Synthesis and pharmacological characterization of new tetrahydrofuran based compounds as histamine receptor ligands

Dissertation

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Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

Meinen Eltern

“Ideas won't keep; something must be done about them.”

Alfred North Whitehead (1861 – 1947)

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List of Abbreviation

ATR	attenuated total reflection
aq	aqueous
B	base
Bn	benzyl
brsm	based on recovered starting material
Bu	butyl
calcd	calculated
cat	catalytic
CI	chemical ionization (MS)
cPr	cyclopropyl
d	day(s)
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropylazodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPIBF	diphenyl isobenzofuran
DPPA	diphenyl phosphoryl azide
dr	diastereomeric ratio
EA	ethyl acetate
EDC	1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron impact (MS)
ent	enantiomer
equiv	equivalent(s)
ESI	electrospray ionization (MS)
Et	ethyl
GC	gas chromatography
h	hour(s)
HPLC	high-pressure liquid chromatogaphy
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IR	infra red spectroscopy
LAH	lithium aluminium hydride
M	molar / metal
Me	methyl
min	minute(s)
mp	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
nd	not determined
no	number
NOE	nuclear Overhauser effect
Nu	nucleophile
OTf	triflate
PE	hexanes
ppm	parts per million
Pr	propyl
quant	quantitative
R	arbitrary residue
rt	room temperature
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TosMIC	tosylmethyl isocyanide
Ts	tosyl
wt	weight

A. Introduction

G-protein coupled receptor

The G-protein coupled receptors (GPCSs) are trans-membrane proteins and constitute the largest and most diverse family of cell surface signal-transducing proteins in mammals. The analysis of the human genome revealed that about 2% of the genes encode for approximately 800 GPCRs.[1-4] GPCRs respond to a wide range of stimuli and transmit signals to the interior of the cell. About one half of the identified GPCRs respond to external signals such as light, pheromones, tastes and odors and are referred to as chemosensory receptors (csGPCRs). The other half (endoGPCRs) is addressed by endogenous ligands including biogenic amines, peptides, glycoproteins, lipids, nucleotides, ions and proteases.[1,5] Endogenous ligands are known for more than 260 endoGPCRs. For the remaining about 140 receptors, ligands have not been identified yet and are termed *orphan* receptors.[2,6] The important role of GPCRs in drug discovery is demonstrated by the fact that more than 30% of all marketed drugs target a GPCR.[7]

A common structural feature of all GPCRs is the existence of seven transmembrane α-helices connected by three intracellular and three extracellular loops with an intracellular C- and an extracellular N-terminus. Moreover, GPCRs interact with heterotrimeric guanine nucleotide-binding (G) proteins inside the cell.[7]

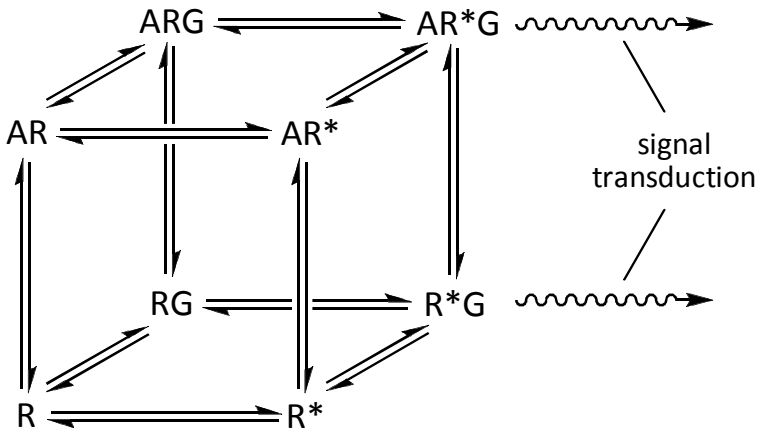
Classically, GPCRs were classified into six groups from A to F according to structural differences and functional properties.[8] More recently, the classification system was developed further based on sequence comparison and comprises five classes.[9] These classes are termed: Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2 and Secretin (shortened to the acronym GRAFS). The very large Rhodopsin family, also referred to as class A of GPCRs, is subdivided into α, β, γ, δ.

In 2000, the first crystal structure of bovine rhodopsin was solved.[10] Since then, a number of other GPCR crystal structures, including activated and agonist-bound GPCRs, could be elucidated.[11-13] As a result, more detailed information of the spatial orientation of the protein domains was available which helped to further analyze the exact mechanisms of GPCR signal transduction.

GPCR activation model and ligand classification

Among many other different models, the cubic ternary model is regarded as the most adequate description of the interactions of the three component system, comprising a GPCR (R), a G-protein (G) and an agonist (A) (Figure 1).[14-18] It incorporates the two-state model of GPCR activation which proposes the ability of the receptor to adopt an inactive conformation (R) and an active conformation (R*). These two states are in equilibrium, whereby the inactive state is prevailing in absence of an agonist. Due to the sufficient low energy barrier, spontaneous receptor activation by R to R* isomerization, independent from agonist binding is possible and is referred to as *constitutive activity*, which is a common property of wild-type GPCRs.[19] G-proteins couple especially to GPCRs in the active state, which induces GDP/GTP exchange at G-proteins enabling signal transduction and amplification.

Figure 1. Two-state cubic ternary complex model of GPCR activation.[14-18]

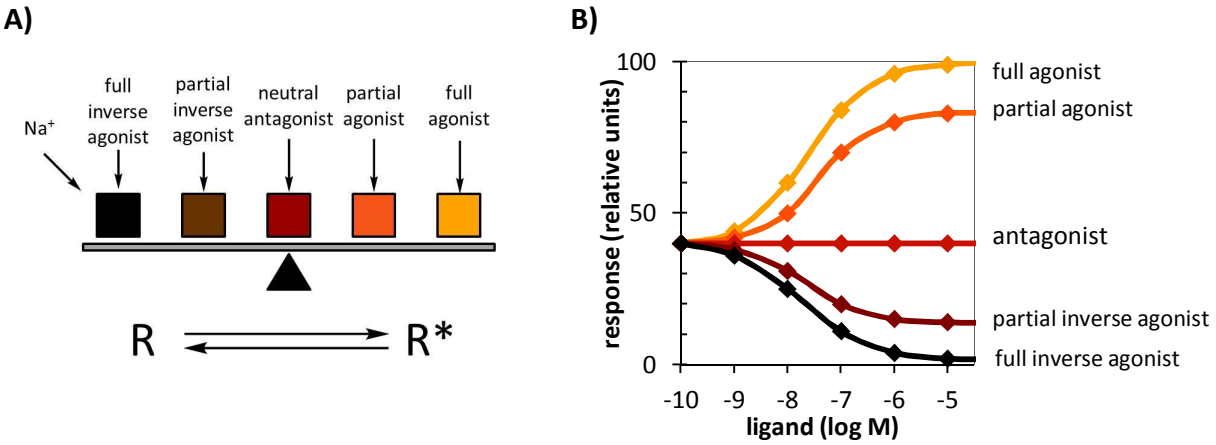


R = inactive state of the receptor, R* = active state of the receptor, G = G-protein, A = agonist.

On the basis of this model, ligands can be classified into full agonists, partial agonist, neutral antagonists, partial inverse agonists and full inverse agonists (Figure 2).[20] Full agonists have a higher affinity for the R* state and stabilize the active conformation. As a consequence, basal G-protein activity is further increased. Full inverse agonists, on the opposite, decrease the functional response by interacting with the inactive conformation of the receptor and stabilize the R state. Partial agonists and partial inverse agonists show a lower ability to stabilize the respective states. The effect on the functional response is smaller in comparison with the full agonists and full inverse agonists. Neutral antagonists have the same binding

affinities for both conformations and have no influence on the R/R* equilibrium but they inhibit the effects of both agonists and invers agonists.[20] In addition, Na^+ stabilizes the inactive state in several constitutively active GPCRs, similar to inverse agonists.[21] Based on the concept of constitutive activity, ligands acting at GPCRs and classified previously as antagonists have to be redefined as either neutral antagonists or inverse agonists.[22]

Figure 2. Ligand classification.

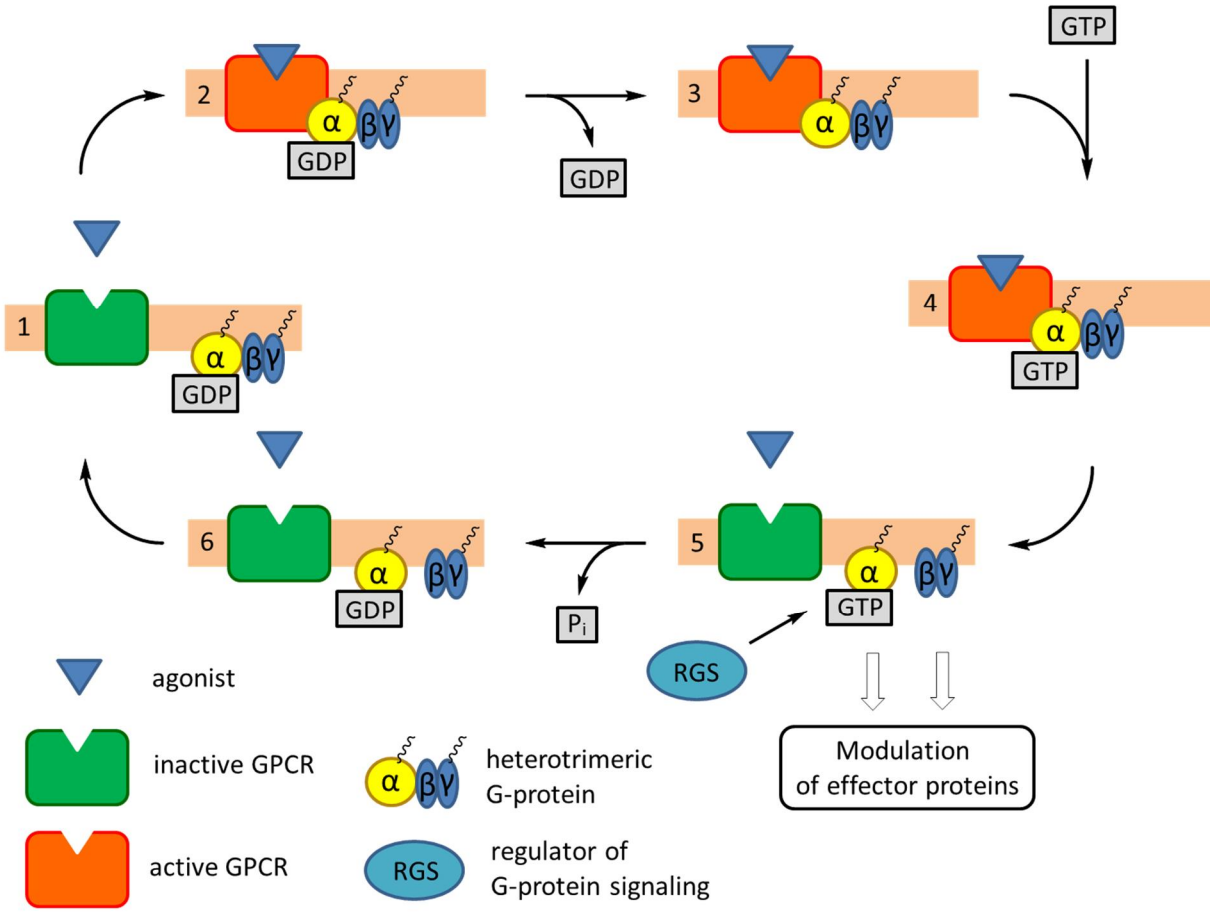


A) Ligand classification according to their capability of shifting the equilibrium to either side of both states; R = inactive state of the receptor, R* = active state of the receptor; reproduced accoding to Seifert *et al*.[19] **B)** dose response curves of full agonist, partial agonist, neutral antagonist, partial inverse agonist and full inverse agonist.

G-protein mediated signal transduction

The heterotrimeric G-protein consists of a G_α-subunit and a $G_{\beta\gamma}$-heterodimer and is divided into four families based on similarities of the G_α amino acid sequence and connected signaling pathways: G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$.[23] When the GPCR in the R* state (agonist free or agonist occupied) binds to the G-protein, a conformational change triggers the release of GDP from the G_α binding site (Figure 3).[24] In addition, the agonist affinity of the receptor is increased. The formed ternary complex is composed of the agonist, the receptor and the nucleotide-free G-protein. Subsequently, GTP binds to the G_α-subunit, leading to separation of the GPCR from the G-protein. Furthermore, the heterotrimer dissociates into G_α-GTP and $G_{\beta\gamma}$ which activate or inhibit effector proteins, resulting in various cellular responses. This is accompanied by a decrease of agonist affinity of the receptor. The G_α-subunit catalyzes the cleavage of GTP into GDP and phosphate, followed by reassociation of G_α-GDP and the $G_{\beta\gamma}$ complex. A family of proteins called regulators of G-protein signaling (RGS) is able to modulate the GTPase activity independent from GPCRs.[25]

Figure 3. The G-protein cycle. Reproduced according to Igel.[26]



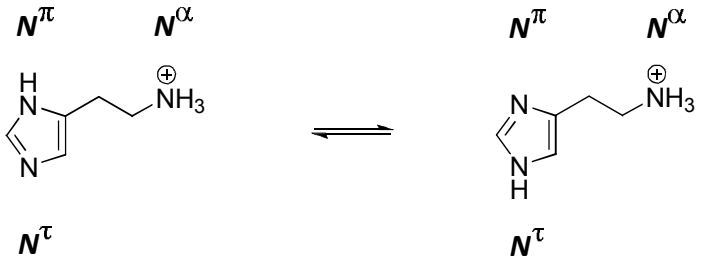
The G_{α}-protein interacts with effector proteins to continue the signaling cascade.[27] The $G_{\alpha s}$-subunits activate adenylate cyclases which generate cAMP from ATP. The increased intracellular cAMP level, in turn, effects a stimulation of cAMP-dependent protein kinases and subsequently cAMP-responsive-element-binding protein (CREB) to modulate gene transcription. In contrast, $G_{\alpha i}$ mainly inhibits the adenylate cyclases. A decreased cAMP production from ATP results in a decreased activity of protein kinases. $G_{\alpha q/11}$ stimulates membrane-bond phospholipase C (PLC_{β}) which then hydrolyses phosphoinositol biphosphate (PIP_2) to generate the second messenger inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 promotes the release of Ca^{2+} from the endoplasmatic reticulum into the cytosol by binding to the IP_3 receptor (Ca^{2+}-ion channel). This results in an increased intracellular calcium level. Further modulation of cell processes is mediated by the activation of protein kinase C (PKC) by DAG. $G_{\alpha 12/13}$ regulates intracellular proteins function such as actin cytoskeletal transformation through the use of guanine nucleotide exchange factors.[28,29] Besides the G_{α}-subunits also the $G_{\beta\gamma}$-heterodimer can actively interact and activate effector molecules.[30]

Although GPCR interaction with G-proteins accounts for the largest proportion of signal transduction from the extracellular to the intracellular region, recent work has demonstrated that GPCRs participates in further protein-protein interactions, which induces intracellular responses, in conjunction with G-proteins or even G-protein independently.[31]

Histamine, histamine receptors and histamine receptor ligands

Histamine (**1**) consists of two basic centers, a primary aliphatic amine and an imidazole ring. At physiological pH the amino group (pK_a = 9.4) is protonated to give a monocation predominantly and the heterocycle (pK_a = 5.8), having one *N*-proton, equilibrates between its two tautomers N^{π}-*H*-histamine (**1A**) and N^{τ}-*H*-histamine (**1B**) (Figure 4).[32,33]

Figure 4. Tautomeric forms of histamine (**1**) at physiological pH.



***N*$^{\pi}$-*H*-histamine (1A)** ***N*$^{\tau}$-*H*-histamine (1B)**

Three years after the first-time synthesis of histamine by Windaus und Vogt in 1907,[34] Sir Dale and Barger,[35] and independently Kutscher,[36] succeeded in the isolation from ergot and observed first physiological effects.[37]

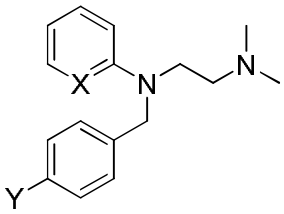
Histamine is a biogenic amine which is formed from the amino acid L-histidine by decarboxylation catalyzed by the enzyme histidine decarboxylase.[38] It is mainly located in mast cells, basophils, blood platelets, enterochromaffin-like (ECL) cells of the stomach, endothelial cells and also in neurons.[39,40] It mediates multiple physiological effects through the interaction with four histamine receptor (HR) subtypes, termed H_1, H_2, H_3 and H_4, all belonging to rhodopsin-like family A of G-protein-coupled receptors (GPCRs).[41]

Histamine H_1 receptor and its ligands

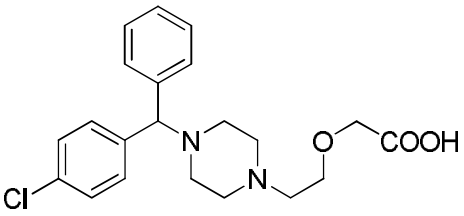
In the beginning of the last century it became apparent that histamine plays an active role in allergy and anaphylaxis.[38] This led to intensive efforts to search for compounds which inhibit these reactions. Since then, a plethora of so-called antihistamines have been developed and became blockbuster drugs for decades for the treatment of allergic disorders. Meanwhile, it is known that these classical *antihistamine*s are inverse agonists at the H_1R.[22]

The H_1R is mainly located in smooth muscle cells, endothelial cells, adrenal medulla, lymphocytes, heart and in the CNS and regulates smooth muscle contraction, stimulation of NO formation, endothelial cell contraction, vascular permeability, stimulation of hormone release and negative inotropism.[39,42] Predominantly, the receptor signals through the $G_{\alpha q/11}$-subunits resulting in calcium-mobilizing and activation of PKC.[39] In 1991, the bovine H_1 cDNA and two years later the human hH_1R was cloned. [43,44]

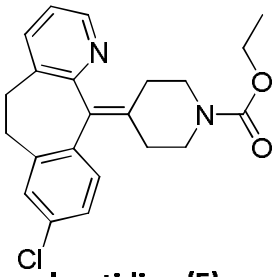
Figure 5. H_1 receptor antagonists.



phenbenzamine (2) (X = CH, Y = H)
mepyramine (3) (X = N, Y = OMe)



cetirizine (4)

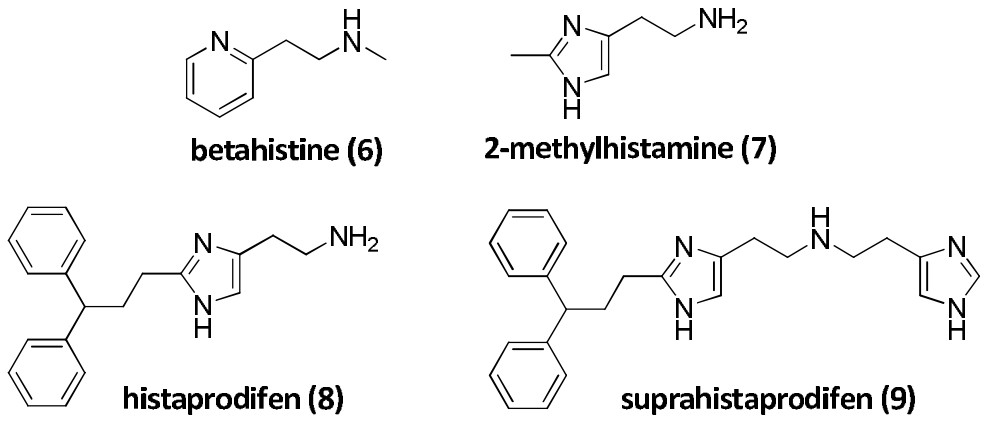


loratidine (5)

The first synthesized histamine receptor antagonists were brought to the market in the 1940s.[38] Phenbenzamine (Antergan™) (**2**) and the further developed mepyramine (Neoantergan™) (**3**) were the basis of numerous H_1R antagonists for the treatment of allergic diseases (Figure 5). However, these fist-generation antihistamines cause sedation.[45] The reason is their capability to cross easily the blood-brain barrier due to their hydrophobic properties. This side-effect was exploited for example for the treatment of motion sickness.[38] Second-generation H_1R antagonists such as cetirizine (**4**, Zyrtec™) and loratidine (**5**, Claritin™) are almost devoid of CNS penetration and are less sedative which made them one of the most prescribed drugs against allergy.[46]

For pharmacological studies mepyramine (**3**) represents the most relevant reference H_1R antagonist and radioligand ([^{3}H]mepyramine) for labeling H_1 receptors in a variety of tissues.[47]

Figure 6. H_1 receptor agonists.



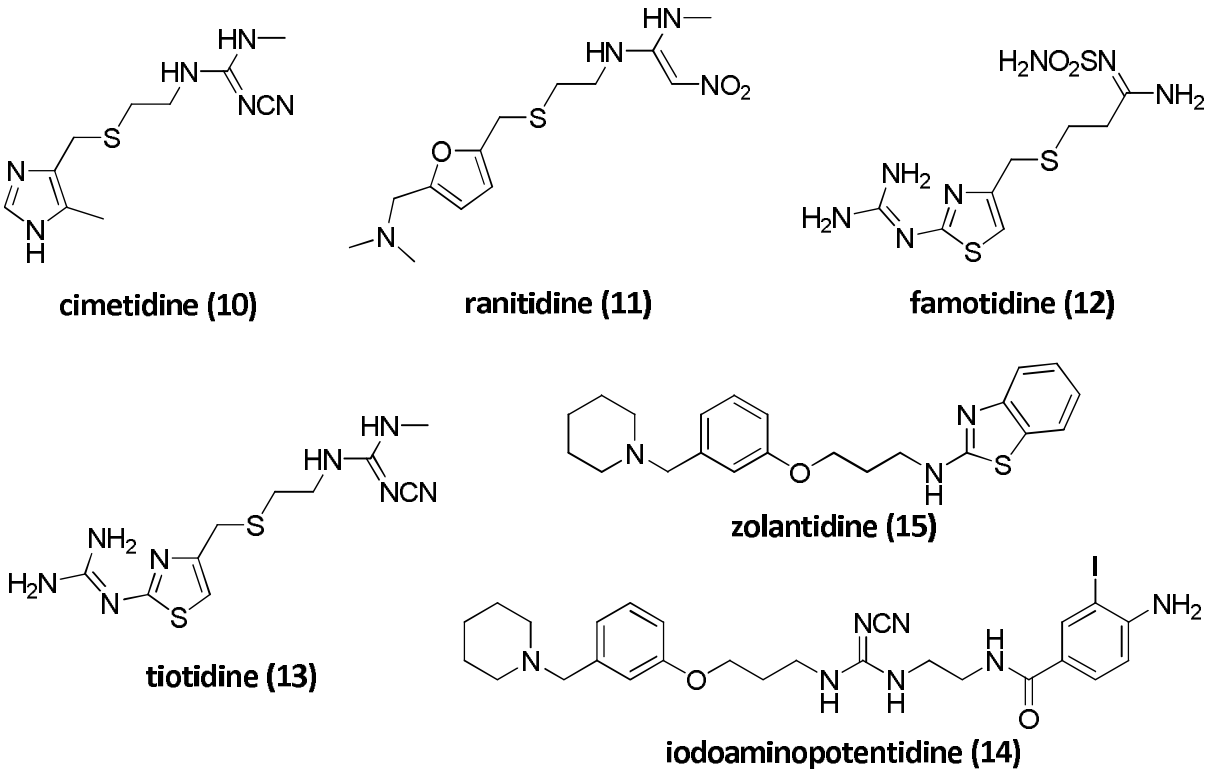
By contrast, H_1R agonists as drugs for therapeutic applications are of much less significance than the antagonist counterparts. Only betahistine (**6**, Aequamen^{TM}) is used for the treatment of Menière's disease (Figure 6).[48] Further compounds, like 2-methylhistamine (**7**), revealed some selective H_1R agonistic properties over H_2R and were used as pharmacological tools to analyze receptor functions in biological systems.[49] Later, it turned out that these compounds also showed H_4R agonistic activity.[50] High potencies and good subtype selectivity were found for histaprodifen (**8**)[51] and especially for suprahistaprodifen (**9**).[52]

Histamine H_2 receptor and its ligands

Since not all effects caused by histamine were inhibited by the *antihistamines*, the existence of different histamine targets was taken into considerations.[53] In 1966, Ash and Schield introduced the term H_1 receptor to distinguish it from non-H_1 receptors.[54]

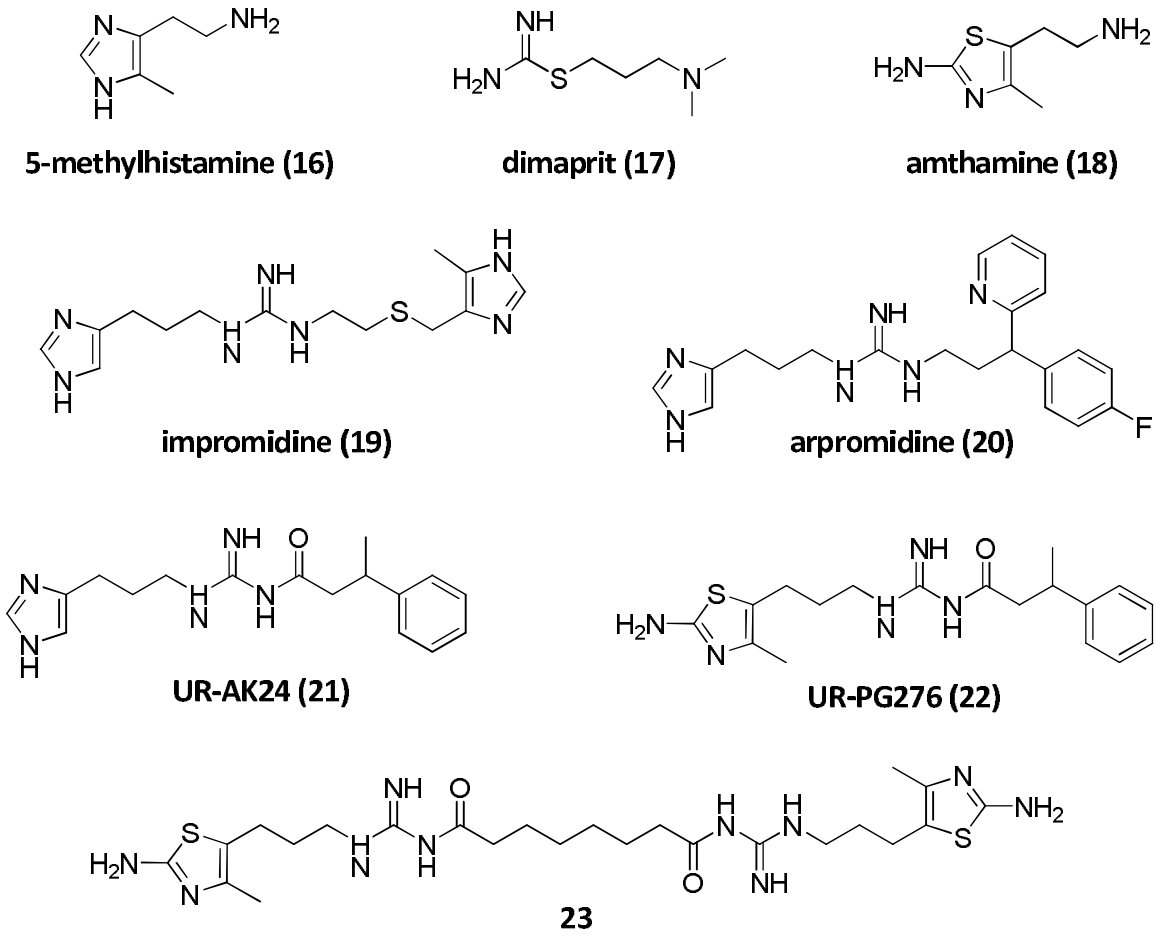
High expression levels for the H_2R are found in gastric parietal cells and a variety of other tissues including leucocytes, heart, airways, smooth muscles and brain.[42] This receptor subtype plays a crucial physiological role in stimulating gastric acid secretion. Additionally, it is associated with positive chronotropic and inotropic effects on atrial and ventricular tissues, it effects relaxation of airway, uterine and vascular smooth muscles and it inhibits a variety of functions within the immune system.[39,42] The H_2R predominantly couples to the $G_{\alpha s}$-protein effecting a stimulation of adenylate cyclase to produce cAMP from ATP. cAMP, in turn, activates cAMP-dependent protein kinases.[39] The cDNA of the H_2R was cloned for the first time in 1991.[55]

Figure 7. H_2 receptor antagonists.



In 1972, burimamide (**24**, Figure 9, page 12) was the first compound which was termed H_2R antagonist by Black.[56] However, due to its insufficient bioavailability it was not considered as a drug candidate. A successive development gave rise to cimetidine (**10**, Tagamet™) which was the first H_2R antagonist brought to the market and became the most prescribed drug for several years (Figure 7).[57] Fewer side effects were observed for ranitidine (**11**, Zantic™) and famotidine (**12**, Pepdul™) which additionally showed that the imidazole function is not essential and can be displaced by different aromatic rings.[42,53] Nowadays proton pump inhibitors like omeprazole are superior in treatment of acid-related gastrointestinal disorders.[58] As pharmacological tools further potent and selective H_2R antagonists are established, *e.g.* tiotidine (**13**) and iodoaminopotentidine (**14**).[42] Moreover, [^{3}H]tiotidine and [^{125}I]iodoaminopotentidine are the most important H_2 radioligands at the present time.[59,60] Most of H_2R antagonists are rather polar compounds and do not cross the blood-brain barrier. To investigate H_2 receptor function in the CNS, zolantidine (**15**) was specifically designed capable of penetrating the brain.[61]

Figure 8. H_2 receptor agonists.



Numerous H_2R agonists have been identified but are not routinely used in therapy so far. The first described agonist that discriminated between the H_2 and H_1 receptor was 5-methylhistamine (**16**, former nomenclature: 4-methylhistamine) (Figure 8). Meanwhile it turned out that it acts as a high-affinity full H_4R agonist as well.[49,62] Dimaprit (**17**), a further amine-type agonist, which is almost as active as histamine (**1**), shows good selectivity over the H_1R and acts as a H_3R antagonist but was also identified as a moderate H_4R agonist.[61,62] Amthamine (**18**), a thiazole analogue of histamine and a cyclic analogue of dimaprit (**17**), is a full histamine H_2R agonist and exhibits a slightly higher potency than histamine at the isolated guinea pig right atrium.[63] Moreover, amthamine (**18**) is devoid of histamine H_1R, H_3R and H_4R stimulatory activities at relevant concentrations.[62] Guanidine-containing H_2R agonists reveal much higher potencies compared to amino-type compounds. Impromidine (**19**) was the first H_2R agonist which is more potent than histamine and was investigated for the treatment of severe catecholamine-insensitive congestive heart failure.[64,65] Arpromidine

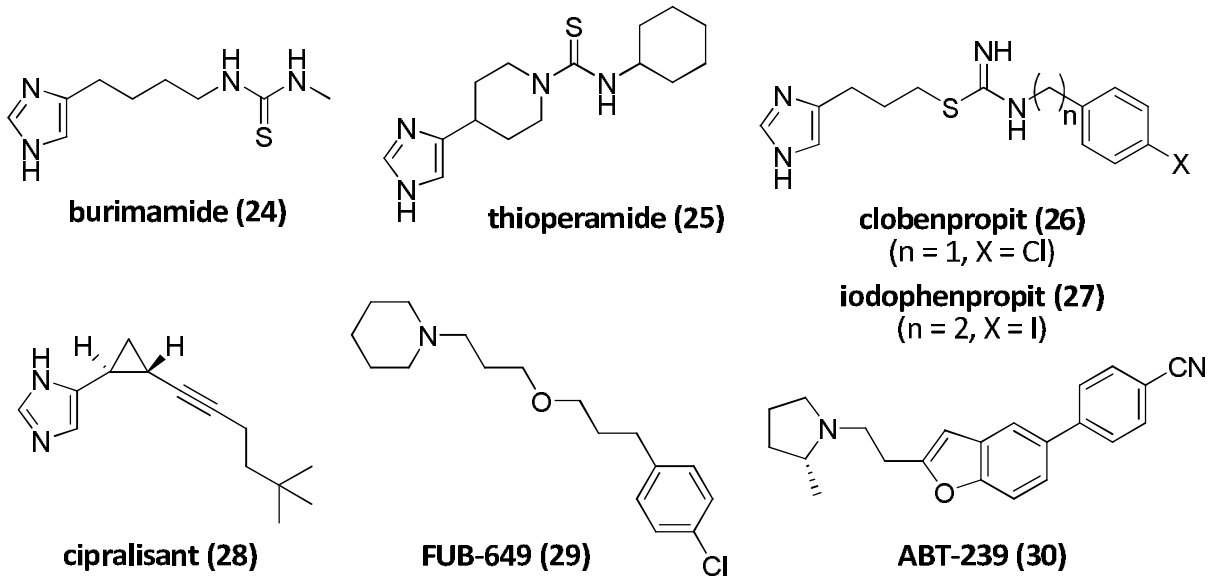
(**20**) shows up 400 times the potency of histamine at the guinea pig right atrium and is of therapeutic value as positive inotropic vasodilators.[66] The pharmacokinetic drawbacks of low bioavailability and poor CNS penetration of these compounds caused by the strong basic guanidine group were overcome by the introduction of a less basic acylguanidine moiety resulting in N^G-acylated imidazolylpropylguanidines like UR-AK24 (**21**).[67] Although these compounds are very potent H_2R agonists they also show considerable activity at the other HR subtypes especially at the H_3R and H_4R. Selectivity was improved by bioisosteric replacement of the imidazole ring by a 2-amino-4-methylthiazol-5-yl moiety according to amthamine (**18**) to form N^G-acylated aminothiazolylpropylguanidines like UR-PG276 (**22**) as valuable pharmacological tools.[68] Very recently, novel bivalent H_2R agonists, like compound **23**, were synthesized. The combination of two pharmacophoric hetarylpropylguanidine moieties with octanedioyl or decanedioyl spacers led to the most potent agonists at the guinea pig right atrium known so far, exceeding up to 4000 times the activity of histamine in increasing heart rate.[69]

Histamine H_3 receptor and its ligands

In the 1970s, it became apparent that histamine can inhibit its own release in the brain.[70] However, potent H_1 and H_2 antagonists were not able to reverse this effect. Those findings led to the assumption of a further histamine receptor subtype.[38] The H_3R was pharmacologically characterized in 1983 by Arrang et al.[71] The H_3R is mainly located on neurons, predominantly in the CNS and to a lesser extent in the peripheral nervous system.[72] It acts as a presynaptic autoreceptor that inhibits the synthesis and release of histamine from histaminergic neurons and as a heteroreceptor it controls the release of other neurotransmitters, *e.g.* acetylcholine, dopamine, noradrenaline, and serotonin.[73] It regulates sleep/wakefulness, feeding and memory processes.[74] Therefore, the H_3R is considered a potential target for therapeutic applications against obesity, and a variety of CNS disorders such as Alzheimer's disease, attention-deficit/hyperactivity disorder (ADHD), migraine, narcolepsy, schizophrenia, epilepsy, and depression.[38,72] The cDNA encoding the human H_3R was cloned by Lovenberg in 1999.[75] The overall similarity between the human H_3 receptor and the H_1 and H_2 receptors is very low. The resemblance amounts to 22% and 21%,

respectively. The H_3 receptor couples to $G_{\alpha i/o}$ resulting in the inhibition of adenylate cyclase. Therefore H_3 receptor activation lowers cAMP levels and reduces downstream events.[76]

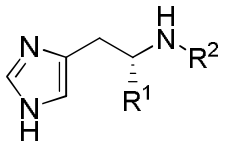
Figure 9. Imidazole-containing and imidazole-free H_3 receptor antagonists.



Originally developed as a H_2R antagonist, burimamide (**24**) revealed a 100-flold higher affinity at the H_3R (Figure 9).[77] In 1987, the potent and highly selective H_3R inverse agonist thioperamide (**25**) was designed which became the most important reference compound for many years and was applied in numerous preclinical studies.[72,78] The potent H_3R antagonists clobenpropit (**26**) and iodophenpropit (**27**), which is derived from the agonist imetit (**33**) (Figure 10), illustrates a trend that potent antagonists can be obtained from related agonists by attaching lipophilic chains and increasing the distance of the basic moieties.[79] Researches tried to optimize the special arrangement of the ligands at the receptor binding site by introducing rigid structural motifs limiting the conformational freedom. This was realized in cipralisant (**28**), the first H_3R antagonists that reached clinical phase II trials for the treatment of ADHD.[80,81] Many of the discovered antagonists lacked of sufficient penetration of the blood-brain barrier because of the polar and hydrogen-bonding properties of the imidazole ring. In addition, imidazole-containing ligands interact with cytochrome P450 which is an unwanted property of drugs.[82] Recent efforts of the academic and pharmaceutical industry research to develop imidazole-free H_3R antagonists resulted in the syntheses of several potent and selective ligands, *e.g.* FUB-649 (**29**)[83] and ABT-239 (**30**).[84] Further advantages of

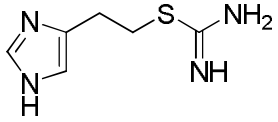
non-imidazole compounds are lower species variations in the receptor affinity and better receptor-subtype selectivity.[38]

Figure 10. H_3 receptor agonists.

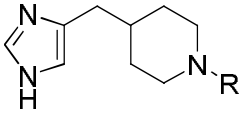


N^{α}-methylhistamine (31)
(R^1 = H, R^2 = Me)

(*R*)-α-methylhistamine (32)
(R^1 = Me, R^2 = H)



imetit (33)



immepip (34) (R = H)
methimepip (35) (R = Me)

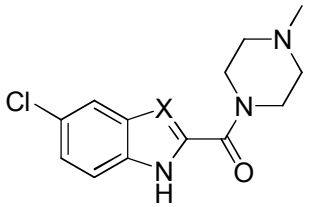
Histamine binds with high affinity to the H_3R. As a consequence, only small structural differences for H_3R agonists in comparison to histamine are tolerated and imidazole seems to be an essential pharmacophore.[72] Methylation of the basic amine group gave rise to N^{α}-methylhistamine (**31**), a high affinity H_3R agonist which is about three times more active than histamine (Figure 10).[85] The chiral (*R*)-α-methylhistamine (**32**) is another methyl derivative of histamine which was frequently used in pharmacological studies.[78] However, high basicity, hydrophilicity and low bioavailability limited its use under *in vivo* conditions.[72] Imetit (**33**), the isothiourea analogue of histamine showed high selectivity over the H_1R and H_2R.[79] Further decrease of side-chain flexibility by incorporation of the basic amino group into a piperidine ring gave rise to immepip (**34**) which is also a potent H_3R agonist with good brain penetration properties.[86] After discovering the H_4 receptor it became apparent that many compounds like N^{α}-methylhistamine (**31**), (*R*)-α-methylhistamine (**32**), imetit (**33**) and immepip (**34**), which were classified as H_3R agonists, also act at the H_4 receptor to a certain extent.[87] Based on these findings the potent H_3R agonist methimepip (**35**) could be developed which showed 2000-fold selectivity over the H_4R.[88]

The most frequently used H_3R radioligands are [^{3}H]N^{α}-methylhistamine, [^{3}H]*R*-α-methyl-histamine and [^{125}I]iodophenpropit.[89]

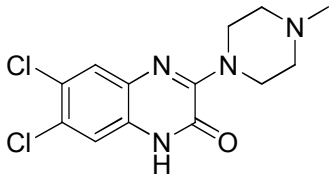
Histamine H_4 receptor and its ligands

The H_4R is the most recently discovered member of the family of histamine receptors and was identified in 2000 and 2001, when several research groups cloned the gene encoding the hH_4R.[41] The H_4R couples to pertussis toxin-sensitive $G_{i/o}$ proteins and thereby inhibits forskolin-induced cAMP production.[90] It is mainly expressed in mast cells, eosinophils, leukocytes, monocytes, CD8+T cells, basophils, dendritic cells, in the spleen and bone marrow and seems to play a crucial role in inflammatory and immunological processes including asthma, atopic dermatitis, allergic rhinitis, pruritus, colitis, pain, cancer and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.[81] The rather high degree of homology with the hH_3R (36% at the protein level, 58% within the transmembrane domains) explains the high affinity of many H_3R ligands, in particular imidazole-containing compounds, for the H_4R.[91] In contrast, only 26% and 27% homology within the transmembrane regions was found with the H_1R and H_2R, respectively.[92]

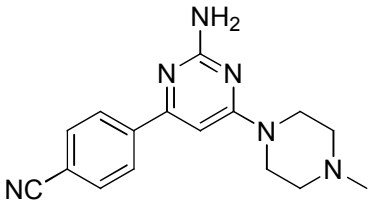
Figure 11. H_4 receptor antagonists.



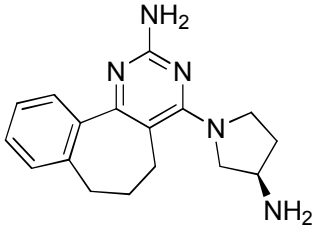
JNJ-7777120 (36) (X = CH)
VUF-6002 (37) (X = N)



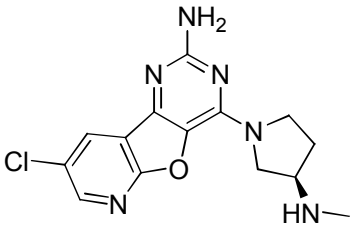
VUF-10214 (38)



39



A-943931 (40)



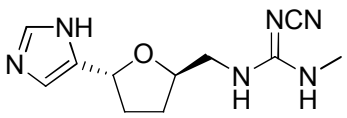
JNJ-40279486 (41)

Thioperamide (**25**), for instance, previously considered as a selective H_3R inverse agonist, turned out to act at the H_4R as an inverse agonist as well with comparable affinities (pK_i = 6.9).[62] Shortly afterwards, high-throughput screening by Johnson & Johnson led to the identification of the highly potent (pK_i = 8.4) non-imidazole indole carboxamide JNJ-7777120 (**36**) which behaves as a neutral antagonist with >1000-fold selectivity over the other receptor subtypes (Figure 11).[93] It became the reference antagonist of choice to investigate

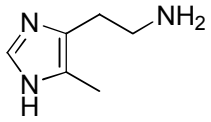
H_4R function but short *in vivo* half-life makes it impractical for prolonged studies of chronic diseases.[94] Further potent and selective indole and also benzimidazole derivatives such as VUF-6002 (**37**) (pK_i = 7.6) and related compounds were synthesized.[40] Quinoxaline turned out to be a further promising lead structure for the synthesis of potent H_4R antagonists. VUF-10214 (**38**) was identified as a potent H_4R ligand with nanomolar affinities (pK_i = 8.3) and showed significant anti-inflammatory properties in rat *in vivo* models.[95] Compounds containing a 2-aminopyrimidine scaffold like compound **39** were found to possess potent antagonistic activity (pK_b = 8.53) with good CNS penetration and were shown to be effective in inflammation and pain models.[96] Some limitation of theses ligands like rapid metabolisation *in vivo* and rapid demethylation to metabolites with significant H_4R activity could be improved by structural modifications. Additionally, selectivity over off-target sites was increased by annulation of the pyrimidine ring to furnish rotationally constrained antagonists like A-943931 (**40**) with high potencies and selectivity (> 190-fold) for the H_4R across multiple species (pK_b > 8).[97] In this series of constrained 2-aminopyrmidines very recently JNJ-40279486 (**41**) was designed and also found to be a potent (pK_i = 8.0) and selective hH_4R antagonist demonstrating acceptable pharmacokinetic profile in a mouse model of inflammation.[98] Meanwhile several H_4R antagonists are announced as candidates for clinical trials. The first compound which finally entered clinical studies for the treatment of allergic respiratory diseases (completing the phase I ascending dose trial) and has been found to be safe and well tolerated is UR-63325 developed at Palau Pharma (undisclosed structure).[99]

Several potent H_1R, H_2R and H_3R ligands turned out to act as H_4R agonists as well. Some even proved to be H_4R selective. The first reported H_4R agonist with moderate affinity and about 40-fold selectivity over the H_3R was OUP-16 (**42**) (Figure 12).[100] Originally developed as a selective H_2R agonist, 5-methylhistamine (**16**) proved to be a potent human H_4R full agonist with > 100-fold selectivity over the other hHR subtypes and has become the most frequently used hH_4R agonist due to its easy accessibility.[49,62,87] The antipsychotic drug clozapine turned out to moderately activate the H_4R. Lead optimization by Smits *et al.* resulted in VUF-6884 (**43**), a high affinity hH_4R ligand (pK_i = 7.6) with full agonistic activity (pEC_{50} = 7.7). It binds poorly to the hH_2R and hH_3R (pK_i > 5) but shows high affinity for the hH_1R (pK_i = 8.1) with inverse agonistic activity.[101] Based on the H_2R agonist, H_3 antagonist, and low affinity H_4R

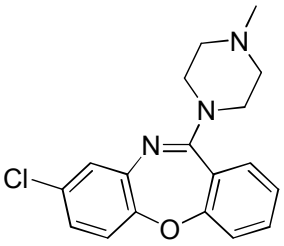
Figure 12. H_4 receptor agonists.



