Harnessing P450 hydroxylation of multi-ring amines for target synthesis

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Abstract

Harnessing P450 hydroxylation of multi-ring amines for target synthesis

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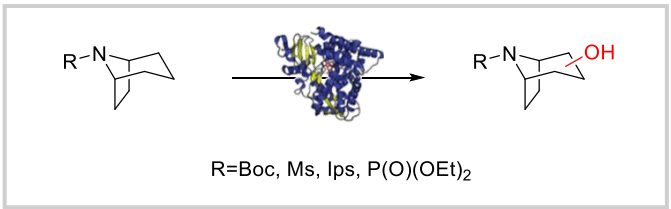
Merton College Trinity Term 2023

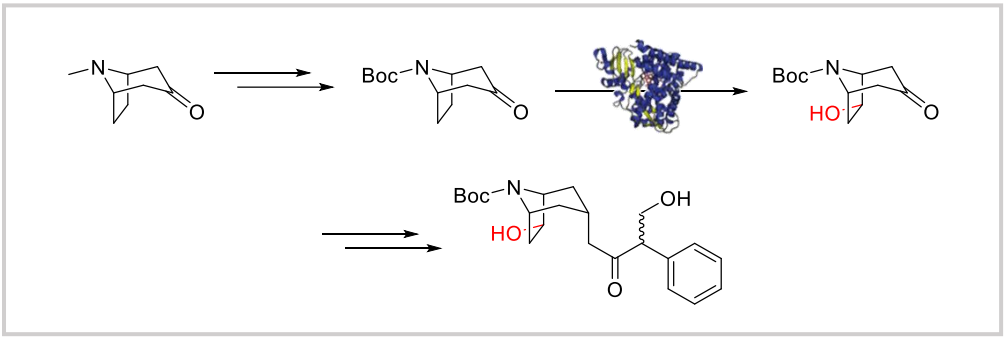
This thesis describes synthetic studies towards the carbon framework of the natural product phlegmadine A and the application of variant P450 enzymes in the synthesis of tropane-based natural product anisodamine.

The **Introduction** provides a short summary of existing C–H activation and biocatalytic strategies in synthesis, as well as an overview of P450 enzymes.

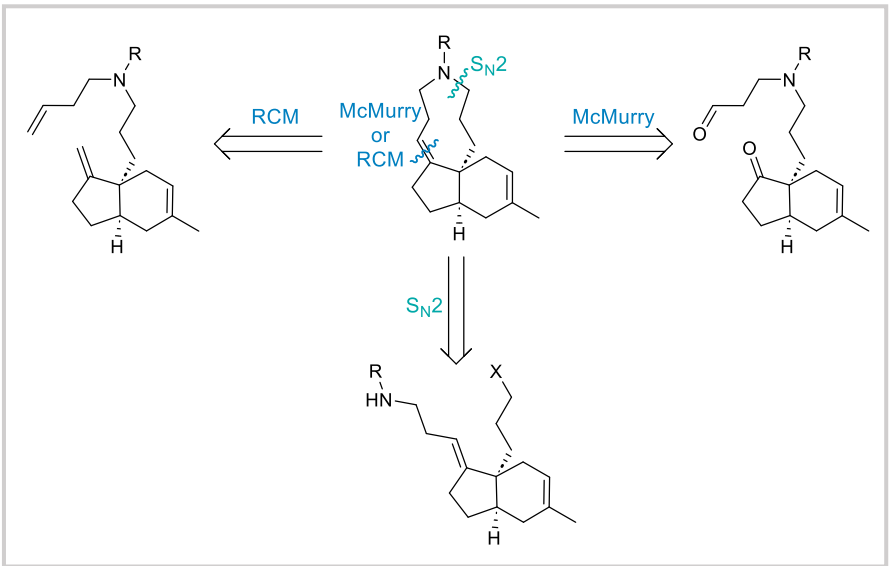
Chapter 2: The first project concerns enzyme-catalysed hydroxylation of variably protected tropanes. Substrate engineering was deployed to alter the selectivity patterns of the P450 enzymes in the variant library; the *N*-Boc, *N*-Ms, *N*-Ips and *N*-PO(OEt)$_2$ derivatives of tropane were tested against the initial library. Different selectivity trends were observed for these derivatives against the same library of variants.



Chapter 3: The late-stage oxidation of the tropane motif was then utilised in the synthesis of the natural product anisodamine. The synthesis of this natural product follows the three-phase process of preparing the cyclic core, screening against a $P450_{BM3}$ variant library and then performing the final chemical synthetic steps.



Chapter 4: The final project describes methods to prepare the tricyclic carbon skeleton of lobscurinol, starting from the cyclopentenone unit. Various disconnections of the nine-membered ring are explored, and the challenges encountered in the preparation of their precursors are discussed.



Abbreviations

°C	degree Celsius
A	alanine
Ac	acetyl
acac	acetylacetonate
ACCN	1,1'-azobiscyclopentanecarbonitrile
AIBN	azobisisobutyronitrile
ALA	alpha-lipoic acid
API	active pharmaceutical ingredient
aq.	aqueous
Ar	aryl
Arg	arginine
atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
C	cysteine
calc.	calculated
CBS	Corey–Bakshi–Shibata catalyst
CDI	carbonyldiimidazole
CF_3PDP	1,1′-bis((5-(2,6-bis(trifluoromethyl)phenyl)pyridin-2-yl)methyl)-2,2′-bipyrrolidine
cod	1,5-cyclooctadiene
CSA	camphorsulfonic acid
cm^{-1}	wavenumbers
conc.	Concentrated or concentration
conv.	conversion
COSY	correlation spectroscopy
CYP	cytochrome P450
d	doublet
D	aspartic acid
DA	Diels–Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarbonylate
DEP	diethyl phosphoryl
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethyoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N*,*N*′-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)-butane
dppf	1,1′-bis(diphenylphosphino)-ferrocene
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E	glutamic acid
E^+	electrophile
e^-	electron
E1cB	unimolecular conjugate base elimination
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron ionisation
equiv.	equivalents
ESI	electrospray ionisation

Et	ethyl
F	phenylalanine
FAD	flavin dinucleotide
FDA	Food and Drug Administration
FID	Flame ionisation detector
FMN	flavin mononucleotide
g	grams
G	glycine
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
GDH	glucose dehydrogenase
h	hours
H	histidine
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
hν	radiation
i	*iso*-
I	isoleucine
IPA	isopropanol
Ips	2-propanesulfonyl
IPTG	isopropyl β-D-1-thiogalactopyranoside
IR	infrared spectroscopy
J	coupling constant
K	lysine
KHMDS	potassium bis(trimethylsilyl)amide
L	litres (volume)
L	leucine (enzyme variant)
LA	Lewis acid
lit.	literature
LRMS	low-resolution mass spectrometry
LTP	long-term potentiation
m	multiplet (NMR)
m	medium (IR)
m	milli (mass/volume)
M	molar (concentration)
M	methionine (enzyme variant)
m-	*meta*-
m-CPBA	3-chloroperbenzoic acid
Me	methyl
Mn(PDP)	[*N*,*N*'-Bis(2-pyridylmethyl)]-2,2'-bipyrrolidinebis(acetonitrile)Mn(II)
min	minutes
mol	moles
mp	melting point
$mP450_{BM3}$	mutant P450 enzyme from *Bacillus megaterium*
MS	mass spectrometry
MS	Molecular sieves (reagent)
Ms	methanesulfonyl
m/*z*	mass/charge ratio
n-	*normal*-
N	asparagine
NADH	nicotinamide adenine dinucleotide
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NHC	*N*-heterocycliccarbene
NHMDS	sodium bis(trimethylsilyl)amide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o-	*ortho*-
P	proline
p-	*para*-
PCC	pyridinium chlorochromate
PCR	polymerase chain reaction
PG	protecting group
Ph	phenyl
Phth	phthalimide
PKR	Pauson–Khand reaction
PMA	phosphomolybdic acid
ppm	parts-per-million
PPTS	pyridinium *p*-toluenesulphonate
Pr	propyl
Py	pyridine
q	quartet
Q	glutamine
quant.	quantitative yield
quin	quintet
R	generic group (chemical structure)
R	arginine (enzyme variant)
R_f	retention factor
R_t	retention time
RCM	ring-closing metathesis
rpm	revolutions per minute
R-PTTL	*N*-phthaloyl-(*R*)-*tert*-leucinate
RT	room temperature
s	singlet (NMR)
s	strong (IR)
S	serine
s-	*sec*-
sat.	saturated
sec	seconds
sext.	sextet
Sia	disiamylborane
SM	starting material
S_N2	bimolecular nucleophile substitution
t	triplet
T	threonine
t-	*tert*-
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFDO	mono(trifluoromethyl) methyldioxirane
Tg	3,5-dimethylhepta-2,5-dien-4-one
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TON	turnover number
Troc	2,2,2-trichloroethoxycarbonyl
Ts	4-toluenesulfonyl
UV	ultraviolet
V	valine
WT	wildtype
w	weak
W	tryptophan
w/v	weight-to-volume ratio
X	any halogen
Y	tyrosine
δ	chemical shift
μ	micro

ν_{max}	infrared absorption maximum

$P450_{BM3}$ variant abbreviations

The haem domain of the $P450_{BM3}$ wildtype has 477 amino acid residues, of which 25 are mutated in this thesis. When the n^{th} residue (X) has been mutated into a different amino acid (Z), the mutation is denoted XnZ. For example, in the wildtype the 74^{th} amino acid is alanine (A); the mutation A74G denotes that the alanine has been mutated into a glycine (G). The G265GG mutation refers to an insertion of a glycine residue between Gly265 and His266 in the wild-type sequence; however, the numbering of subsequent residues is not changed, e.g. Thr268 in the wild-type sequence remains Thr268 in the insertion mutant.

Abbreviation	Relationship to subset abbreviations	Mutations
GV	-	A74G/F87V
GVQ	**GV** + L188Q	A74G/F87V/L188Q
RP	-	R47L/Y51F/I401P
KU3	-	N239H/I259V/A276T
RT2	**KU3** + R47L/Y51F/A191T/L353I	R47L/Y51F/A191T/N239H/I259V/A276T/L353I
RLYF	-	R47L/Y51F
K19	-	H171L/Q307H/N319Y
R19	**RLYF** + **K19**	R47L/Y51F/H171L/Q307H/N319Y
KSK19	**K19** + F87A	F87A/H171L/Q307H/N319Y
RK	**RLYF** + **KSK19** **R19** + F87A	R47L/Y51F/F87A/H171L/Q307H/N319Y

Table 1: The mutations present in common $P450_{BM3}$ variant abbreviations.

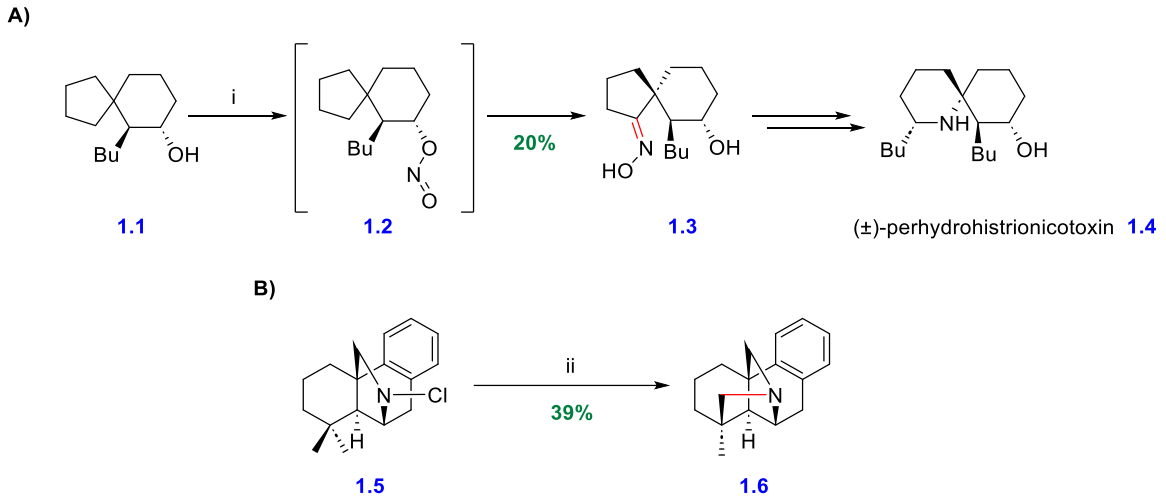
Chapter 1: Introduction

1.1 Chemical C(sp^3)–H activation

Enantiomerically pure alcohols are key intermediates in the synthesis of chiral substrates used in the pharmaceutical and agrochemical industries,[1,2] and their efficient formation is of great value to organic synthesis. To this end, late-stage C–H oxidation is an efficient method of incorporating alcohol groups, since it allows the synthetic route to focus on skeleton-building without the need for a protecting group strategy or unnecessary redox manipulations during the synthesis, and various reviews cover how late-stage functionalisation strategies can be applied to the industrial syntheses of drug-like compounds.[3–6] Aliphatic hydroxylation could be viewed as the most basic form of C–H functionalisation; oxidising an unfunctionalised aliphatic carbon to the corresponding alcohol makes it amenable to typical organic manipulations as it may be further substituted, alkylated, acylated, oxidised or eliminated, as desired. Performing this transformation with high efficiency and selectivity, however, constitutes a formidable challenge owing to the strength of C–H bonds and the occurrence of many C–H bonds of similar energy in organic compounds, especially in complex molecules. The most documented methods of C(sp^3)–H functionalisation are based on three main strategies: hydrogen-atom transfer, metal-catalysed carbene and nitrene insertions, and directed transition-metal-catalysed C–H activation.

1.1.1 Hydrogen atom transfer *via* intramolecular radical reactions

Early approaches to the functionalisation of unactivated C(sp^3)–H bonds involved the use of free radical reactivity. For example, the Barton reaction (discovered in 1960) was used to introduce an oxime selectively in the well-known synthesis of (±)-perhydrohistrionicotoxin **1.4** (Scheme 1A).[7] Prior to that, though, the Hofmann–Löffler–Freytag reaction (discovered in 1883) had been long known and is probably the earliest discovered example of a synthetically valuable C–H functionalisation; this reaction was, for example, employed to synthesise the bridged nitrogen structure of tertiary amine **1.6**, an intermediate useful for the preparation of the kobusine-type alkaloids (Scheme 1B).[8]



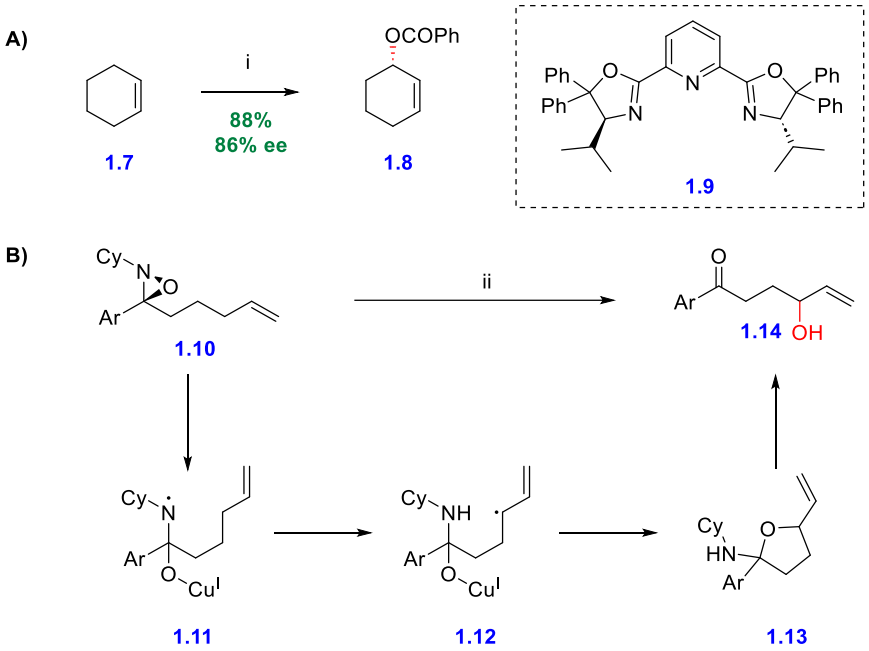
Scheme 1: i) NOCl, pyridine, DCM, 0 °C, then *hv*; ii) CF_3CO_2H, *hv*, RT, 5 h.

In these reactions, an H-atom is transferred from a C–H bond to a radical species centred on oxygen, nitrogen, or an sp^2-carbon (vinyl, aryl), thermodynamically driven by the formation of a stronger X–H bond than the C–H bond broken.[9] Kinetically, intramolecular reactions are often favoured over analogous intermolecular reactions due to their higher effective concentration and lower entropic cost in achieving the transition state. In most cases, 1,5-hydrogen atom transfer (1,5-HAT) is the predominant pathway since it achieves a near-linear arrangement of $[C\cdots H\cdots X]^{\bullet}$ within a six-membered cyclic transition state and entropic losses are lower than for more remote 1,n-abstractions.[9] This approach is an example of late-stage functionalisation which avoids the need for protecting groups during the earlier synthesis; however, these particular reactions require photochemical initiation and often harsh acidic or basic conditions which can limit the substrate scope. These early reactions do, however, show that the efficient functionalisation of unactivated C(sp^3)–H bonds results in profound synthetic advantages, unmatched by stepwise functional group interconversions.

The Karasch–Sosnovsky reaction, first reported in 1958,[10] is a radical oxidation which converts an allylic alkene into an allylic alcohol using a copper catalyst and a perester. Singh *et al*. published an enantioselective variant of the Karasch–Sosnovsky reaction in 1998, using chiral copper ligand **1.9**, and were able to convert cyclic olefins to (*S*)-allylic benzoates in up to 86% ee (Scheme 2A).[11]

More recently, in 2012, Aubé *et al*. reported intramolecular oxidation of activated C–H bonds to form allylic and benzylic alcohols (Scheme 2B).[12] In this reaction, Cu(I) promotes the fragmentation of oxaziridine **1.10** to form *N*-centred radical **1.11** which could undergo 1,5-hydrogen abstraction forming

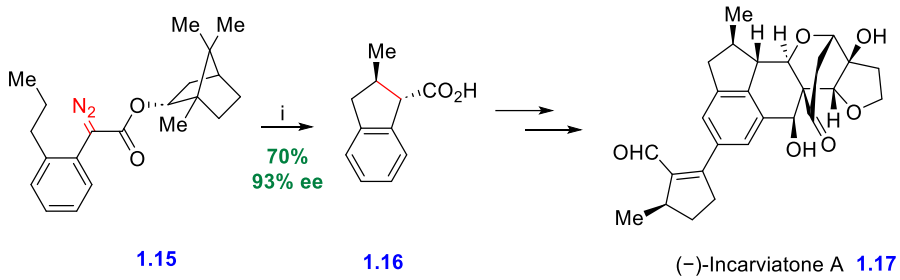
an allylic radical **1.12**. This then undergoes radical recombination to form cyclic intermediate **1.13**, which is hydrolysed to form product **1.14**. Although highly chemoselective, this process is limited to this specific class of substrates.



Scheme 2: i) **1.9**-$(CuOTf)_2$ (0.6 mol%), MeCN, $PhCO_3t$-Bu, RT; ii) $[Cu(PPh_3)Cl]_4$ (5 mol%), THF, 66 °C.

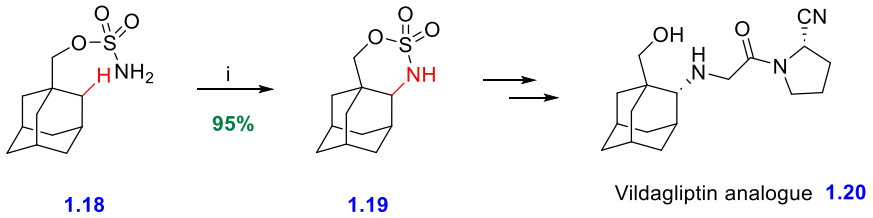
1.1.2 Carbenes and nitrenes, and their metal-bound equivalents

First used synthetically by Doering in 1954,[13] carbenes have also been explored as reactive intermediates for the activation of C(sp^3)–H bonds. Along with nitrenes, the lack of a complete octet configuration renders them highly electrophilic and sufficiently energetic to break unactivated C–H bonds.[9] Transition metal carbenoids are stabilised versions of the free reactive intermediates leading to more controlled reactions. For instance, the combination of a diazo precursor and Rh(II) catalysis is reliable for accomplishing intramolecular insertions.[14] The synthesis of natural product (–)-incarviatone A (Scheme **3**) made use of a highly diastereoselective Rh-catalysed intramolecular C–H insertion to construct the indane core.[15]



Scheme 3: (i) Rh_2(*R*-PTTL)$_4$ (1 mol%), toluene, 0 °C, 14 h, then LiOH, MeOH, 60 °C, 20 h.

Transition-metal-catalysed nitrenoid C(sp^3)–H insertions use sulfamate and carbamate precursors.[16] For example, intramolecular C–N bond formation from such substrates can be achieved using $Rh_2(OAc)_4$ as a catalyst and $PhI(OAc)_2$ as a stoichiometric oxidising agent,[17, 18, 19] as in the synthesis of vildagliptin analogue **1.20** (Scheme 4).[20] The regioselectivity in this and similar reactions arises from the proximity of the C–H to the carbenoid centre, combined with the strong preference for insertion into activated C–H bonds when these are present and sterically accessible.



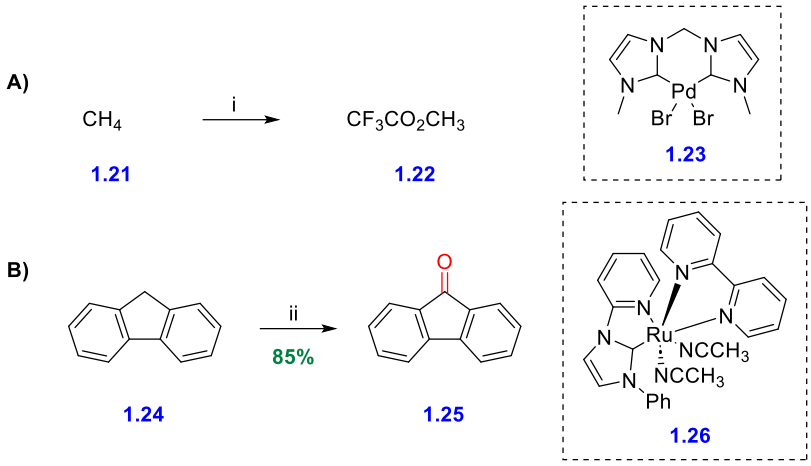
Scheme 4: (i) $Rh_2(OAc)_4$ (1 mol%), $PhI(OAc)_2$, DCM.

These reactions often proceed under milder conditions than those typical of classical free-radical processes, have good functional group tolerance, and can achieve extremely high regio- and stereochemical control by varying the ligands of the metal-centred reagents. The reagents are usually employed catalytically and the reactions are therefore atom efficient and relatively environmentally benign compared to earlier methods.

1.1.3 Transition-metal-catalysed C−H activation

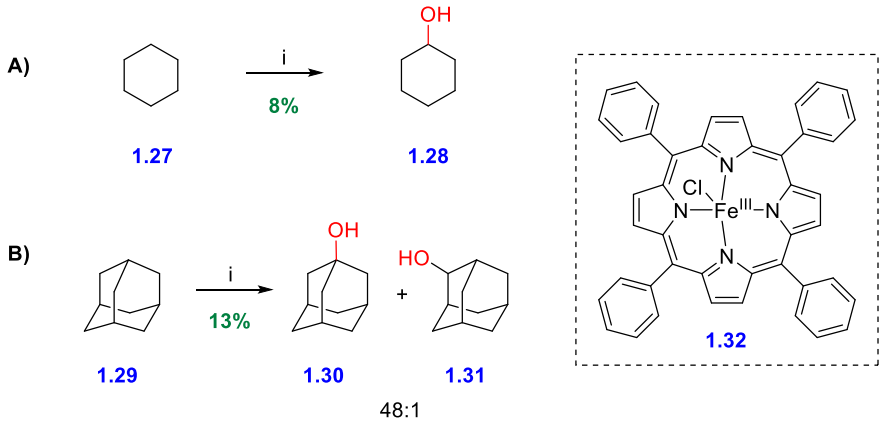
Metal–chelated *N*-heterocyclic carbenes (NHCs) have been established as effective catalysts to activate C(sp^3)−H bonds. In 2002, Strassner *et al*. reported the first example of Pd−NHC complexes for the conversion of methane into the corresponding methyl esters (Scheme 5A).[21] Further to this, in 2017, Choudhury *et al*. reported a mixed NHC/bipyridine Ru(II) catalyst for the selective oxidation of benzylic

C(sp^3)–H bonds to ketones such as that depicted in Scheme 5B.[22] NHCs have been extensively used and reviewed regarding C–H activation,[23] and can be easily modified to vary the steric environment around the metal by *N*-substitution and backbone modification, allowing tuning of the ligand for the optimum performance in catalysis; however, NHCs have not yet been used in stereoselective hydroxylation reactions.



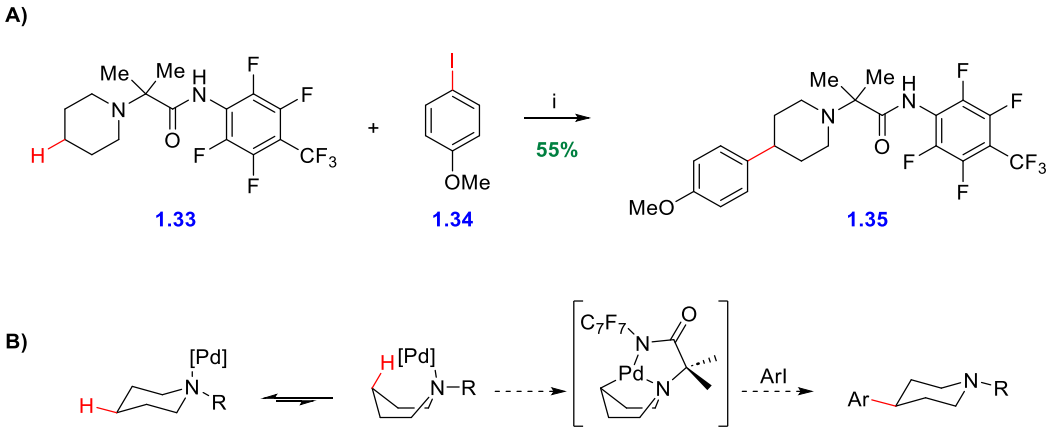
Scheme 5: i) **1.23** (10 mol%), CF_3CO_2H, $(CF_3CO)_2O$, $K_2S_2O_8$, 90 °C; ii) **1.26** (3 mol%), $NaIO_4$, CH_3CN, H_2O, 70 °C.

Pioneered by Breslow in 1970,[24] metalloporphyrin-based catalysts are designed to mimic C–H activating haem-iron groups found in Nature. One of the first metalloporphyrin-based catalyst to be developed was by Groves *et al.*, in the hydroxylation of cyclohexane **1.27** (Scheme 6A) and adamantane **1.28** (Scheme **6**B).[25, 26] Since then, higher yielding iron, manganese, cobalt, osmium and ruthenium porphyrin-based catalytic systems have been developed.[27–31]



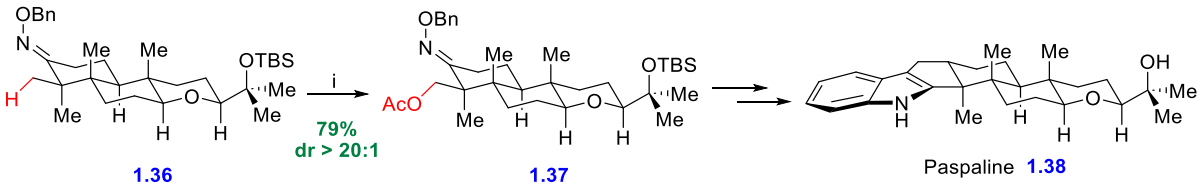
Scheme 6: i) PhIO, **1.32** (10 mol%), DCM, RT.

Porphyrin-based metal catalysts often show poor regio- and chemo-selectivity; however, asymmetric C–H activation makes use of a chiral metal-based catalyst to influence the regio- and stereochemical outcome of the reaction. Coordination between a transition metal and a Lewis-basic directing group brings the metal centre into close proximity to attached C–H bonds, leading to agostic interactions which lower the energy barrier for bond cleavage.[9] Pd catalysts have been employed in amine functionalisation, directed by an electron-withdrawing group installed on the nitrogen atom. For example, Pd-catalysed transannular C–H activation was used for the derivatisation of piperidine, a heterocycle of central importance in medicinal chemistry (Scheme 7A); subsequent removal of the amide directing group was achieved by reductive cleavage with SmI_2.[32] The authors suggested that coordination of the two nitrogen atoms to palladium generates a bidentate bicyclo[2.2.1]palladacycle, enabling selective transannular C–H activation (Scheme 7B).



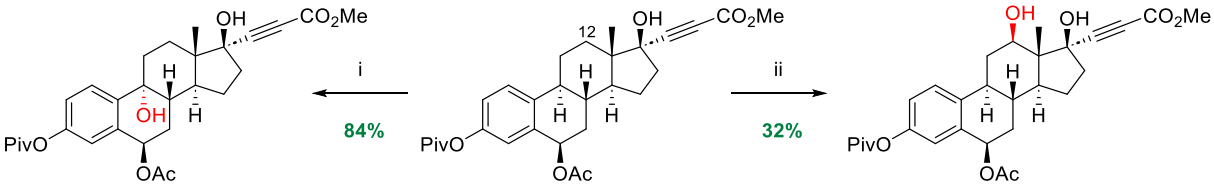
Scheme 7: A) (i) $Pd(OAc)_2$ (10 mol%), CsOPiv, neat, 80 °C; B) Proposed mode of action of the directing group.

Alongside C–C and C–N bond formation, metal-catalysed C−O bond formations have been accomplished as illustrated in the synthesis of paspaline, in which selective activation of the equatorial methyl group in precursor 1.36 was attributed to its proximity to the oxime directing group (Scheme **8**).[33]



Scheme 8: (i) $Pd(OAc)_2$ (15 mol%), $PhI(OAc)_2$, $AcOH/Ac_2O$ (1:1), 100 °C.

While C–H aminations, alkylations and halogenation reactions tolerate aromatic functionality,[34, 35, 36] hydroxylations of unactivated methylene C–H bonds usually tolerate only electronically deactivated aromatics with strongly electron-withdrawing substituents (such as, nitro, trifluoromethyl, triflyl).[37, 38] White *et al*. developed the regio- and chemoselective Mn(CF_3-PDP) catalyst system, enabling late-stage aliphatic C–H oxidation in the presence of aromatic rings, for example, in ethinylestradiol derivative **1.40** (Scheme 9).[39] In contrast to TFDO,[40] which hydroxylates the doubly activated tertiary benzylic site, White's Mn catalyst effectively oxidises the non-activated C-12 methylene position to afford diastereomerically pure alcohol products.



1.39 **1.40** **1.41**

Scheme 9: i) TFDO, DCM, −20 °C; ii) (*R*,*R*)-Mn(CF_3-PDP)$(MeCN)_2$ (0.05 mol%), $ClCH_2CO_2H$, H_2O_2, 0 °C.

Transition-metal catalysts based on iridium,[41] rhodium[42] and nickel[43] have also been reported for C–H activation reactions, and the various directed transition-metal catalysed C–H activation methodologies have been extensively reviewed.[9, 44]

There are many other methods for C–H activation in organic synthesis, including Du Bois' catalytic hydroxylation of hydrocarbons using perfluorinated oxaziridines,[45–47] and Baran's quinuclidine-mediated electrochemical method which oxidises unactivated secondary and tertiary C–H bonds on large scales.[48] This hugely prominent field in modern organic chemistry has been extensively reviewed elsewhere.[48–54]

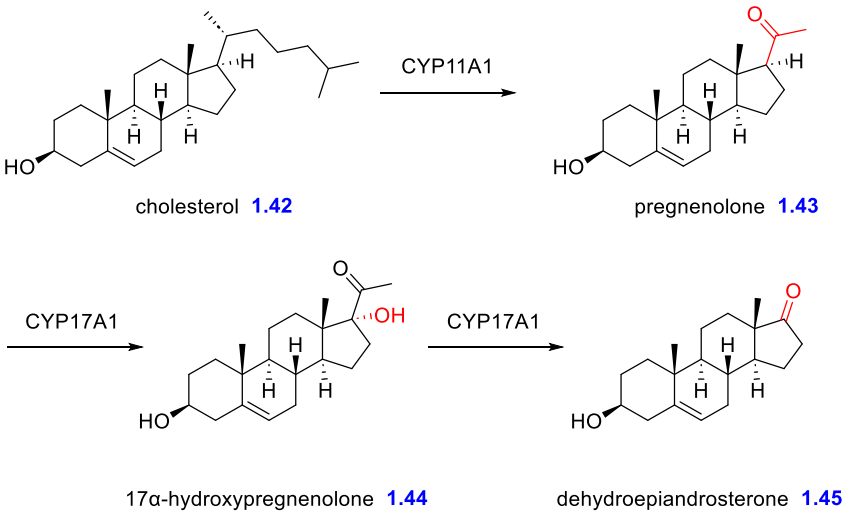
Complementary to the use of chemical reagents, the field of biocatalysis has employed Nature's vast catalytic repertoire to facilitate, among many types of processes, transformations at chemically inaccessible sites. The constraints imposed by substrate orientation in the enzyme active site mean that biocatalytic transformations usually proceed with high regio- and stereoselectivity, and the enzyme can be engineered to achieve a desired reactivity by optimising the amino acid residues, most commonly in and around the active site. The use of oxidative enzymes to produce valuable chiral building blocks is

an effective and environmentally benign alternative to traditional chemical methods because the reactions proceed under mild, aqueous conditions, use abundant and non-toxic aerial oxygen as the stoichiometric oxidising agent, and, unlike many expensive and rare heavy-metal catalysts, enzymes are plentiful and their supply is sustainable.[55, 56] The main obstacles towards their widespread application include expression levels in heterologous organisms, the need for co-factor recycling systems for reactions *in vitro*, issues with scale-ability (especially at high concentrations of hydrophobic organic compounds), and the challenge of engineering them for a particular task.[57]

1.2 P450 enzymes

1.2.1 Biological function

Discovered in the late 1950s, the cytochrome P450 superfamily of enzymes are monooxygenases that catalyse the oxidation of organic compounds by, among other means, C–H activation. They have been identified in all kingdoms of life, and play a significant role in the biological functionalisation of natural products, including biosynthesis, and degradation and detoxification of biological metabolites and xenobiotics.[57, 58] For instance, the conversion of cholesterol to dehydroepiandrosterone (which acts as a precursor to other steroid hormones) involves three P450-catalysed steps: oxidative side-chain cleavage, hydroxylation, and a second oxidative cleavage reaction (Scheme 10).[59, 60]

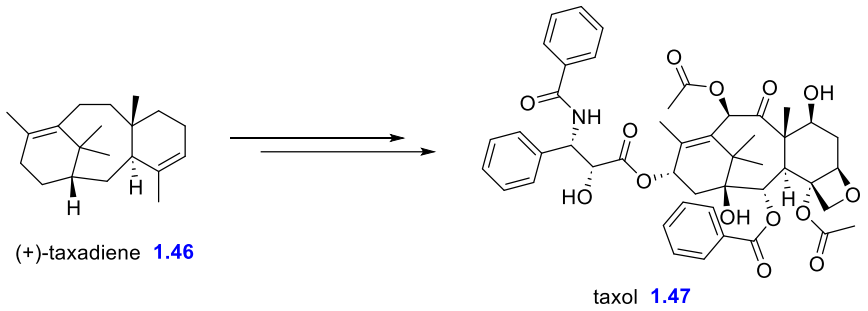


cholesterol **1.42** pregnenolone **1.43**

17α-hydroxypregnenolone **1.44** dehydroepiandrosterone **1.45**

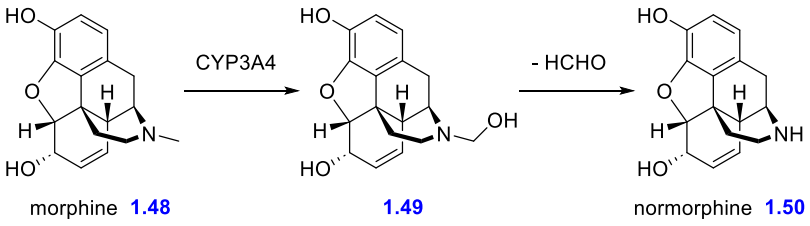
Scheme 10: P450s are crucial in the biosynthesis of steroids.

Similarly, in the Pacific yew *Taxus brevifolia*, cytochrome P450 enzymes introduce all the oxygen ring-substituents found in paclitaxel (taxol), starting from the diterpene precursor taxadiene (Scheme **11**).[61,62]



Scheme 11: P450 enzymes are responsible for introducing all the oxygen atoms in taxol.

As mentioned, P450 enzymes can also metabolise xenobiotics. For example, morphine is deactivated by mammalian CYP3A4, furnishing the demethylated derivative normorphine **1.50** *via* hydroxylation of the *N*-methyl group followed by loss of formaldehyde (Scheme 12).[63]



Scheme 12: P450-mediated metabolism of morphine to normorphine.

1.2.2 Structure of active site and catalytic cycle

The P450 enzymes are hemoproteins, employing a haem group (Figure 1) located in their active site; a cysteine thiolate and water act as the two axial ligands of the hexacoordinate Fe(III) centre. The enzyme derives its name (pigment 450) from this haem group's characteristic absorption wavelength when its ferrous form is complexed to carbon monoxide.[64, 65]

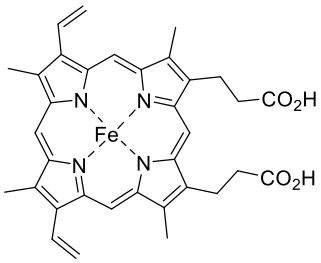


Figure 1: Structure of iron-protoporphyrin located in P450 active site.

The catalytic cycle of the enzyme is believed to be as follows (Figure 2):[57, 66]

- Beginning from resting state **A**, ligand binding triggers displacement of the axial water molecule. This switch from a hexacoordinated to a pentacoordinated state is accompanied by a change of the ferric centre from a low-spin (S = 1/2) to high-spin (S = 5/2) state (**B**), resulting in an increase in the species' reduction potential.

- The Fe(III) receives an electron from a molecule of NADPH and is reduced to the Fe(II) species (**C**). This electron transfer step is rate-limiting for the catalytic cycle.[67]

- Molecular oxygen binds to this species, producing **D**, which receives another electron to form Fe(III)-peroxo species **E**, which is rapidly protonated to give Fe(III)-hydroperoxy species **F**.

- Another protonation and heterolytic cleavage with loss of water generates Compound I (**G**), a Fe(IV) oxo (ferryl) species in which a radical cation is delocalised over the porphyrin and thiolate ligands. Compound I is the active species in P450-catalysed oxidation.[68]

- Abstraction of a hydrogen atom from the substrate forms an alkyl radical and Fe(IV) hydroxide complex **H**. The alkyl radical then undergoes radical rebound onto the iron-bound OH group, forming the alcohol product and regenerating the Fe(III) centre.

- Finally, the binding of water or another molecule of substrate returns the enzyme to states **A** or **B** respectively, closing the cycle.

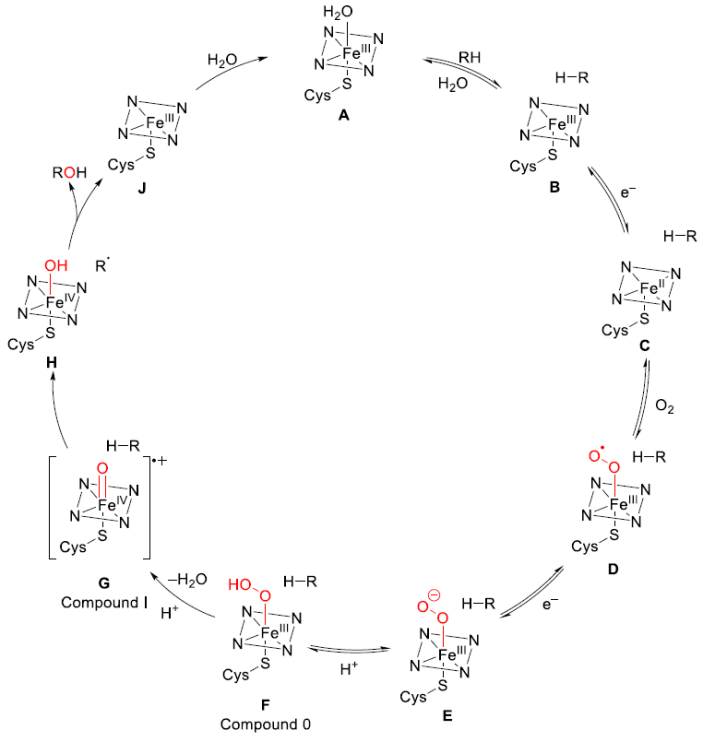
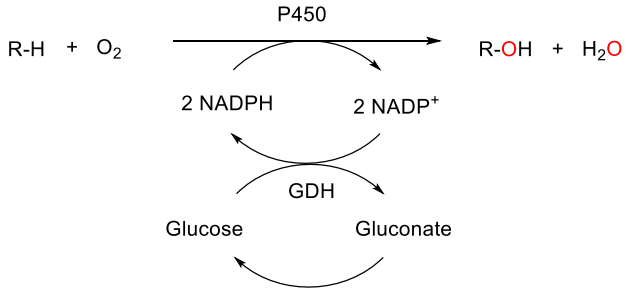


Figure 2: Cytochrome P450 catalytic cycle.

Ultimately, this results in the incorporation of a single oxygen atom into an organic substrate:[69]

$$RH + O_2 + 2e^- + 2H^+ \rightarrow ROH + H_2O$$

In synthetic application, the $2e^-$ and $2H^+$ commonly derive from glucose, which is added to the reaction mixture along with glucose dehydrogenase (GDH) to recycle the nicotinamide adenine dinucleotide phosphate ($NADP^+$) cofactor (Scheme 13).



Scheme 13: The source of electrons and protons in the catalytic cycle of P450-mediated hydroxylation.

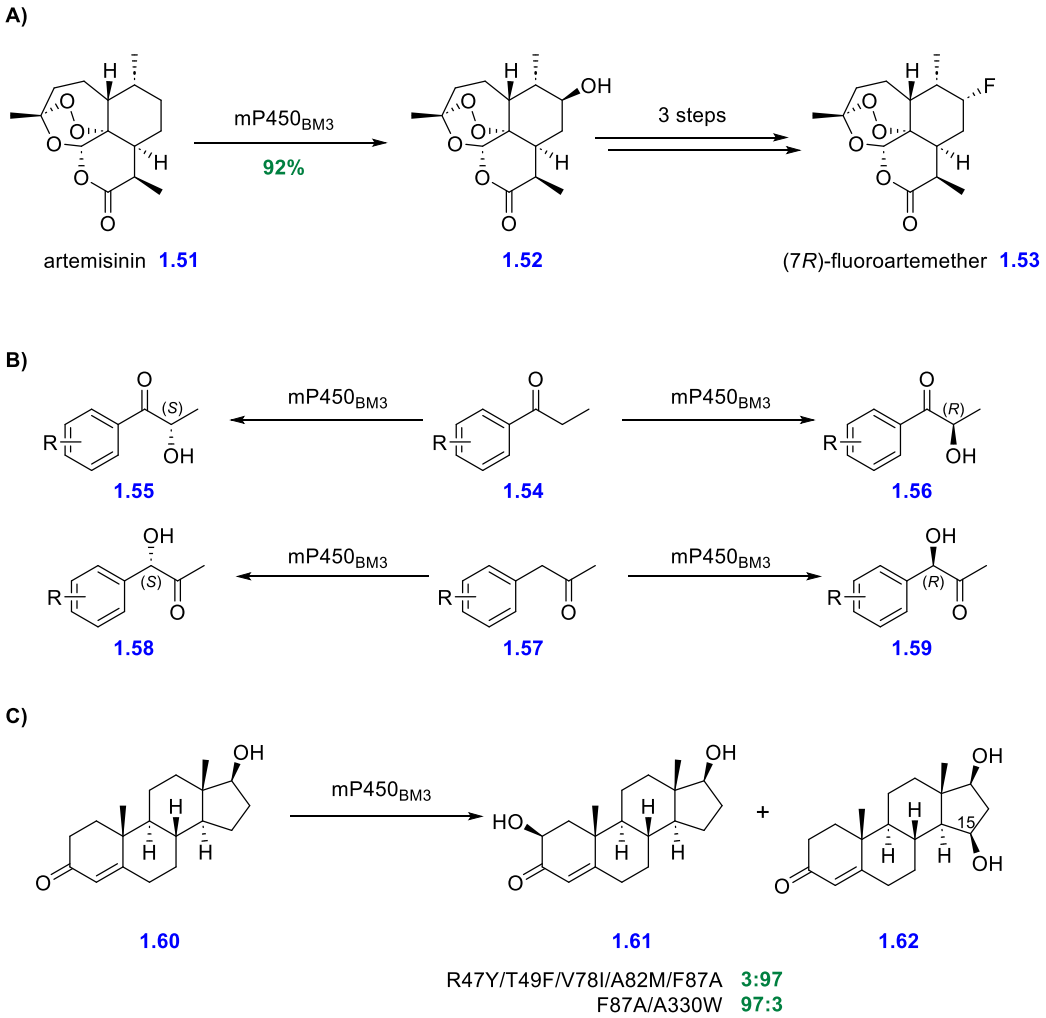
1.2.3 Applications in chemical synthesis

Due to their ability to hydroxylate unactivated C–H bonds, cytochrome P450s are attractive biocatalysts for application in organic synthesis. Microbial P450s are stable, soluble and readily expressed in *E.*

coli;[70] indeed, these enzymes are ideal for laboratory synthesis because they have a broad substrate range, maximising the likelihood of finding promising initial hits for further selectivity optimisation.[57] $P450_{BM3}$ (the third P450 enzyme isolated from *Bacillus megaterium*) is commonly employed[57] in such studies as it uniquely possesses its own reductase domain, making it self-sufficient; this means it only requires an NADPH cofactor to operate, whereas other P450 enzymes require a redox partner, such as an iron-sulfur containing ferredoxin in bacterial P450s, or an FAD/FMN-dependent oxidoreductase in mammalian microsomal enzymes.[71] Mutant variants have been produced, through both error-prone PCR and site-directed mutagenesis, that demonstrate improved reactivity and wider substrate scope than wild-type enzymes. Such cytochrome P450 libraries have found synthetic application in three main areas:

- Hydroxylation of small, relatively unfunctionalised molecules to create otherwise inaccessible fragment molecules to underpin drug discovery and for further elaboration;
- Kinetic resolution of racemic substrates;
- Enzymatic hydroxylation at strategic points on natural product-like scaffolds to open new synthetic approaches to target molecules.

The P450-mediated hydroxylation of artemisinin **1.51** by Zhang *et al*. is an example of the third area of application;[72] the hydroxylated derivative **1.52** was converted into (7*R*)-fluoroartemether **1.53**, thus blocking a potential site of metabolism (Scheme 14A). The Reetz group has also demonstrated the application of $P450_{BM3}$ enantioselective hydroxylation of small molecules;[73–78] for example in the oxidative α-hydroxylation of ketones **1.54** and **1.57** to form chiral acyloins with high regioselectivity (up to 99%) and enantioselectivity (up to 99% *ee*) (Scheme 14B).[79] The same group carried out P450 screening of the steroid testosterone **1.60** (Scheme 14C),[80] and found that the regioselectivity of the hydroxylation could be tailored by the topology of the binding pocket: the R47Y/T49F/V78I/A82M/F87A variant selectively hydroxylated α- to the unsaturated ketone (**1.61**), while the F87A/A330W variant reversed this selectivity, giving hydroxylation at the C15 position on the cyclopentane ring (**1.62**) as the major product.



Scheme 14: P450-mediated hydroxylation of A) artemisinin, B) small molecules, and C) testosterone.

1.2.4 Wong and Robertson group research

For over 20 years, the Wong group has investigated selective P450 oxidation by engineering $P450_{BM3}$ variants, each with subtle differences in the size, shape, and polarity of the active site, enabling C–H bond functionalisation to occur at unactivated positions which would otherwise be chemically inaccessible. The Robertson and Wong groups have collaborated[57, 81–85] to explore $P450_{BM3}$ hydroxylation of various *N*-protected cyclic amines, including monocyclic and bridged- and spiro-bicyclic substrates, as well as spirocyclic *N*-benzyl lactams.[86, 87]

Expanding the scope of this research to assist in natural product synthesis, the groups have worked on target syntheses of biologically active alkaloids and their analogues. Past examples include ferruginol, clausenamide, trigoxyphins K and L, viridiol, balanol, alvocidib, and eleutherobin (Figure 3). They have

also studied the metabolites produced *via* oxidation of common drugs including lidocaine, naproxen, chlorzoxazone, testosterone, diclofenac and amitriptyline.[88]

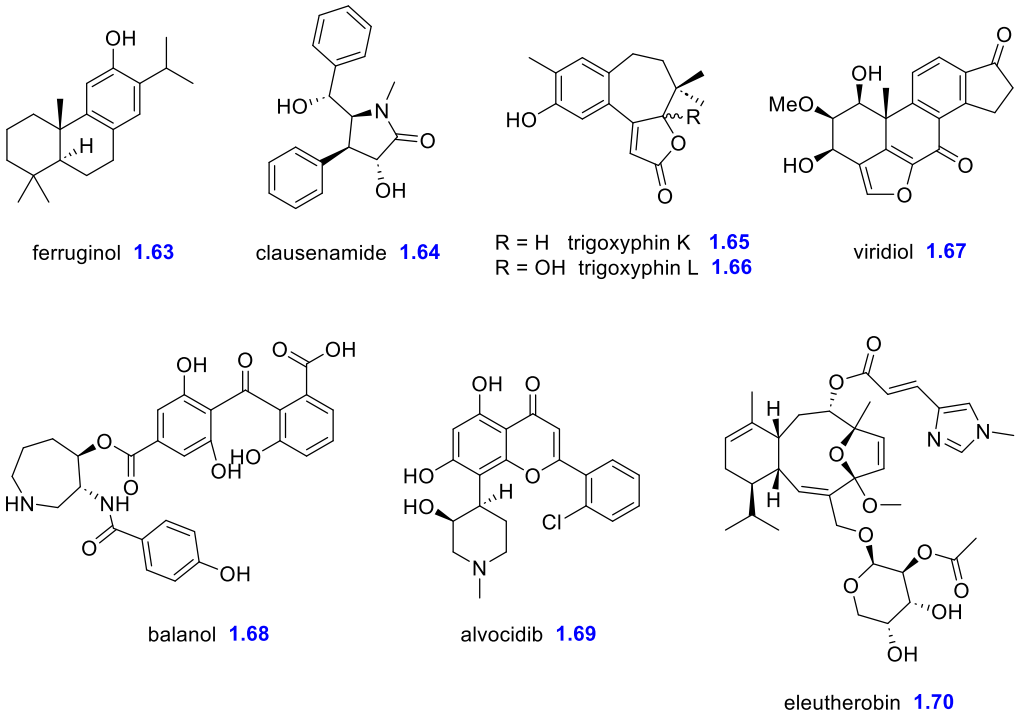
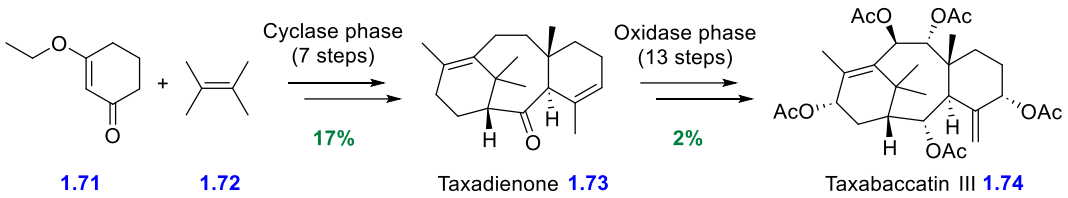


Figure 3: Examples of natural products studied in the Robertson and Wong group collaboration.

Through an understanding of the reactivity and selectivity patterns exhibited by the P450 library when confronted with diverse structural substrate classes, P450s have the potential to enter the synthetic chemistry toolbox as general oxidation catalysts alongside traditional chemical reagents. The work described in this thesis stems from this collaboration and involves P450-mediated oxidation studies of *N*-protected nortropanes, followed by the potential application of P450-mediated late-stage oxidation in natural product synthesis.

Conceptually related work in this area accomplished the total synthesis of terpenoid natural products in two phases: a cyclase phase which assembles the carbocyclic core, followed by an oxidase phase which adds the necessary oxygen functionality. In 2010, Baran applied this two-phase approach to the synthesis of highly oxidised taxanes, conceptually mimicking the biosynthesis of such molecules and highlighting the benefits of sequential C–H functionalisation in organic synthesis (Scheme 15).[89] During the cyclase phase, the partially-oxidised taxadiene (taxadienone) was assembled from commercially available alkene **1.72** and enone **1.71**.[90] Then in the second, oxidase, phase the core was elaborated in a sequence

of chemical C–H oxidations, affording taxabaccatin III **1.74**.[91] The synthesis demonstrates the potential for this two-phase strategy to achieve divergent access to a series of highly oxidised natural products.



Scheme 15: Enantioselective two phase synthesis of taxabaccatin III.

Although Baran published a conceptually similar synthesis of taxol in 2020,[92] the authors commented that accessing these compounds *via* chemical synthesis will likely never be competitive with a fully enzymatic approach, and concluded that the hybrid chemical/biochemical approach was more advantageous to solely chemical means.[93]

This project intends to explore both phases of enzyme-assisted total synthesis:

- Chapter 2 describes enzymatic methods for the oxidase phase, using a library of variant P450 enzymes;
- Chapter 3 describes the synthesis of a natural product post-enzymatic oxidation;
- Chapter 4 describes progress in the assembly of an alkaloid core prior to enzymatic oxidation.

The use of $P450_{BM3}$ enzymes on a wide range of substrates will increase knowledge of the enzymes' activity and selectivity when faced with diverse substrates, helping to build a reactivity profile and moving these variants closer to application as general oxidation catalysts.

Chapter 2:

In which variably protected tropanes are oxidised regioselectively by the $P450_{BM3}$ library

Chapter 2: Regioselective oxidation of tropane

2.1 Previous work on oxidation of *N*-protected nortropanes

The influential 'escape from flatland' publication in 2009 described the movement of the chemical industry to include more sp^3-rich scaffolds *vs*. the predominant sp^2, to improve on key pharmacokinetic properties and ultimately reduce the failure rate of drug candidates.[94] Over the subsequent decade, there has been growing interest in introducing more 3-dimensionality and saturation into molecular substructures within the pharmaceutical and agrochemical industries; for example, spirocycles are desirable scaffolds for drug discovery due to their 3D conformational structures, and their relative rigidity reduces entropic loss upon ligand-protein binding.[95–97]

Nitrogen-containing heterocycles are extremely common structural components of drug fragments, present in 59% of USA FDA-approved small-molecule drugs, including antibiotics, antidepressants and anti-HIV agents.[98, 99, 100] Among these structures, saturated cyclic amines account for a high proportion of medicinal molecules and are considered prominent bioactive motifs in natural products. Additionally, as discussed in Chapter 1, late-stage functionalisation of complex scaffolds *via* C–H activation has become an integral tool in organic synthesis; with the development of highly chemoselective methodologies, with high functional group tolerance and without the requirement for pre-installation of specific functionalities, late-stage functionalisation can offer a rapid way to generate compounds of interest. Combining these ideas, the development of efficient late-stage functionalisation of saturated cyclic amines is of great interest and importance in organic synthesis. The functionalisation of the chemically-activated α-position of saturated cyclic amines has been extensively studied and reviewed,[101–105] while functionalisation of the β- and γ-positions within saturated cyclic amines has been reviewed by Fan's group.[106]

The tropane ring forms the core structure of a wide range of natural products and synthesised drugs, which have been intensively studied due to their variety of pharmacological activity.[107] The pharmaceutical industry manufactures over 20 active pharmaceutical substances containing the tropane

moiety,[108] which are used as mydriatics, antiemetics, bronchodilators, antispasmodics and local anasthetics.[109–113] Among active pharmaceutical ingredients which contain the tropane moiety in their structure, the most significant in terms of production volume and value are natural products atropine, hyoscyamine and scopolamine, and their *N*-alkylated derivatives. For example, the quaternary ammonium salt scopolamine butylbromide (Buscopan®, **2.4**) is used in the treatment of intestinal tract problems and around 21 tons are manufactured per year (Figure 4).[114]

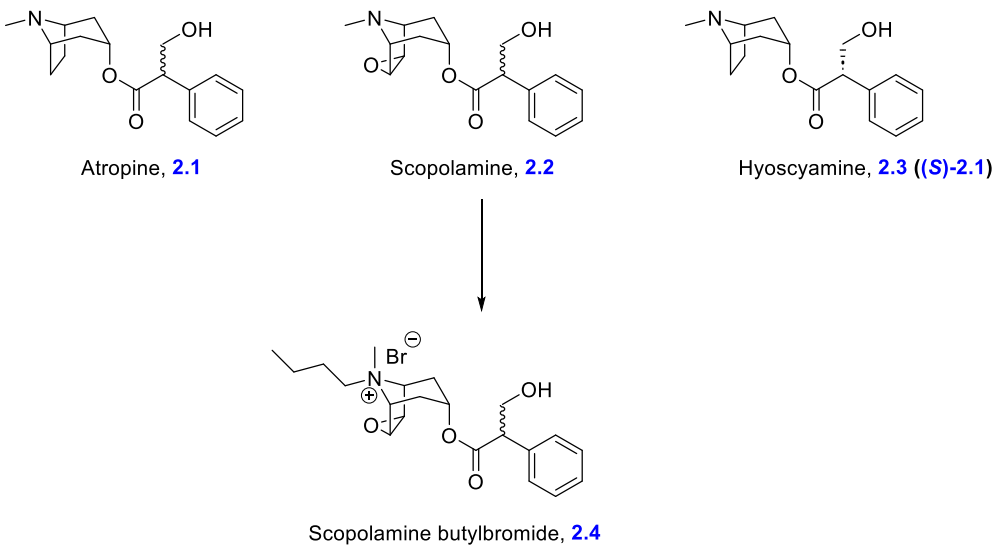
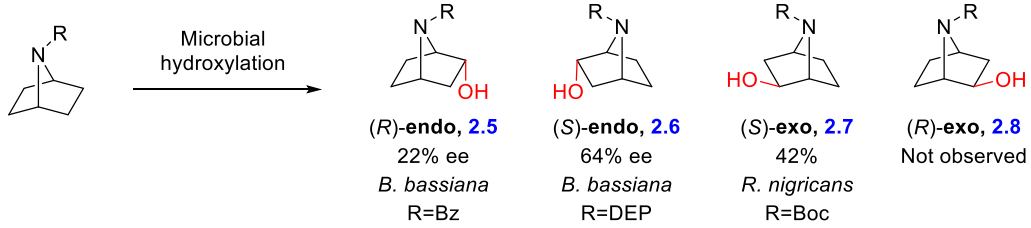


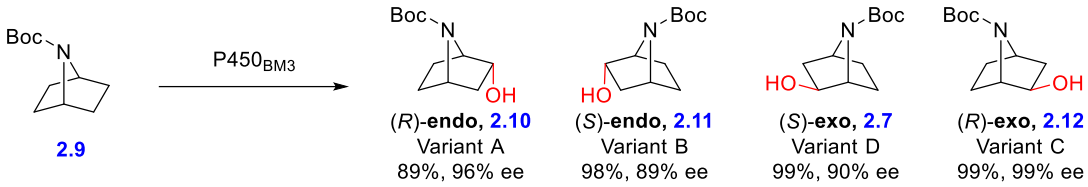
Figure 4: Tropane alkaloids atropine, scopolamine and hyoscyamine, and therapeutic quaternary ammonium salt scopolamine butylbromide.

Although the direct C–H hydroxylation of 8-azabicyclo[3.2.1]octane has not been previously reported, biocatalytic hydroxylation of 7-azabicyclo[2.2.1]heptane derivatives have been reported using the fungi *Beauveria bassiana* and *Rhizopus nigricans* (Scheme 16).[115–117] The former led to products with the highest enantioselectivites for the (*S*)-*endo* alcohol (64% ee) and the (*R*)-*endo* alcohol (22% ee), while the latter microorganism gave the highest selectivity for the (*S*)-*exo* alcohol (42% ee). No (*R*)-*exo* alcohol was observed.



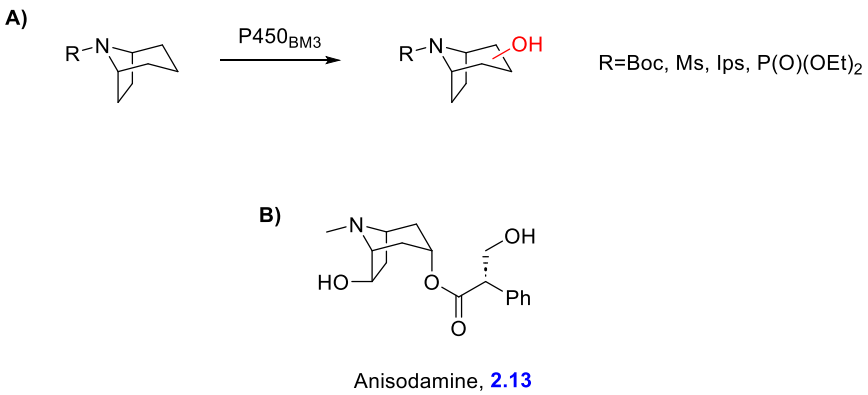
Scheme 16: Highest enantioselectivity observed for the hydroxylation products from the work by Hemenway,[115] Olivo,[116] and Marshall.[117]

Twenty-five years later, work within our group combined enzyme engineering with substrate docking studies to achieve enantioselective functionalisation of all unactivated C–H bonds of *N*-Boc-7-azabicyclo[2.2.1]heptane by cytochrome $P450_{BM3}$ variants (Scheme 17).[86]



Scheme 17: The oxidation products of *N*-Boc-7-azabicyclo[2.2.1]heptane by cytochrome $P450_{BM3}$ variants as discovered within our group. The percentages refer to the regioselectivity and enantioselectivity (ee), respectively, for the diastereomers shown.
Variant A: KU3/S72W/A330P; Variant B: GQ/A82M/T260L/I263G/A328L/S332F;
Variant C: GV/S72F/A184I/L188F/I263G/A328G; Variant D: R19/F87I.

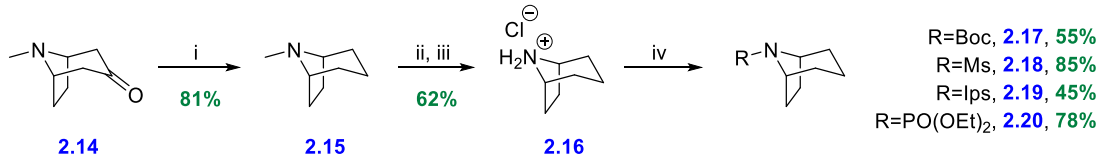
When investigating P450 functionalisation, the most interesting outcomes are when oxidation takes place at unactivated C–H bonds, since these sites are relatively inaccessible to chemical reagents. In general, an unactivated C–H bond is one whose cleavage results in a non-stabilised radical; in this context these are the C–H bonds non-adjacent to nitrogen. The current project set out to explore the selective functionalisation of unactivated sites in 8-azabicyclo[3.2.1]octane (tropane) derivatives by engineered $P450_{BM3}$ variants (Scheme 18A), and the use of the so-formed products in the synthesis of the natural product anisodamine (Scheme 18B). This chapter discusses the results of P450 screening. The tropane motif was prepared chemically with four protecting groups: Ms ($–SO_2Me$), Ips ($–SO_2i$-Pr), and DEP ($–PO(OEt)_2$). These derivatives were then screened against a common panel of $P450_{BM3}$ variants. Library screening and substrate engineering were deployed to identify key residues and the most effective protecting group for each metabolite, aiming for high conversion of starting material and high product selectivity.



Scheme 18: A) P450 oxidation of differentially protected nortropanes; B) Anisodamine.

2.2 Substrate synthesis

P450 enzymes do not react cleanly with free amines because the nitrogen lone electron pair coordinates to the iron centre in the active site haem group, either deactivating the enzyme or becoming oxidatively degraded;[118] therefore, differentially protected tropanes were prepared as depicted in Scheme 19. The protecting group also offers a means to vary how the substrate is anchored in the active site *via* differential electrostatic, van der Waals and H-bond interactions with the local residues; this 'substrate engineering' allows the generation of different oxidation products when exposed to the same enzyme. Wolff–Kishner reduction of tropinone **2.14** afforded tropane **2.15**, and demethylation gave nortropane hydrochloride **2.16**. Protection using Boc anhydride, methane- or isopropyl-sulfonyl chloride or diethyl chlorophosphate yielded protected tropanes **2.17**–**2.20**. These four substrates were screened with a panel of 48 $P450_{BM3}$ variants initially to obtain a broad oxidation profile and an overview of how their enzymatic reactivities differed.



Scheme 19: i) NH_2NH_2, KOH, ethylene glycol, 200 °C, 18 h; ii) 1-chloroethyl chloroformate, DCE, 90 °C, 18 h; iii) MeOH, 70 °C, 1 h; iv) Boc_2O or RCl, NEt_3, DCM, RT, 18 h.

2.3 Enzymatic screening

The 48 chosen P450 variants were derived from six base variants:

GV	A74G/F87V
K19	H171L/Q307H/N319Y
KU3	N239H/I259V/A276T
RLYF	R47L/Y51F
RP	R47L/Y51F/I401P
RT2	R47L/Y51F/A191T/N239H/I259V/A276T/L353I

These 48 variants had previously given varied metabolite profiles as well as high selectivities in the oxidations of a wide range of organic substrates, including steroids and amines.[81–83, 119–125] Between two to four additional mutations at active site residues V78, F81, A82, F87, A184, L188, I263, A264, G265, E267, A328, P329 and A330 (Figure 5) were introduced by mutagenesis previously developed in the group. The different combinations of mutations at these residues generated diverse binding pocket topologies in the expectation of diverse outcomes from the oxidation reactions.

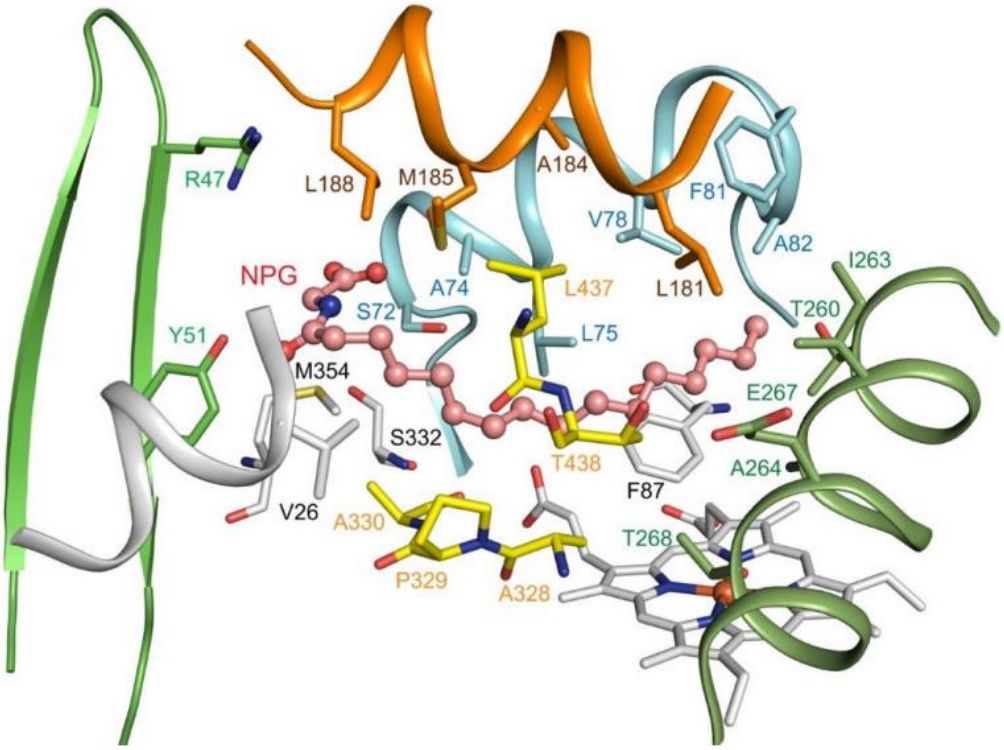


Figure 5: The active site of wildtype $P450_{BM3}$, bound to its natural substrate *N*-palmitoylglycine, with key amino acid residues labelled. PDB ID: 1JPZ.

Screening reactions (1.0 μmol substrate) were carried out at a 2000:1 substrate-to-enzyme ratio in phosphate buffer (pH 7.9) at RT for 24 hours. Glucose, GDH and $NADP^+$ were added to regenerate the NADPH cofactor. Reactions were analysed by GC to determine an approximate conversion of substrate into various products before preparative scale reactions (0.2 mmol substrate) were performed to enable isolation and identification by NMR spectroscopic analysis of the oxidised products. These preparative reactions contained the same components (at their respective concentrations) as the screening reactions, and the oxidation profiles of the scale-up reactions were consistent with those seen during screening. The relative configuration of the oxidised products was established by NMR spectroscopy; however,

the absolute configuration and enantiomeric enrichment of chiral compounds was not established during screening due to difficulty separating enantiomers by chiral GC.

2.3.1 *N*-Boc-protected tropane

Initial screening of *N*-Boc-protected tropane **2.17** indicated the formation of six major oxidised products as detected by GC analysis. Three enzymes RLYF/K19/F87A/A184I, K19/A82M/F87A/A264G and K19/F87V/I263G (Table 2), were chosen for scale-up reactions because of their near perfect conversions and excellent expression. Since many of the screened variants had impressive conversion, these particular enzymes were chosen because their diverse range of products meant that multiple metabolites could be isolated and characterised upon scale-up. The three variants were prepared according to the general procedure (see 5.2.3 Enzymatic Oxidations; General Procedure 2 – Preparative scale reactions) and each introduced to 40 mg of *N*-Boc-tropane **2.17**. Between them, these variants generated all the major products detected during screening in sufficiently high yield for full characterisation by NMR spectroscopic and MS analysis.

Entry	Variant	Retention Time (min)							
		3.04	**3.68**	**3.95**	**4.09**	**4.13**	**4.63**	**5.08**	**Other**
1	RLYF/K19/F87A/A184I	-	-	-	-	-	70%	22%	8%
2	K19/A82M/F87A/A264G	1%	22%	1%	74%	1%	-	-	1%
3	K19/F87V/I263G	1%	-	30%	5%	30%	1%	29%	4%

Table 2: Enzymes selected for scale-up with *N*-Boc-tropane **2.17**. GC R_t for substrate (3.04 min) and six oxidised products (3.68–5.08 min). Percentages refer to fractional area of the total GC peak integration.

The six major products were identified as γ-ketone **2.21**, *exo*-α-alcohol **2.22**, *endo*-γ-alcohol **2.23**, *exo*-γ-alcohol **2.24**, γ-keto/*exo*-α-alcohol **2.25** and *exo,exo*-α,γ-diol **2.26** (Figure 6). Compounds **2.21**, **2.23** and **2.24** were already reported and their ^{1}H and ^{13}C NMR spectra could therefore be compared to published data.[126, 127]

These products were identified first by the presence of additional ^{13}C NMR spectroscopic resonances in the 60–80 ppm region and/or the 200–210 ppm region, to determine whether alcohol and/or ketone

functionality had been added, respectively. When oxidation occurred only at the γ-position (**2.21**, **2.23** and **2.24**), the molecule remained symmetrical and the bridgehead protons gave a broad singlet in the 4.0–4.5 ppm region of the ^{1}H NMR spectrum. A large geminal coupling constant of J = 16.0 Hz for the two pairs of diastereotopic β-protons adjacent to the carbonyl group confirmed the assignment of **2.21** (and the γ-ketone of **2.25**). The stereochemical configuration of **2.24** and **2.23** was determined in each case by coupling constants typical of axial (J = 14.0, 3.0 Hz) and equatorial (J = 3.0 Hz only) protons, respectively.

When oxidation occurred at the α-position (**2.22**, **2.25** and **2.26**), the bridgehead protons separated into two broad singlets. Hydroxylation at the α-position was established by COSY correlation of the C**H**OH to both the bridgehead protons. The *exo*-configuration in α-OH of **2.22**, **2.25** and **2.26** was identified by nOe correlations of the C**H**OH proton with the β- and γ-protons, and the *exo*-γ-OH of **2.26** by the C**H**OH diaxial coupling constants. It was notable that no product arising from oxidation at the β-position was observed.

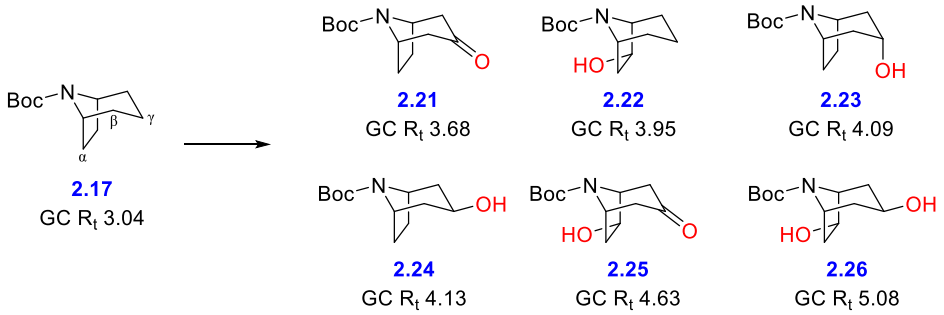


Figure 6: Products characterised from the screening of *N*-Boc-tropane **2.17**, including their GC retention times (GC R_t). Reagents and conditions: $P450_{BM3}$ (2000:1 substrate:enzyme ratio), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h.

The Boc protecting group was well tolerated across the panel of variants and gave generally good conversions: 38 out of 48 enzymes gave a conversion of >50%. Table 3 shows selected data for this screen, which reveals some key residues affecting the conversion and selectivity. Full data for all enzymatic screening can be found in the Appendices, Table 28–Table 32.

