Rigid 3D Scaffolds by a Diversity-Generating Functional-Structural-Skeletal Elaboration Approach

by

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Abstract

This thesis describes the development of novel three-dimensional, heterocyclic organic scaffolds, and their derivatization to new C(sp^3)-rich compounds as the basis for library generation. An eight step synthetic route from 4-tetrahydropyranone or *N*-protected 4-piperidone to α,β-conjugate carbonyl intermediates is detailed. Optimization studies and large scale syntheses routes have been developed. Five novel scaffolds were achieved through functional, structural and skeletal rearrangement of enone intermediates to generate *in-silico* compound libraries. From these, a total of 1068 compounds were selected following chemical novelty, diversity and druglikeliness principles. Sixty-six compounds were selected from the *in-silico* library to synthesise and characterise.

Eventually, the achieved experimental libraries were analysed for lipophilicity, hERG interaction and biological activity towards a range of targets.

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List of abbreviation

[1,5]-HT	[1,5]-hydride transfer
.ca	circa
°C	degrees Celsius
Δ	heat
A	Molar refractivity
Å	ångström
ADME	absoption, distribution, metabolism and excretion
atm	atmospheres
BBB	blood-brain barrier
Boc	*tert*-butoxy carbonyl
CADD	computer-aided drug design
CNS	central nervous system
COD	cyclooctadiene
COSY	correlation spectroscopy
Cy	cyclohexyl
DCE	dichloroethane

DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMF	*N*-*N*-dimethylformamide
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
d.r.	diastereomeric ratio
DS	Dean-Stark
E	electrophile
EDG	electro-donating group
ee	enantiomeric excess
EI	electron impact
eq.	equivalents
ES	electrospray
equiv.	equivalent(s)
EWG	electro-withdrawing groups
Fsp^3	fraction of sp^3-hybridised carbons
FT-IR	Fourier transform infrared

g	gram(s)
h	hour(s)
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
HTS	high throughput screening
hv	light
Hz	hertz
hex	hexyl
i	iso
IR	infrared
J	coupling constant
L	litre
LA	Lewis acid
LCMS	liquid chromatography – mass spectrometry

LDA	lithium diisopropylamide
LLAMA	lead-likeliness and molecular analysis
LLP	lead-likeliness penalty
LOS	lead-oriented synthesis
m-CPBA	*meta*-chloroperbenzoic acid
[M]	metal
M	molar
Hz	hertz
MMFF94	Merck molecular force field 94
m	multiplet
mp	melting point
Ms	methanesulfonyl
min	minutes
Ms	methanesulfonyl
MS	mass spectrometry
MSM	methylsulfonylmethane
MW	molecular weight

m/*z*	mass/charge
NAR	number of aromatic rings
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbenes
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	4-nitrobenzenesulfonyl
Nu	nucleophile
o	*ortho*
OD600	Optical density at 600 nm
p	*para*
p	pressure
PDD	phenotypic drug discovery
POS	Probability of success
ppm	parts per million

Py	pyridine
R&D	research and Development
rac	racemic
RDS	rate determining step
RO3	rule of three
RO5	rule of five
ROTB	rotable bonds
RT	room temperature
SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
T	temperature
T	tertiary
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCE	trichloroethylene
TEA	triethylamine

Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic acid
THF	tetrahydrofuran
TIC	total ion current
TMS	trimethylsilyl
TIPS	triisopropylsilyl
TPSA	topological polar surface area
Ts	4-methylbenzenesulfonyl
TSA	total surface area
quant.	quantitative
UV	ultraviolet
ν	wavenumber

1. Recent advances in drug development

1.1. The process of drug discovery

The search for novel medicines has been a topic of great interest throughout human history. Modern drug discovery has been underpinned by technological progress, advances in the understanding of biotechnology and anatomy along with intellectual contributions to chemical knowledge for drug development.[2]

A 9-60% increase of drug approval has been reported by several drug organizations over the last decade compared to the years 2000-2010, indicating a progressive development in the pharmaceutical industry.[3] However, the cost of drug development has risen over time, registering a 29-66% increase in the pharmaceutical R&D expenditure over the same period.[4] It is estimated that the cost for a new drug to be developed is from 800 million to 1.2 billion dollars, taking into account laboratory research and the clinical trials, included the failures and withdrawn pharmaceuticals.[5]

Moreover, a successful drug requires on average from 10 to 15 years of study from its discovery to its licencing stage and further implementation in the market,[6] making the drug development timescale another major obstacle in this field in addition to its capital costs.

Eventually, only 0.1% of drug candidates are likely to be approved from pre-clinical testing to human testing,[7] and 12% of drug candidates that are submitted to Phase I of Clinical Trials have a chance to be commercialised.[8] These issues suggest the need to improve the current drug discovery approaches.

Drug discovery has often occurred through the determination of the biological activity of specific compounds. There are three main approaches when the target (that is the protein, nucleic acid, a membrane or a cell wall object of the study) is known, depending on the

available data of the latter: target-based drug design, ligand-based drug design and *de novo* drug design (Figure 1).

Figure 1: Drug discovery process scheme

Target-based drug design (TBDD) is the most adopted strategy[9] and it deals with a biological target whose spatial structure is known. Molecular docking is widely used in TBDD, allowing the prediction of the preferred orientation of a molecule when bound to the target.

Ligand-based drug design (LBDD) is instead the approach used when the three-dimensional structure of the target is not defined. Studies are based on the available data of a series of binders with known potency. In these cases, quantitative structure-activity relationships (QSAR) investigations and pharmacophore modelling are the strategies of choice.[10] QSAR methods correlate all the properties of a molecule related to its structure to its chemical, physical and biological activity.[11] A pharmacophore model is, according to IUPAC: "an ensemble of steric and electronic features that is necessary to ensure the optimal

supramolecular interactions with a specific biological target and to trigger (or block) its biological response."[12]

De novo drug design consists of the computational generation of novel molecular entities by exploration of different atoms, conformations and hybridization states when the only available information is the structure of the receptor or a pseudo-receptor originated *in silico.* Atom-based sampling uses an atom as an input for the software-based library generation,[13] while fragment-based sampling uses a fragment (defined as low molecular weight ligand, 150 Da on average) as a starting point to build the rest of the molecule. The latter is the preferred method as it generates a smaller series of compounds that are more likely to be drug-like and chemically accessible.[14]

Sometimes, the target identity is unknown or a disease mechanism is too complicated to be reduced to one drug-target interaction. In these cases, novel drugs are achieved through phenotypic drug discovery (PDD), that involves organoids or cell-based models and screenings instead of single biomolecules.[15]

A novel approach to drug discovery that has been recently promoted is *library design*.[16] Contrarily to TBDD, LBDD *de novo* drug design and PDD, *library design* does not consider a target as object of study but aims to generate new chemical entities with wide structural diversity. Hits (that are compounds with a strong biological activity) are then identified through pharmacological screening of the compound library against a broad range of targets.

Once a line of drug discovery research has been selected for a particular study, a broad list of ligands can be generated computationally. Two ways of designing new chemical libraries were devised to maximise success: fragment-based screening (FBS) and diversity-oriented synthesis (DOS).[17]

Fragment-based screening involves the generation of molecules that have a weight <300 Da, and the compounds that are found to be even weakly active are used as starting blocks to computationally build more complex drug-like compounds.[18] This is the preferred drug design approach, as compared to other drug-discovery procedures it requires fewer compounds to be screened with biological assays. However, fragment-based libraries are made more often when the nature of the target and drug-target interactions are known, so studies are conducted towards more specific chemical frameworks. The FBS approach tends instead to be less successful for "blind screening", that is the screening of targets whose structure is unknown.[19] As a matter of fact, it has been observed in these cases that molecules with a higher molecular weight have a better chance to yields hits than fragments because they are more likely to build interactions with a biological structure.

Diversity-oriented synthesis is the production of a compound library aimed to maximise the skeletal, stereochemical, functional group and appendage (side group around a common scaffold) diversity. This strategy consists in designing the creation of intermediates with versatile structures, so that they can generate multiple scaffolds with divergent synthesis. Thus, a great coverage of novel chemical space is obtained with only one synthetic pathway enabling great progress in drug discovery.[20] Screening of DOS libraries provided several hits for unconventional targets as protein-protein interactions (PPI), that are responsible for important cellular processes and diseases such as cancers, Alzheimer's disease and viral proteins action.[21] They are new drug targets that were discovered in the 2000s and it is estimated that only 2% of them have been associated with a drug. They are difficult to study and considered to be "undruggable" as they do not have defined binding pockets,[22] and FBS is not appropriate in screening for PPI as these modulators tend to be very exposed to water and fragments tend to bind weakly to these sites. As a consequence, DOS is considered to be

the most promising library design method, being applicable for the creation of more diverse chemical structures and for the designing of drugs for biochemical systems that are yet to be studied in depth.

Compound library enumeration can generate a large number of compounds, and an analysis of all of them would be either impossible or very demanding in terms of time and financial resources. For this reason, the size of a library is often reduced with the aid of algorithms, aiming to select the most promising compounds and thus reducing the effort required for chemical synthesis and biological testing.[23] Use of artificial intelligence in drug discovery is known as computer-aided drug design (CADD)[24] and has been reported to decrease of 20-50% the expected costs of pharmaceutical development.[25]

Several softwares[26] have been created to predict physicochemical properties, ADME parameters, toxicity and even possible targets for an assigned molecule. Unfortunately, the prediction accuracy is often limited and very variable, as it depends on the type and size of the dataset under study and the estimation method (characterised either by a calculation of molecular properties or by a comparison with similar structures).

Along with *in-silico* predictors, several rules of thumb have been created to link specific physicochemical properties with druglikeliness. These measures cannot, however, predict any pharmacological activity. The most followed set of rules is known as Lipinski's rule of five (RO5), that states that compounds that have HBA ≤ 5, HBD ≤ 10, MW < 500 Da and logP ≤ 5 are more likely to be orally administrable drugs. Instead, chemicals that exceed these parameters are associated with poorer absorption.[27]

It was observed that, during hit and lead optimization in the Drug Discovery process, it is common to increase the molecular size and logP in order to increase the affinity with a target,

physicochemical properties and/or compatibility with the species in question. This operation tends to be more successful if realised from starting hits that have reduced dimensions and lipophilicity. Therefore, a new set of physicochemical properties limitations known as rule of three (RO3) has been proposed as an alternative set of guidelines to RO5[28] and bear properties as follow: HBA ≤ 3, HBD ≤ 3, MW < 300 Da, logP ≤ 3 and rotable bonds ≤ 3. Compounds that comply with RO3 are called "leadlike". The RO3 aims to increase the probability of success (often abbreviates as POS)[29] for CADD-designed libraries, therefore maximising their advance in the Drug Discovery process to hits and leads.

After a compound library is designed (with the aid of rules of thumb and/or docking), the next step is the synthetic pathway design followed by chemical synthesis. A way to greatly amplify the size of a library is the parallel synthesis approach. Having available a large quantity of a scaffold, it is possible to set a series of several same-type reactions with the help of automated systems. The crude compounds are then submitted for preparative purification,[30] that considerably speeds up the library making process compared to flash column chromatography.

Once a chemical library is synthesised, the molecules that have a binding activity with the target, known as hits, are identified through biophysical assessment. One of the newest techniques (datable to 2008) to aid this purpose is high-throughput screening. With the help of robotics, different binders and targets in different experimental conditions can be filled into assay plates with a number of wells that varies from 96 to 6144, and a large number of compounds can be analysed in a reduced time (up to 10,000 in a day).[31] If hits are identified, their physicochemical and metabolic properties are optimised to lead compounds, then eventually be submitted for preclinical development and clinical phases.

1.2. Three-dimensionality in drug discovery

It was estimated that the number of drug-like molecules that could be potentially produced exceeds 10^{60}.[32] It is therefore impossible to make a chemical sample and analyse the biological activity of all of them. Is there a way we can expand the known chemical structures (named chemical space) to novel structures that better serve our purpose of making medicines? To answer this question, an investigation on the differences between the properties of successfully approved drugs and compounds that did not get through all the drug discovery steps was undertaken.

It was observed that a higher sp^3 fraction and the presence of stereogenic centers were associated with a higher chance to pass the stages of clinical testing. It has been observed that the average sp^3 fraction increased from 0.36 to 0.47 from discovery compounds to approved drugs.[33] Compounds with a higher sp^3 fraction also resulted in less off-target effects, that are the main cause of toxicity.[34] This can be explained by the direct correlation between sp^3 fraction and three-dimensionality: compounds that are more complex, rigid and spheric-shaped interact with a target in a more specific manner, so with more selectivity and specificity unlike compounds that are more flat-shaped. The same drop in drug promiscuity was indeed found by differentiating withdrawn drug-like compounds and those that entered clinical phases according to three-dimensional descriptors.[35] Three-dimensional compounds also presented better ADMET properties, in particular solubility and aggregation, and this may be ascribed mainly to a decrease of lipophilicity given the reduction of aromatic rings and multiple bonds, other than greater solvation.

The three-dimensional chemical space can be represented by a principal-moment inertia (PMI) plot (Figure 2), that measures a molecule's resistance against acceleration on the

principal axes I_1, I_2 and I_3 and describes a triangular space in which the corners represent the degree of linearity, planarity and sphericity. The "3D score" of a molecule is identified as I_1/I_3 added to I_2/I_3.[36]

It has been estimated that for 75% of ZINC fragments and 80% of known drugs[36,37] was calculated a 3D value < 1.2, that is associated with a linear/planar shape and is represented by the left side of the PMI plot (Figure 2, white region). The more three-dimensional space associated with a 3D value > 1.2 (Figure 2, orange region) still remains relatively unexplored. Therefore, the creation of 3D-libraries would bring to the discovery of promising drug-like compounds that fill out new chemical space.

Figure 2: PMI plot; 3D space (orange) is less explored, most fragments fill out the linear/planar region (white)

Since the first observation of the correlation between sp^3 fraction and druglikeliness,[33] many 3D-rich drug-like libraries have been produced with DOS. An interesting study in this regard concerns the generation of bioactive molecules from 2,4-methanoproline scaffolds (Scheme

1).[38] Seven three-dimensional drug-like libraries, with a total of 234 compounds, have been designed *in-silico*, physically created with parallel synthesis and analysed computationally from five scaffolds.[39] Three hits were later found with an antimalarial activity < 2 µM.[40]

Scheme 1: Published 3D drug-like libraries generation from substituted bridged pyrrolidine

1.3. Principles of gold catalysis

Gold catalysis has been experiencing a considerable growth in the last three decades and now has become a main subject of interest in the branch of metal-catalysed transformations [41] and production of pharmaceuticals.[42] The reason behind this outcome lies in the impact of relativistic effects to gold, that is more pronounced than other metals and is responsible for the different reactivity of gold complexes with respect to other metal-based catalysts.

The relativistic effects describe the considerable increase in the mass of a particle when its velocity approaches the speed of light.[43] This can be rationalised by the mathematical expression for the relativistic mass (Figure 3), in which the speed of an electron in s and p orbitals has been directly correlated to the atomic number. This factor is negligible for atoms with a low molecular weight ($m \simeq m_0$) but is important for heavy atoms like gold ($m > m_0$).[44]

$$m = \frac{m_0}{\sqrt{1-(\frac{v}{c})^2}} \xrightarrow{\text{for } e^- \text{ (s)}} m = \frac{m_0}{\sqrt{1-(\frac{Z}{n})^2}}$$

m= e^- relativistic mass
m_0 = e^- non-relativistic mass
v= e^- speed
c= speed of light
Z= atomic number
n= number (e.g. for 1s orbitals n= 137)

Figure 3: Mathematical expression for relativistic mass

An increased mass of the electrons in the s and p orbitals implicates a smaller Bohr radius and therefore those orbitals are “contracted” and lowered in energy. [45]

A decrease in energy of the orbital 6s increases the ionization energy and the electronegativity of gold. The latter is the highest amongst metals and comparable to that of carbon and iodine. The orbital 6s is the LUMO of gold in Au(I) species and its lowering in energy justifies their superior Lewis acidity compared to that of Cu and Ag.

The relativistic contraction of s and p orbitals determines a better shielding of d and f orbitals from the nucleus, that experience a consequent “expansion”. This enhances the ability to make a back-bond on orbitals of appropriate energy and symmetry. Gold interacts selectively with triple bonds even in the presence of other coordinating functional groups and can therefore be defined as alkynophile.[46] The gold-triple bond bonding can be described by the DCD (Dewar-Chatt-Duncanson) model (Figure 4). Theoretical calculations showed a strong σ-bonding, a minor π back-donation and a consistent polarization of the alkyne triple bond toward the metal fragment.[47] Gold acts therefore as a potent carbophilic Lewis acid and induces electrophilic activation of the triple bond via electron charge transfer (Scheme 2, **5**).[48]

Figure 4: DCD model for Au-alkyne interactions

On the contrary, other metal catalysts normally provides nucleophilic activation.

The d and f orbital expansion increases the backbonding from gold, enabling a partial carbene character to gold carbocation intermediates (Scheme 2, **8** and **9**).

Scheme 2: Gold-mediated activation of triple bonds

Though the existence of gold carbenes has been debated, as intermediates exhibit strong electrophilic reactivity and the Au-C bond order is close to 1, physical and chemical similarities have been found between gold complexes and Fischer metal carbenes.[49]

Organogold chemistry has mostly been developed on Au(I), while Au(III) has been studied to a lesser extent as its complexes tend to be less stable and more toxic.[50] Though the reason for the different reactivity between the two oxidation states has not been completely rationalised, theoretical studies determined a smaller π-back-donation component for Au(III) than for Au(I). This corresponds to an increased vinyl cationic character and an easier nucleophilic attack to the carbon of the triple bond further away from gold.

Gold-complexes are less nucleophilic than those of other metals and do not readily give oxidative addition, explaining the lack of a ready cycle Au(I)/Au(III) and the stability of gold-complexes towards water and oxygen. This makes gold catalysis appealing as it simplifies experimental procedures.[51] They are also tolerant towards a broad range of functional groups and generally biocompatible, making them applicable for Green Chemistry procedures and the production of pharmaceuticals. [52]

Gold catalysis has been exploited for the creation of both 2D and 3D frameworks. Examples of gold-catalysed transformations used for the achievement of natural products and drugs with a high sp^3-character can be found in the total synthesis of the renal anticancer *Englerin A* **12** (Scheme 3a)[53] and hepatitis C inhibitors **16** (Scheme 3b).[54]

Scheme 3: Gold-catalysis for the total synthesis of 3D natural products and pharmaceuticals

1.4. Polycyclization cascade of *N*-allyl ynamides

An appealing starting point for the creation of novel 3D drug-like chemical libraries is presented by the recent work of Adcock *et al.*,[55] where the synthesis of a novel sp^3-rich tetracyclic framework through an Au(III)-mediated polycyclization cascade of *N*-allyl sulfonylynamides has been accomplished (Scheme 4a).

The mechanism (Scheme 4b) has been rationalised as follows: gold coordination triggers the formation of gold keteneiminium **20**, followed by 1,5-hydride shift through space (**21**) or sigmatropic hydride transfer (**22**). After that, gold carbene **24** is achieved by either intermediate **21** with back donation from the metal and nucleophilic attack of the vinyl gold intermediate on the oxonium or alternatively with conrotatory 4π-electrocyclic ring closure from pentadienyl cation **23**. Final cyclopropanation and protodeauration yields tetracycle **18**.

The reaction is achieved using benchstable non-toxic dichloro(2-pyridinecarboxylate)gold.[56]

Scheme 4: Gold-catalysed polycyclization cascade of *N*-allyl sulfonylynamides

The resulting products contain a fused cyclopropane ring, whose use is increasing in drug development. It is present as a motif in 46 FDA approved drugs that work against a wide range of diseases (bacterial and viral infections, heart diseases, inflammations, bone disorders and cancer). A cyclopropyl ring system is associated with desirable ADMET properties. It is for example an excellent isosteric group to isopropyl and phenyl groups, but with a higher aqueous solubility and a higher metabolic stability, being less prone to CYP450-mediated oxidations than other functional groups like methyl or *N*-ethyl. Moreover, when designing a CNS active drug, a cyclopropyl provides a better BBB permeability.[57] The presence of a sulfonyl pyrrolidine ring is also appealing for a drug design project: nitrogen-containing heterocycles are widely present in vitamins, alkaloids and hormones and exhibit diverse biological activities.[58] Sulfonamide groups are also contained in a vast range of drugs, especially with anti-bacterial activity.[59]

The scope of Au-polycyclization products has been extended to 25 compounds with yields from fair to excellent. The reaction is completely selective, as the cyclopropane ring and the opposite bridgehead proton are in a *syn* relationship. Ynamides containing benzylic ethers originated diastereomeric mixtures with variable ratios (from 1.1:1 to 5.2:1), in contrast to dioxolane groups that gave only one compound. In these cases, the use of an achiral gold catalyst afforded products as racemic mixtures.

The scope mainly focused on substrates with aromatic rings. However, early studies have been conducted on cyclic non-aromatic substrates to afford a few tetracycles bearing a cyclohexene, dihydropyran or a tetrahydropyridine ring, enabling the possibility of extending the procedure to further non-aromatic products so to create new intermediates applicable for DOS that have a higher sp^3 fraction than aromatic tetracycles.

In the initial study, tetrahydropyridine motifs were prepared as tosyl derivatives as they can stand very acidic, basic, oxidant and reducing conditions.[60] Mesyl and nosyl protecting groups were also used, but only to a limited extent (3 compounds).

1.5. Scope of the project

This project aims to develop new three-dimensional drug-like libraries with desirable physicochemical properties for early drug discovery development, achieved through gold-catalysed polycyclization cascade as shown in Scheme 4 applied on non-aromatic ynamides as **27** (Scheme 5).

The aim presents several objectives, the first of which is the large scale application of a multistep synthetic pathway. The following challenge is the generation of new chemical scaffolds. This can be achieved through the exploration of the post-catalytic reactivity, that

has not been realised previously to this project. Then, scaffold-derived libraries have to be designed towards compounds with desirable ADMET properties.

Scheme 5: Scope of the project

Scale-up of chemical reactions requires equipment suitable for the usage of large quantities of compounds and solvents. Possible changes in reactivity form a small to a large scale, along with increased safety issues regarding reaction, work-up and compounds purifications may occur, therefore needing procedural modifications.

We surmised compound **29**, achieved from deprotection of the dioxolane group, might serve as a good starting point for a library synthesis. It includes an α,β-unsaturated carbonyl and an amine that are very versatile functional groups. The heterocycle fused to the cyclopentene and the cyclopropane ring also constitute a starting point for skeletal diversification.

Oxidation of an enone (Scheme 6) can result in an epoxidation (**31**),[61] a Baeyer-Villiger oxidation (**32**, **33**)[62] or diol formation (**34**) followed by oxidative cleavage (**35**, **36**), [63] depending on the oxidant of choice. Reduction at the carbonyl generates an allyl alcohol **37**, while hydrogenation at the double bond yields saturated ketone **38**. Lastly, new groups can be incorporated in the structure via 1,2-addition (**39**),[64] carbonyl alpha substitution reaction (**40**),[65] Michael addition (**41**),[66] vinylogous Michael addition (**42**)[67] and Diels-Alder cycloaddition (**43**, **44**).[68]

Scheme 6: General scheme of α,β-unsaturated carbonyl derivatizations

It was hypothesised that the presence of a α,β-unsaturated carbonyl adjacent to the cyclopropane ring could trigger reactions of 1,6-conjugated addition (Scheme 7; **48**, **50**) with the use of a Brønsted[69] or Lewis acid[70] and a soft nucleophile or under hydroboration conditions.[71] This type of transformation has been explored on other substrates to a very

limited extent in the Literature.[72] Therefore, an investigation on these transformations would provide interesting new insights.

The three-membered ring cleavage can also be potentially achieved through reductive pathways (Scheme 7; **51**, **52**, **53**) via Li or Na in liquid ammonia[73], samarium diiodide[74] or with hydrogenation reaction.[75]

Scheme 7: Cyclopropane cleavage reactions a) proposed 1,6-conjugated addition on cyclopropyl enone b) reductive ring cleavage

The 5- and 6-membered rings can also be subjected to oxidation of the α-positions to heteroatoms (Scheme 8). This would lead to the formation of lactones and lactams,[76] that are widely found groups in biologically active molecules.[77] Linear chains can also be achieved from lactones with further ring cleavage (**55**).[78]

Scheme 8: General scheme of oxidation reactions on heterocycles

Reactions showed in Schemes 6,7 and 8 will be tested on a tetracyclic chemical intermediate such as **29**. The reactions with the best results will be then considered to generate new chemical scaffolds. From these, drug-like chemical libraries can be achieved by derivatization of amine, alcohol and ketone groups.

The drug-like library design will be realised through CADD by using softwares adopted for drug discovery. A virtual library will be first created by scaffold derivatization through a compound library enumeration program. A small set of compounds to be experimentally synthesised will be selected based on *in-silico* physicochemical properties predictions and application of the *rules of thumb* used in drug design. Physical library compounds will then be analysed for ElogD and hERG channel binding to assess their potentiality to advance in drug discovery clinical phases. Finally, biological activities towards a range of targets will be measured through HTS to find potential hits.

2. Chapter 2: Generation of novel *N*-containing tetracyclic frameworks

2.1 Introduction

In this chapter is described the design, optimization and scope to novel non-aromatic tetracyclic frameworks achieved with gold-catalysed cyclization cascade of *N*-allyl ynamides. Structures were planned to be built from tetrahydropyran and piperidine- containing building blocks (Scheme 9), as it has been observed that the presence of heteroatoms increases druglikeliness. In addition, five and six-membered rings are the most common in drug design, counting for about 30% each amongst natural compounds and ring-containing fragments.[79] Tetrahydropyran motifs are for example found as substructures in glycomimetic inhibitors which bind sugar moieties,[80] while piperidine scaffold is the most frequent heterocycle found in FDA drugs, and it is contained in more than 70 commercialised drugs.[81]

Scheme 9: Aim of the project

2.1.1 Multistep synthesis to tetracyclic frameworks

The synthesis of novel non-aromatic tetracycles was based on a pathway previously designed by the ex-Davies group members Holly V. Adcock and Elli Chatzopoulou (showed in Scheme 10).[55,82,83] It starts off with reaction with PBr_3/DMF of a cyclic ketone followed by a Sonogashira coupling with trimethylsilylacetylene (**63**, **64**). After that, an aldehyde protection as a dioxolane is carried out (**65**, **66**) and then removal of the silyl group to give terminal alkyne (**67**, **68**). The ynamide structures **72**, **73** and **74** were obtained by a copper-mediated coupling, developed by Hsung *et al.*,[84] between a bromoalkyne (**69**, **70**) and a sulfonamide (**71**). Lastly,

the polycyclization was accomplished with 5% catalyst loading of gold picolinate dichloride to yield tetracycles **75**, **76** and **77**.

Scheme 10: Outline of the synthetic pathway to sp^3-rich tetracycles[83]

In order to achieve sufficient quantities of chemical scaffolds and derived libraries, the process needed to be applicable on a multi-gram scale. This required careful considerations about chemical availability, atom economy, chemical and environmental hazards, including for purification and waste. [85]

Steps initially identified to require development work were the low yielding 2 step synthesis to the trimethylsilyl enynal and the ynamide formation, as yields for nonaromatic substrates were moderate (45-53%). A modification of the pathway was initially proposed with a

Sonogashira coupling reaction from a terminal ynamide (Scheme 11). It was later discarded as an analogous transformation from a phenyl intermediate resulted unsuccessful in a previous project.[83]

Scheme 11: Proposed Sonogashira couplings from terminal ynamide (not tested)

It was eventually decided to carry out the synthetic pathway as in Scheme 10 up to the stage of terminal alkyne. Other methodologies were considered to be tested for the synthesis of the ynamide, that are reviewed in the next Section.

2.1.2 Synthesis of ynamides

Ynamides have become a very popular class of building blocks in recent years, as they are precursors of complex chemical architectures and multifunctional compounds. The presence of a polarised triple bond (Scheme 12) makes ynamides very versatile substrates, as regioselective addition may be triggered by an electrophile at the β-position or a nucleophile at the α-position.[86]

Scheme 12: Polarization of the ynamide group and general reactivity

Despite being a reactive class of alkynes, ynamides are stable to moisture and aqueous workups, air, silica and heat. They are also preferred as chemical intermediates to ynamines, that are hydrolytically unstable.[87] Although the synthetic development of ynamides has occasionally been reported to be limited by their difficult preparation, sensitivity and handling,[88] there is nowadays plenty of established procedures for their synthesis (resumed in Scheme 13 and 14 and discussed in the following paragraph). Most techniques rely on the use of terminal alkynes **88** and a compound bearing a nitrogen linked to an electron-withdrawing group **90** (Scheme 13).

Scheme 13: Main ynamide synthesis methods from terminal alkynes

One of the first successful techniques for ynamide synthesis was introduced by R. P. Hsung's research group[89a] and is a copper-catalysed coupling in a basic media between a bromoalkyne intermediate **89** and a sulfonamide, carbamate, indole or camphor lactam (Scheme 13a). The outcome of the reaction depends on the conditions: a coupling with CuCN (5%), K_3PO_4 as base and *N,N'*-dimethylenediamine as ligand was reported to be successful for only cyclic carbamates. With a substitution with $CuSO_4$ (20%) and 1,10-phenantroline, the procedure could be extended for all aforementioned substrates. In addition, K_2CO_3 resulted to be a better base than K_3PO_4 when coupling with sulfonamides.[89b-c] To this day, this method is the most popular for ynamide synthesis. However, the potential instability of bromoalkyne intermediates is the main limiting factor. A room temperature procedure could be achieved through bromoalkynes and strong base (Scheme 13b),[90] allowing the use of temperature sensitive substrates. Its simple setup also led multigram scale production of ynamides. It has been reported that volatile bromoalkynes also have the disadvantage of lachrymatory properties.[91] An alternative procedure that circumvents the bromoalkyne formation was identified by Stahl's research group.[92] The primary difference with the previous method is that Stahl's procedure is carried out under aerobic conditions, allowing the direct synthesis of ynamides from terminal alkynes (Scheme 13c). The requirement of an oxygen atmosphere for the reaction represents a safety hazard to take into consideration especially at large scale. Moreover, the need of an excess of nitrogenated coupling partner (sulfonamide, carbamate, urea or indole) to compensate the eventual formation of homocoupling products may cause complications during separation of product and unreacted reagent. In 2010, Evano and his group tried to address the drawbacks of the previously described procedures via alkynylation of *gem*-dibromoalkenes **93**, that are the synthetic equivalents of bromoalkynes.[91] They are usually synthesised from aldehydes **92** (Scheme 13d) but they can also be directly achieved

from terminal alkynes by using a strong base and zinc dibromide (Scheme 13e).[93] The ynamide synthesis turned out to be effective with a limited scope of nitrogenated nucleophiles: while sulfonamides, pyrrolidinones and oxazolidinones gave up to excellent yields, acyclic amides and ureas could not be used as substrates. A baseless procedure was developed for substrates that are sensitive to temperature and basic conditions (Scheme 13f) and was accomplished through potassium alkynyltrifluoroborates **94**.[94] Although this reaction type was successful as an ynamide synthesis in mild conditions, the synthesis of potassium alkynyltrifluoroborates was reported to be laborious. These salts are also toxic and corrosive. The procedure was later modified by employing copper acetylides **95** (Scheme 13g),[95] that are easy to make and stable over time and to elevated temperature. Nonetheless, the reaction had to be performed under aerobic conditions in order to activate the substrate, and the substrate scope was limited to only amides and oxazolidinones. Alternative strategies have been implemented through chlorinated intermediates as a way to handle more stable compounds than brominated analogues. Zhao *et al.*[96] managed to set up metal-less conditions using chloroalkynes **96** (Scheme 13h) or 1,2-dichloroalkenes **97** (Scheme 13i) with a broad reaction scope. A similar method was applied using 1,1-dichloroalkenes **98** (Scheme 13j).[97] Dichloroalkenes derived from nitrogenated compounds have been used to synthesise ynamides structures through halogen elimination and cross-coupling reactions. In Scheme 14 are illustrated Negishi (a),[98] Sonogashira (b)[99] and Suzuki-Miyaura couplings (c).[100] These procedures could be extended only to aromatic substrates, and an ynamide synthesis with a wider scope was recently achieved through nitrogen-derived 1,2-dichloroalkenes **104** (Scheme 14d).[101] Some substrates generated products only with halide elimination, while others needed transmetallation with a zinc salt or transmetallation followed by Negishi coupling conditions.

Scheme 14: Ynamides synthesis methods from nitrogenated compound derivatization a) through 1,1-dichloroalkenes b) through 1,2-dichloroalkenes

2.2 Results and discussion

In this section, optimization and upscaling of the procedure to afford new tetracyclic acetals is described. Initially, the synthetic pathway was tested for pyran substrates. Later on, the approach was extended to the piperidine building block.

2.2.1 Route to enynal intermediate

Initially, we investigated the optimization of the synthesis of trimethylsilyl alkyne intermediate **63**. Its precursor bromoacrylaldehyde **61** was synthesised with a Vilsmeier-Haack reaction using PBr_3 and DMF (Scheme 15). Its structure was confirmed by ^{1}H NMR and was not purified as it is reported to be an unstable intermediate that can be converted from the crude mixture.[102]

Scheme 15: Synthesis of 4-((trimethylsilyl)ethynyl)-5,6-dihydro-2H-pyran-3-carbaldehyde

The Sonogashira coupling was tested immediately after but only degradation was observed (Table 1, Entry 1). The synthesis of bromoacrylaldehyde **61** was repeated and the product purified, obtaining with a 17% yield. This result is comparable to previous studies[83,103] and the low yield may be explained by the highly acidic conditions and the high sensitivity of PBr_3 and $POCl_3$ towards moisture.[104] No trimethylsilyl alkyne **63** was detected for the Sonogashira coupling when conducting the reaction at room temperature or at 50 °C (Entries 2 and 3). Product **63** was formed at 50 °C when a mixture of TEA/organic solvent (Entries 4-5) was used. Repetition with unpurified **61** confirmed that the substrate needs to be purified for the cross-coupling to work (Entry 6). As second reaction of the multi-step synthesis, a 5% load of palladium catalyst would make the whole procedure very expensive and so lower loadings were attempted. The reduction of palladium and copper catalysts to 2% and 1% respectively led to a yield decrease to 54% (Entry 7). The quantity of solvent was then halved to check if the catalyst load reduction could be compensated by an increase in concentration, recovering the yield to 68% (Entry 8). The use of less solvent is beneficial for economy, safety[105] and time in processing. When the concentration was raised to 1 M, a drop in yield was observed (Entry 9) and a side-product with MW= 306 was detected in LCMS analysis. The molecular weight of the side-product matches the presence of an additional trimethylsilylalkynyl group compared to product **63**. Therefore, the most probable structure is **106** (Scheme 16).

Unfortunately, it could not be isolated as it coelutes as column chromatography with the alkyne homocoupling side-product.

Table 1: Survey of Sonogashira coupling conditions from bromoacrylaldehyde 61

Entry	Catalysts	Solvents	T (°C)	T (h)	Yield 63[a]
1[b]	[Pd]= 5%, [Cu]= 3%	TEA (0.25M)	50	1.0	0
2	[Pd]= 5%, [Cu]= 3%	TEA (0.25M)	20	5.0	0
3	[Pd]= 5%, [Cu]= 3%	TEA (0.25M)	50	1.0	0
4	[Pd]= 5%, [Cu]= 3%	TEA/THF 1:1 (0.25M)	50	3.0	60
5	[Pd]= 5%, [Cu]= 3%	TEA/1,4-dioxane (0.25M)	50	3.0	64
6[b]	[Pd]= 5%, [Cu]= 3%	TEA/1,4-dioxane (0.25M)	50	3.0	0
7	[Pd]= 2%, [Cu]= 1%	TEA/1,4-dioxane (0.25M)	50	5.0	54
8	[Pd]= 2%, [Cu]= 1%	TEA/1,4-dioxane (0.5M)	50	2.0	68
9	[Pd]= 2%, [Cu]= 1%	TEA/1,4-dioxane (1.0M)	50	1.5	42

[a]Yields are related to purified product unless specified [b]Reaction was conducted with unpurified **61**

The same reaction was repeated later with nosyl-protected piperidine bromoacrylaldehyde **107** (vide infra) and this time NMR analysis confirmed the structure of the side-product **109**.

Scheme 16: Outcome of a Sonogashira coupling with solvent concentration

The formation of bis-trimethylsilyl-1,3-enynes have also been reported in other studies involving Sonogashira couplings.[106] A recent study[107] aimed to selectively synthesise these

compounds from aromatic substrates (Scheme 17, **110**) found it was successfully accomplished at low concentration (0.1 M), multiple equivalents of trimethylsilylacetylene (2.2 eq.) and high temperatures (110 °C). Structures were confirmed with the double bond having a E configuration.

Scheme 17: Literature-known synthesis of bis-trimethylsilyl-1,3-enynes

The reaction has been established by the authors as a palladium-catalysed coupling, so the proposed mechanism (Scheme 18) can explain the formation of compound **106**.

Scheme 18: Mechanism for competitive reaction to bis-trimethylsilyl-1,3-enyne 106

While the first two steps of the synthesis successfully yielded product **63**, the procedure was still raising several issues. The low yield of **61** could not be increased and use of more equivalents of PBr_3 and DMF gave complete degradation. The use of additives, specifically sodium perchlorate, is reported to improve the results only for aromatic substrates.[108] The substitution of dichloromethane as solvent with chloroform did not provide any significant improvement (Scheme 19). No other solvents were tested for this reaction, as it is widely

reported that Vilsmeier-Haack reactions are optimised in chlorinated solvents.[109] Trichloroethylene and DCE[110] are carcinogenic solvents and therefore not considered for this research.

Scheme 19: Bromination reaction in chloroform

Phosphorus tribromide use raises safety issues as it reacts violently with water. It is also an expensive reagent (46£/100g at 99% purity, Alfa Aesar website)[111] for the first step of the synthetic pathway and 3.0 equivalents are needed. We decided therefore to test whether the analogous vinyl chloride (**116**) would be more suitable instead. However, there are no reports of chloroacrylaldehydes used for Sonogashira cross-couplings.

Compound **116** was successfully synthesised according to the procedures established by Komendatova *et al*., in the absence of solvent (Table 2, Entry 1)[112] Chloroacrylaldehyde **116** was also observed to be more stable to moisture and temperature than bromoacrylaldehyde **61**. The latter easily degrades turning overnight from a red oil to a black solid even at -20 °C. On the contrary, chloride **116** could be kept in a freezer for up to a week without any substantial loss (ca. 5% after flash column chromatography) of compound.

The chlorination was repeated but this time in DCM at 0.4 M (Entry 2).[113] The presence of solvent led to a considerable improvement in yield. This may be due to the fact that a higher concentration of Vilsmeier reagent is also associated with a lower pH (as $POCl_3$ hydrolyses to HCl and H_3PO_4 in presence of moisture), resulting in a higher degradation of reagent and product. Optimization of reagent equivalents and solvent concentration was performed. Better yields are obtained with a higher content of $POCl_3$ and DMF and a higher dilution of the

reaction (Entries 3, 4, 5 and 6). In specific, the best results are achieved with the use of 4.0 eq. of $POCl_3$, 6.0 eq. of DMF and 0.2 M concentration of dichloromethane (Entry 6). These conditions were selected as standard for all further Vilsmeier-Haack reactions in the project. Adding further equivalents of reagents and solvent would lead to a considerable higher cost and a larger volume of reaction and quenching solution, generating issues for a large scale process.

The result is superior to reported in the literature where compound **116** was obtained in 44% yield using trichloroethylene as solvent.[114]

Table 2: Optimization studies of Vilsmeier-Haack reaction

Entry	$POCl_3$ (eq.)	DMF (eq.)	[CH_2Cl_2]	T (h)	Yield 116[a]
1	1.4	2.0	-	3	20%
2	1.4	2.0	0.4 M	4	35%
3	2.0	3.0	0.4 M	4	46%
4	2.0	3.0	0.45 M	4	40%
5	2.0	3.0	0.5 M	4	37%
6	4.0	6.0	0.2 M	4	65%

[a] Reactions were tested with 5.0 mmol of **59** [b] Yields are related to purified product

No actual yield of purified compound is mentioned in scientific publications with procedures that employ DCM or chloroform[112,113,115], where crude mixtures were used and yields reported for 2-steps transformations. In this study, instead, **116** was successfully isolated without decomposing at 98.3% purity with column chromatography in 65% yield. Giles et al.[114b]

observed rapid decomposition of the halide after column chromatography, but it is supposed that it may have been due to the unwanted presence of excess moisture.

A basic solution is used in the workup to hydrolyse the dimethyl iminium intermediate, quench the excess $POCl_3$ and neutralise the acidic side-products. Sodium acetate and bicarbonate are the most used salts for this purpose in Vilsmeier-Haack reactions. In this study, sodium carbonate was used as less volume of saturated solution was required compared to NaOAc and $NaHCO_3$ (this can be confirmed by comparisons of pK_b and solubilities values),[116] easing the procedure at large scale.

The use of chloride substrate **116** for the Sonogashira coupling (Scheme 20) at 60 °C was successful in higher yield than the cross-coupling with the bromide substrate (77% versus 42%), presumably because of the better thermal stability of the chloride analogue.

Scheme 20: Sonogashira coupling with chloroacrylaldehyde

The Vilsmeier-Haack reaction on 4-tetrahydropyranone was progressively increased in scale ultimately to 500 mmol (Table 3), the maximum allowable using the available equipment. Also, the total time for the reaction itself, quenching, extraction, solvent evaporation and column chromatography was realised in eight hours, that is the maximum allowed for a daytime process at Symeres. Scaling up the Vilsmeier-Haack reaction led to progressively lower yield (Table 3), more than halving from 5 to 500 mmol. The reason behind this outcome has been mainly attributed to the volatility of product **116**, along with modifications of the purification settings when upscaling. Forty grams of silica were used for purification with automated flash column chromatography of a reaction crude obtained from 20 mmol of ketone. The biggest

packed column available for the largest scale (500 mmol) was 330g in size, and therefore the column size was smaller in relation to the quantity of reaction crude for a bigger reaction scale compared to a smaller scale. For a big scale purification, a slower gradient Heptane/EtOAc was used as eluent to avoid the coelution of the product with reaction impurities. Purified fractions from large scale purification had a consequently a higher content of heptane, that had to be removed under higher vacuum for a longer time. After complete solvent removal, chloroacrylaldehyde **116** was detected by TLC in the collection bottle, indicating that it is relatively volatile. This may justify why the final yield resulted lower at high scale. Moreover, more residual DMF was stripped from the crude mixture prior to purification with heptane and high vacuum at larger scale, after observing that the presence of DMF enlarged the band at column chromatography.

Table 3: Upscaling studies of Vilsmeier-Haack reaction

Entry	Scale (mmol)	Capacity reaction flask (mL)	t (h)	Yield 116[a]
1	5	100	5h	65%
2	40	500	6h	54%
3	100	1000	6.5h	43%
4	200	2000	7h	39%
5	400	5000	7.5h	32%
6	500	6000	8h	27%

[a] Yields are related to purified product

The Vilsmeier-Haack reaction setup from 500 mmol of 4-tetrahydropyranone is shown in the Appendix. Given the large quantity of solvent, a mechanical stirrer was used instead of a standard PTFE magnetic stirrer for the reaction and the quenching of the dimethyl iminium salt with basic solution. As the quenching generates heat, the process was conducted in a flask cooled down with ice and sodium chloride, and the temperature of the mixture was controlled by an external probe. Addition of reaction mixture was hold when the temperature was higher than 20 °C and resumed as soon as it dropped to 17 °C. The transfer of large volumes of solvent was realised with a PTFE tube and a vacuum pump.

The subsequent Sonogashira coupling was successfully upscaled to 135 mmol, with no need of special equipment. A comparable yield (75%) was achieved as in small scale (77%), therefore no procedural changes were applied.

2.2.2 Dioxolane formation

After the Sonogashira coupling, the aldehyde group was protected as a 1,3-dioxolane. Cyclic acetals are usually obtained with diol and toluenesulfonic acid as catalyst in refluxing toluene. A Dean-Stark trap is used to remove the water formed as a by-product.[117] Pure aldehyde is required in these reactions because the presence of impurities leads easily to partial degradation. However, compound **63** and the Sonogashira homocoupling side product are very apolar and inefficient separation on flash column chromatography was seen in pure hexane. Switching to heptane as solvent was beneficial, in addition to being safer, allowing recovery of **63** in 95% purity. Further recrystallization in MeOH resulted in 100% purity.

Initial conditions were tested for acetal protection (Table 4, Entry 1) that led to incomplete conversion even after 4h. Interestingly, a lower reaction time (Entry 2) resulted in lower conversion but afforded higher yield of **65**. Supposing that the high reaction temperature

caused degradation, it was decided to direct the optimization towards two strategies: the first by pushing the equilibrium towards the dioxolane and the second by testing alternative methods that do not require heating. To enhance the acetal formation, both acid and diol loading were increased and the solvent concentration was changed from 0.2 M to 0.35 M, leading to a great improvement in yield (Table 4, Entry 3). Incomplete conversion was still seen and repeating with dry toluene and ethylene glycol afforded acetal **65** in excellent yield (Entry 4). At 101 mmol, 90% of dioxolane was afforded. The slight yield decrease could be attributed to the reduced ratio of solvent used for extraction and product quantity.

Table 4: Acetalization tests

Entry	Catalyst (eq.)	Diol (eq.)	T (°C)	t (h)	Solvent	Yield 63:65 (%)[a]
1	*p*-TsOH (0.05)	1.2	111	4.0	PhMe [0.2M]	16:40
2	*p*-TsOH (0.05)	1.2	111	2.5	PhMe [0.2M]	29:61
3	*p*-TsOH (0.07)	2.0	111	2.0	PhMe [0.35M]	10:81
4	*p*-TsOH (0.07)	2.0	111	1.5	PhMe (dry) [0.35M]	0:98
5	HCl (0.1)	500	20	24	-[b]	45:50
6	$PhSO_2NHOH$ (0.7), TEA (1.0)	2.0	20	24	CH_2Cl_2 [0.2M]	95:0

[a] Yields are related to purified product, [b]In this case diol was used as solvent

As alternative methods for acetalization, a recent procedure that employs HCl as catalyst and diol as solvent[118] was tested (Entry 5). After 24h at rt the conversion was around 50%. Further

optimization of this procedure was not performed, as conditions in Entry 4, tested at the same time, already gave excellent results.

A base-catalysed acetalization was also tested as a comparison to acid-catalysed methods.[119] However, no conversion was observed (Entry 6). Eventually, conditions showed in Table 4 Entry 4 were selected as standard for the synthesis of **65**.

2.2.3 Desilylation reaction

The deprotection of the trimethylsilyl protecting group was successfully accomplished in an alkaline aqueous solution of K_2CO_3 in methanol at room temperature in quantitative yield (Scheme 21).

Scheme 21: Base-mediated TMS deprotection on alkyne

The reaction itself did not require any optimization. However, a few adjustments had to be made for the workup, as extraction of aqueous phase with dichloromethane or ethyl acetate did not result in a clear phase separation and multiple extractions were required. Addition of brine in the separating funnel resulted in a better salts dissolution and organic/aqueous phase separation, through after addition of much organic solvent (ca 250 ml of CH_2Cl_2 for a 10 mmol scale). Extraction with dichloromethane gave slightly better results than with ethyl acetate, giving a yield of 99% against 91%. This may be due to the volatility of the product: when 100 mg of product were left at a high vacuum of 6×10^{-2} mbar, only 58% of **67** was recovered after 6 h. The volatility of the terminal alkyne may explain the low yield for desilylation reaction in a previous study (Scheme 7).

The reaction was repeated and then the solvent was removed prior to the aqueous workup, following the procedure reported by Caddick *et al.*,[120] to test if the extraction from a solventless crude residue could result in an easier formation of a biphasic mixture in the separating funnel. Unknown side products with MW 204, 281, 303, 390, 496, and 709 were detected at LCMS analysis, along with the product obtained at 23% yield. Considerable reduction in yield is reported in other studies where TMS-deprotection reactions were left for longer periods after their completion.[121] It is therefore possible that concentration of the reaction mixture gives the same result, so the presence of potassium carbonate in a solventless mixture may trigger processes of base-catalysed oligomerization. An alternative TMS-deprotection with a fluoride source such as KF or TBAF was considered, but it was later discarded as potassium fluoride is more expensive than K_2CO_3 (the first worth £102/10g and the latter £44.1/10g)[122] and K_2CO_3 is generally more available in laboratories.

Using less methanol avoided the need of multiple extractions. No loss of yield was seen going from 0.2 M to 0.35 M. Large scale TMS-deprotection reaction could then be carried out on 91.1 mmol of **65**, giving 90% of product. Slight reduction of yield may be attributed to its relative volatility, as observed in the upscaling of chloroacrylaldehyde **116** synthesis, and/or the reduction of the ratio solvent/compound during workup extraction.

We also attempted the acetalization and desilylation steps in reverse order. However, the deprotection reaction resulted in the almost complete degradation of the substrate to an insoluble black solid (Scheme 22). A similar outcome was observed by You *et al.*,[123] suggesting that terminal enynals are not stable in basic environments.

Scheme 22: Base-mediated TMS deprotection on aldehyde

2.2.4 Ynamide formation

For this work, it was planned to generate sulfonamide-containing ynamides via bromoalkyne intermediate, according to the procedure reported for the scope of aromatic substrates (Scheme 23).[55,82,83]

Scheme 23: Reported ynamide synthesis from phenylalkynes

A series of *N*-allyl sulfonamides was synthesised (Scheme 24) in order to have a range of substrates to couple with a bromoalkyne. The synthesis of sulfonamides was achieved through reaction of allylamine and sulfonyl chlorides in DCM in presence of a base. In previous work,[55] pyridine was used as base in 0.1 M DCM. In this study, the base was changed to triethylamine as pyridine was affording products in low yields. The reagent concentration was also increased to 1 M. This way, sulfonamide synthesis was more efficient providing products from very good to excellent yields and with reduced reaction times.

[a] Reaction was conducted with: Pyridine (1.1 eq.) in DCM (0.1 M), rt, 1 h

Scheme 24: Sulfonamides scope

The scope of the sulfonamide groups was designed in order to achieve the greatest chemical variety and usefulness for a Drug Design project. *N*-Allyl mesylamine **123** was selected as, being the sulfonamide with the lowest molecular weight, has the most chance to be incorporated in drug-like compound libraries that comply with RO3 and RO5 space. Compounds **124**, **125**, **127** and **128** were selected after an *in-silico* assessment of final compounds druglikeliness, that is discussed in Section 4.2.2. Nosyl sulfonamide **126** was chosen instead to generate scaffolds with a free amine further in the synthesis. *Ortho*- and *para*-nitrobenzene sulfonamides can be easily cleaved in mild conditions,[124] and therefore are more applicable for amine scaffold generation than tosyl or mesyl groups.

As compounds **123** and **126** were selected for the development of scaffolds on large scale, their synthesis was applied to a scale of up to 1.0 mol (75.0 ml of **121**) with no changes in reaction yield. However, because the addition of sulfonyl chloride and TEA generates heat, these reagents were added dropwise via dropping funnels over 10 minutes.

One coupling test between aryl bromoalkyne **130** and pivaloyl allyl amine **131** was attempted (Scheme 25) to assess the possibility of an extension to non-sulfonamide ynamides, without success. Terminal alkyne **129** was provided by ex Davies group member Holly V. Adcock.

Scheme 25: Failed ynamide synthesis from pivaloyl allyl amine

The inclusion of *N*-allyl carbamates was excluded. Although Boc is amongst the most useful protecting groups for amines, it is very likely for it to interfere in the gold-catalysed reaction leading to oxazolone **136** (Scheme 26) instead of the desired polycycle **137**. This hypothesis is supported by the fact that there are several works of metal-catalysed transformations in which a Boc group is actively involved in the process.[125] A Cbz protecting group would also be likely to bind the gold complex preventing the desired transformation from occurring, though there are no reported examples of Au-catalysed cyclizations of *N*-Cbz-protected substrates.

Scheme 26: Proposed mechanism for a possible Boc-ynamide cyclization in presence of [Au] (not investigated)

Generation of compound **69** failed on a first attempt (Scheme 27). The reaction was repeated using freshly recrystallised NBS, and this time bromoalkyne was successfully obtained. It is possible that impurities present in non-recrystallised NBS are involved in radical reactions that lead to the destruction of substrate and product.

Scheme 27: First bromoalkyne attempt from tetrahydropyran substrate

Unfortunately, an unidentifiable mixture was detected with ^{1}H-NMR analysis after solvent evaporation, indicating that bromoalkynes built on a non-aromatic scaffold such as **69** are highly unstable. The degradation pathway is unknown, although it can be assumed that a displacement of the multiple bond system occurs. It would be more likely to happen in a non-aromatic framework than in an aromatic bromoalkyne where the breakage of the aryl system is less probable. It is observed that aromatic bromoalkyne **130** is obtained in excellent yields and that can be stored in the freezer up to 5 days. The reaction was repeated in acetone-d_6 and ^{1}H-NMR analysis confirmed complete conversion of **67** and formation of **69** along with minor unknown impurities. It was, however, still impossible to isolate the product in order to use it for the copper-catalysed coupling with a sulfonamide.

To overcome this initial failure, it was decided to test an ynamide formation through chloroalkyne intermediate **138**, which was successfully obtained in mild conditions and with complete conversion (Scheme 28).

Scheme 28: Chloroalkyne synthesis

The crude residue was initially used without further purification to avoid chloroalkyne degradation. However, the mixture did not yield any ynamide **139** with caesium carbonate and DMF, following the procedure showed in Figure 13h. Also a Cu-catalysed synthesis failed, even when increasing the temperature to 110 °C (Scheme 29).

Scheme 29: Failed ynamide syntheses through chloroalkyne

The two reactions were repeated with chloroalkyne purified by flash column chromatography with eluent hexane/ethyl acetate 7:3 and 1% triethylamine to avoid dioxolane cleavage. It was observed that compound **67** was obtained along with **138** in a ratio 1.6:1 (Scheme 28), that was not present in the crude mixture after reaction completion. This means that purification on silica leads to a partial chlorine loss. The yield of reaction described in Figure 26 after column was calculated as 36% with qNMR using 1,2,3,4-tetrachloronitrobenzene as internal standard. Use of purified chloroalkyne did not eventually lead to any ynamide product.

A further attempt was made through a Negishi coupling between bromoacrylaldehyde **140** and 1,2-dichloroalkene **141** (Scheme 30). Compound **140** was selected as halide substrate by derivatization of a protected piperidine scaffold and not the tetrahydropyran as it did not exhibit any volatility, unlike the oxygenated equivalents **61** and **116**, and was therefore

supposed to be less problematic for the acetalization done at high temperature. Although the compound was successfully synthesised and purified, it was obtained in a very poor yield, due to the high sensitivity of the bromide. Compound **141** was instead successfully synthesised and purified in high yields. The Negishi cross-coupling eventually turned out to be inappropriate for this substrate.

Scheme 30: Failed ynamide syntheses through Negishi coupling

While the described exploration of ynamide syntheses remained unsuccessful, the efforts for the generation and stabilization of bromoalkyne intermediate gave eventually positive results. The observation of a visible degradation of **69** upon complete solvent evaporation from crude mixture (Scheme 31) led to the idea that the bromoalkyne could be utilised only when still in solution.

Bromoalkyne formation was therefore repeated and, after completion, was filtered on a nylon membrane filter to remove $AgNO_3$ and concentrated to 3 M solution in acetone. The mixture did not however yield any ynamide **139**.

Scheme 31: Bromoalkyne formation test and ynamide formation attempt with bromoalkyne in acetone solution

It was then hypothesised that acetone and succinimide (generated as by-product) could interfere with catalytic activity. A few drops of toluene were added to the reaction crude prior to evaporation to prevent over concentration and degradation. Toluene was chosen as it is less volatile than acetone and it is the solvent used for the copper-catalysed ynamide synthesis. Toluene does not solvate succinimide, enabling the separation of the latter from the main product by filtration.

It was observed at ^{1}H-NMR spectroscopy that a considerable amount of side products were formed during the reaction (Figure 5a). Ethylene glycol and other peaks associated with aldehyde compounds were identified, suggesting that occurring side-reactions involve aldehyde deprotection. Interestingly, the same signals were observed when stirring terminal alkyne with a catalytic amount (10%) of $AgNO_3$ in acetone (Figure 5c), in absence of NBS. This means that under these conditions, [Ag] may be involved in a Lewis-acid mediated aldehyde deprotection. A reaction with terminal alkyne was also performed with NBS but in absence of $AgNO_3$ (Figure 5d), that resulted in complete conversion to a mixture of unknown products. The same pattern resulted when stirring **67** with a solution of H_2O_2, indicating that NBS could act as an oxidating agent on the terminal alkyne other than initiating radical reactions.

Figure 5: ^{1}H NMR analysis of crude residues of a) Reaction of 67 with NBS and $AgNO_3$ b) Purified 67 c) Reaction of 67 with $AgNO_3$ d) Reaction of 67 with NBS

Instead, when bromoalkyne was stirred with either NBS or $AgNO_3$, it was recovered unaltered, meaning that side-reactions only occur on terminal alkyne. Side-reactions occurring during alkyne bromination were not further investigated in this project. Basing on what reported in the literature, it may be speculated that the presence of moisture may trigger addition to the double bond[126] (Scheme 32a) or hydration of the double bond followed by bromination of the ketone[127] (Scheme 32b).

Scheme 32: Literature example of an addition on double bond with H_2O and NBS

An optimization study was planned in order to minimize the quantity of side-products in the silver-catalysed bromination reaction. Reactions were conducted in acetone-d_6 and then the mixture was analysed by ^{1}H-NMR spectroscopy at reaction completion. Reactions were performed, unlike in the previous tests, under inert atmosphere to minimize the possible interference of moisture and oxygen. The water content reported on the solvent's label was 0.05%).[128] These changes increased the yield from 68% to 86% (Table 5, Entries 1-2) compared to reactions realised in wet solvent and in air. Temperature control tests gave better results at 0 °C (Entry 3) compared to -20 °C (Entry 4). The former gave quantitative calculated yield, with no detectable impurities. On the contrary, lower temperature led to incomplete conversion even after 2 h. Along with the conditions stated in Entries 1-4, a bromoalkyne synthesis under basic conditions was tested to assess if the absence of a silver catalyst and/or NBS could lead to a better result. DBU was found to be an efficient base (Entry 5) and bromoalkyne was successfully recovered after filtration on silica but was contaminated with DBU and ynamide synthesis failed thereafter. The substitution of NBS with 1,2-dibromotetrachloroethane as brominating agent led to incomplete conversion and a poor yield. Deprotonation with *n*-BuLi and then halogenation resulted in ever worse conversion, even with an excess of base.

In conclusion, the best method for bromoalkyne synthesis from pyran-based intermediate **67** was the silver-catalysed transformation with the use of NBS as brominating agent, in dry acetone as solvent, under inert atmosphere at 0 °C.

Table 5: Bromoalkyne synthesis tests

67 **69**

Entry[a]	Reagents	Solvent [0.1 M]	T (°C)	T (min)	Yield[b]
1	NBS, $AgNO_3$	Acetone-d6	20	60	68%[c]
2	NBS, $AgNO_3$	Acetone-d6	20	60	86%
3	NBS, $AgNO_3$	Acetone-d6	0	80	100%
4	NBS, $AgNO_3$	Acetone-d6	-20	120	51%
5	NBS, DBU	Acetone-d6	20	120	82%
6	$(Cl_2CBr)_2$ $AgNO_3$	Acetone-d6	20	120	46%
7	$(Cl_2CBr)_2$, *n*-BuLi	THF	(-78) to 20	120	27%

[a] Reactions were conducted from 0.25 mmol of **67** under inert atmosphere and dry solvent. Five drops of PhMe were always added to the crude mixtures prior to evaporation [b] Yields are calculated with qNMR using CH_3NO_2 or MSM as internal standard [c] Reaction was conducted with undried solvent and in air

For small scale syntheses (0.25-15 mmol) acetone was dried over 4Å molecular sieves and stored overnight. Longer times were avoided as it is reported that MS catalyse aldol condensation of acetone,[129] and therefore increasing the water content even after 16h other than adding unwanted chemicals.[130] For larger scale reactions (15-60 mmol) commercially available HPLC grade acetone (with 99.8% purity)[131] from unopened bottles was used. Since it was previously observed that ynamide synthesis is not successful if succinimide is still present

in the reaction mixture, the crude mixture of bromoalkyne reaction was filtered through silica eluting with toluene. Product was however not detected, unlike prior to filtration. Instead, ^{1}H NMR spectroscopy showed the presence of ethylene glycol and an aldehyde group (same as in Figure 5a) after filtration, indicating the acidity of the silica pad is enough to trigger acetal deprotection and further undefined transformations. The pKa of the silica used for filtration is reported as 6.5-7.0 by the supplier. [132]

To avoid bromoalkyne degradation, silica gel was deactivated with 1% triethylamine.[133] This way, bromoalkyne was recovered and succinimide was completely removed along with silver nitrate. However, only 38% of product (calculated by qNMR) was recovered, along with 53% of terminal alkyne **67** (Scheme 33).

Scheme 33: TEA-mediated debromination of 69

It is reported in a few articles that bromoalkynes react instantaneously with TEA even at -30 °C.[134] The mechanism (Scheme 34) was established as a nucleophilic attack of triethylamine to the α-carbon of the triple bond, formation of vinyl ammonium **151** and then elimination of bromide to lead to ynammonium bromide **152**.

Scheme 34: TEA-mediated formation of ynammonium bromides from bromoalkynes

No salt **153** was detected when reacting **69** with triethylamine. The difference in results observed in this work and in previous works may depend on the different polarization of the bromoalkyne group. If the electrophilic center is more shifted towards the bromine atom rather than the α-carbon of the triple bond, nucleophilic attack of TEA would generate acetylide **155** that would then protonate in the presence of water (Scheme 35).

Scheme 35: TEA-mediated debromination of 69

Tikhomirov *et al.*[134a] came to the same conclusion when studying the reaction of bromophenylacetylene with potassium aziridinide, as they observed the formation of phenylacetylene instead of the expected ynamine product **159** (Scheme 36).

Scheme 36: Reported formation of terminal alkyne from bromoalkyne with amides

A few tests were done to determine the quantity of base that leads to the least bromoalkyne loss. After reaction completion and solvent evaporation, the crude reaction was filtered on a 2 cm pad of silica in a pipette, corresponding to 285 mg of silica, and eluting with 10 mL of PhMe and variable quantities of TEA. Results are shown in Figure 6. The bromoalkyne recovery after filtration is very sensitive to even small variations of base content. The quantity of TEA

that successfully deactivates the silica while minimizing debromination was observed to be 0.5% v/v.

Figure 6: Bromoalkyne yield (qNMR) after filtration as a function of %TEA in PhMe

A change from TEA to a less nucleophilic base such as DIPEA was considered. However, it was not carried out as TEA was easily removed under reduced pressure. The presence of a less volatile base would instead interfere with the copper-catalysed ynamide synthesis, as observed when using DBU (Table 5, Entry 5).

The involvement of $AgNO_3$ in the debromination is unlikely as no transformation occurred when bromoalkyne **69** was stirred with $AgNO_3$ in presence of 2% of TEA and toluene. The same result was observed when compound **69** was stirred in toluene with 2% TEA with succinimide

(that has a pKa of 9.5), indicating that the protonation of the acetylide is likely to occur because of water rather than succinimide.

The evaporation and filtration steps of the workup are not done under inert conditions, as keeping bromoalkyne in toluene and TEA did not lead to a considerable debromination. The formation of terminal alkyne must occur in the presence of TEA on the silica pad. The hypothesis is supported by the observable change of colour of the bromination crude upon filtration with TEA=1%. It shifts from pale yellow, observed for bromoalkyne, to dark red (that is the colour of impurities created when forming the terminal alkyne) (Figure 7a). As a comparison, the silica pad after filtration with TEA=0.5% is clear with an orange column head (Figure 7b).

Silica gel for column chromatography is stated to contain 3-5% moisture by weight.[135] Different procedures for filtration were then tested to check the impact of different pH and moisture absorption capacity. Specifically, celite (pH 10.0),[136] neutral alumina (pH 7.0-8.0)[137] and basic alumina (pH 10.0)[138] were used (Table 6). In these cases, no triethylamine was added in the eluent used for filtration. Alumina filtration pads are shown in Figure 7c.

Replacement of silica also implies a reduction of particle size, pore size and surface area, therefore impacting the filtration.

Only 25% of bromoalkyne was collected after filtration (Table 6, Entry 2), along with all the succinimide. Neutral alumina has proved to be good for the scope (Entry 3), although to a lesser extent than silica. In the case of basic alumina (Entry 4), no yield was determined as proton NMR spectroscopy showed two sets of superimposing signals. One set is ascribable to bromoalkyne and the other to an unidentified compound. No terminal alkyne was observed in this case.

Figure 7: Comparison between a) silica pad after filtration of 69 with PhMe + 1% TEA (left) and celite pad after filtration with PhMe (right) b) silica pad after filtration of 69 with PhMe + 0.5% TEA c) neutral alumina after filtration of 69 with PhMe (left) and basic alumina after filtration of 69 with PhMe (right)

Table 6: Filtration procedures of bromination crude mixtures

67 **69**

Entry[a]	**Filtration**	**Yield**[b]
1[c]	Silica gel	86%
2	Celite	25%
3	Neutral alumina	74%
4	Basic alumina	N.A.

[a] Reactions conditions: **67** (0.25 mmol), NBS (1.1 eq.), $AgNO_3$ (0.1 eq.), dry acetone (0.1 M), 0 °C, 80 min. Five drops of PhMe were added prior to evaporation of solvent under reduced pressure. Crude mixtures were then filtered on a 2 cm pad on a pipette with PhMe [b] Yields are calculated with qNMR using durene as internal standard [c] 0.5% of TEA was added in the eluent

The last study concerning bromoalkyne formation was the direct synthesis from intermediate **65** by silver-mediated cleavage of trimethylsilyl acetylenes followed by bromination.[139] The reaction was carried out in the same optimized conditions as for bromoalkyne formation from terminal alkyne (Table 6, Entry 1) but at room temperature, as it was hypothesised that silylated alkyne is not subjected to the same side-reactions with NBS and $AgNO_3$ as terminal alkyne. This was then confirmed by ^{1}H-NMR spectroscopy of the reaction crude.

The sub-product from desilylation, trimethylsilanol, is a volatile liquid. Hence, it does not interfere with product purification as it is easily removed during solvent evaporation. The yield obtained with qNMR after filtration is comparable to that obtained from silver-catalysed bromination of terminal alkyne (Scheme 37).

Scheme 37: Bromoalkyne synthesis from terminal alkyne 67 and from trimethylsilyl alkyne intermediate 65

In conclusion, bromoalkyne **69** can be successfully synthesised from silyl alkyne **65** with silver nitrate and NBS at room temperature. The product easily degrades upon complete solvent evaporation, but this can be prevented by addition of toluene drops after reaction completion. Bromoalkyne is afforded pure with filtration on a silica pad eluting with PhMe + 0.5% TEA, with a yield calculated by qNMR of 85%.

After successfully resolving all issues related to bromoalkyne synthesis and obtaining the pure intermediate, a series of sulfonyl ynamides was prepared (Scheme 38). Having confirmed that the synthesis to **139** and **143** were not complete after 9 h, reactions were left to stir overnight at 65 °C, according to the original procedure. As the one-pot desilylation-bromination reaction

was developed late in the project, all ynamides were synthesised using terminal alkyne as a precursor for bromoalkyne intermediate. The ratio of bromoalkyne/sulfonamide was increased, compared to previous studies where the amide was the limiting reagent, from 1.2:1 to 1:1. This raised the yield of **143** from 45 to 51%.

Ynamide products were obtained in fair yields (51-61%), expressed as 2-step from **67**, and are slightly higher for aromatic ynamides than aliphatic ones. Products were obtained in higher yields compared to a previous work (45-53%).[83] In Scheme 38 are also reported in parentheses the calculated yields of only the Cu-catalysed step, assuming the 85% yield calculated for bromination of terminal alkyne with qNMR.

Scheme 38: Trihydropyran ynamides scope in this work; yields are related to 2-step procedure, in parenthesis calculated 1-step

Purification by flash column chromatography with eluent heptane/ethyl acetate always resulted in coelution of ynamide and unreacted sulfonamide. A change to PhMe/MeOH (with

the addition of 1% triethylamine to preserve the dioxolane group) in an improvement and allowed a fast purification (comparable to a filtration) of pure ynamide.

Ynamides **160**, **161** and **162** were synthesised from 5.0 mmol of **67** as intermediates in the synthesis of drug-like compound libraries (described in Section 4.2.2). Compounds **139** and **143** were selected as scaffold precursors, therefore their synthesis was upscaled to 60 mmol. The only procedural difference when dealing with larger quantities was the use of larger silica pads for the bromoalkyne crude reaction filtration (specifics are reported in Experimental Section).

It is reported in several studies that the use of microwave leads to higher yields as well as reduced reaction times,[140] and so we decided to test this for the preparation of **143**. The temperature was set to 120 °C and the reaction was complete in 30 minutes, while conventional heating leads to complete conversion in 16 h. The ynamide quantity with the two heating methods resulted comparable both at small and large scale. Hence, the use of microwave could give for this reaction a consistent time saving and enable the completion of the reaction within a day-time process. The maximum volume allowed in the biggest reaction vials suitable for the microwave reactor (Biotage® Initiator+)[141] is 20 mL.[142] Thus, when upscaling ynamide syntheses to 60 mmol, only conventional heating was used to avoid splitting the reaction in multiple vials.

^{1}H and ^{13}C-NMR analysis in $CDCl_3$ showed the formation of unknown impurities 16 h after making the sample (an example is shown in Figure 8), revealing how these ynamides are acid-sensitive (given a small amount of HCl in $CDCl_3$). This is also confirmed by comparison between LCMS analysis in acidic conditions (water/acetonitrile gradient as eluent with addition of 0.1% of formic acid) and in basic conditions (water/acetonitrile gradient as eluent with addition of

ammoniumbicarbonate 10 mM). The latter reflects the purity obtainable by ^{1}H NMR (95% for **142**), while in presence of acid the analysis of the same sample shows a mixture of compounds and a purity of 39%. For these reasons, ynamides were characterised for NMR analysis in solutions of chloroform either previously neutralised with sodium carbonate or contained in sealed 0.6 mL vials with analysis certification from the supplier showing absence of phosgene/HCl and a low water content[143] and kept stored in the dark.

Figure 8: ^{1}H-NMR of freshly purified 139 in $CDCl_3$ (above) and after 16 h (below)

2.2.5 Gold-catalysed polycyclization

The catalyst was successfully obtained from potassium gold trichloride and picolinic acid with good yields (Scheme 39). An important precaution that had to be taken is that catalyst **165** needed to be dried over high vacuum ($p < 10^{-2}$ bar) from the water used as reaction solvent for at least 6 h, in order to avoid its degradation from yellow to inactive grey solid. Once the catalyst is dried, it is stable over atmospheric moisture.

Scheme 39: Au(III) catalyst synthesis

The Au(III)-catalysed polycyclization reaction was first tested for the synthesis of compound **168** with 5% loading of [Au(Pic)Cl_2], obtaining a yield of 84% (Scheme 40). The reaction was repeated with 3% loading of [Au(Pic)Cl_2], obtaining a negligible yield loss to 80%. To further improve the applicability and the atom economy of the cycloisomerization procedure, a catalyst loading of 3% was set as standard and used for the synthesis of all the other polycycles. Only the completion to compound **170** needed 5% loading of [Au(Pic)Cl_2] and longer reaction times, due to the possible coordination of the isoxazole nitrogen to gold. All reactions were successful in toluene at 70 °C except for the synthesis of **168** where the temperature was increased to 80 °C to reach full conversion. The solvent concentration was changed from previous reports[55] (Section 1.4, Scheme 4) from 0.1 M to 0.25 M, as in the former case only 10% conversion was observed.

Reaction yields are generally inferior to what reported for published non-aromatic tetracyclic acetals (80-95%), that were mostly tosylated. They are however comparable to mesylated (49-75%) and nosylated (61-80%) products.[55,83]

Scale-up of the formation of catalyst **165** and polycycles **166** and **168** were carried out smoothly to a scale of respectively 5g, 9g and 8g without significative differences in yields compared to smaller scales. Reaction setup is shown in the Appendix.

[a] The reaction was run with 5% catalyst load for 3 h [b] The reaction was run at 80 °C

Scheme 40: Tetracyclic pyran-based acetals scope

Nevertheless, upscaling raised issues in purification. When using automated purification, a pressure increase could be observed, which could cause a potential detachment of the tubes from the column. This issue could be resolved by securing the column with metal tubing (Figure 9a) instead of plastic tubes (Figure 9b) or by purification with filtration followed by recrystallization.

a) b)

Figure 9: Silica column for flash chromatography a) fixed on metal endpieces b) fixed on plastic tubes

A summary scheme of the 6/7-step synthesis to tetracyclic acetals is shown in Scheme 41.

Scheme 41: Summary scheme of multistep synthesis to tetracyclic acetals (max scale) from 4-oxotetrahydropyran

2.2.6 Piperidine-derived substrates

After establishing an optimised synthetic pathway from 4-tetrahydropyranone to the tetracyclic structures in Scheme 41, the following work was to extend the procedure to the nitrogenated analogue 4-piperidinone (Scheme 42). The use of a nitrogenated scaffold was planned as it adds points of diversity, increasing the structural differentiation achievable with DOS.

Scheme 42: Extension of the multi-step synthesis to piperidine-derived tetracycles

We carefully considered which protecting groups for piperidine nitrogen should be used and were eventually selected as nosyl, Boc and Cbz.[144] *P*-Nosyl was selected as precursor to **176** (Scheme 43), able to stand all reactions conditions throughout the synthesis, whether acidic, basic and/or metal-catalysed. However, since hydrogenation reactions were planned for the elaboration steps to obtain scaffolds with an increased sp^3 character, a complementary study of other protecting groups was required as the presence of the nitro group would indeed result in the formation of a non-deprotectable aniline (**175**).

Scheme 43: Hypothetical hydrogenation to 175 (unwanted) and planned nosyl deprotection to 176

A Cbz protection would provide a double deprotection-alkene hydrogenation[145] opportunity to **179**. Also, if the reducing conditions are pushed further, a fully sp^3 aminoalcohol scaffold **180** could be potentially achieved (Scheme 44).

Scheme 44: Planned scaffold achievements from tetracycle 177

A concern of the Cbz group for the multistep synthesis compatibility with the strongly acidic media would be the Vilsmeier-Haack reaction. However, the synthesis of the corresponding β-chloroacrylaldehyde **182** has been reported[146] (Scheme 45), implying that a Cbz protection for the piperidine nitrogen was likely to be successful for this study.

Scheme 45: Literature reported Vilsmeier-Haack reaction on *N*-Cbz 4-piperidinone

Boc group was also added as a potential protecting group for the piperidine nitrogen. No obstacles were expected as the Vilsmeier-Haack reaction has also been previously described for *N*-Boc 4-piperidinone.[147] A possible interference of a Boc protection in the gold-catalysed cyclization was considered improbable as, unlike for the protection of the ynamidic nitrogen (Scheme 26), in this case (Scheme 46) the protecting group would be far from the reaction site. A following 1-pot Boc-acetal removal to a free amine with an enone functionality **185** was envisaged.

Scheme 46: Planned scaffold realization with *N*-Boc protection

Other protecting groups were ruled out as they were not likely to survive throughout all the 7 steps. For example, a 9-fluorenylmethyl would be potentially unstable in basic environments.[148] and a triflate protection would be highly prone to hydrolysis during aqueous workup and basic solutions.[149] An Alloc protection was ruled out relative to Boc and Cbz that offer two transformations in one step.

Protection reactions on 4-piperidinone were successfully realised following literature procedures.[150] (Scheme 47).

Scheme 47: Protections reactions on 4-piperidinone

Results of the synthetic sequence towards tetracyclic frameworks from *N*-protected 4-piperidinones are shown in Scheme 48. Nosylated intermediates were characterised to bromoalkyne **200**. Bromoacrylaldehyde **107** was synthesised instead of the corresponding chloride as the Vilsmeier-Haack reaction studies described in Section 2.2.1 were realised at a later stage. Reaction yields of *p*-nosyl derivatives were generally lower than those obtained for the dihydropyran-based route, due to the limited solubility of the intermediates that made the purification more difficult. Compounds **107** and **108** required flash column chromatography while nosylated intermediates **188**, **194** and **197** could be purified by recrystallization. Despite the successful synthesis of bromoalkyne **200**, no ynamide structure was obtained on attempted Cu-catalysed amidation, possibly due to the insolubility of the bromoalkyne in toluene. A Negishi cross-coupling (previously described in Section 2.1.2, Scheme 14d) was also attempted, with no results. For these reasons, the use of nosyl as a protecting group was eventually abandoned.

Scheme 48: Summary scheme of multistep synthesis to tetracyclic acetals (max scale) from *N*-protected 4-piperidones

The use of Boc and Cbz protecting groups was instead successful for each step of the synthesis, leading ultimately to 4 tetracycles **207**-**210**. The synthesis of β-bromoacrylaldehydes (Scheme 49) was initially attempted but failed given the excessively acidic reaction media that resulted in the cleavage of the carbamates.

Scheme 49: β-Bromoacrylaldehydes synthesis attempt from carbamates

Chlorinated analogues **189** and **182** were instead obtained following the optimised conditions of the Vilsmeier-Haack reaction achieved in this study, in yields comparable to those reported in literature.[146-147] Scaling-up the reactions did not result in a yield decrease, unlike that observed for the synthesis of **61**, likely due to decreased volatility of the product. Because *N*-Boc tetracycle **207** was used for scaffold generation later in the project, a large scale synthesis from 500 mmol was carried out from **186**. For Cbz and nosyl protected analogues, the multistep synthesis was instead started from 80 mmol.

Sonogashira coupling was then carried out smoothly from vinyl chloride intermediates, followed by dioxolane formation that was carried out in very good yields.

Desilylation of the alkyne generated a small amount of unknown side products that were visible at TLC by UV. In these cases, purification of compounds **195** and **196** had to be carried out to afford the correspondent bromoalkynes.

A yield of 66% and 90% was calculated with qNMR for the bromination to **198** at reaction completion respectively from trimethylsilyl alkyne **192** and terminal alkyne **195**. Impurities (amongst which an aldehyde) were detected, unlike for the synthesis of compounds **69** and **200** under the same reaction conditions. The synthesis of *N*-Boc-piperidine bromoalkyne **198** from terminal alkyne (Scheme 48) gave a lower yield than the oxygenated analogue **69** under the same conditions (Scheme 41). ^{1}H-NMR analysis showed the presence of impurities, including an aldehyde signal. Analogous results were observed when conducting the synthesis of **69** at room temperature, but at 0 °C the reaction was found to proceed clearly.

Compound **198** was found to be more sensitive towards TEA than **69**. The plot of bromoalkyne recovery/% workup TEA (Figure 10) was substantially different from that previously observed for the dihydropyran-based analogue (Figure 6). Specifically, the least product loss after filtration was associated with an addition of 0.15% of TEA, that is circa ¼ of that previously observed for compound **69**. The curve for the *N*-Cbz-piperidine bromoalkyne **199** showed a similar trend, although with slightly higher yields. The rationale for the substantial difference of reactivity between carbamate-based bromoalkynes and the dihydropyran-based one is still unclear. Direct desilylation-bromination reaction from **192** (Scheme 48) was accomplished later in the project, giving better results than the bromoalkyne formation from terminal alkyne and no impurities detected at ^{1}H-NMR. The reaction was therefore extended to a scale of 60 mmol.

Figure 10: Yield of 198 and 199 (qNMR) as a function of %TEA in PhMe

For the scope of ynamides, mesyl and cyclopropylsulfonyl group were incorporated in the structures as they are recurrent structures in pharmaceuticals. Compound **210** was

synthesised to demonstrate the possibility of achieving tetracyclic structures with two nitrogen atoms bearing orthogonal protecting groups, thus enabling the prospect of derivatizing two different amines in different steps and therefore making potentially a large number of compounds. Piperidine-derived ynamides were synthesised in fair yields, according to that previously observed for dihydropyran-based analogues. Tetracyclic acetals were obtained from fair to good yields depending on the sulfonamide structure, being higher for the nosyl derivative **210** than for the aliphatic ones.

A gold-catalysed cyclization was tested from homoallyl sulfonamide **214** (Scheme 50a) in order to extend the procedure to more scaffold precursors. The reaction was previously accomplished by the ex-Davies group member Holly V. Adcock (Scheme 50b) from aryl substrate **216**. The two diastereoisomers **217** and **218** with a [5,6]-ring junction were synthesised and isolated. In comparison, for the cyclization of *N*-Boc piperidine homoallyl ynamide **214**, realised in this work, an inseparable mixture of compounds was obtained. The formation of tetracycles was confirmed by LCMS and ^{1}H-NMR spectroscopy, that showed the characteristic signals of the cyclopropane ring. However, ^{1}H-NMR analysis showed a complicated mixture and no compound could be isolated.

Scheme 50: Au-catalysed polycyclization of omoallyl ynamides a) from *N*-Boc piperidine substrate (this work) b) from aryl substrates (previously reported)

A common feature observed for all the Boc and Cbz protected compounds is the broadening of the signals in the ^{1}H-NMR and the signals splitting to doublets at ^{13}C-NMR at room temperature, indicating the presence of two major rotamers.[151] These effects are more accentuated for *N*-Boc-protected compounds than Cbz. All signals relative to carbamates could be identified and the compounds characterised at room temperature with very concentrated samples. Analysis at ^{13}C-NMR were obtained after 4000 scans.

Compounds **192** and **207** were also analysed at 90 °C as representative compounds (See Appendix), respectively of intermediates and tetracyclic carbamates, to show peak resolution of carbamates at high temperature.

2.3 Summary

Nine tetracyclic intermediates with an acetal functionality were synthesised through a seven-step synthesis from 4-tetrahydropyranone and *N*-protected piperidinone (Scheme 51). Compounds **166**, **168** and **207** were selected to be used as chemical scaffold precursors and were synthesised from 500 mmol of building block with a 5.0%, 7.2% and 9.3% overall yield respectively.

Scheme 51: Tetracyclic precursors to chemical scaffolds

Chapter 3: Generation of novel 3D chemical scaffolds

3.1 Introduction

The new synthesised tetracyclic structures were used to generate chemical scaffolds for drug-like library generation. A general aim was the scaffold achievement as α,β-conjugated carbonyls, in order to achieve the maximum chemical versatility.

Compound **168** was planned to be used as precursor to amine **220** (Scheme 52) potentially obtainable with deprotection of the ketone followed by the use of a thiol as nucleophile in a basic medium.[124]

Scheme 52: Potentially achievable amine scaffold by denosylation; framework modifications are highlighted in red

Compound **166** (Scheme 53) was intended for the study of unexplored reactions for these systems: reductions, oxidations and cyclopropane ring expansion were selected for investigation.

Scheme 53: Potentially achievable scaffolds from pyran-derived tetracyclic acetals; framework modifications are highlighted in red

The *N*-protected piperidine intermediates **207** and **208** were planned to be used as precursors to the aminoketone scaffold **227** (Scheme 54) by ketone deprotection, carbamate cleavage and hydrogenation of the double bond.

Scheme 54: Potentially achievable scaffolds from N-protected tetracyclic acetals; framework modifications are highlighted in red

3.2 Results and discussion

In this section, the synthetic exploration to novel chemical scaffolds from the intermediates achieved from gold-catalysed polycyclization cascade described in Sections 2.2.5 and 2.2.6 is discussed.

3.2.1 Amine formation via *p*-nosyl group deprotection

The dioxolane group was successfully hydrolysed from compound **168** to enone **228** with acid catalysis in excellent yields (Scheme 55). Unfortunately, when the latter was undergone to denosylation conditions, the crude rapidly turned into an insoluble black solid and no compound was detectable by ^{1}H-NMR analysis.

Scheme 55: *p*-TsOH mediated acetal deprotection

It is hypothesised that this outcome may be resulted from a thia-Michael addition that leads to polymerization[152] (Scheme 56), that occurs instead of the *p*-nosyl group cleavage.

Scheme 56: Possible basic-mediated enone polymerization

To avoid degradation, we decided to reduce the enone **228** to allyl alcohol and then test the denosylation reaction. The enone was reduced by Luche reduction (Scheme 57),[153] as $LiAlH_4$ was likely to give azo compounds[154] and $NaBH_4$ would have given a mixture of saturated alcohol and allyl alcohol.[155] The reduction was totally diastereoselective towards compound **233**.

Scheme 57: Reduction of enone 228 to allyl alcohol

The mechanism of the reduction of **228** is shown in Scheme 58. The use of $NaBH_4$ in the presence of $CeCl_3$ generates instead *in situ* alkoxyborohydrides, that are stronger reducing

agents than $NaBH_4$ alone and chemoselective towards the carbonyl group. At the same time, the nosyl group is not affected like when treated with $LiAlH_4$.

Scheme 58: Luche reduction mechanism

Determination of the diastereoisomer obtained as product in Scheme 57 was first attempted by *J* coupling calculation (Figure 11) and use of equations that describe its correlation with dihedral torsion angles.[156]

Figure 11: ^3J coupling between protons H_d-H_e for compound 223

Comparison with 3D-models generated with different softwares[157] (See Appendix) was however inconclusive. As a matter of fact, authors claim that diastereoisomers of structures that are similar to **233** (Scheme 59, **238** and **239**) are both reported to have the same ^3J coupling between the protons CHOH-CH,[158] demonstrating that for these systems the *J* coupling cannot provide any structure confirmation. Moreover, variations of the molecular structure around the fused cyclopentanol ring can significantly change the ^3J coupling. For

example, compounds **238** and **239** have ^{3}J coupling of 6.0 Hz while compound **240** has a ^{3}J coupling of 2.2 Hz.

Scheme 59: ^{3}J couplings of structures with structural affinity to 233

The structure of **233** could be determined by NOESY experiment that confirmed spatial vicinity of proton H_e and H_g' and not for H_e and H_g (Figure 12). This would be likely only for isomer **233**. For complete assignments of ^{1}H and ^{13}C-NMR spectra see Supplementary information.

Figure 12: NOESY correlations found for compound 233

A further confirmation of the structure of compound **233** came later in the project by comparison of chemical shifts and multiplicities at ^{1}H-NMR spectroscopy and NOESY analysis of allyl alcohol **401**, whose structure was resolved by X-ray christallography (See Section 5.2.1).

Attempted denosylation of **233** led to degradation (Scheme 60). Despite seeing the formation of aminoalcohol **241** by LCMS analysis, only thiol and solvent were recovered after solvent evaporation.

Scheme 60: Denosylation of 233

Because the denosylation failed for both the enone and the allyl alcohol, the reaction was tested on dioxolane **168**. Little conversion to **242** was observed at room temperature when thiophenol was used as deprotecting agent (Table 7, Entry 1), while the use of thioglycolic acid led to better results (Entry 2) that were further improved with mild heating (Entry 7).

Table 7: Denosylation tests

Entry[a]	RSH (eq.)	T	T	Yield[b]
1	PhSH (2.5)	rt	16h	8%
2	$SHCH_2COOH$ (2.5)	rt	16h	24%
3	$SHCH_2COOH$ (1.2)	50°C	8h	32%
4	$SHCH_2COOH$ (1.5)	50°C	8h	50%
5	$SHCH_2COOH$ (1.7)	50°C	6h	76%
6	$SHCH_2COOH$ (2.0)	50°C	3h	60%
7	$SHCH_2COOH$ (2.5)	50°C	3h	47%

[a] Reactions were conducted from 0.21 mmol of **168** under inert atmosphere and dry DMF-d_7 (0.3 M) using 5.0 eq. of Cs_2CO_3 [b] Yields are calculated with qNMR using TMS as internal standard

The deprotection with thiogycolic acid also resulted in the formation of an aniline side-product (**243,** Scheme 61). This compound was identified by LCMS analysis and was not possible to isolate. However, the corresponding enone (**244**) after acetal deprotection was successfully

characterised. Because the formation of the side-product may be generated by an excess of reducing agent, parallel reactions were set up and conducted with different quantities of thiol (Entries 3-7), with the best conditions found in Entry 5.

Scheme 61: Nitro group reduction side reaction

An aqueous workup was not practical for the denosylation reaction as compound **242** was soluble both in aqueous solution and organic solvents. The product also could not be properly recovered with column chromatography, after which only 25% of product was afforded. For these reasons, the crude mixture was used for the following step after removing salts with filtration on a nylon membrane filter. The accepted mechanism for the denosylation reaction[127] (Scheme 62) goes through thiolate addition and formation of the Meisenheimer complex **249**. Further elimination affords product amine.

Scheme 62: Denosylation mechanism

The reduction of **168** to side-product **243** is instead likely to occur through a nitroso intermediate (**255**) and following hydroxylamine (**257**). Following studies of thiol-mediated reduction of nitro compounds the reaction may occur through nucleophilic attack of the thiol

to the nitro group (Scheme 63),[159] via a S_NAr mechanism (Scheme 64)[160] or a radical mechanism (Scheme 65).[161]

Scheme 63: Nitro group reduction proposed mechanism by nucleophilic substitution

Scheme 64: Nitro group reduction proposed mechanism by S_NAr

Scheme 65: Nitro group reduction proposed radical mechanism

The reduction can also occur through formation of an azodioxy dimer from **255** and **257** (Scheme 66). These intermediates have been observed with nitrosobenzenes under basic conditions.[162] Two unknown compounds with masses 696 and 715 (about 5% each) were found through LCMS analysis of the crude mixture of reaction as shown in Table 10 Entry 3 and are consistent with the formation of dimers.

Scheme 66: Nitro group reduction proposed mechanism by dimerization

It is stated in the aforementioned works[159-162] that all mechanisms can occur at the same time, although some may play a more considerable role depending on the compound structure and solvent polarity.

Compound **168** was originally considered to be used as a chemical scaffold for the generation of a library of acetals. These compounds are usually not desired for drug design as, since they are prone to hydrolysis in the acidic stomach environment, are not appealing as orally administered drugs. Despite this, cyclic acetals are generally more resistant to acid deprotection and can be accepted as oral drug candidates if they withstand gastric acidity for four hours, that is the maximum time needed for food to be cleared in the stomach.[163]

To verify the possible applicability of dioxolanes in drug discovery for this project, a representative compound (chosen as **166**) was stirred in a solution of simulated gastric fluid (JT Baker® purchased from Avantor) diluted to pH=2 (Scheme 67). Unfortunately, the acetal completely converted to its corresponding ketone **273** after only 2 h. For this reason, the idea of making a library of acetal compounds was discarded.

Scheme 67: Acetal cleavage mediated by simulated gastric fluid

However, a few products of the gold-catalysed cycloisomerization were included in the experimental library as even compounds with labile functionalities can lead to hits. Moreover, drugs can also be given parenterally even if *per os* is the preferred route of administration.[164]

Acetals included in the library were chosen as the mesylated compound **166** and **207** (Scheme 68). Compound **170** was also added to incorporate a sulfamylamide other than only sulfonamides.

Scheme 68: Acetals added to the drug-like library

Further transformations were carried out on acetal **242** to generate scaffolds as a ketone and or an alcohol. Addition of HCl 4N afforded deprotected hydrochloride salt **274** (Scheme 69). The product was obtained as a fine-grained solid incorporated in a viscous oily matrix that is generated from the sub- and side-products of the denosylation reaction. The hydrochloride salt could not be efficiently separated from the impurities with filtration and only a few milligrams of compound were recovered. Purification with preparative reverse phase LCMS also failed as impurities coeluted along with the product. Therefore, compound **274** was used for further reactions as the crude mixture.

Scheme 69: Acid-mediated ammonium scaffold synthesis

Attempted reduction of hydrochloride salt to aminoalcohol **275** was unsuccessful (Scheme 70). Therefore, enone **274** was used as a scaffold for compound library generation.

Scheme 70: Attempted reduction of enone 274

Derivatization of **274** to the amide by acid coupling was unsuccessful, while use of acyl chlorides successfully yielded compound library **276** (Scheme 71). The pathway to the amide is shown from **168** as intermediates **242** and **274** are not purified, therefore an over 3 steps yield was determined. Further reduction of **276** yielded compound **277** enabling the possibility to make a library of allyl alcohols.

Scheme 71: Two-step allyl alcohol compound library synthesis

Etherification reactions were tested on compound **278** to assess the versatility of the allyl alcohol group (Scheme 72). Unfortunately, no side chain could be linked with Williamson ether synthesis or by Ag_2O-mediated etherification.[165] The use of bases led to partial degradation of the reagent, while reaction with silver oxide did not yield to any conversion.

Scheme 72: Attempted alkylation of allyl alcohol

3.2.2 Conjugated carbonyl formation

Acetal **166** was deprotected to enone **273** following a protocol[166] that utilizes *p*-toluenesulfonic acid in a mixture of acetone and water (Table 8, second column). The reaction was heated to 65 °C as the ketone was not soluble in the solvent mixture at room temperature. Despite the good results achieved at small scale, complete degradation was observed when the reaction was scaled to 60 mmol. The cause for this outcome is not known and no signals were registered at LCMS analysis. It can be supposed that it is due to the reactivity of the enone. It would be plausible, for example, a 1,4- or 1,6-conjugate addition.[167] Further substitution may then trigger a conjugate-addition polymerization. The deprotection procedure was successfully changed by using a stronger acid and lower temperature to avoid heating (Table 8, third column). Though the yield was found to be lower at smaller scale than when applying the previous method, this procedure was more robust and applicable to a larger scale.

Table 8: Acetal deprotection tests

166 **273**

Scale (mmol)	Yield method A[a]	Yield method B[b]
0.1	91	79
1.0	87	71
5.0	76	76
30.0	degradation	72

[a] Conditions: *p*-TsOH (0.3 eq.), Acetone/H_2O 3:1 (0.1 M), 65 °C, 3 h

[b] HCl 4 N in 1,4-dioxane (0.1 M), H_2O (1.0 eq.), 0 °C, 2 h

Derivatizations of the α,β-conjugated carbonyl were tested to assess the potential to generate drug-like compounds. Grignard reaction of **273** (Scheme 73) did not yield any desired product, registering partial sulfonamide cleavage instead.

Scheme 73: Attempted Grignard reaction on enone 273

Both Borch reaction and titanium isopropoxide reductive amination in different solvent mixtures were explored to generate amines, but all trials resulted in no conversion (Scheme 74).

Scheme 74: Attempted reductive amination on enone 273

Since the one-step derivatization of compound **273** to drug-like compounds resulted impossible, further modifications on the enone were planned to achieve chemical scaffolds.

3.2.3 Saturated ketone and alcohol formation *via* hydrogenation reaction

Enone **273** was subjected to hydrogenation conditions, using palladium on carbon as catalyst (Scheme 75). The reaction yielded a mixture of three compounds with mild heating. Even after several hours, no further hydrogenation of C=C or C=O bonds was observed.

Scheme 75: Pd/C-catalysed hydrogenation of enone 273

Compound **283** was the only diastereoisomer derived from the hydrogenation of only the double bond of the enone. The configuration of the new stereocenters could be determined with 2D NMR analysis (See Appendix). Data was collected in both $CDCl_3$ and C_6D_6 as the different chemical shift of protons in different solvents allowed the separation of superimposed signals. Key NOESY correlations for the diastereomeric determination are shown in Figure 13.

Figure 13: NOESY correlations found for compound 283

The structure determination was later confirmed by X-ray analysis (Figure 14).

Figure 14: Crystal structure of 283 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham)

The total diastereoselectivity towards of the catalytic hydrogenation of the double bond towards compound **283** can be due to the steric hindrance given by the pyrrolidine ring of enone **273**. This implies that the most accessible face for the activated metal surface to interact is opposite to the one that contains the pyrrolidine ring (Figure 15).

Figure 15: Elucidation of catalytic hydrogenation diastereoselectivity

The formation of side-products **284** and **285** was an unexpected outcome. Metal-catalysed hydrogenolysis of oxygenated rings are known processes that lead to alcohols.[168] In this study, the tetrahydropyran ring opening may be followed by elimination (Scheme 76), possibly triggered by the water content in the solvent (EtOH). Further hydrogenation of the formed double bond affords compound **284**.

Scheme 76: Proposed mechanism for the formation of compound 284

It is interesting to observe that compound **284** is still unsaturated, indicating that after the 6-membered ring cleavage the cyclopropane ring cleavage is favoured compared to the hydrogenation of the double bond. This is possibly due to the steric hindrance given by the alkyl groups.

It was observed in other studies that hydrogenation-induced cyclopropane cleavage of 3/5-fused systems selectively leads to the product with the newly created methyl group adjacent to the quaternary carbon on a 5,5-*cis* junction (Examples in Scheme 77). In these cases, the products come from the C-C cleavage on the least hindered side of the cyclopropane.[169]

Scheme 77: Literature examples of hydrogenation reaction on 3/5-fused systems

In this work, the formation of an analogous compound (Table 9, **295** and **298**) was not observed, nor a product of ring expansion (**296** or **299**). Product **284** also bears a *cis*-ring junction, and it was calculated as more stable than its *trans*-isomer **297**. Although compound **296** would be the theoretical product with the lowest calculated energy, the cyclopropane hydrogenation on the concave side of the 5,3-ring junction would be more unlikely than the breakage of the other C-C bonds. The regio- and stereoselectivity of the cyclopropane cleavage towards compound **284** can therefore be explained by energetic and steric factors. More information on the energies of the transition states could potentially be provided by DFT calculations (not realised for this work).

Table 9: All theoretical product from cyclopropane hydrogenation of 284 and relative energies calculated with MarvinSketch (lowest energy of 500 conformers with force field MMFF94)

284 -13.5 kcal/mol	**295** -10.8 kcal/mol	**296** -15.6 kcal/mol
297 6.9 kcal/mol	**298** 14.2 kcal/mol	**299** -6.5 kcal/mol

The identification of compound **284** could be possible through 2D-NMR analysis (See Appendix), with the most important correlation being at NOESY between H_e and H_l (Figure 16). The formation of compounds **284** and **285** was not further investigated as the project was more focused on the selective synthesis of scaffold **283**. This compound bears indeed an additional heterocyclic ring than the side-products and was therefore considered more promising for the creation of drug-like libraries.

Figure 16: NOESY correlations found for compound 284

Despite not being the main goal of this work, the synthesis of compounds **284** and **285** was an interesting result as it shows a simple strategy for a heterocyclic ring cleavage-hydrogenation procedure, that is not broadly available in the literature. Moreover, Pd/C-catalysed

hydrogenation of **273** enabled accessible structures that could be difficult to obtain by other methods.

The hydrogenation of enone **273** was repeated with platinum oxide as catalyst and saturated ketone **283** was obtained in a very good yield (Scheme 78). The amount of ring cleavage side-products was calculated as 5-10% by LCMS, and the main product was successfully purified with recrystallization in ethanol. Interestingly, saturated alcohol **300** was obtained when the PtO_2-catalysed hydrogenation was carried out for a longer time. The same conditions with a higher catalyst loading produced a diastereomeric mixture of saturated alcohols. The two compounds could be separated by flash column chromatography followed by recrystallization.

273	Conditions:	283	300	301
	PtO_2= 6% w/w, t= 45min	82%	0%	0%
	PtO_2= 6% w/w, t= 3h	0%	73%	0%
	PtO_2= 30% w/w, t= 3h	0%	31%	18%

Scheme 78: PtO_2 catalysed hydrogenations of 273

These results are in accordance with that reported in a previous study,[170] where hydrogenation of methyl vinyl ketone **302** (Scheme 79) led only to the corresponding saturated ketone **303** when using a Pd-based catalyst. Instead, when using a Pt-based catalyst, the reduction could be pushed further to the saturated alcohol product **304** after conducting the reaction for several hours. The same article reported that the hydrogenation of the double bond was both kinetically and thermodynamically favoured than that on the carbonyl group. The different selectivity depends on how strongly the carbonyl group binds to the surface.

Scheme 79: Literature reported Pd- and Pt-catalysed hydrogenations of methyl vinyl ketone

Synthesis of alcohol **300** was also achieved through reduction of carbonyl **283** with $NaBH_4$ (Scheme 80). Because the yield was higher than for the hydrogenation reaction, the reduction with hydride was selected for reaction scale-up to 1g of ketone.

Scheme 80: Hydride reduction of ketone 283

The addition of titanium isopropoxide in the sodium borohydride reduction reaction mixture led to a 1:1 ratio mixture of diastereoisomers. The two alcohol diastereoisomers could be identified by their *J* couplings in the ^{1}H-NMR spectra by comparison between predicted 3D structures and predicted dihedral angles (See Appendix). The resolution of overlapping resonances and determination of multiplicities could be carried out with multiple ^{1}H-NMR spectra obtained from analysis in different solvents. One compound shows proton H_f (bonded to the new stereocentre, Figure 17) coupled with H_g (on the tetrahydropyran ring-junction) with a *J*= 3.6 Hz, while the other compound shows *J*= 10.0 Hz. The dihedral angles predicted for *J*= 3.6 Hz match those predicted by 3D structures of **300**, where the conformation of the central five-membered ring is *syn*-clinal, and not by 3D structures of **301** that would require an *anti*-clinal conformation. Likewise, a *J*= 10.0 Hz matches the *anti*-periplanar conformations

for compound **301**, being instead highly improbable for compound **300** as most equations do not predict a *J* coupling this high for any *syn*-clinal conformation.

Figure 17: *J* couplings and Newman projections of 300 (left) and 301 (right)

For compound **300**, NOESY analysis provided further evidence of its structure (Figure 18). Proton H_f shows strong NOESY correlations with H_e and H_g, while the alcohol proton shows correlation with proton H_j', that is on the same side of the plane. On the contrary, no useful NOESY correlations were found for compound **301**.

Figure 18: NOESY correlations found for compound 300

The structure of compound **300** was eventually confirmed by X-ray analysis (Figure 19) of colourless needles obtained with slow recrystallization in dichloromethane. Interestingly, the observed structure occupies a chiral space group. Rapid recrystallization of **300** in hot ethanol

afforded the product as a white solid and was confirmed to be a racemic mixture by SFC analysis using a chiral column.

Figure 19: Crystal structure of 300 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham)

The selective reduction of the double bonds was also tested with Stryker's reagent[171] (Scheme 81) to assess the possibility of accessing scaffold **283** with a procedure that does not require hydrogen gas or heating. Unfortunately, the reaction was unsuccessful.

Scheme 81: Reduction attempt with Stryker's reagent

In contrast to the α,β-unsaturated carbonyl **273**, ketone **283** successfully yielded a product of Grignard reaction (**305**) and a product of reductive amination (**306**, detected by LCMS), enabling the possibility of creating two chemical libraries (Scheme 82).

Scheme 82: Small scale Grignard reaction and reductive amination on saturated ketone 283

A Williamson ether synthesis could be carried out from alcohol **300** (Scheme 83). Compound **301** was not tested as this project was focused more on the use of scaffolds that were achieved stereoselectively.

Scheme 83: Small scale Williamson ether synthesis from alcohol 300

3.2.4 Framework modifications via oxidation reactions

As mentioned in the introduction, oxidation reaction studies were planned with the primary goal of achieving lactones and/or lactams (Scheme 84) which are structures of great interest in drug discovery. The activation of the methylene group adjacent to the cyclopropane can also be potentially explored,[172] along with cyclopropane ring opening.[173] A review of literature for similar transformations revealed ruthenium tetroxide[174] and PCC[175] as suitable reagents to investigate.

Scheme 84: Planned oxidation of ketones 273 and 283

Enone **273** did not give any conversion with use of PCC as oxidant, while reaction with RuO_4 (generated in situ) gave a mixture of compounds (Scheme 85). Isolation of identifiable products from these reactions proved unsuccessful.

Scheme 85: Oxidation attempts of 283 with PCC and RuO_4

Oxidations of enone **273** with *m*-CPBA was attempted, hoping for the formation of lactone **315** along with epoxidation[176] to **316** (Scheme 86). However, the reaction only led to an inseparable complex mixture. The same outcome was observed when attempting an alkene α-hydroxylation with SeO_2 to **317** (that could also compete with oxidation of a methylene group to carbonyl **318** or oxidation of the double bond to 1,2-diol to **319**).[177]

Scheme 86: Oxidation tests with *m*-CPBA and SeO_2 on compound 273 and expected products

Concerning the application of potential Baeyer-Villiger Reaction oxidation from **283**, use of *m*-CPBA as oxidant (Scheme 87, B) successfully led to lactone **320** in low yields while use of PCC resulted in little conversion (Scheme 87, A). A reaction with $AgBF_4$ along with PIDA was carried out in an attempt to make an oxidative cyclopropane cleavage[178] (Scheme 88a) but instead product **320** was observed.

Conditions:

A: PCC (1.0 eq.), CH_2Cl_2 (0.1 M), rt, 4 d		8%
B: *m*-CPBA (2.0 eq.), CH_2Cl_2 (0.1 M), 0 °C, 3 h		28%
C: $AgBF_4$ (1.0 eq.), PIDA (1.0 eq.), $CHCl_3$ (0.1 M), rt, 7 h		21%
D: $AgBF_4$ (1.0 eq.), $CHCl_3$ (0.1 M), rt, 1 h		0%
E: PIDA (1.0 eq.), $CHCl_3$ (0.1 M), rt, 16 h		0%
F: $Cu(BF_4)_2$ (1.0 eq.), PIDA (1.0 eq.), $CHCl_3$ (0.1 M), rt, 7 h		mixture
G: $Sc(OTf)_3$ (1.0 eq.), PIDA (1.0 eq.), $CHCl_3$ (0. 1M), rt, 7 h		mixture

Scheme 87: Chemoselective Baeyer-Villiger oxidation of 283

No conversion was observed when stirring compound **283** with only $AgBF_4$ or only PIDA. This indicates that the oxidation with PIDA can only occur with Lewis acid activation. The proposed mechanism for this transformation (Scheme 88b) follows that reported for the Baeyer-Villiger oxidation with hypervalent bromane.[179] Replacement of $AgBF_4$ with other Lewis acids only led to complex mixtures (Scheme 87, F, G).