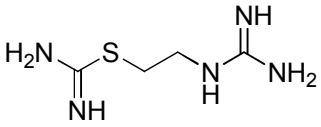
OUP-16 (42)



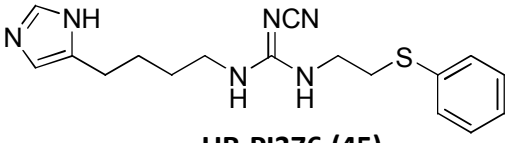
5-methylhistamine (16)



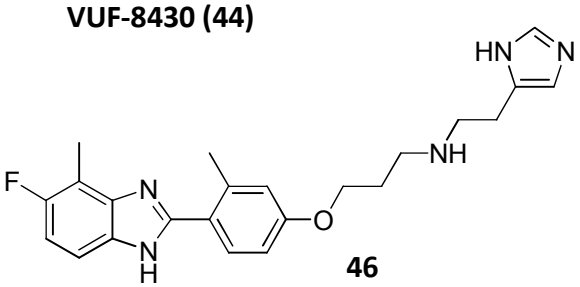
VUF-6884 (43)



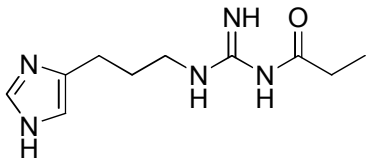
VUF-8430 (44)



UR-PI376 (45)



46



UR-PI294 (47)

partial agonist dimaprit (**17**) structure-activity relationship investigations revealed VUF-8430 (**44**) as high affinity (pK_i = 7.5) hH_4R full agonist (pEC_{50} = 7.3) with 30-fold selectivity over the hH_3R with negligible affinity for the hH_1R and hH_2R.[102,103] Derived from the originally developed H_2R agonistic N^G-acylated imidazoylpropylguanidines, cyanoguanidino compound UR-PI376 (**45**) was designed and identified as a potent hH_4R agonist (pEC_{50} = 7.5) devoid of any agonistic activity at the other three hHR subtypes which makes it superior to other selective hH_4R agonists.[104] It shows negligible hH_1R and hH_2R affinities and 25-fold selectivity over the hH_3R. A drawback, however, are species-dependent discrepancies.[87] In the course of the development of new H_4R antagonists on the basis of 2-arylbenzimidazoles by Johnson & Johnson a number of compounds were synthesized revealing full agonistic activity at the hH_4R.[105] These include **46** which is one of the most potent hH_4R agonist known so far having sub-nanomolar affinity. In addition, it shows negligible affinity at the hH_1R (pK_i > 5), > 600-fold selectivity over the hH_2R (pK_i = 6.9) and > 1700-fold selectivity over the hH_3R (pK_i = 6.4). [^{125}I]Iodophenpropit (**27**), tritiated histamine (**1**), JNJ-7777120 (**36**), and the recently developed acylguanidine UR-PI294 (**47**) were used as radioligands in binding studies.[81] Despite the lack of selectivity of UR-PI294 (**47**) and other ligands to the hH_3R they can be used for pharmacological experiments on the H_4R in native or recombinant systems devoid of hH_3Rs.

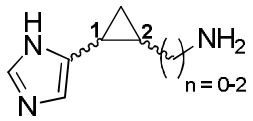
Stereochemical diversity-oriented conformational restricted ligands

Frequently, endogenous ligands such as histamine (**1**) possess flexible structures owing to rotations around single bonds and can adopt a variety of conformations. At different receptor subtypes distinct conformations are preferred which have lower affinities at the respective other subtypes.[106] A reasonable strategy to improve affinity and selectivity is to create analogues with a conformational restricted linker which only allows a concrete spatial arrangement of the functional groups that are essential for receptor binding.[107-109] To acquire potent and selective histamine receptor ligands, the imidazole ring and the basic nitrogen must have a defined orientation that superimpose the bioactive conformation in which these pharmacophoric elements effectively interact with certain amino acid residues in the binding pocket of the receptor. Due to the difficulties with the structural analysis of membrane-bound proteins the bioactive conformation of the natural ligand is usually not known with precision. To investigate the bioactive conformation and to refine the models of interaction a stereochemical diversity-oriented conformational restriction strategy proved to be a valuable method. In most cases restriction of the flexible linker is achieved by a displacement with rigid carbo- and heterocycles.

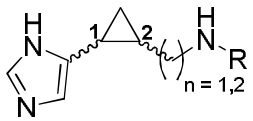
Cyclopropane-based conformationally restricted HR ligands

The above mentioned approach was successfully applied by Kazuta *et al.* to identify novel H_3R agonists.[110] From a series of cyclopropane-based conformationally restricted histamine analogues **48** with divers stereochemistry the "folded" *cis*-analogue AEIC revealed to be the most potent agonist at the hH_3R (K_i = 1.3 nM, EC_{50} = 10 nM) which had virtually no effect on the H_4R subtype (Figure 13).

Figure 13. Cyclopropane-based conformationally restricted histamine analogues.



48



49

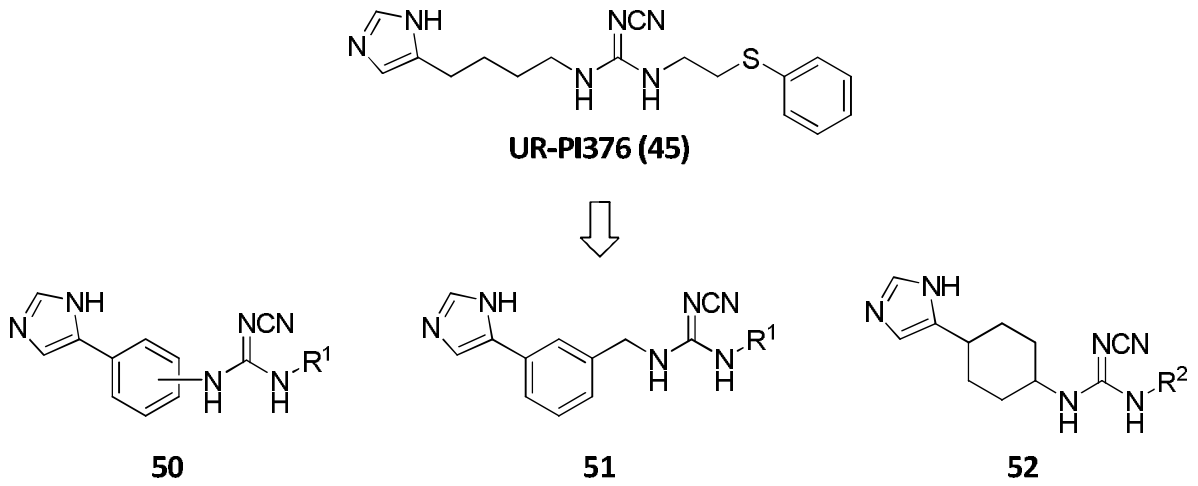
AEIC: (1*R*,2*S*)-**48**, n = 2; **49**: R = 4-chlorobenzyl, cyclohexylmethyl.

The same concept was followed by Watanabe *et al.* for the search of H_3R and H_4R antagonists.[111] By attaching hydrophobic side-chains at the amino group of the cyclopropane-based conformationally restricted histamine **48**, both selective H_3R and H_4R antagonists were obtained (Figure 13). Among them, the (1*R*,2*S*)-*trans*-isomer of **49** (R = 4-chlorobenzyl, n = 1) was found to be a potent H_4R antagonist (K_i = 118 nM) with > 8.5-fold selectivity over the H_3R.

Cyclohexane-based conformationally restricted HR ligands

Based on the selective H_4R agonist UR-PI376 (**45**), Geyer and Buschauer explored structural rigidified analogues having the flexible tetramethylene chain replaced by conformationally constrained spacers.[112] While phenyl linker yielded only the very weakly active compounds **50** and **51** at both hH_3R and hH_4R, less rigid 1,4-cyclohexylene linker exhibited *cis*- and *trans*-configured molecules **52** revealing EC_{50} or K_B values ≥ 110 nM at the hH_3R and hH_4R (Figure 14). *Cis*-configurated diastereomers prefer the hH_4R and are partial agonists, whereas *trans*-isomers are antagonists at the hH_4R. At the hH_3R the *trans*-diastereomers are superior to the *cis*-isomers by a factor of 10. It was suggested that an appropriate balance between constraint and flexibility is important to further elucidate the requirements of high hH_4R affinity and selectivity.

Figure 14. Cyclohexane-based conformationally restricted HR ligands.

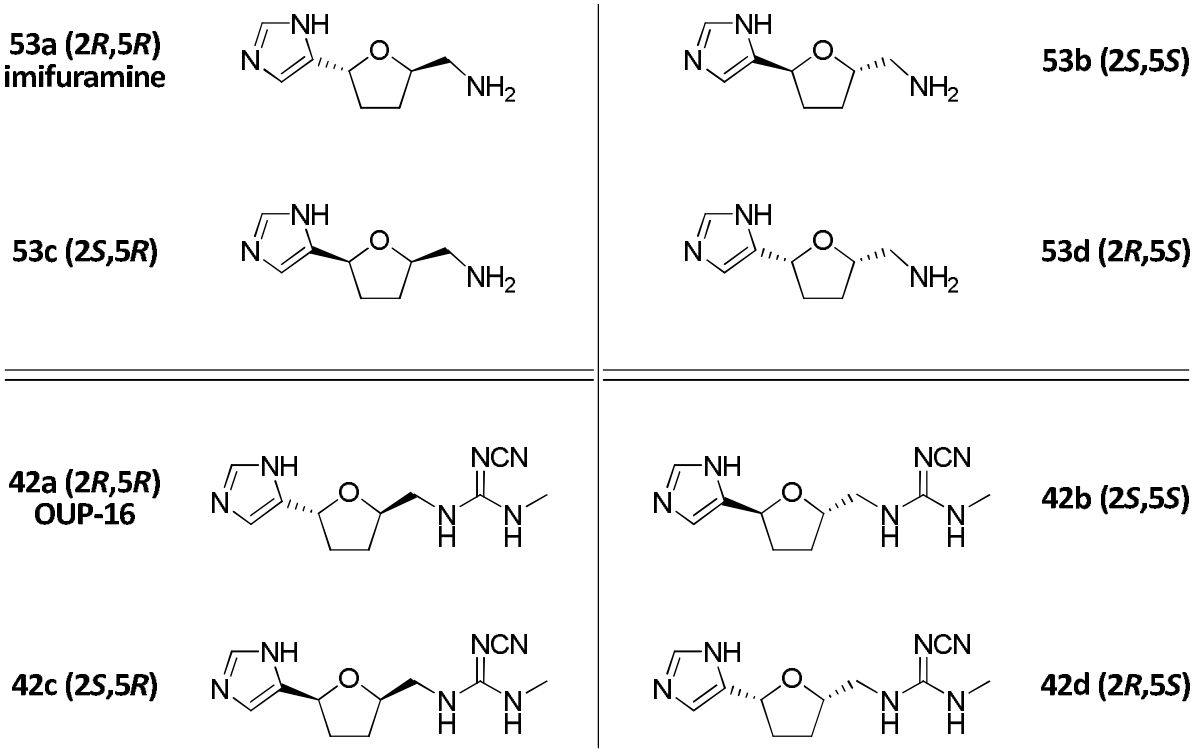


R^1 = -CH_3, -cPr, -$CH_2CH(CH_3)_2$, -$(CH_2)_3$-Ph, -$(CH_2)_2$-S-Ph; R^2 = -CH_3, -$(CH_2)_2$-S-Ph.

Tetrahydrofuran-based conformationally restricted HR ligands

In 2003, Hashimoto *et al*. synthesized a series of tetrahydrofuranylimidazoles and examined the binding affinity and functional activity for the human H_3 and H_4 receptors by *in vitro* studies (Figure 15).[100,113,114] In general the amino compounds – imifuramine (**53a**) and its stereoisomers **53b**, **53c**, **53d** – behaved as partial to full agonists at the hH_3R and hH_4R with selectivity for the hH_3R. When the amino group was replaced with a less basic cyanoguanidine moiety (**42a**, **42b**, **42c**, **42d**) agonistic activity at the hH_3R decreased. In contrast, the potencies and intrinsic activities increased at the hH_4R for most isomers. Especially imifuramine (**53a**) and its enantiomer **53b** showed full agonistic activities ($0.9 < \alpha < 1.0$) at the hH_3R with EC_{50} values of 45 and 105 nM and had 45- and 300-fold higher potency than at the hH_4R, respectively. The cyanoguanidine analogue of imifuramine, (2*R*,5*R*)-configured compound OUP-16 (**42a**), exhibited the highest agonistic activity with a EC_{50} value of 77 nM at the hH_4R with 41-fold selectivity over the hH_3R. 45-fold selectivity for the hH_4R was observed for (2*R*,5*S*)-isomer **42d**. Until that time, **42a** and **42d** were the first described selective H_4R agonists. These findings imply the usefulness of stereoselective syntheses to develop selective HR ligands. (K_i, EC_{50} and α values of all compounds: page 73)

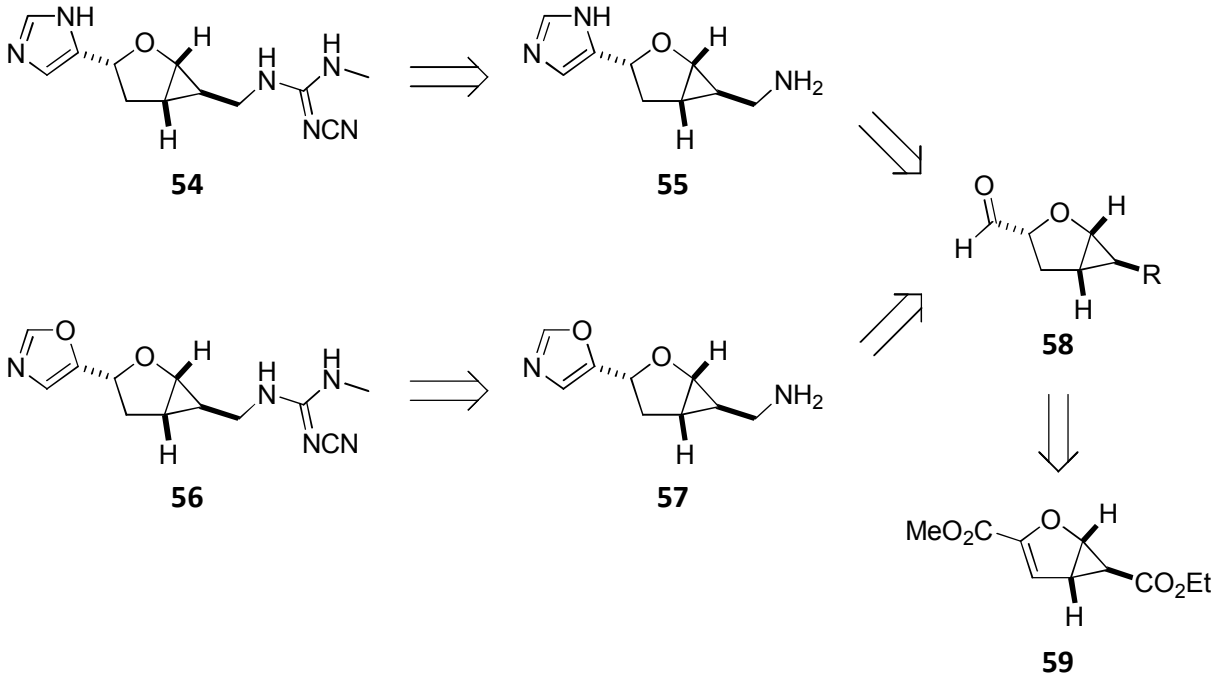
Figure 15. Tetrahydrofuran-based conformationally restricted H_3R and H_4R ligands.[100]



Aim of this work

There is still a need for the development of selective ligands targeting histamine receptors, especially the H_4R, in order to further elucidate its biological roles which would offer new opportunities for the therapy of several diseases. Based on the work of Hashimoto *et al.* this work aims at the enantioselective synthesis and pharmacological evaluation of potential histamine receptor ligands containing a modified tetrahydrofuran-spacer with a conformational restricted structure (Scheme 1).

Scheme 1. Retrosynthesis of the target compounds.



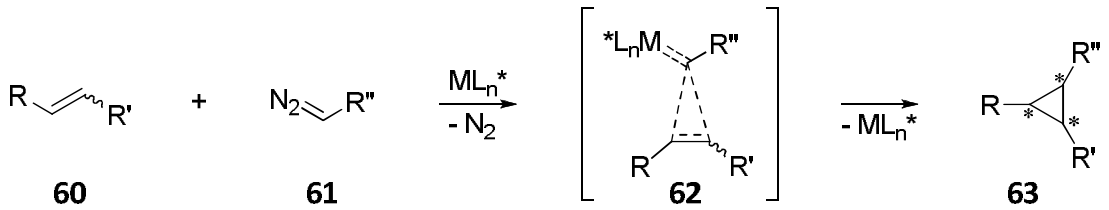
For that reason, the core structure consists of a fused ring system and is formed by an asymmetric cyclopropanation reaction, established in our group, which gives rise to the bicyclic building block **59**.[115] The formation of the imidazole moiety represents a key step in the synthetic route and is realized by conversion of aldehyde **58** by means of a TosMIC strategy.[116-119] Finally, the amino group of **55** and the cyanoguanidino group of **54** are introduced by further functional group interconversions including a Mitsunobu-type Gabriel reaction.[120] In parallel, analogues **57** and **58** with an oxazole moiety as a potential bioisoster are synthesized and pharmacologically characterized. All target compounds are accessible as both enantiomers depending on the choice of the respective chiral ligand in the asymmetric cyclopropanation step.

B. Main Part

Cyclopropanation

Cyclopropane rings are encountered in a multitude of natural products and due to its chemical properties employed as versatile building blocks in synthetic applications.[121,122] A well-documented method of the cyclopropanation arsenal is the transition metal-catalyzed decomposition of diazo alkanes **61** (Scheme 2).[123] This includes diazo compounds bearing an electron-withdrawing group especially diazo esters which reacts with electron-rich alkenes **60** catalyzed by metals such as Rh, Ru, Co and Cu. In this process, under release of nitrogen, a metal carbene complex is generated which undergoes a [2+1]-cycloaddition to an olefin (transition state **62**). The formation of two C-C bonds creates up to three new stereogenic centers (compound **63**). A controlled introduction of stereochemistry is achieved using chiral transition metal complexes (ML_n*). A large number of ligands have been developed for that reason. The complex of copper(I) and a bidentate bis(oxazoline) ligand, disclosed by Evans and coworkers, has become a standard for asymmetric cyclopropanation reactions.[124,125]

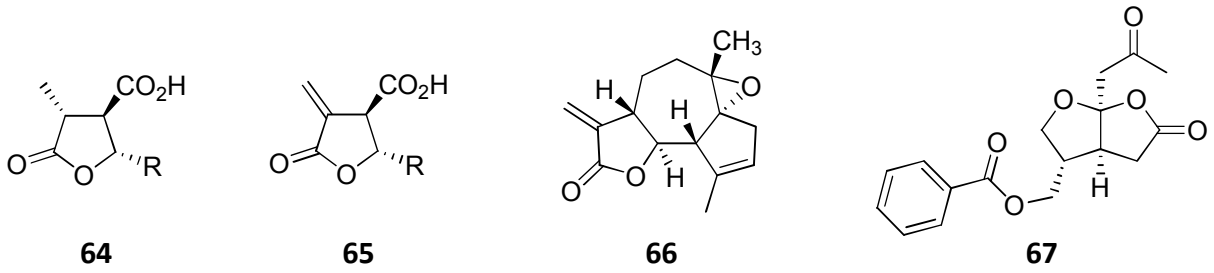
Scheme 2. Cyclopropanation by transition metal-catalyzed decomposition of diazo alkanes.



Based on a racemic cyclopropanation of 2-furoic methyl ester (**73**) with ethyl diazoacetate (**75**) using $Rh_2(OAc)_4$ as a catalyst reported by Wenkert *et al.*[126] Reiser *et al.* developed a copper(I)-catalyzed asymmetric cyclopropanation of the same furan **73**. This was achieved by using ethyl diazoacetate (**75**) in the presence of (*S*,*S*)-isopropyl bis(oxazoline) (**71**) as a chiral ligand showing high enantio- and diastereoselectivity (Scheme 4, page 23).[115]

The bicyclic building block **59** or its enantiomer ***ent*-59**, which are used in the following for the preparation of the desired target molecules, were already successfully employed for total syntheses of several natural products such as paraconic acids **64** and **65**[127,128] or Arglabin™ (**66**) (Figure 16).[129] Recently, (-)-Paeonilide (**67**) was synthesized starting from the 3-substituted analogue of **59**.[130]

Figure 16. Natural products synthesized from cyclopropanation adducts by Reiser *et al.*

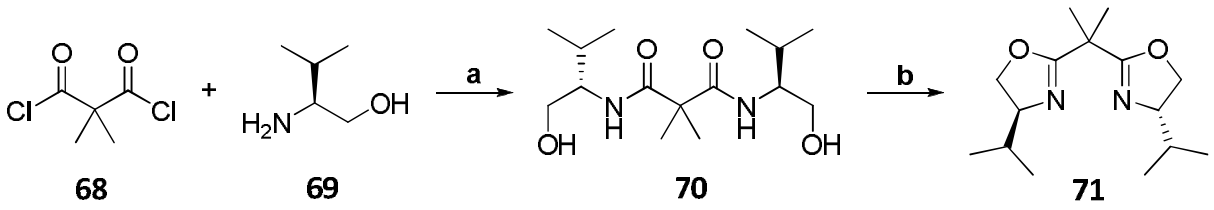


64 **65** **66** **67**

64a: R = *n*-$C_{13}H_{27}$: (-)-Roccellaric acid; **4b:** R = *n*-$C_{11}H_{23}$: (+)-Nephrosteranic acid; **65a**: R = *n*-$C_{12}H_{24}CO_2H$: (-)-Protopraesorediosic acid; **65b**: R = *n*-$C_{13}H_{27}$: (-)-Protolichesterinic acid; **65c**: R = *n*-C_5H_{11}: (-)-Methylenolactocin; **66**: Arglabin™; **67**: (-)-Paeonilide.

The bis(oxazoline) ligand **71** for the cyclopropanation reaction was accessible *via* a two-step synthesis starting from 2,2-dimethylpropanedioyl dichloride (**68**) and L-valinol (**69**) forming the diamide intermediate **70** (Scheme 3). Subsequent cyclisation afforded ligand **71**.[131] Using D-valinol gave rise to the enantiomer ***ent*-71**.

Scheme 3. Preparation of bis(oxazoline) ligand **71**.[131]



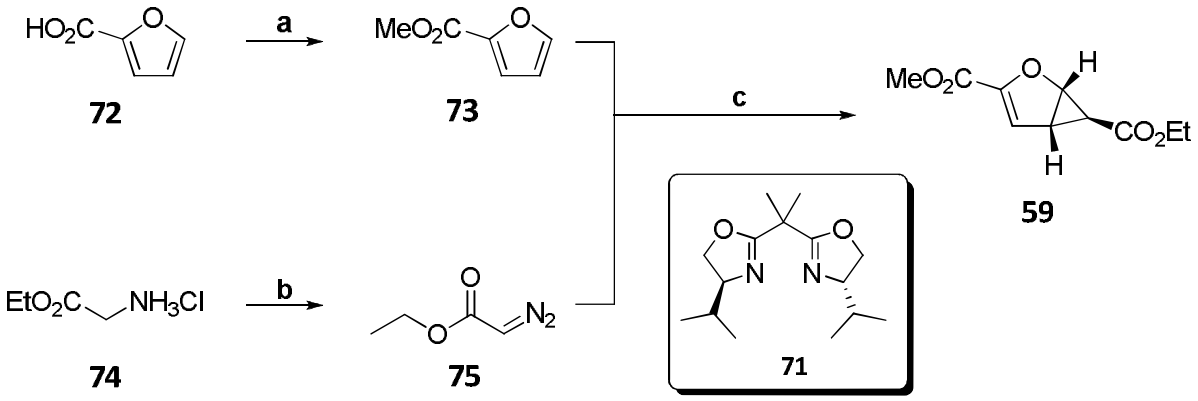
68 **69** **70** **71**

Reagents and conditions: a) L-valinol (2 equiv), NEt_3 (5 equiv), DCM, 0 °C to rt, 70 min, 84%; b) DMAP (0.1 equiv), NEt_3 (4 equiv), TsCl (2 equiv), DCM, rt, 27 h, 83%.

The substrate for the cyclopropanation, 2-furoic methyl ester (**73**), was prepared from commercially available furan carboxylic acid **72** by a sulfuric acid catalyzed esterification in 89% yield (Scheme 4). Ethyl diazoacetate (**75**) was obtained from glycine ethyl ester hydrochloride (**74**) *via* diazotization in 95% yield as a solution in DCM (9 - 12 wt%).[132]

The bicyclic building block **59** was obtained by the above mentioned copper(I)-catalyzed asymmetric cyclopropanation of 2-furoic methyl ester (**73**) using ethyl diazoacetate (**75**) in the presence of (*S*,*S*)-isopropyl bis(oxazoline) (**71**) (Scheme 4). The active copper(I) complex was generated *in situ* by reduction of copper(II) triflate with phenylhydrazine. The reaction was accomplished with high regio- and diastereoselectivity: preferentially, the less substituted and more electron-rich double bond was cyclopropanated and only the *exo* isomer with the ester functionality oriented on the convex face of the bicyclic framework was observed. The enantiopurity was improved from 85 - 90% to >99% *ee* by a single recrystallization. On a 50 g scale an isolated yield of 37% (brsm 62%) of compound **59** was achieved.

Scheme 4. Preparation of starting materials and cyclopropanation.

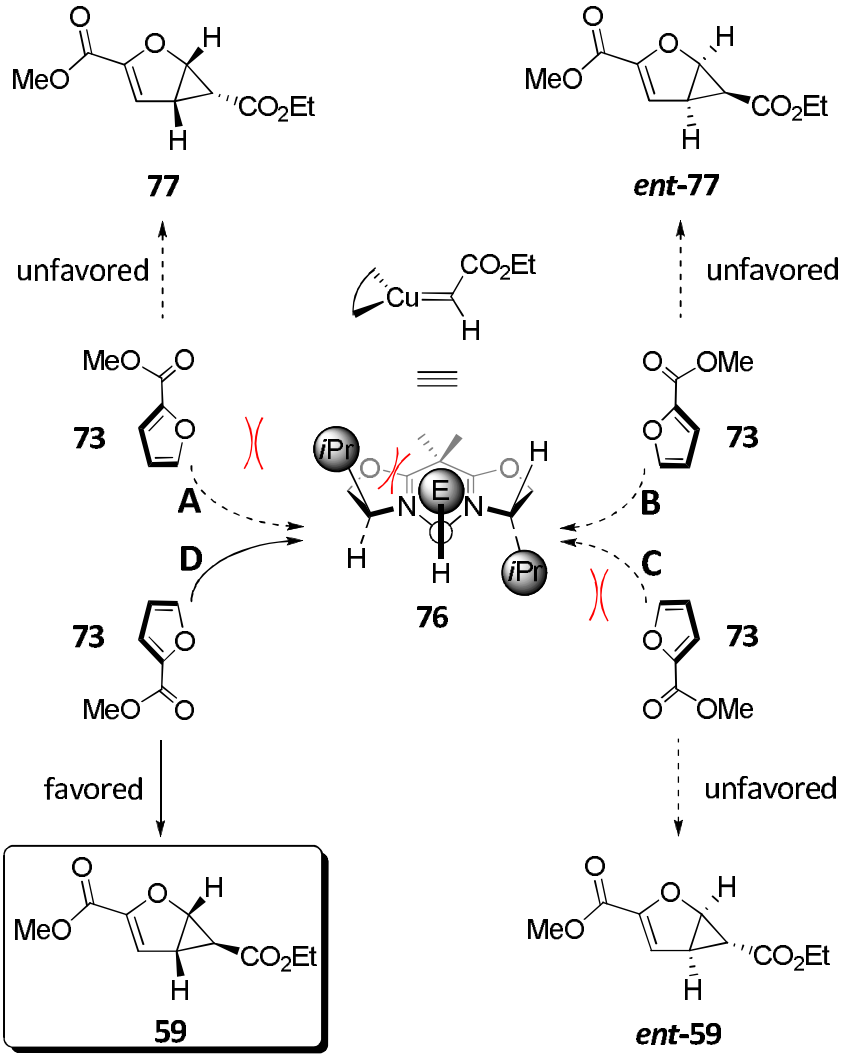


Reagents and conditions: a) H_2SO_4 (cat.), MeOH, Δ, 20 h, 89%; b) $NaNO_2$ (1.3 equiv), H_2SO_4 (cat.), DCM/H_2O, - 20 °C to 0 °C, 95%; c) i. **71** (1.0 mol%), $Cu(OTf)_2$ (0.75 mol%), $PhNHNH_2$ (0.9 mol%), DCM, 0 °C, 7 d, 54%, 85-90% *ee*; ii. recrystallization (DCM, *n*-pentane), 37%, > 99% *ee*.

The following mechanistic aspects deduced from Pfaltz[133] and Andersson[134] provide an explanation for the stereochemical results of the asymmetric cyclopropanation of 2-furoic methyl ester (**73**) (Scheme 5). First the bis(oxazoline) copper(I) complex reacts with ethyl diazoacetate (**75**) to afford a metal carbene complex **76** under release of nitrogen. The ligand forms a plane which is perpendicular to the plane formed by the trigonal copper carbenoid. Due to the C2-symmetry of the ligand, two opposite quadrants are sterically blocked by the bulky isopropyl substituents. Therefore, trajectory A and C are unfavored. 2-Furoic methyl ester (**73**) attacks the carbenoid center with its less substituted and more electron-rich double bond. This causes a change of the hybridization of the carbenoid carbon to sp^3 arranging it in a tetrahedral geometry. In consequence, trajectory B is also not favored

because the approach of 2-furoic methyl ester (**73**) increases the repulsive steric interaction between the ester function at the former carbenoid center and the isopropyl group of the oxazoline ring. By contrast, the steric interaction between the ethyl ester group and the oxazoline hydrogen atom of the ligand is much smaller. In summary, this results in a preference for trajectory D. Moreover, the high enatioselectivity results also from the structural properties of the olefin: (1) the double bond approaches *via* trajectory D with the methyl ester group pointing away from the ligand framework, (2) the approach of the substrate to the reaction center *via* trajectory D is directed due to an attractive interaction of the endocyclic oxygen atom of **73** and the metal atom.

Scheme 5. Mechanistic aspects of the asymmetric cyclopropanation reaction.

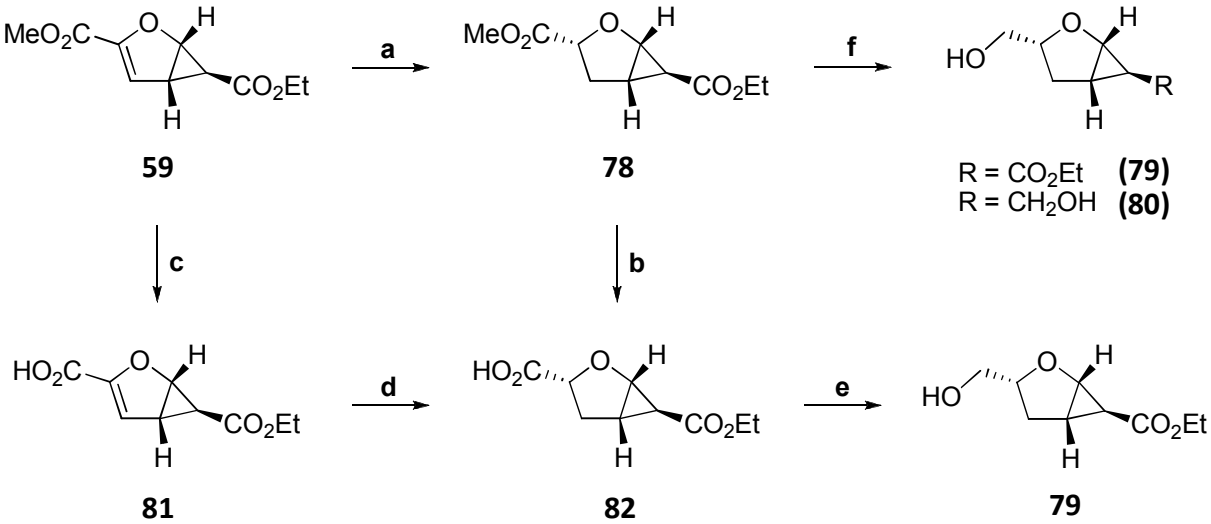


Route I - Introduction of an aldehyde functionality

On the basis of the bicyclic building block **59** the synthesis of the target compounds is divided into two parts: The functional group interconversion of the methyl ester group to the imidazole moiety and the transformation of the ethyl ester function to the amino and cyanoguanidino group, respectively. A key step in the synthesis is the preparation of the imidazole moiety. The imidazole ring is incorporated in countless natural products and is part of many pharmaceutical drugs and compounds with industrial and technological importance.[135-137] Therefore numerous methods for the construction of the imidazole ring were developed since its first synthesis from glyoxal and ammonia by Debus more than 150 years ago.[138,139] A convenient way for the *de novo* synthesis of 4(5)-monosubstituted and 1,4- or 1,5-disubstituted imidazole compounds is the application of tosylmethyl isocyanide (TosMIC) chemistry which was initially described by van Leusen.[116] Some related methodologies have been developed which all have an aldehyde as the starting material in common.[117-119] Therefore, generation of an aldehyde function was the next task in the reaction route.

Having the bicyclic building block **59** in hand a sequence of double bond hydrogenation, methyl ester saponification and carboxylic acid reduction was contemplated in order to realize a chemoselective reduction of the CO_2Me group (Scheme 6).

Scheme 6. Preparation of alcohol **79**.



Reagents and conditions: a) i) Pd/C (10%), EA, H_2 (balloon), rt, 1.5 h, ii) recrystallization (DCM, *n*-pentane) 73%; b) LiOH (1.2 equiv), THF/H_2O, rt, 1 h, 92%; c) LiOH (1.1 equiv), THF/H_2O, rt, 1 h, 94%; d) Pd/C (10%), EA, H_2 (balloon), rt, 1.5 h, 70%; e) BH_3•DMS (1.5 equiv), THF, 0 °C to rt, 4 h, 77%; f) LAH (0.6 equiv), THF, 45 min, 87% **79**, 5% **80**.

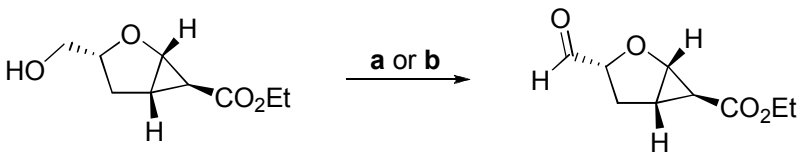
The double bond was hydrogenated according to Weisser *et al.* using palladium on charcoal in EA.[140] The hydrogenation proceeded *via syn*-addition exclusively from the less hindered convex face of the bicyclic framework to form **78** as a single stereoisomer in 73% yield after recrystallization. The choice of mild conditions by employing a small stoichiometric excess of LiOH in aqueous THF effected selective saponification of the methyl ester group to yield **82** in 92%.[141] The reverse reaction order, first saponification to **81**, then hydrogenation, afforded **82** in comparable yields as well but separation of unreacted **81** from **82** proved to be difficult.[141]

Subsequently, the reducing agent borane dimethyl sulfide complex, which enables chemoselective reduction of carboxylic acids to alcohols without affecting ester functions, was successfully applied to obtain alcohol **79** in 77% yield.[142]

It is assumed that the selectivity in the LiOH-mediated saponification reaction is also attributed to a chelation of the lithium ion by the methyl ester carbonyl oxygen atom and the endocyclic oxygen atom that activates the methyl ester group for nucleophilic attack. In consequence, it was expected that the strong reducing agent LAH behaves in a similar way so that the hydride ion reduces the methyl ester faster than the ethyl ester. Indeed, by an accurate addition of two reduction equivalents a selective reduction of compound **59** to alcohol **79** was accomplished in 87% yield. The instable dihydroxyl product **80** was obtained in 5% yield and characterized as its diprotected derivative **115** (page 36).

To oxidize alcohol **79** to the corresponding aldehyde **83** two standard procedures were examined (Scheme 7). Swern oxidation, using oxalyl chloride, DMSO and NEt_3 afforded **83** in 65% yield.[143] Oxidation mediated by Dess-Martin periodinane, which was prepared in two steps from 2-iodobenzoic acid,[144] furnished **83** in 88% yield. In addition to the improved yield Dess-Martin oxidation exhibited a shorter reaction time and was more convenient to perform.

Scheme 7. Preparation of aldehyde **83.**



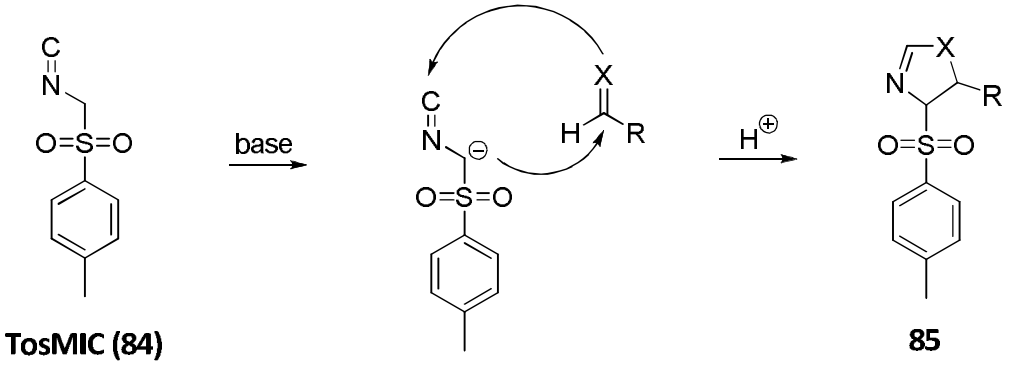
79 **83**

Reagents and conditions: a) $(COCl)_2$ (1.5 equiv), DMSO (2.5 equiv), NEt_3 (5 equiv), DCM, -78 °C, 1.5 h, 65%; b) Dess-Martin periodinane (1.05 equiv), DCM, rt, 1 h, 88%.

Route I - Introduction of the imidazole ring

TosMIC (**84**), introduced by van Leusen, is a versatile synthon in organic chemistry.[145] Among the synthetically useful applications are: the conversion of aldehydes and ketones to homologous nitriles[146] and carboxylic acids[147] and the synthesis of ketones,[148] α-diketones[149] and azoles[150,151] such as oxazoles, pyrroles, 1,2,4-triazoles, thiazoles and imidazoles. TosMIC accommodates a reactive isocyanide carbon and a methylene group which is activated by a tosyl group (Scheme 8). Bases induce a [3+2] anionic cycloaddition of the C–N=C moiety with polarized double bonds to give five-membered heterocycles **85**.

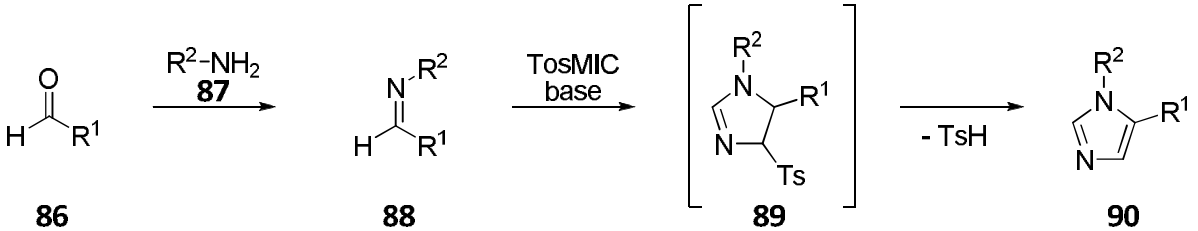
Scheme 8. Cycloaddition reaction of TosMIC (**84**).



TosMIC (84) **85**

The first reported synthesis of imidazole derivatives using TosMIC proceeds through a cycloaddition with *N*-protected aldimines **88** derived from corresponding aldehydes **86** (Scheme 9).[116] The intermediate 4-tosyl-2-imidazoline **89** eliminates *p*-toluenesulfinic acid (TsH) resulting in the formation of 1,5-disubstituted imidazoles **90**. Complete transformation in a single operation is effected by using K_2CO_3 as a base in a mixture of MeOH and DME. Alternatively, amine **87** can be applied which corresponds to the aldimine, to prevent amine exchange.

Scheme 9. TosMIC-mediated method (A) for the preparation of imidazoles.[116,119]



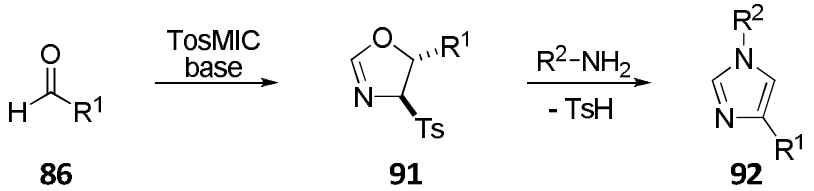
86 **88** **89** **90**

R^1 = alkyl, alkenyl, aryl; R^2 = alkyl, aryl, tosyl.

According to ten Have *et al.*, 4(5)-monosubstituted imidazoles are obtained when the reaction is carried out with *p*-toluenesulfonamide (**87**, R^2 = tosyl) to form an activated imine **88** possessing an electron withdrawing tosyl group.[119] The initially formed 1-tosylimidazole **90** (Scheme 9, R^2 = tosyl) spontaneously splits off the tosyl group.