Entry	Enzyme variant	Conv.	2.21	2.22	2.23	2.24	2.25	2.26	Others	TON
1	GV/L188Q	100%	4%	12%	1%	20%	12%	16%	**34%**	686
2	RLYF/K19/F87A/A184I	100%					**70%**	22%	8%	1399
3	GV/A184I/A328G	99%	19%	8%		25%	15%	23%	**30%**	495
4	GV/A184I/I263G/A328G	99%		10%	1%	2%	2%	**81%**	3%	1601
5	GV/A184I/I263G	99%		11%		17%	1%	**67%**	3%	1322
6	RLYF/K19/F87A/A184I/ A264G	99%	29%	3%	5%	11%	14%	15%	**52%**	568
7	K19/A82M/F87A/A264G	98%	22%	2%	**74%**	2%			22%	1444
8	RLYF/K19/F87A	97%	2%	4%	6%	4%	**41%**	15%	27%	801
9	GV/A184I/A264G	97%	7%	23%	13%	**49%**		2%	13%	943
10	K19/A82M/F87A	96%	6%	2%	**83%**	8%			7%	1580
11	GV/A184I	95%	5%	27%	9%	**37%**	2%	10%	10%	699
12	K19/A82M/F87A/I263G	64%		26%	2%	**73%**				933
13	K19/A82M/F87A/I263G/ A264G	63%	3%	30%	10%	**54%**			6%	679
14	RLYF/K19/F87A/A328G	61%	10%	17%	31%	**42%**				506
15	K19/A82M/F87A/A264G/ A328G	55%	3%	9%	**69%**	18%			4%	760
16	GV/A184I/A264G/A328G	47%	2%	22%	4%	**73%**				684
17	RLYF/K19/F87A/A184I/ A264G/A328G	45%	6%	22%	16%	**55%**			7%	486
18	K19/A82M/F87A/I263G/ A264G/A328G	31%	1%	38%	1%	**59%**			3%	364
19	RT2	22%		9%	**91%**					410
20	RP/V78I/E267V	6%			**70%**				30%	78
21	KU3/A328I/A330P	3%			**100%**					55

Table 3: Selected conversion and selectivity data for the P450 screening of substrate **2.17**. Selectivity is calculated by peak area ((single metabolite/all metabolites)x100). Colour intensity compares the cell's value to those in the same column for conversion and TON, or for selectivity, to all other selectivities. TON refers to the turnover number for the formation of the (major) metabolite in bold.

The data suggest that mutation of Phe87 to a residue with a smaller side chain – to Ala and Val within the panel of $P450_{BM3}$ variants – is critical for *N*-Boc tropane oxidation activity; variants based on RT2, RP and KU3, which do not have a mutation at F87, showed little activity (entries 19–21). The F87A and F87V mutations created space just above the haem for substrate binding. Of the active mutants, there is not a simple relationship between the addition of a single mutation and the resulting conversion. For example, addition of A264G or A328G onto the GV base variant did not affect the conversion negatively (entries 3, 9, 11), but combinations of these mutations led to a significantly reduced conversion (entry 16). This pattern was also seen with the K19 and RLYF/K19 base variants, where the inclusion of A264G had little effect (entries 7 and 10; entries 12 and 13; entries 6 and 8), but further addition of A328G diminished the conversion (entries 15, 18 and 17, respectively). These observations imply complex interactions between residues in the 3D structure of the P450 enzyme.

The formation of over-oxidation products, such as diol **2.25** and keto-alcohol **2.26**, is noteworthy as oxidation generally slows substantially after mono-hydroxylation; that it can occur within the 24 h timeframe of the screening reactions suggests that re-screening the primary metabolites would be productive in generating more complex products. Indeed, oxidation of a chiral primary metabolite produced in some enantiomeric excess, can be followed by a kinetic resolution during subsequent oxidation(s), resulting in impressive enantiomeric excesses in the secondary metabolites. An increase in selectivity for these metabolites was observed following the addition of I263G (entries 5 and 11; entries 3 and 4) or A184I (entries 2 and 8). Since this substrate is prone to further oxidation, a time course study of the reaction would determine whether a shorter reaction time should be used in order to increase the selectivity for primary oxidation products.

2.3.2 *N*-Ms-protected tropane

Following the same procedure as with the *N*-Boc substrate, the *N*-Ms-protected tropane **2.18** was screened against the same library of 48 variants. Scale-up reactions performed as described for the *N*-Boc-tropane led to the identification of four major products, characterised as α-ketone **2.27**, γ-ketone **2.28**, *endo*-γ-alcohol **2.29** and *endo*-α-alcohol **2.30** (Figure 7). Strikingly, products analogous to **2.27** and **2.30** were not accessible from the *N*-Boc-tropane, despite that substrate's greater reactivity. The structure of **2.27** was identified by the two diastereotopic α-protons with a large geminal coupling constant (J = 18.5 Hz) and with COSY correlations to both bridgehead protons; meanwhile, the relative configuration of **2.30** was determined by the absence of nOe correlation between the C**H**OH and β- and γ-protons. The metabolites **2.29** and **2.30** were inseparable by GC and thereby had to be analysed as one unit.

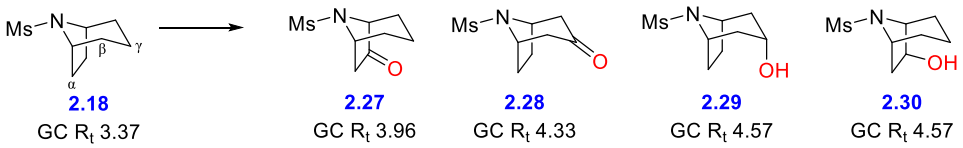


Figure 7: Products characterised from the screening of *N*-Ms-tropane **2.18**, including their GC retention times on the GC (GC R_t). Reagents and conditions: $P450_{BM3}$ (2000:1 substrate:enzyme), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h.

With this substrate, the variants proved far less active, with only seven out of 48 giving a conversion of >50%. Table 4 shows selected data for this screen.

Entry	Enzyme variant	Conv.	2.27	2.28	2.29/2.30	Others	TON
1	K19/A82M/F87A/A330W	100%	27%	**55%**	13%	5%	1108
2	K19/A82M/F87A/A264G	97%	9%	**71%**	8%	12%	1386
3	RK/A184I	76%	4%	**48%**	37%	11%	737
4	GV/A184I	63%		30%	**58%**	12%	735
5	K19/A82M/F87A	55%	3%	**72%**	19%	6%	786
6	K19/F87V/Q403P	26%		**60%**	36%	4%	314
7	GV/A184I/A328G	15%		30%	**61%**	9%	182
8	K19/F87V	15%		**53%**	43%	4%	158
9	GV/A184I/A264G	14%		35%	**48%**	17%	130
10	RK	9%		**79%**	21%		144
11	GV/A184I/I263G	8%			**100%**		162
12	RK/A184I/A264G	7%		**51%**	29%	20%	73
13	K19/F87V/A328V	4%			**100%**		78
14	RK/A184I/A264G/A328G	3%		**53%**	26%	21%	32
15	GV/A184I/A264G/A328G	2%		**52%**		48%	18
16	RK/A328G	2%		**100%**			44
17	RK/A184I/I263G/A264G	1%		**100%**			16
18	GV/L188Q	0%					0
19	K19/F87V/I263G	0%					0
20	K19/A82M/F87A/I263G	0%					0

Table 4: Selected conversion and selectivity data for the P450 screening of *N*-mesyl-tropane **2.18**. Selectivity is calculated by peak area ((single metabolite/all metabolites)x100). The columns are coloured according to the value of each cell and show the darkest hue for the highest number. TON refers to the turnover number for the formation of the metabolite in bold (the highest yielding metabolite).

The data in Table 4 suggest that A184I is a significant mutation for this substrate. While GV/A184I gave a moderate conversion of 63% (entry 4), addition of any further mutations suppressed the conversion to ≤15% (entries 7, 9, 11 and 15). Similarly, the inclusion of A184I in the RK base variant improved the conversion dramatically from 9% to 76% (entries 3 and 10); again, however, additional mutations decreased the conversion so that the variants in entries 12, 14 and 17 were practically inactive. Without A184I on the RK base variant, other mutations failed to promote conversion of starting material (for example, entry 16). This suggests that A184I is a crucial mutation for *N*-Ms-tropane activity, but not compatible with other mutations. The variants with highest overall activity were modifications of K19/A82M/F87A, which itself gave a conversion of 55% (entry 5). The inclusion of A264G or A330W led to an increase in

conversion to 97% and 100%, respectively (entries 22 and 23), while the selectivity profile remained relatively unchanged.

Overall, the *N*-Ms-tropane substrate was not processed well by the P450 variants screened. The average conversion was 14% and many of the base variants showed little or no activity. All GVQ (GV/L188Q) variants were completely inactive (for example, entry 18), and those based on K19/F87V also showed low reactivity, with a highest TON of 314 (entry 6). The I263G mutation appeared to be incompatible with the conversion of *N*-Ms-tropane (entries 4 and 11, entries 8 and 19, entries 5 and 20).

2.3.3 *N*-Ips-protected tropane

The *N*-Ips-protected tropane **2.19** was screened against the same 48 variants. Scale-up reactions allowed the five major products to be characterised as γ-ketone **2.31**, α-ketone **2.32**, *exo*-β-alcohol **2.33**, *exo*-γ-alcohol **2.34** and *endo*-γ-alcohol **2.35** (Figure 8). The configuration of the β-alcohol was determined from the C**H**OH coupling constant (J = 5.0 Hz).

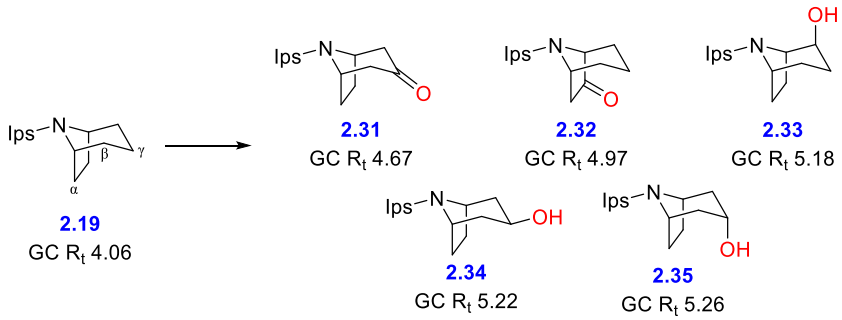


Figure 8: Products characterised from the screening of *N*-Ips-tropane **2.19**, including their retention time on the GC (GC R_t). Reagents and conditions: $P450_{BM3}$ (2000:1 substrate:enzyme), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h.

Table 5 shows selected data for this screen. Again, not all variants were active, although there was greater average activity than for the *N*-Ms substrate, with 12 out of 48 giving a conversion of >50%.

Entry	Enzyme variant	Conv.	2.31	2.32	2.33	2.34	2.35	Others	TON
1	K19/A82M/F87A	100%	6%		3%		**91%**		1824
2	RK	100%	38%		2%	14%	**45%**	1%	900
3	RK/A184I/A264G	100%	19%			7%	**74%**		1484
4	RK/A328G/P329G/A330G	100%	10%	3%	12%	17%	**55%**	3%	1092
5	GV/A184I	92%	5%		3%	31%	**61%**		1130
6	GV/A184I/I263G	84%	5%		16%	**79%**			1323
7	GV/A184I/A264G	34%					**100%**		687
8	RP/V78I/E267V	28%			2%	1%	**97%**		539
9	RK/A328G	16%		35%	2%	13%	**50%**		164
10	GV/L188Q	13%		7%	4%	11%	**78%**		209
11	RK/A184I/I263G/A264G	12%					**100%**		241
12	K19/A82M/F87A/I263G	10%			14%	40%	**46%**		96
13	GV/A184I/I263G/A264G/A328G	0%							0
14	KU3/A328I/A330P	0%							0
15	RT2	0%							0

Table 5: Selected conversion and selectivity data for the P450 screening of *N*-Ips-tropane **2.19**. Selectivity is calculated by peak area ((single metabolite/all metabolites)x100). The columns are formatted according to the value of each cell and show the darkest hue for the highest number. TON refers to the turnover number for the formation of the metabolite in bold (the highest yielding metabolite).

In contrast to the reactions of the *N*-Ms-tropane substrate, the Ips derivative did show some improvements with mutations additional to the A184I mutation. For example, the GV/A184I variant gave a conversion of 92% (entry 5) and while the addition of A264G led to a reduction in conversion to 34%, the selectivity for **2.35** rose to essentially 100% (entry 7). If, instead, the I263G mutation was added to the GV variant, the major product changed from **2.35** to **2.34** (entry 6). Further mutations on top of this, however, abolished the activity (entry 13).

Similarly, the addition of A184I/A264G to RK-based variants improved selectivity for **2.35** without compromising conversion (entries 2 and 3), further suggesting that the A184I/A264G combination is advantageous for this substrate. Another combination of favourable mutations was P329G/A330G, which brought the conversion up from 16% to 100% (entries 4 and 9); variant RK/A328G/P329G/A330G gave many product peaks on the GC which indicated that the three glycine mutations had greatly enlarged the substrate pocket, promoting conversion at multiple sites with little selectivity.

The Ips protecting group was unique in affording a β-alcohol for which the highest selectivity observed was 16% with GV/A184/I263G (entry 6), while K19/A82M/F87A/I263G and RK/A328G/P329G/A330G gave 14% (entry 12) and 12% (entry 4), respectively. Furthermore, seven

out of the nine variants that gave >8% selectivity for **2.33** contained the I263G mutation, suggesting that it is beneficial for obtaining this regioselectivity (for example, compare entries 1 and 12). This mutation is known to cause a significant conformational change in the I helix, leading to this helix retreating from the haem, creating extra space for substrate binding.[128] A Gly mutation of the adjacent residue, i.e. A264G, abolished β-alcohol formation (entries 3, 7 and 11). As a starting point for improving on these data, introduction of the P329G/A330G couplet to GV/A184I/I263G, and addition of the I263G mutation to RK/A328G/P329G/A330G may increase the selectivity for β-alcohol **2.33**.

Overall, the average conversion of the *N*-Ips-tropane substrate lay between the Boc and the Ms substrates at 33% and many of the base variants showed little or no activity. All GVQ (GV/L188Q) and RP variants gave low activity (entries 10 and 8), and those based on KU3 and RT2 were inactive (entries 14 and 15). Once again, the I263G mutation appeared to hamper the conversion of the substrate; it brought the RK/A184I variant down from 100% conversion to 12% (entries 3 and 11), and impaired both the conversion and selectivity of the K19/F87A/A82M variant, reducing the TON from 1824 to 96 (entries 1 and 12).

2.3.4 *N*-phosphoryl-protected tropane

The *N*-phosphoryl-protected tropane **2.20** was screened against 48 variants. The three major products were characterised as γ-ketone **2.36**, *exo*-α-alcohol **2.37** and *endo*-γ-alcohol **2.38** (Figure 9), all regioselectivities found previously in products **2.21**–**2.35**.

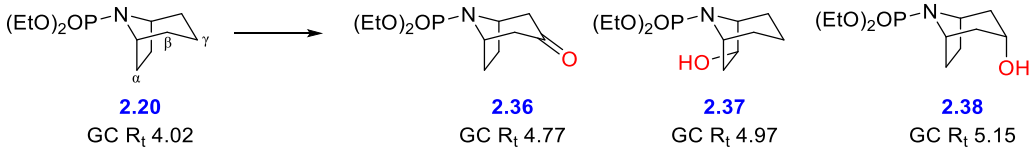


Figure 9: Products characterised from the screening of *N*-phosphoryl-tropane **2.20**, their retention time on the GC (GC R_t). Reagents and conditions: $P450_{BM3}$ (2000:1 substrate:enzyme), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h.

Table 6 shows selected data for this screen. In this case, 16 out of 48 variants gave a conversion of >50%, similar to the *N*-Ips alternative.

Entry	Enzyme variant	Conv.	2.36	2.37	2.38	Others	TON
1	GV/A184I	100%	10%	1%	**82%**	7%	1640
2	K19/A82M/F87A/A330W	100%	**47%**	1%	35%	17%	940
3	RK	100%	35%		**64%**	1%	1280
4	RK/A184I/A264G	100%	**57%**		37%	6%	1140
5	RK/A328G/P329G/A330G	96%	13%	3%	**79%**	5%	1522
6	K19/A82M/F87A/A264G	83%	4%	32%	**43%**	21%	714
7	K19/F87V	76%	3%	1%	**89%**	7%	1349
8	K19/A82M/F87A	54%	3%	4%	**70%**	23%	766
9	RK/A184I/A264G/A328G	50%	7%	19%	**69%**	5%	698
10	GV/A184I/A264G/A328G	46%		**57%**	19%	24%	528
11	RK/A184I/I263G/A264G	36%	2%	14%	**69%**	15%	502
12	GV/A184I/I263G	36%		10%	**84%**	6%	597
13	GV/L188Q	34%		2%	**90%**	8%	620
14	K19/F87V/I263G	26%		5%	**87%**	8%	450
15	RK/A328G	25%		5%	**95%**		474
16	RP/V78I/E267V	18%			**100%**		362
17	K19A82M/F87A/A264G/A328G	15%		**74%**	16%	10%	226
18	GV/A184I/I263G/A264G/A328G	5%		**49%**	16%	35%	53
19	RT2	1%				**100%**	15
20	KU3/A328I/A330P	0%					0
21	K19/A82M/F87A/I263G	0%					0

Table 6: Selected conversion and selectivity data for the P450 screening of *N*-phosphoryl-tropane **2.20**. Selectivity is calculated by peak area ((single metabolite/all metabolites)x100). The columns are formatted according to the value of each cell and show the darkest hue for the highest number. TON refers to the turnover number for the formation of the metabolite in bold (the highest yielding metabolite).

For this protected tropane, the A328G mutations appeared detrimental to enzyme activity. Addition of A264G/A328G onto the GV base variant lowered the conversion from 100% to 46% (entries 1 and 10) and in another instance from 36% to 5% (entries 12 and 18), as well as decreasing the selectivity in both cases. In contrast, the addition of A264G/A328G on K19/F87A/A82M decreased the conversion from 54% to 15% (entries 8 and 17), but also changed the major product from **2.38** to **2.37**, an interesting switch in regioselectivity. Insertion of only A264G increased the conversion (entry 6), suggesting these trends are attributable to the A328G mutation. Indeed, the A328G mutation alone was capable of lowering the conversion on the RK base variant (entries 3 and 15; entries 4 and 9), although in both cases it boosted the selectivity for **2.38**.

Conversely, inclusion of the A330W mutation increased the conversion from 54% to 100% (entries 2 and 8), and a point mutation from F87A to F87V slightly improved both conversion and selectivity for

2.38 (entries 7 and 8). As seen for the Ips-protected substrate, the combination of mutations P329G/A330G was favourable, bringing the conversion up from 25% to 96% (entries 5 and 15).

Overall, the average conversion of the *N*-PO(OEt)$_2$-tropane substrate was most similar to that of the *N*-Ips-tropane substrate at 38%. As seen for the previous protecting groups, insertion of the I263G mutation was detrimental to the conversion (entries 1 and 12; entries 8 and 21; entries 7 and 14; entries 4 and 11), all GVQ (GV/L188Q) and RP variants gave low activity (entries 13 and 16), and those based on KU3 and RT2 were inactive (entries 19 and 20).

2.4 Conclusions and future work

In this study, substrate engineering by varying the nitrogen substituent led to diverse oxidation regioselectivity around the tropane motif, accessing every unactivated position on the tropane ring. Figure 10 shows the P450$_{BM3}$ variant and protecting group combination that gave the highest TON for each metabolite. Despite the high activity of *N*-Boc-tropane, its low selectivity results in relatively low TONs, and (excepting the over-oxidised metabolites) only the *exo*-α-alcohol is most efficiently generated using the Boc protecting group. From this initial screening, the *exo*-γ-alcohol, *endo*-γ-alcohol, *exo*-β-alcohol and α-ketone were all best achieved with the ipsyl protecting group, and the *endo*-α-alcohol and γ-ketone with the mesyl protecting group, while none of the metabolites achieved a highest TON from the phosphoryl alternative under these conditions.

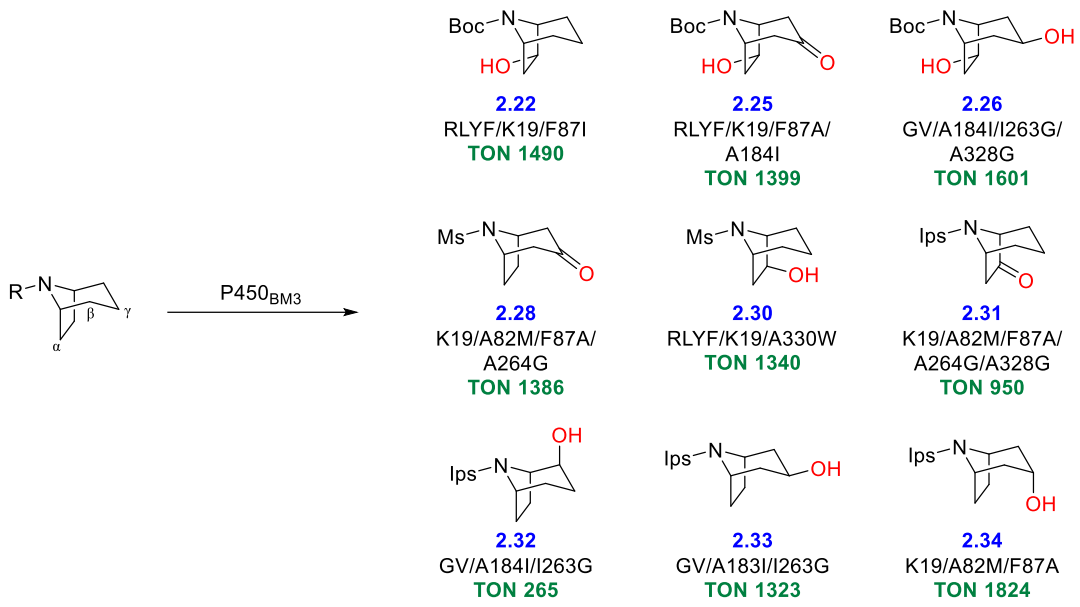


Figure 10: Highest TON obtained by enzymatic oxidation of protected amines **2.17**–**2.20**, with relevant $P450_{BM3}$ variants. Reagents and conditions: $P450_{BM3}$ (2000:1 substrate:enzyme), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h.

Overall, the Boc-protected amine **2.17** was the most active (Figure 11), with an average conversion of 76%, and 56% of enzymes showing a conversion of >90% (4%, 21% and 15% for **2.18**, **2.19** and **2.20**, respectively). The high activity came with relatively low selectivity, however; none of the enzymes achieved a clean product from the *N*-Boc-tropane so it would not be the ideal protecting group to generate a target metabolite using the conditions screened. This is a phenomenon commonly observed in the Wong group's research because the enzyme library has evolved over time from $P450_{BM3}$ variants that were initially trialled against, and therefore now tend to favour, Boc-protected amine substrates. Reaction engineering such as altering the enzyme loading and reaction time could be carried out in future work to investigate whether the selectivity could be improved in other conditions. Additionally, future screening should be carried out using other variants in order to generate a less biased data set.

The results show the potential of tuning the regio- and stereo-selectivity of cyclic amine hydroxylation simply by changing the *N*-protecting group (Figure 11), supporting de Raadt's 2001 publication on the concept of protecting groups in biohydroxylation.[129] Oxidation on the γ-carbon was very readily achieved, the major products for Boc-protected tropane being the γ-alcohols **2.23** and **2.24**, while for the mesyl substrate the γ-ketone (**2.28**) was most favoured, and for the ipsyl and phosphoryl substrates, the *endo*-γ-alcohols (**2.35** and **2.38** respectively)

were favoured. Oxidation occurred diastereoselectively; the selective production of γ-alcohol metabolites can be controlled by appropriate choice of protecting group and/or variant used, and the same can be said for the diastereomeric α-alcohols.

The various protecting groups have distinct advantages; while Boc gave the highest average conversion and a greater number of oxidation products, other protecting groups are useful for achieving less common structural isomers. For example, the ipsyl protecting group procured metabolite **2.32** and the mesyl protecting group procured metabolite **2.30**, despite its generally sluggish activity.

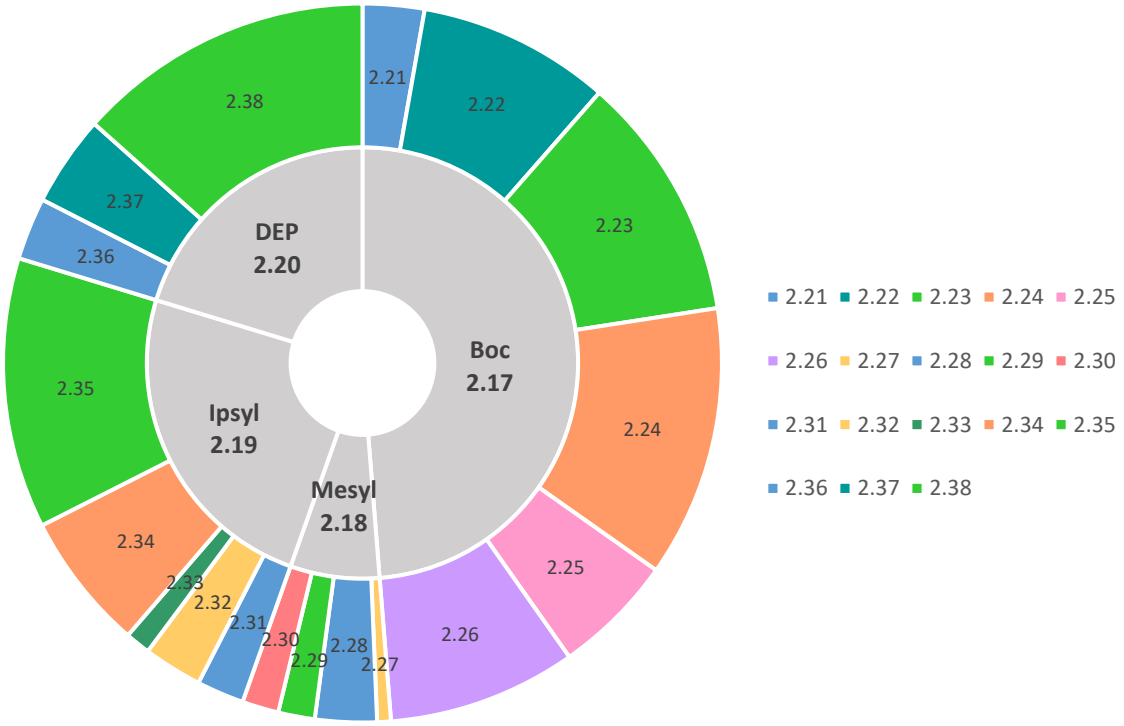


Figure 11: The relative average TONs of the metabolites from enzymatic oxidation of substrates **2.17**–**2.20**. Colours denote regioselectivity.

Future work could include optimising the TONs for selected metabolites *via* further screening and mutagenesis, which should include enantiomeric excess data by establishing a chiral GC method for distinguishing the enantiomers of chiral metabolites. Furthermore, Molecular Dynamics (MD) simulations could be used to rationalise the screening results and guide how further mutagenesis could improve TONs; the ability to estimate regioselectivity outcomes *in silico* would substantially increase the accessibility of these enzymatic reactions by narrowing the scope of experimental work needed to locate the ideal enzyme for a particular substrate and transformation.

Following the identification of oxidised products, analysis of the screening results with respect to the mutations present revealed several general observations:

- Mutations at the I helix (I263 and A264) and the β_1 strand (A328, P329 and A330) seemed to be important in changing the product selectivity, demonstrating the importance of changing the substrate binding orientation in the substrate pocket;
- Concerning activating mutations, A184I, A264G, A330W and P329G/A330G tended to increase conversion compared to their parent variants;
- Meanwhile, I263G and A328G tended to decrease conversion, however;
- The inclusion of I263G and the P329G/A330G combination increased the chances of forming the β-alcohol **2.33**, from the *N*-ipsyl-tropane substrate;
- There is often not a simple relationship between the addition of a single mutation and the resulting conversion, implying a complex interplay between mutations and substrate in determining the reactivity and selectivity profiles;
- Of the original base variants, KU3, RP and RT2 were found to be relatively inactive, leaving only GV (A74G/F87V/L188Q), K19 (H171L/Q307H/N319Y) and RLYF (R47L/Y51F) as operational base variants for these tropane substrates.

The combined results from screening $P450_{BM3}$ variants with a wide range of substrates have the potential to build a predictive understanding of the enzymes' likely activity when faced with new substrates, and hence the adoption of these variants as general oxidation catalysts. Currently, however, controlling the selectivity remains a challenge since individual mutations do not have predictable effects and substrates must be evaluated on a case-by-case basis. This means that screening results are both difficult to predict and to rationalise since a single mutation can drastically alter the outcome, with non-additive outcomes from mutation combinations. Overall, detailed conclusions are only relevant to the precise substrate and enzymes screened, and it has not so far proven possible to extrapolate results. Furthermore, results from combined MD/docking studies carried out in our groups have so far shown only loose correlation with the empirical data which is unsurprising given the assumptions and simplifications made. A potential solution to understanding these complex screening datasets would be to perform a regression study or other appropriate statistical analysis.

Chapter 3:

In which natural product anisodamine is synthesised *via* $P450_{BM3}$ functionalisation

Chapter 3: Synthesis of anisodamine

3.1 Introduction to anisodamine

3.1.1 Isolation, biological activity and structural features

The anticholinergic drug 6β-hydroxyhyoscyamine (Figure 12), also known as anisodamine, is a member of the large class of tropane alkaloids first isolated in the 1830s[130–132] and the subject of many total synthesis and methodology studies since.[108]

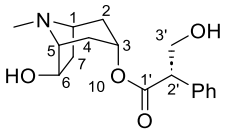


Figure 12: Anisodamine, **3.1**

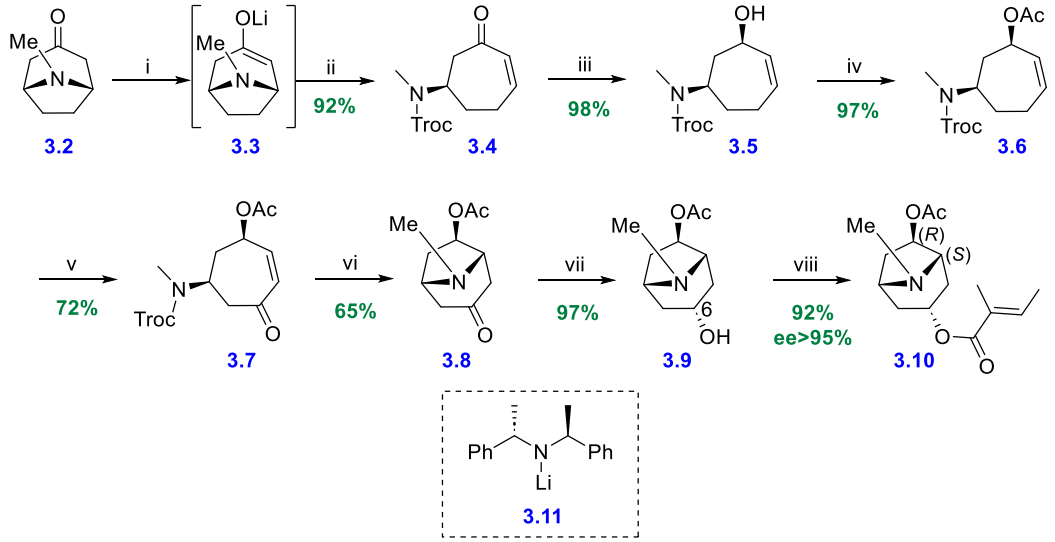
This ester of tropic acid and 6β-hydroxytropinone was first isolated from the Chinese herb *Scopolia tangutica* Maxim and subsequently synthesised in 1975.[133] As a naturally occurring atropine derivative and a non-specific cholinergic antagonist, it is marketed in China as a treatment for septic shock and to improve blood flow in various circulatory disorders.[134, 135] Since the natural compound is very scarce, pharmaceutical formulations of anisodamine, as used in clinical practice, comprise four individual entities (two diastereomeric pairs of enantiomers): the (6*S*,2′*S*), (6*R*,2′*S*), (6*S*,2′*R*) and (6*R*,2′*R*) stereoisomers, of which only the active (3*S*,6*S*,2′*S*)-6β-hydroxy-hyoscyamine has been isolated from plant material.[136] For this reason, an asymmetric synthesis of the single active naturally-occurring 6*S*,3*S*,2′*S* isomer would be of significant interest.

3.1.2 Previous synthetic approaches

Anisodamine is currently manufactured as a racemic mixture of diastereomers from (±)-6β-hydroxytropinone and (±)-tropic acid,[137-139] while in the literature, enantioenriched intermediates of anisodamine have been prepared by asymmetric synthesis,[107, 140–144] from (*R*)- or (*S*)-malic acid,[145] and by resolution.[146–148]

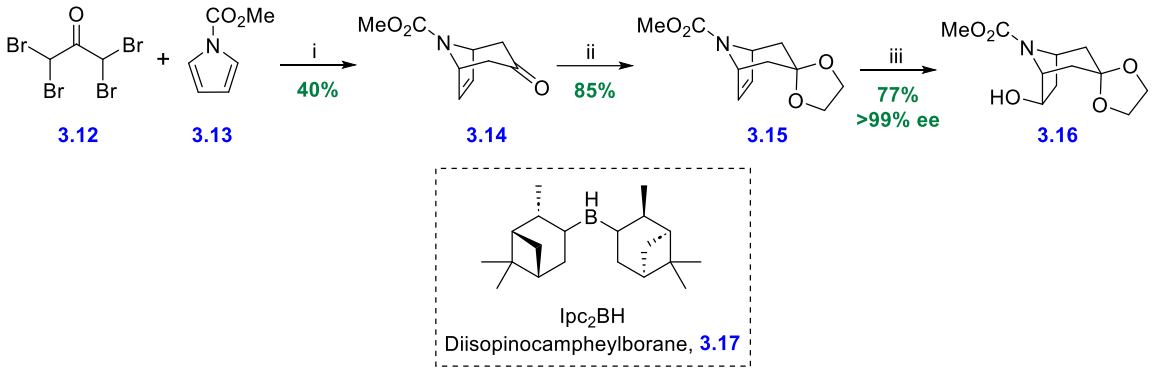
Asymmetric syntheses

In 1996, Majewski *et al*. devised a method to synthesise the 3,6-dihydroxytropanes stereoselectively, as illustrated in Scheme 20.[140, 141] The authors found that deprotonation of tropinone **3.2** with a chiral lithium amide led to ring-opening upon acylation, to produce the cycloheptenone **3.4** in >95% ee. Stereoselective Luche reduction, protection of the resulting alcohol, and allylic oxidation allowed re-closure of the tropane ring. This hydroxylated tropane **3.8** was then reduced to give *endo*-alcohol **3.9**, which was esterified to deliver the final product.



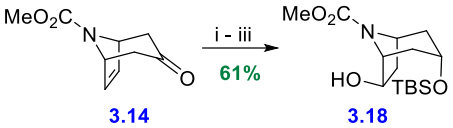
Scheme 20: i) LiCl, **3.11**; ii) TrocCl, −78 °C, 30 min; iii) $NaBH_4$, $CeCl_3$, MeOH, 0 °C → RT, 1 h; iv) Ac_2O, Et_3N, DMAP, DCM, RT, 24 h; v) H_2SeO_3, Celite®, dioxane, 101 °C, 18 h, then PDC, DCM, RT, 12 h; vi) Zn, EtOH, −78 °C, 2 h; vii) H_2/PtO_2, RT, 12 h; viii) Tg_2O, Py, DMAP, benzene, RT, 3.5 days.

An alternative enantioselective desymmetrisation of tropinone derivatives was achieved by Cramer *et al*. in their 2003 report of their investigation of the enantioselective hydroboration of tropenone **3.14** to the chiral alcohol **3.16** (Scheme 21).[143] Protected tropenone **3.14** was prepared *via* (4+3)-cycloaddition from pyrrole **3.13**.[142] After ketone protection, asymmetric hydroboration and oxidation furnished alcohol **3.16** with almost perfect enantioselectivity.



Scheme 21: i) $ZnEt_2$, toluene, −12 °C → RT, 18 h, then Zn/Cu, NH_4Cl, MeOH, RT, 2.5 h; ii) PPTS, ethylene glycol, benzene, 80 °C, 8 h; iii) (–)-**3.17**, THF, −28 °C, 18 h, then 3 M NaOH, H_2O_2, MeOH, 55 °C, 1 h.

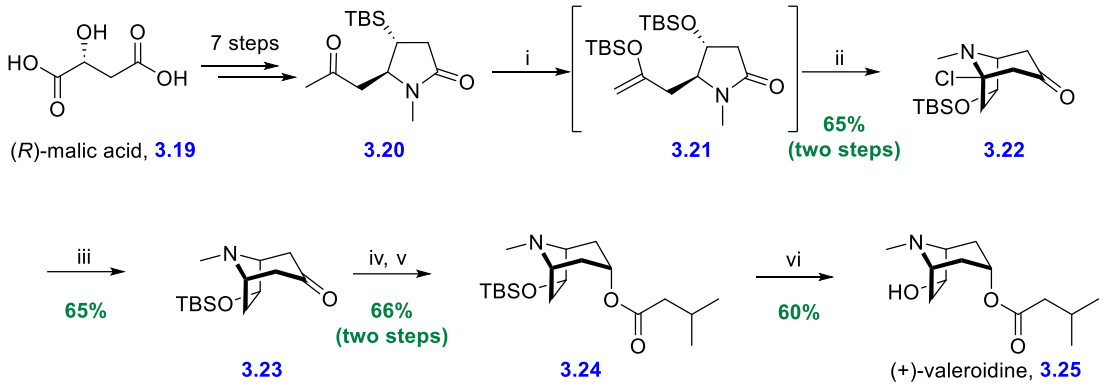
Kulkarni *et al.* built on this method in 2008,[144] with the variation that the asymmetric hydroboration was carried out on the TBS-protected alcohol rather than the protected ketone (Scheme 22).



Scheme 22: i) L-Selectride®; ii) TBSCl, DMF; iii) (–)-**3.17**, THF, −25 °C, 18 h, then NaOH, H_2O_2, MeOH, 55 °C, 1 h.

From (R)- or (S)-malic acid

An alternative to asymmetric synthesis is to exploit the chiral pool; that is, beginning with a naturally-occurring enantiomerically pure starting material. In 2014, based on this idea, a novel and flexible method for the enantiospecific construction of hydroxylated 8-azabicyclo[3.2.1] octane ring systems was established by Mao *et al.*[145] The method was applied to the syntheses of various tropane alkaloids, including (+)-(1*S*,3*R*,5*S*,6*R*)-valeroidine (**3.25**) (Scheme 23). From keto-lactam **3.20**, the key step consisted of silyl enol ether formation and cyclisation into the activated lactam. Radical dechlorination of the resulting 1-halotropan-3-one **3.22** then diastereoselective hydrogenation led to a dihydroxytropane derivative, which was esterified and deprotected to yield the natural product.

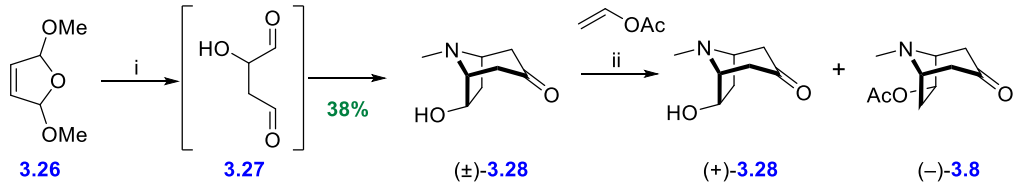


Scheme 23: i) TBSOTf, Et_3N, DCM, 0 °C, 18 h; ii) Tf_2O, DTBMP, $ZnCl_2$, DCM, −78 °C to RT, 1 h; iii) ACCN, Bu_3SnH, toluene, 85 °C, 5 h; iv) PtO_2, H_2 (5 atm), EtOH, 30 h; v) isovaleryl chloride, Et_3N, DCM, 18 h; vi) TsOH, acetone, 50 °C, 24 h.

Resolution

While asymmetric synthesis aims to produce a single enantiomer from the beginning, resolution prepares enantiopure compounds from racemates. Among the many approached to resolving racemates, the use of lipases has found wide use because of the enzymes' ability to form and cleave acetate esters of a wide variety of chiral alcohols with high enantioselectivity by kinetic resolution.[149–152]

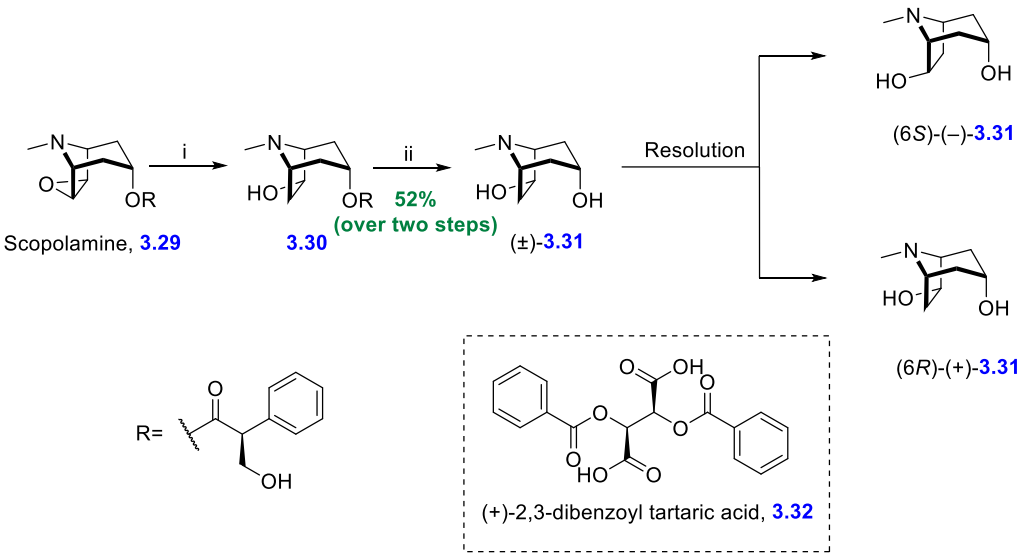
For example, in their 2003 paper, Cramer *et al*. demonstrated the feasibility of this approach to generate enantiomerically enriched tropane alkaloids.[146] The racemic hydroxytropinone (±)-**3.28** was prepared by a modified Robinson procedure as shown in Scheme 24. Subsequent screening with vinyl acetate and a variety of lipases at different temperatures (20–55 °C) resulted in the formation of alcohol (+)-**3.28** and ester (–)-**3.8** in variable conversions (27–97%) and enantiomeric excesses ranging from 24%–95% ee. Chirazyme L-6 lipase gave the highest conversions and enantioselectivities among the different lipases investigated, obtaining (+)-6-hydroxytropinone [(+)-**3.28**] in 35% yield and >99% ee after a single recrystallisation.



Scheme 24: i) 3 N HCl, then $MeNH_2$, NaOAc, acetonedicarboxylic acid, RT, 2 d; ii) vinyl acetate, 4 Å MS, solvent, lipase.

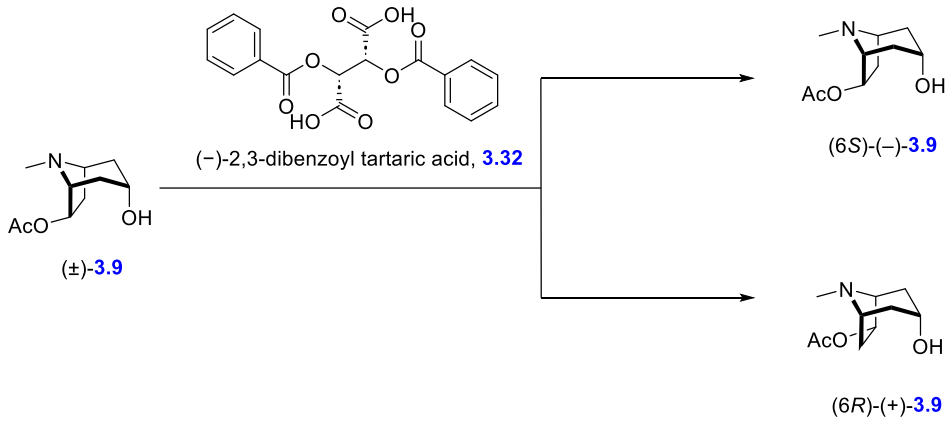
The classical procedure of forming a pair of separable diastereomeric derivatives from which the enantiomers may then be obtained has been employed in this context. For example,

2,3-dibenzoyl-tartaric acid was employed by Fodor *et al*. in 1953 (Scheme 25).[148] Hydrogenolysis of scopolamine **3.29**, then hydrolysis of the tropic ester **3.30** gave (±)-3,6-dihydroxytropane **3.31** and (−)-tropic acid. The racemic tropane derivative was resolved *via* fractional recrystallisation of its dibenzoyl-(+)-tartrate salt.



Scheme 25: i) H_2, Raney nickel, H_2O, RT, 16 h; ii) 10% HBr, H_2O, 100 °C, 16 h.

Essentially the same procedure was employed by Niu *et al*. in 2008 (Scheme 26)[147] to separate the enantiomers of 3-hydroxy-6-acetoxytropane. The absolute configurations of (−)-**3.9** and (+)-**3.9** were determined as (6*S*)-**3.9** and (6*R*)-**3.9**, respectively, according to the relationship between the absolute configuration and optical activity of the chiral tropane compounds.[153]

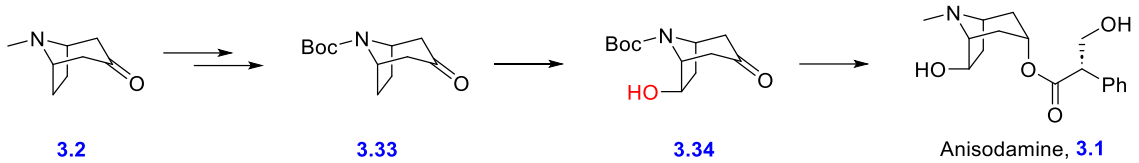


Scheme 26: Resolution of (±)-3α-hydroxy-6β-acetoxytropane.

3.1.3 Project aims

This project initiated the total synthesis of anisodamine to highlight and exploit the results of the previous chapter by incorporating one of the metabolites of $P450_{BM3}$ oxidation into a natural product synthesis.

The initial proposal for the synthesis was to replace the *N*-methyl group in commercially available tropinone with Boc, so that the substrate would be compatible with enzymatic oxidation. Following hydroxylation, the ketone would be reduced stereoselectively then selective esterification with tropic acid would afford the natural product (Scheme 27).

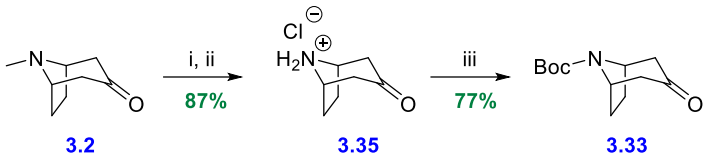


3.2 3.33 3.34 Anisodamine, 3.1

Scheme 27: Proposed synthesis of anisodamine.

3.2 Enzymatic screening

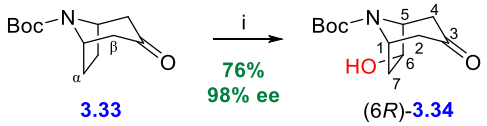
Screening of the tropane motif in the previous chapter had revealed that the γ-position is readily oxidised, and so it was deemed more efficient to start with tropinone, to avoid removing the ketone in the preparation of the substrate, only to have it installed again by the enzyme. After demethylation of tropinone, the free amine was Boc-protected (Scheme 28). The Boc protecting group was chosen because the previous chapter on oxidising variably protected tropane, supported by earlier work in the Wong group, had shown that this protecting group is well tolerated across the library of $P450_{BM3}$ variants and gives a diverse reaction profile. The *N*-Boc-protected tropinone was screened against a panel of 24 $P450_{BM3}$ variants, derived *via* mutagenesis, as described previously. Full data for this screen can be found in Appendices, Table 32.



Scheme 28: i) 1-chloroethyl chloroformate, DCE; ii) MeOH, 87% over two steps; iii) Boc_2O, imidazole, DCM, 77%.

In order to isolate the single major metabolite, reactions were carried out on a 0.2 mmol scale using $P450_{BM3}$ variant RLYF/K19/F87A/A184I – chosen for its high conversion and excellent expression – and the major product was characterised as 6-hydroxy-*N*-Boc tropinone **3.34** (Scheme 29). This oxidation at an unactivated site provides an excellent demonstration of the potential benefits of the enzymatic approach when comparing with chemical reagents that readily oxidise the activated positions such as those adjacent to the carbonyl.[154]

This regioselective oxidation of *N*-Boc-protected tropinone was readily scaled to provide up to 500 mg batches of (*6R*)-**3.34** in 70–80% yield. The enantiomeric excess was later assessed by Dr Ziyue Xiong to be 98.5% *via* Mosher ester analysis and the absolute configuration as 6*R*- by correlation of reported specific rotation data with the value obtained for diol **3.31** later in the route, see below.[155]



Scheme 29: i) RLYF/K19/F87A/A184I (2000:1 substrate:enzyme molar ratio), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h.

The 24-variant enzyme library showed moderate activity towards this substrate with seven showing >50% conversion, and high selectivity with 14 showing a >90% preference for the major product, the 6-*exo*-alcohol **3.34**. Since the target product was obtained in both high conversion and high selectivity, it was not necessary to perform any further screening. Table 7 shows selected data for this screen and reveals some key residues which affect the conversion and selectivity.

Entry	Enzyme Variant	Conv.	3.34	Others	TON
1	K19/F87V	100%	100%		2000
2	RLYF/K19/F87A/A184I	98%	96%	4%	1877
3	RLYF/K19/F87A	94%	95%	5%	1776
4	RLYF/K19/F87I	91%	99%	1%	1792
5	K19/F87V/Q403P	81%	100%		1622
6	K19/F87A/I263G	74%	98%	2%	1443
7	RLYF/K19/F87A/G265GG	37%	97%	3%	724
8	RLYF/K19/F87A/I263G/A264G	22%	94%	6%	407
9	K19/F87V/E267V	19%	93%	7%	358
10	K19/F87A/I263A	13%	71%	29%	187
11	RLYF/K19/F87A/A328G	9%	90%	10%	158
12	K19/A82M/F87A/I263G	3%	64%	36%	41
13	K19/F87V/A328V	3%	69%	31%	46
14	RLYF/K19	1%		100%	0
15	RLYF/K19/A184I/A328L	1%		100%	0

Table 7: Selected conversion and selectivity data for the P450 screening of substrate **3.33**, ordered by conversion. Selectivity is calculated by peak area [(single metabolite/all metabolites)x100]. The columns are coloured according to the value of each cell and show the darkest hue for the highest number. TON refers to the turnover number for the formation of **3.34**.

From this, mutations within the I helix such as I263, seem to be important in influencing the product selectivity. Variants K19/F87A/I263G and K19/F87A/I263A showed 74% and 13% conversion respectively, demonstrating the importance of I263 in changing the substrate binding orientation in the substrate pocket (entries 6 and 10). Despite the benefit of the I263G mutation on this scaffold, an additional A82M mutation (entry 12) decreased the conversion to 3%. A82 is outside the area of the active site, demonstrating the oblique impact of off-site mutations.

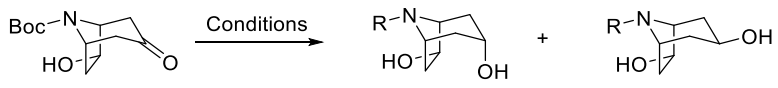
The large phenylalanine (F) at residue 87 blocks the active site, preventing the substrate from approaching and thus preventing substrate oxidation. Mutation to a smaller residue, such as valine (V), alanine (A) or isoleucine (I), provides improved access to the active site. This is evident in the reactions with K19/F87V, RLYF/K19/F87A and RLYF/K19/F87I which gave

100%, 94% and 91% conversion, respectively (entries 1, 3 and 4), compared to RLYF/K19 which gave a minimal conversion (entry 14). Similarly, addition of mutation F87A to the low converting variant RLYF/K19/A328L/A184I (1%) led to a much higher conversion of 98% (entries 2 and 15), which again demonstrates the importance of the F87 mutation for substrate turnover.

Additional mutations can be detrimental to the conversion, however, since K19/F87V (entry 1) was found to be superior to all the screened daughter mutations: K19/F87V/Q403P, K19/F87V/E267V and K19/F87V/A328V (entries 5, 9, 13), although the former two maintained high selectivity. A similar trend was seen for RLYF/K19/F87A (entry 3) whose performance was impaired by additional mutations G265GG, I263G/A264G or A328G (entries 7, 8, 11). The inclusion of an A184I mutation, however, slightly increased the conversion to 98% (entry 2). Despite these variations in conversion, none of these mutations undermined the selectivity which remained at 90% or above.

3.3 Chemical elaboration post-P450

The functional groups in keto-alcohol **3.34** had then to be manipulated to achieve the natural product, starting with reduction of the ketone to the *endo*-alcohol (Table 8). At first, reduction using $LiAlH_4$[156] gave a mixture of diastereomers (entry 1); however, the use of the bulkier reducing agent DIBAL-H[157] produced the desired diol (entry 2), and the use of L-Selectride® improved the yield while maintaining the stereoselectivity.

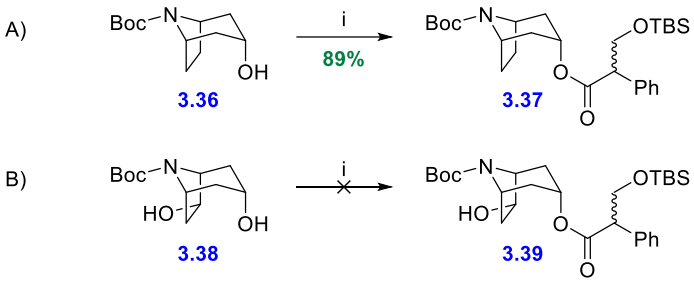


3.34 *endo* *exo*

Entry	Reducing agent	R	Yield	Result (*endo*:*exo*)
1	$LiAlH_4$	Me	77%	29:71
2	DIBAL-H	Boc	53%	100:0
3	L-Selectride®	Boc	66%	100:0

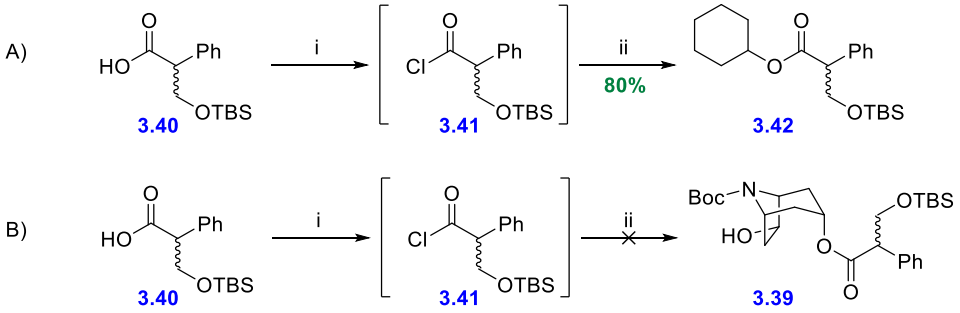
Table 8: Stereoselective reduction of ketone **3.34**.

Esterification with a protected form of (*S*)-tropic acid and subsequent deprotection would complete the synthesis of anisodamine, so esterification conditions were tested on the mono-alcohol **3.36** using racemic TBS-protected-tropic acid **3.40**,[158, 159] giving the desired product **3.37** in 89% yield (Scheme 30A). When these conditions were repeatedly tried with the diol **3.38**, only starting material was recovered (Scheme 30B).



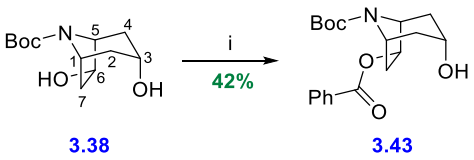
Scheme 30: i) DCC, DMAP (25 mol%), *O*-TBS-(±)-tropic acid **3.40**, DCM, 0 °C to RT, 4 h.

A test esterification of cyclohexanol with the corresponding tropic acid chloride, prepared *in situ*, was successful (Scheme 31A).[160] When the same procedure was applied to diol **3.38**, only starting material was recovered (Scheme 31B).



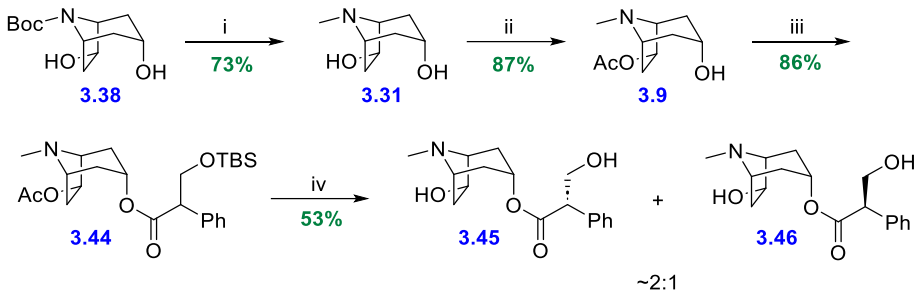
Scheme 31: i) $(COCl)_2$, DCM, RT for 30 min; ii) cyclohexanol or diol **3.38**, DMAP, NEt_3, RT for 18 h.

To simplify the system, the less complex, more reactive esterification partner benzoyl chloride, was used (Scheme 32)[161] and, here, it was found that esterification was selective for the 6-*exo*-alcohol, rather than the (desired) 3-*endo*-alcohol. In the ^{1}H NMR spectrum, the H-6 resonance shifted substantially downfield, from 4.70 to 5.77 ppm, while the H-3 resonance shifted only slightly, from 3.99 to 4.18 ppm.



Scheme 32: i) DMAP (25 mol%), NEt_3, benzoyl chloride, DCM, RT, 18 h.

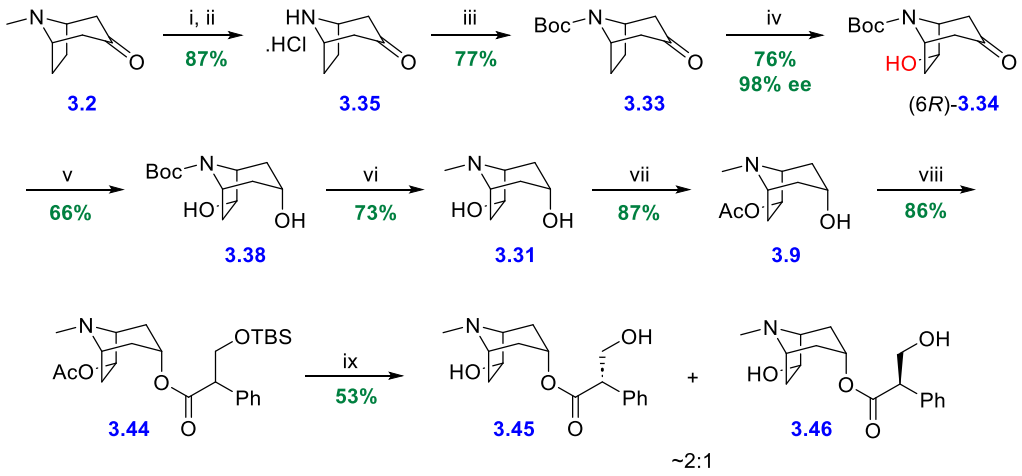
Due to the national lockdown, the final steps of the synthesis were completed by Dr Ziyue Xiong in our satellite group in the Oxford Suzhou Centre for Advanced Research. Since esterification at this point had given the unwanted regioselectivity, after modification of the Boc group, the 6-hydroxyl group in diol **3.31** was acetylated selectively, then esterification with the (±)-tropic acid derivative **3.40** was achieved in high yield (Scheme 33). Finally, global deprotection under acidic conditions furnished diastereomers **3.45** and **3.46** in a 2:1 ratio. The products were distinguished by comparison with reported NMR data for the separate diastereomers.[162]



Scheme 33: i) $LiAlH_4$, THF, 66 °C, 14 h; ii) Ac_2O, THF, RT, 12 h; iii) (±)-**3.40**, DCC, DMAP (20 mol%), $CHCl_3$, RT, 14 h; iv) conc HCl, H_2O, 100 °C, 2.5 h.

3.4 Final synthesis

The whole route for this proof-of-principle synthesis of anisodamine, completed in collaboration with group member Dr Ziyue Xiong and published in 2022, is presented in Scheme 34.[86]



Scheme 34: i) 1-Chloroethyl chloroformate, DCE; ii) MeOH; iii) Boc_2O, imidazole, DCM; iv) RLYF/K19/F87A/A184I (2000:1 substrate:enzyme), phosphate buffer, GDH, $NADP^+$, glucose, RT, 24 h; v) L-Selectride®, THF, −78 °C, 2 h; vi) $LiAlH_4$, THF, 66 °C, 14 h; vii) Ac_2O, THF, RT, 12 h; viii) (±)-**3.40**, DCC, DMAP (20 mol%), $CHCl_3$, RT, 14 h; ix) conc HCl, H_2O, 100 °C, 2.5 h.

Overall, the route gave diastereomers (3*R*,6*R*,2′*S*)-**3.45** and (3*R*,6*R*,2′*R*)-**3.46** in 15% overall yield (30 mg) from *N*-Boc-nortropinone **3.2** (215 mg). The single-step enzymatic oxidation of substrate **3.33** into (6*R*)-**3.34** (76%) represents a substantial improvement on the analogous asymmetric chemical synthesis of (6*R*)-acetoxytropinone from tropinone, which requires five steps (44%).[145] The need to replace the methyl group in tropinone with Boc, in readiness for the enzymatic step, and subsequently convert this Boc back into the necessary methyl substituent contributes four of the nine steps. Therefore, incorporating the protecting group into the substrate as part of the synthesis would eliminate these extra steps and provide a more efficient overall synthesis. This hypothesis was the origin of the following chapter, which describes progress in the assembly of an alkaloid core prior to enzymatic oxidation.

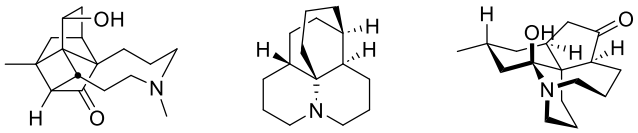
Chapter 4:

In which routes towards the carbon skeleton of lobscurinol are explored

Chapter 4: Synthesis of the carbon skeleton of phlegmadine A

4.1 Phlegmadine A: Isolation, biological activity, structural features

Phlegmadine A (Figure 13) is a newly-reported alkaloid of the *Lycopodium* family whose members contain complex polycyclic structures with dense stereochemical arrays, known for their ability to inhibit acetylcholine esterase.[163–165] Phlegmadine A is part of the fawcettimine subclass of *Lycopodium* alkaloids which consists of over 80 natural products,[166] typically with tetracyclic skeletons containing a single quaternary carbon and derived biosynthetically from the lycopodane core (Figure 13) through an oxidative rearrangement. The eponymous alkaloid, fawcettimine (Figure 13) – a tetracyclic structure with five stereogenic centres and a carbinol-amine moiety – was isolated in 1959 by Burnell from a moss in the Blue Mountain range of Jamaica.[167]

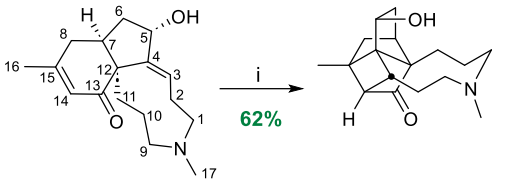


Phlegmadine A **4.1** Lycopodane **4.2** Fawcettimine **4.3**

Figure 13: Structures of phlegmadine A, lycopodane and fawcettimine.

Over 60 years later, phlegmadine A was reported to be isolated from *Phlegmariurus phlegmaria*, commonly known as the coarse tassel fern, and its structure elucidated by Zhao *et al.*[168] using a combination of NMR spectroscopy and single-crystal X-ray crystallography. *P. phlegmaria* is a traditional Chinese medicinal plant used for the treatment of arthritis, rheumatic pain, sore throat and traumatic injury.[169] The Zhao group also isolated various biogenetically related compounds from the same plant, including 14-hydroxylobscurinol, lobscurinol, fawcettimine, phlegmadine A, phlegmadine B and phlegmadine C.[168, 170] Phlegmadine A has a particularly unusual structure; it contains seven stereocentres including three quaternary carbon atoms, comprising a complex 6-5-4-9 tetracyclic bridged system including, uniquely among *Lycopodium* alkaloids, a cyclobutane ring. Although a dedicated enzyme is yet to be identified, it is generally believed

that such cyclobutane derivatives originate from the direct coupling of two olefinic carbon bonds.[171–174] Indeed, Zhao *et al*. showed that phlegmadine A may be obtained chemically from lobscurinol by an intramolecular [2 + 2] photocycloaddition as shown in Scheme 35.

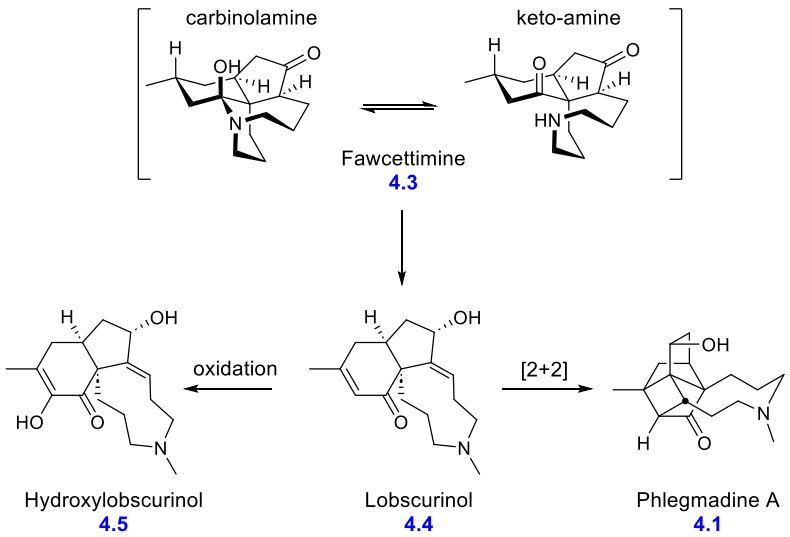


Scheme 35: i) hν (λ = 200–400 nm), DCM, RT, 9 h.

Zhao *et al*. also investigated the effect of the isolated compounds on long-term potentiation (LTP) impairment in the hippocampus; that is, their ability to rectify inhibition of memory. An activity-dependent synaptic plasticity model was used as a cellular mechanism for learning and memory.[175–177] In this study, 14-hydroxylobscurinol in particular showed "significant protective effects" against LTP impairment, suggesting that it could improve the synaptic plasticity, making it a potential candidate for neurodegenerative disorders such as Alzheimer's disease.

4.2 Previous synthetic approaches towards similar targets

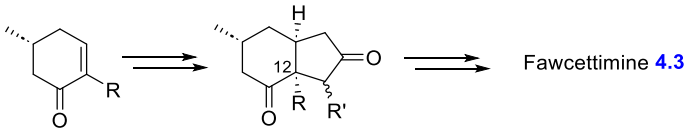
Given the conversion of lobscurinol to phlegmadine A, Zhao *et al.* suggested a biosynthetic pathway from fawcettimine to phlegmadine A and 14-hydroxylobscurinol *via* the equilibrium of the carbinolamine and its ring-chain tautomer (Scheme 36).[178]



Scheme 36: Hypothetical outline biosynthetic pathway for phlegmadine A and 14-hydroxylobscurinol.

While neither phlegmadine A nor lobscurinol have been synthesised previously, there are numerous reported syntheses of *Lycopodium* alkaloid 5-6-9 ring systems. The challenges inherent in preparing these alkaloids include their unusual framework, embellished with stereochemical intricacies and considerable functionalisation.

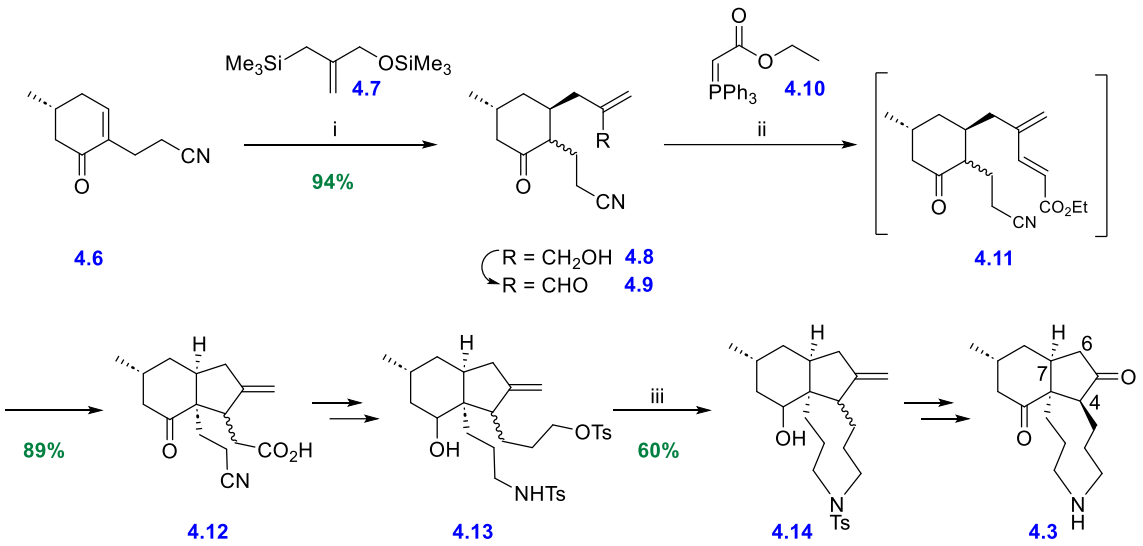
The most common strategy to form the 5-6-9 ring system employs S_N2-equivalent reactions to form the C–N bonds in the nine-membered ring following assembly of the fused 6-5 rings. In turn the *cis*-fused 6,5-carbocyclic core with one all-carbon quaternary centre (C-12), is most frequently accessed by exploiting the configuration of enantiomerically pure 5-methylcyclohex-2-enones to promote addition of reagents to the side opposite to the methyl group (Scheme 37).



Scheme 37: Commonly used strategy for *cis*-fused 5,6 ring system.

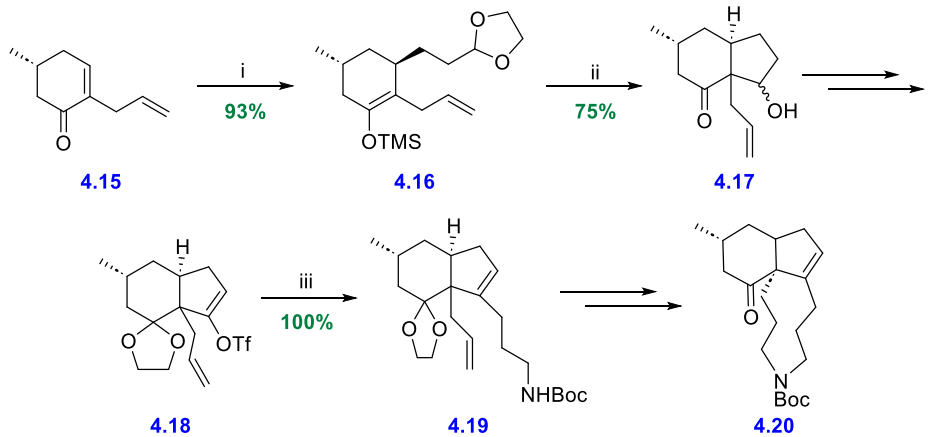
In 1986, for example, Heathcock *et al*. began with 2,5-dialkylcyclohex-2-en-l-one **4.6** and used the configuration of the methyl group to direct the stereochemical outcome of the subsequent steps (Scheme 38),[179, 180] beginning with a Sakurai allylation leading to allylic alcohol **4.8**. Oxidation followed by a Wittig reaction and *cis*-selective cyclisation *in situ*, afforded hydrindanone **4.12**. After further transformations, the nine-membered ring was achieved by intramolecular S_N2 reaction (**4.13** → **4.14**).

In the final step, base-catalysed epimerisation at C-4 converted all material to the more stable isomer, (±)-fawcettimine. The total synthesis consisted of 16 steps with an overall yield of 10%, and was accomplished with no need for protecting groups. This paper is considered a landmark fawcettimine synthesis because it established that the (4*S*)-configuration is thermodynamically preferred relative to the (4*R*)-epimer; later papers also set the configuration by late-stage catalytic epimerisation of a C-5 ketone.



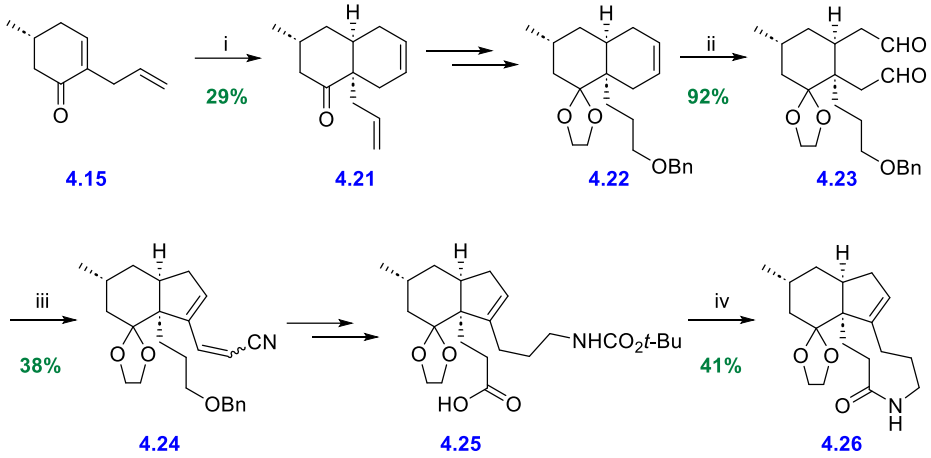
Scheme 38: i) $TiCl_4$, **4.7**, DCM, −78 °C, 3 h, then H_2O; ii) EtOH, 70 °C, 18 h then NaOEt, NaOH, 70 °C, 18 h; iii) KH, 18-crown-6, toluene, 110 °C, 16 h.