Scheme 88: a) Expected oxidative cyclopropane cleavage b) LA/PIDA mediated Baeyer-Villiger

The purification of compounds **320** by flash column chromatography or preparative LCMS resulted in partial degradation. The lactone was characterised with a purity of 74% measured by LCMS.

The regioselectivity of lactone **320** was confirmed by HMBC analysis (Figure 20) that showed correlation between the carbon atom of the carbonyl group and the proton resonances of the oxygenated ring and of the ring junction.

Figure 20: HMBC correlations found for compound 320

3.2.5 Framework modifications via addition reactions

Ring-opening of β-cyclopropyl α,β-unsaturated carbonyls is very limited in the literature, with only few examples available and only restricted on simple structures. A multicomponent coupling with cyclopropyl cleavage was noted by Gianino *et al.* on β-cyclopropylacrylaldehyde[180] (Scheme 89).

Scheme 89: Reported ring-opening of β-cyclopropyl α,β-unsaturated carbonyls mediated by Zn and titanocene

The establishment of a simple procedure for the 3-membered ring opening on structures bearing a fused cyclopropyl ring, as in this project, would allow a ring expansion to further novel frameworks. A strategy to achieve this goal would be through a Brønsted/Lewis acid mediated 1,6-conjugate addition (Scheme 90).

Scheme 90: Expected transition states for a 1,6-conjugated addition to a cyclopropyl enone substrate

This idea was applied by the ex-Davies group member MSc James I. Bowen, who in a previous project achieved the synthesis of compounds **333** and **334** (Scheme 91).[181] However, thiophenol attacked the carbonyl group and the conjugate addition was eventually carried out by tosylate anion.

Scheme 91: Reported 1,6-conjugated addition on aromatic tetracycles

When compound **273** was subjected to the same conditions, only partial degradation was observed. The same outcome resulted when replacing tosyl acid with a Lewis acid. Heating was avoided to prevent unwanted degradation, and thiophenol was used as solvent as well as reagent to enhance the reactivity. In this case, thioacetal **340** could be isolated in a small quantity that increased to 52% when using a softer Lewis acid (Scheme 92). Two new

compounds with masses 582 and 692 were detected at LCMS analysis if the reaction was allowed to occur for several hours after complete conversion to thioacetal. The corresponding peaks were successfully isolated, the first corresponding to compound **341**, while the latter was not identified as it gave an extremely messy ^{1}H-NMR analysis with the almost totality of signals corresponding to aromatic protons. This means that the isolated peak may correspond to a mixture, an unstable compound or an oligomer that cleaves during mass analysis.

Scheme 92: Cu-catalysed reaction of 273 with PhSH

The formation of compound **341** can be justified by a 1,4-conjugate addition instead of a 1,6-conjugate addition (Scheme 93). This indicates a difference of reactivity of thiophenol towards aromatic and non-aromatic tetracyclic ketones. The reaction mechanism was envisaged as mediated by Cu(I) as Cu(II) salts are reported to easily disproportionate in the presence of thiols.[182] It was unfortunately impossible to determine the configuration of the new stereocenters of compound **341**. One- and two-dimensional NMR analysis in $CDCl_3$ and C_6D_6 (See Appendix) allowed resonance assignments, but no useful correlations were found at COSY, NOESY or HMBC analysis that could help to determine the structure. DFT calculations could potentially give insights regarding the energy pathways towards different diastereoisomers (not realised for this project). As compound **341** is an oil, crystal structure would not be available for the diastereoselectivity determination.

Scheme 93: Conjugate addition mechanism of PhSH on enone 273

The ElogD of the compound was > 5.3 and was therefore considered too apolar to be a good type of scaffold, therefore the conjugate addition with thiophenol was not further investigated. The reaction was instead tested with other soft nucleophiles. Reaction with ketone **273** and acetylacetone did not yield any conversion (Scheme 94) in any conditions, neither with addition of a base.

Scheme 94: Conjugate addition attempt with acetylacetone

Reaction of **273** with nitromethane (Scheme 95) gave instead partial conversion to two compounds, whose masses correspond to the product obtained with Henry reaction and the

compound achieved by following 1,4-conjugate addition. The new compounds could not be separated by flash column chromatography nor by preparative LCMS/UPLC methods as the peaks corresponding to the products superimposed to the unreacted ketone.

Scheme 95: Conjugate addition reaction with nitromethane

3.2.6 Reactions mediated by samarium Iodide

A final attempt to cleave the cyclopropane ring was attempted with single electron transfer reducing agent samarium iodide which has been used for ring openings[183] and closures[184] in total syntheses. An example is found in the synthesis of cyclocitrinol,[185] where a cyclopropane cleavage is mediated by SmI_2 with the assistance of an α,β-conjugated carbonyl and a carbonyl as vicinal groups (Scheme 96).

Scheme 96: Reported SmI_2-mediated cyclopropane cleavage in the total synthesis of cyclocitrinol

An expected outcome from the reaction of SmI_2 with enone **273** was the cyclopropane ring opening by radical mechanism mediated by the α,β-conjugated carbonyl group to give compound **361** (Scheme 97). What was instead observed by LCMS analysis was the formation of four compounds, of which one with mass M+4, two with mass 2M+2 and one with mass

2M+4. All peaks were superimposed so no relative intensity could be calculated. Separation of the reaction mixture was unsuccessful. It can be hypothesised that the reaction may generate different radical intermediates that eventually form dimers by radical coupling. Further reduction may then be responsible for the formation of the peak 2M+4.

Scheme 97: Reduction of 273 with SmI_2 and speculated intermediates

3.2.7 Aminoalcohol formation

The formation of enone scaffold **362** was successfully accomplished by one-pot double deprotection of tetracycle **207** (Scheme 98). Unlike compound **274**, scaffold **362** was easily purified by filtration.

Scheme 98: Double deprotection of 207

The same transformation was tested on compound mixture **215**, and we hoped to achieve a mixture of hydrochloride salts that could potentially be separated by recrystallization. Instead,

traces (ca 2 mg) of one enone (stereochemistry not confirmed) were isolated along with mesyl homoallyl amide that was found to be the main product (Scheme 99). Separation of compound **364** by multiple solvent extraction was unsuccessful as the sulfonamide was always found to be partially soluble in the aqueous phase (that contains the hydrochloride salt).

Scheme 99: Double deprotection of 215

Reduction of hydrochloride salt **362** with $LiAlH_4$ afforded aminoalcohol **365** (Scheme 100).

Scheme 100: Reduction of scaffold 362 to aminoalcohol

NMR analysis of the reaction mixture showed the presence of a side product, although it was not detected by LCMS analysis as only one broad peak was observed. However, a few mg of a side product could be isolated after derivatization of the amine to a urea using unpurified **365** (Scheme 100). The presence of a peak at ^{13}C-NMR at 212.3 ppm and a pattern at ^{13}C-NMR and HSQC in the aliphatic region comparable to compound **283** confirm the side product to be ketone **367** (stereochemistry not confirmed). The side-reaction is therefore a 1,4-reduction.

Scheme 101: Derivatization of aminoalcohol scaffold and side-product formation

Purification of scaffold **365** was carried out by preparative UPLC, and because the peak of the main product superimposed to that of the side product, mixed fractions were collected. Purified fraction contained 34% of product, while the actual reaction yield was determined by qNMR as 79%.

The diastereoselectivity of the reaction was confirmed with two-dimensional NMR analysis (See Appendix) as previously undertaken for compound **233** (Section 3.2.1). The same NOESY correlation was found between proton H_f and proton H_h' on the same side of the molecule (Figure 21). Synthesis of caffold **365** was achieved with one more equivalent of hydride than theoretically required to reach complete conversion, and in a lower yield (determined after preparative UPLC purification) than other observed reductions to allyl alcohols in this work (some reaching 90%). A counterion analysis of the hydrochloride salt **362** (See Appendix) confirmed the presence of one chloride ion per molecule, confirming that that compound **362** is monohydrochloride and therefore the need of more hydride equivalents is not caused by the presence of multiple HCl molecules in the enone structure.

Figure 21: NOESY correlations found for compound 365

3.2.8 Aminoalcohol reduction via hydrogenation reactions

A one pot deprotection-double bond hydrogenation was attempted from compound **208** (Scheme 102). When using H_2 and PtO_2 as catalyst no reaction occurred, while Pd/C only

cleaved the Cbz group. The low yield of compound **368** was likely given by filtration of the mixture at reaction completion on celite eluting with CH_2Cl_2. The high polarity of the compound (confirmed by its high solubility in D_2O and low in $CDCl_3$) would have required the use of a membrane filter and elution with a more polar solvent, that was used for all the other hydrogenation workups in this project.

Scheme 102: Hydrogenation tests on compound 208

No double bond hydrogenation was observed, neither when increasing the temperature and the catalyst loading. This may be due to the presence of two spirocyclic allylic positions preventing access to the alkene (Figure 22).

Figure 22: 3D model of the minimum energy conformer out of 100 conformers for compound 208 realised with MarvinSketch software. Explicit hydrogens were omitted for clarity

It was then planned to test a hydrogenation reaction from an α,β-conjugated carbonyl, and since it was observed to be procedurally easier to achieve from a Boc protected intermediate rather than a Cbz, only Boc-protected intermediates were used for scaffold production.

Hydrogenation of the hydrochloride salt was unsuccessful, while the same reaction on the derived enonamine resulted in an inseparable mixture (Scheme 103) of three isomers with mass M+2.

Scheme 103: Hydrogenation tests on compounds 362 and 365

Considering that the formation of a mixture could result from reactions between the ketone and the amine group, the reactions were repeated after derivatizing the amine to amide **370** and urea **371** (Scheme 104). However, also in these cases the desired ketone could not be separated from the side-products.

Scheme 104: Hydrogenation tests on amide and urea derivatives towards ketones

Hydrogenation reactions were eventually repeated until completion to the corresponding saturated alcohols (Scheme 105). This time, compound **372** was obtained in traces while alcohol **373** was successfully isolated in a low yield from the separation of the obtained complex mixture. The stereoselectivity was confirmed by 2D-NMR analysis and by comparison with the NMR analysis of compound **273**. The synthesis of **373** was finally tested at room

temperature and with a higher pressure of hydrogen. In this case, no side-products were observed and the synthesis of the alcohol was achieved in good yields.

Scheme 105: Hydrogenation tests on amide and urea derivatives towards alcohols

The optimization of the hydrogenation reaction on piperidine-derived tetracycles was successfully realised at the end of this project, therefore compound **373** was not used as a scaffold to make further chemical libraries by derivatization of the alcohol group, due to a lack of time available. It was however added to the experimental library.

3.3 Summary

Five chemical scaffolds were synthesised from four tetracycles (**167**, **166**, **207** and **208**) obtained with gold-catalysed polycyclization (Scheme 106). Denosylation and ketone deprotection of **167** were carried out to synthesise aminoketone **274**, while scaffold **283** was generated with ketone deprotection and hydrogenation of **166.** Further reduction of **300** afforded alcohol **300**, whose structure was confirmed with X-ray christallography. Aminoalcohol **365** could be synthesised by a one-pot Boc cleavage and ketone deprotection from **207**. Small scale derivatization of the nitrogen to urea and hydrogenation afforded compound **373**. No scaffold was obtained from ketone deprotection and following hydrogenation of **208**, affording instead a complex mixture.

Scheme 106: Scaffold generation; points of derivatizations are highlighted in red

Enone **273**, synthesised from tetracycle **166**, could be used to carry out a thiol addition to thioacetal **340** and spiro compound **341** (Scheme 107). A Baeyer-Villiger oxidation to lactone **320** was possible from ketone **283**.

Scheme 107: Further derivatizations from enone scaffold 273

Chapter 4: Virtual library generation

4.1 Introduction

The creation of virtual libraries can be realised through a compound library enumeration software. Programs commonly used are: KNIME,[186] OSIRIS DataWarrior,[187] Reactor (Chemaxon)[188] and Flare™.[189] After that, algorithms can be applied to select the compounds that have a higher chance to give promising results in a drug discovery project. Several "rules of thumb" have been established to assess the drug-likeliness of a compound[190] (Table 8), based on the observation of the properties of approved drugs. These include Lipinski's rules, Veber's rules,[191] Muegge's rules,[192] Egan's rules[193] and Ghose filters.[194]

Table 8: Resume of the most common drug-likeliness "rules of thumb" parameters

	Lipinski	Veber	Muegge	Egan	Ghose
MW	< 500 Da	-	200 < MW < 600	180 < MW < 480	180 < MW < 480
logP	≤ 5	-	-2 < logP < 5	≤ 5.88	-0.4 < logP < 5.6
HBA, HBD	≤ 10; ≤ 5	-	≤ 10; ≤ 5	-	-
PTSA	-	≤ 140.0	≤ 150.0	≤ 131.6	-
ROTB	-	≤ 10	≤ 15	-	-
Rings, C, heteroatoms	-	-	≤ 7; > 4, > 1	-	-
atoms	-	-	-	-	20 < n < 70

4.2 Results and discussion

The four chemical scaffolds achieved in a multi-gram scale (**274**, **283**, **300** and **365**) could be used to potentially create five different drug-like libraries. In this Section will be detailed the

process that led to the creation of *in-silico* libraries, entirely realised with the free software OSIRIS DataWarrior.

4.2.1 Compound library enumeration

For the virtual library creation, a list of commercially available reactants was downloaded in .sdf format from the chemical suppliers Merck,[195] Enamine,[196] InterBioScreen Ltd,[197] Maybridge[198] and UpFluorochem.[199] Duplicates were removed with Osiris DataWarrior, along with reagents containing metals and functional groups considered to be not-druglike (CN, NO_2, double and triple bonds, carbonyls, imines, hydrazones, boronic acids) with the filter "*Nasty functions"*. Very expensive reagents (> 100£/ g) were also ruled out. An example of this procedure realised for acyl chlorides is shown in Figure 23.

Figure 23: Numbers related to downloaded acyl chlorides and filtration on OSIRIS DataWarrior

Eventually, a total of 10,744 compounds was achieved from library enumeration from scaffold derivatization and an *in-silico* list of 1297 acyl chlorides, 1297 aldehydes, 114 carbamoyl chlorides, 4100 primary amines, 48 Grignard reagents and 1180 primary alkyl halides (Scheme 108). The technical details regarding the building of the virtual library with OSIRIS DataWarrior is discussed in the Appendix.

Scheme 108: Scheme of scaffolds derivatizations and numbers related to *in-silico* reagents

4.2.2 Compound library filtration by drug-likeliness

The "rules of thumb for drug-likeliness" discussed in Section 4.1 were applied to the "raw library" of 10,744 compounds, selecting the compounds with the following parameters: 180 < MW < 480, -0.4 < logP < 5.0, HBA ≤ 10; HBD ≤ 5, PTSA ≤ 131.6, ROTB ≤ 10, rings ≤ 7 and 20 < atoms < 70. Limitations on the molar refractivity < 130, that is one of the Ghose filters, were not applied as OSIRIS DataWarrior is not provided with a parameter predictor. A restriction on 0-3 aromatic rings was also added, following recent observations on drug developability studies.[200] The overall filtration by "drug-likeliness rules of thumb" restricted the library list to 7274 compounds.

A further parameter used for the selection of the virtual library compounds is the *DataWarrior druglikeliness*.[201] It is an algorithm built exclusively for the OSIRIS DataWarrior software and it is a score that keeps into account the frequency in which molecular fragments are found in traded drugs and the potency of the selected drug. It is advised from the software creators to select compounds with a positive druglikeliness score, as it is compatible with most drugs. To verify the applicability of this parameter, the score was calculated for a collection of publicly

available virtual "targeted libraries" realised by Enamine®[202], containing in total 260,025 compounds realised via docking and visual evaluation and specific for the studies of ion-channel active DNA-active, PPI-active or CNS-active compounds, immuno-oncology agents, kinases or anti-virals. It was found that 84% of the molecules have a positive druglikeliness score. For this study, the minimum has been decreased from 0 to -1 as it has been observed that in a list of 3035 FDA approved drugs (the most provided for HTS),[203] the range -1-0 of druglikeliness score is in proximity to the maximum of the bell curve (Figure 24).

Figure 24: Bell-curve of the drug-likeliness score calculated with "OSIRIS DataWarrior" of 3035 FDA-approved drugs; the red arrow shows the proximity of the range -1 to 0 to the maximum range (0-1)

OSIRIS DataWarrior was also used to make a toxicity risk predictor[204] for mutagenicity, tumorigenicity, irritability and reproductivity risks. Erasure of the compounds labelled as "non drug-like" and toxic yielded 2874 compounds.

4.2.3 Compound library filtration by globularity score

The virtual library was filtered in order to keep the compounds with the greatest tridimensionality. OSIRIS DataWarrior has two parameters available for this scope: the *molecular shape index* is a 2D-parameter and considers the atom count and bond lengths, while the *globularity score* is determined from the atom coordinates of 128 predicted

molecular conformers. For the library filtration, the latter was used as it is a more sophisticated calculation. The *globularity score* was set as > 0.3, returning a library of 1987 compounds. The limit was not raised further as most of the virtual compounds derived from aminoalcohol **365** would have been ruled out, therefore reducing chemical variability.

4.2.4 Compound library filtration by structural similarity

Even if the 1987 compounds contained in the library satisfy all the requirements for drug-likeliness and tridimensionality, further selection had to be carried out as the library was considered too large to be analysed for *in-silico* pharmacological analysis. The library size was aimed to be finally cut to the maximum size advised to be stored in the platform "CDD vault"[205] per project, that corresponds to around 1000 compounds.

It was eventually decided to downsize the library based on reducing chemical similarities. These are determined first by associating the structure of a molecule to a bidimensional descriptor, known as fingerprint. An example is shown in Scheme 109, where the fingerprint of 3-isopropylpyridine was built in a previous study after deconstruction into further substructures.[206]

Scheme 109: Molecular fingerprint of 3-isopropylpyridine

OSIRIS DataWarrior has different descriptors, each one built on an algorithm that relies on different properties. Descriptor *FragFp* breaks down a structure into fragments chosen out of a list of 512 substructures, while *PathFp* considers vicinal atoms up to the seventh bond. *SphereFp* encodes fragments in the space around a specified atom, and the same algorithm

with inclusion of stereochemistry descriptors and with doubled resolution makes the descriptor *SkelSpheres*. *OrgFunctions* describes molecules through a selection of 957 functional groups, including features regarding electronic and steric factors. The most complex descriptor is *Flexophore* and it describes the potential as a pharmacophore, keeping into account the possible conformers. The library filtration was planned to be based on chemical structure, and because *SkelSpheres* was described as the most accurate molecular descriptor, this parameter was used for chemical similarity analysis. The structure similarity chart describes a circular space in which the dots representing the compounds are the closer in space the higher is their Tanimoto index,[207] that indicates the degree of similarity between two fingerprints and is a measurement of their structural similarity. Those that have similar substructures (such as halo-substituted aromatics or aliphatic chains) are connected with a line and are visualised as denser spots on the chart (Figure 25, red circles). For each series of connected spots, only the central one was selected as representative of the chemical space occupied by a certain scaffold derivatization, while the other spots were eliminated. OSIRIS DataWarrior provides the filter *neighbour count* that enables a decrease in the connections between adjacent spots. However, it was observed that the use of the filter caused the removal of entire regions in the plot creating "holes". Because of this, the filtration was carried out manually, selecting specific compounds to be preserved in the library in order to achieve the described chemical space homogeneously (Figure 25, right). Eventually, the final *in-silico* library resulted in 1068 compounds.

Figure 25: Structure similarity chart of a library of 1987 compounds (left) and after manual filtration (right) of 1068 compounds

4.2.5 Compound library analysis by PCA

After building the virtual library, its occupied virtual space was determined and compared with the known chemical space occupied by a catalogue of commercial drugs. This was achieved by principal component analysis (PCA), where a list of determined properties is translated into a vector through a matrix factorization, representing a compound in a three-dimensional space. Every axis of the coordinate system considers the maximum attainable variance. Unlike for the structure similarity chart that could be built with only one descriptor, the PCA plot could be built from as much as information as possible regarding the structure of library molecules. For the PCA calculation were considered the descriptors *FragFp*, *PathFp*, *SphereFp* and *SkelSpheres*, as they are all indicators of the compounds three-dimensional structure. *OrgFunctions* and *Flexophore* descriptors could not be used as they could not be translated to a vector by the software. The final space occupied by the virtual library (Figure 26, dark green spheres) is different from that occupied by a selected list of 3035 FDA-approved drugs, indicating that this project was successful in creating novel molecules that fill out new chemical space.

Figure 26: PCA analysis of the virtual library (dark green spheres) compared with a list of 3035 FDA-approved drugs (red spheres)

4.3 Summary

A virtual compounds library was built from the four chemical scaffolds discussed in chapter 3, using the software OSIRIS DataWarrior (Scheme 110).

Scheme 110: Virtual library generation and filtration

In-silico derivatization of amine, ketone and alcohol groups with a total of 8036 commercially available reagents generated a “raw library” of 10,744 compounds. Application of “rules of thumb” for druglikeliness and OSIRIS DataWarrior algorithms (druglikeliness filter, globularity and structural similarity) resulted in the selection of 1068 compounds that were submitted as an in-silico library in the platform “CDD vault”.

Chapter 5: Experimental library generation

5.1 Introduction

Of all the virtual library compounds, an illustrative subset of compounds was planned to be synthesised. The quantity of each scaffold in hand gave the potential to create 64 compounds, that were mainly chosen amongst the compounds that presented a high drug-likeliness score on OSIRIS DataWarrior (Figure 27, grey circles).

Figure 27: MW/Druglikeliness plot of the virtual library (grey circles) compared with a list of 3035 FDA-approved drugs (red circles)

An additional factor for the selection of the planned experimental library was reagent availability. Lastly, each series of compounds derived form a scaffold was confirmed to have the maximum structural diversity as possible. For this scope, side-chains were chosen as aliphatic, heteroatom-containing aliphatic, EDG and EWG-substituted phenyls, aromatic and aliphatic heterocycles.

5.2 Results and discussion

In this Section will be detailed the experimental synthesis of 68 drug-like library compounds, selected from the virtual library discussed in Chapter 4.

5.2.1 Dihydropyran-based allyl alcohols synthesis

Four sulfonamide-derived α,β-conjugated carbonyls (Scheme 111, **273**, **385**, **386** and **387**) were synthesised from acetal deprotection of the products achieved from gold-catalysed polycyclization **166**, **167**, **169** and **170** (Scheme 41).

Conditions: a) HCl 4N, 1,4-dioxane (0.25 M), rt, 2 h b) 1. $SHCH_2COOH$ (1.7 eq.), Cs_2CO_3 (5.0 eq.), DMF, (0.3 M), 50 °C, 3 h 2. HCl 4N, 1,4-dioxane (0.25 M), rt, 2h 3. RCl (1.2 eq.), TEA (2.0 eq.), CH_2Cl_2 (0.1 M), rt, 1 h

Scheme 111: Derivatizations to α,β-conjugated carbonyls

Other enones were obtained from derivatization of the pyrrolidine nitrogen from scaffold **274** with acyl or carbamoyl chlorides. Sulfonamide **384** was also synthesised with this method as 2-chlorobenzylsulfonyl chloride is a higher-cost reagent than other sulfonyl chlorides. A thiourea (**389**) was also included as these derivatives are also used for medical applications.[208] The yields for the scope of α,β-conjugated carbonyls are reported for 3-steps from **168**, being the two previous steps carried out from unpurified intermediates.

The presence of two atropoisomers was observed for amide derivatives, presenting two sets of peaks (with ratio either 85:15, 66:34 or 55:45) for the side chain and the spatially proximal protons of the tetracyclic framework (Figure 28). The signal splitting was resolved for all amides at ^{1}H-NMR at 80 °C in DMSO (See Appendix). ^{13}C-NMR spectrum also showed atropoisomeric spitting for all resonances.

Figure 28: Representation of the protons that give atropoisomeric splitting at ^{1}H-NMR for amide-derived α,β-conjugated carbonyls

Reduction of sulfonamide-derived α,β-conjugated carbonyls by $LiAlH_4$ was totally diastereoselective towards allyl alcohols **287**, **395-398** (Scheme 112). The configuration of the alcohol was determined by two-dimensional NMR analysis (COSY, NOESY, HSQC and HMBC, that are comparable to the analysis shown for compounds **223** and **375**. Luche reduction to **278** resulted in the formation of the same stereoisomer.

Conditions: a) $LiAlH_4$ (2.0 eq.), THF (0.1 M), 0 °C, 1 h b) $CeCl_3 \cdot 7H_2O$ (2.0 eq), $NaBH_4$ (3.0 eq.), MeOH (0.1 M), 0 °C, 1 h

Scheme 112: Dihydropyran-derived allyl alcohols library by reduction of α,β-conjugated carbonyl compounds

Reduction of urea derivatives **276** and **388** with $LiAlH_4$ afforded one alcohol respectively (**277** and **401**) in very good yields. The diastereoselectivity of compound **401** was confirmed by X-ray crystallography (Figure 29). The structure of compound **277** was confirmed as multiplicities of resonances and two-dimensional correlations of the tetracyclic system at NMR spectroscopy match those of compound **401**. Luche reduction of enone **276** afforded a mixture of two diastereoisomers **399** and **277** with ratio 1.6:1, that were separated by preparative LCMS. The same reaction on compound **388** gave an analogous result affording

compound **400** and **401** in a ratio 2:1, that were singularly isolated. Reduction of the thiourea-derived enone 389 was unsuccessful, only resulting in degradation.

Figure 29: Crystal structure of 401 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham)

Luche reduction was carried out to achieve amide-derived allyl alcohols. Unfortunately, unlike in the case of urea-derivatives, the resulting mixtures achieved from **390** and **391** could not be resolved. Also, an additional impurity was observed after two preparative LCMS purification attempts, impeding the characterization of the diastereomeric mixtures. Only reduction of **392** resulted in the formation of only isomer **405**. This compound did not give atropoisomeric splitting at NMR analysis.

The determination of the configuration of the new stereocenter on **405** was done by NOESY correlation between proton H_l' and H_j (Figure 30). The assignation of the resonance corresponding to protons H_l and H_l' could not be done by NOESY correlations with H_m and H_m' due to superimposition of peaks. Resonances for H_l and H_l' were assigned after comparison of homoallylic couplings observed at COSY NMR with those of the sulfonamide and urea-derived allyl alcohols whose structure was confirmed (**287**, **395-398**). Specifically, homoallylic coupling was observed between H_j and the proton on the dihydropyran ring on the same side of the plane (H_n' for this compound). Another correlation is visible between diastereotopic proton

H_n and proton H_l. These observations are in agreement with previous studies on ^5J homoallylic couplings,[209] where interactions were found to be minima at 0 and 180° and maxima at 90°.

Figure 30: COSY correlations originated by ^{5}J homoallyl couplings found for compound 405

Aminoalcohols **406** and **407** were synthesised by reduction of amides **393** and **394** by $LiAlH_4$ in very low yields (Scheme 113). A side-product with a free amine **241** was also achieved, indicating that $LiAlH_4$ is also involved in a mechanism of side-group cleavage. Compound **241** may also be the main product of the reactions, but could have been mostly lost during the workup due to its high aqueous solubility.

Scheme 113: Dihydropyran-derived aminoalcohols

A ^{3}J coupling of 1.5 Hz between C<u>H</u>(OH) and C<u>H</u>NRR' was observed for aminoalcohols **406** and **407**, and configuration of the new stereocenters were confirmed with two-dimensional NMR analysis as carried out with the rest of the compounds of the library.

It is interesting to notice that reduction by $LiAlH_4$ of ketone **283** (resulted from hydrogenation of **273**) gives an alcohol product (**300**, Scheme 80) with opposite diastereoselectivity to the product from the reduction of α,β-carbonyl **273** (**278**, Scheme 112). In this work, diastereoselectivities could be explained by 3D optimization of possible transition states realised with MarvinSketch software. A transition state of the reduction by $LiAlH_4$ of compound **273** to **278** was built adding a further coordination of the aluminium atom to one of the oxygen atoms of the sulfonamide group (Figure 31) and of the lithium to two solvent molecules (following the coordinations of $LiAlH_4$ found in ether solvents).[210] The forming alcohol group is on the same side of the plane as that containing the proton of the adjacent CH group, according to experimental data.

Figure 31: 3D-models of the TS with the minimum energy out of 100 conformers for the reduction of 273 with $LiAlH_4$ to 278 realised with MarvinSketch. Explicit hydrogens are omitted for clarity

An analogous TS was built for the hydrogenation of ketone **283** to **300** with $LiAlH_4$, (Figure 32) and it shows a potential hydride addition on the opposite side of the plane compared to the TS illustrated in Figure 31.

Figure 32: 3D-models of the TS with the minimum energy out of 100 conformers for the reduction of 283 with $LiAlH_4$ to 300 with coordination on the sulfonamide, realised with MarvinSketch. Explicit hydrogens are omitted for clarity

Coordination with the oxygen of the 6-membered ring is also possible. It would be supported by the fact that the energy calculated for the TS in this case (Figure 33) would be much lower than the TS shown in Figure 35 (237.8 kcal/mol against 497.3 kcal/mol). An analogous TS for the reduction of compound **273** was not possible. The reason may be due to the fact that the oxygen atom of the enone would be too far away to give coordination with the lithium.

Figure 33: 3D-models of the TS with the minimum energy out of 100 conformers for the reduction of 283 with $LiAlH_4$ to 300 with the coordination on the oxygen of the 6 -membered ring, realised with MarvinSketch. Explicit hydrogens are omitted for clarity

A more precise study would be given by DFT methods. Other coordinations of Li and Al are not indeed excluded and neither the involvement of more THF molecules or $LiAlH_4$ bridged dimers.[211]

The presence of $CeCl_3$ or $Ti(O\mathit{i}Pr)_4$ would further modify the transition states, partially preventing the reduction from one side of the plane. This would justify the formation of diastereoisomeric mixtures that led to the characterization of compounds **301**, **399** and **400**.

5.2.2 Addition of organometallic reagents

Ketone **283** was successfully derivatised to tertiary alcohols (Scheme 114) with Grignard reaction or use of organolithium reagents with complete diastereoselectivity, generally with good to very good yields.

Scheme 114: Grignard reaction scope

Synthesis of compounds **409** and **413** were in a lower yield due to the presence of unknown side-products. A side-product with mass 584 (18% by UPLC analysis) was detected with reaction with cyclopropyl magnesium bromide. ^{1}H-NMR analysis showed two sets of signals, indicating it is a dimer. It may be generated by nucleophilic attack of alkoxide **415** to the ketone **283** with formation of hemiacetal **416** (Scheme 115a). Deprotonation of ketone **283** to

enolate **417** or **420** is also possible (Scheme 115b), followed by nucleophilic attack of the carbonyl group and Grignard reagent addition to compound **419** or **422**. The determination of the side-product structure would require further spectroscopic studies.

All reactions carried out with an organometallic reagent reached a conversion of around 66%, even with a reagent excess. This leads to the idea that organometallic reagent may also act as bases and not only as nucleophiles.

Scheme 115: Possible formation of side-product (MW 584) by a) hemiacetal formation b) aldol addition followed by Grignard reaction

Concerning diastereoisomer determination, two-dimensional NMR analysis did not generally give sufficient indication: weak NOESY correlations of the group bonded to the new quaternary carbon were always found with the neighbouring protons. However, these could be theoretically possible for both configurations. Only compound **411** showed spatial vicinity of the -OH proton with a proton on the tetrahydropyran ring on the same side of the plane (H_n', Figure 34). Crystals of compounds **410**, **411, 412** and **433** were obtained, but only crystals

of **413** were suitable for X-ray crystallography (Figure 35) that confirmed the diastereoisomer assessment for this compounds library found with NOESY analysis of **411**.

Figure 34: NOESY correlations found for compound 411

Figure 35: Crystal structure of 413 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham)

Rationalization of a transition state for the addition of organometallic reagents would be challenging as Grignard reagents can exist in several chemical species, given by the Schlenk equilibrium. Recent computational and experimental studies[212] found the presence of dinuclear intermediates with chlorine bridges, with magnesium coordination number variable from 4 to 5 depending on its coordination to the solvent, that was assessed to be with 1 or 2 molecules of THF. The lowest free energy solvation state was found to be a dinuclear dihalide

bridged structure with each Mg atom having coordination 4, and this was used to build the TS proposed in Figure 36, realised with MarvinSketch.

Figure 36: 3D-models of the TS with the minimum energy out of 100 conformers for the addition of MeMgBr on ketone 283, realised with MarvinSketch. Explicit hydrogens are omitted for clarity

5.2.3 Reductive amination

A series of secondary amines was made through reductive amination mediated by titanium (IV) isopropoxide (Scheme 116). All planned reactions were successful except that for the synthesis of compound **427**. Products were achieved from poor to very good yields. The failure may be due to the coordination of the titanium to the amidic group of the amine that prevents the substrate activation or the formation of the imine intermediate. No product was obtained even after adding an excess of Ti(O*i*Pr)$_4$.

Initially, the reaction was carried out with titanium isopropoxide and amine without further additives to achieve the aromatic derivatives. The formation of enamine side-product was always observed, resulting from an elimination mechanism (proposed in Scheme 117), that occurs instead of the protonation of the hemiaminal that leads to the formation of the imine intermediate.

Conditions: a) $NaBH_4$ (2.0 eq.), MeOH (0.1 M), rt, 16 h b) H_2 (1 atm), PtO_2 (5% w/w), EtOH (0.1 M), 50 °C, 40 min

Scheme 116: Reductive amination scope

Scheme 117: Proposed mechanism for the formation of amine and enamine by Ti(O*i*Pr)$_4$ reductive amination

Enamines could not be directly quantified by LCMS or ^{1}H-NMR as the corresponding peaks were always superimposed with those of the product amine. It was however possible to recover some of ketone **283** after flash column chromatography following the enamine

hydrolysis on silica (Scheme 118). It was confirmed by LCMS and ^{1}H-NMR that the conversion of the reductive amination is complete, therefore the ketone does not result from an incomplete reaction. No ketone with a *trans*-ring junction (**439**) was observed.

Scheme 118: Enamine acid-hydrolysis on silica to ketone 283

The only enamine that was possible to isolate was that derived from reductive amination with methylammonium chloride with an addition of 2.0 eq of TEA (Scheme 119). Compound **440** was then purified by recrystallization.

Scheme 119: Selective formation of enamine 440

The quantity of recovered ketone with flash column chromatography was observed to be minimal for the synthesis of amines with an EDG (**428** and **430**, 6-10%) and maximum when using an amine with a EWG group (**429,** 58%). Synthesis of amine **449** was therefore chosen as a reaction model for an optimization, that was carried out with different additives to test the reductive amination outcome in different pH conditions (Table 9). The best result was obtained with addition of 1 equivalent of acetic acid, so conditions in Entry 2 were used for all subsequent reductive amination reactions.

Table 9: Reductive amination optimization studies

Entry	Reagent (1.0 eq.)	Additive (1.0 eq.)	Yield **429**	Yield **283** (recovered)
1	(*o*-F)BnNH$_2$	-	12	58
2	(*o*-F)BnNH$_2$	CH$_3$COOH	33	11
3	(*o*-F)BnNH$_2$	(COOH)$_2$	30	25
4	(*o*-F)BnNH$_2$	CH$_2$(COOH)$_2$	27	20
5	(*o*-F)BnNH$_3$Cl	-	19	36
6	(*o*-F)BnNH$_3$Cl	Pyridine	5	41
7	(*o*-F)BnNH$_3$Cl	TEA	2	10

Compound **424** was synthesised from methylammonium chloride and 1.0 eq of TEA as methylamine is usually commercially available in aqueous solution.[213] The syntheses of **425** and **426** were attempted with the optimised conditions, but the reactions resulted totally chemoselective towards the respective enamines. Fortunately, reduction by following hydrogenation reactions successfully yielded amine products (Scheme 116, conditions b) with the same diastereoselectivity as the titanium isopropoxide-mediated reductive amination, therefore avoiding the formation of mixtures of isomers.

For all synthesised amines were observed strong NOESY correlations of the proton bonded to the new stereocentre with the neighbouring protons on the ring junctions, while the side groups bonded to the secondary amine never show the same spatial vicinity. This suggests

that the reductive amination products have a structure like that illustrated in Figure 37 (compound **425** is shown as an example).

Figure 37: NOESY correlations found for compound 425

The stereochemistry was confirmed by X-ray crystallography of compound **424** (Figure 38).

Figure 38: Crystal structure of 424 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham)

The diastereoselectivity of the reductive amination can be explained by a possible coordination of the titanium to the imine group, making a complex that favours the nucleophilic attack of the hydride from the convex side of the plane (proposed in Figure 39).

Figure 39: Proposed 3D-models of the TS with the minimum energy out of 100 conformers for reduction of the imine generated from 283 and $MeNH_3^+Cl^-$, realised with MarvinSketch. Explicit hydrogens are omitted for clarity

5.2.4 Williamson ether synthesis

Scaffold **300** was derivatised to generate a series of ethers (Scheme 120), generally from good to very good yields. Compounds **442** and **447** were achieved in lower yields than the rest of the library, the first resulted from an incomplete conversion of alcohol (despite the use of an excess of hydride) and the second for the presence of several unknown side-products.

Unfortunately, several reactions were unsuccessful (Scheme 121) and the overall success rate for the Williamson ether synthesis from **300** resulted to be 53%. The reasons for the failure of other reactions is still unknown, although it is supposed that the effects of steric hindrance of the alcohol may play a significant role. Also, the halides that were stored at low temperatures (such as piperonyl bromide) are unstable at the reaction temperature. The presence of moisture in the reactant containers is not excluded, although the unsuccessful reactions were always repeated with an excess of hydride and with halides from freshly opened bottles. The reactions were also carried out in parallel with other successful reactions to demonstrate the absence of an interference of possible moisture in the solvent.

Scheme 120: Successful examples for the formation of a library of ethers from alcohol scaffold 300

Scheme 121: Unsuccessful examples for the formation of a library of ethers from alcohol scaffold 315

A singularity observed in this library is that compound **450** was isolated in a hydrated form. This was confirmed by LCMS and HRMS analysis that showed the presence of both masses [M] and [M+H_2O]. No peak at 1.5 ppm was observed at ^{1}H-NMR in $CDCl_3$, seeing instead additional proton signals at 9.0 and 10.0 ppm. Each water peak gives NOESY and HMBC correlations with the compound signals shown in Figure 40 (for complete signal assignments see Appendix). Compound hydrates are known in the literature with regard to pharmaceutical compounds,[214] and they are involved in structure polymorphism. A theoretical study of benzofuran hydrates claims that several structures with different hydrogen bonds are possible, as hydrogen atoms

of the water molecule can interact not only with heteroatoms but also with the π molecular orbitals of the aromatic system.[215]

Figure 40: NOESY and HMBC correlations found for hydrated compound 450

5.2.5 Piperidine nitrogen derivatization

Thirteen allyl alcohols were derived from amine derivatization of aminoalcohol scaffold **365**, generally in good yields (2 steps from ketone **362**, Scheme 122).

Attempted synthesis of urea **464** did not yield any product. Formation of compound **478** was observed at LCMS its purification was unsuccessful due to overpressure in the column and tubing system used for preparative UPLC. Thiazole derivative **468** was instead achieved in a low purity (68%), not sufficient for compound characterization or HTS.

It was shown in Section 3.2.7 that purification of scaffold **365** yielded a low quantity of aminoalcohol. Purification of the resulting compound libraries was more feasible as better separation was seen on UPLC and so the tetrahydropyridine-based library was realised by performing reactions with unpurified scaffold.

Conditions: a) A) RCl (1.2 eq.), TEA (1.0 eq.), CH_2Cl_2 (0.1 M), 0 °C, 1h b) RCHO (1.2 eq.), $NaBH_3CN$ (1.0 eq.), CH_3COOH (1.0 eq.), DCE (0.1 M), 6 h, rt; Yields are reported 2 steps from **382**

Scheme 122: Tetrahydropyridine-based allyl alcohol scope

In most cases, especially for ureas and amides, flash column chromatography was required prior to preparative UPLC separation to isolate products with a purity >90%.

The amides of this library (**465**, **466** and **467**) show atropoisomerism. Compounds **466** and **467** were also analysed in DMSO-d_6, and all splitted peaks were resolved at ^{1}H and ^{13}C-NMR analyses carried out at 90 °C.

Urea **366** was selected from the virtual library to be experimentally synthesised even if it has a relatively low sp^3 fraction (0.37) because of the concave shape of the dibenzoazepine ring.[216]

Compound **466** was included in the library despite not complying to all Lipinski's rules as it showed a very high druglikeliness score on OSIRIS DataWarrior. Also, it was observed that Lipinski's rules do not include around 6% of oral drugs and that are unlikely to be applicable for the discovery of compounds whose target is a PPI.[217] The company AbbVie Inc. created an equation (Equation 1) to assess the druglikeliness of compounds "beyond rule of 5" (bRO5): [218] with AB-MPS being "AbbVie multiparametric score", NAR= number of aromatic rings and NRB= number of rotable bonds.

$$\text{AB-MPS} = \text{Abs}(\text{cLogD}-3) + \text{NAR} + \text{NRB}$$

Equation 1: AbbVie "beyond rule of 5" algorithm

In the previous study was found that compounds that have a score ≤14 are associated with a more probability of success. For compound **561** the score results was AB-MPS = |3.5-3| + 1 + 3 = 4.5, making it drug-like following this new prediction.

5.3 Summary

The experimental library was built from five derivatizations out of the four synthesised chemical scaffolds. Amine derivatization from compound **274** (Scheme 123) followed by ketone reduction afforded a series of thirteen allyl alcohols. Reductions were diastereoselective: use of $LiAlH_4$ on sulfonamides, ureas and amides (Scheme 123 a, b and d) allowed the formation of the alcohol with the -OH group in a *syn*-relationship with the cyclopropane ring, while Luche reduction afforded a mixture of diastereoisomers when reducing ureas (Scheme 123b). Reduction of amides resulted in a formation of complex mixtures (Scheme 123 b). Successful reductions were 77% of the reactions carried out.

Scheme 123: Tetrahydropyridine-based allyl alcohol series

Ketone **283** could be derivatised to seven tertiary alcohols with Grignard or organolithium reagents (Scheme 124). Titanium-catalysed reductive amination (Scheme 124) partially afforded enamines (**435**) that could be converted to amines with catalytic hydrogenations. Reactions were diastereoselective and the structures were confirmed by X-ray

crystallography. All reactions with organolithium were successful, while a reductive amination with an amide-containing amine failed.

Scheme 124: Reaction with organometallics and reductive amination from 283

Nineteen Williamson syntheses were tested on alcohol **300**, and ten ethers were successfully synthesised (Scheme 125). The reason for the low success rate for the etherification has not been rationalised, though it is speculated that it can be due to thermal sensitivity of the halides.

Scheme 125: Williamson ether synthesis from 300

Aminoalcohol **365** was successfully derivatised into amides and ureas with acyl/carbamoyl chlorides and tertiary amines with reductive amination. Out of all the reactions carried out, only the synthesis of an urea failed.

Scheme 126: Compounds derived from aminoalcohol 365

Chapter 6: Processing of experimental compound library

6.1 Introduction

It has been discussed in Section 1.1 and 4.2.2 how some physicochemical properties are critical for drug design. Parameters such as solubility, lipophilicity, presence of charged functional groups, chemical stability and toxicity are important for the ADME process related to a drug and can be predicted with algorithms. An open-access tool that includes a comprehensive assessment of molecular properties is LLAMA[219]. This web-based software allows to visualise compounds in the RO3/RO5 space and in a PMI plot and assesses structural similarities with known structures in chemical databases. The software package LLAMA also assigns a "leadlikeliness penalty score" score based on calculated molecular parameters. The program favours compounds with 17<heavy atoms<24, -1<AlogP<3, 1≤NAR≤3 and with no reactive functional groups. Penalties are also assigned to other compounds for the presence of heavy atoms superior to 24, so because of their size and not because of bad physicochemical properties. The likelihood of library compounds to be absorbed intestinally and to penetrate the BBB can be predicted with the free-access software SwissADME, where property estimations were carried out with a vector machine algorithm developed by Daina *et al.*[220] built on a model set of 1033 molecules.[221]

An important parameter that is always measured when optimizing hit and lead structures is the ElogD, that is the logP value measured at pH= 7.4 (physiological pH).[222] A low ElogD is associated with a high solubility in water, which may reduce the amount of drug that passes through the intestinal villi, while a very high logP may result in a more difficult clearance of the drug from the body increasing the systemic toxicity.[223] For this reason, pharmaceuticals are designed to reach optimal lipophilicity. It has been observed that the range 1.35-1.8 is

ideal for gastrointestinal absorption[224] while the range 1.5 to 2.7 is suggested for BBB-active drugs.[225]

A crucial analysis in drug development concerns the toxicity assessment towards the hERG (human ether-à-go-go related gene) channel, that is a very promiscuous protein known to bind around 20% of known drugs.[226] The hERG channel is a potassium channel involved in cardiac functionality, specifically for ventricular repolarization. If the interaction between a molecule and the hERG channel determines a change in activity of the latter, it may cause prolongation of the QT interval (between heart contraction and relaxation) ending up in cardiac failure. For this reason, the hERG channel inhibition is one of the first tests carried out on drug candidates for toxicity assessment.

6.2 Results and discussion

In this Section is discussed the computational analysis of drug-related properties of the compound libraries prepared in the previous chapter. Scaffolds **273**, **283**, **300**, **365**, **301** and **373** were also included in the library, along with other intermediates. Dioxolanes **166**, **170 and 207** were added to the library as examples of sulfonamide- and sulfamyl-derived acetals. As mentioned in Section 3.2.1, there are a few examples of acetals with applications in drug-discovery despite their susceptibility to hydrolysis. The same principles can be applied to α,β-conjugated carbonyls: their high reactivity as Michael acceptors is not appealing for the creation of stable drugs, but despite this several biologically active molecules were found to bear an enone functionality.[227] For this reason, compounds **385**, **387**, **390** and **393** were also added to the library. Finally, compounds **340**, **341** and **389** were also included as sulfur-rich α,β-conjugated carbonyl derivatives. The final experimental library contained a total of 68 compounds.

The library was also experimentally analysed for ElogD, hERG and drug-target interaction to appreciate their physicochemical properties and biological activities.

6.2.1 Lead-likeliness and tridimensionality analysis

General molecular properties of the experimental library compounds were analysed with LLAMA. With a plot AlogP/MW (Figure 41) was possible to easily visualize the compounds included in the lead-like space and Lipinski's space. A good portion of the library, with 22 compounds out of 68, was categorised as lead-like, while 63 follow Lipinski's rules. The library is therefore overall complying to the main Literature "druglikeliness rules of thumb".

Figure 41: AlogP/MW plot of experimental library realised with LLAMA

Around 58% of the library (Figure 42) has a LLAMA-derived leadlikeliness score inferior to 3, therefore having a good chance for possible hits to advance in the drug discovery process.

Figure 42: Histogram of experimental library based on leadlikeliness penalty realised with LLAMA

The structural novelty of the library was assessed comparing their Murcko framework to a 2% of randomly selected compounds in the ZINC database. No compound was found having similarity with those synthesised in this project, confirming the structure of the molecules is unprecedented. The three-dimensionality of the library was assessed by an analysis of the sp^3-fraction, being superior to 0.4 for 94% of the library (Figure 43).

Figure 43: Histogram of experimental library based on sp^3-fraction realised with LLAMA

A PMI plot was realised to compare the tridimensionality of the library compounds (Figure 44) to that ZINC fragments shown in Figure 2 (Section 1.2) . It was observed that 59% of the library falls into the relatively unexplored three-dimensional area (inside light blue triangle), compared to the remaining are of the plot occupied by the ZINC fragments. It was also

observed that leadlike compounds are more concentrated in the 3D region, while compounds associated with a higher leadlike penalty are more located towards the upper left corner, that indicates more linearity.

Figure 44: PMI plot of the experimental library; dark triangle contains relatively unexplored 3D region

A plot WLogP/TPSA was made with SwissADME to determine the compounds expected to have a high gastroinstestinal absorption (Figure 45). Gladly, 98% of the library falls in the requirements (white + yellow region). Twenty-four per cent of the library was found to the in the region of the compounds associated with a high probability to penetrate the central nervous system (Figure 45, yellow region). This is not necessarily a sought-after property, as it depends on the drug target. However, it is considered to be favourable to have a fraction of the library associated with this property so to have a degree of diversification in the library. Eighty-four per cent of the compounds were predicted to be P-glycoprotein substrates, that

are plasma proteins responsible for the drug clearance in cells (Figure 45, blue circles). Compounds that are unlikely to bind P-glycoproteins are overlined in red (18%).

Figure 45: "Hard-boiled egg" plot for HIA and BBB barriers and glycoprotein interactions

6.2.2 Lipophilicity assessment

The ElogD7.4 value was measured for 39 compounds of the library. Other library compounds did not show any UV activity (necessary for the detection) or had an ElogD7.4 out of the calibration curve, that was built between values of 0.3 and 5.0. This library subset shows a good coverage of values (bold red line in Figure 46 a-b), ranging from 0.3 to 4.5. Eight compounds have a ElogD7.4 included in the range 1.35-1.8, therefore considered to have an optimal gastrointestinal absorption,[224] while 11 have a ElogD7.4 from 1.5 to 2.7 and therefore predicted to be BBB-active drugs.[225]

The experimental ElogD7.4 values were compared to those predicted by 12 software packages, some of which are equipped with algorithms able to determine both logP and ElogD7.4.[228] Most tools predict ElogD values that resulted inferior to the experimental one

(Figure 46 a-b, bold red line), especially for ElogDs>2. The accuracy of the models was determined through determination of the squared correlation coefficient Q^2 and the standard error of prediction SEP (Equation 2), following what reported by Erős et al.[229] Data in Table 10 shows the values of the softwares in crescent order of good predictability for the library of this study. The algorithm that is the most comparable to the experimental data (having the greatest Q^2 and the smallest SEP, Table 10) is Molinspiration (whose graph is shown in Figure 46a, bold orange line).

Figure 46: Experimental ElogD values (red line) compared to software predictions a) Chemicalize, Molinspiration (orange line), MarvinSketch, ADMETLab, admetSAR, b) DataWarrior, iLogP, XlogP, WlogP, SILICOS_IT, Average SwissADME, AlogP2.1

$$Q^2 = \frac{\Sigma\,(calc - exp)^2}{\Sigma\,(\overline{exp} - exp)^2}$$

$$SEP = \sqrt{\frac{\Sigma\,(calc - exp)^2}{m}}$$

calc= single calculated ELogD7.4 value
exp= single experimentally measured ELogD7.4 value
$\overline{exp}$ = mean of experimentally measured ELogD7.4 value
m= number of molecules

Equation 2: Determination of the square correlation coefficient and standard error of prediction

Table 10: Q^2 and SEP values of software predictions for the experimental library

Software	Q^2	SEP
Chemicalize (ElogD7.4)	-2.56	2.20
MarvinSketch (ElogD7.4)	-2.54	2.17
Chemicalize (logP)	-2.01	2.00
MarvinSketch (logP)	-1.62	1.87
XLOGP	-1.08	1.66
SILICOS-IT	-0.30	1.32
ALOGPS2.1	-0.10	1.21
iLOGP	-0.10	1.21
MLOGP	0.26	0.99
DataWarrior	0.48	0.85
Average_Swiss	0.50	0.81
admetSAR	0.59	0.64
ADMETLab 2.0 LogP	0.60	0.73
ADMETLab 2.0 LogD	0.65	0.69
WLOGP	0.68	0.65
Molinspiration	0.75	0.57

A regression statistics study was carried out in an attempt to build an equation that could be used to predict the ElogD values from a calculated set of physicochemical properties, following the procedure used for previous studies of structure-logP correlation studies.[230] The MW, TPSA, TSA, HBA, HBD, molecular refractivity and 24 different atom/ring counting were predicted for the 39 compounds which the ELogD was experimentally measured. In absence of mathematical instruments that include non-linear systems, a regression statistics study was

carried out with maximum 16 variables at a time (that is the maximum capacity of Microsoft Excel "Data Analysis Tools") to obtain a linear correlation of multiple variables. The square and cubic root of MW, PTSA, TSA and molecular refractivity were manually calculated and also tested for linear regression, as well as the square values. The straight line that showed the best correlation with experimental data is described in Equation 3:

ELogD= $0.126\sqrt{MW}$ + $2.5\sqrt{TSA}$ – 0.09A – 0.03 heavy atoms – 0.68 HBA – 0.83 HBD + 0.045 "carbo rings" – 0.1 "ring closures" + 0.6 amides + 0.67 amines + 0.025 stereocenters – 0.58 ROTB

Equation 3: Linear regression for ElogD prediction

The aforementioned curved trendline is shown in Figure 47, along with the calculated ELogD values (light blue) compared with the experimental ones (orange).

Figure 47: Experimental ElogD values compared to software predictions realised with linear regression on Microsoft Excel

The linear correlation was obtained with a r value of 0.924, which is associated to be a good predictive acceptance.[231] However, it can be observed that calculated ELogD values are quite scattered, decreasing the precision of the method. The accuracy also decreases for ELogD>2.5.

It is not expected for this study to achieve a higher r value and precision, as the available data is limited only to 39 compounds. Instead, published works[230-231] use hundreds or thousands of inputs to set up a new algorithm. The ElogD estimation could potentially be improved by using more potent softwares that can generate higher-order polynomials. This would however require expertise in computational mathematics.

6.2.3 hERG channel inhibition

The hERG-related cardiotoxicity was predicted with 6 software packages.[232,233] Though a high hERG inhibition generates a safety flag, it does not automatically result in the rejection of a compound in a drug discovery program because its therapeutic window (dosage needed against its target) may be lower than the concentration that results in a harmful hERG channel binding.

Compounds that were calculated to be hERG-channel active are listed in Table 11. These were observed to contain aromatic rings, amine groups and/or a high logP, that are characteristics already observed with reported chemicals that bind the hERG channel.[234]

Seven of the compounds listed in the table (Scheme 127) were selected to be experimentally measured for hERG channel interaction (See appendix for analysis). Amine **241** and thioacetal **360** did not show any hERG activity, while compounds **340**, **366** and **493** gave borderline values so that, although they give a weak hERG binding, their activity may be biologically relevant. Of

the compounds that have a eLogD>4.0, biphenyl ether **448** and benzylaminic compound **472** resulted to be positive hERG binders.

Table 11: Predicted hERG inhibitors by different softwares

Software	Strong inhibition	Medium inhibition
Chemaxon	-	**375, 446, 448, 463, 472, 473**
Way2Drug	**241, 380**	**374, 389, 407, 409, 411, 412, 465, 470, 471**
pkCSM	**350, 351, 375, 406, 428, 429, 448, 463, 473**	-
ADMETLab2.0	**351, 446**	**312, 441, 469, 471**
admetSAR	**273, 278, 302, 340, 341, 364, 371, 385, 389, 395, 396, 407, 413, 425, 428, 429, 430, 431, 442, 443, 445, 447, 448, 449, 469, 470, 471, 472, 473**	-
Amed Cardiotoxicity	**473**	**302, 489, 472**

Scheme 127: Compounds experimentally analysed for hERG activity

6.2.4 *In-silico* target prediction and drug-target interaction

A Reaxys[235] search for scaffold **475** (Scheme 128) returned 146 chemicals with available pharmacological data.

Scheme 128: Chemical framework used for the chemical similarity search

Chemical similarity with the library compounds of this work was then determined by Tanimoto dissimilarity calculation[236] (carried out with JChem for Excel), resulting in molecules belonging to the class of duocarmycins being the most chemically similar to the tetracyclic structures synthesised in this study. Specifically, the greatest similarity with the library compounds was observed with duocarmycin **476** (known as CBI-TMI, Scheme 129)[237] with a Tanimoto dissimilarity index ranging from 0.54 for allyl alcohol **405** to 0.89 for ketone **283**, with an average of 0.75.

Scheme 129: Structure of CBI-TMI and library compounds with the lowest and greatest Tanimoto dissimilarity

A docking study was carried out to assess the potential of the library compounds to act as mimics to CBI-TMI. Duocarmycins can act as antitumor and antibiotic agents thanks to their ability to alkylate DNA sequences rich in adenine and thymine.[238] The interactions of both enantiomers of the library molecules with a TA-rich DNA sequence used in previous studies for duocarmycin interactions (d-G1ACTAATTGAC11)[239] were determined with the software AutoDockTools 1.5.7[240] and compared with CBI-TMI **476**. The binding energy was calculated as an inhibition constant and resulted being K_i= 40.21 nM for **476** and 20.8 nM < K_i < 82.7 µM for the library compounds. One enantiomer of allyl alcohol **406** (Scheme 113, **477**) showed a comparable binding constant to the DNA sequence to that of with K_i= 40.9 nM, while the other enantiomer (**478**) was calculated with a binding constant halved with K_i= 20.8 nM (See Appendix). This shows that compound **478** may be more biologically active than **476** even as

racemic mixture. Figure 50 shows the docking structure of the DNA-**478** binding, highlighting three hydrogen bonds with two phosphate groups and a thymine.

477 **478**

Scheme 130: Structures of the enantiomers for compound 406

Figure 48: Image after docking of interaction between DNA sequence and 478; HB is shown in yellow and light blue dotted lines

6.2.5 High-throughput screening

The synthesised 68 compounds of the library were analysed for antimicrobial activity through high-throughput screening. Analyses were realised by Alex Kingdon at the School of Biosciences (University of Birmingham). The biological assays were focused on ESKAPE pathogens, that are ranked by the WHO as “priority pathogens list” and present a strong anti-microbial resistance.[241] Bacterial growth was determined by either optical density at 600 nm

(OD600)[242] or by resazurin fluorescence.[243] Unfortunately, no compound gave a sufficient inhibition to be considered a hit (that has been assessed as superior to 50% for drug concentrations of 20 µM). In Table 12 are listed the compounds that give the maximum inhibition for each microbial assay.

Table 12: Library compounds that show the maximum microbial inhibition

Microorganism	Compound (rac mixture)	% inhibition (detection method)
Enterococcus faecium	**406**	28.4% (fluorescence)
	447	35.3% (OD600)
Staphylococcus aureus	**406**	42.9 % (OD600)
Klebsiella pneumoniae	**409**	28.2% (OD600)
Acinetobacter baumannii	**366**	22.8 % (fluorescence)
Pseudomonas aeruginosa	**368**	28.0 % (OD600)
BCG	**472**	7.50% (fluorescence)
Mycobacterium smegmatis	**170**	35.6% (fluorescence)

Charts showing inhibition of all the compounds in the library are shown in the Appendix. Other biological assays are in progress.

6.3 Summary

The physicochemical properties of the compounds in the drug-like library were predicted with the software packages LLAMA and SwissADME. The library has a good coverage of RO3 and RO5 compounds, being respectively 32% and 93%. The three-dimensionality of the library was confirmed by the high sp^3-fraction of the compounds and by their position in the three-dimensional space of the PMI plot. Compounds are generally expected to have a good gastrointestinal absorption and p-glycoprotein mediated clearance. The ElogD was experimentally measures and compared with *in-silico* predictors, finding *Molinspiration* to be the software that matches the most the experimental data. Linear regression to assess a trend for ElogD values resulted instead inconclusive. The seven compounds of the library with the highest ElogD were measured for hERG inhibition, finding that the compounds containing the most phenyl rings had the higher chance to bind the heart protein. Docking studies predict a compound of the library to be a better binder for AT-rich DNA-sequences involved in antitumor studies than their binders duocarmycins. The library was finally analysed with high-throughput screening for activity against ESKAPE pathogens, not finding any hit.

7. Outlook and future work

Four novel three-dimensional chemical scaffolds were achieved from derivatization of tetracyclic acetal frameworks built from a 7 step synthesis from 4-tetrahydropyranone or *N*-Boc/Cbz-piperidinone (Scheme 131).

Scheme 131: Summary of this project

Each reaction of the multistep synthesis was optimised and applied on a multi-gram scale, resulting eventually in a scope of nine tetracyclic acetals with a 5.0-9.3% overall yield. Three of these intermediates were used to generate chemical scaffolds by acid-mediated acetal and Boc deprotection, hydrogenation reactions, nosyl deprotection and ketone reduction.

A compound library was built by Grignard reaction, titanium isopropoxide mediated reductive amination, Williamson ether synthesis, ketone reduction and amine derivatization. A virtual library of 1068 compounds was created with the software “OSIRIS Datawarrior” by compound library enumeration and filtration by druglikeliness “rules of thumb” developed by Lipinski, Veber, Muegge, Egan and Ghose followed by toxicity assessment predictions and chemical similarity. PCA analysis confirmed that the virtual library explores new chemical space compared to that occupied by known drugs. PMI analysis show that library compounds have a greater degree of tridimensionality, associated with a greater success chance for clinical phases, than most of ZINC fragments. Structures of scaffolds and library compounds achieved from reactions that involve the formation of a new stereocenter were confirmed by two-dimensional NMR spectroscopy and a total 5 X-ray structures.

The experimental library was built from compounds derived from the scaffolds, to which were added scaffolds and intermediates to make a total of 66 compounds. PMI analysis demonstrated that the library exhibits more spherical-like features than most known drug-like fragments, accessing relatively unexplored three-dimensional space that is associated with natural compounds and pharmaceuticals. Thirthy-nine compounds were measured for ElogD analysis, giving a 0.3-4.5 range that is compatible with most known drugs.bSeven compounds were measured for hERG-channel inhibition, resulting in two compounds being potential binders and so showing potential cardiotoxicity. All experimental library was

analysed with HTS against 7 bacterial strains and no hits compounds were found. Other biological assays are still in progress.

Further derivatizations could be potentially realised on the tertiary alcohols and amines synthesised as library compounds in this work (structures **479** and **438**) to ethers **480** and amides/ureas **481** respectively (Scheme 132a-b). An ether compound library (structure **482**) can also be realised from scaffold **373**.

Scheme 132: Proposed derivatizations of compound libraries

A transformation that could be studied in a future project on ketone **283** is the α-alkylation, potentially forming a new scaffold (compound **483** or/and **484**, Scheme 133).

Scheme 133: Proposed α-alkylation on ketone 283

An interesting further development of this project would be the extension of the multistep synthesis to tetracyclic acetals from acyclic intermediates. For this project, 4-tetrahydropyranone and *N*-protected piperidone were chosen as building blocks because,

being cyclic and symmetric substrates, do not raise any of these regioselectivity issues. The use of substituted cycles would generate multiple regioisomers with a ratio depending on the ring size (Scheme 134a).[244] An additional stereocenter would imply the formation of diastereoisomeric mixtures with the Au-catalysed polycyclization cascade, raising purification issues. Mixtures of regioisomers are formed also from linear ketones, with a variable ratio E:Z (Scheme 134b). It is reported[108-114] that Vilsmeier-Haack reactions from ethyl ketones with an aromatic substitution yield chloroacrylaldehydes with a ratio E:Z > 95:5, therefore being potentially appliable for this study.

Scheme 134: Regiochemistry of known Vilsmeier-Haack reactions a) given by asymmetric compounds b) given by rotational bonds

An early test has been made in a previous project[83] with a phenyl substitution (compound **491**), only resulting in acetal cleavage and formation of a complex mixture (Scheme 135). It is uncertain if the acyclic ynamide is unstable in the reaction conditions or if the failure is due to steric hindrance.

Scheme 135: Previously tested Au-catalysed polycyclization on acyclic substrate

The multistep synthesis could be carried out from a β-substituted ketone. In this project, the Vilsmeier-Haack reaction was tested on compound **495** (Scheme 136a), yielding vinyl chloride **496** instead of the expected product **497**. It is doubtful whether different reaction conditions would resolve the issue or if ethyl arylmethylketones have a different reactivity than the ketones previously mentioned. If the latter was the case, a future project could be directed towards acyclic non-aromatic substrates as **501** (Scheme 136b).

Scheme 136: Previously tested Au-catalysed polycyclization on acyclic substrate

8 Experimental Section

8.1 General Experimental

Commercially available chemicals and reagents were purchased from Acros, Alfa Aesar, Apollo Scientific, Combi-Blocks, Enamine, Fluorochem or Merck and used without further purification unless reported.

All metal-catalysed reactions were conducted under inert atmosphere (argon or nitrogen) in heat gun-dried glassware. The solvents used were purified using a Pure Solv-MD solvent purification system and were transferred under inert atmosphere. Reactions carried out at T<rt were conducted with cooling baths (0 °C in ice/water or -20 °C in dry ice). Reactions carried out at T>rt were conducted on paraffin oil baths or stirrer hotplates, with temperature controlled via an external probe.

Experimental procedures are related to the maximum scale achieved.

Compounds purification: Fluorochem silica gel 60 (0.043-0.063 mm) was used for purification of compounds with flash column chromatography. Automated flash column chromatography purifications were realised either with a Reveleris® X2 flash chromatography system (BUCHI) with detection UV= 210 and 300 mM and ELSD or with a CombiFlash NEXTGEN 300+ (TELEDYNE ISCO) with detection UV= 254 and 280 mM. All drug-like library compounds were purified with a preparative-LCMS or preparative-UPLC method unless specified.

Retention factors (R_f): Merck silica gel 60F254 analytical plates for thin layer chromatography (TLC) were used and developed using UV fluorescence (254 and 366 mM) or $KMnO_4$. Eluents used are specified for all compounds.

IR: spectra were recorded either on a Perkin–Elmer Spectrum 100 FTIR spectrometer (Perkin-Elmer) whose spectra were processed with *PerkinElmer Spectrum*, or on an Inc. Cary 630 FTIR (Agilent Technologies) whose spectra were processed with *Spectragryph* version v1.2.15. Only selected absorbencies (ν_{max}) are reported in a range of 4000-600 cm^{-1}.

HRMS (ES): Waters Xevo G2-XS or Waters Synapt G2-Si was used with either Methanol/Water or Acetonitrile/Water as the mobile phase. HRMS were recorded using a lock-mass (Leucine Enkephalin) to compensate for any mass error (gives 4 decimals). Alternatively, a LC-MS Q Exactive Focus high resolution mass spectrometer (Thermo Scientific) was used (gives 4 or 5 decimals). In this case, the mass spectrometer was calibrated by infusion of a Pierce calibration solution containing n-butylamine, caffeine, MRFA and Ultramark 1621 (Thermo Fisher Scientific product nr 88323) for positive ion mode; a Pierce calibration solution containing sodium dodecyl sulfate, sodium taurocholate, and Ultramark 1621 (Thermo Fisher Scientific product nr 88324) was used for negative ion mode (gives 4 or 5 decimals).

HRMS (EI): Waters GCT Premier GCMS was used. The sample was dissolved into DCM and injected using an Agilent Technologies 7683B Series Injector and 7890A Oven; the sample was injected though a (5%-phenyl)-methylpolysiloxane column; injector temperature 270°C, oven gradient 50 °C to 270 °C ramped over 20 minutes. Perfluorokerosene was used as reference ions for accurate mass measurements (gives 4 decimals).

HRMS (ASAP): Waters Xevo G2-XS was used. The sample was deposited onto the tip of a glass capillary, inserted into the ASAP probe then placed into the ionisation source. The probe was heated from 50°C to 650°C, with the sample measurement taken when the sample ions were observed; the source was operated in constant current mode (4µA). HRMS were recorded using a lock-mass (Leucine Enkephalin) to compensate for any mass error (gives 4 decimals).

Low-resolution MS: GCMS spectra were recorded on an Agilent 6890N with a RXi-5MS 20m, ID 180µm, df 0.18µ column, T= 250 °C. The measured masses range 50-500. Data are evaluated using Xcalibur Qual Browser version 4.2.47 (Thermo Fisher). Waters MassLynx (V4.1 version) was used for HRMS reported as neutrals.

All LCMS spectra were recorded on an Agilent InfinityLab LC/MSD with a XSelect CSH C18 (30x2.1mm 3.5µ) column with 1mL/min flow. Detection was accomplished with DAD (210, 220 and 220-320 nm), PDA (210-320 nm) and MSD (ESI pos/neg). The measured mass range is 100-1000. MS data are reported as m/z (relative intensity).

All LCMS analysis of drug-like library compounds were carried out with linear gradient as follows: t=0 min 5% B, 4.5 min 98%B, t=6 min 98% B. Analysis of other compounds were carried out with linear gradient as follows: t=0 min 5% B, 1.6 min 98%B, t=3 min 98% B. Eluents were used as either A= 0.1% formic acid in water and B= 0.1% formic acid in acetonitrile, with data recorded as T=40 °C or A= 10 mM ammoniumbicarbonate in water and B= acetonitrile. Compound purities were measured with LCMS analysis.

NMR: Spectra were recorded on Bruker AVIII300 (^{1}H = 300 MHz) or Bruker AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) or on Bruker AVIII500 (^{1}H = 500 MHz) in $CDCl_3$, Acetone-d_6, Benzene-d_6, DMSO-d_6 or CD_3OD purchased from Sigma Aldrich. Chemical shifts (δ) are reported in ppm downfield from TMS signal. ^{1}H and ^{13}C NMR spectra reference signal are related to non-deuterated residual signals in deuterated solvents and calibrated with references $\delta_C \equiv 77.16$ (s) ppm and $\delta_H \equiv 7.26$ (t) ppm for $CDCl_3$; $\delta_C \equiv 39.51$ (sept) ppm and $\delta_H \equiv 2.50$ (quint) ppm for DMSO-d_6; $\delta_C \equiv 206.68$ (s), 29.92 (sept) ppm and $\delta_H \equiv 2.05$ ppm for Acetone-d_6, $\delta_C \equiv 128.4$ (t) ppm and $\delta_H \equiv 7.16$ (s) ppm for C_6D_6; $\delta_C \equiv 20.4$ (sept) ppm and $\delta_H \equiv 2.09$ (quint) ppm for Toluene-d_8; $\delta_C \equiv 49.15$ (sept) ppm and $\delta_H \equiv 4.78$ (s), 3.31 (quint) ppm for Methanol-d_4; $\delta_H \equiv 4.80$ ppm for D_2O. Coupling constants (*J*) are reported in Hz. Reference $\delta_H \equiv 0.00$ ppm for added TMS was specifically for ^{1}H NMR spectra containing signals that totally superimpose to undeuterated solvent signals. In this case data is labelled as ^{1}H NMR (field, solvent, TMS). Multiplicity is denoted in ^{1}H-NMR by: d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent), br (broad). ^{13}C-NMR peaks are denoted by: C (quaternary) CH (tertiary), CH_2

(secondary), CH_3 (primary) and br (broad peak). 1D ^{13}C-NMR spectra were recorded using the UDEFT or PENDANT pulse sequences from the Bruker standard pulse program library. 2D ^{1}H-NMR spectra were recorded using the Bruker standard pulse program library.

NMR and MS Spectra were processed using *MestReNova* version 14.2.1.

8.2 General Procedures

General Procedure 1 (GP1): Preparation of *N*-protected 4-Piperidinones

The procedure is a modified version of that reported by Ellis *et al.*[245]

4-Piperidinone monohydrate hydrochloride (1.0 eq.) was dissolved in a mixture of H_2O and $CHCl_3$ 1:1 (0.5 M). Oxycarbonyl or sulfonyl chloride (1.2 eq.) was added followed by K_2CO_3 (2.5 eq.) and the mixture was stirred at rt for 16 h. The organic phase was then separated and the aqueous phase was extracted with CH_2Cl_2 (3 × ca. 1 mL/mmol of ketone). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a light yellow solid or oil. The desired *N*-protected 4-piperidinone was finally afforded without further purification or, if needed, by recrystallization.

General Procedure 2 (GP2): Preparation of β-Bromoacrylaldehydes

The procedure is a modified version of that reported by Binder *et al.*[246]

Dry DMF (3.0 eq.) was added in a heat gun-dried 3-neck bottom flask under inert atmosphere, followed by the dropwise addition of PBr_3 (2.7 eq.) at 0 °C. Dichloromethane (0.1 M) was added and the mixture was allowed to stir at rt for 1 h at 0 °C. Ketone (1.0 eq.) was added and the mixture was allowed to stir for 16 h. The reaction was then quenched slowly in a flask containing a saturated solution of $NaHCO_3$vuntil neutralization. The aqueous layer was

separated and extracted with CH_2Cl_2 (ca. 3 × 1mL/mmol of ketone). The organic fractions were merged, dried over Na_2SO_4 and filtrated. The solvent was removed under reduced pressure, then heptane (ca. 1 mL/mmol of ketone) was added before being removed under reduced pressure to give crude as a red oil. The desired β-bromoacrylaldehyde was finally afforded via flash column chromatography.

NOTE: Products are highly sensitive to light and moisture. Use them immediately after purification.

General Procedure 3 (GP3): Preparation of β-Chloroacrylaldehydes

The procedures are modified versions of that reported by Komendatova *et al.*[112-113]

Procedure A (1.00-150 mmol): Dry DMF (6.0 eq.) was added in a heat gun-dried 3-neck bottom flask under inert atmosphere, followed by the dropwise addition of $POCl_3$ (4.0 eq.) through a syringe at 0 °C. Dichloromethane (0.6 M) was added and the mixture was allowed to stir at rt for 2 h. Ketone (1.0 eq.) was added followed by CH_2Cl_2 (0.3 M) and the mixture was allowed to stir for further 2 h. The reaction was then quenched slowly in a flask containing a saturated solution of Na_2CO_3 (ca. 10mL/mmol of ketone) at 0 °C until neutralization. The biphasic mixture was then stirred until no more formation of bubbles was observed. The aqueous layer was separated and extracted with CH_2Cl_2 (ca. 3 × 1mL/mmol of ketone). The organic fractions were merged, dried over Na_2SO_4 and filtrated. The solvent was removed under reduced pressure, then heptane (ca. 1 mL/mmol of ketone) was added before being removed under

reduced pressure to give crude as a red oil. The desired β-chloroacrylaldehyde was finally afforded via flash column chromatography.

Procedure B (100-500 mmol): Dry DMF (6.0 eq.) was added in a heat gun-dried 3-neck bottom flask under inert atmosphere and provided with a mechanical stirrer, followed by the dropwise addition of $POCl_3$ (4.0 eq.) through a dropping funnel at 0°C. Dichloromethane (0.6 M) was added and the mixture was allowed to stir at rt for 2h. Ketone (1.0 eq.) was added followed by CH_2Cl_2 (0.3 M) and the mixture was allowed to stir for further 2h. The reaction was then slowly transferred via vacuum pump in a 5-10 L flask containing a saturated solution of Na_2CO_3 (ca. 10mL/mmol of ketone) at 0 °C while stirring. The temperature of the mixture was controlled via an external probe and kept at T<20 °C. The biphasic mixture was stirred until no more formation of bubbles was observed. If necessary, more saturated solution of Na_2CO_3 was added until neutralization. The organic phase was then separated via vacuum pump and the aqueous layer was extracted with CH_2Cl_2 (ca. 2 × 0.5mL/mmol of ketone). The organic fractions were merged, dried over Na_2SO_4 and filtrated on a Büchner funnel with sintered disc. . The solvent was removed under reduced pressure, then heptane (ca. 0.5 mL/mmol of ketone) was added before being removed under reduced pressure to give crude as a red oil. The desired β-chloroacrylaldehyde was finally afforded via flash column chromatography.

NOTE: Products are sensitive to light and moisture. It is advised to keep them in freezer and use it for the next step within a week.

General Procedure 4 (GP4): Preparation of Trimethylsilyl enynals

The procedure is a modified version of that reported by Baldridge *et al*.[247]

β-Haloacrylaldehyde (1.0 eq.) was dissolved in 1,4-dioxane and triethylamine 1:1 (0.5 M). The mixture was then degassed with inert gas (N_2 or Ar) for 10 minutes. $Pd(PPh_3)_2Cl_2$ (0.02 eq.) and CuI (0.01 eq.) were added followed by trimethylsilyl acetylene (2.0 eq.). The reaction was stirred at a specified temperature until completion by TLC (ca. 2-3 h). The mixture was cooled down to rt and filtered on celite eluting with CH_2Cl_2. The solvent was then removed under reduced pressure to give crude as a black oil. The desired trimethylsilyl enynal was finally afforded via flash column chromatography.

General Procedure 5 (GP5): Preparation of Trimethylsilyl acetals

The procedure is a modified version of that reported by Kato *et al*.[248]

Trimethylsilyl enynal (1.0 eq.) was dissolved in toluene (0.35 M). Ethylene glycol (2.0 eq.) and para-toluensulfonyl acid hydrate (0.07 eq.) were added and the flask was connected to a Dean-Stark apparatus. The mixture was heated to reflux and stirred until completion (ca. 2.5h) by TLC/GCMS/LCMS, before cooling it down to rt. Saturated solution of $NaHCO_3$ was added (ca. 3 mL/mmol enynal), the organic phase was separated and the aqueous layer was

extracted with CH_2Cl_2 (ca. 3 × 2 mL/mmol enynal) The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a dark orange oil. The desired trimethylsilyl acetal was finally afforded without further purification or, if needed, by flash column chromatography or recrystallization.

General Procedure 6 (GP6): Preparation of Terminal Alkynes

The procedure is a modified version of that reported by Morn-Poladura *et al*.[249]

Trimethylsilyl acetal (1.0 eq.) was dissolved in MeOH (0.35 M). Potassium carbonate (0.75 eq.) was added and the mixture was stirred at rt until completion by TLC/GCMS/LCMS (ca. 1h). Saturated solution of NH_4Cl was added (ca. 1 mL/mmol trimethylsilyl acetal), then CH_2Cl_2 was added (ca. 3 mL × mmol acetal) and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (ca. 3 × 2 mL/mmol of trimethylsilyl acetal). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a red oil. The desired terminal alkyne was finally afforded without further purification or, if needed, by flash column chromatography.

General Procedure 7 (GP7): Preparation of Bromoalkynes

The procedures are modified versions of those reported by Plamont *et al*.[250]

Trimethylsilyl acetal or terminal alkyne (1.0 eq.) was dissolved in dry acetone (0.1M) under inert atmosphere. Silver nitrate (0.1 eq.) and NBS (1.1 eq.) were added, then the flask was covered with aluminium foil. The reaction was stirred at a specified temperature until reaction completion by TLC (ca. 1 h). Toluene was added (ca. 0.2 mL/mmol reagent) and acetone was removed under reduced pressure. NOTE: do not let product reach complete dryness. The mixture was filtered over a silica pad (ca. 1-5 cm) eluting with PhMe added with a specified quantity of TEA (0.15-0.5%). The solvent was removed under reduced pressure to give the desired bromoalkyne that was immediately used for the following step without further purification.

NOTE: Products are unstable: do not store. Products vapours are irritant.

General Procedure 8 (GP8): Preparation of Sulfonamides

The procedures are modified versions of that reported by Pickford *et al*.[251]

Procedure A (1.0-150 mmol): *N*-allyl amine (1.0 eq.) was added to CH_2Cl_2 (1.0 M) and the solution was cooled down to 0 °C. Sulfonyl chloride (1.1 eq.) was added portionwise, followed by triethylamine (1.1 eq.) dropwise. The mixture was allowed to stir at rt for 30 min before adding water (ca 1 mL × mmol of allylamine). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (ca 1 mL/mmol of allylamine × 3). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as an orange oil/solid. The desired sulfonamide was finally afforded via flash column chromatography.

Procedure B (0.15-1.0 mol): *N*-allyl amine (1.0 eq.) was added to CH_2Cl_2 (1.0 M) and the solution was cooled down to 0°C. Sulfonyl chloride (1.1 eq.) was added portionwise, then triethylamine (1.1 eq.) was added dropwise through a dropping funnel while monitoring the temperature with an external probe so that T<20 °C). The mixture was allowed to stir at rt for 30 min before adding water (ca 1 mL × mmol of allylamine). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (ca 0.2 mL/mmol of allylamine × 3). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as an orange oil/solid. The desired sulfonamide was finally afforded via flash column chromatography.

General Procedure 9 (GP9): Preparation of Ynamides

The procedure is a modified version of that reported by Hsung *et al.*[84c]

Freshly prepared bromoalkyne (1.0 eq.) was dissolved in toluene (1.0 M). Sulfonamide (1.0 eq.) was added followed by $CuSO_4{\cdot}5H_2O$ (0.2 eq.), 1,10-phenantroline (0.4 eq.) and K_2CO_3 (2.0 eq.). The mixture was stirred at 65 °C for 16 h. The reaction was then cooled down to rt and filtered through a pad of celite eluting with CH_2Cl_2. The solvent was removed under reduced pressure to give crude as a dark brown oil. The desired ynamide was finally afforded via flash column chromatography.

General Procedure 10 (GP10): Preparation of Polycycles by Gold-catalysed Polycyclization

The procedure is a modified version of that reported by Adcock *et al.*[55]

Ynamide (1.0 eq.) was dissolved in toluene (0.25 M). Dichloro(2-pyridinecarboxylato)*gold* (3-5% mol) was added and the mixture was stirred at a specified temperature for 1h. The reaction was cooled down to rt and filtered through a pad of celite eluting with CH_2Cl_2. The solvent was removed under reduced pressure to give crude as black oil. The desired polycycle was finally afforded via flash column chromatography or filtration on silica followed by recrystallization.

General Procedure 11 (GP11): Preparation of α,β-Conjugated Carbonyl Compounds

Procedure A: Polycycle (1.0 eq.) was dissolved in a solution of 4 N HCl (0.25 M). Water (1.0 eq.) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure to give crude as an orange oil. The desired α,β-conjugated carbonyl was finally afforded via flash column chromatography, recrystallization or filtration.

Procedure B: Polycycle **168** (1.0 eq.) was dissolved in dry DMF (0.3 M) in a flame dried Schlenk tube under inert atmosphere. Cs_2CO_3 (5.0 eq.) was added followed by thioglycolic acid (1.7 eq.). The mixture was stirred for 3h at 50 °C before cooling it down to rt and filtrating it on a membrane filter (pore size 0.45 µm) eluting with CH_2Cl_2. The solvent was removed under reduced pressure to give ***Rac*-(1aR,3aS,8bS)-1a,2,3,3a,7,8-hexahydro-1H,5H-spiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane] 242** as a red oil (75% by qNMR). R_f= 0.2 (CH_2Cl_2:MeOH 9:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2956, 2925, 2855, 1698, 1498, 1425, 1330, 1280, 1225, 1154, 1111, 1047, 1023, 1009, 964, 822, 799, 751, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 – 4.21 (m, 2H), 4.15 – 4.06 (m, 2H), 3.99 – 3.74 (m, 5H), 3.68 (s, 1H), 3.63 (dd, *J* = 11.5, 4.8 Hz, 1H), 3.19 (dd, *J* = 11.6, 1.2 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.80 (app. dtt, *J* = 17.2, 5.2, 2.6 Hz, 1H), 1.55 – 1.46 (m, 1H), 1.26 (dd, *J* = 8.9, 3.2 Hz, 1H), 1.06 – 0.97 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.5 (C), 132.9 (C), 115.1 (C), 73.3 (CH), 66.3 (CH_2), 65.6 (CH_2), 63.8 (CH_2), 62.7 (CH_2), 52.5 (CH_2), 42.9 (C), 22.9 (CH_2), 22.3 (CH), 14.6 (CH_2); MS (LCMS, ES+): 237 (11), 236 (100); HRMS (ES+) *m/z* calculated for $C_{13}H_{18}NO_3$ $[M+H]^+$ 236.1281, found 236.1280. The crude mixture was dissolved in a solution of HCl 4N in 1,4-dioxane (0.1M). The reaction was stirred at 0 °C for 2 h. The solvent was removed under reduced pressure to give **Rac-(1aR,3aS,8bS)-4-oxo-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-3-ium chloride 274** as a dark red oil; IR: ν_{max} (neat, cm^{-1}) 3405, 2987, 2162, 1075, 1628, 1408, 1250, 1052, 899, 840, 624; ^{1}H NMR (400 MHz, D_2O): δ 4.34 – 4.19 (m, 3H), 3.99 (dd, *J* = 12.7, 6.2 Hz, 1H), 3.88 – 3.77 (m, 2H), 3.42 (dd, *J* = 12.7, 3.1 Hz, 1H), 2.32 (d, *J* = 19.6 Hz, 1H), 2.26 – 2.12 (m, 2H), 1.87 (dd, *J* = 8.5, 6.5 Hz,

1H), 1.58 (app. t, *J* = 5.8 Hz, 1H); 2H missing; ^{13}C NMR (101 MHz, $CDCl_3$): δ 226.5 (C), 175.8 (C), 136.5 (C), 69.5 (CH), 65.6 (CH_2), 64.3 (CH_2), 55.9 (CH_2), 26.4 (CH_2), 25.3 (CH), 23.0 (CH_2), 2C missing; MS (LCMS, ES+): 192 (100); HRMS (ES+) *m/z* calculated for $C_{11}H_{14}ClNO_2$ [M+H] 192.1025, found 192.1019. The crude mixture was dissolved in CH_2Cl_2 (0.1 M) and TEA (1.0 eq.) was added. The mixture was stirred at 0 °C for 15 min before adding sulfonyl/acyl/carbamoyl/thiocarbamoyl chloride (1.2 eq.) followed by TEA (1.0 eq.). The reaction was stirred for further 30 min at rt, then water (ca. 1 mL × 0.25 mmol of **180**) was added. The aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **180**)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a red oil. The desired α,β-conjugated carbonyl was finally afforded by flash column chromatography.

Procedure C: α,β-Unsaturated carbonyl **362** was dissolved in CH_2Cl_2 (0.1 M) and TEA (1.0 eq.) was added. Acyl/carbamoyl chloride (1.2 eq.) was added, followed by TEA (2.0 eq.). The reaction mixture was stirred at rt for 30 min before adding water (ca. 2.0 mL × mmol α,β-conjugated carbonyl). The aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **362**)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as an orange oil. The desired allyl alcohol was finally afforded by flash column chromatography or preparative LCMS.

General Procedure 12 (GP12): Preparation of Allyl Alcohols

Procedure A: α,β-Conjugated carbonyl (1.0 eq.) was dissolved in THF (0.1 M). $LiAlH_4$ (1.5 eq., 2.4 M in THF) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of α,β-conjugated carbonyl)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a pale-yellow oil. The desired allyl alcohol was finally afforded by flash column chromatography or preparative LCMS.

Procedure B: α,β-Conjugated carbonyl (1.0 eq.) was dissolved in MeOH (0.1 M). $CeCl_3 \cdot 7H_2O$ (1.0 eq.) was added followed by $NaBH_4$ (2.0 eq.). The mixture was stirred at 0°C for 1h. The reaction was quenched with water (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of α,β-conjugated carbonyl)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a pale-yellow oil. The desired allyl alcohol was finally afforded by flash column chromatography or preparative LCMS.

Procedure C: α,β-Conjugated carbonyl **362** (1.0 eq.) was dissolved in THF (0.1 M). $LiAlH_4$ (3.0 eq., 2.4 M in THF) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of α,β-conjugated carbonyl)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a white solid. The crude residue was dissolved in CH_2Cl_2 (0.1 M). Acyl/carbamoyl chloride (1.2 eq.) was added, followed by TEA (1.2 eq.). The reaction mixture was stirred at rt for 30 min before adding water (ca. 2.0 mL × mmol α,β-conjugated carbonyl). The aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **362**)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as an orange oil. The desired allyl alcohol was finally afforded by flash column chromatography or preparative LCMS.

Procedure D: α,β-Conjugated carbonyl **362** (1.0 eq.) was dissolved in THF (0.1 M). $LiAlH_4$ (3.0 eq., 2.4 M in THF) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of α,β-conjugated carbonyl)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced

pressure to give crude as a white solid. The crude residue was dissolved in DCE/MeOH 3:1 (0.1 M) under inert atmosphere. Aldehyde (1.2 eq.) was added and the mixture was stirred at rt for 6h. $NaBH_4$ (1.5 eq.) was then added and the mixture was stirred for 16h. Water was added (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **362**). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a pale-yellow oil. The desired tertiary alcohol was finally afforded by flash column chromatography, recrystallization or preparative UPLC.

General Procedure 13 (GP13): Preparation of Tertiary Alcohols

Ketone **283** (1.0 eq.) was dissolved in THF (0.1 M) under inert atmosphere. Grignard reagent (2.0 eq.) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **283**). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a pale-yellow oil. The desired tertiary alcohol was finally afforded by flash column chromatography.

General Procedure 14 (GP14): Preparation of Secondary Amines by Reductive Amination

Procedure A: Ketone **283** (1.0 eq.) was dissolved in DCE/MeOH 3:1 (0.1 M) under inert atmosphere. Amine (1.2 eq.) was added followed by CH_3COOH glacial (1.0 eq.) and the mixture was stirred at rt for 6 h. $NaBH_4$ (1.5 eq.) was then added and the mixture was stirred for 16h. Water was added (ca. 3 mL × 0.25 mmol of **283**), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **283**). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a white oil. The desired secondary amine was finally afforded by flash column chromatography, recrystallization or preparative UPLC.

Procedure B: Ketone **283** (1.0 eq.) was dissolved in DCE/MeOH 3:1 (0.1 M) under inert atmosphere. Amine (1.2 eq.) was added followed by CH_3COOH glacial (1.0 eq.) and the mixture was stirred at rt for 6 h. The solvent was removed under reduced pressure and the crude residue was dissolved in EtOH. The solution was degassed under inert atmosphere for 5 minutes and then the reaction vessel was then loaded with a balloon filled with H_2. After bubbling the mixture with H_2 for 2 minutes, the reaction was stirred at 50°C for 45 min. The reaction was cooled down to rt and the hydrogen-filled balloon was removed. The mixture was degassed for 5 minutes under inert atmosphere and then filtered over a membrane filter. The solvent was removed under reduced pressure to give crude as a pale yellow oil. The desired secondary amine was finally afforded by preparative UPLC.

General Procedure 15 (GP15): Preparation of Ethers

Alcohol **300** (1.0 eq.) was dissolved in dry DMF (0.3 M) under inert atmosphere. NaH (1.5 eq.) was added and the mixture was stirred at 50 °C for 1 h. Alkyl halide (1.2 eq.) was then added and the mixture was stirred at 50 °C for 1 h. Water was added (ca. 2.0 mL × mmol α,β-conjugated carbonyl), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL × 0.25 mmol of **300**). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a red oil. The desired tertiary alcohol was finally afforded by preparative UPLC.

8.2.1 Preparation of *N*-Protected 4-Piperidinones

***Tert*-butyl 4-oxopiperidine-1-carboxylate 187**

The procedure is a modified version of that reported by Ashwood *et al.*[252]

4-Piperidinone monohydrate hydrochloride (12.3 g, 80.0 mmol, 1.0 eq.) and $NaHCO_3$ (8.06 g, 96 mmol, 1.2 eq.) were added to water (160 mL, 0.5 M) and stirred until dissolution. Di-tert-butyl dicarbonate (19.3 g, 88.0 mmol, 1.1 eq.) was then added and the mixture was stirred for 2 h at 30 °C. The reaction was then warmed to 50 °C and stirred for further 2 h before cooling it down to rt. EtOAc (80 mL) was added, then the aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The organic fractions were merged, dried over Na_2SO_4 and filtrated. The solvent was removed under reduced pressure to afford *N*-protected 4-piperidinone **187**

as an off-white solid (13.7 g, 69.0 mmol, 86%) that was used for the following step without further purification; m.p. 74–75 °C; R_f= 0.20 (Hexane:EtOAc 7:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 2979, 2861, 1680, 1415, 1364, 1234, 1162, 988, 859, 771, 628, 554; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.71 (t, *J* = 6.2 Hz, 4H), 2.43 (t, *J* = 6.2 Hz, 4H), 1.48 (s, 9H). Data match that reported by Watson *et al.*[253]

Benzyl 4-oxopiperidine-1-carboxylate 181

Prepared according to **GP1** from 4-piperidinone monohydrate hydrochloride (12.3 g, 80.0 mmol) and benzyl chloroformate (16.4 g, 96.0 mmol). *N*-protected 4-piperidinone **181** was afforded as a pale yellow oil (15.9 g, 85%) and used for the following step without further purification; R_f= 0.26 (Hexane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 1695, 1498, 1474, 1426, 1364, 1310, 1272, 1226, 1118, 1060, 989, 934, 910, 863, 815, 752, 697, 604; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 5H), 5.18 (s, 2H), 3.80 (t, *J* = 6.3 Hz, 4H), 2.46 (t, *J* = 6.5 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.4 (C), 155.3 (C), 136.4 (C), 128.7 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 67.8 (CH_2), 43.3 (2 × CH_2), 41.2 (2 × CH_2). Data matches that reported by Sasano *et al.*[254]

1-((4-Nitrophenyl)sulfonyl)piperidin-4-one 188

Prepared according to **GP1** from 4-piperidinone monohydrate hydrochloride (12.3 g, 80.0 mmol) and 4-nitrobenzenesulfonyl chloride (21.3 g, 96.0 mmol). Recrystallization in 1-4-dioxane afforded *N*-protected 4-piperidinone **188** as a light yellow solid (20.2 g, 89%); m.p. 193–194 °C; R_f= 0.22 (Hexane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 1717, 1608, 1534, 1474, 1420, 1399, 1362, 1300, 1223, 1163, 1114, 1087, 1020, 984, 961, 938, 855, 828, 765, 739, 701, 686, 627; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 – 8.38 (m, 2H), 8.03 – 7.97 (m, 2H), 3.48 (t, *J* = 6.2 Hz, 4H), 2.58 (t, *J* = 6.3 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.7 (C),

150.5 (C), 142.8 (C), 128.8 (2 × CH), 124.8 (2 × CH), 45.9 (2 × CH_2), 40.9 (2 × CH_2); ^{1}H NMR (400 MHz, DMSO + 0.03 v/v TMS): δ 8.48 – 8.39 (m, 2H), 8.11 – 8.04 (m, 2H), 3.41 (t, *J* = 6.2 Hz, 4H), 2.42 (t, *J* = 6.2 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6 + 0.03 v/v TMS): δ 205.2 (C), 150.1 (C), 141.9 (C), 128.9 (2 × CH), 124.8 (2 × CH), 44.9 (2 × CH_2), 39.8 (2 × CH_2) superimposed to DMSO signal. MS (LCMS, ES+): *m/z* 325 $[M+H_2O+Na]^+$ (77), 307 $[M+Na]^+$ (41), 285 $[M+H]^+$ (100), 100 (34); HRMS (ASAP+) *m/z* calculated for $C_{11}H_{13}N_2O_5S$ [M+H] 285.0545, found 285.0550·; HRMS (EI+) *m/z* calculated for $C_{11}H_{12}N_2O_5S$ [M] 284.0467, found 284.0469.

3.2.2 Preparation of Ketone 495

1-(Pyridin-4-yl)propan-2-one 495

Picoline (931 mg, 10.0 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (5.0 mL, 2.0 M) and acyl chloride (711 µL, 10.0 mmol, 1.0 eq.). The mixture was heated to 35 °C and stirred for 2h before cooling it down to 0 °C. A saturated solution of Na_2CO_3 was added dropwise until neutralisation, then the mixture was stirred for 2h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5mL). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a red oil. Flash column chromatography afforded ketone **495** as yellow oil (108.1 mg, 6%) R_f= 0.2 (Hexane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3069, 2897, 1714, 1558; ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.52 (m, 2H), 7.14 – 7.10 (m, 2H), 3.71 (s, 2H), 2.20 (s, 3H). Data matches that reported by Fragis *et al.*[255]

8.2.3 Preparation of β-Haloacrylaldehydes

4-Bromo-5,6-dihydro-2H-pyran-3-carbaldehyde 61

Prepared according to **GP2** from tetrahydro-4H-pyran-4-one (8.00 g, 80.0 mmol). Flash column chromatography [Heptane:EtOAc 4:1] afforded β-haloacrylaldehyde **65** as a yellow oil (2.60 g, 17%); R_f= 0.46 (Hexane:EtOAc 4:1) [UV]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 4.33 (t, *J* = 2.5 Hz, 2H), 3.84 (t, *J* = 5.5 Hz, 2H), 2.82 (tt, *J* = 5.5, 2.5 Hz, 2H). Data match that reported by Binder et al.[86a]

4-Bromo-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde 107

Prepared according to **GP2** from **188** (22.7 g, 80.0 mmol). Flash column chromatography [Heptane:EtOAc 4:1] afforded β-haloacrylaldehyde **107** as an orange solid (5.10 g, 17%); Decomposition at 88-89 °C; R_f= 0.40 (Hexane:EtOAc 7:3) [UV]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.45 – 8.34 (m, 2H), 8.06 – 7.95 (m, 2H), 3.85 (t, *J* = 2.4 Hz, 2H), 3.38 (t, *J* = 5.7 Hz, 2H), 2.95 (tt, *J* = 5.6, 2.4 Hz, 2H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS) δ 9.77 (s, 1H), 8.48 – 8.37 (m, 2H), 8.14 – 8.02 (m, 2H), 3.77 (t, *J* = 2.4 Hz, 2H), 3.35 (t, *J* = 5.8 Hz, 2H) superimposed to H_2O signal, 2.89 (tt, *J* = 5.8, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 190.8 (CH), 150.2 (C), 141.4 (C), 139.7 (C), 130.9 (C), 129.1 (2×CH), 124.9 (2×CH), 44.5 (CH_2), 43.4 (CH_2), 36.8 (CH_2); MS (LCMS, ES+): *m/z* 431 (100), 429 (93), 391 (79), 389 (74); (LCMS, ES-): 375 (100) $[M-H^+]^-$, 373 (96).

4-Chloro-5,6-dihydro-2H-pyran-3-carbaldehyde 116

Prepared according to **GP3** from tetrahydro-4H-pyran-4-one (**GP3A**: 10.0 g, 100 mmol, **GP3B** 50.1 g, 500.0 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-90:10] afforded β-haloacrylaldehyde **116** as a light yellow oil (**GP3A**:

6.30 g, 43%; **GP3B**, 19.8 g, 27%); purity: 98.0 [LCMS, PDA]; R_f= 0.60 (Hexane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}): 2856, 1731, 1670, 1631, 1465, 1416, 1383, 1353, 1286, 1243, 1199, 1116, 1097, 1055, 1020, 992, 899, 833, 713; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 4.34 (t, *J* = 2.3 Hz, 2H), 3.86 (t, *J* = 5.6 Hz, 2H), 2.67 (tt, *J* = 5.3, 2.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.9 (CH), 147.7 (C), 132.8 (C), 64.8 (CH_2), 64.4 (CH_2), 35.0 (CH_2); MS (GCMS, EI+): 148 (16) $[M]^+$, 146 (48), 119 (23), 117 (71), 102 (16), 100 (49), 81 (44), 53 (100), 51 (47); MS (LCMS, ES+): *m/z* 228 (48), 142 (77), 102 (100). Data match that reported by Giles *et al*.[99a-b]

Tert-butyl 4-chloro-5-formyl-3,6-dihydropyridine-1(2H)-carboxylate 189

Prepared according to **GP3** from **187** (**GP3A**: 15.9 g, 80.0 mmol, **GP3B** 99.6 g, 500.0 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-90:10] afforded β-haloacrylaldehyde **189** as a light yellow oil (**GP3A**: 9.43 g, 48%; **GP3B**, 59.0 g, 48%); purity: 90.4 [LCMS, PDA]; R_f= 0.50 (Hexane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2975, 2932, 2863, 1676, 1629, 1456, 1413, 1365, 1331, 1283, 1230, 1160, 1121, 1068, 1040, 987, 941, 895, 859, 829, 766, 718, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 4.12 (t, *J* = 2.5 Hz, 2H), 3.61 (t, *J* = 5.8 Hz, 2H), 2.67 (tt, *J* = 5.5, 2.3 Hz, 2H), 1.46 (s, 9H), data matches that reported by Shao *et al*.;[256] ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.2 (CH), 80.8 + 80.6 (2 rotamers, C), 42.6 (CH_2), 41.3 (CH_2), 35.4 (CH_2), 28.5 (3 × CH_3). 3C missing; MS (GCMS, EI+): 191 (14) [M-*tert*-butyl]$^+$, 189 (42), 172 (16), 110 (22), 57 (100) [*tert*-butyl]$^+$; MS (LCMS, ES+): *m/z* 233 (33), 231 (100), 190 (88), 192 (36).

Benzyl 4-chloro-5-formyl-3,6-dihydropyridine-1(2H)-carboxylate 182

Prepared according to **GP3** from **181** (18.7 g, 80.0 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-90:10] afforded β-haloacrylaldehyde **182** as a light yellow oil (11.2 g, 50%); purity: 90.6 [LCMS, PDA]; R_f= 0.45

(Hexane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2864, 1699, 1672, 1630, 1497, 1424, 1384, 1361, 1331, 1286, 1223, 1200, 1117, 1068, 1030, 988, 952, 911, 852, 807, 755, 726, 697, 670; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.42 – 7.27 (m, 5H), 5.15 (s, 2H), 4.22 (t, *J* = 2.4 Hz, 2H), 3.69 (t, *J* = 5.8 Hz, 2H), 2.69 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 187.9 (CH), 154.1 + 153.8 (C), 148.0 + 147.0 (C), 135.2 (C), 130.2 + 129.8 (C), 127.6 (2 × CH), 127.2 (CH), 127.1 (2 × CH), 66.6 (CH_2), 41.4 (CH_2), 39.7 + 39.5 (CH_2), 34.0 (CH_2); MS (LCMS, MS+): 304 (28) $[M+Na]^+$, 302 (86), 238 (33) $[M-CHO_2]^+$, 236 (100); (LCMS, ES-): 280 (39) $[M-H^+]^-$, 278 (100), 113 (46); HRMS (ES+) *m/z* calculated for $C_{14}H_{14}ClNNaO_3$ $[M+Na]^+$ 302.0554, found 302.0565.

8.2.4 Preparation of vinyl chloride 496

(E)-4-(2-Chloroprop-1-en-1-yl)pyridine 496

Dry DMF (194 µL, 2.52 mmol, 4.2 eq.) was added in a heat gun-dried 3-neck bottom flask under inert atmosphere, followed by the addition of $POCl_3$ (123 µL, 1.32 mmol, 2.2 eq.) through a syringe at 0 °C. Ketone **495** (81.1 mg, 0.6 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (300 µL) and the solution was added to the reaction. The mixture was heated at 70 °C and stirred for 5 h. The reaction was cooled down to rt and then quenched with a saturated solution of Na_2CO_3 (2 mL) at 0 °C until neutralisation. The aqueous layer was separated and extracted with CH_2Cl_2 (ca. 3 × 1mL/mmol of ketone). The organic fractions were merged, dried over Na_2SO_4 and filtrated. The solvent was removed under reduced pressure to give crude as a dark red oil. Flash column chromatography (Hexane:EtOAc 9:1) vinyl chloride **496** as yellow oil (28.6 mg, 31%) R_f= 0.35 (Hexane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3181, 2897, 2842,

1550, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 – 8.54 (m, 2H), 7.50 – 7.44 (m, 2H), 6.41 (d, *J* = 1.4 Hz, 1H), 2.32 (d, *J* = 1.2 Hz, 3H).

3.2.5 Preparation of Trimethylsilyl Enynals

4-((Trimethylsilyl)ethynyl)-5,6-dihydro-2H-pyran-3-carbaldehyde 63

Prepared according to **GP4** from **61** (2.60 g, 13.6 mmol) at T= 50 °C or **116** (19.8 g, 135 mmol) at T=60 °C. Flash column chromatography [Heptane] followed by recrystallization in MeOH afforded trimethylsilyl enynal **63** as a light orange solid (1.93 g, 68% from **61**; 21.1 g, 75% from **116**); m.p. 53–54 °C ; R_f= 0.6 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2965, 2860, 2833, 2139, 1655, 1602, 1463, 1443, 1414, 1388, 1363, 1284, 1254, 1206, 1154, 1111, 987, 906, 835, 757, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H), 4.36 (t, *J* = 2.6 Hz, 2H), 3.78 (t, *J* = 5.5 Hz, 2H), 2.48 (tt, *J* = 5.4, 2.5 Hz, 2H), 0.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.8 (CH), 141.6 (C), 136.7 (C), 106.4 (C), 99.7 (C), 63.6 (CH_2), 63.5 (CH_2), 31.1 (CH_2), -0.2 (3 × CH_3); MS (GCMS, EI+): 179 (40) $[M-CHO]^+$, 163 (100), 97 (28), 75 (50), 73 (93); MS (LCMS, ES+): 210 (15), 209 (100) $[M+H]^+$, 179 (13); HRMS (ES+) *m/z* calculated for $C_{11}H_{17}O_2Si$ $[M+H]^+$ 209.09923, found 209.09939.

***Tert*-butyl 5-formyl-4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2H)-carboxylate 190**

Prepared according to **GP4** from **189** (59.0 g, 240 mmol) at T= 60 °C. Flash column chromatography [Heptane] afforded trimethylsilyl enynal **190** as an orange solid (53.9 g, 73%); m.p. 79–80 °C; R_f= 0.6 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2962, 2930, 2901, 2844, 1699, 1677, 1607, 1456, 1414, 1366, 1331, 1288, 1234, 1164, 1118, 1046, 978, 840, 760, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 4.19 – 4.07 (m, 2H), 3.51 (t, *J* = 5.7 Hz, 2H), 2.49 (tt, *J* = 6.2, 2.5 Hz, 2H), 1.46 (s, 9H), 0.22 (s, 9H); ^{13}C NMR (101

MHz, $CDCl_3$): δ 189.1 (CH), 153.5 (C), 139.6 (C), 136.5 (C), 105.4 (C), 99.4 (C), 79.1 (C), 40.7 (CH_2), 38.1 (CH_2), 30.9 (CH_2), 27.7 (3 × CH_3), -1.03 (3 × CH_3); MS (LCMS, ES+): 253 (20), 252 (100); HRMS (ES+) *m/z* calculated for $C_{16}H_{25}NO_3NaSi$ [M+Na] 330.1501, found 330.1503; calculated for $C_{16}H_{26}NO_3Si$ $[M+H]^+$ 308.16765, found 308.16718; calculated for $C_{12}H_{18}NO_3Si$ $[M\text{-}tert\text{-butyl}+H]^+$ 252.10505, found 252.10468; calculated for $C_{11}H_{18}NOSi$ $[M\text{-Boc}+H]^+$ 208.11522, found 208.11500.