In the presence of a catalytic amount of a weak base such as NaCN or K_2CO_3 in a protic solvent like EtOH the [3+2] cycloaddition of TosMIC and aldehyde **86** affords isolable *trans*-configured 4-tosyloxazolines **91** (Scheme 10).[152] 4(5)-monosubstituted or 1,4-disubstituted imidazoles **92** can be obtained when those oxazolines **91** are heated with a saturated solution of ammonia in methanol or monoalkylamines in benzene or xylene at 90 - 110 °C in a sealable pressure tube.[117]

Scheme 10. TosMIC-mediated method (B) for the preparation of imidazoles.[117]

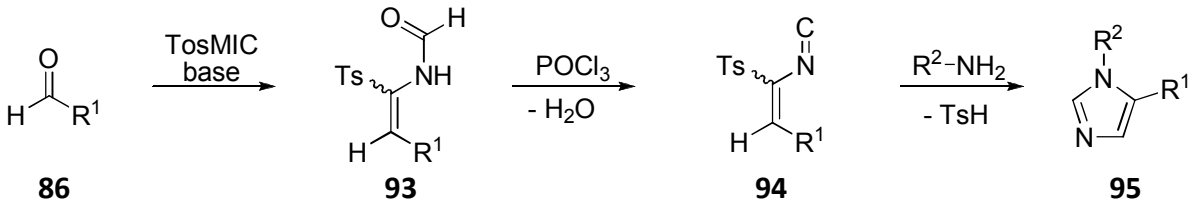


86 **91** **92**

R^1 = alkyl, alkenyl, aryl; R^2 = H, alkyl.

In an aprotic solvent such as DME and with ^{t}BuOK as a strong base the cycloadduct of aldehyde **86** and TosMIC undergoes ring opening to provide *N*-(1-tosyl-1-alkenyl)formamide **93** (Scheme 11) which is the acyclic isomer of oxazoline **91** (Scheme 10).[118] Two sets of signals were frequently observered in NMR spectra which were assumed in many scientific publications to arise from *E*/*Z*-isomers at the newly formed C=C bond although van Leusen *et al.* attributed this fact to restricted rotation around the amide bond based on temperature dependent ^{1}H-NMR analysis. Subsequent dehydration with $POCl_3$ give rise to α,β-unsaturated sulfonyl isocyanides **94**. Treating with a primary aliphatic amine or ammonia affords the formation of 1,5-disubstituted or 4(5)-monosubstituted imidazoles **95**.

Scheme 11. TosMIC-mediated method (C) for the preparation of imidazoles.[118]

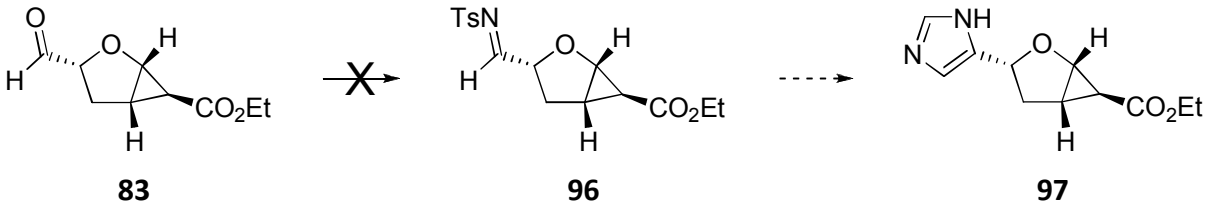


R^1 = alkyl, alkenyl, aryl; R^2 = H, alkyl.

Formation of the imidazole ring *via* method (A)

To obtain 4(5)-monosubstituted imidazole **97** *via* method (A) first *N*-tosylaldimine **96** was intended to prepare (Scheme 12). Due to the limited nucleophilicity of *N*-sulfonamides toward aldehydes harsh reaction conditions are generally required for their direct condensation like the use of strong Lewis and Brønsted acids to eliminate water, high temperature and long reaction times. Additionally, enolizable aldehydes are known to suffer from side reactions. As a result, various direct and indirect condensation methods have been developed for the preparation of *N*-sulfonylimines since they are versatile intermediates in organic synthesis.[153-165]

Scheme 12. Envisaged TosMIC-mediated method (A) for the preparation of imidazole **97**.[119]



When aldehyde **83** was conducted with *p*-toluenesulfonamide in anhydrous DCM in the presence of $MgSO_4$ under reflux conditions crude NMR showed full conversion of the aldehyde and indicated, among other undefined side products, the formation of a small amount of the desired imine **96** which was confirmed by mass spectroscopy. However, the isolation was not feasible owing to the sensibility of the imine toward hydrolytic cleavage. It was tried to improve the outcome of the reaction by addition of *p*-toluenesulfonic acid as a Brønsted acid or $AlCl_3$ as a Lewis acid. Both resulted in an acceleration of the formation of unwanted side products.

In the following experiments, procedures were applied which are known to manage the conversion of enolizable aldehydes.

Fan *et al.* reported a method which enables the direct condensation of enolizable aldehydes with *p*-toluenesulfonamide through a Barbier-type reaction using benzyl bromide and zinc dust.[162] However, the desired product **96** could not be detected by NMR, only *p*-toluenesulfonamide was isolable.

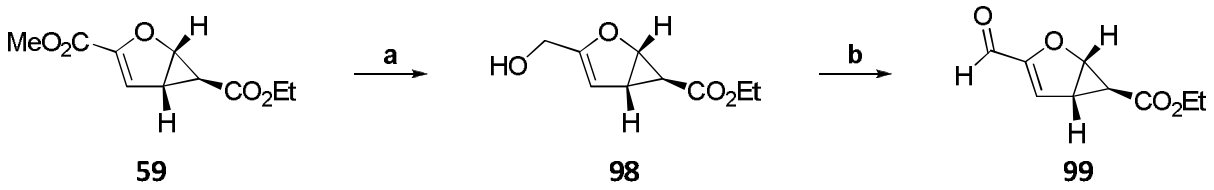
Chemla *et al.* published a two-step procedure for the formation of *N*-sulfonyl aldimines using *p*-toluenesulfonamide in the presence of sodium benzenesulfinate in formic acid and water to produce an intermediate that was treated with $NaHCO_3$.[158] But in the present case the reaction again did not afford the desired imine **96**. Most of the employed *p*-toluenesulfonamide was recovered.

Another mild, indirect method is known as the Kresze reaction.[153] *N*-sulfinyl *p*-toluenesulfonamide[166] is used instead of *p*-toluenesulfonamide to generate the product *via* a [2+2] cycloaddition and extrusion of sulfur dioxide in the presence of the Lewis acid trifluoride etherate.[154] In the crude NMR spectrum of this reaction with aldehyde **83** small amounts of the desired imine **96**, unreacted aldehyde and a multiple amount of *p*-toluenesulfonamide could be identified. *N*-tosylaldimine **96** seemed to be unstable under these conditions and prone to hydrolysis after its formation.

The Kresze reaction had been engaged also for the *in situ* generation of sulfonylaldimines which had been further converted directly. Therefore, it was tried to perform a Kresze reaction with aldehyde **83** which was immediately treated with TosMIC and K_2CO_3 to accomplish imidazole **97** directly in a one-pot two-step synthesis. A complex product mixture was obtained with no indication of desired imidazole **97**.

Due to the problems associated with enolizable aldehydes it was decided to skip the hydrogenation step in the reaction sequence (Scheme 6) to retain the double bond in the molecule resulting in the α,β-unsaturated aldehyde **99** that has no acidic α-hydrogen atom. As illustrated in Scheme 13 compound **59** was first selectively reduced with LAH to afford allyl alcohol **98** in 79% yield. Subsequently, Dess-Martin oxidation accomplished the preparation of aldehyde **99** in 49% yield. Both **98** and **99** proved to be slightly unstable when subjected to column chromatography and upon storing at room temperature for a prolonged period.

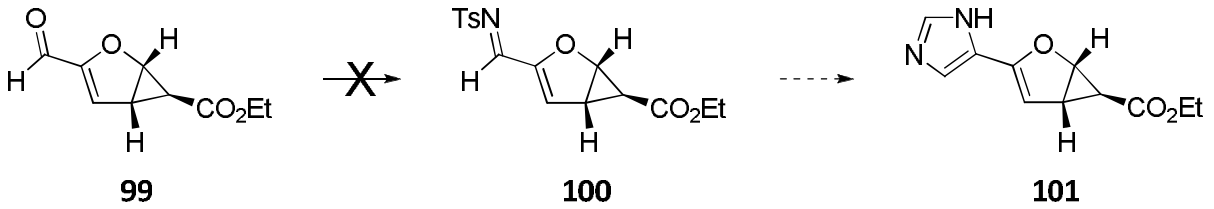
Scheme 13. Preparation of α,β-unsaturated aldehyde **99**.



Reagents and conditions: a) LAH (0.6 equiv), THF, 0 °C, 1 h, 79%; b) Dess-Martin periodinane (1.06 equiv), DCM, rt, 1.5 h, 49%.

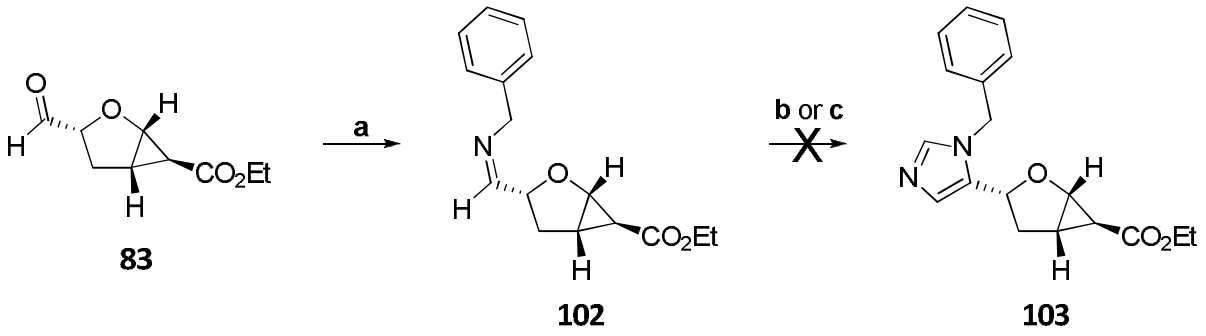
Aldehyde **99** was reacted with *p*-toluenesulfonamide in the presence of the dehydration agent $TiCl_4$ and NEt_3 in DCM at 0 °C.[155] Conversion of the aldehyde and formation of new products was indicated by TLC but crude NMR did not show evidence for the formation of imine **100** (Scheme 14). Column chromatography could not reveal any characterizable compounds apart from the starting material *p*-toluenesulfonamide. Comparable results were obtained applying the above mentioned Barbier-type and Kresze methods.[154,162]

Scheme 14. Envisaged TosMIC-mediated method (A) for the preparation of imidazole **101**.[119]



The installation of the 1,5-distubstituted imidazole ring was investigated next. For this reason, it was considered to use benzylamine to prepare a *N*-benzyl imine which is then subjected to a cycloaddition with TosMIC under van Leusen conditions.[116] The resulting *N*-protected imidazole is cleavable by hydrogenation in a subsequent operation.[167] Formation of *N*-benzyl imine **102** was achieved quantitatively by treating aldehyde **83** with benzylamine in DCM in the presence of $MgSO_4$ (Scheme 15). Attempts of purification by column chromatography led to hydrolysis of the imine. The crude product was applied in a van Leusen reaction using TosMIC and K_2CO_3 or benzylamine as a base in MeOH or a mixture of DME and MeOH. No conversion was observed at room temperature. Nor could higher temperatures and longer reaction times promote the generation of imidazole **103**.

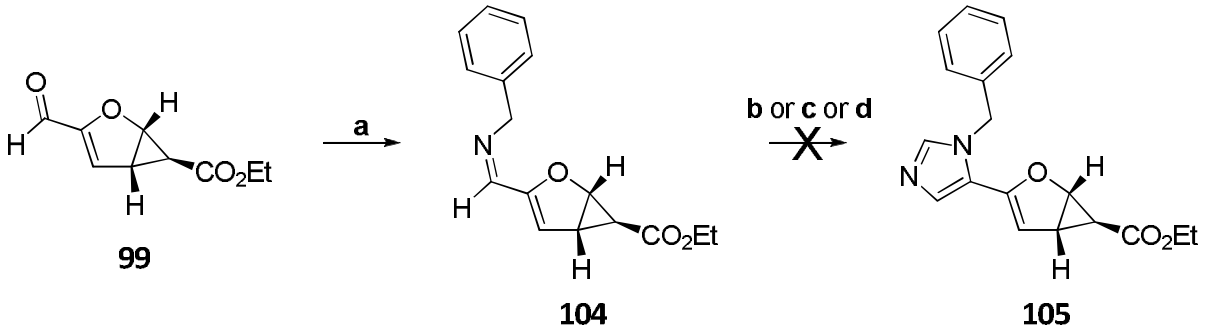
Scheme 15. Envisaged TosMIC-mediated method (A) for the preparation of imidazole **103**.[116]



Reagents and conditions: a) benzylamine (1.0 equiv), $MgSO_4$, DCM, reflux, 1.5 h, quant.; b) TosMIC (1.5 equiv), K_2CO_3 (2.0 equiv), MeOH/DME (2:1), rt - reflux, 1 - 17 h; c) TosMIC (2.0 equiv), benzylamine (2.0 equiv), MeOH, rt - reflux, 6 - 18 h.

In parallel, the analogous α,β-unsaturated *N*-benzyl imine **104** was prepared from aldehyde **99** and used in the next step without purification (Scheme 16). Again, it was not possible to convert imine **104** to the desired imidazole **105** under van Leusen conditions with TosMIC and K_2CO_3 in a DME/MeOH mixture. Using benzylamine instead of K_2CO_3 remained unsuccessful as well. Also the initial reaction of the reported two-step procedure employing NaH in DME did not provide the expected intermediate, not even at elevated temperature.

Scheme 16. Envisaged TosMIC-mediated method (A) for the preparation of imidazole **105**.[116]



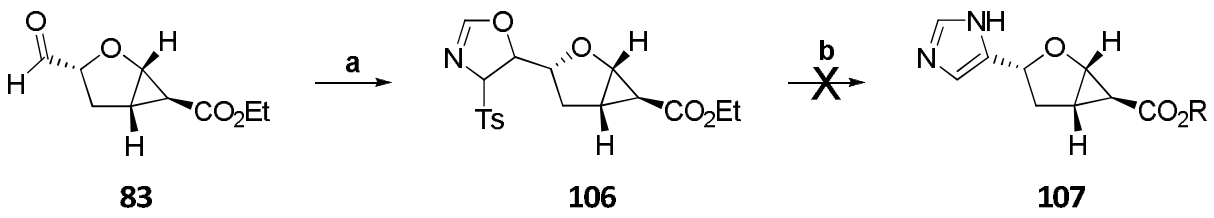
Reagents and conditions: a) benzylamine (1.1 equiv), $MgSO_4$, DCM, reflux, 1.5 h, quant.; b) TosMIC (1.5 equiv), K_2CO_3 (2.0 equiv), MeOH/DME (2:1), rt to reflux, 3 - 20 h; c) TosMIC (2.0 equiv), benzylamine (2.0 equiv), MeOH, rt to reflux, 20 h; d) TosMIC (1.1 equiv), NaH (2.4 equiv), DME, -20 °C to rt, 2 h.

Obviously, electrophilicity of the *N*-alkylated imines **102** and **104** is drastically reduced, thus TosMIC is not reactive enough to cycloadd to the C=N bond of those imines.

Formation of the imidazole ring *via* method (B)

Following method (B), the aldehyde **83** was allowed to react with TosMIC in the presence of NaCN in EtOH to yield 4-tosyloxazoline **106** in 70% as a 2:1 mixture of presumably *trans*-configured diastereomers (Scheme 17). Aiming at the formation of an unprotected monosubstituted imidazole ring, oxazoline **106** was heated in a saturated solution of ammonia in MeOH or EtOH at various temperatures from 80 to 110 °C and various reaction times from 0.5 h to 20 h in a sealable pressure tube. It was considered that these conditions might allow tansesterification or amide formation at the ethyl ester group as known from literature precedents.[168] However, none of the expected imidazole containing compounds **107** could be identified from the reaction mixture by NMR and mass analysis.

Scheme 17. Envisaged TosMIC-mediated method (B) for the preparation of imidazole **107**.[117]



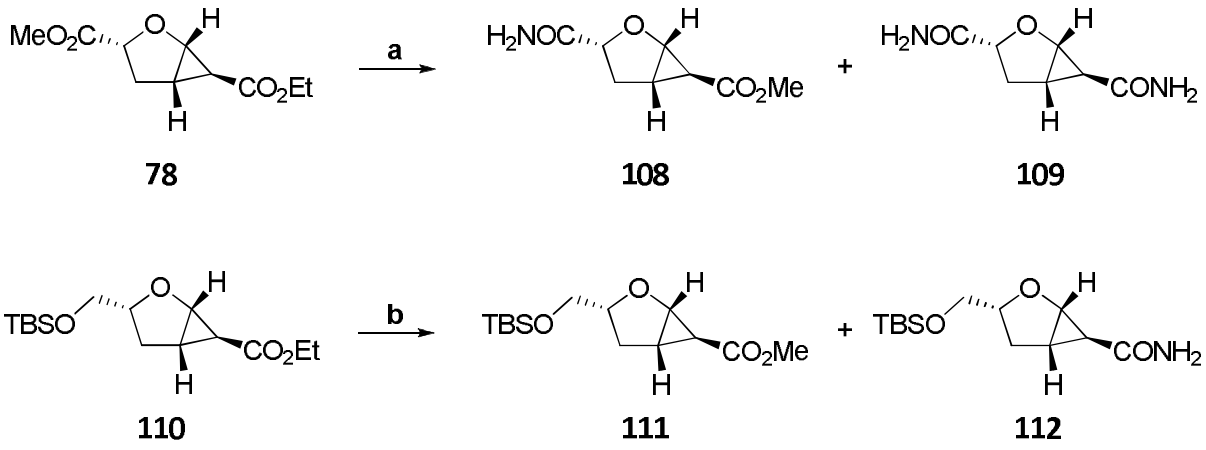
83 **106** **107**

Reagents and conditions: a) TosMIC (1.1 equiv), NaCN (0.18 equiv), EtOH, rt, 1 h 70%; b) saturated NH_3 in MeOH or EtOH, 80 to 110°C, 0.5 - 20 h; R = Et, Me, NH_2.

Two test reactions were carried out in order to exclude any unexpected side reactions of the bicyclic core such as ring opening of the cyclopropane moiety. Additionally, information about the behavior of the ethyl ester group should be gained when treated with ammonia at elevated temperature and pressure (Scheme 18). Reaction of diester **78** with a saturated solution of ammonia in MeOH at 95 °C in a sealable pressure tube for 17 h gave rise to a transesterification of the ethyl ester group and amide formation at the methyl ester function to furnish compound **108** in 28% yield. Compound **109**, bearing two amide functions, was isolated in 67% yield. When TBS-protected compound **110** was employed, analogous reactions to methylester **111** and amide **112** were performed.

Neither the bicyclic scaffold was affected under these conditions nor was any other transformations observed.

Scheme 18. Test reactions with ammonia.

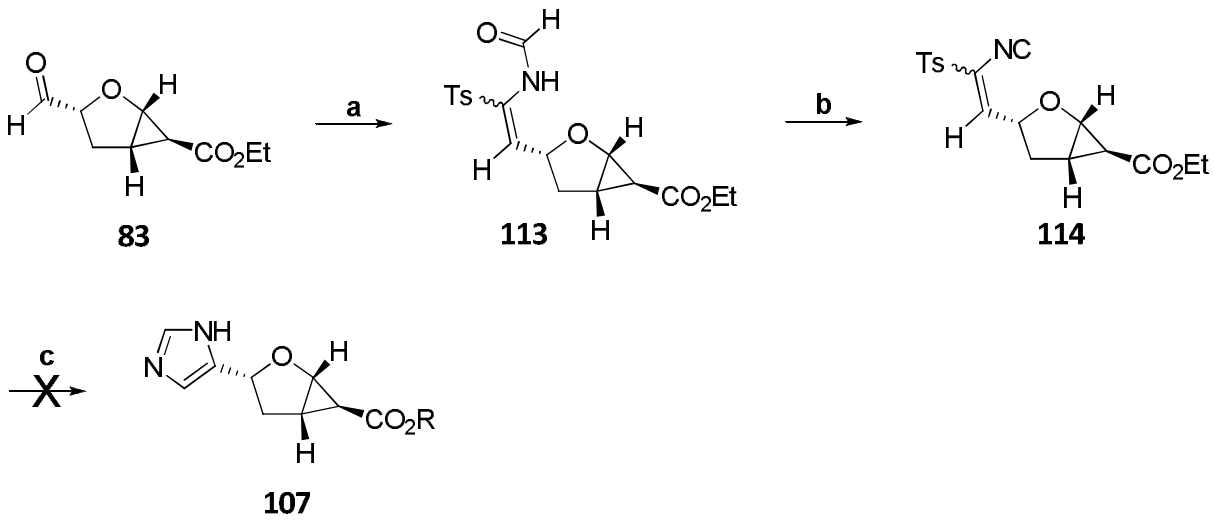


Reagents and conditions: a) saturated NH_3 in MeOH (100 equiv), 95 °C, 17 h, 28% **108**, 67% **109**; b) saturated NH_3 in MeOH (100 equiv), 80 °C, 16 h, 38% **111**, 55% **112**.

Formation of the imidazole ring *via* method (C)

Method (C) seemed to be promising for the formation of the desired heterocycle since the imidazole forming step requires less drastic conditions in comparison to method (B). Treating aldehyde **83** with ^{t}BuOK in DME at -35 °C afforded the acyclic *N*-(1-tosyl-1-alkenyl)formamide **113** in 54% yield (Scheme 19). Two sets of signals were observed in NMR spectra as explained above (page 28). The following dehydration with $POCl_3$ in DME gave rise to sulfonyl isocyanides **114**, proved by NMR, IR and mass analysis. However, compound **114** turned out to be unstable on silica gel. Therefore, the crude reaction mixture was treated without further purification with 2 - 300 equivalents of ammonia saturated in MeOH at room temperature but did not show any conversion to the desired product. Higher temperature, however, provided a complex mixture of substances. None of the expected imidazole-containing compounds **107** could be identified by NMR or mass analysis.

Scheme 19. Envisaged TosMIC-mediated method (C) for the preparation of imidazole **107**.[118]



Reagents and conditions: a) ^{t}BuOK (1.3 equiv), TosMIC (1.0 equiv), DME, -35 °C, 0.5 h, 54%; b) NEt_3 (4.7 equiv), $POCl_3$ (1.5 equiv), DME, rt, 0.5 h; c) saturated NH_3 in MeOH (2 -300 equiv), rt to 90 °C, 6 h; R = Et, Me, NH_2.

To summarize, starting from aldehyde **83** the introduction of the imidazole moiety by different methods using TosMIC chemistry failed. Preparation *via* tosylimines from enolazible and non-enolizable aldehydes suffered from hydrolysis of the generated imine and formation of side products. A benzyl substituent led to deactivation of the imino group whereby TosMIC was not able to form 1,5-disubstituted imidazoles by cycloaddition. Finally, tosyloxazoline **106** and tosylisocanide **114** did not react with ammonia in the expected way to accomplish 4(5)-monosubstituted imidazoles **107**. Although it was shown that harsh ammoniacal conditions had no influence on the core structure, it remained unclear, whether the amide functionality, whose formation was confirmed by test reactions, might interfere with the imidazole forming step in the latter two cases.

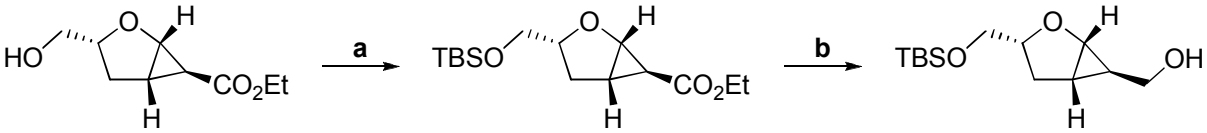
For that reason, it was considered to displace the ethyl ester moiety by a protection group which is inert toward ammonia.

Synthesis of imidazole-containing ligands - Route II

To circumvent the difficulties associated with the imidazole forming step in the previous section it was decided to reduce the ethyl ester function to the corresponding hydroxyl group which is then converted to a base-resistant benzyl ether protection group.

For this purpose, alcohol **79** was protected almost quantitatively as silyl ether **110** by using TBSCl under basic conditions with DMAP as a catalyst (Scheme 20). **110** was also obtained in comparable yields from diester **78** in two steps without purification of the crude intermediate by column chromatography. In this case diprotected compound **115** was isolated in up to 5% yield resulting from dialcohol **80** (Scheme 6). Subsequently, reduction of the ethyl ester moiety using an excess of LAH afforded alcohol **116** in almost quantitative yield as well.

Scheme 20. Preparation of alcohol **116**.

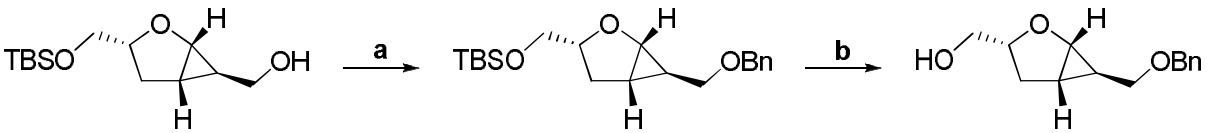


79 **110** **116**

Reagents and conditions: a) NEt_3 (1.5 equiv), TBSCl (1.2 equiv), DMAP (0.05 equiv), DCM, rt, 18 h, 95%; b) LAH (0.8 equiv), THF, 0 °C, 45 min, 95%.

The protection of alcohol **116** succeeded in 85% yield by employing benzyl bromide under basic conditions in DMF to give compound **117** (Scheme 21). The cleavage of the siliylether was accomplished by the use of TBAF in THF excellent yield. The resulting alcohol **118** represents the benzyl ether analogue of compound **79**.

Scheme 21. Preparation of alcohol **118**.

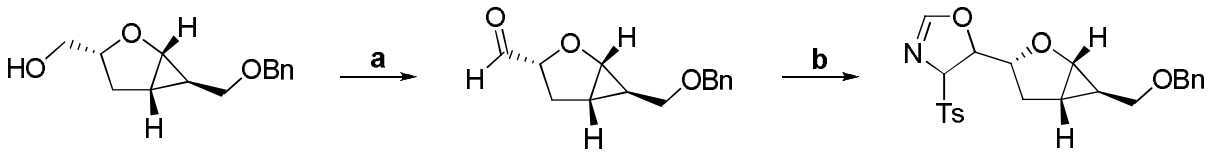


116 **117** **118**

Reagents and conditions: a) NaH (2.0 equiv), BnBr (2.0 equiv), DMF, 0 °C to rt, 2 h, 85%; b) TBAF•$3H_2O$ (1.5 equiv), THF, rt, 13 h, 95%.

In analogy with the reactions depicted in Scheme 7 and Scheme 17 oxidation of alcohol **118** was performed by Dess-Martin reagent in 90% yield to give aldehyde **119**. This compound underwent a [3+2] anionic cycloaddition with TosMIC under basic conditions to form 4-tosyloxazoline **120** as a mixture of presumably *trans*-configured isomers in 77% yield and a diastereomeric ratio of 3:2 (Scheme 22).

Scheme 22. Preparation of tosyloxazolin **120**.

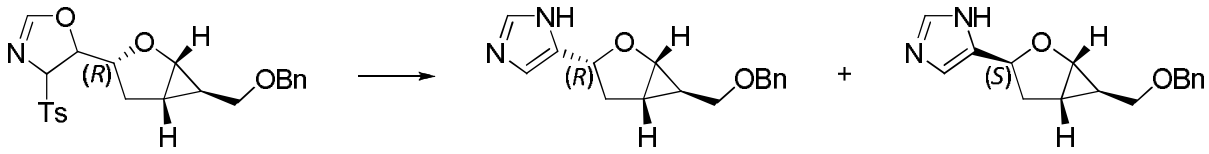


118 **119** **120**

Reagents and conditions: a) Dess-Martin periodinane (1.1 equiv), DCM, rt, 2 h, 90%, b) TosMIC (1.1 equiv), NaCN (0.22 equiv), EtOH, rt, 2 h, 77%.

In the following key step oxazoline **120** was treated with a solution of ammonia in MeOH under elevated temperature in a sealable pressure tube (Table 1). The desired imidazole formation was achieved in up to 68% yield. Beside the formation of the expected imidazole **121a** the corresponding epimer **121b** was identified as well. Several experiments confirmed the dependence of the combined yield and the ratio of both isomers on the reaction temperature. Heating to 100 °C afforded almost equal amounts of the isomers (entry 2) while lower temperatures encouraged the formation of **121a** with unchanged configuration of the relevant stereogenic center (entry 1).

Table 1. Preparation of imidazole **121**.



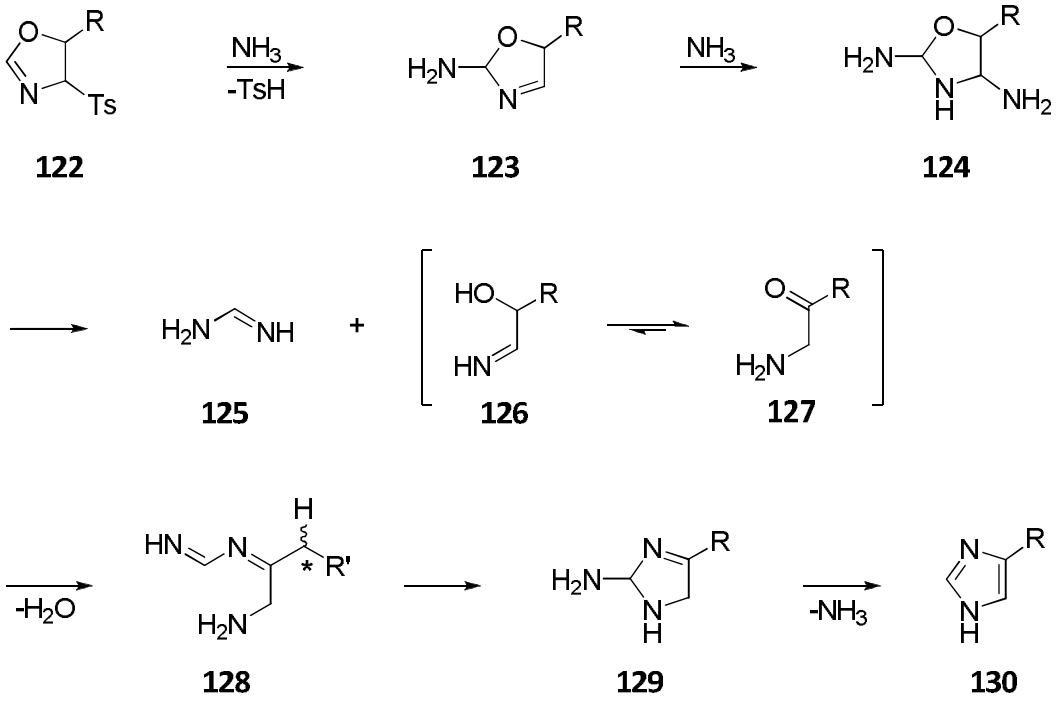
120 **121a** **121b**

entry	NH_3 (equiv)[a]	t (h)	T (°C)	yield (%)	*dr* (121a : 121b)[b]
1	70	16	95	68	84 : 16
2	70	16	100	49	53 : 47

[a] saturated in MeOH.
[b] determined by ^{1}H-NMR.

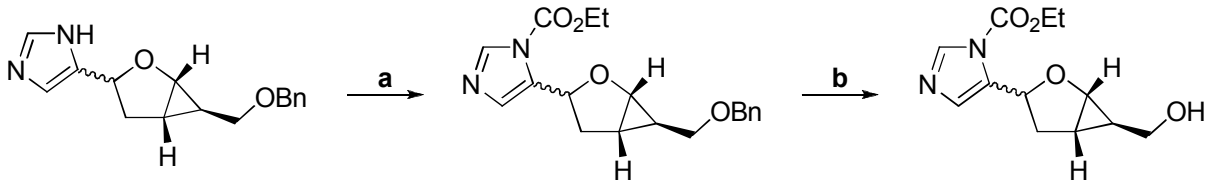
The epimerisation in the present case can be explained by the following proposed mechanism according to Horne *et al.* (Scheme 23).[117] Initially, aminooxazoline **123** is generated by the attack of ammonia on the immino function of tosyloxazoline **122** under release of sulfinic acid. Addition of a second molecule of ammonia and heating effects fragmentation of intermediate **124** to formamidine (**125**) and iminoalcohol **126** which isomerizes to α-amino ketone **127**. Finally, 4(5)-monosubstituted imidazole **130** is formed by a sequence of intermolecular condensation and intramolecular cyclization which is related to the well documented imidazole syntheses with α-halogen ketones and amidines[169] and the Bredereck synthesis of α-hydroxy, α-halogen and α-amino ketones with formamide.[170] It is suspected that intermediate **128**, possessing a delocalized π-system, comprises an α-acidic proton at the adjacent carbon. Proton abstraction by suitable bases such as the intermediately generated formamidine (**125**) causes the observed equilibration of the stereogenic center.

Scheme 23. Proposed mechanism for imidazole formation.[117]



Separation of the two isomers by column chromatography was not possible at this stage. Referring to a concept of Harusawa *et al.* protection of the imidazole ring should facilitate the separation of the isomers at a later stage of the synthetic route.[171] Ethyl chloroformate was employed to convert imidazole **121** to its base-sensitive carbamate-protected derivative **131** in 73% yield (Scheme 24). Cleavage of the benzylether was realized by hydrogenolysis under catalytic transfer hydrogenation using palladium hydroxide on carbon and cyclohexene as the hydrogen donor to give alcohol **132** in 73% yield.[172]

Scheme 24. Preparation of alcohol **132**.



121 **131** **132**

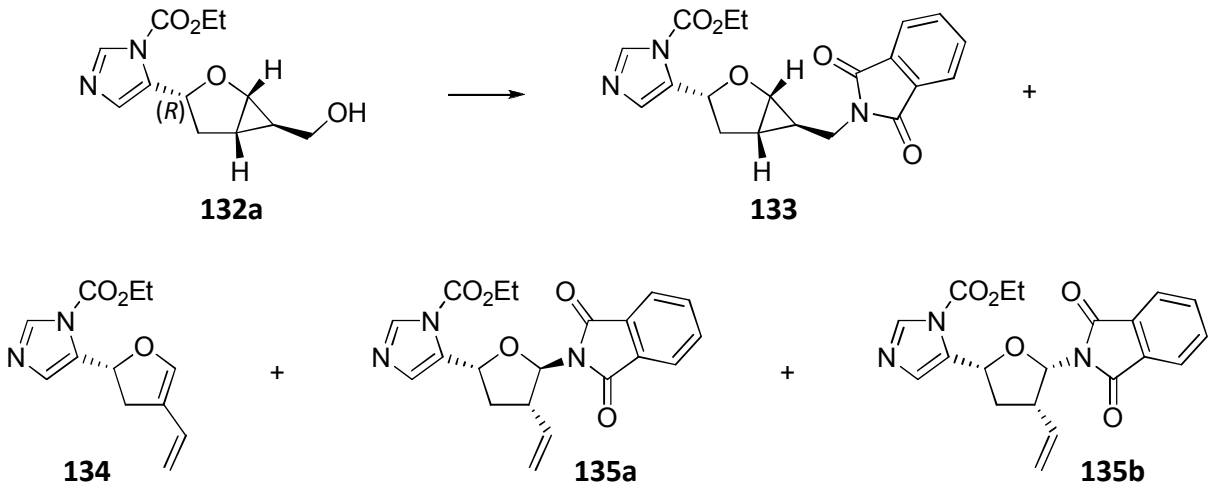
Reagents and conditions: a) ethyl chloroformate (1.9 equiv), pyridine (1.9 equiv), DMAP (0.16 equiv), benzene, 50 °C, 10 min, 73%; b) $Pd(OH)_2/C$, cyclohexene (40 equiv), EtOH, reflux, 1 h, 73%.

At this point separation of the isomers became necessary since the next step provided several side-products which were otherwise tedious to separate and to characterize. Partial separation of the less polar alcohol **132a** from the isomeric mixture could be achieved by a single column chromatographical run. On the other hand, several purification steps were required to achieve an analytically pure sample of isomer **132b**.

To displace the hydroxyl group of the 3*R*-isomer **132a** with an amino moiety a phthaloylimination under Mitsunobu conditions and subsequent hydrazinolysis was performed.[120] By treating **132a** with phthalimide in the presence of PPh_3 and DIAD, desired phthalimide **133** was obtained in low yields of 29% (Table 2). In addition, further ring-opening compounds were formed. Phthalimides **135a** and the corresponding epimer **135b** could be isolated in 51% and 10% yield, respectively. Diene **134** was observed as well but was not separable from the triphenylphosphine oxide byproduct.

In order to optimize the conditions for the preparation of the desired phthalimide **133** several test reactions using model compound **116** were carried out, presented in section *Mitsunobu reaction* (page 48). A mechanistic view on the formation of these side products is also given there.

Table 2. Mitsunobu-type Gabriel reaction.

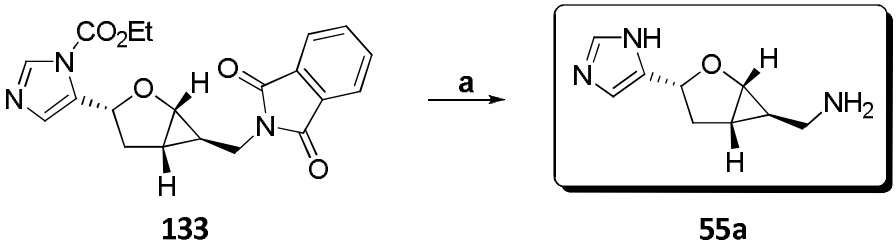


PPh_3	phthalimide	DIAD	yield (%)			
			133	134	135a	135b
1.5 equiv	1.5 equiv	1.5 equiv	29	nd	51	10

Conditions: THF, rt, 18 h.

Cleavage of the phthalimide moiety of compound **133** by means of hydrazinolysis proceeded smoothly with simultaneous removal of the base-sensitive carbamate protection group at the imidazole ring to give the desired target compound aminoimidazole **55a** in 77% yield (Scheme 25).[120]

Scheme 25. Preparation of aminoimidazole **55a**.

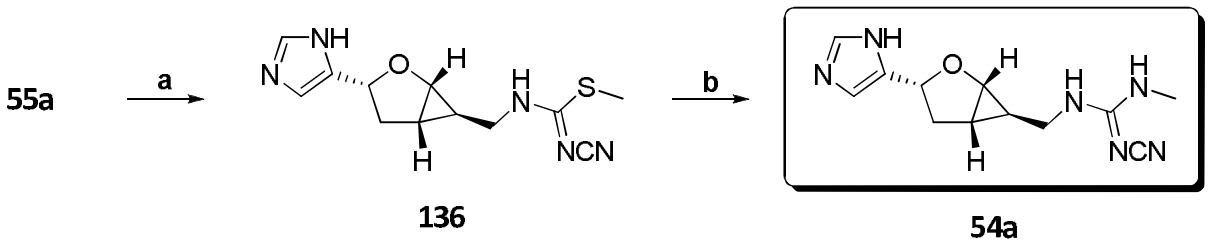


Reagents and conditions: a) hydrazine hydrate (5.4 equiv), EtOH, reflux, 1 h, 77%.

The conversion to the analogous cyanoguanidine-containing compound **54a** required two additional steps (Scheme 26). First, aminoimidazole **55a** was treated with an excess of dimethyl *N*-cyanodithioiminocarbonate ($(MeS)_2C$=N-CN) in MeOH to furnish isothiourea **136**

which was then directly converted without purification to the desired cyanoguanidinoimidazole **54a** by adding an ethanolic solution of $MeNH_2$.

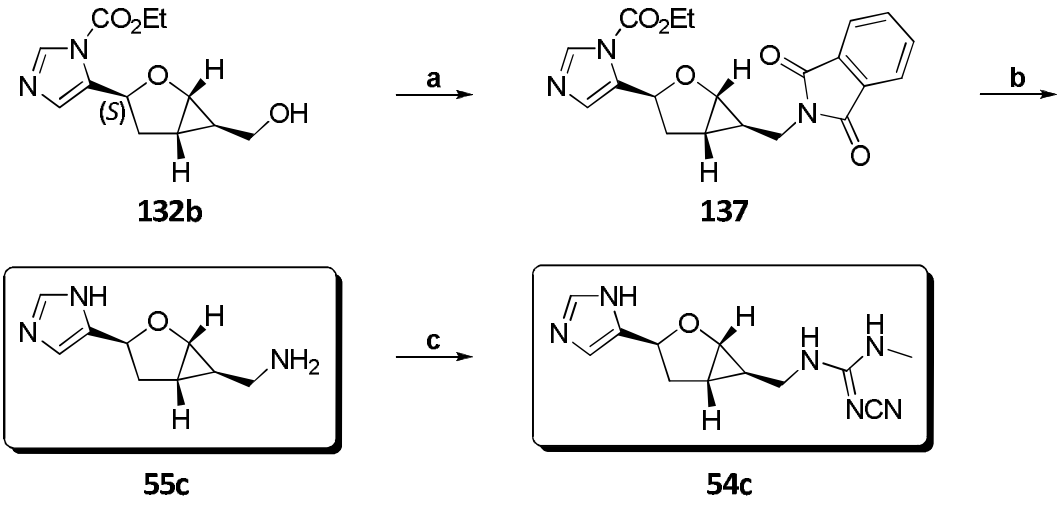
Scheme 26. Preparation of cyanoguanidinoimidazole **54a**.



Reagents and conditions: a) dimethyl *N*-cyanodithioiminocarbonate (2.4 equiv), MeOH, rt, 18 h; b) $MeNH_2$ in EtOH (150 equiv), rt, 18 h, 69% over two steps.

The respective 3*S*-configured target compounds, aminoimidazole **55c** and cyanoguanidinioimidazole **54c**, were derived from the corresponding 3*S*-configured alcohol **132b** running through an analogous synthetic pathway *via* phthalimide **137** (Scheme 27).

Scheme 27. Preparation of aminoimidazole **55c** and cyanoguanidinoimidazole **54c**.