Similarly, Yang *et al*. assembled the 5-6 fused ring system in **4.17** *via* a Helquist annulation to form the cyclopentenyl ring, introducing the amine side chain *via* Suzuki–Miyaura cross-coupling (Scheme **39**).[181]



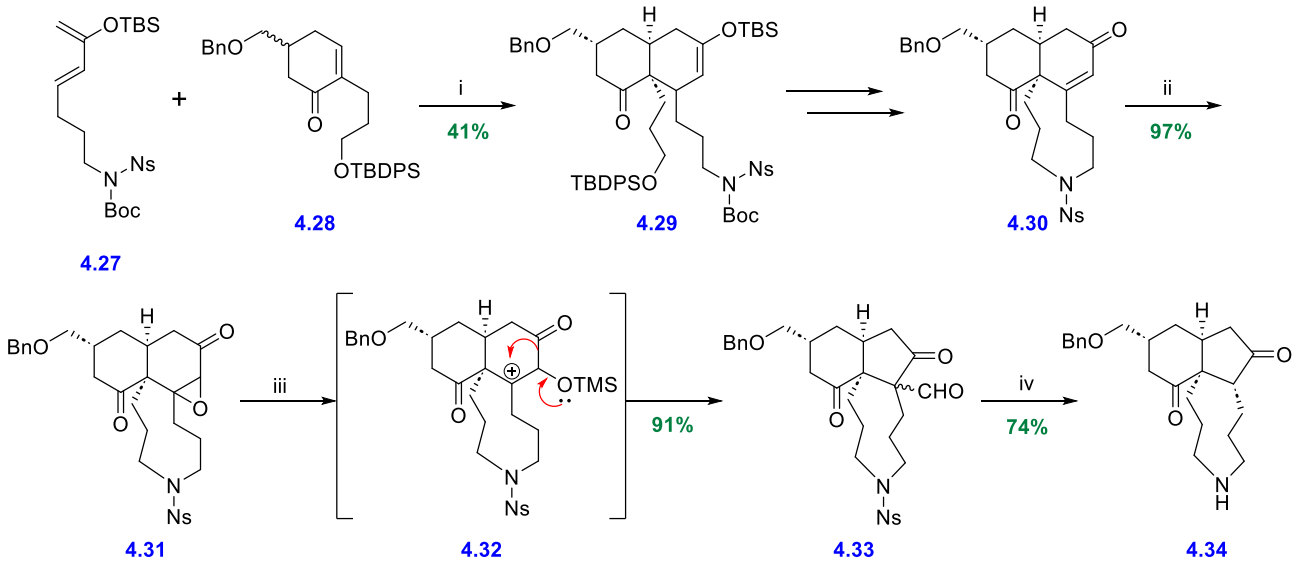
Scheme 39: i) Mg, 2-(2-bromoethyl)-1.3-dioxolane, THF, DMAP, $CuBr.SMe_2$, −78 °C then TMSCl, NEt_3, −10 °C; ii) aq HCl, THF, RT; iii) $H_2C{=}CHCH_2NHBoc$, 9-BBN, THF, RT then $[Pd(dppf)Cl_2]$, $AsPh_3$, Cs_2CO_3, DMF, 50 °C.

In contrast, Harayama *et al*. employed ring contraction of an octalin precursor to form the 5-6 fused rings (Scheme 40).[182, 183] In the initial Diels–Alder (DA) reaction of enone **4.15**, preferential approach of butadiene to the face opposite the C-5 methyl group gave *cis*-fused octalin derivative **4.21**. Dihydroxylation and periodate cleavage, followed by regioselective intramolecular aldol condensation and a Wittig reaction, supplied the 5-6 fused ring system in conjugated nitrile **4.24**. After further redox manipulations, carbamate **4.25** was coupled under acidic conditions to give the nine-membered lactam **4.26**, only two steps away from the (±)-fawcettimine target which the authors obtained in 26 steps and 0.1% overall yield.



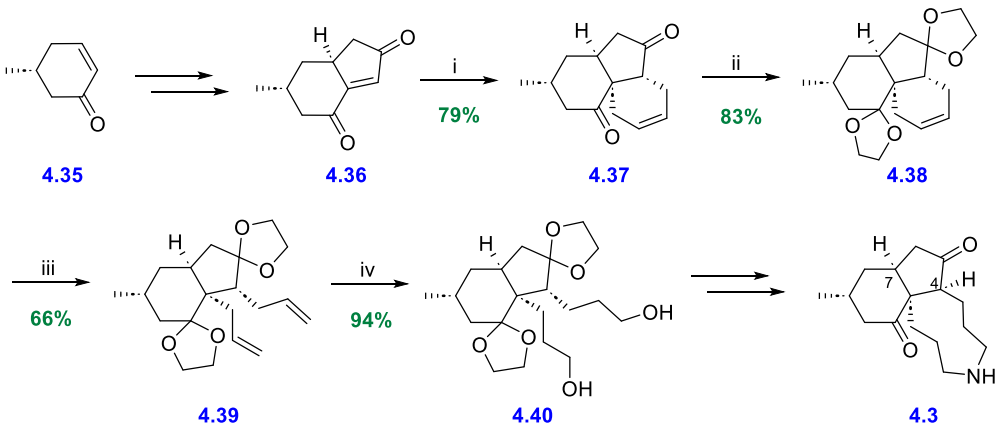
Scheme 40: i) Butadiene, $BF_3.OEt_2$, xylene, 190 °C, 22 h; ii) OsO_4, NMO, $HIO_4.2H_2O$, DCM, RT, 12 h; iii) morpholine-camphoric acid, HMPA, Et_2O, diethyl (cyanomethyl)phosphonate; iv) *N*-hydroxysuccinimide-DCC, CF_3CO_2H, NEt_3, MeCN, RT, 18 h.

This ring-contraction approach inspired Tanimura *et al*. who, in 2017,[184] envisaged that the side chain of the *cis*-hydrindane core might be installed as a part of the diene unit (Scheme 41). A DA reaction constructed *cis*-decalin **4.29**, which, in turn, was converted into the *cis*-hydrindane core of the natural product *via* a ring contraction of the derived epoxyketone and deformylation of the so-formed **4.33**. The DA reaction in this sequence also proceeded *via* approach of the diene to the enone face opposite to the C-5 substituent, in this case, a benzyloxymethyl group, to furnish *cis*-decalin **4.29** as an inseparable mixture of the *endo*-and *exo*-isomers (dr = 1.5:1).



Scheme 41: i) $ZnCl_2$, DCM, RT; ii) aq H_2O_2, aq NaOH, MeOH, THF, 0 °C; iii) TMSOTf, DCM, −78 °C; iv) PhSH, Cs_2CO_3, MeCN, MeOH, 50 °C.

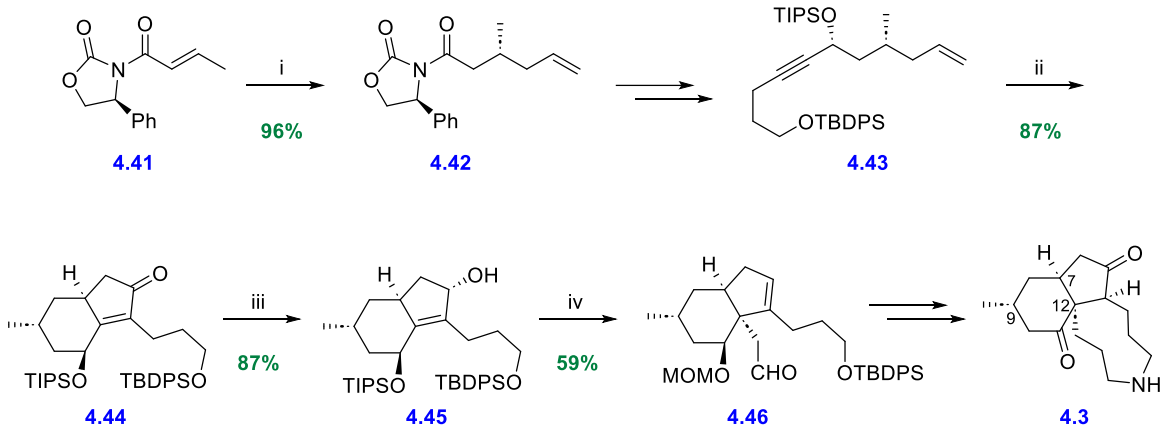
In 2014 Xu *et al*. exploited the symmetry of the two three-carbon chains connecting the nitrogen to the hydrindane system by performing a DA reaction on enedione **4.36** (Scheme 42),[185] with ring-cleavage and Wittig reactions to give the requisite number of carbons. As in previous work, the existing stereogenic centre in Xu's starting material dictated the C-7 configuration; the nine-membered ring was formed by double *N*-alkylation and the desired C-4 configuration was achieved by epimerisation under the reaction conditions to give the more stable product.



Scheme 42: i) Butadiene, BHT, toluene, 110 °C; ii) ethylene glycol, TsOH, benzene, 66 °C; iii) OsO_4, NMO, $NaIO_4$, aq THF, then $MePPh_3I$, BuLi, THF; iv) 9-BBN, THF, then NaOH, H_2O_2.

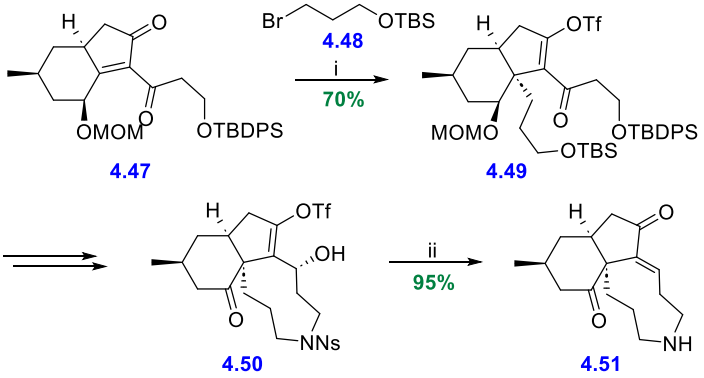
Other researchers employed a Pauson–Khand reaction (PKR) to set the C-7 stereogenic centre, as first reported by Nakayama *et al.* in 2009 (

Scheme 43).[186] Conventionally forming the nine-membered ring by an intramolecular S_N2 reaction, the authors executed an otherwise unusual synthesis of fawcettimine, incorporating a diastereoselective Hosomi–Sakurai allylation to form **4.42**, a PKR to form bicyclic **4.44**, and a Claisen rearrangement which gave aldehyde **4.46**, to exert the necessary stereocontrol for carbons C-7, C-9 and C-12.



Scheme 43: i) Allyltrimethylsilane, $TiCl_4$, DCM, −78 °C; ii) $Co_2(CO)_8$, NMO, DCM, RT under CO; iii) (*R*)-CBS, BH_3, THF, RT; iv) phenyl vinyl sulfone, KH, NaH, THF, RT, then $NaHCO_3$, 1,2-dichlorobenzene, 170 °C.

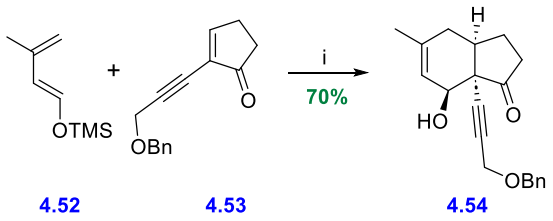
Also making use of the PKR, Kaneko *et al*. published in 2019 a 22-step asymmetric total synthesis of fawcettimine-type *Lycopodium* alkaloid, lycopoclavamine-A,[187] in 14% overall yield. Key steps following the PKR included a stereoselective conjugate addition (→ **4.49**), a Mitsunobu reaction to close the nine-membered ring (→ **4.50**), and an E1cB-like reaction to form the double bond within the nine-membered ring (Scheme 44).



Scheme 44: i) **4.48**, 2-thienylcyano cuprate, $BF_3.OEt_2$, *t*-BuLi, THF, −78 °C, 5 h, then NaH, Comins' reagent, THF, 0 °C, 3 h; ii) aq NaOH, dioxane/methanol, RT, 15 min.

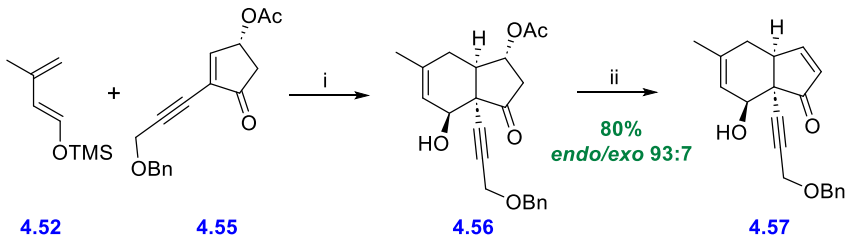
In a reversal of the order of ring-forming steps, the 5-6 ring system has also been assembled using a DA reaction to construct the cyclohexene ring. Prior to 2013, the six-membered ring in fawcettimine had

always been present in the starting material or constructed simultaneously with the five-membered ring in a PKR. Zaimoku *et al*., however, employed the typical method for forming a *cis*-fused 6-membered ring – that is, a DA reaction – in their synthesis of various *Lycopodium* alkaloids,[188] postulating that the DA reaction could compose the six-membered ring as well as setting three of the necessary stereocentres (Scheme 45). The group initially endeavoured to carry out the DA reaction between α-***alkyl***cyclopentenones and diene **4.52**; however, the reaction was extremely slow even under elevated temperatures, and the use of Lewis acids induced substrate decomposition. Instead, they took inspiration from Danishefsky *et al*.[189] who reported the high reactivity of α-***alkynyl*** enones as dienophiles in DA reactions. Thus, reaction of diene **4.52** with α-alkynylcyclopentenone **4.53** gave the *endo*-adduct **4.54** as the major product (70%).



Scheme 45: i) neat, 80 °C.

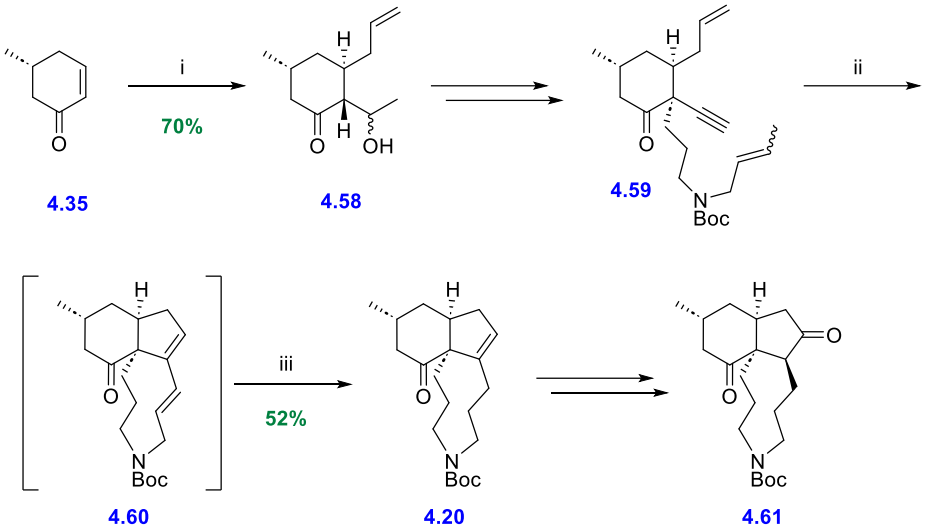
The same group later reported a similar DA reaction with chiral cyclopentenone **4.55** leading to major diastereomer **4.56** resulting from *endo*-cycloaddition on the enone face opposite the acetoxyl substituent (Scheme 46).[190] This time, the reaction proceeded in the absence of heating, suggesting that the acetoxy group activated the dienophile inductively.



Scheme 46: i) THF, RT; ii) *i*-Pr_2NEt.

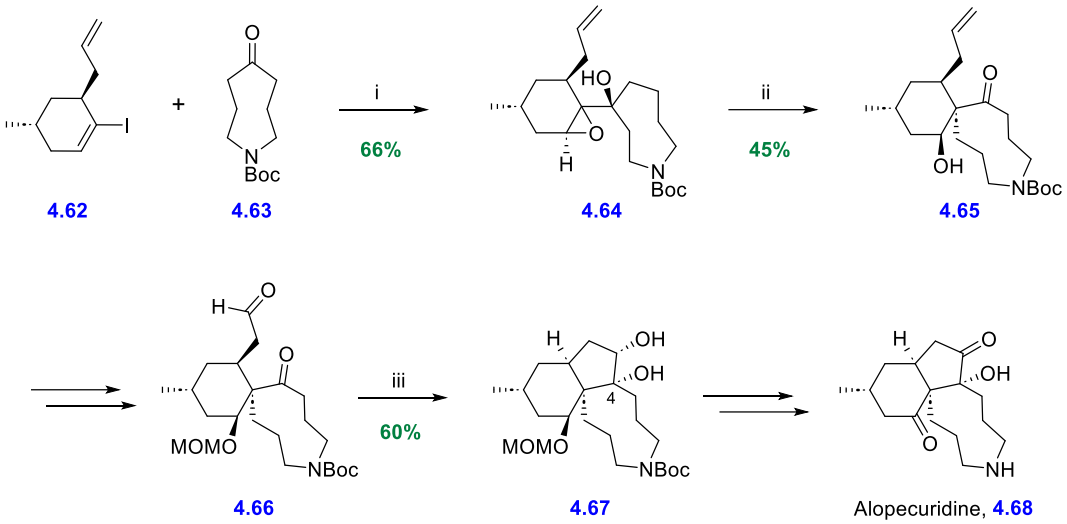
Enyne metathesis offers a strategic alternative, forming the five- and nine-membered rings in one step.[88] Using this strategy, Ramharter devised an efficient synthesis of Boc-protected (+)-fawcettimine in 13 steps and 13% overall yield (Scheme 47).[88] The most impressive step in this route is the tandem

catalysis cascade combining enyne RCM and selective hydrogenation steps (Scheme 47) that creates two new rings in a single step to give tricyclic **4.20**. The stereochemical control in this synthesis again derives from the C-5 substituent in the starting cyclohexenone **4.35**.[191, 192, 193]



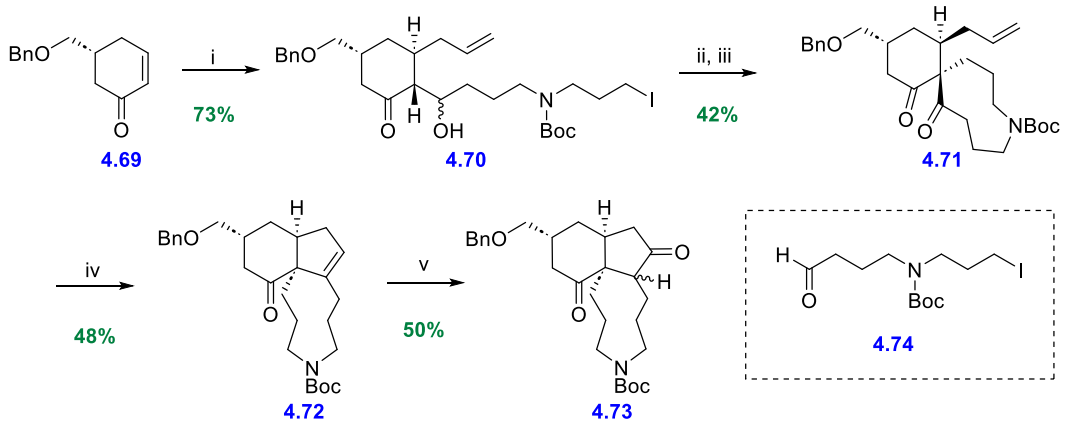
Scheme 47: i) $TiCl_4$, allyltrimethylsilane, DCM, −78 °C, then acetaldehyde; ii) Grubbs II (20 mol%), 1,2-dichloroethane, 80 °C then iii) H_2, 10 atm, 70 °C.

Other reported strategic alternatives include pinacol coupling and carbonyl-olefin metathesis of 6,9-spirocyclic precursors to form the five-membered ring. For example, in 2011 Zhang *et al*. left the formation of the five-membered ring until last (Scheme 48),[194] at which point a SmI_2-mediated pinacol coupling in dicarbonyl compound **4.66** simultaneously established the C-4 tertiary alcohol configuration. The azonane ring was achieved through semipinacol ring expansion of compound **4.64** which, in turn, originated from iodoalkene **4.62** and carbamate **4.63**.



Scheme 48: i) *t*-BuLi, $CeCl_3$, −78 °C, then *m*-CPBA, $NaHCO_3$, DCM, 0 °C; ii) $BF_3.Et_2O$, Et_2O, −30 °C; iii) HMPA, SmI_2, THF, 0 °C.

A related approach was described by Hong *et al*. in 2015 for the synthesis of huperzine Q (Scheme 49).[195] Again, the route began with an enantiomerically-enriched starting material, with 1,4-addition of an allylic cuprate being followed by enolate trapping with an iodoaldehyde leading to trisubstituted cyclohexanone derivative **4.70**. Alcohol oxidation then intramolecular enolate-alkylation afforded diketone **4.71**. Regioselective carbonyl-olefin metathesis furnished the cyclopentene ring, which was elaborated into a cyclopentanone moiety through a hydroboration/oxidation process.



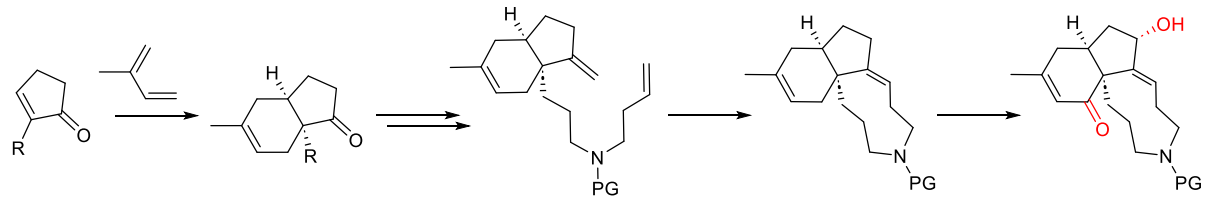
Scheme 49: i) Allyl MgBr, CuI, Me_2S, THF, −78 °C, 1 h, then add **4.74**, −78 °C, 3 h; ii) Dess–Martin periodinane, DCM, RT, 1.5 h; iii) DBU, DMF, RT, 72 h; iv) Schrock catalyst, ethylene balloon, benzene, reflux, 5 h; v) $BH_3.SMe_2$, Et_2O, reflux, 10 h, then NMO, TPAP, DCM.

4.3 Proposed synthesis for this work

This sub-project set out to synthesise the carbon skeleton of lobscurinol, with a view to use P450 enzymes to install late-stage functionalisation and perform final manipulations to give lobscurinol. This

general approach would: (1) extend the diversity of substrates evaluated by our $P450_{BM3}$ library leading to a greater understanding of the library's capabilities; (2) explore the ability of these enzymes to effect kinetic resolution of racemic substrates relevant to enantioselective alkaloid synthesis; and (3) highlight a late-stage hydroxylation approach to natural product synthesis by focusing on the synthesis of a relatively unfunctionalised tricyclic core.

As initially formulated, the synthesis of the core 5-6-9 ring system was to be achieved *via* a DA reaction to form the 5-6 bicyclic system, then closure of the nine-membered lactam by RCM which was expected to afford the more accessible *Z*-alkene (Scheme 50). At this point, $P450_{BM3}$ screening would be performed, aiming, ideally, to achieve hydroxylation at the allylic positions indicated in red in Scheme 50. It was appreciated, however, that obtaining the allylic ketone next to a quaternary carbon may be unachievable by the P450 enzyme; therefore, if oxidation does not occur there, the products of oxidation at other positions around the cyclohexenyl ring would be manipulated to move the oxy-functionalised centre into position chemically.



Scheme 50: Proposed synthetic route to the lobscurinol core.

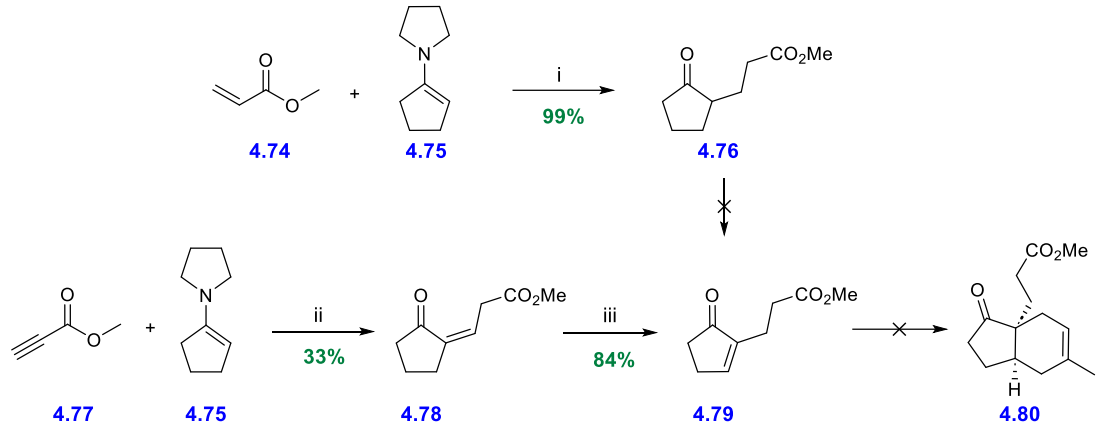
4.4 RCM tactic

4.4.1 Diels–Alder reaction with an intact enone side chain

The planned synthetic route to lobscurinol involved a DA reaction between enone **4.79** and isoprene (Scheme 51), for which the closest precedent employs 2-methylcyclopentenone as the dienophile.[196]

The synthesis of enone **4.79** was initially attempted from the Michael adduct **4.76** addition of cyclopentanone and methyl acrylate;[197] however, subsequent introduction of the conjugated double bond proved troublesome. Numerous conditions were attempted – including using NBS,[198] Ac_2O,[199] or SO_2Cl_2 then 2,4,6-collidine[200] at a variety of temperatures and with various additives – but these attempts invariably resulted in over-halogenation or poor selectivity.

Instead, the cycloaddition of enamine **4.75** and methyl propiolate **4.77**[201] afforded the desired compound **4.79** after alkene isomerisation.[202]



Scheme 51: (i) Dioxane, reflux, 4 h, then H_2O and reflux, 30 min; (ii) dioxane, 10 °C, 1 h, then H_2O and AcOH, 10 °C, 18 h; (iii) HCl, MeOH, reflux, 1 h.

The planned DA reaction did not proceed despite trialling various Lewis acids (at a variety of loadings) and reaction temperatures (Appendices, Table 34).[203–205] This led to the conclusion that the steric bulk of a non-methyl side chain inhibits the approach of the diene resulting in the DA transition state being inaccessible. In the Wenkert paper, the α-substituent of the cyclopentenone starting material was either a methyl group or a proton and a further survey of the literature showed DA reactions of α-substituted cyclopentenones have only been achieved with an α-ester,[206–216] -nitrile,[217, 218] -bromine[219–223] or -alkynyl[188–190, 224] substituents (Figure 14). The relatively small size and of these substituents coupled with their dienophile activating electron-withdrawing effect accounts for the appreciable reactivity of such enones towards dienes.

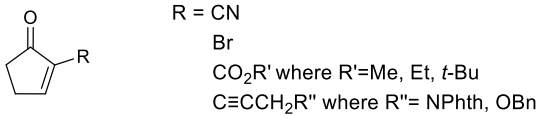
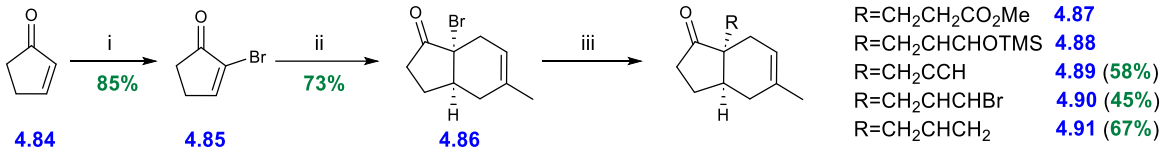


Figure 14: Precedented starting materials for the DA reaction of α-substituted cyclopentenones.

4.4.2 Diels–Alder reaction prior to installation of the side chain

Consequently, another route was followed, which started with the precedented DA reaction[225] of 2-bromocyclopentenone **4.85**[226] with isoprene (Scheme 52) to give key intermediate **4.86**, whose

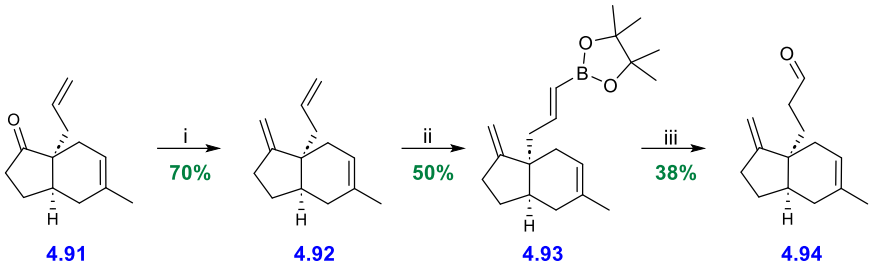
instability became problematic when the reaction was scaled up. The specific enolate could be generated from bromoketone **4.86** based on previous results in the group.[227] Michael addition of this enolate with methyl acrylate[228] gave a mixture of products due to oligomerisation following the first 1,4-addition, while alkylation towards TMS-enol ether **4.88** was unsuccessful due to the instability of the allylic iodide electrophile. Simple allylation and propargylation variants were successful, giving intermediates **4.89**, **4.90** and **4.91**, which were used to explore methods for elaborating the side chain. The polar, aprotic solvent system of DME/DMPU was found to be necessary for effective alkylation, solvating the Li^+ counterion and increasing the charge density and nucleophilicity of the enolate (Appendices, Table 35). The relative ring-fusion configuration of these intermediates was established (NOESY) to be *cis*, which is consistent with precedent reporting alkylations of related bicyclic enolates.[229]



Scheme 52: (i) Pyridine-*N*-oxide, MeCN, NBS, 0 °C → RT, 18 h; (ii) $EtAlCl_2$ (20 mol%), isoprene, DCM, 0 °C, 18 h; (iii) MeLi, DME, −78 °C, 1 h, then DMPU, methyl acrylate *or* (3-iodoprop-1-en-1-yl)oxy)trimethylsilane *or* propargyl bromide *or* 1,3-dibromoprop-1-ene *or* allyl bromide, RT, 18 h.

Developing the side chain of compounds **4.89**, **4.90** and **4.91** proved unexpectedly difficult; while various methods were evaluated for installing amine functionality (see Appendices, Table 36), only the terminal alkene **4.91** gave viable routes forward. The unsuccessful attempts included hydroboration of terminal alkyne **4.89**,[230–233] hydrolysis of vinyl bromide **4.90**,[234–239] and hydroamination of terminal alkene **4.91**,[240] as well as variants in which the ketone in intermediate **4.91** was protected so as to avoid carbonyl reduction during hydroboration.[241–244] It was thought that the congested quaternary centre and the ketone functionality could be interfering with the approach of reagents to the side chain.

A positive outcome from these experiments was the selective cross metathesis reaction between triene **4.92**[245] and pinacol vinylboronate, the product of which was expected to be readily hydrolysed to give the aldehyde **4.94** (Scheme 53). Triene **4.92**, rather than ketone **4.91**, was used for the cross-metathesis reaction in order to avoid potential complications associated with orchestrating differential reactivity of two carbonyl groups.



Scheme 53: (i) $MePh_3PBr$, *t*-BuOK, THF, 70 °C, 18 h; (ii) pinacol vinylboronate, Grubbs II (10 mol%), toluene, 110 °C, 1 h; (iii) anhydrous Me_3NO, THF, 70 °C, 3 h.

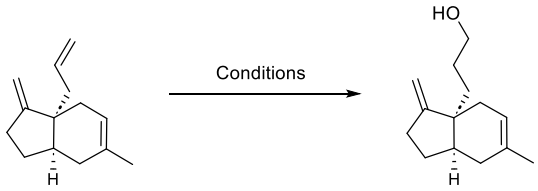
The hydrolysis of pinacol vinylboronate **4.93** to give aldehyde **4.94** was attempted (Table 9). When water was present, the product mixture showed signs of cyclisation induced by $NaBO_3$,[246] giving an alcohol (unidentified) by IR spectroscopy (entries 1 and 2). When trimethylamine *N*-oxide was tried,[247–249] the product could be detected but could not be purified effectively (entry 3). Exclusion of water from the system by using anhydrous trimethylamine *N*-oxide gave the product in low yield (entry 4), significantly improved by reducing the reaction time (entry 5).

Entry	Conditions	Result
1	$NaBO_3.4H_2O$, THF/H_2O, RT, 18 h	Product cyclised during the reaction
2	$NaBO_3.4H_2O$, THF/H_2O, 40 °C, 18 h	Product cyclised during the reaction
3	$Me_3NO.2H_2O$, THF, 70 °C, 18 h	Incomplete, inseparable **4.93** and **4.94**
4	Anhydrous Me_3NO, THF, 70 °C, 18 h	14% **4.94**
5	Anhydrous Me_3NO, THF, 70 °C, 3 h	38% **4.94**

Table 9: Attempts to hydrolyse vinyl pinacolborane **4.93** leading to aldehyde **4.94**.

The cross metathesis and hydrolysis steps were deemed too inefficient for continuing the route and a different approach was attempted based on selective hydroboration of triene **4.92**, since this would give the necessary handle for development of the side chain (Table 10). In the event, 9-BBN proved too bulky a reagent and the reaction did not proceed (entry 1); use of the smaller $BH_3.SMe_2$ gave non-selective

reaction (entry 2); lowering the loading of borane to 0.25 equiv. showed that the primary alkene was not attacked first and that hydroboration occurred at all three alkenes with similar rates.



4.92 4.95

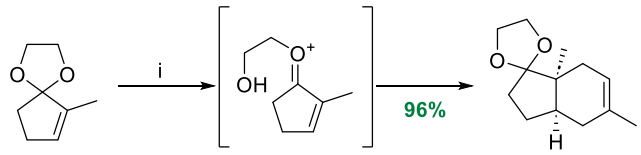
Entry	Conditions	Result
1	9-BBN, THF, 50 °C, 24 h	No reaction
2	$BH_3.SMe_2$, THF, RT, 1 h	All alkenes react

Table 10: Hydroboration attempts.

4.4.3 An alternative specific enolate precursor

The route was revised to avoid unstable bromoketone **4.86**, and plans were made to use a TMS enol ether as an alternative precursor to the enolate, and take the opportunity to explore new methods to install the quaternary carbon.

Following Gassman's earlier work, Grieco had shown that ionic DA reactions can be carried out at room temperature using the ethylene ketals of α,β-unsaturated ketones as the dienophile, in 4.0–5.0 M solutions of $LiClO_4$ in diethyl ether, with 1% of CSA added (Scheme 55).[250] The Brønsted acid catalyses the reversible formation of the oxygen stabilised allyl cation **4.97** in the highly polar $LiClO_4$/ether medium, activating the dienophile, and the high internal solvent pressures of the medium accelerates the rate so that these reactions can occur rapidly under mild conditions.[251]

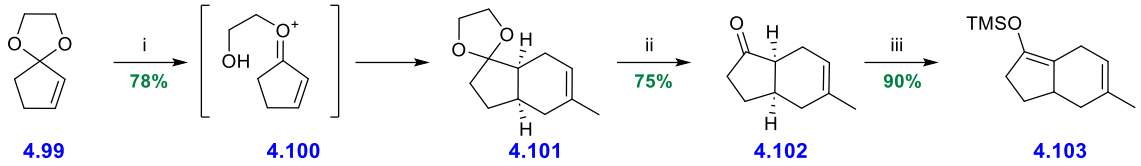


4.96 4.97 4.98

Scheme 54: i) 4.0 M $LiClO_4$ in Et_2O, isoprene, 1.0 mol% CSA, 30 min, RT.

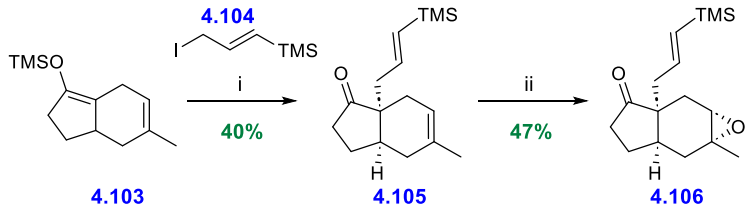
Thus, the revised route (Scheme 55) started with a DA reaction between cyclopentenone ethylene ketal **4.99** and isoprene,[252] made possible under mild conditions by virtue of the reactive activated oxonium

intermediate **4.100** (*cf.* **4.97**), generated *in situ* reversibly. This was followed by ketal hydrolysis to afford ketone **4.102**.[252] To control the site of subsequent ketone α-alkylation, the more stable fully-substituted TMS enol ether **4.103** was prepared under equilibrating conditions.[253]



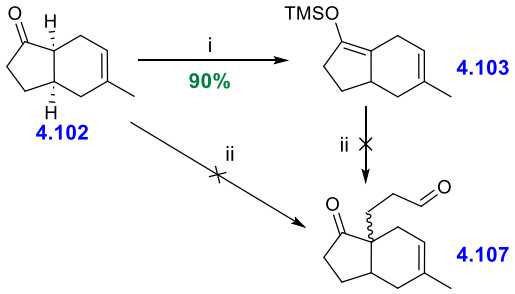
Scheme 55: (i) $LiClO_4$, isoprene, CSA (1.0 mol%), Et_2O, RT, 1 h; (ii) aq HCl, methanol, 0 °C 1 h; (iii) NEt_3, TMSOTf, DCM, RT, 1 h.

Compound **4.103** was then used to generate the lithium enolate regiospecifically from which vinyl silane derivative **4.105** was obtained (Scheme 56). Epoxidation of this side-chain was then attempted, based on precedent from Stork in which a 3-ketoalkyl chain was appended to a carbonyl in this manner, capitalising on the vinyl silane's function as a latent carbonyl.[254] The expected increase in alkene reactivity towards electrophiles imparted by the TMS group was insufficient to compete with the electron-rich trisubstituted cyclohexene double bond and epoxide **4.106** was obtained instead.



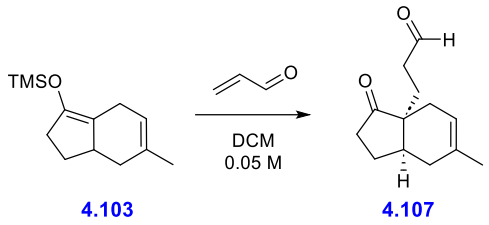
Scheme 56: i) MeLi, **4.104**, DME, THF, RT, 18 h; ii) mCPBA, DCM, 0 °C to RT, 18 h.

Furthermore, with acrolein as the electrophile, neither direct Michael addition from ketone **4.102** nor Mukaiyama–Michael addition from TMS enol ether **4.103** processed the starting material at all (Scheme **57**), despite precedent describing similar reactions in the absence of added reagents.[255, 256]



Scheme 57: i) TMSOTf, NEt_3, DCM, RT, 1 h; ii) acrolein, DCM, 0 °C or RT.

In attempts to promote the Mukaiyama–Michael reaction with various Lewis acid additives, diethylaluminium chloride,[257] $TiCl_4$[258] and $SnCl_4$[259] gave no reaction, but $InCl_3$[260] showed some promise, with 20% of the material converting to the desired Michael-adduct **4.107**. Further attempts to optimise the $InCl_3$-catalysed addition only increased the conversion to product slightly, to 25% (Table 11). Doubling the loading of Lewis acid (entry 2) did not have an appreciable effect on product formation. To neutralise any HCl potentially present in the $InCl_3$, the hindered base DTBMP was added (entry 3); however, this completely inhibited the reaction, suggesting that adventitious protic impurities may play a positive role. Increasing the concentration of the reaction (entries 4, 7 and 9) attempting to promote Michael addition over protonation, or alternatively reducing the loading of DTBMP to below that of $InCl_3$ (entry 5), aiming to restrict complete quenching of the acid, did not improve the reaction. The solvent was changed to the more polar acetonitrile to encourage charge separation, in an attempt to favour Mukaiyama–Michael addition over proto-desilylation (entry 6), but again this did not produce the desired result. The only change in conditions that increased the percentage of product was to add the premixed $InCl_3$-acrolein *via* syringe pump rather than through a manual syringe (entry 8), which had the advantage of ensuring that a low concentration of acrolein was maintained at all times.

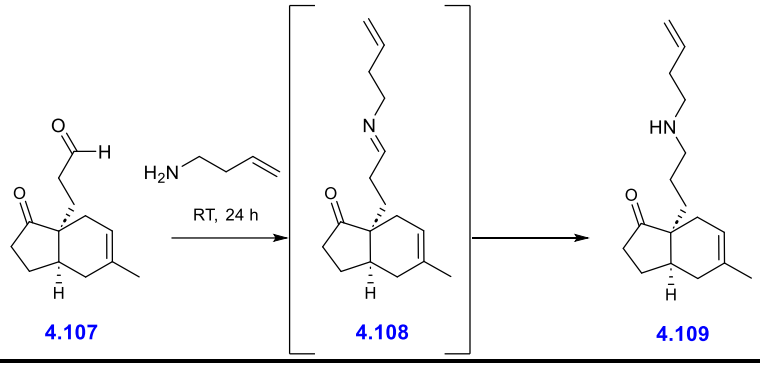


Entry	$InCl_3$ (equiv.)	Conc. (M)	Base (equiv.)	Solvent	Mode of addition of premixed $InCl_3$-acrolein	Product 4.107 (%)	4.102 (%)
1	0.05	0.05	–	DCM	Dropwise	20	80
2	0.1	0.05	–	DCM	Dropwise	21	79
3	0.05	0.05	DTBMP (0.15)	DCM	Dropwise	0	0
4	0.05	0.50	DTBMP (0.15)	DCM	Dropwise	0	0
5	0.05	0.05	DTBMP (0.02)	DCM	Dropwise	0	0
6	0.05	0.05	–	MeCN	Dropwise	6	94
7	0.05	2.00	–	DCM	Dropwise	0	0
8	0.05	0.05	–	DCM	Syringe pump	25	75
9	0.05	0.20	–	DCM	Syringe pump	4	96

Table 11: Attempts to optimise the Mukaiyama–Michael reaction.

With a sample of key intermediate **4.107** in hand, a reductive amination was pursued (Table 12), in the expectation that the more electrophilic and unhindered aldehyde would react preferentially, at least initially. Indeed, selective reductive amination of an aldehyde in the presence of a ketone has been traditionally achieved by using a mild reducing agent such as $NaBH_3CN$,[261–263] which is capable of reducing the iminium intermediate but neither the aldehyde nor ketone starting material. Thus, these common reaction conditions were trialled; however, amination did not occur in the solvent system of MeOH/THF. A paper by Shah *et al.*[264] advocated using DCE as a solvent, and acetic acid as a catalyst; this paper also maintained that the milder reducing agent $NaBH(OAc)_3$ gave consistently higher yields

and fewer side products than $NaBH_3CN$. Under these revised conditions, the reductive amination was convoluted and the numerous products were indefinable. The same disappointing result occurred when no reducing agent was added, suggesting that the imine intermediate is unstable with respect to cyclisation and other reactions with the ketone.



Entry	Solvent	Reducing agent	Other	Result
1	MeOH + THF	$NaBH_3CN$	–	No reaction
2	MeOH + THF	$NaBH_3CN$	AcOH (1.0 mol%)	No reaction
3	MeOH + THF	$NaBH(OAc)_3$	–	No reaction
4	DCE	$NaBH(OAc)_3$	–	Complex mixture
5	DCE	$NaBH(OAc)_3$	AcOH (1.0 mol%)	Complex mixture
6	DCM	–	$MgSO_4$, NEt_3	Complex mixture

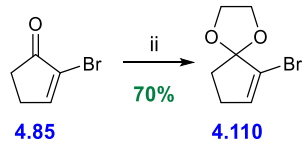
Table 12: Conditions attempted for reductive amination from ketoaldehyde **4.107**.

4.4.4 Diels–Alder cycloaddition with ketal and side chain intact

Rather than developing the side chain *following* the DA reaction, which seemed to be plagued with complications, the strategy was revised to install most of the side-chain functionality before performing the cycloaddition. Earlier attempts to do this had been thwarted by the α-substituent of the

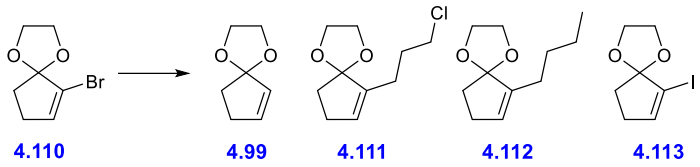
cyclopentenone; however, following the success of the DA reaction of unsubstituted cyclopentenone ketal **4.99** (Scheme 55), it was decided to evaluate the method with ketals bearing α-substituents.

Thus, by performing the DA reaction with the ethylene ketal rather than the ketone, it was hoped that the α-substituent could be introduced before ionic cycloaddition. To this end, bromo-enone **4.85** was converted into its ethylene ketal[265] in readiness for C-2 functionalisation (Scheme 58).



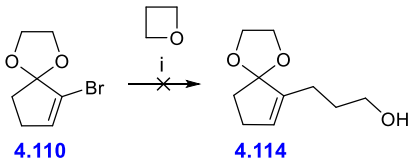
Scheme 58: (i) Ethylene glycol, $(EtO)_3CH$, TsOH (10 mol%), toluene, 80 °C, 1 h, 75%.

The next step was to alkylate the cyclopentenone bromoketal which was first tackled by lithium-halogen exchange and trapping of the so-formed vinyllithium species.[266] With 1-chloro-3-iodopropane as the electrophile (Table 13),[267] varying the loading of butyllithium (1.0, 1.05, 1.1, 1.5, or 2.0 equiv.), concentration (0.2 M, 0.45 M, or 0.5 M), solvent (THF or ether), loading of alkyl iodide (1.0, 1.2, or 2.9 equiv.), identity of the electrophile (changed to allyl iodide and allyl bromide[268]), or additive (0.1 equiv. HMPA, 1.05 equiv. CuI,[269] 1.0 equiv. phenyl thiocopper),[270, 271] the desired product was not detected. Instead, proto-debromination or butylation were observed using 1-chloro-3-iodopropane (entry 1), and proto-debromination or halogen exchange using allyl halides (entries 2 and 3). A reaction employing oxetane as the electrophile[272] and an attempted radical addition to acrylonitrile[273] were equally unsuccessful (Scheme 59; entry 4 and Scheme 60; entry 5, respectively).

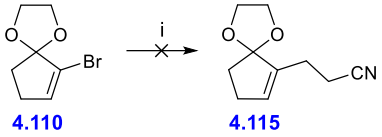


Entry	Electrophile	Result
1	$ClCH_2CH_2CH_2I$	Only **4.99** or **4.112**
2	CH_2=$CHCH_2I$	Only **4.99** or **4.113**
3	CH_2=$CHCH_2Br$	Only **4.99**
4	Oxetane	Complex mixture
5	CH_2=CHCN	No reaction

Table 13: Results from the attempted functionalisation of bromoketal **4.110** *via* lithium-halogen exchange with butyllithium.

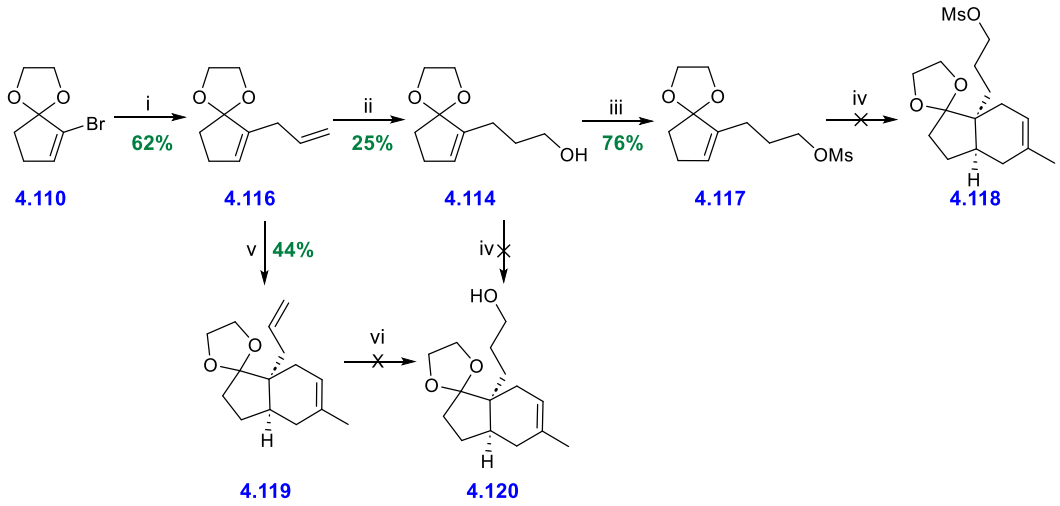


Scheme 59: i) BuLi, $BF_3.OEt_2$, oxetane, THF, −78 °C, 3 h.



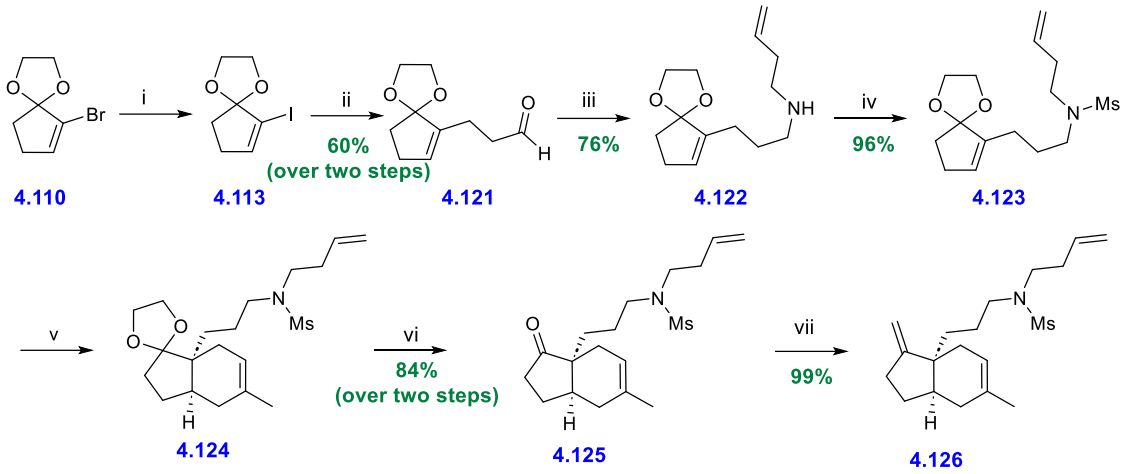
Scheme 60: i) Acrylonitrile, AIBN (12 mol%), Bu_3SnH, benzene, 80 °C, 18 h.

Functionalisation of the bromo ketal was finally achieved *via* a Stille cross-coupling (Scheme 61);[275] however, after subsequent hydroboration, oxidation[274] and *O*-mesylation, the DA reaction[252] failed. Attempts to carry out the DA reaction earlier in the sequence were also stalled by ineffective hydroboration of ketal-diene **4.119** and a failed DA reaction from propyl alcohol **4.114**, both returning only the starting material. A more promising step in this sequence was the successful DA reaction of α-substituted ketal **4.116**, which demonstrated a route to a bicyclic bearing the side-chain and avoiding bromo-enone **4.86**, as well as being the first DA reaction of an alkyl cyclopentenone beyond 2-methyl cyclopentenone.



Scheme 61: (i) Allyl-$SnBu_3$, $PdCl_2(PPh_3)_2$ (5.0 mol%), PPh_3 (10 mol%), LiCl, DMF, 140 °C, 3 h; (ii) 9-BBN, THF, RT, 18 h, then H_2O_2, aq NaOH, RT, 18 h; (iii) MsCl, NEt_3, DCM, RT, 1 h; (iv) $LiClO_4$, isoprene, CSA (5.0 mol%), Et_2O, 40 °C, 18 h; (v) $LiClO_4$, isoprene, CSA (1.0 mol%), Et_2O, 40 °C, 18 h; (vi) 9-BBN, H_2O_2, aq NaOH, THF, 66 °C, 18 h.

The successful Stille reaction of bromoketal **4.110** to give allylated product **4.116** suggested that other cross-coupling reactions could be used to access further DA substrates. To facilitate this, the bromine in **4.110** was exchanged[276] for iodine (→ **4.113**, Scheme 62), then a Heck reaction[277] afforded aldehyde **4.121**. This coupling reaction did not occur at the temperature (50 °C) reported for similar reactions; however, at 100 °C the coupling progressed well and the isolated yield was further improved by including triethylamine in the column eluent to minimise ketal hydrolysis on the partially acidic silica stationary phase. Reductive amination[278] of the aldehyde and mesylation[279] of the so-formed amine provided amine **4.122** as a substrate for the DA reaction[252] containing all the side-chain components necessary for the projected RCM reaction. The cycloaddition was successful but required an increase in the reaction temperature, compared with that reported (RT), as well as the loading of CSA (Table 14). Finally, the ketal was removed,[252] and a Wittig methylenation[280] carried out as before (*cf.* Scheme 53) to give triene **4.126**.



Scheme 62: (i) BuLi, I_2, THF, −78 °C, 30 min then RT, 1 h; (ii) allyl alcohol, $NaHCO_3$, Bu_4NCl, $Pd(OAc)_2$ (2.0 mol%), DMF, 100 °C, 18 h; (iii) 1-aminobut-3-ene, MeOH, RT, 1 h then $NaBH_4$, RT, 1 h; (iv) MsCl, NEt_3, DCM, RT, 1 h; (v) $LiClO_4$, isoprene, CSA (5.0 mol%), Et_2O, 40 °C, 18 h; (vi) aq HCl, MeOH, RT, 1 h; (vii) $MePh_3PBr$, *t*-BuOK, THF, 70 °C, 18 h.

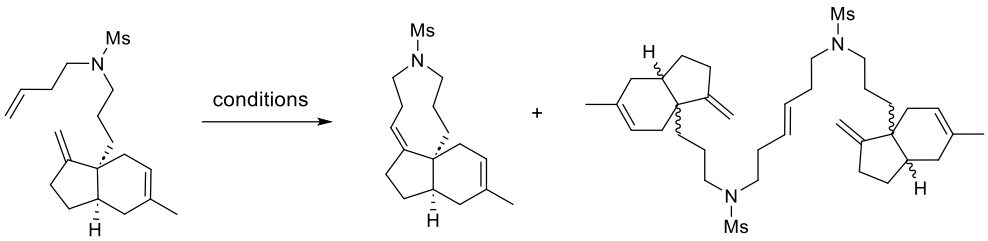
Entry	CSA (%)	Temperature (°C)	Outcome
1	1.0	RT	No reaction
2	1.0	40	No reaction
3	5.0	40	Reaction proceeds

Table 14: Optimisation of the DA reaction, step (v) in Scheme 62.

4.4.5 RCM reaction

The crucial RCM step to complete the lobscurinol core was ultimately unsuccessful despite a number of trials (Table 15). Only the dimer (**4.128**) of starting material **4.127** was obtained and no evidence was found to support formation of the desired tricyclic product **4.128**. Grubbs I, Grubbs II and Hoveyda–Grubbs II catalysts gave no reaction at RT (entries 1, 3 and 5), whereas higher temperatures of 60 °C or 110 °C gave dimer **4.128** (entries 4, 6 and 7). The elevated temperature allowed the catalyst to perform metathesis at the terminal alkene, but the hindered alkene adjacent to the quaternary centre was apparently inaccessible to the bulky ruthenium carbene intermediate, and so continuation of the metathesis reaction at this centre could not occur. While there is precedent for RCM reactions involving a disubstituted alkene next to a quaternary centre to form five- and six-membered rings,[281, 282, 283, 284] similarly congested larger

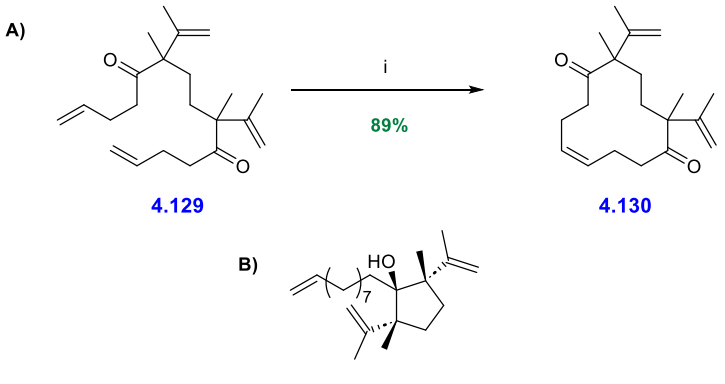
rings have not been formed *via* this method. Indeed, Santelli *et al*. achieved a RCM reaction which formed a 12-membered ring (Scheme 63A);[285] however, only the terminal alkenyl groups in the starting material **4.129** were involved in the metathesis reaction, and no reaction leading to a tetrasubstituted alkene occurred. Furthermore, all attempts to observe a metathesis reaction from substrate **4.131** reportedly failed (Scheme 63B), suggesting that the alkenes adjacent to a quaternary centre are too hindered for metathesis to occur for that substrate.



4.126 4.127 4.128

Entry	Solvent	Catalyst (2.0 mol%)	Temperature (°C)	Addition method of catalyst	Outcome
1	DCE	Grubbs I	25	Instant	No reaction
2	DCE	Grubbs I	60	Instant	No reaction
3	DCE	Grubbs II	25	Instant	No reaction
4	DCE	Grubbs II	60	Instant	80% **4.128**
5	DCE	Hoveyda–Grubbs II	25	Instant	No reaction
6	DCE	Hoveyda–Grubbs II	60	Instant	84% **4.128**
7	Toluene	Grubbs II	110	Dropwise *via* syringe pump, 1 mL/h	89% **4.128**

Table 15: Conditions attempted to form the nine-membered ring from triene **4.126** by a RCM reaction.



4.129 4.130

4.131

Scheme 63: A) i) Grubbs II, DCM, 40 °C, 16 h; B) Unreactive substrate **4.131**.

4.5 McMurry tactic

With this setback, a change of tactic from RCM to an intramolecular McMurry coupling of the two carbonyl groups was considered since this would avoid the requirement to engage the sterically-hindered exomethylene double bond with bulky intermediates. Additionally, while RCM is generally reversible, the irreversible McMurry reaction was thought to have more chance of accessing the somewhat strained medium ring; the low-valent titanium reagent can pre-coordinate to the two aldehydes, bringing them together and separating the entropic barrier towards cyclisation from the C–C bond-forming step. In this way, the McMurry is effective at forming strained alkenes including those in larger rings that are inaccessible to RCM (Figure **15**). For example, in Berlage's formal synthesis of bicyclic strigol,[286] a McMurry reaction was used to couple an aldehyde with a ketone adjacent to a quaternary carbon centre (Figure 11, **4.140**), similar to the circumstance in this approach to the lobscurinol core.

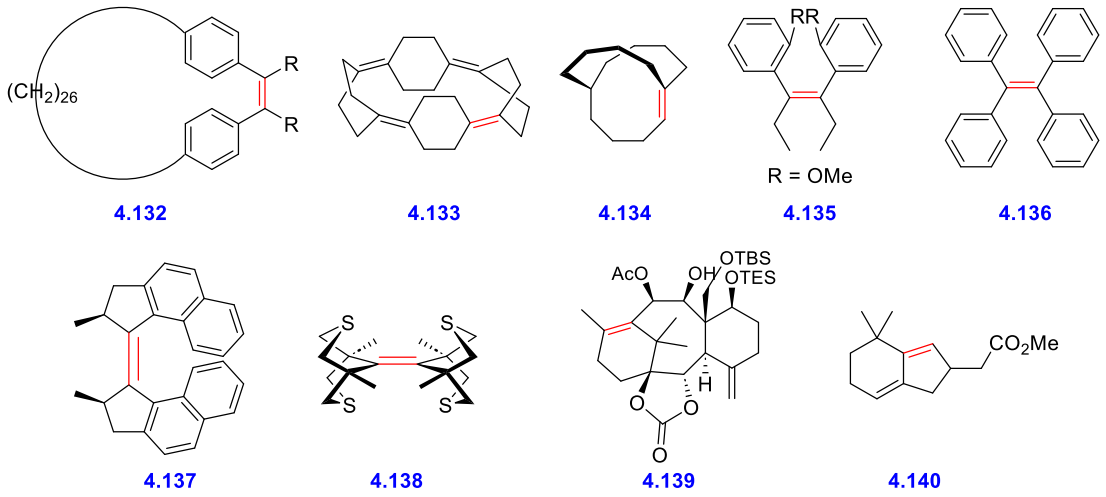
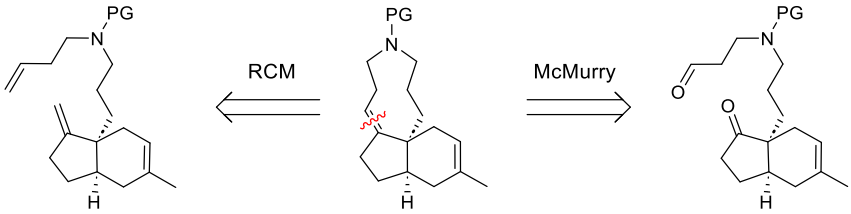


Figure 15: Examples of large rings (**4.132**,[287] **4.133**,[287] **4.134**[288]) and hindered alkenes (**4.135**,[289] **4.136**,[290] **4.137**[291–293]), including those adjacent to a quaternary carbon (**4.138**,[294] **4.139**,[295, 296] **4.140**[286]), formed by McMurry reactions, with the newly-formed alkene in each case highlighted in red.

This change of tactic requires two carbonyl groups in the precursor (Scheme 64). The presence of the cyclohexene double bond meant that double ozonolysis or an equivalent reaction of the substrate in hand (**4.126**) could not be considered. Additionally, any preparatory reactions would

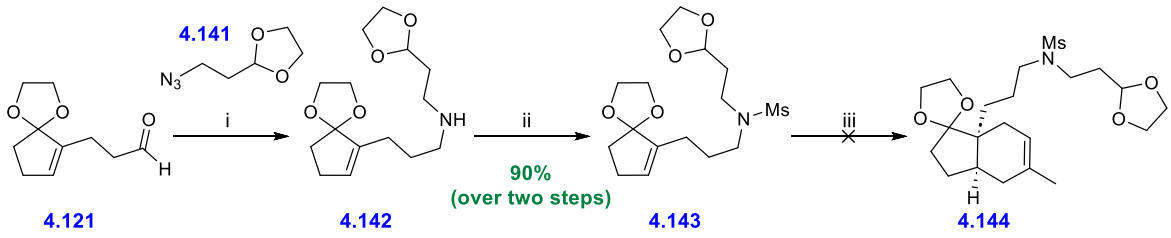
need to be compatible with the cyclopentanone carbonyl group or its ketal, and the amine substituent requires a latent aldehyde.



Scheme 64: Change of ring-closing tactic from alkene metathesis to McMurry reaction.

4.5.1 Formation of the precursor

The first attempt to assemble the McMurry precursor began with a Staudinger–aza-Wittig reaction using aldehyde **4.121** (Scheme 65).[297] This method was more efficient than the reductive amination previously employed, giving a higher yield and averting the need to prepare the acetal-amine. After mesylation of the amine, the standard cycloaddition was planned. The DA reaction did not proceed in the presence of the acetal however, even with the increased temperature and loading of CSA used to facilitate the reaction previously, possibly because the acid catalyst was effectively sequestered by the acetal group. Thus, for this route, the required side-chain aldehyde could not be present in masked form as the acetal at the time of the DA reaction.



Scheme 65: i) Azide **4.141**, PPh_3, THF, RT, 3 h, then add **4.121**, 66 °C, 3 h, then $NaBH_4$ added at 0 °C, RT, 30 min; ii) MsCl, NEt_3, DCM, RT, 1 h; iii) $LiClO_4$, isoprene, CSA (5.0 mol%), Et_2O, THF, 40 °C, 18 h.

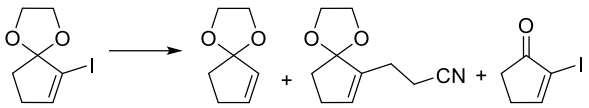
As an alternative, starting with iodoketal **4.113** conditions for installing a cyanoethyl side chain were explored (Table 16). In their 2008 paper, Liu *et al*. reported the generation of α-carbonyl vinyl radicals from α-iodo-cycloalkenones and their participation in intermolecular addition reactions with electron-deficient olefins such as acrylonitrile.[273] The Liu conditions were repeated with iodoketal **4.113**,

giving a yield of 37% (entry 1) comparable to the yield reported (42%) for the reaction of the corresponding ketone. To maintain a low concentration of α-carbonyl vinyl radical and disfavour self-coupling and premature direct reduction, a solution of tributyltin hydride and AIBN in benzene was added in portions over four hours (slow addition *via* a syringe pump gave a more complicated reaction and favoured formation of ketal **4.99** (entry 2), paralleling similar observations in the Liu paper).

Despite Liu's paper reporting no improvement in yield when the amount of acrylonitrile was increased above 10 equivalents, here it was found that 50 equivalents of acrylonitrile increased the isolated yield to 57% (entry 3). Using acrylonitrile as the solvent, however, triggered exothermic polymerisation instead of the desired reaction (entry 9), although it functioned moderately well as a 1:1 co-solvent (entry 10). Increasing the temperature of the reaction to 110 °C by changing the solvent to toluene (entry 8) resulted in removal of the ketal group, suggesting benzene or, at least, a lower reaction temperature is necessary for the success of the reaction.

There is precedent for using photolytic initiation of such reactions with an α-iodoketone substrate in the presence of hexamethylditin, to give the radical addition adduct;[299–301] however, in our hands this system gave no desired product (entries 5–7) and the addition of tributyltin hydride (entry 4) did not improve the working yield.

There is also precedent for performing a similar vinyl radical addition to acrylonitrile in the absence of AIBN and at RT.[302] These were tried on the current system (entries 11 and 12), but with little success. It has also been found that tris(trimethylsilyl)silane can be a useful substitute for tributyltin hydride because the former is a weaker H-atom donor and its use can suppress the formation of direct reduction products.[303] This proved not to be the case in practice (entry 13), the ketone **4.145** being the sole product observed; therefore, the least inefficient conditions remained those detailed in entry 3, which gave a 57% isolated yield of adduct **4.115**.

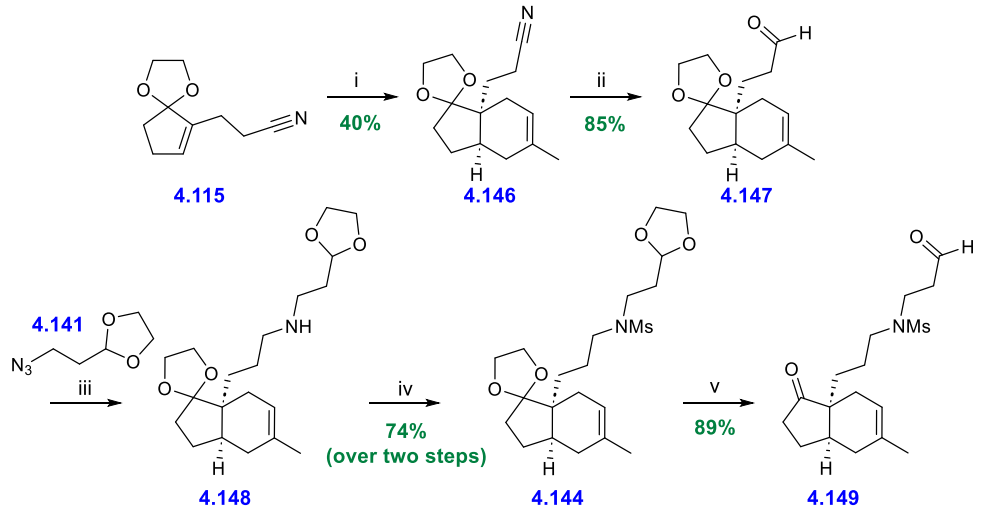


4.113 4.99 4.115 4.145

Entry	Acrylonitrile (equiv.)	Radical initiator	Solvent	Temperature (°C)	Outcome (4.99/4.115/ 4.145)	Yield of 4.115 (%)
1	10	Bu_3SnH + AIBN[a]	Benzene	80	49:51:0	37
2	10	Bu_3SnH + AIBN[b]	Benzene	80	60:40:0	22
3	50	Bu_3SnH + AIBN[a]	Benzene	80	40:60:0	57
4	10	Bu_3SnH + AIBN + $(Bu_3Sn)_2$ + UV lamp[c]	Benzene	80	53:47:0	40
5	10	$(Bu_3Sn)_2$ + UV lamp[c]	Benzene	80	100:0:0	–
6	25	$(Bu_3Sn)_2$ + UV lamp[c]	Benzene	80	100:0:0	–
7	50	$(Bu_3Sn)_2$ + UV lamp[c]	Benzene	80	100:0:0	–
8	10	Bu_3SnH + AIBN[b]	Toluene	110	0:0:100	–
9	74 (solvent)	Bu_3SnH + AIBN[a]	Acrylonitrile	80	Polymerisation	–
10	37 (co-solvent)	Bu_3SnH + AIBN[a]	Acrylonitrile + benzene	80	48:52:0	41
11	5	Bu_3SnH[a]	Benzene	80	82:18:0	15
12	5	Bu_3SnH[a]	Benzene	RT	94:6:0	5
13	5	$(Me_3Si)_3SiH$[a]	Benzene	80	0:0:100	–

Table 16: Optimisation of radical reaction. [a]Addition method = 8 aliquots in 30 min intervals; [b]Addition method = syringe pump (1mL/hr); [c]Addition method = immediate.

The cyanoethyl-substituted ketal 4.115 was a successful substrate in the DA reaction (Scheme **66**); following this, a DIBAL-H reduction[304] of the nitrile gave aldehyde **4.147** which was converted to the amine by the reductive aza-Wittig reaction employed previously.[305] Amine mesylation and acetal hydrolysis were performed in readiness for the McMurry reaction.



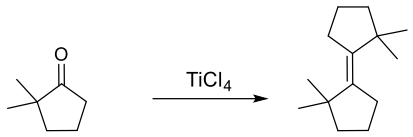
Scheme 66: (i) $LiClO_4$, isoprene, CSA (1.0 mol%), Et_2O, THF, RT, 18h; (ii) DIBAL-H, DCM, −78 °C, 1 h; (iii) azide **4.141**, PPh_3, THF, RT, 3 h, then add **4.147**, 66 °C, 3 h, then add $NaBH_4$ at 0 °C, RT, 30 min; (iv) NEt_3, MsCl, DCM, RT, 18 h; (v) aq HCl, MeOH, RT, 1 h.

4.5.2 McMurry reaction

With many reagent combinations having been reported for the McMurry reaction, the dimerisation of a sterically-demanding model ketone **4.150** was evaluated in order to confirm that a viable reagent was being generated (Table 17).

Low-valent titanium was formed initially by reaction of $TiCl_4$ with Zn in THF at 100 °C, before adding the ketone and heating at reflux for 2 h.[306] One factor that was evidently crucial to the success of the reaction was the addition technique of the low-valent Ti system; instant addition of the ketone proved detrimental to the reaction, whereas pre-activation of the Ti with a reducing agent allowed the reaction to proceed. Using this method, the deoxygenative coupling to yield alkene **4.151** was achieved in up to 23% yield, and the source of Zn did not substantially affect the outcome (entries 1–3); however, the source of Mg, as an alternative reducing agent for Ti(IV), was important to the success of the reaction (entries 8 and 9). In an effort to improve the yield, pyridine was used as an additive reportedly capable of activating the low-valence Ti system.[307, 308] This modification led to THF opening and oligomerisation (entry 4), while changing the solvent to DME gave no reaction (entries 5 and 6). Since $TiCl_4$ is notoriously capable of opening THF, it was suggested that the Ti(IV) reagent was not being reduced efficiently. When the reaction was attempted with Mg turnings and $HgCl_2$ to generate a

magnesium amalgam (entries 7–9) – conditions used with success previously in the group[227] – the yield remained low. The use of $LiAlH_4$ also gave no reaction (entry 10).[309] It was decided that $TiCl_4$ is an unreliable source of low-valent titanium and is predisposed to contain HCl impurities once the bottle is opened. Additionally, Corey *et al*. remarked that the $TiCl_4$/Zn system is effective for aromatic ketones, but less so for aliphatic systems.[310]



4.150 **4.151**

Entry	Solvent	Reducing agent	Additive	Temperature (°C)	Outcome
1	THF	Zn powder	–	66	**4.151**, 19%
2	THF	Zn dust	–	66	**4.151**, 23%
3	THF	Zn/Cu couple[311]	–	66	**4.151**, 20%
4	THF	Zn dust	Pyridine	66	THF opening
5	DME	Zn dust	Pyridine	85	No reaction
6	DME	Zn dust	–	85	No reaction
7	THF	Mg powder	$HgCl_2$	66	No reaction
8	THF	Mg turnings	$HgCl_2$	RT	Diol (36%)
9	THF	Mg turnings	$HgCl_2$	66	**4.151** 44%
10	DME	$LiAlH_4$	–	85	No reaction

Table 17: Conditions trialled for the McMurry reaction with a model ketone **4.150**.

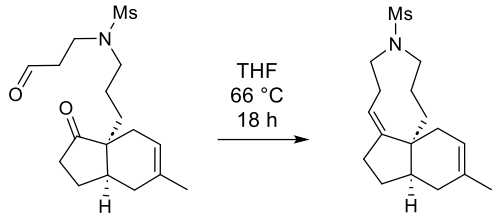
A more reliable source of activated titanium for the McMurry reaction is $TiCl_3(DME)_{1.5}$,[312] prepared by heating $TiCl_3$ in DME at reflux; however, due to commercial transport and therefore purchase restrictions limiting the availability of pure $TiCl_3$ in Europe, this could not be obtained. Instead, $TiCl_3(THF)_3$ was prepared by heating pyrophoric $3TiCl_3.AlCl_3$ in THF,[313] using toluene as a heat sink to prevent the exothermic reaction provoking a runaway reaction. The resulting

pale blue precipitate was tested with the ketone **4.150** model (Table 18, entry 1),[312, 314] but this was ineffective. The use of $3TiCl_3.AlCl_3$ itself[315, 316] and $TiCl_4.2THF$[317–319] proved more successful in this model reaction (entries 2 and 3).

Entry	Solvent	Source of Ti	Temperature (°C)	Outcome
1	THF	$TiCl_3(THF)_3$	66	No reaction
2	THF	$3TiCl_3.AlCl_3$	66	40%
3	THF	$TiCl_4.2THF$	66	40%

Table 18: Different sources of titanium investigated for the 2,2-dimethylcyclopentanone **4.150** model.

Three different set of conditions for the McMurry reactions, which had been successful in forming alkene **4.151** were attempted with ketoaldehyde **4.149**. In the event, all the attempts (Table 19) returned unreacted starting material indicating either a failure to produce a viable reagent in these reactions or, for some reason, a failure for the reaction to progress.