Benzyl 5-formyl-4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2H)-carboxylate 191

Prepared according to **GP4** from **182** (11.2 g, 40.0 mmol) at T= 60 °C. Flash column chromatography [Heptane] afforded trimethylsilyl enynal **191** as an orange oil (10.5 g, 77%); R_f= 0.55 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}): 2959, 1702, 1675, 1607, 1498, 1455, 1425, 1389, 1361, 1330, 1288, 1249, 1228, 1204, 1149, 1113, 1041, 1029, 989, 911, 891, 841, 759, 731, 696; ^1H NMR (400 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 10.12 (s, 1H), 7.36 – 7.28 (m, 5H), 5.14 (s, 2H), 4.21 (t, *J* = 2.5 Hz, 2H), 3.57 (t, *J* = 5.7 Hz, 2H), 2.49 (s, 2H), 0.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.6 (CH), 155.3 (C), 140.1 + 139.6 (C), 137.7 + 137.0 (C), 136.4 (C), 128.5 (2 × CH), 128.2 (CH), 128.1 (2 × CH), 107.0 (C), 99.7 (C), 67.4 (CH_2), 41.3 (CH_2), 39.8 + 39.5 (CH_2), 31.4 (CH_2), -0.4 (3 × CH_3); MS (LCMS, ES+): 343 (26), 342 (100) $[M+H]^+$, 299 (15), 298 (53), 250 (11) $[M\text{-benzyl}]^+$; MS (LCMS, ES-): 341 (24), 340 (100) $[M-H]^-$; HRMS (ES+) *m/z* calculated for $C_{19}H_{23}NO_3NaSi$ [M+Na] 364.1345, found 364.1359.

1-((4-Nitrophenyl)sulfonyl)-4-((trimethylsilyl)ethynyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde 108

Prepared according to **GP4** from **107** (5.10 g, 13.6 mmol) at T= 60 °C. Flash column chromatography [Heptane:EtOAc 7:3] followed by recrystallization in MeOH afforded trimethylsilyl enynal **108** as a pale-yellow solid (3.79 g, 71%); m.p. 145-146 °C; R_f= 0.41 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2852, 1669, 1610, 1529, 1456, 1351, 1315, 1252, 1206, 1165, 1133, 1109, 1086, 993, 958, 895, 840, 762, 687; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.39 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 2H), 3.85 (t, *J* = 2.4 Hz, 2H), 3.29 (t, *J* = 5.7 Hz, 2H), 2.62 (tt, *J* = 5.6, 2.4 Hz, 2H), 0.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.1 (CH), 150.5 (C), 142.2 (C), 138.1 (C), 137.0 (C), 129.0 (2 × CH), 124.7 (2 × CH), 108.4 (C), 98.9 (C), 42.9 (CH_2), 42.1 (CH_2), 31.8 (CH_2), -0.3 (3 × CH_3); MS (LCMS, ES+): 456 (17), 411 (24), 410 (100) $[M+H_2O]^+$, 393 (33) $[M+H]^+$; MS (LCMS, ES-): 391 (35) $[M-H]^-$, 327 (100); HRMS (ES+) *m/z* calculated for $C_{17}H_{21}N_2O_5SSi$ 393.0940 [M+H], found 393.0941; HRMS (EI+) *m/z* calculated for $C_{17}H_{20}N_2O_5SSi$ 392.0862 [M], found 392.0865.

(Z)-4-(2,4-bis(trimethylsilyl)but-1-en-3-yn-1-yl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde 109

Obtained as a side-product with procedure **GP4** from **107** (78.5 mg, 0.20 mmol) at T= 50 °C. Flash column chromatography [Heptane:EtOAc 7:3] afforded trimethylsilyl enynal **109** as a black oil (9.81 mg, 10%); R_f= 0.45 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 1666, 1621, 1521, 1413, 1346, 1308, 1241, 1163, 936, 999; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.41 – 8.36 (m, 2H), 8.05 – 7.99 (m, 2H), 6.06 (s, 1H), 3.84 (t, *J* = 2.4 Hz, 2H), 3.31 (t, *J* = 5.7 Hz, 2H), 2.77 – 2.67 (m, 2H), 0.21 (s, 9H), 0.18 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.0 (CH), 151.7 (C), 149.4 (CH), 145.8 (C),

136.3 (C), 131.8 (C), 128.5 (2 × CH), 124.4 (2 × CH), 106.1 (C), 96.3 (C), 45.9 (CH_2), 44.1 (CH_2), 16.3 (CH_2), 1.7 (3 × CH_3), 0.3 (3 × CH_3); HRMS (ES+) *m/z* calculated for $C_{22}H_{31}N_2O_5SSi_2$ 491.1492 [M+H], found 491.1481.

8.2.6 Preparation of Trimethylsilyl Acetals

((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran-4-yl)ethynyl)trimethylsilane 65

Prepared according to **GP5** from **63** (21.1 g, 101 mmol). Trimethylsilyl dioxolane **65** was afforded as a dark orange oil (23.0 g, 90%) and used for the following step without further purification; R_f= 0.55 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2958, 2885, 2142, 1426, 1382, 1251, 1206, 1161, 1101, 1076, 1041, 996, 968, 936, 838, 758, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (s, 1H), 4.24 (t, *J* = 2.5 Hz, 2H), 4.00 – 3.95 (m, 2H), 3.94 – 3.89 (m, 2H), 3.74 (t, *J* = 5.5 Hz, 2H), 2.28 (tt, *J* = 5.4, 2.6 Hz, 2H), 0.18 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.0 (C), 119.9 (C), 101.9 (CH), 101.4 (C), 99.8 (C), 65.7 (2 × CH_2), 63.9 (CH_2), 63.3 (CH_2), 29.8 (CH_2), 0.03 (3 × CH_3); MS (GCMS, EI+): 163 (15), 149 (10), 73 (100); MS (LCMS, ES+): 254 (18), 253 (100) $[M+H]^+$; HRMS (ES+) *m/z* calculated for $C_{13}H_{21}O_3Si$ $[M+H]^+$ 253.12545, found 253.12520.

***Tert*-butyl 5-(1,3-dioxolan-2-yl)-4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2H)-carboxylate 192**

Prepared according to **GP5** from **190** (53.9 g, 175 mmol). Trimethylsilyl dioxolane **192** was afforded as a dark orange solid (51.8 g, 84%) and used for the following step without further purification; m.p. 113–114 °C; R_f= 0.58 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2958, 2893, 2138, 1693, 1405, 1367, 1331, 1284, 1246, 1205, 1159, 1122, 1045, 980, 935, 836, 757, 714; ^{1}H NMR (400 MHz, $CDCl_3$, 22°C): δ 5.85 (s, 1H), 4.03 –

3.87 (m, 6H), 3.43 (t, *J* = 5.8 Hz, 2H), 2.26 (dt, *J* = 6.4, 3.5 Hz, 2H), 1.42 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, 22°C) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 154.7 (C), 139.2 + 138.2 (C), 121.1 + 120.4 (C), 101.9 (CH), 101.6 (C), 100.1 (C), 79.9 (C), 65.7 (2 × CH_2), 41.0 + 40.5 (CH_2), 39.2 (CH_2), 30.2 (CH_2), 28.5 (3 × CH_3), -0.04 (3 × CH_3); ^{1}H NMR (400 MHz, Tol-d_8, 25°C): δ 6.13 (s, 1H), 4.25 (s, 2H), 3.46 (s, 2H), 3.38 – 3.12 (m, 4H), 2.04 (dt, *J* = 6.0, 3.5 Hz, 2H), 1.41 (s, 9H), 0.16 (s, 9H); ^{1}H NMR (400 MHz, Tol-d_8, 90°C) (two signals with the same intensity were observed for certain protons due to the presence of two major rotamers; in these cases, the two signals are reported in square parenthesis followed by the merged integration in round figure): δ 6.03 (s, 1H), 4.17 – 4.14 (m, 2H), 3.58 – 3.51 (m, 2H), 3.47 – 3.41 (m, 2H), 3.27 (t, *J* = 5.8 Hz, 2H), 2.09 – 2.05 (m, 2H), [1.39(5) (s) superimposed to 1.39(4) (s), 9H], [0.14(2) (s) superimposed to 0.14(1) (s), 9H]; ^{13}C NMR (101 MHz, Tol-d_8, 90°C): δ 154.8 (C), 140.5 (C), 120.9 (C), 103.3 (CH), 102.7 (C), 99.9 (C), 79.4 (C), 65.7 (2 × CH_2), 41.8 (CH_2), 40.5 (CH_2), 30.8 (CH_2), 28.7 (3 × CH_3), 0.1 (3 × CH_3); MS (GCMS, EI+): 295 (21), 294 (39), 222 (18), 178 (37), 73 (100), 57 (31); MS (LCMS, ES+): 374 (24) $[M+Na]^+$, 297 (21), 296 (100), 252 (20); HRMS (ES+) *m/z* calculated for $C_{18}H_{30}NO_4Si$ $[M+H]^+$ 352.19386, found 352.19330; calculated for $C_{14}H_{22}NO_4Si$ [M-*tert*-butyl+H]$^+$ 296.13126, found 296.13077; calculated for $C_{13}H_{22}NO_2Si$ [M-Boc+H]$^+$ 252.14143, found 252.14098; HRMS (EI+) *m/z* calculated for $C_{18}H_{29}NO_4Si$ $[M]^+$ 351.1866, found 351.1864.

Benzyl 5-(1,3-dioxolan-2-yl)-4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2H)-carboxylate 193

Prepared according to **GP5** from **191** (10.5 g, 30.7 mmol). Trimethylsilyl dioxolane **193** was afforded as a dark orange oil (10.5 g, 89%) and used for the following step without further purification; R_f= 0.5 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2958, 2890, 2144, 1702, 1498, 1427, 1386, 1362, 1330, 1288, 1248, 1229, 1206, 1159, 1116, 1099, 1046, 1029, 998, 983, 967, 942, 933, 841, 759, 735, 715, 697, 647, 622, 604; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.16 (m, 5H), 5.80 (s, 1H), 5.06 (s, 2H), 4.02 (t, *J* = 2.5 Hz, 2H), 3.91 (s, 2H), 3.87 – 3.80 (m, 2H), 3.45 (t, *J* = 5.8 Hz, 2H), 2.22 (s, 2H), 0.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.3 + 155.0 (C), 138.7 + 137.7 (C), 136.7 (C), 128.4 (2 × CH), 127.9 (2 × CH) superimposed to 127.8 (CH), 121.0 + 120.3 (C), 101.7 (CH), 101.3 (C), 100.2 + 100.1 (C), 67.0 (CH_2), 65.5 (2 × CH_2), 40.9 + 40.7 (CH_2), 40.1 + 39.8 (CH_2), 30.0 + 29.8 (CH_2), -0.2 (3×CH_3); HRMS (ES+) *m/z* calculated for $C_{21}H_{27}NO_4NaSi$ [M+Na] 408.1607, found 408.1622; HRMS (EI+) *m/z* calculated for $C_{21}H_{28}NO_4Si$ [M+H] 385.1709, found 385.1708.

5-(1,3-Dioxolan-2-yl)-1-((4-nitrophenyl)sulfonyl)-4-((trimethylsilyl)ethynyl)-1,2,3,6-tetrahydropyridine 194

Prepared according to **GP5** from **108** (3.79 g, 9.66 mmol). Recrystallization in MeOH afforded trimethylsilyl dioxolane **194** as a white solid (3.42 g, 81%); m.p. 113–114 °C; R_f= 0.38 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2959, 2886, 2142, 1605, 1523, 1465, 1441, 1399, 1352, 1309, 1250, 1205, 1169, 1118, 1075, 1048, 1006, 981,

935, 899, 839, 788, 759, 734, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 9.0 Hz, 2H), 5.76 (s, 1H), 4.05 – 3.98 (m, 2H), 3.97 – 3.90 (m, 2H), 3.84 (t, *J* = 2.4 Hz, 2H), 3.29 (t, *J* = 5.8 Hz, 2H), 2.29 (td, *J* = 5.7, 2.9 Hz, 2H), 0.15 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (C), 143.3 (C), 136.2 (C), 128.8 (2 × CH), 124.5 (2 × CH), 120.8 (C), 108.4 (C, invisible at ^{13}C, identified at HMBC), 101.5 (CH), 100.3 (C), 65.7 (2 × CH_2), 42.5 (CH_2) superimposed to 42.4 (CH_2), 29.7 (CH_2), -0.1 (3 × CH_3); MS (UPLC, ES+): 459 (18) $[M+Na]^+$, 438 (27), 437 (100) $[M+H]^+$; HRMS (ES+) *m/z* calculated for $C_{19}H_{24}N_2NaO_6SSi$ $[M+Na]^+$ 459.1017, found 459.1015.

8.2.7 Preparation of Terminal Alkynes

5-(1,3-Dioxolan-2-yl)-4-ethynyl-3,6-dihydro-2H-pyran 67

Prepared according to **GP6** from **65** (23.0 g, 91.1 mmol). Terminal alkyne **67** was afforded as a red solid (14.8 g, 90%) and used for the following step without further purification; m.p. 53–54 °C; R_f= 0.3 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3243, 2954, 2883, 1837, 1702, 1653, 1471, 1431, 1382, 1339, 1288, 1260, 1227, 1205, 1145, 1121, 1093, 1070, 1035, 992, 932, 844, 754; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (s, 1H), 4.28 – 4.21 (m, 2H), 4.02 – 3.89 (m, 4H), 3.76 (t, *J* = 5.5 Hz, 2H), 3.18 (s, 1H), 2.30 (tt, *J* = 5.5, 2.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.0 (C), 118.9 (C), 101.7 (CH), 82.5 (CH), 80.3 (C), 65.6 (2 × CH_2), 63.8 (CH_2), 63.3 (CH_2), 29.6 (CH_2); MS (GCMS, EI+): 77 (16), 73 (100), MS (LCMS, ES+): 182 (12), 181 (100) $[M+H]^+$, 130 (16), 83 (19); HRMS (ES+) *m/z* calculated for $C_{10}H_{13}O_3$ $[M+H]^+$ 181.08592, found 181.08597.

***Tert*-butyl 5-(1,3-dioxolan-2-yl)-4-ethynyl-3,6-dihydropyridine-1(2H)-carboxylate 195**

Prepared according to **GP6** from **192** (51.8 g, 147 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-50:50] afforded

terminal alkyne **195** as a light yellow solid (36.2 g, 88%); m.p. 107–108 °C; R_f= 0.35 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3280, 3255, 2974, 2932, 2888, 1689, 1416, 1366, 1331, 1284, 1239, 1162, 1117, 1091, 1041, 982, 963, 932, 900, 860, 767, 734, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (s, 1H), 4.07 – 3.98 (m, 4H), 3.98 – 3.91 (m, 2H), 3.48 (t, *J* = 5.8 Hz, 2H), 3.20 (s, 1H), 2.31 (td, *J* = 5.8, 3.0 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 154.8 (C), 140.2 + 139.2 (C), 120.1 + 119.4 (C), 101.8 (CH), 82.9 (CH), 80.5 (C), 80.0 (C), 65.7 (2 × CH_2), 41.0 + 40.5 (CH_2), 39.2 (CH_2), 30.1 (CH_2), 28.5 (3 × CH_3); MS (LCMS, ES+): 224 (100), 180 (17); HRMS (ES+) *m/z* calculated for $C_{15}H_{21}NO_4Na$ [M+Na] 302.1368, found 302.1374; HRMS (ES+) *m/z* calculated for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.15433, found 280.15411; calculated for $C_{11}H_{14}NO_4$ [M-*tert*-butyl+H]$^+$ 224.09173, found 224.09161; calculated for $C_{10}H_{14}NO_2$ [M-Boc+H]$^+$ 180.10191, found 180.10175.

Benzyl 5-(1,3-dioxolan-2-yl)-4-ethynyl-3,6-dihydropyridine-1(2H)-carboxylate 196

Prepared according to **GP6** from **193** (10.5 g, 27.2 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-50:50] afforded terminal alkyne **196** as a dark orange oil (6.39 g, 75%); R_f= 0.33 (Heptane:EtOAc 7:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3279, 3258, 2953, 2891, 1698, 1624, 1498, 1427, 1392, 1361, 1331, 1287, 1230, 1209, 1146, 1113, 1094, 1044, 1029, 997, 982, 966, 942, 861, 764, 753, 736, 697, 675, 650, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.17 (m, 5H), 5.79 (s, 1H), 5.06 (s, 2H), 4.03 (d, *J* = 2.6 Hz, 2H), 3.91 (s, 2H), 3.86 – 3.80 (m, 2H), 3.47 (t, *J* = 5.7 Hz, 2H), 3.15 (s, 1H), 2.28 – 2.19 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks

corresponding to the same carbon atom are reported separated by a plus sign): δ 155.4 + 155.1 (C), 139.6 + 138.7 (C), 136.7 (C), 128.5 (2 × CH), 128.0 (2 × CH) superimposed to 127.9 (CH), 120.1 + 119.4 (C), 101.5 (CH), 83.1 + 83.0 (CH), 80.2 (C), 67.1 (CH_2), 65.5 (2 × CH_2), 41.0 + 40.8 (CH_2), 40.1 + 39.8 (CH_2), 29.9 + 29.7 (CH_2); HRMS (ASAP+) *m/z* calculated for $C_{18}H_{20}NO_4$ [M+H] 314.1392, found 314.1397; HRMS (EI+) *m/z* calculated for $C_{18}H_{19}NO_4$ [M] 313.1314, found 313.1313.

5-(1,3-Dioxolan-2-yl)-4-ethynyl-1-((4-nitrophenyl)sulfonyl)-1,2,3,6-tetrahydropyridine 197

Prepared according to **GP6** from **194** (3.42 g, 7.83 mmol). Recrystallization in MeOH afforded **197** as a white solid (1.97 g, 69%); m.p. 153–155 °C; R_f= 0.3 (Heptane:EtOAc 7:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3259, 2893, 1608, 1533, 1455, 1433, 1398, 1342, 1308, 1256, 1209, 1161, 1143, 1124, 1084, 1014, 1006, 959, 980, 931, 851, 70, 744, 664, 625, 608; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 – 8.32 (m, 2H), 8.03 – 7.93 (m, 2H), 5.76 (s, 1H), 4.07 – 3.98 (m, 2H), 3.97 – 3.89 (m, 2H), 3.88 – 3.82 (m, 2H), 3.31 (t, *J* = 5.9 Hz, 2H), 3.19 (s, 1H), 2.31 (tt, *J* = 5.8, 2.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (C), 143.2 (C), 137.4 (C), 128.8 (2 × CH), 124.5 (2 × CH), 119.8 (C), 101.3 (CH), 83.9 (CH), 79.4 (C), 65.7 (2 × CH_2), 42.5 (CH_2) superimposed to 42.3 (CH_2), 29.5 (CH_2); HRMS (ES+) *m/z* calculated for $C_{16}H_{17}N_2O_6S$ [M+H] 365.0807, found 365.0807.

2-(2-Ethynylphenyl)-1,3-dioxolane 129

This terminal alkyne was provided by ex Davies group member Dr Holly V. Adcock.

8.2.8 Preparation of Haloalkynes

4-(Bromoethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran 69

Prepared according to **GP7** from **67** (15.1 g, 60.0 mmol) at T= rt or **65** (10.8 g, 60.0 mmol) at T= 0 °C using PhMe+0.5% TEA as eluent for filtration. Bromoalkyne **69** was afforded as a pale yellow solid (85% by qNMR from **67**; 86% qNMR from **65**) and immediately used for the following step without further purification; R_f= 0.48 (Heptane:EtOAc 7:3) [UV]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (s, 1H), 4.23 (t, *J* = 2.6 Hz, 2H), 4.00 – 3.90 (m, 4H), 3.76 (t, *J* = 5.5 Hz, 2H), 2.29 (tt, *J* = 5.4, 2.6 Hz, 2H); ^{1}H NMR (300 MHz, Acetone-d_6): δ 5.70 (s, 1H), 4.15 – 4.11 (m, 2H), 4.00 – 3.93 (m, 2H), 3.92 – 3.86 (m, 2H), 3.70 (t, *J* = 5.5 Hz, 2H), 2.24 (tt, *J* = 5.5, 2.6 Hz, 2H); MS (LCMS, ES+): 261 (100), 259 (100) $[M]^+$, 228 (20), 226 (21), 219 (72), 217 (21).

***Tert*-butyl 4-(bromoethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 198**

Prepared according to **GP7** from **195** (21.1 g, 60.0 mmol) at T= rt or **192** (16.8 g, 60.0 mmol) at T= 0 °C using PhMe+0.15% TEA as eluent for filtration. Bromoalkyne **198** was afforded as a yellow oil (87% by qNMR from **195**; 66% by qNMR from **192**) and immediately used for the following step without further purification; R_f=0.5 (Hexane:EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (s, 1H), 4.04 – 3.98 (m, 4H), 3.97 – 3.91 (m, 2H), 3.47 (t, *J* = 5.8 Hz, 2H), 2.29 (td, *J* = 6.5, 5.9, 3.1 Hz, 2H), 1.46 (s, 9H); ^{1}H NMR (400 MHz, Acetone-d_6): δ 5.75 (s, 1H), 4.05 – 3.99 (m, 2H), 3.97 (t, *J* = 2.5 Hz, 2H), 3.95 – 3.90 (m, 2H), 3.47 (t, *J* = 5.7 Hz, 2H), 2.27 (tt, *J* = 5.6, 2.6 Hz, 2H), 1.44 (s, 9H); MS (LCMS, ES+): 304 (100), 302 (96), 274 (41), 272 (42).

Benzyl 4-(bromoethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 199

Prepared according to **GP7** from **196** (1.57 g, 5.00 mmol) at T= 0 °C using PhMe+0.15% TEA as eluent for filtration. Bromoalkyne **199** was afforded as a yellow oil (75% by qNMR) and immediately used for the following step without further purification; R_f= 0.38 (Heptane:EtOAc 7:3) [UV]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.20 (m, 5H), 5.75 (s, 1H), 5.08 (s, 2H), 4.02 (t, *J* = 2.5 Hz, 2H), 3.95 (td, *J* = 7.7, 5.5 Hz, 2H), 3.91 – 3.82 (m, 2H), 3.49 (t, *J* = 5.8 Hz, 2H), 2.25 (s, 2H).

4-(Bromoethynyl)-5-(1,3-dioxolan-2-yl)-1-((4-nitrophenyl)sulfonyl)-1,2,3,6-tetrahydropyridine 200

Prepared according to **GP7** from **197** (364 mg, 1.00 mmol) at T= 0°C using PhMe+0.15% TEA as eluent for filtration. Bromoalkyne **200** was afforded as a white solid (90% by qNMR) and immediately used for the following step without further purification; R_f= 0.35 (Heptane:EtOAc 7:3) [UV]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 8.7, 1.7 Hz, 2H), 7.95 – 7.88 (m, 2H), 5.64 (s, 1H), 4.01 – 3.92 (m, 2H), 3.92 – 3.82 (m, 2H), 3.81 – 3.72 (m, 2H),3.24 (t, *J* = 5.9 Hz, 2H), 2.24 (tt, *J* = 5.7, 2.5 Hz, 2H).

2-(2-(Bromoethynyl)phenyl)-1,3-dioxolane 130

Prepared according to **GP7** from **129** (174.2 g, 1.00 mmol) at T= rt using PhMe+0.5% TEA as eluent for filtration. Bromoalkyne **130** was afforded as a colourless oil (245.5 mg, 97%); R_f= 0.5 (Heptane:EtOAc 4:1) [UV]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.38 (app. td, *J* = 7.6, 1.7 Hz, 1H), 7.31 (app. td, *J* = 7.4, 1.6 Hz, 1H), 6.14 (s, 1H), 4.23 – 4.03 (m, 4H).

4-(Chloroethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran 138

Prepared according to a procedure reported by Gulia *et al.*[257] Terminal alkyne **67** (180.0 mg, 1.0 mmol, 1.0 eq.) was dissolved in CH_3CN (10.0 mL, 0.1 M). NCS (267 mg, 2.0 mmol, 2.0 eq.), $AgNO_3$ (51.0 mg, 0.3 mmol, 0.3 eq.) and TBAF (157 mg, 0.6 mmol, 0.6 eq.) were added and the mixture was stirred for 1h. The solvent was removed under reduced pressure and the crude residue was filtered on a silica pad (1 cm) eluting with EtOAc. Flash column chromatography afforded chloroalkyne **138** as a yellow oil. (77.3 mg, 36%) and immediately used for the following step without further purification; R_f= 0.45 (Heptane:EtOAc 7:3) [UV]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (s, 1H), 4.22 (t, *J* = 2.6 Hz, 2H), 3.99 – 3.89 (m, 4H), 3.75 (t, *J* = 5.5 Hz, 2H), 2.26 (tt, *J* = 5.5, 2.6 Hz, 2H). Unstable compound.

8.2.9 Preparation of Sulfonamides

***N*-allylmethanesulfonamide 123**

Prepared according to **GP8B** from mesyl chloride (85.1 mL, 1.10 mol). Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **123** as a pale yellow oil (123 g, 91%); R_f= 0.23 (Heptane:EtOAc 7:3) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3283, 1645, 1412, 1306, 1139, 1062, 967, 837, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (ddt, *J* = 17.4, 10.0, 1.4 Hz, 1H), 5.30 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.24 – 5.18 (m, 1H), 4.70 (s, 1H), 3.79 – 3.73 (m, 2H), 2.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6 (CH), 118.0 (CH_2), 45.8 (CH_2), 38.2 (CH_3); MS (GCMS, EI+): 120 (18) $[M-CH_3]^+$, 79 (16) $[CH_3SO_2]^+$, 57 (13), 56 (100); MS (LCMS, MS+): *m/z* 153 (100) $[M+H_2O]^+$; MS (LCMS, MS-): *m/z* 134 (100) $[M-H^+]^-$. Data matches that reported by O'Sullivan *et al.*[258]

***N*-allylcyclopropanesulfonamide 124**

Prepared according to **GP8A** from cyclopropyl chloride (2.24 mL, 22.0 mmol). Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **124** as a pale yellow oil (3.09 g, 96%); R_f= 0.28 (Heptane:EtOAc 7:3) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3281, 1730, 1646, 1422, 1374, 1321, 1300, 1246, 1191, 1139, 1063, 1043, 994, 921, 889, 838, 785, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.2, 10.1, 5.7 Hz, 1H), 5.29 – 4.98 (m, 3H), 3.71 – 3.59 (m, 2H), 2.41 – 2.31 (m, 1H), 1.06 – 0.96 (m, 2H), 0.96 – 0.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.9 (CH), 116.9 (CH_2), 45.5 (CH_2), 30.0 (CH), 5.2 (2 × CH_2); HRMS (ES+) *m/z* calculated for $C_6H_{11}NO_2SNa$ $[M+Na]^+$ 184.04027, found 184.04041; calculated for $C_6H_{12}NO_2S$ $[M+H]^+$ 162.05833, found 162.05843.

***N*-allyl-4-methoxybenzenesulfonamide 125**

Prepared according to **GP8A** from 4-metoxybenzenesulfonyl chloride (558 mg, 3.44 mmol). Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **125** as a white solid (558 mg, 78%); m.p. 47-48 °C; R_f= 0.38 (Heptane:EtOAc 7:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3262, 3022, 2910, 2845, 1899, 1644, 1596, 1578, 1495, 1462, 1431, 1300, 1324, 1260, 1181, 1150, 1112, 1095, 1057, 1014, 935, 857, 801, 720, 667, 627; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.77 (m, 2H), 7.00 – 6.95 (m, 2H), 5.72 (ddt, *J* = 16.4, 11.0, 5.8 Hz, 1H), 5.16 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 9.6 Hz, 1H), 4.55 (s, 1H), 3.87 (s, 3H), 3.57 (app. td, *J* = 6.1, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1 (C), 133.2 (CH), 131.7 (C), 129.4 (2 × CH), 117.8 (CH_2), 114.4 (2 × CH), 55.8 (CH_3), 45.9 (CH_2); MS (GCMS, EI+): 227 (37) $[M]^+$, 171 (100), 155 (27), 135 (17), 123 (53), 108 (70), 107 (77), 92 (42), 77 (62), 64 (23), 63 (16), 56 (31); HRMS (ASAP+) *m/z* calculated for $C_{10}H_{14}NO_3S$ [M+H] 228.0694, found 228.0700.

***N*-allyl-4-nitrobenzenesulfonamide 126**

Prepared according to **GP8B** from 4-nitrobenzenesulfonyl chloride (244 g, 1.10 mol). Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **126** as a light yellow solid (206 g, 85%); m.p. 103-104 °C; R_f= 0.4 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3258, 3103, 1701, 1606, 1522, 1434, 1345, 1158, 1087, 1046, 1002, 942, 851, 736, 680, 607; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 – 8.33 (m, 2H), 8.10 – 8.02 (m, 2H), 5.71 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.72 (app. t, *J* = 6.2 Hz, 1H), 3.72 – 3.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (C), 146.2 (C), 132.5 (CH), 130.0 (CH), 128.5 (2 × CH), 124.6 (2 × CH), 118.6 (CH_2), 46.0 (CH_2); MS (GCMS, MS+): *m/z* 210 (19) [M-C_3H_6]$^+$, 106 (45), 91 (100). MS (LCMS, MS+): *m/z* 243 (100) [M+H]$^+$, 142 (31), 100 (42); MS (LCMS, MS-): *m/z* 241 [M-H$^+$]$^-$. Data matches that reported by Pickford *et al.*[256] and Torres *et al.*[259]

***N*-allyl-3,5-dimethylisoxazole-4-sulfonamide 127**

Prepared according to **GP8A** from 3,5-dimethylisoxazole-4-sulfonyl chloride (430 mg, 2.20 mmol). Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **127** as a colourless oil (398 mg, 91%); R_f= 0.33 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3292, 1594, 1497, 1439, 1408, 1370, 1327, 1263, 1177, 1120, 1067, 1029, 994, 924, 881, 834, 756, 737, 685; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.22 (app. dq, *J* = 17.0, 1.3 Hz, 1H), 5.17 (app. dq, *J* = 10.1, 1.3 Hz, 1H), 4.69 (t, *J* = 6.1 Hz, 1H), 3.63 (app. tt, *J* = 6.0, 1.5 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C), 157.7 (C), 132.7 (CH), 118.4 (CH_2), 116.3 (C), 45.5 (CH_2), 12.8 (CH_3), 10.9 (CH_3); MS (GCMS, EI+): 160 (100), 137 (12), 124 (20), 118 (69), 109 (15), 102 (13), 97 (13), 82 (20), 56 (65); HRMS (ES+) *m/z* calculated for $C_8H_{13}N_2O_3S$ [M+H]$^+$ 217.06414, found 217.06395.

***N*-allylpiperidine-1-sulfonamide 128**

Prepared according to **GP8A** from piperidine-1-sulfonyl chloride (404 mg, 2.20 mmol). Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **131** as a white solid (335 mg, 82%); m.p. 43-44 °C; R_f= 0.56 (Heptane:EtOAc 7:3) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}3291, 3082, 3012, 2916, 2866, 2849, 1646, 1442, 1390, 1320, 1261, 1212, 1156, 1143, 1104, 1027, 995, 982, 924, 845, 716, 675, 619; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddt, *J* = 16.2, 10.2, 5.8 Hz, 1H), 5.27 – 5.20 (m, 1H), 5.14 (app. dq, *J* = 10.1, 1.3 Hz, 1H), 4.52 (s, 1H), 3.63 (t, *J* = 4.3 Hz, 2H), 3.18 – 3.12 (m, 4H), 1.63 – 1.57 (m, 4H), 1.55 – 1.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.9 (CH), 117.3 (CH_2), 46.9 (2 × CH_2), 46.1 (CH_2), 25.4 (2 × CH_2), 23.8 (CH_2); MS (GCMS, MS+): *m/z* 203 (10) $[M-H]^+$, 148 (8), 84 (100), 83 (58), 56 (26), 55 (30); MS (LCMS, MS+): *m/z* 206 (18), 205 (100), 193 (11); MS (LCMS, MS-): *m/z* 203 (100); HRMS (ES+) *m/z* calculated for $C_8H_{17}N_2O_2S$ $[M+H]^+$ 205.10053, found 205.10040.

***N*-(but-3-en-1-yl)methanesulfonamide 213**

3-Butene-1-amine (0.915 mL, 10.0 mmol) was added to CH_2Cl_2 (10.0 mL, 1.0 M) and the solution was cooled down to 0 °C. Mesyl chloride (851 µL, 11.0 mmol) was added dropwise, followed by triethylamine (1.53 mL, 11.0 mmol) dropwise. The mixture was allowed to stir at rt for 30 min before adding water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as an orange oil. Flash column chromatography [Heptane:EtOAc 4:1] afforded sulfonamide **213** as a colourless oil (1.06 g, 71%); R_f= 0.28 (Heptane:EtOAc 7:3) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3281, 2935, 1641, 1433, 1411, 1307, 1138, 1073, 970, 916, 864, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (ddt, *J* = 17.2, 10.5, 6.9 Hz, 1H), 5.22 – 5.10 (m, 2H), 4.40 (s, 1H), 3.21 (q, *J* = 6.4 Hz, 2H),

2.96 (s, 3H), 2.38 – 2.30 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3 (CH), 118.6 (CH_2), 42.3 (CH_2), 40.6 (CH_3), 34.4 (CH_2); MS (LCMS, MS+): *m/z* 150 (100) $[M+H]^+$, 108 (21); MS (LCMS, MS): *m/z* 148 (21) $[M-H]^-$, 113 (100). Data matches that reported by Carballo *et al.*[260]

8.2.10 Preparation of Dichlorovinyl Sulfonamide 141

(Z)-*N*-allyl-*N*-(1,2-dichlorovinyl)methanesulfonamide 141

Prepared according to a procedure reported by Mansfield *et al*.[126] Sulfonamide **126** (135 mg, 1.00 mmol, 1.0 eq.) was dissolved in DMF (1.4 mL, 0.7 M). TCE (199 µL, 1.10 mmol, 1.1 eq.) was added followed by Cs_2CO_3 (977 mg, 3.0 mmol, 3.0 eq.) and the mixture was stirred at 50 °C for 2 h. The reaction was cooled down to rt and water (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a black oil. Flash column chromatography [Heptane:EtOAc 4:1] afforded dichlorovinylsulfonamide **144** as a light yellow oil (173 mg, 75%); R_f= 0.48 (Heptane:EtOAc 7:3) [$KMnO_4$]; ^1H NMR (400 MHz, $CDCl_3$): δ 5.94 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.42 (app. dq, *J* = 17.2, 1.3 Hz, 1H), 5.35 (app. dq, *J* = 10.1, 1.0 Hz, 1H), 4.35 (app. dt, *J* = 6.6, 1.1 Hz, 2H), 3.28 (s, 4H). Unstable compound.

8.2.11 Preparation of Ynamides

_N_-((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran-4-yl)ethynyl)-N-allylmethanesulfonamide 143

Prepared according to **GP9** using freshly prepared bromoalkyne **69** (from **67**, 10.8 g, 60.0 mmol, **GP7**) and sulfonamide **123** (8.11 g, 60.0 mmol). Flash column chromatography [Toluene:MeOH:TEA 98.5:0.5:1] afforded ynamide **143** as a pale yellow oil (9.59 g, 2 steps 51%); R_f= 0.45 (Toluene:MeOH 24:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2930, 2884, 2226, 1646, 1464, 1424, 1353, 1244, 1162, 1110, 1074, 1038, 995, 962, 933, 837, 781, 733, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.71 (s, 1H), 5.43 – 5.30 (m, 2H), 4.23 (t, *J* = 2.5 Hz, 2H), 4.08 (dt, *J* = 6.4, 1.3 Hz, 2H), 3.98 – 3.86 (m, 4H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.08 (s, 3H), 2.26 (tt, *J* = 5.4, 2.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2 (C), 130.9 (CH), 120.8 (CH_2), 118.9 (C), 102.0 (CH), 86.7 (C), 68.9 (C), 65.5 (2 × CH_2), 63.9 (CH_2), 63.4 (CH_2), 54.3 (CH_2), 39.1 (CH_3), 29.7 (CH_2); MS (LCMS, MS+): *m/z* 315 (18), 314 (100); HRMS (ES+) *m/z* calculated for $C_{14}H_{19}NO_5S$ $[M+H]^+$ 314.10567, found 314.10556.

_N_-((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran-4-yl)ethynyl)-N-allyl-4-methoxybenzenesulfonamide 163

Prepared according to **GP9** using freshly prepared bromoalkyne **69** (from **67**, 901 mg 5.00 mmol, **GP7**) and sulfonamide **125** (1.14 g, 5.0 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded ynamide **163** as a white solid (1.24 g, 2 steps 61%); m.p. 113-114 °C; R_f= 0.45 (Toluene:MeOH 98:2) [UV]; IR: ν_{max} (neat, cm^{-1}) 3526, 2942, 2880, 2845, 1719, 1670, 1594, 1497, 1460, 1416, 1332, 1304, 1258, 1153, 1087, 1021, 919, 834, 803, 729, 669; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.82 (m, 2H), 7.03 – 6.99 (m, 2H), 5.78 – 5.65 (m, 2H), 5.27 – 5.19 (m,

2H), 4.23 (t, *J* = 2.5 Hz, 2H), 3.98 (tt, *J* = 4.9, 2.2 Hz, 4H), 3.89 (d, *J* = 5.4 Hz, 5H), 3.75 (t, *J* = 5.5 Hz, 2H), 2.22 (tt, *J* = 5.4, 2.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9 (C), 136.3 (C), 130.9 (CH), 130.0 (2 × CH), 129.1 (C), 120.2 (CH_2), 119.2 (C), 114.5 (2 × CH), 102.0 (CH), 87.5 (C), 68.6 (C), 65.4 (2 × CH_2), 63.8 (CH_2), 63.3 (CH_2), 55.8 (CH_3), 54.2 (CH_2), 29.7 (CH_2); MS (LCMS, MS+): *m/z* 407 (22), 406 (100); HRMS (ES+) *m/z* calculated for $C_{20}H_{24}NO_6S$ $[M+H]^+$ 406.13189, found 406.13112.

_N_-((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran-4-yl)ethynyl)-N-allyl-4-nitrobenzenesulfonamide 139

Prepared according to **GP9** using freshly prepared bromoalkyne **69** (from **67**, 10.8 g, 60.0 mmol, **GP7**) and sulfonamide **126** (14.5 g, 60.0 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded ynamide **139** as a yellow solid (13.9 g, 2 steps 55%); m.p. 127-128°C; R_f= 0.5 (Toluene:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3110, 2953, 2889, 2852, 2229, 1704, 1676, 1654, 1606, 1533, 1473, 1426, 1366, 1351, 1306, 1259, 1226, 1172, 1102, 1072, 1038, 992, 971, 932, 899, 836, 764, 734, 680; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 5.74 – 5.65 (m, 2H), 5.29 – 5.22 (m, 2H), 4.23 (t, *J* = 2.5 Hz, 2H), 4.05 (dt, *J* = 6.4, 1.2 Hz, 2H), 4.01 – 3.95 (m, 2H), 3.92 – 3.87 (m, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 2.21 (tt, *J* = 5.4, 2.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.8 (C), 143.0 (C), 138.2 (C), 130.1 (CH), 129.2 (2 × CH), 124.6 (2 × CH), 121.1 (CH_2), 118.5 (C), 102.0 (CH), 85.9 (C), 69.2 (C), 65.6 (2 × CH_2), 63.8 (CH_2), 63.4 (CH_2), 54.8 (CH_2), 29.6 (CH_2); MS (LCMS, MS+): *m/z* 443 (38), 422 (23), 421 (100); HRMS (ES+) *m/z* calculated for $C_{19}H_{21}N_2O_7S$ $[M+H]^+$ 421.10640, found 421.10608.

***N*-((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran-4-yl)ethynyl)-N-allyl-3,5-dimethylisoxazole-4-sulfonamide 161**

Prepared according to **GP9** using freshly prepared bromoalkyne **69** (from **67**, 901 mg, 5.00 mmol, **GP7**) and sulfonamide **127** (11.1 g, 5.00 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded ynamide **161** as a pale yellow oil (1.16 g, 2 steps 59%); R_f= 0.4 (Toluene:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2935, 2883, 2228, 1648, 1586, 1494, 1437, 1406, 1378, 1355, 1260, 1187, 1119, 1074, 1037, 995, 933, 836, 757, 680; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H), 5.49 (s, 1H), 5.29 – 5.20 (m, 2H), 4.13 (t, *J* = 2.5 Hz, 2H), 4.02 (dt, *J* = 6.3, 1.3 Hz, 2H), 3.90 – 3.84 (m, 2H), 3.83 – 3.76 (m, 2H), 3.66 (t, *J* = 5.5 Hz, 2H), 2.60 (s, 3H), 2.36 (s, 3H), 2.13 (tt, *J* = 5.4, 2.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 183.0 (C), 165.6 (C), 145.9 (C), 138.6 (CH), 128.4 (CH_2), 126.4 (C), 122.8 (C), 109.6 (CH), 93.6 (C), 77.2 (C), 73.3 (2 × CH_2), 71.6 (CH_2), 71.1 (CH_2), 61.8 (CH_2), 37.6 (CH_2), 20.9 (CH_3), 19.1 (CH_3); MS (LCMS, ES+): *m/z* 396 (18), 395 (100); HRMS (MS+) *m/z* calculated for $C_{18}H_{23}N_2O_6S$ $[M+H]^+$ 397.12713, found 397.12631.

***N*-((5-(1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyran-4-yl)ethynyl)-N-allyl-3,5-dimethylisoxazole-4-sulfonamide 162**

Prepared according to **GP9** using freshly prepared bromoalkyne **69** (from **67**, 901 mg 5.00 mmol, **GP7**) and sulfonamide **128** (1.02 g, 5.00 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded ynamide **162** as a pale yellow oil (1.01 g, 2 steps 53%); R_f= 0.6 (Toluene:MeOH 24:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3294, 2938, 2854, 2223, 1646, 1443, 1377, 1330, 1279, 1246, 1222, 1146, 1110, 1073, 1053, 995, 928, 836, 756, 709, 651; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.71 (s, 1H), 5.36 – 5.26 (m, 2H), 4.22 (t, *J* = 2.6 Hz, 2H), 4.02 (d, *J* = 6.4

Hz, 2H), 3.98 – 3.91 (m, 2H), 3.90 – 3.83 (m, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.37 – 3.30 (m, 4H), 2.23 (tt, *J* = 5.4, 2.5 Hz, 2H), 1.67 – 1.53 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.8 (C), 131.8 (CH), 119.9 (CH_2), 119.4 (C), 102.1 (CH), 88.5 (C), 68.1 (C), 65.5 (2 × CH_2), 63.9 (CH_2), 63.4 (CH_2), 55.6 (CH_2), 48.0 (2 × CH_2), 29.9 (CH_2), 25.5 (2 × CH_2), 23.7 (CH_2); MS (LCMS, MS+): *m/z* 384 (18), 383 (100); HRMS (ES+) *m/z* calculated for $C_{18}H_{27}N_2O_5S$ [M+H] 383.1635, found 383.1629.

***Tert*-butyl 4-((N-allylmethylsulfonamido)ethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 201**

Prepared according to **GP9** using freshly prepared bromoalkyne **198** (from **195**, 16.8 g, 60.0 mmol, **GP7**) and sulfonamide **123** (8.11 g, 60.0 mmol). Flash column chromatography [Toluene:MeOH:TEA 98.5:0.5:1] afforded ynamide **201** as a pale yellow oil (13.1 g, 2 steps 53%); R_f= 0.5 (Toluene:MeOH 24:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2974, 2929, 2887, 2228, 1689, 1454, 1416, 1363, 1285, 1239, 1161, 1105, 1042, 960, 932, 859, 829, 772, 736, 688; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.77 (s, 1H), 5.39 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.36 – 5.33 (m, 1H), 4.08 (s, 2H), 4.05 – 3.97 (m, 4H), 3.91 (d, *J* = 6.3 Hz, 2H), 3.48 (s, 2H), 3.08 (s, 3H), 2.27 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 154.8 (br, C), 136.4 (C, invisible at ^{13}C, identified at HMBC), 130.9 (CH), 120.8 (CH_2), 119.9 (C, invisible at ^{13}C, identified at HMBC), 102.2 (CH), 87.1 (C), 80.0 (C), 69.2 (C), 65.7 (2 × CH_2), 54.3 (CH_2), 41.3 + 40.7 (CH_2), 39.3 (br, CH_2) superimposed to 39.2 (CH_3), 30.2 (br, CH_2), 28.6 (3 × CH_3); MS (LCMS, MS+): *m/z* 413 (17), 357 (100); HRMS (ES+) *m/z* calculated for $C_{19}H_{29}N_2O_6S$ $[M+H]^+$ 413.17408, found

413.17331; calculated for $C_{15}H_{21}N_2O_6S$ [M-*tert*-butyl+H]$^+$ 357.11148, found 357.11087; calculated for $C_{14}H_{21}N_2O_4S$ [M-Boc+H]$^+$ 313.12165, found 313.12113.

***Tert*-butyl 4-((N-(but-3-en-1-yl)methylsulfonamido)ethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 214**

Prepared according to **GP9** using freshly prepared bromoalkyne **198** (from **195**, 1.40 g 5.00 mmol, **GP7**) and sulfonamide **213** (746 mg, 5.00 mmol). Flash column chromatography [Toluene:MeOH:TEA 98.5:0.5:1] afforded ynamide **214** as a yellow oil (1.04 g, 2 steps 49%); R_f= 0.55 (Toluene:MeOH 24:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2974, 2930, 2885, 2225, 1689, 1454, 1417, 1362, 1286, 1239, 1161, 1105, 1044, 929, 859, 829, 769, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 – 5.69 (m, 2H), 5.21 – 5.06 (m, 2H), 4.02 – 3.84 (m, 6H), 3.51 (t, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 5.8 Hz, 2H), 3.04 (s, 3H), 2.44 (qd, *J* = 6.9, 3.5 Hz, 2H), 2.26 (td, *J* = 5.9, 3.0 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 154.7 (br, C), 133.6 (CH), 120.2 + 119.4 (br, C), 118.3 (CH_2), 102.1 (CH), 86.9 (C), 79.9 (C), 69.3 (C), 65.5 (2 × CH_2), 50.7 (CH_2), 41.2 (br, CH_2), 40.7 (br, CH_2), 38.62 (CH_3), 32.6 (CH_2), 30.1 (br, CH_2), 28.4 (3 × CH_3), 1C missing; MS (LCMS, MS+): *m/z* 427 (49), 371 (100) [M-*tert*-butyl+H]$^+$, 327 (17) [M-Boc+H]$^+$; HRMS (ES+) *m/z* calculated for $C_{20}H_{30}N_2O_6SNa$ [M+Na] 449.1722, found 449.1718.

Benzyl 4-((N-allylmethylsulfonamido)ethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 202

Prepared according to **GP9** using freshly prepared bromoalkyne **199** (from **196**, 940 mg 3.00 mmol, **GP7**) and sulfonamide **123** (406 mg, 3.00 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded ynamide **202** as a pale yellow oil (670 mg, 2 steps 50%); R_f= 0.4 (Toluene:MeOH 24:1) [UV]; IR: ν_{max} (neat, cm^{-1}2933, 2889, 2229, 1697, 1626, 1498, 1429, 1358, 1328, 1288, 1231, 1204, 1164, 1126, 1104, 1073, 1043, 1029, 892, 962, 933, 911, 854, 800, 782, 765, 756, 729, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 5H), 5.90 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.75 (s, 1H), 5.41 – 5.27 (m, 2H), 5.14 (s, 2H), 4.14 – 4.06 (m, 4H), 3.99 (d, *J* = 6.2 Hz, 2H), 3.94 – 3.87 (m, 2H), 3.55 (t, *J* = 5.7 Hz, 2H), 3.07 (s, 3H), 2.29 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.5 + 155.1 (C), 136.8 (C), 135.8(4) + 134.8(2) (C), 130.8 (CH), 128.5 (2 × CH), 128.0 (2 × CH) superimposed to 127.9 (CH), 120.8 (CH_2), 120.2 + 119.5 (C), 102.0 (CH), 87.3 + 87.1 (C), 69.0 (C), 67.2 (CH_2), 65.5 (2 × CH_2), 54.2 (CH_2), 41.2 + 41.0 (CH_2), 40.3 + 40.0 (CH_2), 39.1 (CH_3), 30.2 + 29.8 (CH_2); HRMS (ES+) *m/z* calculated for $C_{22}H_{27}N_2O_6S$ [M+H] 447.1590, found 447.1597.

Benzyl 4-((N-allylcyclopropanesulfonamido)ethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 203

Prepared according to **GP9** using freshly prepared bromoalkyne **199** (from **196**, 940 mg 3.00 mmol, **GP7**) and sulfonamide **124** (484 mg, 3.00 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded

ynamide **203** as a pale yellow oil (723 mg, 2 steps 51%); R_f= 0.43 (Toluene:MeOH 24:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2890, 2228, 1698, 1498, 1427, 1358, 1288, 1230, 1204, 1157, 1126, 1103, 1072, 1042, 983, 932, 883, 826, 801, 762, 734, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.25 (m, 5H), 5.91 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.75 (s, 1H), 5.40 – 5.26 (m, 2H), 5.13 (s, 2H), 4.14 – 4.05 (m, 4H), 3.99 (d, *J* = 6.0 Hz, 2H), 3.93 – 3.84 (m, 2H), 3.55 (t, *J* = 5.8 Hz, 2H), 2.58 (tt, *J* = 7.9, 4.8 Hz, 1H), 2.28 (s, 2H), 1.34 – 1.27 (m, 2H), 1.12 – 1.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.5 + 155.1 (C), 136.8 (C), 135.0 + 134.0 (C), 131.3 (CH), 128.5 (2 × CH), 128.0 (2 × CH) superimposed to 127.9 (CH), 120.5 + 119.8 (C) superimposed to 120.2 (CH_2), 102.0 (CH), 88.1 + 87.9 (C), 68.2 (C), 67.1 (CH_2), 65.5 (2 × CH_2), 54.4 (CH_2), 41.1 + 40.9 (CH_2), 40.2 + 39.9 (CH_2), 30.1 + 29.8 (CH_2), 30.0 (CH) 5.8 (2 × CH_2); HRMS (ES+) *m/z* calculated for $C_{24}H_{28}N_2O_6SNa$ $[M+Na]^+$ 495.1566, found 495.1569.

Benzyl 4-(((N-allyl-4-nitrophenyl)sulfonamido)ethynyl)-5-(1,3-dioxolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate 204

Prepared according to **GP9** using freshly prepared bromoalkyne **199** (from **196**, 940 mg 3.00 mmol, **GP7**) and sulfonamide **129** (727 mg, 3.00 mmol). Flash column chromatography [Toluene:MeOH:TEA 98:1:1] afforded ynamide **204** as a yellow oil (997 mg, 2 steps 60%); R_f= 0.6 (Toluene:MeOH 24:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2951, 2889, 2231, 1697, 1607, 1531, 1498, 1470, 1428, 1403, 1372, 1348, 1313, 1289, 1230, 1203, 1173, 1127, 1104, 1087, 1041, 1011, 983, 967, 931, 911, 854, 808, 802, 764, 732, 698, 683, 627, 607; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 – 8.38 (m, 2H), 8.13 – 8.08 (m, 2H), 7.39 – 7.29 (m, 5H), 5.75 – 5.64 (m, 2H), 5.29 – 5.22 (m, 2H), 5.15 (s, 2H), 4.10 (t, *J* = 2.4 Hz,

2H), 4.07 – 4.01 (m, 4H), 3.95 – 3.89 (m, 2H), 3.56 (t, *J* = 5.7 Hz, 2H), 2.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 150.7 (C), 142.9 (C), 136.8 + 135.7 (C), 130.1 (CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.4 (C), 128.1 (2 × CH) superimposed to 128.0 (CH), 124.6 (2 × CH), 124.4 (C), 121.1 (CH_2), 119.9 + 119.2 (C), 102.0 (CH), 86.4 (C), 69.3 (C), 67.3 (CH_2), 65.6 (2 × CH_2), 54.7 (CH_2), 41.2 + 41.1 (CH_2), 40.2 + 39.9 (CH_2), 30.1 + 29.8 (CH_2); HRMS (MS+) *m/z* calculated for $C_{27}H_{27}N_3O_8SNa$ $[M+Na]^+$ 576.1417, found 576.1412.

8.2.12 Preparation Gold(III) catalyst 165

Dichloro(2-pyridinecarboxylato)gold 165

The procedure is a modified version of that reported by Annibale *et* al.[261] Potassium gold (III) chloride (5.0 g, 12.9 mmol, 1.0 eq.) was dissolved in water (0.1 M). Picolinic acid (1.59 g, 12.9 mmol, 1.0 eq.) was dissolved in water (0.1M) and the solution was added dropwise to the potassium salt solution while stirring. The mixture was stirred for 3h before filtering the precipitate on a Büchner funnel. The solid was dried over vacuum and P_2O_5 overnight at rt. Gold(III) catalyst **165** was afforded as a yellow solid (3.62, 72%); m.p. 171-172 °C; IR: ν_{max} (neat, cm^{-1}) 3053, 2291, 2108, 1888, 1696, 1604, 1568, 1472, 1434, 1309, 1283, 1260, 1222, 1130, 1101, 1054, 982, 912, 844, 810, 759, 712, 669; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (dd, *J* = 5.9, 1.3 Hz, 1H), 8.53 (td, *J* = 7.7, 1.3 Hz, 1H), 8.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 148.6 (CH), 139.0 (CH), 127.6 (CH), 125.1 (CH).

Note: Keep catalyst away from humidity as it leads to deactivation.

8.2.13 Preparation of Polycycles by Gold-catalysed Polycyclization

***Rac*-(1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,7,8-hexahydro-1H,5H-spiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane] 166**

Prepared according to **GP10** from ynamide **143** (4.95 g, 15.8 mmol) and 3% Au-catalyst loading, conducting the reaction at 70 °C. Filtration on a silica pad eluting with EtOAc followed by recrystallization in EtOH afforded polycycle **166** as a white solid (2.97 g, 60%); m.p. 135–136 °C; R_f= 0.35 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2924, 2888, 2856, 2820, 2300, 2085, 1918, 1685, 1472, 1421, 1384, 1356, 1321, 1270, 1206, 1182, 1142, 1096, 1052, 1010, 969, 945, 903, 859, 819, 750, 675; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 – 4.23 (m, 2H), 4.23 – 4.17 (m, 1H), 4.16 (s, 1H), 4.09 (app. dt, *J* = 15.5, 2.7 Hz, 1H), 4.01 (app. td, *J* = 7.4, 6.5, 4.1 Hz, 1H), 3.96 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.83 – 3.73 (m, 2H), 3.69 (d, *J* = 11.0 Hz, 1H), 2.83 (s, 3H), 1.99 (app. dtt, *J* = 14.0, 5.2, 2.7 Hz, 1H), 1.78 (app. dtt, *J* = 17.0, 5.2, 2.6 Hz, 1H), 1.45 (app. dt, *J* = 9.0, 4.6 Hz, 1H), 1.29 (dd, *J* = 8.3, 6.3 Hz, 1H), 0.74 (dd, *J* = 6.3, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6 (C), 134.5 (C), 72.9 (CH), 66.3 (CH_2), 66.0 (CH_2), 63.7 (CH_2), 62.6 (CH_2), 54.0 (CH_2), 40.4 (C), 37.7 (CH_3), 22.6 (CH_2), 21.1 (CH), 12.4 (CH_2); MS (LCMS, ES+): *m/z* 315 (15), 314 (100); HRMS (MS+) *m/z* calculated for $C_{14}H_{20}NO_5S$ $[M+H]^+$ 314.10567, found 314.10501.

***Rac*-(1aR,3aS,8bS)-3-((4-methoxyphenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-1H,5H-spiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane] 167**

Prepared according to **GP10** from ynamide **160** (682 mg, 3.00 mmol) and 3% Au-catalyst loading, conducting the reaction at 70 °C. Flash

column chromatography [linear gradient Heptane:EtOAc 100:0-70:30] afforded polycycle **167** as a white solid (766 mg, 63%); m.p. 169–170 °C; R_f= 0.4 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2949, 2890, 2841, 1675, 1594, 1495, 1462, 1412, 1382, 1341, 1306, 1258, 1181, 1157, 1095, 1047, 1019, 949, 900, 859, 834, 817, 734, 670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.72 (m, 2H), 7.02 – 6.96 (m, 2H), 4.38 (app. td, *J* = 6.5, 4.0 Hz, 1H), 4.35 – 4.30 (m, 1H), 4.24 (app. dt, *J* = 15.7, 2.5 Hz, 1H), 4.11 – 3.97 (m, 4H), 3.94 – 3.84 (m, 4H),3.81 – 3.69 (m, 2H), 3.63 (d, *J* = 11.5 Hz, 1H), 1.87 (app. dtt, *J* = 16.8, 5.2, 2.7 Hz, 1H), 1.67 (app. dtt, *J* = 17.0, 5.1, 2.5 Hz, 1H), 1.29 – 1.25 (m, 1H), 0.81 (dd, *J* = 8.3, 6.1 Hz, 1H), -0.44 (dd, *J* = 6.2, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.2 (C), 136.9 (C), 134.0 (C), 130.7 (C), 129.4 (2 × CH), 115.0 (C), 114.5 (2 × CH), 74.0 (CH), 66.2 (CH_2) superimposed to 66.1 (CH_2), 63.7 (CH_2), 62.5 (CH_2), 55.8 (CH_3), 54.4 (CH_2), 40.4 (C), 22.6 (CH_2), 19.8 (CH), 11.1 (CH_2); MS (LCMS, ES+): *m/z* 833 (14) $[2M+Na]^+$, 407 (31), 406 (100); HRMS (MS+) *m/z* calculated for $C_{20}H_{24}NO_6S$ $[M+H]^+$ 406.13189, found 406.13105.

***Rac*-(1aR,3aS,8bS)-3-((4-nitrophenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-1H,5H-spiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane] 168**

Prepared according to **GP10** from ynamide **139** (9.00 g, 21.4 mmol) and 3% Au-catalyst loading, conducting the reaction at 80°C. Filtration on a silica pad eluting with EtOAc followed by recrystallization in EtOH afforded polycycle **168** as a light yellow solid (7.20 g, 80%); m.p. 187–188°C; R_f= 0.45 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3100, 3063, 2977, 2949, 2922, 2886, 2842, 1673, 1603, 1525, 1469, 1448, 1427, 1403, 1387, 1348, 1324, 1309, 1293, 1272, 1225, 1208, 1187, 1170, 1141, 1107, 1090, 1043, 1021, 1006, 975, 964, 951, 927, 900, 870, 855, 827, 812, 798, 748, 734, 692, 680; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 – 8.33 (m, 2H), 8.05 – 7.97 (m, 2H), 4.32 (app td, *J* = 6.9, 4.5 Hz, 1H), 4.26

– 4.19 (m, 2H), 4.11 – 4.01 (m, 4H), , 3.93 – 3.86 (m, 1H), 3.81 – 3.69 (m, 2H), 3.63 (d, *J* = 11.5 Hz, 1H), 1.88 (app. dtt, *J* = 14.0, 5.3, 2.7 Hz, 1H), 1.69 (app. ddt, *J* = 17.3, 5.3, 2.7 Hz, 1H), 1.32 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 0.91 (dd, *J* = 8.3, 6.3 Hz, 1H), -0.45 (dd, *J* = 6.3, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (C), 144.5 (C), 136.3 (C), 134.5 (C), 128.4 (2 × CH), 124.6 (2 × CH), 114.8 (C), 74.0 (CH), 66.3 (CH_2) superimposed to 66.2 (CH_2), 63.7 (CH_2), 62.4 (CH_2), 54.5 (CH_2), 40.2 (C), 22.5 (CH_2), 19.5 (CH), 11.3 (CH_2); MS (LCMS, ES+): *m/z* 484 (19), 422 (25), 421 (100); HRMS (MS+) *m/z* calculated for $C_{19}H_{21}N_2O_7S$ $[M+H]^+$ 421.10640, found 421.10629.

***Rac*-(1aR,3aS,8bS)-3-((3,5-dimethylisoxazol-4-yl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-1H,5H-spiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane] 169**

Prepared according to **GP10** from ynamide **161** (1.18 g, 3.00 mmol) and 5% Au-catalyst loading, conducting the reaction at 70 °C. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-70:30] afforded polycycle **169** as a colourless oil (757 mg, 64%); R_f= 0.48 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2962, 2926, 2883, 2828, 2298, 2121, 1996, 1167, 1591, 1466, 1443, 1404, 1372, 1340, 1270, 1228, 1177, 1152, 1127, 1091, 1020, 974, 952, 898, 854, 816, 759, 740, 683; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (app. dt, *J* = 15.6, 2.4 Hz, 1H), 4.09 (s, 1H), 4.08 – 4.04 (m, 2H), 4.04 – 4.00 (m, 1H), 4.00 – 3.92 (m, 2H), 3.83 – 3.75 (m, 2H), 3.75 – 3.67 (m, 2H), 2.64 (s, 3H), 2.41 (s, 3H), 1.99 – 1.90 (m, 1H), 1.73 (app. dtt, *J* = 17.1, 5.2, 2.5 Hz, 1H), 1.37 (app. dt, *J* = 8.7, 4.6 Hz, 1H), 1.14 (dd, *J* = 8.3, 6.3 Hz, 1H), 0.32 (dd, *J* = 6.3, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C), 157.6 (C), 136.3 (C), 134.6 (C), 116.6 (C), 114.9 (C), 72.9 (CH), 66.0 (CH_2) superimposed to 65.9 (CH_2), 63.6 (CH_2), 62.5 (CH_2), 53.9 (CH_2), 40.0 (C), 22.6 (CH_2), 19.4 (CH), 13.1 (CH_3), 11.5(0) (CH_3) superimposed to 11.4(6) (CH_2); MS (LCMS, ES+): *m/z* 396 (14), 395 (100); HRMS (MS+) *m/z* calculated for $C_{18}H_{23}N_2O_6S$ $[M+H]^+$ 395.12713, found 395.12687.

***Rac*-(1aR,3aS,8bS)-3-(piperidin-1-ylsulfonyl)-1a,2,3,3a,7,8-hexahydro-1H,5H-spiro[cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-4,2'-[1,3]dioxolane]] 170**

Prepared according to **GP10** from ynamide **162** (1.21 g, 3.00 mmol) and 3% Au-catalyst loading, conducting the reaction at 70 °C. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-70:30] afforded polycycle **170** as a white solid (851 mg, 70%); m.p. 112–113 °C; R_f= 0.43 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2938, 2892, 2853, 1676, 1452, 1445, 1427, 1412, 1383, 1355, 1336, 1320, 1305, 1275, 1221, 1185, 1161, 1145, 1106, 1092, 1054, 1020, 978, 948, 930, 918, 902, 858, 833, 816, 797, 730, 709, 672, 633, 606; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 – 4.20 (m, 3H), 4.17 (app. td, *J* = 6.4, 5.0 Hz, 1H), 4.07 (app. dt, *J* = 15.5, 2.6 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.82 – 3.72 (m, 3H), 3.61 (d, *J* = 10.6 Hz, 1H), 3.25 – 3.12 (m, 4H), 2.02 – 1.92 (m, 1H), 1.76 (app. dtt, *J* = 17.1, 5.2, 2.5 Hz, 1H), 1.63 – 1.56 (m, 4H), 1.56 – 1.49 (m, 2H), 1.37 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 1.21 (ddd, *J* = 8.4, 6.0, 0.7 Hz, 1H), 0.94 (dd, *J* = 6.0, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7 (C), 134.1 (C), 115.1 (C), 73.9 (CH), 66.4 (CH_2), 65.7 (CH_2), 63.7 (CH_2), 62.6 (CH_2), 53.8 (CH_2), 47.2 (2 × CH_2), 40.2 (C), 25.5 (2 × CH_2), 23.9 (CH_2), 22.6 (CH_2), 20.0 (CH), 12.1 (CH_2); MS (LCMS, ES+): *m/z* 384 (24), 383 (100); HRMS (MS+) *m/z* calculated for $C_{18}H_{26}N_2O_5NaS$ [M+Na] 405.1460, found 405.1461.

***Rac*-tert-butyl (1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,7,8-hexahydro-1H-spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane]-6(5H)-carboxylate 207**

Prepared according to **GP10** from ynamide **201** (10.5 g, 30.0 mmol) and 3% Au-catalyst loading, conducting the reaction at 70 °C. [linear gradient Heptane:EtOAc 100:0-0:100] afforded polycycle **207** as a white solid (6.90 g, 66%); m.p. 206–

207 °C; R_f= 0.4 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2982, 2904, 1679, 1479, 1458, 1401, 1366, 1326, 1280, 1253, 1223, 1183, 1155, 1115, 1056, 1008, 963, 904, 851, 820, 796, 777, 752, 695, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (s, 2H), 4.14 (s, 1H), 4.05 (app. td, *J* = 6.7, 4.4 Hz, 1H), 4.02 – 3.90 (m, 3H), 3.88 – 3.73 (m, 1H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.53 (s, 2H), 2.81 (s, 3H), 1.95 (d, *J* = 17.2 Hz, 1H), 1.76 (app. dtt, *J* = 16.6, 5.4, 2.4 Hz, 1H), 1.45 (s, 10H), 1.31 – 1.25 (m, 1H), 0.71 (app. t, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.2 + 154.9 (C), 137.7 + 137.0 (C), 133.2 + 132.5 (C), 114.8 (C), 80.0 (C), 73.7 (br, CH), 66.3 (CH_2), 66.1 (CH_2), 53.9 (CH_2), 40.5 + 40.3 (br, CH_2) superimposed to 40.2 (C), 39.8 + 39.4 (CH_2), 37.5 (br, CH_3), 28.5 (3 × CH_3), 22.3 (br, CH_2), 20.0 (CH), 12.4 (CH_2); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ 4.13 – 4.03 (m, 3H), 4.00 – 3.93 (m, 1H), 3.88 – 3.78 (m, 2H), 3.73 – 3.64 (m, 2H), 3.61 (d, *J* = 11.1 Hz, 1H), 3.49 – 3.36 (m, 2H), 2.91 (s, 3H), 1.95 – 1.85 (m, 1H), 1.79 (app. ddt, *J* = 17.1, 5.5, 2.8 Hz, 1H), 1.52 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 1.40 (s, 9H), 1.28 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.73 (app. t, *J* = 5.5 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6, 90°C): δ 4.14 – 4.04 (m, 3H), 3.98 – 3.92 (m, 1H), 3.90 – 3.81 (m, 2H), 3.74 – 3.65 (m, 2H), 3.60 (d, *J* = 10.9 Hz, 1H), 3.49 – 3.35 (m, 2H), 2.86 (s, 3H), 1.95 – 1.85 (m, 1H), 1.82 – 1.73 (m, 1H), 1.47 (app. dt, *J* = 8.9, 4.7 Hz, 1H), 1.40 (d, *J* = 1.4 Hz, 9H), 1.28 – 1.24 (m, 1H), 0.74 (dd, *J* = 6.1, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, 23°C) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 154.0 (C), 138.0 + 137.8 (C), 131.5 + 131.1 (C), 114.2 (C), 79.0 (C), 72.9 (CH), 65.5 (CH_2), 65.3 (CH_2), 53.4 (CH_2), 36.4 (CH_3), 28.1 (3 × CH_3), 21.6 (CH_2), 19.6 (CH), 11.9 (CH_2), 3C missing; ^{13}C NMR (101 MHz, DMSO-d_6, 90 °C): δ 153.8 (C), 137.2 (C), 131.3 (C), 114.0 (C), 78.5 (C), 72.5 (CH), 65.1 (CH_2), 64.8 (CH_2), 52.8

(CH_2), 37.0 (CH_3), 27.7 (3 × CH_3), 21.1 (CH_2), 19.2 (CH), 11.4 (CH_2); 3C missing; MS (LCMS, ES+): *m/z* 435 (20) $[M+Na]^+$, 358 (17), 357 (100); HRMS (MS+) *m/z* calculated for $C_{19}H_{29}N_2O_6S$ $[M+H]^+$ 413.17408, found 413.17354; calculated for $C_{15}H_{21}N_2O_6S$ [M-*tert*-butyl+H]$^+$ 357.11148, found 357.11084; calculated for $C_{14}H_{21}N_2O_4S$ [M-Boc+H]$^+$ 313.12165, found 313.12103.

***Rac*- benzyl (1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,7,8-hexahydro-1H-spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane]-6(5H)-carboxylate 208**

Prepared according to **GP10** from ynamide **202** (473 mg, 1.00 mmol) and 3% Au-catalyst loading, conducting the reaction at 70 °C. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded polycycle **208** as a pale yellow oil (303 mg, 64%); R_f= 0.28 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2892, 1695, 1497, 1424, 1328, 1278, 1223, 1151, 1181, 1108, 1059, 1022, 1007, 950, 902, 865, 822, 799, 748, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.20 (m, 5H), 5.07 (s, 2H), 4.22 – 4.10 (m, 2H), 4.08 – 3.93 (m, 3H), 3.91 – 3.78 (m, 3H), 3.60 (d, *J* = 11.1 Hz, 1H), 3.58 – 3.47 (m, 2H), 2.74 (s, 3H), 1.88 (app. d, *J* = 15.0 Hz, 1H), 1.72 (app. d, *J* = 15.6 Hz, 1H), 1.41 – 1.31 (m, 1H), 1.30 – 1.08 (m, 1H), 0.65 (app. t, *J* = 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.8 + 155.4 (C), 137.7 + 137.0 (C), 136.7 (C), 132.8 + 132.1 (C), 128.5 (2 × CH), 128.1 (CH), 128.0 (2 × CH), 114.6 (C), 73.6 + 73.4 (C), 67.2 (CH_2), 66.2 (CH_2), 66.0 (CH_2), 53.8 (CH_2), 40.3 (CH_2) superimposed to 40.1 (CH_2), 37.7 + 37.4 (CH_3), 31.9 + 29.0 (C), 22.3 + 20.0 (CH_2), 14.2 (CH), 12.3 (CH_2); HRMS (MS+) *m/z* calculated for $C_{22}H_{26}N_2O_6NaS$ [M+Na] 469.1409, found 469.1411.

***Rac*- benzyl (1aR,3aS,8bS)-3-(cyclopropylsulfonyl)-1a,2,3,3a,7,8-hexahydro-1H-spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane]-6(5H)-carboxylate 209**

Prepared according to **GP10** from ynamide **203** (473 mg, 1.00 mmol) and 3% Au-catalyst loading, conducting the reaction at 70 °C. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded polycycle **209** as a colourless oil (369 mg, 78%); R_f= 0.3 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2954, 2893, 1696, 1425, 1337, 1279, 1224, 1149, 1007, 889, 821, 699, 609; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.15 (s, 2H), 4.34 – 4.22 (m, 2H) superimposed to 4.20 (s, 1H), 4.11 – 4.02 (m, 2H), 4.00 – 3.84 (m, 3H), 3.75 (d, *J* = 11.2 Hz, 1H), 3.69 – 3.52 (m, 2H), 2.29 (app. tt, *J* = 8.0, 4.8 Hz, 1H), 2.06 – 1.92 (m, 1H), 1.81 (s, 1H), 1.45 – 1.39 (m, 1H), 1.27 – 1.24 (m, 1H), 1.23 – 1.16 (m, 2H), 1.01 – 0.93 (m, 2H), 0.89 (dd, *J* = 6.2, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.9 + 155.6 (C), 138.0 + 136.7 (C) superimposed to 136.8 (C), 132.8 + 132.0 (2 rotamers, C), 128.6 (2 × CH), 128.3 (CH) superimposed to 128.1 (2 × CH), 114.7 (C), 74.1 + 73.9 (CH), 67.4 (CH_2), 66.2 (CH_2, br), 66.1 (CH_2), 54.2 (CH_2), 40.5 + 40.3 (CH_2 + C), 40.1 (CH_2), 28.4 + 28.2 (CH), 22.5 + 22.2 (CH_2), 20.2 (CH), 12.0 (CH_2), 5.1 (CH_2), 5.0 (CH_2); HRMS (MS+) *m/z* calculated for $C_{24}H_{29}N_2O_6S$ [M+H] 473.1746, found 473.1758.

***Rac*- benzyl (1aR,3aS,8bS)-3-((4-nitrophenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-1H-spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane]-6(5H)-carboxylate 210**

Prepared according to **GP10** from ynamide **204** (554 mg, 1.00 mmol) and 3% Au-catalyst loading, conducting the reaction at 80 °C. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded polycycle **210** as a light yellow solid (454 mg, 82%); m.p. 163-164 °C; R_f= 0.45 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2894, 1697, 1605, 1529, 1497, , 1278, 1349, 1224, 1167, 1108, 1093, 1022, 949, 903, 855, 820, 798, 765, 733, 699, 686, 622; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 – 8.23 (m, 2H), 7.95 – 7.87 (m, 2H), 7.29 – 7.19 (m, 5H), 5.04 (s, 2H), 4.24 (s, 1H), 4.18 – 4.09 (m, 1H), 4.02 – 3.92 (m, 4H), 3.89 – 3.75 (m, 2H), 3.53 (d, *J* = 11.5 Hz, 1H) superimposed to 3.51 – 3.41 (m, 2H), 1.82 – 1.71 (m, 1H), 1.65 – 1.57 (m, 1H), 1.23 – 1.19 (m, 1H), 0.83 – 0.77 (m, 1H), -0.57 (dd, *J* = 13.4, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) (two signals with the same intensity were observed for certain carbons due to the presence of two major rotamers; in these cases, the two peaks corresponding to the same carbon atom are reported separated by a plus sign): δ 155.8 + 155.5 (C), 150.3 (C), 144.4 (br, C), 137.6 (C), 136.8 (C), 133.1 + 132.3 (C), 128.6 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 128.1 (2 × CH), 124.6 (2 × CH), 114.6 (C), 74.1 + 74.0 (CH), 67.4 (CH_2), 66.4 (br, CH_2), 66.3 (CH_2), 54.5 (CH_2), 45.9 (C, invisible at ^{13}C, identified at HMBC), 40.4 + 40.2 (CH_2), 40.0 (CH_2), 22.3 + 22.0 (CH_2), 19.7 (CH), 11.4 (CH_2); HRMS (MS+) *m/z* calculated for $C_{27}H_{27}N_3O_8NaS$ [M+Na] 576.1417, found 576.1420.

8.2.14 Preparation of α,β-Unsaturated Carbonyl Compounds

***Rac*-(1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 273**

Prepared according to **GP11A** from **166** (9.40 g, 30.0 mmol). Recrystallization in Acetone afforded α,β-conjugated carbonyl **273** as a white solid (5.82 g, 72%); m.p. 144–145 °C; R_f= 0.3 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2930, 2840, 1688, 1616, 1423, 1330, 1263, 1149, 1050, 961, 843, 753, 715, 654; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 (s, 1H), 4.31 – 4.27 (m, 2H), 3.98 (d, *J* = 10.4 Hz, 1H), 3.89 – 3.82 (m, 2H), 3.77 (ddd, *J* = 10.4, 3.3, 2.2 Hz, 1H), 3.20 (s, 3H), 2.27 (app. ddt, *J* = 18.8, 5.1, 2.6 Hz, 1H), 2.11 (app. ddt, *J* = 16.3, 5.8, 2.8 Hz, 1H), 1.65 – 1.59 (m, 2H), 1.39 – 1.34 (m, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.2 (C), 166.4 (C), 135.3 (C), 69.0 (CH), 63.1 (CH_2), 62.4 (CH_2), 53.1 (CH_2), 42.8 (CH_3), 40.2 (C), 24.2 (CH_2), 21.9 (CH), 15.4 (CH_2); MS (LCMS, ES+): 561 (19) $[2M+Na]^+$, 292 (12) $[M+Na]^+$, 271 (12), 270 (100); HRMS (ES+) *m/z* calculated for $C_{12}H_{16}NO_4S$ $[M+H]^+$ 270.07946, found 270.07898.

***Rac*-(1aR,3aS,8bS)-3-((2-chlorophenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 384**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and 2-chlorobenzene sulfonyl chloride (211 mg, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-Conjugated carbonyl **384** as a white solid (209 mg, 3 steps 57%); m.p. 89-90 °C; R_f= 0.48 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2927, 2868, 2340, 2288, 2114, 1700, 1626, 1576, 1511, 1449, 1417, 1387, 1337, 1294, 1251, 1216, 1157, 1098, 1031, 978, 953, 899, 839, 809, 763, 741, 706, 662; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.39 (ddd, *J* = 8.4, 6.6, 2.0 Hz, 1H), 4.43 (s, 1H), 4.25 – 4.11 (m, 2H), 4.08 (d, *J* = 10.8 Hz, 1H), 4.03 (dd, *J* =

11.1, 4.2 Hz, 1H), 3.83 – 3.78 (m, 2H), 2.23 (app. dtt, *J* = 18.9, 5.0, 2.3 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.65 – 1.54 (m, 2H), 1.29 (app. t, *J* = 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.6 (C), 165.5 (C), 138.4 (C), 135.2 (C), 133.9 (CH), 132.6 (C), 131.8 (CH), 126.9 (CH), 124.2 (CH), 69.1 (CH), 63.1 (CH_2), 62.4 (CH_2), 54.3 (CH_2), 39.9 (C), 24.1 (CH_2), 21.6 (CH), 15.0 (CH_2); MS (LCMS, ES+): 753 (29) $[2M+Na]^+$, 367 (17), 366 (100); HRMS (ES+) *m/z* calculated for $C_{17}H_{17}ClNO_4S$ $[M+H]^+$ 366.05613, found 366.05519.

***Rac*-(1aR,3aS,8bS)-3-((4-methoxyphenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 385**

Prepared according to **GP11A** from **167** (122 mg, 0.30 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **385** as a white solid (82.4 mg, 76%); m.p. 151-152 °C; R_f= 0.43 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2895, 2840, 2286, 2116, 1700, 1593, 1498, 1418, 1338, 1259, 1154, 1097, 1021, 894, 833, 669; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.85 (m, 2H), 7.03 – 6.94 (m, 2H), 4.39 (s, 1H), 4.31 – 4.23 (m, 2H), 3.87 (s, 3H), 3.85 – 3.78 (m, 3H), 3.72 (dd, *J* = 11.1, 4.8 Hz, 1H), 2.21 (app. ddq, *J* = 18.5, 5.0, 2.6 Hz, 1H), 2.05 (app. dtd, *J* = 16.1, 5.7, 2.8 Hz, 1H), 1.53 (app. dt, *J* = 9.4, 4.9 Hz, 1H), 1.44 (dd, *J* = 8.5, 6.2 Hz, 1H), 0.82 (app. t, *J* = 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.6 (C), 165.1 (C), 163.2 (C), 135.5 (C), 131.3 (C), 130.0 (2 × CH), 114.2 (2 × CH), 69.3 (CH), 63.2 (CH_2), 62.6 (CH_2), 55.7 (CH_3), 53.4 (CH_2), 39.8 (C), 24.2 (CH_2), 21.8 (CH), 14.8 (CH_2); MS (LCMS, ES+): 745 (27) $[2M+Na]^+$, 363 (18), 362 (100); HRMS (ES+) *m/z* calculated for $C_{18}H_{20}NO_5S$ $[M+H]^+$ 362.10567, found 362.10473.

***Rac*-(1aR,3aS,8bS)-3-((4-nitrophenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 228**

Prepared according to **GP11A** from **168** (2.10 g, 5.0 mmol). Recrystallization in Acetone afforded α,β-conjugated carbonyl **228** as a light yellow solid (1.69 g, 90%); m.p. 194-195 °C; R_f= 0.4 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3104, 2965, 2931, 2889, 2855, 1698, 1625, 1606, 1528, 1475, 1421, 1348, 1310, 1293, 1169, 1098, 1049, 1029, 993, 960, 935, 894, 857, 836, 767, 736, 711, 686; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 – 8.34 (m, 2H), 8.26 – 8.22 (m, 2H), 4.58 (s, 1H), 4.28 – 4.21 (m, 2H), 3.99 (d, *J* = 10.4 Hz, 1H), 3.85 – 3.81 (m, 2H), 3.68 (ddd, *J* = 10.5, 4.0, 1.6 Hz, 1H), 2.26 (app. ddt, *J* = 18.8, 5.2, 2.6 Hz, 1H), 2.08 (app. ddt, *J* = 18.9, 5.9, 3.2 Hz, 1H), 1.64 – 1.59 (m, 2H), 1.24 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.4 (C), 165.8 (C), 150.2 (C), 146.2 (C), 135.6 (C), 129.3 (2 × CH), 124.2 (2 × CH), 69.5 (CH), 63.1 (CH_2), 62.4 (CH_2), 53.3 (CH_2), 39.6 (C), 24.2 (CH_2), 21.8 (CH), 15.0 (CH_2); MS (LCMS, ES+): 775 $[2M+Na]^+$ (10), 378 (19), 377 (100); HRMS (ES+) *m/z* calculated for $C_{17}H_{17}N_2O_6S$ $[M+H]^+$ 377.08018, found 377.07970.

***Rac*-(1aR,3aS,8bS)-3-((4-aminophenyl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 244**

Compound **168** (100.0 mg, 0.24 mmol, 1.0 eq.) was dissolved in dry DMF (790 µL, 0.3 M) in a flame dried Schlenk tube under inert atmosphere. Cs_2CO_3 (391 mg, 5.0 eq.) was added followed by thioglycolic acid (38.4 µL, 2.5 eq.). The mixture was stirred for 3 h at 50 °C before cooling it down to rt and filtrating it on a membrane filter (pore size 0.45 µm) eluting with

CH_2Cl_2. The solvent was removed under reduced pressure and then HCl 4N in dioxane (2.4 mL, 0.1M) was added. The mixture was stirred for 2 h before removing the solvent under reduced pressure giving crude as a red oil. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **244** as a light yellow oil (28.3 mg, 32%); R_f= 0.3 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3472, 3367, 3233, 2958, 2924, 2886, 2856, 2320, 2110, 1700, 1621, 1593, 1501, 1445, 1418, 1384, 1321, 1253, 1225, 1185, 1149, 1089, 1045, 989, 959, 933, 900, 867, 836, 767, 737, 711, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.64 (m, 2H), 6.74 – 6.63 (m, 2H), 4.37 – 4.22 (m, 3H), 3.85 – 3.78 (m, 2H), 3.77 – 3.71 (m, 2H), 2.20 (app. dtt, *J* = 18.7, 5.3, 2.4 Hz, 1H), 2.03 (app. ddt, *J* = 22.0, 5.8, 2.8 Hz, 1H), 1.51 (app. ddt, *J* = 8.3, 5.4, 2.9 Hz, 1H), 1.39 (dd, *J* = 8.5, 6.2 Hz, 1H), 1.25 (app. t, *J* = 7.1 Hz, 1H), 0.70 (app. t, *J* = 5.7 Hz, 1H); N$\underline{H_2}$ protons missing; ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.7 (C), 165.1 (C), 151.0 (C), 135.5 (C), 130.0 (2 × CH), 127.3 (C), 114.2 (2 × CH), 69.3 (CH), 63.2 (CH_2), 62.6 (CH_2), 53.6 (CH_2), 39.9 (C), 24.1 (CH_2), 21.8 (CH), 14.8 (CH_2); MS (LCMS, ES+): 348 (17), 347 (100); MS (LCMS, ES-): 346 (16), 345 (100) $[M-H]^-$; HRMS (ES+) *m/z* calculated for $C_{17}H_{19}N_2O_4S$ $[M+H]^+$ 347.10600, found 347.10529.

***Rac*-(1aR,3aS,8bS)-3-((3,5-dimethylisoxazol-4-yl)sulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 386**

Prepared according to **GP11A** from **169** (118 mg, 0.30 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **386** as a light yellow oil (57.8 mg, 55%); R_f= 0.48 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2930, 2893, 2853, 1704, 1623, 1591, 1409, 1371, 1337, 1293, 1259, 1226, 1178, 1123, 1106, 1046, 978, 889, 867, 837, 756, 733, 711, 685; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (s, 1H), 4.25 – 4.19 (m, 2H), 3.97 (d, *J* = 11.0 Hz, 1H), 3.85 – 3.79 (m, 2H), 3.75

(ddd, *J* = 10.7, 3.9, 1.6 Hz, 1H), 2.64 (s, 3H), 2.44 (s, 3H), 2.25 (app. dtt, *J* = 18.8, 5.1, 2.3 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.65 – 1.58 (m, 2H), 1.34 – 1.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3 (C), 173.7 (C), 165.7 (C), 158.1 (C), 135.4 (C), 116.8 (C), 69.0 (CH), 63.1 (CH_2), 62.4 (CH_2), 53.6 (CH_2), 39.9 (C), 24.2 (CH_2), 21.7 (CH), 15.0 (CH_2), 13.0 (CH_3), 11.2 (CH_3); MS (LCMS, ES+): 352 (16), 351 (100); MS (LCMS, ES-): 350 (16), 349 (100); HRMS (ES+) *m/z* calculated for $C_{16}H_{19}N_2O_5S$ $[M+H]^+$ 351.10092, found 351.10024.

***Rac*-(1aR,3aS,8bS)-3-(piperidin-1-ylsulfonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 387**

Prepared according to **GP11A** from **170** (115 mg, 0.30 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **387** as a white solid (83.3 mg, 82%); m.p. 122-123 °C; R_f= 0.45 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2938, 2854, 1703, 1624, 1446, 1421, 1337, 1161, 1143, 1106, 1054, 1024, 933, 901, 837, 712, 618, 595; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 – 4.27 (m, 2H), 4.26 (s, 1H), 3.93 (d, *J* = 11.5 Hz, 1H), 3.90 – 3.81 (m, 2H), 3.75 – 3.68 (m, 1H), 3.38 – 3.26 (m, 4H), 2.26 (app. dtt, *J* = 18.7, 4.9, 2.3 Hz, 1H), 2.16 – 2.05 (m, 1H), 1.72 – 1.59 (m, 4H), 1.59 – 1.52 (m, 4H), 1.41 – 1.34 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9 (C), 165.7 (C), 135.3 (C), 69.9 (CH), 63.24 (CH_2), 62.5 (CH_2), 55.0 (CH_2), 47.0 (2 × CH_2), 40.1 (C), 25.5 (2 × CH_2), 24.3 (CH_2), 23.8 (CH_2), 22.2 (CH), 14.8 (CH_2); HRMS (ES+) *m/z* calculated for $C_{16}H_{23}N_2O_4S$ [M+H] 339.1379, found 339.1383.

***Rac*-(1aR,3aS,8bS)-3-(morpholine-4-carbonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 276**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and morpholine carbonyl chloride (117 µL, 1.00 mmol). Flash column

chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **276** as a white solid (140 mg, 3 steps 46%); m.p. 104–105 °C; R_f= 0.28 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3504, 2963, 2891, 2854, 1698, 1616, 1457, 1409, 1349, 1271, 1222, 1108, 1067, 1023, 955, 903, 868, 844, 758, 730, 659; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 1H), 4.35 – 4.22 (m, 2H), 3.90 – 3.81 (m, 2H), 3.81 – 3.75 (m, 2H), 3.69 – 3.64 (m, 4H), 3.45 – 3.36 (m, 2H), 3.36 – 3.27 (m, 2H), 2.26 (app. dtt, *J* = 18.7, 4.8, 2.3 Hz, 1H), 2.12 (dddd, *J* = 18.7, 8.3, 5.3, 2.4 Hz, 1H), 1.57 – 1.46 (m, 2H), 1.15 – 1.06 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.9 (C), 165.7 (C), 163.4 (C), 135.5 (C), 69.3 (CH), 66.7 (2 × CH_2), 63.2 (CH_2), 62.7 (CH_2), 54.4 (CH_2), 46.9 (2 × CH_2), 38.5 (C), 24.3 (CH_2), 22.1 (CH), 15.0 (CH_2); MS (LCMS, ES+): 306 (17), 305 (100); HRMS (ES+) *m/z* calculated for $C_{16}H_{21}N_2O_4$ $[M+H]^+$ 305.14958, found 305.14902.

***Rac*-(1aR,3aS,8bS)-N-methyl-4-oxo-N-phenyl-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-3(1H)-carboxamide 368**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and *N*-methyl-*N*-phenyl carbamoyl chloride (170 mg, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **368** as a white solid (156 mg, 3 steps 48%); m.p. 128–129 °C; R_f= 0.4 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3546, 2875, 2389, 2292, 2080, 2000, 1866, 1700, 1644, 1494, 1368, 1292, 1191, 1104, 958, 862, 754, 699; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 2H), 7.24 – 7.18 (m, 2H), 7.14 – 7.08 (m, 1H), 4.80 (s, 1H), 4.34 – 4.25 (m, 2H), 3.86 – 3.77 (m, 2H), 3.29 (d, *J* = 11.2 Hz, 1H), 3.25 (s, 3H), 2.96 (dd, *J* = 11.2, 5.1 Hz, 1H), 2.20 (app. dtt, *J* = 18.5, 4.8, 2.2 Hz, 1H), 2.02 (app. ddq, *J* = 18.5, 5.6, 2.8 Hz, 1H), 1.44 (dd, *J* = 8.4, 5.8 Hz, 1H), 1.33 (app. dt, *J* = 8.4, 5.0 Hz, 1H), 1.08 (app. t, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5 (C), 165.3 (C), 160.5 (C), 146.0 (C), 135.5 (C), 129.6 (2 × CH), 125.7 (2 × CH), 125.1 (CH), 68.4 (CH),

63.2 (CH_2), 62.7 (CH_2), 54.4 (CH_2), 39.7 (CH_3), 38.12 (C), 24.1 (CH_2), 21.6 (CH), 15.5 (CH_2); MS (LCMS, ES+): 671 (42) $[2M+Na]^+$, 326 (20), 325 (100); HRMS (ES+) *m/z* calculated for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.15467, found 325.15363.

Rac-(1aR,3aS,8bS)-N,N-diethyl-4-oxo-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-3(1H)-carbothioamide 389

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and *N*,*N*-diethylthiocarbamoyl chloride (152 mg, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-Conjugated carbonyl **389** as a yellow solid (172 mg, 3 steps 56%); m.p. 139-140 °C; R_f= 0.55 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2972, 2932, 2877, 2286, 2107, 1916, 1701, 1667, 1621, 1489, 1459, 1417, 1355, 1269, 1197, 1142, 1104, 1004, 979, 956, 916, 885, 862, 824, 778, 747, 714, 654; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [4.75 (s, 0.16) + 4.69 (s, 0.79), 1H], 4.35 – 4.23 (m, 2H), 4.19 – 3.94 (m, 2H), 3.94 – 3.72 (m, 5H), 3.72 – 3.51 (m, 1H), 2.26 (app. ddt, *J* = 18.8, 5.2, 2.7 Hz, 1H), 2.10 (app. ddq, *J* = 18.7, 5.5, 2.8 Hz, 1H), [1.72 – 1.47 (m, 2.73) + 1.48 – 1.34 (m, 0.14), 3H], 1.34 – 1.19 (m, 6H); ^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ [4.64 (s, 0.23) + 4.58 (s, 0.71), 1H], 4.24 – 4.08 (m, 2H), 4.03 – 3.58 (m, 8H), 2.35 – 2.16 (m, 2H), 1.93 – 1.80 (m, 1H), 1.76 – 1.63 (m, 1H), 1.31 (app. t, *J* = 5.7 Hz, 1H), 1.26 – 1.12 (m, 6H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80°C): δ 4.60 (s, 1H), 4.26 – 4.12 (m, 2H), 4.07 – 3.64 (m, 8H), 2.36 – 2.17 (m, 2H), 1.87 (app. td, *J* = 6.8, 3.0 Hz, 1H), 1.71 (dd, *J* = 8.5, 5.9

Hz, 1H), 1.33 (app. t, *J* = 5.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{1}H NMR (400 MHz, Acetone-d_6): δ [4.68 (s) superimposed to 4.65 (s), 1H], 4.25 – 4.14 (m, 2H), 4.11 – 4.02 (m, 1H), 4.01 – 3.64 (m, 7H), 2.40 – 2.19 (m, 2H), 1.94 – 1.83 (m, 1H), 1.73 (dd, *J* = 8.5, 5.8 Hz, 1H), 1.44 (app. t, *J* = 5.6 Hz, 1H), 1.35 – 1.19 (m, 6H); ^{13}C NMR (101 MHz, Acetone) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as "maj"= major and "min"= minor and separated with a plus sign): δ 188.5 (C), 167.6 (C), 159.0 (C), 135.4 (C), 71.0 (min) + 70.5 (maj) (CH), 63.8 (min) superimposed to 63.8 (maj) (CH_2), 62.8 (min) superimposed to 62.7 (maj) (CH_2), 54.0 (maj) + 53.4 (min) (CH_2), 50.7 (min) + 49.9 (maj) (CH_2), 49.3 (CH_2), 43.1 (min) + 39.9 (max) (C), 24.8 (min) superimposed to 24.7 (maj) (CH_2), 22.8 (min) + 21.5 (maj) (CH), 16.0 (maj) + 14.5 (min) (CH_2), 13.2 (CH_3), 11.6 (CH_3); MS (LCMS, ES+): 368 (21), 367 (100); MS (LCMS, ES-): 366 (32), 365 (100); HRMS *m/z* calculated for $C_{16}H_{23}N_2O_2S$ $[M+H]^+$ 307.14748, found 307.14676.

***Rac*-(1aR,3aS,8bS)-3-(cyclopropanecarbonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 390**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and cyclopropyl carbonyl chloride (90.7 µL, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **390** as a white solid (160 mg, 3 steps 54%); m.p. 97–98 °C; R_f= 0.2 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3006, 2963, 2930, 2880, 2852, 1696, 1621, 1416, 1346, 1292, 1253, 1205, 1106, 1086, 1056, 1030, 980, 956, 865, 834, 765, 714, 682; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square

parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [4.85 (s, 0.13) + 4.54 (s, 0.81), 1H], 4.37 – 4.27 (m, 2H), 4.03 (d, *J* = 12.6 Hz, 1H), 3.94 – 3.84 (m, 2H), 3.81 (dd, *J* = 12.7, 5.1 Hz, 1H), 2.30 (dddd, *J* = 14.8, 7.1, 5.3, 2.4 Hz, 1H), 2.18 – 2.08 (m, 1H), 2.08 – 2.00 (m, 1H), 1.68 – 1.60 (m, 2H), 1.23 (app. t, *J* = 4.8 Hz, 1H), 1.18 – 1.10 (m, 1H), 0.94 – 0.84 (m, 2H), [0.81 – 0.78 (m, 0.13) + 0.76 – 0.70 (m, 0.80), 1H]; ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 23 °C): δ [4.78 (s, 0.85) + 4.63 (s, 0.15), 1H], 4.25 – 4.10 (m, 2H), [4.02 – 4.00 (m, 0.22) + 3.62 (dd, *J* = 12.4, 5.3 Hz, 0.82), 1H], 3.86 – 3.70 (m, 3H), 2.34 – 2.19 (m, 2H), [2.02 (ddd, *J* = 12.5, 8.0, 4.7 Hz, 0.83) + 1.67 (m, 1.11), 2H], 1.80 (app. dt, *J* = 10.0, 5.3 Hz, 1H), [1.21 (app. t, *J* = 5.5 Hz, 0.87) + 1.13 (t, *J* = 5.6 Hz, 0.14), 1H], 0.87 – 0.60 (m, 4H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80 °C): δ 4.72 (s, 1H), 4.24 – 4.13 (m, 2H), 3.85 – 3.72 (m, 3H), 3.65 (s, 1H), 2.34 – 2.19 (m, 2H), 2.05 (s, 1H), 1.79 (app. dt, *J* = 9.6, 5.3 Hz, 1H), 1.67 (dd, *J* = 8.5, 5.9 Hz, 1H), 1.19 (s, 1H), 0.84 (s, 1H), 0.78 – 0.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as "maj"= major and "min"= minor and separated with a plus sign): δ 201.5 (maj) + 201.3 (min) (C), 174.4 (maj) + 174.0 (min) (C), 166.7 (maj) + 164.8 (min) (C), 135.9 (min) 135.2 (maj) (C), 67.8 (min) + 67.6 (maj) (CH), 63.2 (CH_2), 62.7 (min) + 62.6 (maj) (CH_2), 52.2 (min) + 51.9 (maj) (CH_2) 40.3 (maj) + 38.3 (min) (C), 24.1(5) (maj) superimposed to 24.1 (min) (CH_2), 21.0 (min) + 20.6 (maj) (CH), 16.3 (maj) + 15.5 (min) (CH_2), 13.1 (maj) + 12.8 (min) (CH), 8.5 (maj) + 8.4 (min) (CH_2), 8.3 (min) + 8.2 (maj) (CH_2); MS (LCMS, ES+): 541 (19) $[2M+Na]^+$, 261 (18), 260 (100); HRMS *m/z* calculated for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.12812, found 260.12774.

***Rac*-(1aR,3aS,8bS)-3-(2-(thiophen-2-yl)acetyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 391**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and 2-(thiophen-2-yl)acetyl chloride (161 mg, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **391** as a dark yellow solid (155 mg, 3 steps 49%); m.p. 110–111 °C; R_f= 0.45 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 2927, 2881, 2853, 1693, 1642, 1622, 1404, 1337, 1287, 1252, 1196, 1105, 1084, 1056, 978, 956, 893, 846, 789, 698; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.97 – 6.86 (m, 2H), 4.34 (s, 1H), 4.33 – 4.29 (m, 2H), [4.24 (s, 0.38) + 4.20 (s, 0.66), 1H], [4.12 (s, 0.67) + 4.08 (s, 0.34), 1H], [4.00 (s, 0.35) + 3.97 (s, 0.62), 1H], 3.84 (m, 3H), 2.26 (app. dtt, *J* = 18.8, 5.1, 2.4 Hz, 1H), 2.11 (app. dtt, *J* = 18.9, 5.3, 2.3 Hz, 1H), 1.64 (app. dt, *J* = 9.9, 5.0 Hz, 1H), 1.57 (dd, *J* = 8.6, 5.8 Hz, 1H), 1.10 (app. t, *J* = 5.5 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 23°C): δ 7.37 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.95 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.91 (d, *J* = 3.3 Hz, 1H), [4.71 (s, 0.87) + 4.65 (s, 0.14), 1H], 4.25 – 4.16 (m, 2H), [4.14 (s) superimposed to 4.13 (s), 1H], [4.07 (s, 0.71) + 4.03 (s, 0.31), 1H], [3.90 – 3.85 (m, 0.54) + 3.82 – 3.74 (m, 2.55), 3H], 3.68 (dd, *J* = 12.5, 5.2 Hz, 1H), 2.33 – 2.21 (m, 2H), 1.83 (app. dt, *J* = 9.7, 5.3 Hz, 1H), 1.67 (dd, *J* = 8.5, 5.7 Hz, 1H), 1.18 (app. t, *J* = 5.5 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80°C): δ 7.33 (d, *J* = 5.0 Hz, 1H), 7.02 – 6.89 (m, 2H), 4.65 (s, 1H), 4.31 – 4.16 (m, 2H), 4.15 – 4.01 (m, 2H), 3.85 – 3.69 (m, 4H), 2.34 – 2.19 (m, 2H), 1.85 – 1.76 (m, 1H), 1.68 (app. t, *J* = 7.4 Hz, 1H), 1.16 (app. t, *J* = 5.9 Hz, 1H); ^{13}C NMR

(101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as “maj”= major and “min”= minor and separated with a plus sign): δ 201.4 (maj) + 200.8 (min) (C), 170.5 (maj) + 169.9 (min) (C), 166.9 (maj) + 164.7 (min) (C), 136.4 (maj) + 135.9 (min) (C), 135.2 (C), 126.9 (min) + 126.8 (maj) (CH), 126.4 (maj) superimposed to 126.3 (min) (CH), 124.9 (min) superimposed to 124.9 (maj) (CH), 67.9 (min) + 67.4 (maj) (CH), 63.2 (min) superimposed to 63.1 (maj) (CH_2), 62.6 (min) + 62.5 (maj) (CH_2), 52.2 (min) + 52.1 (maj) (CH_2), 40.3 (maj) + 38.1 (min) (C), 36.5 (min) + 36.1 (maj) (CH_2), 24.1 (maj) superimposed to 24.1 (min) (CH_2), 21.0 (min) + 20.5 (maj) (CH), 16.2 (maj) + 15.2 (min) (CH_2); MS (LCMS, ES+): 317 (18), 316 (100); HRMS *m/z* calculated for $C_{17}H_{18}NO_3S$ $[M+H]^+$ 316.10019, found 316.09950.

***Rac*-(1aR,3aS,8bS)-3-(3,4,5-trimethoxybenzoyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 392**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and 3,4,5-trimethoxybenzoyl chloride (231 mg, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-conjugated carbonyl **392** as a white solid (170 mg, 3 step 44%); m.p. 136–137 °C; R_f= 0.33 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 2945, 2839, 1781, 1724, 1599, 1581, 1514, 1488, 1464, 1435, 1338, 1287, 1275, 1257, 1194, 1164, 1154, 1117, 989, 882, 853, 797, 695, 680, 621; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [7.15 (s, 1.37) + 6.75 (s, 0.48), 2H], [5.13 (s, 0.21) + 4.59 (d, *J* =

12.9 Hz, 0.69), 1H], [4.37 – 4.24 (m, 2.72) + 4.07 – 4.00 (m, 0.33), 3H], 3.91 – 3.79 (m, 11H), 3.74 – 3.60 (m, 1H), 2.25 (d, *J* = 18.3 Hz, 1H), 2.13 (app. dtd, *J* = 16.5, 5.5, 2.6 Hz, 1H), 1.63 – 1.49 (m, 2H), 1.19 – 1.00 (m, 1H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80 °C) δ: 7.01 – 6.87 (m, 2H), [4.64 (s, 0.83) + 4.23 – 4.12 (m, 2.13), 3H], 4.05 – 3.69 (m, 13H), 2.33 – 2.19 (m, 2H), 1.80 – 1.71 (m, 1H), 1.63 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.16 (app. t, *J* = 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as "maj"= major and "min"= minor and separated with a plus sign): δ 201.8 (C), 172.2 (C), 165.9 (C), 153.0 (C), 139.7 (C), 135.1 (C), 131.1 (C), 105.2 (2 × CH), 70.4 (CH), 63.2 (CH_2), 62.5 (CH_2), 60.9 (CH), 56.4 (3 × CH_3), 50.2 (CH_2), 38.7 (C), 24.3 (CH_2), 20.9 (CH), 13.8 (CH_2); MS (LCMS, ES+): 793 (15), $[2M+Na]^+$, 387 (24), 386 (100); MS (LCMS, ES-): 384 (56) $[M-H]^-$, 113 (100); HRMS *m/z* calculated for $C_{21}H_{24}NO_6$ $[M+H]^+$ 386.15981, found 386.15918.

***Rac*-(1aR,3aS,8bS)-3-(benzo[d][1,3]dioxole-4-carbonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 393**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and 2,3-(methylenedioxy)benzoyl chloride (185 mg, 1.00 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-Conjugated carbonyl **393** as a white solid (153 mg, 3 steps 45%); m.p. 108–109 °C; R_f= 0.35 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 2881, 2827, 2287, 2109, 1994, 1913, 1702, 1633, 1594, 1508, 1449, 1403, 1320, 1292, 1252, 1210, 1105, 1056, 959, 923, 861, 833, 806, 785, 743, 712; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are

separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [7.17 (dd, *J* = 7.6, 1.5 Hz, 0.60) + 6.96 (dd, *J* = 7.0, 2.3 Hz, 0.40), 1H], 6.89 – 6.79 (m, 2H), [6.01 (s) superimposed to 6.00 (s), 1H], [5.95 (s) superimposed to 5.94 (s), 1H], [5.06 (s, 0.36) + 4.44 (s, 0.62) 1H], [4.36 – 4.29 (m, 0.70) + 4.27 – 4.10 (m, 2.30), 3H], [3.96 – 3.76 (m, 2.64) + 3.60 (d, *J* = 11.5 Hz, 0.35), 3H], 2.32 – 2.20 (m, 1H), 2.11 (app. ddt, *J* = 18.6, 5.6, 3.3 Hz, 1H), 1.69 – 1.51 (m, 2H), [1.27 (app. t, *J* = 4.8 Hz, 0.66) + 1.12 (m, 0.36), 1H]; ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 24 °C): δ 7.03 – 6.83 (m, 3H), 6.13 – 6.02 (m, 2H), [4.87 (s, 0.46) + 4.50 (s, 0.55), 1H], [4.25 – 4.02 (m, 2.62) + 3.87 (d, *J* = 12.7 Hz, 0.46), 3H], [3.84 – 3.69 (m, 2.64) + 3.45 (d, *J* = 11.5 Hz, 0.47), 3H], 2.33 – 2.18 (m, 2H), [1.83 (app. dt, *J* = 9.8, 5.0 Hz, 0.56) + 1.77 (app. dt, *J* = 9.8, 5.1 Hz, 0.49), 1H], [1.71 (dd, *J* = 8.5, 5.9 Hz, 0.56) + 1.64 (dd, *J* = 8.4, 5.9 Hz, 0.46), 1H], [1.21 (app. t, *J* = 5.6 Hz, 0.56) + 1.16 (app. t, *J* = 5.6 Hz, 0.49), 1H]; ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80 °C): δ 7.33 (d, *J* = 5.0 Hz, 1H), 7.02 – 6.89 (m, 2H), [4.87 (s, 0.46) + 4.50 (s, 0.55), 1H], [4.26 – 4.01 (m, 2.62) + 3.87 (d, *J* = 12.7 Hz, 0.46), 3H], [3.85 – 3.69 (m, 2.64) + 3.45 (d, *J* = 11.5 Hz, 0.47), 3H], 2.34 – 2.19 (m, 2H), [1.83 (app. dt, *J* = 9.8, 5.0 Hz, 0.56) + 1.77 (app. dt, *J* = 9.8, 5.1 Hz, 0.49), 1H], [1.71 (dd, *J* = 8.5, 5.9 Hz, 0.56) + 1.64 (dd, *J* = 8.4, 5.9 Hz, 0.46), 1H], [1.21 (app. t, *J* = 5.6 Hz, 0.56), 1.16 (app. t, *J* = 5.6 Hz, 0.49), 1H]; ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80°C): δ 7.09 – 6.81 (m, 3H), 6.07 (s, 1H), 6.03 (s, 1H), 5.17 – 4.25 (m, 1H), 4.13 (s, 2H), 4.02 – 3.35 (m, 4H), 2.34 – 2.17 (m, 2H), 1.78 (s, 1H), 1.68 (app. t, *J* = 7.2 Hz, 1H), 1.19 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as “maj”= major and “min”= minor and separated with a plus sign): δ 200.8 (C), 167.4 (min) + 167.2 (maj) (C), 165.7 (maj) + 165.2 (min) (C), 147.8 (min) + 147.4 (maj) (C), 144.5 (min) + 143.2 (maj) (C), 135.8 (min) + 135.0 (maj) (C), [122.0 + 121.9 + 121.1, maj and min signals

superimposed, 2CH], 118.7 (maj) + 118.0 (min) (C), 110.3 (min) + 109.9 (maj) (CH), 101.4 (min) + 101.2 (maj) (CH_2), 68.4 (maj) + 67.6 (min) (CH), 63.2 (min) superimposed to 63.1 (maj) (CH_2), 62.7 (min) + 62.4 (maj) (CH_2), 53.0 (min) + 51.3 (maj) (CH_2), 39.1 (maj) + 37.9 (min) (C), 24.1 (CH_2) 21.1 (min) + 20.5 (maj) (CH), 15.0 (maj) superimposed to 14.9 (min) (CH_2); MS (LCMS, ES+): 701 (13) $[2M+Na]^+$, 341 (22), 340 (100); MS (LCMS, ES-): 339 (19), 338 (100) $[M-H]^-$, 113 (13); HRMS *m/z* calculated for $C_{19}H_{18}NO_5$ $[M+H]^+$ 340.11795, found 340.11736.