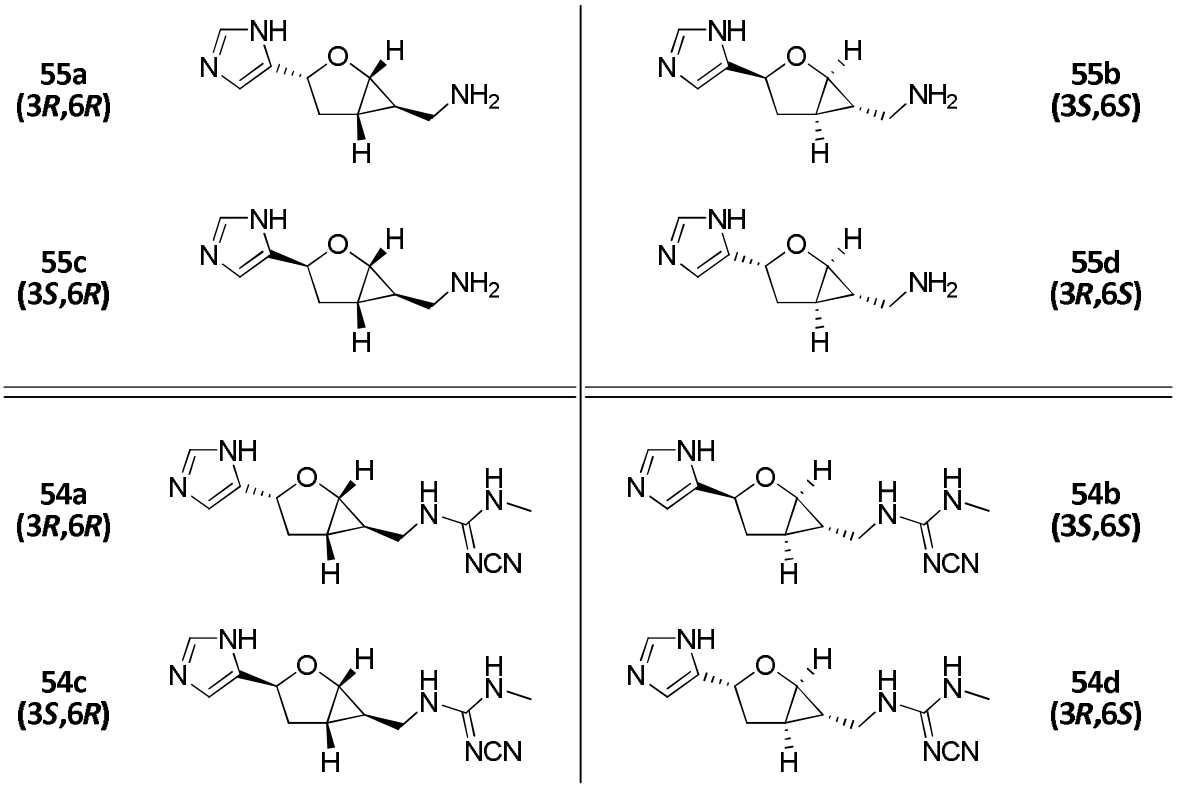


Reagents and conditions: a) PPh_3 (1.5 equiv), phthalimide (1.5 equiv), DIAD (1.5 equiv), rt, 18 h, 27%; b) hydrazine hydrate (5.4 equiv), EtOH, reflux, 1.5 h, 68%; c) i) dimethyl *N*-cyanodithioiminocarbonate (3.0 equiv), MeOH, rt, 18 h; ii) $MeNH_2$ in EtOH (150 equiv), rt, 18 h, 64%.

Consequently, the target molecules, aminoimidazoles **55a** and **55c** and cyanoguanidinoimidazoles **54a** and **54c** were synthesized in 15 and 17 steps, respectively from commercially available 2-furan carboxylic acid (**72**). By employing (*R*,*R*)-isopropyl bis(oxazoline) ligand ***ent*-71** in the asymmetric cyclopropanation reaction (Scheme 4),

additionally, the respective enantiomers, aminoimidazoles **55b** and **55d** and cyanoguanidinoimidazoles **54b** and **54d**, were accessible as well (Figure 17).

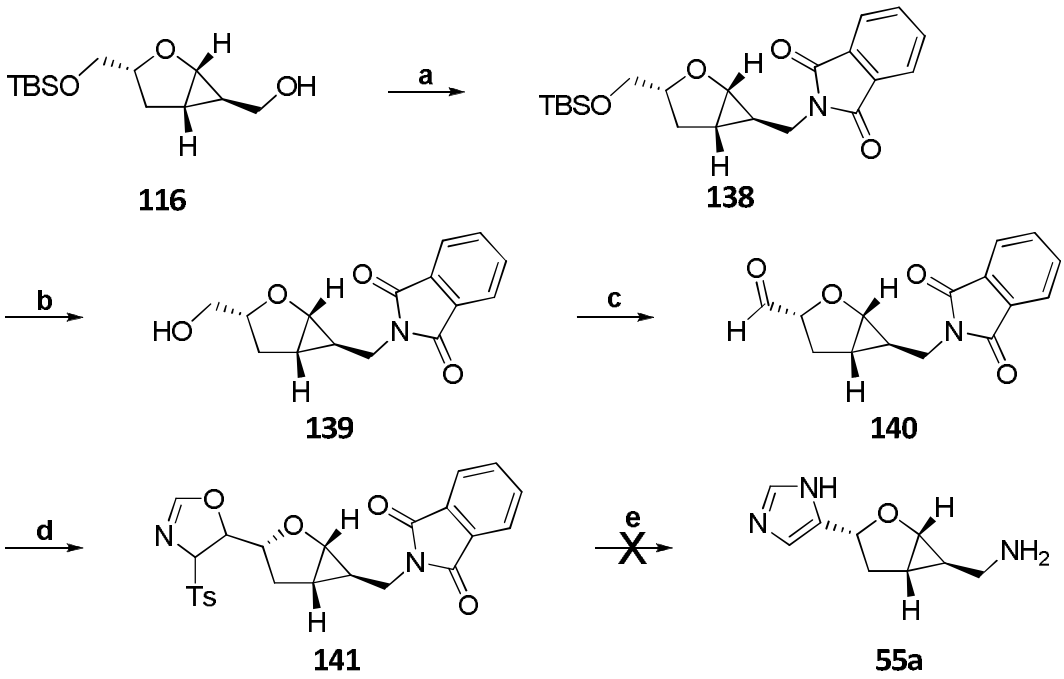
Figure 17. Synthesized imidazole-containing target compounds.



Synthesis toward imidazole- containing ligands - Route III

To shorten the synthetic route of the target compounds depicted in Figure 17 by three steps an alternative pathway was conceived circumventing some protecting-deprotecting reactions. Starting from alcohol **116** it was intended to avoid an *O*-benzylation of the hydroxyl group, as described in the previous section, and to prepone the phthaloylimination step. The phthalimide moiety itself acts then as a protecting group which was expected to be cleaved simultaneous with the imidazole formation step.

Scheme 28. Alternative synthetic pathway.



Reagents and conditions: a) PPh_3 (1.5 equiv), DIAD (1.5 equiv), phthalimide (1.5 equiv), THF, 50 °C, 1 h, 31%; b) TBAF•$3H_2O$ (1.5 equiv), THF, 0 °C to rt, 1.5 h, 70%; c) $NaHCO_3$ (2.0 equiv), Dess-Martin periodinane (1.7 equiv), DCM, rt, 5 h, 79%; d) TosMIC (1.1 equiv), NaCN (0.18 equiv), EtOH/DCM, rt, 1 h, 81%; e) NH_3 in MeOH, 100 °C, 20h.

Mitsunobu-type Gabriel reaction (see section *Mitsunobu reaction,* page 48) afforded phthalimide **138** in 31% yield (Scheme 28). The subsequent deprotection of the silylether gave rise to alcohol **139** in 70% yield which turned out to be acid-sensitive. For that reason, addition of $NaHCO_3$ was vital for the Dess-Martin oxidation in the following step to obtain aldehyde **140** in 79% yield. Base-induced [3+2] cycloaddition with TosMIC furnished tosyloxazoline **141** as a 1:1 mixture of diastereomers. However, treatment with a saturated solution of ammonia in MeOH in a sealable pressure tube under elevated temperature did

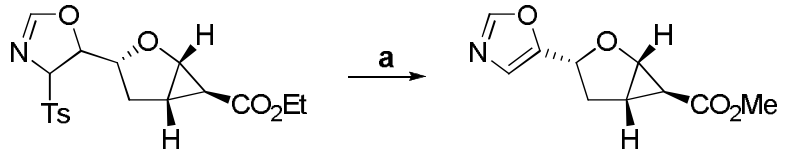
not form the desired aminoimidazole **54a**. Only a mixture of inseparable polar compounds was detected.

Synthesis of oxazole-containing ligands

In the course of developing potent histamine receptor ligands, which show selectivity for certain subtypes, the search for appropriate bioisosteres, besides altering the spacer properties between the pharmacophores, has become a common method (see *Introduction*).[68,173] Especially, the imidazole ring has been successfully modified by introducing various substitution patterns or was replaced by different kinds of heterocycles such as thiazoles. It was decided to exchange the imidazole ring of the above described amino- and cyanoguanidinoimidazoles (Figure 17) by an oxazole ring as an isostere. The effects of these replacements were then analyzed by determining the functional activities on the H_3R and H_4R subtypes.

Since 5-substituted oxazole derivatives are accessible in a similar way than the corresponding imidazole analogues *via* the TosMIC strategy developed by van Leusen a previous synthetic approach was adjusted.[152] Starting from tosyloxazoline **106**, which was originally envisaged for the formation of the imidazole ring, elimination of sulfinic acid afforded oxazole **142** in 31% yield (Scheme 29).

Scheme 29. Preparation of oxazole **142**.[152]

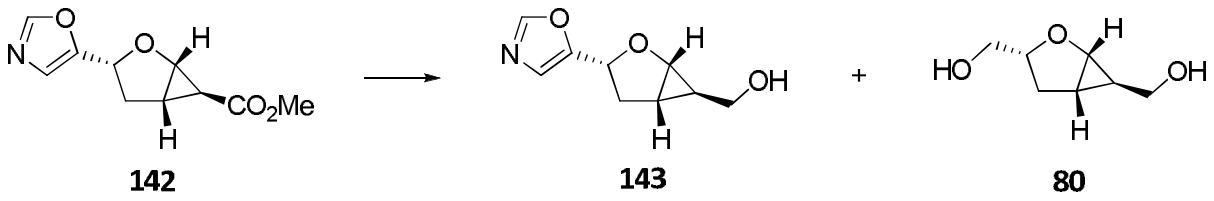


106 **142**

Reagents and conditions: a) K_2CO_3 (2.0 equiv), MeOH, reflux, 0.5 h, 31%.

The subsequent transformations of the ethyl ester moiety were in line with parts of the reaction sequence of section *Synthesis of imidazole-containing ligands - Route II.* The reduction of the ethyl ester group with an excess of LAH first gave rise to the expected alcohol **143** in only moderate yield (Table 3). The unstable diol **80** was identified as a side product. By decreasing the amount of LAH to a slight excess the yield of alcohol **143** could be increased to 71%.

Table 3. Ester reduction to alcohol **143**.



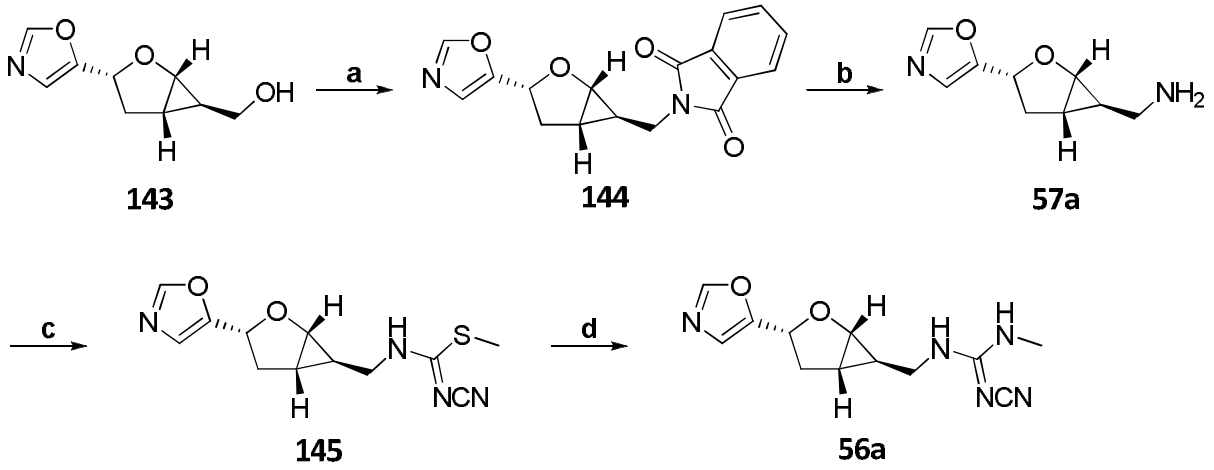
142 **143** **80**

entry[a]	LAH (equiv)	yield (%)		
		142	**143**	**80**
1	1.5	-	44	56[b]
2	0.6	12[b]	71 (81)[b]	6[b]

[a] LAH, 0 °C, 0.5 h.
[b] determined by ^{1}H-NMR.

Mitsunobu-type Gabriel reaction afforded phthalimide **144** (Scheme 30). The expected ring-opening side products were again observed but the yield of the relevant phthalimide **144** was significantly higher (55%) compared to the analogous Mitsunobu reactions that furnished compound **133** in 29% (Table 2, page 40) and compound **138** in 31% yield (Scheme 32, page 49). Cleavage of the phthalimide moiety revealed **57a** in 72% yield. The conversion with dimethyl *N*-cyanodithioiminocarbonate to isothiourea **145** proceeded quantitatively. Subsequent treatment with a solution of $MeNH_2$ in EtOH finally gave rise to cyanoguanidine **56a** in 90% yield.

Scheme 30. Preparation of aminooxazole **57a** and cyanoguanidinooxazole **56a**.



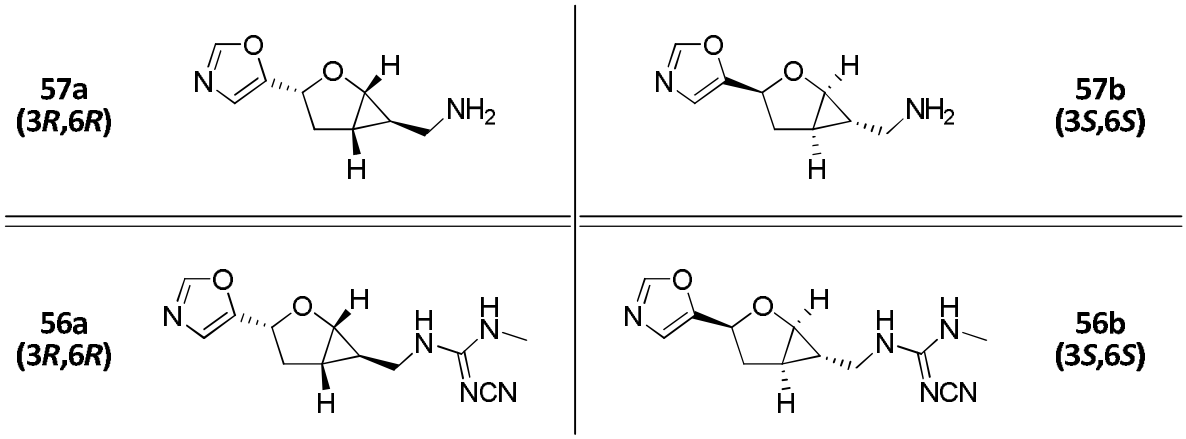
143 **144** **57a**

145 **56a**

Reagents and conditions: a) PPh_3 (1.5 equiv), phthalimide (1.5 equiv), DIAD (1.5 equiv), THF, 0 °C, 0.5 h, 55%; b) hydrazine hydrate (5.0 equiv), EtOH, reflux, 1.5 h, 72%; c) dimethyl *N*-cyanodithioiminocarbonate (2.0 equiv), EtOH, rt, 18 h, quant.; d) $MeNH_2$ in EtOH, rt, 18 h, 90%.

By following this reaction sequence the target molecules, aminooxazole **57a** and cyanoguanidinooxazole **56a** were synthesized in 10 and 12 steps, respectively, from commercially available 2-furan carboxylic acid (**72**). Enantiomer **57b** and **56b** were obtained using the (*R*,*R*)-isopropyl bis(oxazoline) ligand **71** in the asymmetric cyclopropanation reaction. Unlike the imidazole analogues no epimerization emerged in the course of the oxazole formation. As a result only 3,6-*trans*-configured compounds were accessible (Figure 18).

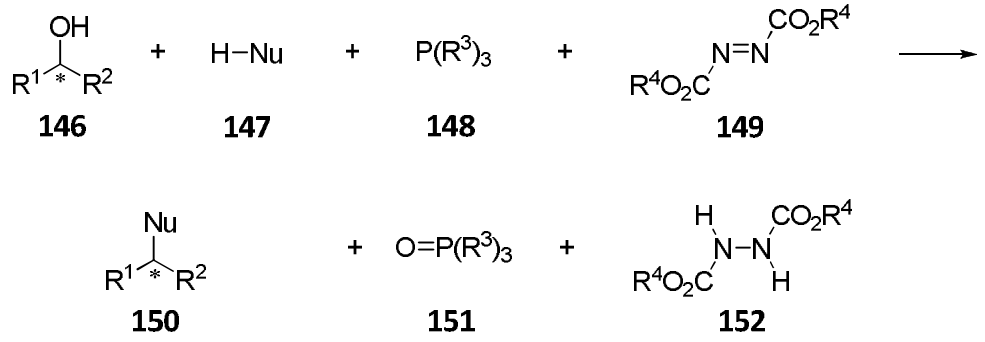
Figure 18. Synthesized oxazole-containing target compounds.



Mitsunobu reaction

The Mitsunobu reaction, discovered in 1967,[174] is a valuable method to convert hydroxyl groups into a wide range of different functional groups, like esters, azides, cyanides, imides, amines, ethers, or thioesters.[175,176] This formal condensation reaction of a primary or secondary alcohol **146** and a suitable nucleophile precursor **147** (pK_a < 11) is driven by a redox process where a trialkylphosphine **148** is oxidized to trialkylphosphine oxide **151** and a diazo compound **149** is reduced to the corresponding hydrazine compound **152** (Scheme 31). A big advantage of the Mitsunobu reaction is its stereospecifity in the case of secondary alcohols. The transformation proceeds with inversion of the stereogenic center. Therefore, it has become a widespread tool in natural product syntheses.[176]

Scheme 31. Mitsunobu reaction.



R^1 = alkyl, R^2 = H, alkyl, R^3 = aryl, alkyl, R^4 = alkyl.

Mitsunobu-type Gabriel reaction

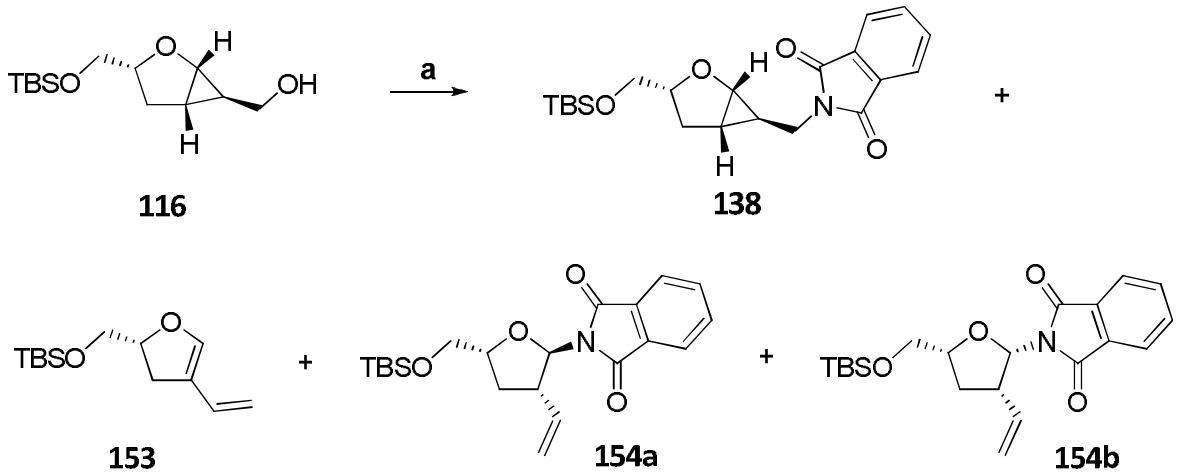
In 1972, the method was expanded to phthalimide as the nucleophile precursor which opened up a mild two-step methodology to convert a hydroxyl into an amine group.[120] The Mitsunobu-type Gabriel reaction, followed by hydrazinolysis of the alkylated phthalimide reveals the corresponding amine.

The Mitsunobu reaction of compound **132** in section *Synthesis of imidazole-containing ligands - Route II* (Table 2, page 40) was investigated more closely on the model compound **116** and is described in the following.

When alcohol **116** was converted under standard Mitsunobu reaction conditions, using 1.5 equivalents each of triphenylphosphine, diisopropyl azodicarboxylate (DIAD) and phthalimide in THF at 0 °C, the desired product **138** was isolated in only 30% yield (Table 4,

entry 1, page 52). Beside the formation of the desired phthalimide **138**, three compounds were encountered additionally: diene **153**, phthalimide **154a** and the corresponding epimer **154b** (Scheme 32).

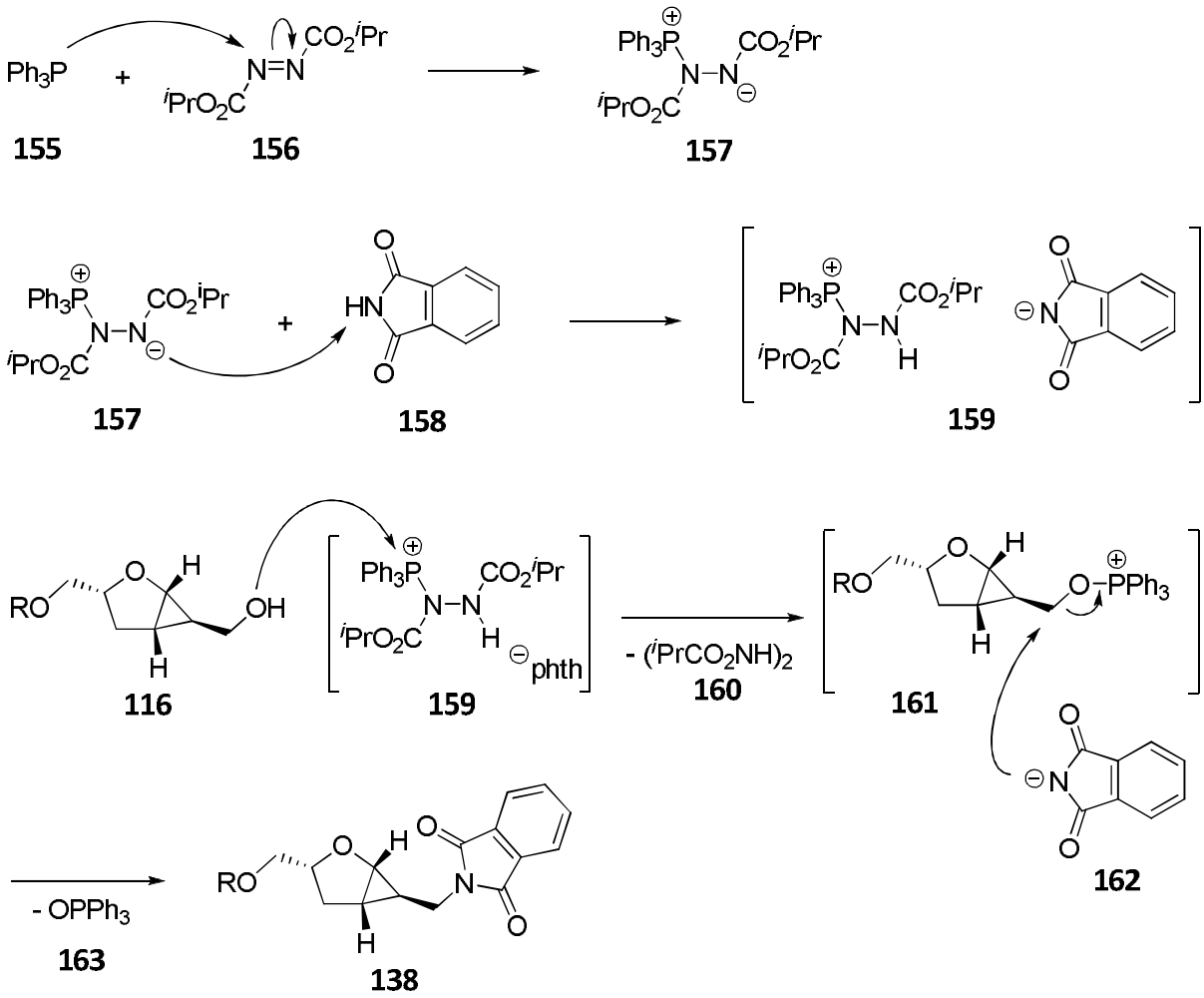
Scheme 32. Mitsunobu-type Gabriel reaction.



Reagents and conditions: a) PPh_3 (1.5 equiv), DIAD (1.5 equiv), phthalimide (1.5 equiv), THF, 0 °C, 6 h, 30% **138**.

These side products have a ring-opening of the cyclopropyl moiety in common. The following mechanistic considerations explain the formation of all products in detail: In the irreversible first step triphenylphosphine (**155**) attacks one of the diazo-nitrogen atoms of DIAD (**156**) to create a betaine intermediate **157** (Scheme 33). A pK_a value of 8.3[177] for phthalimide (**158**) enables the betaine **157** to abstract the acidic proton, leading to the formation of ion pair **159**. This sequence proceeds within seconds as evidenced by the decolorization of DIAD upon addition.[178] Reaction with alcohol **116** under release of hydrazine **160** gives rise to the key alkoxyphosphonium salt **161**, which is in equilibrium with other species (not shown in the scheme).[179,180] This equilibrium depends on the pK_a value of the acidic compound and on the polarity of the solvent. Up to now, it is still under discussion whether such species play a role in the Mitsunobu reaction or whether they are present just as *spectators*. In the further course different pathways are possible. As a good leaving group, triphenylphosphine oxid (**163**) is displaced by the deprotonated phthalimide (**162**) through nucleophilic attack to form the desired product **138**.

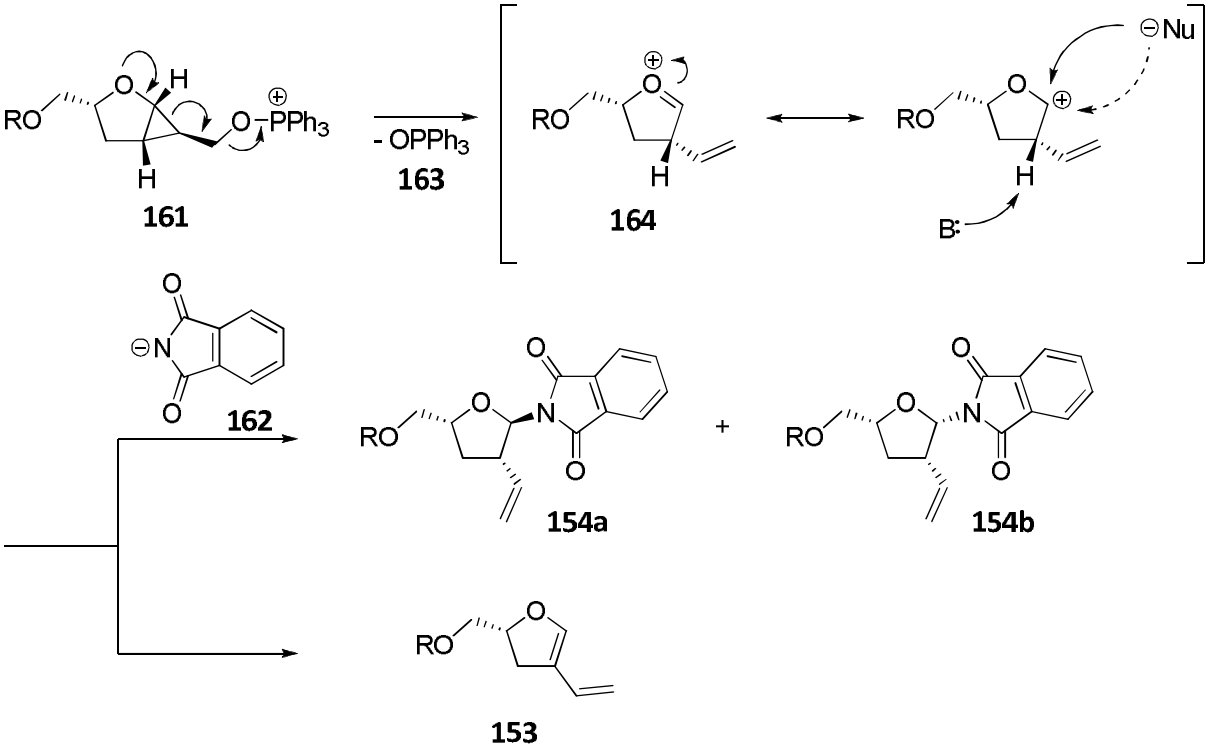
Scheme 33. Mitsunobu reaction – mechanism I.



R = TBS, phth = phthalimide.

In parallel with such a S_N2-type reaction a cyclopropylcarbinyl-homoallylic rearrangement takes place due to the stabilization of the emerging positive charge by the endocyclic oxygen atom (Scheme 34). Such kind of ring opening reactions of similar cyclopropylcarbinols was reported previously in the fields of terpene and sugar chemistry.[181-183] The carbenium ion can be trapped by the phthalimide nucleophile **162** from two sides resulting in a pair of stereoisomers, phthalimide **154a** and its epimer **154b**. In this regard, the formation of **154a** is preferred due to the steric hindrance of the two substituents on the heterocycle. The diastereomers **154a** and **154b** were isolated in a 4:1 ratio. In competition with this S_N1-type mechanism an E1 elimination takes place. The proton is abstracted by a base to give oxacyclic diene **153**.

Scheme 34. Mitsunobu reaction – mechanism II.



R = TBS, Nu = nucleophile, B = base.

In order to improve the yield of phthalimide **138** different reaction conditions were investigated (Table 4). Initially, diethyl azodicarboxylate (DEAD), which is also a common reagent for this reaction, was used instead of DIAD under the same conditions but only slight differences in product distribution were observed (entry 2). The addition order of the reagents has a strong influence on the product distribution in certain cases.[184] Commonly, DEAD or DIAD is added to a solution of alcohol, PPh_3 and the acidic compound (Table 4, method A). Alternatively, PPh_3 and the azodicarboxylate are premixed and nucleophile and alcohol are added successively (method B). However, altering the order of addition did not show any effects (entry 3). A reaction temperature of -40 °C caused a slight increase of yield for the products which arise after ring opening whereas the yield of phthalimide **138** remained at the same level (entry 4). Nevertheless, further decrease of the reaction temperature to -78 °C resulted in an incomplete conversion of the starting material (entry 5). As a consequence, the isolated yields of all products dropped but the product ratio shifted in favor of compounds **154a**, **154b** and **153** and in disfavor of phthalimide **138**. Higher amounts of the reagents gave rise to larger quantities of triphenylphosphine oxide (**163**) and

Table 4. Optimization of the reaction conditions.

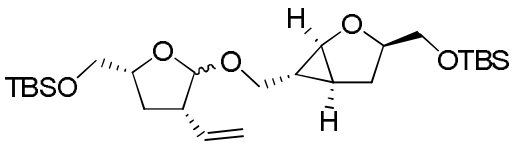
entry	method[a]	PPh_3, DIAD (equiv)	phthalimide (equiv)	T (°C)	solvent[b]	yield (%)		
						138	**154**[c]	**153**
1	A	1.5	1.5	0	THF	30	45	7
2	A	1.5[d]	1.5	0	THF	29	42	8
3	B	1.5	1.5	0	THF	30	45	10
4	B	1.5	1.5	-40	THF	30	52	12
5[e]	B	1.5	1.5	-78	THF	14	37	7
6	A	6.0	6.0	0	THF	nd	52	nd
7	A	1.5	3.0	0	THF	26	46	13
8[e]	A	1.5	3.0	0	MeCN	20	20	9
9	A	1.5	3.0	0	toluene	23	52	15
10	A	1.5	1.5	50	THF	31	39	23
11[f]	A	1.5	1.5	50	MeCN	16	48	13

[a] addition order: A) 1. **116**, 2. PPh_3, 3. phthalimide, 4. DIAD; B) 1. PPh_3, 2. DIAD, 3. phthalimide, 4. **116**.
[b] c = 0.05 mol/L.
[c] combined yield of **154a** and **154b**.
[d] DEAD instead of DIAD.
[e] unreacted starting material **116** recovered.
[f] 17% yield **165**.

hydrazine byproducts, which strongly hampered the isolation of both diene **153** and phthalimide **138** (entry 6). However, the combined yield of compounds **154a** and **154b** amounted to 52% which suggests that a substantial improvement for product **138** was not achieved. The mechanistic studies of the Mitsunobu esterification reaction by Hughes *et al.* revealed that the nucleophilicity in the S_N2 reaction step is influenced by hydrogen bonding.[178] In principal, this effect should also exist for the corresponding phthalimidation reaction and is explained as follows. When equimolar amounts of PPh_3, DIAD and phthalimide are employed in the reaction, complete protonation of betaine **159** occurs (Scheme 33). When 2 equivalents of phthalimide are used, 1 equivalent is deprotonated and 1 equivalent remains unreacted to give a hydrogen bonded species consisting of both. As a consequence, the activity of the nucleophile is reduced. The resulting lowered reaction rate for the S_N2 reaction should be reflected in a lower yield for phthalimide **138** and higher

yields for the ring-opening products. These assumptions are confirmed by the experimental data, but only to a rather small extend (entry 7). Further experiments were carried out, in order to investigate solvent effects. It was assumed, that a much more polar solvent, like acetonitrile, is capable of breaking up the tight ion pair **159** making the phthalimide anion more easily accessible to the S_N2 displacement. But again a considerable amount of starting material was recovered (entry 8). Nevertheless, a shift in the product distribution in favor of phthalimide **138** was observed. Moreover, when E1 and S_N1 mechanisms are in competition, the elimination is supported by more polar solvents. The product ratio of the S_N1 products **154a** and **154b** to E1 product **153** decreased from 3.5 (entry 7) to 2.2 (entry 8). The opposite case, when less polar toluene was used, the ratio of the ring-opening products to phthalimide **138** increased from 2.3 (entry 7) to 2.9 (entry 9). Since low temperature promotes the formation of ring-opening products, running the reaction at elevated temperatures should display the contrary effect. This was partly confirmed as shown in entry 10. The absolute yield of phthalimide **138** was slightly improved to 31% but the yield of the ring-opening products rose as well (entry 10) which gives an even higher product ratio of 2.0 compared to 1.7 (entry 1). As expected, the elimination product **153** profited from the elevated reaction temperature against the S_N1 products, resulting in a product ratio of phthalimides **154a** and **154b** to diene **153** of 1.7. To combine all the putative positive effects for the formation of phthalimide **138**, the reaction was performed in acetonitrile at 50 °C and 1.5 equivalents of each reagent. Interestingly, the yield of phthalimide **138** was not enhanced, but further side products encountered in 17% combined yield, which turned out to be the self-condensation product **165a** and epimer **165b** of alcohol **116** (Figure 19).

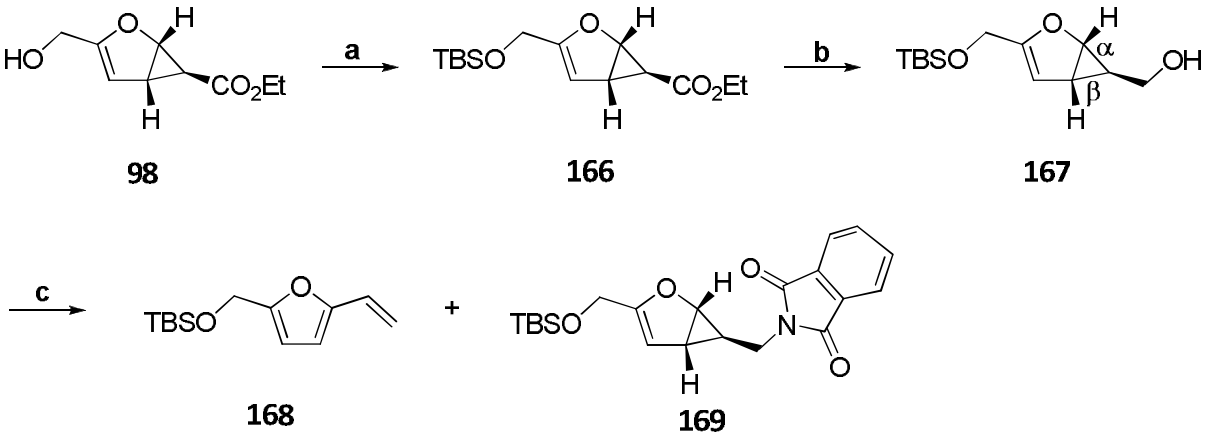
Figure 19. Condensation product **165**.



165

In parallel, the α,β-unsaturated analogue **167** was also investigated in the Mitsunobu reaction. It was synthesized from alcohol **98** in 2 steps *via* a hydroxyl-protection and an ester-reduction reaction (Scheme 35). The treatment of alcohol **98** with PPh_3, phthalimide and DIAD afforded the S_N2-type product, phthalimide **169**, in low 38% yield. Even in this case, ring-opening predominated. However, unlike when saturated alcohol **116** was employed, not the C-C bond of alcohol **167**, which is referred to as α, was broken but the cyclopropane C-C bond termed β was cleaved. This reaction is promoted by rearomatization and gave rise to vinylfuran **168** in 54% yield.

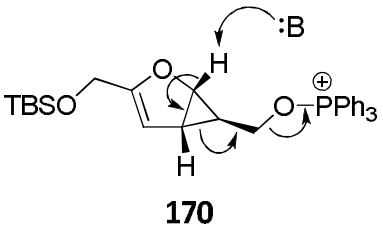
Scheme 35. Preparation of alcohol **167** and Mitsunobu reaction.



Reagents and conditions: a) NEt_3 (1.5 equiv), TBSCl (1.2 equiv), DMAP (0.05 equiv), DCM, rt, 4 h, 99%; b) LAH (0.85 equiv), THF, 0 °C, 1 h, 88%; c) PPh_3 (1.5 equiv), DIAD (1.5 equiv), phthalimide (1.5 equiv), THF, 0 °C, 2 h, 54% **168**, 38% **169.**

Additional products were not observed. This indicates that the release of triphenylphosphine oxide and proton abstraction proceeded in a concerted manner (Figure 20). Therefore, a positively charged intermediate was not generated which could be traped by a phthalimide nucleophile in a S_N1-type reaction.

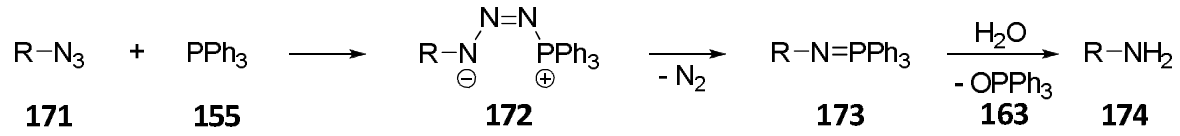
Figure 20. Ring-opening of intermediate **170**.



Conversion of alcohols to azides

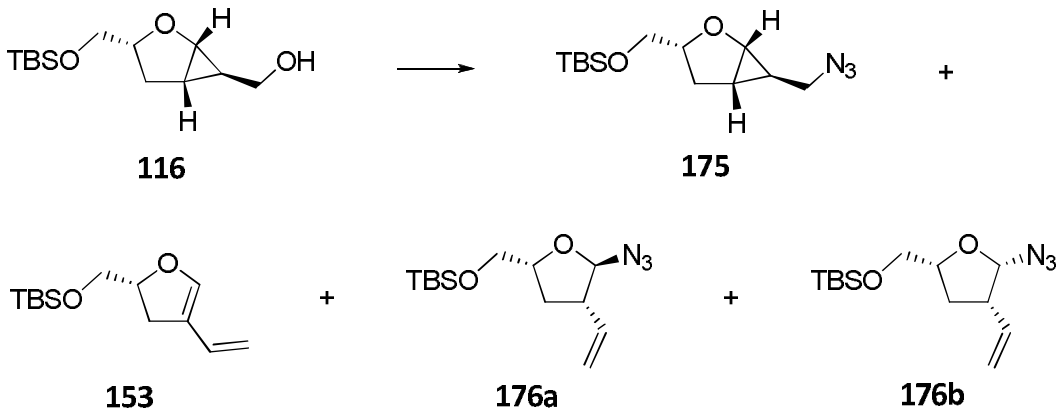
A further convenient two-step method to convert alcohols into the corresponding amines is *via* a Mitsunobu-mediated displacement of the hydroxyl by an azide group[185] and a subsequent reduction of the latter.[186] Apart from hydrazoic acid, appropriate azide sources are diphenyl phosphoryl azide (DPPA), trimethylsilyl azide, sodium azide, zinc azide or nicotinoyl azide.[176] The reduction to the amine is effected by various reagents, including lithium aluminium hydride, sodium borohydride and catalytic hydrogenation.[187] A very mild and selective way to reduce the azide group comprises the Staudinger reaction[188-190] where triphenylphosphine (**155**) and azide **171** form a phosphazide **172**. Cyclization and release of molecular nitrogen result in an iminophosphorane **173** which after hydrolysis gives the desired amine **174** (Scheme 36).

Scheme 36. Staudinger reaction and hydrolysis.



It was contemplated that an azide anion might act as a better nucleophile than the phthalimide anion in the Mitsunobu reaction. This is tantamount to a higher reaction rate of the S_N2 displacement contributing to a product distribution with smaller amounts of ring-opening compounds. The attempt to perform the Mitsunobu-mediated azide formation using hydrazoic acid as the azide source failed (Table 5, entry 1). Conversion of alcohol **116** was not discernible. The same was observed applying sodium azide in DMF (entry 2).[191] Using modified Bose conditions[192], DIAD was added to a THF solution of alcohol **116**, triphenylphosphine and DPPA at 0 °C (entry 3) which afforded a product pattern in analogy to the Gabriel reaction. The desired S_N2 substitution product azide **175** was obtained in poor yield. This was again due to the competing ring opening which resulted in the formation of azide **176a**, its epimer **176b** and oxacyclic diene **153**. A smaller value of 2 for the diastereomeric ratio of azide **176a** and **176b** compared to the ratio of phthalimides **154a** and **154b** under similar conditions is due to a smaller size of the azide anion, facilitating the attack of the occurring carbenium ion from the shielded face.

Table 5. Conversion of alcohol **116** into azide **175**.



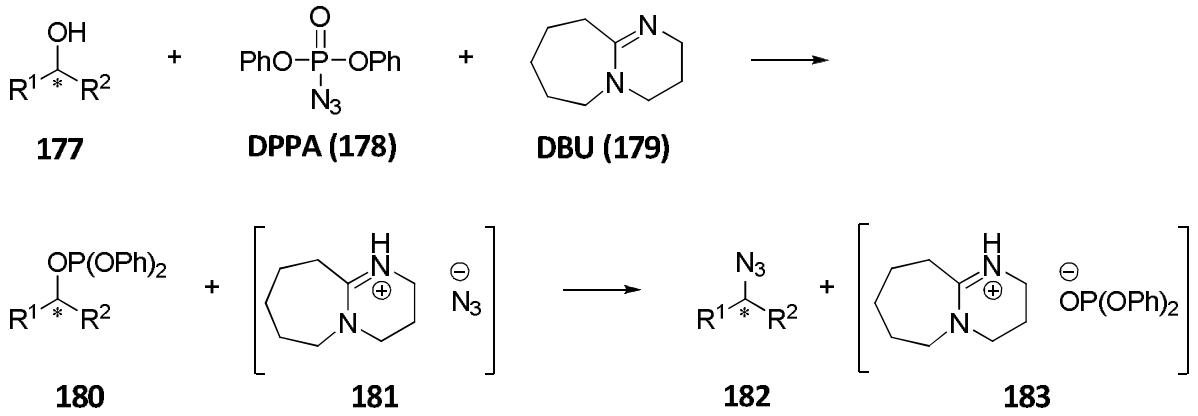
entry	reagents and conditions	yield (%)		
		175	**176** [a]	**153**
1	PPh_3 (1.5 equiv), DIAD (1.5 equiv), HN_3 in toluene (3 equiv), THF, 0 °C to rt, 18 h.	no conversion		
2	PPh_3 (1.5 equiv), DIAD (1.5 equiv), NaN_3 (3 equiv), DMF, rt, 18 h.	no conversion		
3	PPh_3 (2 equiv), DIAD (2 equiv), DPPA (2 equiv), THF, 0 °C, 0.5 h.	21	52	5
4	DPPA (2 equiv), DBU (2 equiv), toluene/DMF 9:1, 50 °C, 1 h.	12	60	5

[a] combined yield of **177a** and **177b**.