4.149 4.127

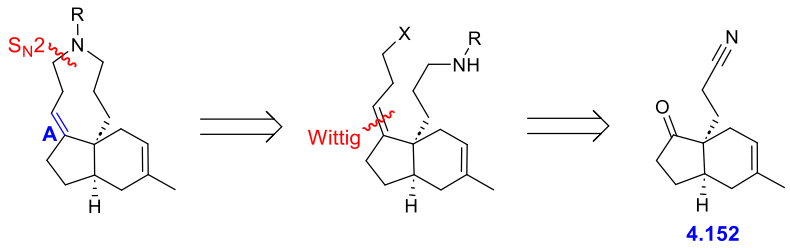
Entry	Source of Ti	Reducing agent	Temp. (°C)	Outcome
1	$TiCl_4$	Zn dust	66	No reaction
2	$TiCl_4$	Mg turnings, $HgCl_2$	25	No reaction
3	$TiCl_4$	Mg turnings, $HgCl_2$	66	No reaction
4	$TiCl_3.AlCl_3$	Zn dust	66	No reaction
5	$TiCl_4.2THF$	Zn dust	66	No reaction

Table 19: McMurry conditions, successful for ketone **4.150**, with the dicarbonyl **4.149**.

At this stage in the project, it had become evident that the process of creating a medium ring whilst simultaneously forming a C–C bond adjacent to a quaternary centre had proven to be over-ambitious, and, therefore, a strategically different approach was considered.

4.6 Alternative strategy

As mentioned above, the attempts to form the nine-membered ring by RCM and McMurry reactions involved bond formation (**A**, Scheme 67) next to a quaternary centre. In an attempt to decouple the two demanding factors (medium ring cyclisation, and creation of the alkylidene cyclopentane double bond) by completing them separately, a new approach was proposed. In the synthesis of fawcettimine-like alkaloids, the nine-membered ring is most commonly assembled *via* *N*-alkylation, under Mitsunobu conditions (Scheme 67). In this approach, the precursor would in turn be generated using a Wittig reaction of bicyclic ketone **4.152**.

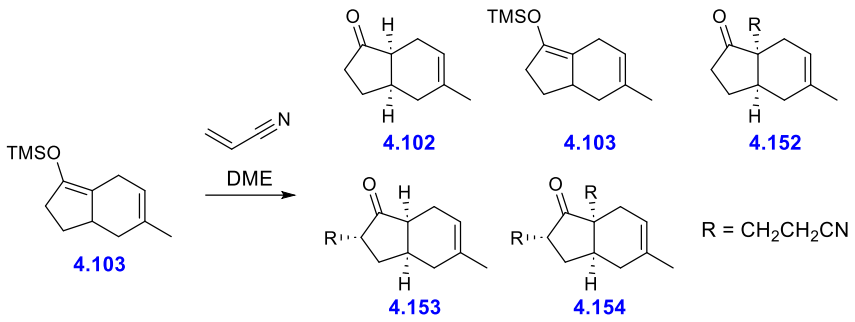


Scheme 67: New approach proposed for the nine-membered ring.

4.6.1 Wittig route to functionalise bicyclic ketone

To this end, the TMS enol ether **4.103** was used to furnish nitrile **4.152,** with the conditions requiring some optimisation as summarised in Table 20. Without pre-treatment of the silyl enol ether with methyllithium to regenerate the enolate, the reaction did not proceed (entries 1 and 2) despite precedent for such reactions with acrylonitrile.[320–324] When methyllithium was used at RT, proto-desilylation dominated (entry 3), while decreasing the temperature to –78 °C assisted the formation of the desired adduct **4.152** (entries 4 and 5). The most compelling conditions were those which maintained this low temperature for 2 h with warming to 0 °C for the remainder of the reaction (entry 4) which gave **4.152**

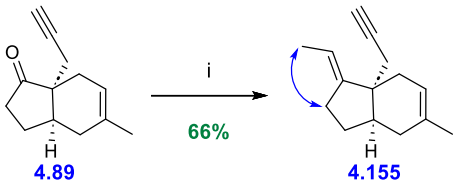
in 47% final isolated yield. Increasing the amount of acrylonitrile gave alkylation on both sides of the ketone (**4.154**, entry 7).



Entry	Pre-treatment	Temp.	Acrylonitrile (equiv.)	4.102	4.103	4.152	4.153	4.154
1	–	0 °C	1		100			
2	–	RT	1		100			
3	MeLi	RT	1	93			7	
4	MeLi	–78 °C, 2h → 0 °C	1	8		**87**	5	
5	MeLi	–78 °C	1	24	31	**41**	4	
6	MeLi	–78 °C, 0.25 h → 0 °C	1	89			11	
7	MeLi	–78 °C, 2h → 0 °C	10				7	93

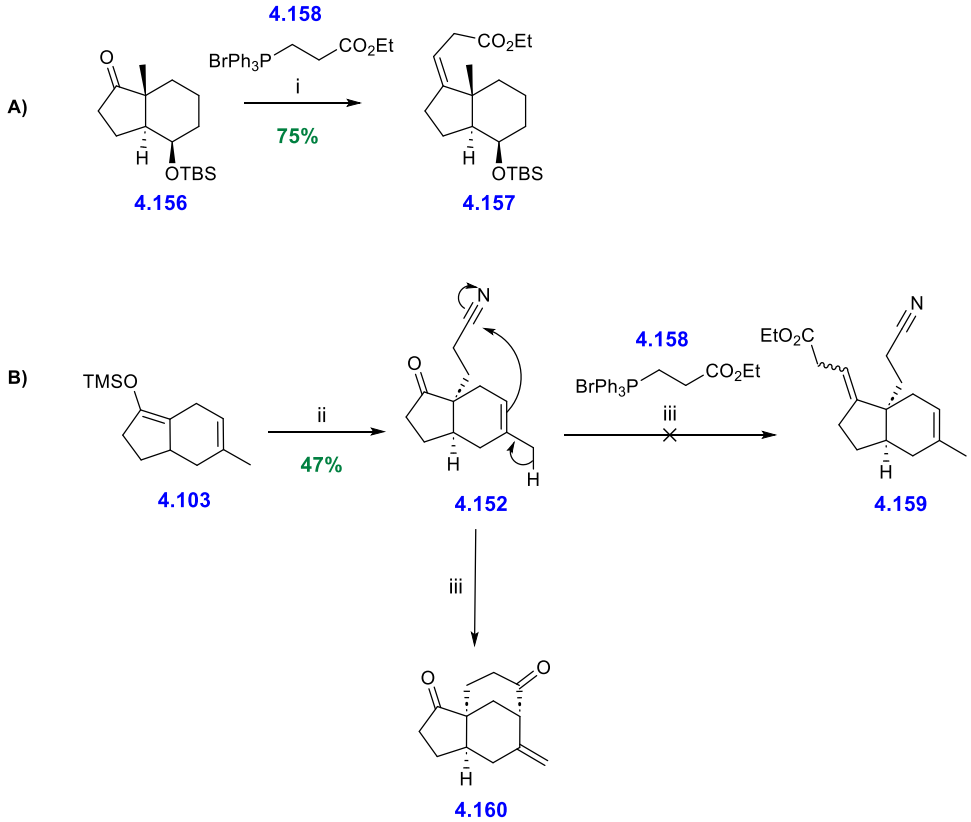
Table 20: Optimisation of reaction to install the cyanoethyl side chain, showing the percentage composition of each component in the crude product mixture, as deduced by ^{1}H NMR spectroscopic integrations.

With nitrile **4.152** secured, the viability of the Wittig reaction was explored. As a test reaction, the keto-alkynyl-substituted ketone **4.89** was subjected to the conditions used in the Wittig methylenation of ketones **4.91** and **4.125** with the ethyltriphenyl phosphonium salt instead (Scheme 68); this was successful and diene-yne **4.155** was obtained in 66% yield (with the depicted configuration confirmed by the NOESY correlation shown), a result that showed that this position is not immune to olefination beyond methylenation.



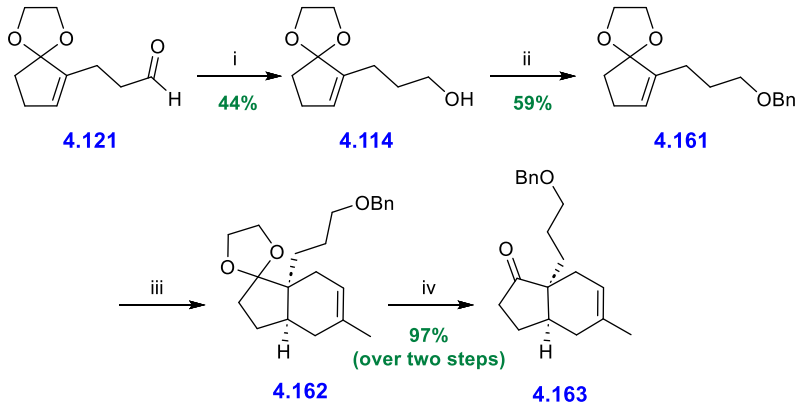
Scheme 68: i) *t*-BuOK, $EtPPh_3Br$, THF, 70 °C, 18 h. The alkene configuration was assigned by NOESY correlations (blue arrows).

For the cyanoethyl substrate, an ylid containing an ester group was used, since there was precedent for this being successful not only with aromatic ketones[325] and cyclobutanone,[326] but also with an α-substituted hexahydro-indanone resulting in a *Z*-alkene (Scheme 69A),[327] similar to the substrate for this work. Unexpectedly, the nitrile group proved reactive under the basic Wittig reaction conditions, cyclising to form the diketone **4.160** (Scheme 69B). This product was identified by two doublets in the ^{1}H NMR spectrum at 5.05 and 5.55 ppm with a coupling constant of J = 1.0 Hz, corresponding to two protons on the same carbon (HSQC), characteristic of a terminal alkene.



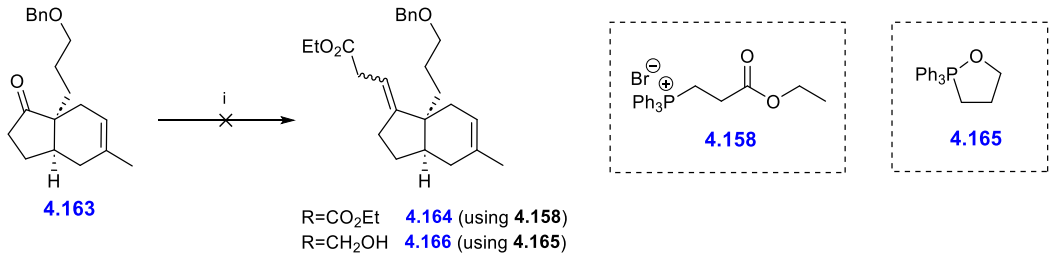
Scheme 69: i) *t*-BuOK, benzene, 80 °C; ii) MeLi, then acrylonitrile, DME, 0 °C, 18 h; iii) *t*-BuOK, THF, 66 °C, 18 h.

Accordingly, the nitrile group was swapped for a protected alcohol side chain by reducing aldehyde **4.121** and protecting the so-formed alcohol before the standard DA reaction and ketal deprotection sequence (Scheme 70).



Scheme 70: i) $NaBH_4$, MeOH, RT, 30 min; ii) BnBr, NaH, THF, RT, 18 h; iii) $LiClO_4$, isoprene, CSA (5.0 mol%), Et_2O, 40 °C, 18 h; iv) aq HCl, MeOH, 0 °C, 1 h.

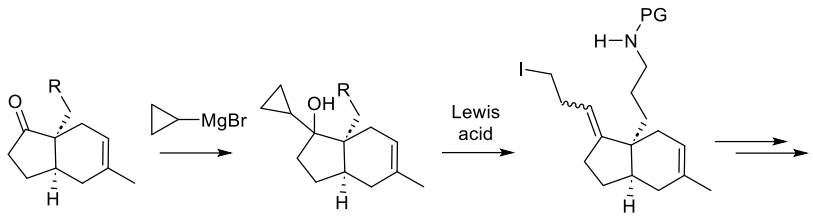
Without the nitrile present, the Wittig reaction still did not proceed, with only starting material being returned (Scheme 71) even under more forcing conditions (180 °C) with an alternative Wittig reagent **4.165**.[328] Ultimately, this approach was abandoned.



Scheme 71: i) *t*-BuOK, **4.158** or **4.165**, THF, 18 h.

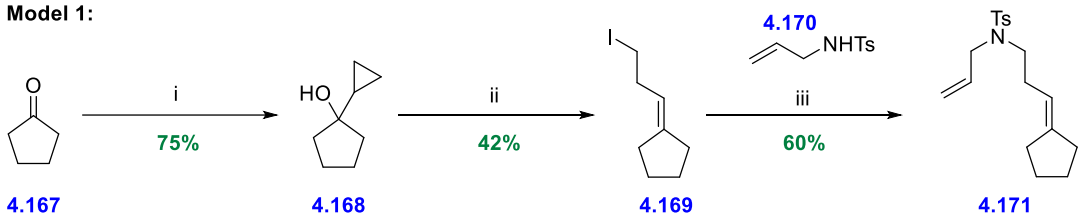
4.6.2 Grignard route to functionalise bicyclic ketone

The Wittig reagents required to form a functionalised alkylidene cyclopentane suffered similarly to the RCM approach to creating this C=C bond by being too bulky and insufficiently nucleophilic. Accordingly, a much more reactive nucleophile class was considered necessary and recourse was made to organometallic chemistry combined with subsequent rearrangement to achieve the overall required conversion. The initial approach set out to explore the use of a cyclopropyl organometallic reagent with ring-opening and alkene formation being achieved with HI or a Lewis-acidic metal iodide (Scheme 72).



Scheme 72: New proposal, proceeding *via* a Grignard reaction to force the stubborn ketone to react.

To model and optimise this proposed sequence, freely-available cyclopentanone was used (Scheme 73; Table 21).[329] The commercially-available cyclopropylmagnesium bromide reagent gave predominantly the aldol condensation product (entry 1); however, formation of the fresh Grignard reagent from cyclopropyl bromide, Mg and 1,2-dibromoethane[330] rendered the reaction successful (entry 2). The alcohol product **4.168** was unstable towards silica gel or alumina chromatography and was therefore carried through without purification; this necessitated that the reaction should be very clean and, for example, forming the nucleophile from cyclopropyl bromide and *tert*-butyllithium[331] was insufficient for this purpose (entry 3).



Scheme 73: i) cyclopropyl MgBr, THF, RT, 1 h; ii) ZnI_2, Et_2O, 40 °C, 1 h; iii) *N*-tosyl allylamine, NaH, DMF, RT, 18 h.

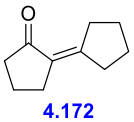
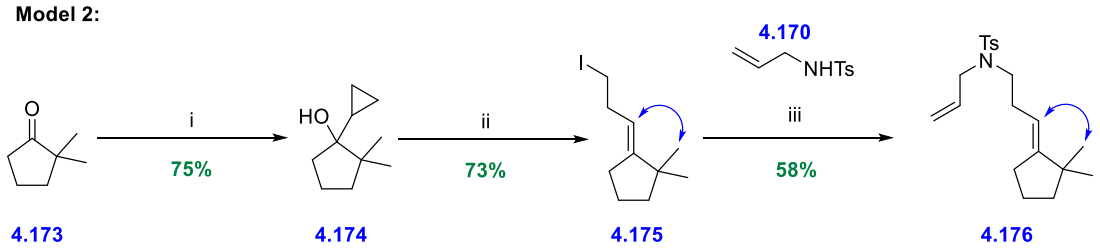
Entry	Organometallic	Outcome (step i)
1	Commercial Grignard solution	 4.172
2	Cyclopropyl bromide + Mg + 1,2-dibromoethane	**4.168**, 75%
3	Cyclopropyl bromide + *t*-BuLi	Unclean crude

Table 21: Various methods for executing the Grignard reaction with cyclopentanone.

A ZnI_2-mediated rearrangement of the cyclopropyl group[332] gave the iodide **4.169**, and substitution with deprotonated *N*-tosyl allylamine gave the final model product **4.171**. NaH was found to be necessary for

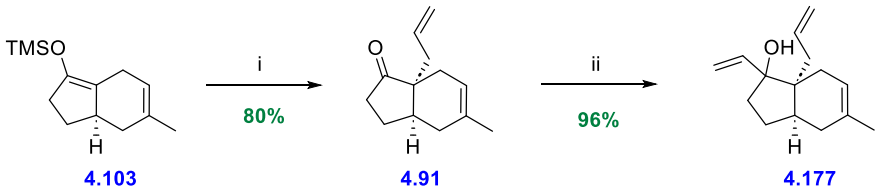
this reaction, with the weaker base K_2CO_3 providing an insufficient concentration of the sulfonamide salt for the substitution to proceed at a reasonable rate. Similarly, among various solvents trialled (for example acetone and ether), the dipolar aprotic DMF was found to be superior. An analogous reaction (not shown) was also accomplished with *N*-Boc-allylamine, Boc being the optimum protecting group for the P450 oxidation work. During these substitution reactions, no competing elimination was seen which boded well for extension to the real system in which deprotonation would need to be effected in the presence of the iodide.

The same sequence was explored on 2,2-dimethylcyclopentanone as a closer model (Scheme 74). It was quickly found that the Grignard addition was only successful when $LaCl_3$ was included in the reaction, presumably to activate the hindered ketone.[371] The second and third reactions in the sequence proceeded as before and diene **4.176** was obtained, with the depicted configuration confirmed by the NOESY correlation shown.



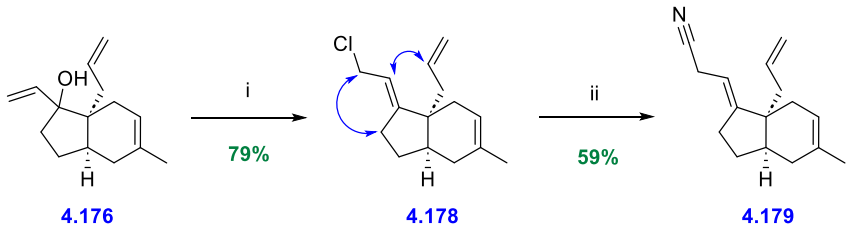
Scheme 74: i) $LaCl_3$.2LiCl, cyclopropyl-MgBr, THF, RT, 1 h; ii) ZnI_2, Et_2O, 40 °C, 1 h; iii) *N*-tosyl allylamine, NaH, DMF, RT, 18 h. The alkene configuration was assigned by NOESY correlations (blue arrows).

Moving on to the bicyclic system, the organometallic reaction was attempted with ketone **4.91** (Scheme **75**) with cyclopropyl- and isopropyl- organometallics; however, no conditions were found under which the desired reaction would take place, regardless of additive, temperature or amount of organometallic reagent (Appendices, Table 37). Eventually, the less sterically-demanding vinyl magnesium bromide was adopted to give the two adjacent quaternary centres in alcohol **4.177**.



Scheme 75: i) MeLi, DME, −78°C to 0 °C, 2 h, then DMPU and allyl bromide, RT, 18 h; ii) vinyl MgBr, $LaCl_3$.2LiCl, THF, RT, 1h.

Preliminary attempts to rearrange this allylic tertiary alcohol determined $SOCl_2$ as the most successful reagent (Scheme 76; Table 22). When triphenylphosphine and I_2 were used,[333] the liberated HI led to decomposition (entry 1). When imidazole was added to mitigate this decomposition (entry 2), only starting material was recovered, perhaps because the triphenylphosphonium iodide was too bulky to react with the tertiary alcohol. Using ZnI_2[331] (entry 3) similarly gave decomposition of the starting material; however, $SOCl_2$[334] served the dual role of activating the alcohol and providing a source of chloride ion, delivering the expected allylic chloride in 79% yield (entry 4). As expected from the model experiments, the rearrangement gave the *E*-alkene configuration (NOESY), undesired for the synthesis, but seemingly unavoidable in this process in which there is no medium ring present to drive formation of the less-strained *Z*-alkene. In order to achieve the necessary terminally-functionalised three-carbon substituent, cyanide displacement followed. Reactions in acetone and acetonitrile were unsuccessful but in DMSO the S_N2 displacement[335] was effective in giving nitrile **4.179**, the first molecule in this project to have all the required core atoms in place and no more (the RCM precursor **4.126** having two additional carbon atoms and the McMurry reaction precursor **4.149** having two additional oxygen atoms).



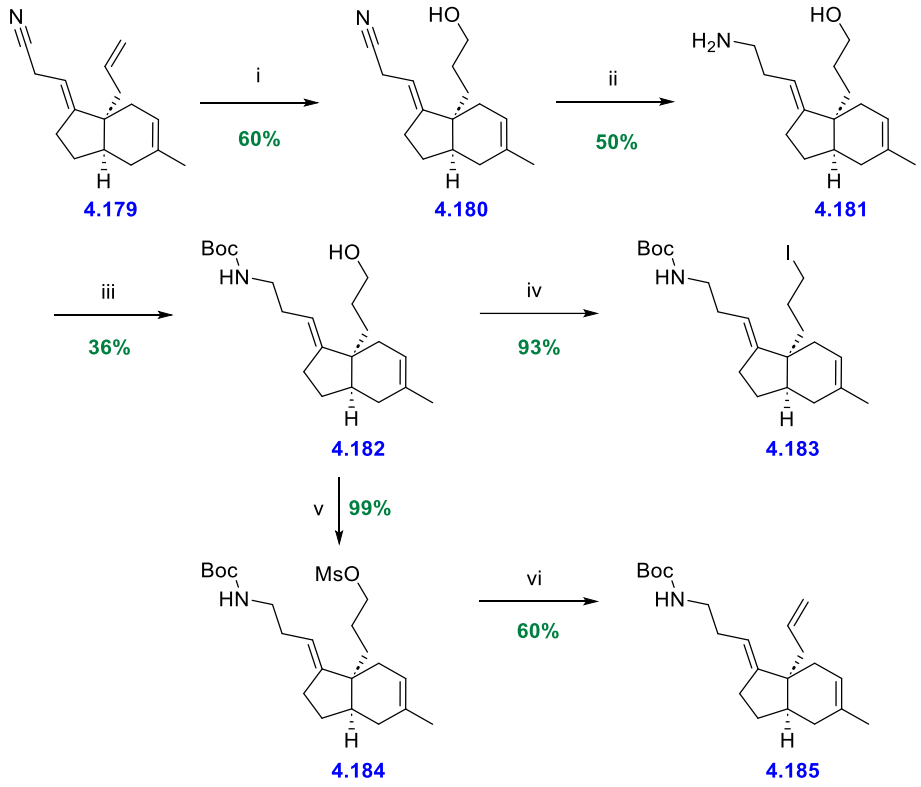
Scheme 76: i) $SOCl_2$, pyridine, DCM, RT, 1 h; ii) NaCN, DMSO, RT, 1 h. (Blue arrows denote diagnostic NOESY correlations.)

Entry	Reagent	Outcome (step i)
1	PPh_3, I_2	Decomposition
2	PPh_3, I_2, imidazole	No reaction
3	ZnI_2	Decomposition
4	$SOCl_2$, pyridine	**4.178**, 79%

Table 22: Rearrangement of tertiary alcohol into allyl halide.

The next obstacle to be faced became manipulating the allyl group, a problem which had been tackled previously using a cross metathesis reaction with pinacol vinylboronate; however, that solution had been abandoned due to its inefficiency, so, here, other solutions were explored.

Bulky hydroborating agents were chosen to promote selective reaction at the terminal alkene in triene **4.179**. Initial hydroboration attempts using 9-BBN, dicyclohexylborane, and disiamylborane were unsuccessful (Appendices, Table 38), but an Ir-catalysed procedure was more fruitful (Scheme 77).[336,337]



Scheme 77: i) Pinacolborane, $[Ir(cod)Cl]_2$ (1.5 mol%), dppb (3.0 mol%), DCM, RT, 18 h, then aq. NaOH, H_2O_2; ii) $LiAlH_4$, Et_2O, RT, 18 h; iii) Boc_2O, NEt_3, DCM, RT, 18 h; iv) PPh_3, I_2, imidazole, DCM, RT, 1 h; v) MsCl, NEt_3, DCM, RT, 30 min; vi) *t*-BuOK, THF, RT, 30 min.

With alcohol **4.180** in hand, nitrile reduction[338] with excess $LiAlH_4$ and amine protection[339] were accomplished (→ **4.182**, Scheme 77) in readiness to close the elusive nine-membered ring by analogy to similar reactions discussed earlier (Table 23). A Mitsunobu reaction directly from alcohol **4.182** was unsuccessful (entries 1 and 2),[340] as was displacement of the mesylate **4.184** (entry 3)[341] which, instead, resulted in elimination to give alkene **4.185**. Literature precedent for formation of the nine-membered ring by S_N2 cyclisation in fawcettimine-like structures implied that displacement of the iodide might be successful;[342,343] therefore, conversion to the iodide **4.183** was achieved.[344] The various attempts to effect

the substitution reaction were performed under dilute conditions (0.01 M) in order to discourage intermolecular reaction.

Since crown ethers complex the metal counterion of ionic reagents to increase the reagent's solubility and increase anion nucleophilicity in aprotic organic solvents,[345] the potassium-selective crown ether 18-C-6 was added (entry 5) and the solvent switched to DMF to further promote solvation of the K^+ ion and activate the carbamate anion (entry 6); however, in both cases, no reaction was observed. When KH was used instead of *t*-BuOK (entry 7),[346] bubbling was observed immediately, implying that the deprotonation step had taken place, but, again, no cyclisation followed. From these experiments, it was concluded that the incorrect configuration of the alkylidene bond renders the transition state for cyclisation too strained for effective cyclisation and, although various potential work-arounds could be considered, time constraints meant that work on completing the route had to cease.

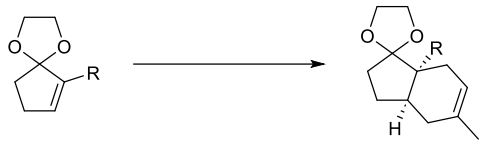
Entry	Starting Material	Conditions	Outcome
1	**4.182**	PPh_3, DEAD, 80 °C, 18 h	No reaction
2	**4.182**	PPh_3, DIAD, 80 °C, 18 h	No reaction
3	**4.184**	*t*-BuOK, THF, RT, 30 min	**4.185**
4	**4.183**	*t*-BuOK, THF, RT, 18 h	No reaction
5	**4.183**	*t*-BuOK, THF, 18-crown-6, RT, 18 h	No reaction
6	**4.183**	*t*-BuOK, DMF, RT, 18 h	No reaction
7	**4.183**	KH, THF, RT, 18 h	No reaction

Table 23: Attempts to close the nine-membered ring *via* intramolecular S_N2 reaction.

4.7 Conclusions and Future Work

In this work, various routes towards the carbon core of lobscurinol have been explored. The ionic DA reaction has been used extensively, beginning when the α,γ-ketoester **4.79** (Scheme 51) did not react with isoprene under any attempted conditions. Instead, the ethylene ketals of α,β-unsaturated ketones were used as the dienophile in the presence of catalytic CSA and highly concentrated solutions of $LiClO_4$

in ether, generating the oxonium ion *in situ* which could then undergo the desired cycloaddition. Through the course of this work, this reaction has been trialled with various groups adjacent to the ketal, as summarised in Table 24. The simple cyclopentenone ethylene ketal and the alkyl nitrile derivative proceeded efficiently at RT (entries 1 and 3). Other substrates required more forcing conditions than those reported by Grieco, sometimes requiring reflux temperature and 5.0 mol% CSA (entries 6 and 7). The reaction was not universally successful, however; the propyl alcohol, Ms-protected alcohol and acetal all returned starting material (entries 4, 5 and 8). This may be due to intramolecular quenching of the active oxonium by the alcohol group, or effective quenching of the catalytic CSA by the acetal.



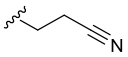
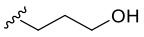
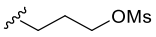
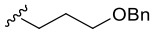
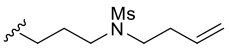
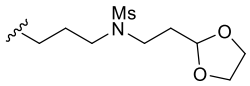
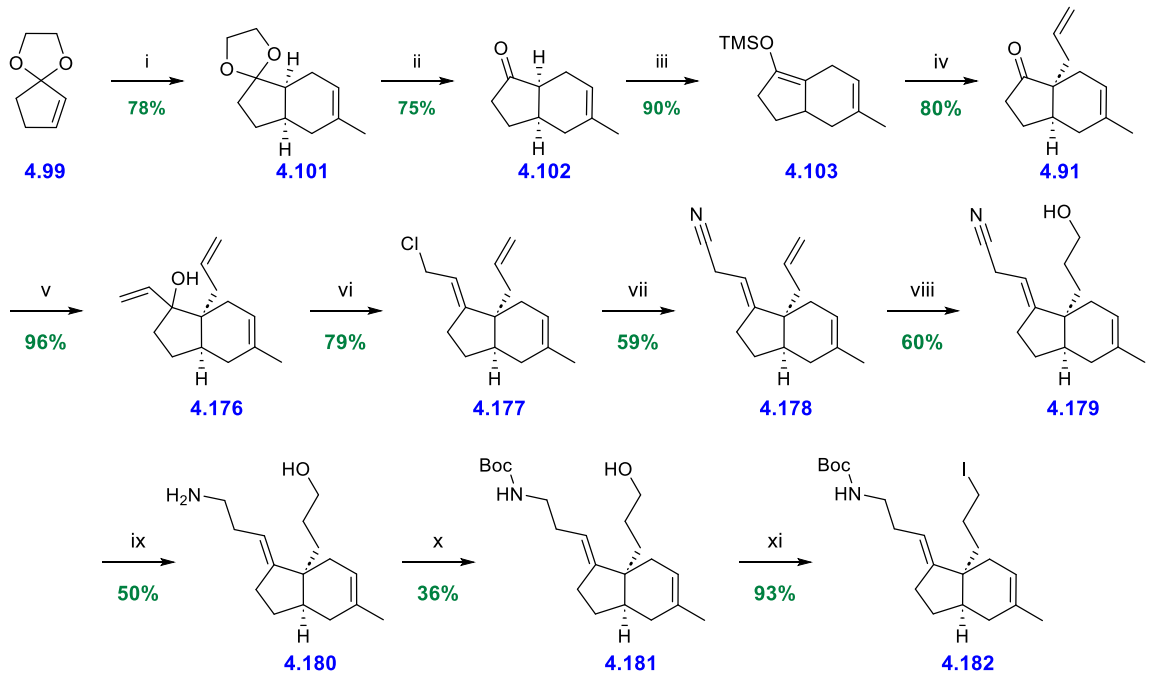
Entry	R	CSA (%mol equiv.)	Temp. (°C)	Yield (%)
1		1.0	20	78
2		1.0	40	44
3		1.0	20	80
4		5.0	40	No reaction
5		5.0	40	No reaction
6		5.0	40	97
7		5.0	40	84
8		5.0	40	No reaction

Table 24: Summary of the substrates tested in the ionic DA reaction during this project.

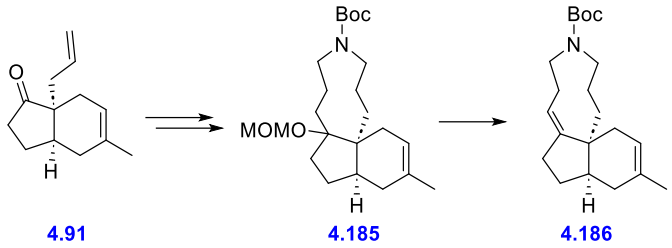
Attempts to form a C–C bond adjacent to the quaternary centre were met with resistance, and the RCM, McMurry and Wittig reactions were all unsuccessful in this regard. In the final stages of this project, the more established approach of closing the medium ring *via* an S_N2 reaction was considered. This latest route is detailed in its entirety in Scheme 78 which shows how the relative ring-fusion configuration of bicyclic **4.91** was installed *via* stereoselective enolate allylation.[229] The final carbons were introduced

by Grignard addition to the ketone, rearrangement of the allylic tertiary alcohol and cyanide displacement to give nitrile **4.178**. From here, functional group interconversions furnished the Boc-protected amine with the pendant alkyl iodide of **4.182**, but attempts to cyclise this intermediate met with no success.



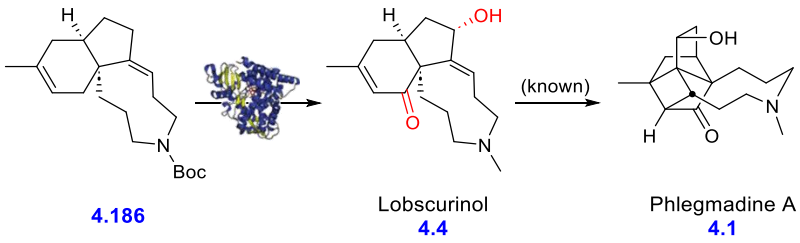
Scheme 78: (i) $LiClO_4$, isoprene, CSA (1.0 mol%), Et_2O, RT, 1 h; (ii) aq HCl, methanol, 0 °C 1 h; (iii) NEt_3, TMSOTf, DCM, RT, 1 h; iv) MeLi, DME, −78°C to 0 °C, 2 h, then DMPU and allyl bromide, RT, 18 h; v) vinyl MgBr, $LaCl_3$.2LiCl, THF, RT, 1h; vi) $SOCl_2$, pyridine, DCM, RT, 1 h; vii) NaCN, DMSO, RT, 1 h; viii) pinacolborane, $[Ir(cod)Cl]_2$ (1.5 mol%), dppb (3.0 mol%), DCM, RT, 18 h, then aq. NaOH, H_2O_2; ix) $LiAlH_4$, Et_2O, RT, 18 h; x) Boc_2O, NEt_3, DCM, RT, 18 h; xi) PPh_3, I_2, imidazole, DCM, RT, 1 h.

With this latest hypothesis that the *E*-configuration of the exocyclic alkene prevents the nine-membered ring from forming, a number of solutions could be considered. For example, to remove the constraint of forming a strained *E*-configured medium ring alkene, the addition chemistry could be modified so that the exocyclic alkene is formed after the ring-closure, as shown in Scheme 79. In this proposed route, elimination may occur to give the endocyclic alkene isomer, which would still be a useful molecule for continuing the project.



Scheme 79: Late-stage elimination approach, easing the cyclisation and delivering the correct *Z*-configured medium ring alkene.

From that point, $P450_{BM3}$ variants would be screened for their ability to install the oxygen functionality in strategically desirable locations (Scheme 80). Since the required oxidations are at allylic positions, it will be important to compare the enzymatic oxidation profiles with those achievable with chemical reagents. Throughout this project, enolate alkylations and DA reactions gave *cis*-fused bicyclic intermediates as racemates. An advantage of using enzymes for further transformations is their ability to distinguish racemic substrates by kinetic resolution,[85] and so the proposed allylic oxidations could potentially be achieved chemically to afford racemic standards for rapid assessment of the enantioselectivity of enzymatic screening reactions. Although oxidation at the allylic positions would be ideal, any introduced hydroxyl functionality on the 5-6 ring system could in principle be used to develop the desired lobscurinol target from which repetition of the known conversion to phlegmadine A will conclude the project.[168]



Scheme 80: Proposed future work.

Chapter 5: Experimental

5.1 General details

All solvents were commercially supplied or provided by the communal solvent purification rigs of the Chemistry Research Laboratory, Oxford. Unless otherwise stated, reagents were obtained from commercial suppliers and used without further purification. All reactions were performed using oven-dried or flame dried glassware, and performed under nitrogen gas.

Photochemical reactions were performed using a Pen-Ray® Light Source, model 11SC-1, emitting the mercury spectrum with the primary energy at 254 nm. Sonication was carried out using a Misonix 3000 sonicator and Fisher Scientific FB-505 ultrasonic processor. Deionised water for enzymatic reactions was obtained from a Millipore ELIX 5 system and was used to prepare all the growth media and buffers.

Flash column chromatography was carried out using Merck Silicagel 60, particle size 40–63 μm, with the eluent system given in parentheses. All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck aluminium-backed Silicagel 60 F254 precoated plates. Spots were visualised under ultra-violet light (λ_{max} = 254 nm) or by staining with aqueous basic $KMnO_4$, PMA, ninhydrin or vanillin solutions, as appropriate. Enzymatic reactions were followed by gas chromatography (GC) using a Thermo Finnigan TRACE gas chromatograph equipped with a flame ionisation detector (FID) and an AS3000 autosampler on a DB-1 capillary GC column (30 m × 0.25 mm i.d. × 0.25 μm film thickness). The injector temperature was 280 °C and the FID was at 250 °C. Chiral GC measurements were conducted on an HP6890 (H_2 as vector gas) or HP6850 (H_2 as vector gas) with a Lipodex® E column.

Compound names are as generated by ChemDraw 21.0.0 and procedures are organised for compounds in numerical order as they appear in each chapter. Proton (^1H) and carbon-13 (^{13}C) spectra were recorded on a Bruker 400 MHz, 500 MHz or 700 MHz spectrometer as specified, in $CDCl_3$ (or other deuterated solvents as specified). Chemical shifts δ_H or δ_C are reported in parts per million (ppm) to the nearest 0.01 ppm and 0.1 ppm respectively, relative to tetramethylsilane (δ = 0) and referenced to the solvent (residual $CHCl_3/CDCl_3$, δ 7.26 and 77.16 ppm respectively). Coupling constants (*J*) are reported in Hz,

rounded to the nearest 0.5 Hz. The ^{1}H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons, assignment). All NMR assignments use arbitrary numbering independent from IUPAC naming and were made on the basis of chemical shifts, integrations and coupling constants, using COSY, HSQC, HMBC and NOESY experiments where necessary. Where an assignment could not be made unambiguously, possible assignments are listed. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), septet (sept), broad (br) or as combinations or multiplets (m).

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film on a diamond ATR module. Selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w), and broad (br) relative to the most intense peak. Low resolution mass spectrometry was recorded on a Waters LCT Premier mass spectrometer (ESI). High resolution mass spectrometry was recorded by the staff of the Chemistry Research Laboratory on a Bruker μTOF mass spectrometer (ESI). Mass to charge ratios *(m/z*) are reported in Daltons. Melting points are recorded in degree Celsius using a Griffin melting point apparatus.

5.2 Protein synthesis

5.2.1 Growth media and buffers

All growth media and buffers were prepared with deionised water from a Millipore ELIX 5-UV system. Media were autoclaved at 121 °C for 30 mins. All components added for bacterial culture growths were first sterilised *via* a 0.22 μm syringe filter.

Media	Components
$FB_{glycerol}$[a]	14.7 g K_2HPO_4, 3.6 g NaH_2PO_4, 2.5 g $(NH_4)_2SO_4$, 2.0 g Na_2SO_4, 1.2 g $Na_3citrate.2H_2O$, 0.5 g NH_4Cl, 5 mL glycerol (after autoclaving, add 2.0 mL 1.0 M $Na_2SO_4.7H_2O$, 3.0 mL trace elements solution, 1.0 mL 10% w/v thiamine.HCl)
Trace elements[a]	0.74 g $CaCl_2.H_2O$, 0.25 g $CoCl_2.6H2O$, 0.10 g $CuSO_4.5H_2O$, 16.7 g $FeCl_3.6H_2O$, 0.132 g $MnSO_4.4H_2O$, 20.1 g Na_2EDTA, 0.18 g $ZnSO_4.7H_2O$
Induction solution[b]	0.475 g IPTG, 0.84 g δ-ALA.HCl, 0.14 g $FeSO_4.7H_2O$, 0.75 g kanamycin
Phosphate buffer[a]	5.38 g KH_2PO_4, 27.8 g K_2HPO_4

Table 25: Components for media. a) Components per litre of water. b) Components per 50 mL solution.

E. coli transformation

The pET-28 plasmid bearing the variant CYP102A1 gene was transformed into BL21.DE3 cells as per manufacturer's instructions, spread onto an LB_{kan} agar plate and incubated in an oven overnight at 37 °C.

5.2.2 Protein expression, harvest and quantification

A 2 L conical flask containing 500 mL of $FB_{glycerol}$ was autoclaved for 2 hours. Following cooling, 1.2 mL of 1 M $MgSO_4$ (filter sterilised), 1.8 mL of FB trace elements solution (components of which

are shown in Table 25), 0.6 mL of 10% thiamine HCl solution (filter sterilised) and 0.6 mL of 30 mg/mL kanamycin were added to the flask. The solution was then inoculated with 500 µL of the starter culture containing *E.coli* BL21.DE3 that had been transformed with the plasmid. The flask was shaken at 160 rpm and 37 °C for 24 hours. The growth media was then cooled to 20 °C for 1 hour. Protein expression was induced by adding 1 mL of induction solution (filter sterilised, components of which are shown in Table 25) and 0.5 g of tryptone. The flask was shaken at 120 rpm for 24 h at 20 °C after which time another 1 mL of induction solution and 0.5 g of tryptone were added and shaking continued for 24 h.

The cells were harvested by centrifugation of the growth media at 4500 rpm for 10 min at 4 °C. The supernatant was discarded, and the pellet was resuspended in 10 mL of phosphate buffer and 30 mL deionised water. A spatula tip of lysozyme was added, and the mixture was shaken at 120 rpm for 1 h at 20 °C. The suspension was transferred to a beaker and the cells were lysed by sonication on ice. The sonication procedure consisted of 10 cycles of 15-second pulses followed by a 30-second cooling period. The lysed suspension was centrifuged for 20 mins at 9500 rpm and 4 °C to remove the cell debris. The supernatant containing the enzyme was purified using ammonium sulfate fractionation. Sufficient ammonium sulfate to achieve 40% saturation was added (2.33 g/10 mL solution) and the mixture was stirred at 4 °C. Once fully dissolved, the mixture was centrifuged at 9500 rpm and 4 °C for 20 mins. The supernatant was poured off and retained and more ammonium sulfate was then added to achieve 60% saturation (1.24 g/10 mL solution). After all the salt had dissolved, the mixture was centrifuged at 9500 rpm and 4 °C for 30 mins and the supernatant discarded. The pellet was resuspended in 1.25 mL phosphate buffer and 3.75 mL deionised water overnight at 0 °C. A CO-difference assay was utilised to determine the concentration of P450 enzyme harvested. The 500 µL sample was prepared by diluting the purified P450 enzyme solution 20-fold. Sodium hydrosulphite was added to reduce the haem iron and the UV-Vis spectrum (200 – 700 nm) was then recorded and used as the baseline. CO was slowly bubbled into the solution and the spectrum of the solution was recorded indicating the protein peak intensity at 450 nm. The concentration of the protein was determined using the following equation:

$$[P450](M) = \frac{(A_{450} - A_{490}) \times 20}{\varepsilon}$$

where ε, the extinction coefficient is 91,000 M^{-1} cm^{-1}.

5.2.3 Enzymatic Oxidations

General Procedure 1 – Initial screening

Substance	Stock concentration	Volume per well (μL)	Final concentration
Glucose	1 M	100	100 mM
Substrate	200 mM (in EtOH)	10	2 mM
GDH	20 mM	10	200 μM
$NADP^+$	40 mM	10	400 μM
Enzyme	10 μM	100	1 μM
Phosphate buffer	-	770	200 mM

Table 26: Components for screening reactions.

Small scale screens of the substrates were conducted on a 1.0 mL scale in a 24 well plate containing 24 $P450_{BM3}$ variants (1 per well). These reactions were performed using 200 mM phosphate buffer (pH 7.9) containing 100 mM glucose, 80 μM $NADP^+$, 2 U/mL GDH, 5 mM substrate and 2 μM enzyme. The solvent used to make the stock solutions was 200 mM phosphate buffer, except for the substrate where it was ethanol. The screening plates were prepared by adding 900 μL of the mixture detailed in Table **26** to each well containing 100 μL of enzyme.

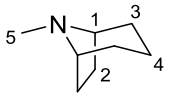
The reactions were shaken at 120 rpm and room temperature for 24 h. Each reaction mixture was then transferred into a 1.5 mL microcentrifuge tube, and 300 μL of ethyl acetate added. The biphasic solution was then mixed *via* centrifugation at 13,000 rpm for 1 minute. 180 μL of the organic layer was separated and transferred into a 200 μL glass GC insert. This was analysed by a Thermo Finnigan Trace1300 gas chromatograph equipped with a flame ionisation detector, an AS3000 autosampler and a DB-1 fused silica column. Helium was used as the carrier gas (1.5 mL/min). The initial and the ending oven temperatures, as well as the gradient of temperature change, were adjusted according to the physical properties of substrates.

General Procedure 2 – Preparative scale reactions

All preparative scale reactions were performed in a conical (Erlenmeyer) flask at 20 °C using the same ratios of reagents as in **General Procedure 1** (Table 26). The mixture was left to stir and monitored *via* GC at regular intervals until deemed appropriate to work up, ranging from 18–24 hours. The reaction mixture was split into falcon tubes with approximately 25 mL in each tube. EtOAc was added to approximately 50 mL and the falcon tubes balanced by adding more EtOAc. The tubes were shaken and then centrifuged for 3 mins at 9500g. The organic layer was pipetted off and the process repeated twice more. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography.

5.3 Synthesis of compounds

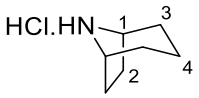
8-Methyl-8-azabicyclo[3.2.1]octane, 2.15



To a stirred solution of tropinone (3.00 g, 21.6 mmol) and KOH (9.68 g, 172 mmol) in ethylene glycol (90.0 mL) at RT was added $NH_2NH_2.H_2O$ (2.70 mL, 86.2 mmol) dropwise. The resulting mixture was heated at 120 °C for 2 h, and then at 200 °C for 18 h. The mixture was cooled to RT then extracted with petrol (5 x 50 mL); the organic extracts were combined and washed with brine (250 mL) and dried ($MgSO_4$) and evaporated *in vacuo* to yield compound **2.15** as a yellow oil (2.17 g, 81%) with no need for further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 – 3.05 (m, 2H, 2 x C(1)H), 2.18 (s, 3H, C(5)H_3), 2.01 – 1.93 (m, 2H, C(2)**H**H′), 1.77 – 1.67 (m, 2H, C(3)**H**H′), 1.57 – 1.51 (m, 2H, C(2)H**H′**), 1.49 – 1.38 (m, 2H, C(4)H_2), 1.29 – 1.36 (m, 2H, C(3)H**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 61.8 (C(1)), 40.9 (C(5)), 31.4 (C(3)), 26.0 (C(2)), 16.3 (C(4)). Spectroscopic data in agreement with literature.[347]

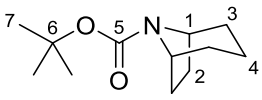
8-Azabicyclo[3.2.1]octane hydrochloride, 2.16



To a stirred solution of amine **2.15** (1.00 g, 8.0 mmol) in DCE (24.0 mL) at 0 °C was added 1-chloroethyl chloroformate (4.30 mL, 40.0 mmol) dropwise. The resulting mixture was heated at 90 °C for 18 h. The mixture was cooled to RT then concentrated *in vacuo*, passed through a short silica plug and eluted with 50:50 diethyl ether:hexane, to give a yellow oil. This was heated to 70 °C in methanol (25.0 mL), and then the solvent evaporated *in vacuo* to yield compound **2.16** as a white solid (0.73 g, 62%) with no need for further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H, N**H**H′Cl), 9.32 (s, 1H, NH**H′**$^+$$Cl^-$), 4.05 – 3.99 (m, 2H, 2 x C(1)H), 2.32 – 2.16 (m, 4H, C(2)**H**H′, C(3)**H**H′), 1.89 – 1.81 (m, 2H, C(2)H**H′**), 1.73 – 1.55 (m, 4H, C(3)H**H′**, C(4)H_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.3 (C(1)), 28.7 (C(3)), 26.3 (C(2)), 15.8 (C(4)). Spectroscopic data in agreement with literature.[348]

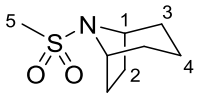
***tert*-Butyl 8-azabicyclo[3.2.1]octane-8-carboxylate, 2.17**



To a stirred solution of nortropane **2.16** (200 mg, 1.80 mmol) in DCM (10.0 mL) at 0 °C was added triethylamine (0.24 mL, 2.7 mmol) and Boc anhydride (580 mg, 2.7 mmol). The resulting mixture was allowed to warm to RT and stirred for 18 h. The mixture was diluted with H_2O, extracted with DCM (4 x 20 mL), washed with brine (2 x 50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by column chromatography (5% EtOAc in pentane) to give compound **2.17** as a colourless oil (210 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H, C(1)H rotamer A), 4.12 (1H, s, C(1)H rotamer B), 1.96 – 1.90 (m, 2H, C(2)**H**H′), 1.75 – 1.71 (m, 3H, C(3)**H**H′, C(4)**H**H′), 1.67 – 1.61 (m, 2H, C(2)H**H′**), 1.56 – 1.52 (m, 1H, C(4)H**H′**), 1.46 (s, 9H, C(7)H_3), 1.43 – 1.36 (m, 2H, C(3)H**H′**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.8 (C(5)), 79.0 (C(6)), 53.9 (C(1)), 30.7 (C(3)), 28.7 (C(7)), 28.1 (C(2)), 16.9 (C(4)). Spectroscopic data in agreement with literature.[349]

8-(Methylsulfonyl)-8-azabicyclo[3.2.1]octane, 2.18

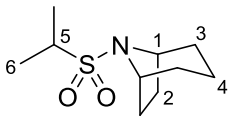


To a stirred solution of nortropane **2.16** (200 mg, 1.35 mmol) in DCM (9.0 mL) at 0 °C was added triethylamine (1.0 mL, 6.75 mmol) and mesyl chloride (0.2 mL, 2.71 mmol). The resulting mixture was

allowed to warm to RT and stirred for 18 h. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL), extracted with DCM (3 x 10 mL), washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by column chromatography (25% EtOAc in pentane) to give compound **2.18** as a colourless oil (186 mg, 73%).

R_f 0.33 (25% ethyl acetate in pentane); **IR** ν_{max} (cm^{-1}) 2939m, 1321s, 1145s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.23 – 4.18 (m, 2H, 2 x C(1)H), 2.88 (s, 3H, C(5)H_3), 2.05 – 2.00 (m, 2H, C(2)**H**H′), 1.85 – 1.51 (m, 8H, C(2)H**H′**, C(3)H_2, C(4)H_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 57.2 (C(1)), 40.6 (C(5)), 32.3 (C(3)), 28.8 (C(2)), 16.6 (C(4)); **HRMS** (ESI+): Found: $[MH]^+$, 190.0897; $C_8H_{16}NO_2S^+$ requires: $[MH]^+$, 190.0896.

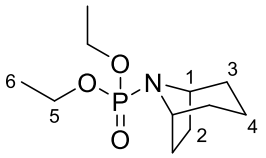
8-(Isopropylsulfonyl)-8-azabicyclo[3.2.1]octane, 2.19



To a stirred solution of nortropane **2.16** (100 mg, 0.68 mmol) in DCM (4.2 mL) at 0 °C was added triethylamine (0.5 mL, 3.40 mmol) and 2-propanesulfonyl chloride (0.2 mL, 0.75 mmol). The resulting mixture was allowed to warm to RT and stirred for 18 h. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL), extracted with DCM (3 x 10 mL), washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by column chromatography (10% EtOAc in pentane) to give compound **2.19** as a colourless oil (67 mg, 45%).

R_f 0.56 (10% ethyl acetate in pentane); **IR** ν_{max} (cm^{-1}) 2942m, 1470w, 1316s, 1136s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.16 (t, *J* = 4.0 Hz, 2H, 2 x C(1)H), 3.12 (sept, *J* = 7.0 Hz, 1H, C(5)H), 2.06 – 2.00 (m, 2H, C(2)**H**H′), 1.82 – 1.73 (m, 2H, C(3)**H**H′), 1.73 – 1.69 (m, 2H, C(2)H**H′**), 1.58 – 1.55 (m, 2H, C(4)H_2), 1.55 – 1.51 (m, 2H, C(3)H**H′**), 1.36 (d, *J* = 7.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 58.1 (C(1)), 54.7 (C(5)), 32.2 (C(3)), 29.3 (C(2)), 23.3 (C(6)), 16.8 (C(4)); **HRMS** (ESI+): found 240.1030, $[MNa]^+$ $C_{10}H_{19}NO_2SNa^+$ requires 240.1029.

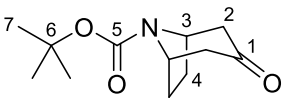
Diethyl (8-azabicyclo[3.2.1]octan-8-yl)phosphonate, 2.20



To a stirred solution of nortropane **2.16** (100 mg, 0.68 mmol) in DCM (4.0 mL) at 0 °C was added triethylamine (0.1 mL, 0.81 mmol) and diethyl chlorophosphate (0.06 mL, 0.75 mmol). The resulting mixture was allowed to warm to RT and stirred for 18 h. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL), extracted with DCM (3 x 10 mL), washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by column chromatography (60% EtOAc in pentane) to give compound **2.20** as a yellow oil (130 mg, 78%).

R_f 0.24 (60% ethyl acetate in pentane); **IR** ν_{max} (cm^{-1}) 2942 m, 1347 w, 1250m, 1028s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.09 – 3.97 (m, 4H, C(5)H_2), 3.91 (br s, 2H, 2 x C(1)H), 1.95 – 1.89 (m, 2H, C(2)**H**H′), 1.78 – 1.62 (m, 4H, C(2)H**H′**, C(3)**H**H′), 1.59 – 1.52 (m, 2H, C(4)H_2), 1.44 – 1.37 (m, 2H, C(3)H**H′**), 1.30 (td, *J* = 7.0, 1.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 62.3 (d, *J* = 5.9 Hz, C(5)), 55.5 (d, *J* = 2.0 Hz, C(1)), 31.9 (d, *J* = 4.4 Hz, C(3)), 29.5 (d, *J* = 4.3 Hz, C(2)), 17.2 (s, C(4)), 16.4 (d, *J* = 7.2 Hz, C(6)); **HRMS** (ESI+): found 248.1410, $[MH]^+$ $C_{11}H_{23}NO_3P^+$ requires 248.1410.

8-(*tert*-Butoxycarbonyl)-3-oxo-8-azabicyclo[3.2.1]octane, 2.21 (also 3.33)



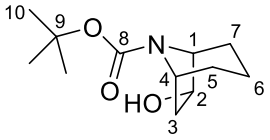
Method A: To a solution of protected amine **2.17** (21 mg in 0.5 mL EtOH, 0.09 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant K19/A82M/F87A/A264G (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers

were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave the alcohol **2.21** as a pale yellow solid (4 mg, 20%).

Method B: To a stirred solution of amine **3.35** (300 mg, 1.8 mmol) in DCM (10 mL) at 0 °C was added triethylamine (0.4 mL, 2.8 mmol) and Boc anhydride (610 mg, 2.8 mmol). The resulting mixture was allowed to warm to RT and stirred for 18 h. The mixture was diluted with H_2O (10 mL), extracted with DCM (2 x 20 mL), then the combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by column chromatography (5% Et_2O in pentane) to give compound **3.33** as a colourless solid (492 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 2H, 2 x C(3)H), 2.67 (s, 2H, C(4)**H**H′), 2.38 – 2.29 (m, 2H, C(4)H**H′**), 2.13 – 2.06 (m, 2H, C(2)**H**H′), 1.66 (d, *J* = 16.0 Hz, 2H, C(2)H**H′**), 1.50 (s, 9H, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.6 (C(1)), 153.6 (C(5)), 80.5 (C(6)), 53.3 (C(3)), 48.2 (C(4)), 29.5 (C(2)), 28.7 (C(7)). Spectroscopic data in agreement with literature.[127]

(±)-8-(*tert*-Butoxycarbonyl)-*exo*-6-hydroxy-8-azabicyclo[3.2.1]octane, 2.22

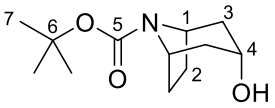


To a solution of protected amine **2.17** (21 mg in 0.5 mL EtOH, 0.09 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant K19/F87V/I263G (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and

evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave the alcohol **2.22** as a colourless solid (5 mg, 25%).

R_f 0.61 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3300 br, 1750 s; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.30 (br, 1H, C(1)H), 4.26 (td, *J* = 6.5, 2.5 Hz, 1H, C(2)H), 3.94 (br, 1H, C(4)H), 2.16 (dd, *J* = 13.5, 7.5 Hz, 1H, C(7)**H**H′), 1.85 (dd, *J* = 13.5, 7.5 Hz, 1H, C(6)**H**H′), 1.69 (br, 2H, C(3)H_2), 1.54 – 1.45 (m, 4H, C(5)H_2, C(6)H**H′**, C(7)H**H′**), 1.47 (s, 9H, 3 x C(10)H_3), 1.37 – 1.29 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.2 (C(8)), 79.3 (C(9)), 74.9 (C(2)), 63.2 (C(1)), 54.4 (C(4)), 40.4 (C(3)), 29.1 (C(5)), 28.5 (C(7)), 27.4 (C(10)), 17.2 (C(6)); **HRMS** (ESI+): found 250.1415, $[MNa]^+$ $C_{12}H_{21}NNaO_3^+$ requires 250.1414.

8-(*tert*-Butoxycarbonyl)-endo-3-hydroxy-8-azabicyclo[3.2.1]octane, 2.23 (also 3.36)

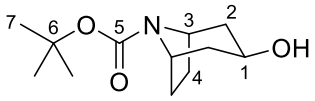


Method A: To a solution of protected amine **2.17** (21 mg in 0.5 mL EtOH, 0.10 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant K19/A82M/F87A/A264G (0.82 mL of a 61 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 2 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and purified by column chromatography (30% ethyl acetate in pentane) to give the alcohol **2.23** as a colourless oil (15 mg, 70%).

Method B: At −78 °C, to a stirred solution of *N*-Boc tropinone **3.33** (100 mg, 0.44 mmol) in THF (1.3 mL) was added DIBAL-H (1.54 mL, 1.0 M, 1.54 mmol). The resulting mixture was stirred 18 h, during which it warmed to RT. The reaction was quenched with H_2O (0.2 mL) and filtered using EtOAc (10 mL). The filtrate was evaporated *in vacuo* before being purified by column chromatography (20% EtOAc in pentane) to give compound **3.36** as a white solid (33 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (p, *J* = 4.0 Hz, 1H, C(4)H), 4.09 – 4.03 (m, 2H, 2 x C(1)H), 2.13 – 1.94 (m, 4H, 2 x C(2)**H**H′, 2 x C(3)**H**H′), 1.91 – 1.83 (m, 2H, 2 x C(2)H**H′**), 1.63 (d, *J* = 14.0 Hz, 2H, 2 x C(3)H**H′**), 1.39 (s, 9H, 3 x C(7)H_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.4 (C(5)), 79.1 (C(6)), 65.39 (C(4)), 52.8 (C(1)), 38.4 (C(3)), 28.5 (C(2)), 28.0 (C(7)). Spectroscopic data in agreement with literature.[126]

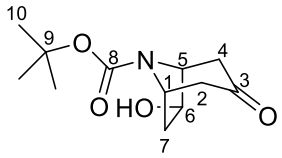
8-(*tert*-Butoxycarbonyl)-*exo*-3-hydroxy-8-azabicyclo[3.2.1]octane, 2.24



To a solution of protected amine **2.17** (21 mg in 0.5 mL EtOH, 0.09 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant K19/F87V/I263G (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave the alcohol **2.24** as a colourless solid (6 mg, 29%).

R_f 0.71 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3377 br, 1749 s; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.17 (br s, 2H, 2 x C(3)H), 4.04 (dd, *J* = 10.5, 5.5 Hz, 1H, C(1)H), 1.88 (q, *J* = 5.7 Hz, 4H, 2 x C(2)**H**H′, 2 x C(4)**H**H′), 1.54 (d, *J* = 7.5 Hz, 4H, 2 x C(2)H**H′**, 2 x C(4)H**H′**), 1.40 (s, 9H, 3 x C(7)H_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.3 (C(5)), 79.4 (C(6)), 64.2 (C(1)), 52.9 (C(3)), 40.5 (C(2)), 28.5 (C(4)), 28.3 (C(7)); **HRMS** (ESI+): found: 250.1415, $[MNa]^+$ $C_{12}H_{21}NNaO_3^+$ requires 250.1414. Spectroscopic data in agreement with literature.[126]

***tert*-Butyl (1*S*,5*S*,6*R*)-6-hydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate, 2.25 (also 3.34)**



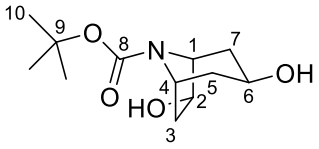
Method A: To a solution of protected amine **2.17** (21 mg in 0.5 mL EtOH, 0.09 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant RLYF/K19/F87A/A184I (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave the alcohol **2.24** as a colourless solid (14 mg, 67%).

Method B: To a 500 mL conical flask was added phosphate buffer (58 mL, 200 mM, pH 7.9), $NADP^+$ (750 μL, 4.0 mM in 200 mM phosphate buffer), GDH (750 μL, 2 U/μL in 200 mM phosphate buffer), glucose (7.5 mL, 1.0 M in 200 mM phosphate buffer), ketone **3.33** (33 mg in 0.75 mL EtOH) and $P450_{BM3}$ enzyme RLYF/K19/F87A/A184I (0.5 mL, 100 μM). The resulting solution was shaken at RT for 24 h. The mixture was extracted with EtOAc (3 x 100 mL); the combined organic extracts were washed with brine (300 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to give compound **3.34** as a colourless oil (32 mg, 76%, 98% ee).

R_f 0.31 (50% EtOAc in pentane); **IR** ν_{max} (cm^{-1}) 3436 br, 1696 s, 1409 m, 1367 w, 1347 w, 1167 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.56 (br s, 1H, C(5)H), 4.32 (br s, 1H, C(1)H), 4.20 (dd, *J* = 7.0, 2.5 Hz, 1H, C(7)H), 2.64 (br s, 2H, C(2)**H**H′, C(4)**H**H′), 2.40 (dt, *J* = 16.0, 2.0 Hz, 1H, C(2)H**H′**), 2.30 (dt, *J* = 16.0, 2.0 Hz, 1H, C(4)H**H′**), 2.11 (dd, *J* = 7.0 Hz, 1H, C(6)**H**H′), 2.07 – 1.97 (m, 1H, C(6)H**H′**), 1.51 (s, 9H, C(10)H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.1 (C(3)), 153.0 (C(8)), 81.0 (C(9)), 74.8 (C(7)), 61.7

(C(1)), 52.5 (C(5)), 48.3 (C(4)), 45.1 (C(2)), 40.5 (C(6)), 26.5 (C(10)); **HRMS** (ESI+): found 242.1386, $[MH]^+$ $C_{12}H_{20}NO_4^+$ requires 242.1387.

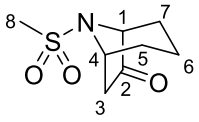
(±)-8-(*tert*-Butoxycarbonyl)-*exo*-3, 6-dihydroxy-8-azabicyclo[3.2.1]octane 2.26



To a solution of protected amine **2.17** (21 mg in 0.5 mL EtOH, 0.09 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant RLYF/K19/F87A/A184I (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave the alcohol **2.26** as a colourless solid (4 mg, 19%).

R_f 0.67 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3309 br, 1739 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.34 (br s, 1H, C(1)H), 4.18 (dd, *J* = 7.5, 2.5 Hz, 1H, C(2)H), 4.05 (br s, 1H, C(4)H), 3.84 (tt, *J* = 11.5, 5.5 Hz, 1H, C(6)H), 2.19 – 2.10 (m, 1H, C(5)**H**H′), 2.07 – 1.99 (m, 1H,C(7)**H**H′), 1.93 – 1.77 (m, 2H, C(5)H**H**′, C(7)H**H**′), 1.48 (s, 9H, 3 x C(10)H_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0 (C(8)), 79.9 (C(9)), 74.4 (C(6)), 63.9 (C(2)), 62.3 (C(1)), 52.9 (C(4)), 40.9 (C(3)), 38.9 (C(5)), 37.2 (C(7)), 28.5 (C(10)); **HRMS** (ESI+): found: 266.1364, $[MNa]^+$ $C_{12}H_{21}NNaO_4^+$ requires 266.1364.

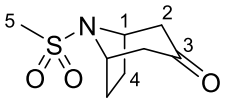
(±)-8-(Methylsulfonyl)-8-azabicyclo[3.2.1]octan-6-one, 2.27



To a solution of protected amine **2.18** (38.0 mg in 1.0 mL EtOH, 0.76 mmol), glucose (10.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 10 mmol), GDH (1.0 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (1.0 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 77.0 mL) was added $P450_{BM3}$ variant KSK19/A82M/A330W (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (100 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (300 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by column chromatography (20% ethyl acetate in pentane) gave compound **2.27** as a colourless oil (13.0 mg, 32%).

R_f 0.78 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 2931m, 1758s, 1317s, 1172s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.73 – 4.62 (m, 1H, C(4)H), 3.99 (d, *J* = 4.0 Hz, 1H, C(1)H), 2.95 (s, 3H, C(8)H_3), 2.76 (ddt, *J* = 18.0, 7.0, 1.0 Hz, 1H, C(3)**H**H′), 2.21 (dt, *J* = 18.0, 1.0 Hz, 1H, C(3)H**H′**), 2.15 – 2.05 (m, 1H, C(5)**H**H′), 1.98 – 1.91 (m, 2H, C(7)H_2), 1.80 – 1.52 (m, 3H, C(5)H**H′**, C(6)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.0 (C(2)), 62.3 (C(1)), 55.5 (C(4)), 42.0 (C(3)), 40.9 (C(8)), 30.1 (C(5)), 29.1 (C(7)), 16.8 (C(6)); **HRMS** (ESI+): found 226.0511; $[MNa]^+$ $C_8H_{13}NO_2SNa^+$ requires 226.0508.

8-(Methylsulfonyl)-8-azabicyclo[3.2.1]octan-3-one, 2.28

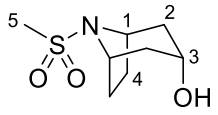


To a solution of protected amine **2.18** (50.0 mg in 1.0 mL EtOH, 0.20 mmol), glucose (10.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 10.0 mmol), GDH (1.0 mL of a 2.0 U/μL solution in

phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (1.0 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 77.0 mL) was added $P450_{BM3}$ RLYF/KSK19 (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (100 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (50% ethyl acetate in pentane) gave compound **2.28** as a colourless oil (28.0 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (dtd, *J* = 7.5, 4.0, 1.5 Hz, 2H, 2 x C(1)H), 3.02 (s, 3H, C(5)H_3), 2.82 (dd, *J* = 16.5, 4.0 Hz, 2H, C(2)**H**H′), 2.47 – 2.37 (m, 2H, C(2)H**H′**), 2.22 – 2.17 (m, 2H, C(4)**H**H′), 1.79 (d, *J* = 7.5 Hz, 2H, C(4)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.6 (C(3), 56.2 (C(1)), 50.1 (C(2)), 41.2 (C(5)), 30.0 (C(4)). Spectroscopic data in agreement with literature.[350]

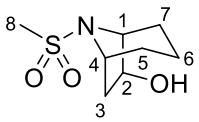
***endo*-8-(Methylsulfonyl)-8-azabicyclo[3.2.1]octan-3-ol, 2.29**



To a solution of protected amine **2.18** (38.0 mg in 1.0 mL EtOH, 0.76 mmol), glucose (10.0 mL of a 1.0 M solution in phosphate buffer, 10 mmol), GDH (1.0 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (1.0 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 77.0 mL) was added $P450_{BM3}$ variant GV/A184I (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (100 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (300 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by column chromatography (20% ethyl acetate in pentane) gave compound **2.29** as a colourless oil (8 mg, 20%).

R_f 0.15 (1:1 ethyl acetate:pentane); **IR** ν_{max} (cm^{-1}) 3507 br, 2927 m, 1315s, 1145s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (dq, *J* = 6.0, 3.0 Hz, 2H, 2 x C(1)H), 4.13 (m, 1 H, C(3)H), 2.87 (s, 3H, C(5)H_3), 2.28 (dd, *J* = 7.5, 1.5 Hz, 2H, C(4)**H**H′), 2.20 – 2.13 (m, 2H, C(2)**H**H′), 2.02 – 1.97 (m, 2H, C(4)H**H′**), 1.85 (ddt, *J* = 5.0, 3.0, 1.5 Hz, 2H, C(2)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 64.6 (C(3)), 56.3 (C(1)), 40.7 (C(2)), 40.4 (C(5)), 28.9 (C(4)); **HRMS** (ESI+): found: 228.0668, $[MNa]^+$ $C_8H_{15}NO_3SNa^+$ requires 228.0665.

(±)-*endo*-8-(Methylsulfonyl)-8-azabicyclo[3.2.1]octan-6-ol, 2.30

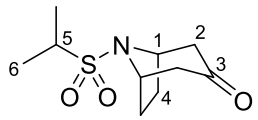


To a solution of protected amine **2.18** (38.0 mg in 1.0 mL EtOH, 0.20 mmol), glucose (10.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 10.0 mmol), GDH (1.0 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (1.0 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 77.0 mL) was added $P450_{BM3}$ variant GV/A184I (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (200 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (800 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave compound **2.30** as a colourless oil (8.0 mg, 20%).

R_f 0.15 (1:1 ethyl acetate:pentane); **IR** ν_{max} (cm^{-1}) 3507br, 2927m, 1758s, 1315s, 1146s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (dq, *J* = 7.5, 2.5 Hz, 1H, C(4)H), 4.34 (td, *J* = 7.5, 2.5 Hz, 1H, C(2)H), 3.99 (d, *J* = 2.5 Hz, 1H, C(1)H), 3.03 (s, 3H, C(8)H_3), 2.77 (d, *J* = 7.5 Hz, 1H, C(2)OH), 2.23 (d, *J* = 7.0 Hz, 1H, C(3)**H**H′), 1.93 (dddt, *J* = 14.0, 7.5, 2.5, 1.0 Hz, 1H, C(3)H**H′**), 1.81 – 1.36 (m, 6H, C(5)H_2, C(6)H_2, C(7)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 75.6 (C(2)), 66.1 (C(1)), 58.0 (C(4)), 41.5 (C(8)), 41.0 (C(3)),

31.3 (C(6)), 29.5 (C(5)), 17.1 (C(7)); **HRMS** (ESI+): found 228.0668, $[MNa]^+$ $C_8H_{15}NO_3SNa^+$ requires 228.0665.

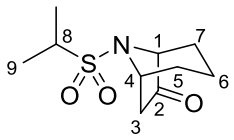
8-(Isopropylsulfonyl)-8-azabicyclo[3.2.1]octan-3-one, 2.31



To a solution of protected amine **2.19** (22.0 mg in 0.5 mL EtOH, 0.10 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant GV/A184I/I263G (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 2 h. After this time, ethyl acetate (150 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (450 mL total volume) through the same procedure. The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (30% ethyl acetate in pentane) gave compound **2.31** as a colourless oil (2.0 mg, 8%).

R_f 0.50 (1:1 ethyl acetate:pentane); **IR** ν_{max} (cm^{-1}) 2974w, 1718s, 1314s, 1135s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.44 (dquin, *J* = 6.5, 4.0 Hz, 2H, 2 x C(1)H), 3.25 (sept, *J* = 7.0 Hz, 1H, C(5)H), 2.81 (dd, *J* = 16.5, 4.0 Hz, 2H, C(2)**H**H′), 2.44 – 2.38 (m, 2H, C(2)H**H′**), 2.19 (ddd, *J* = 11.5, 6.5, 2.5 Hz, 2H, C(4)**H**H′), 1.81 – 1.72 (m, 2H, C(4)H**H′**), 1.41 (d, *J* = 7.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.6 (C(3)), 57.1 (C(1)), 55.3 (C(5)), 50.0 (C(2)), 30.3 (C(4)), 16.8 (C(6)); **HRMS** (ESI+): found 254.0824, $[MNa]^+$ $C_{10}H_{17}NO_2SNa^+$ requires 254.0821.

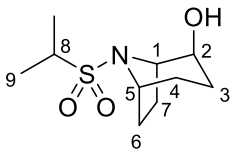
(±)-8-(Isopropylsulfonyl)-8-azabicyclo[3.2.1]octan-6-one 2.32



To a solution of protected amine **2.19** (33.0 mg in 0.75 mL EtOH, 0.15 mmol), glucose (7.5 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 7.50 mmol), GDH (0.75 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.75 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 58 mL) was added $P450_{BM3}$ variant KSK19/A82M/A264G/A328G (3.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (150 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (450 mL total volume) through the same procedure. The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (10% ethyl acetate in pentane) gave compound **2.32** as a colourless oil (8.0 mg, 24%).

R_f 0.95 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 1750s, 1310s, 1180s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.45 (tt, *J* = 4.5, 2.5 Hz, 1H, C(4)H), 4.31 – 4.23 (m, 1H, C(1)H), 3.17 (sept, *J* = 7.0 Hz, 1H, C(8)H), 2.46 – 2.38 (m, 2H, C(5)H_2), 2.29 – 2.23 (m, 2H, C(7)H_2), 2.22 – 2.11 (m, 1H, C(3)**H**H′), 1.91 – 1.88 (m, 1H, C(3)H**H**′), 1.88 – 1.84 (m, 2H, C(6)H_2), 1.35 (d, *J* = 7.0 Hz, 6H, C(9)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.3 (C(2)), 67.4 (C(1)), 57.2 (C(4)), 55.2 (C(8)), 32.3 (C(5)), 31.3 (C(3)), 28.9 (C(7), C(6)), 16.7 (C(9)); **HRMS** (ESI+): Not found.

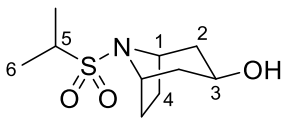
(±)-*exo*-8-(Isopropylsulfonyl)-8-azabicyclo[3.2.1]octan-2-ol, 2.33



To a solution of protected amine **2.19** (22.0 mg in 0.5 mL EtOH, 0.10 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant GV/A184I/I263G (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave compound **2.33** as a colourless oil (1.0 mg, 5%).

R_f 0.48 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 3479br, 1305s, 1135s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (dt, *J* = 6.5, 3.5 Hz, 1H, C(5)H), 4.03 (dd, *J* = 7.0, 3.5 Hz, 1H, C(1)H), 3.91 (ddd, *J* = 11.0, 5.5, 3.5 Hz, 1H, C(2)H), 3.20 – 3.06 (m, 1H, C(8)H), 2.08 – 2.00 (m, 1H, C(6)**H**H′), 2.00 – 1.94 (m, 1H, C(7)**H**H′), 1.93 – 1.85 (m, 2H, C(3)**H**H′, C(7)H**H′**), 1.80 – 1.73 (m, 1H, C(4)**H**H′), 1.62 (dt, *J* = 10.5, 3.5 Hz, 1H, C(6)**H**H′), 1.60 – 1.57 (m, 1H, C(4)H**H′**), 1.43 – 1.37 (m, 1H, C(6)H**H′**), 1.35 (d, *J* = 6.8 Hz, 6H, $C(9)H_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 70.0 (C(2)), 62.0 (C(1)), 57.2 (C(5)), 54.8 (C(8)), 30.8 (C(4)), 29.1 (C(6)), 26.0 (C(3)), 24.1 (C(7)), 16.8 (C(9)); **HRMS** (ESI+): found 256.0979, $[MNa]^+$ $C_{12}H_{20}NO_4^+$ requires 256.0978.