***Rac*-(1aR,3aS,8bS)-3-(1-methyl-1H-pyrazole-5-carbonyl)-1a,2,3,3a,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 394**

Prepared according to **GP11B** from **168** (420 mg, 1.00 mmol) and 1-methyl-1H-pyrazole-5-carbonyl chloride (145 mg, 1.00 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded α,β-Conjugated carbonyl **394** as a light yellow solid (153 mg, 3 steps 51%); m.p. 122–123 °C; R_f= 0.2 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3568, 2925, 2886, 2852, 1701, 1625, 1515, 1460, 1393, 1322, 1294, 1275, 1255, 1222, 1197, 1146, 1104, 1058, 1015, 958, 934, 908, 863, 832, 807, 755, 718; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [7.43 (s, 0.34) superimposed to 7.37 (s, 0.62), 1H], [6.66 (s, 0.61) + 6.46 (s, 0.29), 1H], [5.08 (s, 0.32) + 4.56 (s, 0.67), 1H], [4.38 – 4.19 (m, 2.79) + 4.09 – 4.00 (m, 3.29), 6H], 3.92 – 3.81 (m, 3H), 2.33 – 2.23 (m, 1H), 2.13 (app. dtt, *J* = 18.9, 5.6, 2.4 Hz, 1H), 1.70 – 1.56 (m, 2H), 1.24 – 1.12 (m, 1H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 23 °C): [δ 7.48 (s, 0.38) + 7.43 – 7.31 (m, 0.53),

1H], [6.80 – 6.71 (m, 0.57) + 6.68 (s, 0.31), 1H], [4.92 (s, 0.35) + 4.68 (s, 0.56), 1H], [4.25 – 4.07 (m, 2.54) + 4.03 – 3.94 (m, 0.52), 3H], [3.92 (s) superimposed to 3.88 (s), 3H], 3.83 – 3.69 (m, 3H), 2.32 – 2.19 (m, 2H), 1.88 – 1.77 (m, 1H), [1.71 – 1.64 (m) superimposed to 1.65 – 1.56 (m), 1H], [1.38 (app. t, *J* = 5.7 Hz, 0.55), 1.29 – 1.20 (m, 0.51); ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ 7.37 (s, 1H), 6.66 (s, 1H), 4.72 (s, 1H), 4.20 – 4.09 (m, 2H), 3.99 – 3.70 (m, 4H) superimposed to 3.89 (s, 3H), 2.33 – 2.17 (m, 2H), 1.80 (app. dt, *J* = 8.3, 5.2 Hz, 1H), 1.65 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as "maj"= major and "min"= minor and separated with a plus sign): δ 200.8 (C), 165.9 (C), 162.8 (C), 137.5 (CH), 135.9 (C), 135.1 (C), 108.8 (min) + 106.8 (maj) (CH), 69.5 (maj) + 67.9 (min) (CH), 63.2 (CH_2), 62.7 (min) + 62.4 (maj) (CH_2), 54.2 (min) + 51.0 (maj) (CH_2), 39.5 (min) + 38.6 (maj) (CH_3) superimposed to 39.2 (C), 24.2 (CH_2), 21.4 (min), 20.4 (maj) (CH), 15.0 (CH_2); MS (LCMS, ES+): 621 (25) $[2M+Na]^+$, 301 (15), 300 (100); MS (LCMS, ES-): 299 (11), 298 (100) $[M-H]^-$; HRMS *m/z* calculated for $C_{16}H_{18}N_3O_3$ $[M+H]^+$ 260.12812, found 260.12774.

***Rac*-(1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,5,6,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4(1H)-one hydrochloride 362**

Prepared according to **GP11A** from **207** (3.00 g, 7.27 mmol). Filtration on a Büchner funnel afforded α,β-conjugated carbonyl **362** as a white solid (1.64 g, 74%); Decomposition at 244–245 °C; R_f= 0.2 (CH_2Cl_2:MeOH 3:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2924, 2625, 2576, 2473, 1704, 1626, 1582, 1495, 1459, 1424, 1386, 1330, 1345, 1290, 1256, 1226, 1158, 1103, 1054, 1052, 1037, 1011, 1000, 963, 936, 913, 897, 828, 752, 706, 618; ^{1}H NMR (400 MHz, D_2O): δ 4.49 (s, 1H), 3.94 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.91 – 3.81 (m, 2H), 3.76

(d, *J* = 11.0 Hz, 1H), 3.55 – 3.42 (m, 2H), 3.14 (s, 3H), 2.72 – 2.62 (m, 1H), 2.57 – 2.47 (m, 1H), 1.96 (app. dt, *J* = 9.7, 4.9 Hz, 1H), 1.87 (dd, *J* = 8.5, 6.7 Hz, 1H), 1.39 (dd, *J* = 6.7, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, D_2O): δ 202.2 (C), 169.5 (C), 125.3 (C), 68.7 (CH), 53.6 (CH_2), 40.0 (CH_2), 39.9 (C), 38.7 (CH_2), 37.3 (CH_3), 22.7 (CH), 20.6 (CH_2), 15.5 (CH_2); MS (LCMS, ES+): 537 (18) $[2M+H]^+$, 270 (14), 269 (100); HRMS (ES+) *m/z* calculated for $C_{12}H_{16}N_2O_3S$ $[M-Cl]^+$ 269.09544, found 269.09518.

***Rac*-(1aR,3aS,8bS)-6-(cyclopropanecarbonyl)-3-(methylsulfonyl)-1a,2,3,3a,5,6,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4(1H)-one 370**

Prepared according to **GP11C** from **362** (305 mg, 1.00 mmol) and cyclopropanecarbonyl chloride (109 µL, mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded α,β-Conjugated carbonyl **370** as a white solid (266 mg, 79%); m.p. 90–91 °C; R_f= 0.2 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 3007, 2925, 2890, 2293, 2086, 1700, 1630, 1422, 1324, 1260, 1222, 1181, 1147, 1083, 1049, 992, 963, 873, 851, 825, 782, 749, 708, 653; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [4.46 – 4.23 (m, 2.68) + 4.22 – 4.07 (m, 0.32), 3H], 4.02 – 3.88 (m, 2H), [3.86 – 3.73 (m, 1.34) + 3.73 – 3.62 (m, 0.70), 2H], 3.21 (s, 3H), 2.33 (dd, *J* = 36.3, 18.3 Hz, 1H), 2.22 – 2.04 (m, 1H), 1.77 – 1.71 (m, 1H), 1.68 – 1.58 (m, 2H), 1.37 (s, 1H), 1.04 – 0.95 (m, 2H), 0.85 – 0.75 (m, 2H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 23 °C): δ [4.39 – 4.18 (m, 1.86) + 4.14 – 3.95 (m, 1.21), 3H] 3.91 – 3.82 (m, 1H), [3.77 (dd, *J* = 10.9, 5.0 Hz, 1.14) superimposed to 3.71

– 3.59 (m, 1.83), 3H], 3.25 (s, 1H), 3.08 (s, 3H), 2.39 – 2.15 (m, 2H), 2.12 – 1.91 (m, 1H), 1.86 (app. dt, *J* = 9.6, 5.1 Hz, 1H), 1.72 (dd, *J* = 8.5, 6.1 Hz, 1H), 1.19 (app. t, *J* = 5.7 Hz, 1H), 0.83 – 0.66 (m, 4H); ^{1}H NMR (400 MHz, DMSO-d_6 + 0.03 v/v TMS, 80 °C): δ δ 4.30 (s, 1H), 4.16 (s, 2H), 3.84 – 3.66 (m, 4H), 3.09 (s, 3H), 2.38 – 2.19 (m, 2H), 1.98 (app. dt, *J* = 7.4, 3.5 Hz, 1H), 1.84 (app. dt, *J* = 9.7, 5.1 Hz, 1H), 1.72 (dd, *J* = 8.4, 6.1 Hz, 1H), 1.21 (app. t, *J* = 5.8 Hz, 1H), 0.80 – 0.71 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as "maj"= major and "min"= minor and separated with a plus sign): δ 202.4 (C), 173.2 (C), 168.5 (C), 133.2 (C), 69.3 (CH), 53.2 (CH_2), 42.8 (CH_3), 41.7 (min) + 41.4 (maj) (CH_2), 40.1 (maj) + 39.1 (C), 38.1 (CH_2), 24.9 (min) + 23.8 (maj) (CH_2), 22.1 (maj) + 21.9 (min) (CH), 15.6 (maj) + 15.4 (min) (CH_2), 11.7 (maj) + 11.4 (min) (CH), 8.1 (maj) + 7.7 (min) (2 × CH_2); MS (LCMS, ES+): 695 (15) $[2M+Na]^+$, 338 (18), 337 (100); MS (LCMS, ES-): 336 (17), 335 (100) $[M-H]^-$; HRMS (ES+) *m/z* calculated for $C_{16}H_{21}N_2O_4S$ $[M+H]^+$ 337.12165, found 337.12086.

***Rac*-(1aR,3aS,8bS)-3-(methylsulfonyl)-6-(morpholine-4-carbonyl)-1a,2,3,3a,5,6,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4(1H)-one 371**

Prepared according to **GP11C** from **362** (305 mg, 1.00 mmol) and 4 - morpholinecarbonyl chloride (140 µL, 1.20 mmol). Flash column chromatography [linear gradient heptane:EtOAc 100:0-0:100] afforded α,β-Conjugated carbonyl **371** as a white solid (324 mg, 85%); m.p. 104–105 °C; R_f= 0.25 (Heptane:EtOAc 2:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 2958, 2918, 2891, 2850, 2292, 2094, 1700, 1626, 1416, 1326, 1260, 1225, 1151, 1111, 1068, 1046, 995, 961, 886, 825, 778, 750, 705, 650; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room

temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [4.34 (s, 0.83) + 4.00 – 3.86 (m, 2.70) + 3.65 (t, *J* = 4.9 Hz, 3.86) + 3.32 – 3.14 (m, 6.51), 14H], 3.74 (app. dt, *J* = 10.6, 2.6 Hz, 1H), 3.46 (app. dt, *J* = 13.7, 5.4 Hz, 1H), 3.37 (ddd, *J* = 13.3, 6.7, 4.8 Hz, 1H), 2.31 (app. dtt, *J* = 18.8, 5.0, 2.3 Hz, 1H), 2.15 (app. dtt, *J* = 18.6, 4.9, 2.6 Hz, 1H), [1.72 – 1.51 (m, 1.87) + 1.25 – 1.15 (m, 1.19), 3H], 1.36 – 1.28 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5 (C), 168.3 (C), 163.7 (C), 133.5 (C), 69.2 (CH), 66.7 (2 × CH_2), 53.2 (CH_2), 47.2 (2 × CH_2), 43.8 (CH_2), 42.8 (CH_3), 42.0 (CH_2), 40.2 (C), 23.5 (CH_2), 22.1 (CH), 15.5 (CH_2); MS (LCMS, ES+): 383 (18), 382 (100); MS (LCMS, ES-): 381 (19), 380 (100) $[M-H]^-$; HRMS (ES+) *m/z* calculated for $C_{17}H_{24}N_3O_5S$ $[M+H]^+$ 382.14312, found 382.14254.

***Rac*-(1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,5,6,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4(1H)-one 369**

Compound **362** (305 mg, 1.0 mmol, 1.0 eq.) was dissolved in EtOH (5.0 mL, 0.5 M). K_2CO_3 (145 mg, 1.1 mmol, 1.1 eq.) was added and the reaction was stirred for 30 min. The solvent was removed under reduced pressure to afford α,β-conjugated carbonyl **369** as a light orange oil (244 mg, 91%); R_f= 0.25 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3355, 1661, 1643, 1565, 1461, 1402, 1317, 1274, 1233, 1205, 1154, 1122, 1101, 1063, 1037, 1016, 982, 922, 858, 823, 794, 779, 758, 747, 733, 700, 656, 640, 577, 549, 512, 492, 454; ^{1}H NMR (400 MHz, D_2O): δ 4.38 (s, 1H), 3.92 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.74 (d, *J* = 10.8 Hz, 1H), 3.66 (d, *J* = 2.4 Hz, 1H), 3.40 – 3.32 (m, 2H), 3.12 (s, 3H), 3.01 (dt, *J* = 11.8, 5.6 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.38 – 2.25

(m, 1H), 2.23 – 2.09 (m, 1H), 1.89 – 1.77 (m, 2H), 1.30 (app. t, *J* = 5.6 Hz, 1H); ^{13}C NMR (101 MHz, D_2O): δ 205.8 (C), 173.0 (C), 133.8 (C), 68.8 (CH), 62.5 (CH_2), 53.9 (CH_2), 40.2 (CH_2), 39.9 (C), 39.3 (CH_2), 37.0 (CH_3), 21.8 (CH), 15.1 (CH_2); MS (LCMS, ES+): 539 (35), 538 (36), 537 (100) $[2M+H]^+$, 291 (23) $[M+Na]^+$, 270 (20), 269 (96); HRMS (ASAP+) *m/z* calculated for $C_{12}H_{17}N_2O_3S$ [M+H] 269.0960, found 269.0955.

8.2.15 Preparation of Chemical Scaffolds by Hydrogenation Reaction

(1aR,3aS,4aS,8aS,8bR)-3-(methylsulfonyl)octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4(1H)-one 283:

α,β-Unsaturated carbonyl **273** (1.25 g, 4.64 mmol, 1.0 eq.) was dissolved in EtOH (46.4 mL, 0.1M) and PtO_2 (75.0 mg, 6% w/w) was added. The solution was degassed under inert atmosphere for 5 minutes and then the reaction vessel was then loaded with a balloon filled with H_2. After bubbling the mixture with H_2 for 2 minutes, the reaction was stirred at 50 °C for 45 min. The reaction was cooled down to rt and the hydrogen-filled balloon was removed. The mixture was degassed for 5 minutes under inert atmosphere and then filtered over a membrane filter. The solvent was removed under reduced pressure to give crude as a white solid. Recrystallization in EtOH afforded scaffold **283** as a white solid (1.03 g, 82%); m.p. 124–125 °C; R_f= 0.33 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2967, 2923, 2878, 2849, 2289, 2078, 1990, 1733, 1620, 1465, 1444, 1374, 1336, 1309, 1217, 1190, 1146, 1077, 1046, 1005, 972, 924, 903, 874, 825, 765, 718, 682, 665; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (s, 1H), 3.90 (dd, *J* = 11.8, 7.6 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.71 (ddd, *J* = 11.7, 5.7, 3.7 Hz, 1H),

3.50 – 3.39 (m, 3H), 3.14 (s, 3H), 2.97 – 2.89 (m, 2H), 1.91 (dddd, *J* = 14.6, 10.7, 6.9, 5.6 Hz, 1H), 1.64 (app. dt, *J* = 8.4, 4.2 Hz, 1H), 1.30 (app. dq, *J* = 15.0, 3.5 Hz, 1H), 1.09 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.84 (dd, *J* = 6.0, 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 213.1 (C), 69.6 (CH), 64.9 (CH_2), 63.7 (CH_2), 50.4 (CH_2), 45.9 (CH), 42.5 (CH_3), 34.1 (C), 28.8 (CH), 22.6 (CH_2), 20.8 (CH), 10.2 (CH_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 1H), 3.70 (dd, *J* = 11.2, 7.4 Hz, 2H), 3.22 (ddd, *J* = 11.5, 5.7, 3.4 Hz, 1H), 3.15 (dd, *J* = 11.7, 9.3 Hz, 1H), 2.88 (app. td, *J* = 11.2, 3.6 Hz, 1H), 2.85 – 2.75 (m, 4H), 2.20 (app. qd, *J* = 8.0, 1.5 Hz, 1H), 1.95 (td, *J* = 7.6, 3.3 Hz, 1H), 1.17 (dddd, *J* = 14.6, 10.8, 7.2, 5.7 Hz, 1H), 0.74 (app. dt, *J* = 8.3, 4.2 Hz, 1H), 0.49 – 0.43 (m, 2H), 0.35 – 0.29 (m, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 213.0 (C), 69.7 (CH), 64.9 (CH_2), 64.0 (CH_2), 50.3 (CH_2), 46.1 (CH), 42.6 (CH_3), 34.1 (C), 28.9 (CH), 22.7 (CH_2), 21.0 (CH), 10.0 (CH_2); MS (LCMS, ES+): 273 (14), 272 (100); MS (LCMS, ES-): 271 (12), 270 (100), HRMS (ES+) *m/z* calculated for $C_{12}H_{18}NO_4S$ $[M+H]^+$ 272.09511, found 272.09470.

((1aR,3aS,6aS)-6-ethyl-5-methyl-3-(methylsulfonyl)-1a,2,3,3a-tetrahydrocyclopenta[b]cyclopropa[c]pyrrol-4(1H)-one 284

Prepared according to the procedure for the synthesis of scaffold **283** from **273** (250 mg, 0.93 mmol) replacing the catalyst with Pd/C (25.0 mg, 10% w/w) and with reaction time of 20 minutes. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] followed by recrystallization in EtOH afforded scaffold **284** was afforded as a white solid (33.2 mg, 14%) m.p. 92–93 °C; R_f= 0.28 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2967, 2932, 2875, 1700, 1633, 1459, 1382, 1324, 1247, 1221, 1146, 1056, 1013, 967, 906, 820, 780, 738, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 (s, 1H), 3.95 (d, *J* = 10.3 Hz, 1H), 3.72 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.23 (s, 3H), 2.31 (dq, *J* = 13.1, 7.7 Hz, 1H), 2.02 (dq, *J* = 13.2, 7.8 Hz, 1H), 1.73 (s, 3H), 1.63 (dd, *J* = 8.5, 6.2 Hz, 1H), 1.53 (app. dt, *J* = 8.8, 4.9 Hz, 1H),

1.32 (app. t, *J* = 5.6 Hz, 1H), 1.06 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.1 (C), 169.8 (C), 133.5 (C), 68.8 (CH), 53.0 (CH_2), 42.7 (CH_3), 39.7 (C), 22.2 (CH), 20.4 (CH_2), 15.2 (CH_2), 12.6 (CH_3), 8.2 (CH_3); MS (GCMS, EI+): 255 (50), 176 (100), 149 (41), 148 (29), 133 (17), 121 (15), 118 (14), 105 (14), 93 (14), 91 (28), 79 (22), 77 (18), 65 (12); HRMS (ES+) *m/z* calculated for $C_{12}H_{18}NO_3S$ $[M+H]^+$ 256.10019, found 256.09981.

(3R,3aS,6aS)-4-ethyl-3,5-dimethyl-1-(methylsulfonyl)-2,3,3a,6a-tetrahydrocyclopenta[b]pyrrol-6(1H)-one 285

Prepared according to the procedure for the synthesis of scaffold **283** from **273** (250 mg, 0.928 mmol) replacing the catalyst with Pd/C (25.0 mg, 10% w/w) and with reaction time of 20 minutes. Flash column chromatography [linear gradient heptane:EtOAc 100:0-0:100] followed by recrystallization in EtOH afforded scaffold **285** as a white solid (21.6 mg, 9%); m.p. 67–68 °C; R_f= 0.25 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3015, 2982, 2935, 2890, 2294, 2108, 1691, 1609, 1474, 1441, 1420, 1396, 1321, 1259, 1225, 1152, 1102, 1023, 951, 900, 859, 825, 787, 749, 688, 654; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (d, *J* = 6.3 Hz, 1H), 3.44 (dd, *J* = 10.6, 2.6 Hz, 1H), 3.13 (s, 3H), 3.06 (app. dt, *J* = 10.0, 5.1 Hz, 2H), 2.59 (dq, *J* = 15.0, 7.6 Hz, 1H), 2.31 (dq, *J* = 15.2, 7.8 Hz, 1H), 2.14 (app. qdt, *J* = 7.0, 5.3, 2.6 Hz, 1H), 1.66 (s, 3H), 1.14 (d, *J* = 7.0 Hz, 1H) superimposed to 1.12 (t, *J* = 7.7 Hz, 1H); note: the last two resonances were identified at COSY analysis; ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.3 (C), 174.9 (C), 135.5 (C), 63.3 (CH), 53.3 (CH_2), 53.1 (CH), 42.6 (CH_3), 36.2 (CH), 23.0 (CH_3), 19.6 (CH_2), 11.5 (CH_3), 8.0 (CH_3); MS (GCMS, EI+): 258 (12), 257 (81), 179 (13), 178 (100), 152 (10), 151 (97), 150 (34), 149 (19), 136 (23), 93 (11), 91 (14), 82 (13), 81 (22), 79 (25), 77 (16), 67 (16), 55 (18); HRMS (ES+) *m/z* calculated for $C_{12}H_{20}NO_3S$ $[M+H]^+$ 258.11584, found 258.11569.

(1aR,3aS,4R,4aS,8aS,8bR)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 300

Procedure A: α,β-Unsaturated carbonyl **273** (1.00 g, 3.71 mmol, 1.0 eq.) was dissolved in EtOH (3.7 mL, 0.1M) and PtO_2 (60.0 mg, 6% w/w) was added. The solution was degassed under inert atmosphere for 5 minutes and then the reaction vessel was then loaded with a balloon filled with H_2. After bubbling the mixture with H_2 for 2 minutes, the reaction was stirred at 50 °C for 3 h. The reaction was cooled down to rt and the hydrogen-filled balloon was removed. The mixture was degassed for 5 minutes under inert atmosphere and then filtered over a membrane filter. The solvent was removed under reduced pressure to give crude as a white solid. Recrystallization in EtOH afforded scaffold **300** (740 mg, 73%) as a white solid.

Procedure B: Scaffold **283** (1.00 g, 3.7 mmol, 1.0 eq.) was dissolved in MeOH (3.7 mL, 0.1 M). $NaBH_4$ (168 mg, 4.43 mmol, 1.2 eq.)was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (ca. 5.0 mL), then the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford scaffold **300** (937 mg, 93%) that was used for the following step without further purification; m.p. 115-116 °C; R_f= 0.38 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3542, 3489, 2946, 2896, 2856, 2819, 1475, 1416, 1381, 1315, 1235, 1148, 1108, 1063, 1035, 977, 912, 860, 826, 807, 769, 726; ^{1}H NMR (400 MHz, $CDCl_3$): δ

4.31 – 4.28 (m, 1H), 4.25 (d, *J* = 12.4 Hz, 1H), 3.95 (ddd, *J* = 11.6, 5.2, 2.1 Hz, 1H), 3.87 (d, *J* = 3.6 Hz, 1H), 3.81 – 3.73 (m, 2H), 3.55 (d, *J* = 8.9 Hz, 1H), 3.33 (app. td, *J* = 12.0, 2.5 Hz, 1H), 2.93 (s, 3H), 2.68 (s, 1H), 2.24 (app. dt, *J* = 11.0, 7.7 Hz, 1H), 2.10 (dt, *J* = 8.0, 3.8 Hz, 1H), 1.81 (app. tdd, *J* = 13.0, 11.0, 5.1 Hz, 1H), 1.57 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 1.50 (ddd, *J* = 13.2, 7.3, 2.3 Hz, 1H), 1.01 (dd, *J* = 8.4, 5.4 Hz, 1H), 0.71 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 76.3 (CH), 71.4 (CH), 67.9 (CH_2), 67.0 (CH_2), 53.3 (CH_2), 41.7 (CH), 39.5 (C), 38.1 (CH_3), 33.0 (CH), 29.9 (CH_2), 20.6 (CH), 14.7 (CH_2); ^{1}H NMR (400 MHz, C_6D_6): δ 3.93 (t, *J* = 3.6 Hz, 1H), 3.76 (d, *J* = 12.4 Hz, 1H), 3.71 (d, *J* = 3.7 Hz, 1H), 3.60 – 3.52 (m, 2H) superimposed to 3.49 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.23 (dd, *J* = 12.5, 4.9 Hz, 1H), 2.86 – 2.78 (m, 1H), 2.60 (s, 3H), 2.44 (s, 1H), 1.47 (app. dt, *J* = 10.9, 7.6 Hz, 1H), 1.33 (app. tdd, *J* = 12.7, 10.8, 5.1 Hz, 1H), 1.26 – 1.20 (m, 1H), 1.02 – 0.95 (m, 1H), 0.74 (app. ddt, *J* = 13.2, 7.7, 2.6 Hz, 1H), 0.51 – 0.43 (m, 2H); ^{1}H NMR (400 MHz, Acetone-d_6): δ 4.17 (app. t, *J* = 4.0 Hz, 1H), 4.10 (dd, *J* = 12.3, 2.7 Hz, 1H), 3.84 (d, *J* = 3.9 Hz, 1H), 3.80 (ddd, *J* = 11.3, 4.9, 2.9 Hz, 1H), 3.75 – 3.69 (m, 2H), 3.51 – 3.41 (m, 2H), 3.30 (app. td, *J* = 11.5, 2.9 Hz, 1H), 2.87 (s, 3H), 2.23 (app. dt, *J* = 10.3, 7.5 Hz, 1H), 2.16 (app. ddt, *J* = 8.5, 5.8, 3.1 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.59 (app. dt, *J* = 8.7, 4.5 Hz, 1H), 1.46 (app. ddt, *J* = 13.0, 6.4, 2.9 Hz, 1H), 1.00 (dd, *J* = 8.3, 5.2 Hz, 1H), 0.60 (app. t, *J* = 4.9 Hz, 1H); ^{1}H NMR (400 MHz, MeOD): δ 4.18 – 4.10 (m, 2H), 3.89 (d, *J* = 4.2 Hz, 1H), 3.88 – 3.83 (m, 1H), 3.80 – 3.72 (m, 2H), 3.49 (d, *J* = 9.3 Hz, 1H), 3.37 – 3.32 (m, 1H), 2.90 (s, 3H), 2.23 (app. dt, *J* = 10.7, 7.7 Hz, 1H), 2.14 (app. ddt, *J* = 8.6, 5.8, 2.9 Hz, 1H), 1.80 (app. dtd, *J* = 13.0, 11.2, 4.9 Hz, 1H), 1.60 (app. dt, *J* = 8.8, 4.5 Hz, 1H), 1.43 (ddd, *J* = 13.3, 6.3, 3.0 Hz, 1H), 1.02 (dd, *J* = 8.3, 5.3 Hz, 1H), 0.61 (app. t, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, MeOD): δ 76.9 (CH), 72.3 (CH), 67.6 (CH_2), 67.3 (CH_2), 54.5 (CH_2), 43.3 (CH), 40.3 (C), 38.0 (CH_3), 34.7 (CH), 30.1 (CH_2), 21.7 (CH), 14.8 (CH_2); MS (LCMS, ES+): 569 (15) $[2M+Na]^+$, 275 (12), 274 (100); MS (LCMS, ES-): 318 (79) $[M+HCOOH-H]^-$, 113 (100); HRMS (ES+) *m/z* calculated for $C_{12}H_{20}NO_4S$ $[M+H]^+$ 274.1108, found 274.1102.

(1aR,3aS,4S,4aS,8aS,8bR)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 301

Prepared according to the procedures described for the synthesis of scaffold **300** from **273** (100 mg, 0.37 mmol, 1.0 eq.) with increased PtO_2 loading (30.0 mg, 30%) with Procedure A or by adding Ti(O*i*Pr)$_4$ (105 mg, 0.37 mmol, 1.0 eq.) with Procedure B from **283** (100 mg, 0.37 mmol, 1.0 eq.). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] followed by recrystallization in EtOH afforded scaffold **301** as a white solid (Procedure A: 18.3 mg, 18%; Procedure B: 34.4 mg, 34%); m.p. 85-86 °C; R_f= 0.25 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3497, 2922, 2852, 1710, 1643, 1463, 1417, 1377, 1321, 1266, 1243, 1149, 1100, 1072, 967, 871, 835, 792, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 (dd, *J* = 10.7, 3.3 Hz, 1H), 4.02 (ddd, *J* = 11.4, 4.5, 1.6 Hz, 1H), 3.88 – 3.79 (m, 2H), 3.73 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.47 (d, *J* = 10.4 Hz, 1H), 3.33 – 3.25 (m, 2H), 2.87 (d, *J* = 2.2 Hz, 1H), 2.84 (s, 3H), 1.74 – 1.63 (m, 2H), 1.48 (dd, *J* = 8.7, 4.5 Hz, 1H), 1.45 – 1.41 (m, 1H), 1.19 (app. td, *J* = 11.8, 4.4 Hz, 1H), 1.12 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.55 (dd, *J* = 6.0, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.4 (CH), 71.5 (CH_2), 67.6 (CH), 67.0 (CH_2), 53.1 (CH_2), 50.8 (CH), 40.6 (C), 37.8 (CH), 36.6 (CH_3), 27.8 (CH_2), 18.1 (CH), 12.9 (CH_2); ^{1}H NMR (400 MHz, Acetone-d_6): δ 4.10 (dd, *J* = 10.6, 4.1 Hz, 1H), 3.97 (d, *J* = 7.5 Hz, 1H), 3.90 (ddd, *J* = 11.3, 4.4, 1.5 Hz, 1H), 3.76 (ddd, *J* = 9.8, 7.5, 4.6 Hz, 1H), 3.61 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.53 – 3.50 (m, 1H), 3.28 – 3.19 (m, 2H), 2.91 (s, 3H), 2.83 (s, 1H), 1.70 (app. td, *J* = 11.6, 3.6 Hz, 1H), 1.59 – 1.48 (m, 2H), 1.44 (app. ddt, *J* = 12.5, 3.9, 2.0 Hz, 1H), 1.18 – 1.06 (m, 2H), 0.63 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, Acetone-d_6): δ 73.4 (CH), 71.9 (CH_2), 67.8 (CH), 67.4 (CH_2), 53.2 (CH_2), 52.4 (CH), 38.4 (CH), 37.3 (CH_3), 28.6 (CH_2), 18.5 (CH), 12.5 (CH_2), 1C missing; ^{1}H NMR (400 MHz, MeOD): δ 4.18 (dd, *J* = 10.7, 4.0 Hz, 1H), 4.01 (d, *J* = 7.6 Hz, 1H) superimposed to 3.97 (ddd, *J* = 11.6, 4.5, 1.6 Hz, 1H), 3.78 (dd, *J* = 9.8, 7.5 Hz, 1H), 3.60 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.55 (d, *J* = 10.1 Hz, 1H), 3.36

(s, 1H), 2.92 (s, 3H), 1.71 (app. td, *J* = 11.6, 3.6 Hz, 1H), 1.57 (app. qd, *J* = 10.9, 4.0 Hz, 1H), 1.51 – 1.44 (m, 2H), 1.17 (app. qd, *J* = 12.1, 4.5 Hz, 1H), 1.09 (dd, *J* = 8.3, 5.8 Hz, 1H), 0.63 (dd, *J* = 5.8, 4.5 Hz, 1H); MS (LCMS, ES+): 569 (39) $[2M+Na]^+$, 275 (13), 274 (100); HRMS (ES+) *m/z* calculated for $C_{12}H_{20}NO_4S$ $[M+H]^+$ 274.11076, found 274.1104.

((1aR,3aS,4R,4aS,8aS,8bR)-4-hydroxy-3-(methylsulfonyl)decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)(morpholino)methanone 373

α,β-Unsaturated carbonyl **371** (100 mg, 0.26 mmol, 1.0 eq.) was dissolved in EtOH (2.6 mL, 0.1 M) in a 5 mL vial and PtO_2 (6.0 mg, 6% w/w) was added. The vial was inserted in autoclave and after two cycles of vacuum/H_2 atmosphere, the pressure was set to 5 atm of H_2. The reaction was stirred at rt for 3 h, then the pressure was decreased to 1 atm and the autoclave was filled with inert atmosphere. The reaction vial was removed and the mixture filtered over a membrane filter. The solvent was removed under reduced pressure to give crude as a colourless oil. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded scaffold **373** (68.2 mg, 68%) as a colourless oil; R_f= 0.5 (CH_2Cl_2:MeOH 49:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3276, 2952, 2891, 2856, 2299, 1733, 1638, 1601, 1482, 1423, 1325, 1264, 1212, 1150, 1110, 1066, 1019, 960, 912, 863, 829, 809, 730, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 (s, 1H), 4.26 (app. t, *J* = 3.3 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.93 (d, *J* = 3.7 Hz, 1H), 3.70 – 3.60 (m, 5H), 3.50 (d, *J* = 8.3 Hz, 1H), 3.46 (ddd, *J* = 7.0, 5.4, 2.3 Hz, 1H), 3.38 (ddd, *J* = 13.3, 6.3, 3.2 Hz, 2H), 3.25 – 3.14 (m, 3H), 3.02 – 2.88 (m, 4H), 2.22 – 2.07 (m, 2H), 1.68 – 1.58 (m, 1H), 1.46 (app. dt, *J* = 8.6, 4.5 Hz, 1H), 1.39 (app. ddt, *J* = 12.4, 6.0, 2.6 Hz, 1H), 0.89 (dd, *J* = 8.3, 5.4

Hz, 1H), 0.73 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9 (C), 74.5 (CH), 70.2 (CH), 66.7 (2 × CH_2), 52.7 (CH_2), 47.4 (2 × CH_2), 47.1 (CH_2), 44.2 (CH_2), 42.2 (CH), 38.9 (CH_3), 38.6 (C), 34.6 (CH), 30.0 (CH_2), 20.3 (CH), 13.6 (CH_2); ^{1}H NMR (400 MHz, Acetone-d_6): δ 4.86 (s, 1H), 4.16 (app. t, *J* = 3.5 Hz, 1H), 3.91 – 3.85 (m, 2H), 3.65 – 3.53 (m, 6H), 3.40 (d, *J* = 8.6 Hz, 1H), 3.34 – 3.26 (m, 3H), 3.18 (ddd, *J* = 13.2, 6.2, 3.3 Hz, 2H), 3.03 (app. td, *J* = 12.9, 3.0 Hz, 1H), 2.89 (s, 3H), 2.26 (ddt, *J* = 9.2, 6.1, 2.9 Hz, 1H), 2.18 (app. td, *J* = 10.0, 6.2 Hz, 1H), 1.62 (app. qd, *J* = 12.6, 4.5 Hz, 1H), 1.52 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.44 (app. ddt, *J* = 12.6, 6.0, 2.9 Hz, 1H), 0.93 (dd, *J* = 8.3, 5.1 Hz, 1H), 0.58 (app. t, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, Acetone-d_6): δ 165.6 (C), 75.5 (CH), 71.1 (CH), 67.2 (2 × CH_2), 53.5 (CH_2), 48.2 (2 × CH_2), 47.3 (CH_2), 44.4 (CH_2), 43.1 (CH), 39.2 (CH_3), 38.6 (C), 35.4 (CH), 29.8 (CH_2) superimposed with Acetone-d_6 signal, 21.0 (CH), 13.7 (CH_2); ^{1}H NMR (400 MHz, MeOD): δ 4.11 (app. t, *J* = 3.8 Hz, 1H), 3.92 (d, *J* = 3.9 Hz, 1H), 3.77 – 3.58 (m, 7H), 3.55 (app. dt, *J* = 12.7, 4.1 Hz, 1H), 3.46 (d, *J* = 9.2 Hz, 1H), 3.40 (dd, *J* = 14.0, 6.6 Hz, 1H), 3.29 – 3.23 (m, 4H), 3.03 (app. td, *J* = 12.5, 3.8 Hz, 1H), 2.91 (s, 3H), 2.43 – 2.33 (m, 1H), 2.15 (ddd, *J* = 11.7, 9.1, 5.8 Hz, 1H), 1.70 (app. qd, *J* = 12.4, 4.9 Hz, 1H), 1.57 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.45 (app. ddt, *J* = 13.0, 6.5, 3.4 Hz, 1H), 0.96 (dd, *J* = 8.2, 5.3 Hz, 1H), 0.58 (app. t, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, MeOD): δ 166.4 (C), 76.0 (CH), 71.9 (CH), 67.8 (2 × CH_2), 54.4 (CH_2), 48.6 (2 × CH_2) superimposed with MeOD signal, 47.2 (CH_2), 44.4 (CH_2), 43.4 (CH_3), 39.5 (C), 38.3 (CH), 35.8 (CH), 28.7 (CH_2), 21.6 (CH), 13.9 (CH_2); MS (LCMS, ES+): *m/z* 793 (18) $[2M+Na]^+$, 387 (31), 386 (100); MS (LCMS, ES-): *m/z* 385 (18), 384 (100) $[M-H]^-$; HRMS (MS+) *m/z* calculated for $C_{17}H_{28}N_3O_5S$ $[M+H]^+$ 386.1744, found 386.1735.

(1aR,3aS,8bS)-3-(methylsulfonyl)-1a,2,3,3a,5,6,7,8-octahydro-1H-spiro[cyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-4,2'-[1,3]dioxolane] 368

Polycycle **208** (100 mg, 0.22 mmol, 1.0 eq.) was dissolved in EtOH (2.2 mL, 0.1 M) and Pd/C (10.0 mg, 10% w/w) was added. The solution was degassed under inert atmosphere for 5 minutes and then the reaction vessel was then loaded with a balloon filled with H_2. After bubbling the mixture with H_2 for 2 minutes, the reaction was stirred at 50 °C for 3 h. The reaction was cooled down to rt and the hydrogen-filled balloon was removed. The mixture was degassed for 5 minutes under inert atmosphere and then filtered over a membrane filter. The solvent was removed under reduced pressure to give scaffold **368** as a pale yellow oil (15.1 mg, 22%) that was afforded without further purification; R_f= 0.28 (CH_2Cl_2:MeOH 24:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2892, 1695, 1497, 1424, 1359, 1328, 1223, 1151, 1108, 1059, 1022, 1008, 950, 902, 865, 822, 750, 698; ^{1}H NMR (400 MHz, D_2O): δ 4.26 – 4.20 (m, 2H), 4.20 – 4.12 (m, 2H), 4.02 – 3.96 (m, 1H), 3.91 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.88 – 3.63 (m, 4H), 3.44 (app. dt, *J* = 12.0, 5.7 Hz, 1H), 3.31 (ddd, *J* = 12.8, 7.4, 5.7 Hz, 1H), 3.03 (s, 3H), 2.33 (app. dddt, *J* = 18.3, 8.3, 5.6, 2.4 Hz, 1H), 2.15 (dddd, *J* = 18.0, 7.1, 5.0, 1.8 Hz, 1H), 1.69 (app. dt, *J* = 9.1, 4.8 Hz, 1H), 1.50 (dd, *J* = 8.6, 6.7 Hz, 1H), 0.89 (dd, *J* = 6.7, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, D_2O): δ 140.0 (C), 126.1 (C), 114.1 (C), 72.6 (CH) 66.1(7) (CH_2) superimposed to 66.1(6) (CH_2), 53.8 (CH_2), 40.6 (CH_2), 39.8 (C), 38.8 (CH_2), 36.0 (CH_3), 20.4 (CH), 18.6 (CH_2), 12.2 (CH_2); MS (LCMS, ES+): 314 (15), 313 (100); HRMS (ES+) *m/z* calculated for $C_{14}H_{21}N_2O_4S$ $[M+H]^+$ 313.1217, found 313.1206.

8.2.16 Preparation of Lactone 320

(2aR,4aS,8aS,8bR,9aR)-2-(methylsulfonyl)octahydro-1H,4H,5H-cyclopropa[c]pyrano[4',3':4,5]pyrano[2,3-b]pyrrol-4-one 320

Procedure A: The procedure follows that reported by Isaza *et* al.[262] Ketone **283** (50 mg, 0.18 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1.8 mL, 0.1 M) and the mixture was stirred at rt for 2h. The solvent was removed under reduced pressure to give crude as a white solid. Flash column chromatography [linear gradient Heptane:EtOAc 100:0-70:30] afforded lactone **320** as a white solid (14.5 mg, 28%, 68% purity).

Procedure B: The procedure follows that reported by Ilchenko *et al.*[178] Ketone **283** (50 mg, 0.18 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (1.8 mL, 0.1 M). $AgNO_3$ (31 mg, 0.18 mmol, 1.0 eq.) and PIDA (58 mg, 0.18 mmol, 1.0 eq.) were added and the mixture was stirred at rt for 7h. Flash column chromatography [linear gradient Heptane:EtOAc 100:0 – 70:30] afforded lactone **320** as a white solid (11 mg, 21%, 75% purity by LCMS); m.p. 73– 74 °C; R_f= 0.35 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2922, 2881, 1733, 1472, 1379, 1327, 1234, 1141, 1107, 1081, 1029, 980; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (s, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 3.96 (app. dt, *J* = 11.4, 3.4 Hz, 1H), 3.67 (d, *J* = 8.8 Hz, 1H), 3.55 (dd, *J* = 8.9, 3.7 Hz, 1H), 3.46 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.33 – 3.27 (m, 1H), 3.07 (s, 3H), 2.69 (dd, *J* = 6.2, 3.1 Hz, 1H), 2.46 – 2.39 (m, 1H), 1.77 (app. dt, *J* = 7.8, 4.0 Hz, 1H), 1.39 (app. dt, *J* = 9.2, 4.9 Hz, 1H), 1.24 – 1.18 (m, 1H), 0.99 (dd, *J* = 5.8, 4.2 Hz, 1H), 0.85 (dd, *J* = 7.9, 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (C), 90.4 (CH), 67.0 (CH_2), 65.2 (CH_2), 48.9 (CH_2), 41.0 (CH_3), 40.4 (CH), 33.0 (C),

32.7 (C), 29.8 (CH_2), 18.5 (CH), 14.4 (CH_2); MS (LCMS, MS+): *m/z* 289 (13), 188 (100); HRMS (ES+) *m/z* calculated for $C_{12}H_{18}NO_5S$ $[M+H]^+$ 288.0900, found 288.0896.

8.2.17 Preparation of Sulfur-containing derivatives of 273

α,β-Unsaturated carbonyl **273** (100.0 mg, 0.371 mmol, 1.0 eq.) was added to thiophenol (378.5 µL, 3.71 mmol, 10.0 eq.). The mixture was stirred at rt for 30 minutes, then flash column chromatography afforded thioacetal **340** as a white solid (91.0 mg, 52%). If the mixture was stirred for 16h, preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded compound **341** as a yellow oil (54.0 mg, 25%).

(1aR,3aS,8bS)-3-(methylsulfonyl)-4,4-bis(phenylthio)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 340: m.p. 166-167 °C; R_f= 0.6 (Heptane:EtOAc 7:3) [UV]; IR: ν_{max} (neat, cm^{-1}) 2860, 2322, 1893, 1618, 1579, 1475, 1436, 1338, 1309, 1251, 1219, 1141, 1085, 1004, 957, 925, 847, 781, 741, 693, 660; ^{1}H NMR (400 MHz, $CDCl_3$ + 0.03% TMS): δ 7.45 – 7.37 (m, 3H), 7.29 – 7.25 (m, 2H), 7.19 – 7.14 (m, 2H), 7.10 – 7.01 (m, 3H), 4.62 (d, *J* = 13.6 Hz, 1H), 4.41 (dd, *J* = 13.6, 3.0 Hz, 1H), 4.08 (app. td, *J* = 12.0, 2.0 Hz, 1H), 3.87 (ddd, *J* = 11.7, 4.8, 1.8 Hz, 1H), 3.75 (d, *J* = 2.9 Hz, 1H), 3.58 (d, *J* = 11.3 Hz, 1H), 3.01 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.38 (s, 3H), 1.83 (ddd, *J* = 14.0, 12.1, 4.8 Hz, 1H), 1.63 (app. dt, *J* = 13.9, 2.0 Hz, 1H), 1.52 (app. dt, *J* = 8.8, 4.5 Hz, 1H), 1.12 (dd, *J* = 8.5, 6.3 Hz, 1H), 0.87 (dd, *J* = 6.4, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ + 0.03% TMS): δ 151.1 (C), 138.2 (2 × CH), 134.8 (C), 130.8 (C), 130.2 (C), 130.1 (CH), 129.1 (2 × CH), 129.1 (2 × CH), 128.4 (2 × CH), 126.5 (CH), 72.4 (CH), 63.9 (CH_2), 63.8 (CH_2), 59.9 (C), 49.2 (CH_2), 45.2 (C), 41.3 (CH_3), 35.5 (CH_2), 21.6

(CH), 11.1 (CH_2); MS (LCMS, ES+): 473 (14), 472 (44), 363 (21), 362 (100) $[M-PhSH+H]^+$; HRMS (ES+) *m/z* calculated for $C_{24}H_{26}NO_3S_3$ $[M+H]^+$ 472.10693, found 472.10635.

***N*-(((2'R,5R)-4a,7,7a-tris(phenylthio)-3,4,4a,7a-tetrahydro-1H-spiro[cyclopenta[c]pyran-5,1'-cyclopropan]-2'-yl)methyl)methanesulfonamide 341**: m.p. R_f= 0.66 (Heptane:EtOAc 4:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3339, 3275, 2929, 2852, 2791, 1597, 1577, 1536, 1470, 1438, 1417, 1364, 1319, 1270, 1146, 1108, 1067, 1023, 968, 922, 875, 850, 828, 735, 691, 651; ^{1}H NMR (400 MHz, $CDCl_3$ + 0.03% TMS): δ 7.82 – 7.73 (m, 2H), 7.35 – 7.24 (m, 11H), 7.21 – 7.20 (m, 1H), 7.19 – 7.17 (m, 1H), 4.80 (s, 1H), 3.94 – 3.87 (m, 2H), 3.86 – 3.77 (m, 2H), 3.08 (d, *J* = 12.8 Hz, 1H), 2.76 (app. ddt, *J* = 12.9, 9.0, 6.1 Hz, 2H), 2.66 (s, 3H), 2.60 – 2.50 (m, 1H), 2.16 – 2.07 (m, 2H), 2.00 (dd, *J* = 11.5, 9.3 Hz, 1H), 1.71 (dd, *J* = 11.5, 9.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.8 (C), 138.8 (2 × CH), 136.9 (2 × CH), 135.0 (2 × CH), 131.4 (C), 131.0 (C), 129.8 (C), 129.7 (2 × CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.2 (2 × CH), 128.7 (2 × CH), 121.5 (CH), 72.3 (CH_2), 66.3 (CH_2), 65.5 (C), 64.5 (C), 52.7 (C), 43.7 (CH_2), 41.9 (CH), 40.1 (CH_3), 33.7 (CH_2), 28.9 (CH_2); ^{1}H NMR (400 MHz, C_6D_6): δ 8.16 (d, *J* = 7.1 Hz, 2H), 7.37 – 7.28 (m, 4H), 7.12 – 7.02 (m, 3H), 7.00 – 6.91 (m, 6H), 5.09 (s, 1H), 4.27 (d, *J* = 12.8 Hz, 1H), 4.03 (app. td, *J* = 12.2, 2.8 Hz, 1H), 3.92 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.59 (app. t, *J* = 5.9 Hz, 1H), 3.46 (d, *J* = 12.7 Hz, 1H), 2.60 (dd, *J* = 12.0, 5.9 Hz, 1H), 2.47 – 2.32 (m, 2H), 2.21 – 2.02 (m, 5H), 1.95 (dd, *J* = 14.5, 2.6 Hz, 1H), 1.52 (dd, *J* = 11.3, 8.5 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 151.1 (C), 139.7 (2 × CH), 137.6 (2 × CH), 135.2 (2 × CH), 132.6 (C), 131.9 (C), 131.0 (C), 130.1 (2 × CH), 129.9 (CH), 129.6 (2 × CH), 129.5 (CH), 129.3 (CH), 129.2 (2 × CH), 123.1 (CH), 73.0 (CH_2), 66.9 (CH_2), 66.4 (C), 64.9 (C), 53.2 (C), 44.1 (CH_2), 42.6 (CH), 39.8 (CH_3), 34.4 (CH_2), 29.5 (CH_2); MS (LCMS, ES+): 599 (11) $[M+NH_4]^+$, 473 (25), 472 (100) $[M-PhSH+H]^+$; HRMS (ES+) *m/z* calculated for $C_{30}H_{32}NO_3S_4$ $[M+H]^+$ 582.12596, found 582.12594.

8.2.18 Preparation of Allyl Alcohols

***Rac*-(1aR,3aS,4S,8bS)-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 278**

Prepared according to **GP12A** from **273** (67 mg, 0.25 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded allyl alcohol **278** as a colourless oil (48 mg, 70%); R_f= 0.25 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3493, 3405, 2925, 2886, 2853, 1740, 1458, 1414, 1382, 1321, 1223, 1150, 1101, 1079, 1041, 963, 893, 845, 816, 759, 732, 671; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 – 4.60 (m, 1H), 4.34 (app. dt, *J* = 15.9, 2.9 Hz, 1H), 4.07 (app. dq, *J* = 15.8, 2.3 Hz, 1H), 3.82 (app. dt, *J* = 11.0, 5.4 Hz, 1H) superimposed to 3.75 (app. dt, *J* = 11.0, 5.3 Hz, 1H), 3.62 – 3.37 (m, 3H) superimposed to 3.33 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.05 (d, *J* = 11.8 Hz, 1H), 1.99 (app. dtt, *J* = 15.9, 5.0, 2.5 Hz, 1H), 1.75 (app. ddq, *J* = 17.0, 5.6, 2.8 Hz, 1H), 1.27 (app. dq, *J* = 8.6, 4.3 Hz, 1H) superimposed to 1.21 (dd, *J* = 8.3, 5.4 Hz, 1H), 0.57 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.6 (C), 132.5 (C), 82.3 (CH), 78.2 (CH), 64.7 (CH_2), 63.7 (CH_2), 53.7 (CH_2), 43.3 (C), 36.5 (CH), 22.4 (CH_2), 20.2 (CH), 16.0 (CH_2); MS (GCMS, EI+): 271 (37), 254 (50), 192 (92), 148 (100); MS (LCMS, ES+): 294 (34) $[M+Na]^+$, 274 (24), 254 (100) $[M-H_2O+H]^+$; HRMS (ES+) *m/z* calculated for $C_{12}H_{18}NO_4S$ $[M+H]^+$ 272.09511, found 272.09476.

***Rac*-(1aR,3aS,4S,8bS)-3-((2-chlorophenyl)sulfonyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 395**

Prepared according to **GP12B** from **384** (67 mg, 0.25 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded allyl alcohol **395** as a light yellow oil (29 mg, 31%); R_f= 0.33 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3255, 1520, 1433, 1343, 1309, 1157, 1087, 1045, 1000, 940, 851, 739, 679; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.39 (ddd, *J* = 8.5, 6.7, 2.0 Hz, 1H), 5.07 – 4.96 (m, 1H), 4.37 – 4.28 (m, 1H), 4.18 – 4.05 (m, 2H), 3.96 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.83 – 3.70 (m, 2H), 3.59 (d, *J* = 9.9 Hz, 1H), 2.99 (s, 1H), 1.91 (app. dtq, *J* = 15.8, 5.0, 2.5 Hz, 1H), 1.71 (app. dtq, *J* = 16.8, 5.6, 2.8 Hz, 1H), 1.45 (app. dt, *J* = 9.2, 4.9 Hz, 1H), 1.18 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.59 (app. t, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7 (C), 135.2 (C), 134.0 (CH), 132.5 (CH), 132.4 (C), 132.2 (CH), 131.9 (C), 127.2 (CH), 81.5 (CH), 77.6 (CH), 64.6 (CH_2), 63.7 (CH_2), 53.0 (CH_2), 42.2 (C), 22.4 (CH_2), 19.8 (CH), 14.0 (CH_2); MS (LCMS, ES+): 757 (13) $[2M+Na]^+$, 387 (11) + 385 (28) $[M+NH_4]^+$, 370 (13) + 368 (40) $[M+H]^+$, 352 (37) + 350 (100) $[M-H_2O+H]^+$; HRMS (ES+) *m/z* calculated for $C_{17}H_{22}N_2O_4SCl$ $[M+NH_4]$ 385.0989, found 385.0970.

Note: Keep compound in freezer as it is subjected to degradation at room temperature.

***Rac*-(1aR,3aS,4S,8bS)-3-((4-methoxyphenyl)sulfonyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 396**

Prepared according to **GP12A** from **385** (90 mg, 0.25 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **396** as a white solid (87 mg, 96%); m.p. 73–74 °C; R_f= 0.38 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3516, 2888, 1592, 1494, 1461, 1440, 1331, 1305, 1262, 1225, 1156, 1120, 1092, 1023, 964, 898, 817, 728, 670; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.71 (m, 2H), 7.03 – 6.96 (m, 2H), 5.01 (s, 1H), 4.40 – 4.31 (m, 1H), 4.12 (app. dq, *J* = 16.1, 2.2 Hz, 1H), 3.96 (dd, *J* = 10.4, 5.3 Hz, 1H), 3.88 (s, 3H), 3.82 (d, *J* = 3.8 Hz, 1H), 3.81 – 3.70 (m, 2H), 3.29 (d, *J* = 10.4 Hz, 1H), 2.91 (d, *J* = 2.9 Hz, 1H), 1.87 (app. dtd, *J* = 16.7, 5.4, 2.6 Hz, 1H), 1.67 (app. dtt, *J* = 16.9, 5.6, 2.8 Hz, 1H), 1.44 (app. dt, *J* = 9.3, 4.9 Hz, 1H), 1.08 (dd, *J* = 8.4, 5.9 Hz, 1H), -0.06 (app. t, *J* = 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3

(C), 135.5 (C), 132.7 (C), 129.4 (2 × CH), 129.3 (C), 114.5 (2 × CH), 82.6 (CH), 78.2 (CH), 64.7 (CH_2), 63.7 (CH_2), 55.8 (CH_3), 54.1 (CH_2), 43.3 (C), 22.4 (CH_2), 19.9 (CH), 15.6 (CH_2); MS (LCMS, ES+): 749 (15) $[2M+Na]^+$, 365 (22), 364 (28), 346 (23) $[M-H_2O+H]^+$; MS (LCMS, ES-): 380 (11) $[M+H_2O-H]^-$, 363 (21), 362 (100) $[M-H]^-$; HRMS (ES+) *m/z* calculated for $C_{18}H_{22}NO_5S$ $[M+H]^+$ 364.1213, found 364.1208; calculated for $C_{18}H_{20}NO_4S$ $[M-H_2O+H]^+$ 364.1108, found 346.1104.

***Rac*-(1aR,3aS,4S,8bS)-3-((4-nitrophenyl)sulfonyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 233**

Prepared according to **GP12B** from **228** (94 mg, 0.25 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded allyl alcohol **243** as a yellow solid (70 mg, 74%); m.p. 103-104 °C; R_f= 0.35 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3543, 2851, 2290, 2085, 1905, 1703, 1603, 1527, 1349, 1224, 1164, 1103, 855, 736, 687; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 – 8.34 (m, 2H), 8.03 – 7.97 (m, 2H), 5.03 – 4.95 (m, 1H), 4.33 (app. dtd, *J* = 16.1, 2.6, 1.2 Hz, 1H), 4.10 (app. dq, *J* = 16.3, 2.4 Hz, 1H), 4.02 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.85 (d, *J* = 3.8 Hz, 1H), 3.79 (ddd, *J* = 10.9, 5.9, 4.9 Hz, 1H), 3.72 (ddd, *J* = 11.2, 6.0, 4.9 Hz, 1H), 3.35 (dd, *J* = 10.6, 1.0 Hz, 1H), 2.94 (d, *J* = 3.6 Hz, 1H), 1.87 (app. dtd, *J* = 16.9, 5.1, 2.5 Hz, 1H), 1.66 (app. dtt, *J* = 16.5, 5.5, 2.8 Hz, 1H), 1.47 (app. dtd, *J* = 8.4, 5.0, 1.1 Hz, 1H), 1.14 (ddd, *J* = 8.4, 6.2, 0.6 Hz, 1H), -0.03 – -0.08 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4 (C), 143.5 (C), 135.6 (C), 132.5 (C), 128.5 (2 × CH), 124.6 (2 × CH), 82.1 (CH), 78.4 (CH), 64.6 (CH_2), 63.7 (CH_2), 54.2 (CH_2), 43.1 (C), 22.3 (CH_2), 19.7 (CH), 15.4 (CH_2); MS (LCMS, ES+): 442 (18), 396 (42) $[M+NH_4]^+$, 379 (10), 378 (20), 377 (70), 362 (21), 361 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 413 (10) 377 (100) $[M-H]^-$; HRMS (ES-) *m/z* calculated for $C_{17}H_{17}N_2O_6S$ $[M-H]^-$ 377.08128, found 377.08078.

***Rac*-(1aR,3aS,4S,8bS)-3-((3,5-dimethylisoxazol-4-yl)sulfonyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 397**

Prepared according to **GP12A** from **386** (88 mg, 0.25 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded allyl alcohol **397** as a light yellow oil (74 mg, 84%); R_f= 0.33 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3398, 2925, 2889, 2853, 1585, 1437, 1405, 1371, 1335, 1267, 1224, 1176, 1124, 1080, 1038, 978, 892, 843, 814, 757, 732, 683; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (app. tt, *J* = 3.4, 1.7 Hz, 1H), 4.33 (app. dq, *J* = 16.6, 2.5, 2.1 Hz, 1H), 4.10 (app. dq, *J* = 16.5, 2.4 Hz, 1H), 3.95 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.90 (d, *J* = 3.8 Hz, 1H), 3.85 – 3.71 (m, 2H), 3.38 (dd, *J* = 10.2, 1.0 Hz, 1H), 2.85 (s, 1H), 2.66 (s, 3H), 2.42 (s, 3H), 1.92 (app. dtq, *J* = 15.8, 5.1, 2.5 Hz, 1H), 1.71 (app. dtq, *J* = 16.8, 5.6, 2.8 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.28 (dd, *J* = 8.3, 6.1 Hz, 1H), 0.40 (dd, *J* = 6.2, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9 (C), 157.6 (C), 135.5 (C), 132.7 (C), 115.4 (C), 82.1 (CH), 77.7 (CH), 64.6 (CH_2), 63.7 (CH_2), 53.6 (CH_2), 43.1 (C), 22.4 (CH_2), 19.8 (CH), 15.7 (CH_2), 13.3 (CH_3), 11.7 (CH_3); MS (LCMS, ES+): 336 (21), 335 (100), $[M-H_2O+H]^+$; MS (LCMS, ES-): 352 (17), 351 (100) $[M-H]^-$, HRMS (ES+) *m/z* calculated for $C_{16}H_{20}N_2O_5SNa$ $[M+Na]^+$ 375.09851, found 375.09803.

***Rac*-(1aR,3aS,4S,8bS)-3-(piperidin-1-ylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 398**

Prepared according to **GP12A** from **387** (85 mg, 0.25 mmol). Flash column chromatography [linear gradient Heptane:EtOAc 100:0-0:100] afforded allyl alcohol **398** as a white solid (76 mg, 89%); m.p. 141–142 °C; R_f= 0.3 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3525, 3500, 2935, 2852, 1445, 1412, 1329, 1277, 1217, 1142, 1104, 1082, 1053, 996, 933, 909, 843, 813, 728, 710, 635, 602, 538, 497; ^{1}H NMR (400 MHz, $CDCl_3$):

δ 4.89 (app. dq, *J* = 3.6, 1.9 Hz, 1H), 4.34 (app. dtd, *J* = 16.0, 2.6, 1.2 Hz, 1H), 4.10 (app. dq, *J* = 16.1, 2.3 Hz, 1H), 3.99 (d, *J* = 3.9 Hz, 1H), 3.86 – 3.72 (m, 3H), 3.44 (dd, *J* = 9.8, 1.1 Hz, 1H), 3.18 (app. t, *J* = 5.4 Hz, 4H), 2.87 (s, 1H), 1.94 (app. dtq, *J* = 15.6, 5.0, 2.4 Hz, 1H), 1.73 (app. dtq, *J* = 14.0, 5.5, 2.6 Hz, 1H), 1.66 – 1.58 (m, 4H) superimposed to 1.57 – 1.46 (m, 3H), 1.30 (ddd, *J* = 8.4, 5.9, 0.6 Hz, 1H), 0.76 (dd, *J* = 5.9, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.2 (C), 132.7 (C), 81.9 (CH), 78.3 (CH), 64.6 (CH_2), 63.6 (CH_2), 53.7 (CH_2), 47.1 (2×CH_2), 42.8 (C), 25.4 (2×CH_2), 23.8 (CH_2), 22.3 (CH_2), 20.2 (CH), 15.7 (CH_2); HRMS (ES+) *m/z* calculated for $C_{16}H_{24}N_2O_4SNa$ $[M+Na]^+$ 363.1354, found 363.1353.

***Rac*-((1aR,3aS,4R,8bS)-4-hydroxy-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-3(1H)-yl)(morpholino)methanone 399**

Prepared according to **GP12B** from **276** (91 mg, 0.3 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **399** as a white solid (50 mg, 54%); m.p. 113-114 °C; R_f= 0.53 (CH_2Cl_2:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3399, 2963, 2923, 2884, 2846, 1669, 1636, 1459, 1403, 1352, 1276, 1219, 1197, 1173, 1112, 1086, 1049, 1023, 991, 944, 912, 874, 847, 829, 795, 761, 710, 659; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (d, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 1H), 4.29 (dt, *J* = 15.5, 2.6 Hz, 1H), 4.23 (dt, *J* = 15.8, 2.7 Hz, 1H), 3.87 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.79 (dq, *J* = 11.2, 5.5 Hz, 2H), 3.74 – 3.63 (m, 5H), 3.37 – 3.20 (m, 4H), 1.97 (dtq, *J* = 10.5, 5.1, 2.5 Hz, 1H), 1.83 (dtd, *J* = 17.1, 5.6, 2.8 Hz, 1H), 1.45 (dt, *J* = 9.0, 4.8 Hz, 1H), 1.19 (dd, *J* = 8.3, 5.7 Hz, 1H), 0.74 (t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.4 (C), 136.0 (C), 135.6 (C), 73.6 (CH), 68.3 (CH), 66.8 (2 × CH_2), 65.1 (CH_2), 63.9 (CH_2), 55.1 (CH_2), 47.2 (2 × CH_2), 40.4 (C), 22.7 (CH_2), 20.3 (CH), 13.1 (CH_2); ^{1}H NMR (400 MHz, C_6D_6): δ 4.50 – 4.38 (m, 3H), 4.14 (dt, *J* =

15.7, 2.9 Hz, 1H), 3.64 (dt, *J* = 10.6, 5.1 Hz, 1H), 3.58 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.51 (ddd, *J* = 11.2, 6.6, 4.8 Hz, 1H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.41 – 3.32 (m, 4H), 3.01 (dd, *J* = 5.7, 3.7 Hz, 4H), 2.12 (d, *J* = 4.4 Hz, 1H), 1.54 – 1.39 (m, 2H), 0.99 (dt, *J* = 8.9, 4.6 Hz, 1H), 0.79 (dd, *J* = 8.2, 5.5 Hz, 1H), 0.48 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 164.0 (C, detected by HMBC), 137.0 (C), 135.5 (C), 74.0 (CH), 69.0 (CH), 67.0 (2 × CH_2), 65.5 (CH_2), 64.1 (CH_2), 55.1 (CH_2), 47.8 (2 × CH_2), 41.0 (C), 23.1 (CH_2), 20.6 (CH), 13.2 (CH_2); MS (LCMS, ES+): 329 (10) $[M+Na]^+$, 305 (50), 290 (17), 289 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 306 (18), 305 (100) $[M-H]^-$; HRMS (ES+) *m/z* calculated for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 307.16523, found 307.16457.

Rac-((1aR,3aS,4S,8bS)-4-hydroxy-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-3(1H)-yl)(morpholino)methanone 398

Prepared according to **GP12A** from **276** (76 mg, 0.25 mmol) or **GP12B** from **276** (91 mg, 0.3 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **398** as a white solid (**GP12A**: 67 mg, 88%, **GP12B**: 26 mg, 34%); m.p. 104-105 °C; R_f= 0.58 (CH_2Cl_2:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3419, 2957, 2888, 2847, 2748, 1607, 1457, 1404, 1350, 1268, 1222, 1109, 1083, 1027, 962, 941, 896, 844, 774, 720, 682, 658; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (app. t, *J* = 4.9 Hz, 1H), 4.38 (app. dt, *J* = 16.1, 2.9 Hz, 1H), 4.17 – 4.07 (m, 2H), 4.01 (s, 1H), 3.87 – 3.73 (m, 3H), 3.76 – 3.63 (m, 4H), 3.61 (d, *J* = 10.3 Hz, 1H), 3.35 – 3.25 (m, 2H), 3.26 – 3.16 (m, 2H), 1.96 (app. dtt, *J* = 17.4, 5.1, 2.5 Hz, 1H), 1.76 (app. dtq, *J* = 17.2, 5.8, 2.8 Hz, 1H), 1.43 (app. dt, *J* = 9.0, 4.8 Hz, 1H), 1.22 (dd, *J* = 8.3, 5.8 Hz, 1H), 0.71 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.6 (C), 135.4 (C), 132.5 (C), 81.4 (CH), 78.0 (CH), 66.8 (2 × CH_2), 64.9 (CH_2), 63.8 (CH_2), 52.9 (CH_2), 47.3 (2 × CH_2), 40.1 (C), 22.6 (CH_2), 20.1 (CH), 14.4 (CH_2); ^{1}H NMR (400 MHz,

C_6D_6): δ 4.82 (s, 1H), 4.76 – 4.58 (m, 2H), 4.31 – 4.19 (m, 2H), 3.61 (app. td, *J* = 6.4, 3.2 Hz, 1H), 3.55 (app. dtd, *J* = 11.0, 5.4, 1.9 Hz, 1H), 3.42 – 3.31 (m, 4H), 3.26 (ddd, *J* = 10.4, 4.8, 1.8 Hz, 1H), 3.11 (dd, *J* = 10.2, 1.9 Hz, 1H), 3.03 – 2.95 (m, 2H), 2.91 – 2.83 (m, 2H), 1.59 (app. dtt, *J* = 15.8, 5.2, 2.5 Hz, 1H), 1.34 (app. dtt, *J* = 17.2, 5.9, 2.8 Hz, 1H), 0.87 – 0.77 (m, 2H), 0.34 – 0.28 (m, 1H); MS (LCMS, ES+): 635 (16) $[2M+Na]^+$, 307 (18), 290 (16), 289 (100) $[M-H_2O+H]^+$; HRMS (ES+) *m/z* calculated for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 307.16523, found 307.16465.

***Rac*-(1aR,3aS,4R,8bS)-4-hydroxy-N-methyl-N-phenyl-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-3(1H)-carboxamide 400**

Prepared according to **GP12B** from **368** (65 mg, 0.2 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **400** as a white solid (38 mg, 58%); m.p. 146 – 147 °C; R_f= 0.65 (CH_2Cl_2:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3281, 2923, 2895, 2851, 2795, 1609, 1480, 1438, 1396, 1329, 1288, 1269, 1216, 1194, 1160, 1102, 1050, 1003, 964, 924, 870, 839, 785, 754, 697, 670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 2H), 7.22 – 7.13 (m, 3H), 4.45 (d, *J* = 3.9 Hz, 1H), 4.31 – 4.17 (m, 3H), 3.83 – 3.71 (m, 2H), 3.30 – 3.21 (m, 2H) superimposed to 3.20 (s, 3H), 2.03 (s, 1H), 1.90 (app. ddq, *J* = 13.6, 5.4, 2.7 Hz, 1H), 1.74 (app. dtd, *J* = 17.0, 5.3, 2.6 Hz, 1H), 1.29 (app. dt, *J* = 9.1, 4.7 Hz, 1H), 1.07 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.59 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.7 (C), 146.2 (C), 135.6(5) (C) superimposed to 135.6(2) (C), 129.7 (2 × CH), 125.6 (CH), 125.4 (2 × CH), 74.0 (CH), 68.8 (CH), 65.0 (CH_2), 63.8 (CH_2), 54.4 (CH_2), 40.6 (C), 40.3 (CH_3), 22.6 (CH_2), 20.1 (CH), 13.6 (CH_2); ^{1}H NMR (400 MHz, C_6D_6): δ 7.06 – 6.97 (m, 4H), 6.88 – 6.81 (m, 1H), 4.54 (app. t, *J* = 6.0 Hz, 1H), 4.40 (d, *J* = 15.5 Hz, 1H), 4.33 (d, *J* = 6.1 Hz, 1H), 4.12 (d, *J* = 16.2 Hz, 1H), 3.57 (app. dt, *J* = 10.4, 5.0 Hz, 1H), 3.43 (app. dt, *J* = 11.3, 5.6 Hz, 1H), 3.33 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.24 (d, *J* = 10.5 Hz, 1H), 3.13 (d, *J* = 1.3 Hz,

3H), 2.33 (d, *J* = 5.6 Hz, 1H), 1.37 – 1.27 (m, 2H), 0.80 (app. dt, *J* = 9.1, 4.7 Hz, 1H), 0.69 – 0.65 (m, 1H), 0.36 (app. t, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 160.9 (C), 147.4 (C), 136.9 (C), 135.1 (C), 130.0 (2 × CH), 125.6 (2 × CH), 125.3 (CH), 74.4 (CH), 69.3 (CH), 65.4 (CH_2), 64.0 (CH_2), 54.6 (CH_2), 41.2 (C), 40.5 (CH_3), 22.9 (CH_2), 20.4 (CH), 13.9 (CH_2); ^{1}H NMR (400 MHz, Acetone): δ 7.37 – 7.29 (m, 2H), 7.29 – 7.24 (m, 2H), 7.14 – 7.07 (m, 1H), 4.33 (app. t, *J* = 6.1 Hz, 1H), 4.17 – 4.06 (m, 2H), 4.04 (d, *J* = 6.1 Hz, 1H), 3.72 – 3.61 (m, 3H), 3.39 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.28 (d, *J* = 10.6 Hz, 1H), 3.12 (s, 3H), 2.84 (s, 1H), 1.89 – 1.70 (m, 2H), 1.31 (app. dt, *J* = 9.2, 4.8 Hz, 1H), 1.09 (dd, *J* = 8.2, 5.3 Hz, 1H), 0.53 (app. t, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, Acetone-d_6): δ 161.1 (C, invisible at ^{13}C, detected by HMBC), 147.7 (C), 137.1 (C), 135.6 (C), 130.2 (2 × CH), 125.3 (2 × CH), 125.1 (CH), 74.1 (CH), 68.8 (CH), 65.3 (CH_2), 64.3 (CH_2), 54.9 (CH_2), 41.3 (C), 39.9 (CH_3), 23.2 (CH_2), 20.5 (CH), 13.5 (CH_2); ^{1}H NMR (400 MHz, MeOD + 0.05 v/v TMS): δ 7.36 (t, *J* = 7.9 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.20 – 7.15 (m, 1H), 4.33 (d, *J* = 6.0 Hz, 1H), 4.19 (d, *J* = 2.7 Hz, 2H), 3.99 (s, 1H), 3.80 – 3.68 (m, 2H), 3.36 (dd, *J* = 10.0, 3.9 Hz, 1H), 3.18 (s, 3H), 1.89 (ddq, *J* = 12.7, 5.1, 2.4 Hz, 1H), 1.80 (dtt, *J* = 14.2, 5.7, 2.5 Hz, 1H), 1.34 (dt, *J* = 9.0, 4.7 Hz, 1H), 1.13 (dd, *J* = 8.3, 5.4 Hz, 1H), 0.56 (t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, MeOD + 0.05 v/v TMS): δ 162.2 (C, detected by HMBC), 147.3 (C), 136.9 (C) superimposed to 136.7 (C), 130.8 (2 × CH), 126.6 (CH), 126.4 (2 × CH), 74.4 (CH), 69.3 (CH), 65.8 (CH_2), 65.0 (CH_2), 55.8 (CH_2), 41.6 (C), 40.5 (CH_3), 23.5 (CH_2), 20.9 (CH), 13.8 (CH_2); MS (LCMS, ES+): 310 (19), 309 (100) $[M-H_2O+H]^+$; HRMS (ES+) *m/z* calculated for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 327.17032, found 327.16955.

***Rac*-(1aR,3aS,4S,8bS)-4-hydroxy-N-methyl-N-phenyl-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole-3(1H)-carboxamide 401**

Prepared according to **GP12A** from **368** (50 mg, 0.15 mmol) or **GP12B** from **368** (65 mg, 0.20 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **401** as a white solid (**GP12A**, 43 mg, 88%; **GP12B**: 76 mg, 34%); m.p. 131 – 132 °C; R_f= 0.7 (CH_2Cl_2:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3442, 3385, 2970, 2939, 2898, 2865, 2808, 1635, 1617, 1593, 1491, 1428, 1381, 1329, 1280, 1221, 1115, 1082, 1048, 995, 961, 905, 866, 833, 791, 762, 733, 706, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 2H), 7.23 – 7.18 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 4.79 (app. t, *J* = 4.1 Hz, 1H), 4.39 (dd, *J* = 16.0, 3.0 Hz, 1H), 4.23 – 4.16 (m, 2H), 4.13 (app. dt, *J* = 16.1, 2.2 Hz, 1H), 3.82 – 3.73 (m, 2H), 3.20 (s, 3H), 3.19 – 3.15 (m, 1H), 2.76 (d, *J* = 10.6 Hz, 1H), 1.90 (app. ddt, *J* = 19.1, 5.0, 2.5 Hz, 1H), 1.69 (app. dtq, *J* = 17.3, 5.8, 2.9 Hz, 1H), 1.23 (app. dt, *J* = 9.2, 4.8 Hz, 1H), 1.07 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.46 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9 (C), 145.7 (C), 135.3 (C), 132.6 (C), 129.8 (2 × CH), 125.9 (CH) superimposed to 125.6 (2 × CH), 82.0 (CH), 78.6 (CH), 64.9 (CH_2), 63.8 (CH_2), 52.6 (CH_2), 40.5 (CH_3), 40.2 (C), 22.4 (CH_2), 20.3 (CH), 14.9 (CH_2); ^{1}H NMR (400 MHz, C_6D_6): δ 7.13 – 7.04 (m, 2H), 6.95 (app. t, *J* = 7.4 Hz, 1H), 6.92 – 6.82 (m, 2H), 5.04 (s, 1H), 5.00 (s, 1H), 4.84 (dd, *J* = 16.2, 3.1 Hz, 1H), 4.53 (d, *J* = 4.4 Hz, 1H), 4.35 (app. dt, *J* = 16.0, 2.2 Hz, 1H), 3.68 (app. dt, *J* = 11.0, 5.5 Hz, 1H), 3.57 (app. dt, *J* = 11.0, 5.4 Hz, 1H), 3.18 (s, 3H), 3.14 – 3.08 (m, 1H), 2.78 (d, *J* = 10.5 Hz, 1H), 1.59 (app. dtq, *J* = 15.9, 5.2, 2.5 Hz, 1H), 1.27 (app. dtt, *J* = 16.8, 5.7, 2.8 Hz, 1H), 0.82 – 0.70 (m, 2H), 0.33 – 0.21 (m, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 161.3 (C), 146.8 (C), 137.3 (C), 131.9 (C), 130.0 (2 × CH), 125.8 (2 × CH) superimposed to 125.8 (CH), 82.6 (CH), 79.5 (CH), 65.5 (CH_2), 64.0 (CH_2), 53.0 (CH_2), 40.7 (CH_3), 40.6 (C), 22.8 (CH_2), 20.4 (CH), 14.8 (CH_2); MS (LCMS, ES+): 675 (12) $[2M+Na]^+$, 327 (32), 310 (21), 309 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 369 (13), 326 (12),

325 (66) $[M-H]^-$, 249 (100); HRMS (ES+) *m/z* calculated for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 327.17032, found 327.16954.

***Rac*-((1aR,3aS,4S,8bS)-4-hydroxy-1a,2,3a,4,7,8-hexahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-3(1H)-yl)(3,4,5-trimethoxyphenyl)methanone 405**

Prepared according to **GP12B** from **392** (50 mg, 0.16 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **405** as a white solid (53 mg, 87%); m.p. 155–156 °C; R_f= 0.35 (CH_2Cl_2:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3535, 3415, 2953, 2932, 2878, 2839, 2237, 1670, 1622, 1583, 1507, 1459, 1408, 1341, 1316, 1236, 1119, 1041, 1002, 964, 908, 863, 834, 768, 720, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 2H), 4.92 (s, 1H), 4.43 (app. dt, *J* = 16.0, 3.1 Hz, 1H), 4.38 (d, *J* = 4.1 Hz, 1H), 4.15 (app. dq, *J* = 16.2, 2.3 Hz, 1H), 4.01 (dd, *J* = 11.1, 5.5 Hz, 1H), 3.97 (d, *J* = 1.4 Hz, 1H), 3.88 (s, 6H) superimposed to 3.87 (s, 3H), 3.84 – 3.76 (m, 2H), 3.69 (d, *J* = 11.2 Hz, 1H), 1.97 (app. ddt, *J* = 18.2, 5.3, 2.6 Hz, 1H), 1.77 (app. dtd, *J* = 17.2, 5.8, 2.9 Hz, 1H), 1.55 (dd, *J* = 9.1, 4.7 Hz, 1H) superimposed to H_2O signal, 1.34 (dd, *J* = 8.4, 5.9 Hz, 1H), 0.84 – 0.76 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4 (C), 153.3 (2 × C), 139.6 (C), 135.7 (C), 132.8 (C), 131.4 (C), 104.3 (2 × CH), 82.3 (CH), 77.8 (CH), 64.8 (CH_2), 63.7 (CH_2), 61.0 (CH_3), 56.4 (2 × CH_3), 54.7 (CH_2), 41.5 (C), 22.4 (CH_2), 20.4 (CH), 16.1 (CH_2); ^{1}H NMR (400 MHz, C_6D_6): δ 6.83 (s, 2H), 5.07 (s, 1H), 4.84 (dd, *J* = 16.0, 2.9 Hz, 1H), 4.77 (s, 1H), 4.63 (d, *J* = 4.2 Hz, 1H), 4.37 (app. dq, *J* = 16.0, 2.2 Hz, 1H), 3.93 (s, 3H), 3.69 (app. tq, *J* = 11.0, 5.5 Hz, 2H), 3.59 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.46 (s, 6H), 3.43 (d, *J* = 11.1 Hz, 1H), 1.63 (app. ddq, *J* = 16.5, 5.2, 2.7 Hz, 1H), 1.40 (app. dtd, *J* = 18.9, 5.9, 3.1 Hz, 1H), 1.00 (app. dt, *J* = 9.3, 4.9 Hz, 1H), 0.94 – 0.90 (m, 1H), 0.41 – 0.38 (m, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 171.5 (C), 154.3 (2 ×

C), 141.3 (C), 137.5 (C), 132.4 (C), 132.2 (C), 106.0 (2 × CH), 83.1 (CH), 78.8 (CH), 65.5 (CH_2), 64.1 (CH_2), 60.9 (CH_3), 56.3 (3 × CH_3), 54.9 (CH_2), 41.8 (C), 22.8 (CH_2), 20.6 (CH), 16.1 (CH_2); MS (LCMS, ES+): 798 (12), 797 (31) $[2M+Na]^+$, 389 (13), 388 (58), 371 (25), 370 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 387 (15), 386 (78) $[M-H]^-$, 249 (100); HRMS (ES+) *m/z* calculated for $C_{21}H_{26}NO_6$ [M+H] 388.1760, found 388.1760.

***Rac*-(1aR,3aS,4S,8bS)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 241**

Achieved according to **GP12A** as a side-product from **393** (85 mg, 0.25 mmol) or **394** (75 mg, 0.25 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **241** as a white solid (3.87 mg, 8% from **393**, 12% from **394**); m.p. 65–66°C; R_f= 0.2 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3295, 2903, 2873, 2815, 2312, 2112, 1443, 1405, 1380, 1350, 1318, 1291, 1230, 1130, 1101, 1079, 1030, 994, 963, 933, 892, 858, 829, 715; ^1H NMR (400 MHz, $CDCl_3$): δ 4.70 – 4.60 (m, 1H), 4.34 (app. dt, *J* = 15.9, 2.9 Hz, 1H), 4.07 (app. dq, *J* = 15.8, 2.3 Hz, 1H), 3.82 (app. dt, *J* = 11.0, 5.4 Hz, 1H), 3.75 (app. dt, *J* = 11.0, 5.3 Hz, 1H), 3.53 (d, *J* = 4.9 Hz, 3H), 3.33 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.05 (d, *J* = 11.8 Hz, 1H), 1.99 (app. dtt, *J* = 15.9, 5.0, 2.5 Hz, 1H), 1.75 (app. ddq, *J* = 17.0, 5.6, 2.8 Hz, 1H), 1.27 (app. dq, *J* = 8.6, 4.3 Hz, 1H), 1.21 (dd, *J* = 8.3, 5.4 Hz, 1H), 0.57 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 134.7 (C), 133.3 (C), 80.2 (CH), 78.5 (CH), 65.0 (CH_2), 64.0 (CH_2), 51.2 (CH_2), 43.1 (C), 23.1 (CH_2), 22.0 (CH), 14.2 (CH_2); MS (LCMS, ES+): 196 (11), 195 (10), 194 (100); HRMS (ES+) *m/z* calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$ 413.17408, found 413.17354.

***Rac*-(1aR,3aS,4S,8bS)-3-(benzo[d][1,3]dioxol-4-ylmethyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 406**

Prepared according to **GP12A** from **393** (81 mg, 0.25 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **406** as a white solid (17 mg, 21%); m.p. 116 – 117 °C; R_f= 0.6 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3181, 2897, 2837, 2811, 2360, 2336, 2105, 1676, 1631, 1598, 1459, 1380, 1348, 1259, 1178, 1152, 1097, 1056, 1034, 983, 963, 933, 835, 793, 754, 726, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 – 6.74 (m, 3H), 5.99 – 5.92 (m, 2H), 4.45 (s, 1H), 4.31 (app. dt, *J* = 15.8, 2.5 Hz, 1H), 4.08 (app. dt, *J* = 15.9, 3.0 Hz, 1H), 3.84 (app. dt, *J* = 10.5, 5.1 Hz, 1H), 3.76 – 3.63 (m, 3H), 3.53 (dd, *J* = 10.1, 6.0 Hz, 1H), 2.83 (d, *J* = 1.4 Hz, 1H), 2.34 (dd, *J* = 10.2, 3.2 Hz, 1H), 1.92 (app. dddt, *J* = 16.5, 6.8, 4.7, 2.1 Hz, 1H), 1.70 – 1.56 (m, 3H), 1.32 (dd, *J* = 8.0, 5.3 Hz, 1H), 0.81 (app. t, *J* = 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.5 (C), 146.2 (C), 136.6 (C), 134.4 (C), 123.7 (CH), 121.6 (CH), 120.1 (C), 108.1 (CH), 100.9 (CH_2), 82.1 (CH), 81.8 (CH), 65.0 (CH_2), 63.7 (CH_2), 60.9 (CH_2), 51.6 (CH_2), 46.5 (C), 22.4 (CH_2), 22.3 (CH_2), 21.6 (CH); MS (LCMS, ES+): 329 (17), 328 (100); HRMS (ES+) *m/z* calculated for $C_{19}H_{22}NO_4$ $[M+H]^+$ 328.1543, found 328.1545.

***Rac*-(1aR,3aS,4S,8bS)-3-((1-methyl-1H-pyrazol-5-yl)methyl)-1,1a,2,3,3a,4,7,8-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 407**

Prepared according to **GP11A** from **394** (71 mg, 0.25 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **407** as a colourless oil (21 mg, 29%); R_f= 0.43 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3544, 3461, 3363, 3237, 2958, 2924, 2886, 2856, 1630, 1595, 1501, 1316, 1223, 1094, 1039, 834, 732, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 1.7 Hz, 1H), 6.16 (d,

J = 1.8 Hz, 1H), 4.26 (app. dt, *J* = 15.5, 2.4 Hz, 1H), 4.20 (s, 1H), 4.07 – 4.02 (m, 1H), 3.89 (s, 3H), 3.83 – 3.78 (m, 1H), 3.75 – 3.64 (m, 3H), 3.46 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.82 (d, *J* = 1.7 Hz, 1H), 2.31 (dd, *J* = 10.0, 3.0 Hz, 1H), 1.96 – 1.81 (m, 2H), 1.67 (app. dtt, *J* = 16.9, 5.1, 2.5 Hz, 1H), 1.54 (app. ddt, *J* = 10.8, 4.4, 2.9 Hz, 1H), 1.31 (dd, *J* = 8.0, 5.4 Hz, 1H), 0.78 (app. t, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.0 (C), 138.0 (CH), 136.1 (C), 134.5 (C), 106.3 (CH), 82.7 (CH), 81.3 (CH), 64.9 (CH_2), 63.7 (CH_2), 60.9 (CH_2), 48.3 (CH_2), 46.3 (C), 36.8 (CH_3), 22.2 (CH_2), 22.0 (CH_2), 21.5 (CH); MS (LCMS, ES+): 289 (19), 288 (100); HRMS (ES+) *m/z* calculated for $C_{16}H_{22}N_3O_2$ $[M+H]^+$ 288.17065, found 288.17018.

Rac-(1aR,3aS,4S,8bS)-3-(methylsulfonyl)-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4-ol 365

α,β-Conjugated carbonyl **362** (1.5 g, 4.9 mmol, 1.0 eq.) was dissolved in THF (49 mL, 0.1 M). $LiAlH_4$ 2.4M in THF (0.21 mL, 14.7 mmol, 3.0 eq.) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (30 mL), then the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a white solid. Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **365** as a white solid (450 mg, 34%); m.p. 114 – 115 °C; R_f= 0.2 (CH_2Cl_2:MeOH 9:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3291, 2932, 2888, 2857, 2829, 2802, 2751, 2688, 2286, 1478, 1457, 1411, 1322, 1222, 1148, 1093, 1064, 1031, 1015, 970, 922, 884, 836, 765, 710; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86 (d, *J* = 4.9 Hz, 1H), 3.93 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.86 (d, *J* = 3.8 Hz, 1H), 3.56 (d, *J* = 16.9 Hz, 1H), 3.44 (d, *J* = 10.0 Hz, 1H), 3.28 (d, *J* = 17.4 Hz, 1H), 3.03 (app. dt, *J* = 11.5, 5.4

Hz, 1H), 2.91 (app. dt, *J* = 12.3, 6.2 Hz, 1H), 2.84 (s, 3H), 2.21 (s, 2H), 1.88 (app. dtd, *J* = 16.9, 5.6, 2.6 Hz, 1H), 1.64 (app. dtd, *J* = 17.1, 5.7, 2.9 Hz, 1H), 1.52 (app. dt, *J* = 9.3, 4.9 Hz, 1H), 1.35 (dd, *J* = 8.3, 6.1 Hz, 1H), 0.60 (app. t, *J* = 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.2 (C), 133.3 (C), 82.7 (CH), 78.1 (CH), 53.7 (CH_2), 43.5 (CH_2), 43.4 (C), 42.5 (CH_2), 36.6 (CH_3), 22.6 (CH_2), 20.2 (CH), 15.8 (CH_2); MS (LCMS, ES+): 541 (16) $[2M+H]^+$, 272 (16), 271 (100) $[M+H]^+$; MS (LCMS, ES-): 287 (13) $[M+H_2O-H]^-$, 269 (100) $[M-H]^-$; HRMS (ES) *m/z* calculated for $C_{12}H_{19}N_2O_3S$ $[M+H]^+$ 271.1111, found 271.1109.

Rac-((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)(morpholino)methanone 460

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and 4 - morpholinecarbonyl chloride (36 µL, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **460** as a white solid (73 mg, 2 steps 73%); m.p. 131 – 132 °C R_f= 0.5 (CH_2Cl_2:MeOH 9:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3380, 2848, 2291, 2117, 1619, 1416, 1322, 1227, 1149, 1046, 960, 818, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86 (s, 1H), 3.98 (d, *J* = 17.1 Hz, 1H), 3.93 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.86 (d, *J* = 3.8 Hz, 1H), 3.73 – 3.64 (m, 5H), 3.47 – 3.40 (m, 2H), 3.34 – 3.21 (m, 5H), 3.12 – 2.92 (m, 1H), 2.83 (s, 3H), 2.03 – 1.97 (m, 1H), 1.74 (app. dtq, *J* = 16.3, 5.2, 2.5 Hz, 1H), 1.53 (app. dt, *J* = 9.3, 4.9 Hz, 1H), 1.35 (dd, *J* = 8.4, 6.1 Hz, 1H), 0.61 (app. t, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9 (C), 134.2 (C), 133.7 (C), 82.3 (CH), 78.1 (CH), 66.7 (2 × CH_2), 53.7 (CH_2), 47.3 (2 × CH_2), 45.9 (CH_2), 43.0 (C), 42.7 (CH_2), 36.5 (CH_3), 21.6 (CH_2), 20.4 (CH), 16.1 (CH_2); MS (LCMS, ES+): 789 (11) $[2M+Na]^+$., 367 (18), 366 (100) $[M-H_2O+H]^+$; MS (LCMS,

ES-): 429 (21), 428 (100); HRMS (ES) *m/z* calculated for $C_{17}H_{25}N_3O_5SNa$ $[M+Na]^+$ 406.1407, found 406.1397; calculated for $C_{17}H_{23}N_3O_4S$ $[M-H_2O+H]^+$ 366.1482, found 366.1474.

***Rac*-((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)(4-methylpiperazin-1-yl)methanone 461**

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and 4 -methyl-1-piperazinecarbonyl chloride (62 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **461** as a white solid (71 mg, 69%); m.p. 124 – 125 °C R_f= 0.35 (CH_2Cl_2:MeOH 9:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3485, 2796, 2290, 2115, 1616, 1418, 1322, 1217, 1149, 1046, 759, 654; ^1H NMR (400 MHz, $CDCl_3$): δ 4.87 (s, 1H), 4.01 – 3.91 (m, 2H), 3.87 (d, *J* = 3.8 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.44 – 3.38 (m, 2H), 3.36 – 3.31 (m, 1H), 3.29 – 3.25 (m, 4H), 3.12 – 2.89 (m, 1H), 2.83 (s, 3H), 2.39 (app. t, *J* = 4.9 Hz, 4H), 2.29 (s, 3H), 2.02 – 1.96 (m, 1H), 1.75 (app. ddq, *J* = 16.8, 5.4, 2.6 Hz, 1H), 1.54 (app. dt, *J* = 9.2, 5.0 Hz, 1H), 1.35 (dd, *J* = 8.4, 6.1 Hz, 1H), 0.60 (app. t, *J* = 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9 (C), 134.2 (C), 133.9 (C), 82.4 (CH), 78.1 (CH), 54.9 (2 × CH_2), 53.7 (CH_2), 46.7 (2 × CH_2), 46.3 (CH_3), 46.0 (CH_2), 43.1 (C), 42.8 (CH_2), 36.5 (CH_3), 21.6 (CH_2), 20.4 (CH), 16.1 (CH_2); MS (LCMS, ES+): 815 (18) $[2M+Na]^+$., 398 (29), 397 (100) $[M+H]^+$; MS (LCMS, ES-): 791 (23) $[2M-H]^-$, 395 (100) $[M-H]^-$; HRMS (ES) *m/z* calculated for $C_{18}H_{29}N_4O_4S$ $[M+H]^+$ 397.1904, found 397.1898.

***Rac*-(1aR,3aS,4S,8bS)-4-hydroxy-N-methyl-3-(methylsulfonyl)-N-phenyl-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridine-6(5H)-carboxamide 462**

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and *N*-phenyl-*N*-methylcarbamoyl chloride (53 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **462** as a white solid (65 mg, 2 steps 62%); m.p. 156 – 157 °C R_f= 0.3 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3378, 2879, 2838, 1625, 1593, 1493, 1467, 1431, 1397, 1325, 1260, 1149, 1101, 1049, 1003, 962, 904, 885, 817, 758, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 2H), 7.15 – 7.08 (m, 3H), 4.73 (s, 1H), 3.91 (dd, *J* = 10.1, 5.2 Hz, 1H), 3.81 (d, *J* = 3.8 Hz, 1H) superimposed to 3.80 – 3.72 (m, 1H), 3.49 – 3.42 (m, 2H) superimposed to 3.39 (d, *J* = 10.2 Hz, 1H), 3.33 (ddd, *J* = 13.2, 6.6, 4.8 Hz, 1H), 3.22 (s, 3H), 2.81 (s, 3H), 2.73 (d, *J* = 3.5 Hz, 1H), 1.76 (app. dtt, *J* = 14.1, 4.9, 2.4 Hz, 1H), 1.56 – 1.44 (m, 2H), 1.30 (dd, *J* = 8.4, 6.1 Hz, 1H), 0.58 (dd, *J* = 6.1, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.3 (C), 146.8 (C), 134.0 (C), 133.8 (C), 129.6 (2 × CH), 124.8 (CH), 124.2 (2 × CH), 82.2 (CH), 78.2 (CH), 53.7 (CH_2), 44.8 (CH_2), 43.0 (C), 42.3 (CH_2), 39.7 (CH_3), 36.5 (CH_3), 21.6 (CH_2), 20.3 (CH), 16.1 (CH_2); MS (LCMS, ES+): 829 (17) $[2M+Na]^+$, 387 (23), 386 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 449 (23), 448 $[M+HCOO]^-$(100); HRMS (ES) *m/z* calculated for $C_{20}H_{26}N_3O_4S$ $[M+H]^+$ 404.1639, found 404.1630; calculated for $C_{20}H_{24}N_3O_3S$ $[M-H_2O+H]^+$ 386.1533, found 386.1526.

***Rac*-(5H-dibenzo[b,f]azepin-5-yl)((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)methanone 366**

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and 5*H*-dibenz[b,f]azepine-5-carbonyl chloride (79 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **366** as a white solid (78 mg, 2 steps 61%); m.p. 189 – 190 °C R_f= 0.43 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3559, 2926, 2894, 2877, 2839, 1630, 1567, 1485, 1405, 1321, 1265, 1211, 1150, 1071, 1038, 986, 963, 875, 820, 800, 760, 715, 695; ^1H NMR (400 MHz, DMSO): δ 7.58 – 7.45 (m, 2H), 7.43 – 7.36 (m, 4H), 7.30 – 7.25 (m, 2H), 7.06 (s, 2H), 5.07 (d, *J* = 7.1 Hz, 1H), 4.47 (s, 1H), 3.77 (d, *J* = 3.9 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.39 (d, *J* = 10.4 Hz, 1H), 3.31 – 3.25 (m, 1H), 3.17 (app. dt, *J* = 12.9, 5.0 Hz, 1H), 3.05 (ddd, *J* = 12.3, 6.7, 4.8 Hz, 1H), 2.92 (s, 3H), 1.37 (app. dt, *J* = 9.2, 4.8 Hz, 1H), 1.34 – 1.20 (m, 2H), 1.16 (dd, *J* = 8.3, 5.7 Hz, 1H), 0.62 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO): δ 158.4 (C), 142.4 (2 × C), 134.3 (C), 133.9 (2 × C), 132.6 (C), 131.2 (2 × CH), 129.0 (2 × CH), 128.9 (2 × CH), 127.4 (2 × CH), 126.3 (2 × CH), 79.7 (CH), 76.3 (CH), 52.7 (CH_2), 44.2 (CH_2), 42.9 (CH_2), 42.1 (C), 36.6 (CH_3), 20.6 (CH_2), 19.3 (CH), 14.6 (CH_2); MS (LCMS, ES+): 490 $[M+H]^+$ (23), 473 (34), 472 $[M-H_2O+H]^+$ (100); MS (LCMS, ES-): 535 (31), 534 $[M+HCOO]^-$(100); HRMS (ES) *m/z* calculated for $C_{27}H_{28}N_3O_4S$ $[M+H]^+$ 490.1795, found 490.1788; calculated for $C_{27}H_{27}N_3O_4SNa$ $[M+Na]^+$ 512.1614, found 512.1607; calculated for $C_{27}H_{26}N_3O_3S$ $[M-H_2O+H]^+$ 472.1689, found 472.1684.

***Rac*-(1aR,3aS,8bR)-6-(5H-dibenzo[b,f]azepine-5-carbonyl)-3-(methylsulfonyl)decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4(1H)-one 367**

Obtained as a side-product with procedure **GP12C** from **362** (79 mg, 0.26 mmol) and 5*H*-dibenz[b,f]azepine-5-carbonyl chloride (79 mg, 0.31 mmol). Flash column chromatography [linear gradient heptane:EtOAc 100:0-0:100] afforded allyl alcohol **367** as a light yellow oil (5.1 mg, 2 steps 4%); R_f= 0.45 (Heptane:EtOAc 1:1) [UV]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.38 (m, 2H), 7.32 – 7.28 (m, 3H), 7.22 – 7.12 (m, 4H), 6.94 – 6.83 (m, 2H), 4.26 (s, 1H), 3.59 (d, *J* = 9.7 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.13 – 3.01 (m, 4H), 2.96 – 2.79 (m, 2H), 2.71 – 2.55 (m, 3H), 1.55 – 1.42 (m, 2H), 1.29 (app. dt, *J* = 8.3, 4.2 Hz, 1H), 1.09 – 0.98 (m, 1H), 0.84 (dd, *J* = 8.3, 5.9 Hz, 1H), 0.74 (dd, *J* = 6.0, 4.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.3 (C), 159.9 (2 × C), 134.4 (2 × C), 129.2 (2 × CH), 129.0 (2 × CH), 127.7 (br, 2 × CH), 126.5 (2 × CH), 69.3 (CH), 49.7 (CH_2), 45.0 (CH), 43.1 (CH_2), 42.4 (CH_3), 40.6 (CH_2), 33.7 (C), 30.0 (CH), 22.9 (CH_2), 20.2 (CH), 10.5 (CH_2); 2 CH (aromatic rings) + 1C missing; MS (LCMS, ES+): 490 (11) $[M+H]^+$, 489 (34), 488 (100); MS (LCMS, ES-): 977 (15) $[2M-H]^-$, 488 (100) $[M-H]^-$.

***Rac*-((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)(10H-phenothiazin-10-yl)methanone 463**

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and 10*H*-phenothiazine-10-carbonyl chloride (81 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **463** as a white solid (97 mg, 2 steps 75%); m.p. 213 – 214 °C R_f= 0.5 (Heptane:EtOAc 1:1) [UV];

IR: ν_{max} (neat, cm^{-1}) 3531, 1647, 1585, 1482, 1460, 1408, 1321, 1280, 1241, 1155, 1084, 1066, 1035, 984, 963, 936, 882, 821, 758, 733, 683, 651; ^{1}H NMR (400 MHz, DMSO): δ 7.66 – 7.52 (m, 2H), 7.45 – 7.35 (m, 2H), 7.33 – 7.23 (m, 2H), 7.22 – 7.11 (m, 2H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.47 (dd, *J* = 7.1, 3.8 Hz, 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 3.80 (d, *J* = 3.9 Hz, 1H), 3.67 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.59 (d, *J* = 17.6 Hz, 1H), 3.52 – 3.38 (m, 3H), 2.92 (s, 3H), 1.70 – 1.60 (m, 1H) superimposed to 1.55 (d, *J* = 17.3 Hz, 1H), 1.43 (app. dt, *J* = 9.2, 4.8 Hz, 1H), 1.21 (dd, *J* = 8.3, 5.7 Hz, 1H), 0.65 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO): δ 156.1 (C), 140.8 (2 × C), 133.6 (C), 132.7 (C), 127.8 (2 × CH), 127.7 (2 × CH), 127.1 (2 × C), 125.2 (2 × CH), 121.0 (2 × CH), 79.6 (CH), 76.3 (CH), 52.6 (CH_2), 44.1 (CH_2), 42.3 (C), 42.0 (CH_2), 36.7 (CH_3), 20.8 (CH_2), 19.4 (CH), 14.5 (CH_2); MS (LCMS, ES+): 518 (15) $[M+Na]^+$, 490 $[M+H]^+$ (23), 480 (12), 479 (26), 478 $[M-H_2O+H]^+$ (100); MS (LCMS, ES-): 542 (14), 541 (27), 540 (100) $[M+HCOO]^-$(100); HRMS (ES) *m/z* calculated for $C_{25}H_{25}N_3O_4S_2Na$ $[M+Na]^+$ 518.1179, found 518.1169; calculated for $C_{25}H_{24}N_3O_3S_2$ $[M-H_2O+H]^+$ 478.1254, found 478.1246.

Rac-cyclopropyl((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)methanone 465

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and cyclopropanecarbonyl chloride (28 µL, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **465** as a white solid (55 mg, 2 steps 63%); m.p. 121 – 122 °C; R_f= 0.45 (CH_2Cl_2:MeOH 9:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2878, 1609, 1438, 1322, 1259, 1221, 1150, 1087, 1056, 963, 886, 818, 759, 714; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases,

integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ [4.89 (s, 0.66) + 4.84 (s, 0.34) 1H], [4.40 (d, *J* = 17.1 Hz, 0.64) + 4.21 – 3.97 (m, 1.45) + 3.97 – 3.65 (m, 3.26) + 3.58 – 3.39 (m, 1.58) 7H], [3.24 (s, 0.40) + 3.16 (s, 0.60), 1H], 2.83 (s, 3H), 2.17 – 1.89 (m, 1H), 1.85 – 1.61 (m, 2H), 1.51 (app. ddt, *J* = 13.3, 8.3, 4.6 Hz, 1H), 1.41 – 1.27 (m, 1H), 0.95 (app. dt, *J* = 6.3, 3.2 Hz, 2H), 0.81 – 0.69 (m, 2H), 0.64 (app. dt, *J* = 10.9, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as "maj"= major and "min"= minor and separated with a plus sign): δ 173.0 (maj) + 172.4 (min) (C), 134.5 (C), 133.0 (maj) superimposed to 132.9 (min) (C), 82.1 (maj) superimposed to 82.0 (min) (CH), 78.1 (maj) + 77.7 (min) (CH), 53.6 (maj) + 53.4 (min) (CH_2), 43.7 (CH_2), 42.8 (maj) superimposed to 42.7 (min) (C), 42.3 (min) + 41.6 (maj) (CH_2), 38.6 (CH_2), 37.0 (min) + 36.5 (maj) (CH_3), 22.8 (min) + 21.6 (maj) (CH_2), 20.(31) (maj) superimposed to 20.(26) (min) (CH), 16.0 (maj) + 15.6 (min) (CH_2), 11.7 (maj) + 11.3 (min) (CH), 7.9 (maj) + 7.3 (min) (CH_2); MS (LCMS, ES+): 699 (16) $[2M+Na]^+$, 322 (16), 341 (11), 340 (20), 339 (100) $[M+H]^+$, 321 $[M-H_2O+H]^+$ (93); MS (LCMS, ES-): 384 (16), 383 (100) $[M+HCOO]^-$; HRMS (ES) *m/z* calculated for $C_{16}H_{22}N_2O_4SNa$ $[M+Na]^+$ 361.1192, found 361.1183; calculated for $C_{16}H_{23}N_2O_4S$ $[M+H]^+$ 339.1373, found 339.1368; calculated for $C_{16}H_{21}N_2O_3S$ $[M-H_2O+H]^+$ 321.1267, found 321.1263.