Thompson *et al.* developed an alternative method for the direct conversion of activated alcohols to azides.[193] The alcohol **177** was allowed to react with a combination of DPPA (**178**) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **179**) in toluene or DMF to give the azide product **18** (Scheme 37). Mechanistically, in the first step phosphate **180** and the DBU salt of hydrazoic acid (**181**) are formed. Subsequently, the *in situ* generated azide anion displaces the leaving group. The resulting DBU salt of diphenyl phosphate (**183**) is water soluble and can be removed by aqueous workup, facilitating the purification of the product compared to Mitsunobu procedures. Apart from this operational simplicity, the authors emphasize the improved yields, formation of fewer byproducts and enhancement of integrity of the desired S_N2 displacement. This method activates the alcohol by creating a phosphate intermediate instead of a triphenylphosphonium ion in the Mitsunobu reaction with potentially different leaving group properties. Hence, it was conceivable that it has a beneficial effect on S_N2 product formation in the present case. The reaction was carried out using Danishefsky

conditions (Table 5, entry 4).[194] Once again, the ring-opening products predominated and the yield of desired azide **175** was even lower than in the Mitsunobu-type reaction. A diastereomeric ratio of azide **176a** to **176b** of 1.0 is attributed to the elevated reaction temperature.

Scheme 37. Azide formation according to Thompson.[193]



R^1 = alkyl, R^2 = H, alkyl.

The traditional route to prepare azides from alcohols requires an additional step to convert the hydroxyl group into a sulfonate which can be displaced subsequently by an azide anion.[187] The most commonly employed leaving groups are the methanesulfonate (mesyl) and *p*-toluenesulfonate (tosyl) moieties. However, it was known that the preparation of sulfonates from alcohols is prone to alkene formation and rearrangements in certain cases. In consequence, it was obvious that the reaction of alcohol **116** with *p*-toluenesulfonyl chloride in presence of triethylamine and DMAP as a catalyst afforded mainly ring-opening products, indicated by TLC and crude NMR measurements.

To conclude, the direct conversion of alcohol **116** to phthalimide **138** by Mitsunobu-type Gabriel reaction was accomplished in poor yield due to ring-opening side reactions. Attempts to increase the yield by changing reagents, addition order, concentrations, solvent and reaction temperature were not successful. Reaction of α,β-unsaturated alcohol **167** also showed a preference for ring-opening. However, the formation of vinylfuran **168** as the only ring-opening product discloses a different mechanism for the ring-opening. Switching to the azide methodology showed similar results for the Mitsunobu reaction as well as the Thompson variant. To afford the desired azide by an indirect way *via* tosylation of the

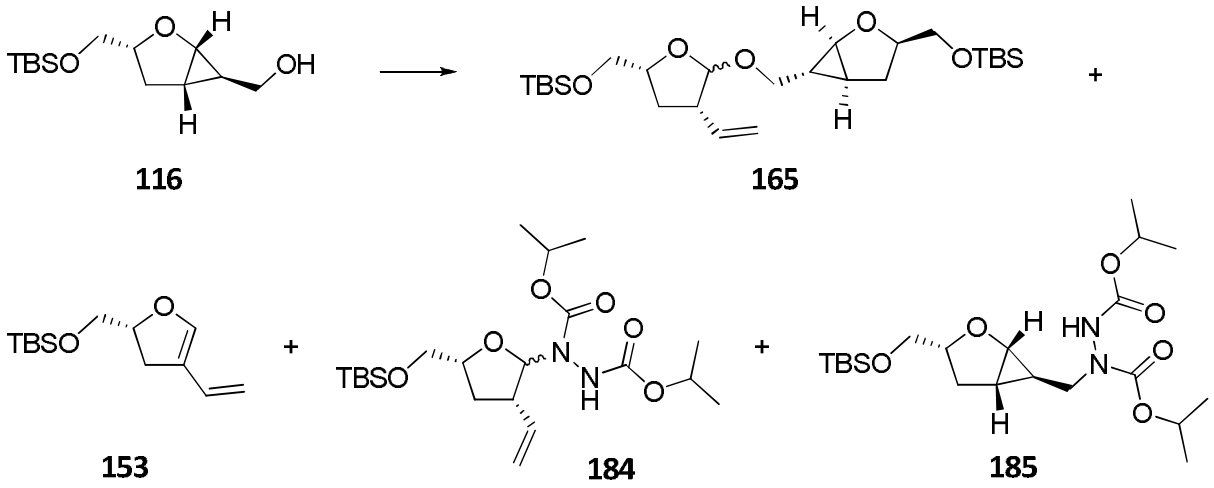
alcohol again caused ring opening. Obviously, all strategies, which include activation of the alcohol to enable its displacement, are facing the problem of ring opening side reactions due to the stabilizing effect of the oxacyclic oxygen atom.

To overcome this difficulty a different synthetic strategy, starting from the cyclopropyl ester, formation of the primary amide and reduction to the desired amine might be a viable alternative.

Dehydration of alcohol to diene

The oxacyclic diene **153**, encountered in the Mitsunobu reaction of alcohol **116**, represents an interesting building block for Diels-Alder reactions to synthesize polycyclic scaffolds. For this reason, it was tried to find conditions and alternative procedures providing the desired diene in higher yields.

Table 6. Mitsunobu dehydration reaction.



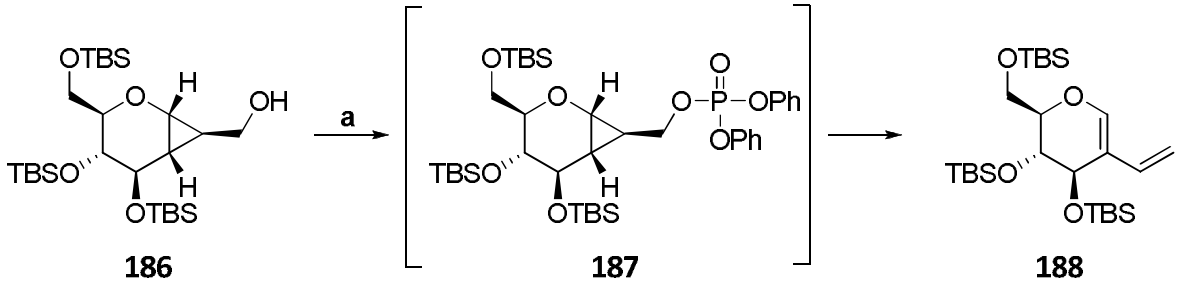
entry	PPh_3/DIAD (equiv)	T (°C)	solvent	yield (%)				
				116[a]	**165**[b]	**153**	**184**[c]	**185**
1	2	0	THF	32	-	38	27	-
2	3	0	THF	-	-	9	54	32
3	4	0	THF	-	-	12	51	35
4	2	0	MeCN	<5	16	16	47	<5
5	2	50	THF	-	-	8	45	45

[a] recovered unreacted starting material; [b] combined yield of **165a** and **165b**; [c] combined yield of **184a** and **184b**.

As shown in Table 4, the maximum yield of diene **153** was 23%. This is due to the nucleophilic substitution reactions trapping the intermediate carbocations before a proton is abstracted to form the C-C double bond (Scheme 34). In order to prevent nucleophilic side reactions the nucleophile source should be omitted. Several precedents in the literature show promising examples for such kind of Mitsunobu dehydration reactions.[176] When the reaction was performed with alcohol **116**, however, separation of the product mixture revealed new compounds in addition to diene **153**, identified as hydrazine **184a**, its epimer

184b and **185** (Table 6). According to literature precedents[176] the alcohol itself can react with the hydrazine intermediates if the betaine is not able to abstract the proton of the nucleophile precursor or a nucleophile is not available. The use of 2 equivalents of each reagent in THF at 0 °C afforded diene **153** in 38% yield which was a small improvement to previous Mitsunobu reactions (Table 6, entry 1). Additionally, hydrazine products **184a** and **184b** were isolated in 27% combined yield and 32% of the starting alcohol was recovered. Therefore the amount of the reagents was increased to 3 and 4 equivalents, respectively (entry 2 and 3). Although the conversion was complete, the yield of diene **153** decreased in favor of the formation of hydrazine **184a**, **184b** and **185**. Performing the reaction in acetonitrile did not result in an improvement with regard to diene **153** but the self-condensation products **165a** and **165b** encountered in 16% combined yield (entry 4). An elevated reaction temperature of 50 °C did not contribute to a higher yield for diene **153** as well but promoted in particular the formation of the S_N2 product **185** (entry 5).

Scheme 38. Dehydration reaction of alcohol **XXX**.[183]



186 **187** **188**

Reagents and conditions: a) $PO(OPh)_2Cl$ (2.7 equiv), pyridine (1.3 equiv), DCM, rt, 83%.

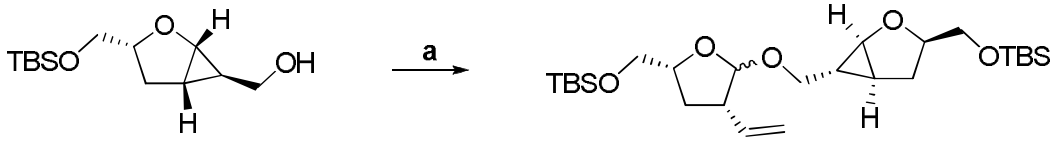
During the course of synthesizing potential inhibitors of glycosyl hydrolases Stick and Stubbs observed the transformation of alcohol **186** to diene **188** in 83% yield (Scheme 38).[183] Alcohol **186** was allowed to react with diphenyl chlorophosphonate and pyridine in DCM. Formation of phosphate **187** immediately initiated ring-opening caused by the ability of the endocyclic oxygen atom to stabilize the positive charge of the generated carbenium ion intermediate. Subsequent elimination afforded oxacyclic diene **188**. These results prompted to employ the same conditions for the reaction with alcohol **116**. However, reaction control by TLC and characteristic signals in crude NMR spectrum indicated the formation of the S_N1 and S_N2 side products. These side products were not isolated and characterized but the yield of diene **153** did not exceed 10%. Using phosphoryl chloride[195] instead of diphenyl

chlorophosphonate in combination with pyridine or DBU showed similar unsatisfactory results.

Classical dehydration catalysts include protic acids like sulfuric acid and phosphoric acid. They enable elimination reactions of primary, secondary and tertiary alcohols through E1 or E2 pathways by protonating the hydroxyl group and making it a good leaving group. Adding a dilute solution of sulfuric acid or phosphoric acid in anhydrous toluene to a solution of alcohol **116** in toluene in one portion at ambient temperature only gave a black insoluble tar. Therefore, the alcoholic solution was cooled to -78 °C before adding the precooled acid solution in the presence of molecular sieves dropwise. Subsequently, the reaction mixture was allowed to warm to room temperature. Reaction control by TLC indicated complete conversion of starting material after 4 h and showed the formation of several side products. The desired diene **153** was only generated in trace amounts. Similar observations were made for applying phosphoric acid and tosylic acid. It is assumed, that an acid catalyzed deprotection of the silylether takes place to reveal another free hydroxyl group, interfering with the expected reaction pathway.

Copper(II) triflate was found to be an efficient catalyst for the dehydration of a variety of tertiary, secondary and primary alcohols.[196] The proposed mechanism starts with an interaction of the alcohol and the electron deficient copper(II) triflate. Two proposed pathways result in the formation of a carbocation which upon deprotonation generates the olefin.

Scheme 39. Self-condensation of alcohol **116**.

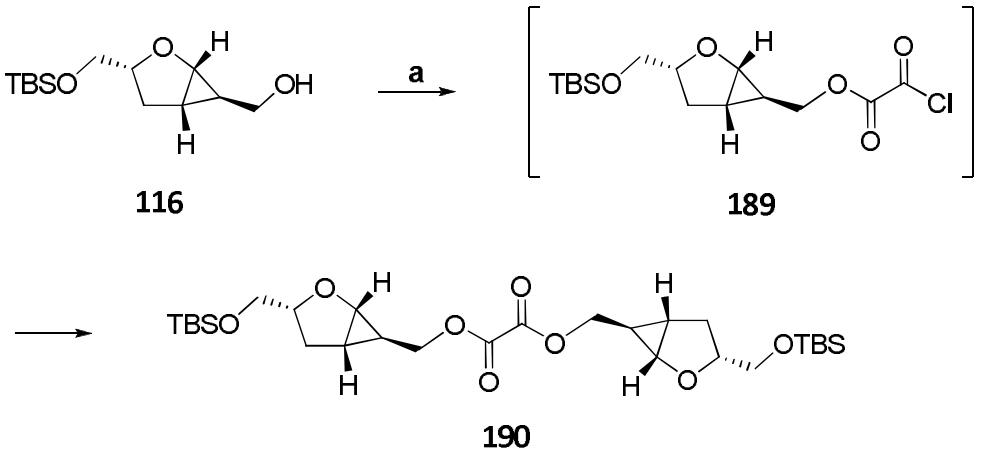


116 **165**

Reagents and conditions: a) $Cu(OTf)_2$ (0.18 equiv), benzene, rt, 1 h, 95%.

When this method was employed to alcohol **116** only a diastereomeric mixture of the asymmetric dimer **165** could be identified (Scheme 39). A value of 95 % yield was calculated based on ^{1}H-NMR measurement by means of 1,2,4,5-tetrachlorobenzene as an internal standard. However, formation of diene **153** was not observed.

Scheme 40. Reaction of alcohol **116** with oxalyl chloride.



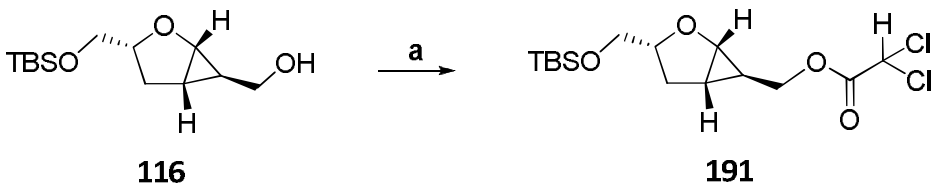
Reagents and conditions: a) $(COCl)_2$ (1.5 equiv), NEt_3 (3 equiv), DCM, 0 °C, 0.5 h, 86%.

Oxalyl chloride was used to effect the dehydration of serine containing peptides.[197] This is explained by the fragmentation of an initially formed Ser-*O*-oxalyl chloride. When alcohol **116** was treated with oxalyl chloride in the presents of triethylamine in DCM only oxalic ester **190** could be isolated in 86% yield (Scheme 40). Obviously, the intermediate **189** is stable enough not to decompose but to react with a second molecule of **116**.

It was not possible to obtain distinct products when oxalyl chloride was exchanged by thionyl chloride which was supposed to effect a related reaction.

Goodall and Parsons developed a method to dehydrate hydroxyamino acids by the reaction of dichloroacetyl chloride in presence of triethylamine or DBU.[198] They were able to isolate the formed dichloroesters or to effect subsequent elimination of dichloroacetic acid upon employing a further equivalent of base. Alcohol **116** reacted to the corresponding dichloroester **191** with 2.2 equivalents of each reagent and base but did not proceed to eliminate, not even when a further equivalent of base was added and the reaction mixture was heated (Scheme 41).

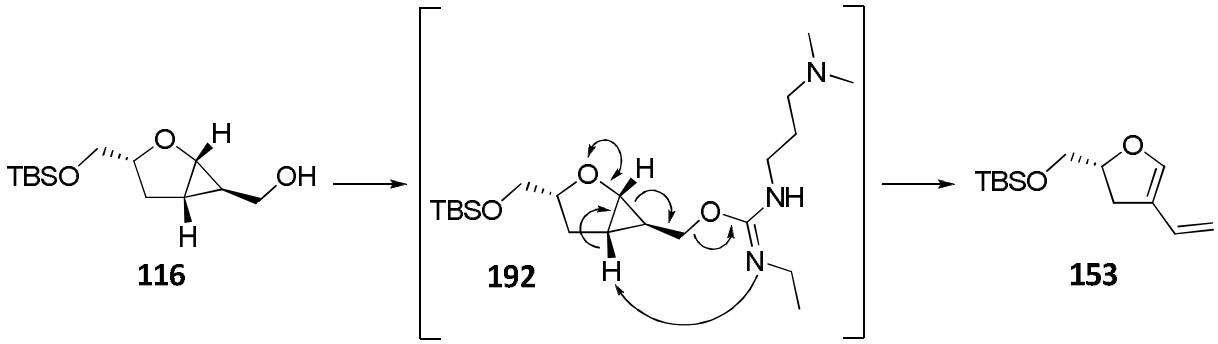
Scheme 41. Reaction of alcohol **116** with dichloroacetyl chloride.



Reagents and conditions: a) $ClCOCHCl_2$ (2.2 equiv), NEt_3 (2.2 equiv), DCM, rt, 1.5 h, 94 %.

Dicyclohexyl- or diisopropylcarbodiimide in combination with copper(I) chloride were found to be efficient dehydrating agents for *β*-hydroxycarbonyl compounds,[199] nitrated alcohols[200] and amino acids.[201] This methodology could be improved by employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and copper(II) chloride.[202,203] These *β*-elimination reactions proceed by generating an *O*-alkylisourea intermediate. A six-membered transition state effects cycloelimination under release of urea. In the case of alcohol **116** the elimination does not take place *via* a six-membered but a seven-membered transition state.

Table 7. Reaction of alcohol **120** with EDC.



entry	EDC (equiv)	$CuCl_2$ (equiv)	T (°C)	solvent	yield (%)[a]
1	2.0	1.1	80	toluene	49
2	2.0	1.1	80	MeCN	62

[a] determined by ^{1}H-NMR with 1,2,4,5-tetrachlorbenzene as internal standard.

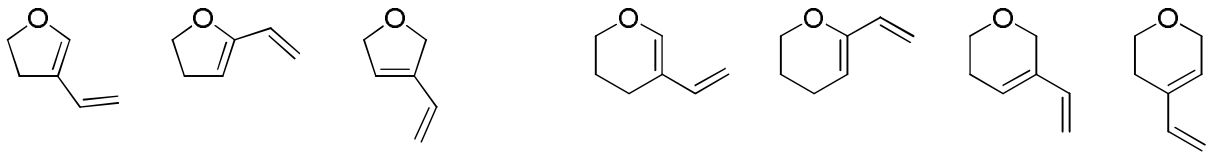
Treatment of alcohol **116** with EDC and copper(II) chloride in toluene at 80 °C afforded diene **153** in 49% yield (Table 7, entry 1). In acetonitrile, an aprotic polar solvent which promotes elimination reactions, the yield could be increased to 62% (entry 2).

To summarize, different procedures and dehydrating agents were examined to achieve diene **153**. Mitsunobu dehydration suffered from the formation of hydrazine side products. Phosphorous based dehydrating agents could not avoid undesired S_N displacement reactions. $Cu(OTf)_2$ as a Lewis acid only afforded self-condensation products. Oxalyl chloride gave the corresponding oxalic ester. Reaction with dichloroacetyl chloride stopped at the stage of the dichloroester, subsequent elimination did not occur. Finally, application of EDC and $CuCl_2$ improved the outcome and yielded diene **153** in 62%.

Furanyldiene in Diels-Alder Reaction

The Diels-Alder reaction is considered as a very powerful tool for stereospecific carbon-carbon bond formation.[204] Chiral oxacyclic dienes with five or six membered rings, such as those depicted in Figure 21, constitute valuable building blocks for the formation of enantiopure polycyclic furanyl and pyranyl derivatives *via* Diels-Alder reactions, which are encountered in many natural products. Preparation of theses oxacyclic moieties comprises enyne metathesis using Grubbs catalyst (**193a**,[205] **193c**,[206] **194c**[206]), isomerization of 2-vinylidene furans (**193b**[207]) and pyrans (**194b**[208]), Wittig alkenylation (**193b**,[209] **194a**[210]), [3+2] cycloaddition of propargyltungsten compounds and aldehydes (**193a**,[211-213] **193c**,[214] **194a**[211,213]), cyclopropylcarbinyl-homoallyl rearrangement (**194a**[183]) and addition of vinyl Grignard reagent to 2-oxo, 3-oxo and 4-oxo pyrans with subsequent dehydration (**194b**,[215] **194a**,[216] **194d**[217]).

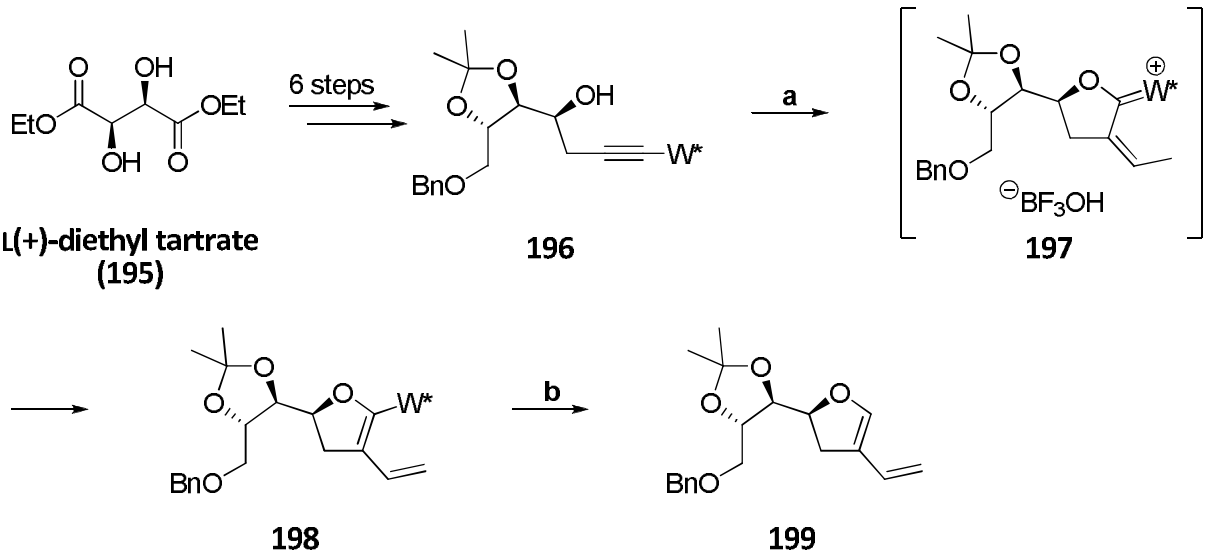
Figure 21. Furanyl (**193a-c**) and pyranyl dienes (**194a-d**).



193a **193b** **193c** **194a** **194b** **194c** **194d**

By means of a tungsten-mediated [3+2] cycloalkenation Liu and coworkers synthesized a furanyl diene of type **193a**[211-213] which distinguishes from diene **153** by a chiral 1,3-dioxolane moiety instead of a methoxysilane group (Scheme 42). To introduce the dioxolane group at C2 of the heterocycle they started the sequence from L(+)-diethyl tartrate (**195**). In the keystep the chiral tungsten alkynol **196** was treated with acetaldehyde in the presence of $BF_3 \bullet Et_2O$ giving rise to an oxacarbenium salt **197** which was deprotonated to afford tungsten furanyl diene **198**. Subsequent hydrodemetalation with Me_3NO in acetonitrile provided the desired chiral oxacyclic diene **199**.

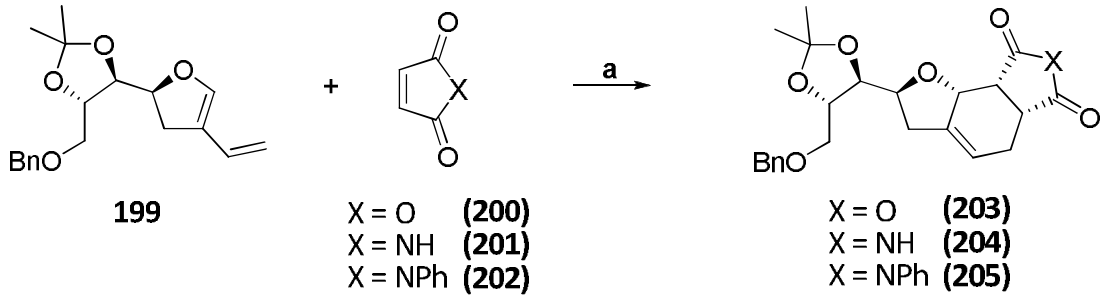
Scheme 42. Synthesis of furanyl diene **199** according to Liu *et al.*[211-213]



Reagents and conditions: a) i) MeCHO (4 equiv), BF_3•Et_2O (1.2 equiv), Et_2O, -78 °C, 5 h; ii) NEt_3 (4.5 equiv), DCM, rt, 0.5 h, 64%; b) Me_3NO (5.2 equiv), MeCN, rt, 4 h, 60%; W* = $CpW(CO)_3$.

The electron rich oxacyclic diene **199** was subjected to a number of Diels-Alder reactions with electron deficient dienophiles under ambient conditions (Scheme 43). The [4+2] cycloadducts were obtained in good yields and with high diastereoselectivity. The latter is attributed to *endo*-facial cycloaddition and the steric effect of the chiral dioxolane moiety.

Scheme 43. Diels-Alder reactions of furanyl diene **199**.

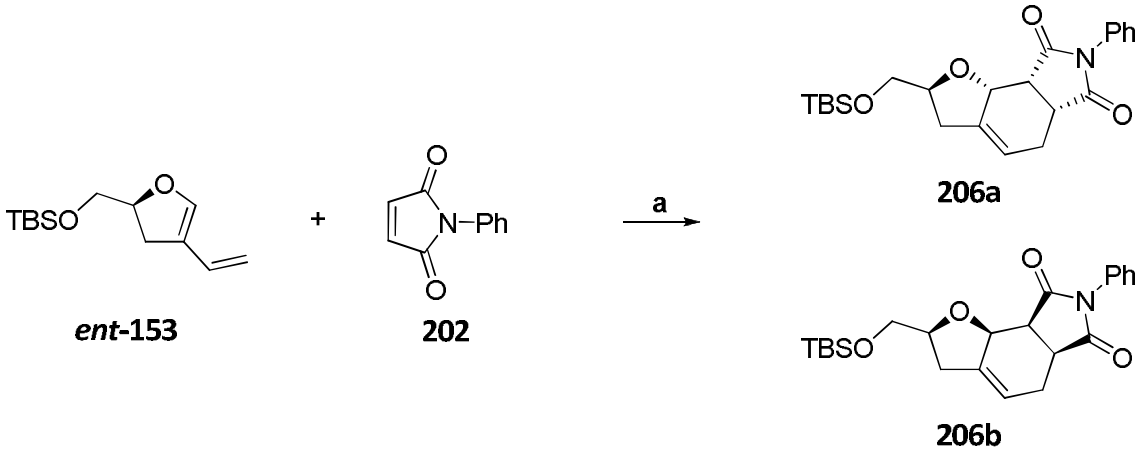


Reagents and conditions: a) DCM or toluene, rt, 12 h, 84 - 87%, *dr* > 20.

For reasons of clarity the (*S*)-configured oxacyclic diene ***ent*-153** was used in the following. The Diels-Alder reaction of diene ***ent*-153** and *N*-phenyl maleimide (**202**) in DCM at room temperature was accomplished in comparable 83% yield (Scheme 44) but was less selective than the reaction of diene **199.** Cycloadducts **206a** and **206b** were produced in 70% and 13% yield which amounts to a diastereomeric ratio of 5.4. The structural elucidation relies on

COSY and NOESY spectra. Dienophile **202** approaches diene ***ent*-153** from the face opposite to the methoxysilane substituent in an *endo* mode to form the major product **206a**. The minor product **206b** possesses an *endo*-configuration as well and emerges from the attack at the more shielded face. The conceivable *exo* cycloadducts were not observed. As a result, the dioxolane moiety in diene **199** is more capable of shielding one face than the methoxysilane substituent in diene ***ent*-153**.

Scheme 44. Diels-Alder reaction of oxacyclic diene ***ent*-153** and *N*-phenyl maleimide (**202**).



***ent*-153** **202** **206a** **206b**

Reagents and conditions: a) DCM, rt, 16 h, 83%, *dr* = 5.4.

In conclusion, oxacyclic diene ***ent*-153** was successfully applied in a [4+2] cycloaddition reaction with electron deficient *N*-phenyl maleimide (**202**) to give the tricyclic compounds **206a** and **206b**. Enantiopure diene ***ent*-153** was obtained in 7 steps from commercially available 2-furan carboxylic acid (**72**) with an overall yield of 23%. The cycloaddition reaction of diene ***ent*-153** showed a strong *endo*/*exo*-selectivity but the shielding ability of the methoxysilane substituent was not sufficient to avoid formation of a second stereoisomer in considerable yields. However, introduction of a bulkier group enables enhancement of stereoselectivity as it was shown for diene **199**.

C. Pharmacological results and discussion

Pharmacological testing was performed at the Institute of Pharmacy in the group of Prof. Buschauer, University of Regensburg.

The binding affinity of the synthesized imidazole compounds (Figure 17, page 42) using [^{3}H]-N^{α}-methylhistamine and [^{3}H]histamine as radio ligands for the human H_3R subtype and [^{3}H]histamine for the human H_4R subtype was evaluated.

The compounds, having submicromolar K_i values were investigated for agonism or antagonism at hH_3R and hH_4R subtypes in [^{35}S]GTPγS binding assays using membrane preparations of Sf9 insect cells co-expressing the hH_3R plus $G\alpha_{i2}$ plus $G\beta_1\gamma_2$ or co-expressing the hH_4R plus $G\alpha_{i2}$ plus $G\beta_1\gamma_2$. In the following agonistic potencies are expressed as EC_{50} values. Intrinsic activities (α) refer to the maximal response induced by the standard agonist histamine. Compounds identified to be inactive as agonists ($\alpha < 0.1$ or negative values, respectively, determined in the agonist mode) were investigated in the antagonist mode. The corresponding K_B values of neutral antagonists and inverse agonists were determined from the concentration-dependent inhibition of the histamine-induced increase in [^{35}S]GTPγS binding. The results are shown in Table 8.

As expected from the findings of Hashimoto *et al.* the aminoimidazoles **55a-d** exhibited significantly stronger binding affinities at the hH_3R than at the hH_4R. At the hH_3R the (6*R*)-configured eutomers **55a** and **55c** showed submicromolar K_i values. Both compounds were about 10-fold more potent than its (6*S*)-configured distomers **55b** and **55d**. At the hH_4R aminoimidazoles **55a** and **55d**, having the (3*R*)-configuration, exhibited weak binding affinities with low micromolar K_i values. In contrast to this, the respective (3*S*)-configured epimers **55b** and **55c** were inactive at this receptor subtype. An unambiguous preference for either the *folded* isomers ((3*R*,6*R*)-*cis*-**55a** and (3*S*,6*S*)-*cis*-**55b**) or the *extended* analogues ((3*S*,6*R*)-*trans*-**55c** and (3*R*,6*S*)-*trans*-**55d**) was not observed at both receptor subtypes. As a result, binding affinity at the hH_3R were 25, >4, >34 and 3-fold higher for aminoimidazoles **55a**, **55b**, **55c** and **55d** than at the hH_4R subtype, respectively. **55a** and **55c** were investigated for their functional activity at the hH_3R. In opposite to the aminoimidazoles **53a-d**, reported by Hashimoto, which all act as full agonists at the receptor subtype, **55a** and **55c** turned out to be almost neutral antagonists with K_B values of 181 and 32 nM.

The elongated spacer length between the pharmacophoric elements and their different spatial arrangement to each other was tolerated to certain extent for the aminoimidazole compounds compared to Hashimoto's THF-based ligands. At both receptor subtypes comparable K_i values were observed, especially at the hH_3R but the quality of action differs.

In contrast, the cyanoguanidinoimidazoles **54a-d** turned out to be inactive at both the H_3R and the H_4R. In this case, the orientation of the pharmacophoric elements, provided by the bicyclic core, was detrimental for receptor binding. An improvement of hH_4R affinity by displacement of the amino group with a cyanoguanidino moiety - as in the case of Hashimoto's THF-based compounds - was not achieved. (K_i, EC_{50} and α values of all tetrahydrofuranylimidazoles according to Hashimoto *et al.,* see page 73)

The synthesized oxazole compounds **56a**, **56b**, **57a** and **57b** were investigated in [^{35}S]GTPγS functional binding assays but did not reveal any activity at both receptor subtypes. Since even oxazole **57a**, whose imidazole analogue **55a** exhibited submicromolar affinities at the hH_3R, was not active at the hH_3R it can be concluded independently from the other structural modifications that an oxazole ring is not a suitable imidazole-bioisoster to improve potency and selectivity at the HR subtypes.

Figure 22. Overview of all synthesized and pharmacologically tested target molecules.

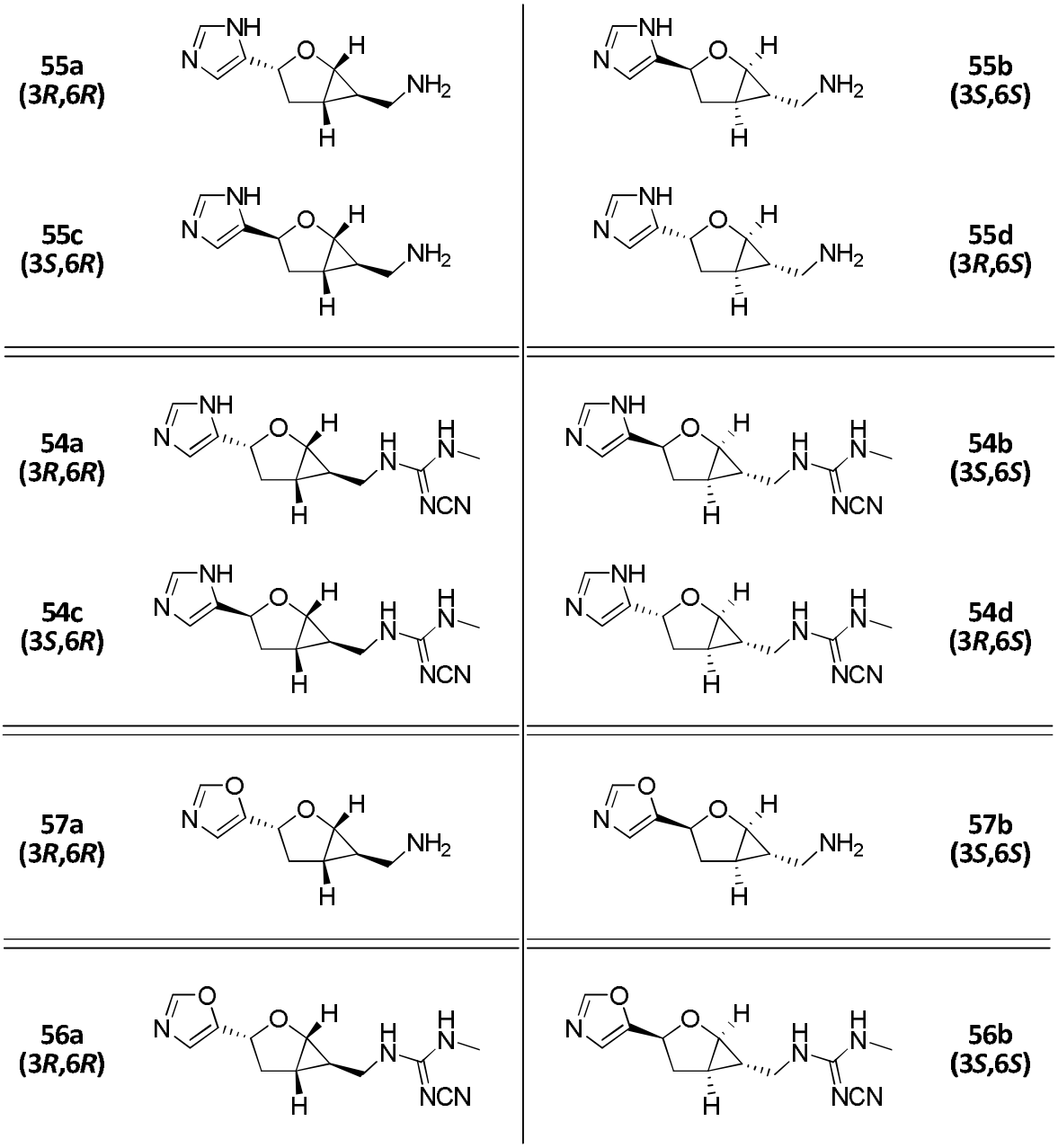


Table 8. Potencies, efficacies and affinities of the synthesized amino- and cyanoguanidinoimidazoles and amino- and cyanoguanidinooxazoles at the hH_3R and hH_4R subtypes in the [^{35}S]GTPγS assay[a] or in radioligand binding experiments.[b]

compound	configuration	hH_3R					hH_4R				
		K_i (nM)	N	K_B (nM)	α	N	K_i (nM)	N	K_B (nM)	α	N
histamine	-	10[c]	-	-	1	-	16[c]	-	-	1	-
55a	3*R*,6*R*	231 ± 106	3	181 ± 119	-0.10	2	5787 ± 853	2	nd	nd	-
55b	3*S*,6*S*	2326 ± 982	2	nd	nd	-	>10000	2	nd	nd	-
55c	3*S*,6*R*	295 ± 154	2	32 ± 17	-0.12	2	>10000	2	nd	nd	-
55d	3*R*,6*S*	2818 ± 1823	2	nd	nd	-	8415 ± 417	2	nd	nd	-
54a	3*R*,6*R*	>10000	2	nd	nd	-	>10000	2	nd	nd	-
54b	3*S*,6*S*	>10000	2	nd	nd	-	>10000	2	nd	nd	-
54c	3*S*,6*R*	>10000	2	nd	nd	-	>10000	2	nd	nd	-
54d	3*R*,6*S*	>10000	2	nd	nd	-	>10000	2	nd	nd	-
57a	3*R*,6*R*	nd	-	>10000	-0.08	2	nd	-	>10000	0.02	2
57b	3*S*,6*S*	nd	-	>10000	-0.06	2	nd	-	>10000	0.13	2
56a	3*R*,6*R*	nd	-	>10000	0.07	2	nd	-	>10000	-0.03	2
56b	3*S*,6*S*	nd	-	>10000	-0.07	2	nd	-	>10000	-0.06	2

[a] [^{35}S]GTPγS functional binding assays with membrane preparations of Sf9 cells expressing the hH_3R + $G\alpha_{i2}$ + $G\beta_1\gamma_2$ or the hH_4R + $G\alpha_{i2}$ + $G\beta_1\gamma_2$ were performed as described in section *Pharmacological methods*. [b] Displacement of [^{3}H]N^{α}-methylhistamine (3 nM) or [^{3}H]histamine (15 nM) from Sf9 cell membranes expressing the hH_3R + $G\alpha_{i2}$ + $G\beta_1\gamma_2$ or the hH_4R + $G\alpha_{i2}$ + $G\beta_1\gamma_2$ was determined as described in section Pharmacological methods. [a][b] Reaction mixtures contained ligands at a concentration from 1 nM to 1 mM as appropriate to generate saturated concentration/response curves. N gives the number of independent experiments performed in triplicate each. The intrinsic activity (α) of histamine was set to 1.00 and α values of other compounds were referred to this value. The α values of neutral antagonists and inverse agonists were determined at a concentration of 10 μM. The K_B values of neutral antagonists and inverse agonists were determined in the antagonist mode versus histamine (100 nM) as the agonist. [c] K_i values for hH_3R and hH_4R taken from Smits *et al.*[218]

Pharmacological data of imifuamine based compounds

Figure 23. Tetrahydrofuranylimidazoles according to Hashimoto *et al*.[100]

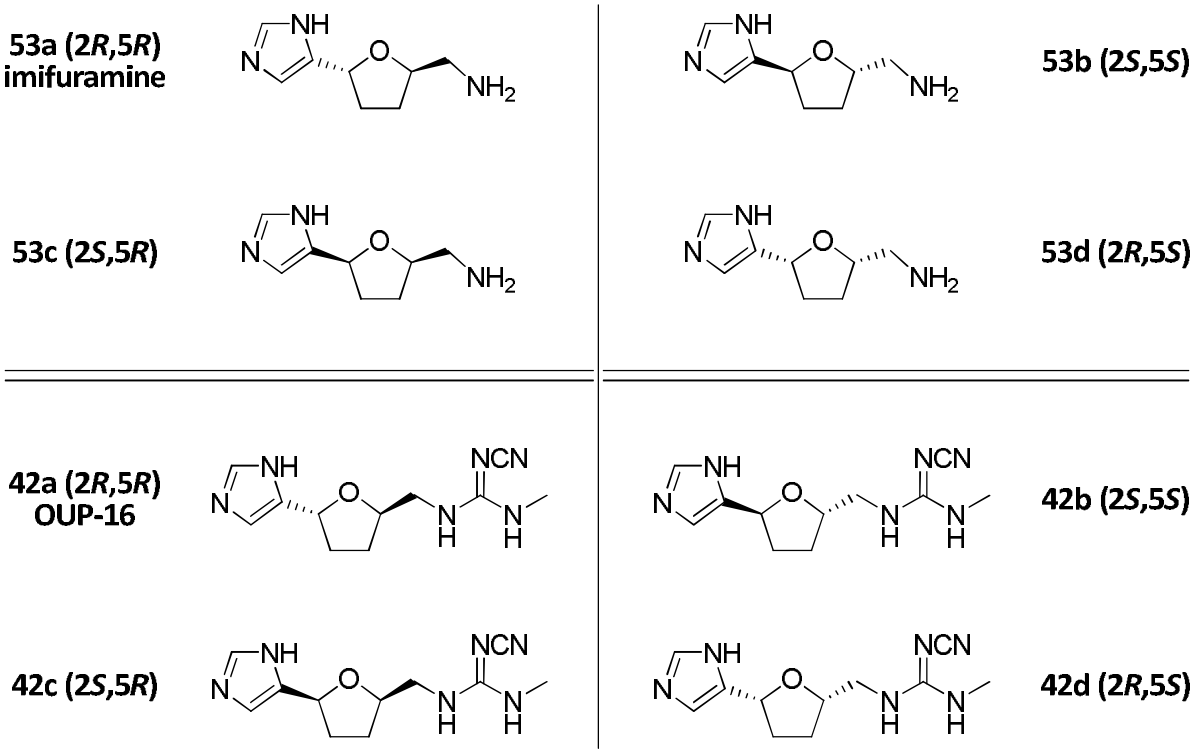


Table 9. EC_{50} values and affinity values of tetrahydrofuranylimidazoles for the hH_3R and hH_4R according to Hashimoto *et al.*[a, 100]

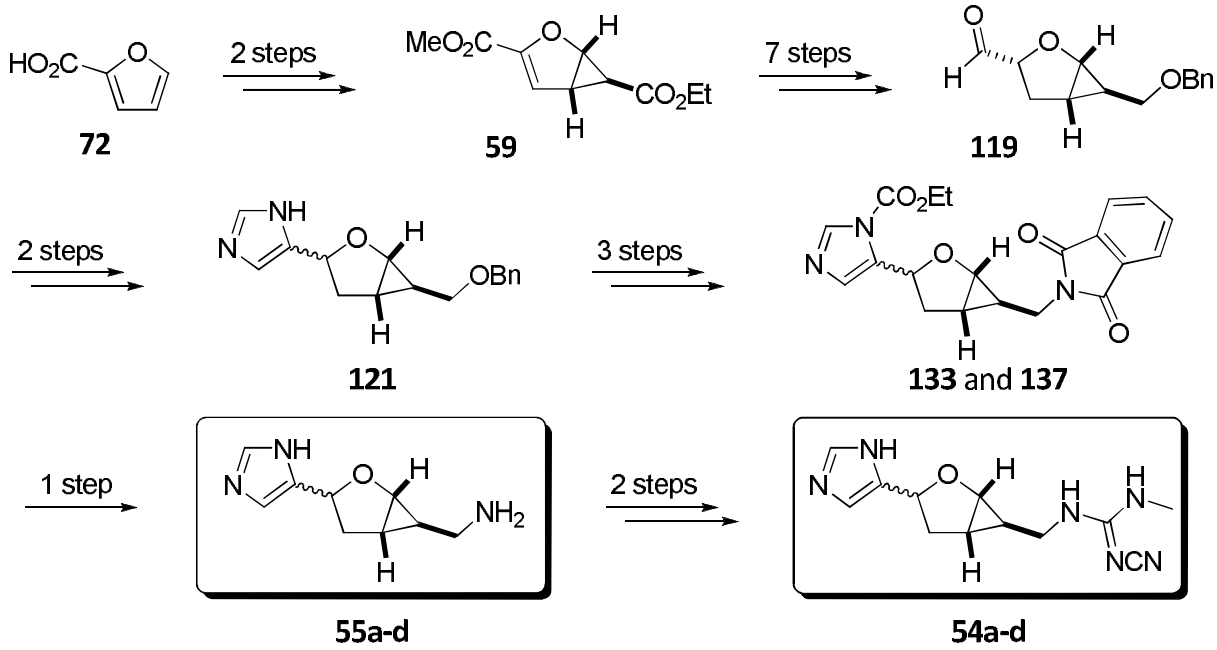
compound	configuration	hH_3R			hH_4R		
		K_i (nM)	EC_{50} (nM)	α	K_i (nM)	EC_{50} (nM)	α
histamine	-	34	4.1	1	-	21	1
(*R*)-α-methyl-histamine	-	-	0.12	0.85	-	550	1.01
(imifuramine) 53a	2*R*,5*R*	229	45	1.04	891	1995	0.70
53b	2*S*,5*S*	219	105	0.91	12882	30903	0.60
53c	2*S*,5*R*	1698	813	0.95	6457	7585	1.02
53d	2*R*,5*S*	2041	776	1.06	2512	5495	0.88
(OUP-16) 42a	2*R*,5*R*	2188	3162	0.79	126	77	0.99
42b	2*S*,5*S*	18620	>10000	-	20417	21380	1.06
42c	2*S*,5*R*	8128	-	<0.1	8128	7586	1.07
42d	2*R*,5*S*	7079	10233	0.43	224	224	1.01

[a] K_i and EC_{50} values calculated from the respective pK_i and pEC_{50} values; the EC_{50} values were determined by the inhibition of the forskolin-stimulated (1 µM) cAMP production, expressing the human H_3 or H_4 receptor. H_3-receptor competition binding was performed using [^{3}H]N^{α}-methylhistamine (1 nM), H_4-receptor competition binding was performed using [^{3}H]histamine (10 nM).