***exo*-8-(Isopropylsulfonyl)-8-azabicyclo[3.2.1]octan-3-ol, 2.34**

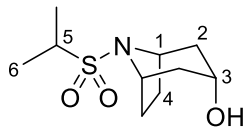


To a solution of protected amine **2.19** (22.0 mg in 0.5 mL EtOH, 0.09 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant GV/A184I/I263G (1.0 mL of a 100 μM

solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (20% ethyl acetate in pentane) gave compound **2.34** as a colourless oil (7.0 mg, 35%).

R_f 0.48 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 3479br, 1306s, 1137s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.22 (br s, 2H, 2 x C(1)H), 4.03 (m, 1H, C(3)H), 3.15 (sept, *J* = 7.0 Hz, 1H, C(5)H), 2.08 – 2.05 (m, 2H, C(4)**H**H′), 2.03 – 2.01 (m, 2H, C(2)**H**H′), 1.72 – 1.69 (m, 2H, C(4)H**H′**), 1.69 – 1.62 (m, 2H, C(2)H**H′**), 1.37 (d, *J* = 7.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 64.0 (C(3)), 57.3 (C(1)), 55.0 (C(5)), 41.7 (C(4)), 29.7 (C(2)), 16.8 (C(6)); **HRMS** (ESI+): found 256.0979, $[MNa]^+$ $C_{10}H_{19}NO_3SNa^+$ requires 256.0989.

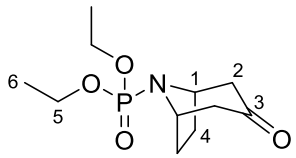
***endo*-8-(Isopropylsulfonyl)-8-azabicyclo[3.2.1]octan-3-ol, 2.35**



To a solution of protected amine **2.19** (22.0 mg in 0.5 mL EtOH, 0.10 mmol), glucose (5.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 5.00 mmol), GDH (0.5 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.5 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 38.5 mL) was added $P450_{BM3}$ variant KSK19/A82M/A330W (0.82 mL of a 61 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 2 h. After this time, ethyl acetate (50 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (150 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by column chromatography (30% ethyl acetate in pentane) gave compound **2.35** as a colourless oil (9.0 mg, 35%).

R_f 0.86 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 3516 br, 2900 m, 1335 s, 1135 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.17 – 4.14 (m, 2H, 2 x C(1)H), 4.14 – 4.10 (m, 1H, C(3)H), 3.13 (sept, *J* = 7.0 Hz, 1H, C(5)H), 2.23 (dd, *J* = 7.0, 1.0 Hz, 2H, C(4)**H**H′), 2.19 – 2.12 (m, 2H, C(2)**H**H′), 2.05 – 2.00 (m, 2H, C(4)H**H′**), 1.87 – 1.80 (m, 2H, C(2)H**H′**), 1.34 (d, *J* = 7.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 64.7 (C(3)), 56.9 (C(1)), 54.8 (C(5)), 40.4 (C(2)), 29.5 (C(4)), 16.8 (C(6)); **HRMS** (ESI+): found 256.0978, $[MNa]^+$ $C_{10}H_{19}NO_3SNa^+$ requires 256.0978.

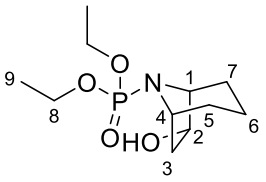
Diethyl (3-oxo-8-azabicyclo[3.2.1]octan-8-yl)phosphonate, 2.36



To a solution of protecte amine **2.20** (50.0 mg in 1.0 mL EtOH, 0.20 mmol), glucose (10.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 10.0 mmol), GDH (1.0 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (1.0 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 77.0 mL) was added $P450_{BM3}$ variant RLYF/KSK19 (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (150 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (450 mL total volume) through the same procedure. The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (50% ethyl acetate in pentane) gave compound **2.36** as a colourless oil (18.0 mg, 34%).

R_f 0.31 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 1716s, 1249m, 1023s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.30 – 4.20 (m, 2H, 2 x C(1)H), 4.16 – 4.01 (m, 4H, C(5)H_2), 2.72 – 2.64 (m, 2H, C(2)**H**H′), 2.37 – 2.27 (m, 2H, C(2)H**H′**), 2.08 – 2.04 (m, 2H, C(4)**H**H′), 1.68 (td, *J* = 7.5, 2.0 Hz, 2H, C(4)H**H′**), 1.32 (td, *J* = 7.0, 1.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.7 (C(3)), 62.8 (C(5)), 54.9 (C(1)), 50.1 (C(2)), 30.5 (C(4)), 16.4 (C(6)); **HRMS** (ESI+): found 262.1203, $[MH]^+$ $C_{11}H_{21}NO_4P^+$ requires 262.1203.

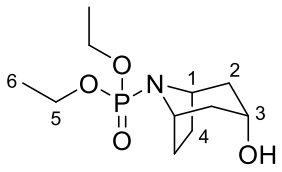
(±)-*exo*-Diethyl (6-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phosphonate, 2.37



To a solution of protected amine **2.20** (30.0 mg in 0.75 mL EtOH, 0.12 mmol), glucose (7.5 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 7.50 mmol), GDH (0.75 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (0.75 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 58 mL) was added $P450_{BM3}$ variant GV/A184I/A264G/A328G (3.0 mL of a 52 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (150 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (450 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (40% ethyl acetate in pentane) gave compound **2.37** as a colourless oil (17.0 mg, 53%).

R_f 0.16 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 3385br, 2942m, 1247s, 1223m, 1024s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.23 (dd, *J* = 7.0, 3.0 Hz, 1H, C(2)H), 4.09 (m, 5H, C(8)H_2, C(4)H), 3.67 (dt, *J* = 7.0, 3.0 Hz, 1H, C(1)H), 2.19 (dd, *J* = 14.0, 7.0 Hz, 1H, C(3)**H**H′), 1.92 (dq, *J* = 8.0, 5.0, 4.0 Hz, 1H, C(5)**H**H′), 1.84 (ddd, *J* = 14.0, 7.0, 2.0 Hz, 1H, C(3)H**H′**), 1.74 – 1.68 (m, 1H, C(6)**H**H′), 1.66 (d, *J* = 2.0 Hz, 1H, C(5)H**H′**), 1.59 (m, 2H, C(7)H_2), 1.43 – 1.37 (m, 1H, C(6)H**H′**), 1.36 – 1.28 (m, 6H, C(9)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 76.2 (C(2)), 64.6 (C(1)), 63.2 (C(8)), 56.2 (C(4)), 42.0 (C(3)), 30.9 (C(6)), 28.9 (C(7)), 27.5 (C(5)), 16.4 (C(9)); **HRMS** (ESI+): found 264.1360, $[MNa]^+$ $C_{11}H_{22}NO_4PNa^+$ requires 264.1359.

***endo*-Diethyl (3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phosphonate, 2.38**

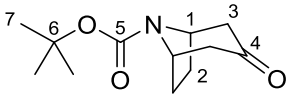


To a solution of protected amine **2.20** (50.0 mg in 1.0 mL EtOH, 0.20 mmol), glucose (10.0 mL of a 1.0 M solution in phosphate buffer, pH 7.5, 10.0 mmol), GDH (1.0 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.5), $NADP^+$ monosodium salt (1.0 mL of a 4.0 mM solution in water), in 200 mM phosphate buffer (pH 8.3, 77.0 mL) was added $P450_{BM3}$ variant RLYF/KSK19 (1.0 mL of a 100 μM solution in phosphate buffer, pH 7.5). The solution was swirled under air for 24 h. After this time, ethyl acetate (100 mL) was added and the mixture centrifuged at 10,000 g for 3 min. The layers were separated and the aqueous phase re-extracted twice with ethyl acetate (300 mL total volume) through the same procedure. The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (50% ethyl acetate in pentane) gave compound **2.38** as a colourless oil (28.0 mg, 53%).

R_f 0.14 (100% ethyl acetate); **IR** ν_{max} (cm^{-1}) 3508 br, 1325s, 1135s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.08 – 4.11 (m, 1H, 2 x C(3)H), 4.05 – 3.93 (m, 4H, C(5)H_2), 3.90 (m, 2H, 2 x C(1)H), 2.19 – 2.10 (m, 2H, C(4)**H**H′), 2.05 (m, 2H, C(2)**H**H′), 1.87 (dt, *J* = 10.0, 3.5 Hz, 2H, C(4)H**H′**), 1.74 – 1.67 (m, 2H, C(2)H**H′**), 1.27 (td, *J* = 7.0, 1.0 Hz, 6H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 65.1 (C(3)), 62.3 (C(5)), 54.3 (C(1)), 39.8 (C(2)), 29.7 (C(4)), 16.4 (C(6)); **HRMS** (ESI+): found 264.1360, $[MH]^+$ $C_{11}H_{23}NO_4P^+$ requires 264.1359.

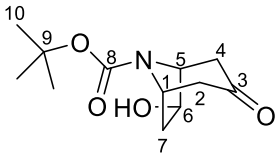
Compounds 3.9 and 3.31 can be found in the Appendices: Synthesis of Compounds Performed by Dr Ziyue Xiong.

***tert*-Butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate, 3.33 (also 2.21)**



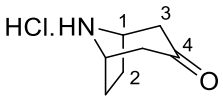
The preparation and data for this compound can be found under compound **2.21** (Method B).

***tert*-Butyl (1*S*,5*S*,6*R*)-6-hydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate, 3.34 (also 2.25)**



The preparation and data for this compound can be found under compound **2.25** (Method B).

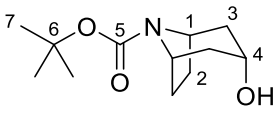
8-Azabicyclo[3.2.1]octan-3-one hydrochloride, 3.35



To a stirred solution of tropinone (0.50 g, 3.6 mmol) in DCE (10.0 mL) at 0 °C was added 1-chloroethyl chloroformate (0.77 mL, 7.2 mmol) dropwise. The resulting mixture was heated at 90 °C for 4 h. The mixture was cooled to RT then evaporated *in vacuo* to give a brown solid. This was passed through a short silica plug and eluted with diethyl ether, to give a yellow oil. This was heated to 70 °C in methanol (10 mL) for 1 h, and then the solvent evaporated *in vacuo* to yield compound **3.35** as a yellow solid (0.50 g, 87%) with no need for further purification.

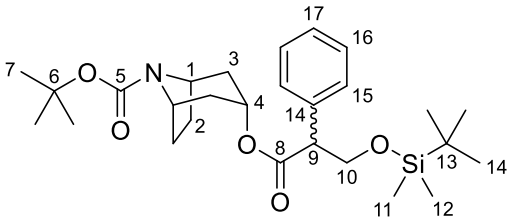
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H, N**H**H′Cl), 10.38 (s, 1H, NH**H**′Cl), 4.38 (s, 2H, 2 x C(1)H), 3.30 (dd, *J* = 16.5, 4.0 Hz, 2H, C(3)**H**H′), 2.52 (d, *J* = 16.5 Hz, 2H, C(3)H**H**′), 2.46 – 2.39 (m, 2H, C(2)**H**H′), 1.94 (t, *J* = 7.5 Hz, 2H, C(2)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.1 (C(4)), 55.0 (C(1)), 46.5 (C(3)), 27.4 (C(2)). Spectroscopic data in agreement with literature.[351]

***endo-tert*-Butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate, 3.36 (also 2.23)**



The preparation and data for this compound can be found under compound **2.23** (Method B).

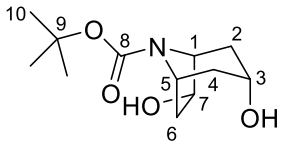
***endo-tert*-Butyl 3-((3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropanoyl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate, 3.37**



At 0 °C, to a stirred solution of **3.40** (32.0 mg, 0.14 mmol), DMAP (9.0 mg, 0.08 mmol) and **3.36** (39.0 mg, 0.14 mmol) in anhydrous DCM (2.0 mL) was added DCC (35.0 mg, 0.17 mmol). The resulting mixture was stirred at 0 °C for 5 min and then at RT for 4 h. A white gel formed (DCU). TLC shows consumption of starting material. The filtrate was evaporated *in vacuo* before being redissolved in ice-cold EtOAc and filtered to remove the DCU. The filtrate was evaporated *in vacuo* and purified by column chromatography (5% EtOAc in pentane) to give compound **3.37** as a yellow oil (47 mg, 89%).

R_f 0.35 (10% EtOAc in pentane); **IR** ν_{max} (cm^{-1}) 1736 s, 1699 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H, 2 x C(15)H, 2 x C(16)H, C(17)H), 5.09 (t, *J* = 5.0 Hz, 1H, C(4)H), 4.21 (t, *J* = 9.0 Hz, 1H, C(10)**H**H′), 4.11 (m, 2H, 2 x C(1)H), 3.85 – 3.71 (m, 2H, C(9)H, C(10)H**H′**), 1.98 – 1.61 (m, 6H, 2 x $C(2)H_2$, 2 x $C(3)H_2$), 1.44 (s, 9H, 3 x $C(7)H_3$), 0.85 (s, 9H, 3 x $C(14)H_3$), 0.02 (2, 3H, $C(11)H_3$), 0.01 (s, 3H, $C(12)H_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8 (C(5)), 170.5 (C(8)), 136.0 (C(17)), 128.8 (C(16)), 128.3 (C(15)), 127.8 (C(14)), 79.4 (C(6)), 68.4 (C(4)), 65.3 (C(10)), 55.3 (C(9)), 35.5 (C(3)), 28.6 (C(7)), 27.7 (C(2)), 25.9 (C(14)), 18.0 (C(13)), −5.3 (C(11)), −5.6 (C(12)); **HRMS** (ESI+): Not found.

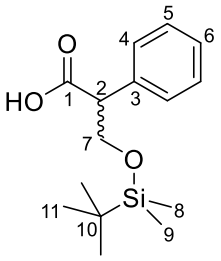
tert-Butyl (1*R*,3*R*,5*S*,6*R*)-3,6-dihydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate, 3.38



To a stirred solution of ketone **3.34** (90.0 mg, 0.37 mmol) in anhydrous THF (1.3 mL) at −78 °C was added L-Selectride® (1.0 M in hexane, 1.3 mL, 1.3 mmol). The resulting mixture was stirred for 2 h, during which it warmed to RT. The mixture was extracted with EtOAc (2 x 10 mL), then the combined organic extracts were washed with water (25 mL) and then brine (25 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give compound **3.38** as a colourless solid (61 mg, 66%).

R_f 0.18 (50% EtOAc in pentane); **mp** 145 °C; **IR** ν_{max} (cm^{-1}) 3400 br s, 1670 s **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.70 (t, *J* = 7.0 Hz, 1H, C(7)H), 4.29 (s, 1H, C(1)H), 4.11 (m, 1H, C(3)H), 3.99 (s, 1H, C(5)H), 2.80 (dd, *J* = 13.5, 7.0 Hz, 1H, C(6)**H**H′), 1.78 (m, 2H, C(2)**H**H′, C(4)**H**H′), 1.62 (m, 2H, C(2)H**H′**, C(4)H**H′**), 1.47 (s, 9H, C(10)H_3), 1.30 (m, 1H, C(6)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8 (C(8)), 80.9 (C(9)), 75.6 (C(7)), 65.2 (C(3)), 64.1(C(1)), 55.1 (C(5)), 41.1 (C(4)), 38.3 (C(2)), 37.0 (C(6)), 28.8 (C(10)); **HRMS** (ESI+): found 266.1364, $[MNa]^+$ $C_{12}H_{21}NO_4Na^+$ requires 266.1363.

(±)-3-((_tert_-Butyldimethylsilyl)oxy)-2-phenylpropanoic acid, 3.40

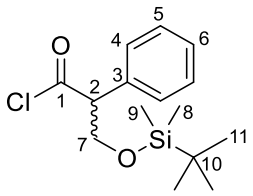


To a stirred solution of racemic tropic acid (300 mg, 1.8 mmol) and imidazole (258 mg, 3.8 mmol) in DMF (3.0 mL), was added TBSCl (570 mg, 3.8 mmol) at RT. The resulting mixture was stirred for 18 h. Then aqueous HCl solution (1.0 M, 8.4 mL) was added and the reaction stirred for a further 15 min. The

reaction mixture was extracted with EtOAc (6 x 10 mL), and the combined organic extracted were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification by column chromatography (10% EtOAc in pentane) gave compound **3.40** as a colourless oil (215 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H, C(4)H, C(5)H, C(6)H), 4.20 – 4.09 (m, 1H, C(7)**H**H′), 3.90 – 3.78 (m, 2H, C(2)H, C(7)H**H′**), 0.86 (s, 9H, C(11)H_3), 0.03 (s, 3H, C(8)H_3), 0.02 (s, 3H, C(9)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 128.9 (C(4)), 128.6 (C(5)), 128.0 (C(6)), 65.3 (C(7)), 54.2 (C(2)), 25.9 (C(11)), 18.1 (C(10)), −5.4 (C(8)), −5.6 (C(9)). Spectroscopic data in agreement with literature.[352]

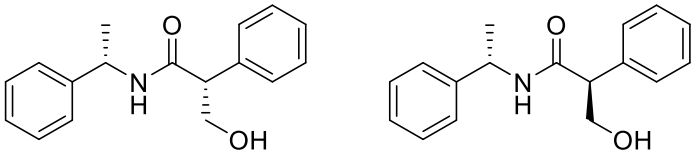
3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpropanoyl chloride, 3.41



To a stirred solution of carboxylic acid **3.40** (20.0 mg, 0.07 mmol) in anhydrous DCM (0.1 mL) was added $(COCl)_2$ (7 μL, 0.08 mmol). The reaction was stirred at RT for 30 min and then the solvent and excess $(COCl)_2$ evaporated *in vacuo* to give compound **3.41** (21 mg, quant.) which was used in the next reaction without further prufication.

R_f 0.72 (20% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2927 w, 2858 w, 1785 m, 1107 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H, 2 x C(4)H, 2 x C(5)H, C(6)H), 4.19 – 4.12 (m, 1H, C(7)**H**H′), 3.90 – 3.78 (m, 2H, C(2)H, C(7)H**H′**), 0.85 (s, 9H, 3 x C(11)H_3), 0.02 (s, 3H, C(8)H_3), 0.01 (s, 3H, C(9)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.0 (C(1)), 129.3 (C(3)), 128.8 (C(4)), 128.6 (C(5)), 128.0 (C(6)), 65.0 (C(7)), 55.0 (C(2)), 26.6 (C(11)), 18.4 (C(10)), −5.0 (C(8)), −5.3 (C(9)); **HRMS** (ESI+): found 299.8879 and 301.1900, $[MH]^+$ $C_{15}H_{24}ClO_2Si^+$ requires 299.8895 and 301.1200.

(*R*)-3-hydroxy-2-phenyl-N-((*S*)-1-phenylethyl)propanamide and (*S*)-3-hydroxy-2-phenyl-N-((*S*)-1-phenylethyl)propanamide

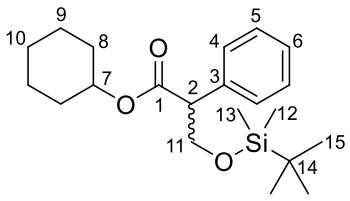


To a stirred solution of (*S*)-1-phenylethylamine (0.14 mL, 1.10 mmol) in anhydrous DCM (17.0 mL) was added DMAP (9.0 mg, 0.10 mmol) and DCC (248 mg, 1.20 mmol). The mixture was cooled to 0 °C and racemic tropic acid (200 mg, 1.2 mmol) was added. The resulting mixture was stirred at 0 °C for 30 min and then at RT for 6 h. A white precipitate formed (DCU) which was filtered off and washed with DCM. The filtrate was evaporated *in vacuo* before purification by column chromatography (60% Et_2O in pentane) to give compounds **5a** and **5b** as colourless foams.

Yield 67 mg (33%); $\mathbf{R_f}$ 0.20 (Et_2O); **m.p.** 160 °C**; IR** ν_{max} (cm^{-1}) 3246 br, 1658 w, 1640 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 10H), 7.12 – 7.07 (m, 2H), 5.64 (s, 1H), 5.12 (quin, *J* = 7.0 Hz, 1H), 4.12 (dd, *J* = 11.1, 8.7 Hz, 1H), 3.76 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.70 (dd, *J* = 8.7, 4.4 Hz, 1H), 1.42 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 129.4, 128.8, 128.7, 128.2, 127.5, 126.0, 65.3, 54.5, 49.1, 22.6; **HRMS** (ESI+): found 270.1487, $[MH]^+$ $C_{17}H_{19}NO_2^+$ requires 270.1489.

Yield 106 mg (21%); $\mathbf{R_f}$ 0.37 (Et_2O); **m.p.** 130 °C**; IR** ν_{max} (cm^{-1}) 3246 br, 1658 w, 1640 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 10H), 5.63 (s, 1H), 5.14 (quin, *J* = 7.1 Hz, 1H), 4.14 (dd, *J* = 11.2, 8.8 Hz, 1H), 3.77 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.66 (dd, *J* = 8.8, 4.3 Hz, 1H), 1.38 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 129.4, 129.0, 128.7, 128.17, 127.9, 126.3, 65.4, 55.7, 49.3, 21.7; **HRMS** (ESI+): found 270.1489, $[MH]^+$ $C_{17}H_{19}NO_2^+$ requires 270.1489.

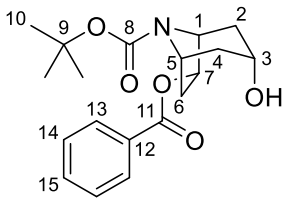
Cyclohexyl 3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropanoate, 3.42



To a stirred solution of carboxylic acid **3.40** (20 mg, 0.07 mmol) in anhydrous DCM (0.1 mL) was added $(COCl)_2$ (7 μL, 0.08 mmol). The reaction was stirred at RT for 30 min and then the solvent and excess $(COCl)_2$ evaporated *in vacuo*. IR showed consumption of acid and formation of acyl chloride. The acyl chloride was redissolved in anhydrous DCM (0.1 mL) and cyclohexanol (10 μL, 0.10 mmol), DMAP (2 mg, 0.02 mol) and triethylamine (50 μL, 0.33 mmol) added. The reaction was stirred at RT for 18 h, before being diluted with DCM and washed with $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and dried before purification by column chromatography (1% Et_2O in pentane) gave compound **3.42** (10 mg, 20%).

R_f 0.51 (5% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1745 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 5H, 2 x C(4)H, 2 x C(5)H, C(6)H), 4.80 (ddt, *J* = 12.5, 8.5, 3.5 Hz, 1H, C(7)H), 4.22 – 4.12 (t, *J* = 10.5, 1H, C(11)**H**H′), 3.76 (q, *J* = 5.5 Hz, 2H, C(2)H, C(11)H**H′**), 1.90 – 1.19 (m, 10H, 2 x C(8)H_2, 2 x C(9)H_2, C(10)H_2), 0.86 (s, 9H, 3 x C(15)H_3), 0.02 (s, 3H, C(12)H_3), 0.00 (s, 3H, C(13)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.1 (C(1)), 136.5 (C(3)), 128.6 (C(4)), 128.6 (C(5)), 128.4 (C(6)), 73.0 (C(7)), 65.7 (C(11)), 55.2 (C(2)), 31.5 (C(8)), 25.9 (C(15)), 25.6 (C(9)), 23.7 (C(10)), 18.4 (C(14), −5.4 (C(12)), −5.7 (C(13)); **HRMS** (ESI+): found 363.2359, $[MH]^+$ $C_{21}H_{35}O_3Si^+$ requires 363.2350.

***tert*-Butyl (1*S*,3*R*,5*S*,6*R*)-3-(benzoyloxy)-6-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate, 3.43**



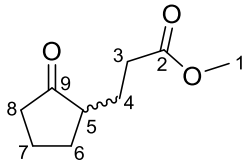
Method A: To a stirred solution of diol **3.38** (20 mg, 0.08 mmol) in anhydrous DCM (0.1 mL) was added benzoyl chloride (7 μL, 0.08 mmol), DMAP (2.0 mg, 0.02 mol) and triethylamine (60 μL, 0.40 mmol) added. The reaction was stirred at RT for 18 h, before being diluted with DCM and washed with $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and dried before purification by column chromatography (20% Et_2O in pentane) gave compound **3.43** as a colourless oil (12 mg, 42%).

Method B: To a stirred solution of diol **4** (10 mg, 0.04 mmol) in anhydrous DCM (0.1 mL) was added benzoyl chloride (4 μL, 0.04 mmol), DMAP (1 mg, 0.01 mol) and pyridine (17 μL, 0.20 mmol) added. The reaction was stirred at RT for 18 h, before being diluted with DCM and washed with $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated *in vacuo* before purification by column chromatography (10% Et_2O in pentane) gave the product as a colourless oil (8 mg, 57%).

R_f 0.13 (30% EtOAc in pentane); **IR** ν_{max} (cm^{-1}) 3462 br, 1748 s, 1698 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.5 Hz, 2H, 2 x C(13)H), 7.58 – 7.50 (m, 1H, C(15)H), 7.47 – 7.36 (m, 2H, 2 x C(14)H), 5.77 (dd, *J* = 5.5, 2.5 Hz, 1H, C(7)H), 4.45 (br s, 1H, C(1)H) 4.25 (br s, 1H, C(5)H), 4.18 (t, *J* = 5.0 Hz, 1H, C(3)H), 2.25 – 1.71 (m, 6H, C(2)H_2, C(4)H_2, C(6)H_2), 1.38 (s, 9H, 3 x C(10H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.8 (C(8)), 154.1 (C(11)), 133.0 (C(15)), 130.3 (C(12)), 129.6 (C(13)), 128.4 (C(14)), 79.7 (C(9)), 79.0 (C(3)), 64.7 (C(7)), 58.9 (C(1)), 53.4 (C(5)); **HRMS** (ESI+): found 348.1791, $[MH]^+$ $C_{19}H_{26}NO_5^+$ requires 348.1806.

Compounds 3.44–3.46 can be found in the Appendices: Synthesis of Compounds Performed by Dr Ziyue Xiong.

(±)-Methyl 3-(2-oxocyclopentyl)propanoate, 4.76

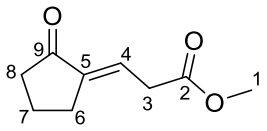


In a pressure tube, to a stirred solution of methyl acrylate (0.13 mL, 1.39 mmol) in dioxane (0.3 mL) was added 1-(cyclopent-1-en-1-yl)pyrrolidine (0.11 mL, 0.73 mmol). The resulting mixture was heated at reflux at 110 °C for 3.5 h. The mixture was cooled to RT and then H_2O (0.3 mL) added before refluxing at 110 °C for a further 30 mins. The reaction mixture was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were washed with 5% HCl (15 mL) at 0 °C, dried over MgSO4,

filtered and dried *in vaccuo* to give compound **4.76** as a yellow oil (184 mg, 99%) with no need for further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H, C(1)H_3), 2.47 – 2.22 (m, 3H, C(8)H_2, C(5)H), 2.16 – 1.97 (m, 3H, C(4)**H**H′, C(6)**H**H′, C(7)**H**H′), 1.89 – 1.84 (m, 1H, C(3)**H**H′), 1.73 – 1.62 (m, 2H, C(3)H**H**′, C(4)H**H**′), 1.54 (dddd, *J* = 14.0, 8.0, 7.0, 5.0 Hz, 1H, C(6)H**H**′), 1.47 – 1.29 (m, 1H, C(7)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.7 (C(9)), 174.2 (C(2)), 51.7 (C(1)), 49.9 (C(5)), 42.3 (C(3)), 34.3 (C(8)), 31.8 (C(4)), 28.2 (C(6)), 25.2 (C(7)). Spectroscopic data in agreement with literature.[353]

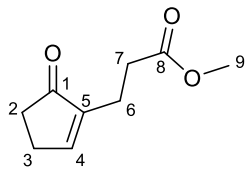
Methyl 3-(2-oxocyclopentylidene)propanoate, 4.78



To a stirred solution of methyl propiolate (0.10 mL, 0.73 mmol) in dioxane (0.80 mL) was added 1-(cyclopent-1-en-1-yl)pyrrolidine (0.13 mL, 0.85 mmol) at 15 °C. The resulting mixture was allowed to stand for 45 mins during which it turned from clear yellow to clear dark red. Then H_2O (0.4 mL) and acetic acid (0.1 mL) were added. The solution was stirred for 18 h at 15 °C and then extracted with Et_2O (4 x 5 mL), and the combined organic extracts were washed with 5% HCl (20 mL) then water (20 mL) then brine (20 mL), dried over Na_2SO_4 and evaporated *in vaccuo*. Purification by column chromatography (10% EtOAc in pentane) gave compound **4.78** as a yellow oil (41 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 – 6.63 (m, 1H, C(4)H), 3.71 (s, 3H, C(1)H_3), 3.19 (d, *J* = 7.5, 2H, C(3)H_2), 2.61 (tdt, *J* = 7.5, 3.0, 1.5 Hz, 2H, C(6)H_2), 2.36 (t, *J* = 7.5 Hz, 2H, C(8)H_2), 1.96 (p, *J* = 7.5 Hz, 2H, C(7)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.0 (C(9)), 172.2 (C(2)), 126.4 (C(4)), 52.3 (C(1)), 38.6 (C(3)), 35.1 (C(8)), 27.0 (C(6)), 19.7 (C(7)). Spectroscopic data in agreement with literature.[354]

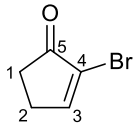
Methyl 3-(5-oxocyclopent-1-en-1-yl)propanoate, 4.79



In a pressure tube, to a stirred solution of intermediate **4.78** (20 mg, 0.12 mmol) in ^{n}BuOH (0.2 mL) was added conc HCl (0.02 mL) at RT. The resulting mixture was stirred at 90 °C for 1 h and then dried *in vaccuo*. The residue was resuspended in water and extracted with Et_2O (3 x 5 mL), and the combined organic extracts were washed with water (15 mL), dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.79** as a yellow oil (21 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (td, *J* = 2.5, 1.5 Hz, 1H, C(4)H), 4.07 (t, *J* = 7.0 Hz, 2H, C(9)H_3), 2.59 – 2.54 (m, 2H, C(2)H_2), 2.52 (t, *J* = 1.0 Hz, 4H, C(7)H_2, C(6)H_2), 2.43 – 2.38 (m, 2H, C(3)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.1 (C(1)), 172.1 (C(8)), 158.2 (C(4)), 143.5 (C(5)), 64.5 (C(9)), 34.7 (C(3)), 32.4 (C(6) or (C(7)), 26.7 (C(2)), 20.7 (C(6) or C(7)). Spectroscopic data in agreement with literature.[355]

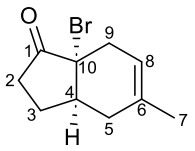
2-Bromocyclopent-2-en-1-one, 4.85



To a stirred solution of cyclopentenone (1.5 mL, 17.9 mmol) and pyridine-*N*-oxide (2.55 g, 26.9 mmol) in acetonitrile (80 mL) was added NBS (4.788 g, 26.9 mmol) at 0 °C. The resulting mixture was allowed to warm to RT and stirred for 18 h before evaporating the solvent *in vaccuo*. Purification by column chromatography (5–10% EtOAc in pentane) gave compound **4.85** as a yellow oil (2.431 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, *J* = 3.0 Hz, 1H, C(3)H), 2.69 (ddd, *J* = 7.0, 3.0, 2.0 Hz, 2H, C(2)H_2), 2.57 – 2.49 (m, 2H, C(1)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.8 (C(5)), 161.9 (C(3)), 126.4 (C(4)), 32.5 (C(1)), 28.1 (C(2)). Spectroscopic data in agreement with literature.[226]

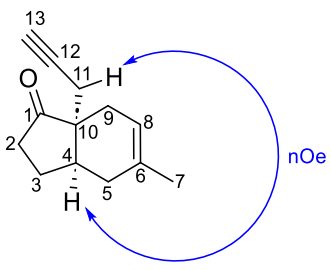
(±)-7a-Bromo-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.86



To a stirred solution of dienophile **4.85** (200 mg, 1.26 mmol) in DCM (6.0 mL) was added ethylalumiumdichloride (0.24 mL, 0.24 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 mins and then isoprene (0.50 mL, 5.00 mmol) was added. The reaction mixture was stirred for 18 h at 0 °C during which it turned from clear colourless to clear orange. The reaction was quenched with triethylamine (0.2 mL) and sat. aq. Rochelle salt (5 mL) at 0 °C, and then stirred vigourously for 5 mins before pouring into H_2O (10 mL) and extracting with DCM (3 x 10 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (5% Et_2O in pentane) gave compound **4.86** as a colourless oil (207 mg, 73%).

R_f 0.58 (15% EtOAc in pentane); **IR** ν_{max} (cm^{-1}) 2921 m, 2851 m, 1748 s; **^{1}H NMR** (400 MHz, $DCCl_3$) δ 5.23 (br s, 1H, C(8)H), 2.99 – 2.89 (m, 1H, C(9)**H**H′), 2.77 – 2.64 (m, 2H, C(9)H**H**′, C(5)**H**H′), 2.58 – 2.49 (m, 1H, C(2)**H**H′), 2.40 (dddd, *J* = 12.5, 9.0, 7.0, 5.5 Hz, 1H, C(3)**H**H′), 2.33 – 2.22 (m, 2H, C(5)H**H**′, C(2)H**H**′), 1.79 – 1.65 (m, 2H, C(4)H, C(3)H**H**′), 1.62 (br s, 3H, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.1 (C(1)), 132.4 (C(6)), 118.2 (C(8)), 67.2 (C(10)), 42.2 (C(5)), 32.8 (C(4)), 32.8 (C(9)), 31.4 (C(2)), 25.7 (C(3)), 23.3 (C(7)); **HRMS** (ESI+): found 229.0223 and 231.0203, $[MH]^+$ $C_{10}H_{14}BrO^+$ requires 229.0223 and 231.0203.

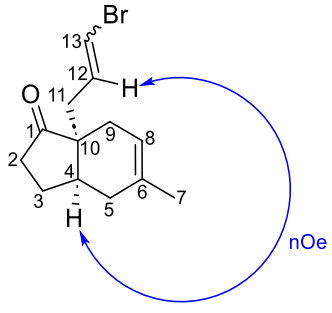
(±)-5-Methyl-7a-(prop-2-yn-1-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.89



To a stirred solution of intermediate **4.86** (100 mg, 0.44 mmol) in DME (2.0 mL) was added methyllithium (0.3 mL, 1.6 M in diethyl ether, 0.48 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h and then DMPU (1.1 mL, 8.77 mmol) and propargyl bromide (0.70 mL, 80% in toluene, 6.58 mmol) were added. The reaction mixture was stirred for 18 h during which it warmed to RT. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and stirred vigorously for 5 mins before pouring into H_2O (10 mL) and extracting with Et_2O (3 x 10 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (5% Et_2O in pentane) gave compound **4.89** as a colourless oil (48 mg, 58%).

R_f 0.21 (10 % Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3300 w, 1739 m, 1631 s; **^{1}H NMR** (400 MHz, $DCCl_3$) δ 5.28 (br s, 1H, C(8)H), 2.65 – 2.52 (m, 2H, C(4)H, C(5)**H**H′), 2.53 – 2.43 (m, 1H, C(2)**H**H′), 2.32 – 2.22 (m, 2H, C(5)H**H′**, C(11)**H**H′), 2.22 – 2.11 (m, 1H, C(2)H**H′**), 2.06 – 1.82 (m, 4H, C(3)**H**H′, C(9)**H**H′, $C(11)H_2$, C(13)H), 1.68 (br s, 3H, $C(7)H_3$), 1.66 – 1.54 (m, 2H, C(3)H**H′**, C(9)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 219.1 (C(1)), 132.2 (C(6)), 116.2 (C(8)), 81.0 (C(12)), 70.2 (C(13)), 48.8 (C(10)), 36.6 (C(4)), 36.1 (C(2)), 29.8 (C(11)), 27.4 (C(9)), 25.1 (C(3)), 23.8 (C(7)), 22.5 (C(5)); configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 189.1275, $[MH]^+$ $C_{13}H_{17}O^+$ requires 189.1274.

(±)-7a-(3-Bromoallyl)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.90

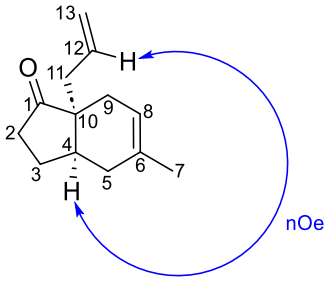


To a stirred solution of intermediate **4.86** (400 mg, 1.75 mmol) in DME (6.0 mL) was added methyllithium (1.2 mL, 1.6 M in diethyl ether, 1.93 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h and then DMPU (4.2 mL, 35.08 mmol) and 1,3-dibromopropene (1.80 mL,

17.54 mmol) were added. The reaction mixture was stirred for 18 h during which it warmed to RT. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and stirred vigorously for 5 mins before pouring into H_2O (5 mL) and extracting with Et_2O (3 x 10 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (5% Et_2O in pentane) gave compound **4.90** as a colourless oil (210 mg, 45%).

R_f 0.35 (5 % Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2912 w, 1736 s, 1621 w, 1436 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 7.0, 1.5 Hz, 1H, C(13)H), 6.09 – 5.96 (m, 1H, C(12)H), 5.31 (br s, 1H, C(8)H), 2.58 – 2.26 (m, 4H, C(11)H_2, C(2)**H**H′, C(3)**H**H′), 2.22 – 2.07 (m, 2H, C(2)H**H**′, C(4)H), 2.07 – 1.98 (m, 1H, C(9)**H**H′), 1.97 – 1.78 (m, 2H, C(3)H**H**′, C(5)**H**H′), 1.76 – 1.72 (m, 1H, C(9)H**H**′), 1.71 – 1.67 (m, 3H, C(7)H_3), 1.66 – 1.60 (m, 1H, C(5)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.5 (C(1)), 132.0 (C(6)), 131.1 (C(12)), 116.6 (C(8)), 109.9 (C(13)), 49.1 (C(10)), 37.8 (C(4)), 36.1 (C(2)), 33.7 (C(11)), 30.4 (C(3)), 27.7 (C(9)), 25.2 (C(5)), 23.9 (C(7)); **HRMS** (ESI+): found 269.0532 and 271.0513, $[MH]^+$ $C_{13}H_{18}BrO^+$ requires 269.0536 and 271.0516.

(±)-7a-Allyl-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.91



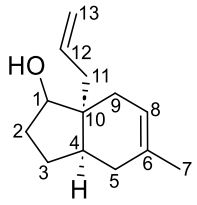
Method A: To a stirred solution of intermediate **4.86** (480 mg, 2.10 mmol) in DME (7 mL) was added methyllithium (1.5 mL, 1.6 M in diethyl ether, 2.32 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h and then DMPU (5.1 mL, 42.0 mmol) and allyl bromide (2.7 mL, 31.57 mmol) were added. The reaction mixture was stirred for 18 h during which it warmed to RT. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and stirred vigorously for 5 mins before pouring into H_2O (10 mL) and extracting with Et_2O (3 x 10 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (2% Et_2O in pentane) gave

compound **4.91** as a colourless oil (232 mg, 58%).

Method B: To a stirred solution of TMS enol ether **4.103** (1.00 g, 4.50 mmol) in DME (25 mL) was added methyllithium (3.1 mL, 1.6 M in diethyl ether, 4.95 mmol) at −78 °C. The mixture was stirred at 0 °C for 2 h and then DMPU (25 mL) and allyl bromide (0.38 mL, 4.50 mmol) were added. The reaction mixture was stirred for 18 h during which it warmed to RT. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and stirred vigorously for 5 mins before extracting with Et_2O (3 x 25 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (25% Et_2O in pentane) gave compound **4.91** as a colourless oil (751 mg, 88%).

R_f 0.36 (10 % Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2950 m, 1737 s, 1640 w; **^{1}H NMR** (500 MHz, $DCCl_3$) δ 5.66 (dddd, *J* = 16.5, 10.0, 8.5, 6.5 Hz, 1H, C(12)H), 5.30 (br s, 1H, C(8)H), 5.06 – 4.98 (m, 2H, $C(13)H_2$), 2.48 – 2.35 (m, 2H, C(2)**H**H′, C(11)**H**H′), 2.26 – 2.20 (m, 1H, C(4)H), 2.19 – 2.04 (m, 3H, C(2)H**H′**, C(9)**H**H′, C(11)H**H′**), 2.01 – 1.86 (m, 2H, C(3)**H**H′, C(5)**H**H′), 1.86 – 1.79 (m, C(9)H**H′**), 1.68 (br s, 3H, $C(7)H_3$), 1.66 – 1.59 (m, 2H, C(3)H**H′**, C(5)H**H′**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 220.9 (C(1)), 134.6 (C(12)), 131.8 (C(6)), 117.8 (C(13)), 117.0 (C(8)), 49.4 (C(10)), 37.9 (C(11)), 36.9 (C(4)), 36.3 (C(2)), 30.0 (C(9)), 27.9 (C(5)), 25.1 (C(3)), 23.9 (C(7)); configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 191.1431, $[MH]^+$ $C_{13}H_{19}O^+$ requires 191.1430.

(±)-7a-Allyl-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ol (Appendices)

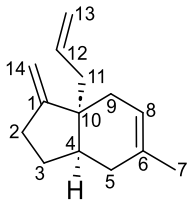


To intermediate **4.91** (200 mg, 1.05 mmol) was added 9-BBN (2.1 mL, 0.5 M in THF, 1.05 mmol) at 0 °C. The resulting mixture was stirred at RT for 1 h and then NaOH (0.7 mL, 3.0 M in H_2O, 2.10 mmol) and H_2O_2 (0.3 mL, 30% in H_2O, 3.84 mmol) were added. The reaction mixture was stirred at reflux for 1 h and then extracted with Et_2O (3 x 5 mL). The organic layers were combined and dried over $MgSO_4$,

filtered and evaporated *in vaccuo*. Purification by column chromatography (20% Et_2O in pentane) gave the *title compound* as a colourless oil (63 mg, 31%).

R_f 0.33 (25 % Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3379 br, 1738 s, 1638 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.97 (dddd, J = 17.0, 10.0, 8.0, 7.0 Hz, 1H, C(12)H), 5.39 – 5.33 (m, 1H, C(8)H), 5.15 – 5.04 (m, 2H, C(13)H_2), 4.01 (dd, J = 9.5, 6.5 Hz, 1H, C(1)H), 2.22 (dd, J = 13.5, 7.0 Hz, 1H, C(11)**H**H′), 2.11 – 1.91 (m, 3H, C(C(2)**H**H′, C(5)**H**H′, C(11)H**H′**), 1.78 – 1.67 (m, 3H, C(2)H**H′**, C(4)H, C(5)H**H′**), 1.66 (s, 3H, C(7)H_3), 1.61 – 1.42 (m, 3H, C(3)H2, C(8)H**H′**), 1.26 (s, 2H, C(9)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8 (C(12)), 131.0 (C(6)), 118.2 (C(8)), 117.5 (C(13)), 79.5 (C(1)), 43.8 (C(10)), 40.8 (C(11)), 39.4 (C(4)), 30.6 (C(2) or C(5)), 29.9 (C(9)), 26.6 (C(3)), 25.3 (C(2) or C(5)), 23.8 (C(7)); **HRMS** (ESI+): Not found.

(±)-7a-Allyl-5-methyl-1-methylene-2,3,3a,4,7,7a-hexahydro-1*H*-indene, 4.92

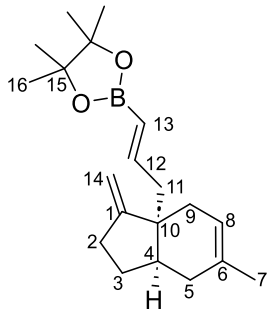


To a stirred solution of methyltriphenylphosphonium bromide (3.85 g, 10.40 mmol) in THF (10.0 mL) was added KO*t*-Bu (9.2 mL, 1.0 M in THF, 9.20 mmol) at RT. The resulting cloudy, yellow mixture was stirred at RT for 5 minutes and then intermediate **4.91** (500 mg, 2.60 mmol) was added. The reaction mixture was stirred for 18 h at 70 °C. The reaction was diluted with pentane (10 mL) and washed with water (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (pentane) gave compound **4.92** as a colourless oil (417 mg, 65%).

R_f 0.80 (pentane); **IR** ν_{max} (cm^{-1}) 1652 m, 1434 m, 911 s, 879 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.69 (m, 1H, C(12)H), 5.26 (br s, 1H, C(8)H), 5.05 – 4.93 (m, 2H, C(13)H_2), 4.83 (td, *J* = 2.5, 1.0 Hz, 1H, C(14)**H**H′), 4.75 (t, *J* = 2.5 Hz, 1H, C(14)H**H′**), 2.48 (ddq, *J* = 17.0, 9.0, 2.0 Hz, 1H, C(2)**H**H′), 2.37 – 2.18 (m, 3H, C(2)H**H′**, C(11)H_2), 2.11 – 1.86 (m, 3H, C(4)H, C(5)**H**H′, C(9)**H**H′), 1.82 – 1.73 (m, 1H,

C(5)H**H′**), 1.73 – 1.60 (m, 5H, C(3)**H**H′, C(7)H_3, C(9)H**H′**), 1.43 (ddt, *J* = 12.0, 11.0, 9.0 Hz, 1H, C(3)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6 (C(1)), 135.8 (C(12)), 131.4 (C(6)), 118.4 (C(8)), 116.4 (C(13)), 103.3 (C(14)), 45.1 (C(10)), 40.1 (C(11)), 39.6 (C(4)), 34.2 (C(9)), 30.4 (C(2)), 30.2 (C(5)), 28.2 (C(3)), 23.8 (C(7)); **HRMS** (ESI+): found 189.1640, $[MH]^+$ $C_{14}H_{21}^+$ requires 189.1638.

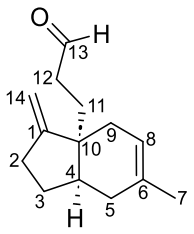
(±)-4,4,5,5-Tetramethyl-2-((*E*)-3-(6-methyl-3-methylene-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)prop-1-en-1-yl)-1,3,2-dioxaborolane, 4.93



To a stirred solution of intermediate **4.92** (417 mg, 2.21 mmol) and pinacol vinyl boronate (1.0 mL, 5.90 mmol) in toluene (5.6 mL) was added Hoveyda–Grubbs Catalyst (375 mg, 0.60 mmol) at RT. The resulting mixture was stirred at 110 °C for 3 h and then the solvent evaporated *in vaccuo*. Purification by column chromatography (2% Et_2O in pentane) gave compound **4.93** as a colourless solid (349 mg, 50%).

R_f 0.52 (5% Et_2O in pentane); **mp** 40 °C; **IR** ν_{max} (cm^{-1}) 2996 s, 1636 m, 1361 s, 1146 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.56 (ddd, *J* = 18.0, 8.0, 6.5 Hz, 1H, C(12)H), 5.43 (dt, *J* = 18.0, 1.5 Hz, 1H, C(13)H), 5.25 (br s, 1H, C(8)H), 4.82 (td, *J* = 2.5, 1.5 Hz, 1H, C(14)**H**H′), 4.76 (t, *J* = 2.5 Hz, 1H, C(14)H**H′**), 2.47 (ddq, *J* = 17.5, 9.0, 2.5 Hz, 1H, C(2)**H**H′), 2.39 – 2.23 (m, 3H, C(2)H**H′**, C(11)H_2), 2.10 – 1.85 (m, 3H, C(3)**H**H′, C(5)**H**H′, C(9)**H**H′), 1.79 – 1.65 (m, 3H, C(C(3)H**H′**, C(4)H, C(5)H**H′**), 1.63 (br s, 3H, C(7)H_3), 1.49 – 1.35 (m, 1H, C(3)H**H′**), 1.25 (s, 12H, 4 x C(16)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4 (C(1)), 151.4 (C(12)), 131.5 (C(6)), 129.1 (C(13)), 118.4 (C(8)), 103.6 (C(14)), 83.1 (C(15)), 45.2 (C(10)), 42.6 (C(11)), 39.7 (C(4)), 34.1 (C(5)), 30.4 (C(9)), 30.0 (C(2)), 28.2 (C(3)), 24.9 (C(16)), 23.8 (C(7)); **HRMS** (ESI+): found 315.2491, $[MH]^+$ $C_{20}H_{32}BO_2^+$ requires 315.2490.

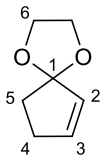
(±)-3-(6-Methyl-3-methylene-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propanal, 4.94



To a stirred solution of intermediate **4.93** (114 mg, 0.36 mmol) in THF (10.0 mL) was added anhydrous Me_3NO (136 mg, 1.81 mmol) at RT. The resulting mixture was stirred at 70 °C for 3 h and then partitioned between brine (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and washed with water (10 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (2% Et_2O in pentane) gave compound **4.94** as a colourless oil (28 mg, 38%).

R_f 0.35 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1738 s, 1653 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (t, J = 2.0 Hz, 1H, C(13)H), 5.25 (br s, 1H (C(8)H), 4.83 (t, J = 2.0 Hz, 1H, C(14)**H**H′), 4.67 (t, J = 2.5 Hz, 1H, C(14)H**H**′), 2.54 – 2.20 (m, 4H, C(2)H_2, C(12)H_2), 2.12 – 1.99 (m, 2H, C(5)H_2), 1.98 – 1.65 (m, 5H, C(4)H, C(9)H_2, C(11)H_2), 1.64 (s, 3H, C(7)H_3), 1.52 – 1.38 (m, 1H, C(3)**H**H′), 1.34 – 1.23 (m, 1H, C(3)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.1 (C(13)), 157.7 (C(1)), 131.3 (C(6)), 118.3 (C(8)), 103.7 (C(14)), 45.0 (C(10)), 39.6 (C(4)), 39.4 (C(12)), 34.5 (C(5)), 30.5 (C(9)), 30.2 (C(2)), 28.3 (C(3)), 27.1 (C(11)), 23.7 (C(7)); **HRMS** (ESI+): found 205.1592, $[MH]^+$ $C_{14}H_{21}O^+$ requires 205.1587.

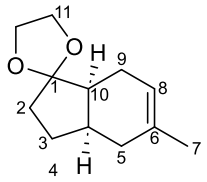
1,4-Dioxaspiro[4.4]non-6-ene, 4.99



This was a side product in attempts to make compound **4.111** and compound **4.115**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (dt, *J* = 5.5 and 2.5 Hz, 1H, C(3)H), 5.70 (dt, J = 5.5 and 1.5 Hz, 1H, C(2)H), 3.94 (br s, 4H, 2 x (C6)H_2), 2.38 – 2.43 (m, 2H, C(4)H_2), 2.04 – 2.08 (m, 2H, C(5)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3 (C(2)), 130.3 (C(3)), 122.2 (C(1)), 64.7 (C(6)), 31.6 (C(4)), 22.65 (C(5)). Spectroscopic data in agreement with literature.[356]

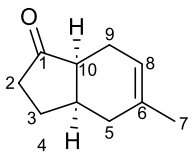
(±)-5-Methyl-2,3,3a,4,7,7a-hexahydrospiro[indene-1,2′-[1,3]dioxolane], 4.101



To a stirred solution of anhydrous lithium perchlorate (14.40 g, 135.3 mmol) in diethyl ether (30.0 mL) was added 2-cyclopenten-1-one ethylene ketal (1.00 mL, 8.46 mmol) and isoprene (3.40 mL, 33.84 mmol), and solution of camphorsulfonic acid (20 mg, 0.08 mmol) in THF (0.17 mL). The resulting reaction mixture was stirred at RT for 15 min and then quenched with triethylamine (24 μL, 0.08 mmol), diluted with H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.101** as a yellow oil (1.26 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 – 5.34 (m, 1H, C(8)H), 3.98 – 3.75 (m, 4H, 2 x C(11)H_2), 2.35 – 2.26 (m, 1H, C(4)H), 2.17 – 2.07 (m, 1H, C(5)**H**H′), 2.07 – 1.67 (m, 7H, C(C(2)H_2, C(3)**H**H′, C(5)H**H**′, C(9)H_2, C(10)H), 1.64 (s, 3H, C(7)H_3), 1.52 – 1.39 (m, 1H, C(3)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.2 (C(6)), 119.2 (C(8)), 114.9 (C(1)), 63.9 (C(11)), 41.4 (C(10)), 35.0 (C(4)), 34.0 (C(2)), 31.9 (C(5)), 27.1 (C(3)), 24.0 (C(7)), 22.3 (C(9)). Spectroscopic data in agreement with literature.[252]

(±)-5-Methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.102

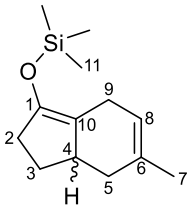


At 0 °C, to a stirred solution of ethylene ketal **4.101** (90 mg, 0.46 mmol) in methanol (2.3 mL) was

added HCl (2.7 M, 140 μL, 0.38 mmol) dropwise. The resulting reaction mixture was stirred at RT for 2 h and then poured into saturated $NaHCO_3$ solution (5 mL) and extracted with petroleum ether 30-40 (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.102** as a colourless oil (69 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 – 5.22 (m, 1H, C(8)H), 2.49 – 2.40 (m, 1H, C(4)H), 2.35 – 2.05 (m, 6H, C(2)H_2, C(5)**H**H′, C(9)H_2, C(10)H), 2.02 – 1.90 (m, 2H, C(3)**H**H′, C(5)H**H′**), 1.77 – 1.66 (m, 1H, C(3)H**H′**), 1.58 – 1.54 (m, 3H, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 219.9 (C(1)), 132.4 (C(6)), 118.9 (C(8)), 46.7 (C(10)), 34.4 (C(2)), 33.0 (C(4)), 31.0 (C(5)), 26.6 (C(3)), 24.0 (C(7)), 21.9 (C(9)). Spectroscopic data in agreement with literature.[252]

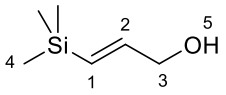
Trimethyl((6-methyl-2,4,7,7a-tetrahydro-1*H*-inden-3-yl)oxy)silane, 4.103



To a stirred solution of intermediate **4.102** (90 mg, 0.60 mmol) in DCM (5.75 mL) was added triethylamine (0.14 mL, 0.99 mmol) and TMSOTf (0.18 mL, 0.99 mmol) at 0 °C. The resulting mixture was stirred at RT for 1 h and then quenched with H_2O (5 mL) and extracted with Et_2O (3 x 5 mL). The organic layers were combined and dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.103** as a colourless oil (120 mg, 90%).

R_f 0.85 (pentane); **IR** ν_{max} (cm^{-1}) 1683 m, 1248 s; **^{1}H NMR** (400 MHz, C_6D_6) δ 5.42 – 5.37 (m, 1H, C(8)H), 3.13 – 3.01 (m, 1H, C(9)**H**H′), 2.73 – 2.63 (m, 2H, C(4)H, C(9)H**H′**), 2.34 (ddt, J = 8.7, 5.7, 2.8 Hz, 2H, C(3)H_2), 2.10 – 1.96 (m, 2H, C(2)**H**H′, C(5)**H**H′), 1.77 – 1.66 (m, 1H, C(5)H**H′**), 1.63 (s, 3H, C(7)H_3), 1.39 – 1.27 (m, 1H, C(3)H**H′**), 0.15 (s, 9H, 3 x C(11)H_3); **^{13}C NMR** (101 MHz, C_6D_6) δ 144.8 (C(1)), 133.8 (C(6)), 132.0 (C(10)), 120.1 (C(8)), 39.9 (C(5)), 39.3 (C(4)), 33.5 (C(3)), 28.0 (C(2)), 25.0 (C(9)), 24.1 (C(7)), 0.7 (C(11)); **HRMS** (ESI+): found 223.1514, $[MH]^+$ $C_{13}H_{23}OSi^+$ requires 223.1513.

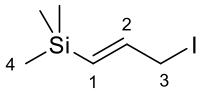
(*E*)-3-(Trimethylsilyl)prop-2-en-1-ol



To a stirred solution of lithium aluminium hydride (88 mg, 2.33 mmol) in DME (0.6 mL) was added 3-(trimethylsilyl)propargyl alcohol (0.23 mg, 1.55 mmol) in DME (1.9 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 18 h and then quenched with water (1 mL) and 1 M HCl (5 mL) and extracted with Et_2O (3 x 5 mL). The organic layers were dried over Na_2SO_4 and filtered through a silica plug, and the filtrate was evaporated *in vaccuo* to give the *title compound* as a colourless oil (200 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (dt, J = 18.5, 4.5 Hz, 1H, C(2)H), 5.92 (dt, J = 18.5, 2.0 Hz, 1H, C(1)H), 4.17 (dd, *J* = 4.5, 2.0 Hz, 2H, C(3)H_2), 0.07 (s, 9H, 3 x C(4)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9 (C(2)), 129.7 (C(1)), 65.6 (C(3)), −1.2 (C(4)). Spectroscopic data in agreement with literature.[357]

(*E*)-(3-Iodoprop-1-en-1-yl)trimethylsilane, 4.104

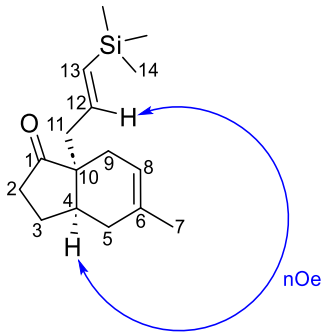


To a stirred solution of triphenyl phosphine (449 mg, 1.71 mmol) in DCM (8.5 mL) was added imidazole (148 mg, 2.17 mmol), iodine (472 mg, 1.86 mmol) and the allylic alcohol above (200 mg, 1.55 mmol) as a 0.2 M solution in DCM (7.5 mL), at 0 °C. The resulting mixture was protected from light by wrapping it in foil and was stirred at 0 °C for 1 h, then quenched with 20% aqueous $Na_2S_2O_3$ (15 mL) and extracted with DCM (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (pentane) to give compound **4.104** as a yellow oil (266 mg, 72%).

R_f 0.81 (pentane); **IR** ν_{max} (cm^{-1}) 1383 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.16 (dt, J = 18.0, 7.5 Hz, 1H, C(2)H), 5.85 (d, J = 18.0 Hz, 1H, C(1)H), 3.88 (d, *J* = 7.5 Hz, 2H, C(3)H_2), 0.07 (s, 9H, 3 x C(4)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4 (C(2)), 134.7 (C(1)), 8.8 (C(3)), −1.4 (C(4)); **HRMS** (ESI+): Not

found.

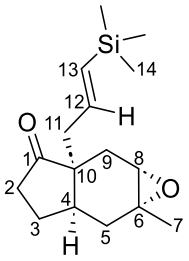
(±)-5-Methyl-7a-((*E*)-3-(trimethylsilyl)allyl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.105



At −78 °C, to a stirred solution of TMS enol ether **4.103** (93 mg, 0.42 mmol) in DME (2.9 mL) was added methyllithium (0.3 mL, 1.6 M, 0.50 mmol). The resulting mixture was stirred at 0 °C for 1 h. At RT, vinyl trimethylsilane **4.104** (100 mg, 9.42 mL) was added as a solution in THF (0.42 mL). The reaction mixture was stirred at RT for 18 h and then quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (pentane) to give compound **4.105** as a colourless oil (44 mg, 40%).

R_f 0.46 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1715 m, 1600 s, 1550 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.91 – 5.81 (m, 1H, C(12)H), 5.66 (dt, *J* = 18.5, 1.5 Hz, 1H, C(13)H), 5.33 – 5.28 (m, 1H, C(8)H), 2.48 – 2.35 (m, 2H, C(2)**H**H′, C(11)**H**H′), 2.29 – 2.21 (m, 1H, C(11)H**H′**), 2.19 – 2.04 (m, 3H, C(2)H**H′**, C(4)H, C(9)**H**H′), 2.02 – 1.86 (m, 2H, C(3)**H**H′, C(5)**H**H′), 1.84 – 1.76 (m, 1H, C(9)H**H′**), 1.72 – 1.68 (m, 1H, C(5)H**H′**), 1.67 (s, 3H, C(7)H_3), 1.65 – 1.57 (m, 1H, C(3)H**H′**), 0.01 (s, 9H, 3 x C(14)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.8 (C(1)), 142.5 (C(12)), 133.9 (C(13)), 131.7 (C(8)), 117.2 (C(6)), 49.3 (C(10)), 41.5 (C(11)), 37.5 (C(4)), 36.1 (C(2)), 30.3 (C(9)), 27.7 (C(5)), 25.2 (C(3)), 23.8 (C(7)), -1.1 (C(14)); configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 263.1827, $[MH]^+$ $C_{16}H_{26}OSi^+$ requires 263.1826.

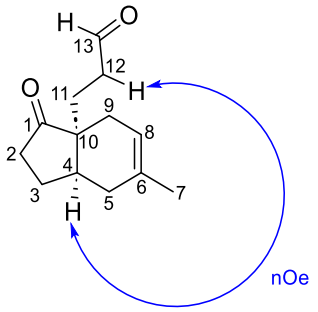
(±)-6a-Methyl-2a-((*E*)-3-(trimethylsilyl)allyl)octahydro-3*H*-indeno[5,6-b]oxiren-3-one 4.106



At 0 °C, to a stirred solution of vinyl trimethylsilane **4.105** (36 mg, 0.14 mmol) in DCM (1.5 mL) was added *m*CPBA (26 mg, 0.15 mmol). The resulting mixture was stirred at 0 °C for 1 h and then quenched with sat. aq. $NHCO_3$ (5 mL) and extracted with DCM (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (10% Et_2O in pentane) to give compound **4.106** as a colourless oil (17 mg, 47%).

R_f 0.43 (25% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1730 m, 1600 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dt, *J* = 18.5, 6.5 Hz, 1H, C(12)H), 5.69 (dt, *J* = 18.5, 1.5 Hz, 1H, C(13)H), 2.90 (t, *J* = 7.0 Hz, 1H, C(8)H), 2.46 – 2.36 (m, 2H, C(2)**H**H′, C(11)**H**H′), 2.26 – 2.21 (m, 1H, C(11)H**H′**), 2.16 – 2.04 (m, 3H, C(2)H**H′**, C(4)H, C(9)**H**H′), 2.02 – 1.86 (m, 2H, C(3)**H**H′, C(5)**H**H′), 1.84 – 1.76 (m, 1H, C(9)H**H′**), 1.72 – 1.68 (m, 1H, C(5)H**H′**), 1.67 (s, 3H, C(7)H_3), 1.65 – 1.57 (m, 1H, C(3)H**H′**), 1.27 (s, 3H, C(7)H_3), 0.04 (s, 9H, 3 x C(14)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.5 (C(1)), 143.5 (C(12)), 133.5 (C(13)), 67.7 (C(8)), 61.2 (C(6)), 49.5 (C(10)), 41.1 (C(11)), 37.0 (C(4)), 36.0 (C(2)), 30.9 (C(9)), 27.9 (C(5)), 25.5 (C(3)), 23.8 (C(7)), -1.0 (C(14)); **HRMS** (ESI+): found 278.1707, $[MH]^+$ $C_{16}H_{27}O_2Si^+$ requires 278.1702.

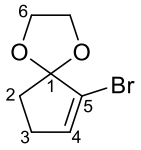
(±)-3-(6-methyl-3-oxo-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propanal, 4.107



For this reaction, the $InCl_3$ was stirred on a high vac for 18 h beforehand, and the DCM was put over sieves for 18 h and then degassed using the freeze-pump-thaw technique. At 0 °C, to a stirred solution of TMS enol ether **4.103** (100 mg, 0.45 mmol) in DCM (0.25 mL), was added premixed acrolein (30 μL, 0.45 mmol) and $InCl_3$ (5 mg, 0.02 mmol) in DCM (8.5 mL) dropwise *via* a syringe pump. The reaction was stirred at RT for 18 h and then quenched with H_2O (10 mL), extracted with DCM (3 x 10 mL), and the solvent removed *in vaccuo* before purification using column chromatography (10% Et_2O in pentane) to give compound **4.107** as a colourless oil (23 mg, 25%).

R_f 0.16 (25% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1735 s, 1708 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.5 Hz, 1H, C(13)H), 5.34 – 5.28 (m, 1H, C(8)H), 2.51 – 2.29 (m, 5H, C(2)H_2, C(3)**H**H′, C(5)**H**H′, C(9)**H**H′), 2.12 – 1.87 (m, 8H, C(3)H**H′**, C(4)H, C(5)H**H′**, C(9)H**H′**, C(11)H_2, C(12)H_2), 1.68 (s, 3H, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.5 (C(1)), 201.8 (C(13)), 131.4 (C(6)), 116.4 (C(8)), 38.9 (C(10)), 37.2 (C(4)), 35.8 (C(3)), 30.2 (C(2)), 29.8 (C(9)), 29.5 (C(11)), 27.4 (C(5)), 24.8 (C(12)), 23.4 (C(7)); configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 207.1381, $[MH]^+$ $C_{13}H_{19}O_2^+$ requires 207.1380.

6-Bromo-1,4-dioxaspiro[4.4]non-6-ene, 4.110



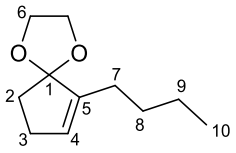
Method A: Using Dean Stark apparatus, to a stirred solution of ketone **4.85** (5.00 g, 25.5 mmol) in toluene (150 mL) was added ethylene glycol (3.50 mL, 63.8 mmol) and pTsOH.H_2O (49 mg, 0.26 mmol). The resulting mixture was stirred at 110 °C for 48 h, during which H_2O (15 mL) was collected. The reaction mixture was cooled and then washed through a silica plug with Et_2O. Removal of solvent and then purification by column chromatography (20% Et_2O in pentane) gave compound **4.110** as a colourless oil (2.54 g, 50%).

Method B: To a stirred solution of ketone **4.85** (10.00 g, 62.52 mmol) in toluene (100 mL) was added ethylene glycol (10.0 mL, 161.5 mmol), pTsOH.H_2O (1.00 g, 5.75 mmol) and triethyl orthoformate

(20.0 mL, 181.75 mmol). The resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was cooled and the solvent removed *in vaccuo*. Purification by column chromatography (60% Et_2O in pentane) gave the title compound as a colourless oil (11.0 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (m, 1H, C(4)H), 4.24 – 4.15 (m, 2H, 2 x C(6)**H**H′), 4.04 – 3.94 (m, 2H, 2 x C(6)H**H′**), 2.37 (m, 2H, C(3)H_2), 2.23 – 2.12 (m, 2H, C(2)H_2); **^{13}C NMR** (101 MHz, CDCl3) δ 136.8 (C(4)), 124.0 (C(5)), 117.8 (C(1)), 66.0 (C(6)), 34.5 (C(2)), 28.8 (C(3)). Spectroscopic data in agreement with literature.[359]

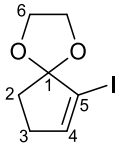
6-Butyl-1,4-dioxaspiro[4.4]non-6-ene, 4.112



This was a side product in attempts to make **4.111**.

R_f 0.68 (25% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1337 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.70 – 5.68 (m, 1H, C(4)H), 4.03 – 3.89 (m, 4H, 2 x C(6)H_2), 2.32 – 2.26 (m, 2H, C(3)H_2), 2.06 – 1.97 (m, 4H, C(2)H_2, C(7)H_2), 1.49 (quin, *J* = 7.5 Hz, 2H, C(8)H_2), 1.35 (h, *J* = 7.5 Hz, 2H, C(9)H_2), 0.91 (t, *J* = 7.3 Hz, 3H, C(10)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13C NMR (101 MHz, CDCl3) δ 143.7 (C(5)), 130.1 (C(4)), 66.0 (C(6)), 35.8 (C(2) or C(7)), 30.2 (C(8)), 27.9 (C(3)), 25.1 (C(2) or C(7)), 22.9 (C(9)), 14.1 (C(10)); **HRMS** (ESI+): not found.

6-Iodo-1,4-dioxaspiro[4.4]non-6-ene, 4.113

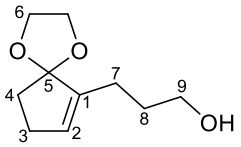


At −78 °C, to a stirred solution of bromo-ketal **4.110** (483 mg, 2.35 mmol) in THF (12 mL) was added butyllithium (1.5 mL, 2.35 mmol). The reaction was stirred at −78 °C for 20 min and then I_2 (1.3 g,

5.12 mmol) was added. The reaction was stirred at RT for 1 h and then quenched with sat. aq. $Na_2S_2O_3$ (15 mL) and extracted with DCM (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (40% Et_2O in pentane) to give compound **4.113** as a yellow oil (478 mg, 80%).

R_f 0.65 (40% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1315 m, 1167 m, 1152 m, 1045 s, 1029 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.41 (t, *J* = 2.5 Hz, 1H, C(4)H), 4.31 – 4.13 (m, 2H, 2 x C(6)**H**H′), 4.03 – 3.91 (m, 2H, 2 x C(6)H**H′**), 2.48 – 2.40 (m, 2H, C(3)H_2), 2.12 (t, *J* = 6.5 Hz, 2H, C(2)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.2 (C(4)), 119.8 (C(1)), 99.8 (C(5)), 65.9 (C(6)), 33.3 (C(2)), 31.8 (C(3)); **HRMS** (ESI+): found 252.9719, $[MH]^+$ $C_7H_9IO_2^+$ requires 252.9720.

3-(1,4-Dioxaspiro[4.4]non-6-en-6-yl)propan-1-ol, 4.114



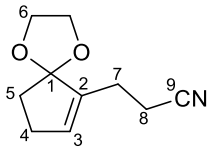
Method A: To a stirred solution of alkene **4.116** (500 mg, 3.00 mmol) in THF (3.0 mL) was added 9-BBN (0.5 M in THF, 6 mL, 3.00 mmol), and the reaction stirred at 50 °C for 18 h. At RT, NaOH (3 M in water, 3.5 mL, 10.52 mmol) and H_2O_2 (30% in water, 1.2 mL, 10.52 mmol) were added and the reaction stirred for a further 2 h, before quenching with $Na_2S_2O_3$ (5 mL) and extracting with Et_2O (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* before purification using column chromatography (75% Et_2O in pentane) to give compound **4.114** as a colourless oil (161 mg, 32%).

Method B: To a stirred solution of $NaBH_4$ (750 mg, 19.80 mmol) in methanol (20 mL) was added ketal **4.121** (900 mg, 4.95 mmol) at 0 °C. The reaction was stirred at RT for 30 h and then quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give the title compound as a yellow oil (399 mg, 44%).

R_f 0.21 (80% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3416 br, 2935 m, 2877 m, 1450 w, 1321 w, 1214 m, 1142, s, 1041 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 – 5.75 (m, 1H, C(2)H), 4.04 – 3.92 (m, 4H, 2 x

C(6)H_2), 3.66 (q, J = 6.0 Hz, 2H, C(9)H_2), 2.35 – 2.28 (m, 2H, C(3)H_2), 2.17 – 2.10 (m, 2H, C(7)H_2), 2.05 – 1.99 (m, 2H, C(4)H_2), 1.84 – 1.74 (m, 2H, C(8)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.5 (C(1)), 131.6 (C(2)), 120.6 (C(5)), 65.3 (C(6)), 62.6 (C(9)), 35.7 (C(4)), 31.4 (C(8)), 28.1 (C(3)), 21.6 (C(7)); **HRMS** (ESI+): found 185.1173, $[MH]^+$ $C_{10}H_{17}O_3^+$ requires 185.1172.

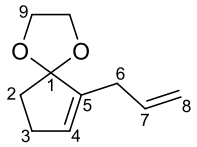
3-(1,4-Dioxaspiro[4.4]non-6-en-6-yl)propanenitrile, 4.115



A solution (solution 1) of iodo-ketal **4.113** (350 mg, 1.58 mmol) and acrylonitrile (5.2 mL, 79.00 mmol) in benzene (7.7 mL) was heated to 80 °C and stirred under reflux. Meanwhile, a solution (solution 2) of AIBN (31 mg, 0.18 mmol) and tributyltin hydride (0.50 mL, 1.89 mmol) in benzene (3.8 mL) was made at RT. Solution 2 was added to solution 1 in portions, 8 times at 30-min intervals. The resulting reaction mixture was then stirred at 80 °C for a further 18 h and then filtered, washing with DCM, and the solvent removed from the filtrate *in vaccuo*. Purification by column chromatography (40% Et_2O in pentane) gave compound **4.115** as a colourless oil (141 mg, 57%).

R_f 0.53 (100% Et_2O); **IR** ν_{max} (cm^{-1}) 2250 w, 1696 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.94 – 5.87 (m, 1H, C(4)H), 4.03 – 3.91 (m, 4H, 2 x C(6)H_2), 2.54 (t, *J* = 7.5 Hz, 2H, C(8)H_2), 2.42 (t, *J* = 7.5 Hz, 2H, C(7)H_2), 2.38 – 2.31 (m, 2H, C(3)H_2), 2.02 (t, *J* = 6.5 Hz, 2H, C(2)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.4 (C(5)), 133.8 (C(4)), 120.0 (C(9)), 119.8 (C(1)), 65.1 (C(6)), 35.5 (C(2)), 28.1 (C(3)), 22.2 (C(7)), 16.8 (C(8)); **HRMS** (ESI+): found 180.1020, $[MH]^+$ $C_{10}H_{13}NO_2^+$ requires 180.1019.

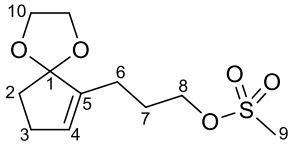
6-Allyl-1,4-dioxaspiro[4.4]non-6-ene, 4.116



At RT, to a stirred solution of bromo-ketal **4.110** (170 mg, 0.83 mmol) in DMF (4.2 mL) was added allyltributylstannane (1.0 mL, 3.32 mmol), bis(triphenylphosphine)palladium dichloride (29 mg, 0.04 mmol), triphenylphosphine (22 mg, 0.08 mmol) and lithium chloride (281 mg, 6.64 mmol). The resulting mixture was stirred at 140 °C for 3 h, then quenched with sat. aq. ammonium chloride (5 mL) and filtered through Celite®. The filtrate was poured into water (10 mL) and extracted with diethyl ether (3 x 15 mL), before being dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (10% Et_2O in pentane) to give compound **4.116** as a colourless oil (85 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.0, 10.0, 6.9 Hz, 1H, C(7)H), 5.76 – 5.68 (m, 1H, C(4)H), 5.15 – 5.00 (m, 2H, C(8)H_2), 4.04 – 3.89 (m, 4H, 2 x C(9)H_2), 2.84 – 2.75 (m, 2H, C(6)H_2), 2.35 – 2.26 (m, 2H, C(3)H_2), 2.09 – 2.00 (m, 2H, C(2)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0 (C(5)), 136.2 (C(7)), 131.7 (C(4)), 120.1 (C(1)), 115.9 (C(8)), 65.3 (C(9)), 35.8 (C(2)), 30.3 (C(6)), 28.0 (C(3)). Spectroscopic data in agreement with literature.[360]

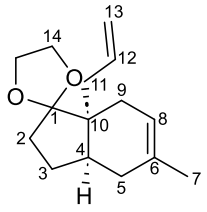
3-(1,4-dioxaspiro[4.4]non-6-en-6-yl)propyl methanesulfonate, 4.117



At RT, to a stirred solution of alcohol **4.114** (160 mg, 0.87 mmol) in DCM (5.0 mL) were added triethylamine (600 μL, 4.35 mmol) and mesyl chloride (135 μL, 1.74 mmol). The reaction was allowed to war to RT over 18 h and then quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (5% Et_2O in pentane) to give compound **4.117** as a colourless oil (168 mg, 76%).