***Rac*-((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)(1-(4-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)methanone 466**

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and 1-(4-trifluoromethyl-pyrimidin-2-yl)-piperidine-4-carbonyl chloride (91 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **466** as a white solid (66 mg, 2 steps 48%); m.p. 142 – 143 °C; R_f= 0.48 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3387, 2924, 2855, 2304, 2097, 2070, 1628, 1592, 1520, 1445, 1326, 1218, 1195, 1147, 1086, 1060, 1031, 981, 960, 904, 882, 816, 760, 716, 671; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, *J* = 4.7 Hz, 1H), 6.71 (d, *J* = 4.6 Hz, 1H), [4.92 (s, 0.64) + 4.87 (s, 0.34), 1H], 4.85 – 4.76 (m, 2H), [4.29 (d, *J* = 17.1 Hz, 0.63) + 4.19 (d, *J* = 18.6 Hz, 0.36) + 4.09 (d, *J* = 18.6 Hz, 0.35) + 4.03 – 3.86 (m, 3.27) + 3.74 – 3.55 (m, 0.71) + 3.53 – 3.38 (m, 1.65), 7H] 3.19 – 2.92 (m, 3H), 2.90 – 2.74 (m, 4H), 1.98 – 1.87 (m, 1H), 1.86 – 1.75 (m, 4H), 1.75 – 1.62 (m, 1H), 1.54 (app. ddt, *J* = 15.1, 9.4, 5.1 Hz, 1H), 1.36 (app. dt, *J* = 15.5, 7.3 Hz, 1H), 0.69 – 0.59 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -70.9 (3 × F); ^{13}C NMR (101 MHz, $CDCl_3$) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as “maj”= major and “min”= minor and separated with a plus sign): δ 173.9 (maj) + 173.4 (min) (C), 161.4 (C), 160.1 (CH), 156.8 (min) + 156.5 (maj) 156.1 (maj) + 155.8 (min) (C-CF_3), 135.0 (maj) + 134.6 (min) (C), 132.9 (maj) +

132.6 (min) (C), 124.8 (min) + 122.1 (maj) + 119.3 (maj) +116.6 (min) ($\underline{C}F_3$), 104.5 (min) + 104.4 (maj) (CH), 82.2 (min) + 82.1 (maj) (CH), 78.2 (maj) + 77.9 (min) (CH), 53.7 (major) + 53.5 (minor) (CH_2), 43.7 (min) + 43.4 (maj) (2 × CH_2), 42.9 (maj, br) superimposed to 42.8 (min, br) + 42.1 (br) + 41.3 (br) (CH_2+C, single resonances not distinguishable), 39.4 (major) + 39.1 (minor) (CH), 38.7 (CH_2), 36.8 (min) + 36.4 (maj) (CH_3), 28.4 (min) + 28.(17) (maj) + 28.(17) (maj) (2 × CH_2), 23.1 (min) + 21.6 (maj) (CH_2), 20.5 (maj, br) + 20.4 (min, br) (CH), 16.2 (maj) + 15.9 (min) (CH_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (d, *J* = 4.8 Hz, 1H), 6.98 (d, *J* = 4.8 Hz, 1H), [5.20 (s, 0.69) + 4.73 – 4.54 (m, 2.92) + 4.19 (d, *J* = 17.7 Hz, 0.77) + 3.96 (d, *J* = 17.3 Hz, 0.38) + 3.86 (dd, *J* = 11.4, 4.0 Hz, 0.84) + 3.80 – 3.63 (m, 2.40), 8H], [3.58 – 3.27 (m, 2.79) + 3.13 – 2.88 (m, 6.38), 9H], [2.06 – 1.92 (m, 0.62) + 1.92 – 1.63 (m, 3.81) + 1.58 – 1.41 (m, 3.15) + 1.30 (ddd, *J* = 8.5, 5.6, 3.2 Hz, 0.79) + 0.75 – 0.67 (m, 0.72), 9H]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (d, *J* = 4.8 Hz, 1H), 6.92 (d, *J* = 4.8 Hz, 1H), 4.71 (s, 1H), 4.63 – 4.57 (m, 2H), 4.26 – 4.16 (m, 1H), 3.93 (d, *J* = 4.0 Hz, 1H), 3.90 – 3.79 (m, 1H), 3.79 – 3.71 (m, 2H), 3.58 – 3.45 (m, 2H), 3.20 – 2.93 (m, 7H), 2.03 – 1.91 (m, 1H), 1.87 – 1.72 (m, 3H), 1.67 – 1.57 (m, 2H), 1.53 (app. dt, *J* = 9.1, 4.9 Hz, 1H), 1.32 (dd, *J* = 8.3, 5.7 Hz, 1H), 0.74 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO): δ 172.5 (C), 160.7 (CH), 154.5 (d, $J_{C\text{-}F}$ = 35.0 Hz, $\underline{C}$-CF_3), 120.2 (d, $J_{C\text{-}F}$ = 275.0 Hz, $\underline{C}F_3$), 103.8 (CH), 79.4 (CH), 76.2 (CH), 52.2 (CH_2), 42.5 (2 × CH_2), 41.6 (CH_2), 37.1 (CH_3), 27.4 (2 × CH_2), 21.0 (CH_2), 19.0 (CH), 14.1 (CH_2), 6C missing; MS (LCMS, ES+): 529 (25), 528 $[M+H]^+$ (100); MS (LCMS, ES-): 573 (27), 572 (100) $[M+HCOO]^-$; HRMS (ES) *m/z* calculated for $C_{23}H_{29}F_3N_5O_4S$ $[M+H]^+$ 528.1887, found 528.1875; calculated for $C_{23}H_{28}F_3N_5O_4SNa$ $[M+Na]^+$ 550.1706, found 550.1690; calculated for $C_{23}H_{27}F_3N_5O_3S$ $[M-H_2O+H]^+$ 510.1781, found 510.1771.

***Rac*-((1aR,3aS,4S,8bS)-4-hydroxy-3-(methylsulfonyl)-1,1a,2,3,3a,4,7,8-octahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-6(5H)-yl)(3,4,5-trimethoxyphenyl)methanone 467**

Prepared according to **GP12C** from **362** (79 mg, 0.26 mmol) and 3,4,5-trimetoxybenzoyl chloride (72 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **467** as a white solid (86 mg, 2 steps 71%); m.p. 156 – 157 °C; R_f= 0.2 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2930, 2882, 2836, 1615, 1580, 1505, 1460, 1414, 1367, 1321, 1226, 1152, 1122, 1057, 1000, 961, 903, 854, 814, 760, 662; Note: two sets of signals with different intensity were observed for certain protons at ^{1}H NMR analysis at room temperature, due to the presence of two rotamers; in these cases, integrations are reported to the second decimal place; above-mentioned resonances are separated with a plus sign and included in square parenthesis along with the merged integrations in round figures; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H), [4.94 (s, 0.42) superimposed to 4.83 (s, 0.56), 1H], [4.49 – 4.08 (m, 1.36) + 4.07 – 3.78 (m, 12.13) + 3.75 (s, 0.79), 14H], 3.54 (s, 1H), 3.47 – 3.38 (m, 1H), 2.95 – 2.79 (m, 4H), 2.15 – 1.91 (m, 1H), 1.87 – 1.70 (m, 1H), 1.60 – 1.53 (m, 1H), 1.39 (s, 1H), 0.65 (app. t, *J* = 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C) (two signals with different intensity were observed for certain carbons due to the presence of two rotamers; in these cases, peaks corresponding to the same carbon atom are reported as “maj”= major and “min”= minor and separated with a plus sign): δ 170.9 (C), 153.4 (C), 104.8 (CH), 104.2 (CH), 82.2 (CH), 78.2 (CH), 61.0 (CH_3), 56.4 (2 × CH_3), 53.7 (CH_2), 46.8 (br, CH_2), 43.0 (CH_2), 39.6 (C), 36.5 (br, CH_3), 21.7 (br, CH_2), 20.5 (CH), 16.3 (br, CH_2), 5C missing; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ 6.78 – 6.62 (m, 2H), [5.25 (s,0.60) + 5.10 (s, 0.40), 1H], [4.68 (s, 0.61), 4.56 (s, 0.42), 1H], [4.28 (d, *J* = 17.9 Hz, 0.60) + 4.07 (d, *J* = 17.2 Hz, 0.44), 1H], 3.79 (s, 8H) superimposed to 3.69 (s, 5H), 3.53 – 3.41 (m, 2H),

3.01 – 2.90 (m, 3H), 1.99 (d, *J* = 17.4 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.55 (app. dt, *J* = 9.1, 4.9 Hz, 1H), 1.31 (dd, *J* = 8.3, 5.7 Hz, 1H), 0.72 (app. t, *J* = 5.3 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C): δ 6.70 (s, 2H), 4.82 (d, *J* = 6.4 Hz, 1H), 4.68 (s, 1H), 4.22 (d, *J* = 17.7 Hz, 1H), 3.91 (d, *J* = 4.0 Hz, 1H), 3.86 (app. dt, *J* = 17.6, 2.3 Hz, 1H), 3.82 (s, 6H), 3.75 (s, 5H), 3.50 (dd, *J* = 10.4, 1.1 Hz, 1H) superimposed to 3.44 (ddd, *J* = 12.8, 7.2, 5.0 Hz, 1H), 2.94 (s, 3H), 2.00 (app. dtt, *J* = 14.7, 5.0, 2.4 Hz, 1H), 1.81 (app. ddq, *J* = 16.7, 5.1, 2.5 Hz, 1H), 1.55 (app. dtd, *J* = 8.4, 4.9, 1.1 Hz, 1H), 1.33 (dd, *J* = 8.3, 5.8 Hz, 1H), 0.74 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, 90 °C): δ 168.8 (C), 152.5 (2 × C), 138.9 (C), 133.6 (C), 132.3 (C), 131.2 (C), 104.9 (2 × CH), 79.3 (CH), 76.1 (CH), 59.7 (CH_3), 56.0 (2 × CH_3), 52.2 (CH_2), 41.7 (CH_2), 37.1 (CH_3), 21.2 (CH_2), 19.1 (CH), 14.1 (CH_2), 1C+1CH_2 missing; MS (LCMS, ES+): 929 (19) $[2M+H]^+$, 467 (10), 466 (21), 465 (100) $[M+H]^+$, 447 (47) $[M-H_2O+H]^+$; MS (LCMS, ES-): 511 (12), 510 (26), 509 (100) $[M+HCOO]^-$; HRMS (ES) *m/z* calculated for calculated for $C_{22}H_{28}N_2O_7SNa$ $[M+Na]^+$ 487.1509, found 487.1497; calculated for $C_{22}H_{29}N_2O_7S$ $[M+H]^+$ 465.1790, found 465.1682; calculated for $C_{22}H_{27}N_2O_6S$ $[M-H_2O+H]^+$ 447.1584, found 447.1577.

***Rac*-(1aR,3aS,4S,8bS)-6-butyl-3-(methylsulfonyl)-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4-ol 469**

Prepared according to **GP12D** from **362** (79 mg, 0.26 mmol) and butyraldehyde (28 µL, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **469** as a light yellow oil (54 mg, 2 steps 64%); 0.38 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3539, 2954, 2930, 2870, 2806, 2768, 1645, 1607, 1464, 1418, 1376, 1325, 1222, 1151, 1084, 1044, 1008, 964, 903, 830, 760, 718; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 – 4.80 (m, 1H), 4.02 – 3.85 (m, 2H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.18 – 2.92 (m, 3H), 2.83 (s, 3H), 2.69 – 2.62 (m, 1H), 2.58 – 2.42 (m,

3H), 1.99 – 1.91 (m, 1H), 1.85 – 1.76 (m, 1H), 1.58 – 1.48 (m, 3H), 1.40 – 1.28 (m, 3H), 0.92 (app. t, *J* = 7.3 Hz, 3H), 0.58 (dd, *J* = 6.1, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.3 (C), 133.2 (C), 82.8 (CH), 78.4 (CH), 58.3 (CH_2), 53.7 (CH_2), 51.2 (CH_2), 49.8 (CH_2), 43.0 (C), 36.6 (CH_3), 29.6 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 20.2 (CH), 15.8 (CH_2), 14.2 (CH_3); MS (LCMS, ES+): 328 (17), 327 (100); HRMS (ES) *m/z* calculated for $C_{16}H_{27}N_2O_3S$ $[M+H]^+$ 327.17369, found 327.1736.

***Rac*-(1aR,3aS,4S,8bS)-6-(((3S,5S,7S)-adamantan-1-yl)methyl)-3-(methylsulfonyl)-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4-ol 470**

Prepared according to **GP12D** from **362** (79 mg, 0.26 mmol) and 1-adamantanecarbaldehyde (51 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **470** as a light yellow solid (62 mg, 2 steps 57%); m.p. 124 – 125 °C; 0.58 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3511, 2895, 2842, 2290, 2119, 1449, 1323, 1212, 1150, 1079, 1042, 963, 893, 832, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (s, 1H), 3.95 (dd, *J* = 10.1, 5.3 Hz, 1H), 3.86 (d, *J* = 3.8 Hz, 1H), 3.43 (d, *J* = 10.1 Hz, 1H), 3.21 (app. dt, *J* = 16.5, 3.0 Hz, 1H), 2.98 (app. d, *J* = 17.9 Hz, 1H), 2.83 (s, 3H), 2.77 (s, 1H), 2.66 – 2.53 (m, 2H), 2.08 (s, 2H), 1.96 – 1.87 (m, 4H), 1.70 – 1.60 (m, 7H), 1.55 – 1.46 (m, 7H), 1.33 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.57 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.2 (C), 133.0 (C), 82.7 (CH), 78.5 (CH), 71.0 (CH_2), 53.8(9) (CH_2) superimposed to 53.8(6) (CH_2), 52.4 (CH_2), 43.2 (C), 41.1 (3 × CH_2), 37.4 (3 × CH_2), 36.4 (CH_3), 35.1 (C), 28.6 (3 × CH), 22.7 (CH_2), 20.1 (CH), 16.0 (CH_2); MS (LCMS, ES+): 420 (27), 419 (100) $[M+H]^+$; MS (LCMS, ES-): 463 (37) $[M+HCOO]^-$, 248 (100); HRMS (ES) *m/z* calculated for $C_{23}H_{35}N_2O_3S$ $[M+H]^+$ 419.2363, found 419.2352.

***Rac*-(1aR,3aS,4S,8bS)-3-(methylsulfonyl)-6-((tetrahydro-2H-pyran-4-yl)methyl)-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4-ol 471**

Prepared according to **GP12D** from **362** (79 mg, 0.26 mmol) and 3,4,5,6-tetrahydro-2*H*-pyran-4-carbaldehyde (32 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **471** as a light yellow oil (58 mg, 2 steps 61%); 0.4 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3512, 2912, 2836, 2758, 2291, 2113, 1929, 1443, 1384, 1322, 1232, 1139, 1086, 1042, 982, 962, 888, 849, 830, 757, 712; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86 (s, 1H), 3.94 (app. td, *J* = 11.2, 4.7 Hz, 3H), 3.87 (d, *J* = 3.8 Hz, 1H), 3.43 (d, *J* = 10.4 Hz, 1H), 3.41 – 3.34 (m, 2H), 3.14 – 3.08 (m, 1H), 2.93 (d, *J* = 16.2 Hz, 1H), 2.83 (s, 3H), 2.62 – 2.50 (m, 2H), 2.33 (d, *J* = 7.1 Hz, 2H), 1.94 (app. ddq, *J* = 13.6, 5.4, 2.5 Hz, 1H), 1.90 – 1.61 (m, 5H), 1.53 (app. dt, *J* = 9.5, 5.0 Hz, 1H), 1.35 – 1.22 (m, 3H), 0.58 (app. t, *J* = 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.2 (C), 133.2 (C), 82.7 (CH), 78.4 (CH), 68.0 (2 × CH_2), 64.9 (CH_2), 53.8 (CH_2), 51.6 (CH_2), 50.2 (CH_2), 43.0 (C), 36.5 (CH_3), 33.0 (CH), 31.(92) (CH_2) superimposed to 31.(86) (CH_2), 22.7 (CH_2), 20.2 (CH), 16.0 (CH_2); MS (LCMS, ES+): 759 (15) $[2M+Na]^+$, 371 (14), 370 (37), 369 (100); MS (LCMS, ES-): 736 (16), 735 (44) $[2M-H]^+$, 385 (20) $[M+H_2O-H]^+$, 368 (20), 367 (100) $[M-H]^+$; HRMS (ES) *m/z* calculated for $C_{18}H_{29}N_2O_4S$ $[M+H]^+$ 369.1843, found 369.1836.

***Rac*-(1aR,3aS,4S,8bS)-6-(3,5-dimethylbenzyl)-3-(methylsulfonyl)-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4-ol 472**

Prepared according to **GP12D** from **362** (79 mg, 0.26 mmol) and 3,5-dimethylbenzaldehyde (42 µL, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **472**

as a white solid (54 mg, 2 steps 54%); m.p. 158 – 159 °C, 0.63 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3413, 2915, 2889, 2862, 2797, 2751, 2106, 1602, 1460, 1429, 1407, 1319, 1253, 1219, 1140, 1099, 1077, 1041, 982, 884, 848, 794, 767, 726, 707, 661; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 2H), 6.89 (s, 1H), 4.89 – 4.81 (m, 1H), 3.95 – 3.84 (m, 2H), 3.63 – 3.51 (m, 2H), 3.43 (d, *J* = 10.1 Hz, 1H), 3.19 – 3.09 (m, 1H), 3.02 (d, *J* = 15.9 Hz, 1H), 2.90 – 2.70 (m, 1H) superimposed to 2.83 (s, 3H), 2.65 (app. dt, *J* = 10.8, 5.3 Hz, 1H), 2.52 (ddd, *J* = 11.6, 7.1, 4.9 Hz, 1H), 2.29 (s, 6H), 1.92 (app. ddq, *J* = 17.2, 5.2, 2.6 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.52 (app. dt, *J* = 9.2, 4.9 Hz, 1H), 1.33 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.58 (app. t, *J* = 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.0 (C), 137.9 (2 × C), 135.3 (C), 133.3 (C), 128.9 (CH), 127.2 (2 × CH), 82.7 (CH), 78.4 (CH), 62.8 (CH_2), 53.7 (CH_2), 51.4 (CH_2), 49.1 (CH_2), 43.0 (C), 36.5 (CH_3), 22.7 (CH_2), 21.4 (2 × CH_3), 20.2 (CH), 15.9 (CH_2); MS (LCMS, ES+): 390 (22), 389 (100); HRMS (ES) *m/z* calculated for $C_{21}H_{29}N_2O_3S$ $[M+H]^+$ 389.1893, found 389.1883.

Rac-(1aR,3aS,4S,8bS)-6-(benzo[b]thiophen-2-ylmethyl)-3-(methylsulfonyl)-1,1a,2,3,3a,4,5,6,7,8-decahydrocyclopropa[3',4']pyrrolo[3',2':3,4]cyclopenta[1,2-c]pyridin-4-ol 473

Prepared according to **GP12D** from **362** (79 mg, 0.26 mmol) and 2-benzothiophenecarboxaldehyde (50 mg, 0.31 mmol). Preparative LCMS purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 to 2:98] afforded allyl alcohol **473** as a white solid (50 mg, 2 steps 46%); m.p. 186 – 187 °C, 0.65 (CH_2Cl_2:MeOH 9:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3518, 2920, 2893, 2854, 2793, 2751, 2283, 2110, 1733, 1489, 1458, 1438, 1414, 1315, 1260, 1247, 1212, 1186, 1151, 1093, 1061, 1025, 974, 955, 886, 828, 800, 752, 729, 681; ^{1}H NMR (400 MHz, DMSO): δ 7.95 – 7.84 (m, 1H), 7.76 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.42 – 7.25 (m, 3H), 5.00 (d, *J* = 7.1 Hz, 1H), 4.56 (s, 1H), 3.91 (d, *J* = 2.4 Hz, 2H), 3.84 (d, *J* = 4.0 Hz,

1H), 3.72 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.46 (d, *J* = 10.5 Hz, 1H), 3.12 (d, *J* = 15.8 Hz, 1H), 2.93 (s, 3H), 2.85 (d, *J* = 15.9 Hz, 1H), 2.65 (app. dt, *J* = 10.9, 5.3 Hz, 1H), 2.55 (app. dt, *J* = 11.5, 5.7 Hz, 1H), 1.90 (d, *J* = 17.4 Hz, 1H), 1.74 (d, *J* = 17.5 Hz, 1H), 1.49 (app. dt, *J* = 8.9, 4.7 Hz, 1H), 1.26 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.68 (app. t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO): δ 144.2 (C), 139.4 (C), 139.3 (C), 135.2 (C), 132.0 (C), 124.2 (CH), 124.0 (CH), 123.2 (CH), 122.4 (CH), 122.1 (CH), 79.9 (CH), 76.6 (CH), 56.7 (CH_2), 52.7 (CH_2), 50.5 (CH_2), 49.0 (CH_2), 42.0 (C), 36.8 (CH_3), 21.9 (CH_2), 19.2 (CH), 14.4 (CH_2); MS (LCMS, ES+): 419 (18), 418 (33), 417 (100); HRMS (ES) *m/z* calculated for $C_{21}H_{25}N_2O_3S_2$ $[M+H]^+$ 417.1301, found 417.1293.

8.2.19 Preparation of Tertiary Alcohols

Rac-(1aR,3aS,4R,4aS,8aS,8bR)-4-methyl-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 408

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and methylmagnesium bromide 1.0 M in THF (30 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **408** as a white solid (59 mg, 79%); m.p. 104 – 105 °C; R_f= 0.25 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3439, 2954, 2898, 2845, 1465, 1447, 1405, 1386, 1324, 1261, 1238, 1144, 1131, 1106, 1095, 1078, 1028, 1013, 936, 916, 891, 868, 846, 765, 742, 658, 599, 586, 564, 517; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (dd, *J* = 12.7, 2.3 Hz, 1H), 3.90 (ddd, *J* = 11.5, 5.0, 2.9 Hz, 1H), 3.80 – 3.70 (m, 2H) superimposed to 3.77 (s, 1H, confirmed at HSQC), 3.57 (d, *J* = 10.2 Hz, 1H), 3.35 (app. td, *J* = 11.6, 2.8 Hz, 1H), 2.88 (s, 3H), 2.32 (s, 1H), 2.30 – 2.23 (m, 1H), 1.88 (ddd, *J* = 8.0, 5.3, 2.3 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.55 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 1.45 (ddd, *J* = 13.2, 6.9, 3.1 Hz, 1H), 1.37 (s, 3H), 0.99 (dd, *J* = 8.4, 5.6 Hz, 1H), 0.57 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 79.7 (C), 75.9 (CH), 66.8 (CH_2), 65.7

(CH_2), 53.6 (CH_2), 45.8 (CH), 38.8 (C), 38.4 (CH_3), 32.9 (CH), 28.6 (CH_2), 25.0 (CH_3), 21.0 (CH), 13.9 (CH_2); MS (LCMS, ES+): 597 (13) $[2M+Na]^+$, 310 (10) $[M+Na]^+$, 289 (17), 288 (100) $[M+H]^+$, 270 (19) $[M-H_2O+H]^+$; HRMS (ES) *m/z* calculated for $C_{13}H_{22}NO_4S$ $[M+H]^+$ 288.12641, found 288.12586.

Rac-(1aR,3aS,4R,4aS,8aS,8bR)-4-cyclopropyl-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 409

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and cyclopropylmagnesium bromide 0.5 M in THF (156 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **409** as a white solid (23 mg, 28%); m.p. 89 – 90 °C; R_f= 0.28 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3518, 3003, 2956, 2898, 2879, 2846, 1465, 1410, 1382, 1309, 1253, 1224, 1202, 1178, 1134, 1085, 1013, 966, 915, 892, 825, 792, 761, 677; ^1H NMR (400 MHz, $CDCl_3$): δ 4.25 (dd, *J* = 12.5, 3.4 Hz, 1H), 4.00 (s, 1H), 3.83 (app. dt, *J* = 11.6, 4.6 Hz, 1H), 3.74 – 3.60 (m, 3H), 3.40 (app. td, *J* = 11.0, 3.4 Hz, 1H), 2.89 (s, 3H), 2.33 (app. q, *J* = 8.1 Hz, 1H), 2.21 (s, 1H), 2.07 (ddd, *J* = 8.3, 5.1, 3.5 Hz, 1H), 1.71 (app. dtd, *J* = 14.7, 10.1, 5.0 Hz, 1H), 1.54 (app. ddt, *J* = 16.8, 8.7, 4.0 Hz, 2H), 0.96 (dd, *J* = 8.4, 5.7 Hz, 1H), 0.73 (app. td, *J* = 8.2, 4.1 Hz, 1H), 0.60 (app. t, *J* = 5.2 Hz, 1H), 0.53 – 0.35 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 78.7 (C), 75.6 (CH), 66.8 (CH_2), 66.6 (CH_2), 53.2 (CH_2), 46.4 (CH), 39.5 (CH_3), 38.1 (C), 32.4 (CH), 28.3 (CH_2), 21.2 (CH), 17.3 (CH), 12.8 (CH_2), -0.4 (CH_2), -0.9 (CH_2); MS (LCMS, ES+): 336 (18) $[M+Na]^+$, 296 (100) $[M-H_2O+H]^+$; HRMS (ES) *m/z* calculated for $C_{15}H_{24}NO_4S$ $[M+H]^+$ 314.14206, found 314.14172; calculated for $C_{15}H_{22}NO_3S$ $[M-H_2O+H]^+$ 296.13149, found 296.13122.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-4-isopentyl-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 410**

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and isopentylmagnesium bromide 2.0 M in Et_2O (47 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **410** as a white solid (68 mg, 72%); m.p. 74 – 75 °C; R_f= 0.35 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1})) 3479, 2927, 2858, 1470, 1396, 1328, 1237, 1144, 1099, 1059, 1013, 954, 893, 846, 819, 756, 724, 670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (dd, *J* = 12.5, 4.3 Hz, 1H), 3.85 – 3.69 (m, 3H) superimposed to 3.83 (s, 1H), 3.56 (d, *J* = 10.4 Hz, 1H), 3.42 (ddd, *J* = 11.3, 9.9, 3.6 Hz, 1H), 2.85 (s, 3H), 2.37 – 2.16 (m, 2H), 2.13 (app. dt, *J* = 8.1, 4.7 Hz, 1H), 1.79 – 1.61 (m, 3H), 1.59 – 1.48 (m, 3H), 1.28 (app. tdd, *J* = 12.6, 6.6, 4.5 Hz, 1H), 1.11 – 1.02 (m, 1H), 0.98 (dd, *J* = 8.3, 5.7 Hz, 1H), 0.89 (dd, *J* = 6.6, 2.8 Hz, 6H), 0.53 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 81.4 (C), 73.0 (CH), 66.3 (CH_2), 65.5 (CH_2), 53.5 (CH_2), 42.3 (CH), 38.2 (CH_3), 38.1 (C), 35.7 (CH_2), 33.2 (CH_2), 32.4 (CH), 28.7 (CH), 27.5 (CH_2), 22.7(5) (CH_3) superimposed to 22.7(0) (CH_3), 21.3 (CH), 13.3 (CH_2); ^{11}H NMR (400 MHz, C_6D_6): δ 3.85 (dd, *J* = 12.5, 3.8 Hz, 1H), 3.67 (s, 1H), 3.60 – 3.49 (m, 3H), 3.41 (d, *J* = 10.1 Hz, 1H), 3.14 (app. td, *J* = 10.5, 3.9 Hz, 1H), 2.23 (s, 4H), 1.83 – 1.70 (m, 3H), 1.59 – 1.48 (m, 2H), 1.38 – 1.28 (m, 2H), 1.09 – 0.99 (m, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.49 (dd, *J* = 8.3, 5.5 Hz, 1H), 0.26 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6): δ 81.6 (C), 73.2 (CH), 66.5 (CH_2), 65.8 (CH_2), 53.5 (CH_2), 43.1 (CH), 38.5 (CH_3), 38.2 (C), 36.5 (CH_2), 33.8 (CH_2), 32.7 (CH), 29.3 (CH), 27.7 (CH_2), 23.2(1) (CH_3) superimposed to 23.2(0) (CH_3), 21.7 (CH), 13.2 (CH_2); ^{1}H NMR (400 MHz, Acetone + 0.03% v/v TMS): δ 3.81 – 3.71 (m, 3H), 3.70 – 3.62 (m, 2H), 3.52 (d, *J* = 10.5 Hz, 1H), 3.40 (ddd, *J* = 11.1, 8.6, 4.4 Hz, 1H), 2.97 (s, 1H), 2.87 (s, 3H), 2.30 (app. q, *J* = 7.7 Hz, 1H), 2.19 (app. dt, *J* = 8.2, 6.1 Hz, 1H), 1.76 – 1.56 (m, 4H), 1.55 – 1.45

(m, 2H), 1.34 – 1.25 (m, 1H), 1.23 – 1.13 (m, 1H), 0.97 (dd, *J* = 8.3, 5.5 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.52 (app. t, *J* = 5.0 Hz, 1H); ^{1}H NMR (400 MHz, MeOD + 0.03% v/v TMS): δ 3.97 – 3.83 (m, 2H), 3.83 – 3.65 (m, 3H), 3.53 (d, *J* = 10.5 Hz, 1H), 3.41 (app. td, *J* = 10.7, 3.7 Hz, 1H), 2.87 (s, 3H), 2.28 (app. td, *J* = 9.1, 6.5 Hz, 1H), 2.15 (app. dt, *J* = 8.4, 5.3 Hz, 1H), 1.82 – 1.68 (m, 2H), 1.67 – 1.40 (m, 4H), 1.29 (app. tdd, *J* = 12.7, 6.5, 4.4 Hz, 1H), 1.08 (app. tdd, *J* = 12.4, 6.9, 4.4 Hz, 1H), 1.01 – 0.86 (m, 7H), 0.54 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, MeOD + 0.03% v/v TMS): δ 82.4 (C), 73.9 (CH), 67.0 (CH_2), 65.7 (CH_2), 54.7 (CH_2), 43.6 (CH), 39.2 (C), 38.0 (CH_3), 36.2 (CH_2), 34.3 (CH_2), 34.0 (CH), 30.0 (CH), 28.2 (CH_2), 23.2 (CH_3), 23.1 (CH_3), 22.3 (CH), 13.4 (CH_2); MS (LCMS, ES+): 710 (15), 709 (37) $[2M+Na]^+$, 366 (47) $[M+Na]^+$, 327 (20), 326 (100) $[M-H_2O+H]^+$; HRMS (ES) *m/z* calculated for $C_{17}H_{30}NO_4S$ $[M+H]^+$ 344.18901, found 344.18841; calculated for $C_{17}H_{28}NO_3S$ $[M-H_2O+H]^+$ 326.17844, found 326.17815.

***Rac*-(1aR,3aS,4S,4aS,8aS,8bR)-3-(methylsulfonyl)-4-phenyldecahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 411**

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and phenylmagnesium bromide 1.0 M in THF (94 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **411** as a white solid (61 mg, 67%); m.p. 178 – 179 °C; R_f= 0.48 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3439, 2954, 2898, 2845, 1465, 1447, 1405, 1387, 1324, 1261, 1238, 1187, 1156, 1144, 1131, 1106, 1095, 1078, 1028, 1013, 979, 966, 953, 936, 891, 868, 846, 765, 742, 658; ^{1}H NMR (400 MHz, $CDCl_3$ + 0.03% v/v TMS): δ 7.49 – 7.43 (m, 2H), 7.35 – 7.28 (m, 2H), 7.23 – 7.18 (m, 1H) superimposed to $CHCl_3$, 4.41 (s, 1H), 3.94 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.79 – 3.71 (m, 2H), 3.66 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.45 (dd, *J* = 12.8, 4.8 Hz, 1H), 3.25 (ddd, *J* = 13.6, 11.5, 2.4 Hz, 1H), 3.20 (s, 1H), 2.40 (app. dt, *J* = 11.2, 7.8 Hz, 1H),

2.28 (dd, *J* = 8.5, 4.7 Hz, 1H), 2.22 (s, 3H), 1.94 (tdd, *J* = 13.3, 11.0, 5.4 Hz, 1H), 1.54 – 1.48 (m, 2H), 0.96 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.74 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ + 0.03% v/v TMS): δ 142.6 (C), 128.5 (2 × CH), 127.4 (CH), 126.0 (2 × CH), 84.5 (C), 76.2 (CH), 67.4 (CH_2), 66.3 (CH_2), 53.3 (CH_2), 47.8 (CH), 41.2 (CH_3), 39.4 (C), 32.6 (CH), 29.8 (CH_2), 20.6 (CH), 13.3 (CH_2); ^{1}H NMR (400 MHz, C_6D_6 + 0.03% v/v TMS): δ 7.46 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.29 – 7.23 (m, 2H) superimposed to C_6H_6, 7.14 (d, *J* = 7.3 Hz, 1H), 4.55 (s, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 3.83 – 3.74 (m, 2H), 3.70 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.32 (s, 1H), 3.09 (dd, *J* = 12.7, 4.6 Hz, 1H), 2.88 (ddd, *J* = 13.6, 11.4, 2.5 Hz, 1H), 2.08 (s, 3H), 1.92 – 1.81 (m, 2H), 1.65 (app. tdd, *J* = 13.3, 10.5, 5.4 Hz, 1H), 1.21 (app. dt, *J* = 8.5, 4.3 Hz, 1H), 0.98 – 0.88 (m, 2H), 0.73 (dd, *J* = 8.3, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6 + 0.03% v/v TMS): δ 143.7 (C), 128.8 (2 × CH), 127.6 (CH), 126.8 (2 × CH), 85.0 (C), 76.3 (CH), 67.6 (CH_2), 66.6 (CH_2), 53.4 (CH_2), 47.9 (CH), 41.9 (CH_3), 39.5 (C), 32.7 (CH), 30.0 (CH_2), 21.1 (CH), 13.1 (CH_2); MS (LCMS, ES+): 721 (13) $[2M+Na]^+$, 372 (32) $[M+Na]^+$, 350 (31) $[M+H]^+$, 332 (100) $[M-H_2O+H]^+$; HRMS (ES) *m/z* calculated for $C_{18}H_{24}NO_4S$ $[M+H]^+$ 350.14206, found 350.14143; calculated for $C_{18}H_{22}NO_3S$ $[M-H_2O+H]^+$ 332.13149, found 332.13095.

Rac-(1aR,3aS,4S,4aS,8aS,8bR)-4-(4-chlorophenyl)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 412

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and 4-chlorophenylmagnesium bromide 1.0 M in Et_2O (132 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **412** as a white solid (88 mg, 88%); m.p. 194 – 195 °C; R_f= 0.55 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3496, 2962, 2896, 2851, 1463, 1431, 1378, 1331, 1288, 1262, 1228, 1139, 1046, 1012, 966, 907, 866, 850, 826, 789,

759, 687; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.44 (m, 2H), 7.38 – 7.32 (m, 2H), 4.44 (s, 1H), 4.01 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.82 – 3.71 (m, 3H), 3.52 (dd, *J* = 12.8, 4.8 Hz, 1H), 3.32 (ddd, *J* = 13.7, 8.6, 2.4 Hz, 2H), 2.50 (s, 1H), 2.38 (s, 3H), 2.29 (dd, *J* = 8.5, 4.6 Hz, 1H), 1.98 (app. tdd, *J* = 13.3, 11.0, 5.4 Hz, 1H), 1.62 – 1.56 (m, 2H), 1.04 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.80 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.4 (C), 133.4 (C), 128.6 (2 × CH), 127.6 (2 × CH), 84.3 (C), 76.0 (CH), 67.5 (CH_2), 66.2 (CH_2), 53.2 (CH_2), 47.9 (CH), 41.2 (CH_3), 39.3 (C), 32.6 (CH), 29.8 (CH_2), 20.7 (CH), 13.5 (CH_2); MS (LCMS, ES+): 384 (11) $[M+H]^+$, 368 (34), 367 (21), 366 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 384 (39), 383(18), 382 (100) $[M-H]^-$, 249 (44); HRMS (ES) *m/z* calculated for $C_{18}H_{23}ClNO_4S$ $[M+H]^+$ 384.10308, found 384.10245; calculated for $C_{18}H_{21}ClNO_3S$ $[M-H_2O+H]^+$ 366.09252, found 366.09218.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-4-benzyl-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 413**

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and benzylmagnesium bromide 1.5 M in THF (76 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **413** as a white solid (45 mg, 48%); m.p. 121– 122 °C; R_f= 0.5 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3513, 3026, 2956, 2917, 2851, 1703, 1601, 1449, 1319, 1221, 1144, 1073, 1015, 961, 846, 751, 699; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.14 (m, 5H), 3.84 (s, 1H), 3.77 (ddd, *J* = 13.1, 11.4, 4.6 Hz, 2H), 3.69 (app. dt, *J* = 11.4, 4.8 Hz, 1H), 3.55 (d, *J* = 10.4 Hz, 1H), 3.47 (dd, *J* = 12.5, 5.6 Hz, 1H), 3.29 (ddd, *J* = 11.3, 9.6, 3.8 Hz, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 2.94 (d, *J* = 13.8 Hz, 1H), 2.81 (s, 3H), 2.53 (s, 1H), 2.11 (app. q, *J* = 8.5 Hz, 1H), 1.99 (app. dt, *J* = 8.4, 5.1 Hz, 1H), 1.62 – 1.48 (m, 2H) superimposed to H_2O, 1.43 (app. ddt, *J* = 13.7, 6.9, 4.3 Hz, 1H), 0.90 (dd, *J* = 8.4, 5.7 Hz, 1H), 0.46 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR

(101 MHz, $CDCl_3$): δ 137.5 (C), 130.6 (2 × CH), 128.5 (2 × CH), 126.7 (CH), 81.5 (C), 73.8 (CH), 66.0 (CH_2), 65.5 (CH_2), 53.8 (CH_2), 44.4 (CH_2), 43.0 (CH), 38.3 (C), 38.2 (CH_3), 32.2 (CH), 27.4 (CH_2), 21.3 (CH), 13.6 (CH_2); 365 (17), 364 (100) $[M+H]^+$, 346 (52) $[M-H_2O+H]^+$; HRMS (ES) *m/z* calculated for $C_{19}H_{26}NO_4S$ $[M+H]^+$ 364.15771, found 364.15719; calculated for $C_{19}H_{24}NO_3S$ $[M-H_2O+H]^+$ 346.14714, found 346.14680.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-3-(methylsulfonyl)-4-(thiophen-2-yl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-ol 414**

Prepared according to **GP13** from **283** (70 mg, 0.26 mmol) and 2-thienyl lithium 1.0 M in THF/hexane (56 µL, 0.52 mmol). Preparative UPLC purification [Gradient solution 0.1% HCOOH in H_2O/ 0.1% HCOOH in CH_3CN 95:5 – 2:98] afforded tertiary alcohol **414** as a white solid (71 mg, 77%); m.p. 187 – 188 °C; R_f= 0.6 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3496, 2962, 2896, 2851, 1331, 1463, 1431, 1378, 1331, 1288, 1262, 1228, 1139, 1046, 1012, 989, 966, 907, 867, 850, 826, 789, 759; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.17 (m, 1H), 6.98 – 6.91 (m, 2H), 4.32 (s, 1H), 3.99 (d, *J* = 12.8 Hz, 1H) superimposed to 3.94 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.76 (d, *J* = 9.7 Hz, 1H), 3.67 (dd, *J* = 9.7, 4.0 Hz, 1H), 3.54 (dd, *J* = 12.9, 4.7 Hz, 2H), 3.27 (ddd, *J* = 13.6, 11.6, 2.4 Hz, 1H), 2.43 – 2.36 (m, 1H) superimposed to 2.39 (s, 3H), 2.27 (dd, *J* = 8.4, 4.6 Hz, 1H), 1.87 (app. tdd, *J* = 13.5, 11.0, 5.3 Hz, 1H), 1.50 (app. td, *J* = 8.5, 4.5 Hz, 2H), 0.95 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.72 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (C), 127.7 (CH), 124.9 (CH), 123.8 (CH), 83.9 (C), 77.5 (CH) partially superimposed to $CHCl_3$, 67.4 (CH_2), 66.3 (CH_2), 53.2 (CH_2), 48.7 (CH), 41.5 (CH_3), 39.0 (C), 32.5 (CH), 29.8 (CH_2), 20.6 (CH), 13.2 (CH_2); MS (LCMS, ES+): 340 (12), 339 (21), 338 (100) $[M-H_2O+H]^+$; MS (LCMS, ES-): 356 (12), 355 (19), 354 (100) $[M-H]^-$, 249 (30); HRMS (ES) *m/z*

calculated for $C_{16}H_{22}NO_4S_2$ $[M+H]^+$ 356.09848, found 356.09787; calculated for $C_{16}H_{20}NO_3S_2$ $[M-H_2O+H]^+$ 338.08791, found 338.0745.

8.2.20 Preparation of Secondary Amines by Reductive Amination

***Rac*-(1aR,3aS,4R,4aR,8aS,8bR)-N-methyl-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 424**

Compound **283** (70 mg, 0.26 mmol, 1.0 eq.) was dissolved in DCE/MeOH 3:1 (0.1 M) under inert atmosphere. Methylammonium chloride (21 mg, 0.31 mmol, 1.2 eq.) was added followed by TEA (36 µL, 0.26 mmol, 1.0 eq.) and the mixture was stirred at rt for 6h. $NaBH_4$ (1.5 eq.) was then added and the mixture was stirred for 16h. Water was added (2.0 mL), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a white oil. Secondary amine **424** was finally afforded by recrystallization in EtOH as a white solid (48 mg, 65%); m.p. 159-160 °C; R_f= 0.55 (CH_2Cl_2:MeOH 49:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3351, 2988, 2949, 2923, 2878, 2854, 2833, 2763, 2371, 2324, 2279, 1480, 1461, 1421, 1323, 1243, 1219, 1146, 1107, 1071, 1016, 985, 963, 936, 901, 865, 833, 812, 779, 753, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.88 (d, *J* = 4.9 Hz, 1H), 3.85 – 3.79 (m, 2H), 3.75 (dd, *J* = 12.4, 4.3 Hz, 1H), 3.51 (d, *J* = 10.4 Hz, 1H), 3.32 (app. td, *J* = 11.2, 2.8 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.77 (s, 3H), 2.55 (s, 3H), 2.19 – 2.10 (m, 2H), 1.83 – 1.68 (m, 2H), 1.56 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.45 (app. dt, *J* = 13.5, 3.4 Hz, 1H), 0.97 (dd, *J* = 8.3, 5.5 Hz, 1H), 0.42 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.1 (CH), 67.5 (CH_2), 67.0 (CH), 66.5 (CH_2), 53.6

(CH_2), 40.8 (CH), 39.2 (C), 37.4 (CH_3), 37.0 (CH_3), 33.5 (CH), 28.6 (CH_2), 21.2 (CH), 13.8 (CH_2); MS (LCMS, ES+): 288 (15), 287 (100); HRMS (ES) *m/z* calculated for $C_{13}H_{23}N_2O_3S$ $[M+H]^+$ 287.14239, found 287.14184.

Rac-(1aR,3aS,4R,4aR,8aS,8bR)-N-(2-ethylbutyl)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 425

Prepared according to **GP14B** from **283** (70 mg, 0.26 mmol) and 2-ethyl-*N*-butylamine (32 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded secondary amine **425** as pale yellow oil (52 mg, 56%); R_f= 0.25 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3350, 2955, 2907, 2873, 1461, 1381, 1330, 1239, 1215, 1150, 1110, 1064, 1015, 986, 959, 895, 844, 751, 712; ^1H NMR (400 MHz, $CDCl_3$): δ 3.97 (dd, *J* = 12.6, 1.9 Hz, 1H), 3.86 (d, *J* = 4.9 Hz, 1H), 3.85 – 3.79 (m, 2H), 3.75 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.50 (d, *J* = 10.4 Hz, 1H), 3.31 (td, *J* = 11.2, 2.8 Hz, 1H), 3.11 (t, *J* = 4.8 Hz, 1H), 2.80 – 2.72 (m, 1H) superimposed to 2.76 (s, 3H), 2.61 (dd, *J* = 11.7, 3.9 Hz, 1H), 2.19 – 2.10 (m, 2H), 1.84 – 1.74 (m, 1H), 1.67 (s, 1H), 1.54 (dt, *J* = 8.6, 4.5 Hz, 1H), 1.44 (ddd, *J* = 13.2, 6.6, 3.0 Hz, 1H), 1.40 – 1.28 (m, 5H), 0.96 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.93 – 0.84 (m, 6H), 0.41 (t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.3 (CH), 67.7 (CH_2), 66.5 (CH_2), 65.2 (CH), 53.6 (CH_2), 53.4 (CH_2), 41.8 (CH), 40.8 (CH), 39.2 (C), 37.1 (CH_3), 33.6 (CH), 28.7 (CH_2), 24.4 (CH_2), 24.2 (CH_2), 21.2 (CH), 13.8 (CH_2), 11.3 (2 × CH_3); MS (LCMS, ES+): 358 (20), 357 (100); HRMS (ES) *m/z* calculated for $C_{18}H_{33}N_2O_3S$ $[M+H]^+$ 357.2206, found 357.2199.

***Rac*-(1aR,3aS,4R,4aR,8aS,8bR)-3-(methylsulfonyl)-N-(tetrahydro-2H-pyran-4-yl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 426**

Prepared according to **GP14B** from **283** (70 mg, 0.26 mmol) and 4-aminotetrahydropyran (32 µL, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded secondary amine **426** as a pale yellow oil (45 mg, 49%); R_f= 0.63 (CH_2Cl_2:MeOH 49:1) [$KMnO_4$];IR: ν_{max} (neat, cm^{-1}) 3320, 2943, 2923,2894, 2853, 2107, 2071, 1477, 1383, 1318, 1237, 1190, 1141, 1067, 1039, 1000, 967, 893, 866, 826, 766, 733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 – 3.82 (m, 5H), 3.80 (d, *J* = 4.7 Hz, 1H), 3.76 (dd, *J* = 12.6, 4.0 Hz, 1H), 3.47 (d, *J* = 10.4 Hz, 1H), 3.46 – 3.25 (m, 4H), 2.84 (app. tt, *J* = 10.4, 4.0 Hz, 1H), 2.74 (s, 3H), 2.21 – 2.11 (m, 2H), 2.07 – 2.00 (m, 1H), 1.85 (ddd, *J* = 13.0, 4.4, 2.3 Hz, 1H), 1.73 (app. dtd, *J* = 13.7, 10.0, 5.0 Hz, 1H), 1.64 (s, 1H), 1.54 (app. dt, *J* = 8.7, 4.5 Hz, 1H), 1.48 – 1.41 (m, 1H), 1.36 (app. ddt, *J* = 12.8, 11.1, 5.6 Hz, 1H), 1.21 (app. qd, *J* = 11.1, 4.3 Hz, 1H), 0.97 (dd, *J* = 8.3, 5.5 Hz, 1H), 0.38 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.6 (CH), 67.9 (CH_2), 67.7 (CH_2), 67.3 (CH_2), 66.4 (CH_2), 60.8 (CH), 53.9 (CH_2), 53.3 (CH), 40.5 (CH), 39.2 (C), 36.7 (CH_3), 35.5 (CH_2), 34.1 (CH_2), 33.6 (CH), 28.9 (CH_2), 21.1 (CH), 13.8 (CH_2); MS (LCMS, ES+): 358 (18), 357 (100); HRMS (ES) *m/z* calculated for $C_{17}H_{29}N_2O_4S$ $[M+H]^+$ 357.1843, found 357.1833.

***Rac*-(1aR,3aS,4R,4aR,8aS,8bR)-N-(3,4-dimethoxybenzyl)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 428**

Prepared according to **GP14A** from **283** (70 mg, 0.26 mmol) and (3,4-dimetoxyphenyl)-methanamine (52 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded secondary amine **248** as a white solid (89 mg, 81%); m.p. 182 – 183 °C; R_f= 0.33

(Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3319, 3003, 2946, 2903, 2859, 2289, 2103, 1589, 1514, 1452, 1416, 1393, 1322, 1260, 1182, 1100, 1068, 1020, 985, 952, 901, 849, 812, 781, 747, 694; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (d, *J* = 1.9 Hz, 1H), 6.89 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 3.96 – 3.82 (m, 12H), 3.70 (dd, *J* = 12.5, 4.8 Hz, 1H), 3.52 (d, *J* = 10.4 Hz, 1H), 3.29 (app. td, *J* = 11.4, 2.7 Hz, 1H), 3.19 (app. t, *J* = 4.8 Hz, 1H), 2.76 (s, 3H), 2.24 (s, 1H), 2.18 – 2.06 (m, 2H), 1.83 (dddd, *J* = 14.2, 11.3, 9.7, 4.5 Hz, 1H), 1.59 – 1.55 (m, 1H), 1.45 (app. ddt, *J* = 13.1, 6.4, 3.0 Hz, 1H), 0.99 (dd, *J* = 8.2, 5.5 Hz, 1H), 0.41 (app. t, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9 (C), 147.7 (C), 134.3 (C), 120.4 (CH), 111.8 (CH), 111.1 (CH), 72.4 (CH), 67.7 (CH_2), 66.5 (CH_2), 62.3 (CH), 56.0 (CH_3), 55.9 (CH_3), 53.9 (CH_2), 53.0 (CH_2), 40.5 (CH), 39.5 (C), 36.6 (CH_3), 33.6 (CH), 28.9 (CH_2), 21.1 (CH), 14.0 (CH_2); MS (LCMS, ES+): 424 (22), 423 (100); HRMS (ES) *m/z* calculated for $C_{21}H_{31}N_2O_5S$ $[M+H]^+$ 423.1948, found 423.1939.

Rac-(1aR,3aS,4R,4aR,8aS,8bR)-N-(2-fluorobenzyl)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 429

Prepared according to **GP14B** from **283** (70 mg, 0.26 mmol) and 2-fluorobenzylamine (50 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded secondary amine **429** as a white solid (44 mg, 44%); m.p. 166 – 167 °C; R_f= 0.35 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3346, 2943, 2917, 2851, 1612, 1580, 1484, 1449, 1416, 1384, 1353, 1325, 1243, 1211, 1181, 1146, 1103, 1064, 1034, 1015, 985, 963, 901, 831, 762, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (app. td, *J* = 7.6, 1.6 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.05 – 6.98 (m, 1H), 4.08 (d, *J* = 13.9 Hz, 1H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.92 – 3.81 (m, *J* = 4.1 Hz, 4H), 3.69 (dd, *J* = 12.6, 4.7 Hz, 1H), 3.53 (d, *J* = 10.3 Hz, 1H), 3.26 (app. td, *J* = 11.6, 2.5 Hz, 1H), 3.19 (app. t, *J*

= 4.6 Hz, 1H), 2.77 (s, 3H), 2.30 (s, 1H), 2.18 – 2.07 (m, 2H), 1.88 – 1.77 (m, 1H), 1.56 (app. dt, *J* = 8.6, 4.5 Hz, 1H), 1.42 (ddd, *J* = 13.1, 6.6, 3.3 Hz, 1H), 0.98 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.42 (app. t, *J* = 5.1 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.06; ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.6 (d, J_{C-F} = 245.2 Hz, CF), 131.1 (d, J_{C-F} = 5.0 Hz, CF-C-CH), 128.5 (d, J_{C-F} = 8.2 Hz, CF-CH-CH), 128.2 (d, J_{C-F} = 15.2 Hz, CF-C), 124.0 (d, J_{C-F} = 3.6 Hz, CF-CH-CH-CH), 115.3 (d, J_{C-F} = 21.9 Hz, CF-CH), 72.4 (CH), 67.7 (CH_2), 66.5 (CH_2), 62.8 (CH), 53.8 (CH_2), 47.4 (d, J_{C-F} = 2.9 Hz, CH_2), 40.4 (CH), 39.4 (C), 37.0 (CH_3), 33.6 (CH), 29.1 (CH_2), 21.1 (CH), 13.9 (CH_2); MS (LCMS, ES+): 382 (22), 381 (100); HRMS (ES) *m/z* calculated for $C_{19}H_{26}FN_2O_3S$ $[M+H]^+$ 381.1643, found 381.1635.

***Rac*-(1aR,3aS,4R,4aR,8aS,8bR)-N-(furan-2-ylmethyl)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 430**

Prepared according to **GP14A** from **283** (70 mg, 0.26 mmol) and furan-2-ylmethanamine (30 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded secondary amine **430** as a white solid (65 mg, 71%); m.p. 152 – 153 °C; R_f= 0.28 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3332, 2960, 2916, 2881, 2837, 2805, 1506, 1465, 1414, 1382, 1364, 1325, 1279, 1253, 1235, 1212, 1147, 1107, 1062, 1031, 1009, 986, 952, 917, 844, 815, 786, 741, 706; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 1.9 Hz, 1H), 6.33 – 6.15 (m, 2H), 4.00 – 3.84 (m, 5H) superimposed to 3.83 (d, *J* = 4.6 Hz, 1H), 3.68 (dd, *J* = 12.5, 4.8 Hz, 1H), 3.52 (d, *J* = 10.3 Hz, 1H), 3.26 (app. td, *J* = 11.6, 2.5 Hz, 1H), 3.17 (app. t, *J* = 4.6 Hz, 1H), 2.76 (s, 3H), 2.29 (s, 1H), 2.16 – 2.05 (m, 2H), 1.83 (dddd, *J* = 14.8, 11.9, 10.1, 4.6 Hz, 1H), 1.55 (app. dt, *J* = 8.6, 4.5 Hz, 1H), 1.42 (ddd, *J* = 13.5, 6.4, 3.2 Hz, 1H), 0.97 (dd, *J* = 8.3, 5.5 Hz, 1H), 0.42 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9 (C), 141.7 (CH), 110.1 (CH), 107.3 (CH), 72.4 (CH), 67.7 (CH_2), 66.5 (CH_2), 62.4 (CH), 53.9 (CH_2), 45.7 (CH_2), 40.5 (CH), 39.5 (C), 37.0 (CH_3), 33.7 (CH),

29.2 (CH_2), 21.0 (CH), 14.0 (CH_2); MS (LCMS, ES+): 354 (17), 353 (100) $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{17}H_{25}N_2O_4S$ $[M+H]^+$ 353.1530, found 353.1519.

***Rac*-(1aR,3aS,4R,4aR,8aS,8bR)-3-(methylsulfonyl)-N-(2-(thiophen-2-yl)ethyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 431**

Prepared according to **GP14A** from **283** (70 mg, 0.26 mmol) and thiophene-2-ethylamine (39 mg, 0.31 mmol). Flash column chromatography [linear gradient heptane:EtOAc 100:0 – 70:30] afforded secondary amine **431** as a white solid (32 mg, 32%); m.p. 126 – 127 °C; R_f= 0.43 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3338, 2954, 2924, 2888, 2839, 2289, 2103, 1483, 1456, 1380, 1352, 1319, 1260, 1219, 1146, 1103, 1073, 1020, 951, 968, 941, 903, 862, 829, 796, 771, 750, 688; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.84 (d, *J* = 3.2 Hz, 1H), 3.90 (dd, *J* = 12.5, 1.6 Hz, 1H), 3.86 (d, *J* = 4.7 Hz, 1H), 3.81 (app. dt, *J* = 11.4, 4.0 Hz, 1H), 3.71 – 3.62 (m, 2H), 3.45 (d, *J* = 10.3 Hz, 1H), 3.26 (app. td, *J* = 11.4, 2.6 Hz, 1H), 3.17 (app. t, *J* = 4.7 Hz, 1H), 3.16 – 3.03 (m, 2H), 3.03 – 2.98 (m, 2H), 2.72 (s, 3H), 2.16 – 2.07 (m, 2H), 1.81 (dddd, *J* = 13.7, 11.3, 9.5, 4.7 Hz, 2H), 1.50 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.40 (app. ddt, *J* = 16.2, 5.9, 2.9 Hz, 1H), 0.94 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.40 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.2 (C), 126.9 (CH), 125.1 (CH), 123.3 (CH), 72.2 (CH), 67.6 (CH_2), 66.5 (CH_2), 64.3 (CH), 53.6 (CH_2), 51.5 (CH_2), 40.8 (CH), 39.2 (C), 37.2 (CH_3), 33.6 (CH), 31.2 (CH_2), 28.9 (CH_2), 21.1 (CH), 13.8 (CH_2); MS (LCMS, ES+): 384 (19), 383 (100) $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{18}H_{27}N_2O_3S_2$ $[M+H]^+$ 383.14576, found 383.14496.

8.2.21 Preparation of Enamine 440

***rac*-(1aR,3aS,8aR,8bR)-*N*-methyl-3-(methylsulfonyl)-1,1a,2,3,3a,7,8,8a-octahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-amine 440**

Compound **283** (70 mg, 0.26 mmol, 1.0 eq.) was dissolved in DCE/MeOH 3:1 (0.1 M) under inert atmosphere. Methylammonium chloride (21 mg, 0.31 mmol, 1.2 eq.) was added followed by TEA (108 µL, 0.78 mmol, 3.0 eq.) and the mixture was stirred at rt for 6h. Water was added (2.0 mL), then the aqueous phase was extracted with CH_2Cl_2 (ca. 3 × 1 mL)**.** The organic fractions were merged, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude as a white oil. Enamine **440** was finally afforded by recrystallization in EtOH as a white solid (19 mg, 21%); m.p. 144-145 °C; R_f= 0.53 (CH_2Cl_2:MeOH 49:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3413, 2925, 2890, 2851, 2815, 1744, 1668, 1529, 1465, 1423, 1381, 1307, 1260, 1233, 1137, 1087, 1056, 1009, 978, 919, 897, 856, 825, 790, 757, 712, 662; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (d, *J* = 13.0 Hz, 1H), 4.34 (d, *J* = 1.3 Hz, 1H), 4.23 (d, *J* = 6.1 Hz, 1H), 4.07 (app. dt, *J* = 13.0, 2.1 Hz, 1H), 4.01 (ddd, *J* = 11.4, 4.4, 2.0 Hz, 1H), 3.67 (dd, *J* = 11.1, 4.7 Hz, 1H), 3.48 – 3.36 (m, 2H), 2.85 (d, *J* = 5.2 Hz, 3H), 2.78 (s, 3H), 2.69 (dd, *J* = 11.5, 4.9 Hz, 1H), 1.51 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 1.41 (app. ddt, *J* = 12.3, 4.5, 2.0 Hz, 1H), 1.25 (app. qd, *J* = 12.1, 4.3 Hz, 1H), 1.07 (dd, *J* = 8.4, 6.0 Hz, 1H), 0.48 (dd, *J* = 6.0, 4.6 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.79 (d, *J* = 13.0 Hz, 1H), 4.40 – 4.34 (m, 1H), 4.26 (app. q, *J* = 5.5 Hz, 1H), 3.96 (app. dt, *J* = 13.1, 2.0 Hz, 1H), 3.86 (ddd, *J* = 11.4, 4.5, 2.0 Hz, 1H), 3.49 – 3.41 (m, 2H), 3.31 – 3.26 (m, 1H), 2.93 (s, 3H), 2.74 (d, *J* = 5.5 Hz, 3H), 2.58 (dd, *J* = 11.7, 4.8 Hz, 1H), 1.50 (app. dt,

J = 8.6, 4.5 Hz, 1H), 1.38 (ddd, *J* = 10.9, 5.0, 2.6 Hz, 1H), 1.12 (app. td, *J* = 12.0, 4.2 Hz, 1H) superimposed to 1.04 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.57 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 137.5 (C), 103.4 (C), 70.8 (CH), 66.0 (CH_2), 65.7 (CH_2), 50.9 (CH_2), 40.0 (CH, invisible at ^{13}C, identified at HSQC, superimposed to solvent signal), 37.6 (C), 35.2 (CH_3), 32.6 (CH_3), 30.5 (CH_2), 18.3 (CH), 12.0 (CH_2); MS (LCMS, ES+): 286 (14), 285 (100); HRMS (ES) *m/z* calculated for $C_{13}H_{21}N_2O_3S$ $[M+H]^+$ 285.1267, found 285.1261.

8.2.22 Preparation of Ethers

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-4-(cyclopropylmethoxy)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 442**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and cyclopropylmethyl bromide (42 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **442** as a pale yellow oil (18 mg, 21%); R_f= 0.4 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3001, 2954, 2914, 2857, 2813, 1462, 1421, 1369, 1317, 1267, 1212, 1193, 1149, 1088, 1048, 1015, 972, 919, 896, 871, 806, 787, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.92 (d, *J* = 4.3 Hz, 1H), 3.89 – 3.82 (m, 2H), 3.76 – 3.69 (m, 2H), 3.59 – 3.43 (m, 3H), 3.34 (app. td, *J* = 11.3, 2.9 Hz, 1H), 2.84 (s, 3H), 2.19 – 2.05 (m, 2H), 1.78 (app. ddt, *J* = 13.2, 11.0, 5.5 Hz, 1H), 1.52 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.35 (app. ddt, *J* = 12.7, 6.1, 3.0 Hz, 1H), 1.06 – 0.96 (m, 1H), 0.93 (dd, *J* = 8.2, 5.5 Hz, 1H), 0.57 (app. t, *J* = 5.0 Hz, 1H), 0.47 (dd, *J* = 8.2, 2.2 Hz, 2H), 0.29 – 0.17 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 82.5 (CH), 75.3 (CH_2), 69.9 (CH), 66.0 (CH_2), 65.8 (CH_2), 52.8 (CH_2), 42.0 (CH), 38.5 (CH_3), 38.2 (C), 33.4 (CH), 28.2 (CH_2), 20.6 (CH), 13.2 (CH_2), 11.3 (CH), 3.0 (CH_2), 2.8 (CH_2); MS (LCMS, ES+): 350 (30) $[M+Na]^+$, 328 (100) $[M+H]^+$, 274 (21) $[M-C_4H_6]^+$; HRMS (ES) *m/z* calculated for $C_{16}H_{26}NO_4S$ $[M+H]^+$ 328.1577, found 328.1576.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-4-(3-methoxypropoxy)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 443**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 1-bromo-3-metoxypropane (47 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **443** as a pale yellow oil (52 mg, 58%); R_f= 0.38 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 2925, 2875, 2840, 1463, 1387, 1321, 1239, 1223, 1188, 1147, 1109, 1064, 1041, 1015, 987, 960, 898, 864, 834, 809, 772, 750, 706; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (dd, *J* = 12.5, 2.8 Hz, 1H), 3.91 (d, *J* = 4.3 Hz, 1H), 3.88 – 3.78 (m, 3H), 3.74 – 3.61 (m, 3H), 3.53 – 3.44 (m, 3H), 3.31 (s, 4H), 2.81 (s, 3H), 2.18 – 2.10 (m, 1H), 2.06 (app. ddt, *J* = 8.6, 5.9, 3.1 Hz, 1H), 1.85 – 1.78 (m, 2H), 1.77 – 1.69 (m, 1H), 1.49 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.33 (app. ddt, *J* = 12.7, 6.1, 2.8 Hz, 1H), 0.93 (dd, *J* = 8.2, 5.5 Hz, 1H), 0.55 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 83.4 (CH), 70.0 (CH), 69.9 (CH_2), 68.2 (CH_2), 66.0 (CH_2), 65.9 (CH_2), 58.6 (CH_3), 53.0 (CH_2), 42.0 (CH), 38.(42) (CH_3), 38.(36) (C), 33.5 (CH), 30.8 (CH_2), 28.5 (CH_2), 20.4 (CH), 13.4 (CH_2); MS (LCMS, ES+): 347 (17), 346 (100) $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{16}H_{28}NO_5S$ $[M+H]^+$ 346.1683, found 346.1678.

***Rac-N*-(tert-butyl)-2-(((1aR,3aS,4R,4aS,8aS,8bR)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrol-4-yl)oxy)acetamide 444**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and *N*-tert-butylchloroacetamide (46 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **444** as a white solid (78 mg, 78%); m.p. 166 – 167 °C; R_f= 0.4 (Heptane:EtOAc 1:1) [$KMnO_4$]; IR: ν_{max} (neat, cm^{-1}) 3314, 2970, 2929, 2901, 2872, 2851, 1664, 1527, 1455, 1395, 1364, 1325, 1292, 1267, 1223, 1150, 1124, 1101, 1065, 1023, 960, 930, 899, 867, 837, 806, 754, 717; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 4.36 (d, *J* = 15.4 Hz, 1H), 4.15 (d, *J* = 12.5 Hz, 1H), 3.97 (d, *J* = 15.4 Hz, 1H), 3.94 – 3.88 (m, 2H), 3.84 (app. t, *J* = 3.6 Hz, 1H), 3.77 – 3.69 (m, 2H), 3.52 (d, *J* = 10.3 Hz, 1H), 3.27 (app. td, *J* = 12.1, 2.0 Hz, 1H), 2.79 (s, 3H), 2.20 (app. dt, *J* = 11.2, 7.5 Hz, 1H), 2.06 (app. dt, *J* = 8.4, 4.3 Hz, 1H), 1.83 – 1.73 (m, 1H), 1.56 (app. dt, *J* = 8.8, 4.6 Hz, 1H), 1.43 – 1.33 (m, 1H) superimposed to 1.36 (s, 9H), 1.05 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.51 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (C), 88.0 (CH), 73.3 (CH_2), 71.0 (CH), 66.6 (CH_2), 66.2 (CH_2), 53.5 (CH_2), 51.0 (C), 41.2 (CH), 39.3 (C), 37.6 (CH_3), 33.7 (CH), 29.6 (CH_2), 28.9 (3 × CH_3), 20.7 (CH), 14.9 (CH_2); MS (LCMS, ES+): 773 (27) $[2M+H]^+$, 388 (16), 387 (100); HRMS (ES) *m/z* calculated for $C_{18}H_{31}N_2O_5S$ $[M+H]^+$ 387.1948, found 387.1943.

Rac-(1aR,3aS,4R,4aS,8aS,8bR)-4-((3-methylbenzyl)oxy)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 445

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 3-methylbenzyl bromide (57 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **445** as a white solid (83 mg, 85%); m.p. 188 – 189 °C; R_f= 0.5 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2356, 2903, 2882, 2849, 1606, 1459, 1420, 1385, 1326, 1282, 1238, 1219, 1183, 1151, 1125, 1067, 1012, 982, 959, 894, 866, 844, 804, 750, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.11 (m, 3H), 7.04 – 6.97 (m, 1H), 4.82 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.02 (dd, *J* = 12.5, 2.9 Hz, 1H), 3.91 – 3.86 (m, 2H) superimposed to 3.83 (ddd, *J* = 11.3, 4.8, 2.9 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.43 (d, *J* = 9.5 Hz, 1H), 3.28 (app. td, *J* = 11.5, 2.8 Hz, 1H), 2.67 (s, 3H), 2.27 (s, 3H), 2.15 – 2.07 (m, 1H), 2.03 (app. ddt, *J* = 8.8, 6.0, 3.1 Hz, 1H), 1.75 (app. dtd, *J* = 16.0, 11.6, 4.7 Hz, 1H), 1.45 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.29 (app. ddt, *J* = 12.6, 6.1, 2.9 Hz, 1H), 0.89 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.48 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.0 (C), 137.9 (C), 128.5 (CH),

128.2 (CH), 128.1 (CH), 124.8 (CH), 82.5 (CH), 72.9 (CH_2), 70.1 (CH), 66.0 (CH_2), 65.9 (CH_2), 53.0 (CH_2), 41.9 (CH), 38.4 (C), 38.2 (CH_3), 33.5 (CH), 28.5 (CH_2), 21.5 (CH_3), 20.5 (CH), 13.5 (CH_2); MS (LCMS, ES+): 378 (10), 273 (10), 272 (100) $[M-C_8H_9]^+$; HRMS (ES) *m/z* calculated for $C_{20}H_{28}NO_4S$ $[M+H]^+$ 378.1734, found 378.1730; calculated for $C_{12}H_{18}NO_4S$ $[M-C_8H_9]^+$ 272.0951, found 272.0948.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-4-((4-chlorobenzyl)oxy)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 307**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 4-chlorobenzyl bromide (64 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **307** as a white solid (84 mg, 81%); m.p. 204 – 205 °C; R_f= 0.48 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2950, 2930, 2881, 2834, 2278, 2109, 2082, 1594, 1488, 1459, 1411, 1322, 1235, 1219, 1149, 1064, 1007, 981, 951, 866, 830, 797, 754, 658; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 2H), 7.33 – 7.26 (m, 2H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.08 (dd, *J* = 12.6, 2.5 Hz, 1H), 3.96 – 3.86 (m, 3H), 3.76 – 3.64 (m, 2H), 3.47 (d, *J* = 9.6 Hz, 1H), 3.32 (app. td, *J* = 11.6, 2.6 Hz, 1H), 2.75 (s, 3H), 2.18 (ddd, *J* = 11.2, 8.4, 6.2 Hz, 1H), 2.08 (ddd, *J* = 8.1, 5.7, 2.4 Hz, 1H), 1.79 (app. qd, *J* = 11.9, 4.7 Hz, 1H), 1.52 (app. dt, *J* = 8.6, 4.5 Hz, 1H), 1.34 (app. ddt, *J* = 13.2, 5.9, 2.7 Hz, 1H), 0.98 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.51 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.7 (C), 133.2 (C), 129.3 (2 × CH), 128.5 (2 × CH), 83.0 (CH), 72.3 (CH_2), 70.4 (CH), 66.1 (CH_2), 66.0 (CH_2), 53.2 (CH_2), 41.8 (CH), 38.7 (C), 37.8 (CH_3), 33.6 (CH), 28.8 (CH_2), 20.5 (CH), 13.9 (CH_2); MS (LCMS, ES+): 420 (5) $[M+Na]^+$, 398 (9) $[M+H]^+$, 272 (100) $[M-C_7H_7Cl]^+$; HRMS (ES) *m/z* calculated for $C_{19}H_{25}ClNO_4S$ $[M+H]^+$ 398.1187, found 398.1186; calculated for $C_{12}H_{18}NO_4S$ $[M-C_7H_7Cl]^+$ 272.0951, found 272.0949.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-3-(methylsulfonyl)-4-((4-phenoxybenzyl)oxy)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 446**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 1-(bromomethyl)-3-phenoxybenzene (82 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **446** as a yellow oil (101 mg, 85%); R_f= 0.6 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2921, 2881, 2842, 1581, 1485, 1444, 1395, 1329, 1251, 1211, 1150, 1068, 1022, 960, 896, 863, 754, 692; ^{1}H NMR (400 MHz, $CDCl_3$ + 0.03% v/v TMS): δ 7.29 – 7.18 (m, 3H), 7.06 – 7.00 (m, 2H), 6.99 – 6.91 (m, 3H), 6.85 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.02 (dd, *J* = 12.6, 2.5 Hz, 1H), 3.88 (d, *J* = 4.0 Hz, 2H), 3.72 (ddd, *J* = 11.3, 4.8, 2.6 Hz, 1H), 3.63 (dd, *J* = 12.5, 5.6 Hz, 1H), 3.49 (dd, *J* = 9.4, 4.3 Hz, 1H), 3.37 (d, *J* = 9.4 Hz, 1H), 3.22 (app. td, *J* = 11.6, 2.7 Hz, 1H), 2.64 (s, 3H), 2.13 – 2.04 (m, 1H), 2.01 (app. ddt, *J* = 8.4, 5.7, 2.8 Hz, 1H), 1.71 – 1.61 (m, 1H), 1.38 (app. dt, *J* = 8.3, 4.3 Hz, 1H), 1.22 (app. ddt, *J* = 12.3, 6.0, 2.7 Hz, 1H), 0.87 (dd, *J* = 8.3, 5.5 Hz, 1H), 0.48 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ + 0.03% v/v TMS): δ 157.7 (C), 157.2 (C), 141.2 (C), 129.9 (2 × CH), 129.6 (CH), 123.5 (CH), 121.9 (CH), 119.4 (2 × CH), 117.6 (CH), 117.3 (CH), 82.9 (CH), 72.4 (CH_2), 70.1 (CH), 66.0 (CH_2), 65.9 (CH_2), 53.0 (CH_2), 42.0 (CH), 38.5 (C), 38.3 (CH_3), 33.6 (CH), 28.6 (CH_2), 20.4 (CH), 13.6 (CH_2); MS (LCMS, ES+): 478 (44) $[M+Na]^+$, 456 (36) $[M+H]^+$, 272 (100) $[M-C_{13}H_{11}O]^+$; HRMS (ES) *m/z* calculated for $C_{25}H_{30}NO_5S$ $[M+H]^+$ 456.1839, found 456.1832; calculated for $C_{25}H_{29}NO_5S$ $[M+Na]^+$ 478.1659, found 478.1652; calculated for $C_{12}H_{18}NO_4S$ $[M-C_{13}H_{11}O]^+$ 272.0951, found 272.0946; calculated for $C_{13}H_{11}O$ $[Ph\text{-}O\text{-}Ph\text{-}CH_2]^+$ 183.0804, found 183.0802.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-3-(methylsulfonyl)-4-(pyridin-4-ylmethoxy)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 447**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 4-(bromomethyl)pyridine hydrochloride (78 mg, 0.31 mmol) with NaH (19 mg, 0.78 mmol, 3.0 eq.). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **447** as a yellow oil (26 mg, 27%); R_f= 0.33 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2913, 2845, 1603, 1559, 1455, 1416, 1329, 1239, 1222, 1154, 1128, 1070, 1030, 991, 964, 862, 806, 756; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 – 8.51 (m, 2H), 7.41 – 7.32 (m, 2H), 4.90 (d, *J* = 13.3 Hz, 1H), 4.81 (d, *J* = 13.3 Hz, 1H), 4.14 (dd, *J* = 12.6, 2.0 Hz, 1H), 3.97 – 3.89 (m, 3H), 3.78 – 3.69 (m, 2H), 3.48 (d, *J* = 9.8 Hz, 1H), 3.32 (app. td, *J* = 11.7, 2.4 Hz, 1H), 2.76 (s, 3H), 2.20 (ddd, *J* = 11.3, 8.3, 6.2 Hz, 1H), 2.11 (app. tt, *J* = 7.0, 2.9 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.56 (app. dt, *J* = 8.7, 4.5 Hz, 1H), 1.37 (app. ddt, *J* = 12.7, 5.5, 2.4 Hz, 1H), 1.02 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.51 (app. t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9 (2 × CH), 148.4 (C), 121.9 (2 × CH), 84.2 (CH), 71.7 (CH_2), 70.6 (CH), 66.2 (CH_2), 66.1 (CH_2), 53.4 (CH_2), 41.8 (CH), 38.9 (C), 37.5 (CH_3), 33.8 (CH), 29.0 (CH_2), 20.5 (CH), 14.3 (CH_2); MS (LCMS, ES+): 366 (21), 365 (100); HRMS (ES) *m/z* calculated for $C_{18}H_{25}N_2O_4S$ $[M+H]^+$ 365.1530, found 365.1521.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-3-(methylsulfonyl)-4-(quinolin-8-ylmethoxy)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 448**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 8-(bromomethyl)quinoline (69 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **448** as a white solid (67 mg, 62%); m.p. 172 – 173 °C; R_f= 0.35 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat,

cm^{-1}) 2935, 2888, 2827, 2764, 2106, 1593, 1577, 1494, 1447, 1407, 1357, 1324, 1239, 1222, 1149, 1101, 1062, 1027, 1008, 983, 948, 898, 843, 814, 784, 784, 754, 715, 650; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (dd, *J* = 4.2, 1.9 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.92 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.74 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 (app. t, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.56 (d, *J* = 13.4 Hz, 1H), 5.46 (d, *J* = 13.4 Hz, 1H), 4.27 (dd, *J* = 12.5, 2.7 Hz, 1H), 4.20 (app. t, *J* = 3.9 Hz, 1H), 4.11 (d, *J* = 4.3 Hz, 1H), 3.87 (ddd, *J* = 11.3, 4.7, 3.0 Hz, 1H), 3.81 – 3.70 (m, 2H), 3.59 (d, *J* = 9.1 Hz, 1H), 3.37 (app. td, *J* = 11.4, 2.9 Hz, 1H), 2.74 (s, 3H), 2.30 – 2.17 (m, 2H), 1.92 (app. ddt, *J* = 15.4, 10.9, 4.7 Hz, 1H), 1.60 (app. dt, *J* = 8.6, 4.4 Hz, 1H), 1.47 – 1.39 (m, 1H), 0.98 (dd, *J* = 8.2, 5.5 Hz, 1H), 0.69 (app. t, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5 (CH), 145.7 (C), 137.5 (C), 136.3 (CH), 128.0 (C), 127.1 (CH), 126.9 (CH), 126.5 (CH), 121.2 (CH), 83.0 (CH), 69.7 (CH), 69.1 (CH_2), 66.2 (CH_2), 66.0 (CH_2), 52.8 (CH_2), 42.3 (CH), 39.2 (CH_3), 38.4 (C), 33.5 (CH), 28.6 (CH_2), 20.5 (CH), 13.2 (CH_2); MS (LCMS, ES+): 416 (26), 415 (100); HRMS (ES) *m/z* calculated for $C_{22}H_{27}N_2O_4S$ $[M+H]^+$ 415.1686, found 415.1680.

Rac-(1aR,3aS,4R,4aS,8aS,8bR)-4-((5-methylisoxazol-4-yl)methoxy)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole 449

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 3-(bromomethyl)-5-methylisoxazole (55 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **449** as a pale yellow oil (63 mg, 66%); R_f= 0.35 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 2345, 2926, 2905, 2885, 2849, 1605, 1479, 1453, 1386, 1323, 1260, 1240, 1222, 1151, 1127, 1086, 1031, 960, 889, 862, 805, 733, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 1H), 4.92 (dd, *J* = 12.2, 1.2 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.11 (dd, *J* = 12.5, 2.4 Hz, 1H), 3.96 (d, *J* = 1.8 Hz, 2H), 3.89 (app. dt, *J* = 11.3, 3.7 Hz, 1H), 3.73 (dd, *J* = 12.6, 5.6 Hz, 1H), 3.66 (dd, *J* = 9.5, 4.3

Hz, 1H), 3.49 (d, *J* = 9.5 Hz, 1H), 3.33 (app. td, *J* = 11.6, 2.5 Hz, 1H), 2.79 (s, 3H), 2.40 (s, 3H), 2.18 (app. dt, *J* = 10.8, 7.4 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.75 (app. qd, *J* = 12.0, 4.6 Hz, 1H), 1.51 (app. dt, *J* = 8.6, 4.5 Hz, 1H), 1.36 (app. ddt, *J* = 12.4, 5.9, 2.7 Hz, 1H), 0.97 (dd, *J* = 8.3, 5.6 Hz, 1H), 0.56 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6 (C), 162.1 (C), 101.4 (CH), 83.7 (CH), 70.0 (CH), 66.1 (CH_2), 65.9 (CH_2), 64.6 (CH_2), 53.0 (CH_2), 41.9 (CH), 38.4(5) (C), 38.4(3) (CH_3), 33.5 (CH), 28.7 (CH_2), 20.5 (CH), 13.6 (CH_2), 12.4 (CH_3); MS (LCMS, ES+): 391 (36) $[M+Na]^+$, 369 (100); HRMS (ES) *m/z* calculated for $C_{17}H_{25}N_2O_5S$ $[M+H]^+$ 369.1479, found 369.1471.

***Rac*-(1aR,3aS,4R,4aS,8aS,8bR)-4-(benzo[d]oxazol-2-ylmethoxy)-3-(methylsulfonyl)decahydro-5H-cyclopropa[c]pyrano[4',3':3,4]cyclopenta[1,2-b]pyrrole hydrate 450**

Prepared according to **GP15** from **300** (71 mg, 0.26 mmol) and 2-(bromomethyl)-benzo[d]oxazole (66 mg, 0.31 mmol). Preparative UPLC purification [Gradient 10 mM NH_4HCO_3 in H_2O/CH_3CN 95:5 – 2:98] afforded ether **450** as a pale yellow solid (58 mg, 53%); m.p. 164 – 165 °C; R_f= 0.4 (Heptane:EtOAc 1:1) [UV]; IR: ν_{max} (neat, cm^{-1}) 3263, 2951, 2913, 2893, 2841, 1654, 1594, 1528, 1497, 1441, 1381, 1236, 1186, 1109, 1023, 985, 967, 930, 902, 858, 833, 801, 664; ^{1}H NMR (400 MHz, $CDCl_3$) (this compound was isolated in monohydrated form): δ 10.01 (s, 1H, hydration H_2O), 9.38 (s, 1H, hydration H_2O), 7.12 (app. td, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.84 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H), 4.76 (d, *J* = 16.6 Hz, 1H), 4.31 (d, *J* = 2.8 Hz, 1H), 4.27 (s, 1H), 4.04 (dd, *J* = 12.2, 4.3 Hz, 1H), 3.99 (app. t, *J* = 3.4 Hz, 1H), 3.91 (d, *J* = 3.4 Hz, 1H), 3.86 – 3.78 (m, 2H), 3.51 (d, *J* = 10.4 Hz, 1H), 3.37 (ddd, *J* = 13.2, 11.7, 2.0 Hz, 1H), 2.79 (s, 3H), 2.26 (app. dt, *J* = 11.5, 7.6 Hz, 1H), 2.16 (app. dt, *J* = 8.4,

4.2 Hz, 1H), 1.89 (app. tdd, *J* = 13.1, 11.4, 4.7 Hz, 1H), 1.60 (dd, *J* = 8.6, 4.4 Hz, 1H), 1.46 (dd, *J* = 13.3, 6.8 Hz, 1H), 1.13 (dd, *J* = 8.4, 5.7 Hz, 1H), 0.52 (app. t, *J* = 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9 (C), 149.4 (C), 127.3 (CH), 125.8 (C), 122.9 (CH), 120.4 (CH), 120.3 (CH), 89.3 (CH), 72.8 (CH_2), 71.3 (CH), 67.0 (CH_2), 66.7 (CH_2), 53.8 (CH_2), 41.2 (CH), 39.7 (C), 36.7 (CH_3), 33.6 (CH), 29.8 (CH_2), 20.7 (CH), 15.8 (CH_2); MS (LCMS, ES+): t=3.292: 424 (19), 423 (100) $[M+H]^+$ (maj) superimposed to t= 3.352: 423 (26) 405 (100) $[M-H_2O+H]^+$ (min); MS (LCMS_AN_base, ES-): 422 (23), 421 (100) $[M-H]^-$; HRMS (ES) *m/z* calculated for $C_{20}H_{27}N_2O_6S$ $[M+H]^+$ 423.1584, found 423.1580; calculated for $C_{20}H_{25}N_2O_5S$ $[M-H_2O+H]^+$ 405.1479, found 405.1476;

9 Appendix

2.2.1: Large scale (500 mmol) Vilsmeier-Haack reaction for the synthesis of 116

Reaction setup: mechanical stirrer (on top), reaction flask in ice bucket (center) on laboratory jack (bottom)

Quench setup of Vilsmeier reaction: mechanical stirrer (on top), reaction flask in ice+NaCl bucket (bottom)

and temperature control probe (top right)

Close-up of the biphasic mixture VIlsmeier reaction/Na_2CO_3 solution stirred in 10L flask

Large scale organic phase separation: 10L separation flask (left) and transfer funnel for organic phase (right)

2.2.5: Gold-catalysed polycyclization of ynamides

Reaction setup from 5g (16.0 mmol) of 166

2.2.6: Characterization of carbamates

Structure elucidation of compound 192:

- **^{1}H NMR:** H_j+H_j'+H_j'' and H_m+H_m'+H_m'' are both singlets that integrate 9H. They are distinguished between each other for their chemical shift, as the protons that belong to the TMS group are the most upfield.

- Protons that belong to -CH_2- groups are identified at HSQC. Protons H_a are those that have the lowest chemical shift are the furthest from an heteroatom. Protons H_b show correlation at COSY analysis with H_a. Protons H_c, H_e and H_e' are superimposed in $CDCl_3$ and DMSO at room temperature. At high temperature in DMSO, however, they are separated. H_c is shown as a triplet, while H_e and H_e' present two sets of multiplets that are symmetrical with each other. Finally, H_d is the only singlet that integrates 1H.
- **^{13}C NMR:** CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis. The signal with the highest chemical shift corresponds to the carbamyl C_k. C_f and C_g, being ethylenic carbons, must have a higher chemical shift than the acetylenic carbons. C_f is predicted to be downfield because of the polarization given by the silicon atom.
- C_f and C_g could be distinguished for the HMBC interaction C_f-H_c (×2) and C_g-H_a (×2)

^{1}H NMR in Tol-d8 at 25°C (top) and at 90°C (bottom) of compound 192

COSY experiment in $CDCl_3$ at 25°C of compound 192

^{13}C NMR in $CDCl_3$ at 25 °C (above) and at 90 °C in toluene-d_8 (below) of compound 192; solvent signals are cut for simplification

^{1}H NMR of piperidine and dioxolane protons at 25 °C (above) and 90 °C (below) of compound 192 (zoomed on 1.9-6.4 ppm); solvent (Tol-d_8) signals is at 2.09 ppm

^{1}H NMR in toluene-d_8 of compound 192 zoomed on TMS group protons (0.12-0.20 ppm) at 25 °C (above) and 90 °C (below)

Figure 12: ^{1}H NMR in toluene-d$_8$ of compound 192 zoomed on on Boc group protons (1.37-1.45 ppm) at 25 °C (above) and 90 °C (below)

^{13}C NMR of compound 192 at 22 °C in $CDCl_3$ (above) and at 90 °C in toluene-d$_8$ (below) zoomed on a) double bond carbons (113.0-149.0 ppm)

^{13}C NMR of compound 192 at 23 °C in $CDCl_3$ (above) and at 90 °C in toluene-d_8 (below) zoomed on dihydropyrane ring carbons C_b and C_c (40.0-43.0 ppm)

HSQC experiment in $CDCl_3$ at 22 °C of compound 192

HSQC experiment in $CDCl_3$ at 22 °C of compound 192

Structure elucidation of compound 207:

- **^{1}H NMR:** H_e is identified at HSQC (CH), at ^{1}H NMR is as a singlet that integrates one at cs= 4.05 ppm (partially superimposed to other signals). The signal that is the most upfield (therefore belonging to the cyclopropane) shows correlation with H_e at NOESY analysis, therefore it is H_a. Proton H_a' is subsequently defined at HSQC. H_b is the proton that shows

correlation at COSY with H_a and H_a'. H_c shows correlation with C_b (identified with HSQC) at HMBC. H_c' is then defined at HSQC (superimposed to other signals).

- Protons H_l and H_l' are distinguished by the NOESY correlations H_l- H_a' and H_l'-H_c. COSY analysis show correlation between (H_l+H_l') and (H_k+H_k'). The upfield singlet that integrates 9H corresponds to the Boc group, while the downfield signal that integrates 3H corresponds to the mesyl group. Finally, protons corresponding to the dioxolane group and the remaining -CH_2- of the pyran ring (H_j and H_j') are all superimposed signals ranging from 3.65 to 4.15 ppm.
- **^{13}C NMR:** CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis, apart from carbon C_j and C_k that are superimposed to the solvent signal. Protons corresponding to the dioxolane group are superimposed to H_j and H_j', but C_g and C_h are distinguished from C_j and C_k as the formers have an additional oxygen in *beta* position, and therefore have a higher chemical shift.
- As concerning the quaternary carbons, C_o is the most downfield carbon. In the vinyl region, C_m and C_i are distinguished from each other as the former presents correlation with H_a and H_b at HMBC. Proceeding upfield, the next quaternary carbon is C_f (adjacent to two oxygen atoms) followed by C_p (adjacent to the carbon of the carbamoyl group) and Cn (with the lowest chemical shift)

^{1}H NMR in DMSO-d$_6$ at 25 °C (above) and at 90 °C (below) of compound 207

^{1}H NMR of compound 207 at rt (above) and at 90 °C (below) zoomed on piperidine and dioxolane protons (partially superimposed); diastereotopic protons are labelled as H$_x$ (above plane) and H$_x$' (below plane)

^{13}C NMR in $CDCl_3$ at 22 °C of compound 207 and expansion on region 36.0-42.0 ppm

^{13}C NMR in DMSO-d_6 at 22 °C (above) and at 90 °C (below) of compound 207; solvent signal is cut for simplification

^{13}C NMR of compound 207 in DMSO-d_6 at 22 °C (above) and at 90 °C (below) zoomed on carbons C_i, C_o and C_m (122.0-162.0 ppm)

^{13}C NMR of compound 207 at rt (above) and at 90 °C (below) zoomed on C_l

COSY in DMSO-d_6 at 22 °C of compound 207

NOESY in DMSO-d_6 at 22 °C of compound 207

HSQC in DMSO-d_6 at 90 °C of compound 207

HMBC in DMSO-d_6 at 22 °C of compound 207

3.2.1: Amine formation via *p*-nosyl group deprotection

Software	3D models **233** **233**	calculated energy	calculated θ H_d-H_e
a) Chem3D		84.6 kcal/mol	143°
b) MarvinSketch		79.0 kcal/mol	135°
c) MolView		83.0 kcal/mol	102°
d) SwissParam		140 kcal/mol	143°
e) Cheminfo		54.2 kcal/mol	136°

Computational 3D models, energy calculations and dihedral angle calculation of compound 233; a) Chem3D model after energy minimization to Minimum RMS Gradient of 0.010 b) MarvinSketch model with lowest energy of 500 conformers with force field MMFF94 c) MolView model after energy minimization calculation d) SwissParam model e) Cheminfo model after energy minimization calculation

Software	3D models **234** **234**	calculated energy	calculated θ H_d-H_e
a) Chem3D		84.6 kcal/mol	3.8°
b) MarvinSketch		79.8 kcal/mol	12.9°
c) MolView		72.2 kcal/mol	19.8°
d) SwissParam		92.9 kcal/mol	23.4°
e) Cheminfo		49.0 kcal/mol	6.3°

Table 8: computational 3D models, energy calculations and dihedral angle calculations of compound 234; a) Chem3D model after energy minimization to Minimum RMS Gradient of 0.010 b) MarvinSketch model with lowest energy of 500 conformers with force field MMFF94 c) MolView model after energy minimization calculation d) SwissParam model e) Cheminfo model after energy minimization calculation

Equation		
	predicted θ 233	**predicted θ 234**
Karplus	**118°**	**52°**
Barfield	**121°**	**61°**
DAD and DAD (cross terms)	**116°** S1= CH_2CH_2OR, S2= OH, S3= CMe_3, S4= NO_2	**56°** S1= OH, S2= CH_2CH_2OR, S3= CMe_3, S4= NO_2
CJG	**124°** S1= CH=CH, S2= OH, S3= CMe_3, S4= NO_2	**34°** S1= OH, S2= C=CH, S3= CMe_3, S4= NO_2
HLA (chemical groups)	**115°** (As DAD)	**56°** (As DAD)
HLA (general)	**115°** S1= CC_3, S2= OH, S3= CC_3, S4= NSC	**55°** S1= OH, S2= CC_3, S3= CC_3, S4= NSC
HLA (beta effect)	**115°** (as HLA general)	**58°** (as HLA general)
HLA (2 substituents)	**109°** (as HLA general)	**61°** (as HLA general)
HLA (3 substituents)	**109°** (as HLA general)	**59°** (as HLA general)
HLA (4 substituents)	**114°** (as HLA general)	**55°** (as HLA general)

Calculated dihedral angles predicted for 233 and 234 for *J*= 3.7 Hz using the software "MestReJ"

Structure elucidation of compound 233:

- **^{1}H NMR**: H_a and H_a' are the most upfield protons (being on the cyclopropane ring). H_a presents NOESY correlation with H_h, while H_a' is then identified at HSQC. H_b shows correlation at COSY with H_a and H_a', and further interactions with a proton bonded to C_c. H_c gives NOESY correlation with H_a, therefore it the proton bonded to C_c that is up the plane. Proton H_c' (down the plane) is then identified at HSQC.
- H_e and H_e' present NOESY correlation with H_h, while the other two aromatic protons are H_f and H_f'. The alcohol proton signal is the only one that does not have any interaction with a carbon at HSQC and that gives exchange crosspeaks at NOESY. Proton H_i is defined by COSY correlation with -OH and H_h.
- Proton H_a' has NOESY correlation with H_m and H_b with H_m'. The two protons with chemical shifts 3.79-3.72 ppm (confirmed to be linked to the same carbon at HSQC) are H_l and H_l' as COSY interactions can be observed. NOESY interactions are seen between H_m - H_l and H_m' - H_l', and thereafter between H_l -H_k and H_l' - H_k'. Finally, NOESY correlation between H_k' – H_i confirms the configuration of the stereocentre C_i.
- **^{13}C NMR**: CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis. The quaternary carbons that are the most downfield are those of the aromatic ring C_g and C_d,

followed by the carbons of the double bond C_j and C_n (distinguished with one another by comparison with HMBC of compound **278**). Carbon C_o is the most upfield being the only aliphatic one.

1H NMR in $CDCl_3$ of compound 233

^{13}C (Jmod)NMR in $CDCl_3$ of compound 233

COSY in $CDCl_3$ of compound 233

NOESY in $CDCl_3$ of compound 233

HSQC in $CDCl_3$ of compound 233

3.2.3: Saturated ketones and alcohols formation via hydrogenation reactions

Structure elucidation of compound 283:

Note: unless specified in the structure, diastereotopic protons are labelled as H_{letter} if above the plane and H_{letter}' if below the plane, taking as reference the enantiomer drawn below. Analysis of compound 359 were realised both in $CDCl_3$ and C_6D_6 to give a complete assignation of signals.

- **^{1}H NMR**: H_e is identified as it the only -CH signal observable at HSQC that corresponds to a singlet at ^{1}H NMR. It gives NOESY correlation with H_a. The latter is a dd at 0.84 ppm in $CDCl_3$ while in C_6D_6 is superimposed to another signal. H_a' is then identified with HSQC.

  H_b corresponds to a CH signal at HSQC and gives COSY interactions with H_a and H_a'. H_b presents COSY interactions with one of the protons of the multiplet (3H, $CDCl_3$) at 3.50-3.39 ppm, that can be H_c or H_c'. Its diastereotopic proton is at 3.84 ppm ($CDCl_3$) as it presents NOESY interactions with H_a, therefore it is H_c. The above-mentioned signal in the multiplet is instead H_c'.

- The singlet at 3.14 ppm (3H, $CDCl_3$) corresponds to the mesyl group.

- The multiplet at 2.93 ppm (2H, $CDCl_3$) are (H_g+H_k) as they correspond to two CH signals at HSQC. It gives correlation at NOESY with H_e, therefore the protons are likely to be on the same side as He and the cyclopropane ring. Both protons are separated at ^{1}H NMR in C_6D_6. H_k correlates at COSY with signals at 1.17 and 0.46 ppm (^{1}H in C_6D_6), while H_g correlates at COSY with signals at 3.70 and 3.15 ppm. Because the latter couples of signals have higher chemical shifts, those protons are (H_h+H_h'). The protons that correlate with H_k are instead (H_j+H_j'). COSY correlations between the signal at 1.17 ppm (C_6D_6) and the signals at 3.22 and 2.88 ppm indicates that these latter are (H_i+H_i'). The signal at 2.88 ppm presents NOESY interaction at 1H in C_6D_6 with H_b. That proton is therefore H_i', while H_i is at 3.22 ppm in C_6D_6 and at 3.71 ppm in $CDCl_3$.
- Observations of the signals splitting and J couplings of protons bonded to C_h, C_i and C_j at ^{1}H NMR in $CDCl_3$ and C_6D_6 led to the determination of the *pseudo*-axial and *pseudo*-equatorial protons. The signal of proton H_i' (C_6D_6, superimposed signal in $CDCl_3$) is described as a td, *J* = 11.2, 3.6 Hz, while H_i is a ddd, *J* = 11.5, 5.7, 3.4 Hz. Proton H_i' couples with *J*= 11.2 Hz with H_i and then with another proton bonded to C_j with the same J coupling, confirmed being the dddd at 1.17 ppm (C_6D_6) by COSY analysis. Instead, H_i couples with *J*= 11.2 Hz with H_i' and then with smaller *J* values with other protons. This means that H_i' is *pseudo*-axial and the conformation of the tetrahydropyran ring can be outlined as in the following figure:

Protons bonded to C_j can consequently be assigned as H_j= dddd, *J* = 14.6, 10.7, 6.9, 5.6 Hz, 1H and H_j'= app.dq, *J* = 15.0, 3.5 Hz. As regarding protons Hi and Hi', it is impossible to assign them without determining the configuration of C_g and C_k first. As a matter of fact, Proton H_i' may give interactions with H_h' at NOESY (C_6D_6), but the corresponding spot may be superimposed with the spot of the interaction H_i-H_i', therefore being not indicative.

NOESY interaction can be observed between H_k and H_k, confirming this way that H_g and H_k are on the same plane side as H_e and the cyclopropane ring.

Finally, NOESY analysis in both $CDCl_3$ and C_6D_6 confirm spatial vicinity of protons H_k and H_i.

- **^{13}C NMR**: CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis in $CDCl_3$. As protons H_g and H_k are superimposed, C_g is identified as the carbon with a higher chemical shift than C_k. The only quaternary carbons are the carbonyl C_f at 213.1 ppm and the aliphatic carbon of the cyclopropane ring junction C_l at 34.1 ppm.

^{1}H NMR in $CDCl_3$ (top) and in C_6D_6 (bottom) of compound 283

^{13}C (Jmod) NMR in $CDCl_3$ of compound 283

COSY in $CDCl_3$ of compound 283

NOESY in $CDCl_3$ of compound 283

HSQC in $CDCl_3$ of compound 283

COSY in C_6D_6 of compound 283

NOESY in C_6D_6 of compound 283

HSQC in C_6D_6 of compound 283

Crystallographic data for compound 283

Experimental

A 5 ml bottom flask was loaded with compound **283** (ca 50 mg) and EtOH was added (ca. 10 ml). The mixture was refluxed until complete dissolution, then was filtered with a syringe on a nylon membrane filter (0.45 µm) in a 2ml vial. The vial was cooled down on ice until formation of crystals.

A suitable crystal was selected and loaded on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 99.9(4) K during data collection. Using Olex2,[263] the structure was solved with the ShelXT[264] structure solution program using Intrinsic Phasing and refined with the ShelXL[265] refinement package using Least Squares minimisation.

Crystal Data for $C_{12}H_{17}NO_4S$ (*M* =271.32 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19),

a = 7.0122(3) Å, b = 8.7304(2) Å, c = 19.7262(5) Å, V = 1207.62(7) Å^3, Z = 4, T = 99.9(4) K, μ(CuKα) = 2.467 mm^{-1}, *Dcalc* = 1.492 g/cm^3, 21762 reflections measured (8.966° ≤ 2Θ ≤ 146.21°), 2395 unique (R_{int} = 0.0403, R_{sigma} = 0.0196) which were used in all calculations. The final R_1 was 0.0265 (I > 2σ(I)) and wR_2 was 0.0665 (all data).

Table 1 Crystal data and structure refinement for **283**

Identification code	ELGI02-042
Empirical formula	$C_{12}H_{17}NO_4S$
Formula weight	271.32
Temperature/K	99.9(4)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.0122(3)
b/Å	8.7304(2)
c/Å	19.7262(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1207.62(7)
Z	4
ρ_{calc}g/cm^3	1.492
μ/mm^{-1}	2.467
F(000)	576.0
Crystal size/mm^3	0.371 × 0.083 × 0.059
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.966 to 146.21
Index ranges	-8 ≤ h ≤ 7, -10 ≤ k ≤ 10, -24 ≤ l ≤ 22
Reflections collected	21762
Independent reflections	2395 [R_{int} = 0.0403, R_{sigma} = 0.0196]
Data/restraints/parameters	2395/0/165
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0265, wR_2 = 0.0658
Final R indexes [all data]	R_1 = 0.0274, wR_2 = 0.0665
Largest diff. peak/hole / e Å^{-3}	0.20/-0.31
Flack parameter	0.48(2)

Notes: The crystal is a mixture of enantiomers and has thus been refined as an inversion twin

with the refined percentage ratio of enantiomers being 52 (2) : 48 (2). In the major enantiomer, C(3) and C(4) are *R* while C(5), C(9) and C(11) are *S* and in the minor enantiomer C(3) and C(4) are *S* while C(5), C(9) and C(11) are *R*. In all cases the relative stereochemistry is the same.

The hydrogen atoms were fixed as riding models and the isotropic thermal parameters (U_{iso}) were based on the U_{eq} of the parent atom.

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **283**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	96(3)	7459(3)	3034.3(11)	20.9(5)
C2	1577(4)	5862(3)	4010.3(11)	18.4(5)
C3	311(3)	7172(2)	3787.9(11)	17.8(5)
C4	1536(4)	8346(2)	3433.4(10)	16.4(4)
C5	1676(3)	10067(2)	3557.8(10)	16.9(4)
C6	-130(4)	10876(3)	3802.2(12)	20.6(5)
C7	-415(4)	10802(3)	4566.7(12)	22.5(5)
C8	2778(3)	10268(3)	4801.7(11)	22.6(5)
C9	3386(3)	10207(3)	4052.8(10)	17.2(4)
C10	4541(3)	8744(2)	3960.8(11)	17.2(5)
C11	3547(3)	7713(2)	3441.2(10)	16.0(5)
C12	6491(4)	4385(3)	3412.0(12)	24.6(5)
N1	3395(3)	6096(2)	3636.2(9)	15.7(4)
O1	1271(2)	11335.1(19)	4909.0(8)	22.5(4)
O2	5961(3)	8400.6(19)	4272.8(8)	23.9(4)
O3	4361(3)	5410.3(18)	2440.8(7)	24.0(4)
O4	3042(2)	3436.4(18)	3201.7(9)	24.2(4)
S1	4187.3(8)	4781.8(5)	3113.8(2)	15.75(13)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **283**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	20.5(12)	20.7(10)	21.5(10)	0.6(9)	-6.2(9)	-1.7(9)
C2	17.3(12)	18.9(10)	19.0(10)	3.4(8)	5.0(9)	-1.4(9)

C3	15.7(11)	18.1(10)	19.6(10)	-0.3(8)	1.2(9)	-1.3(9)
C4	18.1(11)	15.4(10)	15.8(9)	-0.5(8)	-1.9(8)	0.8(9)
C5	17.1(11)	16.6(10)	17.0(9)	0.8(8)	0.0(8)	-0.4(9)
C6	18.2(12)	18.1(10)	25.4(11)	0.3(9)	-1.7(10)	2.4(9)
C7	19.2(13)	22.1(10)	26.3(11)	-3.0(9)	1.8(10)	0.5(9)
C8	23.0(12)	25.1(11)	19.8(10)	-4.5(9)	-1.5(9)	6.8(11)
C9	15.9(11)	15.5(9)	20.3(9)	-1.3(8)	0.4(8)	0.2(9)
C10	16.0(12)	17.9(10)	17.5(10)	0.2(8)	3.5(9)	-0.8(9)
C11	17.8(12)	14.3(10)	16.0(9)	1.2(8)	1.1(8)	-0.5(9)
C12	19.9(13)	29.6(12)	24.4(11)	-5.2(9)	-2.2(9)	6.3(10)
N1	16.4(10)	12.8(9)	18.0(8)	0.3(7)	4.3(8)	0.5(7)
O1	21.5(9)	23.3(8)	22.8(8)	-6.8(6)	-0.4(7)	3.9(7)
O2	16.8(8)	25.8(8)	29.1(8)	-5.0(7)	-4.8(7)	3.9(8)
O3	34.2(10)	22.7(8)	15.0(7)	0.3(6)	2.6(7)	6.0(8)
O4	25.2(9)	15.6(7)	31.7(9)	-3.7(7)	2.0(8)	-4.5(7)
S1	17.5(3)	14.3(2)	15.5(2)	-1.52(17)	-0.2(2)	1.0(2)

Table 4 Bond Lengths for **283**

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
C1	C3	1.515(3)	C8	C9	1.538(3)
C1	C4	1.496(3)	C8	O1	1.424(3)
C2	C3	1.512(3)	C9	C10	1.523(3)
C2	N1	1.487(3)	C10	C11	1.532(3)
C3	C4	1.509(3)	C10	O2	1.208(3)
C4	C5	1.526(3)	C11	N1	1.467(3)
C4	C11	1.515(3)	C12	S1	1.754(3)
C5	C6	1.528(3)	N1	S1	1.6390(18)
C5	C9	1.551(3)	O3	S1	1.4416(15)
C6	C7	1.523(3)	O4	S1	1.4335(16)
C7	O1	1.439(3)			

Table 5 Bond Angles for **283**

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C4	C1	C3	60.15(14)	C10	C9	C5	105.65(17)
N1	C2	C3	104.80(17)	C10	C9	C8	106.91(17)
C2	C3	C1	117.92(19)	C9	C10	C11	109.31(19)
C4	C3	C1	59.30(15)	O2	C10	C9	125.8(2)

C4	C3	C2	108.29(19)	O2	C10	C11	124.7(2)
C1	C4	C3	60.55(15)	C4	C11	C10	102.48(17)
C1	C4	C5	129.6(2)	N1	C11	C4	106.63(18)
C1	C4	C11	116.43(18)	N1	C11	C10	115.03(18)
C3	C4	C5	129.12(19)	C2	N1	S1	120.42(15)
C3	C4	C11	106.11(18)	C11	N1	C2	108.92(17)
C11	C4	C5	107.32(19)	C11	N1	S1	118.96(14)
C4	C5	C6	116.93(19)	C8	O1	C7	109.18(17)
C4	C5	C9	103.22(17)	N1	S1	C12	103.86(11)
C6	C5	C9	113.92(17)	O3	S1	C12	107.82(12)
C7	C6	C5	113.68(19)	O3	S1	N1	109.95(9)
O1	C7	C6	110.06(19)	O4	S1	C12	108.27(12)
O1	C8	C9	111.78(18)	O4	S1	N1	107.92(10)
C8	C9	C5	113.14(18)	O4	S1	O3	118.08(10)

Table 6 Torsion Angles for **283**

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C3	C4	C5	119.0(3)	C5	C4	C11	N1	154.41(16)
C1	C3	C4	C11	-111.65(19)	C5	C6	C7	O1	52.7(3)
C1	C4	C5	C6	49.9(3)	C5	C9	C10	C11	-1.6(2)
C1	C4	C5	C9	175.8(2)	C5	C9	C10	O2	-177.8(2)
C1	C4	C11	C10	-172.55(18)	C6	C5	C9	C8	32.6(3)
C1	C4	C11	N1	-51.3(2)	C6	C5	C9	C10	149.26(18)
C2	C3	C4	C1	112.2(2)	C6	C7	O1	C8	-68.2(2)
C2	C3	C4	C5	-128.8(2)	C8	C9	C10	C11	119.21(19)
C2	C3	C4	C11	0.5(2)	C8	C9	C10	O2	-57.0(3)
C2	N1	S1	C12	-124.55(18)	C9	C5	C6	C7	-35.5(3)
C2	N1	S1	O3	120.30(17)	C9	C8	O1	C7	66.1(2)
C2	N1	S1	O4	-9.8(2)	C9	C10	C11	C4	-19.0(2)
C3	C1	C4	C5	-118.2(3)	C9	C10	C11	N1	-134.3(2)
C3	C1	C4	C11	94.3(2)	C10	C11	N1	C2	90.1(2)
C3	C2	N1	C11	22.7(2)	C10	C11	N1	S1	-126.63(18)
C3	C2	N1	S1	-119.94(17)	C11	C4	C5	C6	-160.46(18)
C3	C4	C5	C6	-31.5(3)	C11	C4	C5	C9	-34.6(2)
C3	C4	C5	C9	94.4(3)	C11	N1	S1	C12	96.45(19)
C3	C4	C11	C10	-107.88(18)	C11	N1	S1	O3	-18.7(2)
C3	C4	C11	N1	13.3(2)	C11	N1	S1	O4	-148.77(17)
C4	C1	C3	C2	-95.6(2)	N1	C2	C3	C1	50.5(3)
C4	C5	C6	C7	84.9(2)	N1	C2	C3	C4	-13.9(2)

C4	C5	C9	C8	-95.2(2)	O1	C8	C9	C5	-47.8(3)
C4	C5	C9	C10	21.4(2)	O1	C8	C9	C10	-163.64(19)
C4	C11	N1	C2	-22.7(2)	O2	C10	C11	C4	157.2(2)
C4	C11	N1	S1	120.52(17)	O2	C10	C11	N1	42.0(3)
C5	C4	C11	C10	33.2(2)					

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **283**

Atom	***x***	***y***	***z***	**U(eq)**
H1A	562.59	6679.09	2725.82	25
H1B	-1036.37	7995.94	2881.84	25
H2A	1788.71	5893.93	4496.07	22
H2B	1008.34	4884.53	3893.25	22
H3	-695.66	7525.66	4094.77	21
H5	2055.48	10546.41	3129.35	20
H6A	-75.1	11942.25	3664.77	25
H6B	-1224.92	10415.54	3581.56	25
H7A	-1495.61	11432.95	4694.69	27
H7B	-684.36	9755.58	4701.11	27
H8A	2364.96	9258.17	4944.42	27
H8B	3865.22	10556.9	5077.5	27
H9	4162.12	11103.93	3938.36	21
H11	4142.99	7815.16	2994.14	19
H12A	7231.84	5309.42	3413.57	37
H12B	7086.18	3643.73	3121.29	37
H12C	6415.87	3983.75	3864.35	37

Structure elucidation of compound 285:

- **^{1}H NMR**: The singlet (3H) that is the most upfield must be corresponding to the mesyl group (H_d × 3). The singlet (3H) at 1.66 ppm corresponds to the methyl group adjacent to C_g. This assignation is justified by its chemical shift and by HMBC correlation with C_g. Groups CH_{3a} and CH_{3k} are both superimposed at 1.13 ppm. The single signals can however be defined from COSY, as a spot is observed for any peak resulted from splitting. This way it's possible to determine the multiplicity and the *J* couplings of the superimposed signals. The signal of H_k (×3) has COSY correlation with H_j and H_j' and it is a triplet with *J*= 7.7 Hz, while H_a (×3) is a doublet with *J*= 7 Hz. H_j and H_j' have COSY correlation with H_k (×3), while the other -CH_2 signal (visible at HSQC) is H_c+H_c'. One of the two protons is superimposed to another signal, identified as H_l as the multiplet (2H) at 3.06 ppm is the only signal that correlates at COSY with H_e (the most upfield proton).
- As compound **361** is derived from the hydrogenation of a cyclopropane breaking the C_a-C_l bond, the configuration of C_b is fixed, with CH_{a3} and H_e in a *syn* relationship.
- The only proton that has not been identified is H_b, and it is the qdt at 2.14 ppm. It presents correlation at NOESY with the signal at 3.06 ppm but not the multiplet at 3.44 ppm, therefore the former signal is H_c' and the latter H_c. The splitting of proton Hc' can be determined at COSY analysis (with a correlation with H_c), defining the signal as a dd, *J*= 5.6, 10.8 Hz. The multiplicity of proton H_l cannot instead be defined. However, the COSY and NOESY

correlations of H_c' and H_l can be distinguished: for the former proton they correspond to four spots homogeneously spread, while for the latter correspond to one single spot that correlates with the right side of the multiplet. With these observations, it can be affirmed that H_l gives NOESY correlations with H_e, thus confirming the configuration of stereocentre C_l.