D. Summary

Based on the results of Hashimoto *et al.*,[100] who synthesized imifuramine analogues and examined these molecules at the human H_3 and H_4 receptor, and following the concept of stereochemical diversity-oriented conformational restriction the aim of this work was to synthesize and investigate related amino- and cyanoguanidinoimidazole compounds containing a modified bicyclic core. The preparation of the aminoimidazole compounds **55a** and **55b** and their corresponding epimers **55c** and **55d** was realized in 15 steps starting from commercially available 2-furan carboxylic acid (**72**). The cyanoguanidino analogues **54a** and **54b** and the corresponding epimers **54c and 54d** were accomplished in 17 steps (Scheme 45). The reaction sequence comprised the following key steps: A copper-catalyzed asymmetric cyclopropanation furnished both enantiomers of compound **59** depending on the stereochemistry of the employed bis(oxazoline) ligand. The imidazole ring was introduced by conversion of aldehyde **119** applying TosMIC chemistry. This included partial epimerization to result both isomers **121a** and **121b**. A Mitsunobu-type Gabriel reaction afforded phthalimides **133** and **137** which were subsequently cleaved to give the target aminoimidazoles **55a-d**. The corresponding cyanoguanidines **54a-d** were obtained after two additional steps.

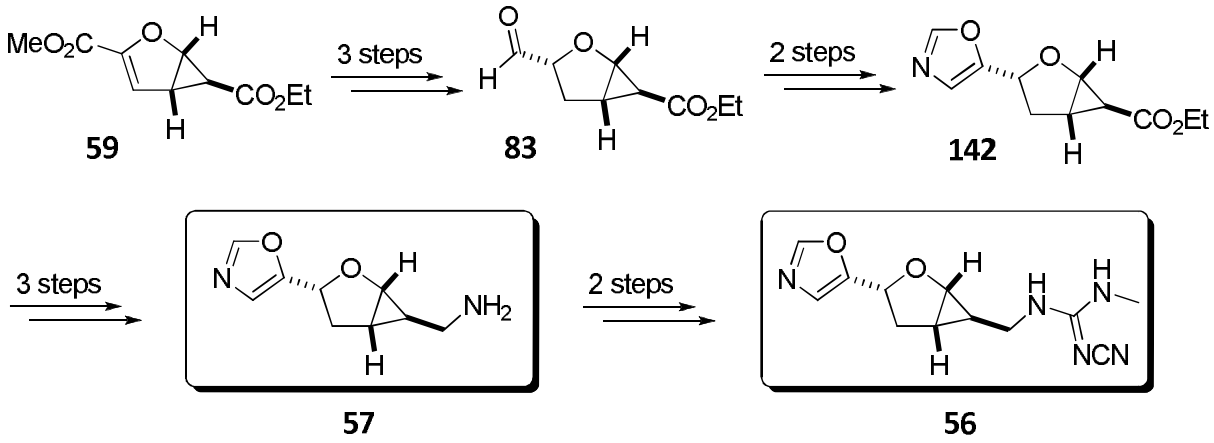
Scheme 45. Synthetic route toward imidazole-containing target compounds.



Radioligand displacement studies revealed a preference of the aminoimidazole compounds for the hH_3R subtype. Among them, **55a** and **55c**, having the (6R)-configation, exhibited submicromolar K_i values at the hH_3R with 10-fold higher affinities than their (6*S*)-enatiomers and 25 and >34-fold selectivity over the hH_4R, respectively. Both act as neutral antagonists at the hH_3R with K_B values of 181 and 32 nM, respectively. The cyanoguanidinoimidazole analogues **54a-d** turned out to be inactive at both the hH_3R and the hH_4R.

In addition, it was aimed to synthesize oxazole analogues as potential bioisosteres and to investigate their pharmacological properties at the H_3R and H_4R subtypes. The preparation of aminooxazole **57** succeeded in 10 steps, the cyanoguanidine derivative **56** was performed in 12 steps starting from 2-furan carboxylic acid (**72**) (Scheme 46). The oxazole ring was prepared by transforming aldehyde **83** into compound **142** using TosMIC chemistry. As expected, epimerisation was not observed under these conditions giving rise to the *trans*-configured target molecules exclusively.

Scheme 46. Synthetic route toward oxazole-containing target compounds.

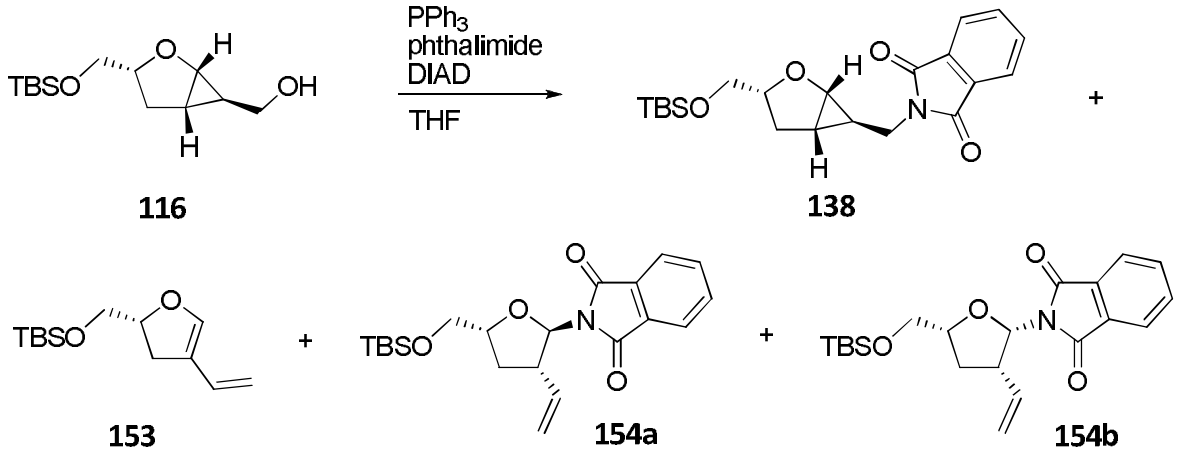


All four synthezised oxazole-containing target molecules were inactive at both the hH_3R and hH_4R in [^{35}S]GTPγS functional binding assays. Hence, discplacement of imidazole with an oxazole moiety could not contribute to an improvement of potency and selectivity at the histamine receptor subtypes.

Summary

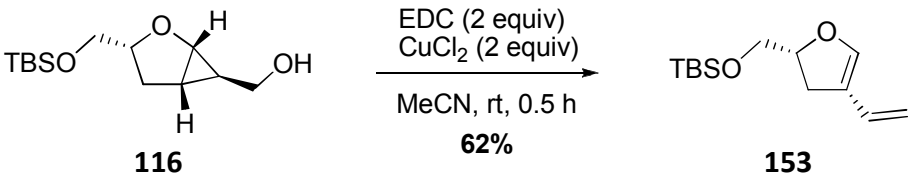
The Mitsunobu-type Gabriel reaction was part of a number of different reaction sequences within this work introducing a phthalimide function as shown exemplarily for alcohol **116** in Scheme 47. Apart from the desired S_N2-product **138** additional ring-opening structures emerged as a result of a cyclopropylcarbinyl-homoallylic rearrangement.

Scheme 47. Mitsunobu-type Gabriel reaction.



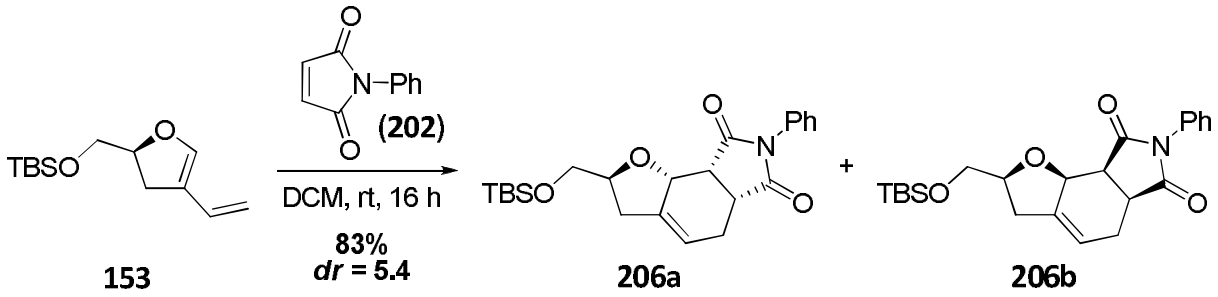
The chiral oxacyclic diene **153** was regarded as a valuable substrate for Diels-Alder reactions to build up polycyclic scaffolds. For that reason, several procedures were tested to enhance the dehydration of alcohol **116**. Best results were obtained by a cycloelimination reaction using EDC and $CuCl_2$ in MeCN (Scheme 48).

Scheme 48. Dehydration of alcohol **116** to diene **153**.



Furanyldiene ***ent*-153** was applied to a Diels-Alder reaction with *N*-phenyl maleimide (**202**) to accomplish the tricyclic compounds **206a** and **206b** in good combined yield (Scheme 49). However, the shielding ability of the methoxysilane substituent was less effective compared to a dioxolane group reported in the literature resulting in a moderate selectivity for *endo*-cycloadduct **206a**.

Scheme 49. Diels-Alder reaction of diene **153**.



153 **206a** **206b**

E. Experimental

General

All reactions were carried out in oven dried glassware under atmospheric conditions unless otherwise stated. Commercially available chemicals were used as received, without any further purification. The following solvents and reagents were purified prior to use: Dichloromethane (DCM) was distilled from $CaCl_2$ and stored over molecular sieves (4 Å). Ethanol (EtOH) and methanol (MeOH) were distilled from magnesium and stored over molecular sieves (3 Å). 1,2-Dimethoxyethane (DME) and tetrahydrofuran (THF) were distilled from sodium wire. Benzene and toluene were dried with CaH_2, distilled and stored over sodium wire. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were dried with CaH_2, distilled and stored over molecular sieves (4 Å). Ethyl acetate (EA) and hexanes (PE) for chromatographic separations were distilled prior to use. Millipore water was used throughout for the preparation of buffers and HPLC eluents. Benzyl bromide, ethyl chloroformate, oxalyl chloride, cyclohexen, benzylamine and dichloroacetyl chloride were distilled prior to use. Triethylamine and pyridine were distilled from KOH.

Chromatography

Analytical thin layer chromatography was performed on Merck TLC aluminium sheets silica gel 60 F_{254}. Visualization was accomplished with UV light (λ = 254 nm). Vaniline, ninhydrin, mostain and permanganate solutions followed by heating or iodine were used for staining. Liquid chromatography was performed using Merck silica gel 60 (0.063 - 0.200 mm) and flash silica gel 60 (0.040 - 0.063 mm).

NMR-Spectroscopy

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C), Bruker Avance III 400 “Nanobay” (400 MHz for ^{1}H, 101 MHz for ^{13}C) or Avance III 600 (600 MHz for ^{1}H, 151 MHz for ^{13}C) FT-NMR-Spectrometer at ambient temperature. Data are given as follows for ^{1}H-NMR: Chemical shift in ppm from internal $CHCl_3$ (7.27 ppm) or CH_3OH (3.31 ppm) as standard on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, qd = quartet of doublet, sept = septet and m = multiplet), integration and

coupling constant (Hz). Data are as follows for ^{13}C-NMR: Chemical shift in ppm from internal $CHCl_3$ (77 ppm) or CH_3OH (49 ppm) as standard on the δ scale. The ^{13}C signals were assigned with DEPT-135: "+" (primary or tertiary carbon, positive intensity in DEPT-135), "-" (secondary carbon, negative intensity in DEPT-135), "C_q" (quaternary carbon, zero intensity in DEPT-135).

Mass spectrometry

Mass spectrometry was performed using Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000 or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS at the analytical department of the University of Regensburg. The percentage set in brackets gives the peak intensity related to the basic peak (I = 100%). High resolution mass spectrometry (HRMS): The molecular formula was proven by the calculated precise mass.

IR spectroscopy

ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System.

Optical rotation

Optical rotations were measured on a P8000T polarimeter (Kruess) at a wavelength of 589 nm in a 5 cm cell of 0.7 mL volume in the specified solvent. Concentrations are indicated in [g/100 mL]

Elemental analysis

Elemental analysis was performed by the analytical department of the University of Regensburg using a Vario EL III or Mikro Rapid CHN (Heraeus).

Melting points

The melting points were measured on a Büchi SMP-20 apparatus in a silicon oil bath. Values thus obtained were not corrected.

Lyophilisation

Lyophilisation was done with a Christ alpha 2-4 LD equipped with a vacuubrand RZ 6 rotary vane vacuum pump.

HPLC

Preparative HPLC was performed at room temperature with a system from Knauer (Berlin, Germany) consisting of two K-1800 pumps, a K-2001 detector (UV detection at 220 nm) and a RP-column (VP Nucleodur 100-5 C18 ec, 250 x 21 mm, 5 µm, Macherey Nagel, Düren, Germany) at a flow rate of 15 mL/min or a RP-column (YMC-Triat C18, 150 x 20.0 m, 5 µm, YMC Europe GmbH Dinslaken, Germany) at a flow rate of 10 mL/min. Mixtures of acetonitrile and 0.1% aq. TFA were used as mobile phase in case of the Nucleodur column and mixtures of acetonitrile and 0.1% aq. NH_3 were used as mobile phase in case of the YMC-Triat column. Acetonitrile was removed from the eluates under reduced pressure (final pressure: 90 mbar) at 45 °C prior to lyophilization.

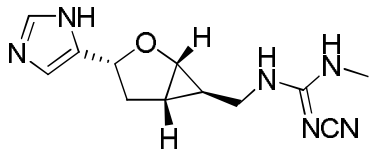
Analytical HPLC analysis was performed with a system from Merck (Darmstadt, Germany), composed of a L-5000 controller, a 655A-12 pump, a 655A-40 autosampler and a L-4250 UV-VIS detector on a Eurospher-100 C18 column (250 × 4 mm, 5 µm, Knauer, Berlin, Germany) at a flow rate of 0.8 mL/min. Mixtures of acetonitrile and 0.05 % aq. TFA were used as mobile phase. Helium degassing was used throughout.
Compound purities were calculated as the percentage peak area of the analyzed compound by UV detection at 210 nm. HPLC conditions, retention times (t_R), capacity factors ($k' = (t_R - t_0)/t_0$) and purities of the synthesized compounds are listed in the appendix.

Syntheses of literature-known compounds and reagents

2,2-Dimethylmalonyl dichloride (**68**),[219] (S)-2-amino-3-methylbutan-1-ol (**69**),[219] N^1,N^3-bis((S)-1-hydroxy-3-methylbutan-2-yl)-2,2-dimethylmalonamide (**70**),[131] (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (**71**),[131] ethyl 2-diazoacetate (**75**),[132] (1*S*,5*S*,6*S*)-6-ethyl 3-methyl 2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (**59**),[115,128] (1*S*,3*R*,5*S*,6*S*)-6-ethyl 3-methyl 2-oxabicyclo[3.1.0]hexane-3,6-dicarboxylate (**78**),[140] (1*S*,3*R*,5*S*,6*S*)-6-(ethoxycarbonyl)-2-oxabicyclo[3.1.0]hexane-3-carboxylic acid (**82**),[141] (1*S*,5*S*,6*S*)-6-(ethoxycarbonyl)-2-oxabicyclo[3.1.0]hex-3-ene-3-carboxylic acid (**81**),[141] Dess-Martin periodinane,[144] *N*-sulfinyl *p*-toluenesulfonamide.[166]

Syntheses

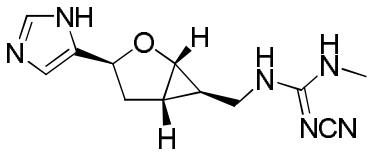
1-(((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-2-cyano-3-methylguanidine (54a)



A solution of compound **55a** (5.0 mg, 0.028 mmol) and dimethyl *N*-cyanodithioiminocarbonate (9.9 mg, 0.067 mmol, 2.4 equiv) in anhydrous MeOH (0.55 mL) was stirred at room temperature for 18 h. Then a 33% solution of $MeNH_2$ in EtOH (0.52 mL) was added and stirred for 18 h at room temperature. The solvent was evaporated to give a residual oil that was purified by column chromatography (EA/MeOH 4:1) to give compound **54a** (5.0 mg, 0.019 mmol, 69%) as a colorless oil. For pharmacological testing the product was further purified by preparative HPLC (YMC-Triat column, mobile phase: MeCN, 0.1% aq. NH_3).

R_f = 0.19 (EA/MeOH 4:1); $[\alpha]_D^{20}$ = + 18.2 (MeOH, c = 0.2); ^{1}H-NMR (300 MHz, MeOD): δ_H = 7.62 (d, *J* = 1.0 Hz, 1H), 6.96 (s, 1H), 5.38 (t, *J* = 7.9 Hz, 1H), 3.89 (dd, *J* = 6.4, 1.1 Hz, 1H), 3.05 (dd, *J* = 14.3, 6.9 Hz, 1H), 2.91 (dd, *J* = 14.3, 7.9 Hz, 1H), 2.79 (s, 3H), 2.55 (dt, *J* = 12.8, 7.4 Hz, 1H), 2.06 (ddd, *J* = 12.8, 8.1, 1.9 Hz, 1H), 1.74 - 1.63 (m, 1H), 1.46 - 1.36 (m, 1H); ^{13}C-NMR (75 MHz, MeOD): δ_C = 161.96 (C_q), 140.02 (C_q), 136.79 (+), 120.08 (C_q), 117.42 (+), 83.90 (+), 65.43 (+), 42.58 (-), 36.41 (-), 33.19 (+), 28.67 (+), 24.09 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3268 (br), 2928, 2160, 1729, 1575, 1485, 1448, 1404, 1369, 1247, 1174, 1097, 1066, 1030, 988, 838, 752, 716, 618, 570; MS (ESI): m/z (%) = 163.1 [$M^+\Delta C_3H_5N_4$] (60), 261.1 [MH^+] (100); HRMS (ESI): calcd for $C_{12}H_{17}N_6O$ [MH^+] 261.1458, found 261.1458.

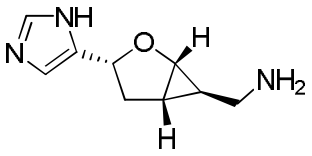
1-(((1*S*,3*S*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-2-cyano-3-methylguanidine (54c)



A solution of compound **55c** (3.0 mg, 0.017 mmol) and dimethyl *N*-cyanodithioiminocarbonate (8.2 mg, 0.05 mmol, 3.0 equiv) in anhydrous MeOH (0.34 mL) was stirred at room temperature for 18 h. Then a 33% solution of $MeNH_2$ in EtOH (0.31 mL) was added. The resulting mixture was stirred for 18 h at room temperature. The solvent was evaporated to give a residual oil that was purified by column chromatography (EA/MeOH 4:1) to give compound **55c** (2.8 mg, 0.011 mmol, 64%) as a colorless oil. For pharmacological testing the product was further purified by preparative HPLC (YMC-Triat column, mobile phase: MeCN, 0.1% aq. NH_3).

R_f = 0.20 (MeOH/saturated NH_3 in MeOH 95:5); $[\alpha]_D^{20}$ = + 36.7 (MeOH, c = 0.1); ^{1}H-NMR (600 MHz, MeOD): δ_H = 7.62 (s, 1H), 7.00 (s, 1H), 4.76 (dd, *J* = 8.7, 7.7 Hz, 1H), 3.94 (dd, *J* = 5.7, 1.1 Hz, 1H), 3.07 (dd, *J* = 14.3, 6.9 Hz, 1H), 2.97 (dd, *J* = 14.3, 7.7 Hz, 1H), 2.81 (s, 3H), 2.29 (dd, *J* = 12.4, 7.1 Hz, 1H), 2.25 - 2.19 (m, 1H), 1.62 - 1.59 (m, 1H), 1.59 - 1.54 (m, 1H); ^{13}C-NMR (151 MHz, MeOD): δ_C = 162.01 (C_q), 136.88 (+), 120.08 (C_q), 63.74 (+), 49.57 (+), 42.71 (-), 35.51 (-), 28.69 (+), 22.28 (+), 21.94 (+), Im-*C*5 and Im-*C*4 signals too weak to be observed; IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2934 (br), 2163, 1582, 1486, 1410, 1372, 1322, 1175, 1121, 1100, 922, 892, 833, 689, 617; MS (ESI): m/z (%) = 261.1 [MH^+] (100), 521.2 [$2MH^+$] (15); HRMS (ESI): calcd for $C_{12}H_{17}N_6O$ [MH^+] 261.1458, found 261.1457.

((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (55a)

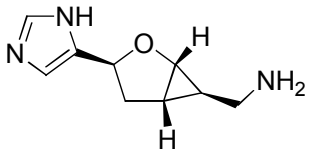


A solution of phthalimide **133** (30 mg, 0.079 mmol) and hydrazine hydrate (21 µL, 0.43 mmol, 5.4 equiv) in anhydrous EtOH (1.6 mL) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (MeOH/saturated NH_3 in MeOH 95:5) to afford compound **55a** (11 mg, 0.061 mmol, 77%) as a colorless amorphous solid. For pharmacological testing the product was further purified by preparative HPLC (Nucleodur column, mobile phase: MeCN, 0.1% aq. TFA).

R_f = 0.20 (MeOH/saturated NH_3 in MeOH 95:5); $[\alpha]_D^{20}$ = + 36.4 (MeOH, c = 0.5); ^{1}H-NMR (300 MHz, MeOD): δ_H = 7.61 (d, *J* = 1.0 Hz, 1H), 6.95 (s, 1H), 5.38 (t, *J* = 7.9 Hz, 1H), 3.82 (dd, *J* = 6.4, 1.2 Hz, 1H), 2.63 - 2.49 (m, 1H), 2.38 (d, *J* = 7.3 Hz, 2H), 2.04 (ddd, *J* = 12.7, 8.0, 1.9 Hz, 1H), 1.61 (tdd, *J* = 6.2, 3.9, 1.9 Hz, 1H), 1.26 (tdd, *J* = 7.4, 4.0, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, MeOD): δ_C = 136.71 (+), 117.55 (+), 83.87 (+), 65.46 (+), 42.61 (-), 36.63 (-), 36.07 (+), 23.99 (+), Im-C_q-signal too weak to be observed; IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3094 (br), 2937, 2869, 2625, 1573, 1454, 1414, 1361, 1306, 1177, 1098, 1067, 1028, 980, 912, 841, 632, 540, 497; MS (ESI): m/z (%) = 163.1 (100) [$MH^+\Delta NH_3$], 180.1 (19) [MH^+], 359.2 (11) [$2MH^+$]; HRMS (ESI): calcd for $C_9H_{14}N_3O$ [MH^+] 180.1131, found 180.1130.

55a•2TFA: ^{1}H-NMR (600 MHz, MeOD): δ_H = 8.83 (d, *J* = 1.0 Hz, 1H), 7.45 (s, 1H), 5.51 (t, *J* = 7.4 Hz, 1H), 4.10 (dd, *J* = 6.3, 0.7 Hz, 1H), 2.90 - 2.63 (m, 3H), 2.14 (ddd, *J* = 13.1, 7.0, 1.5 Hz, 1H), 1.92 - 1.87 (m, 1H), 1.31 - 1.26 (m, 1H); ^{13}C-NMR (151 MHz, MeOD): δ_C = 163.10 (C_q, TFA), 162.87 (C_q, TFA), 136.63 (+), 135.90 (C_q), 119.17 (+, TFA), 117.23 (+, TFA), 116.76 (+), 79.55 (+), 65.65 (+), 40.61 (-), 35.88 (-), 29.34 (+), 24.45 (+).

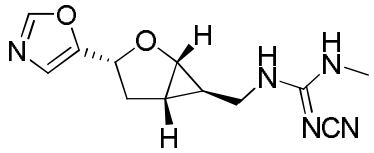
((1*S*,3*S*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (55c)



A solution of phthalimide **137** (16 mg, 0.042 mmol) and hydrazine hydrate (11 µL, 0.23 mmol, 5.4 equiv) in anhydrous EtOH (0.85 mL) was refluxed for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (MeOH/saturated NH_3 in MeOH 97:3) to afford compound **55c** (5.1 mg, 0.028 mmol, 68%) as a colorless amorphous solid. For pharmacological testing the product was further purified by preparative HPLC (Nucleodur column, mobile phase: MeCN, 0.1% aq. TFA).

55c•2TFA: R_f = 0.20 (MeOH/saturated NH_3 in MeOH 95:5); $[\alpha]_D^{20}$ = + 5.5 (DCM, c = 0.2); ^{1}H-NMR (600 MHz, MeOD): δ_H = 8.88 (d, *J* = 1.3 Hz, 1H), 7.50 (d, *J* = 0.9 Hz, 1H), 4.94 (dd, *J* = 8.9, 7.5 Hz, 1H), 4.14 (dd, *J* = 5.8, 1.2 Hz, 1H), 2.82 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.77 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.51 (dd, *J* = 12.7, 7.4 Hz, 1H), 2.22 (ddd, *J* = 12.8, 9.1, 5.6 Hz, 1H), 1.83 - 1.79 (m, 1H), 1.56 (tdd, *J* = 7.9, 3.9, 1.1 Hz, 1H).^{13}C-NMR (151 MHz, MeOD): δ_C = 162.80 (C_q, TFA), 162.56 (C_q, TFA), 136.08 (C_q), 134.59 (+), 119.04 (+, TFA), 117.45 (+), 117.11 (+, TFA), 72.81 (+), 64.08 (+), 40.76 (-), 35.51 (-), 22.52 (+), 20.51 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3240 (br), 2935, 2873, 2627, 1580, 1492, 1420, 1372, 1312, 1180, 1101, 899, 840, 630, 540; MS (ESI): m/z (%) = 180.0 (100) [MH^+], 359.2 (20) [$2MH^+$]; HRMS (ESI): calcd for $C_9H_{14}N_3O$ [MH^+] 180.1131, found 180.1133.

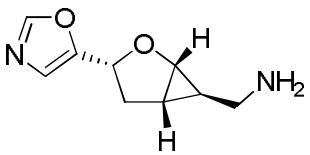
2-cyano-1-methyl-3-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl) guanidine (56a)



Compound **145** (26 mg, 0.09 mmol) was dissolved in a 33% solution of $MeNH_2$ in EtOH (2 ml) and stirred for 18 h at room temperature. The solvent was evaporated under reduced pressure. Purification by column chromatography (DCM then DCM/MeOH 9:1) afforded compound **56a** (22 mg, 0.08 mmol, 90%) as a colorless oil.

R_f = 0.32 (DCM/MeOH 9:1); $[\alpha]_D^{20}$ = + 18.9 (DCM, c = 1.0); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.84 (s, 1H), 6.96 (s, 1H), 5.64 (s, 1H), 5.43 (dd, *J* = 8.3, 7.4 Hz, 1H), 5.20 (s, 1H), 3.95 (dd, *J* = 6.3, 1.0 Hz, 1H), 3.24 - 3.13 (m, 1H), 2.95 - 2.86 (m, 1H), 2.85 (d, *J* = 4.9 Hz, 3H), 2.62 (ddd, *J* = 13.1, 8.6, 7.0 Hz, 1H), 2.14 (ddd, *J* = 13.1, 7.0, 1.4 Hz, 1H), 1.73 - 1.67 (m, 1H), 1.37 (tdd, *J* = 8.0, 4.0, 1.0 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ_C = 160.65 (C_q), 151.72 (C_q), 151.44 (+), 124.01 (+), 118.53 (C_q), 78.46 (+), 65.08 (+), 42.03 (-), 33.91 (-), 30.74 (+), 28.57 (+), 23.15 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3292 (br), 2954, 2929, 2165, 1583, 1507, 1453, 1409 1370, 1174, 1103, 1028, 963, 838, 717; MS (ESI): m/z (%) = 262.1 (25) [MH^+], 523.2 (100) [$2MH^+$]; HRMS (EI): calcd for $C_{12}H_{15}N_5O_2$ [$M^{+\bullet}$] 261.1226, found 261.1222.

((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (57a)

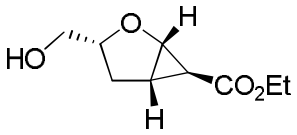


A solution of phthalimide **144** (60 mg, 1.19 mmol) and hydrazine hydrate (48 mg, 0.97 mmol, 5 equiv) in EtOH (4 mL) was refluxed for 1.5 h and then cooled in an ice bath. The white precipitate was removed by filtration through a Celite pad. The filtrate was concentrated *in*

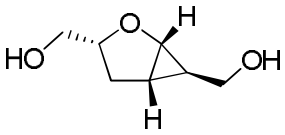
vacuo. Column chromatography (DCM/saturated NH_3 in MeOH 20:1) afforded compound **57a** (25 mg, 0.10 mmol, 72%) as a colorless solid.

mp = 51 °C; R_f = 0.32 (DCM/saturated NH_3 in MeOH 9:1); $[\alpha]_D^{20}$ = + 36.2 (DCM, c = 1.0); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.80 (s, 1H), 6.93 (s, 1H), 5.41 (dd, *J* = 8.1, 7.4 Hz, 1H), 3.82 (dd, *J* = 6.3, 1.2 Hz, 1H), 2.58 (ddd, *J* = 12.9, 8.6, 7.0 Hz, 1H), 2.51 - 2.39 (m, 2H), 2.11 (ddd, *J* = 12.9, 6.9, 1.5 Hz, 1H), 1.59 - 1.51 (m, 1H), 1.28 - 1.22 (m, 1H), 1.25 (br s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 152.16 (C_q), 151.25 (+), 123.68 (+), 78.37 (+), 65.19 (+), 42.33 (-), 34.78 (-), 34.12 (+), 22.68 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3356 (br), 3127, 2949, 1636, 1567, 1508, 1482, 1427, 1377, 1318, 1380, 1103, 1027, 980, 955, 849, 723, 646, 610; MS (ESI): m/z (%) = 181.0 (7) [MH^+], 222.0 (100) [MH^+MeCN]; HRMS (ESI): calcd for $C_9H_{13}N_2O_2$ [MH^+] 181.0972, found 181.0969.

(1*S*,3*R*,5*S*,6*S*)-ethyl 3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (79)
(1*S*,3*R*,5*S*,6*R*)-2-oxabicyclo[3.1.0]hexane-3,6-diyldimethanol (80)



79



80

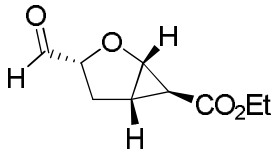
Method A: To a stirred ice-cooled solution of compound **82** (2.25 g, 11.3 mmol) in anhydrous THF (110 mL) under a nitrogen atmosphere borane-dimethyl sulfide complex (1.7 mL, 10 M in DMS, 17 mmol, 1.5 equiv) was added dropwise. Hydrogen evolved during the course of addition. The resulting solution was stirred for 4 h and allowed to warm to room temperature. The solution was quenched with MeOH (5 mL) and stirred overnight. After solvent evaporation the mixture was treated with MeOH (5 mL) and the solvent was evaporated once again. Purification of the crude product by column chromatography (PE/EA 1:1) afforded compound **79** (1.62 g, 8.72mmol, 77%) as a colorless oil.

Method B: To a stirred ice-cooled solution of **78** (2.45 mg, 11.4 mmol) in anhydrous THF (45 mL) under a nitrogen atmosphere, a suspension of LAH (260 mg, 6.87 mmol, 0.6 equiv) in anhydrous THF (5 mL) was added dropwise within 10 min. The reaction mixture was stirred for 45 min at 0 °C. After dropwise addition of water (260 µL) the mixture was stirred for another 30 min. Then a 15% NaOH solution (260 µL) was added followed by water (780 µL). The mixture was warmed to room temperature, treated with $MgSO_4$ and filtered through a Celite pad. The solvent was evaporated under reduced pressure. The crude product was purified by chromatography (PE/EA 1:1) to obtain compound **79** (1.85 g, 9.94 mmol, 87%) and compound **80** (82 mg, 0.57 mmol, 5%) as colorless oils.

79: R_f = 0.34 (PE/EA 1:1), 0.49 (EA); $[\alpha]_D^{20}$ = + 63.7 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.60 - 4.50 (m, 1H), 4.18 (d, *J* = 5.9 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.58 (ddd, *J* = 11.9, 6.0, 3.2 Hz, 1H), 3.41 - 3.31 (m, 1H), 2.37 (ddd, *J* = 13.1, 8.8, 7.0 Hz, 1H), 2.26 - 2.11 (m, 1H), 2.14 (br s, 1H), 1.81 (ddd, *J* = 13.1, 7.7, 1.1 Hz, 1H), 1.72 (dd, *J* = 3.8, 0.8 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).; ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 170.50 (C_q), 87.00 (+), 67.37 (+), 64.91 (-), 60.59 (-), 33.39 (+), 30.31 (-), 27.56 (+), 14.33 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3460 (br), 2978, 2939, 2880, 1713, 1454, 1407, 1386, 1309, 1269, 1175, 1111, 1074, 1048, 980, 878, 851, 808, 712; MS (ESI): m/z (%) = 186.9 (40) [MH^+], 228.0 (100) [MH^+MeCN], 373.1 (40) [$2MH^+$], 390.0 (30) [$2MNH_4^+$]; HRMS (ESI): calcd for $C_9H_{15}O_4$ [MH^+] 187.0965, found 187.0966.

Labile **80** was analytically characterized as diprotected compound **115** (see page 99).

(1*S*,3*R*,5*S*,6*S*)-ethyl 3-formyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (83)



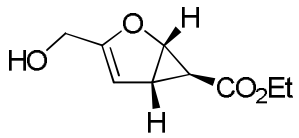
Method A: To a stirred solution of oxalyl chloride (746 µL, 8.70 mmol, 1.5 equiv) in anhydrous DCM (17 mL) under a nitrogen atmosphere at -78 °C a solution of DMSO (1.03 mL, 14.5 mmol, 2.5 equiv) in anhydrous DCM (7 mL) was added. After 15 min, a solution of alcohol **79** (1.08 mg, 5.80 mmol) in anhydrous DCM (34 mL) was added dropwise over a

period of 20 min at. After stirring for 15 min at -78 °C, NEt_3 (4.02 mL, 29.0 mmol, 5 equiv) was added and further stirred for 10 min at -78 °C. The reaction mixture was warmed to room temperature and stirred for another 30 min. Water (50 mL) was added to quench the reaction, the layers were separated and the aqueous phase was extracted with DCM (1 x 25 mL). The organic phases were washed with brine, 1% aqueous H_2SO_4 solution, water and 5% aqueous $NaHCO_3$ solution (1 x 50 mL each) and dried over $MgSO_4$. The solvent was evaporated *in vacuo*. Purification by column chromatography (PE/EA 1:1) afforded compound **83** (694 mg, 3.77 mmol, 65%) as a yellowish oil.

Method B: Dess-Martin periodinane (4.24 g, 10.0 mmol, 1.05 equiv) was added to a solution of alcohol **79** (1.77 g, 9.52 mmol) in DCM (95 mL) at room temperature and stirred for 1 h. After completion the reaction was quenched with a mixture of saturated aqueous $Na_2S_2O_3$ solution (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was stirred for 15 min, afterwards the organic layer was separated and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatography (PE/EA 1:1) to give compound **83** (1.54 mg, 8.37 mmol, 88%) as a yellowish oil.

R_f = 0.31 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 44.8 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 9.59 (s, 1H), 4.64 (dd, *J* = 10.6, 3.8 Hz, 1H), 4.34 (dd, *J* = 5.7, 0.8 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.51 (ddd, *J* = 13.4, 10.6, 5.7 Hz, 1H), 2.36 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.20 (td, *J* = 5.5, 3.9 Hz, 1H), 1.46 (dd, *J* = 3.8, 1.0 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.26 - 1.19 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 203.36 (+), 170.20 (C_q), 85.29 (+), 67.22 (+), 60.85 (-), 30.26 (-), 27.54 (+), 25.21 (+), 14.31 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3435 (br), 2984, 1712, 1451, 1411, 1385, 1323, 1298, 1273, 1177, 1107, 1051, 1035, 976, 926, 870, 849, 796, 749, 702; MS (CI): m/z (%) = 185.0 (15) [MH^+], 202.1 (100) [MNH_4^+]; HRMS (ESI): calcd for $C_9H_{13}O_4$ [MH^+] 185.0808, found 185.0808.

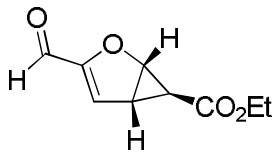
(1*S*,5*S*,6*S*)-ethyl 3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (98)



To a stirred ice-cooled solution of compound **59** (1.09 g, 5.14 mmol) in anhydrous THF (20 mL) under a nitrogen atmosphere, a suspension of LAH (118 mg, 3.11 mmol, 0.6 equiv) in anhydrous THF (5 mL) was added dropwise within 10 min. The reaction mixture was stirred for 1 h at 0 °C. After dropwise addition of water (118 µL) the mixture was stirred for another 30 min. Then 15% NaOH solution (118 µL) was added followed by water (354 µL). The mixture was warmed to room temperature, treated with $MgSO_4$ and filtered through a Celite pad. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EA 3:1 to 1:1) to obtain compound **98** (744 mg, 4.04 mmol, 79%) as a colorless oil.

R_f = 0.34 (PE/EA 1:1); $[\alpha]_D^{20}$ = - 103.3 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.37 (dt, *J* = 2.6, 0.9 Hz, 1H), 4.84 (dd, *J* = 5.6, 1.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.08 (d, *J* = 1.0 Hz, 2H), 2.76 (m, 1H), 2.22 (br s, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.04 (dd, *J* = 2.6, 1.0 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 172.88 (C_q), 159.31 (C_q), 102.83 (+), 67.27 (+), 60.77 (-), 57.37 (-), 31.99 (+), 22.65 (+), 14.27 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3438 (br), 2983, 2940, 2874, 1710, 1650, 1446, 1400, 1379, 1331, 1289, 1268, 1177, 1084, 1041, 1004, 921, 884, 831, 727; MS (CI): m/z (%) = 185.1 (10) [MH^+], 202.1 (100) [MNH_4^+].

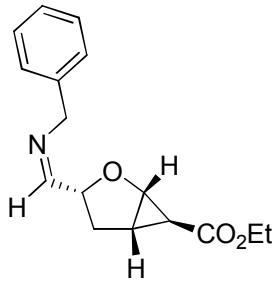
(1*S*,5*S*,6*S*)-ethyl 3-formyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (99)



Dess-Martin periodinane (257 mg, 0.61 mmol, 1.06 equiv) was added to a solution of alcohol **98** (105 mg, 0.57 mmol) in DCM (11 mL) at room temperature and stirred for 1.5 h. After completion the reaction was quenched with a mixture of saturated aqueous $Na_2S_2O_3$ solution (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The obtained mixture was stirred for 15 min, then the organic layer was separated and the aqueous layer was extracted with DCM (2 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (PE/EA 3:1) to give compound **99** (50 mg, 0.27 mmol, 49%) as a yellowish oil.

R_f = 0.40 (PE/EA 1:1); $[\alpha]_D^{20}$ = - 133.0 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 9.36 (d, *J* = 0.5 Hz, 1H), 6.46 (d, *J* = 3.0 Hz, 1H), 4.99 (ddd, *J* = 5.1, 1.1, 0.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.91 (dt, *J* = 5.1, 3.0 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (dd, *J* = 2.8, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 180.43 (+), 171.39 (C_q), 156.99 (C_q), 123.44 (+), 67.84 (+), 61.32 (-), 31.97 (+), 22.33 (+), 14.24 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3102, 2986, 1716, 1692, 1599, 1402, 1376, 1290, 1270, 1182, 1153, 1084, 1042, 996, 913, 827, 759, 731; MS (EI): m/z (%) = 53.1 (32), 81.1 (30), 97.0 (52), 109.0 (100) [$M^+\Delta CO_2Et$], 125.0 (38), 153.0 (61) [$M^+\Delta CHO$], 182.0 (6) [$M^{+\bullet}$]; HRMS (EI): calcd for $C_9H_{10}O_4$ [$M^{+\bullet}$] 182.0579, found 182.0583.

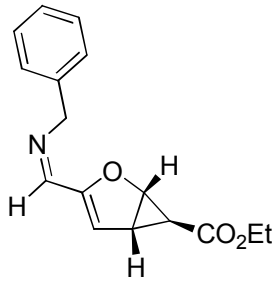
(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((benzylimino)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (102)



To a solution of aldehyde **83** (105 mg, 0.57 mmol) in anhydrous DCM (5 mL) was added $MgSO_4$ and the mixture was stirred for 15 min at room temperature under a nitrogen atmosphere. After addition of benzylamine (63 mg, 0.059 mmol, 1.03 equiv) the reaction mixture was refluxed for 1.5 h and then cooled to room temperature. Filtration and evaporation of the solvent under reduced pressure afforded crude **102** as a colorless oil.