R_f 0.57 (25% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1383 m, 1323 m, 1142 m, 1041 s, 1016 m, 956 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 – 5.74 (m, 1H, C(4)H), 4.26 (t, *J* = 6.5 Hz, 2H, C(8)H_2), 4.02 – 3.89 (m, 4H, 2 x C(10)H_2), 3.00 (s, 4H, C(9)H_3), 2.36 – 2.28 (m, 2H, C(3)H_2), 2.22 – 2.13 (m, 2H, C(6)H_2), 2.05 – 1.93 (m, 4H, C(7)H_2, C(2)H_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.4 (C(5)), 132.0 (C(4)), 120.2 (C(1)), 65.2 (C(10)), 37.5 (C(9)), 35.7 (C(2)), 28.0 (C(3)), 27.7 (C(6)), 21.6 (C(6)); **HRMS** (ESI+): found 263.0944, $[MH]^+$ $C_{11}H_{19}O_5S^+$ requires 263.0948.

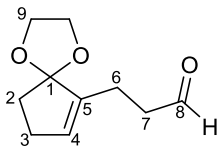
(±)-7a-Allyl-5-methyl-2,3,3a,4,7,7a-hexahydrospiro[indene-1,2′-[1,3]dioxolane], 4.119



To a stirred solution of anhydrous lithium perchlorate (308 mg, 2.89 mmol) in diethyl ether (0.5 mL) was added ketal **4.116** (30 mg, 0.18 mmol) and isoprene (72 μL, 0.72 mmol), and a solution of camphorsulfonic acid (0.42 mg, 0.0018 mmol) in THF (4 μL). The resulting reaction mixture was stirred at RT for 1 h and then quenched with triethylamine (50 μL, 0.16 mmol), diluted with H_2O (5 mL) and extracted with Et_2O (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.119** as a colourless oil (11 mg, 26%).

R_f 0.65 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1684 w, 1637 w, 1437 m, 1043 s, 909 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C(12)H), 5.35 – 5.26 (m, 1H, C(8)H), 5.01 – 4.86 (m, 2H, C(13)H_2), 4.01 – 3.80 (m, 4H, 2 x C(14)H_2), 2.19 – 2.00 (m, 4H, C(9)H_2, C(11)H_2), 2.00 – 1.87 (m, 3H, C(2)**H**H′, C(5)H_2), 1.82 – 1.66 (m, 3H, C(3)H_2, C(4)H), 1.64 (s, 3H, C(7)H_3), 1.52 – 1.40 (m, 1H, C(2)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.8 (C(12)), 130.6 (C(6)), 120.8 (C(1)), 118.5 (C(8)), 115.5 (C(13)), 64.5 (C(14)) 45.6 (C(10)), 39.7 (C(11)), 37.3 (C(4)), 30.6 (C(2)), 29.8 (C(9)), 27.1 (C(5)), 26.0 (C(3)), 23.8 (C(7)); **HRMS** (ESI+): found 235.1692, $[MH]^+$ $C_{15}H_{22}O_2^+$ requires 235.1693.

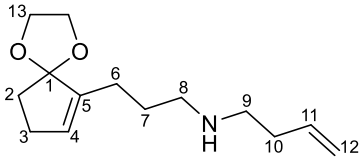
3-(1,4-Dioxaspiro[4.4]non-6-en-6-yl)propanal, 4.121



At RT, to a stirred solution of iodo-ketal **4.113** (2.5 g, 9.92 mmol) in DMF (140 mL) was added allyl alcohol (1.4 mL, 29.76 mmol), $NaHCO_3$ (2.2 g, 26.19 mmol), $^nBu_4NCl$ (2.9 g, 10.44 mmol) and $Pd(OAc)_2$ (47 mg, 0.21 mmol). The reaction was stirred at 100 °C for 18 h and then diethyl ether (100 mL) added and the mixture washed once with ice water (150 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (5% triethylamine, 10% Et_2O in pentane) to give compound **4.121** as a colourless oil (912 mg, 50%).

R_f 0.29 (40% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1723 m, 1676 m, 1386 m, 1143 s, 950 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz, 1H, C(8)H), 5.76 – 5.70 (m, 1H, C(4)H), 4.05 – 3.89 (m, 4H, 2 x C(9)H_2), 2.67 – 2.63 (m, 2H, C(7)H_2), 2.45 – 2.37 (m, 2H, C(6)H_2), 2.34 – 2.25 (m, 2H, C(3)H_2), 2.02 (t, J = 6.5 Hz, 2H, C(2)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.5 (C(8)), 141.5 (C(5)), 131.8 (C(5)), 120.1 (C(1)), 65.3 (C(9)), 42.4 (C(7)), 35.7 (C(2)), 28.0 (C(3)), 18.3 (C(6)); **HRMS** (ESI+): found 183.1015, $[MH]^+$ $C_{10}H_{14}O_3^+$ requires 183.1016.

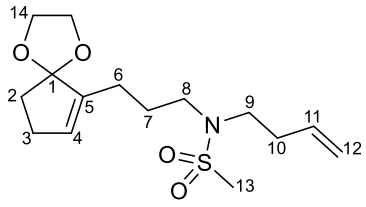
***N*-(3-(1,4-Dioxaspiro[4.4]non-6-en-6-yl)propyl)but-3-en-1-amine, 4.122**



At RT, to a stirred solution of aldehyde **4.121** (900 mg, 4.92 mmol) in MeOH (25 mL) was added but-3-en-1-amine (0.45 mL, 4.91 mmol). The reaction was stirred at RT for 1 h and then $NaBH_4$ (186 mg, 4.92 mmol) was added and the reaction stirred for another 1 h. The reaction was then quenched with NaOH solution (20 mL, 3.0 M) and extracted with DCM (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.122** as a colourless oil (906 mg, 81%).

R_f 0.29 (40% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1382 m, 1147 m, 911 m, 731 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 – 5.68 (m, 2H, C(4)H, C(11)H), 5.12 – 4.99 (m, 2H, C(12)H_2), 3.96 (m, 4H, 2 x C(13)H_2), 2.65 (m, 4H, C(8)H_2, C(9)H_2), 2.34 – 2.22 (m, 4H, C(3)H_2, C(10)H_2), 2.10 – 1.97 (m, 4H, C(2)H_2, C(6)H_2), 1.71 (tt, *J* = 8.8, 6.8 Hz, 2H, C(7)H_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (C(5)), 136.7 (C(11)), 130.6 (C(4)), 120.4 (C(1)), 116.3 (C(12)), 65.3 (C(13)), 49.9 (C(8)), 49.0 (C(9)), 35.8 (C(2)), 34.5 (C(10)), 28.5 (C(7)), 28.0 (C(3)), 23.2 (C(6)); **HRMS** (ESI+): found 238.1800, $[MH]^+$ $C_{14}H_{23}NO_2^+$ requires 238.1802.

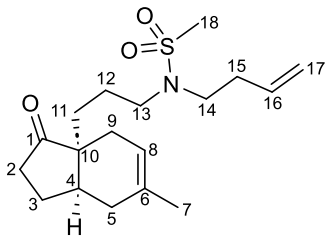
***N*-(3-(1,4-Dioxaspiro[4.4]non-6-en-6-yl)propyl)-*N*-(but-3-en-1-yl)methanesulfonamide, 4.123**



At RT, to a stirred solution of amine **4.122** (906 mg, 3.82 mmol) in DCM (30 mL) was added triethylamine (1.06 mL, 7.64 mmol) and mesyl chloride (0.30 mL, 3.82 mmol). The reaction was stirred at RT for 1 h and then quenched with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3 x 30 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by a silica plug, washing with Et_2O, to give compound **4.123** as a yellow oil (956 mg, 92%).

R_f 0.51 (Et_2O); **IR** ν_{max} (cm^{-1}) 1382 m, 1329 m, 1147 s, 956 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 – 5.69 (m, 2H, C(4)H, C(11)H), 5.16 – 5.03 (m, 2H, C(12)H_2), 4.03 – 3.89 (m, 4H, 2 x C(14)H_2), 3.31 – 3.17 (m, 4H, C(8)H_2, C(9)H_2), 2.83 (s, 3H, C(13)H_3), 2.41 – 2.25 (m, 4H, C(3)H_2, C(10)H_2), 2.11 – 2.03 (m, 2H, C(6)H_2), 2.02 – 1.97 (m, 2H, C(2)H_2), 1.89 – 1.77 (m, 2H, C(7)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0 (C(5)), 134.8 (C(11)), 131.4 (C(4)), 120.2 (C(1)), 117.4 (C(12)), 65.2 (C(14)), 47.8 (C(8)), 47.3 (C(9)), 38.8 (C(13)), 35.7 (C(2)), 33.5 (C(10)), 28.0 (C(3)), 26.9 (C(7)), 22.8 (C(6)); **HRMS** (ESI+): found 316.1574, $[MH]^+$ $C_{15}H_{25}NO_4S^+$ requires 316.1577.

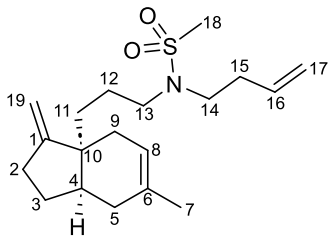
(±)-*N*-(But-3-en-1-yl)-*N*-(3-(6-methyl-3-oxo-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propyl)methanesulfonamide, 4.125



To a stirred solution of anhydrous lithium perchlorate (4.80 g, 45.7 mmol) in diethyl ether (11.5 mL) was added ketal **4.123** (900 mg, 2.85 mmol) and isoprene (1.67 mL, 11.41 mmol), and a solution of camphorsulfonic acid (33 mg, 0.14 mmol) in THF (0.29 mL). The resulting reaction mixture was stirred at 40 °C for 18 h and then diluted with H_2O (20 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.125** as a colourless oil (730 mg, 67%).

R_f 0.60 (Et_2O); **IR** ν_{max} (cm^{-1}) 1697 m, 1382 w, 1329 m, 1148 s ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C(16)H), 5.30 – 5.27 (m, 1H, C(8)H), 5.16 – 5.05 (m, 2H, C(17)H_2), 3.26 – 3.19 (m, 2H, C(14)H_2), 3.19 – 3.03 (m, 2H, C(13)H_2), 2.82 (s, 3H, C(18)H_3), 2.51 – 2.41 (m, 1H, C(2)**H**H′), 2.38 – 2.30 (m, 2H, C(15)H_2), 2.29 – 1.74 (m, 7H, C(2)H**H′**, C(4)H, C(5)**H**H′, C(9)H_2, C(11)H_2), 1.67 (s, 3H, C(7)H_3), 1.63 – 1.36 (m, 5H, C(3)H_2, C(5)H**H′**, C(12)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.9 (C(1)), 134.8 (C(16)), 131.6 (C(6)), 117.5 (C(17)), 116.9 (C(8)), 49.1 (C(10)), 48.5 (C(13)), 47.5 (C(14)), 38.7 (C(18)), 37.0 (C(4)), 36.2 (C(2)), 33.4 (C(15)), 30.1 (C(9)), 29.9 (C(12)), 28.2 (C(5)), 25.0 (C(11)), 23.9 (C(3)), 23.8 (C(7)); **HRMS** (ESI+): found 340.1941, $[MH]^+$ $C_{13}H_{21}NO_3S^+$ requires 340.1941.

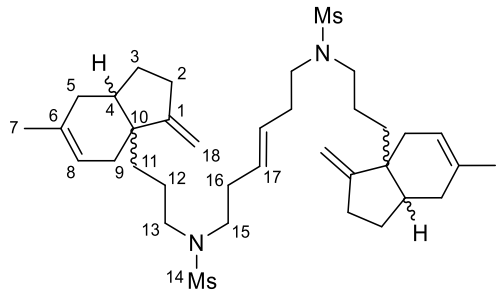
(±)-*N*-(But-3-en-1-yl)-*N*-(3-(6-methyl-3-methylene-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propyl)methanesulfonamide, 4.126



At −78 °C, potassium tert-butoxide (0.2 mL, 1 M in THF, 0.22 mmol) was added to triphenylmethylphosphonium bromide (90 mg, 0.26 mmol). The reaction was stirred at this temperature for 5 minutes and then ketone **4.125** (15 mg, 0.06 mmol) in THF (0.2 mL) was added. The reaction was stirred at reflux for 18 h and then quenched with water (1 mL) and extracted with diethyl ether (3 x 2 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (25% Et_2O in pentane) to give compound **4.126** as a yellow oil (17 mg, quant.).

R_f 0.63 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1382 m, 1333 m, 1148 s, 957 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C(17)H), 5.28 – 5.23 (m, 1H, C(8)H), 4.82 – 4.81 (m, 1H, C(19)**H**H′), 4.67 – 4.66 (m, 1H, C(19)H**H′**), 3.23 (td, *J* = 7.0, 1.5 Hz, 2H, C(15)H_2), 3.20 – 3.07 (m, 2H, C(13)H_2), 2.87 (s, 3 H, C(18)H_3), 2.82 (s, 3H, C(14)H_3), 2.54 – 2.43 (m, 1H, C(2)**H**H′), 2.39 – 2.23 (m, 3H, C(2)H**H′**, C(16)H_2), 2.09 – 1.67 (m, 5H, C(3)**H**H′, C(4)H, C(9)H_2), 1.64 (s, 3H, C(7)H_3), 1.63 – 1.25 (m, 7H, C(3)H**H′**, C(5)H_2, C(11)H_2, C(12)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4 (C(1)), 134.8 (C(17)), 131.3 (C(6)), 118.4 (C(8)), 117.8 (C(18)), 103.1 (C(19)), 48.6 (C(13)), 47.2 (C(15)), 45.3 (C(10)), 39.5 (C(4)), 38.7 (C(14)), 34.7 (C(5)), 33.4 (C(16)), 32.4 (C(9)), 30.7 (C(2)), 30.3 (C(11)), 28.3 (C(3)), 23.7 (C(7)), 23.0 (C(12)); **HRMS** (ESI+): found 338.2148, $[MH]^+$ $C_{14}H_{23}NO_2S^+$ requires 338.2148.

(*E*)-*N*-(3-(6-Methyl-3-methylene-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propyl)-*N*-(6-(*N*-(3-(6-methyl-3-methylene-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propyl)methylsulfonamido)hex-3-en-1-yl)methanesulfonamide, 4.128



This was a side product of attempts to make compound **4.127**. At RT, to a solution of triene **4.126** (10 mg, 0.044 mmol) in solvent (2 mL) was added catalyst (0.002 mmol) in solvent (1 mL). The reaction was stirred at temperature T for 18 h and then DCM added (2 mL) and washed with water (3 x 2 mL). The organic layers were combined, concentrated *in vaccuo* and then purified by column chromatography (60% Et_2O in pentane) to give the dimer **4.128** as a yellow oil.

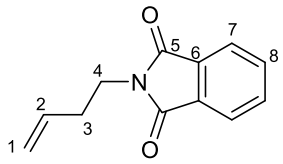
Method number	Solvent	Catalyst	T (°C)	Addition method
1	DCE	Grubbs II	60	Immediate
2	DCE	Hoveyda-Grubbs II	60	Immediate
3	Toluene	Grubbs II	110	Dropwise *via* syringe pump, 1 mL/h

Table 27: Conditions used to synthesise compound **4.128**.

R_f 0.16 (60% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2927 w, 1559 w, 1541 w, 1331 w, 1148 m, 912 s, 724 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.49 – 5.43 (m, 2H, 2 x C(17)H), 5.28 – 5.22 (m, 2H, 2 x C(8)H), 4.84 – 4.78 (m, 2H, 2 x (18)**H**H′), 4.67 – 4.63 (m, 2H, 2 x C(18)H**H′**), 3.22 – 3.08 (m, 8H, 2 x C(13)H_2, 2 x C(15)H_2), 2.82 – 2.78 (m, 6H, 2 x C(14)H_3), 2.54 – 2.22 (m, 8H, 2 x C(2)H_2, 2 x C(16)H_2), 2.08 – 1.67 (m, 10H, 2 x C(3)**H**H′, 2 x C(4)H, 2 x C(5)**H**H′, 2 x C(9)H_2), 1.64 (s, 6H, 2 x C(7)H_3), 1.61 – 1.28 (m, 12H, 2 x C(3)H**H′**, 2 x C(5)H**H′**, 2 x C(11)H_2, 2 x C(12)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5 (C(1)), 131.3 (C(6)), 129.1 (C(17)), 118.5 (C(8)), 103.1 (C(18)), 48.7 (C(13)), 47.6 (C(15)), 45.3 (C(10)), 39.7 (C(4)), 38.7 (C(14)), 34.7 (C(5)), 32.4 (C(16)), 31.1 (C(9)), 30.7 (C(11)), 30.3 (C(2)), 28.3

(C(7)), 23.8 (C(12)); **HRMS** (ESI+): found 661.4060, $[MH]^+$ $C_{36}H_{59}N_2O_4S_2^+$ requires 661.4067.

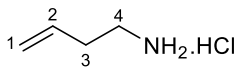
2-(3-Buten-1-yl)-1*H*-isoindole-1,3(2*H*)-dione



At RT, to a stirred solution of 4-bromo-1-butene (1.0 mL, 10.0 mmol) in acetonitrile (16 mL) were added potassium phthalimide (2.3 g, 12.5 mmol) and tetra-n-butylammonium bromide (160 mg, 0.5 mmol). The reaction was stirred at reflux for 5 h and then filtered to remove potassium salts. The solvent was removed in vaccuo. Water (20 mL) was added and the mixture extracted with diethyl ether (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered, evaporated *in vaccuo* and then purified by column chromatography (40% Et_2O in pentane) to give the *title compound* as a colourless solid (1.24 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H, 2 x C(7)H), 7.70 (m, 2H, 2 x C(8)H), 5.88 – 5.71 (m, 1H, C(2)H), 5.12 – 4.95 (m, 2H, C(1)H_2), 3.76 (td, *J* = 7.0, 2.5 Hz, 2H, C(4)H_2), 2.44 (q, *J* = 7.0 Hz, 2H, C(3)H_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5 (C(5)), 134.6 (C(2)), 134.0 (C(8)), 132.2 (C(6)), 123.3 (C(7)), 117.7 (C(1)), 37.5 (C(4)), 33.0 (C(3)). Spectroscopic data in agreement with literature.[361]

1-Aminobut-3-ene hydrochloride salt

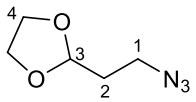


At RT, to a stirred solution of 2-(3-buten-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (1.24 mL, 6.18 mmol) in ethanol (30 mL) was added hydrazine monohydrate (0.6 mL, 12.34 mmol) dropwise. The reaction was stirred at reflux for 1 h and then cooled to RT and concentrated HCl (5 mL) added dropwise. The reaction was stirred for another 10 minutes at RT and then the white precipitate removed by filtration. The ethanol was removed *in vaccuo* and then water (30 mL) added, before extraction with diethyl ether (3 x 30 mL).

The aqueous layer was dried *in vaccuo* to give the *title compound* as a light brown solid (677 mg, quant.).

^{1}H NMR (400 MHz, D_2O) δ 5.84 (m, 1H, C(2)H), 5.31 – 5.20 (m, 1H, C(1)H_2), 3.11 (t, *J* = 7.0 Hz, 2H, C(4)H_2), 2.45 (q, *J* = 7.0 Hz, 2H, C(3)H_2). **^{13}C NMR** (101 MHz, D_2O) δ 133.2 (C(2)), 119.0 (C(1)), 38.6 (C(4)), 31.0 (C(3)). Spectroscopic data in agreement with literature.[362]

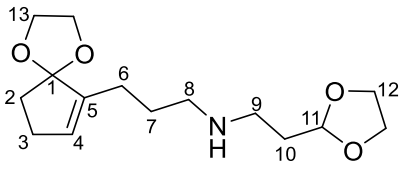
2-(2-Azidoethyl)-1,3-dioxolane, 4.141



At RT, to a stirred solution of 2-(2-bromoethyl)-1,3-dioxolane (1.0 mL, 8.52 mmol) in DMSO (13 mL), was added NaN_3 (1.1 g, 17.04 mmol). The reaction was stirred at 50 °C for 18 h and then cooled to RT, quenched with ice water (20 mL) and extracted with diethyl ether (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.141** as a pale yellow oil (1.2 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (t, *J* = 4.5 Hz, 1H, C(3)H), 4.01 – 3.95 (m, 2H, 2 x C(4)**H**H′), 3.90 – 3.84 (m, 2H, 2 x C(4)H**H′**), 3.42 (t, *J* = 7.0 Hz, 2H, C(1)H_2), 1.95 (td, *J* = 7.0, 4.5 Hz, 2H, C(2)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 102.0 (C(3)), 65.1 (C(4)), 46.6 (C(1)), 33.1 (C(2)). Spectroscopic data in agreement with literature.[363]

***N*-(2-(1,3-Dioxolan-2-yl)ethyl)-3-(1,4-dioxaspiro[4.4]non-6-en-6-yl)propan-1-amine, 4.142**

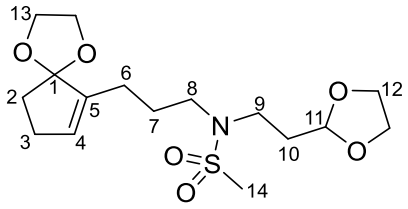


At RT, to a stirred solution of azide **4.141** (39 mg, 0.27 mmol) in THF (0.27 mL) was added triphenyl phosphine (71 mg, 0.27 mmol) in THF (0.27 mL). The reaction was stirred at RT for 3 h and then aldehyde **4.121** (50 mg, 0.27 mmol) added dropwise. The reaction was stirred at reflux for 1 h and then

cooled to RT and concentrated HCl (5 mL) added dropwise. After stirring for another 3 h at 66 °C, $NaBH_4$ (10 mg, 0.27 mmol) was added at 0 °C. The reaction was stirred for another 30 minutes at RT and then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with diethyl ether (3 x 5 mL), and the organic layers dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.142** as a brown oil (64 mg) which was used without further purification.

R_f 0.30 (Et_2O); **IR** ν_{max} (cm^{-1}) 2885 m, 1647 w, 1610 m, 1456 w, 1214 m, 1139 s, 1040 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.73 – 5.66 (m, 1H, C(4)H), 4.97 – 4.84 (m, 1H, C(11)H), 4.02 – 3.78 (m, 8H, 2 x $C(12)H_2$, 2 x $C(13)H_2$), 2.78 – 2.68 (m, 2H, $C(9)H_2$), 2.67 – 2.53 (m, 2H, $C(8)H_2$), 2.34 – 2.23 (m, 2H, $C(3)H_2$), 2.07 – 1.92 (m, 4H, $C(6)H_2$, $C(2)H_2$), 1.90 – 1.79 (m, 2H, $C(10)H_2$), 1.76 – 1.62 (m, 2H, $C(7)H_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (C(5)), 130.5 (C(4)), 120.3 (C(1)), 103.9 (C(11)), 65.2 (C(12)), 64.9 (C(13)), 49.9 (C(8)), 44.9 (C(9)), 35.7 (C(2)), 34.2 (C(10)), 28.4 (C(7)), 27.9 (C(3)), 23.2 (C(6)); **HRMS** (ESI+): found 284.1854, $[MH]^+$ $C_{15}H_{26}NO_4^+$ requires 284.1856.

***N*-(2-(1,3-Dioxolan-2-yl)ethyl)-*N*-(3-(1,4-dioxaspiro[4.4]non-6-en-6-yl)propyl)methanesulfonamide, 4.143**

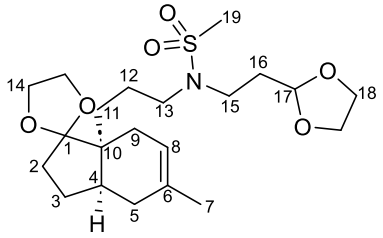


At 0 °C, to a stirred solution of amine **4.142** (64 mg, 0.23 mmol) in DCM (2.0 mL) was added triethylamine (74 μL, 0.46 mmol) and mesyl chloride (17 μL, 0.23 mmol). The reaction was stirred at RT for 1 h and then quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with DCM (3 x 5 mL), and the organic layers dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.143** as an orange oil (64 mg, 77% over two steps) which was used without further purification.

R_f 0.26 (Et_2O); **IR** ν_{max} (cm^{-1}) 2885 w, 1611 w, 1559 w, 1327 m, 1214 w, 1144 s, 1040 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 – 5.73 (m, 1H, C(4)H), 4.91 (t, J = 4.5 Hz, 1H, C(11)H), 4.03 – 3.82 (m, 8H,

2 x C(12)H_2, 2 x C(13)H_2), 3.39 – 3.31 (m, 2H, C(9)H_2), 3.24 – 3.18 (m, 2H, C(8)H_2), 2.83 (s, 3H, C(14)H_3), 2.36 – 2.27 (m, 3H, C(3)H_2), 2.10 – 2.03 (m, 2H, C(6)H_2), 2.03 – 1.97 (m, 4H, C(2)H_2, C(10)H_2), 1.89 – 1.80 (m, 2H, C(7)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0 (C(5)), 131.3 (C(4)), 120.2 (C(1)), 102.3 (C(11)), 65.2 (C(12)), 65.1 (C(13)), 48.0 (C(8)), 43.0 (C(9)), 38.4 (C(14)), 35.7 (C(2)), 33.3 (C(10)), 28.0 (C(3)), 26.9 (C(7)), 22.7 (C(6)); **HRMS** (ESI+): found 362.1627, $[MH]^+$ $C_{16}H_{28}NO_6S^+$ requires 362.1632.

(±)-*N*-(2-(1,3-dioxolan-2-yl)ethyl)-*N*-(3-(5-methyl-3,3a,4,7-tetrahydrospiro[indene-1,2′-[1,3]dioxolan]-7a(2*H*)-yl)propyl)methanesulfonamide, 4.144

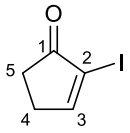


To a stirred solution of azide **4.141** (100 mg, 0.81 mmol) in THF (1.0 mL) was added triphenyl phosphine (190 mg, 0.81 mmol) in THF (1.0 mL). The reaction was stirred at RT for 3 h and then ketal **4.147** (190 mg, 0.81 mmol) added. The reaction was stirred at 66 °C for a further 3 h and then $NaBH_4$ (30 mg, 0.81 mmol) added at 0 °C. After stirring at RT for 30 min, the reaction was quenched with sat. aq. NH_4Cl (5 mL) and extracted with DCM (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give the title compound as a colourless oil. This was then immediately dissolved in DCM (5 mL) and triethylamine (112 μL, 0.81 mmol) and mesyl chloride (63 μL, 0.81 mmol) added. The reaction as stirred at RT for 18 h and then quenched with sat. aq. $NaHCO_3$ (5 mL) before extraction with DCM (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* before purification using column chromatography (1% triethylamine, 10% Et_2O in pentane) to give compound **4.144** as a colourless oil (184 mg, 74% over two steps).

R_f 0.50 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2980 w, 1653 w, 1437 m, 1327 m, 1172 s, 1121 s w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.30 (s, 1H, C(8)H), 4.90 (t, *J* = 4.5 Hz, 1H, C(17)H), 3.99 – 3.82 (m, 4H, 2 x C(14)H_2), 3.31 (t, *J* = 7.5 Hz, 2H, C(13)H_2), 3.10 (t, *J* = 7.5 Hz, 1H, C(15)H_2), 2.81 (s, 3H, C(19)H_3),

2.51 – 2.40 (m, 1H, C(2)**H**H′), 2.26 – 1.66 (m, 10H, C(2)H**H**′, C(3)H_2, C(4)H, C(5)**H**H′, C(9)H_2, C(11)**H**H′, C(12)H_2, C(16)H_2), 1.66 – 1.63 (m, 3H, C(7)H_3), 1.53 – 1.44 (m, 1H, C(5)H**H**′), 1.35 – 1.28 (m, 1H, C(11)H**H**′).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.8 (C(6)), 120.1 (C(1)), 118.1 (C(8)), 102.3 (C(17)), 65.2 (C(18)), 64.1 (C(14)), 63.4 (C(14)), 48.0 (C(13)), 44.2 (C(10)), 43.0 (C(15)), 40.1 (C(4)), 38.4 (C(19)), 33.9 (C(9)), 33.3 (C(16)), 30.5 (C(3)), 30.3 (C(11)), 26.9 (C(12) and (C(5)), 26.0 (C(2)), 23.8 (C(7)); **HRMS** (ESI+): found 430.2254, $[MH]^+$ $C_{21}H_{36}NO_6S^+$ requires 430.2258.

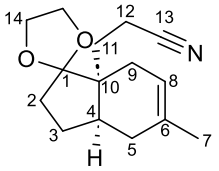
2-Iodocyclopent-2-en-1-one, **4.145**



This was a side product in attempts to make compound **4.115**.

R_f 0.60 (75% Et_2O in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 3.0 Hz, 1H, C(3)H), 2.80 – 2.75 (m, 2H, C(4)H_2), 2.54 – 2.47 (m, 2H, C(5)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.1 (C(1)), 169.6 (C(2)), 103.1 (C(3)), 31.4 (C(4)), 31.1 (C(5)). Spectroscopic data in agreement with literature.[364]

(±)-3-(5-Methyl-3,3a,4,7-tetrahydrospiro[indene-1,2′-[1,3]dioxolan]-7a(2*H*)-yl)propanenitrile, 4.146

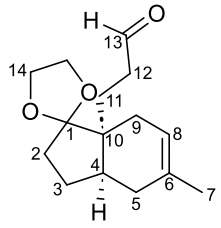


To a stirred solution of anhydrous lithium perchlorate (4.80 g, 45.60 mmol) in diethyl ether (9.0 mL) were added ketal **4.115** (500 mg, 2.81 mmol) and isoprene (1.12 mL, 11.20 mmol), and a solution of camphorsulfonic acid (7 mg, 0.03 mmol) in THF (0.03 mL). The resulting reaction mixture was stirred at RT for 18 h and then quenched with triethylamine (5 mL) and H_2O (20 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* before

purification using column chromatography (20% Et_2O in pentane) to give compound **4.146** as a colourless oil (206 mg, 30%).

R_f 0.50 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2250 w, 1715 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 – 5.25 (m, 1H, C(8)H), 4.03 – 3.81 (m, 4H, 2 x C(14)H_2), 2.50 – 2.30 (m, 2H, C(12)H_2), 2.10 – 1.98 (m, 3H, C(3)**H**H′, C(4)H, C(9)**H**H′), 1.92 – 1.66 (m, 7H, C(2)H**H′**, C(C(3)H**H′**, C(5)H_2, C(9)H**H′**, C(11)H_2), 1.64 (s, 3H, C(7)H_3), 1.52 – 1.41 (m, 1H, C(2)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.9 (C(6)), 121.2 (C(13)), 120.2 (C(1)), 117.6 (C(8)), 64.0 (C(14)), 44.1 (C(10)), 39.5 (C(4)), 33.5 (C(5)), 30.2 (C(3)), 28.1 (C(11)), 26.3 (C(9)), 25.9 (C(2)), 23.7 (C(7)), 12.5 (C(12)); **HRMS** (ESI+): found 248.1644, $[MH]^+$ $C_{15}H_{22}NO_2^+$ requires 248.1645.

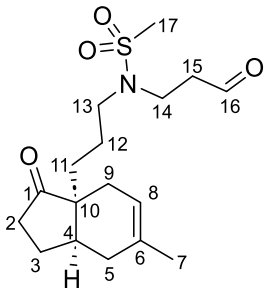
(±)-3-(5-Methyl-3,3a,4,7-tetrahydrospiro[indene-1,2′-[1,3]dioxolan]-7a(2*H*)-yl)propanal, 4.147



To a stirred solution of ketal **4.146** (200 mg, 0.86 mmol) in DCM (8.5 mL) was added DIBAL-H (1 M in cyclohexane, 0.98 mL, 0.98 mmol) at −78°C. The reaction mixture was stirred at −78°C for 1 h and then quenched with sat. aq. NH_4Cl (10 mL), warmed to RT over 10 min, stirred at RT for 1 h and extracted with Et_2O (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give compound **4.147** as a colourless oil (170 mg, 84%).

R_f 0.30 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2960 m, 2886 m, 1719 s, 1456 m, 1437 m, 1155 s, 1031 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (t, *J* = 1.9 Hz, 1H, C(11)H), 5.34 – 5.18 (m, 1H, C(8)H), 4.01 – 3.76 (m, 4H, 2 x C(14)H_2), 2.58 – 2.39 (m, 2H, C(12)H_2), 2.13 – 1.65 (m, 10H, C(2)**H**H′, C(3)H_2, C(4)H, C(5)H_2, C(9)H_2, C(11)H_2), 1.63 (s, 3H, C(7)H_3), 1.56 – 1.37 (m, 1H, C(2)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.8 (C(13)), 130.8 (C(6)), 120.1 (C(1)), 118.1 (C(8)), 64.1 (C(14)), 63.4 (C(14)), 44.2 (C(10)), 40.1 (C(4)), 39.5 (C(12)), 33.9 (C(9)), 30.5 (C(3)), 26.9 (C(5)), 26.0 (C(2)), 24.2 (C(11)), 23.8 (C(7)); **HRMS** (ESI+): found 251.1642, $[MH]^+$ $C_{15}H_{23}O_3^+$ requires 251.1642.

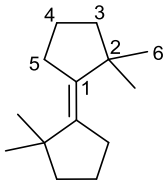
(±)-*N*-(3-(6-methyl-3-oxo-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propyl)-*N*-(3-oxopropyl)methanesulfonamide, 4.149



To a stirred solution of diacetal **4.144** (150 mg, 0.35 mmol) in acetone (1.0 mL), was added HCl (1.0 M in water, 1.05 mL, 1.05 mmol) dropwise. The reaction was stirred at RT for 18 h and then extracted with DCM (3 x 5 mL), and the solvent removed *in vaccuo* before purification using column chromatography (50% Et_2O in pentane) to give compound **4.149** as a colourless oil (89 mg, 75%).

R_f 0.08 (Et_2O); **IR** ν_{max} (cm^{-1}) 2960 w, 1732 s, 1437 m, 1328 s, 1149 s, 723 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 – 9.72 (m, 1H, C(16)H), 5.26 – 5.21 (m, 1H, C(8)H), 3.50 – 3.34 (m, 2H, C(13)H_2), 3.15 – 3.01 (m, 2H, C(14)H_2), 2.85 – 2.72 (m, 5H, C(15)H_2, C(17)H_3), 2.46 – 2.33 (m, 1H, C(2)**H**H′), 2.21 – 1.74 (m, 6H, C(2)H**H′**, C(3)**H**H′, C(4)H, C(5)H_2, C(9)**H**H′, C(11)**H**H′), 1.64 – 1.60 (m, 3H, C(7)H_3), 1.59 – 1.48 (m, 3H, C(3)H**H′**, C(9)H**H′**, C(12)**H**H′), 1.44 – 1.26 (m, 2H, C(11)H**H′**, C(12)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.9 (C(1)), 201.8 (C(13)), 131.6 (C(6)), 116.9 (C(8)), 49.1 (C(10)), 48.5 (C(13)), 42.2 (C(14)), 38.7 (C(17)), 37.0 (C(4)), 36.2 (C(2)), 30.1 (C(9)), 29.9 (C(12)), 28.2 (C(5)), 25.0 (C(11)), 24.8 (C(12)), 23.9 (C(3)), 23.8 (C(7)); **HRMS**: not found.

(*E*)-2,2,2′,2′-Tetramethyl-1,1′-bi(cyclopentylidene), 4.151

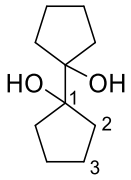


To a stirred solution of Zn dust (418 mg, 6.40 mmol) in THF (2.6 mL), was added $TiCl_4$ (0.32 mL,

2.95 mmol) dropwise. The reaction was stirred at 66 °C for 1 h and then 2,2-dimethyl cyclopentanone (0.1 mL, 0.80 mmol) was added at RT. The reaction was sonicated at 0 °C for 1 h and then stirred at 66 °C for a further 18 h. The reaction mixture was filtered and washed with DCM (10 mL), and the solvent removed *in vaccuo* before purification using column chromatography (pentane) to give compound **4.151** as a colourless oil (36 mg, 23%).

R_f 0.65 (pentane); **IR** ν_{max} (cm^{-1}) 2959 m, 1624 m, 1052 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.46 – 2.39 (m, 2H, C(5)H_2), 1.60 – 1.53 (m, 2H, C(4)H_2), 1.50 – 1.43 (m, 2H, C(3)H_2), 1.12 (s, 3H, C(6)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.5 (C(1)), 45.1 (C(3)), 43.7 (C(2)), 32.1 (C(5)), 26.8 (C(6)), 23.9 (C(4)); **HRMS** (ESI+): found 192.1878, $[MH]^+$ $C_{14}H_{24}^+$ requires 192.1878.

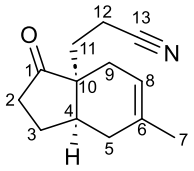
[1,1′-Bi(cyclopentane)]-1,1′-diol



A solution of activated Mg turnings (65 mg, 2.67 mmol) and $HgCl_2$ (20 mg, 0.07 mmol) in degassed THF (2.5 mL) was sonicated at 0 °C for 1 h and then $TiCl_4$ (0.11 mL, 1.00 mmol) added dropwise at −10 °C to give a yellow-green mixture. Cyclopentanone (60 μL, 0.66 mmol) was added as a solution in THF (1.65 mL), before refluxing stirring the reaction for 2 h at RT. The reaction mixture was quenched with sat. aq. K_2CO_3 (2 mL), stirred for another 15 min and then filtered through Celite®, washing with Et_2O (20 mL). The filtrate was washed with brine (10 mL) and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification by column chromatography (50% Et_2O in pentane) to give the *title compound* as a colourless solid (16 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (br s, 2H, 2 x OH), 1.89 – 1.78 (m, 4H, 2 x C(2)H_2), 1.77 – 1.67 (m, 4H, 2 x C(3)H_2), 1.67 – 1.55 (m, 8H, 2 x C(2)H_2, 2 x C(3)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 87.3 (C(1)), 36.5 (C(2)), 25.0 (C(3)). Spectroscopic data in agreement with literature.[365]

(±)-3-(6-Methyl-3-oxo-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propanenitrile, 4.152

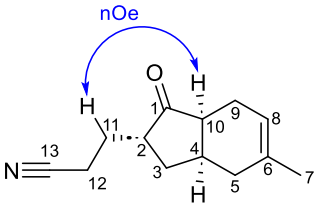


Method A: To a stirred solution of TMS enol ether **4.103** (100 g, 0.45 mmol) in DME (2.25 mL) was added methyllithium (1.6 M in hexanes, 0.28 mL, 0.45 mmol) at −78 °C. The reaction was stirred at 0 °C for 2 h and then acrylonitrile (30 μL, 0.45 mmol) was added and the reaction allowed to warm to RT over 18 h. After quenching with NH_4Cl (5 mL) and extracting with Et_2O (3 x 10 mL), the organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Finally, purification using column chromatography (10% Et_2O in pentane) gave compound **4.152** as a yellow oil (43 mg, 47%).

Method B: To a stirred solution of anhydrous lithium perchlorate (4.80 g, 45.60 mmol) in diethyl ether (9.0 mL) were added nitrile ketal number (500 mg, 2.81 mmol) and isoprene (1.12 mL, 11.20 mmol), and a solution of camphorsulfonic acid (7 mg, 0.03 mmol) in THF (0.03 mL). The resulting reaction mixture was stirred at RT for 18 h and then quenched with H_2O (20 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* before purification using column chromatography (20% Et_2O in pentane) to give compound **4.152** as a colourless oil (100 mg, 14%).

R_f 0.40 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2250 w, 1715 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.34 – 5.29 (m, 1H, C(8)H), 2.37 – 2.10 (m, 6H, C(3)H_2, C(4)H, C(9)**H**H′, C(12)H_2), 2.07 – 1.92 (m, 3H, C(2)**H**H′, C(5)**H**H′, C(11)**H**H′), 1.90 – 1.79 (m, 2H, C(9)H**H′**, C(11)H**H′**), 1.73 – 1.57 (m, 5H, C(2)H**H′**, C(5)H**H′**, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 219.5 (C(1)), 131.9 (C(6)), 116.2 (C(8)), 48.5 (C(10)), 37.2 (C(4)), 35.9 (C(3)), 29.8 (C(9)), 28.4 (C(11)), 27.1 (C(5)), 25.0 (C(2)), 23.7 (C(7)), 12.7 (C(12)); **HRMS** (ESI+): found 226.1198, $[MNa]^+$ $C_{13}H_{17}NONa^+$ requires 226.1202.

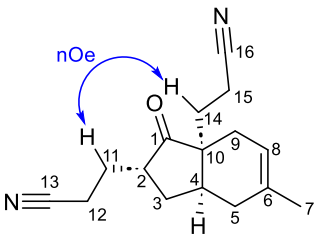
(±)-3-(5-Methyl-1-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl)propanenitrile, 4.153



This is a side product of attempts to make compound **4.152**.

R$_f$ 0.42 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2263 w, 1722 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.35 – 5.25 (m, 1H, C(8)H), 2.30 – 2.17 (m, 6H, C(3)H_2, C(4)H, C(9)**H**H′, C(12)H_2), 2.02 – 1.97 (m, 3H, C(2)**H**H′, C(5)**H**H′, C(11)**H**H′), 1.93 – 1.79 (m, 2H, C(9)H**H′**, C(11)H**H′**), 1.77 – 1.53 (m, 5H, C(2)H**H′**, C(5)H**H′**, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 218.0 (C(1)), 130.3 (C(6)), 116.6 (C(8)), 49.5 (C(2)), 35.2 (C(4)), 34.9 (C(3)), 29.8 (C(9)), 28.4 (C(11)), 26.6 (C(5)), 26.0 (C(10)), 23.6 (C(7)), 12.2 (C(12)); configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 226.1200, $[MNa]^+$ $C_{13}H_{17}NONa^+$ requires 226.1202.

(±)-3,3′-(6-Methyl-3-oxo-1,2,3,4,7,7a-hexahydro-3a*H*-indene-2,3a-diyl)dipropanenitrile, 4.154

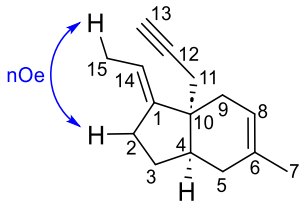


This is a side product of attempts to make compound **4.152**.

R$_f$ 0.45 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2259 w, 2200 m, 1715 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 – 5.29 (m, 1H, C(8)H), 2.33 – 2.11 (m, 7H, C(3)H_2, C(4)H, C(9)**H**H′, C(12)H_2, C(15)**H**H′), 2.07 – 1.93 (m, 6H, C(2)**H**H′, C(5)**H**H′, C(11)**H**H′, C(14)H_2, C(15)H**H′**), 1.93 – 1.79 (m, 2H, C(9)H**H′**, C(11)H**H′**), 1.73 – 1.57 (m, 5H, C(2)H**H′**, C(5)H**H′**, C(7)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 217.4 (C(1)), 133.3 (C(13)), 131.9 (C(6)), 116.1 (C(8)), 49.3 (C(10)), 44.5 (C(2)), 34.2 (C(4)), 32.2 (C(3)), 29.1 (C(9)), 28.1 (C(11)), 28.0 (C(14)), 27.1 (C(5)), 23.6 (C(7)), 12.7 (C(12)), 11.8 (C(12));

configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 257.1644, $[MH]^+$ $C_{16}H_{21}N_2O^+$ requires 257.1648.

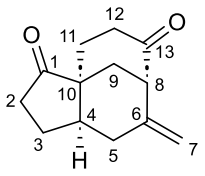
(±)-(*E*)-1-Ethylidene-5-methyl-7a-(prop-2-yn-1-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-indene, 4.155



To a stirred solution of ethyltriphenylphosphonium bromide (104 mg, 0.28 mmol) in THF (0.28 mL) was added KO*t*-Bu (0.28 mL, 1.0 M in THF, 0.28 mmol) at −78 °C. The resulting cloudy, yellow mixture was stirred at RT for 5 minutes and then intermediate **4.89** (35 mg, 0.19 mmol) was added. The reaction mixture was stirred for 18 h at 70 °C. Distilled water (10 mL) was added and the reaction was extracted with Et_2O (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (pentane) gave compound **4.155** as a colourless oil (23 mg, 65%).

R_f 0.75 (pentane); **IR** ν_{max} (cm^{-1}) 3100 m, 2304 s, 1622 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.35 – 5.26 (m, 2H, C(8)H, C(14)H), 2.46 – 2.30 (m, 2H, C(2)**H**H′, C(9)**H**H′), 2.27 – 2.17 (m, 1H, C(4)H), 2.03 – 1.94 (m, 1H, C(9)H**H′**), 1.88 (dt, *J* = 7.0, 1.5 Hz, 3H, C(15)H_3), 1.86 – 1.78 (m, 3H, C(2)H**H′**, C(11)**H**H′, C(13)H), 1.70 (s, 3H, C(7)H_3), 1.66 – 1.57 (m, 1H, C(3)**H**H′), 1.45 – 1.18 (m, 5H, C(3)H**H′**, C(11)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7 (C(1)), 131.7 (C(6)), 117.1 (C(8)), 117.0 (C(14)), 84.7 (C(12)), 75.8 (C(13)), 46.2 (C(4)), 44.9 (C(10)), 32.9 (C(9)), 31.8 (C(2)), 29.8 (C(11)), 28.9 (C(3)), 24.0 (C(7)), 13.7 (C(15)); alkene configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 201.1638, $[MH]^+$ $C_{16}H_{20}^+$ requires 201.1638.

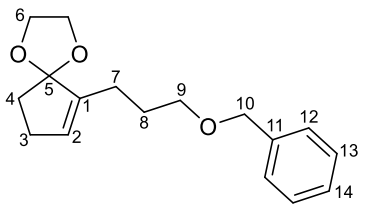
(±)-8-Methyleneoctahydro-3a,7-methanocyclopenta[8]annulene-3,6-dione, 4.160



A solution of ethyl 5-bromovalerate (0.1 mL, 0.63 mmol) and triphenylphosphine (157 mg, 0.60 mmol) in toluene (0.6 mL) was heated to 110 °C and refluxed for 18 h. After cooling to RT, white precipitate **4.158** formed (280 mg, quant.) and was filtered before re-suspending in THF (0.7 mL). At 0 °C, KO*t*-Bu (0.3 mL, 1.0 M in THF, 0.3 mmol) was added and stirred for 20 minutes. Compound **4.152** (40 mg, 0.2 mmol) was added and the reaction was heated to 66 °C for 15 h. After addition of H_2O (5 mL), the mixture was extracted with Et_2O (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo*. Purification by column chromatography (pentane) gave compound **4.160** as a colourless oil (26 mg, 65%).

R_f 0.26 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1732 s, 1740 s, 1651 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.55 (d, *J* = 1.0 Hz, 1H, C(7)**H**H′), 5.05 (d, *J* = 1.0 Hz, 1H, C(7)H**H′**), 3.03 – 2.99 (m, 1H, C(8)H), 2.45 – 2.22 (m, 6H, C(3)H_2, C(4)H, C(9)**H**H′, C(12)H_2), 2.01 – 1.92 (m, 3H, C(2)**H**H′, C(5)**H**H′, C(11)**H**H′), 1.89 – 1.74 (m, 2H, C(9)H**H′**, C(11)H**H′**), 1.70 – 1.59 (m, 2H, C(2)H**H′**, C(5)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 222.2 (C(1)), 212.7 (C(13)), 148.4 (C(6)), 104.5 (C(7)), 48.5 (C(10)), 38.4 (C(4)), 37.4 (C(3)), 33.7 (C(12)), 29.4 (C(9)), 28.1 (C(11)), 28.0 (C(5)), 25.9 (C(2)); **HRMS** (ESI+): found 204.1156, $[MH]^+$ $C_{13}H_{17}O_2^+$ requires 204.1150.

6-(3-(Benzyloxy)propyl)-1,4-dioxaspiro[4.4]non-6-ene, 4.161

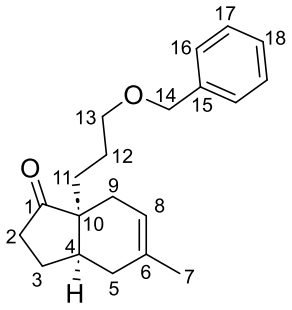


To a stirred solution of alcohol **4.115** (400 mg, 2.17 mmol) in THF (5.0 mL) was added NaH (60% in mineral oil, 130 mg, 3.26 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min and then benzyl

bromide (0.5 mL, 2.93 mmol) added. The reaction was stirred at RT for a further 18 h and then quenched with ice water and extracted with Et_2O (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* before purification using column chromatography (25% Et_2O in pentane) to give compound **4.161** as a colourless oil (349 mg, 59%).

R_f 0.77 (75% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3099 w, 3068 w, 3032 m, 1550 m, 1506 m; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H, 2 x C(12)H, 2 x C(13)H, C(14)H), 5.74 – 5.67 (m, 1H, C(2)H), 4.50 (s, 2H, C(10)H_2), 4.03 – 3.89 (m, 4H, 2 x C(6)H_2), 3.51 (t, *J* = 6.5 Hz, 2H, C(9)H_2), 2.34 – 2.24 (m, 2H, C(3)H_2), 2.16 – 2.07 (m, 2H, C(7)H_2), 2.05 – 1.97 (m, 2H, C(4)H_2), 1.90 – 1.80 (m, 2H, C(8)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9 (C(1)), 138.8 (C(11)), 130.7 (C(2)), 128.5 (C(12)), 127.7 (C(13)), 127.6 (C(14)), 120.4 (C(5)), 72.9 (C(10)), 70.3 (C(9)), 65.3 (C(6)), 35.8 (C(4)), 28.2 (C(8)), 28.0 (C(3)), 22.1 (C(7)); **HRMS** (ESI+): found 275.1623, $[MH]^+$ $C_{17}H_{23}O_3^+$ requires 275.1642.

(±)-7a-(3-(Benzyloxy)propyl)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one, 4.163

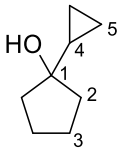


To a stirred solution of anhydrous lithium perchlorate (1.80 g, 17.52 mmol) in diethyl ether (4.4 mL) were added ketal **4.161** (300 mg, 1.09 mmol) and isoprene (0.44 mL, 4.38 mmol), and a solution of camphorsulfonic acid (13 mg, 0.05 mmol) in THF (0.55 mL). The resulting reaction mixture was stirred at 40 °C for 18 h and then H_2O (20 mL) was added. The reaction as stirred at RT for another 1 h before extraction with Et_2O (3 x 20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated *in vaccuo* before purification using column chromatography (25% Et_2O in pentane) to give compound **4.163** as a colourless oil (318 mg, 97%).

R_f 0.66 (40% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 2914 m, 1738 s, 1455 w, 1101 m; **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.39 – 7.23 (m, 5H, 2 x C(16)H, 2 x C(17)H, C(18)H), 5.37 – 5.27 (m, 1H, C(8)H), 4.47 (s, 2H, C(14)H_2), 3.44 – 3.40 (m, 2H, C(13)H_2), 2.61 – 2.53 (m, 1H,C(4)H), 2.34 – 2.08 (m, 3H, C(3)H_2, C(5)**H**H′), 1.93 – 1.75 (m, 4H, C(9)H_2, C(11)H_2), 1.65 (s, 3H, C(7)H_3), 1.63 – 1.35 (m, 5H, C(2)H_2, C(5)HH′, C(12)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 223.0 (C(1)), 138.7 (C(15)), 134.9 (C(6)), 128.5 (C(16)), 127.8 (C(17)), 127.6 (C(18)), 123.6 (C(6)), 72.9 (C(14)), 70.8 (C(13)), 50.2 (C(10)), 41.3 (C(4)), 36.8 (C(3)), 31.0 (C(2)), 26.8 (C(9)), 26.7 (C(11)), 26.1 (C(5)), 24.4 (C(12)), 23.8 (C(7)); **HRMS** (ESI+): found 299.2000, $[MH]^+$ $C_{20}H_{27}O_2^+$ requires 299.2006.

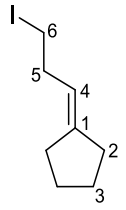
1-Cyclopropylcyclopentan-1-ol, 4.168



To form the Grignard reagent: to a stirred suspension of activated magnesium turnings (225 mg, 9.36 mmol) in THF (3.75 mL) was added cyclopropyl bromide (0.50 mL, 6.24 mmol) dropwise and catalytic 1,2-dibromoethane (27 μL, 0.31 mmol). The reaction was stirred at RT for 30 min, during which it became warm and was exothermic enough to sustain itself without the need for external heating. Separately, cyclopentanone (88 μL, 1.00 mmol) was solvated in THF (2.00 mL) and the prepared Grignard added at 0 °C. The reaction was stirred at RT for 3 h before quenching with H_2O (5 mL) and then extracting with Et_2O (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* to give compound **4.168** as a colourless oil (90 mg, 75%) which was used in the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 – 1.47 (m, 8H, 2 x C(2)H_2, 2 x C(3)H_2), 1.04 (tt, *J* = 8.5, 5.5 Hz, 1H, C(4)H), 0.41 – 0.34 (dt, *J* = 8.5, 5.5 Hz, 2H, 2 x C(5)**H**H′), 0.26 (q, *J* = 5.5 Hz, 2H, 2 x C(5)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 82.1 (C(1)), 38.4 (C(2)), 23.8 (C(3)), 20.0 (C(4)), 1.4 (C(5)). Spectroscopic data in agreement with literature.[366]

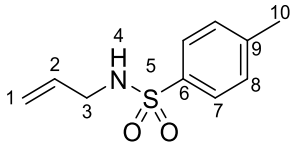
(3-Iodopropylidene)cyclopentane, 4.169



To a stirred solution of alcohol **4.168** (38 mg, 0.30 mmol) in Et_2O (0.30 mL), was added ZnI_2 (83 mg, 0.30 mmol) dropwise. The reaction was stirred at RT for 1 h and then 40 °C for another 1 h. The reaction was quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification using column chromatography (20% Et_2O in pentane) to give compound **4.169** as a colourless oil (16 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (tquin, *J* = 7.5, 2.5 Hz, 1H, C(4)H), 3.13 (t, *J* = 7.5 Hz, 2H, C(6)H_2), 2.56 (qquin, *J* = 7.5, 1.5 Hz, 2H, C(5)H_2), 2.24 – 2.14 (m, 4H, 2 x C(2)H_2), 1.72 – 1.57 (m, 4H, 2 x C(3)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5 (C(1)), 118.6 (C(4)), 34.2 (C(5)), 33.8 (C(2)), 29.0 (C(2)), 26.4 (C(3)), 6.3 (C(6)). Spectroscopic data in agreement with literature.[367]

***N*-Allyl-4-methylbenzenesulfonamide, 4.170**

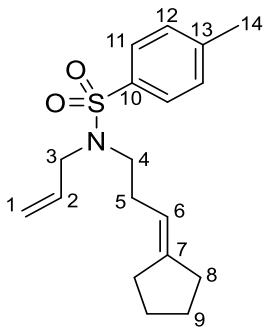


To a stirred solution of allyl amine (0.66 mL, 8.75 mmol) in DCM (25.0 mL), was added triethylamine (2.40 mL, 17.5 mmol) and tosyl chloride (1.00 g, 5.20 mmol) at 0 °C. The reaction was stirred at RT for 18 h and then quenched with aq. sat. NH_4Cl (25 mL) and extracted with DCM (3 x 25 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification by column chromatography (40% Et_2O in pentane) to give compound **4.170** as a colourless solid (1.08 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H, 2 x C(8)H), 7.31 (d, *J* = 8.0 Hz, 2H, 2 x C(7)H), 5.72 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H, C(2)H), 5.13 (m, 2H, C(1)H_2), 4.41 (t, *J* = 6.0 Hz, 1H, N(4)H), 3.59 (tt, *J* = 6.0, 1.5 Hz, 2H, C(3)H_2), 2.43 (s, 3H, C(10)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7

(C(6)), 137.1 (C(9)), 133.1 (C(2)), 129.9 (C(7)), 127.3 (C(8)), 117.9 (C(1)), 45.9 (C(3)), 21.7 (C(10)). Spectroscopic data in agreement with literature.[368]

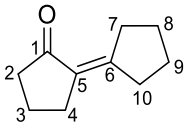
_N_-Allyl-_N_-(3-cyclopentylidenepropyl)-4-methylbenzenesulfonamide, 4.171



To a stirred solution of iodide **4.169** (8 mg, 0.03 mmol) and MW7.92C (14 mg, 0.06 mmol) in DMF (0.5 mL), was added NaH (1 mg, 0.03 mmol, 60% dispersion over mineral oil) at 0 °C. The reaction was stirred at RT for 18 h and then quenched with H_2O (5 mL) extracted with DCM (3 x 5 mL). The solvent was removed *in vaccuo* before purification using column chromatography (20% Et_2O in pentane) to give compound **4.171** as a colourless oil (5 mg, 52%).

R_f 0.61 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1347 m, 1162 s, 736 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H, 2 x C(11)H), 7.29 (d, *J* = 8.0 Hz, 2H, 2 x C(12)H), 5.65 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C(2)H), 5.21 – 5.08 (m, 3H, C(1)H_2, C(6)H), 3.82 (dt, *J* = 6.5, 1.5 Hz, 2H, C(3)H_2), 3.15 – 3.08 (m, 2H, C(4)H_2), 2.42 (s, 3H, C(14)H_3), 2.22 – 2.09 (m, 6H, C(5)H_2, C(8)H_2, C(9)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.2 (C(7)), 143.2 (C(10)), 137.5 (C(13)), 133.5 (C(2)), 129.7 (C(11)), 127.3 (C(12)), 118.7 (C(1)), 115.7 (C(6)), 50.7 (C(3)), 46.9 (C(4)), 33.8 (C(5)), 28.9 (C(8)), 28.8 (C(9)), 21.6 (C(14)); **HRMS** (ESI+): found 320.1679, $[MH]^+$ $C_{18}H_{26}NO_2S^+$ requires 320.1679.

[1,1′-Bi(cyclopentylidene)]-2-one, 4.172

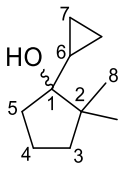


This was a side product obtained in the above reaction, when the commercially available Grignard

reagent was used, or when the organometallic was obtained from butyllithium and cyclopropyl bromide.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 – 2.74 (m, 2H, C(7)H_2), 2.56 – 2.49 (m, 2H, C(4)H_2), 2.33 – 2.25 (m, 4H, C(2)H_2, C(10)H_2), 1.91 (quin, *J* = 7.5 Hz, 2H, C(3)H_2), 1.76 – 1.63 (m, 4H, C(8)H2, C(9)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.6 (C(1)), 158.8 (C(5)), 128.0 (C(6)), 39.9 (C(2)), 34.4 (C(10)), 32.7 (C(7)), 29.7 (C(4)), 27.1 (C(8)), 25.4 (C(9)), 20.2 (C(3)). Spectroscopic data in agreement with literature.[369]

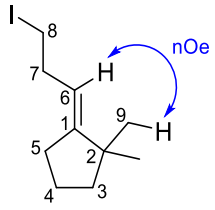
1-Cyclopropyl-2,2-dimethylcyclopentan-1-ol, 4.174



To 2,2-dimethylcyclopentanone (100 μL, 0.79 mmol) was added $LaCl_3$.2LiCl (1.3 mL, 0.6 M in THF, 0.79 mmol) and the mixture stirred at RT for 1 h. Meanwhile, to form the Grignard reagent: to a stirred suspension of activated magnesium turnings (57 mg, 2.37 mmol) in THF (0.95 mL) was added cyclopropyl bromide (127 μL, 1.58 mmol) dropwise and catalytic 1,2-dibromoethane (7 μL, 0.08 mmol). The reaction was stirred at RT for 30 min, during which it became warm and was exothermic enough to sustain itself without the need for external heating. The resultant Grignard was added dropwise to the 2,2-dimethylcyclopentanone solution at 0 °C. The reaction was stirred at RT for 3 h before quenching with H_2O (5 mL) and then extracting with DCM (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* to give compound **4.174** as a colourless oil (90 mg, 75%) which was used in the next reaction without further purification.

R_f 0.40 (20% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3400 br, 1104 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.79 – 1.37 (m, 6H, C(3)H_2, C(4)H_2, C(5)H_2), 1.01 (s, 3H, C(8)H_3), 0.95 (s, 3H, C(8′)H_3), 0.91 (m, 1H, C(6)H), 0.43 – 0.27 (m, 4H, 2 x C(7)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.3 (C(1)), 39.4 (C(5)), 38.6 (C(2)), 35.4 (C(3)), 25.4 (C(8)), 21.9 (C(8′)), 19.1 (C(4)), 15.2 (C(6)), 1.7 (C(7)), 0.1 (C(7′)); **HRMS** (ESI+): found 193.0979, $[MK]^+$ $C_{10}H_{18}OK^+$ requires 193.0989.

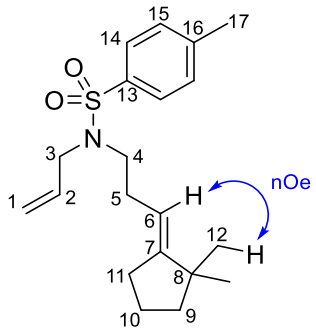
(*E*)-2-(3-Iodopropylidene)-1,1-dimethylcyclopentane, 4.175



To a stirred solution of alcohol **4.174** (62 mg, 0.40 mmol) in Et_2O (1.0 mL), was added ZnI_2 (130 mg, 0.40 mmol) dropwise. The reaction was stirred at RT for 1 h and then 40 °C for another 1 h. The reaction was quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification using column chromatography (10% Et_2O in pentane) to give compound **4.175** as a colourless oil (45 mg, 73%).

R_f 0.85 (20% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 909 s, 500 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.04 (tt, *J* = 7.0, 2.5 Hz, 1H, C(6)H), 3.13 (t, *J* = 7.0 Hz, 2H, C(8)H_2), 2.54 (qt, *J* = 7.0, 1.0 Hz, 2H, C(7)H_2), 2.30 (tdt, *J* = 7.5, 2.5, 1.0 Hz, 2H, C(5)H_2), 1.66 (quin, *J* = 7.5 Hz, 2H, C(4)H_2), 1.49 (t, *J* = 7.5 Hz, 2H, C(3)H_2), 1.03 (s, 6H, 2 x C(9)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.8 (C(1)), 116.9 (C(6)), 42.1 (C(3)), 40.0 (C(2)), 33.8 (C(7)), 29.5 (C(5)), 28.9 (C(9)), 22.4 (C(4)), 6.5 (C(8)); alkene configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): Not found.

(*E*)-*N*-Allyl-*N*-(3-(2,2-dimethylcyclopentylidene)propyl)-4-methylbenzenesulfonamide, 4.176

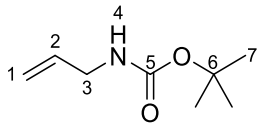


To a stirred solution of iodide **4.175** (12 mg, 0.05 mmol) and MW7.92C (10 mg, 0.05 mmol) in DMF (0.5 mL), was added NaH (1 mg, 0.07 mmol, 60% dispersion over mineral oil) at 0 °C. The reaction was stirred at RT for 18 h and then quenched with H_2O (5 mL) extracted with Et_2O (3 x 5 mL). The

organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification using column chromatography (10% Et_2O in pentane) to give compound **4.176** as a colourless oil (11 mg, 63%).

R_f 0.46 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1345 m, 738 s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H, 2 x C(14)H), 7.29 (d, *J* = 8.0 Hz, 2H, 2 x C(15)H), 5.64 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C(2)H), 5.22 – 5.10 (m, 2H, $C(1)H_2$), 4.96 (tt, *J* = 7.0, 2.5 Hz, 1H, C(6)H), 3.82 (dt, *J* = 6.5, 1.5 Hz, 2H, $C(3)H_2$), 3.14 – 3.06 (m, 2H, $C(4)H_2$), 2.42 (s, 3H, $C(17)H_3$), 2.24 (tdt, *J* = 7.5, 2.5, 1.0 Hz, 2H, $C(11)H_2$), 2.16 (qt, *J* = 7.0, 1.0 Hz, 2H, $C(5)H_2$), 1.67 – 1.58 (m, 2H, $C(10)H_2$), 1.46 (t, *J* = 7.0 Hz, 2H, $C(9)H_2$), 0.98 (s, 6H, 2 x $C(12)H_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6 (C(7)), 143.2 (C(13)), 137.6 (C(16)), 133.6 (C(2)), 129.8 (C(14)), 127.3 (C(15)), 118.7 (C(1)), 113.9 (C(6)), 50.7 (C(3)), 46.9 (C(3)), 42.2 (C(9)), 42.0 (C(8)), 29.3 (C(11)), 18.9 (C(12)), 28.8 (C(5)), 22.5 (C(10)), 21.6 (C(17)); alkene configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 400.1704, $[MK]^+$ $C_{21}H_{31}NO_2SK^+$ requires 400.1707.

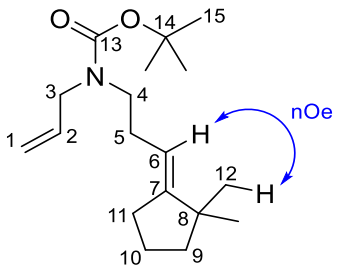
tert-Butyl allylcarbamate



To a stirred solution of allyl amine (0.13 mL, 1.75 mmol) in DCM (5.0 mL), was added triethylamine (0.48 mL, 3.50 mmol) and Boc anhydride (255 mg, 1.17 mmol) at 0 °C. The reaction was stirred at RT for 18 h and then quenched with aq. sat. NH_4Cl (5 mL) and extracted with DCM (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification by column chromatography (40% Et_2O in pentane) to give the *title compound* as a colourless solid (131 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 2H, $C(1)H_2$), 5.23 – 5.06 (m, 1H, C(2)H), 4.58 (br s, 1H, N(4)H), 3.75 (t, *J* = 6.5 Hz, 1H, $C(3)H_2$), 1.45 (s, 9H, 3 x $C(7)H_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9 (C(5)), 135.1 (C(2)), 115.9 (C(1)), 77.4 (C(6)), 43.2 (C(3)), 28.5 (C(7)). Spectroscopic data in agreement with literature.[370]

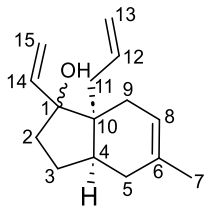
***tert*-Butyl (*E*)-allyl(3-(2,2-dimethylcyclopentylidene)propyl)carbamate**



To a stirred solution of iodide **4.175** (12 mg, 0.05 mmol) and MW7.91C (8 mg, 0.05 mmol) in DMF (0.5 mL), was added NaH (4 mg, 0.1 mmol, 60% dispersion over mineral oil) at 0 °C. The reaction was stirred at RT for 18 h and then quenched with H_2O (5 mL) extracted with Et_2O (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification using column chromatography (10% Et_2O in pentane) to give the *title compound* as a colourless oil (5 mg, 40%).

R_f 0.43 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1700 s; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.81 – 5.73 (m, 1H, C(2)H), 5.15 – 5.01 (m, 3H, C(1)H_2, C(6)H), 3.87 – 3.73 (m, 2H, 4)H_2), 3.24 – 3.09 (m, 2H, C(4)H_2), 2.34 – 2.28 (t, *J* = 7.0 Hz, 2H, C(11)H_2), 2.21 – 2.14 (q, *J* = 7.0 Hz, 2H, C(5)H_2), 1.64 (quin, *J* = 7.0 Hz, 2H, C(10)H_2), 1.49 – 1.42 (m, 11H, C(9)H_2, 3 x C(15)H_3), 1.01 (s, 6H, 2 x C(12)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7 (C(13)), 134.5 (C(2)), 125.8 (C(7)), 116.3 (C(1)), 114.7 (C(6)), 64.6 (C(14)), 49.8 (C(3)), 46.4 (C(4)), 42.3 (C(9)), 41.9 (C(8)), 29.3 (C(11)), 28.8 (C(12)), 28.7 (C(5)), 28.5 (C(15)), 22.3 (C(10)); alkene configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 316.2249, $[MNa]^+$ $C_{18}H_{31}NO_2Na^+$ requires 316.2247.

(±)-7a-Allyl-5-methyl-1-vinyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ol, 4.177

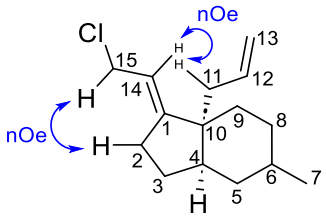


To ketone **4.91** (372 mg, 1.98 mmol) was added $LaCl_3$.2LiCl (6.5 mL, 0.6 M in THF, 3.96 mmol) and the mixture stirred at RT for 1 h. Then vinyl magnesium bromide (1.98 mL, 1.98 mmol) was added

dropwise to the solution at 0 °C. The reaction was stirred at RT for 3 h before quenching with H_2O (5 mL) and then extracting with Et_2O (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vaccuo* to give single (unassigned) diastereomer **4.177** as a colourless oil (432 mg, 96%) which was used in the next reaction without further purification.

R_f 0.50 (25% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3477 br, 3074 w, 1637 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.12 (dd, *J* = 17.5, 10.5 Hz, 1H, C(14)H), 5.97 – 5.85 (m, 1H, C(12)H), 5.36 – 5.31 (m, 1H, C(8)H), 5.22 (dd, *J* = 17.5, 1.5 Hz, 1H, C(15)**H**H′), 5.08 (dd, *J* = 10.5, 1.5 Hz, 1H, C(15)H**H′**), 5.01 – 4.93 (m, 2H, C(13)H_2), 2.16 – 1.65 (m, 10H, C(2)H_2, C(3)**H**H′, C(4)H, C(5)H_2, C(12)H_2, C(11)H_2), 1.63 (s, 3H, C(7)H_3), 1.59 – 1.44 (m, 1H, C(3)H**H′**); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (C(14)), 135.4 (C(12)), 130.8 (C(6)), 118.8 (C(8)), 117.3 (C(13)), 111.6 (C(15)), 86.0 (C(1)), 46.7 (C(10)), 40.3 (C(4)), 38.5 (C(11)), 36.4 (C(2)), 31.4 (C(9)), 26.7 (C(3)), 25.9 (C(5)), 23.6 (C(7)); **HRMS** (ESI+): found 219.1752, $[MH]^+$ $C_{15}H_{22}O^+$ requires 219.1743.

(±)-*E*)-7a-Allyl-1-(2-chloroethylidene)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene, 4.178

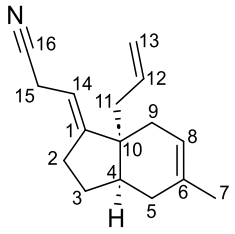


To alcohol **4.177** (10 mg, 0.046 mmol) in DCM (0.4 mL) was added pyridine (7 µL, 0.092 mmol) and thionyl chloride (8 µL, 0.115 mmol) at 0 °C and the mixture stirred at RT for 30 minutes. The reaction was quenched with $NaHCO_3$ (1 mL) and then extracted with DCM (3 x 1 mL). The organic layer was concentrated *in vaccuo* to give compound **4.178** as a colourless oil (11 mg, quant.) which was used in the next reaction without further purification.

R_f 0.81 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3076 w, 3006 w, 1668 w, 1639 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H, C(12)H), 5.39 (tt, *J* = 8.0, 2.5 Hz, 1H, C(14)H), 5.27 – 5.20 (m, 1H, C(8)H), 5.06 – 4.95 (m, 2H, C(13)H_2), 4.09 (dt, *J* = 8.0, 1.5 Hz, 2H, C(15)H_2), 2.52 (ddt, *J* = 17.5, 9.0, 2.5 Hz, 1H, C(2)**H**H′), 2.35 – 2.26 (m, 1H, C(2)H**H′**), 2.24 (dt, *J* = 7.0, 1.5 Hz, 2H,

C(11)H_2), 2.11 – 2.00 (m, 1H, C(9)**H**H′), 1.98 – 1.89 (m, 2H, C(4)H, C(5)**H**H′), 1.82 – 1.74 (m, 1H, C(9)H**H**′), 1.74 – 1.67 (m, 1H, C(3)H**H**′), 1.65 (s, 3H, C(7)H_3), 1.62 – 1.55 (m, 1H, C(5)H**H**′), 1.55 – 1.39 (m, 1H, C(3)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9 (C(1)), 135.1 (C(12)), 131.2 (C(6)), 117.9 (C(8)), 116.9 (C(13)), 115.1 (C(14)), 49.7 (C(10)), 42.5 (C(15)), 39.5 (C(11)), 39.1 (C(4)), 33.9 (C(5)), 29.8 (C(9)), 27.9 (C(3)), 26.7 (C(2)), 23.8 (C(7)); alkene configuration assigned by NOESY correlations (blue arrows); **HRMS** (ESI+): found 237.1403 and 239.1373, $[MH]^+$ $C_{15}H_{22}Cl^+$ requires 237.1405 and 239.1376.

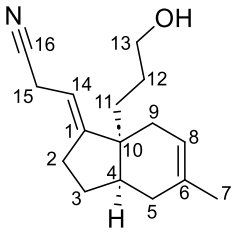
(±)-3-(7a-Allyl-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ylidene)propanenitrile, 4.179



To allylic chloride **4.178** (176 mg, 0.074 mmol) in DMSO (8 mL) was added sodium cyanide (48 mg, 0.93 mmol) and the mixture stirred at RT for 1 h. The reaction was quenched with H_2O (15 mL) and then extracted with Et_2O (3 x 15 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification using column chromatography (5% Et_2O in pentane) to give compound **4.179** as a yellow oil (100 mg, 59%).