- **^{13}C NMR**: CH, CH_2 and CH_3 signals are assigned by correlation at HSQC and HMBC analysis. The only quaternary carbons belong to the α,β-unsaturated carbonyl group and they can be assigned based on their chemical shift.

^{1}H NMR of compound 285

^{13}C NMR of compound 285

COSY of compound 285

COSY of compound 285 (zoom on 1.09-1.14: 0.90-2-80 ppm)

NOESY of compound 285

NOESY of compound 285 (zoom on 2.70-3.24: 1.00-4.50 ppm)

HSQC of compound 285

HMBC of compound 285

Software	3D models **300** **300**	calculated energy	calculated θ H_e-H_f	calculated θ H_f-H_g
a) Chem3D		10.9 kcal/mol	18°	34°
b) MarvinSketch		0.17 kcal/mol	18°	40°
c) MolView		2.2 kcal/mol	36°	35°
d) Cheminfo		11.2 kcal/mol	38°	41°
e) X-ray analysis		12.8 kcal/mol	42°	49°

Computational 3D models, energy calculations and dihedral angle calculation of compound 300; a) Chem3D model after energy minimization to Minimum RMS Gradient of 0.010 b) MarvinSketch model with lowest energy of 500 conformers with force field MMFF94 c) MolView model after energy minimization calculation d) Cheminfo model after energy minimization calculation e) from X-ray analysis

Software	3D models **301** **301**	calculated energy	calculated θ H_e-H_f	calculated θ H_f-H_g
a) Chem3D		10.9 kcal/mol	147°	160°
b) MarvinSketch		-3.9 kcal/mol	154°	166°
c) MolView		- 2.6 kcal/mol	127°	153°
d) Cheminfo		4.2 kcal/mol	147°	159°

Computational 3D models, energy calculations and dihedral angle calculation of compound 301; a) Chem3D model after energy minimization to Minimum RMS Gradient of 0.010 b) MarvinSketch model with lowest energy of 500 conformers with force field MMFF94 c) MolView model after energy minimization calculation d) Cheminfo model after energy minimization calculation

Equation ***J*= 3.6 Hz**		
	predicted θ (Hg-Hf) 300	**predicted θ (Hg-Hf) 301**
Karplus	**52°**	**118°**
Barfield	**61°**	**121°**
DAD and DAD (cross terms)	**46°** S1= CN, S2= OH, S3= CH_2OR, S4= $CHMe_2$	**128°** S1= OH, S2= CN, S3= CH_2OR, S4= $CHMe_2$
CJG	**56°** S1= CN, S2= OH, S3 = CMe_3, S4= CMe_3	**108°** S1= OH, S2= CN, S3 = CMe_3, S4= CMe_3
HLA (chemical groups)	**46°** (As DAD)	**128°** (As DAD)
HLA (general)	**55°** S1= CHCN, S2= OH, S3= CH_2O, S4= CHC_2	**126°** S1= OH, S2= CHCN, S3= CH_2O, S4= CHC_2
HLA (beta effect)	**46°** (as HLA general)	**128°** (as HLA general)
HLA (2 substituents)	**44°** (as HLA general)	**126°** (as HLA general)
HLA (3 substituents)	**47°** (as HLA general)	**124°** (as HLA general)
HLA (4 substituents)	**44°** (as HLA general)	**127°** (as HLA general)

Calculated dihedral angles predicted for 300 and 301 for *J*= 3.6 Hz using the software "MestReJ"

Equation ***J*= 10.0 Hz**		
	predicted θ (Hg-Hf) 300	**predicted θ (Hg-Hf) 301**
Karplus	**n.d. (*J*= 8.0 for θ=0°)**	**170°**
Barfield	**24°**	**161°**
DAD and DAD (cross terms)	**n.d. (*J*= 9.4 for θ=0°)** S1= CN, S2= OH, S3= CH_2OR, S4= $CHMe_2$	**168°** S1= OH, S2= CN, S3= CH_2OR, S4= $CHMe_2$
CJG	**n.d. (*J*= 6.7 for θ=12°)** S1= CN, S2= OH, S3 = CMe_3, S4= CMe_3	**156°** S1= OH, S2= CN, S3 = CMe_3, S4= CMe_3
HLA (chemical groups)	**n.d. (*J*= 9.4 for θ=0°)** (As DAD)	**168°** (As DAD)
HLA (general)	**n.d. (*J*= 9.2 for θ=0°)** S1= CHCN, S2= OH, S3= CH_2O, S4= CHC_2	**168°** S1= OH, S2= CHCN, S3= CH_2O, S4= CHC_2
HLA (beta effect)	**n.d. (*J*= 9.6 for θ=0°)** (as HLA general)	**168°** (as HLA general)
HLA (2 substituents)	**n.d. (*J*= 9.3 for θ=6°)** (as HLA general)	**165°** (as HLA general)
HLA (3 substituents)	**n.d. (*J*= 8.9 for θ=0°)** (as HLA general)	**168°** (as HLA general)
HLA (4 substituents)	**n.d. (*J*= 9.2 for θ=6°)** (as HLA general)	**167°** (as HLA general)

Calculated dihedral angles predicted for 300 and 301 for *J*= 10.0 Hz using the software "MestReJ"

Structure elucidation of compound 300:

- **^{1}H NMR**: Protons on the cyclopropane ring are identified with the NOESY interactions H_a-H_e, H_a'-H_b ($CDCl_3$).
- Protons H_c+H_c' (identified at HSQC) correspond to the doublet at 3.55 ppm ($CDCl_3$)and a multiplet at 3.77 ppm (superimposed to another signal). The former correlates at NOESY with H_a, therefore it is H_c. The multiplet contains instead H_c'.
- The singlet (3H) at 2.93 ppm ($CDCl_3$) corresponds to the mesyl group, while -OH corresponds to the only signal that does not show any correlation at HSQC, that is the singlet at 2.68 ppm.
- H_e shows correlation at COSY (^{1}H NMR in $CDCl_3$) with H_f.
- Out of the three pairs of signals that correspond to -CH_2 at HSQC, those at 1.50 and 1.81 ppm ($CDCl_3$) are those with the lowest chemical shift, and therefore must be H_j+H_j'.

  Signals at 2.10 and 2.24 ppm correspond to the two CH signals left (observable at HSQC). The latter gives COSY correlation with H_j and H_j', therefore is H_k. Proton H_g gives instead resonance at 2.24 ppm ($CDCl_3$). H_k gives NOESY correlation with H_a' and the signal at 1.50 ppm, that is identified this way at H_j. The resonance at 1.81 ppm corresponds instead to H_j'.

Observation of the resonances splitting, *J* couplings of protons bonded to C_h, C_i and C_j ($CDCl_3$ + C_6D_6) and NOESY correlations H_k-H_j ($CDCl_3$) and H_g-H_h ($CDCl_3$ + C_6D_6) led to the determination of the *pseudo*-axial and *pseudo*-equatorial protons.

- The configuration of C_f can be determined by the NOESY interactions between H_e-H_f, H_f-H_g and OH-H_j' (C_6D_6).

^{1}H NMR of compound 315 in $CDCl_3$ (top) and C_6D_6 (bottom)

^{13}C (Jmod) NMR of compound 300 in $CDCl_3$

COSY of compound 300 in $CDCl_3$

NOESY of compound 300 in $CDCl_3$

NOESY of compound 300 in C_6D_6

HSQC of compound 300 in $CDCl_3$

SFC analysis for compound 300

Column	Phenomenex Amylose-1 (100x4.6mm 5µm)
Flow	2.5 ml/min; Column temp: 35 °C; BPR: 170 bar
Eluent A	CO2
Eluent B	Methanol + 20mM ammonia
Gradient	t=0 min 5% B, t=5 min 50% B, t=6 min 50% B
Posttime	0.5 min
Detection PDA	210-320nm
MS	QDa
Detection MS	ESI (scan)
Mass range	100-650 (pos), 1Hz
Time	6 min
Cone	15 V

Crystallographic data for compound 300

Experimental

An NMR tube was loaded with compound **300** (ca. 10 mg) and was dissolved in the minimum amount of CH_2Cl_2 (ca. 0.2 ml). Heptane (ca. 0.4 ml) was slowly added with a pipette in order to form a biphasic mixture. The NMR tube was kept for 3 days at rt until the formation of crystals (see left image).

A suitable crystal was selected and loaded on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 100.00(10) K during data collection. Using Olex2, the structure was solved with the SHELXT, structure solution program using Intrinsic Phasing and refined with the SHELXL, refinement package using Least Squares minimisation.

Table 1 Crystal data and structure refinement for **300**

Identification code	ELGI02-025
Empirical formula	$C_{12}H_{19}NO_4S$
Formula weight	273.34
Temperature/K	100.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.33240(10)
b/Å	13.4843(3)
c/Å	16.9103(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1215.91(5)
Z	4
ρ_{calc}g/cm^3	1.493
μ/mm^{-1}	2.451
F(000)	584.0
Crystal size/mm^3	0.268 × 0.2 × 0.083
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.386 to 146.086
Index ranges	$-6 \leq h \leq 6$, $-16 \leq k \leq 16$, $-20 \leq l \leq 19$
Reflections collected	23362
Independent reflections	2419 [R_{int} = 0.0344, R_{sigma} = 0.0140]
Data/restraints/parameters	2419/0/167
Goodness-of-fit on F^2	1.071
Final R indexes [I>=2σ (I)]	R_1 = 0.0312, wR_2 = 0.0784
Final R indexes [all data]	R_1 = 0.0315, wR_2 = 0.0787
Largest diff. peak/hole / e Å^{-3}	0.28/-0.42
Flack parameter	-0.008(5)

Notes: The structure occupies a chiral space group with a refined Flack parameter of -0.008(5) and is thus a single enantiomer. In all cases, C(3), C(4) and C(10) are *R* while C(5), C(9) and C(11) are *S*.

The hydrogen atom bonded to O(2) was located in the electron density and the position was freely refined. The remaining hydrogen atoms were fixed as riding models and the isotropic thermal parameters (U_{iso}) of all hydrogen atoms were based on the U_{eq} of the parent atom.

Crystal Data for $C_{12}H_{19}NO_4S$ (*M* =273.34 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 5.33240(10) Å, *b* = 13.4843(3) Å, *c* = 16.9103(5) Å, *V* = 1215.91(5) Å^3, *Z* = 4, *T* = 100.00(10) K, μ(Cu Kα) = 2.451 mm^{-1}, *Dcalc* = 1.493 g/cm^3, 23362 reflections measured (8.386° ≤ 2Θ ≤ 146.086°), 2419 unique (R_{int} = 0.0344, R_{sigma} = 0.0140) which were used in all calculations. The final R_1 was 0.0312 (I > 2σ(I)) and wR_2 was 0.0787 (all data).

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **300**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	2409(5)	4089.0(17)	3217.3(13)	20.1(5)
C2	5348(4)	5577.7(17)	2910.2(14)	18.0(5)
C3	4992(4)	4549.8(17)	3242.6(13)	15.5(4)
C4	3287(4)	4603.2(17)	3952.6(13)	15.4(5)
C5	3777(4)	4167.3(17)	4771.5(13)	16.1(5)
C6	6458(5)	3769.6(18)	4883.2(14)	17.8(5)
C7	7103(5)	3700.5(17)	5756.5(14)	20.8(5)
C8	4413(5)	4986.9(19)	6138.7(14)	19.5(5)
C9	3196(4)	5059.8(18)	5327.5(13)	19.2(5)
C10	3735(5)	5983.1(18)	4832.6(14)	20.5(5)
C11	2502(5)	5680.7(17)	4046.6(13)	19.8(5)
C12	4265(5)	8112(2)	3474.7(16)	25.3(6)
N1	3372(5)	6152.0(16)	3317.7(12)	26.2(5)
O1	6960(3)	4664.5(13)	6108.9(9)	19.7(4)
O2	6381(3)	6136.8(13)	4735.7(10)	22.7(4)
O3	2752(6)	7277.3(14)	2193.6(12)	51.2(7)

Atom	*x*	*y*	*z*	U(eq)
O4	-103(4)	7337.1(15)	3347.9(19)	55.4(8)
S1	2380.8(12)	7215.0(4)	3027.4(4)	26.90(18)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **300**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	22.6(11)	22.1(11)	15.6(10)	-1.9(8)	-0.2(10)	-6.9(10)
C2	20.5(11)	16.3(10)	17.0(11)	-0.4(9)	-2.6(9)	-1.8(9)
C3	16.6(10)	14.8(10)	15.3(10)	-0.7(8)	1.1(9)	2.1(9)
C4	13.3(10)	18.7(11)	14.1(11)	-1.5(9)	-0.1(8)	0.0(8)
C5	17.3(11)	17.9(11)	13.2(11)	-0.4(8)	-0.6(9)	-2.4(9)
C6	21.3(11)	14.8(10)	17.4(11)	0.5(9)	-1.5(9)	2.7(9)
C7	25.5(12)	18.5(11)	18.3(11)	3.3(9)	-1.5(10)	3.3(10)
C8	22.0(12)	23.0(11)	13.6(11)	-1.5(9)	1.5(9)	1.1(10)
C9	17.6(11)	25.3(12)	14.6(11)	-3.3(9)	1.5(9)	4.0(9)
C10	26.0(12)	20.4(12)	15.2(11)	-5.2(9)	-0.7(9)	8.9(10)
C11	20.1(11)	24.8(11)	14.5(10)	-2.8(8)	-2.1(10)	10.2(11)
C12	20.1(12)	29.2(13)	26.5(13)	-13.0(10)	3.8(10)	-6.6(10)
N1	44.4(14)	19.3(10)	14.9(10)	1.2(8)	-1.5(9)	17.7(10)
O1	19.9(8)	22.7(8)	16.4(8)	-1.8(6)	-2.3(6)	-1.3(7)
O2	29.3(9)	19.9(8)	18.8(9)	1.3(7)	1.7(7)	-1.3(7)
O3	103(2)	17.5(9)	33.1(11)	8.0(8)	-42.5(13)	-10.7(13)
O4	14.4(9)	19.1(9)	133(3)	9.8(12)	-17.7(12)	1.8(8)
S1	27.5(3)	12.1(3)	41.0(4)	-0.9(2)	-21.2(3)	1.7(3)

Table 4 Bond Lengths for **300**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C3	1.511(3)	C8	C9	1.521(3)
C1	C4	1.499(3)	C8	O1	1.427(3)
C2	C3	1.508(3)	C9	C10	1.527(3)
C2	N1	1.478(3)	C10	C11	1.538(3)
C3	C4	1.508(3)	C10	O2	1.435(3)
C4	C5	1.527(3)	C11	N1	1.462(3)
C4	C11	1.520(3)	C12	S1	1.745(2)
C5	C6	1.538(3)	N1	S1	1.605(2)
C5	C9	1.558(3)	O3	S1	1.426(2)
C6	C7	1.519(3)	O4	S1	1.440(2)
C7	O1	1.432(3)			

Table 5 Bond Angles for **300**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C4	C1	C3	60.11(15)	C8	C9	C10	117.8(2)
N1	C2	C3	102.60(19)	C10	C9	C5	105.15(18)
C2	C3	C1	118.8(2)	C9	C10	C11	100.2(2)
C4	C3	C1	59.53(14)	O2	C10	C9	111.4(2)
C4	C3	C2	109.21(18)	O2	C10	C11	111.1(2)
C1	C4	C3	60.36(15)	C4	C11	C10	103.05(18)
C1	C4	C5	128.9(2)	N1	C11	C4	103.87(18)
C1	C4	C11	116.3(2)	N1	C11	C10	118.5(2)
C3	C4	C5	126.92(19)	C2	N1	S1	124.07(17)
C3	C4	C11	107.15(19)	C11	N1	C2	113.05(18)
C11	C4	C5	108.68(18)	C11	N1	S1	122.78(17)
C4	C5	C6	113.87(19)	C8	O1	C7	109.98(18)
C4	C5	C9	102.47(18)	N1	S1	C12	107.28(14)
C6	C5	C9	112.33(19)	O3	S1	C12	107.92(14)
C7	C6	C5	110.55(19)	O3	S1	N1	108.01(12)
O1	C7	C6	109.68(18)	O3	S1	O4	119.54(17)
O1	C8	C9	113.20(19)	O4	S1	C12	106.69(13)
C8	C9	C5	114.2(2)	O4	S1	N1	106.85(13)

Table 6 Hydrogen Bonds for **300**

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O4[1]	0.92(3)	2.58(4)	3.412(3)	151(3)

[1]1+X,+Y,+Z

Table 7 Torsion Angles for **300**

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C3	C4	C5	118.4(3)	C5	C4	C11	N1	150.5(2)
C1	C3	C4	C11	-111.0(2)	C5	C6	C7	O1	-60.6(2)
C1	C4	C5	C6	88.1(3)	C5	C9	C10	C11	43.7(2)
C1	C4	C5	C9	-150.3(2)	C5	C9	C10	O2	-74.0(2)
C1	C4	C11	C10	-178.7(2)	C6	C5	C9	C8	-35.7(3)
C1	C4	C11	N1	-54.5(3)	C6	C5	C9	C10	95.0(2)
C2	C3	C4	C1	112.8(2)	C6	C7	O1	C8	69.2(2)
C2	C3	C4	C5	-128.8(2)	C8	C9	C10	C11	172.2(2)
C2	C3	C4	C11	1.8(3)	C8	C9	C10	O2	54.5(3)
C2	N1	S1	C12	-89.2(2)	C9	C5	C6	C7	43.6(2)
C2	N1	S1	O3	26.9(3)	C9	C8	O1	C7	-60.2(3)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C2	N1	S1	O4	156.7(2)	C9	C10	C11	C4	-42.2(2)
C3	C1	C4	C5	-115.4(3)	C9	C10	C11	N1	-156.2(2)
C3	C1	C4	C11	95.6(2)	C10	C11	N1	C2	93.5(2)
C3	C2	N1	C11	20.9(3)	C10	C11	N1	S1	-83.0(3)
C3	C2	N1	S1	-162.64(18)	C11	C4	C5	C6	-121.0(2)
C3	C4	C5	C6	9.0(3)	C11	C4	C5	C9	0.5(2)
C3	C4	C5	C9	130.6(2)	C11	N1	S1	C12	87.0(2)
C3	C4	C11	C10	-113.9(2)	C11	N1	S1	O3	-156.9(2)
C3	C4	C11	N1	10.4(2)	C11	N1	S1	O4	-27.1(3)
C4	C1	C3	C2	-96.4(2)	N1	C2	C3	C1	52.0(2)
C4	C5	C6	C7	159.48(19)	N1	C2	C3	C4	-13.1(2)
C4	C5	C9	C8	-158.29(19)	O1	C8	C9	C5	43.6(3)
C4	C5	C9	C10	-27.6(2)	O1	C8	C9	C10	-80.5(3)
C4	C11	N1	C2	-20.0(3)	O2	C10	C11	C4	75.6(2)
C4	C11	N1	S1	163.50(18)	O2	C10	C11	N1	-38.4(3)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **300**

Atom	*x*	*y*	*z*	U(eq)
H1A	1137.31	4416.05	2900.91	24
H1B	2297.55	3371.11	3227.82	24
H2A	7002.82	5833.88	3032.7	22
H2B	5107.54	5585.13	2341.69	22
H3	6449.65	4108.32	3266.71	19
H5	2573.79	3633.27	4873.69	19
H6A	6595.52	3118.64	4642.97	21
H6B	7637.81	4207.55	4621.25	21
H7A	5940.32	3255.36	6018.66	25
H7B	8782.36	3435.76	5819.08	25
H8A	4344.67	5631.72	6392.14	23
H8B	3458.69	4527.09	6461.24	23
H9	1380.59	5051.01	5417.46	23
H10	2923.42	6570.39	5058.43	25
H11	673.12	5729.93	4087.78	24
H12A	5984.54	8002.11	3331.17	38
H12B	4092.59	8068.74	4038.75	38
H12C	3754.75	8758.81	3300.31	38
H2	6790(70)	6590(30)	4360(20)	34

- **Structure elucidation of compound 301:**

- **^{1}H NMR**: Proton H_a is coupled at NOESY with H_e (Acetone-d_6) and H_c ($CDCl_3$).
- Protons H_a' and H_c' are identified by correlations between respectively C_a and C_c with H_a and H_c at HSQC.
- Proton H_b (superimposed with another proton at ^{1}H NMR in $CDCl_3$, Acetone-d_6 and Methanol-d_4) corresponds to a CH signal at HSQC and correlates at COSY with H_a and H_c'.
- Proton H_f correlates at COSY with H_e (Acetone-d_6).
- Protons H_g and H_k correspond to two CH signals at HSQC. Proton H_k correlates at COSY with H_j and H_j' (Acetone-d_6). Because compound **301** was synthesised from **283** (whose 3D structure is known), H_g and H_k are in a *syn* relationship to H_e.
- Diastereotopic proton couples bonded to C_h, C_i and C_j are identified at HSQC. Protons bonded to C_i correlate at COSY with those bonded to C_j, while protons bonded to C_h correlate at COSY with H_g (superimposed to H_k at ^{1}H NMR in $CDCl_3$). Observation of the resonances splitting and *J* couplings of protons bonded to C_g, C_h, C_i, C_j and C_k at ^{1}H NMR in $CDCl_3$, Acetone-d_6 and Methanol-d_4 led to the determination of the *pseudo*-axial and *pseudo*-equatorial protons:
- H_g= (app. qd, *J* = 10.9, 4.0 Hz, 1H), H_k= (app. td, *J* = 11.6, 3.6 Hz, 1H)

- $H_j + H_j'$ = (app. qd, *J* = 12.1, 4.5 Hz, 1H) **ax** + (app. ddt, *J* = 12.5, 3.9, 2.0 Hz, 1H) **eq**
- $H_i + H_i'$ = multiplet (superimposed signal with H_h or H_h'), (ddd, *J* = 11.3, 4.4, 1.5 Hz, 1H) **eq**
- $H_h + H_h'$ = multiplet (superimposed signal with H_i or H_i'), (dd, *J* = 10.6, 4.1 Hz, 1H) **eq**

  The splitting of the resonances of protons bonded to C_i and C_h that are superimposed in a multiplet can be determined at ^{1}H NMR in $CDCl_3$: (app. td, *J* = 11.7, 2.3 Hz, 1H) **ax** + (app. t, *J* = 10.5 Hz, 1H) **ax**.

- Proton H_k strongly correlates at NOESY at ^{1}H NMR in acetone-d_6 with the multiplet (2H) observed at 3.23 ppm. It can be therefore safely assumed that the multiplet contains the signals of the *pseudo*-axial protons and that these are in a *syn*-relationship with H_k.

  The tetrahydropyran ring conformation is therefore the same as described as **300**:

- The configuration of C_f could not be determined solely by 2D-NMR analysis of **301** as no key NOESY correlations could be found. The structure confirmation of the compound could be confirmed only after X-ray analysis of the diastereoisomer **300**.
- **^{13}C NMR**: CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis, the only quaternary carbon corresponding to the 5,5,3-ring junction.

^{1}H NMR of compound 301 in $CDCl_3$ (top), Acetone-d_6 (centre) and Methanol-d_4 (bottom)

^{13}C (Jmod) NMR of compound 301 in $CDCl_3$

COSY of compound 301 in $CDCl_3$

COSY of compound 301 in Acetone-d_6

NOESY of compound 301 in $CDCl_3$

NOESY of compound 301 in Acetone-d_6

HSQC of compound 301 in Acetone-d_6

3.2.4 Framework modifications via oxidation reactions

- **Structure elucidation of compound 320:**

- **^{1}H NMR**: H_a is identified for NOESY correlation with He (that is a singlet integrating 1H). Protons H_a', H_b, H_c and H_c' are assigned with HSQC, COSY and NOESY analysis. Proton H_k gives COSY correlation with H_j and H_j' plus NOESY correlation with H_j. Proton H_g gives NOESY correlation with H_h and H_h' and COSY with Hh. It doesn't give COSY with H_h', that is a doublet and therefore has a dihedral angle with H_g of ~ 90°. Proton H_k correlates at NOESY with H_i.
- **^{13}C NMR**: CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis. Of the two quaternary carbons, the carbonyl is at ~ 170 ppm while the other is in the aliphatic region.

^{1}H NMR of compound 320 in $CDCl_3$

^{13}C (Jmod) NMR of compound 320 in $CDCl_3$

COSY of compound 320 in $CDCl_3$

NOESY of compound 320 in $CDCl_3$

HSQC of compound 320 in $CDCl_3$

HMBC correlations found for compound 320

3.2.5 Framework modifications via addition reactions

- **Resonances assignment of compound 341:**

Note: unless specified in the structure, diastereotopic protons are labelled as H_{letter} if above the plane and H_{letter}' if below the plane, taking as reference the enantiomer drawn below. Analysis of compound **341** were realised both in $CDCl_3$ and C_6D_6 to give a complete assignation of signals.

- **^{1}H NMR**: H_a and H_e correlate at NOESY ($CDCl_3$). H_a' and H_b are identified with COSY correlation with H_a and distinguished from each other by HSQC. Diastereotopic protons (H_c + H_c') are identified by COSY correlation with H_b. The mesyl group is the only singlet signal that integrates 3H. The three diastereotopic protons bonded to C_h, C_i and C_j are identified at HSQC. Protons (H_j+H_j') have, amongst the three remaining diastereotopic couples, the lowest chemical shift. Protons (H_h+H_h') are both doublets, while (H_i+H_i') have additional splittings ($CDCl_3$). Proton H_j' gives a separate signal in C_6D_6, and it is a dd with couplings J = 14.5, 2.6 Hz. This means it is the equatorial proton. Proton H_a' gives NOESY correlation with the multiplet (H_j+H_j') in $CDCl_3$, but not with the isolated "equatorial H_j" in C_6D_6, therefore the NOESY correlation is H_a'-H_j (axial). Proton H_b gives NOESY correlation with (H_j+H_j') ($CDCl_3$), and given the interaction H_a'-H_j, the only possible interaction would be H_b-H_j'. This is also confirmed by

NOESY interaction between the multiplet (H_b+H_c/H_c') and H_j', as protons H_c and H_c' would be too far away to give spatial correlation with H_j'. Moreover, Hj' gives NOESY correlation with Hi and a weaker correlation with Hi'. Instead, the multiplet at 2.10 ppm (Ha + Hj + Hd×3) gives NOESY correlation with Hi' but not with Hi. This means that the axial protons do not show spatial vinicinity, therefore the conformation of the tetrahydropyran ring is a chair and not a "distorted chair" or other conformations characteristic of a saturated 6-membered ring. The tetrahydropyran ring conformation can subsequently be determined as follows:

^{13}C NMR: CH, CH_2 and CH_3 signals are assigned by correlation at HSQC analysis. The only quaternary carbon in the aromatic region that can be identified is C_f, that is the one with the highest chemical shift. Carbons C_g and C_k are identified for respective HMBC interaction with Ha (^{4}J, W interaction, CDCl3) and H_a'(^{3}J) plus Hb (^{3}J, $CDCl_3$).

^{1}H NMR of compound 341 in $CDCl_3$ (top) and C_6D_6 (bottom)

^{13}C NMR of compound 341 in $CDCl_3$

NOESY of compound 341 in $CDCl_3$

NOESY of compound 341 in C_6D_6

HSQC of compound 341 in $CDCl_3$

HMBC of compound 341 in $CDCl_3$

3.2.7 Aminoalcohol formation

- **Structure elucidation of compound 365:**

Signals assignations of protons and carbons atoms were realised as reported for compound **233**.

^{1}H NMR of compound 365 in $CDCl_3$

^{13}C NMR of compound 365 in $CDCl_3$

NOESY of compound 365 in $CDCl_3$

HSQC of compound 365 in $CDCl_3$

HMBC of compound 365 in $CDCl_3$

- **Counterion analysis of compound 362:**

Experimental

The sample was prepared twice by accurately weighing in 0.5 ± 0.3 mg of provided material into a 1 ml flask and dissolving it in H2O.

The calibration curve was prepared by weighing 30.00 ± 3 mg of NaCl into a 100 ml flask and dissolving it in H_2O. These solutions were measured with method: TrinityP1_iso50_CAD and an injection volume of 0.2, 0.5, 2 and 4 µl (twice). Samples were measured using this method with an injection volume of 10µl (triplicate). The amount of Cl- present in the sample was calculated by average of CAD responses.

	TrinityP1_iso50_CAD
column	Trinity P1 150x3.0 mm 3 µ
temp	40 °C
flow	0.9 ml/min
eluent A	20 mM ammonium acetate in water
eluent B	acetonitrile
isocratic	50% B (for 12 min)
post time	off
detection CAD	neb. gas 40°C, filter: 3.6 sec

	%w/w	moleq	
	Cl-	**Cl-**	**n**
ELGI02-066-1	12.2	1.0	
	11.5	1.0	
average	11.9	1.0	6

3.2.8: Aminoalcohol reduction via hydrogenation reactions

- **3D-model of compound 208 realised with MarvinSketch 21.18**

Software	MarvinSketch 21.18
Force field	MMFF94
Optimization limit	Normal
Max number of conformers	100
Diversity limit	0.1
Timelimit	900
Conformer energy	-20.58 kcal/mol

Image visualised with Chem3D 12.0.2:

Atom coordinates

Atoms	x (Å)	y (Å)	z (Å)
C(1)	-0.891	-7.5687	0.4765
C(2)	0.3718	-6.7149	3.6708
N(3)	2.0647	-3.7938	3.6453
C(4)	0.4866	-1.0645	2.4149
C(5)	-1.6512	-1.9251	-0.1211
C(6)	-2.2761	-4.8151	-1.06
C(7)	-3.289	0.459	-2.0728
C(8)	-5.6106	-1.5569	-4.067
C(9)	-4.4267	-4.844	-3.6306
N(10)	-5.4767	-1.0012	-7.4489
C(11)	-4.2816	-3.7081	-9.1307
C(12)	-3.5289	-6.0639	-6.7104
C(13)	-6.0261	-7.6594	-4.8665
O(14)	-4.9488	2.5677	-0.1472
O(15)	-0.9824	2.0456	-3.8261
C(16)	-3.4171	5.4621	-0.5346
C(17)	-1.8026	5.2204	-3.6017
C(18)	4.6447	-3.4975	5.5084
O(19)	5.9255	-5.6581	6.8058
O(20)	5.5786	-0.5206	5.7732
C(21)	8.2268	-0.0655	7.6947
C(22)	8.8532	3.3714	7.8891
S(23)	-8.0708	1.2924	-9.0962
O(24)	-7.2336	1.6408	-12.3121
O(25)	-8.5181	3.9494	-7.1239
C(26)	-11.5375	-0.9177	-8.95
C(27)	7.0326	5.226	9.635
C(28)	7.6121	8.2757	9.8545

C(29)	10.0294	9.5133	8.3404
C(30)	11.8629	7.6994	6.6053
C(31)	11.281	4.6503	6.3861
H(32)	-1.6713	-8.3541	0.5905
H(33)	-0.0525	-7.945	-0.1512
H(34)	-0.4813	-6.6271	4.3803
H(35)	1.08	-7.5153	3.9813
H(36)	1.2457	-3.5E-05	2.0242
H(37)	-0.1039	-0.5960	3.2339
H(38)	-6.6496	-1.3287	-3.7396
H(39)	-3.367	-3.4353	-9.7033
H(40)	-5.0242	-4.096	-9.8635
H(41)	-2.6716	-6.4795	-7.2316
H(42)	-5.8378	-8.6321	-4.422
H(43)	-7.0581	-7.9449	-5.0481
H(44)	-4.1542	6.296	-0.5456
H(45)	-2.7075	5.6745	0.2961
H(46)	-0.8955	5.865	-3.6222
H(47)	-2.4409	5.558	-4.4487
H(48)	9.1066	-0.5843	7.2526
H(49)	8.0421	-0.4816	8.7103
H(50)	-12.3683	-0.3365	-9.4093
H(51)	-11.3951	-1.8678	-9.512
H(52)	-11.787	-1.1465	-7.8897
H(53)	6.1782	4.7947	10.1771
H(54)	6.9614	8.9162	10.468
H(55)	10.2353	10.5911	8.4186
H(56)	12.7181	8.1357	6.0683
H(57)	11.9366	4.0146	5.7729

bond lengths

Atoms	Bond lenght (Å)
C(31)-H(57)	1.1000
C(30)-H(56)	1.1000
C(29)-H(55)	1.1000
C(28)-H(54)	1.1000
C(27)-H(53)	1.1000
C(26)-H(52)	1.1130
C(26)-H(51)	1.1130
C(26)-H(50)	1.1130
C(21)-H(49)	1.1130
C(21)-H(48)	1.1130
C(17)-H(47)	1.1130
C(17)-H(46)	1.1130
C(16)-H(45)	1.1130

C(16)-H(44)	1.1130
C(13)-H(43)	1.0860
C(13)-H(42)	1.0860
C(12)-H(41)	1.0860
C(11)-H(40)	1.1130
C(11)-H(39)	1.1130
C(8)-H(38)	1.1130
C(4)-H(37)	1.1130
C(4)-H(36)	1.1130
C(2)-H(35)	1.1130
C(2)-H(34)	1.1130
C(1)-H(33)	1.1130
C(1)-H(32)	1.1130
C(22)-C(31)	3.1287
C(22)-C(27)	3.1309
C(30)-C(31)	3.1119
C(29)-C(30)	3.1085
C(28)-C(29)	3.1093
C(27)-C(28)	3.1120
S(23)-C(26)	4.1139
S(23)-O(25)	3.3391
S(23)-O(24)	3.3413
N(10)-S(23)	3.8345
C(21)-C(22)	3.4989
O(20)-C(21)	3.3034
C(18)-O(20)	3.1312
C(18)-O(19)	2.8270
N(3)-C(18)	3.1961
C(16)-C(17)	3.4745
O(15)-C(17)	3.2867
O(14)-C(16)	3.2975
C(7)-O(15)	3.3033
C(7)-O(14)	3.3030
C(12)-C(13)	3.4902
C(9)-C(13)	3.4658
C(9)-C(12)	3.4321
C(8)-N(10)	3.4299
C(11)-C(12)	3.4604
N(10)-C(11)	3.4035
C(6)-C(9)	3.3517
C(5)-C(7)	3.4893
C(8)-C(9)	3.5210
C(7)-C(8)	3.6648
C(1)-C(6)	3.4441
C(5)-C(6)	3.1023
C(4)-C(5)	3.4267
N(3)-C(4)	3.3843

C(2)-N(3)	3.3763
C(1)-C(2)	3.5394

bond angles

Atoms	Bond angles (°)
H(57)-C(31)-C(22)	119.6086
H(57)-C(31)-C(30)	119.6086
C(22)-C(31)-C(30)	120.7827
H(56)-C(30)-C(31)	119.9739
H(56)-C(30)-C(29)	119.9739
C(31)-C(30)-C(29)	120.0522
H(55)-C(29)-C(30)	120.0621
H(55)-C(29)-C(28)	120.0621
C(30)-C(29)-C(28)	119.8758
H(54)-C(28)-C(29)	119.9838
H(54)-C(28)-C(27)	119.9838
C(29)-C(28)-C(27)	120.0325
H(53)-C(27)-C(22)	119.6165
H(53)-C(27)-C(28)	119.6165
C(22)-C(27)-C(28)	120.7670
H(52)-C(26)-H(51)	109.5200
H(52)-C(26)-H(50)	109.4618
H(52)-C(26)-S(23)	109.4618
H(51)-C(26)-H(50)	109.4418
H(51)-C(26)-S(23)	109.4418
H(50)-C(26)-S(23)	109.5000
C(26)-S(23)-O(25)	107.0742
C(26)-S(23)-O(24)	107.5397
C(26)-S(23)-N(10)	103.5019
O(25)-S(23)-O(24)	121.2713
O(25)-S(23)-N(10)	108.2300
O(24)-S(23)-N(10)	107.8385
C(31)-C(22)-C(27)	118.4884
C(31)-C(22)-C(21)	120.9138
C(27)-C(22)-C(21)	120.5799
H(49)-C(21)-H(48)	108.6205
H(49)-C(21)-C(22)	110.2596
H(49)-C(21)-O(20)	110.2596
H(48)-C(21)-C(22)	109.7830
H(48)-C(21)-O(20)	109.7830
C(22)-C(21)-O(20)	108.1294
C(21)-O(20)-C(18)	114.7890
O(20)-C(18)-O(19)	123.5510
O(20)-C(18)-N(3)	112.2220
O(19)-C(18)-N(3)	124.2213
H(47)-C(17)-H(46)	106.1275

H(47)-C(17)-C(16)	112.5915
H(47)-C(17)-O(15)	112.5915
H(46)-C(17)-C(16)	110.7757
H(46)-C(17)-O(15)	110.7757
C(16)-C(17)-O(15)	104.0887
H(45)-C(16)-H(44)	106.6577
H(45)-C(16)-C(17)	112.0798
H(45)-C(16)-O(14)	112.0798
H(44)-C(16)-C(17)	110.5584
H(44)-C(16)-O(14)	110.5584
C(17)-C(16)-O(14)	104.9803
C(17)-O(15)-C(7)	104.6824
C(16)-O(14)-C(7)	104.9792
H(43)-C(13)-H(42)	89.8683
H(43)-C(13)-C(12)	135.3763
H(43)-C(13)-C(9)	135.3763
H(42)-C(13)-C(12)	120.1081
H(42)-C(13)-C(9)	120.1081
C(12)-C(13)-C(9)	59.1272
H(41)-C(12)-C(13)	130.0487
H(41)-C(12)-C(9)	140.6412
H(41)-C(12)-C(11)	95.5424
C(13)-C(12)-C(9)	60.0824
C(13)-C(12)-C(11)	121.6747
C(9)-C(12)-C(11)	109.1932
H(40)-C(11)-H(39)	107.1526
H(40)-C(11)-C(12)	111.6101
H(40)-C(11)-N(10)	111.6101
H(39)-C(11)-C(12)	110.3587
H(39)-C(11)-N(10)	110.3587
C(12)-C(11)-N(10)	105.7961
S(23)-N(10)-C(8)	119.6097
S(23)-N(10)-C(11)	120.0653
C(8)-N(10)-C(11)	111.8437
C(13)-C(9)-C(12)	60.7904
C(13)-C(9)-C(6)	125.2118
C(13)-C(9)-C(8)	123.9874
C(12)-C(9)-C(6)	121.5635
C(12)-C(9)-C(8)	107.9729
C(6)-C(9)-C(8)	107.6234
H(38)-C(8)-N(10)	107.0567
H(38)-C(8)-C(9)	117.9547
H(38)-C(8)-C(7)	108.5744
N(10)-C(8)-C(9)	105.0903
N(10)-C(8)-C(7)	115.0046
C(9)-C(8)-C(7)	103.4790
O(15)-C(7)-O(14)	110.7132

O(15)-C(7)-C(5)	107.2956
O(15)-C(7)-C(8)	114.6916
O(14)-C(7)-C(5)	110.2423
O(14)-C(7)-C(8)	110.4923
C(5)-C(7)-C(8)	103.0538
C(9)-C(6)-C(1)	126.3927
C(9)-C(6)-C(5)	111.6785
C(1)-C(6)-C(5)	121.9230
C(7)-C(5)-C(6)	111.8805
C(7)-C(5)-C(4)	122.3561
C(6)-C(5)-C(4)	125.7050
H(37)-C(4)-H(36)	110.4974
H(37)-C(4)-C(5)	108.6191
H(37)-C(4)-N(3)	108.6191
H(36)-C(4)-C(5)	109.0803
H(36)-C(4)-N(3)	109.0803
C(5)-C(4)-N(3)	110.9428
C(18)-N(3)-C(4)	120.9023
C(18)-N(3)-C(2)	118.7214
C(4)-N(3)-C(2)	117.8186
H(35)-C(2)-H(34)	111.5046
H(35)-C(2)-N(3)	107.7756
H(35)-C(2)-C(1)	107.7756
H(34)-C(2)-N(3)	108.7173
H(34)-C(2)-C(1)	108.7173
N(3)-C(2)-C(1)	112.3823
H(33)-C(1)-H(32)	110.3214
H(33)-C(1)-C(6)	108.7690
H(33)-C(1)-C(2)	108.7690
H(32)-C(1)-C(6)	109.1447
H(32)-C(1)-C(2)	109.1447
C(6)-C(1)-C(2)	110.6865

dihedral angles

Atoms	Dihedral angles (°)
C(21)-C(22)-C(31)-C(30)	-178.8721
C(21)-C(22)-C(31)-H(57)	1.1279
C(27)-C(22)-C(31)-C(30)	-0.4035
C(27)-C(22)-C(31)-H(57)	179.5965
C(21)-C(22)-C(27)-C(28)	178.9044
C(21)-C(22)-C(27)-H(53)	-1.0956
C(31)-C(22)-C(27)-C(28)	0.4306
C(31)-C(22)-C(27)-H(53)	-179.5694
C(29)-C(30)-C(31)-C(22)	0.2157
C(29)-C(30)-C(31)-H(57)	-179.7843
H(56)-C(30)-C(31)-C(22)	-179.7843

H(56)-C(30)-C(31)-H(57)	0.2157
C(28)-C(29)-C(30)-C(31)	-0.0454
C(28)-C(29)-C(30)-H(56)	179.9546
H(55)-C(29)-C(30)-C(31)	179.9546
H(55)-C(29)-C(30)-H(56)	-0.0454
C(27)-C(28)-C(29)-C(30)	0.0722
C(27)-C(28)-C(29)-H(55)	-179.9278
H(54)-C(28)-C(29)-C(30)	-179.9278
H(54)-C(28)-C(29)-H(55)	0.0722
C(22)-C(27)-C(28)-C(29)	-0.2698
C(22)-C(27)-C(28)-H(54)	179.7302
H(53)-C(27)-C(28)-C(29)	179.7302
H(53)-C(27)-C(28)-H(54)	-0.2698
N(10)-S(23)-C(26)-H(50)	-180.0000
N(10)-S(23)-C(26)-H(51)	-60.0364
N(10)-S(23)-C(26)-H(52)	59.9996
O(24)-S(23)-C(26)-H(50)	-66.0277
O(24)-S(23)-C(26)-H(51)	53.9359
O(24)-S(23)-C(26)-H(52)	173.9719
O(25)-S(23)-C(26)-H(50)	65.7759
O(25)-S(23)-C(26)-H(51)	-174.2605
O(25)-S(23)-C(26)-H(52)	-54.2245
C(11)-N(10)-S(23)-O(24)	-39.6736
C(11)-N(10)-S(23)-O(25)	-172.5262
C(11)-N(10)-S(23)-C(26)	74.0833
C(8)-N(10)-S(23)-O(24)	174.8930
C(8)-N(10)-S(23)-O(25)	42.0404
C(8)-N(10)-S(23)-C(26)	-71.3502
O(20)-C(21)-C(22)-C(27)	74.5113
O(20)-C(21)-C(22)-C(31)	-107.0522
H(48)-C(21)-C(22)-C(27)	-165.7369
H(48)-C(21)-C(22)-C(31)	12.6996
H(49)-C(21)-C(22)-C(27)	-46.1022
H(49)-C(21)-C(22)-C(31)	132.3343
C(18)-O(20)-C(21)-C(22)	-176.8796
C(18)-O(20)-C(21)-H(48)	63.3685
C(18)-O(20)-C(21)-H(49)	-56.2661
N(3)-C(18)-O(20)-C(21)	179.5313
O(19)-C(18)-O(20)-C(21)	0.3691
C(2)-N(3)-C(18)-O(19)	12.5584
C(2)-N(3)-C(18)-O(20)	-166.5972
C(4)-N(3)-C(18)-O(19)	174.0300
C(4)-N(3)-C(18)-O(20)	-5.1257
O(14)-C(16)-C(17)-O(15)	-32.8822
O(14)-C(16)-C(17)-H(46)	-151.9838
O(14)-C(16)-C(17)-H(47)	89.3544
H(44)-C(16)-C(17)-O(15)	-152.1306

H(44)-C(16)-C(17)-H(46)	88.7678
H(44)-C(16)-C(17)-H(47)	-29.8940
H(45)-C(16)-C(17)-O(15)	89.0194
H(45)-C(16)-C(17)-H(46)	-30.0822
H(45)-C(16)-C(17)-H(47)	-148.7440
C(7)-O(15)-C(17)-C(16)	28.9140
C(7)-O(15)-C(17)-H(46)	148.0156
C(7)-O(15)-C(17)-H(47)	-93.3226
C(7)-O(14)-C(16)-C(17)	22.9435
C(7)-O(14)-C(16)-H(44)	142.1919
C(7)-O(14)-C(16)-H(45)	-98.9581
C(8)-C(7)-O(15)-C(17)	110.2728
C(5)-C(7)-O(15)-C(17)	-135.9280
O(14)-C(7)-O(15)-C(17)	-15.5860
C(8)-C(7)-O(14)-C(16)	-133.4813
C(5)-C(7)-O(14)-C(16)	113.2641
O(15)-C(7)-O(14)-C(16)	-5.3045
C(11)-C(12)-C(13)-C(9)	-95.2006
C(11)-C(12)-C(13)-H(42)	155.5959
C(11)-C(12)-C(13)-H(43)	29.8809
C(9)-C(12)-C(13)-H(42)	-109.2035
C(9)-C(12)-C(13)-H(43)	125.0814
H(41)-C(12)-C(13)-C(9)	132.9732
H(41)-C(12)-C(13)-H(42)	23.7697
H(41)-C(12)-C(13)-H(43)	-101.9453
C(8)-C(9)-C(13)-C(12)	92.8327
C(8)-C(9)-C(13)-H(42)	-157.9637
C(8)-C(9)-C(13)-H(43)	-32.2487
C(6)-C(9)-C(13)-C(12)	-109.8422
C(6)-C(9)-C(13)-H(42)	-0.6386
C(6)-C(9)-C(13)-H(43)	125.0764
C(12)-C(9)-C(13)-H(42)	109.2035
C(12)-C(9)-C(13)-H(43)	-125.0814
C(8)-C(9)-C(12)-C(11)	-3.2892
C(8)-C(9)-C(12)-C(13)	-119.4679
C(8)-C(9)-C(12)-H(41)	122.5612
C(6)-C(9)-C(12)-C(11)	-128.2376
C(6)-C(9)-C(12)-C(13)	115.5837
C(6)-C(9)-C(12)-H(41)	-2.3873
C(13)-C(9)-C(12)-C(11)	116.1787
C(13)-C(9)-C(12)-H(41)	-117.9710
C(7)-C(8)-N(10)-C(11)	112.8501
C(7)-C(8)-N(10)-S(23)	-99.0885
C(9)-C(8)-N(10)-C(11)	-0.2378
C(9)-C(8)-N(10)-S(23)	147.8237
H(38)-C(8)-N(10)-C(11)	-126.4361
H(38)-C(8)-N(10)-S(23)	21.6253

N(10)-C(11)-C(12)-C(9)	3.0747
N(10)-C(11)-C(12)-C(13)	69.1358
N(10)-C(11)-C(12)-H(41)	-145.8312
H(39)-C(11)-C(12)-C(9)	122.4558
H(39)-C(11)-C(12)-C(13)	-171.4831
H(39)-C(11)-C(12)-H(41)	-26.4502
H(40)-C(11)-C(12)-C(9)	-118.5090
H(40)-C(11)-C(12)-C(13)	-52.4479
H(40)-C(11)-C(12)-H(41)	92.5850
C(8)-N(10)-C(11)-C(12)	-1.7276
C(8)-N(10)-C(11)-H(39)	-121.1087
C(8)-N(10)-C(11)-H(40)	119.8562
S(23)-N(10)-C(11)-C(12)	-149.6256
S(23)-N(10)-C(11)-H(39)	90.9933
S(23)-N(10)-C(11)-H(40)	-28.0419
C(5)-C(6)-C(9)-C(8)	-8.3375
C(5)-C(6)-C(9)-C(12)	116.7711
C(5)-C(6)-C(9)-C(13)	-168.7416
C(1)-C(6)-C(9)-C(8)	170.7934
C(1)-C(6)-C(9)-C(12)	-64.0981
C(1)-C(6)-C(9)-C(13)	10.3892
C(4)-C(5)-C(7)-C(8)	-172.1527
C(4)-C(5)-C(7)-O(14)	-54.2141
C(4)-C(5)-C(7)-O(15)	66.4266
C(6)-C(5)-C(7)-C(8)	10.4797
C(6)-C(5)-C(7)-O(14)	128.4183
C(6)-C(5)-C(7)-O(15)	-110.9410
C(7)-C(8)-C(9)-C(6)	14.0394
C(7)-C(8)-C(9)-C(12)	-118.8391
C(7)-C(8)-C(9)-C(13)	174.7417
N(10)-C(8)-C(9)-C(6)	135.0247
N(10)-C(8)-C(9)-C(12)	2.1462
N(10)-C(8)-C(9)-C(13)	-64.2730
H(38)-C(8)-C(9)-C(6)	-105.8305
H(38)-C(8)-C(9)-C(12)	121.2910
H(38)-C(8)-C(9)-C(13)	54.8719
C(5)-C(7)-C(8)-C(9)	-14.3738
C(5)-C(7)-C(8)-N(10)	-128.4026
C(5)-C(7)-C(8)-H(38)	111.7184
O(14)-C(7)-C(8)-C(9)	-132.1368
O(14)-C(7)-C(8)-N(10)	113.8344
O(14)-C(7)-C(8)-H(38)	-6.0446
O(15)-C(7)-C(8)-C(9)	101.8897
O(15)-C(7)-C(8)-N(10)	-12.1391
O(15)-C(7)-C(8)-H(38)	-132.0181
C(2)-C(1)-C(6)-C(5)	17.6818
C(2)-C(1)-C(6)-C(9)	-161.3666

H(32)-C(1)-C(6)-C(5)	137.8252
H(32)-C(1)-C(6)-C(9)	-41.2232
H(33)-C(1)-C(6)-C(5)	-101.7613
H(33)-C(1)-C(6)-C(9)	79.1903
C(4)-C(5)-C(6)-C(1)	1.8111
C(4)-C(5)-C(6)-C(9)	-179.0132
C(7)-C(5)-C(6)-C(1)	179.0726
C(7)-C(5)-C(6)-C(9)	-1.7518
N(3)-C(4)-C(5)-C(6)	4.6204
N(3)-C(4)-C(5)-C(7)	-172.3710
H(36)-C(4)-C(5)-C(6)	124.8022
H(36)-C(4)-C(5)-C(7)	-52.1892
H(37)-C(4)-C(5)-C(6)	-114.6991
H(37)-C(4)-C(5)-C(7)	68.3095
C(2)-N(3)-C(4)-C(5)	-33.1815
C(2)-N(3)-C(4)-H(36)	-153.3632
C(2)-N(3)-C(4)-H(37)	86.1380
C(18)-N(3)-C(4)-C(5)	165.1850
C(18)-N(3)-C(4)-H(36)	45.0032
C(18)-N(3)-C(4)-H(37)	-75.4955
C(1)-C(2)-N(3)-C(4)	54.2632
C(1)-C(2)-N(3)-C(18)	-143.6933
H(34)-C(2)-N(3)-C(4)	-66.1314
H(34)-C(2)-N(3)-C(18)	95.9121
H(35)-C(2)-N(3)-C(4)	172.8663
H(35)-C(2)-N(3)-C(18)	-25.0902
C(6)-C(1)-C(2)-N(3)	-43.4543
C(6)-C(1)-C(2)-H(34)	76.9403
C(6)-C(1)-C(2)-H(35)	-162.0574
H(32)-C(1)-C(2)-N(3)	-163.5977
H(32)-C(1)-C(2)-H(34)	-43.2031
H(32)-C(1)-C(2)-H(35)	77.7992
H(33)-C(1)-C(2)-N(3)	75.9889
H(33)-C(1)-C(2)-H(34)	-163.6166
H(33)-C(1)-C(2)-H(35)	-42.6143

High pressure hydrogenation setting in autoclave of scaffold 371 to 373

4.2.1 Compound library enumeration

Virtual library enumeration was carried out by importing the drawn reactions in format .rxn, adding the label *rac* for products as they are obtained in a racemic mixture. The structure of the scaffolds were not drawn in the reaction scheme as errors in the stereochemistry of the compound libraries were observed otherwise (visualised as question marks on the stereocenters). An example of a drawn reaction that did generate errors in stereochemistry is shown in the figure below. The reaction could not be directly drawn on OSIRIS DataWarrior as there was no available label for racemic mixtures: labels *abs*, *or* and *and* counted respectively one, one and 2^n (with n= chiral centers) stereoisomers associated to one single structure.

Reaction drawn on ChemDraw for compound library enumeration (left) and reaction with imported file on DataWarrior (right) with correct label *racemate*

5.2.1 Dihydropyran-based allyl alcohol synthesis

- **^{1}H NMR signal assignment of compound 393:**

- Protons that give atropoisomeric splitting in DMSO were identified by signal comparison with ^{1}H NMR in $CDCl_3$, HSQC (to distinguish CH signals from CH_2) and NOESY analysis (necessary to distinguish H_a from H_a').

^{1}H NMR of compound 393 in $CDCl_3$

NOESY of compound 393 in $CDCl_3$

HSQC of compound 393 in $CDCl_3$

^{1}H NMR in DMSO at rt (above) and at 80 °C (below) of compound 393

Crystallographic data for compound 401

Experimental

An NMR tube was loaded with compound **401** (ca. 10 mg) and a minimum amount of $CHCl_3$ (ca. 0.3 ml) was added. The NMR tube was kept for 20 days at rt until dryness with formation of crystals (see left image).

A suitable crystal was selected and loaded on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 100.00(10) K during data collection. Using Olex2, the

structure was solved with the SHELXT, structure solution program using Intrinsic Phasing and refined with the SHELXL, refinement package using Least Squares minimisation.

Crystal Data for $C_{19}H_{22}N_2O_3$ (*M* =326.38 g/mol): triclinic, space group P-1 (no. 2), *a* = 10.1385(2) Å, *b* = 13.1220(4) Å, *c* = 13.6347(3) Å, *α* = 104.396(2)°, *β* = 91.428(2)°, *γ* = 112.274(2)°, *V* = 1611.44(7) Å^3, *Z* = 4, *T* = 100.01(10) K, μ(Cu Kα) = 0.740 mm^{-1}, *Dcalc* = 1.345 g/cm^3, 57322 reflections measured (7.582° ≤ 2Θ ≤ 146.158°), 6345 unique (R_{int} = 0.0412, R_{sigma} = 0.0169) which were used in all calculations. The final R_1 was 0.0342 (I > 2σ(I)) and wR_2 was 0.0883 (all data).

Table 1 Crystal data and structure refinement for **401**

Identification code	ELGI02_048_fr2
Empirical formula	$C_{19}H_{22}N_2O_3$
Formula weight	326.38
Temperature/K	100.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	10.1385(2)
b/Å	13.1220(4)
c/Å	13.6347(3)
α/°	104.396(2)
β/°	91.428(2)
γ/°	112.274(2)
Volume/Å^3	1611.44(7)
Z	4
ρ_{calc}g/cm^3	1.345
μ/mm^{-1}	0.740
F(000)	696.0
Crystal size/mm^3	0.161 × 0.138 × 0.083
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.582 to 146.158
Index ranges	-12 ≤ h ≤ 12, -15 ≤ k ≤ 16, -16 ≤ l ≤ 16
Reflections collected	57322
Independent reflections	6345 [R_{int} = 0.0412, R_{sigma} = 0.0169]
Data/restraints/parameters	6345/0/443

Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0342, wR_2 = 0.0845
Final R indexes [all data]	R_1 = 0.0387, wR_2 = 0.0883
Largest diff. peak/hole / e $Å^{-3}$	0.28/-0.21

Table 2 Fractional Atomic Coordinates ($\times10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2\times10^3$) for **401**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
C1	5168.2(14)	1576.6(11)	6802.8(9)	22.8(3)
C2	3540.4(12)	998.8(10)	5065.7(9)	19.4(2)
C3	4984.5(13)	1302.0(10)	5651.9(9)	19.0(2)
C4	5516.2(12)	2530.4(10)	6300.9(8)	16.6(2)
C5	6919.6(12)	3441.3(10)	6291.4(8)	16.2(2)
C6	8359.0(12)	3383.6(10)	6398.0(9)	19.4(2)
C7	9410.3(13)	4293.8(10)	5971.1(9)	21.0(2)
C8	7986.0(12)	5372.0(10)	6017.9(9)	20.3(2)
C9	6749.6(12)	4325.8(10)	6084.9(8)	16.6(2)
C10	5198.1(12)	4155.8(10)	5919.5(8)	16.8(2)
C11	4379.3(12)	2988.2(10)	6144.1(8)	16.3(2)
C12	2081.7(12)	2196.3(10)	5080.7(8)	16.6(2)
C13	-301.1(13)	1478.1(12)	4185.1(9)	23.5(3)
C14	1432.2(12)	746.6(10)	3402.7(8)	18.3(2)
C15	2429.6(13)	1354.8(11)	2859.2(9)	19.9(2)
C16	2748.4(14)	768.1(12)	1961.8(9)	24.2(3)
C17	2068.2(14)	-415.3(12)	1607.0(9)	25.5(3)
C18	1062.0(14)	-1019.0(11)	2147.1(10)	25.0(3)
C19	741.4(13)	-440.0(11)	3045.6(9)	21.6(3)
N1	3334.7(10)	2085.4(8)	5294.4(7)	17.1(2)
N2	1055.5(10)	1337.2(9)	4317.1(7)	19.2(2)
O1	9322.6(9)	5379.6(7)	6389.7(7)	22.17(19)
O2	5024.7(9)	5096.5(7)	6604.7(7)	21.92(19)
O3	1858.9(9)	3031.3(7)	5566.8(6)	20.24(18)
C101	1546.0(13)	6438.3(11)	10476.0(9)	22.5(3)
C102	3625.8(13)	7373.8(10)	9486.8(9)	19.7(2)
C103	3120.3(13)	6860.7(10)	10349.7(9)	19.4(2)
C104	2134.5(12)	5608.1(10)	9895.9(8)	17.6(2)
C105	2337.9(12)	4641.1(10)	10145.1(9)	18.6(2)
C106	2469.0(15)	4464.1(11)	11179.4(9)	24.8(3)
C107	3207.7(15)	3638.0(11)	11122.7(10)	27.1(3)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **401**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C108	2811.5(13)	2925.7(10)	9319.8(9)	20.8(2)
C109	2527.6(12)	3957.5(10)	9312.3(9)	17.5(2)
C110	2472.0(12)	4345.0(10)	8368.2(8)	16.5(2)
C111	1986.2(12)	5351.8(10)	8738.7(8)	16.2(2)
C112	2922.1(11)	6542.6(10)	7581.5(8)	16.1(2)
C113	3691.5(14)	7754.0(11)	6453.4(9)	23.0(3)
C114	2695.5(12)	8378.3(10)	7997.0(8)	16.9(2)
C115	1250.8(13)	7945.1(10)	8129.1(9)	19.1(2)
C116	659.4(13)	8679.8(11)	8666.4(9)	22.1(3)
C117	1491.1(14)	9843.5(11)	9046.1(9)	23.0(3)
C118	2926.1(14)	10272.3(11)	8895.6(9)	23.3(3)
C119	3533.3(13)	9545.0(10)	8377.1(9)	20.9(2)
N101	2807.1(10)	6458.3(8)	8555.4(7)	17.4(2)
N102	3339.1(11)	7632.8(9)	7464.9(7)	18.3(2)
O101	2578.2(10)	2645.9(7)	10264.5(6)	24.4(2)
O102	1458.1(9)	3413.2(7)	7591.3(6)	20.99(18)
O103	2694.0(8)	5697.1(7)	6851.2(6)	18.57(18)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **401**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	25.4(6)	22.4(6)	22.4(6)	11.2(5)	3.1(5)	8.4(5)
C2	20.5(6)	14.1(6)	22.9(6)	4.0(5)	2.1(4)	6.7(5)
C3	21.2(6)	14.7(6)	21.4(6)	5.4(5)	2.0(4)	7.4(5)
C4	18.8(5)	16.9(6)	14.8(5)	4.5(4)	2.6(4)	7.8(5)
C5	18.6(5)	17.0(6)	12.0(5)	1.6(4)	2.0(4)	7.4(5)
C6	19.1(6)	19.7(6)	19.7(6)	3.6(5)	1.0(4)	9.3(5)
C7	18.1(6)	20.4(6)	23.1(6)	2.2(5)	3.0(4)	8.6(5)
C8	18.1(5)	16.4(6)	25.2(6)	4.5(5)	3.7(4)	6.6(5)
C9	17.8(5)	16.7(6)	13.9(5)	1.7(4)	2.8(4)	7.0(5)
C10	18.9(5)	15.2(6)	15.7(5)	1.7(4)	2.6(4)	7.8(4)
C11	17.3(5)	16.7(6)	13.9(5)	2.4(4)	2.5(4)	6.7(5)
C12	17.7(5)	17.3(6)	14.7(5)	6.0(4)	4.9(4)	5.8(5)
C13	17.9(6)	28.3(7)	22.0(6)	3.2(5)	2.6(4)	9.2(5)
C14	18.1(5)	20.3(6)	15.5(5)	1.9(4)	0.1(4)	8.7(5)
C15	20.5(6)	18.2(6)	20.0(6)	4.8(5)	1.3(4)	7.0(5)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **401**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C16	24.2(6)	29.5(7)	20.8(6)	8.4(5)	6.0(5)	11.6(5)
C17	28.2(6)	29.1(7)	18.8(6)	-0.1(5)	2.0(5)	15.3(6)
C18	25.9(6)	19.4(6)	25.5(6)	-0.4(5)	-2.5(5)	9.0(5)
C19	20.0(6)	19.9(6)	22.2(6)	5.3(5)	1.3(5)	5.5(5)
N1	17.2(5)	13.8(5)	17.9(5)	1.2(4)	0.8(4)	5.7(4)
N2	16.3(5)	21.6(5)	17.3(5)	1.8(4)	2.4(4)	7.2(4)
O1	17.4(4)	17.9(4)	26.8(4)	0.9(3)	1.1(3)	5.8(3)
O2	19.2(4)	17.4(4)	27.3(4)	-1.1(3)	2.6(3)	9.9(3)
O3	23.0(4)	20.6(4)	17.9(4)	2.4(3)	3.2(3)	11.3(3)
C101	27.5(6)	21.1(6)	21.0(6)	3.6(5)	7.6(5)	13.0(5)
C102	24.2(6)	15.5(6)	16.3(5)	1.4(4)	-0.8(4)	6.7(5)
C103	24.8(6)	17.2(6)	15.8(5)	2.0(4)	0.9(4)	9.7(5)
C104	20.3(6)	17.2(6)	16.3(5)	3.8(4)	3.9(4)	8.9(5)
C105	19.3(5)	17.4(6)	18.5(6)	5.3(4)	2.2(4)	6.5(5)
C106	35.2(7)	21.0(6)	17.4(6)	4.7(5)	2.6(5)	10.9(5)
C107	37.2(7)	22.4(7)	19.8(6)	4.4(5)	-4.3(5)	11.3(6)
C108	25.1(6)	18.9(6)	19.5(6)	5.2(5)	1.8(4)	10.3(5)
C109	17.6(5)	15.7(6)	18.4(5)	4.3(4)	1.4(4)	6.0(4)
C110	17.4(5)	13.5(5)	16.9(5)	2.5(4)	2.7(4)	5.4(4)
C111	16.2(5)	14.9(6)	16.6(5)	3.5(4)	1.8(4)	6.0(4)
C112	13.5(5)	17.5(6)	17.7(5)	3.1(4)	1.8(4)	7.8(4)
C113	26.9(6)	24.5(6)	18.2(6)	7.4(5)	8.2(5)	9.9(5)
C114	22.2(6)	17.0(6)	14.2(5)	5.2(4)	2.5(4)	10.2(5)
C115	21.2(6)	16.4(6)	17.8(5)	3.8(4)	-0.3(4)	6.3(5)
C116	20.7(6)	24.6(6)	23.4(6)	7.6(5)	3.9(5)	10.9(5)
C117	30.5(7)	22.1(6)	21.2(6)	4.5(5)	3.9(5)	16.7(5)
C118	29.3(6)	14.7(6)	24.3(6)	3.8(5)	-0.5(5)	8.6(5)
C119	20.0(6)	18.7(6)	23.5(6)	6.8(5)	2.2(5)	6.5(5)
N101	21.8(5)	13.1(5)	15.5(5)	2.3(4)	0.9(4)	6.3(4)
N102	22.9(5)	17.4(5)	16.2(5)	5.1(4)	6.3(4)	9.2(4)
O101	34.8(5)	17.6(4)	19.8(4)	5.5(3)	-0.8(3)	9.4(4)
O102	27.5(4)	15.2(4)	15.3(4)	1.8(3)	0.8(3)	4.8(3)
O103	19.2(4)	18.1(4)	17.5(4)	0.3(3)	1.7(3)	9.3(3)

Table 4 Bond Lengths for compound **401**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C3	1.5102(16)	C101	C103	1.5083(17)
C1	C4	1.5042(17)	C101	C104	1.5021(15)
C2	C3	1.5109(16)	C102	C103	1.5041(17)
C2	N1	1.4769(15)	C102	N101	1.4758(14)
C3	C4	1.5100(16)	C103	C104	1.5171(16)
C4	C5	1.4740(16)	C104	C105	1.4755(16)
C4	C11	1.5204(15)	C104	C111	1.5202(15)
C5	C6	1.4950(15)	C105	C106	1.4958(16)
C5	C9	1.3294(17)	C105	C109	1.3289(16)
C6	C7	1.5208(17)	C106	C107	1.5226(18)
C7	O1	1.4345(14)	C107	O101	1.4306(15)
C8	C9	1.4926(16)	C108	C109	1.4895(16)
C8	O1	1.4305(14)	C108	O101	1.4263(15)
C9	C10	1.5054(15)	C109	C110	1.5041(16)
C10	C11	1.5531(16)	C110	C111	1.5546(15)
C10	O2	1.4236(13)	C110	O102	1.4222(13)
C11	N1	1.4740(14)	C111	N101	1.4623(15)
C12	N1	1.3648(15)	C112	N101	1.3638(15)
C12	N2	1.3822(15)	C112	N102	1.3815(15)
C12	O3	1.2348(14)	C112	O103	1.2331(14)
C13	N2	1.4680(15)	C113	N102	1.4648(15)
C14	C15	1.3887(17)	C114	C115	1.3906(17)
C14	C19	1.3898(17)	C114	C119	1.3898(17)
C14	N2	1.4382(14)	C114	N102	1.4366(14)
C15	C16	1.3908(17)	C115	C116	1.3909(17)
C16	C17	1.3852(19)	C116	C117	1.3856(18)
C17	C18	1.3876(19)	C117	C118	1.3882(18)
C18	C19	1.3885(17)	C118	C119	1.3860(17)

Table 5 Bond Angles for compound **401**

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C4	C1	C3	60.12(8)	C104	C101	C103	60.52(8)
N1	C2	C3	104.80(9)	N101	C102	C103	104.56(9)
C1	C3	C2	120.39(10)	C101	C103	C104	59.53(8)
C4	C3	C1	59.74(8)	C102	C103	C101	119.55(10)
C4	C3	C2	108.16(9)	C102	C103	C104	108.27(9)
C1	C4	C3	60.13(8)	C101	C104	C103	59.94(8)

Table 5 Bond Angles for compound **401**

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C1	C4	C11	119.00(10)	C101	C104	C111	117.82(10)
C3	C4	C11	108.31(9)	C103	C104	C111	108.19(9)
C5	C4	C1	129.28(10)	C105	C104	C101	130.87(10)
C5	C4	C3	125.10(10)	C105	C104	C103	124.64(10)
C5	C4	C11	106.82(10)	C105	C104	C111	106.74(9)
C4	C5	C6	126.65(10)	C104	C105	C106	127.37(10)
C9	C5	C4	110.78(10)	C109	C105	C104	110.18(10)
C9	C5	C6	122.35(11)	C109	C105	C106	122.20(11)
C5	C6	C7	108.29(10)	C105	C106	C107	108.23(10)
O1	C7	C6	110.38(9)	O101	C107	C106	111.86(10)
O1	C8	C9	111.15(10)	O101	C108	C109	111.72(10)
C5	C9	C8	122.71(11)	C105	C109	C108	123.17(11)
C5	C9	C10	113.27(10)	C105	C109	C110	113.58(10)
C8	C9	C10	124.03(10)	C108	C109	C110	123.22(10)
C9	C10	C11	103.18(9)	C109	C110	C111	102.75(9)
O2	C10	C9	108.17(9)	O102	C110	C109	108.54(9)
O2	C10	C11	113.74(9)	O102	C110	C111	112.79(9)
C4	C11	C10	105.52(9)	C104	C111	C110	105.00(9)
N1	C11	C4	104.25(9)	N101	C111	C104	104.33(9)
N1	C11	C10	115.47(9)	N101	C111	C110	119.59(9)
N1	C12	N2	118.19(10)	N101	C112	N102	116.10(10)
O3	C12	N1	121.01(10)	O103	C112	N101	121.86(11)
O3	C12	N2	120.79(10)	O103	C112	N102	122.03(10)
C15	C14	C19	120.25(11)	C115	C114	N102	120.73(10)
C15	C14	N2	120.59(11)	C119	C114	C115	120.07(11)
C19	C14	N2	119.11(11)	C119	C114	N102	119.20(10)
C14	C15	C16	119.61(11)	C114	C115	C116	119.69(11)
C17	C16	C15	120.28(12)	C117	C116	C115	120.39(11)
C16	C17	C18	119.94(11)	C116	C117	C118	119.56(11)
C17	C18	C19	120.13(12)	C119	C118	C117	120.54(11)
C18	C19	C14	119.78(12)	C118	C119	C114	119.73(11)
C11	N1	C2	112.87(9)	C111	N101	C102	113.98(9)
C12	N1	C2	125.83(9)	C112	N101	C102	125.16(10)
C12	N1	C11	116.90(9)	C112	N101	C111	120.26(9)
C12	N2	C13	114.84(9)	C112	N102	C113	116.13(9)
C12	N2	C14	122.20(9)	C112	N102	C114	119.45(9)
C14	N2	C13	115.03(9)	C114	N102	C113	115.12(9)

Table 5 Bond Angles for compound **401**

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C8	O1	C7	111.36(9)	C108	O101	C107	111.87(9)

Table 6 Hydrogen Bonds for compound **401**

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O103	0.864(18)	1.985(18)	2.7636(12)	149.4(16)
O102	H102	O3	0.88(2)	1.92(2)	2.7491(12)	157.1(18)

Table 7 Torsion Angles for compound **401**

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	C3	C4	C5	119.27(13)	C101	C103	C104	C105	-121.27(13)
C1	C3	C4	C11	-113.51(10)	C101	C103	C104	C111	112.17(10)
C1	C4	C5	C6	26.84(18)	C101	C104	C105	C106	-22.2(2)
C1	C4	C5	C9	-158.49(11)	C101	C104	C105	C109	163.49(12)
C1	C4	C11	C10	163.86(10)	C101	C104	C111	C110	-171.56(10)
C1	C4	C11	N1	-74.07(12)	C101	C104	C111	N101	61.85(12)
C2	C3	C4	C1	115.15(11)	C102	C103	C104	C101	-114.11(11)
C2	C3	C4	C5	-125.58(12)	C102	C103	C104	C105	124.63(12)
C2	C3	C4	C11	1.65(13)	C102	C103	C104	C111	-1.93(12)
C3	C1	C4	C5	-112.76(13)	C103	C101	C104	C105	111.58(14)
C3	C1	C4	C11	95.50(11)	C103	C101	C104	C111	-95.88(11)
C3	C2	N1	C11	-12.28(12)	C103	C102	N101	C111	-8.71(12)
C3	C2	N1	C12	-167.82(10)	C103	C102	N101	C112	-179.81(10)
C3	C4	C5	C6	-50.95(17)	C103	C104	C105	C106	55.81(17)
C3	C4	C5	C9	123.72(12)	C103	C104	C105	C109	-118.46(12)
C3	C4	C11	C10	-130.75(9)	C103	C104	C111	C110	123.45(10)
C3	C4	C11	N1	-8.67(12)	C103	C104	C111	N101	-3.14(11)
C4	C1	C3	C2	-94.37(12)	C104	C101	C103	C102	94.85(11)
C4	C5	C6	C7	159.80(10)	C104	C105	C106	C107	-158.98(12)
C4	C5	C9	C8	-179.56(10)	C104	C105	C109	C108	177.83(10)
C4	C5	C9	C10	-0.06(13)	C104	C105	C109	C110	-0.45(14)
C4	C11	N1	C2	13.20(12)	C104	C111	N101	C102	7.51(12)
C4	C11	N1	C12	171.08(9)	C104	C111	N101	C112	179.08(9)
C5	C4	C11	C10	6.36(11)	C105	C104	C111	C110	-12.91(12)
C5	C4	C11	N1	128.44(9)	C105	C104	C111	N101	-139.51(9)
C5	C6	C7	O1	49.45(12)	C105	C106	C107	O101	-48.20(14)
C5	C9	C10	C11	4.05(12)	C105	C109	C110	C111	-7.67(13)
C5	C9	C10	O2	124.86(10)	C105	C109	C110	O102	-127.32(11)
C6	C5	C9	C8	-4.63(17)	C106	C105	C109	C108	3.21(19)

Table 7 Torsion Angles for compound **401**

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C6	C5	C9	C10	174.88(10)	C106	C105	C109	C110	-175.07(11)
C6	C7	O1	C8	-69.12(12)	C106	C107	O101	C108	66.53(14)
C8	C9	C10	C11	-176.45(10)	C108	C109	C110	C111	174.05(10)
C8	C9	C10	O2	-55.64(14)	C108	C109	C110	O102	54.40(14)
C9	C5	C6	C7	-14.30(15)	C109	C105	C106	C107	14.66(17)
C9	C8	O1	C7	47.23(13)	C109	C108	O101	C107	-45.26(13)
C9	C10	C11	C4	-6.17(11)	C109	C110	C111	C104	12.17(11)
C9	C10	C11	N1	-120.70(10)	C109	C110	C111	N101	128.71(10)
C10	C11	N1	C2	128.46(10)	C110	C111	N101	C102	-109.39(11)
C10	C11	N1	C12	-73.65(12)	C110	C111	N101	C112	62.19(14)
C11	C4	C5	C6	-178.79(10)	C111	C104	C105	C106	-177.02(11)
C11	C4	C5	C9	-4.12(12)	C111	C104	C105	C109	8.71(13)
C14	C15	C16	C17	0.48(18)	C114	C115	C116	C117	1.73(18)
C15	C14	C19	C18	0.65(18)	C115	C114	C119	C118	0.57(18)
C15	C14	N2	C12	-47.31(16)	C115	C114	N102	C112	-36.71(15)
C15	C14	N2	C13	100.03(13)	C115	C114	N102	C113	108.73(12)
C15	C16	C17	C18	0.14(19)	C115	C116	C117	C118	-0.62(18)
C16	C17	C18	C19	-0.36(19)	C116	C117	C118	C119	-0.53(19)
C17	C18	C19	C14	-0.03(19)	C117	C118	C119	C114	0.55(18)
C19	C14	C15	C16	-0.88(18)	C119	C114	C115	C116	-1.70(17)
C19	C14	N2	C12	135.29(12)	C119	C114	N102	C112	143.59(11)
C19	C14	N2	C13	-77.37(14)	C119	C114	N102	C113	-70.98(14)
N1	C2	C3	C1	71.09(13)	N101	C102	C103	C101	-58.60(13)
N1	C2	C3	C4	6.08(12)	N101	C102	C103	C104	6.15(12)
N1	C12	N2	C13	175.71(10)	N101	C112	N102	C113	170.34(10)
N1	C12	N2	C14	-36.89(16)	N101	C112	N102	C114	-44.56(14)
N2	C12	N1	C2	-22.56(16)	N102	C112	N101	C102	-27.55(15)
N2	C12	N1	C11	-177.24(10)	N102	C112	N101	C111	161.88(10)
N2	C14	C15	C16	-178.24(11)	N102	C114	C115	C116	178.59(10)
N2	C14	C19	C18	178.06(11)	N102	C114	C119	C118	-179.72(10)
O1	C8	C9	C5	-11.06(15)	O101	C108	C109	C105	11.29(16)
O1	C8	C9	C10	169.49(10)	O101	C108	C109	C110	-170.59(10)
O2	C10	C11	C4	-123.10(10)	O102	C110	C111	C104	128.83(10)
O2	C10	C11	N1	122.36(10)	O102	C110	C111	N101	-114.63(11)
O3	C12	N1	C2	156.25(11)	O103	C112	N101	C102	151.10(11)
O3	C12	N1	C11	1.58(16)	O103	C112	N101	C111	-19.48(16)
O3	C12	N2	C13	-3.11(16)	O103	C112	N102	C113	-8.31(16)

Table 7 Torsion Angles for compound **401**

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O3	C12	N2	C14	144.29(11)	O103	C112	N102	C114	136.79(11)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters ($Å^2$×10^3) for compound **401**

Atom	x	y	z	U(eq)
H1A	4305.97	1389.11	7134.32	27
H1B	5964.15	1491.36	7132.26	27
H2A	3542.09	708.22	4338.58	23
H2B	2783.46	423.48	5290.83	23
H3	5675.93	1049.54	5286.73	23
H6A	8295.19	2629.72	6025.27	23
H6B	8685.78	3520.22	7111.62	23
H7A	10380.98	4361.5	6138.28	25
H7B	9189.99	4068.24	5232.99	25
H8A	7994.25	5395.76	5312.62	24
H8B	7870.75	6049.74	6415.86	24
H10	4921.27	4109.3	5210.85	20
H11	3916.73	3097.54	6761.78	20
H13A	-687.97	1550.2	4822.24	35
H13B	-975.12	821.06	3678.16	35
H13C	-127.36	2155.09	3968.73	35
H15	2881.69	2149.77	3093.8	24
H16	3421.07	1171.89	1598.38	29
H17	2285.77	-804.76	1007.4	31
H18	601.45	-1813.1	1906.82	30
H19	66.59	-844.91	3407.14	26
H2	4160(19)	5054(15)	6495(13)	36(4)
H10A	1290.1	6384.32	11147.57	27
H10B	933.7	6657.1	10088.66	27
H10C	3421.56	8049.53	9543.94	24
H10D	4651.47	7584.44	9482.67	24
H103	3820.63	7063.97	10948.08	23
H10E	1523.44	4148.61	11386.41	30
H10F	3029.88	5190.16	11677.7	30
H10G	4218.9	4029.34	11073.14	32
H10H	3138.96	3400.47	11745.33	32
H10I	2185.21	2280.01	8766.32	25

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for compound **401**

Atom	**x**	**y**	**z**	**U(eq)**
H10J	3797.96	3066.52	9205.06	25
H110	3423.62	4613.42	8142.81	20
H111	972.48	5095.06	8471.4	19
H11A	2820.51	7453.38	5988.01	34
H11B	4274.39	7337.87	6210.41	34
H11C	4210.54	8550.15	6498.91	34
H115	682.82	7167.74	7859.47	23
H116	-299.91	8388.27	8771.34	27
H117	1090.65	10334.01	9399.41	28
H118	3484.58	11053.89	9144.77	28
H119	4497.45	9836.59	8283.81	25
H102	1670(20)	3497(16)	6989(15)	48(5)

- **^{1}H NMR signal assignment of compound 405:**

^{1}H NMR in $CDCl_3$ (above) and in C_6D_6 (below) of compound 405

COSY of compound 405 in $CDCl_3$

COSY of compound 405 in C_6D_6

NOESY of compound 405 in $CDCl_3$

NOESY of compound 405 in C_6D_6

- 3D-model of TS for the reduction of 273 with $LiAlH_4$ to 278 realised with MarvinSketch 21.18

273 **278**

Software	MarvinSketch 21.18
Force field	MMFF94
Optimization limit	Normal
Max number of conformers	100
Diversity limit	0.1
Timelimit	900
Conformer energy	463.3 kcal/mol

Image visualised with Chem3D 12.0.2:

Atom coordinates

Atoms	x (Å)	y (Å)	z (Å)
C(1)	5.914	4.4087	-4.1599
C(2)	4.7705	4.4011	-6.662
O(3)	2.2048	4.5713	-6.4867
C(4)	1.1248	2.5457	-5.3643
C(5)	2.3562	1.9384	-3.059
C(6)	4.5461	2.7851	-2.5155
C(7)	1.3943	0.2971	-1.115
C(8)	3.3661	0.5214	0.9147
C(9)	5.3892	1.9031	-0.2288
N(10)	4.4628	-1.7464	1.7014
C(11)	7.0512	-1.9027	1.0531
C(12)	7.6219	0.4426	-0.1049
C(13)	7.4724	2.8286	1.1892
S(14)	2.9462	-4.0908	2.4173
O(15)	2.6032	-5.2696	0.4036
O(16)	0.5583	-3.3096	3.0684
C(17)	4.4706	-5.7426	4.6571
H(18)	1.1581	-1.4975	-2.0007
O(19)	-0.8302	1.3666	-0.3081
Al(20)	0.2921	-4.05	-1.047
H(21)	-1.5893	-5.6261	0.1759
H(22)	1.3575	-4.4839	-3.5201
H(23)	-1.4793	-5.0157	-2.8821
Li(24)	-2.5916	-0.9398	0.655
O(25)	-5.4194	-0.9108	-0.9262

O(26)	-2.9695	-0.7902	38835
C(27)	-5.1555	-1.4357	-3.605
C(28)	-6.4333	0.6016	-4.9049
C(29)	-8.1718	1.5788	-3.0509
C(30)	-6.7441	1.4176	-0.7327
C(31)	-2.9991	1.6335	4.9012
C(32)	-4.5587	1.4168	7.1307
C(33)	-6.4085	-0.4372	6.3745
C(34)	-4.9501	-2.1869	4.8746
H(35)	5.8528	6.2259	-3.4084
H(36)	7.8004	3.8695	-4.2981
H(37)	5.4108	5.9488	-7.6887
H(38)	5.2489	2.771	-7.6587
H(39)	-0.7576	3.0107	-5.0402
H(40)	1.168	1.0119	-6.5972
H(41)	2.6667	1.4899	2.4772
H(42)	8.1538	-2.1707	2.6565
H(43)	7.3306	-3.37	-2.3E-05
H(44)	8.8628	0.3061	-1.5921
H(45)	8.523	4.3086	4.76E-05
H(46)	7.3695	2.8326	3.1341
H(47)	3.3383	-7.2623	5.1557
H(48)	6.1707	-6.376	3.9239
H(49)	4.7554	-4.588	6.2155
H(50)	-3.2477	-1.5113	-4.0503
H(51)	-5.9998	-3.1801	-3.9272
H(52)	-5.1309	1.991	-5.4081
H(53)	-7.3351	-0.0208	-6.5389
H(54)	-8.7673	3.4059	-3.4549
H(55)	-9.7632	0.4238	-2.9422
H(56)	-5.4245	2.8629	-5.8E-05
H(57)	-7.8959	1.3653	8.54E-05
H(58)	-1.1632	2.1957	5.3163
H(59)	-3.776	2.8569	3.5795
H(60)	-3.5096	0.7415	8.6546
H(61)	-5.3708	3.1252	7.6552
H(62)	-7.2948	-1.3048	7.8987
H(63)	-7.7939	0.418	5.2715
H(64)	-4.178	-3.6123	5.9811
H(65)	-6.0049	-2.9856	3.4322

Bond lengths

Atoms	Bond lenght (Å)
C(34)-H(65)	1.9573
C(34)-H(64)	1.9627
C(33)-H(63)	1.9665

C(33)-H(62)	1.9651
C(32)-H(61)	1.9630
C(32)-H(60)	1.9695
C(31)-H(59)	1.9614
C(31)-H(58)	1.9644
C(30)-H(57)	1.9617
C(30)-H(56)	1.9632
C(29)-H(55)	1.9694
C(29)-H(54)	1.9637
C(28)-H(53)	1.9674
C(28)-H(52)	1.9697
C(27)-H(51)	1.9646
C(27)-H(50)	1.9605
C(17)-H(49)	1.9603
C(17)-H(48)	1.9568
C(17)-H(47)	1.9596
C(13)-H(46)	1.9476
C(13)-H(45)	1.9502
C(12)-H(44)	1.9417
C(11)-H(43)	1.9667
C(11)-H(42)	1.9643
C(8)-H(41)	1.9669
C(4)-H(40)	1.9684
C(4)-H(39)	1.9659
C(2)-H(38)	1.9696
C(2)-H(37)	1.9646
C(1)-H(36)	1.9668
C(1)-H(35)	1.9674
O(26)-C(34)	2.6184
O(26)-C(31)	2.6289
C(33)-C(34)	2.7273
C(32)-C(33)	2.7260
C(31)-C(32)	2.7295
O(25)-C(30)	2.6858
O(25)-C(27)	2.7425
C(29)-C(30)	2.7273
C(28)-C(29)	2.7230
C(27)-C(28)	2.7337
Li(24)-O(26)	3.2540
Li(24)-O(25)	3.2400
Li(24)-Al(20)	4.5701
O(19)-Li(24)	3.0577
Al(20)-H(23)	2.7273
Al(20)-H(22)	2.7276
Al(20)-H(21)	2.7421
Al(20)-O(15)	2.9888
H(18)-Al(20)	2.8592

C(7)-O(19)	2.5968
C(7)-H(18)	2.0152
S(14)-C(17)	3.1732
S(14)-O(16)	2.5954
S(14)-O(15)	2.3584
N(10)-S(14)	2.8825
C(12)-C(13)	2.7185
C(9)-C(13)	2.6846
C(9)-C(12)	2.6708
C(8)-N(10)	2.6390
C(11)-C(12)	2.6771
N(10)-C(11)	2.6729
C(6)-C(9)	2.5919
C(5)-C(7)	2.7200
C(8)-C(9)	2.7036
C(7)-C(8)	2.8387
C(1)-C(6)	2.6854
C(5)-C(6)	2.4100
C(4)-C(5)	2.6832
O(3)-C(4)	2.5552
C(2)-O(3)	2.5773
C(1)-C(2)	2.7510

Bond angles

Atoms	Bond angles (°)
H(65)-C(34)-H(64)	109.3355
H(65)-C(34)-O(26)	110.2654
H(65)-C(34)-C(33)	112.2656
H(64)-C(34)-O(26)	107.6512
H(64)-C(34)-C(33)	111.4836
O(26)-C(34)-C(33)	105.6907
H(63)-C(33)-H(62)	108.0176
H(63)-C(33)-C(34)	110.3192
H(63)-C(33)-C(32)	109.7474
H(62)-C(33)-C(34)	112.6133
H(62)-C(33)-C(32)	113.0277
C(34)-C(33)-C(32)	103.0635
H(61)-C(32)-H(60)	108.1823
H(61)-C(32)-C(33)	112.6629
H(61)-C(32)-C(31)	112.6778
H(60)-C(32)-C(33)	110.0541
H(60)-C(32)-C(31)	110.7858
C(33)-C(32)-C(31)	102.4239
H(59)-C(31)-H(58)	109.5155
H(59)-C(31)-O(26)	108.5813
H(59)-C(31)-C(32)	111.9386

H(58)-C(31)-O(26)	109.581
H(58)-C(31)-C(32)	112.5898
O(26)-C(31)-C(32)	104.4451
H(57)-C(30)-H(56)	110.5304
H(57)-C(30)-O(25)	108.9513
H(57)-C(30)-C(29)	112.4511
H(56)-C(30)-O(25)	108.2017
H(56)-C(30)-C(29)	112.0344
O(25)-C(30)-C(29)	104.3705
H(55)-C(29)-H(54)	108.1791
H(55)-C(29)-C(30)	109.9641
H(55)-C(29)-C(28)	110.0616
H(54)-C(29)-C(30)	112.8681
H(54)-C(29)-C(28)	112.7955
C(30)-C(29)-C(28)	102.9032
H(53)-C(28)-H(52)	108.3038
H(53)-C(28)-C(29)	112.7292
H(53)-C(28)-C(27)	111.9268
H(52)-C(28)-C(29)	110.0567
H(52)-C(28)-C(27)	109.7608
C(29)-C(28)-C(27)	104.0117
H(51)-C(27)-H(50)	110.2862
H(51)-C(27)-O(25)	106.7854
H(51)-C(27)-C(28)	112.5111
H(50)-C(27)-O(25)	108.837
H(50)-C(27)-C(28)	112.0606
O(25)-C(27)-C(28)	106.0724
C(34)-O(26)-C(31)	109.6786
C(34)-O(26)-Li(24)	116.0323
C(31)-O(26)-Li(24)	115.3273
C(30)-O(25)-C(27)	106.4846
C(30)-O(25)-Li(24)	113.7703
C(27)-O(25)-Li(24)	113.0167
O(26)-Li(24)-O(25)	112.4845
O(26)-Li(24)-Al(20)	118.2989
O(26)-Li(24)-O(19)	110.1653
O(25)-Li(24)-Al(20)	112.0279
O(25)-Li(24)-O(19)	110.0171
Al(20)-Li(24)-O(19)	91.8652
Li(24)-Al(20)-H(23)	94.688
Li(24)-Al(20)-H(22)	133.821
Li(24)-Al(20)-H(21)	78.0034
Li(24)-Al(20)-O(15)	125.7939
Li(24)-Al(20)-H(18)	73.0092
H(23)-Al(20)-H(22)	65.6241
H(23)-Al(20)-H(21)	69.5689
H(23)-Al(20)-O(15)	133.1827

H(23)-Al(20)-H(18)	106.7621
H(22)-Al(20)-H(21)	125.5158
H(22)-Al(20)-O(15)	94.193
H(22)-Al(20)-H(18)	73.8154
H(21)-Al(20)-O(15)	94.5626
H(21)-Al(20)-H(18)	150.4236
O(15)-Al(20)-H(18)	106.9763
Li(24)-O(19)-C(7)	106.3008
Al(20)-H(18)-C(7)	133.1518
H(49)-C(17)-H(48)	111.2413
H(49)-C(17)-H(47)	109.7816
H(49)-C(17)-S(14)	108.9253
H(48)-C(17)-H(47)	110.2624
H(48)-C(17)-S(14)	108.7476
H(47)-C(17)-S(14)	107.8003
Al(20)-O(15)-S(14)	108.8387
C(17)-S(14)-O(16)	114.9355
C(17)-S(14)-O(15)	114.3535
C(17)-S(14)-N(10)	110.2383
O(16)-S(14)-O(15)	103.346
O(16)-S(14)-N(10)	107.5521
O(15)-S(14)-N(10)	105.7225
H(46)-C(13)-H(45)	113.0948
H(46)-C(13)-C(12)	118.6908
H(46)-C(13)-C(9)	119.1549
H(45)-C(13)-C(12)	117.5354
H(45)-C(13)-C(9)	119.1053
C(12)-C(13)-C(9)	59.2459
H(44)-C(12)-C(13)	117.4812
H(44)-C(12)-C(9)	122.4899
H(44)-C(12)-C(11)	113.9507
C(13)-C(12)-C(9)	59.7453
C(13)-C(12)-C(11)	123.4543
C(9)-C(12)-C(11)	108.7181
H(43)-C(11)-H(42)	110.4553
H(43)-C(11)-C(12)	109.994
H(43)-C(11)-N(10)	109.8149
H(42)-C(11)-C(12)	110.6675
H(42)-C(11)-N(10)	110.7057
C(12)-C(11)-N(10)	105.0771
S(14)-N(10)-C(8)	123.6624
S(14)-N(10)-C(11)	121.4787
C(8)-N(10)-C(11)	112.3567
C(13)-C(9)-C(12)	61.0088
C(13)-C(9)-C(6)	126.9498
C(13)-C(9)-C(8)	122.2384
C(12)-C(9)-C(6)	119.9298

C(12)-C(9)-C(8)	109.0538
C(6)-C(9)-C(8)	107.6771
H(41)-C(8)-N(10)	109.5176
H(41)-C(8)-C(9)	110.5139
H(41)-C(8)-C(7)	111.0957
N(10)-C(8)-C(9)	104.7308
N(10)-C(8)-C(7)	115.7159
C(9)-C(8)-C(7)	104.9362
O(19)-C(7)-H(18)	113.7622
O(19)-C(7)-C(5)	106.0516
O(19)-C(7)-C(8)	109.8962
H(18)-C(7)-C(5)	105.3493
H(18)-C(7)-C(8)	117.7783
C(5)-C(7)-C(8)	102.5743
C(9)-C(6)-C(1)	125.4719
C(9)-C(6)-C(5)	112.024
C(1)-C(6)-C(5)	122.4926
C(7)-C(5)-C(6)	111.8495
C(7)-C(5)-C(4)	126.0387
C(6)-C(5)-C(4)	122.0908
H(40)-C(4)-H(39)	107.9744
H(40)-C(4)-C(5)	110.5916
H(40)-C(4)-O(3)	109.4695
H(39)-C(4)-C(5)	110.5689
H(39)-C(4)-O(3)	106.8353
C(5)-C(4)-O(3)	111.2747
C(4)-O(3)-C(2)	113.471
H(38)-C(2)-H(37)	107.9617
H(38)-C(2)-O(3)	109.3213
H(38)-C(2)-C(1)	111.1966
H(37)-C(2)-O(3)	107.9375
H(37)-C(2)-C(1)	109.7351
O(3)-C(2)-C(1)	110.5942
H(36)-C(1)-H(35)	108.0528
H(36)-C(1)-C(6)	111.4591
H(36)-C(1)-C(2)	109.512
H(35)-C(1)-C(6)	107.9807
H(35)-C(1)-C(2)	109.6962
C(6)-C(1)-C(2)	110.0927

Dihedral angles

Atoms	Dihedral angles (°)
Li(24)-O(26)-C(34)-C(33)	-126.8303
Li(24)-O(26)-C(34)-H(64)	113.9215
Li(24)-O(26)-C(34)-H(65)	-5.2793

C(31)-O(26)-C(34)-C(33)	6.0366
C(31)-O(26)-C(34)-H(64)	-113.2116
C(31)-O(26)-C(34)-H(65)	127.5875
Li(24)-O(26)-C(31)-C(32)	151.1173
Li(24)-O(26)-C(31)-H(58)	-88.0423
Li(24)-O(26)-C(31)-H(59)	31.5383
C(34)-O(26)-C(31)-C(32)	17.8875
C(34)-O(26)-C(31)-H(58)	138.7279
C(34)-O(26)-C(31)-H(59)	-101.6915
C(32)-C(33)-C(34)-O(26)	-27.4519
C(32)-C(33)-C(34)-H(64)	89.2300
C(32)-C(33)-C(34)-H(65)	-147.7021
H(62)-C(33)-C(34)-O(26)	-149.5697
H(62)-C(33)-C(34)-H(64)	-32.8878
H(62)-C(33)-C(34)-H(65)	90.1801
H(63)-C(33)-C(34)-O(26)	89.6637
H(63)-C(33)-C(34)-H(64)	-153.6544
H(63)-C(33)-C(34)-H(65)	-30.5865
C(31)-C(32)-C(33)-C(34)	37.7228
C(31)-C(32)-C(33)-H(62)	159.5613
C(31)-C(32)-C(33)-H(63)	-79.7965
H(60)-C(32)-C(33)-C(34)	-80.1337
H(60)-C(32)-C(33)-H(62)	41.7048
H(60)-C(32)-C(33)-H(63)	162.3470
H(61)-C(32)-C(33)-C(34)	159.0426
H(61)-C(32)-C(33)-H(62)	-79.1189
H(61)-C(32)-C(33)-H(63)	41.5233
O(26)-C(31)-C(32)-C(33)	-34.3843
O(26)-C(31)-C(32)-H(60)	82.9510
O(26)-C(31)-C(32)-H(61)	-155.6938
H(58)-C(31)-C(32)-C(33)	-153.2010
H(58)-C(31)-C(32)-H(60)	-35.8657
H(58)-C(31)-C(32)-H(61)	85.4895
H(59)-C(31)-C(32)-C(33)	82.9058
H(59)-C(31)-C(32)-H(60)	-159.7589
H(59)-C(31)-C(32)-H(61)	-38.4037
Li(24)-O(25)-C(30)-C(29)	150.5775
Li(24)-O(25)-C(30)-H(56)	31.1103
Li(24)-O(25)-C(30)-H(57)	-89.1045
C(27)-O(25)-C(30)-C(29)	25.4154
C(27)-O(25)-C(30)-H(56)	-94.0517
C(27)-O(25)-C(30)-H(57)	145.7335
Li(24)-O(25)-C(27)-C(28)	-127.5038
Li(24)-O(25)-C(27)-H(50)	-6.7551
Li(24)-O(25)-C(27)-H(51)	112.2926
C(30)-O(25)-C(27)-C(28)	-1.8829
C(30)-O(25)-C(27)-H(50)	118.8658

C(30)-O(25)-C(27)-H(51)	-122.0865
C(28)-C(29)-C(30)-O(25)	-39.3206
C(28)-C(29)-C(30)-H(56)	77.5229
C(28)-C(29)-C(30)-H(57)	-157.2651
H(54)-C(29)-C(30)-O(25)	-161.1914
H(54)-C(29)-C(30)-H(56)	-44.3479
H(54)-C(29)-C(30)-H(57)	80.8641
H(55)-C(29)-C(30)-O(25)	77.9141
H(55)-C(29)-C(30)-H(56)	-165.2425
H(55)-C(29)-C(30)-H(57)	-40.0305
C(27)-C(28)-C(29)-C(30)	37.8304
C(27)-C(28)-C(29)-H(54)	159.7504
C(27)-C(28)-C(29)-H(55)	-79.3351
H(52)-C(28)-C(29)-C(30)	-79.6900
H(52)-C(28)-C(29)-H(54)	42.2299
H(52)-C(28)-C(29)-H(55)	163.1444
H(53)-C(28)-C(29)-C(30)	159.2844
H(53)-C(28)-C(29)-H(54)	-78.7956
H(53)-C(28)-C(29)-H(55)	42.1189
O(25)-C(27)-C(28)-C(29)	-22.3604
O(25)-C(27)-C(28)-H(52)	95.3648
O(25)-C(27)-C(28)-H(53)	-144.3476
H(50)-C(27)-C(28)-C(29)	-141.0011
H(50)-C(27)-C(28)-H(52)	-23.2758
H(50)-C(27)-C(28)-H(53)	97.0118
H(51)-C(27)-C(28)-C(29)	94.0456
H(51)-C(27)-C(28)-H(52)	-148.2292
H(51)-C(27)-C(28)-H(53)	-27.9416
O(19)-Li(24)-O(26)-C(31)	32.6405
O(19)-Li(24)-O(26)-C(34)	162.8650
Al(20)-Li(24)-O(26)-C(31)	136.3565
Al(20)-Li(24)-O(26)-C(34)	-93.4191
O(25)-Li(24)-O(26)-C(31)	-90.4972
O(25)-Li(24)-O(26)-C(34)	39.7272
O(19)-Li(24)-O(25)-C(27)	65.9403
O(19)-Li(24)-O(25)-C(30)	-55.6595
Al(20)-Li(24)-O(25)-C(27)	-34.7071
Al(20)-Li(24)-O(25)-C(30)	-156.3070
O(26)-Li(24)-O(25)-C(27)	-170.8390
O(26)-Li(24)-O(25)-C(30)	67.5611
O(19)-Li(24)-Al(20)-H(18)	-9.2478
O(19)-Li(24)-Al(20)-O(15)	89.7310
O(19)-Li(24)-Al(20)-H(21)	176.6952
O(19)-Li(24)-Al(20)-H(22)	-55.0462
O(19)-Li(24)-Al(20)-H(23)	-115.3599
O(25)-Li(24)-Al(20)-H(18)	103.2487
O(25)-Li(24)-Al(20)-O(15)	-157.7724

O(25)-Li(24)-Al(20)-H(21)	-70.8082
O(25)-Li(24)-Al(20)-H(22)	57.4503
O(25)-Li(24)-Al(20)-H(23)	-2.8633
O(26)-Li(24)-Al(20)-H(18)	-123.4063
O(26)-Li(24)-Al(20)-O(15)	-24.4275
O(26)-Li(24)-Al(20)-H(21)	62.5367
O(26)-Li(24)-Al(20)-H(22)	-169.2047
O(26)-Li(24)-Al(20)-H(23)	130.4816
C(7)-O(19)-Li(24)-Al(20)	-9.6653
C(7)-O(19)-Li(24)-O(25)	-123.9486
C(7)-O(19)-Li(24)-O(26)	111.4830
H(18)-Al(20)-O(15)-S(14)	70.6621
H(21)-Al(20)-O(15)-S(14)	-88.8219
H(22)-Al(20)-O(15)-S(14)	145.0077
H(23)-Al(20)-O(15)-S(14)	-154.9081
Li(24)-Al(20)-O(15)-S(14)	-10.3311
C(7)-H(18)-Al(20)-O(15)	-78.4045
C(7)-H(18)-Al(20)-H(21)	56.5393
C(7)-H(18)-Al(20)-H(22)	-167.8888
C(7)-H(18)-Al(20)-H(23)	134.5394
C(7)-H(18)-Al(20)-Li(24)	44.6987
C(8)-C(7)-O(19)-Li(24)	-98.8601
C(5)-C(7)-O(19)-Li(24)	150.9551
H(18)-C(7)-O(19)-Li(24)	35.6380
C(8)-C(7)-H(18)-Al(20)	64.6538
C(5)-C(7)-H(18)-Al(20)	178.2166
O(19)-C(7)-H(18)-Al(20)	-66.0528
N(10)-S(14)-C(17)-H(47)	177.0755
N(10)-S(14)-C(17)-H(48)	-63.3808
N(10)-S(14)-C(17)-H(49)	58.0072
O(15)-S(14)-C(17)-H(47)	-63.9840
O(15)-S(14)-C(17)-H(48)	55.5597
O(15)-S(14)-C(17)-H(49)	176.9477
O(16)-S(14)-C(17)-H(47)	55.3483
O(16)-S(14)-C(17)-H(48)	174.8920
O(16)-S(14)-C(17)-H(49)	-63.7199
N(10)-S(14)-O(15)-Al(20)	-81.6001
O(16)-S(14)-O(15)-Al(20)	31.2782
C(17)-S(14)-O(15)-Al(20)	156.9404
C(11)-N(10)-S(14)-O(15)	-73.2213
C(11)-N(10)-S(14)-O(16)	176.8681
C(11)-N(10)-S(14)-C(17)	50.8602
C(8)-N(10)-S(14)-O(15)	87.4492
C(8)-N(10)-S(14)-O(16)	-22.4615
C(8)-N(10)-S(14)-C(17)	-148.4693
C(11)-C(12)-C(13)-C(9)	-93.4330
C(11)-C(12)-C(13)-H(45)	157.4136