R_f = 0.31 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 30.3 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.67 (dt, *J* = 3.5, 1.4 Hz, 1H), 7.37 - 7.20 (m, 5H), 4.97 - 4.88 (m, 1H), 4.59 (s, 2H), 4.27 (dd, *J* = 5.7, 0.9 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.54 (ddd, *J* = 13.3, 9.6, 6.1 Hz, 1H), 2.35 (ddd, *J* = 13.3, 4.9, 0.5 Hz, 1H), 2.23 (tdd, *J* = 6.1, 3.9, 0.8 Hz, 1H), 1.67 (dd, *J* = 3.8, 1.0 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ_C = 170.46 (C_q), 166.61 (+), 138.51 (C_q), 128.66 (+), 128.05 (+), 127.24 (+), 83.65 (+), 67.23 (+), 64.59 (-), 60.56 (-), 32.05 (-), 29.79 (+), 26.60 (+), 14.33 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2979, 2930, 1715, 1495, 1453, 1406, 1386, 1307, 1261, 1175, 1107, 1028, 969, 908, 851, 802, 731, 698, 648; MS (ESI): m/z (%) = 274.1 (100) [MH^+]; HRMS (ESI): calcd for $C_{16}H_{20}NO_3$ [MH^+] 274.1443, found 274.1437.

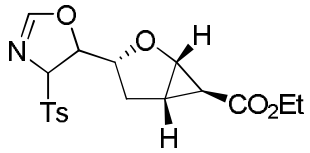
(1S,5S,6S)-ethyl 3-((benzylimino)methyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (104)



To a solution of aldehyde **99** (137 mg, 0.75 mmol) in anhydrous DCM (8 mL) was added $MgSO_4$ and the mixture was stirred for 15 min at room temperature under a nitrogen atmosphere. After addition of benzylamine (90 µL, 0.83 mmol, 1.1 equiv) the reaction mixture was refluxed for 1.5 h and then cooled to room temperature. Filtration and evaporation of the solvent under reduced pressure afforded crude **104** as a colorless oil.

R_f = 0.40 (PE/EA 1:1); $[\alpha]_D^{20}$ = - 96.2 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.74 (t, *J* = 1.2 Hz, 1H), 7.31 – 7.15 (m, 5H), 5.83 (d, *J* = 2.8 Hz, 1H), 4.90 (dd, *J* = 5.4, 0.9 Hz, 1H), 4.66 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.80 (dt, *J* = 5.5, 2.8 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.14 (dd, *J* = 2.7, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 172.06 (C_q), 156.12 (C_q), 150.79 (+), 138.19 (C_q), 128.63 (+), 128.42 (+), 127.31 (+), 113.61 (+), 67.53 (+), 65.08 (-), 60.97 (-), 32.20 (+), 22.82 (+), 14.32 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3062, 3030, 2979, 1714, 1648, 1594, 1495, 1454, 1397, 1380, 1343, 1290, 1269, 1178, 1085, 1042, 995, 934, 893, 829, 732, 698; MS (ESI): m/z (%) = 272.1 (100) [MH^+]; HRMS (ESI): calcd for $C_{16}H_{18}NO_3$ [MH^+] 272.1287, found 272.1281.

(1*S*,3*R*,5*S*,6*S*)-ethyl 3-(4-tosyl-4,5-dihydrooxazol-5-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (106)



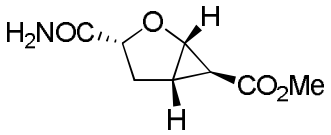
Finely powdered NaCN (70 mg, 1.42 mmol, 0.18 equiv) was added in one portion to a stirred solution of TosMIC (1.70 g, 8.70 mmol, 1.1 equiv) and aldehyde **83** (1.46 g, 7.91 mmol) in anhydrous EtOH (80 mL) at room temperature under a nitrogen atmosphere. After 1 h, the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (1 x 100 mL). The aqueous layer was extracted with $CHCl_3$ (1 x 40 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EA 1:1) afforded a 2:1 diastereomeric mixture of compound **106** (2.10 g, 5.54 mmol, 70%) as a yellowish foam.

Major: R_f = 0.29 (PE/EA 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.80 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 1H), 4.91 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.86 (dd, *J* = 5.9, 1.7 Hz, 1H), 4.60 - 4.52 (m, 1H), 4.17 (d, *J* = 6.0 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.51 - 2.41 (m, 1H), 2.44 (s, 3H), 2.27 - 2.20 (m, 1H), 1.88 (ddd, *J* = 13.6, 8.2, 1.2 Hz, 1H), 1.73 (d, *J* = 3.8, 1H), 1.23 (t, *J* = 7.1, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 169.87 (C_q), 159.32 (+), 145.83 (C_q), 132.87 (C_q), 129.97 (+), 129.63 (+), 86.60 (+), 85.71 (+), 79.54 (+), 67.06 (+), 60.71 (-), 33.52 (+), 30.01 (-), 26.70 (+), 21.82 (+), 14.29 (+);

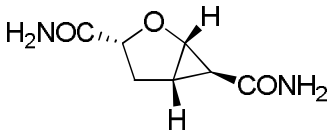
minor: R_f = 0.29 (PE/EA 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.79 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.00 (s, 1H), 4.99 (dd, *J* = 6.4, 1.7 Hz, 1H), 4.88 - 4.81 (m, 1H), 4.63 - 4.55 (m, 1H), 4.15 (d, *J* = 6.0 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.57 - 2.49 (m, 1H), 2.44 (s, 3H), 2.27 - 2.20 (m, 1H), 2.12 (ddd, *J* = 13.4, 8.2, 1.0 Hz, 1H), 1.73, (d, *J* = 3.8, 1H), 1.21 (t, *J* = 7.1, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 170.04 (C_q), 159.15 (+), 145.79 (C_q), 133.02 (C_q), 129.97 (+), 129.53 (+), 87.27 (+), 86.65 (+), 68.76 (+), 67.33 (+), 60.64 (-), 33.15 (+), 30.58 (-), 27.11 (+), 21.82 (+), 14.29 (+);

Data for isomeric mixture: IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978, 2936, 1716, 1618, 1453, 1408, 1387, 1306, 1177, 1149, 1108, 1086, 1075, 975, 934, 852, 813, 707, 668; Elemental analysis calcd (%) for $C_{16}H_{21}NO_6S$ • 1.2 H_2O: C 53.91, H 5.88, N 3.49, S 8.00, found C 53.83, H 5.93, N 3.34, S 7.92.

(1*S*,3*R*,5*S*,6*S*)-methyl 3-carbamoyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (108), (1*S*,3*R*,5*S*,6*S*)-2-oxabicyclo[3.1.0]hexane-3,6-dicarboxamide (109)



108



109

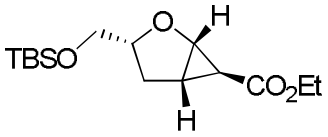
In a sealable pressure tube diester **78** (46 mg, 0.21 mmol) and a saturated solution of NH_3 in MeOH (3 mL) was heated to 95 °C for 17 h. After cooling the reaction mixture was concentrated *in vacuo*. Compound **109** (24 mg, 0.14 mmol, 67%) crystallized as colorless crystals from MeOH/$CHCl_3$. The remaining solution was concentrated and purified by column chromatography (EA) to give compound **108** (11 mg, 0.06 mmol, 28%) as a colorless oil.

108: R_f = 0.35 (EA); $[\alpha]_D^{20}$ = + 66.1 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 6.48 (br s, 1H), 5.80 (br s, 1H), 4.69 (dd, *J* = 10.5, 4.2 Hz, 1H), 4.33 (dd, *J* = 5.7, 1.0 Hz, 1H), 3.64 (s, 3H), 2.60 (ddd, *J* = 13.5, 10.5, 5.9 Hz, 1H), 2.45 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.22 (tdd, *J* = 5.8, 3.9, 0.6 Hz, 1H), 1.73 (dd, *J* = 3.9, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 175.67 (C_q), 170.73 (C_q), 80.68 (+), 67.23 (+), 51.95 (+), 31.34 (-), 27.93 (+), 26.25 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3443, 3229, 2959, 2919, 2855, 1711, 1681, 1439, 1399, 1327, 1303, 1274, 1171, 1114, 1078, 1023, 965, 927, 902, 869, 858, 726, 687, 622; MS (ESI): m/z (%) = 186.0 (10) [MH^+], 202.8 (20) [MNH_4^+], 227.0 (100) [MH^+MeCN]; HRMS (ESI): calcd for $C_8H_{11}NNaO_4$ [MNa^+] 208.0580, found 208.0576.

109: mp = 210 °C; $[\alpha]_D^{20}$ = + 27.6 (MeOH, c = 0.5); ^{1}H-NMR (300 MHz, MeOD): δ_H = 4.68 (dd, *J* = 10.5, 4.5 Hz, 1H), 4.24 (dd, *J* = 5.7, 1.0 Hz, 1H), 2.62 (ddd, *J* = 13.3, 10.5, 6.1 Hz, 1H), 2.26 (dd, *J* = 13.3, 4.5 Hz, 1H), 2.11 (m, 1H), 1.73 (dd, *J* = 3.8, 1.0 Hz, 1H); ^{13}C-NMR (75 MHz,

$CDCl_3$): δ_C = 178.75 (C_q), 174.92 (C_q), 82.03 (+), 67.88 (+), 32.74 (-), 30.39 (+), 26.11 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3360, 3306 (br), 2535, 2487, 2443, 2385, 1635, 1611, 1511, 1442, 1174, 1109, 1079, 1017, 961, 943, 861, 943, 861, 729, 687, 650; MS (ESI): m/z (%) = 171.0 (20) [MH^+], 188.0 (22) [MNH_4^+], 212.0 (100) [MH^+MeCN], 341.1 (30) [$2MH^+$]; HRMS (ESI): calcd for $C_7H_{11}N_2O_3$ [MH^+] 171.0764, found 171.0763.

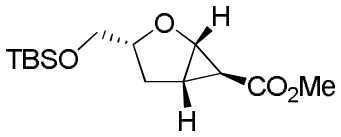
(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (110)



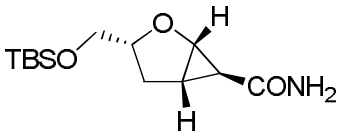
To a stirred solution of alcohol **79** (2.53 g, 13.6 mmol) in DCM (45 mL) under a nitrogen atmosphere anhydrous NEt_3 (2.8 mL, 20 mmol, 1.5 equiv), TBSCl (2.48 g, 16.5 mmol, 1.2 equiv) and DMAP (83 mg, 0.68 mmol, 0.05 equiv) was added successively. The reaction mixture was stirred for 18 h at room temperature and then quenched with a saturated aqueous NH_4Cl solution (40 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (PE/EA 5:1) afforded compound **110** (3.88 g, 12.9 mmol, 95%) as a colorless oil.

R_f = 0.52 (PE/EA 5:1); $[\alpha]_D^{20}$ = + 35.0 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.48 (ddt, *J* = 9.1, 7.0, 4.1 Hz, 1H), 4.13 (d, *J* = 5.9 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.54 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.45 (dd, *J* = 11.0, 4.2 Hz, 1H), 2.33 (ddd, *J* = 13.0, 9.2, 6.9 Hz, 1H), 2.21 - 2.11 (m, 1H), 1.91 (ddd, *J* = 13.0, 6.9, 0.8 Hz, 1H), 1.87 (dd, *J* = 3.9, 0.9 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 170.74 (+), 86.16 (+), 67.32 (+), 65.31 (-), 60.22 (-), 32.22 (+), 30.13 (-), 27.42 (+), 25.94 (+), 18.38 (C_q), 14.23 (+), -5.35 (+), -5.43 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2931, 2858, 1720, 1463, 1408, 1309, 1256, 1176, 1112, 1096, 1054, 979, 839, 778; MS (ESI): m/z (%) = 301.0 (100) [MH^+]; HRMS (EI): calcd for $C_{15}H_{28}SiO_4$ [$M^{+\bullet}$] 300.1757, found 300.1760.

(1*S*,3*R*,5*S*,6*S*)-methyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (111), (1*S*,3*R*,5*S*,6*S*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0] hexane-6-carboxamide (112)



111



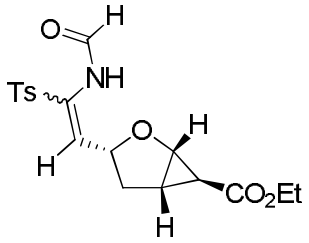
112

In a sealable pressure tube compound **110** (102 mg, 0.34 mmol) dissolved in a saturated solution of NH_3 in anhydrous MeOH (7 mL) was heated at 80 °C for 16 h. After cooling, the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EA 2:1, then EA) to give compound **111** (38 mg, 0.13 mmol, 39%) and compound **112** (51 mg, 0.19 mmol, 55%) as colorless oils.

111: R_f = 0.74 (EA); $[\alpha]_D^{20}$ = + 28.6 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.50 (ddt, *J* = 9.0, 7.1, 4.1 Hz, 1H), 4.15 (d, *J* = 5.9 Hz, 1H), 3.62 (s, 3H), 3.56 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.45 (dd, *J* = 11.1, 4.2 Hz, 1H), 2.34 (ddd, *J* = 13.0, 9.1, 6.9 Hz, 1H), 2.21 - 2.13 (m, 1H), 1.92 (ddd, *J* = 13.3, 7.2, 0.9 Hz, 1H), 1.88 (dd, *J* = 3.9, 0.9 Hz, 1H), 0.90 (s, *J* = 2.9 Hz, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 171.72 (C_q), 86.82 (+), 67.92 (+), 65.77 (-), 52.07 (+), 32.63 (+), 30.61 (-), 28.13 (+), 26.49 (+), 18.95 (C_q), -4.77 (+), -4.87 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2935, 2857, 1724, 1472, 1462, 1439, 1393, 1313, 1256, 1198, 1169, 1134, 1112, 1097, 1056, 980, 837, 778; MS (ESI): m/z (%) = 287.0 (100) [MH^+]; HRMS (ESI): calcd for $C_{14}H_{27}O_4Si$ [MH^+] 287.1673, found 287.1681.

112: R_f = 0.35 (EA); $[\alpha]_D^{20}$ = + 31.7 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.43 (br s, 2H), 4.51 (ddt, *J* = 9.0, 7.4, 3.8 Hz, 1H), 4.15 (d, *J* = 5.8 Hz, 1H), 3.59 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.46 (dd, *J* = 11.1, 4.1 Hz, 1H), 2.42 - 2.29 (m, 1H), 2.27 - 2.19 (m, 1H), 1.91 (ddd, *J* = 12.9, 7.2, 0.8 Hz, 1H), 1.68 (dd, *J* = 3.8, 0.7 Hz, 1H), 0.92 (s, *J* = 2.9 Hz, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 172.22 (C_q), 86.48 (+), 67.44 (+), 65.25 (-), 33.83 (+), 30.23 (-), 27.04 (+), 26.11 (+), 18.56 (C_q), -5.13 (+), -5.24 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3334 (br), 3194, 2952, 2928, 2857, 1660, 1617, 1434, 1361, 1254, 1176, 1125, 1092, 979, 837, 778; MS (ESI): m/z (%) = 287.0 (100) [MH^+]; HRMS (ESI): calcd for $C_{13}H_{26}NO_3Si$ [MH^+] 272.1676, found 272.1684.

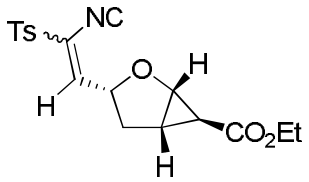
(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((*E*/*Z*)-2-formamido-2-tosylvinyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (113)



A stirred suspension of ^{t}BuOK (79 mg, 0.71 mmol, 1.3 equiv) in anhydrous DME (0.5 mL) was added to a solution of TosMIC (106 mg, 0.54 mmol, 1.0 equiv) in anhydrous DME (0.7 mL) at -35 °C under a nitrogen atmosphere. A solution of aldehyde **83** (100 mg, 0.54 mmol) in anhydrous DME (1 mL) was added dropwise to the mixture at the same temperature. After 30 min the mixture was poured into ice-water acidified by acetic acid (10 mL; pH <3) and extracted with DCM (2 x 10 mL). The organic layers were washed with water (1 x 10 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was separated by column chromatography (PE/EA 3:1 to 1:1) to give compound **113** (111 mg, 0.29 mmol, 54%) as a colorless foam.

Data for isomeric mixture: R_f = 0.54 (PE/EA 1:3); $[\alpha]_D^{20}$ = + 53.3 (DCM, c = 1.0); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 8.00 (s, 0.7H), 7.81 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 0.6H), 7.68 (d, *J* = 8.2 Hz, 1.4H), 7.46 (d, *J* = 10.3 Hz, 0.3H), 7.33 (d, *J* = 8.2 Hz, 0.6H), 7.29 (d, *J* = 8.2 Hz, 1.4H), 6.71 (d, *J* = 7.1 Hz, 0.7H), 6.61 (d, *J* = 7.8 Hz, 0.3H), 5.09 - 4.96 (m, 1H), 4.21 (d, *J* = 5.8 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.69 - 2.53 (m, 1H), 2.42 (s, 0.9H), 2.39 (s, 2.1H), 2.27 (dd, *J* = 9.6, 5.4 Hz, 0.3H), 2.20 (dd, *J* = 9.7, 5.7 Hz, 0.7H), 1.91 (dd, *J* = 13.5, 6.5 Hz, 1H), 1.72 (d, *J* = 3.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$, major isomer labeled with *): δ_C = 170.31* (C_q), 169.88 (C_q), 163.50 (+), 158.50* (+), 145.97 (C_q), 145.50* (C_q), 138.05* (+), 137.21 (C_q), 134.53 (+), 134.30* (C_q), 133.68 (C_q), 132.48* (C_q), 130.46 (+), 130.16* (+), 128.66 (+), 128.24* (+), 80.51* (+), 79.53 (+), 67.39* (+), 67.32 (+), 60.82 (-), 60.70* (-), 35.49 (-), 33.92* (-), 32.81 (+), 31.86* (+), 27.05 (+), 26.73* (+), 21.76* (+), 21.76 (+), 14.30* (+), 14.30 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3287 (br), 2981, 1712, 1658, 1597, 1494, 1409, 1321, 1181, 1149, 1100, 1089, 1067, 970, 850 658, 582; MS (ESI): m/z (%) = 397.1 (100) [MNH_4^+]; HRMS (ESI): calcd for $C_{18}H_{25}N_2O_6S$ [MNH_4^+] 397.1428, found 397.1429.

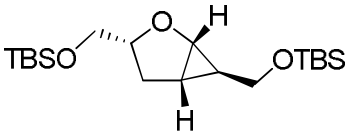
(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((*E*/*Z*)-2-isocyano-2-tosylvinyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (114)



To a stirred solution of **113** (86 mg, 0.24 mmol) in anhydrous DME (3.2 ml) at -5 °C under a nitrogen atmosphere NEt_3 (114 mg, 1.13 mmol, 4.7 equiv) was added in one portion, followed by slow addition of $POCl_3$ (54 mg, 0.35 mmol, 1.5 equiv) in anhydrous DME (1 ml) at -10 °C. After stirring for 30 min at 0°C, the mixture was poured into ice-water (10 mL), immediately extracted with DCM (2 x 10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue (110 mg) was separated from polar compounds by fast column chromatography (PE/EA 2:1) to give crude **114** (40 mg, 0.11 mmol, 48%).

Data for isomeric mixture: R_f = 0.66, 0.65 (PE/EA 1:1); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2133 (N=C), 1718 (C=O); MS (ESI): m/z (%) = 362.0 (100) [MH^+], 379.0 (65) [MH_4^+]; HRMS (ESI): calcd for $C_{18}H_{20}NO_5S$ [MH^+] 362.1057, found 362.1054.

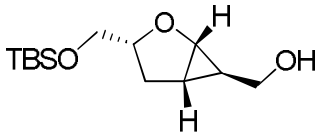
(1*S*,3*R*,5*S*,6*R*)-2-oxabicyclo[3.1.0]hexane-3,6-diylbis(methylene)bis(oxy)bis(*tert*-butyl-dimethylsilane) (115)



Compound **115** was obtained as a colorless oil in 5% yield when crude product of the LAH-reduction of diester **78** was used in the protecting reaction without separation of dialcohol **80** from monoalcohol **79**.

R_f = 0.33 (PE/EA 19:1); $[\alpha]_D^{20}$ = + 26.4 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.43 (tt, *J* = 7.9, 4.9 Hz, 1H), 3.72 (dd, *J* = 6.3, 1.2 Hz, 1H), 3.48 (d, *J* = 4.9 Hz, 2H), 3.44 (dd, *J* = 11.1, 6.2 Hz, 1H), 3.34 (dd, *J* = 11.1, 6.4 Hz, 1H), 2.23 (ddd, *J* = 12.7, 8.2, 7.3 Hz, 1H), 1.69 (ddd, *J* = 12.7, 7.6, 1.5 Hz, 1H), 1.53 - 1.42 (m, 1H), 1.14 - 1.04 (m, 1H), 0.87 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H), 0.01 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 87.79 (+), 66.16 (-), 64.45 (+), 62.43 (-), 34.54 (+), 31.71 (-), 26.09 (+), 26.04 (+), 21.76 (+), 18.52 (C_q), 18.43 (C_q), -5.08 (+), -5.13 (+), -5.19 (+), -5.21 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2929, 2884, 2857, 1472, 1463, 1413, 1389, 1361, 1253, 1179, 1132, 1083, 1006, 939, 831, 813, 773, 666; MS (ESI): m/z (%) = 241.0 (100) [$MH^+\Delta C_6H_{16}OSi$], 373.1 (2) [MH^+], 390.1 (50) [MNH_4^+]; HRMS (ESI): calcd for $C_{19}H_{41}O_3Si_2$ [MH^+] 373.2589, found 373.2586.

((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methanol (116)

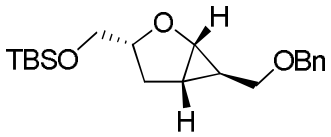


To a stirred ice-cooled solution of **110** (3.88 mg, 12.9 mmol) in anhydrous THF (50 mL) under a nitrogen atmosphere, a suspension of LAH (412 mg, 10.9 mmol, 0.84 equiv) in anhydrous THF (5 mL) was added dropwise within 10 min. The reaction mixture was stirred for 45 min at 0 °C. After dropwise addition of water (0.41 mL) the mixture was stirred for another 30 min. Then a 15% aqueous NaOH solution (0.41 mL) was added followed by water (1.24 mL). The mixture was warmed to room temperature, treated with $MgSO_4$ and filtered through a Celite pad. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EA 3:1, then 1:1) to obtain compound **116** (3.17 g, 12.3 mmol, 95%) as a colorless oil.

R_f = 0.30 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 44.6 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.43 (tt, *J* = 7.9, 4.9 Hz, 1H), 3.73 (dd, *J* = 6.3, 1.1 Hz, 1H), 3.46 (d, *J* = 4.9 Hz, 2H), 3.37 - 3.21 (m, 2H), 2.23 (ddd, *J* = 12.8, 8.3, 7.2 Hz, 1H), 2.21 (br s, 1H), 1.68 (ddd, *J* = 12.8, 7.6, 1.5 Hz, 1H), 1.51 - 1.43 (m, 1H), 1.21 - 1.13 (m, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C =

87.94 (+), 66.01 (-), 64.33 (+), 62.32 (-), 34.78 (+), 31.54 (-), 26.01 (+), 21.98 (+), 18.45 (C_q), -5.25 (+), -5.27 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3386 (br), 2953, 2929, 2858, 1463, 1410, 1254, 1130, 1095, 1023, 837, 777, 669; MS (ESI): m/z (%) = 241.0 (78) [$MH^+\Delta H_2O$], 259.0 (55) [MH^+], 276.1 (20) [MNH_4^+], 300.0 (100) [MH^+MeCN], 481.2 (35) [$2MH^+\Delta 2H_2O$], 499.2 (85) [$2MH^+\Delta H_2O$], 517.2 (50) [$2MH^+$]; HRMS (ESI): calcd for $C_{13}H_{27}O_3Si$ [MH^+] 259.1724, found 259.1731.

(((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(*tert*-butyl)-dimethylsilane (117)

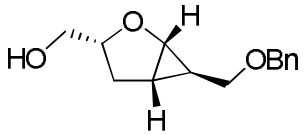


To a solution of alcohol **116** (1.00 g, 3.87 mmol) in anhydrous DMF (25 mL), NaH (309 mg, 60 wt% in mineral oil, 7.74 mmol, 2.0 equiv) was added in one portion at 0 °C under a nitrogen atmosphere. The resulting suspension was stirred at 0 °C for 10 min, then benzyl bromide (919 µL, 7.74 mmol, 2.0 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. MeOH (5 mL) was added carefully to quench the reaction. The solvent was evaporated under reduced pressure. The residue was diluted in DCM and washed with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with DCM (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE/EA 9:1) to obtain compound **117** (1.14 g, 3.28 mmol, 85%) as a colorless oil.

R_f = 0.22 (PE/EA 9:1), 0.53 (PE/EA 3:1); $[\alpha]_D^{20}$ = + 22.5 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.38 - 7.22 (m, 5H), 4.46 (ddd, *J* = 9.8, 8.1, 4.9 Hz, 3H), 3.75 (dd, *J* = 6.2, 1.1 Hz, 1H), 3.50 (d, *J* = 5.0 Hz, 2H), 3.35 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.09 (dd, *J* = 10.6, 7.6 Hz, 1H), 2.27 (ddd, *J* = 12.8, 8.3, 7.2 Hz, 1H), 1.74 (ddd, *J* = 12.8, 7.5, 1.5 Hz, 1H), 1.61 - 1.45 (m, 1H), 1.23 (dddd, *J* = 7.7, 6.7, 4.0, 1.2 Hz, 1H), 0.90 (s, *J* = 2.9 Hz, 9H), 0.06 (d, *J* = 1.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 138.50 (C_q), 128.49 (+), 127.75 (+), 127.68 (+), 87.80 (+), 72.50 (-), 69.61 (-), 66.20 (-), 64.62 (+), 31.99 (+), 31.66 (-), 26.10 (+), 22.45 (+), 18.54 (C_q), -5.18 (+); IR (ATR):

$\tilde{\nu}$ (cm^{-1}) = 3038, 2932, 2858, 1461, 1380, 1254, 1182, 1132, 1091, 1009, 840, 778, 738, 697; MS (ESI): m/z (%) = 241.1 (100) [$M^+\Delta C_7H_7O$], 349.1 (15) [MH^+], 366.1 (65) [MNH_4^+], 714.5 (20) [$2MNH_4^+$]; HRMS (ESI): calcd for $C_{20}H_{33}O_3Si$ [MH^+] 349.2193, found 349.2197.

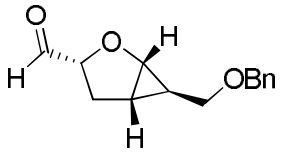
((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (118)



To a solution of compound **117** (3.03 mg, 8.69 mmol) in anhydrous THF (60 mL) a solution of TBAF•$3H_2O$ (4.11 mg, 13.0 mmol, 1.5 equiv) in anhydrous THF (30 mL) was added and stirred for 13 h at room temperature. After evaporating the solvent the crude product was purified by column chromatography (EA) to give **118** (1.94 mg, 8.28 mmol, 95%) as a colorless oil.

R_f = 0.42 (EA); $[\alpha]_D^{20}$ = + 47.2 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.39 - 7.23 (m, 5H), 4.59 - 4.49 (m, 1H), 4.48 (d, *J* = 2.2 Hz, 2H), 3.78 (dd, *J* = 6.2, 1.1 Hz, 1H), 3.56 (ddd, *J* = 11.4, 5.4, 3.2 Hz, 1H), 3.42 - 3.31 (m, 1H), 3.26 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.16 (dd, *J* = 10.5, 7.1 Hz, 1H), 2.26 (ddd, *J* = 12.8, 8.1, 7.3 Hz, 1H), 2.07 (br s, 1H), 1.69 (ddd, *J* = 12.8, 8.0, 1.6 Hz, 1H), 1.55 (dddd, *J* = 7.6, 6.0, 4.0, 1.6 Hz, 1H), 1.20 (tdd, *J* = 7.1, 4.0, 1.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 138.35 (C_q), 128.51 (+), 127.78 (+), 127.74 (+), 88.08 (+), 72.67 (-), 69.47 (-), 65.36 (-), 64.71 (+), 32.57 (+), 31.17 (-), 22.51 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3421 (br), 3027, 2924, 2862, 1497, 1454, 1414, 1360, 1180, 1087, 1071, 1028, 987, 844, 810, 739, 698, 614; MS (ESI): m/z (%) = 235.0 (5) [MH^+], 469.0 (25) [$2MH^+$], 486.1 (75) [$2MH_4^+$], 491.1 (100) [$2MNa^+$]; HRMS (ESI): calcd for $C_{14}H_{18}NaO_3$ [MNa^+] 257.1148, found 257.1153.

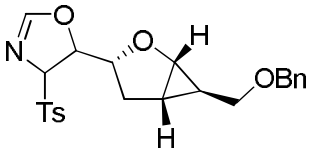
(1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexane-3-carbaldehyde (119)



To a stirred solution of alcohol **118** (4.35 g, 18.6 mmol) in DCM (150 mL) was added in one portion Dess-Martin periodinane (8.66 g, 20.4 mmol, 1.1 equiv) at room temperature. After 2 h saturated aqueous $NaHCO_3$ (60 mL) and saturated aqueous $Na_2S_2O_3$ (60 mL) were added. The mixture was stirred for another 15 min. After completion the reaction was quenched with a mixture of saturated aqueous $Na_2S_2O_3$ solution (60 mL) and saturated aqueous $NaHCO_3$ solution (60 mL). The mixture was stirred for 15 min, then the organic layer was separated and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by column chromatography (PE/EA 1:1) afforded compound **119** (3.87 g, 16.7 mmol, 90%) as a colorless oil.

R_f = 0.31 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 57.5 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 9.57 (d, *J* = 0.8 Hz, 1H), 7.39 - 7.21 (m, 5H), 4.58 (ddd, *J* = 10.2, 3.9, 0.7 Hz, 1H), 4.47 (d, *J* = 1.1 Hz, 2H), 3.95 (dd, *J* = 5.9, 1.3 Hz, 1H), 3.30 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.17 (dd, *J* = 10.5, 7.1 Hz, 1H), 2.40 (ddd, *J* = 13.0, 10.3, 5.9 Hz, 1H), 2.26 (ddd, *J* = 13.0, 4.0, 0.6 Hz, 1H), 1.53 (tdd, *J* = 5.8, 4.0, 0.6 Hz, 1H), 0.97 (tdd, *J* = 6.9, 3.9, 1.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 204.38 (+), 138.19 (Cq), 128.54 (+), 127.81 (+), 127.77 (+), 86.02 (+), 72.77 (-), 69.06 (-), 64.86 (+), 31.08 (-), 25.84 (+), 20.30 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3031, 2942, 2860, 1730, 1497, 1455, 1422, 1362, 1091, 1076, 1030, 988, 738, 699; MS (EI): m/z (%) = 91.1 (100) [$C_7H_7^+$], 231.1 (<1) [$M^{\bullet}\Delta H^+$]; HRMS (ESI): calcd for $C_{14}H_{20}NO_3$ [MNH_4^+] 250.1438, found 250.1439.

5-((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-4-tosyl-4,5-dihydro-oxazole (120)



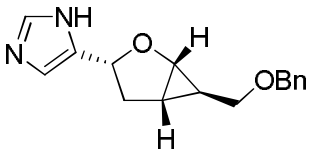
Finely powdered NaCN (28 mg, 0.57 mmol, 0.22 equiv) was added in one portion to a stirred solution of TosMIC (555 mg, 2.84 mmol, 1.1 equiv) and aldehyde **119** (600 mg, 2.58 mmol) in anhydrous EtOH (25 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 2 h. The solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with $CHCl_3$ (2 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EA 1:1) afforded a 3:2 diastereomeric mixture of compound **120** (854 mg, 2.00 mmol, 77%) as yellowish foam.

Major: R_f = 0.41 (PE/EA 1:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.81 (d, *J* = 8.3 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.34 - 7.20 (m, 5H), 7.00 - 6.96 (m, 1H), 4.94 - 4.91 (m, 1H), 4.92 - 4.89 (m, 1H), 4.62 - 4.52 (m, 1H), 4.51 - 4.45 (m, 2H), 3.79 (dd, *J* = 6.2, 0.9 Hz, 1H), 3.31 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.11 (dd, *J* = 10.5, 7.3 Hz, 1H), 2.44 (s, 3H), 2.40 - 2.20 (m, 1H), 1.81 (ddd, *J* = 13.3, 8.8, 1.3 Hz, 1H), 1.65 - 1.53 (m, 1H), 1.30 - 1.18 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 159.28 (+), 145.62 (C_q), 138.15 (C_q), 133.09 (C_q), 129.89 (+), 129.60 (+), 128.47 (+), 127.75 (+), 127.71 (+), 86.80 (+), 86.36 (+), 79.63 (+), 72.70 (-), 69.00 (-), 64.69 (+), 33.03 (+), 30.85 (-), 22.12 (+), 21.79 (+);

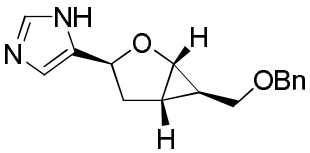
minor: R_f = 0.41 (PE/EA 1:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.80 (d, *J* = 8.3 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.34 - 7.20 (m, 5H), 7.00 - 6.96 (m, 1H), 4.98 (dd, *J* = 6.2, 1.7 Hz, 1H), 4.84 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.58 - 4.50 (m, 1H), 4.47 - 4.42 (m, 2H), 3.76 (dd, *J* = 6.3, 0.8 Hz, 1H), 3.26 (dd, *J* = 10.5, 6.8 Hz, 1H), 3.14 (dd, *J* = 10.5, 7.2 Hz, 1H), 2.44 (s, 3H), 2.43 - 2.33 (m, 1H), 2.01 (ddd, *J* = 13.0, 8.4, 1.6 Hz, 1H), 1.65 - 1.53 (m, 1H), 1.30 - 1.18 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 159.35 (+), 145.62 (C_q), 138.19 (C_q), 133.09 (C_q), 129.89 (+), 129.52 (+), 128.45 (+), 127.75 (+), 127.71 (+), 87.66 (+), 87.31 (+), 79.13 (+), 72.63 (-), 69.04 (-), 64.92 (+), 32.83 (+), 31.19 (-), 22.12 (+), 21.79 (+);

Data for isomeric mixture: IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3033, 2948, 2861, 1616, 1597, 1486, 1455, 1362, 1319, 1304, 1292, 1148, 1108, 1086, 1071, 1028, 939, 848, 813, 739, 700, 664, 651, 587, 533.

5-((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole (121a), 5-((1*S*,3*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole (121b)



121a



121b

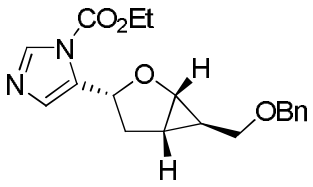
In a sealable pressure tube oxazoline **120** (1.70 g, 3.98 mmol) and a saturated solution of NH_3 in anhydrous MeOH (40 mL, 70 equiv) was heated at 95 °C for 16 h. Within this time the solution turned red. After cooling, the solvent was removed under reduced pressure. The residue was purified by column chromatography (DCM/saturated NH_3 in MeOH 9:1) to give an epimeric mixture of compound **121a** and **121b** (726 mg, 2.69 mmol, 68%) as a colorless oil.

121A: R_f = 0.22 (DCM/saturated NH_3 in MeOH 9:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.28 (br s, 1H), 7.48 (s, 1H), 7.38 - 7.22 (m, 5H), 6.83 (s, 1H), 5.42 (t, *J* = 7.5 Hz, 1H), 4.47 (d, *J* = 1.7 Hz, 2H), 3.86 (dd, *J* = 6.2, 1.2 Hz, 1H), 3.29 - 3.15 (m, 2H), 2.64 - 2.51 (m, 1H), 2.15 (ddd, *J* = 12.8, 7.0, 1.4 Hz, 1H), 1.66 - 1.57 (m, 1H), 1.45 - 1.34 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 139.57 (C_q), 138.27 (C_q), 135.36 (+), 128.54 (+), 127.87 (+), 127.80 (+), 116.10 (+), 81.53 (+), 72.69 (-), 69.71 (-), 64.45 (+), 35.21 (-), 30.89 (+), 22.67 (+).

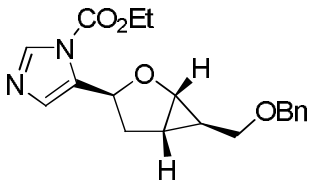
121b: R_f = 0.22 (DCM/saturated NH_3 in MeOH 9:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.28 (br s, 1H), 7.55 (s, 1H), 7.38 - 7.22 (m, 5H), 6.90 (s, 1H), 4.76 (t, *J* = 8.2 Hz, 1H), 4.50 (d, *J* = 2.6 Hz, 2H), 3.90 - 3.78 (m, 1H), 3.42 - 3.31 (m, 1H), 3.23 - 3.11 (m, 1H), 2.38 - 2.23 (m, 2H), 1.59 - 1.48 (m, 1H), 1.19 - 1.05 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 138.22 (C_q), 137.81 (C_q), 135.62 (+), 128.54 (+), 127.86 (+), 127.80 (+), 115.90 (+), 74.14 (+), 72.72 (-), 69.90 (-), 62.56 (+), 34.54 (-), 21.40 (+), 20.80 (+).

Data for isomeric mixture: IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3090 (br), 2936, 2858, 1716, 1670, 1496, 1453, 1362, 1313, 1273, 1087, 1071, 1027, 839, 738, 698, 626; MS (ESI): m/z (%) = 271.0 (100) [MH^+], 312.1 (30) [MH^+MeCN], 541.2 (40) [$2MH^+$]; HRMS (ESI): calcd for $C_{16}H_{19}N_2O_2$ [MH^+] 271.1441, found 271.1446;

ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (131a), ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (131b)



131a



131b

A solution of an epimeric mixture of imidazole **121** (1.10 mg, 4.06 mmol), ethyl chloroformate (733 µL, 7.72 mmol, 1.9 equiv), anhydrous pyridine (623 µL, 7.72 mmol, 1.9 equiv) and DMAP (79 mg, 0.65 mmol, 0.16 equiv) in benzene (80 mL) was stirred for 10 min at 50 °C. After addition of water (5 mL), the solvent was evaporated. A saturated aqueous NH_4Cl solution (50 mL) was added und extracted with DCM (3 x 25 mL). The extract was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residual oil was purified by column chromatography (PE/EA 1:1) to give an epimeric mixture of compound **131a** and **131b** (1.01 g, 2.95 mmol, 73%) as a colorless oil.

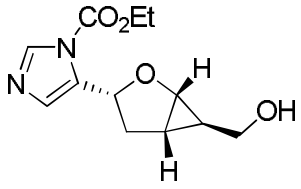
131a: R_f = 0.26 (PE/EA 1:1); ^{1}H-NMR (300 MHz, $CDCl_3$): $[\alpha]_D^{20}$ = - 15.2 (DCM, c = 1.0); δ_H = 8.06 (d, *J* = 1.3 Hz, 1H), 7.37 - 7.27 (m, 5H), 7.28 (t, *J* = 1.2 Hz, 1H), 5.38 (ddd, *J* = 8.4, 6.7, 0.9 Hz, 1H), 4.48 (d, *J* = 3.8 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.88 (dd, *J* = 6.1, 1.2 Hz, 1H), 3.33 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.13 (dd, *J* = 10.6, 7.4 Hz, 1H), 2.61 (ddd, *J* = 12.8, 8.6, 6.9 Hz, 1H), 2.15 (ddd, *J* = 12.8, 6.7, 1.4 Hz, 1H), 1.67 - 1.57 (m, 1H), 1.47 - 1.39 (m, 1H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 148.63 (C_q), 145.81 (C_q), 138.32 (C_q), 137.17 (+), 128.41 (+),

127.70 (+), 127.26 (+), 113.26 (+), 81.75 (+), 72.52 (-), 69.50 (-), 64.68 (+), 64.45 (-), 43.88 (-), 30.63 (+), 22.66 (+), 14.21 (+);

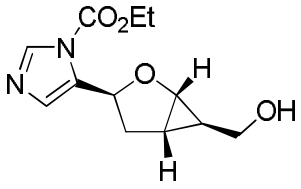
131b: R_f = 0.24 (PE/EA 1:1), 0.54 (EA); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.07 (d, *J* = 1.3 Hz, 1H), 7.35 - 7.26 (m, 5H), 7.33 - 7.31 (m, 1H), 4.72 (dd, *J* = 8.8, 7.4 Hz, 1H), 4.49 (d, *J* = 3.1 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.91 (dd, *J* = 5.5, 1.6 Hz, 1H), 3.38 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.13 (dd, *J* = 10.5, 7.5 Hz, 2H), 2.35 (dd, *J* = 12.3, 7.3 Hz, 1H), 2.24 (ddd, *J* = 12.4, 9.0, 5.0 Hz, 1H), 1.59 - 1.50 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 148.58 (C_q), 143.45 (C_q), 138.34 (C_q), 137.26 (+), 128.44 (+), 127.72 (+), 127.67 (+), 113.85 (+), 74.88 (+), 72.58 (-), 69.71 (-), 64.49 (-), 62.91 (+), 34.52 (-), 22.14 (+), 20.86 (+), 14.21 (+);

Data for isomeric mixture: IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3032, 2937, 2859, 1759, 1482, 1454, 1409, 1388, 1336, 1252, 1207, 1093, 1069, 1019, 843, 769, 740, 699, 607; MS (ESI): m/z (%) = 342.9 (100) [MH^+]; HRMS (ESI): calcd for $C_{19}H_{23}N_2O_4$ [MH^+] 343.1652, found 343.1656.

ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (132a) ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (132b)



132a



132b

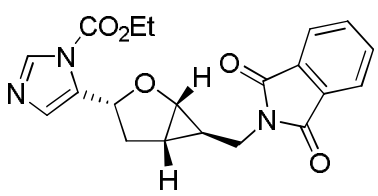
A epimeric mixture of compound **131** (134 mg, 0.39 mmol), $Pd(OH)_2$/C (20%, 95 mg) and cyclohexene (1.6 mL, 16 mmol, 40 equiv) in anhydrous EtOH (15 mL) was refluxed for 1 h. After filtration through a Celite pad the solvent was evaporated. The residue was purified by column chromatography (EA, then EA/MeOH 19:1) to afford an epimeric mixture of alcohol **132a** and **132b** (72 mg, 0.29 mmol, 73%) as a colorless foam.

132a: R_f = 0.38 (EA/MeOH 19:1); $[\alpha]_D^{20}$ = - 4.6 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.06 (d, *J* = 1.3 Hz, 1H), 7.29 (m, 1H), 5.38 (ddd, *J* = 8.5, 6.6, 0.9 Hz, 1H), 4.45 (q, *J* = 7.1 Hz,

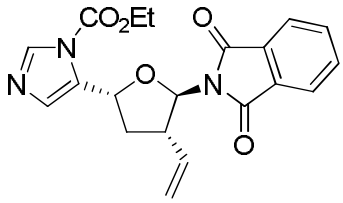
2H), 3.90 (dd, *J* = 6.2, 1.3 Hz, 1H), 3.40 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.33 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.61 (ddd, *J* = 12.8, 8.6, 6.9 Hz, 1H), 2.16 (ddd, *J* = 12.8, 6.7, 1.5 Hz, 1H), 1.75 (br s, 1H), 1.62 (tdd, *J* = 6.8, 4.0, 1.5 Hz, 1H), 1.50 - 1.43 (m, 1H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 148.69 (C_q), 145.65 (C_q), 137.31 (+), 113.54 (+), 81.81 (+), 64.60 (-), 64.51 (+), 62.61 (-), 34.83 (-), 33.45 (+), 22.44 (+), 14.30 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3373 (br), 2982, 2943, 2876, 1758, 1489, 1409, 1336, 1253, 1176, 1103, 1068, 1018, 847, 768, 606; MS (ESI): m/z (%) = 252.9 (40) [MH^+], 294.0 (15) [MH^+MeCN], 505.1 (100) [$2MH^+$]; HRMS (ESI): calcd for $C_{12}H_{17}N_2O_4$ [MH^+] 253.1183, found 253.1190.