R_f 0.32 (10% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3076 w, 3015 w, 2249 m, 1640 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 (dddd, *J* = 16.7, 10.2, 8.2, 6.3 Hz, 1H, C(12)H), 5.19 – 5.14 (m, 1H, C(8)H), 5.09 – 5.03 (m, 1H, C(14)H), 4.99 – 4.90 (m, 2H, C(13)H_2), 2.96 (dt, *J* = 6.5, 1.5 Hz, 2H, C(15)H_2), 2.40 – 2.30 (m, 1H, C(2)**H**H′), 2.22 – 2.10 (m, 3H, C(2)H**H**′, C(11)H_2), 2.02 – 1.61 (m, 6H, C(3)**H**H′, C(4)H, C(5)H_2, C(9)**H**H′), 1.58 (s, 3H, C(7)H_3), 1.56 – 1.50 (m, 1H, C(9)H**H**′), 1.49 – 1.39 (m, 1H, C(3)H**H**′); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7 (C(1)), 134.8 (C(12)), 131.2 (C(6)), 125.6 (C(16)), 117.8 (C(8)), 117.1 (C(13)), 106.5 (C(14)), 49.7 (C(10)), 39.4 (C(4)), 39.3 (C(11)), 33.8 (C(9)), 29.8 (C(5)), 27.8 (C(3)), 27.2 (C(2)), 23.7 (C(7)), 17.1 (C(15)); **HRMS** (ESI+): found 228.1747, $[MH]^+$ $C_{16}H_{22}N^+$ requires 228.1747.

(±)-3-((*E*)-7a-(3-Hydroxypropyl)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ylidene)propanenitrile, 4.180

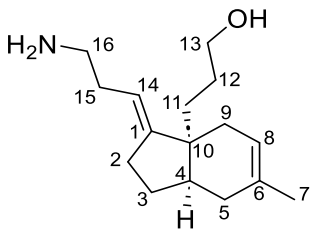


To alkene **4.179** (150 mg, 0.66 mmol) in DCM (2.0 mL) was added $[Ir(cod)Cl]_2$ (9 mg, 0.010 mmol), dppb (9mg, 0.020 mmol) and pinacolborane (116 μL, 0.79 mmol) and the mixture stirred at RT for 24 h. Then H_2O_2 (2.0 mL) and NaOH (2.0 mL) were added, and the orange solution became a grey suspension. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and then extracted with Et_2O (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vaccuo* before purification using column chromatography (20% Et_2O in pentane) to give compound **4.180** as a yellow oil (93 mg, 59%).

R_f 0.43 (Et_2O); **IR** ν_{max} (cm^{-1}) 3450 br, 2977 m, 2944 w, 2250 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21 (m, 1H, C(8)H), 5.05 (tt, *J* = 7.0, 2.5 Hz, 1H, C(14)H), 3.59 (t, *J* = 6.5 Hz, 2H, C(13)H_2), 3.01 (d, *J* = 7.0 Hz, 2H, C(15)H_2), 2.47 – 2.37 (m, 1H, C(2)**H**H′), 2.27 – 2.15 (m, 1H, C(2)H**H′**), 2.12 – 1.88 (m, 4H, C(3)**H**H′, C(4)H, C(5)**H**H′, C(11)**H**H′), 1.84 – 1.72 (m, 1H, C(5)H**H′**), 1.63 (s, 3H, C(7)H_3), 1.60 – 1.35 (m, 4H, C(3)H**H′**, C(9)H**H′**, C(12)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8 (C(1)), 131.0 (C(6)), 119.7 (C(16)), 118.7 (C(16)), 118.0 (C(8)), 106.0 (C(14)), 63.6 (C(13)), 45.5 (C(10)), 39.2 (C(4)), 34.5 (C(11)), 30.8 (C(9)), 30.0 (C(5)), 27.9 (C(3)), 27.3 (C(2)), 27.1 (C912)), 23.7 (C(7)), 17.1 (C(15)); **HRMS** (ESI+): Not found.

(±)-3-(*E*)-3-(3-Aminopropylidene)-6-methyl-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propan-1-

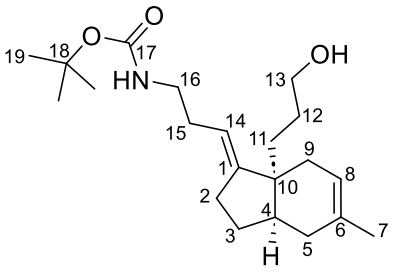
ol, 4.181



To nitrile **4.180** (90 mg, 0.37 mmol) in Et_2O (2.0 mL) was added $LiAlH_4$ (28 mg, 0.73 mmol) and the mixture stirred at RT for 24 h. The reaction was quenched with H_2O (0.03 mL), NaOH (15%, 0.03 mL) and further H_2O (0.18 mL), and stirred for 5 min before filtering through a Celite® plug and concentrating *in vaccuo* to give compound **4.181** as a yellow oil (45 mg, 50%).

R_f 0.11 (Et_2O); **IR** ν_{max} (cm^{-1}) 3363 br, 1659 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.22 (m, 1H, C(8)H), 5.07 – 5.00 (m, 1H, C(14)H), 3.63 – 3.54 (m, 2H, C(13)H_2), 2.73 (t, *J* = 6.5 Hz, 2H, C(16)H_2), 2.46 – 2.35 (m, 1H, C(2)**H**H′), 2.23 – 1.88 (m, 7H, C(2)H**H'**, C(4)H, C(5)H_2, C(9)**H**H′, C(15)H_2), 1.83 – 1.66 (m, 4H, C(3)**H**H′, C(9)H**H′**, C(11)H_2), 1.63 (s, 3H, C(7)H_3), 1.60 – 1.45 (m, 3H, C(3)H**H′**, C(12)H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8 (C(1)), 131.0 (C(6)), 118.2 (C(8)), 115.5 (C(14)), 63.3 (C(13)), 45.7 (C(10)), 41.9 (C(16)), 39.0 (C(4)), 34.9 (C(5)), 32.9 (C(15)), 30.8 (C(3)), 30.2 (C(9)), 28.2 (C(11)), 27.5 (C(12)), 27.2 (C(2)), 23.6 (C(7)); **HRMS** (ESI+): found 272.1994, $[MNa]^+$ $C_{16}H_{27}NONa^+$ requires 272.1985.

(±)-*tert*-Butyl (3-((*E*)-7a-(3-hydroxypropyl)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ylidene)propyl)carbamate, 4.182

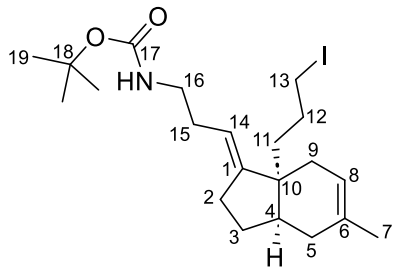


To amine **4.182** (50 mg, 0.20 mmol) in DCM (0.5 mL) was added Boc_2O (43 mg, 0.20 mmol) and triethylamine (34 μL, 0.24 mmol), and the mixture stirred at RT for 24 h before quenching with sat. aq.

NH_4Cl (5 mL), extracting with DCM (3 x 5 mL), drying over $MgSO_4$, concentrating *in vaccuo* and finally purification *via* column chromatography (20% Et_2O in pentane) to give compound **4.182** as a colourless oil (25 mg, 36%).

R_f 0.09 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3369 br, 1693 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.23 – 5.20 (m, 1H, C(8)H), 4.97 (tt, *J* = 7.0, 2.5 Hz, 1H, C(14)H), 3.63 – 3.50 (m, 2H, C(13)H_2), 3.12 (m, 2H, C(16)H_2), 2.44 – 2.32 (m, 1H, C(2)**H**H′), 2.21 – 1.87 (m, 8H, C(2)**H**H′, C(4)H, C(5)**H**H′, C(9)**H**H′, C(11)H_2, C(15)H_2), 1.80 – 1.65 (m, 2H, C(3)**H**H′, C(9)H**H**′), 1.62 (s, 3H, C(7)H_3), 1.59 – 1.44 (m, 4H, C(3))H**H**′, C(5)H**H**′, C(12)H_2), 1.42 (s, 9H, 3 x C(19)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.2 (C(1)), 150.9 (C(17)), 131.1 (C(6)), 118.5 (C(8)), 114.7 (C(14)), 79.3 (C(18)), 63.6 (C(13)), 45.0 (C(10)), 39.3 (C(4)), 34.9 (C(5)), 31.1 (C(11)), 30.5 (C(9)), 29.6 (C(15)), 28.6 (C(19)), 28.2 (C(3)), 27.3 (C(12)), 27.2 (C(2)), 23.7 (C(7)); **HRMS** (ESI+): found 350.2699, $[MH]^+$ $C_{21}H_{36}NO_3^+$ requires 350.2690.

(±)-*tert*-Butyl (3-((*E*)-7a-(3-iodopropyl)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ylidene)propyl)carbamate, 4.183

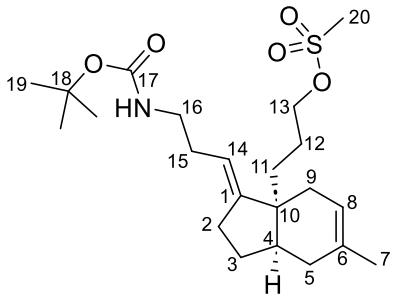


To triphenylphosphine (17 mg, 0.06 mmol) in DCM (0.33 mL) was added iodine (16 mg, 0.07 mmol) and imidazole (5 mg, 0.09 mmol). The reaction was stirred at RT for 10 min before adding alcohol **4.182** (11 mg, 0.03 mmol) in DCM (0.33 mL) and stirring at RT for 1 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with Et_2O (3 x 5 mL) before drying over $MgSO_4$ and purification *via* column chromatography (10% Et_2O in pentane) to give compound **4.183** as a yellow oil (14 mg, 93%).

R_f 0.83 (50% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 3414 w, 3391 w, 2974 m, 1718 s; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.24 – 5.19 (m, 1H, C(8)H), 4.99 (tt, *J* = 7.0, 2.5 Hz, 1H, C(14)H), 4.56 (s, 1H, NH), 3.21 –

3.04 (m, 4H, C(13)H_2, C(16)H_2), 2.43 – 2.33 (m, 1H, C(2)**H**H′), 2.21 – 2.10 (m, 3H, C(2)H**H′**, C(15)H_2), 2.08 – 1.93 (m, 3H, C(5)**H**H′, C(9)**H**H′, C(11)**H**H′), 1.91 – 1.83 (m, 1H, C(4)H), 1.81 – 1.73 (m, 2H, C(9)H**H′**, C(12)**H**H′), 1.69 (m, 2H, C(3)**H**H′, C(5)H**H′**), 1.63 (s, 3H, C(7)H_3), 1.59 – 1.56 (m, 2H, C(11)H**H′**, C(12)H**H′**), 1.48 – 1.45 (m, 1H, C(3)H**H′**), 1.43 (s, 9H, 3 x C(17)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0 (C(1)), 131.1 (C(6)), 118.4 (C(8)), 114.8 (C(14)), 46.2 (C(10)), 39.4 (C(16), C(4)), 32.1 (C(11)), 31.3 (C(3)), 30.4 (C(9)), 29.5 (C(15)), 28.6 (C(17)), 28.1 (C(5)), 27.4 (C(12)), 27.1 (C(2)), 23.7 (C(7)), 14/2 (C(13)); **HRMS** (ESI+): found 460.1705, $[MH]^+$ $C_{21}H_{35}INO_2^+$ requires 460.1707.

(±)-3-((*E*)-3-(3-((*tert*-Butoxycarbonyl)amino)propylidene)-6-methyl-1,2,3,4,7,7a-hexahydro-3a*H*-inden-3a-yl)propyl methanesulfonate, 4.184

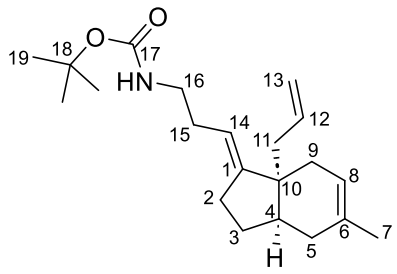


To alcohol **4.182** (25 mg, 0.07 mmol) in DCM (1.5 mL) was added triethylamine (33 μL, 0.24 mmol) and mesyl chloride (14 μL, 0.19 mmol). The reaction was stirred at RT for 30 min, during which a white precipitate formed. The reaction was quenched with diethyl ether (5 mL) and filtered through a Celite® plug before concentrating *in vaccuo* to give compound **4.184** as a brown oil (30 mg, 99%).

R_f 0.29 (75% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1722 s, 1599 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.18 – 5.13 (m, 1H, C(8)H), 4.89 (tt, *J* = 7.0, 3.5 Hz, 1H, C(14)H), 4.58 (br s, 1H, NH), 4.11 (t, *J* = 6.0 Hz, 2H, C(13)H_2), 3.12 – 3.05 (m, 2H, C(16)H_2), 2.94 (s, 3H, C(20)H_3), 2.33 (dd, *J* = 17.5, 9.0 Hz, 1H, C(2)**H**H′), 2.15 – 2.05 (m, 4H, C(2)H**H′**, C(4)H, C(15)H_2), 2.01 – 1.58 (m, 6H, C(3)**H**H′, C(5)**H**H′, C(9)H_2, C(11)H_2), 1.58 – 1.56 (m, 5H, C(7)H_3, C(12)H_2), 1.56 – 1.49 (m, 2H, C(3)H**H′**, C(5)H**H′**), 1.36 (s, 9H, 3 x C(19)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.5 (C(1)), 150.5 (C(17)), 131.5 (C(6)), 118.0 (C(8)), 114.0 (C(14)), 79.2 (C(18)), 71.0 (C(13)), 45.7 (C(10)), 39.7 (C(4)), 37.4 (C(20)), 34.0 (C(5)), 31.6 (C(11)), 30.1 (C(9)), 29.0 (C(15)), 28.0 (C(19)), 28.9 (C(3)), 27.9 (C(12)), 27.9 (C(2)),

23.2 (C(7)); **HRMS** (ESI+): found 428.2455, $[MH]^+$ $C_{22}H_{38}NO_5S^+$ requires 428.2465.

(±)-*tert*-Butyl (3-((*E*)-7a-allyl-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-ylidene)propyl)carbamate, 4.185

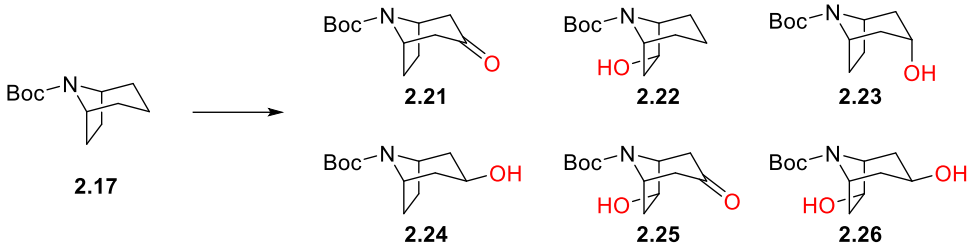


This was a side product of a reaction attempting to make **4.187**. To mesylate **4.184** (30 mg, 0.07 mmol) in THF (1.5 mL), was added KO*t*-Bu (1.0 M in THF, 0.64 mL, 0.64 mmol) at 0 °C. The reaction was stirred at RT for 30 min before quenching carefully with 1 M HCl (5 mL) and extracted with DCM (3 x 5 mL). The organic phases were dried over $MgSO_4$, concentrated *in vaccuo* and purified *via* column chromatography (20% Et_2O in pentane) to give compound **4.185** as a yellow oil (14 mg, 60%).

R_f 0.70 (75% Et_2O in pentane); **IR** ν_{max} (cm^{-1}) 1744 s, 1666 w, 1602 w; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78 – 5.64 (m, 1H, C(12)H), 5.26 – 5.19 (m, 1H, C(8)H), 5.05 – 4.92 (m, 3H, C(13)H, C(14)H), 3.17 – 3.09 (m, 2H, C(16)H_2), 2.43 – 2.33 (m, 1H, C(2)**H**H′), 2.22 – 2.12 (m, 6H, C(2)H**H′**, C(3)**H**H′, C(5)**H**H′, C(9)**H**H′, C(15)H_2), 2.08 – 1.85 (m, 3H, C(3)H**H′**, C(4)H, C(5)H**H′**), 1.79 – 1.66 (m, 3H, C(9)H**H′**, C(11)H_2), 1.63 (ds, 3H, C(7)H_3), 1.43 (s, 9H, 3 x C(19)H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.5 (C(1)), 150.5 (C(17)), 134.7 (C(12)), 131.7 (C(6)), 117.7 (C(13)), 117.0 (C(8)), 114.0 (C(14)), 79.2 (C(18)), 49.3 (C(10)), 37.3 (C(11)), 36.9 (C(4)), 36.3 (C(2)), 30.0 (C(9)), 29.0 (C(15)), 28.0 (C(19)), 27.3 (C(5)), 25.5 (C(3)), 23.1 (C(7)); **HRMS** (ESI+): found 370.2221, $[MK]^+$ $C_{21}H_{33}NO_2K^+$ requires 370.2143.

Appendices

A: Enzyme screening data for *tert*-butyl 8-azabicyclo[3.2.1]octane-8-carboxylate 2.17



Enzyme	Conv.	2.24	2.23	2.22	2.21	2.25	2.26	Others
GVQ	100%	20%	1%	12%	4%	16%	12%	34%
R19/F87I	100%	13%		75%		10%		2%
K19/F87V	100%			3%		30%	23%	43%
K19/F87V/Q403P	100%	11%		8%		28%	20%	33%
RLYF/KSK19/A184I	100%					22%	70%	8%
RK/A184I/I263G/A328G	100%	6%	1%	19%	1%	45%	15%	13%
RK/I263G/A328G	99%	1%		3%		69%	18%	9%
RK/A184I/A264G	99%	11%	5%	3%	29%	15%	14%	24%
GV/A184I/I263G	99%	17%		11%		67%	1%	3%
GV/A184I/A328G	99%	25%		8%	19%	23%	15%	11%
GV/A184I/I263G/A328G	99%	2%	1%	10%		81%	2%	3%
GVQ/A328G	98%	51%	1%	19%	10%	8%	3%	8%
KSK19/A82M/A264G	98%	2%	74%	2%	22%			1%
K19/F87V/I263G	98%	30%	5%	30%	1%	29%	1%	4%
K19/F87V/I263G	97%	4%		11%		55%	19%	12%
GVQ/V78L/I263G	97%	23%	14%	39%		7%		17%
RLYF/KSK19	97%	4%	6%	4%	2%	15%	41%	27%
GV/A184I/A264G	97%	49%	13%	23%	7%	2%		6%
RK/I263G/A264G	97%	43%	2%	24%	7%	7%	1%	16%
K19/F87V/A328V	96%	1%	56%	5%	2%			36%
KSK19/F81W	96%	12%	15%	13%	16%	5%	16%	23%
KSK19/A82M	96%	8%	83%	2%	6%			1%
GV/A184I	95%	37%	9%	27%	5%	10%	2%	10%
KSK19/I263A	94%	46%	16%	29%	3%	4%		2%
RK/I263G/A264G	94%	35%	2%	22%	7%	10%	2%	22%
RK/G265GG	92%	19%		75%		6%		
RK/A184I/I263G/A264G	92%	46%	1%	26%	4%	5%	1%	17%
RK/A184I/I263G/A264G/A328G	88%	46%	1%	32%	4%	8%	1%	9%

KSK19/A82M/I263G/A328G	88%	66%	2%	25%	2%	5%	
RK/A328G/P329G/A330G	71%	33%	11%	36%		2%	18%
GV/A184I/I263G/A264G	68%	50%	8%	38%			4%
GVQ/I263G/A328L	66%	3%	81%		17%		
KSK19/A82M/I263G	64%	73%	2%	26%			
GV/A184I/I263G/A264G/A328G	64%	53%		45%			2%
KSK19/A82M/I263G/A264G	63%	54%	10%	30%	3%		3%
GVQ/I263G/A264G	63%	61%	1%	33%	1%		4%
RK/A328G	61%	42%	31%	17%	10%		
KSK19/A82M/A264G/A328G	55%	18%	69%	9%	3%		1%
KSK19/A82M/A330W	49%		78%	13%			9%
GV/A184I/A264G/A328G	47%	73%	4%	22%	2%		
GVQ/I263G/A264G/A328G	45%	46%	3%	49%			2%
RK/A184I/A264G/A328G	45%	55%	16%	22%	6%		2%
R19/I263A/A328L	33%		96%	4%			
KSK19/A82M/I263G/A264G/A328G	31%	59%	1%	38%	1%		2%
RT2	22%		91%	9%			
R19/A330W	8%		100%				
RP/V78I/E267V	6%		70%				30%
KU3/A328I /A330P	3%		100%				

Table 28: Conversion and selectivity data for the P450 screening of substrate **4.17**.

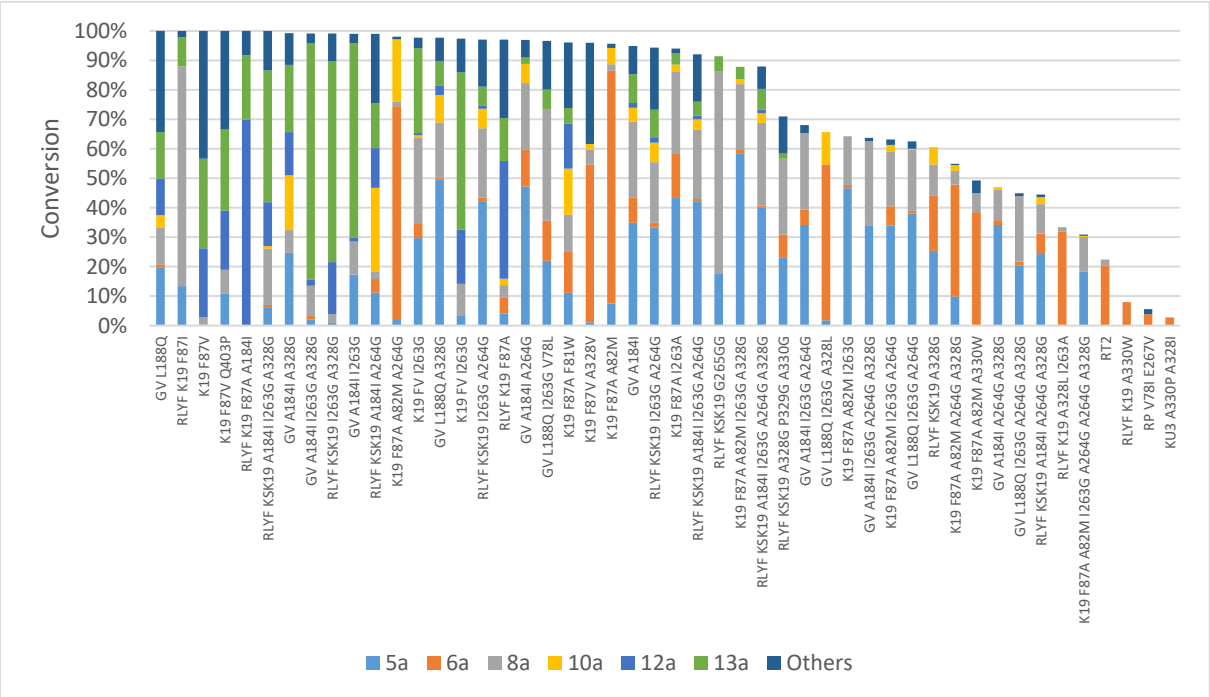
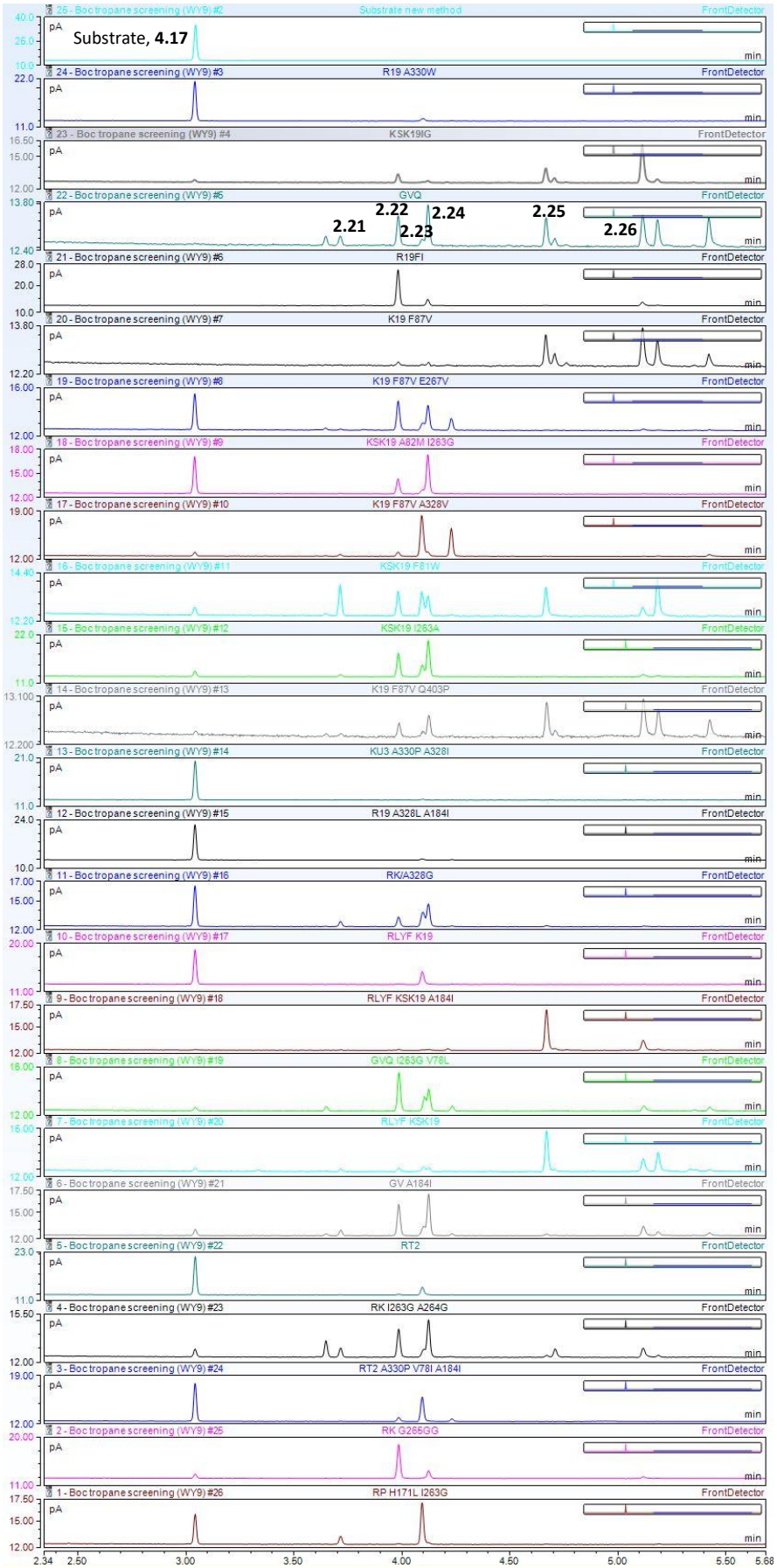
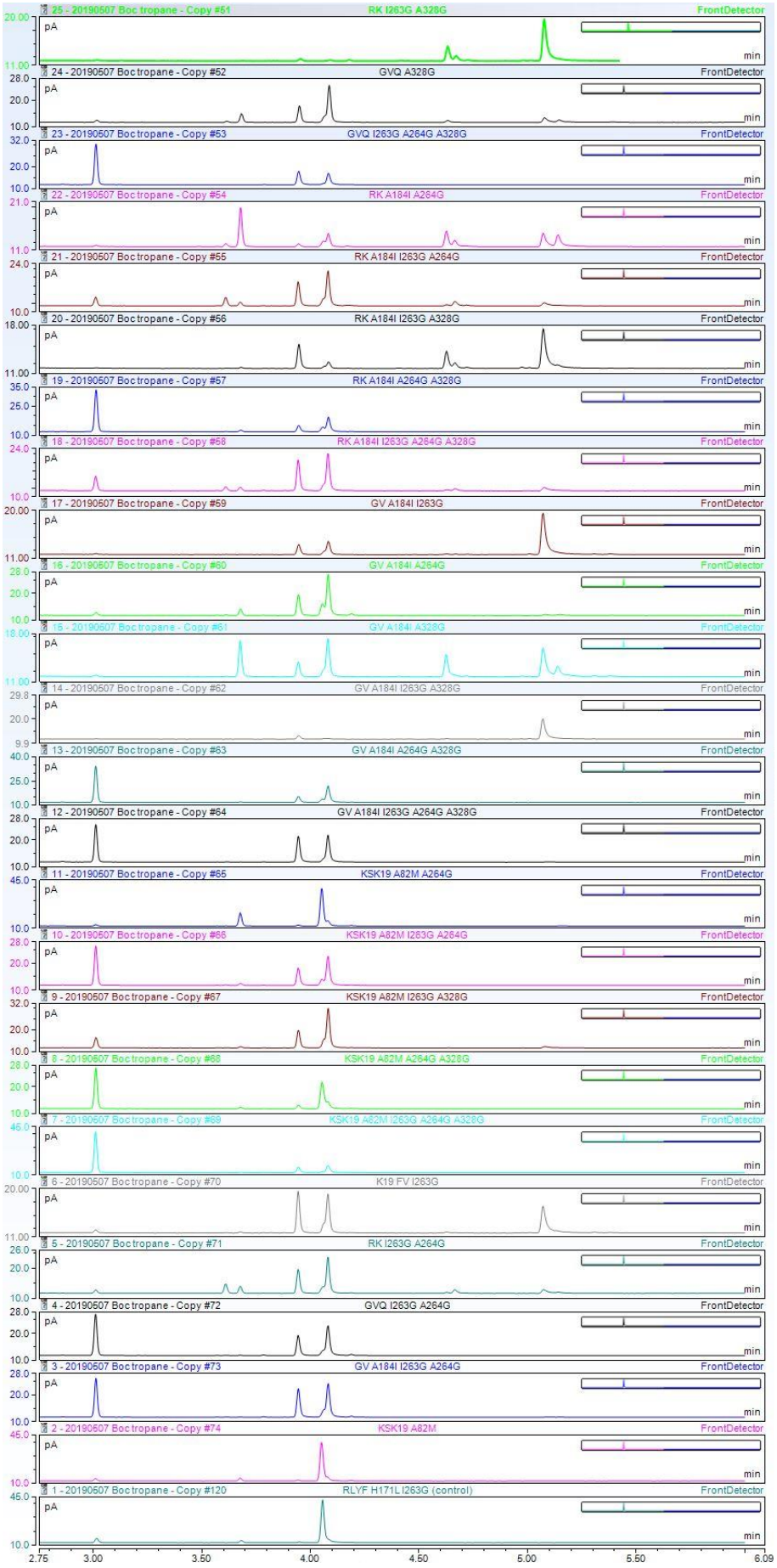


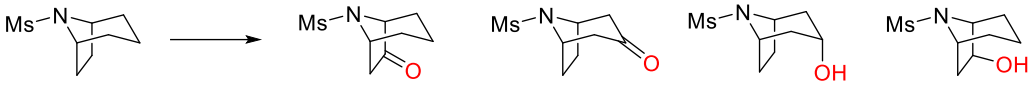
Figure 16: Product distribution for enzymatic screens against *N*-Boc-tropane **4.17**. The oxidised products were detected by GC analysis and the product distributions determined from the integration of peak areas. Oxidised products were subsequently identified by NMR analysis following scale-up of selected mutants.

GC trace of screen




25 - 20190507 Boc tropane - Copy #51 RK I263G A328G FrontDetector
24 - 20190507 Boctropane - Copy #52 GVQ A328G FrontDetector
23 - 20190507 Boctropane - Copy #53 GVQ I263G A264G A328G FrontDetector
22 - 20190507 Boctropane - Copy #54 RK A184I A264G FrontDetector
21 - 20190507 Boctropane - Copy #55 RK A184I I263G A264G FrontDetector
20 - 20190507 Boctropane - Copy #56 RK A184I I263G A328G FrontDetector
19 - 20190507 Boctropane - Copy #57 RK A184I A264G A328G FrontDetector
18 - 20190507 Boctropane - Copy #58 RK A184I I263G A264G A328G FrontDetector
17 - 20190507 Boctropane - Copy #59 GV A184I I263G FrontDetector
16 - 20190507 Boctropane - Copy #60 GV A184I A264G FrontDetector
15 - 20190507 Boctropane - Copy #61 GV A184I A328G FrontDetector
14 - 20190507 Boctropane - Copy #62 GV A184I I263G A328G FrontDetector
13 - 20190507 Boctropane - Copy #63 GV A184I A264G A328G FrontDetector
12 - 20190507 Boctropane - Copy #64 GV A184I I263G A264G A328G FrontDetector
11 - 20190507 Boctropane - Copy #65 KSK19 A82M A264G FrontDetector
10 - 20190507 Boctropane - Copy #66 KSK19 A82M I263G A264G FrontDetector
9 - 20190507 Boctropane - Copy #67 KSK19 A82M I263G A328G FrontDetector
8 - 20190507 Boctropane - Copy #68 KSK19 A82M A264G A328G FrontDetector
7 - 20190507 Boctropane - Copy #69 KSK19 A82M I263G A264G A328G FrontDetector
6 - 20190507 Boctropane - Copy #70 K19 FV I263G FrontDetector
5 - 20190507 Boctropane - Copy #71 RK I263G A264G FrontDetector
4 - 20190507 Boctropane - Copy #72 GVQ I263G A264G FrontDetector
3 - 20190507 Boctropane - Copy #73 GV A184I I263G A264G FrontDetector
2 - 20190507 Boctropane - Copy #74 KSK19 A82M FrontDetector
1 - 20190507 Boctropane - Copy #120 RLYF H171L I263G (control) FrontDetector
pA
min
2.75
3.00
3.50
4.00
4.50
5.00
5.50
6.09

B: Enzyme screening data for 8-(methylsulfonyl)-8-azabicyclo[3.2.1]octane 2.18



2.18 2.27 2.28 2.29 2.30

Enzyme	Conversion	2.29/2.30	2.28	2.27	Others
KSK19/A82M/A330W	100%	13%	55%	26%	5%
KSK19/A82M/A264G	97%	7%	71%	8%	12%
RLYF/KSK19/A184I	76%	37%	48%	3%	11%
GV/A184I	63%	58%	31%		12%
KSK19/A82M	55%	19%	72%	3%	6%
KSK19/A82M/A264G/A328G	52%		79%	4%	18%
K19/F87V/Q403P	26%	36%	60%		4%
RK/A184I/I263G/A328G	24%	43%	42%		15%
K19/F87V	15%	43%	53%		4%
GV/A184I/A328G	15%	61%	30%		9%
GV/A184I/A264G	14%	48%	35%		17%
RK/A328G/P329G/A330G	12%	36%	63%		
GVQ/A328G	10%	23%	61%		6%
RLYF/KSK19	9%	21%	79%		
GV/A184I/I263G	8%	100%			
RK/A184I/A264G	7%	28%	51%		20%
K19/F87V/A328V	4%	99%			
KSK19/F81W	4%	28%	66%		6%
RP/V78I/E267V	3%		100%		
RK/A184I/A264G/A328G	3%	26%	53%		21%
RK/A328G	2%		100%		
GV/A184I/I263G/A328G	2%	90%			10%
GV/A184I/A264G/A328G	2%		52%		48%
KSK19/A82M/I263G/A328G	2%		100%		
RK/A184I/I263G/A264G	1%		100%		
R19/A330W	0%				
K19/F87V/I263G	0%				
GVQ	0%				
R19/F87I	0%				
KSK19/A82M/I263G	0%				
KSK19/I263A	0%				
KU3/A328I/A330P	0%				
R19/I263A/A328L	0%				

GVQ/V78L/I263G	0%
RT2	0%
RK/I263G/A264G	0%
RK/G265GG	0%
GVQ/I263G/A328L	0%
RK/I263G/A328G	0%
GVQ/I263G/A264G/A328G	0%
RK/A184I/I263G/A264G/A328G	0%
GV/A184I/I263G/A264G/A328G	0%
KSK19/A82M/I263G/A264G	0%
KSK19/A82M/I263G/A264G/A328G	0%
K19/F87V/I263G	0%
RK/I263G/A264G	0%
GVQ/I263G/A264G	0%
GV/A184I/I263G/A264G	0%

Table 29: Conversion and selectivity data for the P450 screening of substrate **2.18**.

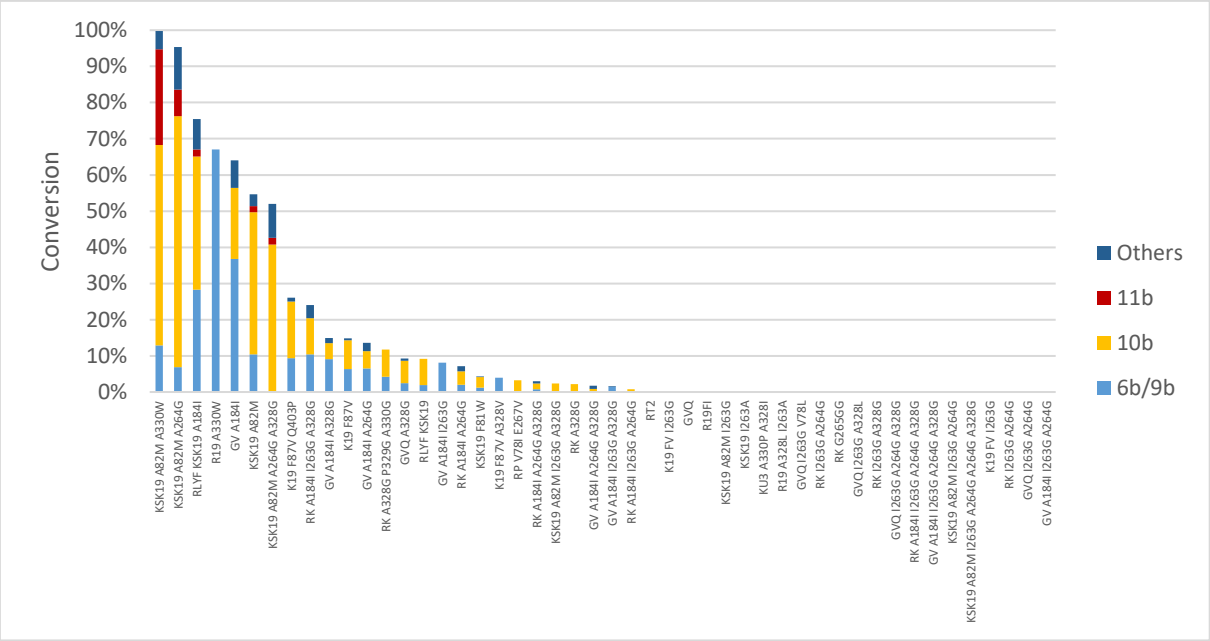
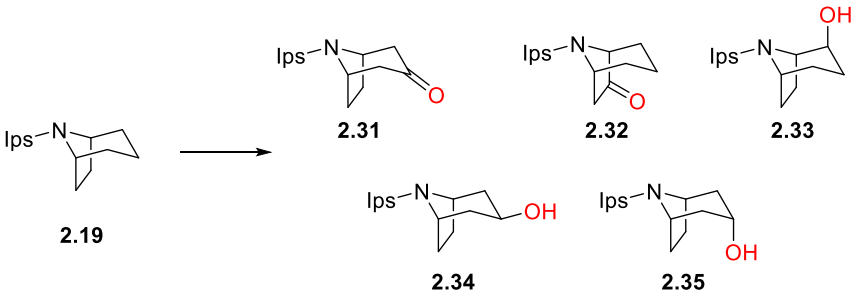


Figure 17: Product distribution for enzymatic screens against *N*-mesyl-tropane **2.18**. The oxidised products were detected by GC analysis and the product distributions determined from the integration of peak areas. Oxidised products were subsequently identified by NMR analysis following scale-up of selected mutants.

GC trace of screen


23 - Mesyl tropane screen (SP3) #1
RK I263G A328G
FrontDetector
22 - Mesyl tropane screen (SP3) #2
GVQ A328G
21 - Mesyl tropane screen (SP3) #3
GVQ I263G A264G A328G
20 - Mesyl tropane screen (SP3) #4
RK A184I A264G
19 - Mesyl tropane screen (SP3) #5
RK A184I I263G A264G
18 - Mesyl tropane screen (SP3) #6
RK A184I I263G A328G
17 - Mesyl tropane screen (SP3) #7
RK A184I A264G A328G
16 - Mesyl tropane screen (SP3) #8
RK A184I I263G A264G A328G
15 - Mesyl tropane screen (SP3) #9
GV A184I I263G
14 - Mesyl tropane screen (SP3) #10
GV A184I A264G
13 - Mesyl tropane screen (SP3) #11
GV A184I A328G
12 - Mesyl tropane screen (SP3) #12
GV A184I I263G A328G
11 - Mesyl tropane screen (SP3) #13
GV A184I A264G A328G
10 - Mesyl tropane screen (SP3) #14
GV A184I I263G A264G A328G
9 - Mesyl tropane screen (SP3) #15
KSK19 A82M A264G
8 - Mesyl tropane screen (SP3) #16
KSK19 A82M I263G A264G
7 - Mesyl tropane screen (SP3) #17
KSK19 A82M I263G A328G
6 - Mesyl tropane screen (SP3) #18
KSK19 A82M A264G A328G
5 - Mesyl tropane screen (SP3) #20
K19 FV I263G
4 - Mesyl tropane screen (SP3) #21
RK I263G A264G
3 - Mesyl tropane screen (SP3) #22
GVQ I263G A264G
2 - Mesyl tropane screen (SP3) #23
GV A184I I263G A264G
1 - Mesyl tropane screen (SP3) #24
KSK19 A82M
pA
min
3.02
3.25
3.50
3.75
4.00
4.25
4.50
4.75
5.00
5.25
5.50
5.75
6.00
6.20

C: Enzyme screening data for 8-(isopropylsulfonyl)-8-azabicyclo[3.2.1]octane 2.19



Enzyme	Conversion	2.34	2.35	2.33	2.31	2.32	Others
RK/A328G/P329G/A330G	100%	17%	55%	12%	10%	4%	3%
RLYF/KSK19	100%	14%	45%	2%	38%		1%
KSK19/A82M/A330W	100%	1%	69%	2%	24%	1%	4%
RK/A184I/A264G	100%	7%	74%		19%		
KSK19/A82M/A264G	100%		82%		17%	2%	
KSK19/A82M	100%		91%	3%	6%		
RLYF/KSK19/A184I	99%	25%	62%	3%	10%	1%	
KSK19/A82M/A264G/A328G	95%		36%		11%	50%	3%
GV/A184I/A328G	93%	41%	51%	3%	5%		
GV/A184I	92%	31%	61%	3%	5%		
GV/A184I/I263G	84%	79%		16%	5%		
KSK19/F81W	70%	14%	83%	3%			
RK/G265GG	43%	45%	39%	12%		2%	1%
RK/A184I/I263G/A328G	43%	84%		16%			
K19/F87V	39%	15%	83%	2%			
K19/F87V/Q403P	38%	15%	83%	1%	1%		
GVQ/A328G	37%	31%	69%				
GV/A184I/A264G	34%		100%				
RK/A184I/A264G/A328G	33%		58%	3%		39%	
RP/V78I/E267V	28%	1%	97%	2%			
KSK19/I263A	24%	46%	39%	15%			
K19/F87V/I263G	17%	47%	44%	8%			
RK/A328G	16%	13%	50%	2%		35%	
RK/I263G/A328G	14%	36%	50%	14%			
K19/F87V/I263G	14%	100%					
GVQ	13%	11%	78%	4%		6%	
KSK19/A82M/I263G/A328G	13%		100%				
RK/A184I/I263G/A264G	12%		100%				
KSK19/A82M/I263G	10%	40%	46%	14%			
GV/A184I/I263G/A328G	9%		100%				

GV/A184I/A264G/A328G	8%		100%	
K19/F87V/A328V	7%	19%	81%	
RK/I263G/A264G	7%	26%	65%	9%
R19/F87I	2%	19%	81%	
GVQ/V78L/I263G	2%	100%		
R19/I263A/A328L	1%		100%	
RK/I263G/A264G	1%	100%		
R19/A330W	0%			
KU3/A328I/A330P	0%			
RT2	0%			
GVQ/I263G/A328L	0%			
GVQ/I263G/A264G/A328G	0%			
RK/A184I/I263G/A264G/A328G	0%			
GV/A184I/I263G/A264G/A328G	0%			
KSK19/A82M/I263G/A264G	0%			
KSK19/A82M/I263G/A264G/A328G	0%			
GVQ/I263G/A264G	0%			
GV/A184I/I263G/A264G	0%			

Table 30: Conversion and selectivity data for the P450 screening of substrate **2.19**.

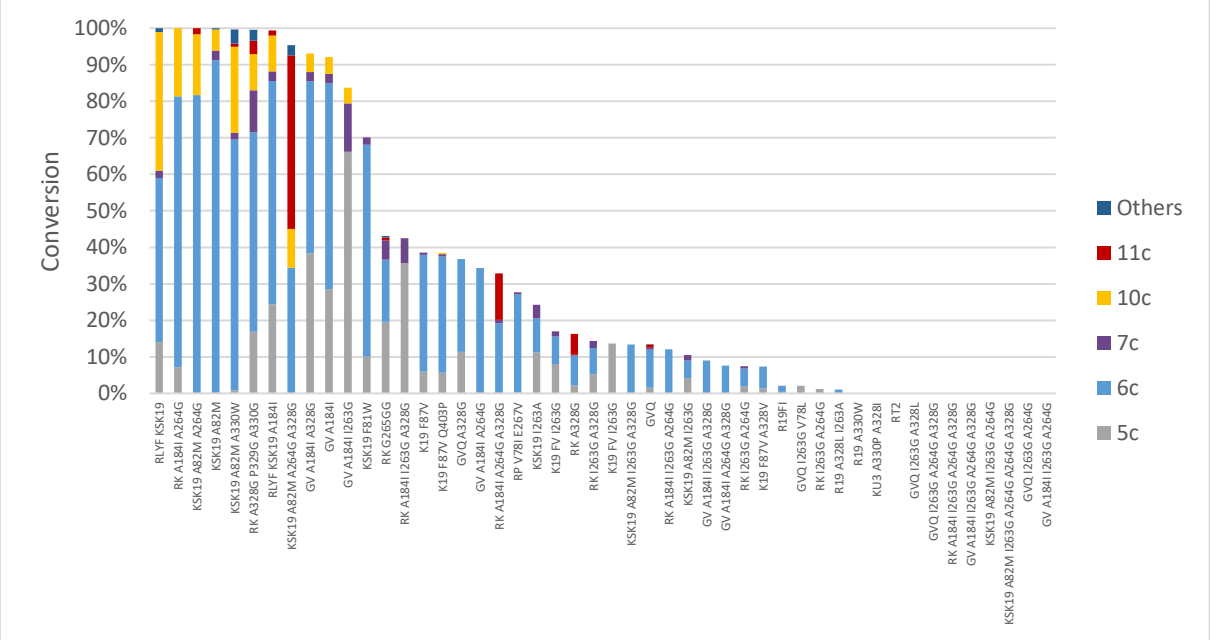
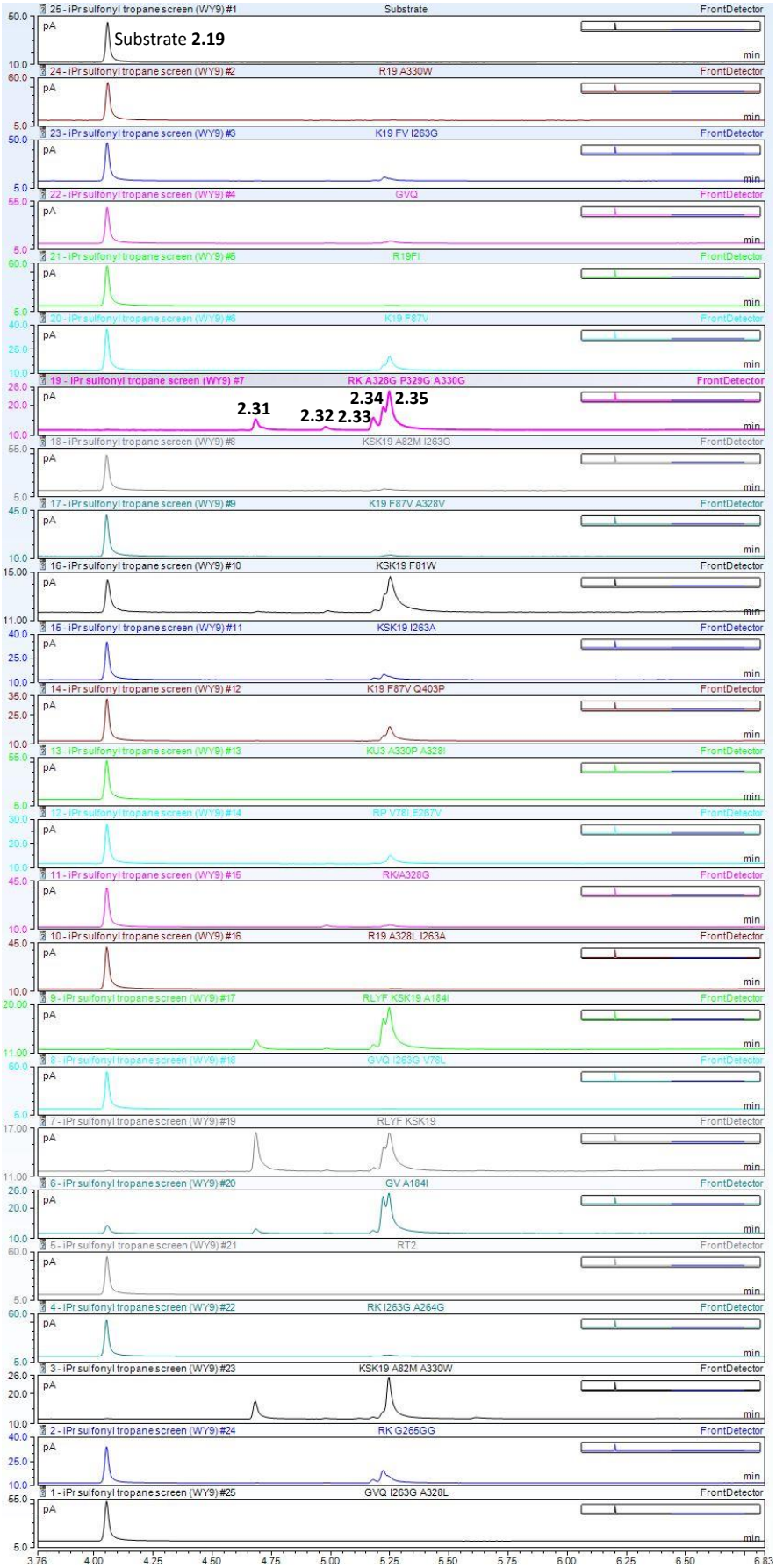
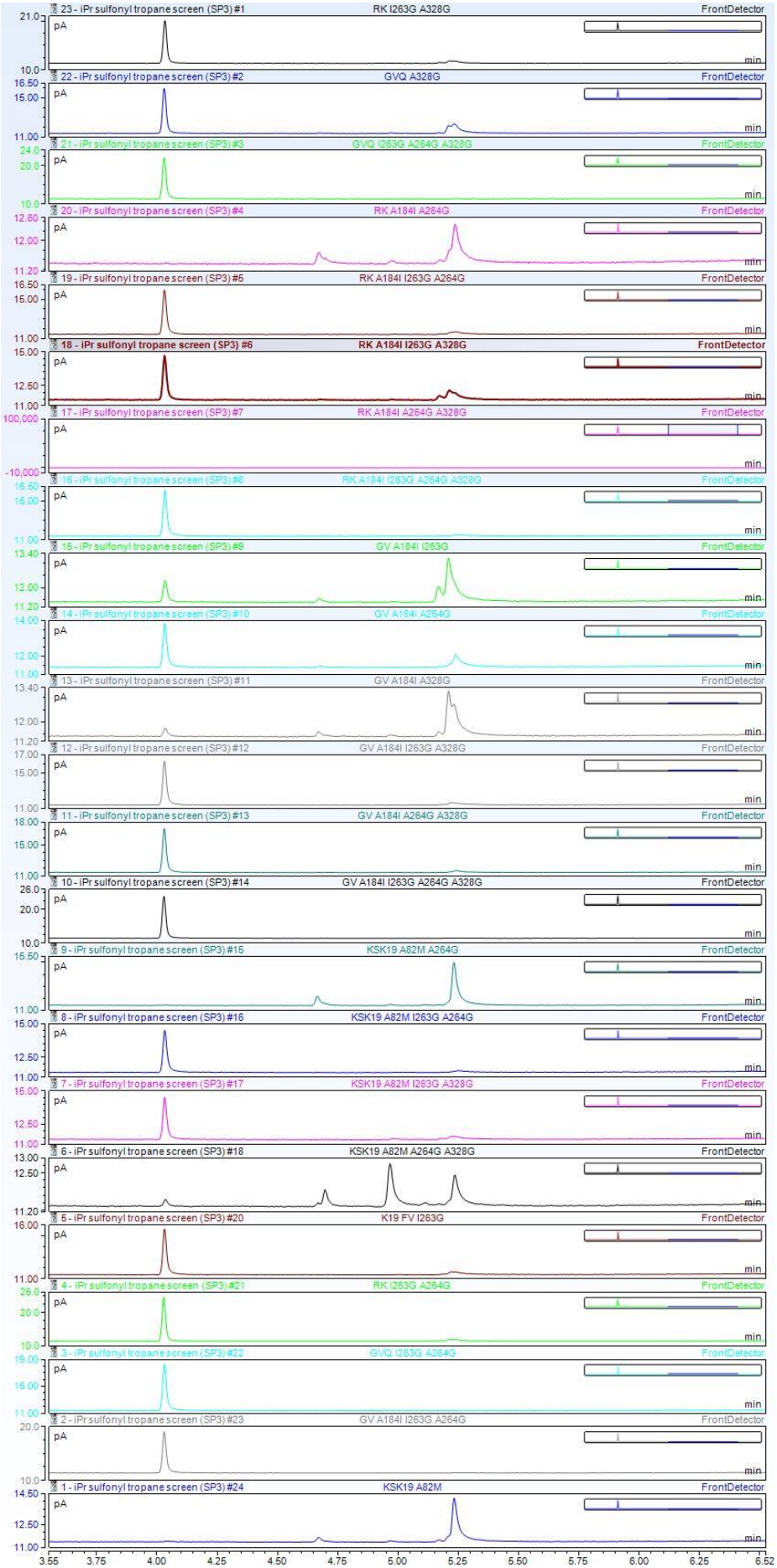


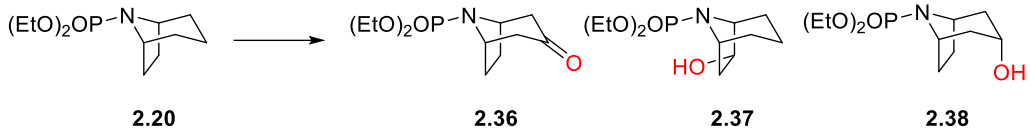
Figure 18: Product distribution for enzymatic screens against *N*-ipsyl-tropane **2.19**. The oxidised products were detected by GC analysis and the product distributions determined from the integration of peak areas. Oxidised products were subsequently identified by NMR analysis following scale-up of selected mutants.

GC trace of screen




23 - iPr sulfonyl tropane screen (SP3) #1
RK I263G A328G
FrontDetector
22 - iPr sulfonyl tropane screen (SP3) #2
GVQ A328G
21 - iPr sulfonyl tropane screen (SP3) #3
GVQ I263G A264G A328G
20 - iPr sulfonyl tropane screen (SP3) #4
RK A184I A264G
19 - iPr sulfonyl tropane screen (SP3) #5
RK A184I I263G A264G
18 - iPr sulfonyl tropane screen (SP3) #6
RK A184I I263G A328G
17 - iPr sulfonyl tropane screen (SP3) #7
RK A184I A264G A328G
16 - iPr sulfonyl tropane screen (SP3) #8
RK A184I I263G A264G A328G
15 - iPr sulfonyl tropane screen (SP3) #9
GV A184I I263G
14 - iPr sulfonyl tropane screen (SP3) #10
GV A184I A264G
13 - iPr sulfonyl tropane screen (SP3) #11
GV A184I A328G
12 - iPr sulfonyl tropane screen (SP3) #12
GV A184I I263G A328G
11 - iPr sulfonyl tropane screen (SP3) #13
GV A184I A264G A328G
10 - iPr sulfonyl tropane screen (SP3) #14
GV A184I I263G A264G A328G
9 - iPr sulfonyl tropane screen (SP3) #15
KSK19 A82M A264G
8 - iPr sulfonyl tropane screen (SP3) #16
KSK19 A82M I263G A264G
7 - iPr sulfonyl tropane screen (SP3) #17
KSK19 A82M I263G A328G
6 - iPr sulfonyl tropane screen (SP3) #18
KSK19 A82M A264G A328G
5 - iPr sulfonyl tropane screen (SP3) #20
K19 FV I263G
4 - iPr sulfonyl tropane screen (SP3) #21
RK I263G A264G
3 - iPr sulfonyl tropane screen (SP3) #22
GVQ I263G A264G
2 - iPr sulfonyl tropane screen (SP3) #23
GV A184I I263G A264G
1 - iPr sulfonyl tropane screen (SP3) #24
KSK19 A82M
pA
min
3.55
3.75
4.00
4.25
4.50
4.75
5.00
5.25
5.50
5.75
6.00
6.25
6.52

D: Enzyme screening data for diethyl (8-azabicyclo[3.2.1]octan-8-yl)phosphonate 2.20



2.20 **2.36** **2.37** **2.38**

Enzyme	Conversion	2.38	2.37	2.36	Others
RLYF/KSK19/A184I	100%	21%		67%	10%
RLYF/KSK19	100%	64%		35%	1%
GV/A184I	100%	82%	1%	10%	6%
KSK19/A82M/A330W	100%	35%	1%	47%	15%
RK/A184I/A264G	100%	37%		57%	5%
GV/A184I/A328G	98%	81%	7%	6%	6%
RK/A328G/P329G/A330G	96%	79%	3%	13%	2%
KSK19/A82M/A264G	83%	43%	32%	5%	22%
GV/A184I/I263G/A264G	83%				100%
K19/F87V	76%	89%	1%	3%	7%
K19/F87V/Q403P	74%	89%	2%	2%	7%
RK/I263G/A328G	73%	93%	2%	2%	3%
RK/A184I/I263G/A328G	62%	86%	4%	3%	6%
GV/A184I/A264G	62%	48%	35%	3%	16%
K19/F87V/A328V	55%	94%		1%	6%
KSK19/A82M	54%	70%	4%	3%	22%
RK/A184I/A264G/A328G	50%	69%	19%	6%	6%
GV/A184I/A264G/A328G	46%	18%	57%		23%
KSK19/F81W	38%	92%		3%	5%
RK/A184I/I263G/A264G	36%	69%	14%	2%	14%
GV/A184I/I263G	36%	84%	10%		7%
GVQ	34%	90%	2%		8%
GVQ/A328G	29%	80%	10%		8%
RK/G265GG	27%	98%	2%		
K19/F87V/I263G	26%	87%	6%		5%
RK/I263G/A264G	26%	75%	14%		7%
RK/A328G	25%	95%	5%		
RK/I263G/A264G	25%	74%	14%		12%
RK/A184I/I263G/A264G/A328G	22%	59%	20%	3%	17%
RP/V78I/E267V	18%	100%			
GV/A184I/I263G/A328G	15%	77%	18%		2%
KSK19/A82M/A264G/A328G	15%	16%	74%		6%
K19/F87V/I263G	11%	94%	6%		

KSK19/I263A	9%	100%		
KSK19/A82M/I263G/A264G	8%	38%	46%	14%
R19/F87I	6%	86%	5%	9%
GV/A184I/I263G/A264G/A328G	5%	16%	49%	13%
KSK19/A82M/I263G/A264G/A328G	5%	21%	73%	6%
GVQ/V78L/I263G	4%	53%	27%	21%
KSK19/A82M/I263G/A328G	4%	52%	27%	18%
GVQ/I263G/A264G	3%	28%	51%	13%
R19/A330W	1%			100%
R19/I263A/A328L	1%			100%
RT2	1%			100%
GVQ/I263G/A328L	1%	100%		
GVQ/I263G/A264G/A328G	1%		62%	38%
KSK19/A82M/I263G	0%			
KU3/A328I/A330P	0%			

Table 31: Conversion and selectivity data for the P450 screening of substrate **2.20**.

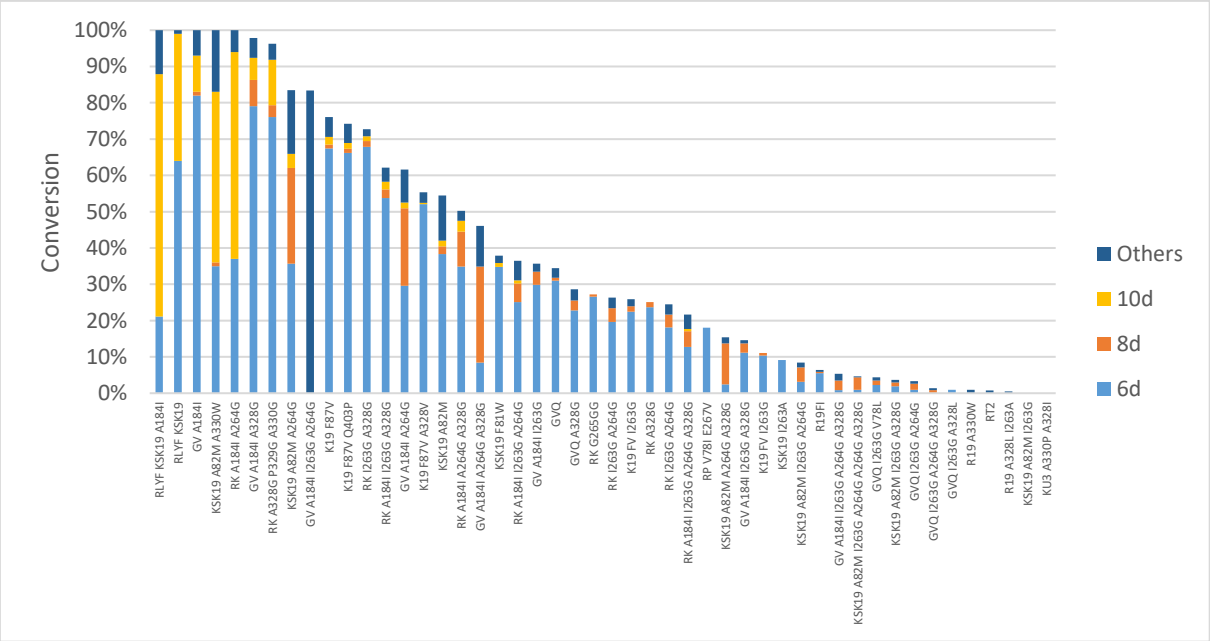
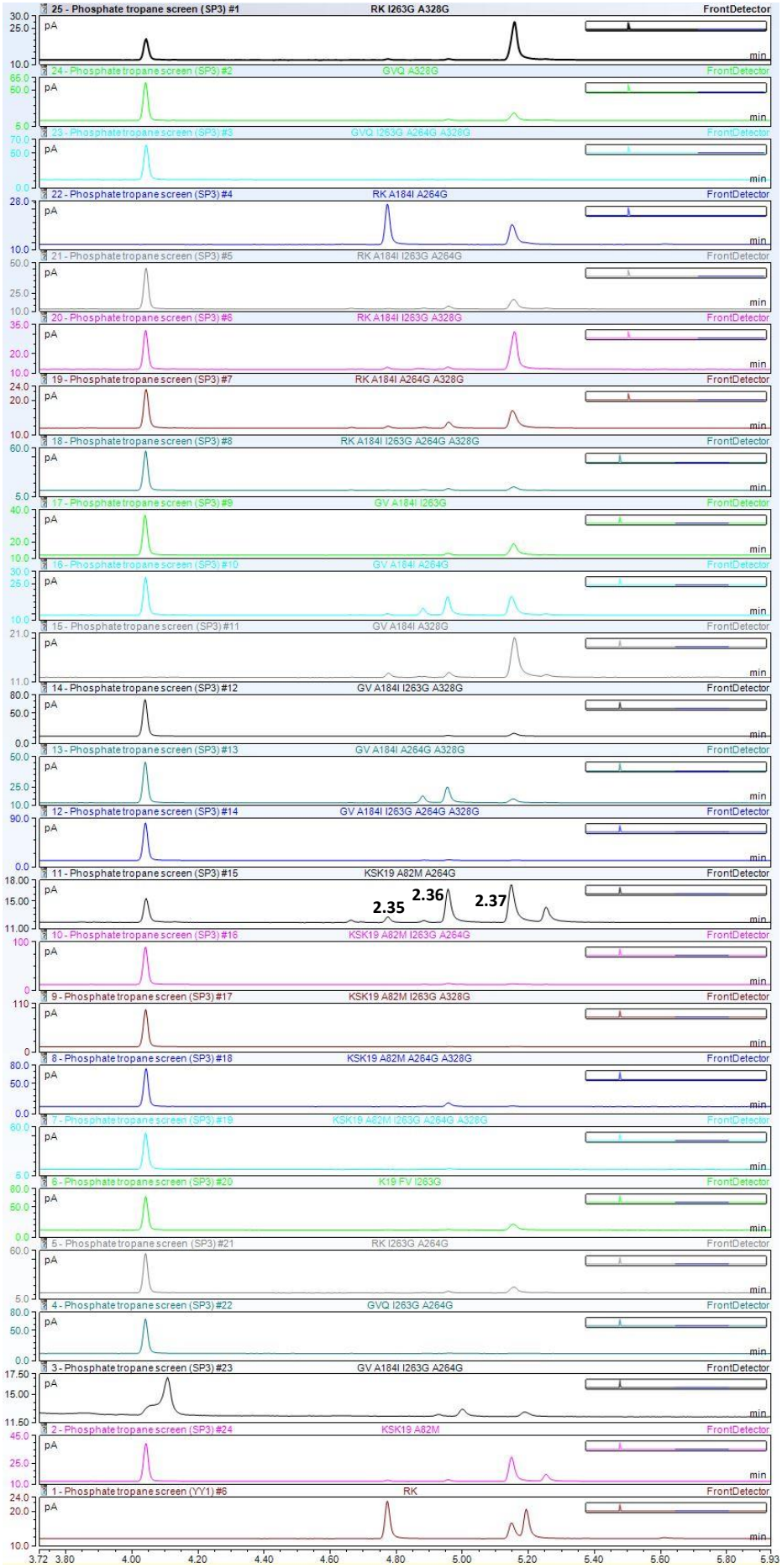


Figure 19: Product distribution for enzymatic screens against *N*-phosphoryl-tropane **2.20**. The oxidised products were detected by GC analysis and the product distributions determined from the integration of peak areas. Oxidised products were subsequently identified by NMR analysis following scale-up of selected mutants.

GC trace of screen


25 - Phosphate tropane screen (SP3) #1
RK I263G A328G
FrontDetector
24 - Phosphate tropane screen (SP3) #2
GVQ A328G
23 - Phosphate tropane screen (SP3) #3
GVQ I263G A264G A328G
22 - Phosphate tropane screen (SP3) #4
RK A184I A264G
21 - Phosphate tropane screen (SP3) #5
RK A184I I263G A264G
20 - Phosphate tropane screen (SP3) #6
RK A184I I263G A328G
19 - Phosphate tropane screen (SP3) #7
RK A184I A264G A328G
18 - Phosphate tropane screen (SP3) #8
RK A184I I263G A264G A328G
17 - Phosphate tropane screen (SP3) #9
GV A184I I263G
16 - Phosphate tropane screen (SP3) #10
GV A184I A264G
15 - Phosphate tropane screen (SP3) #11
GV A184I A328G
14 - Phosphate tropane screen (SP3) #12
GV A184I I263G A328G
13 - Phosphate tropane screen (SP3) #13
GV A184I A264G A328G
12 - Phosphate tropane screen (SP3) #14
GV A184I I263G A264G A328G
11 - Phosphate tropane screen (SP3) #15
KSK19 A82M A264G
2.35
2.36
2.37
10 - Phosphate tropane screen (SP3) #16
KSK19 A82M I263G A264G
9 - Phosphate tropane screen (SP3) #17
KSK19 A82M I263G A328G
8 - Phosphate tropane screen (SP3) #18
KSK19 A82M A264G A328G
7 - Phosphate tropane screen (SP3) #19
KSK19 A82M I263G A264G A328G
6 - Phosphate tropane screen (SP3) #20
K19 FV I263G
5 - Phosphate tropane screen (SP3) #21
RK I263G A264G
4 - Phosphate tropane screen (SP3) #22
GVQ I263G A264G
3 - Phosphate tropane screen (SP3) #23
GV A184I I263G A264G
2 - Phosphate tropane screen (SP3) #24
KSK19 A82M
1 - Phosphate tropane screen (YY1) #6
RK
pA
min
3.72 3.80 4.00 4.20 4.40 4.60 4.80 5.00 5.20 5.40 5.60 5.80 5.93

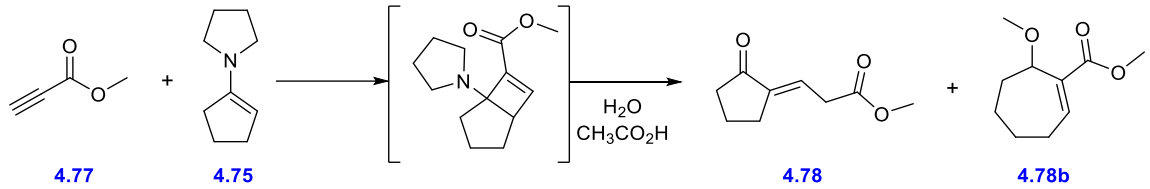
D: Enzyme screening data for *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate 3.33

3.33 3.34

Enzyme	Conversion	3.34	Others
R19/A330W	2%		100%
K19/F87V/I263G	74%	98%	2%
GVQ	48%	97%	3%
R19/F87I	91%	99%	1%
K19/F87V	100%	100%	
RK/A328G/P329G/A330G	19%	93%	6%
KSK19/A82M/I263G	3%	64%	36%
K19/F87V/A328V	3%	69%	31%
KSK19/F81W	39%	95%	5%
KSK19/I263A	13%	71%	7%
K19/F87V/Q403P	81%	100%	
KU3/A330P/A328I	1%		100%
RP/V78I/E267V	1%		100%
RK/A328G	9%	90%	9%
R19/A328L/I263A	1%		100%
RLYF/KSK19/A184I	98%	96%	4%
GVQ I263G V78L	55%	100%	
RLYF/KSK19	94%	95%	5%
GV/A184I	43%	99%	1%
RT2	1%		100%
RK/I263G/A264G	22%	94%	6%
KSK19/A82M/A330W	1%		100%
RK/G265GG	37%	97%	3%
GVQ/I263G/A328L	6%	70%	29%

Table 32: Product distribution for enzymatic screens against *N*-Boc-tropinone **3.33**. The oxidised products were detected by GC analysis and the product distributions determined from the integration of peak areas. Oxidised products were subsequently identified by NMR analysis following scale-up of selected mutants.

E: Reaction optimisation of cycloaddition of enamine 4.75 and methyl propiolate 4.77

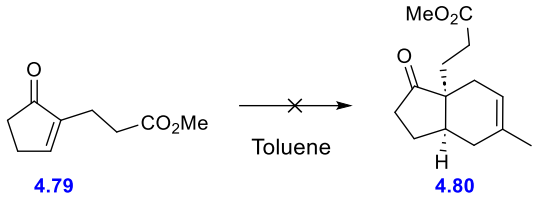


4.77 4.75 4.78 4.78b

Entry	4.75 (equiv.)	Solvent	Temperature (°C)	Time (h)	Outcome (4.78:4.78b)
1	1.0	Dioxane	20	1	0:100
2	1.0	Dioxane	10	1	16:84
3	1.0	Dioxane	0	1	No reaction
4	2.0	Dioxane	10	1	33:66
5	2.0	THF	10	1	No reaction
6	5.0	Dioxane	10	6	Decomposition
7	5.0	Dioxane	10	18	Decomposition

Table 33: Optimisation of cycloaddition of enamine **4.75** and methyl propiolate **4.77**.

F: Reaction trials of the DA reaction between isoprene and enone 4.79

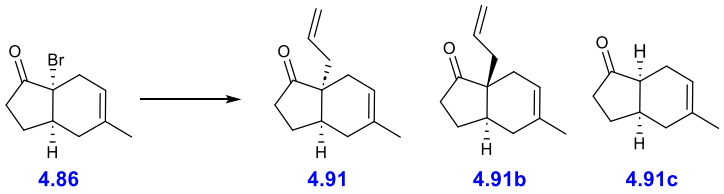


4.79 4.80

Entry	Lewis acid (equiv.)	Temperature (°C)	Outcome
1	Et_2AlCl (0.10)	40	No reaction
2	$AlCl_3$ (0.10)	40	No reaction
3	Et_2AlCl (0.25)	80	No reaction
4	$AlCl_3$ (0.25)	80	No reaction
5	$BF_3.Et_2O$ (0.25)	80	No reaction
6	Et_2AlCl (0.5)	110	No reaction
7	$AlCl_3$ (0.9)	110	No reaction
8	$BF_3.Et_2O$ (0.5)	110	No reaction
9	TMSOTf (1.0)	110	No reaction

Table 34: Various attempts at the DA reaction between isoprene and enone **4.79**.