C(11)-C(12)-C(13)-H(46)	15.2655
C(9)-C(12)-C(13)-H(45)	-109.1533
C(9)-C(12)-C(13)-H(46)	108.6986
H(44)-C(12)-C(13)-C(9)	113.4246
H(44)-C(12)-C(13)-H(45)	4.2713
H(44)-C(12)-C(13)-H(46)	-137.8768
C(8)-C(9)-C(13)-C(12)	95.2665
C(8)-C(9)-C(13)-H(45)	-158.2087
C(8)-C(9)-C(13)-H(46)	-12.6573
C(6)-C(9)-C(13)-C(12)	-107.2762
C(6)-C(9)-C(13)-H(45)	-0.7514
C(6)-C(9)-C(13)-H(46)	144.8000
C(12)-C(9)-C(13)-H(45)	106.5248
C(12)-C(9)-C(13)-H(46)	-107.9238
C(8)-C(9)-C(12)-C(11)	1.4474
C(8)-C(9)-C(12)-C(13)	-116.9901
C(8)-C(9)-C(12)-H(44)	137.8273
C(6)-C(9)-C(12)-C(11)	-123.2701
C(6)-C(9)-C(12)-C(13)	118.2925
C(6)-C(9)-C(12)-H(44)	13.1098
C(13)-C(9)-C(12)-C(11)	118.4375
C(13)-C(9)-C(12)-H(44)	-105.1826
C(7)-C(8)-N(10)-C(11)	113.2988
C(7)-C(8)-N(10)-S(14)	-48.9290
C(9)-C(8)-N(10)-C(11)	-1.6890
C(9)-C(8)-N(10)-S(14)	-163.9168
H(41)-C(8)-N(10)-C(11)	-120.2197
H(41)-C(8)-N(10)-S(14)	77.5524
N(10)-C(11)-C(12)-C(9)	-2.3765
N(10)-C(11)-C(12)-C(13)	63.1836
N(10)-C(11)-C(12)-H(44)	-142.8285
H(42)-C(11)-C(12)-C(9)	-121.9131
H(42)-C(11)-C(12)-C(13)	-56.3530
H(42)-C(11)-C(12)-H(44)	97.6349
H(43)-C(11)-C(12)-C(9)	115.7618
H(43)-C(11)-C(12)-C(13)	-178.6781
H(43)-C(11)-C(12)-H(44)	-24.6902
C(8)-N(10)-C(11)-C(12)	2.5609
C(8)-N(10)-C(11)-H(42)	122.0720
C(8)-N(10)-C(11)-H(43)	-115.6984
S(14)-N(10)-C(11)-C(12)	165.2300
S(14)-N(10)-C(11)-H(42)	-75.2589
S(14)-N(10)-C(11)-H(43)	46.9707
C(5)-C(6)-C(9)-C(8)	-6.2576
C(5)-C(6)-C(9)-C(12)	119.1116
C(5)-C(6)-C(9)-C(13)	-166.3601
C(1)-C(6)-C(9)-C(8)	174.9539

C(1)-C(6)-C(9)-C(12)	-59.6769
C(1)-C(6)-C(9)-C(13)	14.8514
C(4)-C(5)-C(7)-C(8)	-175.8283
C(4)-C(5)-C(7)-H(18)	60.3648
C(4)-C(5)-C(7)-O(19)	-60.5508
C(6)-C(5)-C(7)-C(8)	5.8220
C(6)-C(5)-C(7)-H(18)	-117.9849
C(6)-C(5)-C(7)-O(19)	121.0995
C(7)-C(8)-C(9)-C(6)	9.4252
C(7)-C(8)-C(9)-C(12)	-122.1874
C(7)-C(8)-C(9)-C(13)	170.6680
N(10)-C(8)-C(9)-C(6)	131.7339
N(10)-C(8)-C(9)-C(12)	0.1213
N(10)-C(8)-C(9)-C(13)	-67.0233
H(41)-C(8)-C(9)-C(6)	-110.4124
H(41)-C(8)-C(9)-C(12)	117.9749
H(41)-C(8)-C(9)-C(13)	50.8303
C(5)-C(7)-C(8)-C(9)	-9.0070
C(5)-C(7)-C(8)-N(10)	-123.8778
C(5)-C(7)-C(8)-H(41)	110.4422
H(18)-C(7)-C(8)-C(9)	106.0822
H(18)-C(7)-C(8)-N(10)	-8.7885
H(18)-C(7)-C(8)-H(41)	-134.4686
O(19)-C(7)-C(8)-C(9)	-121.4651
O(19)-C(7)-C(8)-N(10)	123.6641
O(19)-C(7)-C(8)-H(41)	-2.0159
C(2)-C(1)-C(6)-C(5)	-14.0771
C(2)-C(1)-C(6)-C(9)	164.5914
H(35)-C(1)-C(6)-C(5)	105.6601
H(35)-C(1)-C(6)-C(9)	-75.6715
H(36)-C(1)-C(6)-C(5)	-135.8080
H(36)-C(1)-C(6)-C(9)	42.8604
C(4)-C(5)-C(6)-C(1)	0.4017
C(4)-C(5)-C(6)-C(9)	-178.4285
C(7)-C(5)-C(6)-C(1)	178.8266
C(7)-C(5)-C(6)-C(9)	0.0360
O(3)-C(4)-C(5)-C(6)	-16.6740
O(3)-C(4)-C(5)-C(7)	165.1340
H(39)-C(4)-C(5)-C(6)	-135.2341
H(39)-C(4)-C(5)-C(7)	46.5739
H(40)-C(4)-C(5)-C(6)	105.2222
H(40)-C(4)-C(5)-C(7)	-72.9697
C(2)-O(3)-C(4)-C(5)	49.2555
C(2)-O(3)-C(4)-H(39)	170.0347
C(2)-O(3)-C(4)-H(40)	-73.2898
C(1)-C(2)-O(3)-C(4)	-65.0846
H(37)-C(2)-O(3)-C(4)	174.8630

H(38)-C(2)-O(3)-C(4)	57.6706
C(6)-C(1)-C(2)-O(3)	44.2558
C(6)-C(1)-C(2)-H(37)	163.2247
C(6)-C(1)-C(2)-H(38)	-77.4004
H(35)-C(1)-C(2)-O(3)	-74.4346
H(35)-C(1)-C(2)-H(37)	44.5343
H(35)-C(1)-C(2)-H(38)	163.9091
H(36)-C(1)-C(2)-O(3)	167.1373
H(36)-C(1)-C(2)-H(37)	-73.8938
H(36)-C(1)-C(2)-H(38)	45.4811

- 3D-model of TS for the reduction of 283 with $LiAlH_4$ to 300 with coordination to sulfonamide realised with MarvinSketch 21.18

Software	MarvinSketch 21.18
Force field	MMFF94
Optimization limit	Normal
Max number of conformers	100
Diversity limit	0.1
Timelimit	900
Conformer energy	497.26 kcal/mol

Image visualised with Chem3D 12.0.2:

atom coordinates

Atoms	x (Å)	y (Å)	z (Å)
C(1)	-6.0317	2.3811	-5.812
C(2)	-9.0373	1.2882	-3.9592
O(3)	-8.2634	0.6992	-0.6116
C(4)	-7.4036	3.6555	0.9339
C(5)	-4.1721	4.8451	-0.3229
C(6)	-4.252	5.1577	-4.1133

C(7)	-1.1304	2.6783	0.2919
C(8)	1.2144	4.5492	-1.9425
C(9)	-0.6901	5.3364	-4.8898
N(10)	3.967	2.5208	-2.9403
C(11)	4.455	2.9738	-6.5277
C(12)	1.2381	4.2147	-7.7307
C(13)	0.9202	7.6606	-7.21
O(14)	-1.999	-0.5392	-0.8236
H(15)	-0.0698	2.6174	2.8343
S(16)	7.0589	2.6622	-0.4306
O(17)	6.5028	-0.0634	1.3927
O(18)	6.7175	5.2598	1.8381
C(19)	10.8106	2.4851	-2.5143
Li(20)	-0.5255	-3.3576	1.7815
Al(21)	3.3924	0.6394	4.0283
H(22)	2.5011	-1.5602	6.8213
H(23)	5.6138	1.0963	6.9139
H(24)	2.8494	4.0047	5.4491
O(25)	1.2669	-6.6144	-0.3065
O(26)	-3.462	-4.87	4.5343
C(27)	4.2496	-7.8174	1.0013
C(28)	5.7642	-9.6859	-1.7769
C(29)	4.9276	-7.5725	-4.6651
C(30)	1.5742	-6.2671	-3.8466
C(31)	-6.2066	-6.4434	2.9976
C(32)	-8.8779	-6.2714	5.5081
C(33)	-8.2835	-3.0143	7.0892
C(34)	-4.6187	-2.6487	7.0066
H(35)	-6.3415	2.7226	-6.8249
H(36)	-5.3344	1.5154	-5.8679
H(37)	-9.8139	2.0831	-4.0206
H(38)	-9.4159	0.3447	-4.4122
H(39)	-7.3319	3.4887	2.032
H(40)	-8.1825	4.42	0.7157
H(41)	-4.057	5.7932	0.2486
H(42)	-4.8321	6.0345	-4.4787
H(43)	1.6173	5.4426	-1.415
H(44)	4.711	2.0066	-7.0152
H(45)	5.2918	3.6706	-6.7577
H(46)	1.0648	3.5685	-8.5861
H(47)	0.3143	8.2562	-7.8864
H(48)	1.6186	8.4855	-7.1042
H(49)	11.6458	2.5271	-1.7798
H(50)	10.8876	3.3483	-3.2126
H(51)	10.8705	1.5344	-3.09
H(52)	4.0578	-8.4876	1.869
H(53)	4.9091	-7.0036	1.3775

H(54)	6.866	-9.7774	-1.6489
H(55)	5.3979	-10.7331	-1.8659
H(56)	4.9018	-8.173	-5.6018
H(57)	5.6741	-6.766	-4.841
H(58)	1.49	-5.1973	-4.1417
H(59)	0.7716	-6.8154	-4.3887
H(60)	-5.966	-7.5017	2.7508
H(61)	-6.493	-5.9565	2.0387
H(62)	-9.8818	-6.3076	5.029
H(63)	-8.8652	-7.1212	6.2268
H(64)	-8.6583	-3.0088	8.1372
H(65)	-8.8103	-2.1822	6.5707
H(66)	-4.3418	-1.603	6.7448
H(67)	-4.1666	-2.8752	7.9982

bond lenghts

Atoms	**Bond lenght (Å)**
C(34)-H(67)	1.113
C(34)-H(66)	1.113
C(33)-H(65)	1.113
C(33)-H(64)	1.113
C(32)-H(63)	1.113
C(32)-H(62)	1.113
C(31)-H(61)	1.113
C(31)-H(60)	1.113
C(30)-H(59)	1.113
C(30)-H(58)	1.113
C(29)-H(57)	1.113
C(29)-H(56)	1.113
C(28)-H(55)	1.113
C(28)-H(54)	1.113
C(27)-H(53)	1.113
C(27)-H(52)	1.113
C(19)-H(51)	1.113
C(19)-H(50)	1.113
C(19)-H(49)	1.113
C(13)-H(48)	1.086
C(13)-H(47)	1.086
C(12)-H(46)	1.086
C(11)-H(45)	1.113
C(11)-H(44)	1.113
C(8)-H(43)	1.113
C(6)-H(42)	1.113
C(5)-H(41)	1.113
C(4)-H(40)	1.113

C(4)-H(39)	1.113
C(2)-H(38)	1.113
C(2)-H(37)	1.113
C(1)-H(36)	1.113
C(1)-H(35)	1.113
O(26)-C(34)	3.5191
O(26)-C(31)	3.5171
C(33)-C(34)	3.6839
C(32)-C(33)	3.669
C(31)-C(32)	3.6699
O(25)-C(30)	3.5703
O(25)-C(27)	3.4719
C(29)-C(30)	3.6904
C(28)-C(29)	3.6753
C(27)-C(28)	3.6747
Li(20)-O(26)	4.2998
Li(20)-O(25)	4.2637
Li(20)-Al(21)	6.0311
Al(21)-H(24)	3.6931
Al(21)-H(23)	3.6702
Al(21)-H(22)	3.6652
Al(21)-O(17)	4.137
H(15)-Al(21)	4.1623
O(14)-Li(20)	4.1111
S(16)-C(19)	4.2952
S(16)-O(18)	3.4657
S(16)-O(17)	3.326
N(10)-S(16)	3.9848
C(7)-H(15)	2.7554
C(7)-O(14)	3.5144
C(12)-C(13)	3.4995
C(9)-C(13)	3.6576
C(9)-C(12)	3.612
C(8)-N(10)	3.5619
C(11)-C(12)	3.6518
N(10)-C(11)	3.6487
C(6)-C(9)	3.6499
C(5)-C(7)	3.7848
C(8)-C(9)	3.5963
C(7)-C(8)	3.7404
C(6)-C(1)	3.7098
C(5)-C(6)	3.8041
C(5)-C(4)	3.6657
O(3)-C(4)	3.4449
C(2)-O(3)	3.486
C(1)-C(2)	3.6961

bond angles

Atoms	Bond angles (°)
H(51)-C(19)-H(50)	109.52
H(51)-C(19)-H(49)	109.4618
H(51)-C(19)-S(16)	109.4618
H(50)-C(19)-H(49)	109.4418
H(50)-C(19)-S(16)	109.4418
H(49)-C(19)-S(16)	109.5
H(65)-C(33)-H(64)	105.9949
H(65)-C(33)-C(34)	112.7208
H(65)-C(33)-C(32)	112.7208
H(64)-C(33)-C(34)	110.8306
H(64)-C(33)-C(32)	110.8306
C(34)-C(33)-C(32)	103.863
H(63)-C(32)-H(62)	105.2772
H(63)-C(32)-C(33)	113.4309
H(63)-C(32)-C(31)	113.4309
H(62)-C(32)-C(33)	111.1316
H(62)-C(32)-C(31)	111.1316
C(33)-C(32)-C(31)	102.6195
H(67)-C(34)-H(66)	107.4418
H(67)-C(34)-O(26)	111.3392
H(67)-C(34)-C(33)	111.3392
H(66)-C(34)-O(26)	110.2434
H(66)-C(34)-C(33)	110.2434
O(26)-C(34)-C(33)	106.2657
H(61)-C(31)-H(60)	106.293
H(61)-C(31)-O(26)	112.4308
H(61)-C(31)-C(32)	112.4308
H(60)-C(31)-O(26)	110.7075
H(60)-C(31)-C(32)	110.7075
O(26)-C(31)-C(32)	104.369
H(57)-C(29)-H(56)	105.8691
H(57)-C(29)-C(30)	112.8441
H(57)-C(29)-C(28)	112.8441
H(56)-C(29)-C(30)	110.8829
H(56)-C(29)-C(28)	110.8829
C(30)-C(29)-C(28)	103.6475
H(55)-C(28)-H(54)	104.9273
H(55)-C(28)-C(29)	113.7833
H(55)-C(28)-C(27)	113.7833
H(54)-C(28)-C(29)	111.2809
H(54)-C(28)-C(27)	111.2809
C(29)-C(28)-C(27)	101.9998
H(59)-C(30)-H(58)	106.8448
H(59)-C(30)-O(25)	111.9014

H(59)-C(30)-C(29)	111.9014
H(58)-C(30)-O(25)	110.4826
H(58)-C(30)-C(29)	110.4826
O(25)-C(30)-C(29)	105.2905
H(53)-C(27)-H(52)	106.1995
H(53)-C(27)-O(25)	112.5215
H(53)-C(27)-C(28)	112.5215
H(52)-C(27)-O(25)	110.746
H(52)-C(27)-C(28)	110.746
O(25)-C(27)-C(28)	104.211
C(4)-O(3)-C(2)	109.9518
H(38)-C(2)-H(37)	110.2195
H(38)-C(2)-O(3)	108.8562
H(38)-C(2)-C(1)	108.8562
H(37)-C(2)-O(3)	109.1822
H(37)-C(2)-C(1)	109.1822
O(3)-C(2)-C(1)	110.5373
C(34)-O(26)-C(31)	109.4407
C(34)-O(26)-Li(20)	116.8865
C(31)-O(26)-Li(20)	114.2404
C(30)-O(25)-C(27)	109.4664
C(30)-O(25)-Li(20)	116.58
C(27)-O(25)-Li(20)	116.1904
O(26)-Li(20)-O(25)	109.3871
O(26)-Li(20)-Al(21)	115.9924
O(26)-Li(20)-O(14)	113.7062
O(25)-Li(20)-Al(21)	114.5552
O(25)-Li(20)-O(14)	111.3469
Al(21)-Li(20)-O(14)	90.8343
Al(21)-O(17)-S(16)	109.617
C(19)-S(16)-O(18)	115.7548
C(19)-S(16)-O(17)	112.2218
C(19)-S(16)-N(10)	111.7615
O(18)-S(16)-O(17)	103.8207
O(18)-S(16)-N(10)	111.2509
O(17)-S(16)-N(10)	100.7457
Li(20)-Al(21)-H(24)	130.6715
Li(20)-Al(21)-H(23)	140.2276
Li(20)-Al(21)-H(22)	74.2276
Li(20)-Al(21)-O(17)	97.9606
Li(20)-Al(21)-H(15)	70.5932
H(24)-Al(21)-H(23)	70.9175
H(24)-Al(21)-H(22)	102.5883
H(24)-Al(21)-O(17)	120.6935
H(24)-Al(21)-H(15)	63.578
H(23)-Al(21)-H(22)	67.8372
H(23)-Al(21)-O(17)	93.8404

H(23)-Al(21)-H(15)	132.054
H(22)-Al(21)-O(17)	124.4968
H(22)-Al(21)-H(15)	107.5486
O(17)-Al(21)-H(15)	121.5579
Al(21)-H(15)-C(7)	126.5378
Li(20)-O(14)-C(7)	109.7503
H(45)-C(11)-H(44)	106.2965
H(45)-C(11)-C(12)	112.4275
H(45)-C(11)-N(10)	112.4275
H(44)-C(11)-C(12)	110.7061
H(44)-C(11)-N(10)	110.7061
C(12)-C(11)-N(10)	104.3749
H(48)-C(13)-H(47)	90.1619
H(48)-C(13)-C(12)	134.7517
H(48)-C(13)-C(9)	134.7517
H(47)-C(13)-C(12)	119.8682
H(47)-C(13)-C(9)	119.8682
C(12)-C(13)-C(9)	60.5721
H(40)-C(4)-H(39)	109.9655
H(40)-C(4)-C(5)	109.0747
H(40)-C(4)-O(3)	109.0747
H(39)-C(4)-C(5)	109.2759
H(39)-C(4)-O(3)	109.2759
C(5)-C(4)-O(3)	110.1634
H(36)-C(1)-H(35)	111.5531
H(36)-C(1)-C(6)	107.7356
H(36)-C(1)-C(2)	107.7356
H(35)-C(1)-C(6)	108.7001
H(35)-C(1)-C(2)	108.7001
C(6)-C(1)-C(2)	112.4506
H(46)-C(12)-C(13)	133.5226
H(46)-C(12)-C(9)	135.9814
H(46)-C(12)-C(11)	101.4126
C(13)-C(12)-C(9)	61.8807
C(13)-C(12)-C(11)	111.4452
C(9)-C(12)-C(11)	108.4623
S(16)-N(10)-C(8)	113.7655
S(16)-N(10)-C(11)	120.7346
C(8)-N(10)-C(11)	107.944
C(13)-C(9)-C(12)	57.5472
C(13)-C(9)-C(6)	126.5627
C(13)-C(9)-C(8)	115.2021
C(12)-C(9)-C(6)	132.3044
C(12)-C(9)-C(8)	107.0914
C(6)-C(9)-C(8)	109.3739
H(43)-C(8)-N(10)	108.0687
H(43)-C(8)-C(9)	113.8533

H(43)-C(8)-C(7)	110.2007
N(10)-C(8)-C(9)	107.7176
N(10)-C(8)-C(7)	111.5277
C(9)-C(8)-C(7)	105.4899
H(15)-C(7)-O(14)	111.5779
H(15)-C(7)-C(5)	118.1558
H(15)-C(7)-C(8)	108.7198
O(14)-C(7)-C(5)	105.8991
O(14)-C(7)-C(8)	115.0401
C(5)-C(7)-C(8)	96.9156
H(42)-C(6)-C(9)	113.591
H(42)-C(6)-C(1)	100.9092
H(42)-C(6)-C(5)	113.7531
C(9)-C(6)-C(1)	114.0411
C(9)-C(6)-C(5)	101.2741
C(1)-C(6)-C(5)	113.8799
H(41)-C(5)-C(7)	108.7358
H(41)-C(5)-C(6)	116.3431
H(41)-C(5)-C(4)	101.0446
C(7)-C(5)-C(6)	103.0486
C(7)-C(5)-C(4)	117.8387
C(6)-C(5)-C(4)	110.4733

dihedral angles

Atoms	Dihedral angles (°)
Li(20)-O(26)-C(34)-C(33)	134.6758
Li(20)-O(26)-C(34)-H(66)	15.219
Li(20)-O(26)-C(34)-H(67)	-103.9284
C(31)-O(26)-C(34)-C(33)	2.8308
C(31)-O(26)-C(34)-H(66)	-116.626
C(31)-O(26)-C(34)-H(67)	124.2266
Li(20)-O(26)-C(31)-C(32)	-157.6065
Li(20)-O(26)-C(31)-H(60)	83.2455
Li(20)-O(26)-C(31)-H(61)	-35.4739
C(34)-O(26)-C(31)-C(32)	-24.3817
C(34)-O(26)-C(31)-H(60)	-143.5297
C(34)-O(26)-C(31)-H(61)	97.7509
C(32)-C(33)-C(34)-O(26)	19.7953
C(32)-C(33)-C(34)-H(66)	139.252
C(32)-C(33)-C(34)-H(67)	-101.6005
H(64)-C(33)-C(34)-O(26)	138.8594
H(64)-C(33)-C(34)-H(66)	-101.6839
H(64)-C(33)-C(34)-H(67)	17.4636
H(65)-C(33)-C(34)-O(26)	-102.5241
H(65)-C(33)-C(34)-H(66)	16.9327
H(65)-C(33)-C(34)-H(67)	136.0801

C(31)-C(32)-C(33)-C(34)	-33.8147
C(31)-C(32)-C(33)-H(64)	-152.8788
C(31)-C(32)-C(33)-H(65)	88.5047
H(62)-C(32)-C(33)-C(34)	-152.6702
H(62)-C(32)-C(33)-H(64)	88.2657
H(62)-C(32)-C(33)-H(65)	-30.3508
H(63)-C(32)-C(33)-C(34)	88.9461
H(63)-C(32)-C(33)-H(64)	-30.118
H(63)-C(32)-C(33)-H(65)	-148.7345
O(26)-C(31)-C(32)-C(33)	35.8679
O(26)-C(31)-C(32)-H(62)	154.7234
O(26)-C(31)-C(32)-H(63)	-86.8929
H(60)-C(31)-C(32)-C(33)	155.0159
H(60)-C(31)-C(32)-H(62)	-86.1287
H(60)-C(31)-C(32)-H(63)	32.2551
H(61)-C(31)-C(32)-C(33)	-86.2647
H(61)-C(31)-C(32)-H(62)	32.5907
H(61)-C(31)-C(32)-H(63)	150.9745
Li(20)-O(25)-C(30)-C(29)	138.1714
Li(20)-O(25)-C(30)-H(58)	18.8724
Li(20)-O(25)-C(30)-H(59)	-100.0466
C(27)-O(25)-C(30)-C(29)	3.7219
C(27)-O(25)-C(30)-H(58)	-115.5771
C(27)-O(25)-C(30)-H(59)	125.504
Li(20)-O(25)-C(27)-C(28)	-161.2172
Li(20)-O(25)-C(27)-H(52)	79.661
Li(20)-O(25)-C(27)-H(53)	-39.0258
C(30)-O(25)-C(27)-C(28)	-26.5714
C(30)-O(25)-C(27)-H(52)	-145.6932
C(30)-O(25)-C(27)-H(53)	95.6201
C(28)-C(29)-C(30)-O(25)	20.5458
C(28)-C(29)-C(30)-H(58)	139.8449
C(28)-C(29)-C(30)-H(59)	-101.2362
H(56)-C(29)-C(30)-O(25)	139.574
H(56)-C(29)-C(30)-H(58)	-101.1269
H(56)-C(29)-C(30)-H(59)	17.792
H(57)-C(29)-C(30)-O(25)	-101.8518
H(57)-C(29)-C(30)-H(58)	17.4472
H(57)-C(29)-C(30)-H(59)	136.3662
C(27)-C(28)-C(29)-C(30)	-35.7818
C(27)-C(28)-C(29)-H(56)	-154.81
C(27)-C(28)-C(29)-H(57)	86.6158
H(54)-C(28)-C(29)-C(30)	-154.5319
H(54)-C(28)-C(29)-H(56)	86.4398
H(54)-C(28)-C(29)-H(57)	-32.1343
H(55)-C(28)-C(29)-C(30)	87.1898
H(55)-C(28)-C(29)-H(56)	-31.8384

H(55)-C(28)-C(29)-H(57)	-150.4125
O(25)-C(27)-C(28)-C(29)	38.5228
O(25)-C(27)-C(28)-H(54)	157.2729
O(25)-C(27)-C(28)-H(55)	-84.4489
H(52)-C(27)-C(28)-C(29)	157.6446
H(52)-C(27)-C(28)-H(54)	-83.6053
H(52)-C(27)-C(28)-H(55)	34.6729
H(53)-C(27)-C(28)-C(29)	-83.6686
H(53)-C(27)-C(28)-H(54)	35.0815
H(53)-C(27)-C(28)-H(55)	153.3597
O(14)-Li(20)-O(26)-C(31)	60.1982
O(14)-Li(20)-O(26)-C(34)	-69.4115
Al(21)-Li(20)-O(26)-C(31)	163.6002
Al(21)-Li(20)-O(26)-C(34)	33.9906
O(25)-Li(20)-O(26)-C(31)	-64.9699
O(25)-Li(20)-O(26)-C(34)	165.4204
O(14)-Li(20)-O(25)-C(27)	138.2464
O(14)-Li(20)-O(25)-C(30)	6.8428
Al(21)-Li(20)-O(25)-C(27)	36.9577
Al(21)-Li(20)-O(25)-C(30)	-94.4459
O(26)-Li(20)-O(25)-C(27)	-95.2309
O(26)-Li(20)-O(25)-C(30)	133.3655
O(14)-Li(20)-Al(21)-H(15)	31.8763
O(14)-Li(20)-Al(21)-O(17)	-88.8557
O(14)-Li(20)-Al(21)-H(22)	147.4511
O(14)-Li(20)-Al(21)-H(23)	165.2587
O(14)-Li(20)-Al(21)-H(24)	54.247
O(25)-Li(20)-Al(21)-H(15)	145.8868
O(25)-Li(20)-Al(21)-O(17)	25.1548
O(25)-Li(20)-Al(21)-H(22)	-98.5385
O(25)-Li(20)-Al(21)-H(23)	-80.7309
O(25)-Li(20)-Al(21)-H(24)	168.2575
O(26)-Li(20)-Al(21)-H(15)	-85.1524
O(26)-Li(20)-Al(21)-O(17)	154.1157
O(26)-Li(20)-Al(21)-H(22)	30.4224
O(26)-Li(20)-Al(21)-H(23)	48.23
O(26)-Li(20)-Al(21)-H(24)	-62.7817
H(15)-Al(21)-O(17)-S(16)	43.3868
H(22)-Al(21)-O(17)-S(16)	-168.2477
H(23)-Al(21)-O(17)-S(16)	-102.6177
H(24)-Al(21)-O(17)-S(16)	-32.5676
Li(20)-Al(21)-O(17)-S(16)	115.4573
C(7)-H(15)-Al(21)-O(17)	27.6854
C(7)-H(15)-Al(21)-H(22)	-125.3546
C(7)-H(15)-Al(21)-H(23)	158.9798
C(7)-H(15)-Al(21)-H(24)	139.0148
C(7)-H(15)-Al(21)-Li(20)	-59.7897

C(7)-O(14)-Li(20)-Al(21)	-18.8763
C(7)-O(14)-Li(20)-O(25)	-135.7432
C(7)-O(14)-Li(20)-O(26)	100.1418
N(10)-S(16)-C(19)-H(49)	180
N(10)-S(16)-C(19)-H(50)	60.0364
N(10)-S(16)-C(19)-H(51)	-59.9996
O(17)-S(16)-C(19)-H(49)	-67.6694
O(17)-S(16)-C(19)-H(50)	172.3669
O(17)-S(16)-C(19)-H(51)	52.3309
O(18)-S(16)-C(19)-H(49)	51.2519
O(18)-S(16)-C(19)-H(50)	-68.7117
O(18)-S(16)-C(19)-H(51)	171.2523
N(10)-S(16)-O(17)-Al(21)	-75.0525
O(18)-S(16)-O(17)-Al(21)	40.2
C(19)-S(16)-O(17)-Al(21)	165.9239
C(11)-N(10)-S(16)-O(17)	-132.2504
C(11)-N(10)-S(16)-O(18)	118.1957
C(11)-N(10)-S(16)-C(19)	-12.8941
C(8)-N(10)-S(16)-O(17)	96.9473
C(8)-N(10)-S(16)-O(18)	-12.6066
C(8)-N(10)-S(16)-C(19)	-143.6964
C(8)-C(7)-H(15)-Al(21)	-66.4982
C(5)-C(7)-H(15)-Al(21)	-175.4976
O(14)-C(7)-H(15)-Al(21)	61.4238
C(8)-C(7)-O(14)-Li(20)	114.5082
C(5)-C(7)-O(14)-Li(20)	-139.7531
H(15)-C(7)-O(14)-Li(20)	-9.9416
C(11)-C(12)-C(13)-C(9)	-100.1287
C(11)-C(12)-C(13)-H(47)	150.2745
C(11)-C(12)-C(13)-H(48)	25.2505
C(9)-C(12)-C(13)-H(47)	-109.5968
C(9)-C(12)-C(13)-H(48)	125.3792
H(46)-C(12)-C(13)-C(9)	128.0939
H(46)-C(12)-C(13)-H(47)	18.4971
H(46)-C(12)-C(13)-H(48)	-106.5269
C(8)-C(9)-C(13)-C(12)	94.9141
C(8)-C(9)-C(13)-H(47)	-155.4891
C(8)-C(9)-C(13)-H(48)	-30.4651
C(6)-C(9)-C(13)-C(12)	-121.4285
C(6)-C(9)-C(13)-H(47)	-11.8317
C(6)-C(9)-C(13)-H(48)	113.1923
C(12)-C(9)-C(13)-H(47)	109.5968
C(12)-C(9)-C(13)-H(48)	-125.3792
C(8)-C(9)-C(12)-C(11)	-4.4265
C(8)-C(9)-C(12)-C(13)	-109.4147
C(8)-C(9)-C(12)-H(46)	125.7921
C(6)-C(9)-C(12)-C(11)	-142.938

C(6)-C(9)-C(12)-C(13)	112.0737
C(6)-C(9)-C(12)-H(46)	-12.7195
C(13)-C(9)-C(12)-C(11)	104.9883
C(13)-C(9)-C(12)-H(46)	-124.7932
C(7)-C(8)-N(10)-C(11)	134.493
C(7)-C(8)-N(10)-S(16)	-88.6573
C(9)-C(8)-N(10)-C(11)	19.1893
C(9)-C(8)-N(10)-S(16)	156.039
H(43)-C(8)-N(10)-C(11)	-104.2315
H(43)-C(8)-N(10)-S(16)	32.6182
N(10)-C(11)-C(12)-C(9)	15.6522
N(10)-C(11)-C(12)-C(13)	81.9052
N(10)-C(11)-C(12)-H(46)	-131.5747
H(44)-C(11)-C(12)-C(9)	134.8011
H(44)-C(11)-C(12)-C(13)	-158.9459
H(44)-C(11)-C(12)-H(46)	-12.4258
H(45)-C(11)-C(12)-C(9)	-106.4783
H(45)-C(11)-C(12)-C(13)	-40.2253
H(45)-C(11)-C(12)-H(46)	106.2948
C(8)-N(10)-C(11)-C(12)	-21.3234
C(8)-N(10)-C(11)-H(44)	-140.4723
C(8)-N(10)-C(11)-H(45)	100.8071
S(16)-N(10)-C(11)-C(12)	-154.5876
S(16)-N(10)-C(11)-H(44)	86.2635
S(16)-N(10)-C(11)-H(45)	-32.4571
C(5)-C(6)-C(9)-C(8)	10.2
C(5)-C(6)-C(9)-C(12)	148.0386
C(5)-C(6)-C(9)-C(13)	-135.1621
C(1)-C(6)-C(9)-C(8)	-112.5465
C(1)-C(6)-C(9)-C(12)	25.2921
C(1)-C(6)-C(9)-C(13)	102.0914
H(42)-C(6)-C(9)-C(8)	132.5598
H(42)-C(6)-C(9)-C(12)	-89.6016
H(42)-C(6)-C(9)-C(13)	-12.8024
C(4)-C(5)-C(7)-C(8)	169.642
C(4)-C(5)-C(7)-O(14)	51.0963
C(4)-C(5)-C(7)-H(15)	-74.7889
C(6)-C(5)-C(7)-C(8)	47.7427
C(6)-C(5)-C(7)-O(14)	-70.803
C(6)-C(5)-C(7)-H(15)	163.3118
H(41)-C(5)-C(7)-C(8)	-76.2856
H(41)-C(5)-C(7)-O(14)	165.1687
H(41)-C(5)-C(7)-H(15)	39.2835
C(7)-C(8)-C(9)-C(6)	20.4296
C(7)-C(8)-C(9)-C(12)	-128.2813
C(7)-C(8)-C(9)-C(13)	170.1274
N(10)-C(8)-C(9)-C(6)	139.6572

N(10)-C(8)-C(9)-C(12)	-9.0536
N(10)-C(8)-C(9)-C(13)	-70.6449
H(43)-C(8)-C(9)-C(6)	-100.5231
H(43)-C(8)-C(9)-C(12)	110.7661
H(43)-C(8)-C(9)-C(13)	49.1748
C(5)-C(7)-C(8)-C(9)	-41.5282
C(5)-C(7)-C(8)-N(10)	-158.1949
C(5)-C(7)-C(8)-H(43)	81.778
O(14)-C(7)-C(8)-C(9)	69.6482
O(14)-C(7)-C(8)-N(10)	-47.0185
O(14)-C(7)-C(8)-H(43)	-167.0456
H(15)-C(7)-C(8)-C(9)	-164.4149
H(15)-C(7)-C(8)-N(10)	78.9184
H(15)-C(7)-C(8)-H(43)	-41.1087
C(5)-C(6)-C(1)-C(2)	38.5087
C(5)-C(6)-C(1)-H(35)	158.9133
C(5)-C(6)-C(1)-H(36)	-80.0595
C(9)-C(6)-C(1)-C(2)	154.0783
C(9)-C(6)-C(1)-H(35)	-85.5172
C(9)-C(6)-C(1)-H(36)	35.51
H(42)-C(6)-C(1)-C(2)	-83.7633
H(42)-C(6)-C(1)-H(35)	36.6412
H(42)-C(6)-C(1)-H(36)	157.6684
C(4)-C(5)-C(6)-C(1)	-40.6019
C(4)-C(5)-C(6)-C(9)	-163.4595
C(4)-C(5)-C(6)-H(42)	74.2931
C(7)-C(5)-C(6)-C(1)	86.14
C(7)-C(5)-C(6)-C(9)	-36.7176
C(7)-C(5)-C(6)-H(42)	-158.9651
H(41)-C(5)-C(6)-C(1)	-154.999
H(41)-C(5)-C(6)-C(9)	82.1434
H(41)-C(5)-C(6)-H(42)	-40.1041
C(6)-C(5)-C(4)-O(3)	55.1678
C(6)-C(5)-C(4)-H(39)	175.2323
C(6)-C(5)-C(4)-H(40)	-64.5241
C(7)-C(5)-C(4)-O(3)	-62.8478
C(7)-C(5)-C(4)-H(39)	57.2167
C(7)-C(5)-C(4)-H(40)	177.4603
H(41)-C(5)-C(4)-O(3)	178.9113
H(41)-C(5)-C(4)-H(39)	-61.0241
H(41)-C(5)-C(4)-H(40)	59.2195
C(2)-O(3)-C(4)-C(5)	-69.7095
C(2)-O(3)-C(4)-H(39)	170.226
C(2)-O(3)-C(4)-H(40)	49.9824
C(1)-C(2)-O(3)-C(4)	66.4622
H(37)-C(2)-O(3)-C(4)	-53.6587
H(38)-C(2)-O(3)-C(4)	-174.0232

C(6)-C(1)-C(2)-O(3)	-50.2228
C(6)-C(1)-C(2)-H(37)	69.8982
C(6)-C(1)-C(2)-H(38)	-169.7373
H(35)-C(1)-C(2)-O(3)	-170.6273
H(35)-C(1)-C(2)-H(37)	-50.5063
H(35)-C(1)-C(2)-H(38)	69.8581
H(36)-C(1)-C(2)-O(3)	68.3455
H(36)-C(1)-C(2)-H(37)	-171.5336
H(36)-C(1)-C(2)-H(38)	-51.1691

3D-model of TS for the reduction of 283 with $LiAlH_4$ to 300 with coordination on the oxygen of the 6-membered ring realised with MarvinSketch 21.18

Software	MarvinSketch 21.18
Force field	MMFF94
Optimization limit	Normal
Max number of conformers	100
Diversity limit	0.1
Timelimit	900
Conformer energy	237.8 kcal/mol

Image visualised with Chem3D 12.0.2:

atom coordinates

Atoms	x (Å)	y (Å)	z (Å)
C(1)	-4.7868	2.628	-2.8257
C(2)	-6.8641	1.1221	-0.9725

O(3)	-5.6951	0.3421	1.9206
C(4)	-4.5645	2.8494	3.216
C(5)	-2.0845	3.8876	1.5617
C(6)	-2.9247	4.7874	-1.3928
C(7)	0.3522	1.8431	1.0071
C(8)	2.0743	3.4908	-1.1379
C(9)	-0.107	5.0883	-2.7416
N(10)	3.274	1.6935	-3.2582
C(11)	2.8968	2.8172	-6.0672
C(12)	0.4435	4.7031	-5.7652
C(13)	0.6705	7.5387	-4.5022
O(14)	-0.7149	-0.5806	-0.4145
H(15)	1.5696	1.2896	2.933
S(16)	5.8463	-0.445	-2.5196
O(17)	5.8709	-2.5267	-4.6563
O(18)	5.4816	-1.2429	0.3453
C(19)	8.8276	1.6946	-2.825
Li(20)	-2.8941	-1.9356	1.8083
Al(21)	0.4387	-0.563	5.4453
H(22)	0.513	1.9448	7.3191
H(23)	-1.1881	-2.0653	7.6587
H(24)	3.0208	-2.2698	5.8843
O(25)	-3.4696	-5.5049	1.2935
C(26)	-1.0532	-7.1549	2.4896
C(27)	-0.4483	-9.3583	0.3476
C(28)	-0.9319	-7.8524	-2.3496
C(29)	-3.5541	-6.2217	-1.8025
H(30)	-5.3607	3.151	-3.6231
H(31)	-4.0954	1.84	-3.1994
H(32)	-7.7476	1.7832	-0.827
H(33)	-7.1244	0.169	-1.4849
H(34)	-4.2423	2.6144	4.2551
H(35)	-5.3492	3.6384	3.2345
H(36)	-1.7354	4.6976	2.2406
H(37)	-3.5431	5.7116	-1.4402
H(38)	2.8741	4.0651	-0.619
H(39)	2.6855	2.0032	-6.7962
H(40)	3.8016	3.3392	-6.4517
H(41)	-0.0461	4.3962	-6.6846
H(42)	-0.0705	8.2979	-4.7344
H(43)	1.4403	8.3036	-4.4603
H(44)	9.7391	1.0956	-2.6032
H(45)	8.8911	2.0959	-3.8612
H(46)	8.7539	2.5387	-2.1032
H(47)	-1.3387	-7.6198	3.4597
H(48)	-0.1669	-6.5133	2.6938
H(49)	0.6036	-9.7139	0.4248

H(50)	-1.0769	-10.2695	0.4627
H(51)	-1.077	-8.5712	-3.1868
H(52)	-0.0739	-7.2104	-2.6506
H(53)	-3.5704	-5.2935	-2.4165
H(54)	-4.4659	-6.8016	-2.0688

bond lengths

Atoms	**Bond lenght (Å)**
C(29)-H(54)	1.113
C(29)-H(53)	1.113
C(28)-H(52)	1.113
C(28)-H(51)	1.113
C(27)-H(50)	1.113
C(27)-H(49)	1.113
C(26)-H(48)	1.113
C(26)-H(47)	1.113
C(19)-H(46)	1.113
C(19)-H(45)	1.113
C(19)-H(44)	1.113
C(13)-H(43)	1.086
C(13)-H(42)	1.086
C(12)-H(41)	1.086
C(11)-H(40)	1.113
C(11)-H(39)	1.113
C(8)-H(38)	1.113
C(6)-H(37)	1.113
C(5)-H(36)	1.113
C(4)-H(35)	1.113
C(4)-H(34)	1.113
C(2)-H(33)	1.113
C(2)-H(32)	1.113
C(1)-H(31)	1.113
C(1)-H(30)	1.113
O(25)-C(29)	3.179
O(25)-C(26)	3.161
C(28)-C(29)	3.136
C(27)-C(28)	3.1267
C(26)-C(27)	3.1319
Li(20)-O(25)	3.6519
O(14)-Li(20)	3.395
O(3)-Li(20)	3.6119
Al(21)-H(24)	3.1262
Al(21)-H(23)	3.1309
Al(21)-H(22)	3.1314
Al(21)-Li(20)	5.1205
Al(21)-H(15)	3.32

S(16)-C(19)	3.6823
S(16)-O(18)	2.9962
S(16)-O(17)	2.9832
N(10)-S(16)	3.4257
C(7)-H(15)	2.3447
C(7)-O(14)	3.0057
C(12)-C(13)	3.1124
C(9)-C(13)	3.1159
C(9)-C(12)	3.0974
C(8)-N(10)	3.0274
C(11)-C(12)	3.1091
N(10)-C(11)	3.0488
C(6)-C(9)	3.1383
C(5)-C(7)	3.2288
C(8)-C(9)	3.1436
C(7)-C(8)	3.2065
C(6)-C(1)	3.1912
C(5)-C(6)	3.2007
C(5)-C(4)	3.1567
O(3)-C(4)	3.0402
C(2)-O(3)	3.2164
C(1)-C(2)	3.165

bond angles

Atoms	**Bond angles (°)**
C(29)-H(54)	1.113
C(29)-H(53)	1.113
C(28)-H(52)	1.113
C(28)-H(51)	1.113
C(27)-H(50)	1.113
C(27)-H(49)	1.113
C(26)-H(48)	1.113
C(26)-H(47)	1.113
C(19)-H(46)	1.113
C(19)-H(45)	1.113
C(19)-H(44)	1.113
C(13)-H(43)	1.086
C(13)-H(42)	1.086
C(12)-H(41)	1.086
C(11)-H(40)	1.113
C(11)-H(39)	1.113
C(8)-H(38)	1.113
C(6)-H(37)	1.113
C(5)-H(36)	1.113
C(4)-H(35)	1.113
C(4)-H(34)	1.113

C(2)-H(33)	1.113
C(2)-H(32)	1.113
C(1)-H(31)	1.113
C(1)-H(30)	1.113
O(25)-C(29)	3.179
O(25)-C(26)	3.161
C(28)-C(29)	3.136
C(27)-C(28)	3.1267
C(26)-C(27)	3.1319
Li(20)-O(25)	3.6519
O(14)-Li(20)	3.395
O(3)-Li(20)	3.6119
Al(21)-H(24)	3.1262
Al(21)-H(23)	3.1309
Al(21)-H(22)	3.1314
Al(21)-Li(20)	5.1205
Al(21)-H(15)	3.32
S(16)-C(19)	3.6823
S(16)-O(18)	2.9962
S(16)-O(17)	2.9832
N(10)-S(16)	3.4257
C(7)-H(15)	2.3447
C(7)-O(14)	3.0057
C(12)-C(13)	3.1124
C(9)-C(13)	3.1159
C(9)-C(12)	3.0974
C(8)-N(10)	3.0274
C(11)-C(12)	3.1091
N(10)-C(11)	3.0488
C(6)-C(9)	3.1383
C(5)-C(7)	3.2288
C(8)-C(9)	3.1436
C(7)-C(8)	3.2065
C(6)-C(1)	3.1912
C(5)-C(6)	3.2007
C(5)-C(4)	3.1567
O(3)-C(4)	3.0402
C(2)-O(3)	3.2164
C(1)-C(2)	3.165
H(54)-C(29)-H(53)	106.8884
H(54)-C(29)-O(25)	111.86
H(54)-C(29)-C(28)	111.86
H(53)-C(29)-O(25)	110.465
H(53)-C(29)-C(28)	110.465
O(25)-C(29)-C(28)	105.3625
H(52)-C(28)-H(51)	105.6411
H(52)-C(28)-C(29)	113.0688

H(52)-C(28)-C(27)	113.0688
H(51)-C(28)-C(29)	110.9782
H(51)-C(28)-C(27)	110.9782
C(29)-C(28)-C(27)	103.2543
H(50)-C(27)-H(49)	105.3706
H(50)-C(27)-C(28)	113.3376
H(50)-C(27)-C(26)	113.3376
H(49)-C(27)-C(28)	111.0921
H(49)-C(27)-C(26)	111.0921
C(28)-C(27)-C(26)	102.7832
H(48)-C(26)-H(47)	106.5722
H(48)-C(26)-O(25)	112.1618
H(48)-C(26)-C(27)	112.1618
H(47)-C(26)-O(25)	110.5932
H(47)-C(26)-C(27)	110.5932
O(25)-C(26)-C(27)	104.8376
C(29)-O(25)-C(26)	105.7316
C(29)-O(25)-Li(20)	111.2143
C(26)-O(25)-Li(20)	109.6559
H(24)-Al(21)-H(23)	93.8943
H(24)-Al(21)-H(22)	109.4882
H(24)-Al(21)-Li(20)	119.4053
H(24)-Al(21)-H(15)	97.4447
H(23)-Al(21)-H(22)	88.4855
H(23)-Al(21)-Li(20)	92.0242
H(23)-Al(21)-H(15)	168.4333
H(22)-Al(21)-Li(20)	130.9308
H(22)-Al(21)-H(15)	89.8764
Li(20)-Al(21)-H(15)	80.4336
O(25)-Li(20)-O(14)	113.5129
O(25)-Li(20)-O(3)	119.9021
O(25)-Li(20)-Al(21)	117.6908
O(14)-Li(20)-O(3)	105.4529
O(14)-Li(20)-Al(21)	86.5755
O(3)-Li(20)-Al(21)	108.2775
H(46)-C(19)-H(45)	109.52
H(46)-C(19)-H(44)	109.4618
H(46)-C(19)-S(16)	109.4618
H(45)-C(19)-H(44)	109.4418
H(45)-C(19)-S(16)	109.4418
H(44)-C(19)-S(16)	109.5
C(19)-S(16)-O(18)	109.4258
C(19)-S(16)-O(17)	109.8391
C(19)-S(16)-N(10)	103.1402
O(18)-S(16)-O(17)	120.0018
O(18)-S(16)-N(10)	106.3198
O(17)-S(16)-N(10)	106.7007

Al(21)-H(15)-C(7)	125.199
Li(20)-O(14)-C(7)	103.8901
H(43)-C(13)-H(42)	89.9719
H(43)-C(13)-C(12)	135.1542
H(43)-C(13)-C(9)	135.1542
H(42)-C(13)-C(12)	120.023
H(42)-C(13)-C(9)	120.023
C(12)-C(13)-C(9)	59.6432
H(41)-C(12)-C(13)	129.3387
H(41)-C(12)-C(9)	141.3982
H(41)-C(12)-C(11)	95.8628
C(13)-C(12)-C(9)	60.2334
C(13)-C(12)-C(11)	122.3091
C(9)-C(12)-C(11)	108.0894
H(40)-C(11)-H(39)	105.7234
H(40)-C(11)-C(12)	112.9874
H(40)-C(11)-N(10)	112.9874
H(39)-C(11)-C(12)	110.9437
H(39)-C(11)-N(10)	110.9437
C(12)-C(11)-N(10)	103.3967
S(16)-N(10)-C(8)	121.1418
S(16)-N(10)-C(11)	121.441
C(8)-N(10)-C(11)	112.1749
C(13)-C(9)-C(12)	60.1234
C(13)-C(9)-C(6)	122.8389
C(13)-C(9)-C(8)	120.9814
C(12)-C(9)-C(6)	124.5549
C(12)-C(9)-C(8)	108.1484
C(6)-C(9)-C(8)	110.7948
H(38)-C(8)-N(10)	110.3717
H(38)-C(8)-C(9)	118.3114
H(38)-C(8)-C(7)	109.8274
N(10)-C(8)-C(9)	102.6724
N(10)-C(8)-C(7)	112.1031
C(9)-C(8)-C(7)	103.2817
H(15)-C(7)-O(14)	112.4872
H(15)-C(7)-C(5)	113.5929
H(15)-C(7)-C(8)	113.0744
O(14)-C(7)-C(5)	108.8998
O(14)-C(7)-C(8)	106.7769
C(5)-C(7)-C(8)	101.2351
H(37)-C(6)-C(9)	113.6377
H(37)-C(6)-C(1)	102.619
H(37)-C(6)-C(5)	114.7495
C(9)-C(6)-C(1)	113.3156
C(9)-C(6)-C(5)	100.8354
C(1)-C(6)-C(5)	112.174

H(36)-C(5)-C(7)	109.2029
H(36)-C(5)-C(6)	116.1543
H(36)-C(5)-C(4)	99.5579
C(7)-C(5)-C(6)	102.5659
C(7)-C(5)-C(4)	118.3369
C(6)-C(5)-C(4)	111.7137
H(35)-C(4)-H(34)	109.7763
H(35)-C(4)-C(5)	109.2384
H(35)-C(4)-O(3)	109.2384
H(34)-C(4)-C(5)	109.3461
H(34)-C(4)-O(3)	109.3461
C(5)-C(4)-O(3)	109.883
Li(20)-O(3)-C(4)	104.1774
Li(20)-O(3)-C(2)	114.0048
C(4)-O(3)-C(2)	108.5677
H(33)-C(2)-H(32)	112.5271
H(33)-C(2)-O(3)	106.9441
H(33)-C(2)-C(1)	106.9441
H(32)-C(2)-O(3)	108.358
H(32)-C(2)-C(1)	108.358
O(3)-C(2)-C(1)	113.7983
H(31)-C(1)-H(30)	114.3609
H(31)-C(1)-C(6)	105.5117
H(31)-C(1)-C(2)	105.5117
H(30)-C(1)-C(6)	107.7351
H(30)-C(1)-C(2)	107.7351
C(6)-C(1)-C(2)	116.2334

dihedral angles

Atoms	Dihedral angles (°)
Li(20)-O(25)-C(29)-C(28)	109.8471
Li(20)-O(25)-C(29)-H(53)	-9.4636
Li(20)-O(25)-C(29)-H(54)	-128.3988
C(26)-O(25)-C(29)-C(28)	-9.1131
C(26)-O(25)-C(29)-H(53)	-128.4238
C(26)-O(25)-C(29)-H(54)	112.641
Li(20)-O(25)-C(26)-C(27)	-137.1557
Li(20)-O(25)-C(26)-H(47)	103.6193
Li(20)-O(25)-C(26)-H(48)	-15.1996
C(29)-O(25)-C(26)-C(27)	-17.1681
C(29)-O(25)-C(26)-H(47)	-136.3931
C(29)-O(25)-C(26)-H(48)	104.788
C(27)-C(28)-C(29)-O(25)	31.955
C(27)-C(28)-C(29)-H(53)	151.2658
C(27)-C(28)-C(29)-H(54)	-89.7991
H(51)-C(28)-C(29)-O(25)	150.9175

H(51)-C(28)-C(29)-H(53)	-89.7718
H(51)-C(28)-C(29)-H(54)	29.1634
H(52)-C(28)-C(29)-O(25)	-90.5835
H(52)-C(28)-C(29)-H(53)	28.7273
H(52)-C(28)-C(29)-H(54)	147.6625
C(26)-C(27)-C(28)-C(29)	-42.721
C(26)-C(27)-C(28)-H(51)	-161.6834
C(26)-C(27)-C(28)-H(52)	79.8175
H(49)-C(27)-C(28)-C(29)	-161.6041
H(49)-C(27)-C(28)-H(51)	79.4334
H(49)-C(27)-C(28)-H(52)	-39.0657
H(50)-C(27)-C(28)-C(29)	79.9831
H(50)-C(27)-C(28)-H(51)	-38.9794
H(50)-C(27)-C(28)-H(52)	-157.4784
O(25)-C(26)-C(27)-C(28)	37.0175
O(25)-C(26)-C(27)-H(49)	155.9007
O(25)-C(26)-C(27)-H(50)	-85.6865
H(47)-C(26)-C(27)-C(28)	156.2426
H(47)-C(26)-C(27)-H(49)	-84.8743
H(47)-C(26)-C(27)-H(50)	33.5385
H(48)-C(26)-C(27)-C(28)	-84.9385
H(48)-C(26)-C(27)-H(49)	33.9446
H(48)-C(26)-C(27)-H(50)	152.3574
Al(21)-Li(20)-O(25)-C(26)	-20.1759
Al(21)-Li(20)-O(25)-C(29)	-136.7581
O(3)-Li(20)-O(25)-C(26)	-155.4416
O(3)-Li(20)-O(25)-C(29)	87.9762
O(14)-Li(20)-O(25)-C(26)	78.7273
O(14)-Li(20)-O(25)-C(29)	-37.8549
C(7)-O(14)-Li(20)-Al(21)	-37.4934
C(7)-O(14)-Li(20)-O(3)	70.531
C(7)-O(14)-Li(20)-O(25)	-156.2866
C(2)-O(3)-Li(20)-Al(21)	141.9281
C(2)-O(3)-Li(20)-O(14)	50.4361
C(2)-O(3)-Li(20)-O(25)	-79.0919
C(4)-O(3)-Li(20)-Al(21)	23.7624
C(4)-O(3)-Li(20)-O(14)	-67.7296
C(4)-O(3)-Li(20)-O(25)	162.7424
H(15)-Al(21)-Li(20)-O(3)	-89.2608
H(15)-Al(21)-Li(20)-O(14)	15.8889
H(15)-Al(21)-Li(20)-O(25)	130.721
H(22)-Al(21)-Li(20)-O(3)	-7.8323
H(22)-Al(21)-Li(20)-O(14)	97.3173
H(22)-Al(21)-Li(20)-O(25)	-147.8506
H(23)-Al(21)-Li(20)-O(3)	81.9181
H(23)-Al(21)-Li(20)-O(14)	-172.9323
H(23)-Al(21)-Li(20)-O(25)	-58.1002

H(24)-Al(21)-Li(20)-O(3)	177.538
H(24)-Al(21)-Li(20)-O(14)	-77.3124
H(24)-Al(21)-Li(20)-O(25)	37.5197
Li(20)-Al(21)-H(15)-C(7)	18.9119
H(22)-Al(21)-H(15)-C(7)	-112.7514
H(23)-Al(21)-H(15)-C(7)	-30.9358
H(24)-Al(21)-H(15)-C(7)	137.6051
N(10)-S(16)-C(19)-H(44)	-180
N(10)-S(16)-C(19)-H(45)	-60.0364
N(10)-S(16)-C(19)-H(46)	59.9996
O(17)-S(16)-C(19)-H(44)	-66.5503
O(17)-S(16)-C(19)-H(45)	53.4133
O(17)-S(16)-C(19)-H(46)	173.4493
O(18)-S(16)-C(19)-H(44)	67.1513
O(18)-S(16)-C(19)-H(45)	-172.8851
O(18)-S(16)-C(19)-H(46)	-52.8491
C(11)-N(10)-S(16)-O(17)	-47.5473
C(11)-N(10)-S(16)-O(18)	-176.7312
C(11)-N(10)-S(16)-C(19)	68.1676
C(8)-N(10)-S(16)-O(17)	160.0415
C(8)-N(10)-S(16)-O(18)	30.8576
C(8)-N(10)-S(16)-C(19)	-84.2436
C(8)-C(7)-H(15)-Al(21)	-176.0216
C(5)-C(7)-H(15)-Al(21)	69.3236
O(14)-C(7)-H(15)-Al(21)	-54.9632
C(8)-C(7)-O(14)-Li(20)	-171.2128
C(5)-C(7)-O(14)-Li(20)	-62.652
H(15)-C(7)-O(14)-Li(20)	64.188
C(11)-C(12)-C(13)-C(9)	-93.5279
C(11)-C(12)-C(13)-H(42)	157.1276
C(11)-C(12)-C(13)-H(43)	31.6628
C(9)-C(12)-C(13)-H(42)	-109.3445
C(9)-C(12)-C(13)-H(43)	125.1907
H(41)-C(12)-C(13)-C(9)	134.0498
H(41)-C(12)-C(13)-H(42)	24.7053
H(41)-C(12)-C(13)-H(43)	-100.7595
C(8)-C(9)-C(13)-C(12)	94.2476
C(8)-C(9)-C(13)-H(42)	-156.4079
C(8)-C(9)-C(13)-H(43)	-30.9431
C(6)-C(9)-C(13)-C(12)	-114.0643
C(6)-C(9)-C(13)-H(42)	-4.7198
C(6)-C(9)-C(13)-H(43)	120.745
C(12)-C(9)-C(13)-H(42)	109.3445
C(12)-C(9)-C(13)-H(43)	-125.1907
C(8)-C(9)-C(12)-C(11)	1.5708
C(8)-C(9)-C(12)-C(13)	-115.8762
C(8)-C(9)-C(12)-H(41)	127.1191

C(6)-C(9)-C(12)-C(11)	-131.2246
C(6)-C(9)-C(12)-C(13)	111.3285
C(6)-C(9)-C(12)-H(41)	-5.6762
C(13)-C(9)-C(12)-C(11)	117.4469
C(13)-C(9)-C(12)-H(41)	-117.0047
C(7)-C(8)-N(10)-C(11)	134.1167
C(7)-C(8)-N(10)-S(16)	-71.1407
C(9)-C(8)-N(10)-C(11)	23.9061
C(9)-C(8)-N(10)-S(16)	178.6487
H(38)-C(8)-N(10)-C(11)	-103.1095
H(38)-C(8)-N(10)-S(16)	51.6331
N(10)-C(11)-C(12)-C(9)	12.2916
N(10)-C(11)-C(12)-C(13)	77.9997
N(10)-C(11)-C(12)-H(41)	-137.025
H(39)-C(11)-C(12)-C(9)	131.2779
H(39)-C(11)-C(12)-C(13)	-163.014
H(39)-C(11)-C(12)-H(41)	-18.0387
H(40)-C(11)-C(12)-C(9)	-110.1961
H(40)-C(11)-C(12)-C(13)	-44.4881
H(40)-C(11)-C(12)-H(41)	100.4873
C(8)-N(10)-C(11)-C(12)	-23.1537
C(8)-N(10)-C(11)-H(39)	-142.14
C(8)-N(10)-C(11)-H(40)	99.334
S(16)-N(10)-C(11)-C(12)	-177.8104
S(16)-N(10)-C(11)-H(39)	63.2033
S(16)-N(10)-C(11)-H(40)	-55.3226
C(5)-C(6)-C(9)-C(8)	20.0282
C(5)-C(6)-C(9)-C(12)	151.7945
C(5)-C(6)-C(9)-C(13)	-134.1902
C(1)-C(6)-C(9)-C(8)	-100.0336
C(1)-C(6)-C(9)-C(12)	31.7326
C(1)-C(6)-C(9)-C(13)	105.7479
H(37)-C(6)-C(9)-C(8)	143.3309
H(37)-C(6)-C(9)-C(12)	-84.9029
H(37)-C(6)-C(9)-C(13)	-10.8876
C(4)-C(5)-C(7)-C(8)	169.5642
C(4)-C(5)-C(7)-O(14)	57.2885
C(4)-C(5)-C(7)-H(15)	-68.9165
C(6)-C(5)-C(7)-C(8)	46.1383
C(6)-C(5)-C(7)-O(14)	-66.1374
C(6)-C(5)-C(7)-H(15)	167.6576
H(36)-C(5)-C(7)-C(8)	-77.631
H(36)-C(5)-C(7)-O(14)	170.0932
H(36)-C(5)-C(7)-H(15)	43.8882
C(7)-C(8)-C(9)-C(6)	8.2093
C(7)-C(8)-C(9)-C(12)	-131.5167
C(7)-C(8)-C(9)-C(13)	162.9796

N(10)-C(8)-C(9)-C(6)	124.9111
N(10)-C(8)-C(9)-C(12)	-14.8149
N(10)-C(8)-C(9)-C(13)	-80.3186
H(38)-C(8)-C(9)-C(6)	-113.3259
H(38)-C(8)-C(9)-C(12)	106.9481
H(38)-C(8)-C(9)-C(13)	41.4444
C(5)-C(7)-C(8)-C(9)	-32.7797
C(5)-C(7)-C(8)-N(10)	-142.6048
C(5)-C(7)-C(8)-H(38)	94.3138
O(14)-C(7)-C(8)-C(9)	81.0996
O(14)-C(7)-C(8)-N(10)	-28.7256
O(14)-C(7)-C(8)-H(38)	-151.807
H(15)-C(7)-C(8)-C(9)	-154.6611
H(15)-C(7)-C(8)-N(10)	95.5138
H(15)-C(7)-C(8)-H(38)	-27.5676
C(5)-C(6)-C(1)-C(2)	36.3779
C(5)-C(6)-C(1)-H(30)	157.3179
C(5)-C(6)-C(1)-H(31)	-80.1211
C(9)-C(6)-C(1)-C(2)	149.7506
C(9)-C(6)-C(1)-H(30)	-89.3094
C(9)-C(6)-C(1)-H(31)	33.2516
H(37)-C(6)-C(1)-C(2)	-87.2999
H(37)-C(6)-C(1)-H(30)	33.6401
H(37)-C(6)-C(1)-H(31)	156.2011
C(4)-C(5)-C(6)-C(1)	-47.1321
C(4)-C(5)-C(6)-C(9)	-168.0074
C(4)-C(5)-C(6)-H(37)	69.4616
C(7)-C(5)-C(6)-C(1)	80.6175
C(7)-C(5)-C(6)-C(9)	-40.2579
C(7)-C(5)-C(6)-H(37)	-162.7888
H(36)-C(5)-C(6)-C(1)	-160.3774
H(36)-C(5)-C(6)-C(9)	78.7472
H(36)-C(5)-C(6)-H(37)	-43.7837
C(6)-C(5)-C(4)-O(3)	63.8596
C(6)-C(5)-C(4)-H(34)	-176.1183
C(6)-C(5)-C(4)-H(35)	-55.9636
C(7)-C(5)-C(4)-O(3)	-54.8789
C(7)-C(5)-C(4)-H(34)	65.1431
C(7)-C(5)-C(4)-H(35)	-174.7021
H(36)-C(5)-C(4)-O(3)	-172.8976
H(36)-C(5)-C(4)-H(34)	-52.8756
H(36)-C(5)-C(4)-H(35)	67.2792
C(2)-O(3)-C(4)-C(5)	-65.2011
C(2)-O(3)-C(4)-H(34)	174.7769
C(2)-O(3)-C(4)-H(35)	54.6221
Li(20)-O(3)-C(4)-C(5)	56.635
Li(20)-O(3)-C(4)-H(34)	-63.387

Li(20)-O(3)-C(4)-H(35)	176.4582
C(1)-C(2)-O(3)-C(4)	53.5361
C(1)-C(2)-O(3)-Li(20)	-62.0856
H(32)-C(2)-O(3)-C(4)	-67.0631
H(32)-C(2)-O(3)-Li(20)	177.3152
H(33)-C(2)-O(3)-C(4)	171.3977
H(33)-C(2)-O(3)-Li(20)	55.776
C(6)-C(1)-C(2)-O(3)	-39.8347
C(6)-C(1)-C(2)-H(32)	80.7644
C(6)-C(1)-C(2)-H(33)	-157.6963
H(30)-C(1)-C(2)-O(3)	-160.7747
H(30)-C(1)-C(2)-H(32)	-40.1755
H(30)-C(1)-C(2)-H(33)	81.3637
H(31)-C(1)-C(2)-O(3)	76.6643
H(31)-C(1)-C(2)-H(32)	-162.7365
H(31)-C(1)-C(2)-H(33)	-41.1973

5.2.2 Addition of organometallic reagents

- **Structure elucidation of compound 411:**

- **^{1}H NMR:** Protons of the tetracyclic framework were assigned as already described for compound **300**. Phenyl signals are distinguished by HMBC; correlations: Cf-(H_i+H_i'), C_g-(H_i+H_i'),
- C_h-H_j.

^{1}H NMR in $CDCl_3$ of compound 411

NOESY in $CDCl_3$ of compound 411

HMBC in $CDCl_3$ of compound 411 (zoomed on 6.70-8.10 ppm; 85.0-150.0 ppm)

Crystallographic data for compound 413

Experimental

An NMR tube was loaded with compound **413** (ca. 10 mg) and a minimum amount of EtOAc (ca. 0.2 ml) was added. The mixture was heated until dissolution, then heptane (ca. 0.4 ml) was slowly added with a pipette in order to form a biphasic mixture. The NMR tube was kept for 7 days at rt until the formation of crystals (see left image).

A suitable crystal was selected and loaded on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 100.00(10) K during data collection. Using Olex2, the

structure was solved with the SHELXT, structure solution program using Intrinsic Phasing and refined with the SHELXL, refinement package using Least Squares minimisation.

Crystal Data for $C_{19}H_{25}NO_4S$ (*M* =363.46 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 9.8473(4) Å, *b* = 11.0719(5) Å, *c* = 16.0747(6) Å, *β* = 96.073(4)°, *V* = 1742.76(12) Å^3, *Z* = 4, *T* = 100.01(10) K, μ(Cu Kα) = 1.855 mm^{-1}, *Dcalc* = 1.385 g/cm^3, 7564 reflections measured (9.718° ≤ 2Θ ≤ 145.98°), 3378 unique (R_{int} = 0.0253, R_{sigma} = 0.0303) which were used in all calculations. The final R_1 was 0.0364 (I > 2σ(I)) and wR_2 was 0.0970 (all data).

Table 1 Crystal data and structure refinement for **413**

Identification code	ELGI02-076
Empirical formula	$C_{19}H_{25}NO_4S$
Formula weight	363.46
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.8473(4)
b/Å	11.0719(5)
c/Å	16.0747(6)
α/°	90
β/°	96.073(4)
γ/°	90
Volume/Å^3	1742.76(12)
Z	4
ρ_{calc}g/cm^3	1.385
μ/mm^{-1}	1.855
F(000)	776.0
Crystal size/mm^3	0.237 × 0.192 × 0.116
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.718 to 145.98
Index ranges	-9 ≤ h ≤ 12, -10 ≤ k ≤ 13, -19 ≤ l ≤ 17
Reflections collected	7564
Independent reflections	3378 [R_{int} = 0.0253, R_{sigma} = 0.0303]
Data/restraints/parameters	3378/0/231
Goodness-of-fit on F^2	1.071

Final R indexes [I>=2σ (I)]	R_1 = 0.0364, wR_2 = 0.0920
Final R indexes [all data]	R_1 = 0.0415, wR_2 = 0.0970
Largest diff. peak/hole / e Å^{-3}	0.29/-0.43

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **413**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	4641.6(17)	72.2(15)	3846.7(10)	21.1(3)
C2	4720.0(16)	843.0(14)	2329.1(9)	17.3(3)
C3	5428.3(16)	236.9(14)	3098.3(9)	17.4(3)
C4	5577.3(15)	1134.6(14)	3812.9(9)	15.1(3)
C5	6840.4(15)	1445.8(14)	4393.6(9)	15.9(3)
C6	7917.2(17)	466.9(15)	4588.6(10)	21.0(3)
C7	8817.9(17)	291.6(15)	3885.9(10)	21.7(3)
C8	8272.6(16)	2176.9(15)	3286.7(10)	18.9(3)
C9	7405.0(15)	2560.7(14)	3969.7(9)	15.0(3)
C10	6128.2(15)	3282.7(14)	3627.7(9)	14.3(3)
C11	4945.3(15)	2322.0(14)	3496.6(9)	13.7(3)
C12	1660.3(17)	2322.6(17)	2575.5(12)	25.9(4)
C13	5742.2(15)	4224.9(14)	4268.0(9)	16.2(3)
C14	6779.3(15)	5218.6(14)	4448.9(9)	16.0(3)
C15	6783.0(16)	6215.0(15)	3922.2(10)	19.6(3)
C16	7743.5(19)	7124.3(15)	4068.1(11)	24.5(4)
C17	8715.1(18)	7063.6(15)	4758.6(11)	24.3(4)
C18	8720.0(17)	6079.1(16)	5291.1(10)	22.1(3)
C19	7762.8(16)	5164.6(15)	5140.1(10)	18.9(3)
N1	4416.5(13)	2074.7(12)	2621.5(8)	15.6(3)
O1	9357.1(11)	1404.9(11)	3618.8(7)	22.9(3)
O2	6383.5(12)	3860.7(10)	2868.2(6)	17.4(2)
O3	3034.0(12)	2568.3(12)	1301.8(7)	25.7(3)
O4	3367.9(12)	4075.9(10)	2446.8(7)	23.2(3)
S1	3150.5(4)	2843.0(3)	2175.4(2)	17.17(12)

Table 3 Anisotropic Displacement Parameters (Å^2×10^3) for **413**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	24.1(8)	19.6(8)	18.9(7)	3.5(6)	-1.9(6)	-7.1(7)
C2	19.3(8)	16.1(8)	15.6(7)	-2.7(6)	-1.7(6)	-0.6(6)
C3	19.0(8)	14.6(8)	17.6(7)	-1.3(6)	-3.6(6)	-1.6(6)
C4	15.9(7)	14.6(8)	14.2(7)	-0.4(6)	-0.7(5)	-2.4(6)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **413**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C5	17.3(7)	16.6(8)	13.2(7)	-0.5(6)	-1.4(5)	-0.4(6)
C6	23.1(8)	19.1(8)	19.2(7)	-0.2(6)	-5.7(6)	2.1(7)
C7	19.5(8)	18.9(8)	25.1(8)	-3.1(7)	-4.3(6)	5.1(6)
C8	15.9(8)	19.1(8)	22.0(8)	0.3(6)	3.1(6)	0.9(6)
C9	12.9(7)	15.9(7)	15.7(7)	-2.5(6)	-1.5(5)	-1.1(6)
C10	14.6(7)	14.6(7)	13.4(7)	-0.4(6)	1.0(5)	-1.9(6)
C11	13.5(7)	15.5(7)	11.8(7)	-1.2(5)	-0.5(5)	-1.1(6)
C12	14.3(8)	27.2(9)	35.8(9)	-0.4(8)	1.1(7)	-0.5(7)
C13	16.2(7)	15.7(8)	17.0(7)	-2.1(6)	3.0(6)	-0.5(6)
C14	16.6(7)	14.3(8)	17.3(7)	-3.7(6)	3.5(6)	0.3(6)
C15	21.5(8)	16.5(8)	19.9(7)	-1.7(6)	-2.4(6)	1.1(6)
C16	33.3(10)	16.1(8)	23.5(8)	1.4(6)	1.1(7)	-3.2(7)
C17	26.1(9)	18.0(8)	28.1(9)	-4.7(7)	0.2(7)	-7.9(7)
C18	20.8(8)	22.8(9)	21.2(8)	-3.7(7)	-4.4(6)	-0.3(7)
C19	22.8(8)	16.3(8)	17.5(7)	-1.3(6)	0.8(6)	0.5(6)
N1	16.0(6)	15.0(7)	14.6(6)	-1.4(5)	-4.0(5)	0.5(5)
O1	14.6(5)	23.0(6)	30.7(6)	-2.7(5)	0.6(5)	2.6(5)
O2	18.8(6)	19.3(6)	14.3(5)	2.4(4)	3.0(4)	-2.0(5)
O3	28.5(7)	30.0(7)	16.7(6)	1.9(5)	-6.4(5)	4.6(5)
O4	22.5(6)	15.4(6)	30.3(6)	0.4(5)	-4.5(5)	1.6(5)
S1	15.9(2)	16.8(2)	17.7(2)	1.28(14)	-3.23(14)	0.83(14)

Table 4 Bond Lengths for **413**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C3	1.509(2)	C10	C13	1.541(2)
C1	C4	1.499(2)	C10	O2	1.4241(17)
C2	C3	1.511(2)	C11	N1	1.4731(18)
C2	N1	1.483(2)	C12	S1	1.7604(18)
C3	C4	1.514(2)	C13	C14	1.508(2)
C4	C5	1.514(2)	C14	C15	1.391(2)
C4	C11	1.519(2)	C14	C19	1.396(2)
C5	C6	1.525(2)	C15	C16	1.384(2)
C5	C9	1.542(2)	C16	C17	1.388(2)
C6	C7	1.521(2)	C17	C18	1.386(2)
C7	O1	1.426(2)	C18	C19	1.387(2)
C8	C9	1.521(2)	N1	S1	1.6133(13)
C8	O1	1.4267(19)	O3	S1	1.4295(12)

Table 4 Bond Lengths for **413**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C9	C10	1.541(2)	O4	S1	1.4421(12)
C10	C11	1.575(2)			

Table 5 Bond Angles for **413**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C4	C1	C3	60.45(10)	O2	C10	C11	112.58(11)
N1	C2	C3	103.89(12)	O2	C10	C13	110.29(12)
C1	C3	C2	118.32(14)	C4	C11	C10	105.59(12)
C1	C3	C4	59.43(10)	N1	C11	C4	104.46(12)
C2	C3	C4	109.18(13)	N1	C11	C10	115.79(12)
C1	C4	C3	60.12(10)	C14	C13	C10	114.38(12)
C1	C4	C5	128.65(13)	C15	C14	C13	120.43(14)
C1	C4	C11	117.37(13)	C15	C14	C19	118.18(15)
C3	C4	C11	108.11(12)	C19	C14	C13	121.39(14)
C5	C4	C3	128.65(13)	C16	C15	C14	121.29(15)
C5	C4	C11	106.87(12)	C15	C16	C17	120.07(16)
C4	C5	C6	118.22(13)	C18	C17	C16	119.28(16)
C4	C5	C9	102.76(12)	C17	C18	C19	120.54(15)
C6	C5	C9	112.60(13)	C18	C19	C14	120.63(15)
C7	C6	C5	112.67(13)	C2	N1	S1	121.07(10)
O1	C7	C6	112.23(13)	C11	N1	C2	114.26(12)
O1	C8	C9	110.64(13)	C11	N1	S1	120.33(10)
C8	C9	C5	110.59(13)	C7	O1	C8	110.04(12)
C8	C9	C10	112.74(12)	N1	S1	C12	107.45(8)
C10	C9	C5	104.73(12)	O3	S1	C12	107.82(8)
C9	C10	C11	105.14(12)	O3	S1	N1	107.60(7)
C13	C10	C9	111.25(12)	O3	S1	O4	119.50(8)
C13	C10	C11	108.38(12)	O4	S1	C12	107.58(8)
O2	C10	C9	109.12(12)	O4	S1	N1	106.35(7)

Table 6 Hydrogen Bonds for **413**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O4	0.86(2)	2.18(2)	2.9846(16)	155(2)
O2	H2	S1	0.86(2)	2.80(2)	3.4490(12)	134(2)

Table 7 Torsion Angles for **413**

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	C3	C4	C5	117.57(18)	C8	C9	C10	C11	95.01(14)

Table 7 Torsion Angles for **413**

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	C3	C4	C11	-111.71(14)	C8	C9	C10	C13	-147.88(13)
C1	C4	C5	C6	49.9(2)	C8	C9	C10	O2	-25.98(17)
C1	C4	C5	C9	174.51(15)	C9	C5	C6	C7	-41.28(18)
C1	C4	C11	C10	173.85(12)	C9	C8	O1	C7	66.39(16)
C1	C4	C11	N1	-63.58(16)	C9	C10	C11	C4	3.17(14)
C2	C3	C4	C1	112.21(15)	C9	C10	C11	N1	-111.83(14)
C2	C3	C4	C5	-130.22(16)	C9	C10	C13	C14	65.64(17)
C2	C3	C4	C11	0.49(17)	C10	C11	N1	C2	112.46(15)
C2	N1	S1	C12	80.41(14)	C10	C11	N1	S1	-90.70(14)
C2	N1	S1	O3	-35.45(14)	C10	C13	C14	C15	83.03(18)
C2	N1	S1	O4	-164.62(12)	C10	C13	C14	C19	-96.52(17)
C3	C1	C4	C5	-117.57(18)	C11	C4	C5	C6	-161.11(13)
C3	C1	C4	C11	96.10(14)	C11	C4	C5	C9	-36.44(15)
C3	C2	N1	C11	3.46(17)	C11	C10	C13	C14	-179.24(12)
C3	C2	N1	S1	-153.19(11)	C11	N1	S1	C12	-74.84(13)
C3	C4	C5	C6	-29.9(2)	C11	N1	S1	O3	169.30(11)
C3	C4	C5	C9	94.73(17)	C11	N1	S1	O4	40.13(13)
C3	C4	C11	C10	-121.04(12)	C13	C10	C11	C4	-115.87(13)
C3	C4	C11	N1	1.53(16)	C13	C10	C11	N1	129.12(13)
C4	C1	C3	C2	-96.60(15)	C13	C14	C15	C16	-178.68(15)
C4	C5	C6	C7	78.39(17)	C13	C14	C19	C18	179.17(14)
C4	C5	C9	C8	-83.79(14)	C14	C15	C16	C17	-1.1(3)
C4	C5	C9	C10	37.93(14)	C15	C14	C19	C18	-0.4(2)
C4	C11	N1	C2	-3.18(16)	C15	C16	C17	C18	0.7(3)
C4	C11	N1	S1	153.65(10)	C16	C17	C18	C19	-0.3(3)
C5	C4	C11	C10	20.75(15)	C17	C18	C19	C14	0.1(3)
C5	C4	C11	N1	143.32(12)	C19	C14	C15	C16	0.9(2)
C5	C6	C7	O1	50.01(18)	N1	C2	C3	C1	62.61(17)
C5	C9	C10	C11	-25.29(14)	N1	C2	C3	C4	-2.28(16)
C5	C9	C10	C13	91.83(14)	O1	C8	C9	C5	-56.90(16)
C5	C9	C10	O2	-146.27(12)	O1	C8	C9	C10	-173.77(12)
C6	C5	C9	C8	44.49(17)	O2	C10	C11	C4	121.86(13)
C6	C5	C9	C10	166.21(12)	O2	C10	C11	N1	6.86(18)
C6	C7	O1	C8	-62.58(16)	O2	C10	C13	C14	-55.58(17)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **413**.

Atom	*x*	*y*	*z*	U(eq)
H1A	3665.9	222.87	3771.65	25
H1B	4924.73	-572.79	4235.2	25
H2A	5311.77	874.17	1884.01	21
H2B	3886.82	419.5	2128.71	21
H3	6189.99	-311.59	3030.71	21
H5	6539.25	1711.67	4925.89	19
H6A	8486.27	681.02	5096.88	25
H6B	7465.24	-289.78	4688.42	25
H7A	9566.69	-243.99	4075.65	26
H7B	8288.39	-90.31	3414.67	26
H8A	7706.02	1756.12	2848.72	23
H8B	8649.2	2886.97	3042.13	23
H9	7958.53	3044.94	4388.63	18
H11	4195.85	2546.11	3821.43	16
H12A	1551.16	1474.33	2464.28	39
H12B	883.24	2751.36	2312.06	39
H12C	1733.7	2458.42	3168.42	39
H13A	4874.1	4585.64	4060.74	19
H13B	5618.5	3814.18	4787.59	19
H15	6127.34	6271.4	3462.95	24
H16	7737.88	7776.51	3703.25	29
H17	9355.73	7677.01	4862.57	29
H18	9370.39	6031.05	5753.61	26
H19	7776.46	4509.31	5502.8	23
H2	5600(30)	4070(20)	2627(14)	41(6)

3D-model of TS for synthesis of 428 via addition of MeMgBr to ketone 283

Software	MarvinSketch 21.18
Force field	MMFF94
Optimization limit	Normal
Max number of conformers	100
Diversity limit	0.1
Timelimit	900
Conformer energy	24.66 kcal/mol

Image visualised with Chem3D 12.0.2:

atom coordinates

Atoms	x (Å)	y (Å)	z (Å)
C(1)	-4.804	-0.4783	-4.8703
C(2)	-7.7473	-2.452	-2.5728
O(3)	-7.4337	-1.7142	1.1885
C(4)	-7.1742	1.9538	2.3
C(5)	-3.8577	3.8618	0.6002
C(6)	-3.8328	3.4907	-3.6319
C(7)	-0.0524	2.2698	1.6866
C(8)	2.6274	3.827	-1.2332
C(9)	0.1009	4.5416	-4.5023
N(10)	5.2936	1.1926	-2.7568
C(11)	5.5259	1.4618	-6.8058
C(12)	1.9966	3.2844	-7.9273
C(13)	1.1586	7.3099	-7.3982
S(14)	8.9064	-0.3445	-0.4075
O(15)	7.7238	-0.94	3.3474
O(16)	10.5529	-3.2739	-2.5188
C(17)	11.9771	3.461	-0.4496
C(18)	1.0702	2.4063	5.7308
O(19)	-0.2594	-1.6429	1.375

Mg(20)	1.0734	-2.8845	5.7001
Br(21)	-1.3234	-8.4283	3.8459
Br(22)	-3.8977	-3.3069	9.6219
Mg(23)	-6.687	-5.2623	4.3746
C(24)	-10.9372	-8.3333	5.3043
H(25)	-5.1681	-0.4284	-5.9209
H(26)	-3.8714	-1.072	-4.7417
H(27)	-8.7513	-2.1183	-2.9184
H(28)	-7.6062	-3.5469	-2.7139
H(29)	-8.0977	2.4908	1.9875
H(30)	-7.0551	1.9727	3.4064
H(31)	-3.9777	4.9009	0.9806
H(32)	-4.5874	4.1163	-4.1591
H(33)	3.1941	4.6642	-0.7678
H(34)	5.608	0.4502	-7.2627
H(35)	6.4213	2.0316	-7.1411
H(36)	1.8578	2.6802	-8.819
H(37)	0.391	7.7891	-7.9987
H(38)	1.7403	8.2269	-7.4123
H(39)	12.906	3.195	0.1028
H(40)	12.2328	3.7191	-1.5017
H(41)	11.4916	4.3347	0.0401
H(42)	2.0651	2.8682	5.9191
H(43)	0.4831	2.9842	6.4792
H(44)	-1.1133	-7.09	3.2352
H(45)	-3.3661	-2.8559	8.3096
H(46)	-11.8459	-7.6956	5.3846
H(47)	-11.0636	-9.0545	4.466
H(48)	-10.7905	-8.8913	6.256

bond lengths

Atoms	**Bond lenght (Å)**
C(24)-H(48)	1.113
C(24)-H(47)	1.113
C(24)-H(46)	1.113
Br(22)-H(45)	1.486
Br(21)-H(44)	1.486
C(18)-H(43)	1.113
C(18)-H(42)	1.113
C(17)-H(41)	1.113
C(17)-H(40)	1.113
C(17)-H(39)	1.113
C(13)-H(38)	1.086
C(13)-H(37)	1.086
C(12)-H(36)	1.086

C(11)-H(35)	1.113
C(11)-H(34)	1.113
C(8)-H(33)	1.113
C(6)-H(32)	1.113
C(5)-H(31)	1.113
C(4)-H(30)	1.113
C(4)-H(29)	1.113
C(2)-H(28)	1.113
C(2)-H(27)	1.113
C(1)-H(26)	1.113
C(1)-H(25)	1.113
C(18)-Mg(20)	5.2909
O(3)-Mg(23)	4.8268
Mg(23)-C(24)	5.3254
Mg(23)-Br(22)	6.256
Mg(23)-Br(21)	6.2507
Mg(20)-Br(22)	6.3459
Mg(20)-Br(21)	6.3179
O(19)-Mg(20)	4.693
C(7)-O(19)	3.9305
C(7)-C(18)	4.1993
S(14)-C(17)	4.8901
S(14)-O(16)	3.9686
S(14)-O(15)	3.9815
N(10)-S(14)	4.5754
C(12)-C(13)	4.1457
C(9)-C(13)	4.1435
C(9)-C(12)	4.1116
C(8)-N(10)	4.046
C(11)-C(12)	4.1274
N(10)-C(11)	4.0646
C(6)-C(9)	4.1637
C(5)-C(7)	4.2656
C(8)-C(9)	4.193
C(7)-C(8)	4.2581
C(6)-C(1)	4.2696
C(5)-C(6)	4.2484
C(5)-C(4)	4.1868
O(3)-C(4)	3.8415
C(2)-O(3)	3.8458
C(1)-C(2)	4.2234

bond angles

Atoms	Bond angles (°)
C(24)-H(48)	1.113

C(24)-H(47)	1.113
C(24)-H(46)	1.113
Br(22)-H(45)	1.486
Br(21)-H(44)	1.486
C(18)-H(43)	1.113
C(18)-H(42)	1.113
C(17)-H(41)	1.113
C(17)-H(40)	1.113
C(17)-H(39)	1.113
C(13)-H(38)	1.086
C(13)-H(37)	1.086
C(12)-H(36)	1.086
C(11)-H(35)	1.113
C(11)-H(34)	1.113
C(8)-H(33)	1.113
C(6)-H(32)	1.113
C(5)-H(31)	1.113
C(4)-H(30)	1.113
C(4)-H(29)	1.113
C(2)-H(28)	1.113
C(2)-H(27)	1.113
C(1)-H(26)	1.113
C(1)-H(25)	1.113
C(18)-Mg(20)	5.2909
O(3)-Mg(23)	4.8268
Mg(23)-C(24)	5.3254
Mg(23)-Br(22)	6.256
Mg(23)-Br(21)	6.2507
Mg(20)-Br(22)	6.3459
Mg(20)-Br(21)	6.3179
O(19)-Mg(20)	4.693
C(7)-O(19)	3.9305
C(7)-C(18)	4.1993
S(14)-C(17)	4.8901
S(14)-O(16)	3.9686
S(14)-O(15)	3.9815
N(10)-S(14)	4.5754
C(12)-C(13)	4.1457
C(9)-C(13)	4.1435
C(9)-C(12)	4.1116
C(8)-N(10)	4.046
C(11)-C(12)	4.1274
N(10)-C(11)	4.0646
C(6)-C(9)	4.1637
C(5)-C(7)	4.2656
C(8)-C(9)	4.193
C(7)-C(8)	4.2581

C(6)-C(1)	4.2696
C(5)-C(6)	4.2484
C(5)-C(4)	4.1868
O(3)-C(4)	3.8415
C(2)-O(3)	3.8458
C(1)-C(2)	4.2234
H(48)-C(24)-H(47)	109.52
H(48)-C(24)-H(46)	109.4618
H(48)-C(24)-Mg(23)	109.4618
H(47)-C(24)-H(46)	109.4418
H(47)-C(24)-Mg(23)	109.4418
H(46)-C(24)-Mg(23)	109.5
O(3)-Mg(23)-C(24)	114.5619
O(3)-Mg(23)-Br(22)	113.1331
O(3)-Mg(23)-Br(21)	116.6947
C(24)-Mg(23)-Br(22)	112.9332
C(24)-Mg(23)-Br(21)	114.0489
Br(22)-Mg(23)-Br(21)	81.1804
H(45)-Br(22)-Mg(23)	60.8987
H(45)-Br(22)-Mg(20)	32.1981
Mg(23)-Br(22)-Mg(20)	81.4724
H(44)-Br(21)-Mg(23)	72.5387
H(44)-Br(21)-Mg(20)	43.672
Mg(23)-Br(21)-Mg(20)	81.7357
C(18)-Mg(20)-Br(22)	93.5834
C(18)-Mg(20)-Br(21)	151.5132
C(18)-Mg(20)-O(19)	74.9665
Br(22)-Mg(20)-Br(21)	79.9673
Br(22)-Mg(20)-O(19)	111.3887
Br(21)-Mg(20)-O(19)	81.601
Mg(20)-O(19)-C(7)	100.0987
H(43)-C(18)-H(42)	98.1742
H(43)-C(18)-Mg(20)	121.5652
H(43)-C(18)-C(7)	121.5652
H(42)-C(18)-Mg(20)	114.5485
H(42)-C(18)-C(7)	114.5485
Mg(20)-C(18)-C(7)	87.8262
H(41)-C(17)-H(40)	109.52
H(41)-C(17)-H(39)	109.4618
H(41)-C(17)-S(14)	109.4618
H(40)-C(17)-H(39)	109.4418
H(40)-C(17)-S(14)	109.4418
H(39)-C(17)-S(14)	109.5
C(17)-S(14)-O(16)	108.0186
C(17)-S(14)-O(15)	108.1212
C(17)-S(14)-N(10)	103.2957
O(16)-S(14)-O(15)	120.9672

O(16)-S(14)-N(10)	107.6025
O(15)-S(14)-N(10)	107.4548
H(38)-C(13)-H(37)	89.9376
H(38)-C(13)-C(12)	135.2275
H(38)-C(13)-C(9)	135.2275
H(37)-C(13)-C(12)	120.0511
H(37)-C(13)-C(9)	120.0511
C(12)-C(13)-C(9)	59.4733
H(36)-C(12)-C(13)	128.2595
H(36)-C(12)-C(9)	142.6661
H(36)-C(12)-C(11)	94.9732
C(13)-C(12)-C(9)	60.2365
C(13)-C(12)-C(11)	124.5375
C(9)-C(12)-C(11)	107.6336
H(35)-C(11)-H(34)	106.3944
H(35)-C(11)-C(12)	112.3328
H(35)-C(11)-N(10)	112.3328
H(34)-C(11)-C(12)	110.6659
H(34)-C(11)-N(10)	110.6659
C(12)-C(11)-N(10)	104.5399
S(14)-N(10)-C(8)	123.074
S(14)-N(10)-C(11)	119.2498
C(8)-N(10)-C(11)	111.6949
C(13)-C(9)-C(12)	60.2902
C(13)-C(9)-C(6)	123.773
C(13)-C(9)-C(8)	120.3289
C(12)-C(9)-C(6)	122.179
C(12)-C(9)-C(8)	108.6353
C(6)-C(9)-C(8)	111.3016
H(33)-C(8)-N(10)	108.1629
H(33)-C(8)-C(9)	120.3087
H(33)-C(8)-C(7)	107.9866
N(10)-C(8)-C(9)	102.3827
N(10)-C(8)-C(7)	115.7739
C(9)-C(8)-C(7)	102.5758
O(19)-C(7)-C(18)	97.0528
O(19)-C(7)-C(5)	107.7193
O(19)-C(7)-C(8)	110.0492
C(18)-C(7)-C(5)	118.1403
C(18)-C(7)-C(8)	118.7014
C(5)-C(7)-C(8)	104.4955
H(32)-C(6)-C(9)	113.556
H(32)-C(6)-C(1)	103.3505
H(32)-C(6)-C(5)	114.7586
C(9)-C(6)-C(1)	112.8859
C(9)-C(6)-C(5)	101.054
C(1)-C(6)-C(5)	111.6417

H(31)-C(5)-C(7)	110.9501
H(31)-C(5)-C(6)	115.0031
H(31)-C(5)-C(4)	101.6116
C(7)-C(5)-C(6)	102.4674
C(7)-C(5)-C(4)	115.6694
C(6)-C(5)-C(4)	111.6706
H(30)-C(4)-H(29)	111.0852
H(30)-C(4)-C(5)	108.1238
H(30)-C(4)-O(3)	108.1238
H(29)-C(4)-C(5)	108.8674
H(29)-C(4)-O(3)	108.8674
C(5)-C(4)-O(3)	111.7885
Mg(23)-O(3)-C(4)	120.0297
Mg(23)-O(3)-C(2)	121.1432
C(4)-O(3)-C(2)	118.1431
H(28)-C(2)-H(27)	111.7159
H(28)-C(2)-O(3)	107.6018
H(28)-C(2)-C(1)	107.6018
H(27)-C(2)-O(3)	108.6423
H(27)-C(2)-C(1)	108.6423
O(3)-C(2)-C(1)	112.6785
H(26)-C(1)-H(25)	114.0239
H(26)-C(1)-C(6)	105.7694
H(26)-C(1)-C(2)	105.7694
H(25)-C(1)-C(6)	107.8476
H(25)-C(1)-C(2)	107.8476
C(6)-C(1)-C(2)	115.7954

dihedral angles

Atoms	Dihedral angles (°)
C(7)-C(18)-Mg(20)-O(19)	-1.5733
C(7)-C(18)-Mg(20)-Br(21)	-37.2791
C(7)-C(18)-Mg(20)-Br(22)	-112.7681
H(42)-C(18)-Mg(20)-O(19)	-117.6606
H(42)-C(18)-Mg(20)-Br(21)	-153.3664
H(42)-C(18)-Mg(20)-Br(22)	131.1446
H(43)-C(18)-Mg(20)-O(19)	124.6895
H(43)-C(18)-Mg(20)-Br(21)	88.9837
H(43)-C(18)-Mg(20)-Br(22)	13.4947
C(2)-O(3)-Mg(23)-Br(21)	63.4101
C(2)-O(3)-Mg(23)-Br(22)	155.026
C(2)-O(3)-Mg(23)-C(24)	-73.5874
C(4)-O(3)-Mg(23)-Br(21)	-106.9359
C(4)-O(3)-Mg(23)-Br(22)	-15.32
C(4)-O(3)-Mg(23)-C(24)	116.0666

Br(21)-Mg(23)-C(24)-H(46)	-180
Br(21)-Mg(23)-C(24)-H(47)	-60.0364
Br(21)-Mg(23)-C(24)-H(48)	59.9996
Br(22)-Mg(23)-C(24)-H(46)	89.6275
Br(22)-Mg(23)-C(24)-H(47)	-150.4089
Br(22)-Mg(23)-C(24)-H(48)	-30.3729
O(3)-Mg(23)-C(24)-H(46)	-41.8554
O(3)-Mg(23)-C(24)-H(47)	78.1082
O(3)-Mg(23)-C(24)-H(48)	-161.8558
Br(21)-Mg(23)-Br(22)-Mg(20)	43.1068
Br(21)-Mg(23)-Br(22)-H(45)	69.4911
C(24)-Mg(23)-Br(22)-Mg(20)	155.573
C(24)-Mg(23)-Br(22)-H(45)	-178.0427
O(3)-Mg(23)-Br(22)-Mg(20)	-72.2386
O(3)-Mg(23)-Br(22)-H(45)	-45.8543
Br(22)-Mg(23)-Br(21)-Mg(20)	-43.3081
Br(22)-Mg(23)-Br(21)-H(44)	-87.2112
C(24)-Mg(23)-Br(21)-Mg(20)	-154.5657
C(24)-Mg(23)-Br(21)-H(44)	161.5312
O(3)-Mg(23)-Br(21)-Mg(20)	68.2215
O(3)-Mg(23)-Br(21)-H(44)	24.3184
O(19)-Mg(20)-Br(22)-Mg(23)	34.0614
O(19)-Mg(20)-Br(22)-H(45)	-12.7167
Br(21)-Mg(20)-Br(22)-Mg(23)	-42.724
Br(21)-Mg(20)-Br(22)-H(45)	-89.5021
C(18)-Mg(20)-Br(22)-Mg(23)	109.3124
C(18)-Mg(20)-Br(22)-H(45)	62.5342
O(19)-Mg(20)-Br(21)-Mg(23)	-70.8758
O(19)-Mg(20)-Br(21)-H(44)	2.4483
Br(22)-Mg(20)-Br(21)-Mg(23)	42.7332
Br(22)-Mg(20)-Br(21)-H(44)	116.0574
C(18)-Mg(20)-Br(21)-Mg(23)	-36.1424
C(18)-Mg(20)-Br(21)-H(44)	37.1817
C(7)-O(19)-Mg(20)-Br(21)	165.3636
C(7)-O(19)-Mg(20)-Br(22)	89.6609
C(7)-O(19)-Mg(20)-C(18)	1.7062
C(8)-C(7)-O(19)-Mg(20)	121.9827
C(5)-C(7)-O(19)-Mg(20)	-124.6687
C(18)-C(7)-O(19)-Mg(20)	-2.0921
C(8)-C(7)-C(18)-Mg(20)	-115.6601
C(8)-C(7)-C(18)-H(42)	0.4272
C(8)-C(7)-C(18)-H(43)	118.0771
C(5)-C(7)-C(18)-Mg(20)	116.2818
C(5)-C(7)-C(18)-H(42)	-127.6309
C(5)-C(7)-C(18)-H(43)	-9.981
O(19)-C(7)-C(18)-Mg(20)	1.8282
O(19)-C(7)-C(18)-H(42)	117.9155

O(19)-C(7)-C(18)-H(43)	-124.4346
N(10)-S(14)-C(17)-H(39)	-180
N(10)-S(14)-C(17)-H(40)	-60.0364
N(10)-S(14)-C(17)-H(41)	59.9996
O(15)-S(14)-C(17)-H(39)	66.3197
O(15)-S(14)-C(17)-H(40)	-173.7167
O(15)-S(14)-C(17)-H(41)	-53.6807
O(16)-S(14)-C(17)-H(39)	-66.1945
O(16)-S(14)-C(17)-H(40)	53.7691
O(16)-S(14)-C(17)-H(41)	173.8051
C(11)-N(10)-S(14)-O(15)	-170.0435
C(11)-N(10)-S(14)-O(16)	-38.3122
C(11)-N(10)-S(14)-C(17)	75.7942
C(8)-N(10)-S(14)-O(15)	39.4604
C(8)-N(10)-S(14)-O(16)	171.1917
C(8)-N(10)-S(14)-C(17)	-74.7019
C(11)-C(12)-C(13)-C(9)	-91.7217
C(11)-C(12)-C(13)-H(37)	158.9801
C(11)-C(12)-C(13)-H(38)	33.4334
C(9)-C(12)-C(13)-H(37)	-109.2981
C(9)-C(12)-C(13)-H(38)	125.1551
H(36)-C(12)-C(13)-C(9)	135.6858
H(36)-C(12)-C(13)-H(37)	26.3876
H(36)-C(12)-C(13)-H(38)	-99.1591
C(8)-C(9)-C(13)-C(12)	95.3025
C(8)-C(9)-C(13)-H(37)	-155.3994
C(8)-C(9)-C(13)-H(38)	-29.8526
C(6)-C(9)-C(13)-C(12)	-110.8576
C(6)-C(9)-C(13)-H(37)	-1.5594
C(6)-C(9)-C(13)-H(38)	123.9873
C(12)-C(9)-C(13)-H(37)	109.2981
C(12)-C(9)-C(13)-H(38)	-125.1551
C(8)-C(9)-C(12)-C(11)	5.3278
C(8)-C(9)-C(12)-C(13)	-114.906
C(8)-C(9)-C(12)-H(36)	129.8509
C(6)-C(9)-C(12)-C(11)	-126.3657
C(6)-C(9)-C(12)-C(13)	113.4005
C(6)-C(9)-C(12)-H(36)	-1.8426
C(13)-C(9)-C(12)-C(11)	120.2337
C(13)-C(9)-C(12)-H(36)	-115.2432
C(7)-C(8)-N(10)-C(11)	134.1225
C(7)-C(8)-N(10)-S(14)	-73.4226
C(9)-C(8)-N(10)-C(11)	23.4178
C(9)-C(8)-N(10)-S(14)	175.8726
H(33)-C(8)-N(10)-C(11)	-104.5922
H(33)-C(8)-N(10)-S(14)	47.8626
N(10)-C(11)-C(12)-C(9)	8.6591

N(10)-C(11)-C(12)-C(13)	74.2295
N(10)-C(11)-C(12)-H(36)	-141.2384
H(34)-C(11)-C(12)-C(9)	127.8352
H(34)-C(11)-C(12)-C(13)	-166.5944
H(34)-C(11)-C(12)-H(36)	-22.0623
H(35)-C(11)-C(12)-C(9)	-113.4096
H(35)-C(11)-C(12)-C(13)	-47.8391
H(35)-C(11)-C(12)-H(36)	96.6929
C(8)-N(10)-C(11)-C(12)	-20.6748
C(8)-N(10)-C(11)-H(34)	-139.8509
C(8)-N(10)-C(11)-H(35)	101.3938
S(14)-N(10)-C(11)-C(12)	-174.3062
S(14)-N(10)-C(11)-H(34)	66.5177
S(14)-N(10)-C(11)-H(35)	-52.2375
C(5)-C(6)-C(9)-C(8)	25.121
C(5)-C(6)-C(9)-C(12)	155.7053
C(5)-C(6)-C(9)-C(13)	-130.7718
C(1)-C(6)-C(9)-C(8)	-94.2424
C(1)-C(6)-C(9)-C(12)	36.3419
C(1)-C(6)-C(9)-C(13)	109.8649
H(32)-C(6)-C(9)-C(8)	148.5344
H(32)-C(6)-C(9)-C(12)	-80.8813
H(32)-C(6)-C(9)-C(13)	-7.3583
C(4)-C(5)-C(7)-C(8)	163.1496
C(4)-C(5)-C(7)-C(18)	-62.3586
C(4)-C(5)-C(7)-O(19)	46.1273
C(6)-C(5)-C(7)-C(8)	41.4234
C(6)-C(5)-C(7)-C(18)	175.9152
C(6)-C(5)-C(7)-O(19)	-75.5989
H(31)-C(5)-C(7)-C(8)	-81.8179
H(31)-C(5)-C(7)-C(18)	52.6738
H(31)-C(5)-C(7)-O(19)	161.1597
C(7)-C(8)-C(9)-C(6)	-0.0425
C(7)-C(8)-C(9)-C(12)	-137.3274
C(7)-C(8)-C(9)-C(13)	156.7942
N(10)-C(8)-C(9)-C(6)	120.2953
N(10)-C(8)-C(9)-C(12)	-16.9896
N(10)-C(8)-C(9)-C(13)	-82.868
H(33)-C(8)-C(9)-C(6)	-119.8364
H(33)-C(8)-C(9)-C(12)	102.8788
H(33)-C(8)-C(9)-C(13)	37.0003
C(5)-C(7)-C(8)-C(9)	-25.3117
C(5)-C(7)-C(8)-N(10)	-135.9031
C(5)-C(7)-C(8)-H(33)	102.7171
C(18)-C(7)-C(8)-C(9)	-159.4927
C(18)-C(7)-C(8)-N(10)	89.9159
C(18)-C(7)-C(8)-H(33)	-31.4639

O(19)-C(7)-C(8)-C(9)	90.0918
O(19)-C(7)-C(8)-N(10)	-20.4996
O(19)-C(7)-C(8)-H(33)	-141.8794
C(5)-C(6)-C(1)-C(2)	37.3074
C(5)-C(6)-C(1)-H(25)	158.1871
C(5)-C(6)-C(1)-H(26)	-79.445
C(9)-C(6)-C(1)-C(2)	150.3482
C(9)-C(6)-C(1)-H(25)	-88.7721
C(9)-C(6)-C(1)-H(26)	33.5958
H(32)-C(6)-C(1)-C(2)	-86.5573
H(32)-C(6)-C(1)-H(25)	34.3224
H(32)-C(6)-C(1)-H(26)	156.6903
C(4)-C(5)-C(6)-C(1)	-43.9165
C(4)-C(5)-C(6)-C(9)	-164.169
C(4)-C(5)-C(6)-H(32)	73.2482
C(7)-C(5)-C(6)-C(1)	80.502
C(7)-C(5)-C(6)-C(9)	-39.7505
C(7)-C(5)-C(6)-H(32)	-162.3333
H(31)-C(5)-C(6)-C(1)	-159.0226
H(31)-C(5)-C(6)-C(9)	80.7249
H(31)-C(5)-C(6)-H(32)	-41.8578
C(6)-C(5)-C(4)-O(3)	53.9107
C(6)-C(5)-C(4)-H(29)	-66.3967
C(6)-C(5)-C(4)-H(30)	172.8138
C(7)-C(5)-C(4)-O(3)	-62.7504
C(7)-C(5)-C(4)-H(29)	176.9422
C(7)-C(5)-C(4)-H(30)	56.1528
H(31)-C(5)-C(4)-O(3)	177.0012
H(31)-C(5)-C(4)-H(29)	56.6938
H(31)-C(5)-C(4)-H(30)	-64.0957
C(2)-O(3)-C(4)-C(5)	-59.1283
C(2)-O(3)-C(4)-H(29)	61.1791
C(2)-O(3)-C(4)-H(30)	-178.0314
Mg(23)-O(3)-C(4)-C(5)	111.5038
Mg(23)-O(3)-C(4)-H(29)	-128.1888
Mg(23)-O(3)-C(4)-H(30)	-7.3993
C(1)-C(2)-O(3)-C(4)	50.4774
C(1)-C(2)-O(3)-Mg(23)	-120.0455
H(27)-C(2)-O(3)-C(4)	-69.9604
H(27)-C(2)-O(3)-Mg(23)	119.5167
H(28)-C(2)-O(3)-C(4)	168.9284
H(28)-C(2)-O(3)-Mg(23)	-1.5945
C(6)-C(1)-C(2)-O(3)	-38.6993
C(6)-C(1)-C(2)-H(27)	81.7385
C(6)-C(1)-C(2)-H(28)	-157.1503
H(25)-C(1)-C(2)-O(3)	-159.579
H(25)-C(1)-C(2)-H(27)	-39.1412

H(25)-C(1)-C(2)-H(28)	81.97
H(26)-C(1)-C(2)-O(3)	78.0531
H(26)-C(1)-C(2)-H(27)	-161.5091
H(26)-C(1)-C(2)-H(28)	-40.3979

5.2.3 Reductive amination

- **Structure elucidation of compound 425:**

- **^{1}H NMR:** Protons of the pyrrolidine and cyclopropane rings were assigned as already described for compound **300**. The triplet at 0.88 ppm corresponds to the methyl groups of the alkyl chain. The resonances of the protons of the rest of the alkyl chain are identified by COSY and HSQC analysis (to confirm diastereotopic proton couples). Proton H_n is distinguished from H_n' for its NOESY correlation with the multiplet signal (H_k+H_o). The other pyran ring signals are assigned for COSY (H_n'-H_m) and NOESY (H_m-H_h) correlations.

^{1}H NMR in $CDCl_3$ of compound 425

COSY in $CDCl_3$ of compound 425

Figure 41: NOESY in $CDCl_3$ of compound 425

HSQC in $CDCl_3$ of compound 425

Crystallographic data for compound 424

Experimental

An NMR tube was loaded with compound **424** (ca. 10 mg) and a minimum amount of EtOH (ca. 0.2 ml) was added. The mixture was heated until dissolution, then heptane (ca. 0.4 ml) was slowly added with a pipette in order to form a biphasic mixture. The NMR tube was kept for 7 days at rt until the formation of crystals (see left image).

A suitable crystal was selected and loaded on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 100.00(10) K during data collection. Using Olex2, the structure was solved with the SHELXT, structure solution program using Intrinsic Phasing and refined with the SHELXL, refinement package using Least Squares minimisation.

Crystal Data for $C_{13}H_{22}N_2O_3S$ (*M* =286.38 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 6.4530(3) Å, *b* = 26.6140(16) Å, *c* = 8.3055(5) Å, *β* = 108.965(6)°, *V* = 1348.96(14) Å^3, *Z* = 4, *T* = 100.00(10) K, μ(CuKα) = 2.198 mm^{-1}, *Dcalc* = 1.410 g/cm^3, 4990 reflections measured (11.748° ≤ 2Θ ≤ 145.248°), 2584 unique (R_{int} = 0.0282, R_{sigma} = 0.0398) which were used in all calculations. The final R_1 was 0.0393 (I > 2σ(I)) and wR_2 was 0.1022 (all data).

Table 1 Crystal data and structure refinement for **424**

Identification code	ELGI02-050
Empirical formula	$C_{13}H_{22}N_2O_3S$
Formula weight	286.38
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	$P2_1/n$

a/Å	6.4530(3)
b/Å	26.6140(16)
c/Å	8.3055(5)
α/°	90
β/°	108.965(6)
γ/°	90
Volume/Å^3	1348.96(14)
Z	4
ρ_{calc}g/cm^3	1.410
μ/mm^{-1}	2.198
F(000)	616.0
Crystal size/mm^3	0.333 × 0.261 × 0.014
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	11.748 to 145.248
Index ranges	-7 ≤ h ≤ 7, -32 ≤ k ≤ 30, -4 ≤ l ≤ 9
Reflections collected	4990
Independent reflections	2584 [R_{int} = 0.0282, R_{sigma} = 0.0398]
Data/restraints/parameters	2584/0/178
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0393, wR_2 = 0.0971
Final R indexes [all data]	R_1 = 0.0473, wR_2 = 0.1022
Largest diff. peak/hole / e Å^{-3}	0.31/-0.44

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **424**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C(1)	2721(3)	6660.7(8)	1241(2)	21.4(4)
C(2)	5395(3)	7083.6(7)	3907(2)	18.9(4)
C(3)	5018(3)	6837.8(7)	2194(2)	19.3(4)
C(4)	4399(3)	6295.2(7)	2289(2)	16.6(4)
C(5)	5346(3)	5844.9(7)	1637(2)	17.3(4)
C(6)	7536(3)	5954.7(7)	1347(2)	19.4(4)
C(7)	8772(3)	5471.2(8)	1314(2)	22.0(4)
C(8)	7200(3)	5026.7(7)	3074(2)	21.2(4)
C(9)	5595(3)	5450.4(7)	3058(2)	18.1(4)
C(10)	6056(3)	5754.0(7)	4719(2)	16.2(4)
C(11)	4402(3)	6189.4(7)	4095(2)	15.5(4)
C(12)	1290(3)	6974.5(7)	5651(2)	20.2(4)

C(13)	9097(3)	5985.3(8)	7243(2)	21.3(4)
N(1)	4970(3)	6675.9(6)	4982.4(19)	16.5(3)
N(2)	8328(2)	5927.1(6)	5387.6(19)	17.2(3)
O(1)	9206(2)	5201.6(5)	2878.5(17)	21.9(3)
O(2)	4214(2)	6365.3(6)	7521.8(17)	24.2(3)
O(3)	5249(2)	7256.3(6)	7341.7(18)	29.1(3)
S(1)	4080.6(7)	6814.5(2)	6535.1(6)	18.53(15)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **424**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C(1)	22.7(9)	22.1(10)	17.3(9)	1.4(8)	3.4(7)	6.5(8)
C(2)	18.0(9)	16.4(9)	22.6(10)	0.9(7)	7.3(7)	-0.5(7)
C(3)	23.3(9)	16.2(9)	20.1(9)	3.5(7)	9.4(7)	2.6(7)
C(4)	15.2(8)	17.0(9)	16.6(9)	0.6(7)	3.7(7)	1.5(7)
C(5)	16.0(8)	19.0(9)	14.6(8)	-1.1(7)	1.8(6)	2.1(7)
C(6)	20.3(9)	23.5(10)	14.5(8)	1.2(7)	6.1(7)	2.4(7)
C(7)	22.3(9)	27.9(11)	16.6(9)	-0.4(8)	7.4(7)	4.7(8)
C(8)	21.7(9)	17.6(9)	23.1(10)	-0.9(8)	5.7(7)	2.4(7)
C(9)	16.7(8)	16.3(9)	20.4(9)	-0.3(7)	4.9(7)	0.3(7)
C(10)	16.2(8)	15.9(8)	16.7(8)	1.5(7)	5.5(7)	-0.2(7)
C(11)	15.1(8)	15.0(9)	15.8(9)	-0.3(7)	4.2(6)	-1.1(7)
C(12)	19.4(9)	19.0(9)	23.7(10)	1.6(8)	9.0(7)	3.4(7)
C(13)	17.5(9)	27.0(10)	18.0(9)	-0.7(8)	3.9(7)	0.7(7)
N(1)	19.7(7)	13.4(7)	17.5(8)	-0.7(6)	7.5(6)	0.6(6)
N(2)	14.8(7)	20.4(8)	15.4(8)	-0.3(6)	3.5(6)	0.4(6)
O(1)	20.0(7)	24.5(7)	20.0(7)	1.2(6)	5.0(5)	6.1(5)
O(2)	22.5(7)	31.8(8)	19.1(7)	7.1(6)	7.7(5)	4.9(6)
O(3)	29.4(7)	32.0(8)	25.9(7)	-14.2(6)	9.1(6)	-9.0(6)
S(1)	18.2(2)	21.9(3)	15.2(2)	-2.61(16)	5.17(17)	-0.24(16)

Table 4 Bond Lengths for **424**

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
C(1)	C(3)	1.511(3)	C(8)	C(9)	1.528(3)
C(1)	C(4)	1.505(2)	C(8)	O(1)	1.433(2)
C(2)	C(3)	1.512(3)	C(9)	C(10)	1.542(3)
C(2)	N(1)	1.487(2)	C(10)	C(11)	1.546(2)
C(3)	C(4)	1.507(3)	C(10)	N(2)	1.463(2)

C(4)	C(5)	1.523(3)	C(11)	N(1)	1.476(2)
C(4)	C(11)	1.525(2)	C(12)	S(1)	1.7618(19)
C(5)	C(6)	1.537(2)	C(13)	N(2)	1.465(2)
C(5)	C(9)	1.548(3)	N(1)	S(1)	1.6154(15)
C(6)	C(7)	1.519(3)	O(2)	S(1)	1.4362(15)
C(7)	O(1)	1.430(2)	O(3)	S(1)	1.4392(15)

Table 5 Bond Angles for **424**

Atom	**Atom**	**Atom**	**Angle/˚**	**Atom**	**Atom**	**Atom**	**Angle/˚**
C(4)	C(1)	C(3)	59.97(12)	C(10)	C(9)	C(5)	105.59(15)
N(1)	C(2)	C(3)	104.18(14)	C(9)	C(10)	C(11)	100.43(14)
C(1)	C(3)	C(2)	117.27(16)	N(2)	C(10)	C(9)	112.47(14)
C(4)	C(3)	C(1)	59.80(12)	N(2)	C(10)	C(11)	112.86(15)
C(4)	C(3)	C(2)	109.24(15)	C(4)	C(11)	C(10)	104.40(14)
C(1)	C(4)	C(3)	60.23(13)	N(1)	C(11)	C(4)	104.48(14)
C(1)	C(4)	C(5)	126.84(16)	N(1)	C(11)	C(10)	117.24(14)
C(1)	C(4)	C(11)	117.33(15)	C(2)	N(1)	S(1)	119.73(12)
C(3)	C(4)	C(5)	126.26(16)	C(11)	N(1)	C(2)	113.85(14)
C(3)	C(4)	C(11)	108.23(15)	C(11)	N(1)	S(1)	120.27(12)
C(5)	C(4)	C(11)	109.39(15)	C(10)	N(2)	C(13)	112.79(14)
C(4)	C(5)	C(6)	113.70(16)	C(7)	O(1)	C(8)	110.40(14)
C(4)	C(5)	C(9)	102.52(14)	N(1)	S(1)	C(12)	107.63(9)
C(6)	C(5)	C(9)	112.05(14)	O(2)	S(1)	C(12)	107.60(9)
C(7)	C(6)	C(5)	110.89(16)	O(2)	S(1)	N(1)	107.14(8)
O(1)	C(7)	C(6)	110.97(15)	O(2)	S(1)	O(3)	119.30(9)
O(1)	C(8)	C(9)	113.19(16)	O(3)	S(1)	C(12)	107.84(10)
C(8)	C(9)	C(5)	114.16(15)	O(3)	S(1)	N(1)	106.85(8)
C(8)	C(9)	C(10)	116.46(15)				

Table 6 Hydrogen Bonds for **424**

D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
N(2)	H(2)	O(1)	0.89(3)	2.27(3)	3.026(2)	143(2)

Table 7 Torsion Angles for **424**

A	**B**	**C**	**D**	**Angle/˚**	**A**	**B**	**C**	**D**	**Angle/˚**
C(1)	C(3)	C(4)	C(5)	115.9(2)	C(5)	C(6)	C(7)	O(1)	-59.2(2)
C(1)	C(3)	C(4)	C(11)	-111.62(16)	C(5)	C(9)	C(10)	C(11)	42.18(16)

C(1)	C(4)	C(5)	C(6)	95.5(2)	C(5)	C(9)	C(10)	N(2)	-78.06(18)
C(1)	C(4)	C(5)	C(9)	-143.29(18)	C(6)	C(5)	C(9)	C(8)	-37.9(2)
C(1)	C(4)	C(11)	C(10)	172.39(15)	C(6)	C(5)	C(9)	C(10)	91.29(17)
C(1)	C(4)	C(11)	N(1)	-63.95(19)	C(6)	C(7)	O(1)	C(8)	66.4(2)
C(2)	C(3)	C(4)	C(1)	110.99(17)	C(8)	C(9)	C(10)	C(11)	170.02(15)
C(2)	C(3)	C(4)	C(5)	-133.09(18)	C(8)	C(9)	C(10)	N(2)	49.8(2)
C(2)	C(3)	C(4)	C(11)	-0.6(2)	C(9)	C(5)	C(6)	C(7)	44.3(2)
C(2)	N(1)	S(1)	C(12)	75.03(15)	C(9)	C(8)	O(1)	C(7)	-58.7(2)
C(2)	N(1)	S(1)	O(2)	-169.50(13)	C(9)	C(10)	C(11)	C(4)	-36.44(16)
C(2)	N(1)	S(1)	O(3)	-40.57(16)	C(9)	C(10)	C(11)	N(1)	-151.43(15)
C(3)	C(1)	C(4)	C(5)	-115.0(2)	C(9)	C(10)	N(2)	C(13)	-151.56(16)
C(3)	C(1)	C(4)	C(11)	96.32(18)	C(10)	C(11)	N(1)	C(2)	113.30(17)
C(3)	C(2)	N(1)	C(11)	1.27(19)	C(10)	C(11)	N(1)	S(1)	-94.33(17)
C(3)	C(2)	N(1)	S(1)	-151.26(13)	C(11)	C(4)	C(5)	C(6)	-113.78(16)
C(3)	C(4)	C(5)	C(6)	18.2(3)	C(11)	C(4)	C(5)	C(9)	7.39(18)
C(3)	C(4)	C(5)	C(9)	139.41(18)	C(11)	C(10)	N(2)	C(13)	95.68(18)
C(3)	C(4)	C(11)	C(10)	-122.33(15)	C(11)	N(1)	S(1)	C(12)	-75.73(15)
C(3)	C(4)	C(11)	N(1)	1.34(18)	C(11)	N(1)	S(1)	O(2)	39.74(16)
C(4)	C(1)	C(3)	C(2)	-97.41(18)	C(11)	N(1)	S(1)	O(3)	168.67(14)
C(4)	C(5)	C(6)	C(7)	159.96(15)	N(1)	C(2)	C(3)	C(1)	64.9(2)
C(4)	C(5)	C(9)	C(8)	-160.21(15)	N(1)	C(2)	C(3)	C(4)	-0.34(19)
C(4)	C(5)	C(9)	C(10)	-31.00(17)	N(2)	C(10)	C(11)	C(4)	83.52(17)
C(4)	C(11)	N(1)	C(2)	-1.65(19)	N(2)	C(10)	C(11)	N(1)	-31.5(2)
C(4)	C(11)	N(1)	S(1)	150.72(12)	O(1)	C(8)	C(9)	C(5)	44.9(2)
C(5)	C(4)	C(11)	C(10)	18.57(18)	O(1)	C(8)	C(9)	C(10)	-78.6(2)
C(5)	C(4)	C(11)	N(1)	142.23(15)					

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **424**

Atom	***x***	***y***	***z***	**U(eq)**
H(1A)	1555.58	6762.59	1670.95	26
H(1B)	2298.3	6634.58	11.69	26
H(2A)	6887.46	7205.78	4374.32	23
H(2B)	4393.68	7362.15	3814.18	23
H(3)	5994.53	6923.63	1544.96	23
H(5)	4280.22	5724.27	574.29	21
H(6A)	7262.3	6130.78	275.09	23
H(6B)	8424.07	6170.16	2250.28	23
H(7A)	7911.79	5262.35	377.97	26

H(7B)	10144.64	5549.41	1128.53	26
H(8A)	7534.33	4844.99	4140.48	25
H(8B)	6504.22	4793.67	2159.96	25
H(9)	4154.13	5293.92	2834.67	22
H(10)	5685.68	5554.21	5579.09	19
H(11)	2941.09	6082.67	4075.6	19
H(12A)	1129.61	7241.23	4841.92	30
H(12B)	743.71	7082.9	6540.28	30
H(12C)	475.6	6686.43	5090.6	30
H(13A)	8418.69	6275.07	7545.86	32
H(13B)	10659.73	6027.54	7640.54	32
H(13C)	8717.91	5691.57	7756.78	32
H(2)	9120(40)	5698(11)	5080(30)	31(7)

- **3D-model of TS for reduction of the imine generated from 283 and $MeNH_3^+Cl^-$ realised with MarvinSketch 21.18**

Software	MarvinSketch 21.18
Force field	MMFF94
Optimization limit	Normal
Max number of conformers	100
Diversity limit	0.1
Timelimit	900
Conformer energy	585.04 kcal/mol

Image visualised with Chem3D 12.0.2:

atom coordinates:

Atoms	x (Å)	y (Å)	z (Å)
C(1)	-4.0422	2.4871	-3.6475
C(2)	-6.2041	0.5769	-2.145
O(3)	-5.2557	-0.2665	0.738
C(4)	-4.7599	2.1118	2.5271
C(5)	-2.3439	3.9506	1.3799

C(6)	-2.827	4.8625	-1.7622
C(7)	0.8082	2.8342	1.5771
C(8)	2.356	5.0379	-0.4869
C(9)	0.1021	5.833	-2.669
N(10)	4.6601	3.7435	-2.2338
C(11)	4.3584	4.4406	-5.3324
C(12)	1.3426	5.4958	-5.599
C(13)	0.4684	8.4227	-4.5641
S(14)	7.9918	3.8244	-0.8306
O(15)	7.5423	3.3378	2.1993
O(16)	9.658	1.8585	-2.5297
C(17)	9.246	7.4031	-1.3694
N(18)	1.1413	-0.2237	0.4033
Ti(19)	-2.0715	-2.6076	0.8259
O(20)	-3.4112	-6.2981	1.1992
O(21)	-0.9761	-3.1937	-2.9005
O(22)	-0.9255	-2.48	4.6107
C(23)	-6.2292	-6.9367	0.2151
C(24)	-6.3094	-10.0836	-0.6386
C(25)	-8.4293	-6.3784	2.5546
C(26)	-0.2284	-5.9406	-3.9972
C(27)	2.981	-6.0931	-4.5404
C(28)	-1.8344	-6.2616	-6.8195
C(29)	-1.8832	-4.5701	6.6051
C(30)	0.2616	-7.0104	6.7678
C(31)	-2.1697	-3.0962	9.4979
B(32)	1.4814	4.3393	5.7072
H(33)	1.7849	2.7123	3.7544
C(34)	3.7174	-1.8304	1.5044
H(35)	-4.5415	2.9576	-4.5239
H(36)	-3.1864	1.8375	-3.938
H(37)	-7.1675	1.1273	-2.0576
H(38)	-6.3181	-0.35	-2.7506
H(39)	-5.6876	2.7242	2.5827
H(40)	-4.4743	1.7416	3.5371
H(41)	-2.4121	4.7922	2.105
H(42)	-3.6014	5.6552	-1.8652
H(43)	2.7842	5.8558	0.1346
H(44)	4.5168	3.5342	-5.9587
H(45)	5.1064	5.1886	-5.6783
H(46)	1.1402	5.0049	-6.5464
H(47)	-0.4023	8.9126	-4.99
H(48)	0.9613	9.3855	-4.4675
H(49)	10.2754	7.5018	-0.9581
H(50)	9.2589	7.631	-2.4588
H(51)	8.5684	8.1159	-0.8483
H(52)	1.2707	-0.0194	-0.6134

H(53)	-6.4785	-6.2855	-0.6524
H(54)	-5.3085	-10.5401	-0.4694
H(55)	-7.0682	-10.6155	-0.0221
H(56)	-6.5788	-10.1691	-1.7152
H(57)	-7.9133	-6.0115	3.4699
H(58)	-8.9701	-7.3229	2.7876
H(59)	-9.1554	-5.6106	2.2052
H(60)	-0.4932	-6.7482	-3.2785
H(61)	3.2428	-7.0984	-4.94
H(62)	3.5269	-5.9201	-3.5861
H(63)	3.2693	-5.3134	-5.2804
H(64)	-1.5996	-7.2519	-7.2701
H(65)	-2.9293	-6.1898	-6.633
H(66)	-1.5223	-5.4531	-7.5178
H(67)	-2.8617	-4.9994	6.2934
H(68)	-0.0951	-7.7704	7.4985
H(69)	0.3643	-7.4809	5.7643
H(70)	1.2489	-6.6151	7.0959
H(71)	-2.5194	-3.8317	10.2565
H(72)	-2.9069	-2.2661	9.4193
H(73)	-1.1811	-2.6878	9.8055
H(74)	2.4554	5.2761	5.6696
H(75)	1.5547	3.6604	6.8741
H(76)	0.2743	4.9403	5.6093
H(77)	3.4029	-2.8364	1.862
H(78)	4.175	-1.2643	2.3463
H(79)	4.4617	-1.9442	0.6847

bond lengths

Atoms	**Bond lenght (Å)**
C(34)-H(79)	1.113
C(34)-H(78)	1.113
C(34)-H(77)	1.113
B(32)-H(76)	1.352
B(32)-H(75)	1.352
B(32)-H(74)	1.352
C(31)-H(73)	1.113
C(31)-H(72)	1.113
C(31)-H(71)	1.113
C(30)-H(70)	1.113
C(30)-H(69)	1.113
C(30)-H(68)	1.113
C(29)-H(67)	1.113
C(28)-H(66)	1.113
C(28)-H(65)	1.113

C(28)-H(64)	1.113
C(27)-H(63)	1.113
C(27)-H(62)	1.113
C(27)-H(61)	1.113
C(26)-H(60)	1.113
C(25)-H(59)	1.113
C(25)-H(58)	1.113
C(25)-H(57)	1.113
C(24)-H(56)	1.113
C(24)-H(55)	1.113
C(24)-H(54)	1.113
C(23)-H(53)	1.113
N(18)-H(52)	1.045
C(17)-H(51)	1.113
C(17)-H(50)	1.113
C(17)-H(49)	1.113
C(13)-H(48)	1.086
C(13)-H(47)	1.086
C(12)-H(46)	1.086
C(11)-H(45)	1.113
C(11)-H(44)	1.113
C(8)-H(43)	1.113
C(6)-H(42)	1.113
C(5)-H(41)	1.113
C(4)-H(40)	1.113
C(4)-H(39)	1.113
C(2)-H(38)	1.113
C(2)-H(37)	1.113
C(1)-H(36)	1.113
C(1)-H(35)	1.113
N(18)-C(34)	3.2296
O(3)-Ti(19)	3.9532
B(32)-H(33)	2.5598
H(33)-C(7)	2.3894
C(7)-N(18)	3.2923
Ti(19)-N(18)	4.0229
C(29)-C(31)	3.2593
C(29)-C(30)	3.253
O(22)-C(29)	3.0436
C(26)-C(28)	3.2631
C(26)-C(27)	3.2586
O(21)-C(26)	3.0508
C(23)-C(25)	3.2597
C(23)-C(24)	3.2616
O(20)-C(23)	3.0524
Ti(19)-O(22)	3.9566
Ti(19)-O(21)	3.928

Ti(19)-O(20)	3.9438
S(14)-C(17)	3.8302
S(14)-O(16)	3.0867
S(14)-O(15)	3.1015
N(10)-S(14)	3.616
C(12)-C(13)	3.2252
C(9)-C(13)	3.2299
C(9)-C(12)	3.1996
C(8)-N(10)	3.168
C(11)-C(12)	3.2062
N(10)-C(11)	3.1903
C(6)-C(9)	3.2162
C(5)-C(7)	3.3498
C(8)-C(9)	3.2363
C(7)-C(8)	3.3929
C(6)-C(1)	3.267
C(5)-C(6)	3.3072
C(5)-C(4)	3.2457
O(3)-C(4)	3.0171
C(2)-O(3)	3.15
C(1)-C(2)	3.2527

bond angles

Atoms	Bond angles (°)
H(79)-C(34)-H(78)	109.52
H(79)-C(34)-H(77)	109.4618
H(79)-C(34)-N(18)	109.4618
H(78)-C(34)-H(77)	109.4418
H(78)-C(34)-N(18)	109.4418
H(77)-C(34)-N(18)	109.5
B(32)-H(33)-C(7)	127.8973
H(76)-B(32)-H(75)	109.52
H(76)-B(32)-H(74)	109.4618
H(76)-B(32)-H(33)	109.4618
H(75)-B(32)-H(74)	109.4418
H(75)-B(32)-H(33)	109.4418
H(74)-B(32)-H(33)	109.5
H(73)-C(31)-H(72)	109.52
H(73)-C(31)-H(71)	109.4618
H(73)-C(31)-C(29)	109.4618
H(72)-C(31)-H(71)	109.4418
H(72)-C(31)-C(29)	109.4418
H(71)-C(31)-C(29)	109.5
H(70)-C(30)-H(69)	109.52
H(70)-C(30)-H(68)	109.4618
H(70)-C(30)-C(29)	109.4618

H(69)-C(30)-H(68)	109.4418
H(69)-C(30)-C(29)	109.4418
H(68)-C(30)-C(29)	109.5
H(67)-C(29)-C(31)	110.2257
H(67)-C(29)-C(30)	107.7155
H(67)-C(29)-O(22)	110.975
C(31)-C(29)-C(30)	110.6594
C(31)-C(29)-O(22)	107.3804
C(30)-C(29)-O(22)	109.9057
H(66)-C(28)-H(65)	109.52
H(66)-C(28)-H(64)	109.4618
H(66)-C(28)-C(26)	109.4618
H(65)-C(28)-H(64)	109.4418
H(65)-C(28)-C(26)	109.4418
H(64)-C(28)-C(26)	109.5
H(63)-C(27)-H(62)	109.52
H(63)-C(27)-H(61)	109.4618
H(63)-C(27)-C(26)	109.4618
H(62)-C(27)-H(61)	109.4418
H(62)-C(27)-C(26)	109.4418
H(61)-C(27)-C(26)	109.5
H(60)-C(26)-C(28)	111.718
H(60)-C(26)-C(27)	107.939
H(60)-C(26)-O(21)	111.275
C(28)-C(26)-C(27)	109.6308
C(28)-C(26)-O(21)	106.193
C(27)-C(26)-O(21)	110.0869
H(59)-C(25)-H(58)	109.52
H(59)-C(25)-H(57)	109.4618
H(59)-C(25)-C(23)	109.4618
H(58)-C(25)-H(57)	109.4418
H(58)-C(25)-C(23)	109.4418
H(57)-C(25)-C(23)	109.5
H(56)-C(24)-H(55)	109.52
H(56)-C(24)-H(54)	109.4618
H(56)-C(24)-C(23)	109.4618
H(55)-C(24)-H(54)	109.4418
H(55)-C(24)-C(23)	109.4418
H(54)-C(24)-C(23)	109.5
H(53)-C(23)-C(25)	107.9396
H(53)-C(23)-C(24)	110.7952
H(53)-C(23)-O(20)	109.6105
C(25)-C(23)-C(24)	109.6643
C(25)-C(23)-O(20)	110.8478
C(24)-C(23)-O(20)	107.9951
C(29)-O(22)-Ti(19)	120.9005
C(26)-O(21)-Ti(19)	122.9373

C(23)-O(20)-Ti(19)	118.6108
O(3)-Ti(19)-N(18)	106.8586
O(3)-Ti(19)-O(22)	103.6196
O(3)-Ti(19)-O(21)	106.9712
O(3)-Ti(19)-O(20)	106.4186
N(18)-Ti(19)-O(22)	81.3764
N(18)-Ti(19)-O(21)	76.4703
N(18)-Ti(19)-O(20)	146.694
O(22)-Ti(19)-O(21)	146.2557
O(22)-Ti(19)-O(20)	92.1792
O(21)-Ti(19)-O(20)	92.5734
H(52)-N(18)-C(34)	109.28
H(52)-N(18)-C(7)	100.2402
H(52)-N(18)-Ti(19)	108.4786
C(34)-N(18)-C(7)	114.9115
C(34)-N(18)-Ti(19)	107.843
C(7)-N(18)-Ti(19)	115.6031
H(51)-C(17)-H(50)	109.52
H(51)-C(17)-H(49)	109.4618
H(51)-C(17)-S(14)	109.4618
H(50)-C(17)-H(49)	109.4418
H(50)-C(17)-S(14)	109.4418
H(49)-C(17)-S(14)	109.5
C(17)-S(14)-O(16)	109.9304
C(17)-S(14)-O(15)	109.3583
C(17)-S(14)-N(10)	105.5464
O(16)-S(14)-O(15)	121.0683
O(16)-S(14)-N(10)	105.6343
O(15)-S(14)-N(10)	104.0075
H(48)-C(13)-H(47)	89.9285
H(48)-C(13)-C(12)	135.247
H(48)-C(13)-C(9)	135.247
H(47)-C(13)-C(12)	120.0586
H(47)-C(13)-C(9)	120.0586
C(12)-C(13)-C(9)	59.4279
H(46)-C(12)-C(13)	129.7612
H(46)-C(12)-C(9)	140.7372
H(46)-C(12)-C(11)	95.6836
C(13)-C(12)-C(9)	60.3586
C(13)-C(12)-C(11)	121.7996
C(9)-C(12)-C(11)	108.8579
H(45)-C(11)-H(44)	106.065
H(45)-C(11)-C(12)	112.6524
H(45)-C(11)-N(10)	112.6524
H(44)-C(11)-C(12)	110.8016
H(44)-C(11)-N(10)	110.8016
C(12)-C(11)-N(10)	103.9825

S(14)-N(10)-C(8)	116.5514
S(14)-N(10)-C(11)	117.3311
C(8)-N(10)-C(11)	112.1796
C(13)-C(9)-C(12)	60.2134
C(13)-C(9)-C(6)	120.7081
C(13)-C(9)-C(8)	120.9048
C(12)-C(9)-C(6)	125.4146
C(12)-C(9)-C(8)	108.7558
C(6)-C(9)-C(8)	111.7177
H(43)-C(8)-N(10)	109.1721
H(43)-C(8)-C(9)	117.6417
H(43)-C(8)-C(7)	108.2463
N(10)-C(8)-C(9)	103.5981
N(10)-C(8)-C(7)	113.6941
C(9)-C(8)-C(7)	104.5975
H(33)-C(7)-N(18)	103.6584
H(33)-C(7)-C(5)	117.083
H(33)-C(7)-C(8)	113.6394
N(18)-C(7)-C(5)	112.5668
N(18)-C(7)-C(8)	109.8897
C(5)-C(7)-C(8)	100.1944
H(42)-C(6)-C(9)	113.1215
H(42)-C(6)-C(1)	101.8688
H(42)-C(6)-C(5)	112.7008
C(9)-C(6)-C(1)	113.2942
C(9)-C(6)-C(5)	102.5939
C(1)-C(6)-C(5)	113.7101
H(41)-C(5)-C(7)	105.7397
H(41)-C(5)-C(6)	113.6761
H(41)-C(5)-C(4)	98.773
C(7)-C(5)-C(6)	106.5755
C(7)-C(5)-C(4)	119.3951
C(6)-C(5)-C(4)	112.5374
H(40)-C(4)-H(39)	110.5769
H(40)-C(4)-C(5)	108.5515
H(40)-C(4)-O(3)	108.5515
H(39)-C(4)-C(5)	109.0513
H(39)-C(4)-O(3)	109.0513
C(5)-C(4)-O(3)	111.0582
Ti(19)-O(3)-C(4)	108.7397
Ti(19)-O(3)-C(2)	114.9246
C(4)-O(3)-C(2)	112.4044
H(38)-C(2)-H(37)	111.4654
H(38)-C(2)-O(3)	107.8079
H(38)-C(2)-C(1)	107.8079
H(37)-C(2)-O(3)	108.7313
H(37)-C(2)-C(1)	108.7313

O(3)-C(2)-C(1)	112.3272
H(36)-C(1)-H(35)	112.7174
H(36)-C(1)-C(6)	106.792
H(36)-C(1)-C(2)	106.792
H(35)-C(1)-C(6)	108.2921
H(35)-C(1)-C(2)	108.2921
C(6)-C(1)-C(2)	114.057

dihedral angles

Atoms	Dihedral angles (°)
Ti(19)-N(18)-C(34)-H(77)	0
Ti(19)-N(18)-C(34)-H(78)	-119.9636
Ti(19)-N(18)-C(34)-H(79)	120.0004
C(7)-N(18)-C(34)-H(77)	130.5443
C(7)-N(18)-C(34)-H(78)	10.5807
C(7)-N(18)-C(34)-H(79)	-109.4553
H(52)-N(18)-C(34)-H(77)	-117.7328
H(52)-N(18)-C(34)-H(78)	122.3035
H(52)-N(18)-C(34)-H(79)	2.2676
C(2)-O(3)-Ti(19)-O(20)	-97.649
C(2)-O(3)-Ti(19)-O(21)	0.3333
C(2)-O(3)-Ti(19)-O(22)	165.9098
C(2)-O(3)-Ti(19)-N(18)	80.9461
C(4)-O(3)-Ti(19)-O(20)	135.376
C(4)-O(3)-Ti(19)-O(21)	-126.6417
C(4)-O(3)-Ti(19)-O(22)	38.9348
C(4)-O(3)-Ti(19)-N(18)	-46.0289
H(74)-B(32)-H(33)-C(7)	-92.2156
H(75)-B(32)-H(33)-C(7)	147.8208
H(76)-B(32)-H(33)-C(7)	27.7848
B(32)-H(33)-C(7)-C(8)	78.7556
B(32)-H(33)-C(7)-C(5)	-37.4005
B(32)-H(33)-C(7)-N(18)	-161.9993
C(8)-C(7)-N(18)-Ti(19)	-141.7638
C(8)-C(7)-N(18)-C(34)	91.5684
C(8)-C(7)-N(18)-H(52)	-25.4225
C(5)-C(7)-N(18)-Ti(19)	-31.0208
C(5)-C(7)-N(18)-C(34)	-157.6887
C(5)-C(7)-N(18)-H(52)	85.3204
H(33)-C(7)-N(18)-Ti(19)	96.4506
H(33)-C(7)-N(18)-C(34)	-30.2172
H(33)-C(7)-N(18)-H(52)	-147.2081
O(20)-Ti(19)-N(18)-C(7)	-152.6545
O(20)-Ti(19)-N(18)-C(34)	-22.4942
O(20)-Ti(19)-N(18)-H(52)	95.7542
O(21)-Ti(19)-N(18)-C(7)	133.733

O(21)-Ti(19)-N(18)-C(34)	-96.1067
O(21)-Ti(19)-N(18)-H(52)	22.1417
O(22)-Ti(19)-N(18)-C(7)	-71.9069
O(22)-Ti(19)-N(18)-C(34)	58.2534
O(22)-Ti(19)-N(18)-H(52)	176.5019
O(3)-Ti(19)-N(18)-C(7)	29.8
O(3)-Ti(19)-N(18)-C(34)	159.9604
O(3)-Ti(19)-N(18)-H(52)	-81.7912
O(22)-C(29)-C(31)-H(71)	180
O(22)-C(29)-C(31)-H(72)	60.0364
O(22)-C(29)-C(31)-H(73)	-59.9996
C(30)-C(29)-C(31)-H(71)	-60.0462
C(30)-C(29)-C(31)-H(72)	179.9902
C(30)-C(29)-C(31)-H(73)	59.9542
H(67)-C(29)-C(31)-H(71)	58.9988
H(67)-C(29)-C(31)-H(72)	-60.9649
H(67)-C(29)-C(31)-H(73)	178.9991
O(22)-C(29)-C(30)-H(68)	-180
O(22)-C(29)-C(30)-H(69)	-60.0364
O(22)-C(29)-C(30)-H(70)	59.9996
C(31)-C(29)-C(30)-H(68)	61.5713
C(31)-C(29)-C(30)-H(69)	-178.4651
C(31)-C(29)-C(30)-H(70)	-58.4291
H(67)-C(29)-C(30)-H(68)	-58.9806
H(67)-C(29)-C(30)-H(69)	60.9831
H(67)-C(29)-C(30)-H(70)	-178.981
Ti(19)-O(22)-C(29)-C(30)	92.826
Ti(19)-O(22)-C(29)-C(31)	-146.7415
Ti(19)-O(22)-C(29)-H(67)	-26.2134
O(21)-C(26)-C(28)-H(64)	-180
O(21)-C(26)-C(28)-H(65)	-60.0364
O(21)-C(26)-C(28)-H(66)	59.9996
C(27)-C(26)-C(28)-H(64)	61.1
C(27)-C(26)-C(28)-H(65)	-178.9364
C(27)-C(26)-C(28)-H(66)	-58.9004
H(60)-C(26)-C(28)-H(64)	-58.5085
H(60)-C(26)-C(28)-H(65)	61.4551
H(60)-C(26)-C(28)-H(66)	-178.5089
O(21)-C(26)-C(27)-H(61)	180
O(21)-C(26)-C(27)-H(62)	60.0364
O(21)-C(26)-C(27)-H(63)	-59.9996
C(28)-C(26)-C(27)-H(61)	-63.5321
C(28)-C(26)-C(27)-H(62)	176.5043
C(28)-C(26)-C(27)-H(63)	56.4683
H(60)-C(26)-C(27)-H(61)	58.367
H(60)-C(26)-C(27)-H(62)	-61.5967
H(60)-C(26)-C(27)-H(63)	178.3674

Ti(19)-O(21)-C(26)-C(27)	-108.7251
Ti(19)-O(21)-C(26)-C(28)	132.6751
Ti(19)-O(21)-C(26)-H(60)	10.9004
O(20)-C(23)-C(25)-H(57)	0
O(20)-C(23)-C(25)-H(58)	-119.9636
O(20)-C(23)-C(25)-H(59)	120.0004
C(24)-C(23)-C(25)-H(57)	119.1527
C(24)-C(23)-C(25)-H(58)	-0.811
C(24)-C(23)-C(25)-H(59)	-120.847
H(53)-C(23)-C(25)-H(57)	-120.0518
H(53)-C(23)-C(25)-H(58)	119.9846
H(53)-C(23)-C(25)-H(59)	-0.0514
O(20)-C(23)-C(24)-H(54)	0
O(20)-C(23)-C(24)-H(55)	119.9636
O(20)-C(23)-C(24)-H(56)	-120.0004
C(25)-C(23)-C(24)-H(54)	-120.8934
C(25)-C(23)-C(24)-H(55)	-0.9297
C(25)-C(23)-C(24)-H(56)	119.1062
H(53)-C(23)-C(24)-H(54)	120.0553
H(53)-C(23)-C(24)-H(55)	-119.9811
H(53)-C(23)-C(24)-H(56)	0.0549
Ti(19)-O(20)-C(23)-C(24)	152.1865
Ti(19)-O(20)-C(23)-C(25)	-87.661
Ti(19)-O(20)-C(23)-H(53)	31.3889
O(20)-Ti(19)-O(22)-C(29)	-14.2512
O(21)-Ti(19)-O(22)-C(29)	-112.1747
N(18)-Ti(19)-O(22)-C(29)	-161.4069
O(3)-Ti(19)-O(22)-C(29)	93.2221
O(20)-Ti(19)-O(21)-C(26)	-26.5986
O(22)-Ti(19)-O(21)-C(26)	71.2064
N(18)-Ti(19)-O(21)-C(26)	121.5758
O(3)-Ti(19)-O(21)-C(26)	-134.63
O(21)-Ti(19)-O(20)-C(23)	-83.3793
O(22)-Ti(19)-O(20)-C(23)	130.0385
N(18)-Ti(19)-O(20)-C(23)	-152.3973
O(3)-Ti(19)-O(20)-C(23)	25.1537
N(10)-S(14)-C(17)-H(49)	-180
N(10)-S(14)-C(17)-H(50)	-60.0364
N(10)-S(14)-C(17)-H(51)	59.9996
O(15)-S(14)-C(17)-H(49)	68.6517
O(15)-S(14)-C(17)-H(50)	-171.3847
O(15)-S(14)-C(17)-H(51)	-51.3487
O(16)-S(14)-C(17)-H(49)	-66.5202
O(16)-S(14)-C(17)-H(50)	53.4434
O(16)-S(14)-C(17)-H(51)	173.4794
C(11)-N(10)-S(14)-O(15)	174.7054
C(11)-N(10)-S(14)-O(16)	-56.8232

C(11)-N(10)-S(14)-C(17)	59.6175
C(8)-N(10)-S(14)-O(15)	37.5408
C(8)-N(10)-S(14)-O(16)	166.0122
C(8)-N(10)-S(14)-C(17)	-77.5471
C(11)-C(12)-C(13)-C(9)	-94.8622
C(11)-C(12)-C(13)-H(47)	155.8521
C(11)-C(12)-C(13)-H(48)	30.2834
C(9)-C(12)-C(13)-H(47)	-109.2858
C(9)-C(12)-C(13)-H(48)	125.1455
H(46)-C(12)-C(13)-C(9)	133.2671
H(46)-C(12)-C(13)-H(47)	23.9813
H(46)-C(12)-C(13)-H(48)	-101.5874
C(8)-C(9)-C(13)-C(12)	95.1148
C(8)-C(9)-C(13)-H(47)	-155.5994
C(8)-C(9)-C(13)-H(48)	-30.0308
C(6)-C(9)-C(13)-C(12)	-115.8889
C(6)-C(9)-C(13)-H(47)	-6.6031
C(6)-C(9)-C(13)-H(48)	118.9655
C(12)-C(9)-C(13)-H(47)	109.2858
C(12)-C(9)-C(13)-H(48)	-125.1455
C(8)-C(9)-C(12)-C(11)	1.0009
C(8)-C(9)-C(12)-C(13)	-115.5071
C(8)-C(9)-C(12)-H(46)	126.6778
C(6)-C(9)-C(12)-C(11)	-135.1321
C(6)-C(9)-C(12)-C(13)	108.3599
C(6)-C(9)-C(12)-H(46)	-9.4552
C(13)-C(9)-C(12)-C(11)	116.508
C(13)-C(9)-C(12)-H(46)	-117.8151
C(7)-C(8)-N(10)-C(11)	129.3723
C(7)-C(8)-N(10)-S(14)	-91.34
C(9)-C(8)-N(10)-C(11)	16.4602
C(9)-C(8)-N(10)-S(14)	155.748
H(43)-C(8)-N(10)-C(11)	-109.6579
H(43)-C(8)-N(10)-S(14)	29.6298
N(10)-C(11)-C(12)-C(9)	8.6605
N(10)-C(11)-C(12)-C(13)	74.8851
N(10)-C(11)-C(12)-H(46)	-140.2324
H(44)-C(11)-C(12)-C(9)	127.7445
H(44)-C(11)-C(12)-C(13)	-166.031
H(44)-C(11)-C(12)-H(46)	-21.1485
H(45)-C(11)-C(12)-C(9)	-113.6151
H(45)-C(11)-C(12)-C(13)	-47.3906
H(45)-C(11)-C(12)-H(46)	97.4919
C(8)-N(10)-C(11)-C(12)	-15.9526
C(8)-N(10)-C(11)-H(44)	-135.0366
C(8)-N(10)-C(11)-H(45)	106.323
S(14)-N(10)-C(11)-C(12)	-154.8973

S(14)-N(10)-C(11)-H(44)	86.0188
S(14)-N(10)-C(11)-H(45)	-32.6216
C(5)-C(6)-C(9)-C(8)	10.7541
C(5)-C(6)-C(9)-C(12)	145.8176
C(5)-C(6)-C(9)-C(13)	-140.839
C(1)-C(6)-C(9)-C(8)	-112.2555
C(1)-C(6)-C(9)-C(12)	22.808
C(1)-C(6)-C(9)-C(13)	96.1514
H(42)-C(6)-C(9)-C(8)	132.447
H(42)-C(6)-C(9)-C(12)	-92.4895
H(42)-C(6)-C(9)-C(13)	-19.1462
C(4)-C(5)-C(7)-C(8)	167.047
C(4)-C(5)-C(7)-N(18)	50.3635
C(4)-C(5)-C(7)-H(33)	-69.6174
C(6)-C(5)-C(7)-C(8)	38.2413
C(6)-C(5)-C(7)-N(18)	-78.4422
C(6)-C(5)-C(7)-H(33)	161.577
H(41)-C(5)-C(7)-C(8)	-83.0364
H(41)-C(5)-C(7)-N(18)	160.2801
H(41)-C(5)-C(7)-H(33)	40.2993
C(7)-C(8)-C(9)-C(6)	12.9322
C(7)-C(8)-C(9)-C(12)	-129.6285
C(7)-C(8)-C(9)-C(13)	164.4618
N(10)-C(8)-C(9)-C(6)	132.2879
N(10)-C(8)-C(9)-C(12)	-10.2727
N(10)-C(8)-C(9)-C(13)	-76.1824
H(43)-C(8)-C(9)-C(6)	-107.1754
H(43)-C(8)-C(9)-C(12)	110.264
H(43)-C(8)-C(9)-C(13)	44.3543
C(5)-C(7)-C(8)-C(9)	-30.3971
C(5)-C(7)-C(8)-N(10)	-142.7065
C(5)-C(7)-C(8)-H(43)	95.8066
N(18)-C(7)-C(8)-C(9)	88.2694
N(18)-C(7)-C(8)-N(10)	-24.04
N(18)-C(7)-C(8)-H(43)	-145.527
H(33)-C(7)-C(8)-C(9)	-156.1061
H(33)-C(7)-C(8)-N(10)	91.5845
H(33)-C(7)-C(8)-H(43)	-29.9024
C(5)-C(6)-C(1)-C(2)	37.0108
C(5)-C(6)-C(1)-H(35)	157.6468
C(5)-C(6)-C(1)-H(36)	-80.7113
C(9)-C(6)-C(1)-C(2)	153.6496
C(9)-C(6)-C(1)-H(35)	-85.7144
C(9)-C(6)-C(1)-H(36)	35.9274
H(42)-C(6)-C(1)-C(2)	-84.5233
H(42)-C(6)-C(1)-H(35)	36.1127
H(42)-C(6)-C(1)-H(36)	157.7546

C(4)-C(5)-C(6)-C(1)	-40.9257
C(4)-C(5)-C(6)-C(9)	-163.6554
C(4)-C(5)-C(6)-H(42)	74.3654
C(7)-C(5)-C(6)-C(1)	91.7597
C(7)-C(5)-C(6)-C(9)	-30.97
C(7)-C(5)-C(6)-H(42)	-152.9492
H(41)-C(5)-C(6)-C(1)	-152.1651
H(41)-C(5)-C(6)-C(9)	85.1052
H(41)-C(5)-C(6)-H(42)	-36.874
C(6)-C(5)-C(4)-O(3)	53.9085
C(6)-C(5)-C(4)-H(39)	-66.2905
C(6)-C(5)-C(4)-H(40)	173.1719
C(7)-C(5)-C(4)-O(3)	-72.1273
C(7)-C(5)-C(4)-H(39)	167.6737
C(7)-C(5)-C(4)-H(40)	47.1361
H(41)-C(5)-C(4)-O(3)	174.1708
H(41)-C(5)-C(4)-H(39)	53.9717
H(41)-C(5)-C(4)-H(40)	-66.5658
C(2)-O(3)-C(4)-C(5)	-63.2733
C(2)-O(3)-C(4)-H(39)	56.9257
C(2)-O(3)-C(4)-H(40)	177.4632
Ti(19)-O(3)-C(4)-C(5)	65.1313
Ti(19)-O(3)-C(4)-H(39)	-174.6696
Ti(19)-O(3)-C(4)-H(40)	-54.1321
C(1)-C(2)-O(3)-C(4)	58.7997
C(1)-C(2)-O(3)-Ti(19)	-66.2837
H(37)-C(2)-O(3)-C(4)	-61.5868
H(37)-C(2)-O(3)-Ti(19)	173.3297
H(38)-C(2)-O(3)-C(4)	177.431
H(38)-C(2)-O(3)-Ti(19)	52.3475
C(6)-C(1)-C(2)-O(3)	-44.7065
C(6)-C(1)-C(2)-H(37)	75.68
C(6)-C(1)-C(2)-H(38)	-163.3378
H(35)-C(1)-C(2)-O(3)	-165.3425
H(35)-C(1)-C(2)-H(37)	-44.956
H(35)-C(1)-C(2)-H(38)	76.0262
H(36)-C(1)-C(2)-O(3)	73.0156
H(36)-C(1)-C(2)-H(37)	-166.5979
H(36)-C(1)-C(2)-H(38)	-45.6156

5.2.4 Williamson ether synthesis

- **Structure elucidation of compound 450:**

- Protons and carbon signals of the tetracyclic framework were assigned as explained for compound **300**. Proton signals of the benzoxazole group were grouped based on their multiplicities (dd or ddd/dt), while carbon signals were grouped based on their positive or negative signal at Jmod. Benzoxazole signals within the same group could not be distinguished as it is difficult to predict their chemical shifts. Comparison with assigned benzoxazoles available in Literature was not possible as chemical shifts may significantly change with modifications on the substituent in position 2.[266]

^{1}H NMR in $CDCl_3$ of compound 450

^{13}C NMR in $CDCl_3$ of compound 450

NOESY in $CDCl_3$ of compound 450

NOESY correlations found for compound 450 zoomed on region (8.2-10.8; 0-11) ppm

HMBC in $CDCl_3$ of compound 450

HMBC correlations found for compound 450 zoomed on region (8.2-10.8; 0-190) ppm

6.2.3 hERG channel inhibition

The hERG assays were realised by Mike Morton (ApconiX)[267] using IonWorks™ Quattro automated patch-clamp. Compounds were analysed at a concentration of 30 µM and incubated with hERG channel for 3 minutes at rt. After, IC50 values were determined while using the activity of quinidine 1 µM as control. Compounds with %hERG channel inhibition < 30% are considered inactive. An inhibition >50% is considered active and may be biologically significant.

6.2.4 *In-silico* drug-target interaction

Docking calculated parameters for binding DNA sequence -G1ACTAATTGAC11 and compound **476**:

Random number generator was seeded with values 5148, 1636136652.

```
Docking parameter file (DPF) used for this docking:
  C:/Users/Elena/caromynomycin1.dpf
DPF> autodock_parameter_version 4.2       # used by autodock to validate parameter set
  Autodock parameter version 4.2.
DPF> outlev 1                             # diagnostic output level

Output Level = 1  ADT-COMPATIBLE OUTPUT DURING DOCKING.
DPF> intelec                              # calculate internal electrostatics

Electrostatic energies will be calculated for all non-bonds between moving atoms.
DPF> seed pid time                        # seeds for random generator

Random number generator was seeded with values 5148, 1636136652.
DPF> ligand_types A C HD OA N             # atoms types in ligand

DPF> fld DNA_model1giusto.maps.fld        # grid_data_file

Opening Grid Map Dimensions file:         DNA_model1giusto.maps.fld
Grid Point Spacing =                      0.375 Angstroms

Even Number of User-specified Grid Points = 66 x-points
                                            44 y-points
                                            68 z-points

Coordinates of Central Grid Point of Maps =  (0.739, -0.348, 7.410)
Macromolecule file used to create Grid Maps =      DNA_model1giusto.pdbqt
Grid Parameter file used to create Grid Maps =     C:/Users/Elena/Carmynomycin1.gpf
Minimum coordinates in grid = (-11.636, -8.598, -5.340)
Maximum coordinates in grid = (13.114, 7.902, 20.160)

1,4-interactions will be _ignored_ in the non-bonded internal energy calculation.


Total charge on ligand                    =      -0.001 e
REMARK  4 active torsions:
REMARK  status: ('A' for Active; 'I' for Inactive)
REMARK    1  A    between atoms: O_2  and  C_3
REMARK    2  A    between atoms: C_4  and  O_5
REMARK    3  A    between atoms: C_7  and  O_8
REMARK    4  A    between atoms: C_15  and  C_16
REMARK       I    between atoms: C_16  and  N_17


Number of Rotatable Bonds in Small Molecule =      4 torsions
Number of atoms in ligand:  33

Number of non-hydrogen atoms in ligand:  32
```

```
Number of vibrational degrees of freedom of ligand:  93


Number of torsional degrees of freedom = 4
Estimated loss of torsional free energy upon binding = +1.1932 kcal/mol


DPF> about -0.112 -0.022 -0.017          # small molecule center

Small molecule center of rotation =    (-0.112, -0.022, -0.017)

DPF> tran0 random                    # initial coordinates/A or random

Initial translation =                        (-0.558, 5.288, 13.187) Angstroms
DPF> quaternion0 random                # initial orientation

Each run will begin with a new, random initial orientation.
Initial quaternion,  (x,y,z,w) =   ( -0.173, -0.108, 0.950, 0.236 ),
DPF> dihe0 random                    # initial dihedrals (relative) or random

DPF> torsdof 4                       # torsional degrees of freedom

Number of torsional degrees of freedom = 4
Free energy coefficient for torsional degrees of freedom = 0.2983, the factory default value.

Estimated loss of torsional free energy upon binding = +1.1932 kcal/mol

DPF> rmstol 2.0                      # cluster_tolerance/A

Maximum RMS tolerance for conformational cluster analysis = 2.00 Angstroms
DPF> extnrg 1000.0                   # external grid energy

External grid energy (beyond grid map walls) = 1000.00

DPF> e0max 0.0 10000                 # max initial energy; max number of retries

Using user-specified maximum number of retries for simanneal initialization, 10000 retries.
If the simanneal initial energy is greater than e0max, 0.000,
then a new, random initial state will be created.

DPF> ga_pop_size 300                 # number of individuals in population

A population of 300 individuals will be used
DPF> ga_num_evals 2500000            # maximum number of energy evaluations

There will be at most 2500000 function evaluations used.
DPF> ga_num_generations 27000        # maximum number of generations
```

The GA will run for at most 27000 generations.
DPF> ga_elitism 1 # number of top individuals to survive to next generation

The 1 best will be preserved each GA generation.
DPF> ga_mutation_rate 0.02 # rate of gene mutation

The mutation rate is 0.020000.
DPF> ga_crossover_rate 0.8 # rate of crossover

The crossover rate is 0.800000.
DPF> ga_window_size 10 #

The GA's selection window is 10 generations.
DPF> ga_cauchy_alpha 0.0 # Alpha parameter of Cauchy distribution

The alpha parameter (for the Cauchy distribution) is being set to 0.000000.
DPF> ga_cauchy_beta 1.0 # Beta parameter Cauchy distribution

The beta parameter (for the Cauchy distribution) is being set to 1.000000.
DPF> set_ga # set the above parameters for GA or LGA

DPF> sw_max_its 300 # iterations of Solis & Wets local search

Solis & Wets algorithms will perform at most 300 iterations.
DPF> sw_max_succ 4 # consecutive successes before changing rho

Solis & Wets algorithms expand rho every 4 in a row successes.
DPF> sw_max_fail 4 # consecutive failures before changing rho

Solis & Wets algorithms contract rho every 4 in a row failures.
DPF> sw_rho 1.0 # size of local search space to sample

rho is set to 1.000000.
DPF> sw_lb_rho 0.01 # lower bound on rho

rho will never get smaller than 0.010000.
DPF> ls_search_freq 0.06 # probability of performing local search on individual

Local search will be performed with frequency 0.060000.
DPF> set_psw1 # set the above pseudo-Solis & Wets parameters

Creating a new Local Search object using the pseudo-Solis-Wets algorithm (pSW1) with the current settings.

DPF> unbound_model bound # state of unbound ligand

DPF> ga_run 50 # do this many hybrid GA-LS runs

```
centering ligand on specified point: -0.112 -0.022 -0.017
Furthest true ligand atom from "about" center is 7.557 Angstroms (maxrad).
Number of requested GA dockings = 50 runs
Unbound model to be used is 'same as bound' [AutoDock 4.2 default].

  BEGINNING GENETIC ALGORITHM DOCKING 1 of 50
Run: 1 Seed: 483677769 604312309 [ Run 1 of 50 GA/GALS ]
Beginning LAMARCKIAN GENETIC ALGORITHM (LGA), with a maximum of 2500000 energy
evaluations.

Final-Value: -12.166

FINAL GENETIC ALGORITHM DOCKED STATE
  ____________________________________________________

Detailed state:  trans 0.044 2.253 4.105 quatxyzw 0.241791 -0.589935 0.188473 0.746989
center -0.112 -0.022 -0.017 ntor 4 171.3890 -146.4195 -173.5412 81.7574
State:      0.044   2.253   4.105   0.364 -0.887  0.283 83.340    171.39 -146.42 -173.54   81.76

DOCKED: MODEL       36
DOCKED: USER    Run = 36
DOCKED: USER    DPF = C:/Users/Elena/caromynomycin1.dpf
DOCKED: USER
DOCKED: USER    Estimated Free Energy of Binding    =  -10.09 kcal/mol  [=(1)+(2)+(3)-(4)]
DOCKED: USER    Estimated Inhibition Constant, Ki   =   40.21 nM (nanomolar)  [Temperature
= 298.15 K]
DOCKED: USER
DOCKED: USER    (1) Final Intermolecular Energy     =  -11.28 kcal/mol
DOCKED: USER       vdW + Hbond + desolv Energy     =  -11.39 kcal/mol
DOCKED: USER       Electrostatic Energy            =   +0.11 kcal/mol
DOCKED: USER    (2) Final Total Internal Energy     =   -0.75 kcal/mol
DOCKED: USER    (3) Torsional Free Energy           =   +1.19 kcal/mol
DOCKED: USER    (4) Unbound System's Energy  [=(2)] =   -0.75 kcal/mol
DOCKED: USER
DOCKED: USER
DOCKED: USER    NEWDPF move DUOCARMYCIN_CBI_TMI_1.pdbqt
DOCKED: USER    NEWDPF about -0.112000 -0.022000 -0.017000
DOCKED: USER    NEWDPF tran0 0.044022 2.253163 4.104788
DOCKED: USER    NEWDPF quaternion0 0.241791 -0.589935 0.188473 0.746989
DOCKED: USER    NEWDPF axisangle0 0.363685 -0.887338 0.283487 83.339592
DOCKED: USER    NEWDPF quat0 0.363685 -0.887338 0.283487 83.339592
DOCKED: USER    NEWDPF dihe0 171.39 -146.42 -173.54 81.76
DOCKED: USER  keepresnum = 1
DOCKED: USER
DOCKED: REMARK  4 active torsions:
DOCKED: REMARK  status: ('A' for Active; 'I' for Inactive)
DOCKED: REMARK    1  A    between atoms: O_2  and  C_3
DOCKED: REMARK    2  A    between atoms: C_4  and  O_5
```

```
DOCKED: REMARK    3  A    between atoms: C_7  and  O_8
DOCKED: REMARK    4  A    between atoms: C_15  and  C_16
DOCKED: REMARK       I    between atoms: C_16  and  N_17
DOCKED: USER                          x       y       z     vdW  Elec       q    Type
DOCKED: USER                          _______ _______ _______ _____ _____    _______ ____
DOCKED: ROOT
DOCKED: ATOM      1  C          0      2.335   0.481  -2.612 -0.13 -0.28    +0.181 C
DOCKED: ATOM      2  O          0      2.190  -0.697  -1.815 -0.17 +0.62    -0.326 OA
DOCKED: ENDROOT
DOCKED: BRANCH   2   3
DOCKED: ATOM      3  C          0      1.657  -0.304  -0.627 -0.28 -0.19    +0.118 A
DOCKED: ATOM      4  C          0      2.493  -0.106   0.477 -0.33 -0.20    +0.140 A
DOCKED: ATOM      5  C          0      1.966   0.294   1.692 -0.45 -0.19    +0.134 A
DOCKED: ATOM      6  C          0      0.593   0.501   1.821 -0.54 -0.11    +0.082 A
DOCKED: ATOM      7  C          0     -0.248   0.307   0.709 -0.43 -0.03    +0.021 A
DOCKED: ATOM      8  N          0     -0.203   0.893   2.876 -0.27 +0.50    -0.348 N
DOCKED: ATOM      9  C          0      0.301  -0.098  -0.519 -0.33 -0.04    +0.028 A
DOCKED: ATOM     10  C          0     -1.567   0.594   1.131 -0.41 -0.03    +0.023 A
DOCKED: ATOM     11  C          0     -1.515   0.945   2.444 -0.45 -0.16    +0.114 A
DOCKED: ATOM     12  HN         0      0.105   1.097   3.772 -0.23 -0.27    +0.166 HD
DOCKED: BRANCH   4  13
DOCKED: ATOM     13  O          0      3.833  -0.308   0.354 -0.19 +0.45    -0.324 OA
DOCKED: ATOM     14  C          0      4.379   0.886  -0.210 -0.20 -0.25    +0.182 C
DOCKED: ENDBRANCH   4  13
DOCKED: BRANCH   5  15
DOCKED: ATOM     15  O          0      2.787   0.486   2.761 -0.37 +0.52    -0.325 OA
DOCKED: ATOM     16  C          0      3.530  -0.722   2.933 -0.47 -0.29    +0.182 C
DOCKED: ENDBRANCH   5  15
DOCKED: BRANCH  11  17
DOCKED: ATOM     17  C          0     -2.670   1.321   3.271 -0.39 -0.40    +0.276 C
DOCKED: ATOM     18  N          0     -3.771   0.544   3.280 -0.29 +0.41    -0.298 N
DOCKED: ATOM     19  C          0     -4.002  -0.717   2.526 -0.38 -0.15    +0.110 C
DOCKED: ATOM     20  C          0     -4.934   0.739   3.997 -0.57 -0.06    +0.046 C
DOCKED: ATOM     21  C          0     -5.466  -0.570   2.028 -0.28 -0.04    +0.032 A
DOCKED: ATOM     22  C          0     -5.894   0.812   1.525 -0.15 -0.02    +0.012 A
DOCKED: ATOM     23  C          0     -6.069   0.426   3.032 -0.35 -0.07    +0.054 A
DOCKED: ATOM     24  C          0     -7.448   0.235   3.585 -0.28 +0.02    -0.015 A
DOCKED: ATOM     25  C          0     -8.479  -0.253   2.818 -0.26 +0.00    -0.004 A
DOCKED: ATOM     26  C          0     -7.667   0.572   4.927 -0.40 -0.04    +0.035 A
DOCKED: ATOM     27  C          0     -9.739  -0.411   3.372 -0.22 +0.00    -0.000 A
DOCKED: ATOM     28  C          0     -9.966  -0.077   4.696 -0.26 -0.00    +0.000 A
DOCKED: ATOM     29  C          0     -8.938   0.413   5.476 -0.38 -0.00    +0.003 A
DOCKED: ATOM     30  C          0     -6.547   1.082   5.744 -0.47 -0.25    +0.196 C
DOCKED: ATOM     31  C          0     -5.219   1.111   5.254 -0.60 -0.08    +0.055 C
DOCKED: ATOM     32  O          0     -6.770   1.476   6.875 -0.42 +0.34    -0.286 OA
DOCKED: ATOM     33  O          0     -2.632   2.331   3.947 -0.43 +0.42    -0.265 OA
DOCKED: ENDBRANCH  11  17
DOCKED: ENDBRANCH   2   3
```

DOCKED: TORSDOF 4
DOCKED: TER
DOCKED: ENDMDL

_____
_____

INFORMATION ENTROPY ANALYSIS FOR THIS CLUSTERING
_____

Information entropy for this clustering = 0.12 (rmstol = 2.00 Angstrom)

_____

STATISTICAL MECHANICAL ANALYSIS
_____

Partition function, Q = 50.83 at Temperature, T = 298.15 K
Free energy, A ~ -2327.54 kcal/mol at Temperature, T = 298.15 K
Internal energy, U = -9.74 kcal/mol at Temperature, T = 298.15 K
Entropy, S = 7.77 kcal/mol/K at Temperature, T = 298.15 K

_____

LOWEST ENERGY DOCKED CONFORMATION from EACH CLUSTER
_____

Keeping original residue number (specified in the input PDBQ file) for outputting.

MODEL 36
USER Run = 36
USER Cluster Rank = 1
USER Number of conformations in this cluster = 9
USER
USER RMSD from reference structure = 3.648 A
USER
USER Estimated Free Energy of Binding = -10.09 kcal/mol [=(1)+(2)+(3)-(4)]
USER Estimated Inhibition Constant, Ki = 40.21 nM (nanomolar) [Temperature = 298.15 K]
USER
USER (1) Final Intermolecular Energy = -11.28 kcal/mol
USER vdW + Hbond + desolv Energy = -11.39 kcal/mol
USER Electrostatic Energy = +0.11 kcal/mol
USER (2) Final Total Internal Energy = -0.75 kcal/mol

```
USER    (3) Torsional Free Energy          =   +1.19 kcal/mol
USER    (4) Unbound System's Energy  [=(2)] =   -0.75 kcal/mol
USER
USER
USER
USER    DPF = C:/Users/Elena/caromynomycin1.dpf
USER    NEWDPF move DUOCARMYCIN_CBI_TMI_1.pdbqt
USER    NEWDPF about -0.112000 -0.022000 -0.017000
USER    NEWDPF tran0  0.044022 2.253163 4.104788
USER    NEWDPF axisangle0     0.363685 -0.887338 0.283487 83.339592
USER    NEWDPF quaternion0  0.241791 -0.589935 0.188473 0.746989
USER    NEWDPF dihe0 171.39 -146.42 -173.54 81.76
USER
USER                    x      y      z    vdW   Elec       q     RMS
ATOM     1  C         0      2.335   0.481  -2.612 -0.13 -0.28    +0.181     3.648
ATOM     2  O         0      2.190  -0.697  -1.815 -0.17 +0.62    -0.326     3.648
ATOM     3  C         0      1.657  -0.304  -0.627 -0.28 -0.19    +0.118     3.648
ATOM     4  C         0      2.493  -0.106   0.477 -0.33 -0.20    +0.140     3.648
ATOM     5  C         0      1.966   0.294   1.692 -0.45 -0.19    +0.134     3.648
ATOM     6  C         0      0.593   0.501   1.821 -0.54 -0.11    +0.082     3.648
ATOM     7  C         0     -0.248   0.307   0.709 -0.43 -0.03    +0.021     3.648
ATOM     8  N         0     -0.203   0.893   2.876 -0.27 +0.50    -0.348     3.648
ATOM     9  C         0      0.301  -0.098  -0.519 -0.33 -0.04    +0.028     3.648
ATOM    10  C         0     -1.567   0.594   1.131 -0.41 -0.03    +0.023     3.648
ATOM    11  C         0     -1.515   0.945   2.444 -0.45 -0.16    +0.114     3.648
ATOM    12  HN        0      0.105   1.097   3.772 -0.23 -0.27    +0.166     3.648
ATOM    13  O         0      3.833  -0.308   0.354 -0.19 +0.45    -0.324     3.648
ATOM    14  C         0      4.379   0.886  -0.210 -0.20 -0.25    +0.182     3.648
ATOM    15  O         0      2.787   0.486   2.761 -0.37 +0.52    -0.325     3.648
ATOM    16  C         0      3.530  -0.722   2.933 -0.47 -0.29    +0.182     3.648
ATOM    17  C         0     -2.670   1.321   3.271 -0.39 -0.40    +0.276     3.648
ATOM    18  N         0     -3.771   0.544   3.280 -0.29 +0.41    -0.298     3.648
ATOM    19  C         0     -4.002  -0.717   2.526 -0.38 -0.15    +0.110     3.648
ATOM    20  C         0     -4.934   0.739   3.997 -0.57 -0.06    +0.046     3.648
ATOM    21  C         0     -5.466  -0.570   2.028 -0.28 -0.04    +0.032     3.648
ATOM    22  C         0     -5.894   0.812   1.525 -0.15 -0.02    +0.012     3.648
ATOM    23  C         0     -6.069   0.426   3.032 -0.35 -0.07    +0.054     3.648
ATOM    24  C         0     -7.448   0.235   3.585 -0.28 +0.02    -0.015     3.648
ATOM    25  C         0     -8.479  -0.253   2.818 -0.26 +0.00    -0.004     3.648
ATOM    26  C         0     -7.667   0.572   4.927 -0.40 -0.04    +0.035     3.648
ATOM    27  C         0     -9.739  -0.411   3.372 -0.22 +0.00    -0.000     3.648
ATOM    28  C         0     -9.966  -0.077   4.696 -0.26 -0.00    +0.000     3.648
ATOM    29  C         0     -8.938   0.413   5.476 -0.38 -0.00    +0.003     3.648
ATOM    30  C         0     -6.547   1.082   5.744 -0.47 -0.25    +0.196     3.648
ATOM    31  C         0     -5.219   1.111   5.254 -0.60 -0.08    +0.055     3.648
ATOM    32  O         0     -6.770   1.476   6.875 -0.42 +0.34    -0.286     3.648
ATOM    33  O         0     -2.632   2.331   3.947 -0.43 +0.42    -0.265     3.648
TER
```

ENDMDL

binding_energy=-10.09
ligand_efficiency=-0.32
inhib_constant=40.21
inhib_constant_units=nM
intermol_energy=-11.28
vdw_hb_desolv_energy=-11.39
electrostatic_energy=0.11
total_internal=-0.75
torsional_energy=1.19
unbound_energy=-0.75
filename=caromynomycin1.dlg
cIRMS=0.0
refRMS=3.65
rseed1=None
rseed2=None
1 hydrogen bonds formed:
DUOCARMYCIN_CBI_TMI_1: : 0:HN : DNA_model1giusto:B: DT18:O2

Docking calculated parameters for binding DNA sequence -G1ACTAATTGAC11 and compound

477:

```
Random number generator was seeded with values 1080, 1636891993.
Docking parameter file (DPF) used for this docking:
  C:/Users/Elena/ELGI02_056_fr327.dpf
DPF> autodock_parameter_version 4.2       # used by autodock to validate parameter set

  Autodock parameter version 4.2.
DPF> outlev 1                             # diagnostic output level

Output Level = 1  ADT-COMPATIBLE OUTPUT DURING DOCKING.
DPF> intelec                              # calculate internal electrostatics

Electrostatic energies will be calculated for all non-bonds between moving atoms.
DPF> seed pid time                        # seeds for random generator

Random number generator was seeded with values 1080, 1636891993.
DPF> ligand_types A C HD OA N             # atoms types in ligand

DPF> fld DNA_model1giusto.maps.fld        # grid_data_file

Opening Grid Map Dimensions file:         DNA_model1giusto.maps.fld
Grid Point Spacing =                      0.375 Angstroms

Even Number of User-specified Grid Points = 62 x-points
                                            42 y-points
                                            62 z-points

Coordinates of Central Grid Point of Maps =  (1.131, -0.096, 8.332)
Macromolecule file used to create Grid Maps =       DNA_model1giusto.pdbqt
Grid Parameter file used to create Grid Maps =      C:/Users/Elena/ELGI02_056_fr327.gpf
Minimum coordinates in grid = (-10.494, -7.971, -3.293)
Maximum coordinates in grid = (12.756, 7.779, 19.957)

1,4-interactions will be _ignored_ in the non-bonded internal energy calculation.

Total charge on ligand                    =      -0.001 e
REMARK  2 active torsions:
REMARK  status: ('A' for Active; 'I' for Inactive)
REMARK    1  A    between atoms: C_7  and  O_25
REMARK       I    between atoms: N_10  and  C_14
REMARK    2  A    between atoms: C_14  and  C_15


Number of Rotatable Bonds in Small Molecule =       2 torsions
```

```
Number of atoms in ligand:  26

Number of non-hydrogen atoms in ligand:  25

Number of vibrational degrees of freedom of ligand:  72


Number of torsional degrees of freedom = 2
Estimated loss of torsional free energy upon binding = +0.5966 kcal/mol


DPF> about -0.079 -0.057 -0.076          # small molecule center

Small molecule center of rotation =    (-0.079, -0.057, -0.076)

DPF> tran0 random                    # initial coordinates/A or random

Initial translation =                        (-9.121, -0.392, 2.086) Angstroms
DPF> quaternion0 random              # initial orientation

Each run will begin with a new, random initial orientation.
Initial quaternion,  (x,y,z,w) =   ( -0.646, 0.718, 0.067, -0.248 ),
DPF> dihe0 random                    # initial dihedrals (relative) or random

DPF> torsdof 2                       # torsional degrees of freedom

Number of torsional degrees of freedom = 2
Free energy coefficient for torsional degrees of freedom = 0.2983, the factory default value.

Estimated loss of torsional free energy upon binding = +0.5966 kcal/mol

DPF> rmstol 2.0                      # cluster_tolerance/A

Maximum RMS tolerance for conformational cluster analysis = 2.00 Angstroms
DPF> extnrg 1000.0                   # external grid energy

External grid energy (beyond grid map walls) = 1000.00

DPF> e0max 0.0 10000                 # max initial energy; max number of retries

Using user-specified maximum number of retries for simanneal initialization, 10000 retries.
If the simanneal initial energy is greater than e0max, 0.000,
then a new, random initial state will be created.

DPF> ga_pop_size 300                 # number of individuals in population

A population of 300 individuals will be used
DPF> ga_num_evals 2500000            # maximum number of energy evaluations
```

```
There will be at most 2500000 function evaluations used.
DPF> ga_num_generations 27000          # maximum number of generations

The GA will run for at most 27000 generations.
DPF> ga_elitism 1                      # number of top individuals to survive to next generation

The 1 best will be preserved each GA generation.
DPF> ga_mutation_rate 0.02             # rate of gene mutation

The mutation rate is 0.020000.
DPF> ga_crossover_rate 0.8             # rate of crossover

The crossover rate is 0.800000.
DPF> ga_window_size 10                 #

The GA's selection window is 10 generations.
DPF> ga_cauchy_alpha 0.0               # Alpha parameter of Cauchy distribution

The alpha parameter (for the Cauchy distribution) is being set to 0.000000.
DPF> ga_cauchy_beta 1.0                # Beta parameter Cauchy distribution

The beta parameter (for the Cauchy distribution) is being set to 1.000000.
DPF> set_ga                            # set the above parameters for GA or LGA

DPF> sw_max_its 300                    # iterations of Solis & Wets local search

Solis & Wets algorithms will perform at most 300 iterations.
DPF> sw_max_succ 4                     # consecutive successes before changing rho

Solis & Wets algorithms expand rho every 4 in a row successes.
DPF> sw_max_fail 4                     # consecutive failures before changing rho

Solis & Wets algorithms contract rho every 4 in a row failures.
DPF> sw_rho 1.0                        # size of local search space to sample

rho is set to 1.000000.
DPF> sw_lb_rho 0.01                    # lower bound on rho

rho will never get smaller than 0.010000.
DPF> ls_search_freq 0.06               # probability of performing local search on individual

Local search will be performed with frequency 0.060000.
DPF> set_psw1                          # set the above pseudo-Solis & Wets parameters

Creating a new Local Search object using the pseudo-Solis-Wets algorithm (pSW1) with the
current settings.
```

```
DPF> unbound_model bound              # state of unbound ligand

DPF> ga_run 50                        # do this many hybrid GA-LS runs

centering ligand on specified point: -0.079 -0.057 -0.076
Furthest true ligand atom from "about" center is 5.993 Angstroms (maxrad).
Number of requested GA dockings = 50 runs
Unbound model to be used is 'same as bound' [AutoDock 4.2 default].

  BEGINNING GENETIC ALGORITHM DOCKING 1 of 50
Run: 1 Seed: 1513763855 485636297 [ Run 1 of 50 GA/GALS ]
Beginning LAMARCKIAN GENETIC ALGORITHM (LGA), with a maximum of 2500000 energy
evaluations.

Final-Value: -7.968

FINAL GENETIC ALGORITHM DOCKED STATE
  ____________________________________________________


Detailed state:  trans -5.998 1.841 5.063 quatxyzw 0.861548 -0.163860 -0.382051 0.291414
center -0.079 -0.057 -0.076 ntor 2 20.1646 -82.3508
State:     -5.998   1.841   5.063   0.901 -0.171 -0.399 146.115     20.16  -82.35

DOCKED: MODEL       43
DOCKED: USER    Run = 43
DOCKED: USER    DPF = C:/Users/Elena/ELGI02_056_fr327.dpf
DOCKED: USER
DOCKED: USER    Estimated Free Energy of Binding    =  -10.08 kcal/mol  [=(1)+(2)+(3)-(4)]
DOCKED: USER    Estimated Inhibition Constant, Ki   =   40.91 nM (nanomolar)  [Temperature
= 298.15 K]
DOCKED: USER
DOCKED: USER    (1) Final Intermolecular Energy     =  -10.68 kcal/mol
DOCKED: USER       vdW + Hbond + desolv Energy     =  -10.29 kcal/mol
DOCKED: USER       Electrostatic Energy            =   -0.39 kcal/mol
DOCKED: USER    (2) Final Total Internal Energy     =   -0.43 kcal/mol
DOCKED: USER    (3) Torsional Free Energy           =   +0.60 kcal/mol
DOCKED: USER    (4) Unbound System's Energy  [=(2)] =   -0.43 kcal/mol
DOCKED: USER
DOCKED: USER
DOCKED: USER    NEWDPF move ELGI02_056_fr327.pdbqt
DOCKED: USER    NEWDPF about -0.079000 -0.057000 -0.076000
DOCKED: USER    NEWDPF tran0 -5.997568 1.841204 5.063103
DOCKED: USER    NEWDPF quaternion0 0.861548 -0.163860 -0.382051 0.291414
DOCKED: USER    NEWDPF axisangle0 0.900638 -0.171295 -0.399385 146.114771
DOCKED: USER    NEWDPF quat0 0.900638 -0.171295 -0.399385 146.114771
DOCKED: USER    NEWDPF dihe0 20.16 -82.35
DOCKED: USER  keepresnum = 1
```

```
DOCKED: USER
DOCKED: REMARK  2 active torsions:
DOCKED: REMARK  status: ('A' for Active; 'I' for Inactive)
DOCKED: REMARK    1  A    between atoms: C_7  and  O_25
DOCKED: REMARK       I    between atoms: N_10  and  C_14
DOCKED: REMARK    2  A    between atoms: C_14  and  C_15
DOCKED: USER                          x       y       z     vdW  Elec       q    Type
DOCKED: USER                     _______ _______ _______ _____ _____    ______ ____
DOCKED: ROOT
DOCKED: ATOM      1  C         0    -10.313   1.774   9.070 -0.21 -0.18    +0.172 C
DOCKED: ATOM      2  O         0     -9.460   2.739   9.687 -0.62 +0.31    -0.387 OA
DOCKED: ATOM      3  C         0     -8.105   2.326   9.494 +0.00 -0.18    +0.204 C
DOCKED: ATOM      4  C         0     -7.849   2.155   8.017 -0.55 +0.02    -0.023 C
DOCKED: ATOM      5  C         0     -8.821   1.990   7.133 -0.51 +0.05    -0.060 C
DOCKED: ATOM      6  C         0    -10.275   1.957   7.545 -0.37 -0.06    +0.061 C
DOCKED: ATOM      7  C         0     -6.500   2.148   7.328 -0.51 -0.17    +0.173 C
DOCKED: ATOM      8  C         0     -6.847   2.533   5.871 -0.40 -0.11    +0.133 C
DOCKED: ATOM      9  C         0     -8.242   1.850   5.762 -0.49 -0.01    +0.013 A
DOCKED: ATOM     10  N         0     -5.998   1.837   4.898 -0.24 +0.42    -0.339 N
DOCKED: ATOM     11  C         0     -6.466   0.436   4.882 -0.33 -0.18    +0.132 C
DOCKED: ATOM     12  C         0     -7.982   0.485   5.078 -0.40 -0.03    +0.020 A
DOCKED: ATOM     13  C         0     -8.892   1.519   4.442 -0.26 -0.03    +0.024 A
DOCKED: ATOM     14  C         0     -4.997   2.367   4.168 -0.42 -0.33    +0.257 C
DOCKED: ATOM     15  O         0     -4.785   3.563   4.206 -1.19 +0.28    -0.267 OA
DOCKED: ENDROOT
DOCKED: BRANCH  14  16
DOCKED: ATOM     16  C         0     -4.158   1.494   3.324 -0.53 -0.09    +0.068 A
DOCKED: ATOM     17  C         0     -4.729   0.789   2.259 -0.37 -0.17    +0.120 A
DOCKED: ATOM     18  C         0     -3.929  -0.032   1.468 -0.35 -0.15    +0.106 A
DOCKED: ATOM     19  O         0     -6.008   0.729   1.795 -0.20 +0.43    -0.322 OA
DOCKED: ATOM     20  C         0     -2.575  -0.144   1.738 -0.37 -0.05    +0.040 A
DOCKED: ATOM     21  O         0     -4.709  -0.605   0.505 -0.20 +0.46    -0.323 OA
DOCKED: ATOM     22  C         0     -2.011   0.555   2.791 -0.54 -0.01    +0.004 A
DOCKED: ATOM     23  C         0     -2.789   1.373   3.580 -0.61 -0.03    +0.020 A
DOCKED: ATOM     24  C         0     -5.911   0.187   0.465 -0.14 -0.50    +0.352 C
DOCKED: ENDBRANCH  14  16
DOCKED: BRANCH   7  25
DOCKED: ATOM     25  O         0     -5.628   3.118   7.912 -0.14 +0.22    -0.389 OA
DOCKED: ATOM     26  H         0     -5.255   2.715   8.707 -0.34 -0.31    +0.210 HD
DOCKED: ENDBRANCH   7  25
DOCKED: TORSDOF 2
DOCKED: TER
DOCKED: ENDMDL
INFORMATION ENTROPY ANALYSIS FOR THIS CLUSTERING
  ____________________________________________________


Information entropy for this clustering = 0.28  (rmstol = 2.00 Angstrom)
```

STATISTICAL MECHANICAL ANALYSIS

Partition function, Q = 50.65 at Temperature, T = 298.15 K
Free energy, A ~ -2325.40 kcal/mol at Temperature, T = 298.15 K
Internal energy, U = -7.60 kcal/mol at Temperature, T = 298.15 K
Entropy, S = 7.77 kcal/mol/K at Temperature, T = 298.15 K

LOWEST ENERGY DOCKED CONFORMATION from EACH CLUSTER

Keeping original residue number (specified in the input PDBQ file) for outputting.

```
MODEL     43
USER    Run = 43
USER    Cluster Rank = 1
USER    Number of conformations in this cluster = 2
USER
USER    RMSD from reference structure       = 6.588 A
USER
USER    Estimated Free Energy of Binding    =  -10.08 kcal/mol  [=(1)+(2)+(3)-(4)]
USER    Estimated Inhibition Constant, Ki   =   40.91 nM (nanomolar)  [Temperature = 298.15
K]
USER
USER    (1) Final Intermolecular Energy     =  -10.68 kcal/mol
USER        vdW + Hbond + desolv Energy     =  -10.29 kcal/mol
USER        Electrostatic Energy            =   -0.39 kcal/mol
USER    (2) Final Total Internal Energy     =   -0.43 kcal/mol
USER    (3) Torsional Free Energy           =   +0.60 kcal/mol
USER    (4) Unbound System's Energy  [=(2)] =   -0.43 kcal/mol
USER
USER
USER
USER    DPF = C:/Users/Elena/ELGI02_056_fr327.dpf
USER    NEWDPF move ELGI02_056_fr327.pdbqt
USER    NEWDPF about -0.079000 -0.057000 -0.076000
USER    NEWDPF tran0  -5.997568 1.841204 5.063103
USER    NEWDPF axisangle0     0.900638 -0.171295 -0.399385 146.114771
USER    NEWDPF quaternion0  0.861548 -0.163860 -0.382051 0.291414
```

```
USER    NEWDPF dihe0 20.16 -82.35
USER
USER                    x      y      z    vdW   Elec       q     RMS
ATOM      1  C         0   -10.313   1.774   9.070 -0.21 -0.18   +0.172     6.588
ATOM      2  O         0    -9.460   2.739   9.687 -0.62 +0.31   -0.387     6.588
ATOM      3  C         0    -8.105   2.326   9.494 +0.00 -0.18   +0.204     6.588
ATOM      4  C         0    -7.849   2.155   8.017 -0.55 +0.02   -0.023     6.588
ATOM      5  C         0    -8.821   1.990   7.133 -0.51 +0.05   -0.060     6.588
ATOM      6  C         0   -10.275   1.957   7.545 -0.37 -0.06   +0.061     6.588
ATOM      7  C         0    -6.500   2.148   7.328 -0.51 -0.17   +0.173     6.588
ATOM      8  C         0    -6.847   2.533   5.871 -0.40 -0.11   +0.133     6.588
ATOM      9  C         0    -8.242   1.850   5.762 -0.49 -0.01   +0.013     6.588
ATOM     10  N         0    -5.998   1.837   4.898 -0.24 +0.42   -0.339     6.588
ATOM     11  C         0    -6.466   0.436   4.882 -0.33 -0.18   +0.132     6.588
ATOM     12  C         0    -7.982   0.485   5.078 -0.40 -0.03   +0.020     6.588
ATOM     13  C         0    -8.892   1.519   4.442 -0.26 -0.03   +0.024     6.588
ATOM     14  C         0    -4.997   2.367   4.168 -0.42 -0.33   +0.257     6.588
ATOM     15  O         0    -4.785   3.563   4.206 -1.19 +0.28   -0.267     6.588
ATOM     16  C         0    -4.158   1.494   3.324 -0.53 -0.09   +0.068     6.588
ATOM     17  C         0    -4.729   0.789   2.259 -0.37 -0.17   +0.120     6.588
ATOM     18  C         0    -3.929  -0.032   1.468 -0.35 -0.15   +0.106     6.588
ATOM     19  O         0    -6.008   0.729   1.795 -0.20 +0.43   -0.322     6.588
ATOM     20  C         0    -2.575  -0.144   1.738 -0.37 -0.05   +0.040     6.588
ATOM     21  O         0    -4.709  -0.605   0.505 -0.20 +0.46   -0.323     6.588
ATOM     22  C         0    -2.011   0.555   2.791 -0.54 -0.01   +0.004     6.588
ATOM     23  C         0    -2.789   1.373   3.580 -0.61 -0.03   +0.020     6.588
ATOM     24  C         0    -5.911   0.187   0.465 -0.14 -0.50   +0.352     6.588
ATOM     25  O         0    -5.628   3.118   7.912 -0.14 +0.22   -0.389     6.588
ATOM     26  H         0    -5.255   2.715   8.707 -0.34 -0.31   +0.210     6.588
TER
ENDMDL
```

binding_energy=-10.08
ligand_efficiency=-0.4
inhib_constant=40.91
inhib_constant_units=nM
intermol_energy=-10.68
vdw_hb_desolv_energy=-10.29
electrostatic_energy=-0.39
total_internal=-0.43
torsional_energy=0.6
unbound_energy=-0.43
filename=ELGI02_056_fr327.dlg
cIRMS=0.0
refRMS=6.59
rseed1=None
rseed2=None
3 hydrogen bonds formed:
ELGI02_056_fr327: : 0:H : DNA_model1giusto:A: DT4:O2
DNA_model1giusto:B: DA19:H3 : ELGI02_056_fr327: : 0:O
DNA_model1giusto:B: DG20:H22 : ELGI02_056_fr327: : 0:O

Docking calculated parameters for binding DNA sequence -G1ACTAATTGAC11 and compound

478:

```
Random number generator was seeded with values 17896, 1638558181.
Docking parameter file (DPF) used for this docking:
  C:/Users/Elena/ELGI02_056_fr327_enantiomer2.dpf
DPF> autodock_parameter_version 4.2       # used by autodock to validate parameter set

  Autodock parameter version 4.2.
DPF> outlev 1                             # diagnostic output level

Output Level = 1  ADT-COMPATIBLE OUTPUT DURING DOCKING.
DPF> intelec                              # calculate internal electrostatics

Electrostatic energies will be calculated for all non-bonds between moving atoms.
DPF> seed pid time                        # seeds for random generator

Random number generator was seeded with values 17896, 1638558181.
DPF> ligand_types A C HD OA N             # atoms types in ligand

DPF> fld DNA_model1giusto.maps.fld        # grid_data_file

Opening Grid Map Dimensions file:         DNA_model1giusto.maps.fld
Grid Point Spacing =                      0.375 Angstroms

Even Number of User-specified Grid Points = 64 x-points
                                            42 y-points
                                            58 z-points

Coordinates of Central Grid Point of Maps =  (1.241, 0.184, 7.803)
Macromolecule file used to create Grid Maps =       DNA_model1giusto.pdbqt
Grid Parameter file used to create Grid Maps =
  C:/Users/Elena/ELGI02_056_fr327_enantiomer2.gpf
Minimum coordinates in grid = (-10.759, -7.691, -3.072)
Maximum coordinates in grid = (13.241, 8.059, 18.678)

1,4-interactions will be _ignored_ in the non-bonded internal energy calculation.

Total charge on ligand                    =      +0.999 e
REMARK  3 active torsions:
REMARK  status: ('A' for Active; 'I' for Inactive)
REMARK    1  A    between atoms: C_7  and  O_14
REMARK    2  A    between atoms: N_10  and  C_15
REMARK    3  A    between atoms: C_15  and  C_16
```

```
Number of Rotatable Bonds in Small Molecule =       3 torsions
Number of atoms in ligand:  25

Number of non-hydrogen atoms in ligand:  24

Number of vibrational degrees of freedom of ligand:  69


Number of torsional degrees of freedom = 3
Estimated loss of torsional free energy upon binding = +0.8949 kcal/mol


DPF> about -0.040 -0.105 0.019          # small molecule center

Small molecule center of rotation =    (-0.040, -0.105, +0.019)

DPF> tran0 random                    # initial coordinates/A or random

Initial translation =                        (8.448, 7.848, 10.801) Angstroms
DPF> quaternion0 random                # initial orientation

Each run will begin with a new, random initial orientation.
Initial quaternion,  (x,y,z,w) =   ( -0.768, 0.627, -0.105, 0.081 ),
DPF> dihe0 random                    # initial dihedrals (relative) or random

DPF> torsdof 3                      # torsional degrees of freedom

Number of torsional degrees of freedom = 3
Free energy coefficient for torsional degrees of freedom = 0.2983, the factory default value.

Estimated loss of torsional free energy upon binding = +0.8949 kcal/mol

DPF> rmstol 2.0                     # cluster_tolerance/A

Maximum RMS tolerance for conformational cluster analysis = 2.00 Angstroms
DPF> extnrg 1000.0                  # external grid energy

External grid energy (beyond grid map walls) = 1000.00

DPF> e0max 0.0 10000                # max initial energy; max number of retries

Using user-specified maximum number of retries for simanneal initialization, 10000 retries.
If the simanneal initial energy is greater than e0max, 0.000,
then a new, random initial state will be created.

DPF> ga_pop_size 300                # number of individuals in population

A population of 300 individuals will be used
```

```
DPF> ga_num_evals 2500000              # maximum number of energy evaluations

There will be at most 2500000 function evaluations used.
DPF> ga_num_generations 27000          # maximum number of generations

The GA will run for at most 27000 generations.
DPF> ga_elitism 1                      # number of top individuals to survive to next generation

The 1 best will be preserved each GA generation.
DPF> ga_mutation_rate 0.02             # rate of gene mutation

The mutation rate is 0.020000.
DPF> ga_crossover_rate 0.8             # rate of crossover

The crossover rate is 0.800000.
DPF> ga_window_size 10                 #

The GA's selection window is 10 generations.
DPF> ga_cauchy_alpha 0.0               # Alpha parameter of Cauchy distribution

The alpha parameter (for the Cauchy distribution) is being set to 0.000000.
DPF> ga_cauchy_beta 1.0                # Beta parameter Cauchy distribution

The beta parameter (for the Cauchy distribution) is being set to 1.000000.
DPF> set_ga                            # set the above parameters for GA or LGA

DPF> sw_max_its 300                    # iterations of Solis & Wets local search

Solis & Wets algorithms will perform at most 300 iterations.
DPF> sw_max_succ 4                     # consecutive successes before changing rho

Solis & Wets algorithms expand rho every 4 in a row successes.
DPF> sw_max_fail 4                     # consecutive failures before changing rho

Solis & Wets algorithms contract rho every 4 in a row failures.
DPF> sw_rho 1.0                        # size of local search space to sample

rho is set to 1.000000.
DPF> sw_lb_rho 0.01                    # lower bound on rho

rho will never get smaller than 0.010000.
DPF> ls_search_freq 0.06               # probability of performing local search on individual

Local search will be performed with frequency 0.060000.
DPF> set_psw1                          # set the above pseudo-Solis & Wets parameters

Creating a new Local Search object using the pseudo-Solis-Wets algorithm (pSW1) with the
current settings.
```

```
DPF> unbound_model bound              # state of unbound ligand

DPF> ga_run 50                        # do this many hybrid GA-LS runs

centering ligand on specified point: -0.040 -0.105 0.019
Furthest true ligand atom from "about" center is 5.601 Angstroms (maxrad).
Number of requested GA dockings = 50 runs
Unbound model to be used is 'same as bound' [AutoDock 4.2 default].

  BEGINNING GENETIC ALGORITHM DOCKING 1 of 50
Run: 1 Seed: 1117371348 1905436500 [ Run 1 of 50 GA/GALS ]
Beginning LAMARCKIAN GENETIC ALGORITHM (LGA), with a maximum of 2500000 energy
evaluations.

Final-Value: -10.691

FINAL GENETIC ALGORITHM DOCKED STATE
  ____________________________________________________


Detailed state:  trans -2.979 1.207 2.005 quatxyzw -0.598309 0.279365 0.230327 -0.714794
center -0.040 -0.105 0.019 ntor 3 -79.1992 140.8410 -18.8669
State:     -2.979   1.207   2.005  -0.856  0.399  0.329 -88.747    -79.20  140.84  -18.87

DOCKED: MODEL       49
DOCKED: USER    Run = 49
DOCKED: USER    DPF = C:/Users/Elena/ELGI02_056_fr327_enantiomer2.dpf
DOCKED: USER
DOCKED: USER    Estimated Free Energy of Binding    =  -10.48 kcal/mol  [=(1)+(2)+(3)-(4)]
DOCKED: USER    Estimated Inhibition Constant, Ki   =   20.75 nM (nanomolar)  [Temperature
= 298.15 K]
DOCKED: USER
DOCKED: USER    (1) Final Intermolecular Energy     =  -11.38 kcal/mol
DOCKED: USER       vdW + Hbond + desolv Energy     =   -9.75 kcal/mol
DOCKED: USER       Electrostatic Energy            =   -1.62 kcal/mol
DOCKED: USER    (2) Final Total Internal Energy     =   -0.24 kcal/mol
DOCKED: USER    (3) Torsional Free Energy           =   +0.89 kcal/mol
DOCKED: USER    (4) Unbound System's Energy  [=(2)] =   -0.24 kcal/mol
DOCKED: USER
DOCKED: USER
DOCKED: USER    NEWDPF move ELGI02_056_fr327_enntiomer2.pdbqt
DOCKED: USER    NEWDPF about -0.040000 -0.105000 0.019000
DOCKED: USER    NEWDPF tran0 -2.978762 1.207012 2.005193
DOCKED: USER    NEWDPF quaternion0 -0.598309 0.279365 0.230327 -0.714794
DOCKED: USER    NEWDPF axisangle0 -0.855541 0.399472 0.329352 -88.747345
DOCKED: USER    NEWDPF quat0 -0.855541 0.399472 0.329352 -88.747345
DOCKED: USER    NEWDPF dihe0 -79.20 140.84 -18.87
```

```
DOCKED: USER  keepresnum = 1
DOCKED: USER
DOCKED: REMARK  3 active torsions:
DOCKED: REMARK  status: ('A' for Active; 'I' for Inactive)
DOCKED: REMARK    1  A    between atoms: C_7  and  O_14
DOCKED: REMARK    2  A    between atoms: N_10  and  C_15
DOCKED: REMARK    3  A    between atoms: C_15  and  C_16
DOCKED: USER                    x       y       z     vdW  Elec       q    Type
DOCKED: USER                _______ _______ _______ _____ _____    ______ ____
DOCKED: ROOT
DOCKED: ATOM      1  C         0     -7.328   1.377   5.530 -0.44 -0.20    +0.172 C
DOCKED: ATOM      2  O         0     -6.697   2.657   5.566 -0.27 +0.34    -0.387 OA
DOCKED: ATOM      3  C         0     -5.282   2.456   5.587 -0.48 -0.21    +0.204 C
DOCKED: ATOM      4  C         0     -4.886   1.625   4.392 -0.69 +0.03    -0.023 C
DOCKED: ATOM      5  C         0     -5.746   0.872   3.724 -0.49 +0.08    -0.059 C
DOCKED: ATOM      6  C         0     -7.201   0.780   4.120 -0.41 -0.08    +0.061 C
DOCKED: ATOM      7  C         0     -3.503   1.517   3.782 -0.54 -0.26    +0.184 C
DOCKED: ATOM      8  C         0     -3.555   0.168   3.028 -0.37 -0.36    +0.269 C
DOCKED: ATOM      9  C         0     -5.049   0.188   2.591 -0.43 -0.03    +0.023 A
DOCKED: ATOM     10  N         0     -2.784   0.205   1.775 -0.40 -0.13    +0.101 N
DOCKED: ATOM     11  C         0     -3.581   1.027   0.837 -0.22 -0.45    +0.279 C
DOCKED: ATOM     12  C         0     -5.050   0.723   1.137 -0.33 -0.05    +0.030 A
DOCKED: ATOM     13  C         0     -5.585  -0.658   1.465 -0.35 -0.03    +0.024 A
DOCKED: ENDROOT
DOCKED: BRANCH   7  14
DOCKED: ATOM     14  O         0     -2.503   1.487   4.803 -0.24 +0.58    -0.389 OA
DOCKED: ATOM     15  H         0     -1.761   2.017   4.483 -0.34 -0.40    +0.210 HD
DOCKED: ENDBRANCH   7  14
DOCKED: BRANCH  10  16
DOCKED: ATOM     16  C         0     -1.556   0.959   2.057 -0.30 -0.43    +0.314 C
DOCKED: BRANCH  16  17
DOCKED: ATOM     17  C         0     -0.451   0.476   1.153 -0.49 -0.01    +0.006 A
DOCKED: ATOM     18  C         0      0.831   0.315   1.652 -0.50 -0.16    +0.113 A
DOCKED: ATOM     19  C         0      1.849  -0.132   0.813 -0.43 -0.15    +0.105 A
DOCKED: ATOM     20  O         0      1.351   0.522   2.897 -0.47 +0.48    -0.322 OA
DOCKED: ATOM     21  C         0      1.575  -0.415  -0.515 -0.33 -0.07    +0.040 A
DOCKED: ATOM     22  O         0      3.007  -0.205   1.533 -0.33 +0.46    -0.323 OA
DOCKED: ATOM     23  C         0      0.293  -0.251  -1.006 -0.31 -0.00    +0.003 A
DOCKED: ATOM     24  C         0     -0.719   0.187  -0.173 -0.33 -0.02    +0.012 A
DOCKED: ATOM     25  C         0      2.601  -0.191   2.915 -0.27 -0.55    +0.352 C
DOCKED: ENDBRANCH  16  17
DOCKED: ENDBRANCH  10  16
DOCKED: TORSDOF 3
DOCKED: TER
DOCKED: ENDMDL
```

INFORMATION ENTROPY ANALYSIS FOR THIS CLUSTERING

Information entropy for this clustering = 0.38 (rmstol = 2.00 Angstrom)

STATISTICAL MECHANICAL ANALYSIS

Partition function, Q = 50.84 at Temperature, T = 298.15 K
Free energy, A ~ -2327.62 kcal/mol at Temperature, T = 298.15 K
Internal energy, U = -9.82 kcal/mol at Temperature, T = 298.15 K
Entropy, S = 7.77 kcal/mol/K at Temperature, T = 298.15 K

LOWEST ENERGY DOCKED CONFORMATION from EACH CLUSTER

Keeping original residue number (specified in the input PDBQ file) for outputting.

```
MODEL      49
USER    Run = 49
USER    Cluster Rank = 1
USER    Number of conformations in this cluster = 22
USER
USER    RMSD from reference structure       = 3.603 A
USER
USER    Estimated Free Energy of Binding    =  -10.48 kcal/mol  [=(1)+(2)+(3)-(4)]
USER    Estimated Inhibition Constant, Ki   =   20.75 nM (nanomolar)  [Temperature = 298.15
K]
USER
USER    (1) Final Intermolecular Energy     =  -11.38 kcal/mol
USER        vdW + Hbond + desolv Energy     =   -9.75 kcal/mol
USER        Electrostatic Energy            =   -1.62 kcal/mol
USER    (2) Final Total Internal Energy     =   -0.24 kcal/mol
USER    (3) Torsional Free Energy           =   +0.89 kcal/mol
USER    (4) Unbound System's Energy  [=(2)] =   -0.24 kcal/mol
USER
USER
USER
```

```
USER    DPF = C:/Users/Elena/ELGI02_056_fr327_enantiomer2.dpf
USER    NEWDPF move ELGI02_056_fr327_enntiomer2.pdbqt
USER    NEWDPF about -0.040000 -0.105000 0.019000
USER    NEWDPF tran0  -2.978762 1.207012 2.005193
USER    NEWDPF axisangle0     -0.855541 0.399472 0.329352 -88.747345
USER    NEWDPF quaternion0  -0.598309 0.279365 0.230327 -0.714794
USER    NEWDPF dihe0 -79.20 140.84 -18.87
USER
USER                    x      y      z    vdW   Elec       q     RMS
ATOM     1  C         0    -7.328   1.377   5.530 -0.44 -0.20    +0.172     3.603
ATOM     2  O         0    -6.697   2.657   5.566 -0.27 +0.34    -0.387     3.603
ATOM     3  C         0    -5.282   2.456   5.587 -0.48 -0.21    +0.204     3.603
ATOM     4  C         0    -4.886   1.625   4.392 -0.69 +0.03    -0.023     3.603
ATOM     5  C         0    -5.746   0.872   3.724 -0.49 +0.08    -0.059     3.603
ATOM     6  C         0    -7.201   0.780   4.120 -0.41 -0.08    +0.061     3.603
ATOM     7  C         0    -3.503   1.517   3.782 -0.54 -0.26    +0.184     3.603
ATOM     8  C         0    -3.555   0.168   3.028 -0.37 -0.36    +0.269     3.603
ATOM     9  C         0    -5.049   0.188   2.591 -0.43 -0.03    +0.023     3.603
ATOM    10  N         0    -2.784   0.205   1.775 -0.40 -0.13    +0.101     3.603
ATOM    11  C         0    -3.581   1.027   0.837 -0.22 -0.45    +0.279     3.603
ATOM    12  C         0    -5.050   0.723   1.137 -0.33 -0.05    +0.030     3.603
ATOM    13  C         0    -5.585  -0.658   1.465 -0.35 -0.03    +0.024     3.603
ATOM    14  O         0    -2.503   1.487   4.803 -0.24 +0.58    -0.389     3.603
ATOM    15  H         0    -1.761   2.017   4.483 -0.34 -0.40    +0.210     3.603
ATOM    16  C         0    -1.556   0.959   2.057 -0.30 -0.43    +0.314     3.603
ATOM    17  C         0    -0.451   0.476   1.153 -0.49 -0.01    +0.006     3.603
ATOM    18  C         0     0.831   0.315   1.652 -0.50 -0.16    +0.113     3.603
ATOM    19  C         0     1.849  -0.132   0.813 -0.43 -0.15    +0.105     3.603
ATOM    20  O         0     1.351   0.522   2.897 -0.47 +0.48    -0.322     3.603
ATOM    21  C         0     1.575  -0.415  -0.515 -0.33 -0.07    +0.040     3.603
ATOM    22  O         0     3.007  -0.205   1.533 -0.33 +0.46    -0.323     3.603
ATOM    23  C         0     0.293  -0.251  -1.006 -0.31 -0.00    +0.003     3.603
ATOM    24  C         0    -0.719   0.187  -0.173 -0.33 -0.02    +0.012     3.603
ATOM    25  C         0     2.601  -0.191   2.915 -0.27 -0.55    +0.352     3.603
TER
ENDMDL
```

binding_energy=-10.48
ligand_efficiency=-0.44
inhib_constant=20.75
inhib_constant_units=nM
intermol_energy=-11.38
vdw_hb_desolv_energy=-9.75
electrostatic_energy=-1.62
total_internal=-0.24
torsional_energy=0.89
unbound_energy=-0.24
filename=ELGI02_056_fr327_enantiomer2.dlg
clRMS=0.0
refRMS=3.6
rseed1=None
rseed2=None
1 hydrogen bonds formed:
ELGI02_056_fr327_enntiomer2: : 0:H : DNA_model1giusto:B: DT18:O2

6.2.5 High throughput screening

Experimental:

An assay plate is created containing 5 uL of each drug at 800 uM in 80% DMSO. These will be diluted 40x by addition of cells, leaving a final DMSO concentration of 2% and drug concentrations of 20 uM. Bacterial strains are cultured until they reach mid-log growth (OD600 - 05). They are diluted to OD600 = 0.05 for addition into the assay plate. Then 195 ul of diluted culture is added into the assay plate. The plate is then incubated for 24-hours at 37 degrees C. For ESKAPE pathogens, the OD600 is used a measure to determine growth/inhibition. For Mycobacteria, resazurin is added to the cells, re-incubated for 3 or 24 hours and then the fluorescence (ex-544, em-590), is used to determine inhibition.

Plot %inhibition of *Enterococcus faecium* for compound library with detection OD600 and fluorescence:

Plot %inhibition of *Staphylococcus aureus* for compound library with detection OD600:

Plot %inhibition of *Klebsiella pneumoniae* for compound library with detection OD600:

Plot %inhibition of *Acinetobacter baumannii* for compound library with fluorescence detection:

Plot %inhibition of *Pseudomonas aeruginosa* for compound library with detection OD600:

Plot %inhibition of *BCG* for compound library with fluorescence detection:

Plot %inhibition of *mycobacterium smegmatis* for compound library with fluorescence detection:

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