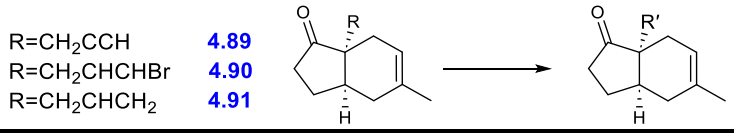
G: Reaction optimisation of allylation from bromoketone 4.86

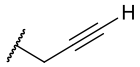
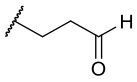
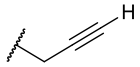
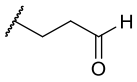
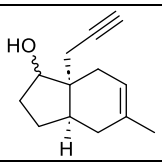
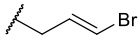
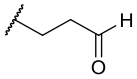
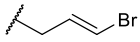
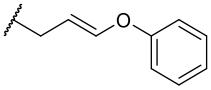
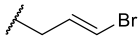
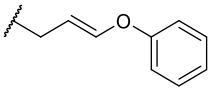
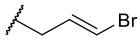
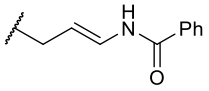
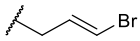
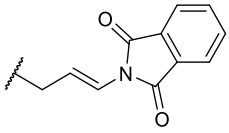
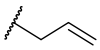
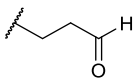
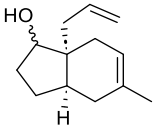
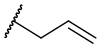
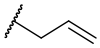
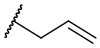
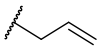


Entry	Allyl bromide (equiv.)	Conc. (M)	Solvent	Additive (equiv.)	Outcome (4.91:4.91b:4.91c)
1	1.1	0.45	THF	–	0:0:100
2	5.0	0.09	THF	–	24:9:67
3	15.0	0.18	THF	–	44:36:20
4	15.0	0.18	THF	DMPU (5.0)	62:21:16
5	15.0	0.18	THF	DMPU (20.0)	83:17:0
6	15.0	0.18	DME	–	82:18:0
7	15.0	0.18	DME	NaI (0.1)	52:28:20
8	15.0	0.18	DME	DMPU (20.0)	85:15:0
9	30.0	0.18	DME	–	71:23:6

Table 35: Optimisation of allylation of the specific enolate generated from bromoketone **4.86**.

H: Reactions to develop the side chain of compounds 4.89, 4.90 and 4.91



Entry	R	Conditions	R′	Outcome
1	 **4.89**	Sia_2BH, diglyme, rt, 24 h, then H_2O_2, NaOH[230, 231]		No reaction
2	 **4.89**	9-BBN, THF, rt, 4 h, then H_2O_2, NaOH[232, 233]		
3	 **4.90**	2.5 M HCl, rt, 18 h[234, 235]		No reaction
4	 **4.90**	PhOH, $Ni(acac)_2$, CuI, Cs_2CO_3, 100 °C, 18 h[236]		No reaction
5	 **4.90**	PhOH, CuCl, Cs_2CO_3, 60°C, 18 h[237]		No reaction
6	 **4.90**	$PhCONH_2$, CuTC, Cs_2CO_3, 90 °C, 18 h[238]		No reaction
7	 **4.90**	Potassium phthalimide, CuI, 130 °C, 18 h[239]		No reaction
8	 **4.91**	9-BBN, THF, 50 °C, 1 h, then H_2O_2, NaOH[244]		
9	 **4.91**	Triethyl orthoformate, 1,3-propanediol, NBS, MeOH, DCM, 30 °C, 18 h[243]	 (Protection of ketone)	No reaction
10	 **4.91**	$(TMSOCH_2)_2$, TMSOTf, DCM, rt, 2 h[240]	 (Protection of ketone)	No reaction

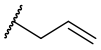
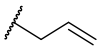
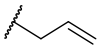
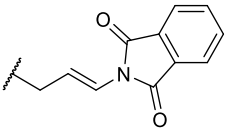
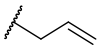
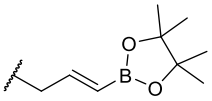
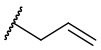
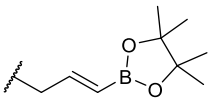
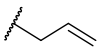
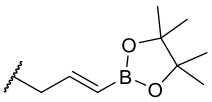
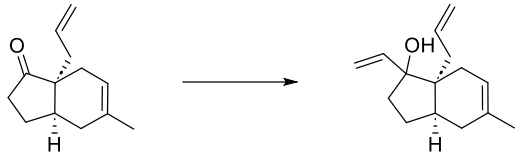
11	 **4.91**	Ethylene glycol, TsOH, toluene, 110 °C, 18 h[242]	 (Protection of ketone)	No reaction
12	 **4.91**	$P(OEt)_3$, PhthNOH, AIBN, 70 °C, 18 h[240]		Complex mixture
13	 **4.91**	Pinacol vinylboronate, Grubbs I, DCM, 40 °C, 18 h[245]		No reaction
14	 **4.91**	Pinacol vinylboronate, Grubbs II, DCM, 40 °C, 18 h[245]		Desired product (37%)
15	 **4.91**	Pinacol vinylboronate, Hoveyda–Grubbs II, DCM, 40 °C, 18 h[245]		Desired product (30%)

Table 36: Various attempts to develop the side chain of compounds **4.89**, **4.90** and **4.91**.

I: Organometallic reactions of compound 4.91

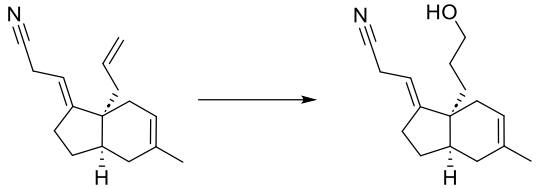


4.91 4.177

Entry	Organometallic (equiv.)	Additive	Temp. (°C)	Result
1	Cyclopropyl-MgBr (1.0)	None	25	No reaction
2[371]	Cyclopropyl-MgBr (1.0)	$LaCl_3.2LiCl$	25	No reaction
3[372]	Cyclopropyl-MgBr (3.0)	Diethyl phosphite	25	No reaction
4	Cyclopropyl-MgBr (10.0)	$LaCl_3.2LiCl$	25	No reaction
5[373]	Cyclopropyl-MgBr (10.0)	$LaCl_3.2LiCl$	66	No reaction
6[374]	Cyclopropyllithium (20.0)	None	40	No reaction
7	Isopropyl-MgBr (1.0)	$LaCl_3.2LiCl$	25	No reaction
8	Isopropyl-MgBr (10.0)	$LaCl_3.2LiCl$	66	No reaction
9	Vinyl-MgBr (2.0)	$LaCl_3.2LiCl$	25	**4.177**, 96%

Table 37: Attempts to add three carbons to ketone **4.91**.

J: Hydroboration attempts of compound 4.179

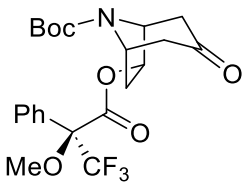


Entry	Conditions	Temp.(°C)	Outcome
1	9-BBN, THF	25	No reaction
		50	No reaction
2	$BH_3.SMe_2$, cyclohexene, THF[375]	25	No reaction
3		50	No reaction
4	2-methyl-2-butene, BH_3.THF, THF[376]	25	No reaction
5		50	No reaction
6		90	No reaction
7	Pinacolborane, $[Ir(cod)Cl]_2$, dppb, DCM[336, 337]	25	60%

Table 38: Evaluation of hydroboration reactions with substrate **4.179**.

K: Synthesis of Compounds Performed by Dr Ziyue Xiong

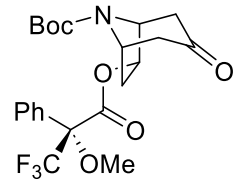
***tert*-Butyl (1*S*,5*S*,6*R*)-3-oxo-6-{[(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy}-8-azabicyclo[3.2.1]octane-8-carboxylate**



This reaction was carried out by Dr Ziyue Xiong. To a stirred solution of alcohol **3.34** (10 mg, 0.041 mmol) in dry $CHCl_3$ (1 mL) was added (*S*)-(–)-MTPA (29 mg, 0.12 mmol), DCC (26 mg, 0.13 mmol) and DMAP (15 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 14 h, diluted with $CHCl_3$ (10 mL), and the solution washed with water (10 mL). The separated aqueous layer was then extracted with $CHCl_3$ (2 x 10 mL); the combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed by rotary evaporation. The crude residue was purified by preparative TLC (hexane:ethyl acetate = 2:1) to give the *title compound* (19 mg, ~quant) as a colourless solid.

R*f* 0.55 (petroleum ether/ethyl acetate, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) (rotameric) δ 7.52 – 7.37 (m, 5H), 5.22 – 5.11 (m, 1H), 4.68 (br s), 4.58 (br s), 4.55 (br s) and 4.41 (br s, 2H), 3.51 (2 x s, 3H), 2.82 – 2.56 (m, 2H), 2.55 (d, *J* = 16.0 Hz, 1H), 2.36 (d, *J* = 16.0 Hz, 1H), 2.27 – 2.18 (m, 2H), 1.46 (s, ~4H), 1.42 (s, ~5H).

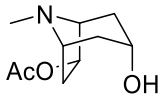
***tert*-Butyl (1*S*,5*S*,6*R*)-3-oxo-6-{[(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy}-8-azabicyclo[3.2.1]octane-8-carboxylate**



This reaction was carried out by Dr Ziyue Xiong. To a stirred solution of alcohol **3.34** (10 mg, 0.041 mmol) in dry $CHCl_3$ (1 mL) was added (*R*)-(+)-MTPA (29 mg, 0.12 mmol), DCC (26 mg, 0.13 mmol) and DMAP (15 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 14 h, diluted with $CHCl_3$ (10 mL), and the solution washed with water (10 mL). The separated aqueous layer was then extracted with $CHCl_3$ (2 x 10 mL); the combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed by rotary evaporation. The crude residue was purified by preparative TLC (hexane:ethyl acetate = 2:1) to give the *title compound* (19 mg, ~quant) as a colourless solid.

R*f* 0.50 (petroleum ether:ethyl acetate = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) (rotameric) δ 7.51 – 7.40 (m, 5H), 5.17 (app. t, *J* = 5.0 Hz, 1H), 4.66 (br s, 1H), 4.55 (br s, ~0.5H), 4.50 (br s, ~0.5H), 3.54 (s, 3H), 2.83 – 2.56 (m, 2H), 2.58 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.40 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.19 – 2.14 (m, 2H), 1.47 (br s, 9H).

(1*R*,3*R*,5*S*,6*R*)-3-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-6-yl acetate, 3.9

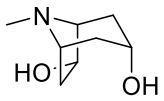


This reaction was carried out by Dr Ziyue Xiong. To a stirred solution of diol **3.31** (100 mg, 0.64 mmol) in THF (6 mL) at room temperature was added acetic anhydride (1 mL, 10.6 mmol). The resulting mixture was stirred for 12 h and then concentrated under vacuum. The residue was dissolved in chloroform (10 mL) and the solution washed with saturated aq. $NaHCO_3$ solution (10 mL). The separated aqueous layer was extracted with chloroform (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed by rotary evaporation to give compound **3.9** (110 mg, 87%) was obtained as a colourless oil and was used directly in the next step.

^{1}H NMR (400 MHz, CDCl3) δ 5.58 (dd, *J* = 7.5, 3.0 Hz, 1H, C**H**OAc), 4.07 (t, *J* = 5.0 Hz, 1H, C**H**OH), 3.30 – 3.25 (m, 1H, bridgehead H), 3.12 (br s, 1H, bridgehead H), 2.68 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.48 (s, 3H, NC**H**$_3$), 2.17 – 2.06 (m, 3H), 2.04 (s, 3H, **Ac**), 1.73 (br d, *J* = 15.5 Hz, 1H), 1.53 (br d, *J* = 15.5

Hz, 1H); **^{13}C NMR** (101 MHz, CDCl3) δ 171.3, 79.7, 65.5, 64.4, 59.3, 38.4, 36.6, 35.2, 34.2, 29.9; **HRMS** (ESI+): found: 200.1276, $[M+H]^+$ for $C_{10}H_{18}NO_3^+$ requires 200.1281.

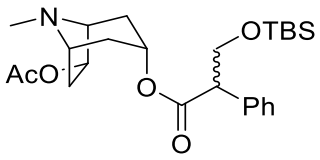
(1*R*,3*R*,5*S*,6*R*)-8-Methyl-8-azabicyclo[3.2.1]octane-3,6-diol, 3.31



This reaction was carried out by Dr Ziyue Xiong. To a stirred solution of diol **3.38** (360 mg, 1.48 mmol) in dry THF (9 mL) at 0 °C under N_2 was added $LiAlH_4$ (7.4 mL, 1.0 M in THF, 7.4 mmol) dropwise. The resulting mixture was stirred at 0 °C for 10 min then heated at reflux for 14 h. The mixture was cooled to 0 °C, then water (1.33 mL) was added followed by ethyl acetate (20 mL). The mixture was stirred for 10 min then the suspension was filtered through a pad of Celite®, rinsing through with methanol (10 mL), and the filtrates combined and the solvent removed by rotary evaporation. The crude product was purified by silica gel chromatography (dichloromethane/methanol/aq. ammonia solution, 75:25:1 then 50:50:1) to give compound **3.31** (170 mg, 73%) as a colourless solid.

R*f* 0.17 (dichloromethane/methanol/aq. ammonia, 30:10:0.4); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ +13 (*c* = 0.3 g/100 mL, EtOH), lit.[201] $[\alpha]_D^{20}$ –9 (*c* = 0.85 g/100 mL, EtOH) for 3*S*,6*S*-; **^{1}H NMR** (400 MHz, CD_3OD) δ 4.77 (dd, *J* = 7.5, 3.0 Hz, 1H), 3.91 (t, *J* = 5.0 Hz, 1H), 3.30 – 3.25 (m, 1H, bridgehead H), 3.02 (br s, 1H, bridgehead H), 2.64 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.53 (s, 3H, NC**H**$_3$), 2.09 – 1.93 (m, 3H), 1.73 (br d, *J* = 15.0 Hz, 1H), 1.59 (br d, *J* = 15.0, 2.0 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3OD) δ 76.8, 69.8, 64.4, 62.0, 40.4, 39.3, 37.3, 36.1; **HRMS** (ESI+): found: 158.1173, $[M+H]^+$ for $C_8H_{16}NO_2^+$ requires 158.1176.

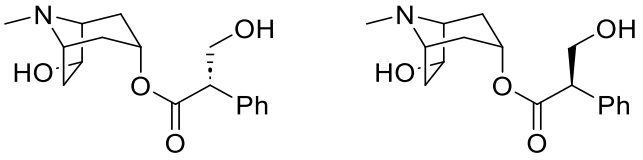
(1*R*,3*R*,5*S*,6*R*)-6-Acetoxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 3′-(*tert*-butyldimethylsilyloxy)-2′-phenylpropanoate, 3.44



This reaction was carried out by Dr Ziyue Xiong. To a stirred solution of acetate **3.9** (67 mg, 0.34 mmol) in dry chloroform (2 mL) at room temperature was added (±)-3-(*tert*-butyldimethylsilyloxy)-2-phenyl propanoic acid 37 (140 mg, 0.50 mmol), DCC (100 mg, 0.49 mmol) and DMAP (8 mg, 0.065 mmol). The resulting mixture was stirred at room temperature for 14 h and was then filtered through a pad of Celite®, rinsing through with chloroform. The solvent was removed by rotary evaporation and the residue was purified by silica gel chromatography (chloroform/methanol, 80:1 then 60:1 then 40:1) to give the inseparable 2'- diastereomers (dr ~3:1) of ester **3.44** (133 mg, 86%) as a colourless oil.

R*f* 0.33 (dichloromethane/methanol, 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 5.36 (dd, *J* = 7.5, 3.0 Hz, 0.25H), 5.18 (dd, *J* = 7.5, 3.0 Hz, 0.75H), 5.03 (t, *J* = 5.5 Hz, 0.25H), 5.02 (t, *J* = 5.5 Hz, 0.75H), 4.24 (t, *J* = 9.0 Hz, 1H), 3.90 – 3.72 (m, 2H), 3.25 (m, 0.75H), 3.16 – 3.09 (m, 0.5H) 3.07 (br s, 0.75H), 2.48 (dd, *J* = 8.0, 6.5 Hz, 1H), 2.45 (s, 2.25H), 2.44 (s, 0.75H), 2.16 – 1.95 (m, 3H) overlaying 2.03 (s, 0.75H) and 2.02 (s, 2.25H), 1.75 (br d, *J* = 15.5 Hz, 0.25H), 1.65 – 1.53 (m, 1.5H), 1.36 (br d, *J* = 15.5 Hz, 0.25H), 0.85 (s, 6.75H), 0.84 (s, 2.25H), 0.02, 0.01, and 0.00 (3 x s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) (resonances attributable solely to the minor diastereomer are starred) δ 171.8, 171.5*, 170.9*, 170.8, 135.9*, 135.7, 128.8, 128.4, 127.7, 79.3, 79.2*, 67.5, 67.3*, 65.4, 65.0*, 64.9*, 64.8, 58.9, 58.9*, 55.2, 38.3, 36.5, 36.1*, 32.4, 32.2*, 30.9*, 30.6, 29.8*, 25.9, 21.5*, 21.4, 18.4, 18.3*, –5.4 (two peaks); **HRMS** (ESI+): found: 462.2656, $[M+H]^+$ for $C_{25}H_{40}NO_5Si^+$ requires 462.2670.

(1*R*,3*R*,5*S*,6*R*,2′*S*)- and (1*R*,3*R*,5*S*,6*R*,2′*R*)-Anisodamine 3.45 and 3.46



This reaction was carried out by Dr Ziyue Xiong. To a stirred solution of ester **3.44** (85 mg, 0.18 mmol) in water (3 mL) at room temperature was added hydrochloric acid (concentrated, 240 μL). The mixture was heated at reflux for 2.5 h then cooled to room temperature. Hydrochloric acid (5%, 5 mL) was added and the solution extracted with chloroform (2 x 10 mL). Aq. NaOH solution (1 M) was then added dropwise to the separated aqueous layer until pH = 8. The aqueous layer was then extracted with chloroform (6 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed by rotary evaporation. The residue was purified by preparative TLC (chloroform/methanol/aq. ammonia solution, 50:10:0.6) to give the diastereomers **3.45** and **3.46** (2′*S*-/2′*R*-, ~2:1) as a colourless oil (30 mg, 53%).

R*f* 0.40 (chloroform/methanol/aq. ammonia solution, 50:10:0.6); **^{1}H NMR** (400 MHz, CD_3OD) δ 7.39 – 7.26 (m, 5H, Ph), 4.95 (t, *J* = 5.5 Hz, 1H), 4.53 (dd, *J* = 7.5, 3.0 Hz, ~0.33H), 4.19 – 4.10 (m, ~1.67H), 3.82 – 3.72 (m, 2H), 3.34 – 3.28 (m, ~0.67H occluded by NMR solvent), 3.21 – 3.17 (m, ~0.33H), 3.05 – 3.01 (m, ~0.33H), 2.95 – 2.92 (m, ~0.67H), 2.52 (s, ~2H), 2.51 (s, ~1H), 2.43 (dd, *J* = 14.0, 8.0 Hz, ~0.67H), 2.17 – 1.88 (m, ~3H), 1. 81 – 1.73 (m, ~0.66H), 1.64 (br d, *J* = 15.5 Hz, ~0.67H), 1.56 (br d, *J* = 15.5 Hz, ~0.67H); 1.43 (br d, *J* = 15.5 Hz, ~0.33H); **^{13}C NMR** (101 MHz, CD_3OD) (resonances attributable solely to the minor diastereomer are starred) δ 173.2, 173.1*, 137.3, 129.9, 129.2, 128.8, 76.4*, 76.2, 69.3*, 69.2, 68.5, 64.7, 64.6*, 61.4, 61.3*, 56.2, 39.9, 38.9, 38.7*, 34.5, 34.3*, 32.9; **HRMS** (ESI+): found: 306.1689, $[M+H]^+$ for $C_{17}H_{24}NO_4^+$ requires 306.1700.

References

1 H. Liu, B.-S. Chen, F. Z. R. de Souza, L. Liu; *Mar. Drugs*, **2018**, 16 (2),62–76.

2 Z. Tan, H. Ma, Q. Li, L. Pu, Y. Cao, X. Qu, C. Zhu, H. Ying; *Enzyme Microb. Technol.*, **2016**, 93, 191–199.

3 M. Moir, J. J. Danon, T. A. Reekie, M. Kassiou; *Expert Opin. Drug Discov.*, **2019**, 14 (11), 1137–1149.

4 A. P. Montgomery, J. M. Joyce, J. J. Danon, M. Kassiou; *Expert Opin. Drug Discov.*, **2023**, 18 (6), 597–613.

5 A. Kinner, P. Nerke, R. Siedentop, T. Steinmetx, T. Classen, K. Rosenthal, M. Nett, J. Pietruszka, S. Lutz; *Biomedicines*, **2022**, 10 (5), 964–994.

6 W. L. Liu, B. K. Hong, J. Wang, X. G. Lei; *Acc. Chem. Res.*, **2021**, 52 (11), 2569–2586.

7 E. J. Corey, J. F. Arnett, G. N. Widiger; *J. Am. Chem. Soc.*, **1975,** 97 (2), 430–431.

8 Y. Shibanuma, T. Okamoto; *Chem. Pharm. Bull.*, **1985**, 33 (8), 3187–3194.

9 J. C. K. Chu, T. Rovis; *Angew. Chem. Int. Ed. Engl.*, **2018**, 57, 62–101.

10 M. S. Kharasch, G. Sosnovsky; *J. Am. Chem. Soc*., **1958**, 80 (3), 756.

11 G. Sekar, A. DattaGupta, V. K. Singh; *J. Org. Chem*., **1998**, 63, 2961–2967.

12 H. F. Motiwala, B. Gülgeze, J. Aubé; *J. Org. Chem*., **2012**, 77, 7005–7022.

13 W. V. E. Doering, A. K. Hoffmann; *J. Am. Chem. Soc*., **1954**, 76 (23), 6162–6165.

14 K. Godula, D. Sames; *Science*, **2006**, 312, 67–72.

15 B. Hong, C. Li, Z. Wang, J. Chen, H. Li, X. Lei; *J. Am. Chem. Soc*., **2015**, 137, 11946–11949.

16 R. Breslow, S. H. Gellman; *J. Am. Chem. Soc.*, **1983**, 105, 6728–6729.

17 C. G. Espino, J. Du Bois; *Angew. Chem. Int. Ed*., **2001**, 40, 598–600.

18 C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois; *J. Am. Chem. Soc.*, **2004**, 126, 15378–15379.

19 J. L. Roizen, M. E. Harvey, J. Du Bois; *Acc. Chem. Res*., **2012**, 45, 911–922.

20 R. Hrdina, F. M. Metz, M. Larrosa, J.-P. Berndt, Y. Y. Zhygadlo, S. Becker, J. Becker; *Eur. J. Org. Chem.*, **2015**, 6231– 6236.

21 M. Muehlhofer, T. Strassner, W. A. Herrmann; *Angew. Chem. Int. Ed*., **2002**, 41 (10), 1745–1747.

22 S. K. Gupta, J. Choudhury; *Chem. Cat. Chem.*, **2017**, 9 (11), 1979–1984.

23 Q. Zhao, G. Meng, S. P. Nolan, M. Szostak; *Chem. Rev.*, **2020**, 120 (4), 1981–2048.

24 R. Breslow, L. E. Overmann; *J. Am. Chem. Soc*., **1970**, 94 (2), 1075–1077.

25 J. T. Groves, T. E. Nemo, R. S. Myers; *J. Am. Chem. Soc*., **1979**, 101, 1032–1033.

26 J.T. Groves, T. E. Nemo, *J. Am. Chem. Soc*., **1983**, 105 (20), 6243–6248.

27 C. L. Hill, B. C. Schardt; *J. Am. Chem. Soc*., **1980**, 102 (20), 6374–6375.

28 J. T. Groves, W. J. Kruper Jr, R. C. Haushalter; *J. Am. Chem. Soc*., **1980**, 102 (20), 6375–6377.

29 P. Battioni, J. P. Renaud, J. F. Bartoli, M. Reina-Artiles, M. Fort, D. Mansuy; *J. Am. Chem. Soc*., **1988**, 110 (25), 8462–8470.

30 C.-M. Che, V. Kar-Yan Lo, C.-Y. Zhou, J.-S. Huang; *Chem. Soc. Rev*., **2011**, 40, 1950–1975.

31 H. Lu, X. P. Zhang; *Chem. Soc. Rev*., **2011**, 40, 1899–1909.

32 J. J. Topczewski, P. J. Cabrera, N. I. Saper, M. S. Sanford; *Nature*, **2016**, 531, 220–224.

33 R. J. Sharpe, J. S. Johnson; *J. Am. Chem. Soc*., **2015**, 137, 4968–4971.

34 S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White; *Nat. Chem.*, **2015**, 7, 987–994.

35 A. Padwa, D. J. Austin, A. T. Price, M. A. Semones, M. P. Doyle, M. N. Protopopova, W. R. Winchester, A. Tran; *J. Am. Chem. Soc.*, **1993**, 115, 8669–8680.

36 R. K. Quinn, Z. A. Konst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal, E. J. Alexanian; *J. Am. Chem. Soc.*, **2016**, 138 (2), 696–702.

37 M. S. Chen, M. C. White; *Science*, **2010**, 327, 556–571.

38 P. E. Gormisky, M. C. White; *J. Am. Chem. Soc.*, 2013, 135 (38), 14052–14055.

39 J. Zhao, T. Nanjo, E. C. de Lucca Jr, M. C. White; *Nat. Chem.*, **2019**, 11, 213–221.

40 L. D'Accolti, C. Fusco, G. Lampignano, F. Capitelli, R. Curci; *Tetrahedron Lett*., **2008**, 49, 5614–5617.

41 E. M. Simmons, J. F. Hartwig; *Nature*, **2012**, 483, 70-73.

42 X. Huang, Y. Wang, J. Lan, J. You; *Angew. Chem. Int. Ed.*, **2015**, 54, 9404-9408.

43 V. G. Zaitsev, D. Shabashov, O. Daugulis; *J. Am. Chem. Soc*., **2005**, 127, 13154-13155.

44 S. Rej, A. Das, N. Chatani; *Coordination Chemistry Reviews*, **2021**, 431, 213683–213719.

45 B. H. Brodsky, J. Du Bois; *J. Am. Chem. Soc.*, **2005**, 127, 15391–15393.

46 N. D. Litvinas, B. H. Brodsky, J. Du Bois; *Angew. Chem. Int. Ed.*, **2009**, 48, 4513–4516.

47 A. M. Adams, J. Du Bois; *Chem. Sci.*, **2014**, 5, 656–659.

48 Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr, P. S. Baran; *J. Am. Chem. Soc.*, **2017**, 139, 7448–7451.

49 K. Godula, D. Sames; *Science*, **2006**, 312, 67–72.

50 J. A. Labinger, J. E. Bercaw; *Nature*, **2002**, 417, 507–514.

51 A. R. Dick, M. S. Sanford; *Tetrahedron*, **2006**, 62, 2439–2463.

52 A. E. Shilov, G. B. Shul'pin; *Chem. Rev*., **1997**, 97, 2879–2932.

53 D. J. Abrams, P. A. Provencher, E. J. Sorensen; *Chem. Soc. Rev*., **2018**, 57, 8925–8967.

54 M. C. White, J. P. Zhao; *J. Am. Chem. Soc*., **2018**, 140 (43), 13988–14009.

55 Bi. Chen, F. Z. Ribeiro de Souza, *RSC Adv.*, **2019**, 9, 2102–2115.

56 E. O'Reilly, S. J. Aitken, G. Grogan, P. P. Kelly, N. J. Turner, S. L. Flitsch, *J. Org. Chem.*, **2012**, 8, 496–500.

57 C. J. C. Whitehouse, S. G. Bell and L. L. Wong, *Chem. Soc. Rev.*, **2012**, 41, 1218–1260.

58 V. B. Urlacher, M. Girhard, *Trends Biotechnol.*, **2012**, 30, 26–36.

59 M. R. Waterman, D. S. Keeney; *Horm. Res.*, **1992**, 38, 217–221.

60 I. Hanukoglu; *J. Steroid Biochem. Mol. Biol.*, **1992**, 43 (8), 779–804.

61 R. Kaspera, R. Croteau; *Phytochem. Rev.*, **2006**, 5, 433–444.

62 Y.-J. Zhao, Q.-Q. Cheng, P. Su, X. Chen, X.-J. Wang, W. Gao, L.-Q. Huang; *Appl. Microbiol. Biotechnol.*, **2014**, 98 (6), 2371–2383.

63 D. Projean, P.-E. Morin, T. M. Tu, J. Ducharme; *Xenobiotica*, **2003**, 33 (8), 841–854.

64 T. Omura, R. J. Sato; *Biol. Chem.*, **1964**, 239 (7), 2370–2378.

65 T. Omura, R. J. Sato; *Biol. Chem.*, **1964**, 239 (7), 2379.

66 P. O. de Montellano; *Chem. Rev*., **2010**, 110, 932–948.

67 Y. Imai, R. Sato, T. Iyanagi, *J. Biochem.*, **1977**, 82, 1237–1246.

68 J. Rittle, M. T. Green; *Science*, **2010**, 330, 933–937.

69 R. Bernhardt, *J. Biotechnol.*, **2006**, 124, 128–145.

70 X. Ren, J. A. Yorke, E. Taylor, T. Zhang, W. Zhou, L. L. Wong, *Chem. Eur. J.*, **2015**, 21, 15039–15047.

71 I. F. Sevrioukova, H. Li, H. Zhang, J. A. Peterson, T. L. Poulos; *Proc. Natl. Acad. Sci. USA*, **1999**, 96 (5), 1863–1868.

72 K. Zhang, B. M. Shafer, M. D. Demars, H. A. Stern, R. J. Fasan; *J. Am. Chem. Soc.*, **2012**, 134 (45), 18695–18704.

73 R. Agudo, G.-D. Roiban, M. T. Reetz; *Chem. Bio. Chem.*, **2012**, 13 (10), 1465–1473.

74 G.-D. Roiban, R. Agudo, M. T. Reetz; *Tetrahedron*, **2013**, 69 (26), 5306–5311.

75 G.-D. Roiban, R. Agudo, A. Ilie, R. Lonsdale, M.T. Reetz; *Chem. Commun.*, **2014**, 50 (92), 14310–14313.

76 G.-D. Roiban, R. Agudo, M. T. Reetz; *Angew. Chem. Int. Ed.*, **2014**, 53 (33), 8659–8663.

77 A. Ilie, R. Agudo, G.-D. Roiban, M. T. Reetz; *Tetrahedron*, **2015**, 71 (3), 470–475.

78 A. Li, A. Ilie, Z. Sun, R. Lonsdale, J.-H. Xu, M. T. Reetz; *Angew. Chem. Int. Ed.*, **2016**, 55 (39), 12205–12208.

79 R. Agudo, G.-D. Roiban, R. Lonsdale, A. Ilie, M.T. Reetz; *J. Org. Chem.*, **2015**, 80 (2), 95–956.

80 S. Kille, F. Zilly, J. Acevedo, M. Reetz; *Nat. Chem.*, **2011**, 3, 738–743.

81 J. A. O'Hanlon, X. Ren, M. Morris, L. L. Wong, J. Robertson, *Org. Biomol. Chem.*, **2017**, 15, 8780–8787.

82 X. Ren, J. A. O'Hanlon, M. Morris, J. Robertson, L. L. Wong; *ACS Catal.*, **2016**, 6 (10), 6833–6837.

83 X. Ren, J. A. Yorke, E. Taylor, T. Zhang, W. Zhou, L. L. Wong; *Chem. Eur. J.*, **2015**, 21 (42), 15039–15047.

84 L. A. Harwood, L. L. Wong, J. Robertson, *Angew. Chem. Int. Ed.*, **2021**, 61, 4434–4447.

85 P. Fernandez Rodriguez, *Streamlined synthesis of taxol analogues*, PhD thesis, Department of Chemistry, University of Oxford, **2017**.

86 Y. Zhang, Z. Xiong, Y. Li, M. Wilson, K. E. Christensen, E. Jaques, P. Hernández-Lladó, J. Robertson, L. L. Wong; *Nat. Synth.*, **2022**, 1, 936–945.

87 Alethea Lee, *Late-Stage C−H Activation of Spiropiperidines via Evolved P450BM3 Mutants and its Application to Fragment-Based Drug Discovery*, PhD thesis, Department of Chemistry, University of Oxford, **2022**.

88 J. Ramharter, H. Weinstabl, J. Mulzer; *J. Am. Chem. Soc.*, **2010**, 132, 14338–14339.

89 Y. Ishihara, P. S. Baran; *Synlett*, **2010**, 12, 1733–1745.

90 A. Mendoza, Y. Ishihara, P. S. Baran; *Nat. Chem.*, **2012**, 4, 21–25.

91 C. Yuan, Y. Jin, N. C. Wilde, P. S. Baran; *Angew. Chem. Int. Ed*., **2016**, 128 (29), 8420–8424.

92 Y. Kanda, H. Nakamura, S. Umemiya, R. K. Puthukanoori, V. R. M. Appala, G. K. Gaddamanugu, B. R. Paraselli, P. S. Baran; *J. Am. Chem. Soc*., **2020**, 142 (23), 10526–10533.

93 Y. Kanda, Y. Ishihara, N. C. Wilde, P. S. Baran; *J. Org. Chem*., **2020**, 85, 10293–10320.

94 F. Lovering, J. Bikker, C. Humblet; *J. Med. Chem.*, **2009**, 52 (21), 6752–6756.

95 A. C. Smith, S. Cabral, D. W. Kung, C. R. Rose, J. A. Southers, C. N. García-Irizarry, D. B. Damon, S. W. Bagley, D. A. Griffith; *J. Org. Chem*., **2016**, 81 (9), 3509–3519.

96 C. M. Marson; *Chem. Soc. Rev*., **2011**, 40, 5514–5533.

97 Y. Zheng, C. M. Tice, S. B. Singh; *Bioorg. Med. Chem. Lett.*, **2014**, 24 (16), 3673–3682.

98 E. Vitaku, D. T. Smith, J. T. Njardarson; *J. Med. Chem*., **2014**, 57 (24), 10257–10274.

99 R. D. Taylor, M. MacCoss, A. D. G. Lawson; *J. Med. Chem*., **2014**, 57 (14), 5845–5859.

100 F. M. D. Ismail, D. O. Levitsky, V. M. Dembitsky; *Eur. J. Med. Chem.*, **2009**, 44 (9), 3373–3387.

101 E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes; *Chem. Eur. J*., **2012**, 18, 10092–10142.

102 Campos, K. R., *Chem. Soc. Rev*., **2007**, 36, 1069–1084.

103 M. X. Cheng, S. D. Yang; *Synlett*, **2017**, 28, 159–174.

104 J. W. Beatty, C. R. J. Stephenson; *Acc. Chem. Res*., **2015**, 48, 1474–1484.

105 D. Seidel; *Acc. Chem. Res*., **2015**, 48, 317–328.

106 Y. He, Z. Zheng, J. Yang, X. Zhang, X. Fan; *Org. Chem. Front.*, **2021**, 8, 4582.

107 S. Singh; *Chem. Rev.*, **2000**, 100 (3), 925–1024.

108 G. Grynkiewicz, M. Gadzikowska, *Pharmacol. Rep.*, **2008**, 60, 439–463.

109 R. Christen: Tropane alkaloids: old drugs used in modern medicine. In: Studies in Natural Products Chemistry, Bioactive Natural Products, Part C. Ed. Rahman A, Elsevier Science and Technology, Amsterdam, **2000**, 22, 717–749.

110 L. Gyermek: Tropane alkaloids. In: Pharmacology of Antimuscarinic Agents. Ed. Gyermek L, CRC Press, Boca Raton, **1997**, 47–160.

111 R. S. Holzman; *Anesthesiology*, **1998**, 89, 241–249.

112 C. D. Leake, E. W. Pelikan; *J. Clin. Pharmacol.*, **1976**, 16, 669–671.

113 W. Sneader: Plant products analogues and compounds derived from them. In: Drug Discovery; A History. Ed. Sneader W, Wiley & Sons, Ltd, Chichester, **2005**, 115–150.

114 M. Lounasmaa, T. Tamminen: The tropane alkaloids. In: The Alkaloids. Ed. Brossi A, Academic Press, New York, **1993**, 44, 1–114.

115 H. F. Olivo, M. S. Hemenway; *J. Org. Chem.*, **1999**, 64 (24), 8968–8969.

116 M. S. Hemenway, H. F. Olivo; *J. Org. Chem.*, **1999**, 64 (17), 6312–6318.

117 C. R. Davis, R. A. Johnson, J. I. Cialdella, W. G. Liggett, S. A. Mizsak, V. P. Marshall; *J. Org. Chem.*, **1997**, 62 (7), 2244–2251.

118 P. R. O. de Montellano; *Cytochrome P450*, **2015**, Ed. 4, Springer, Chapter 5, Pages 177–259.

119 Y. Li, L. L. Wong, *Angew. Chem. Int. Ed*., **2019**, 58, 9551–9555.

120 C. J. C. Whitehouse, S. G. Bell, S. G. H. G. Tufton, R. J. P. Kenny, L. C. I. Ogilvie, L. L. Wong; *Chem. Commun.*, **2008**, 8, 966–968.

121 L. D. Syntrivanis, L. L. Wong, J. Robertson; *Eur. J. Org. Chem.*, **2018**, 2018 (45), 6369–6378.

122 C. J. C. Whitehouse, W. Yang, J. A. Yorke, B. C. Rowlatt, A. J. F. Strong, C. F. Blankford, S. G. Bell, M. Bartlam, L. L. Wong, Z. Rao; *Chem. Bio. Chem.*, **2010**, 11 (18), 2549–2556.

123 C. J. C. Whitehouse, W. Yang, J. A. Yorke, H. G. Tufton, L. C. I. Ogilvie, S. G. Bell, Weihong. Zhou, M. Bartlam, Z. Rao, L. L. Wong; *Dalton Trans.*, **2011**, 40, 10383–10396.

124 W. Chen, M. J. Fisher, A. Leung, Y. Cao, L. L. Wong; *ACS Catal.*, **2020**, 10 (15), 8334–8343.

125 C. J. Whitehouse, S. G. Bell, W. Yang, J. A. Yorke, C. F. Blanford, A. J. F. Strong, E. J. Morse, M. Bartlam, Z. Rao, L. L. Wong; *Chem. Bio. Chem.*, **2009**, 10 (10), 1654–1656.

126 T. Nagase, T. Takahashi, T. Sasaki, A. Nagumo, K. Shimamura, Y. Miyamoto, H. Kitazama, M. Kanesaka, R. Yoshimoto, K. Aragane, S. Tokita, N. Sato; *J. Med. Chem*, **2009**, 52 (14), 4111–4114.

127 Y. Li, F. Jia, Z. Li; *Chem. Eur. J.*, **2012**, 19 (1), 8286.

128 W. Chen, M. J. Fisher, A. Leung, Y. Cao, L. L. Wong; *ACS Catal*., **2020**, 10 (15), 8334–8343.

129 A. de Raadt, H Griengl, H. Weber; *Chem. Eur. J.*, **2001**, 7 (1), 27–31.

130 Fodor G: The tropane alkaloids. In: The Alkaloids; Chemistry and Physiology, vol. XIII. Ed. Manske RHF, Academic Press, New York, **1971**, 351–396.

131 Henry TA: The tropane alkaloids. In: The Plant Alkaloids. Ed. Henry TA, JA Churchill Ltd, London, **1949**, 69–118.

132 Sneader W: Plant products analogues and compounds derived from them. In: Drug Discovery; A History. Ed. Sneader W, Wiley & Sons, Ltd, Chichester, **2005**, 115–150.

133 J. X. Xie; *Sci. Bull.*, **1975**, 20, 197–198.

134 J. M. Poupko, S. I. Baskin and E. Moore, *J. Appl. Toxicol*., **2007**, 27, 116–121.

135 Y. Yu, C. Zhu, Y. Hong, L. Chen, Z. Huang, J. Zhou, X. Tian, D. Liu, B. Ren, C. Zhang, C. Hu, X. Wang, R. Yin, Y. Gao, Z. Zhang; *Crit. Care*, **2021**, 25, 349–359.

136 K. Ishimaru, K. Shimomura; *Phytochemistry*, **1989**, 28, 3507–3509.

137 S. Clementson, M. Jessing, H. Pedersen, P. Vital**,** J. L. Kristensen; *J. Am. Chem. Soc.*, **2019**, 141, 8783–8786.

138 R. Shang, D. Ji, L. Chu, Y. Fu, L. Liu; *Angew. Chem*. **2011**, 50, 4470–4474.

139 F. Orsini, F. Pelizzoni; *Synth. Commun.*, **1987**, 17 (12), 1389–1402.

140 M. Majewski, R. Lazny; *Synlett*, **1996**, 785–786.

141 M. Majewski, R. Lazny, A. Ulaczyk; *Can. J. Chem.* **1997**, 75, 754–761.

142 A. El-Wareth, A. O. Sarhan; *Monatshefte für Chemie*, **1999**, 130, 563–572.

143 N. Cramer, S. Laschat, A. Baro, W. Frey; *Synlett*, **2003**, 2175–2177.

144 K. Kulkarni, A. Y. Zhao, A. W. Purcell, P. Perlmutter; *Synlett*, **2008**, 2209–2212.

145 Z. Y. Mao, S. Y. Huang, L. H. Gao, A. E. Wang, P. Q. Huang; *Sci. China Chem.*, **2014**, 57, 252–264.

146 N. Cramer, S. Laschat, A. Baro; *Synlett*, **2003**, 14, 2178–2181.

147 Y.-Y. Niu, L. Zhu, Y.-Y, Cui, H.-Z. Liu, H.-Z. Chen, Y. Lu; *Bioorg. Med. Chem.*, **2008**, 16, 10251–10256.

148 G. Fodor, O. Kovacs; *J. Chem. Soc*., **1953**, 2341–2344.

149 A. Berthod; *Anal. Chem*., **2006**, 78 (7), 2093–2099.

150 E. Busto, V. Gotor-Fernández, V. Gotor; *Chem. Soc. Rev*., **2010**, 39, 4504–4523.

151 M. Kapoor, M. N. Gupta; *Process Biochem.*, **2012**, 47, 555–569.

152 A. Ghanem, H. Y. Aboul-Enein; *Chirality*, **2005**, 17, 1–15.

153 Z. H. Yan, Y. Lu, A. Valler, H. Z. Liu, Z. N. Chen; *J. Shanghai Second Med. Univ.*, **2001**, 21, 199.

154 Z.-H. Chen, J.-M. Tian, Z.-M. Chen, Y.-Q. Tu; *Chem. Asian J.* **2012**, 7, 2199–2202.

155 T. R Hoye, C. S Jeffrey, F. Shao; *Nat. Protoc.*, **2007**, 2 (10), 2451–2458.

156 S. W. McCall, T. A. Grillo, D. L. Comins, *Org. Lett*, **2008**, 10 (15), 3255–3257.

157 R. Noyori, Y. Hayakawa; *Tetrahedron*, **1985**, 41 (24), 5879–5886.

158 X. Wang, J. Li, C. Xu, Y. Li, T. Gong, X. Sun, Y. Fu, Q. He, Z. Zhang; *Bioconjugate Chem*., **2014**, 25 (11), 2046–2054.

159 B. Neises, W. Steglich; *Angew. Chem. Int. Ed. Engl*., **1978**, 17 (7), 522–524.

160 B. Latli, M. Stiasni, M. Hrapchak, Z. Li, N. Grinberg, H. Lee, C. A. Busacca, C. H. Senanayake; *J. Label. Compd. Radiopharm.*, **2016**, 59 (13), 557–564.

161 G. Cheng, X. Wang, R. Zhu, C. Shao, J. Xu, Y. Hu; *J. Org. Chem.*, **2011**, 76 (8), 2694–2700.

162 R. Ushimaru, M. W. Ruszczycky, W.-C. Chang, F. Yan, Y.-N. Liu, H.-W. Liu; *J. Am. Chem. Soc.*, **2018**, 140 (24), 7433–7436.

163 A. P. Kozikowski, W. Tückmantel; *Acc. Chem. Res*., **1999**, 32, 641–650.

164 D. M. Wong, H. M. Greenblatt, H. Dvir, P. R. Carlier. Y. F. Han, Y. P. Pang, I. Silman, J. L. Sussman; *J. Am. Chem. Soc*., **2003**, 125, 363–373.

165 Y. Xu, J. Shen, X. Luo, I. Silman, J. L. Sussman, K. Chen, H. L. Jiang, *Am. Chem. Soc*., **2003**, *125*, 11340–11349.

166 X. Ma, D. R. Gang; *Nat. Prod. Rep.*, **2004**, 21, 752–772.

167 R. H. Burnell; *J. Chem. Soc*., **1959**, 3091.

168 Z. Zhang, C. Wang, X. Wu, Y. Huang, W. Zhou, Q. Zhao, *J. Org. Chem.*, **2019**, 84, 11301−11305.

169 Wu, Z. Y. Xinhua Outline of Materia Medica, 1st ed.; Shanghai Science and Technology Press: Shanghai, 1990; Vol. 3, p 621.

170 Z-J. Zhang, Q-F. Zhu, X-D. Wu, Q-S. Zhao; *Tetrahedron Lett.*, **2020**, 61 (2), 151381–151384.

171 V. M. Dembitsky; *J. Nat. Med*., **2007**, 62, 1−33.

172 N. Tanaka, M. Okasaka, Y. Ishimaru, Y. Takaishi, M. Sato, M. Okamoto, T. Oshikawa, S. U. Ahmed, L. M. Consentino, K-H. Lee; *Org. Lett*., **2005**, 7, 2997−2999.

173 M. J. Martin, R. Fernandez, A. Francesch, P. Amade, S. S. de Matos-Pita, F. Reyes, C. Cuevas; *Org. Lett*., **2010**, 12, 912−914.

174 C. S. Yang, X. B. Wang, J. S. Wang, J. G. Luo, J. Luo, L. Y. Kong; *Org. Lett*., **2011**, 13, 3380−3383.

175 T. V. Bliss, T. Lomo; *J. Physiol*., **1973**, 232, 331−356.

176 M. A. Lynch; *Physiol. Rev*., **2004**, 84, 87−136.

177 J. R. Whitlock, A. J. Heynen, M. G. Shuler, M. F. Bear; *Science*, **2006**, 313, 1093−1097.

178 Y. Inubushi, H. Ishii, T. Harayama, R. H. Burnell, W. A. Ayer, B. Altenkirk; *Tetrahedron Lett.*, **1967**, 8 (12), 1069–1072.

179 C. H. Heathcock, K. M. Smith, T. A. Blumenkopf; *J. Am. Chem. Soc.*, **1986**, 108 (16), 5022–5024.

180 C. H. Heathcock, K. M. Smith, T. A. Blumenkopf; *J. Org. Chem.*, **1989**, 54 (7), 1548–1562.

181 Y.-R. Yang, L. Shen, K. Wei, Q.-S. Zhao; *J. Org. Chem*., **2010**, 75, 1317–1320.

182 T. Harayama, M. Takatani, Y. Inubushi; *Tetrahedron Lett.*, **1979**, 44, 4307–4310.

183 T. Harayama, M. Takatani, Y. Inubushi; *Chem. Pharm. Bull.*, **1980**, 28 (8), 2394–2402.

184 S. Tanimura, S. Yokoshima, T. Fukuyama; *Org. Lett.*, **2017**, 19, 3684–3686.

185 K. Xu, B. Cheng, Y. Li, T. Xu, C. Yu, J. Zhang, Z. Ma, H. Zhai; *Org. Lett.*, **2014**, 16, 196–199.

186 A. Nakayama, N. Kogure, M. Kitajima, H. Takayama; *Org. Lett.*, **2009**, 11 (23), 5554–5557.

187 H. Kaneko, S. Takahashi, N. Kogure, M. Kitajima, H. Takayama; *J. Org. Chem*., **2019**, 84, 5645−5654.

188 G. Pan, R. Williams; *J. Org. Chem*., **2012**, 77, 4801−4811.

189 S.-J. Min, G. O. Jones, K. N. Houk, S. J. Danishefsky; *J. Am. Chem. Soc*., **2007**, 129, 10078–10079.

190 H. Zaimoku, T. Taniguchi; *Chem. Eur. J.*, **2014**, 20, 9613–9619.

191 A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen; *Chem.Commun*., **2006**, 4928–4930.

192 R. D. Carpenter, J. C. Fettinger, K. S. Lam, M. J. Kurth, *Angew. Chem., Int. Ed*., **2008**, 120 (34), 6507–6510.

193 D. Caine, K. Procter, R. A. Cassell, *J. Org. Chem*., **1984**, 49, 2647–2648.

194 X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, H. Shao, X. Meng; *Angew. Chem. Int. Ed.*, **2011**, 50, 3916–3919.

195 B. Hong, H. Li, J. Wu, J. Zhang, X. Lei; *Angew. Chem. Int. Ed.*, **2015**, 54, 1011–1015.

196 F. Fringuelli, F. Pizzo, A. Taticchi, T. D. J. Halls, and E. Wenkert, *J. Org. Chem.*, **1982**, 47, 5056–5065.

197 S. M. Allin, S. N. Gaskell, M. R. J. Elsegood, W. P. Martin, *J. Org. Chem.*, **2008**, 73, 6448–6451.

198 Based on work undertaken by DPhil student Patricia Fernández Rodríguez 2017.

199 K. B. Wiberg, L. K. Olli, N. Golembeski, R. D. Adams; *J. Am. Chem. Soc.*, **1980**, 102 (25), 7467–7475.

200 E. W. Warnhoff, D. G. Martin, William S. Johnson; *Org. Synth.*, **1957**, 37, 8.

201 C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *J. Org. Chem.*, **1963**, 28, 3134–3140.

202 M. P. L. Caton, E. C. J. Coffee, T. Parker, G. L. Watkins, *Synth. Commun.*, **1974**, 4, 303–306.

203 F. Fringuelli, F. Pizzo, A. Taticchi, T. D. J. Halls, E. Wenkert; *J. Org. Chem*., **1982**, 47, 5056–5065.

204 F. Fringuelli, F. Pizzo, A. Taticchi, E. Wenkert; *J. Org. Chem*., **1983**, 48, 2802–2808.

205 H. Nakamura, M. Kawakami, C. Tsukano; *Synlett*, **2019**, 30, 2253–2257.

206 C. Schotes, M. Althaus, R. Aardoom, A. Mezzetti; *J. Am. Chem. Soc.*, **2012**, 134 (2), 1331–1343.

207 C. Schotes, A. Mezzetti; *Chimia*, **2011**, 65, 4, 231–234.

208 C. Schotes, A. Mezzetti; *J. Org. Chem*., **2011**, 76 (14), 5862–5866.

209 C. Schotes, A. Mezzetti; *J. Am. Chem. Soc.*, **2010**, 132 (11), 3652–3653.

210 H-J. Liu, G. Ulibarri, E. N. C. Browne; *Can. J. Chem.*, **1992**, 70 (5), 1545–1554.

211 H. J. Liu, M. G. Kulkarni; *Tetrahedron Letters*, **1985**, 26 (40), 4847–4850.

212 Y-J. Ping, Y-M. Zhou, L-L. Wu, Z-R. Li; X. Gu; *Org. Chem. Front.*, **2021**, 8 (9), 1910–1917.

213 V. N. G. Lindsay, R. A. Murphy, R. Sarpong; *Chem. Commun.*, **2017**, 53 (74), 10291–10294.

214 P. R. Leger, R. A. Murphy, E. Pushkarskaya, R. Sarpong; *Chem. Eur. J.*, **2015**, 21 (11), 4377–4383.

215 J. Choi, H. Park, H. J. Yoo, S. Kim, E. J. Sorensen; *J. Am. Chem. Soc.*, **2014**, 136 (28), 9918–9921.

216 K. S. Halskov, B. S. Donslund, S. Barfuesser, K. A. Jorgensen, Karl Anker; *Angew. Chem., Int. Ed.*, **2014**, 53 (16), 4137–4141.

217 J-L. Zhu, H-J. Liu, K-S. Shia; *Chem. Commun.*, **2000**, 17, 1599–1600.

218 S-I. Murahashi; *Sci. Synth.*, **2004**, 19, 345–402.

219 J. J. Lee, W. H. Kim, S. J. Danishefsky; *Tetrahedron Lett*., **2010**, 51 (35), 4653–4654.

220 K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa, H. Yamamoto; *J. Am. Chem. Soc.*, **2010**, 132 (16), 5625–5627.

221 J-J. Liu, K-S. Shia; *Tetrahedron Lett.*, **1995**, 36 (11), 1817–1820.

222 J-A. Funel, L. Ricard, J. Prunet, Joelle; *Chem. Commun.*, **2005**, 38, 4833–4835.

223 Z. Liu, X. Lin, N. Yang, Z. Su, C. Hu; *J. Am. Chem. Soc.*, **2016**, 138 (6), 1877–1883.

224 H. Zaimoku, T. Taniguchi; *Chem. Eur. J.*, **2014**, 20 (31), 9613–9619.

225 H.-J. Liu, K.-S. Shia; *Tetrahedron Lett.*, **1995**, 36 (11), 1817-1820.

226 T. Ohfusa, A. Nishida, *Tetrahedron*, **2011**, 67, 1893–1906.

227 A. Sobanska, *Application of the glyoxylate ene reaction to natural product synthesis*, PhD thesis, Department of Chemistry, University of Oxford, **1996**.

228 G. Zhu, C. Zhou, S. Chen, S. Fu**,** B. Liu, *Org. Lett.*, **2019**, 21, 7809–7812.

229 T. V. Lee and J. Toczek, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 759–762.

230 H. C. Brown, G. Zwiegal; *J. Am. Chem. Soc.*, **1961**, 83, 3834–3840.

231 H. C. Brown, G. Zwiegal; *J. Am. Chem. Soc.*, **1959**, 81, 1512.

232 H. C. Brown, C. G. Secuten, R. Liottal; *J. Am. Chem. Soc.*, **1979**, 101, 96–99.

233 A. Mahmood, H. Z. Alkhathlan, S. Parvez, M. Khan, S. A. Shahzad; *Molecules*, **2015**, 20 (6), 9890–9905.

234 T. Sasaki, S. Eguchi, F. Nakata; *Tetrahedron Lett.*, **1978**, 19 (23), 1999–2002.

235 M. Larchevêque, G. Valette, T. Cuvigny; *Tetrahedron lett.*, **1979**, 35, 1745–1749.

236 D. Kundu, P. Maity, B. C. Ranu; *Org. Lett.*, **2014**, 16 (4), 1040–1043.

237 H. Harada, R. K. Thalji, R. G. Bergman, J. A. Ellman; *J. Org. Chem.*, **2008**, 73 (17), 6772–6779.

238 R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman, J. A. Porco; *J. Am. Chem. Soc.*, **2003**, 125 (26), 7889–7901.

239 T. Ogawa, T. Kiji, K. Hayami, H. Suzuki; *Chem. Lett.*, **1991**, 1443–1446.

240 S. W. Lardy, V. A. Schmidt; *J. Am. Chem. Soc.* **2018**, 140 (39), 12318–12322.

241 *Peloton Therapeutics, Inc*. **2016**, WO2016/145032, A2.

242 H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, G. C. Buzby, R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Siuda, Leland L. Smith, J. Tokolics, D. H. P. Watson; *J. Chem. Soc.*, **1964**, 4472–4492.

243 B. Karimi, G. R. Ebrahimian, H. Seradj; *Org. Lett.*, **1999**, 1 (11), 1737–1739.

244 P. Becker, T. Duhamel, C. Martínez, K. Muñiz; *Angew. Chem. Int. Ed.*, **2018**, 57 (18), 5166–5170.

245 Y. Gao, Z. Cao, Q. Zhang, R. Guo, F. Ding, Q. You, J. Bi, Y. Zhang; *J. Nat. Prod.*, **2019**, 82 (7), 1908–1916.

246 R. Hemelaere, F. Carreaux, B. Carboni; *J. Org. Chem*., **2013**, 78 (13), 6786–6792.

247 K. C. Nicolaou, G. Scott Tria, D. J. Edmonds, M. Kar; *J. Am. Chem. Soc.*, **2009**, 131 (43), 15909–15917.

248 K. C. Nicolaou, A. F. Stepan, T. Lister, A. Li, A. Montero, G. Scott Tria, C. I. Turner, Y. Tang, J. Wang, R. M. Denton, D. J. Edmonds; *J. Am. Chem. Soc*., **2008**, 130 (39), 13110–13119.

249 K. C. Nicolaou, Y. Tang, J. Wang, A. F. Stepan, A. Li, A. Montero; *J. Am. Chem. Soc*., **2007**, 129 (48), 14850–14851.

250 P. A. Grieco, J. L. Collins, S. T. Handy; *Synlett*, **1995**, 1155–1157.

251 P. A. Grieco, J. J. Nunes, M. D. Gaul; *J. Am. Chem. Soc.*, **1990**, 112, 4595–4596.

252 H. C. Hailes, B. Isaac, M. H. Javaid, *Tetrahedron*, **2001**, 57 (52), 10329–10333.

253 N. Isaka, M. Tamiya, A. Hasegawa, M. Ishiguro; *Eur. J. Org. Chem.*, **2012**, 2012 (4), 665– 668.

254 G. Stork, M. E. Jung; *J. Am. Chem. Soc.*, **1974**, 86, 3682–3684.

255 A. Lubineau, E. Meyer; *Tetrahedron*, **1988**, 44, 6065–6070.

256 Sonia Fresu, *Synthesis of Bridged Bicycles and Macrocycles from Cycloalkanones via Tandem Reactions and Ring Expansion*, PhD thesis, Department of Chemistry, University of Dortmund, **2004**.

257 H. Hagiwara, Y. Yamada, H. Sakai, T. Suzuki, M. Ando; *Tetrahedron*, **1998**, 54, 10999–11010.

258 C. Cavé, J. Valancogne, R. Casas, J. d'Angelo; *Tetrahedron Lett.*, **1998**, 39, 3133–3136.

259 D. Li, J. Yang, B. Liu, J. Gong, Z. Yang; *Org. Lett.*, **2021**, 23, 4532–4537.

260 From work done within the group by Shuyang Li.

261 G. C. Hirst, T. O. Johnson Jr., L. E. Overman; *J. Am. Chem. Soc.*, **1993**, 115 (7), 2992–2993.

262 K. Shibata, S. Takegawa, N. Koizumi, N. Yamakoshi, E. Shimazawa; *Chem. Pharm. Bull*., **1992**, 40 (4), 935–941.

263 R. V. Stevens, N. Beaulieu, W. H. Chan, A. R. Daniewski, T. Takeda, Ad. Waldner, P. G. Williard, U. Zutter*; J. Am. Chem. Soc.*, **1986**, 108 (5), 1039–1049.

264 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah; *J. Org. Chem.*, **1996**, 61 (11), 3849–3862.

265 Q. Wang, C. Zhang, J. Yang; *Chin. Chem. Lett.*, **2020**, 31 (17), 1906–1910.

266 S. M. Ng, S. J. Bader, M. L. Snapper; *J. Am. Chem. Soc.*, **2006**, 128 (22), 7315–7319**.**

267 A. R. Matlin, C. F. George, S. Wolff, W. C. Agosta; *J. Am. Chem. Soc.*, **1986**, 108 (12), 3385–3394.

268 G.Majetich, A. J.Leigh, S. Condon; *Tetrahedron Lett.*, **1991**, 32 (5), 605–608.

269 M. Ladlow, G. Pattenden; *J. Chem. Soc. Perkin Trans. 1*, **1988**, 1107–1118.

270 G. A. Molander, C. T. Bibeau; *Tetrahedron Lett.*, **2002**, 43 (31), 5385–5388.

271 G. Majetich, J. Seop Song, A. J. Leigh, S. M. Condon; *J. Org. Chem.*, **1993**, 58, 5, 1030–1037.

272 B. Wu, A. Mallinger, J. Robertson; *Org. Lett.*, **2010**, 12, 12, 2818–2821.

273 K. Liu, C. Chau, C. Sha, *Chem. Commun.*, **2008**, 91–93.

274 H. Cheng. X. Wang, L. Chang, Y. Chen, L. Chu, Z. Zuo; *Sci. Bull.*, **2019**, 64 (24), 1896–1901.

275 PCT Int. Appl. 2005087700, **2005**.

276 G. K. Tranmer, C. Yip, S. Handerson, R. W. Jordan, W. Tam; *Can. J. Chem.*, **2000**, 78, 527–535.

277 J. Tuyêt**;** *Tetrahedron Lett.*, **1991**, 32 (19), 2121–2124.

278 V. Durel, C. Lalli, T. Roisnel, P. van de Weghe; *J. Org. Chem.*, **2016**, 81 (3), 849–859.

279 G. Gros, E. Fowler, J. Hasserodt; *Tetrahedron*, **2014**, 70 (37), 6554–6560.

280 R. M. Coates, J. Z. Ho, M. Klobus, L, Zhu; *J. Org. Chem.*, **1998**, 63 (25), 9166–9176.

281 O. H. Ko, J. H. Hong; *Arch. Pharm.*, **2004**, 337 (11), 579–586.

282 A. Srikrishna, R. R. Babu; *Tetrahedron Lett.*, **2007**, 48, 6916–6919.

283 L. A. Paquette, X. Peng, J. Yang, Jiong, H.-J. Kang; *J. Org. Chem.*, **2008**, 73 (12), 4548–4558.

284 D. Oguro, N. Mori, H. Takikawa, H. Watanabe; *Tetrahedron*, **2018**, 74 (39), 5745–5751.

285 C. Aouf, N. Galy, H. Doucet, M. Santelli; *Appl. Organometal. Chem*., **2010**, 24, 794–797.

286 U. Berlage; *Tetrahedron lett.*, **1987**, 28 (27), 3091–3094.

287 A. Fürstner, A. Hupperts; *J. Am. Chem. Soc.*, **1995**, 117, 4468–4475.

288 A. Fürstner, B. Boganović; *Angew. Chem. Int. Ed. Engl*., **1996**, 35, 2442–2469.

289 S. Rele, S. Chattopadhyay, S. K. Nayak; *Tetrahedron Lett.*, **2001**, 42, 9093–9095.

290 N. Stuhr-Hansen; *Tetrahedron Lett.*, **2005**, 46, 5491–5494.

291 M. K. J. Ter Wiel, R. A. Van Delden, A. Meetsma, B. L. Feringa*; J. Am. Chem. Soc*., **2003**, 125, 15076–15086.

292 M. K. J. Ter Wiel, R. A. Van Delden, B. L. Feringa; *Chem. Commun*., **2004**, 200–201.

293 M. K. J. Ter Wiel, B. L. Feringa; *Synthesis*, **2005**, 1789–1796.

294 P. R. Brooks, R. Bishop, D. C. Craig, M. L. Scudder, J. A. Counter; *J. Org. Chem.*, **1993**, 58, 5900–5906.

295 T. Mukaiyama, Y. Ogawa, K. Kuroda, J. Matsuo; *Chem. Lett.* **2004**, 33 (11), 1412–1413.

296 Y. Ogawa, K. Kuoda, J. Matsuo, T. Mukaiyama; *Bull. Chem. Soc. Jpn.*, **2005**, 78, 677–697.

297 K. Hemming, M. J. Bevan, C. Loukou, S. D. Patel, D. Renaudeau; *Synlett*, **2000**, 11, 1565–1568.

298 B. L. Nilsson, L. E. Overman, J. R. de Alaniz, J. M. Rohde, *J. Am. Chem. Soc.*, **2008**, 130 (34), 11297–11299.

299 S. Z. Peng, C. K. Sha; *Org. Lett*., **2015**, 17 (14), 3486–3489.

300 H. Y. Lee, C. K. Sha; *J. Org. Chem*., **2012**, 77 (1), 598–605.

301 C. H. Chen, Y. K. Chen, C. K. Sha; *Org. Lett*., **2010**, 12 (7), 1377–1379.

302 K. Miura, D. Takeshi, H. A. Hosomi; *Tetrahedron Lett.*, **1994**, 35 (51), 9605–9608.

303 B. Giese, B. Kopping, C. Chatgilialoglu; *Tetrahedron Lett.*, **1989**, 30 (6), 1989, 681–684.

304 G. R. Dake, E. E. Fenster, B. O. Patrick; *J. Org. Chem*., **2008**, 73 (17), 6711–6715.

305 K. Hemming, M. J. Bevan, C. Loukou, S. D. Patel, D. Renaudeau; *Synlett*, **2000**, 11, 1565–1568.

306 H. Zhu, L. Huang, X. Xu, Y.-M. Shen; *Synth. Commun.*, **2010**, 40, 3322–3331.

307 X. F. Duan, J. Zeng, J. W. Lü, Z. B. Zhang; *J. Org. Chem.*, **2006**, 71 (26), 9873–9876.

308 H. Meier, B. Rose, D. Schollmeyer; *Liebigs Ann./Recl*. **1997**, 1173.

309 A. Bongso, R. Roswanda, Y. M. Syah; *RSC Adv*., **2022**, 12, 15885–15909.

310 E. J. Coery, R. L. Danheiser, S. Chandrasekaran; *J. Org. Chem*., **1976**, 41 (2), 260–265.

311 L. R. Krepski, A. Hassner; *J. Org. Chem.*, **1978**, 43 (14), 2879–2882.

312 J. E. McMurry, T. Lectka, J. G. Rico; *J. Org. Chem.*, **1989**, 54 (15), 3748–3749.

313 N. A. Jones, S. T. Liddle, C. Wilson, P. L. Arnold; *Organometallics*, **2007**, 26, 755–757.

314 D. Ma, C. B. Miao, J. Sun; *J. Am. Chem. Soc.*, **2019**, 141 (35), 13783–13787.

315 Y. D. Lima, D. W. Seo, S. H. Lee, H. H. Ju, T. W. Hong, D. M. Kim, H. C. Jud, W. G. Kim; *Int. J. Hydrog. Energy*, **2013**, 38, 7667–7673.

316 H. Tong, Y. Hong, Y. Dong, M. Häussler, Z. Li, J. W. Y. Lam, Y. Dong, H. H. Y. Sung, I. D. Williams, B. Z. Tang; *J. Phys. Chem.*, **2007**, 111 (40), 11817–11823.

317 P. Lhoták, R. Zieba, V. Hromádko, I. Stibor, J. Sykora; *Tetrahedron Lett.*, **2003**, 44, 45219–4522.

318 B. M. Fox, X. Xiao, S. Antony, G. Kohlhagen, Y. Pommier, B. L. Staker, L. Stewart, M. Cushman; *J. Med. Chem.*, **2003**, 46 (15), 3275–3282.

319 J. M. Takacs, **2001**, John Wiley and Sons Ltd. *Encyclopaedia of reagents for organic synthesis*.

320 K. Lia, C. Wanga, G. Yina, S. Gao; *Org. Biomol. Chem*., **2013**, 11, 7550–7558.

321 D. C. Behenna, E. J. Corey; *J. Am. Chem. Soc.*, **2008**, 130 (21), 6720–6721.

322 G. Brooks, W. Burgess, D. Colthurst, J. D. Hinks, E. Hunt, M. J. Pearson, B. Shea, A. K, Takle, J. M. Wilson, G. Woodnutt; *Bioorg. Med. Chem.*, **2001**, 9 (5), 1221–1231.

323 D. Belotti, J. Cossy, J. P. Pete, C. Portella; *J. Org. Chem*., **1986**, 51 (22), 4196–4200.

324 Satshi et. al. PCT Int Appl. 2009069610, **2009**.

325 T. R. Huffman, Y. Wu, A. Emmerich, R. A. Shenvi; *Angew. Chem., Int. Ed. Engl.*; **2019**, 58 (8), 2371–2376.

326 S. A. Green, S. Vásquez-Céspedes, R. A. Shenvi; *J. Am. Chem. Soc.* **2018**, 140 (36), 11317–11324.

327 M. de Los Angeles Rey, J. A. Martínez-Pérez, A. Fernández-Gacio, K. Halkes, Y. Fall, J. Granja, A. Mouriño; *J. Org. Chem*., **1999**, 64 (9), 3196–3206.

328 A. R. Hands, A. J. H. Mercer; *J. Chem. Soc. C*, **1967**, 1099–1100.

329 R. R. Paccani, D. Donati, S. Fusi, L. Latterini, G. Farina, V. Zanirato, M. Olivucci; *J. Org. Chem.*, **2012**, 77 (4), 1738–1748

330 A. Sirvent, S. Hernández-Ibáñez, M. Yus, F. Foudalo; *Synthesis*, **2021**, 53, 1749–1759.

331 P. S. Engel, A. M. Culotta; *J. Am. Chem. Soc*., **1991**, 113 (7), 2686–2696.

332 Z. M. Ismail, H. M. R. Hoffmann; *J. Org. Chem.*, **1981**, 46, 3549–3550.

333 J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford; *ACS Catalysis*, **2019**, 9 (10), 9568–9574.

334 H. Hopf, C. Mlynek, D. Klein, M. Traetteberg, P. Bakken; *Eur. J. Org. Chem.*, **2001**, 1385–1391.

335 D. L. Ladd, J. Weinstock, M. Wise, G. W. Gessner, J. L. Sawyer, K. E. Flaim; *J. Med. Chem.*, **1986**, 29 (10), 1904–1912.

336 Y. Yamamoto, R. Fujikawa, T. Umemoto, N. Miyaura; *Tetrahedron*, **2004**, 60, 10695–10700.

337 F. W. W. Hartrampf, D. Traumer; *J. Org. Chem.*, **2017**, 82, 8206–8212.

338 K. Y. Seah, S. J. Macnaughton, J. W. P. Dallimore, J. Robertson; *Org. Lett.*, **2014**, 16, 884–887.

339 T. Fiala, J. Wang, M. Dunn, P. Sebej, S. J. Choi; *J. Am. Chem. Soc*., **2020**, 142 (20), 9285–9301.

340 X. Zeng, Z. Jia, F. G. Qiu; *Tetrahedron Lett.*, **2020**, 61, 1–4.

341 M. Ishizaki, Y. Niimi, O. Hashino, H. Hara, T. Takahasi; *Tetrahedron*, **2005**, 61, 4053–4065.

342 J.-Z. Huang, X.-K. Jie, K. Wei, H. Zhang, M.-C. Wang, Y.-R. Yang; *Synlett*, **2013**, 24 (10), 1303–1306.

343 X. Linghu, J. J. Kennedy-Smith, F. D. Toste; *Angew. Chem.* **2007**, 119, 7815–7817.

344 J.-Z. Huang, X.-K. Jie, K. Wei, H. Zhang, M.-C. Wang, Y.-R. Yang; *Synlett*, **2013**, 24, 1303–1306.

345 D. J. Sam, H. E. Simmons; *J. Am. Chem. Soc*., **1974**, 96 (7), 2252–2253.

346 P. R. Leger, R. A. Murphy, E. Pushkarskaya, R. Sarpong; *Chem. Eur. J.*, **2015**, 21, 4377–4383.

347 H. Iida, Y. Watanabe, C. Kibayashi, *J. Org. Chem.*, **1985**, 50, 1818–1825.

348 A. Naylor, N. Howarth, J. R. Malpass, *Tetrahedron*, **1993**, 49, 451–468.

349 K. Shing, Y. Liu, B. Cao, X. Chang, T. You, and C. Che, *Angew. Chem. Int. Ed.*, **2018**, 57, 11947–11951.

350 H. Kubas, U. Meyer, M. Hechenberger, K.-U. Klein, P. Plitt, R. Zemribo, H. W. Spexgoor, S. G. A. van Assema, U. Abel; *Bioorg. Med. Chem. Lett.*, **2013**, 23, 6370–6376.

351 R. Lazny, A. Nodzewska, P. Klosowski, *Tetrahedron*, **2004**, 60 (1), 121–130.

352 R. Ushimaru, M. W. Ruszczycky, W. Chang, F. Yan, Y. Liu; H. Liu, *J. Am. Chem. Soc.*, **2018**, 140 (24), 7433–7436.

353 S. M. Allin, S. N. Gaskell, M. R. J. Elsegood, W. P. Martin, *J. Org. Chem.*, **2008**, 73, 6448–6451.

354 J. Duan, F. Cao, X. Wang, C. Ma; *Chem. Commun.*, **2013**, 49, 1124–1126.

355 M. P. L. Caton, E. C. J. Coffee, T. Parker & G. L. Watkins, *Synth. Commun.*, **1974**, 4, 303–306.

356 J. Otera, N. Dan-oh, H. Nozaki; *Tetrahedron*, **1992**, 48 (8), 1449–1456.

357 T. Anzo, A. Suzuki, K. Sawamura, T. Motozaki, M. Hatta, K. Takao, K. Tadano, *Tetrahedron Lett.*, **2007**, 48, 8442–8448.

358 D. Wei, B. Carboni, J. Sortais, C. Darcel; *Adv. Synth. Catal.*, **2018**, 360 (19), 3649–3654.

359 A. C. Wright, Y. E. Du, B. M. Stoltz; *J. Org. Chem.*, **2019**, 84 (17), 11258–11260.

360 A. C. Brickwood, M. G. B. Drew, L. M. Harwood, T. Ishikawa, P. Marais, V. Morisson; *J. Chem. Soc., Perkin Trans. 1*, **1999**, 913–922.

361 X. M. Chen, X. S. Ning, Y. B. Kang; *Org. Lett.*, **2016**, 18 (20), 5368–5371.

362 K. Zawatzky, M. Kamuf, O. Trapp; *Chirality*, **2015**, 27 (2), 156–162.

363 G. W. Gribble, F. L. Switzer, *Synth. Commun.*, **1987**, 17 (4), 377–383.

364 M. E. Krafft, J. W. Cran, *Synlett*, **2005**, 8, 1263–1266.

365 J. Li, Q. Niu, S. Li, Y. Sun, Q. Zhou, X. Lv, X. Wang, *Tetrahedron Lett.*, **2017**, 58 (13), 1250–1253.

366 P. S. Engel, A. M. Culotta; *J. Am. Chem. Soc*., **1991**, 113 (7), 2686–2696.

367 N. E. Schore, M. J. Knudsen; *J. Org. Chem.*, **1987**, 52 (4), 569–580.

368 J. A. Johnson, B. M. Petersen, A. Kormos, E. Echeverría, Y.-S. Chen, J. Zhang; *J. Am. Chem. Soc*., **2016**, 138 (32), 10293–10298.

369 T. Iio, K. Nagai, T. Kozuka, A. M. Sammi, K. Sato, T. Narumi, N. Mase; *Synlett*, **2020**, 31 (19), 1919–1924.

370 S. Engl, O. Reiser; *Eur. J. Org. Chem.*, **2020**, 2020 (10), 1523–1533.

371 A. Krasovsky, F. Kopp, P. Knochel; *Angew. Chem. Int. Ed*., **2006**, 45, 497–500.

372 W. Qi, P. Wang, L. Fan, S. Zhang; *J. Org. Chem.*, **2013**, 78, 5918–5924.

373 V. Zanirato, G. P. Pollini, C. De Risi, F. Valente, A. Melloni, S. Fusi, J. Barbetti, M. Olivucci; *Tetrahedron*, **2007**, 63, 4975–4982.

374 R. Rettenmaier, F. S. Waksmunski, D. B. R. Johnston, T. B. Windholz; *J. Med. Chem.*, **1969**, 12, 388–393.

375 F. W. W. Hartrampf, T. Furukawa, D. Trauner; *ACS Catalysis*, **2017**, 56 (3), 893–896.

376 H. C. Brown, A. W. Moerikofer; *J. Am. Chem. Soc*., **1961**, 83, 3417–3422.