132b: R_f = 0.36 (EA/MeOH 19:1); $[\alpha]_D^{20}$ = + 10.5 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.05 (d, *J* = 1.2 Hz, 1H), 7.32 - 7.29 (m, 1H), 4.70 (dd, *J* = 8.6, 7.5 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.91 (dd, *J* = 5.5, 1.6 Hz, 1H), 3.41 (dd, *J* = 11.5, 6.8 Hz, 1H), 3.32 (dd, *J* = 11.5, 7.1 Hz, 1H), 2.32 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.21 (ddd, *J* = 12.4, 9.0, 5.0 Hz, 1H), 1.58 - 1.47 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 148.66 (C_q), 143.43 (C_q), 137.38 (+), 113.98 (+), 75.10 (+), 64.64 (-), 62.86 (-), 62.42 (+), 34.59 (-), 24.90 (+), 20.54 (+), 14.30 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3349 (br), 2939, 2869, 1760, 1487, 1409, 1342, 1254, 1123, 1018, 852, 768, 607; MS (ESI): m/z (%) = 252.8 (100) [MH^+], 505.1 (30) [$2MH^+$]; HRMS (ESI): calcd for $C_{12}H_{17}N_2O_4$ [MH^+] 253.1183, found 253.1188.

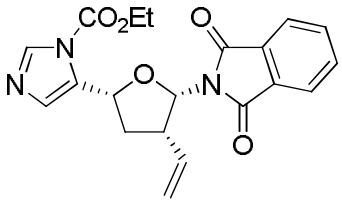
ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (133), ethyl 5-((2*R*,4*S*,5*R*)-5-(1,3-dioxoisoindolin-2-yl)-4-vinyltetrahydrofuran-2-yl)-1*H*-imidazole-1-carboxylate (135a), ethyl 5-((2*R*,4*S*,5*S*)-5-(1,3-dioxoisoindolin-2-yl)-4-vinyltetrahydrofuran-2-yl)-1*H*-imidazole-1-carboxylate (135b)



133



135a



135b

DIAD (211 mg, 0.98 mmol, 1.5 equiv) was added to a solution PPh_3 (257 mg, 0.98 mmol, 1.5 equiv) in anhydrous THF (7 mL) at room temperature under a nitrogen atmosphere. After stirring for 10 min phthalimide (144 mg, 0.98 mmol, 1.5 equiv) was added and stirred for

another 10 min. After addition of alcohol **132a** (165 mg, 0.65 mmol) in THF the reaction mixture was stirred overnight. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (PE/EA 5:1 to EA) to obtain **135a** (126 mg, 0.33 mmol, 51%), **135b** (25 mg, 0.07 mmol, 10%) and **133** (72 mg, 0.19 mmol, 29%) as colorless oils.

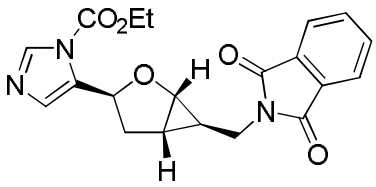
135a: R_f = 0.37 (PE/EA 1:1); $[\alpha]_D^{20}$ = - 23.6 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.10 (d, *J* = 1.2 Hz, 1H), 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.40 (dd, *J* = 1.3, 0.7 Hz, 1H), 5.93 (d, *J* = 7.5 Hz, 1H), 5.86 (ddd, *J* = 17.1, 10.3, 8.0 Hz, 1H), 5.50 (dd, *J* = 10.6, 4.9 Hz, 1H), 5.13 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.10 - 5.04 (m, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.01 - 3.85 (m, 1H), 2.65 (ddd, *J* = 12.2, 7.2, 5.0 Hz, 1H), 2.24 (dt, *J* = 12.2, 11.3 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 167.92 (C_q), 148.63 (C_q), 143.33 (C_q), 137.37 (+), 136.39 (+), 134.37 (+), 132.02 (C_q), 123.60 (+), 117.58 (-), 114.40 (+), 85.06 (+), 76.33 (+), 64.59 (-), 46.68 (+), 39.34 (-), 14.27 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2985, 2927, 2853, 1760, 1716, 1468, 1410, 1367, 1332, 1252, 1210, 1084, 1019 977, 919, 891, 845, 769, 736, 721, 655, 611, 531; MS (ESI): m/z (%) = 381.9 (100) [MH^+], 422.9 (45) [MH^+MeCN], 763.2 (90) [$2MH^+$]; HRMS (ESI): calcd for $C_{20}H_{20}N_3O_5$ [MH^+] 382.1375, found 382.1365.

135b: R_f = 0.33 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 73.6 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.09 (d, *J* = 1.3 Hz, 1H), 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.61 - 7.53 (m, 1H), 6.21 (d, *J* = 8.6 Hz, 1H), 5.69 (ddd, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.11 - 5.04 (m, 1H), 5.06 - 5.00 (m, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.56 - 3.41 (m, 1H), 2.93 - 2.77 (m, 1H), 2.51 - 2.40 (m, 1H), 1.42 (t, *J* = 7.1 Hz, 3H).; ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 167.77 (C_q), 148.78 (C_q), 143.44 (C_q), 136.78 (+), 134.30 (+), 133.84 (+), 131.98 (C_q), 123.61 (+), 118.82 (-), 114.31 (+), 82.69 (+), 77.63 (+), 64.53 (-), 47.93 (+), 36.93 (-), 14.33 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2985, 2955, 2925, 1762, 1720, 1468, 1410, 1364, 1326, 1258, 1228, 1113, 1090, 1018, 901, 838, 792, 770, 722, 604, 530; MS (ESI): m/z (%) = 381.9 (100) [MH^+], 763.2 (10) [$2MH^+$]; HRMS (ESI): calcd for $C_{20}H_{20}N_3O_5$ [MH^+] 382.1397, found 382.1403.

133: R_f = 0.27 (PE/EA 1:1); $[\alpha]_D^{20}$ = - 12.4 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 8.03 (d, *J* = 1.2 Hz, 1H), 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.24 (t, *J* = 1.0 Hz, 1H), 5.36 (t, *J* = 7.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.05 (dd, *J* = 6.2, 0.9 Hz, 1H), 3.51 (dd, *J* = 14.3, 7.1 Hz, 1H), 3.38 (dd, *J* = 14.3, 8.2 Hz, 1H), 2.59 (ddd, *J* = 12.9, 8.4, 7.1 Hz, 1H), 2.07

(ddd, *J* = 12.7, 7.2, 1.6 Hz, 1H), 1.76 (ddd, *J* = 7.0, 3.9, 1.5 Hz, 1H), 1.57 - 1.48 (m, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.30 - 1.20 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 168.45 (C_q), 148.65 (C_q), 145.26 (C_q), 137.27 (+), 134.06 (C_q), 132.31 (+), 123.37 (+), 113.43 (+), 82.36 (+), 65.09 (+), 64.54 (-), 38.00 (-), 35.03 (-), 30.67 (+), 23.63 (+), 14.28 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2977, 2931, 1760, 1711, 1467, 1433, 1409, 1391, 1357, 1336, 1253, 1211, 1137, 1102, 1019, 950, 846, 769, 721, 614, 530; MS (ESI): m/z (%) = 381.9 (100) [MH^+], 763.3 (75) [$2MH^+$]; HRMS (ESI): calcd for $C_{20}H_{20}N_3O_5$ [MH^+] 382.1397, found 382.1396.

ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (137)

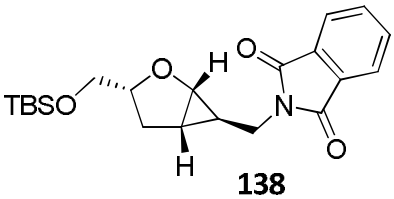


DIAD (54 mg, 0.25 mmol, 1.5 equiv) was added to a solution PPh_3 (65.5 mg, 0.25 mmol, 1.5 equiv) in anhydrous THF (1.3 mL) at room temperature under a nitrogen atmosphere. After stirring for 10 min phthalimide (37 mg, 0.25 mmol, 1.5 equiv) was added and stirred for another 10 min. After addition of alcohol **132b** (42 mg, 0.17 mmol) the reaction mixture was stirred for 18 h. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (PE/EA 3:1 to 1:1) to obtain compound **137** (17 mg, 0.04 mmol, 27%) as a colorless oil.

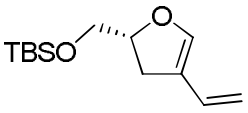
R_f = 0.43 (PE/EA 1:3); $[\alpha]_D^{20}$ = + 17.1 (DCM, c = 0.2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 8.07 (d, *J* = 1.3 Hz, 1H), 7.90 - 7.82 (m, 2H), 7.76 - 7.67 (m, 2H), 7.30 (s, 1H), 4.68 (t, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.11 (dd, *J* = 5.7, 1.2 Hz, 1H), 3.54 (dd, *J* = 14.2, 6.9 Hz, 1H), 3.42 (dd, *J* = 14.3, 7.8 Hz, 1H), 2.36 - 2.19 (m, 2H), 1.73 - 1.62 (m, 1H), 1.48 - 1.38 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ_C = 168.50 (C_q), 148.68 (C_q), 143.44 (C_q), 137.38 (+), 134.12 (+), 132.33 (C_q), 123.43 (+), 113.93 (+), 75.15 (+), 64.59 (-), 63.38 (+), 38.09 (-), 34.48 (-), 21.89 (+), 21.56 (+), 14.30 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978, 2936, 2873, 1758, 1707, 1467,

1391, 1336, 1251, 1139, 1087, 1017, 944, 850, 769, 721, 611, 541, 501; MS (ESI): m/z (%) = 381.9 (100) [MH^+], 763.3 (10) [$2MH^+$]; HRMS (ESI): calcd for $C_{20}H_{20}N_3O_5$ [MH^+] 382.1397, found 382.1405.

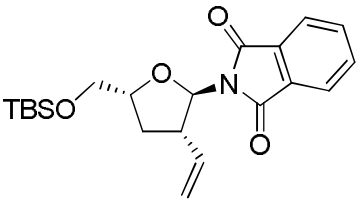
2-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methyl)isoindoline-1,3-dione (138), (*R*)-*tert*-butyldimethyl((4-vinyl-2,3-dihydrofuran-2-yl)methoxy)silane (153), 2-((2*R*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)isoindoline-1,3-dione (154a), 2-((2*S*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)-methyl)-3-vinyltetrahydrofuran-2-yl)isoindoline-1,3-dione (154b)



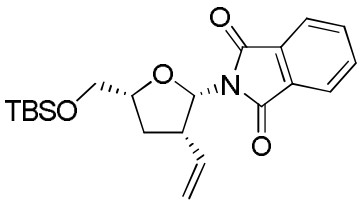
138



153



154a



154b

DIAD (1.58 g, 8.72 mmol, 1.5 eq) was added dropwise to a solution of alcohol **116** (1.50 g, 5.82 mmol), PPh_3 (2.29 g, 8.72 mmol, 1.5 equiv) and phthalimide (1.28 mg, 8.72 mmol, 1.5 equiv) in anhydrous THF (116 mL) at 50 °C. After stirring at 50 °C for 1 h the mixture was cooled to room temperature quenched with water (50 mL). The phases were separated and the organic layer was extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EA 9:1, then 5:1) to obtain compound **153** (100 mg, 0.42 mmol, 7%) as a colorless oil and compound **154b** (115 mg, 0.30 mmol, 5%), compound **154a** (1.04 g, 2.67 mmol, 46%) and compound **138** (665 mg, 1.72 mmol, 29%) as colorless solids.

153: R_f = 0.77 (PE/EA 5:1), 0.59 (PE/EA 9:1); $[\alpha]_D^{20}$ = - 125.8 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 6.46 (ddd, *J* = 18.0, 11.0, 0.6 Hz, 1H), 6.41 (m, 1H), 4.85 (dd, *J* = 10.7, 1.1 Hz, 1H), 4.85 - 4.76 (m, 1H), 4.70 (dddd, *J* = 10.5, 7.3, 5.9, 4.9 Hz, 1H), 3.73 (dd, *J* = 10.9,

5.9 Hz, 1H), 3.65 (dd, *J* = 10.9, 4.8 Hz, 1H), 2.73 (dddd, *J* = 14.4, 10.4, 1.8, 0.7 Hz, 1H), 2.48 (dddd, *J* = 14.6, 7.3, 1.7, 0.6 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 144.97 (+), 129.08 (+), 116.31 (C_q), 109.70 (-), 83.00 (+), 65.64 (-), 30.71 (-), 26.01 (+), 18.50 (C_q), -5.14 (+), -5.19 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2929, 2857, 1641, 1472, 1463, 1253, 1105, 1006, 980, 834, 776, 667;

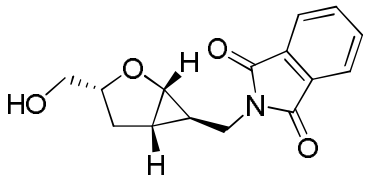
154b: R_f = 0.40 (PE/EA 5:1); $[\alpha]_D^{20}$ = + 95.5 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.83 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.0 Hz, 2H), 6.13 (d, *J* = 8.4 Hz, 1H), 5.62 (ddd, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.15 (dt, *J* = 17.1, 1.4 Hz, 1H), 4.99 (ddd, *J* = 10.2, 1.5, 1.0 Hz, 1H), 4.18 (ddt, *J* = 10.7, 6.5, 5.2 Hz, 1H), 3.97 (dd, *J* = 10.5, 6.6 Hz, 1H), 3.82 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.41 - 3.26 (m, 1H), 2.39 (dt, *J* = 12.1, 11.2 Hz, 1H), 2.13 (ddd, *J* = 11.7, 7.6, 5.5 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 167.89 (C_q), 134.26 (+), 134.12 (+), 131.99 (C_q), 123.50 (+), 118.46 (-), 83.27 (+), 82.56 (+), 65.93 (-), 47.39 (+), 34.02 (-), 26.14 (+), 18.62 (C_q), -5.04 (+), -5.11 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2956, 2928, 2857, 1787, 1772, 1720, 1470, 1416, 1370, 1351, 1327, 1255, 1117, 1101, 1059, 1005, 924, 891, 838, 777, 720; MS (ESI): m/z (%) = 388.0 (100) [MH^+], 729.4 (15) [$2MH^+$]; HRMS (ESI): calcd for $C_{21}H_{30}NO_4Si$ [MH^+] 388.1939, found 388.1941;

154a: R_f = 0.38 (PE/EA 5:1); $[\alpha]_D^{20}$ = - 41.5 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.84 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.0 Hz, 2H), 5.79 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H), 5.74 (d, *J* = 7.6 Hz, 1H), 5.09 (dt, *J* = 17.7, 1.4 Hz, 1H), 5.04 (ddd, *J* = 7.9, 1.4, 0.9 Hz, 1H), 4.53 (dq, *J* = 5.2, 4.1 Hz, 6H), 3.87 - 3.73 (m, 7H), 3.73 (dd, *J* = 11.0, 4.2 Hz, 10H), 3.67 (dd, *J* = 11.0, 4.4 Hz, 1H), 2.35 (ddd, *J* = 12.6, 7.6, 5.3 Hz, 1H), 1.89 (ddd, *J* = 12.2, 11.1, 10.1 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 167.95 (C_q), 136.90 (+), 134.31 (+), 132.06 (C_q), 123.57 (+), 117.25 (-), 85.23 (+), 80.85 (+), 65.07 (-), 46.15 (+), 35.26 (-), 26.08 (+), 18.51 (C_q), -5.10 (+), -5.21 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2929, 2857, 1775, 1717, 1470, 1405, 1368, 1328, 1253, 1084, 996, 921, 872, 836, 777, 718, 665, 530; MS (ESI): m/z (%) = 388.0 (70) [MH^+], 405.0 (70) [MNH_4^+], 775.4 (20) [$2MH^+$], 792.4 (100) [$2MNH_4^+$]; HRMS (ESI): calcd for $C_{21}H_{30}NO_4Si$ [MH^+] 388.1939, found 388.1942;

138: mp = 63 - 65 °C; R_f = 0.25 (PE/EA 5:1); $[\alpha]_D^{20}$ = + 28.9 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.46 - 4.34 (m, 1H), 3.89 (dd, *J* = 6.2, 0.6 Hz, 1H), 3.47 (dd, *J* = 14.3, 6.9 Hz, 1H), 3.41 (d, *J* = 4.9 Hz, 2H), 3.28 (dd, *J* = 14.3, 8.4 Hz, 1H), 2.20 (ddd, *J* = 12.7, 8.1, 7.3 Hz, 1H), 1.70 - 1.53 (m, 2H), 1.36 - 1.25 (m,

1H), 0.82 (s, 9H), -0.02 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 168.28 (C_q), 133.94 (+), 132.23 (C_q), 123.22 (+), 87.79 (+), 65.97 (-), 64.86 (+), 37.87 (-), 31.45 (-), 31.13 (+), 25.97 (+), 23.09 (+), 18.42 (C_q), -5.30 (+), -5.31 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2929, 2856, 1772, 1712, 1468, 1433, 1391, 1356, 1330, 1253, 1188, 1137, 1088, 1007, 990, 950, 836, 777, 720, 529; MS (ESI): m/z (%) = 388.1 (50) [MH^+], 405.0 (100) [MNH_4^+]; HRMS (ESI): calcd for $C_{21}H_{30}NO_4Si$ [MH^+] 388.1939, found 388.1940.

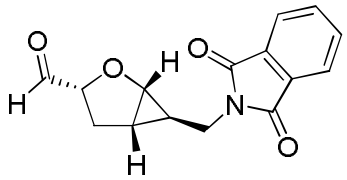
2-(((1*S*,3*R*,5*S*,6*R*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (139)



To a solution of phthalimide **138** (150 mg, 0.65 mmol) in anhydrous THF (5 mL) a solution of TBAF•3H_2O (305 mg, 0.97 mmol, 1.5 equiv) in anhydrous THF (1.5 mL) was added dropwise and stirred for 1.5 h at 0 °C. The mixture was allowed to warm to room temperature and the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (EA/MeOH 9:1) to afford compound **139** (124 mg, 0.45 mmol, 70%) as a colorless oil.

mp = 85 °C; R_f = 0.44 (EA); $[\alpha]_D^{20}$ = + 17.8 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.81 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.54 - 4.40 (m, 1H), 3.91 (dd, *J* = 6.3, 0.6 Hz, 1H), 3.55 - 3.42 (m, 1H), 3.48 (dd, *J* = 14.3, 7.0 Hz, 2H), 3.36 - 3.23 (m, 1H), 3.30 (dd, *J* = 14.3, 8.3 Hz, 2H), 2.21 (dt, *J* = 12.9, 7.6 Hz, 1H), 2.11 (t, *J* = 6.2 Hz, 1H), 1.69 - 1.56 (m, 1H), 1.63 (br s, 1H), 1.27 (tdd, *J* = 7.9, 3.6, 0.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 168.38 (C_q), 134.05 (+), 132.18 (C_q), 123.33 (+), 88.23 (+), 65.15 (-), 64.86 (+), 37.83 (-), 31.76 (+), 31.04 (-), 23.30 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3459 (br), 2937, 2876, 1770, 1703, 1467, 1434, 1392, 1356, 1188, 1138, 1076, 951, 860, 794, 720, 614, 530; MS (ESI): m/z (%) = 274.0 (2) [MH^+], 291.0 (7) [MNH_4^+], 547.1 (100) [$2MH^+$]; HRMS (ESI): calcd for $C_{15}H_{16}NO_4$ [MH^+] 274.1074, found 274.1074.

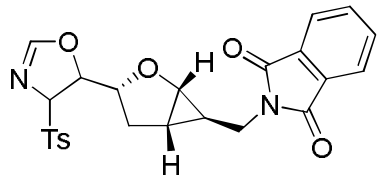
(1*S*,3*R*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexane-3-carbaldehyde (140)



To stirred suspension of alcohol **139** (42 mg, 0.15 mmol) and $NaHCO_3$ (26 mg, 0.31 mmol, 2.0 equiv) in DCM (3 mL) was added Dess-Martin periodinane (108 mg, 0.25 mmol, 1.7 equiv) and stirred for 5 h at room temperature. The mixture was quenched with a mixture of saturated aqueous $Na_2S_2O_3$ solution (2 mL) and saturated aqueous $NaHCO_3$ solution (2 mL) and stirred for another 15 min. The phases were separated and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE/EA 1:3) provided compound **140** (33 mg, 0.12 mmol, 79%) as a colorless solid.

mp = 107 - 110 °C; R_f = 0.43 (PE/EA 1:3); $[\alpha]_D^{20}$ = + 46.3 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 9.53 (d, *J* = 0.8 Hz, 1H), 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.59 (ddd, *J* = 10.2, 4.1, 0.4 Hz, 1H), 4.13 (dd, *J* = 5.9, 1.1 Hz, 1H), 3.50 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.40 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.41 (ddd, *J* = 13.1, 10.3, 6.1 Hz, 1H), 2.21 (dd, *J* = 13.1, 4.2 Hz, 1H), 1.69 (td, *J* = 5.9, 4.0 Hz, 1H), 1.16 - 1.02 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 203.86 (+), 168.34 (C_q), 134.18 (+), 132.18 (C_q), 123.47 (+), 86.43(+), 65.24 (+), 37.60 (-), 31.04 (-), 25.73 (+), 21.38 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2935, 1770, 1708, 1467, 1434, 1393, 1358, 1331, 1194, 1139, 1108, 1080, 948, 856, 793, 720, 530; MS (APCI): m/z (%) = 253.9 (30) [$M^+\Delta H_2O$], 271.9 (100) [MH^+], 285.9 (25) [MNH_4^+]; HRMS (EI): calcd for $C_{15}H_{13}NO_4$ [$M^{+\bullet}$] 271.0845, found 271.0844.

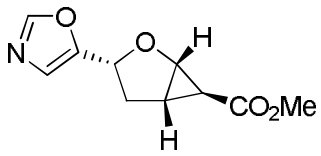
2-(((1*S*,3*R*,5*S*,6*R*)-3-(4-tosyl-4,5-dihydrooxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-isoindoline-1,3-dione (141)



Finely powdered NaCN (3 mg, 0.06 mmol, 0.18 equiv) was added in one portion to a stirred solution of TosMIC (72 mg, 0.37 mmol, 1.1 equiv) and aldehyde **140** (91 mg, 0.34 mmol) in anhydrous EtOH (3 mL) and anhydrous DCM (1 mL). The reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (1 x 5 mL). The aqueous layer was extracted with $CHCl_3$ (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EA 1:1) afforded compound **141** (127 mg, 0.27 mmol, 81%) as a yellowish foam.

Data for isomeric mixture: R_f = 0.25 (PE/EA 1:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.93 - 7.65 (m, 6H), 7.38 (d, *J* = 8.6 Hz, 1.2H), 7.35 (d, *J* = 8.6 Hz, 0.8H), 6.96 (s, 1H), 4.97 - 4.89 (m, 1H), 4.87 - 4.78 (m, 1H), 4.62 (ddd, *J* = 9.1, 7.6, 3.4 Hz, 0.6H), 4.53 (td, *J* = 8.4, 3.2 Hz, 0.4H), 3.98 (dd, *J* = 6.4, 0.7 Hz, 0.6H), 3.92 (dd, *J* = 6.4, 0.8 Hz, 0.4H), 3.55 - 3.41 (m, 1H), 3.41 - 3.30 (m, 1H), 2.45 (s, 1.8H), 2.44 (s, 1.2H), 2.42 - 2.24 (m, 1H), 1.96 (ddd, *J* = 13.1, 8.5, 1.6 Hz, 0.4H), 1.80 - 1.64 (m, 1.6H), 1.43 - 1.30 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 168.43 (C_q) and 168.40 (C_q), 159.45 (+) and 159.37 (+), 145.74 (C_q) and 145.71 (C_q), 134.16 (+), 133.14 (C_q) and 133.08 (C_q), 132.25 (C_q) and 132.22 (C_q), 130.01 (+) and 129.95 (+), 129.71 (+) and 129.59 (+), 123.47 (+) and 123.45 (+), 87.87 (+) and 87.40 (+), 87.34 (+) and 86.32 (+), 79.43 (+) and 78.99 (+), 65.15 (+) and 65.11 (+), 37.66 (-) and 37.59 (-), 32.66 (+) and 31.68 (+), 31.18 (-) and 30.71 (-), 23.22 (+) and 22.58 (+), 21.87 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2927, 2873, 1770, 1710, 1617, 1434, 1393, 1357, 1321, 1187, 1148, 1109, 1085, 951, 914, 859, 813, 721, 648, 588, 531; MS (ESI): m/z (%) = 467.1 (100) [MH^+], 484.1 (90) [MNH_4^+]; HRMS (ESI): calcd for $C_{24}H_{23}N_2O_6S$ [MH^+] 467.1271, found 467.1264.

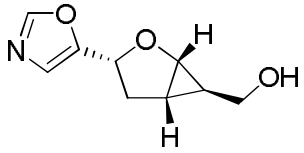
(1*S*,3*R*,5*S*,6*S*)-methyl 3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (142)



To a solution of oxazoline **106** (396 mg, 1.04 mmol) in anhydrous MeOH (10 mL), K_2CO_3 (289 mg, 2.09 mmol, 2 equiv) was added under a nitrogen atmosphere. The reaction mixture was refluxed for 30 min, quenched with water (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification by column chromatography (PE/EA 1:1) afforded compound **142** (67 mg, 0.32 mmol, 31%) as a colorless solid.

mp = 61 °C; R_f = 0.36 (PE/EA 1:3); $[\alpha]_D^{20}$ = + 30.6 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.84 (s, 1H), 6.97 (s, 1H), 5.47 (dd, *J* = 9.4, 6.1 Hz, 1H), 4.30 (dd, *J* = 5.9, 0.6 Hz, 1H), 3.65 (s, 3H), 2.72 (ddd, *J* = 13.4, 9.5, 6.6 Hz, 1H), 2.37 - 2.30 (m, 1H), 2.26 (ddd, *J* = 13.5, 6.1, 0.7 Hz, 1H), 1.98 (dd, *J* = 3.9, 0.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 170.80 (C_q), 151.63 (C_q), 151.51 (+), 124.18 (+), 77.16 (+), 67.36 (+), 51.89 (+), 33.00 (-), 31.18 (+), 27.25 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3435 (br), 3129, 2954, 1716, 1507, 1440, 1394, 1311, 1274, 1198, 1171, 1107, 1070, 963, 860, 715; MS (EI): m/z (%) = 95.0 (100), 180.1 (39) [M^+ΔCHO], 209.1 (<1) [$M^{+\bullet}$]; HRMS (EI): calcd for $C_{10}H_{11}NO_4$ [$M^{+\bullet}$] 209.0688, found 209.0694.

(1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanol (143)

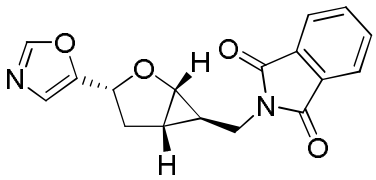


To a stirred ice-cooled solution of oxazole **142** (65 mg, 0.31 mmol) in anhydrous THF (3 mL) under a nitrogen atmosphere, LAH (9.3 mg, 0.25 mmol, 0.8 equiv) was added in small portions within 5 min. The reaction mixture was stirred for 30 min at 0 °C. After addition of

water (10 µL) the mixture was stirred for another 30 min. Then a 15% aqueous NaOH solution (10 µL) was added followed by water (30 µL). The mixture was warmed to room temperature, treated with $MgSO_4$ and filtered through a Celite pad. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EA) to obtain compound **143** (40 mg, 0.22 mmol, 71%) as a colorless solid.

mp = 95 °C; R_f = 0.19 (EA); $[\alpha]_D^{20}$ = + 25.8 (DCM, c = 1.0); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 7.81 (s, 1H), 6.93 (s, 1H), 5.41 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.90 (dd, *J* = 6.2, 1.2 Hz, 1H), 3.39 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.33 (dd, *J* = 11.5, 7.1 Hz, 1H), 2.59 (ddd, *J* = 13.0, 8.7, 6.9 Hz, 1H), 2.13 (ddd, *J* = 13.0, 6.7, 1.4 Hz, 1H), 2.11 (br s, 1H), 1.69 - 1.62 (m, 1H), 1.40 (tdd, *J* = 7.1, 4.0, 1.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 152.18 (C_q), 151.31 (+), 123.62 (+), 78.11 (+), 64.70 (+), 62.12 (-), 33.85 (-), 33.45 (+), 22.08 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3369 (br), 3125, 2945, 2881, 1508, 1461, 1414, 1353, 1262, 1176, 1106, 1026, 990, 966, 910, 885, 846, 645; MS (CI): m/z (%) = 182.1 (99) [MH^+], 199.1 (100) [MNH_4^+]; HRMS (LSI): calcd for $C_9H_{12}NO_3$ [MH^+] 182.0817, found 182.0816.

2-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (144)

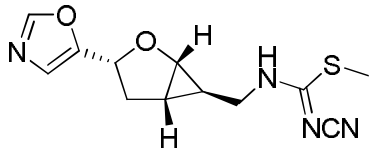


DIAD (96 mg, 0.45 mmol, 1.5 equiv) was added dropwise to a solution of oxazole **143** (54 mg, 0.30 mmol), PPh_3 (117 mg, 0.45 mmol, 1.5 equiv) and phthalimide (66 mg, 0.45 mmol, 1.5 equiv) in anhydrous THF (6 mL) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 30 min the mixture was allowed to warm to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (PE/EA 3:1 to EA) to obtain compound **144** (51 mg, 0.17 mmol, 55%) as a colorless solid.

mp = 83 °C; R_f = 0.51 (EA); $[\alpha]_D^{20}$ = + 18.9 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (s, 1H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.92 (s, 1H), 5.45 - 5.37 (m,

1H), 4.08 (dd, *J* = 6.3, 1.0 Hz, 1H), 3.56 (dd, *J* = 14.4, 6.9 Hz, 1H), 3.36 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.59 (ddd, *J* = 13.1, 8.6, 7.1 Hz, 1H), 2.09 (ddd, *J* = 13.1, 7.2, 1.4 Hz, 1H), 1.84 - 1.75 (m, 1H), 1.59 - 1.51 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 168.33 (C_q), 151.59 (C_q), 151.30 (+), 134.08 (+), 132.18 (C_q), 123.87 (+), 123.36 (+), 78.48 (+), 65.23 (+), 37.73 (-), 33.92 (-), 30.69 (+), 23.24 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3141, 3938, 1769, 1708, 1509, 1467, 1433, 1392, 1357, 1329, 1260, 1225, 1197, 1136, 1101, 1071, 1026, 950, 851, 798, 720, 645, 531; MS (EI): m/z (%) = 77.1 (8), 95.1 (100), 104.1 (6), 130.1 (6), 160.1 (18), 310.1 (1) [$M^{+\bullet}$]; HRMS (EI): calcd for $C_{17}H_{14}N_2O_4$ [$M^{+\bullet}$] 310.0954, found 310.0956.

methyl-*N*'-cyano-*N*-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl) -carbamimidothioate (145)

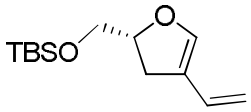


A solution of aminooxazole **57a** (19 mg, 0.11 mmol) and dimethyl *N*-cyanodithioiminocarbonate (34 mg, 0.22 mmol, 2 equiv) in EtOH was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (DCM then DCM/MeOH 9:1) to afford compound **145** (29 mg, 0.11 mmol, quantitative) as a colorless oil.

R_f = 0.51 (PE/EA 9:1); $[\alpha]_D^{20}$ = + 14.3 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.84 (s, 1H), 7.16 (s, 0.5H), 6.96 (s, 1H), 6.53 (s, 0.5H), 5.43 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.96 (dd, *J* = 6.3, 0.9 Hz, 1H), 3.45 - 2.86 (m, signal broadening due to rotamers, 2H), 2.73 - 2.32 (m, signal broadening due to rotamers, 3H), 2.62 (ddd, *J* = 13.0, 8.6, 7.0 Hz, 1H), 2.15 (dd, *J* = 13.0, 6.9 Hz, 1H), 1.77 - 1.68 (m, 1H), 1.50 - 1.37 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 151.67 (C_q), 151.44 (+), 123.99 (+), 78.34 (+), 64.99 (+), 44.01 (signal broadening due to rotamers, -), 33.82 (-), 30.09 (+), 23.30 (+), 14.64 (signal broadening due to rotamers, +), **C**=N and **C**≡N signals too weak to be observed; IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3263 (br), 3126, 3011, 2939, 2174, 1716, 1554, 1511, 1430, 1357, 1285, 1182, 1104, 938, 846, 645; MS (ESI): m/z (%) = 279.0

(30) [MH^+], 296.0 (40) [MNH_4^+], 557.1 (100) [$2MH^+$]; HRMS (EI): calcd for $C_{12}H_{14}N_4O_2S$ [$M^{+\bullet}$] 278.0837, found 278.0833.

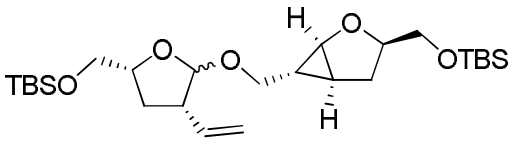
2-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (138), (*R*)-*tert*-butyldimethyl((4-vinyl-2,3-dihydrofuran-2-yl)methoxy)silane (153)



A solution of alcohol **116** (40 mg, 0.15 mmol), EDC (49 mg, 0.31 mmol, 2 equiv) and $CuCl_2$ (22 mg, 0.17 mmol, 1.08 equiv) in anhydrous MeCN (3 mL) was stirred at 80 °C under a nitrogen atmosphere for 0.5 h. The reaction mixture was quenched with water (3 mL) and the mixture was extracted with EA (3 x 3 mL) and DCM (2 x 3 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford 22 mg (0.09 mmol, 62%) of analytically pure compound **153**.

For analytical data see page 111.

***tert*-butyl(((2*R*,4*S*)-5-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo-[3.1.0]hexan-6-yl)methoxy)-4-vinyltetrahydrofuran-2-yl)methoxy)dimethylsilane (165)**



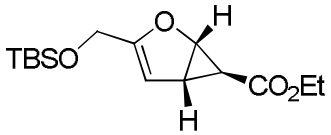
To alcohol **116** (45 mg, 0.17 mmol) dissolved in benzene (1.5 ml), $Cu(OTf)_2$ (11 mg, 0.03 mmol, 0.18 equiv) was added. The heterogeneous mixture was stirred for 1 h at room temperature. The reaction mixture was treated with water and extracted with EA (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification

by column chromatography (PE/EA 19:1) yielded compound **165** (40 mg, 0.08 mmol, 94%) as a colorless oil.

Major: R_f = 0.36 (PE/EA 9:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.77 (ddd, *J* = 17.2, 10.2, 8.3 Hz, 1H), 5.13 - 4.97 (m, 2H), 4.81 (d, *J* = 2.5 Hz, 1H), 4.50 - 4.39 (m, 1H), 4.18 - 4.07 (m, 1H), 3.79 - 3.70 (m, 1H), 3.67 (dd, *J* = 4.8, 0.7 Hz, 2H), 3.56 - 3.45 (m, 2H), 3.42 (dd, *J* = 10.9, 7.2 Hz, 1H), 3.12 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.85 - 2.71 (m, 1H), 2.34 - 2.11 (m, 2H), 1.77 - 1.60 (m, 2H), 1.60 - 1.41 (m, 1H), 1.21 - 1.06 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ_C = 139.00 (+), 115.31 (-), 108.19 (+), 87.78 (+), 78.91 (+), 67.08 (-), 66.38 (-), 65.46 (-), 64.57 (+), 49.82 (+), 33.13 (-), 31.99 (+), 31.84 (-), 26.08 (+), 22.51 (+), 18.53 (C_q), -5.16 (+); minor: R_f = 0.36 (PE/EA 9:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.85 (ddd, *J* = 17.3, 10.2, 8.3 Hz, 1H), 5.14 - 4.98 (m, 2H), 4.87 (d, *J* = 4.6 Hz, 1H), 4.50 - 4.39 (m, 1H), 4.18 - 4.07 (m, 1H), 3.79 - 3.70 (m, 1H), 3.56 - 3.45 (m, 2H), 3.69 - 3.62 (m, 2H), 3.35 (dd, *J* = 10.9, 7.0 Hz, 1H), 3.18 (dd, *J* = 10.7, 6.7 Hz, 1H), 2.81 - 2.67 (m, 1H), 2.32 - 2.12 (m, 2H), 2.11 - 1.96 (m, 1H), 1.77 - 1.60 (m, 1H), 1.60 - 1.41 (m, 1H), 1.21 - 1.06 (m, 1H), 0.89 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ_C = 136.17 (+), 116.28 (-), 103.85 (+), 87.72 (+), 80.58 (+), 68.09 (-), 66.30 (-), 66.01 (-), 64.85 (+), 49.32 (+), 33.20 (-), 31.72 (-), 31.68 (+), 26.11 (+), 21.94 (+), 18.55 (C_q), -5.11 (+);

Data for isomeric mixture: $[\alpha]_D^{20}$ = + 4.2 (DCM, c = 1.0); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2928, 2857, 1472, 1463, 1389, 1361, 1254, 1136, 1096, 1038, 1006, 836, 776, 667; MS (ESI): m/z (%) = 499.3 (5) [MH^+], 516.3 (100) [MNH_4^+], 521.2 (70) [MNa^+]; HRMS (ESI): calcd for $C_{26}H_{54}NO_5Si_2$ [MNH_4^+] 516.3535, found 516.3525.

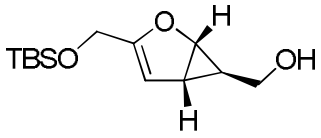
(1*S*,5*S*,6*S*)-ethyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (166)



To a stirred solution of alcohol **98** (683 mg, 3.71 mmol) in DCM (12 mL), anhydrous NEt_3 (771 µL, 5.56 mmol, 1.5 equiv) and TBSCl (683 mg, 4.53 mmol, 1.2 equiv) was added in one portion, followed by DMAP (23 mg, 0.19 mmol, 0.05 equiv). The mixture was stirred 4 h at room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl solution (15 mL) and extracted with DCM (2 x 15 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The residue was separated by column chromatography (PE/EA 5:1) to give compound **166** (1.10 g, 3.69 mmol, 99%) as a colorless oil.

R_f = 0.52 (PE/EA 5:1); $[\alpha]_D^{20}$ = - 93.4 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.33 (dt, *J* = 2.2, 1.0 Hz, 1H), 4.85 (dd, *J* = 5.6, 1.0 Hz, 1H), 4.16 (q, *J* = 14.0 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.76 (dt, *J* = 5.4, 2.6 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.04 (dd, *J* = 2.6, 1.0 Hz, 1H), 0.89 (s, *J* = 3.0 Hz, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ_C = 172.88 (C_q), 159.88 (C_q), 102.09 (+), 67.47 (+), 60.68 (-), 58.39 (-), 32.06 (+), 25.94 (+), 22.78 (+), 18.48 (C_q), 14.41 (+), -5.23 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2931, 2887, 2858, 1716, 1652, 1606, 1464, 1399, 1378, 1306, 1289, 1256, 1174, 1157, 1116, 1084, 1045, 1003, 939, 888, 835, 779, 726; MS (ESI): m/z (%) = 299.1 (95) [MH^+], 321.1 (100) [MNa^+], 619.3 (25) [$2MNa^+$]; HRMS (ESI): calcd for $C_{15}H_{27}O_4Si$ [MH^+] 299.1673, found 299.1676.

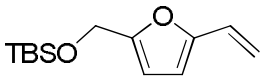
((1*S*,5*R*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hex-3-en-6-yl)-methanol (167)



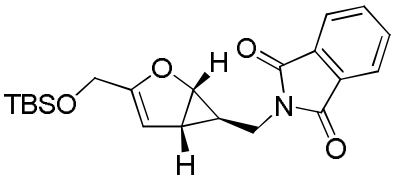
To a stirred ice-cooled solution of ester **166** (1.10 g, 3.69 mmol) in anhydrous THF (15 mL) under a nitrogen atmosphere, a suspension of LAH (119 mg, 3.31 mmol, 0.85 equiv) in anhydrous THF (4 mL) was added dropwise within 10 min. The reaction mixture was stirred for 1 h at 0 °C. After dropwise addition of water (120 µL) the mixture was stirred for another 30 min. Then a 15% aqueous NaOH solution (120 µL) was added followed by water (360 µL). The mixture was warmed to room temperature, treated with $MgSO_4$ and filtered through a Celite pad. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EA 3:1) to obtain compound **167** (835 mg, 3.26 mmol, 88%) as a colorless oil.

R_f = 0.18 (PE/EA 3:1); $[\alpha]_D^{20}$ = - 57.7 ($CHCl_3$, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.22 (dt, *J* = 2.3, 1.1 Hz, 1H), 4.37 (dd, *J* = 6.0, 1.3 Hz, 1H), 4.20 - 4.04 (m, 2H), 3.54 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.40 (dd, *J* = 11.5, 7.8 Hz, 1H), 2.07 (dt, *J* = 5.7, 2.7 Hz, 1H), 1.54 (s, *J* = 14.3 Hz, 1H), 0.89 (s, 9H), 0.67 (tdd, *J* = 7.7, 2.9, 1.3 Hz, 1H), 0.07 (d, *J* = 0.8 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 158.12 (C_q), 102.46 (+), 64.07 (+), 62.76 (-), 58.64 (-), 25.99 (+), 25.48 (+), 22.86 (+), 18.53 (C_q), -5.17 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3352 (br), 2953, 2929, 2885, 2857, 1657, 1472, 1463, 1403, 1255, 1218, 1160, 1118, 1084, 1018, 959, 939, 836, 816, 778, 740, 667; MS (ESI): m/z (%) = 257.0 (35) [MH^+], 513.1 (100) [$2MH^+$]; HRMS (ESI): calcd for $C_{13}H_{25}O_3Si$ [MH^+] 257.1567, found 257.1568.

***tert*-butyldimethyl((5-vinylfuran-2-yl)methoxy)silane (168), 2-(((1*S*,5*R*,6*R*)-3-((*tert*-butyl-dimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hex-3-en-6-yl)methyl)isoindoline-1,3-dione (169)**



168



169

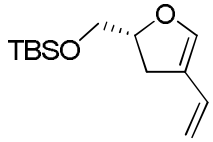
DIAD (115 µg, 0.59 mmol, 1.5 equiv) was added dropwise to a solution of alcohol **167** (100 mg, 0.39 mmol), PPh_3 (153 mg, 0.59 mmol, 1.5 equiv) and phthalimide (86 mg, 0.59 mmol, 1.5 equiv) in anhydrous THF (7 mL) at 0 °C under a nitrogen atmosphere. After stirring for 2 h at 0 °C the mixture was allowed to come to room temperature. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (PE/EA 19:1, then 5:1) to obtain compound **168** (50 mg, 0.21 mmol, 54%) as a colorless oil and compound **169** (57 mg, 0.15 mmol, 38%) as a colorless solid.

168: R_f = 0.57 (PE/EA 19:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 6.46 (dd, *J* = 17.5, 11.3 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 5.64 (dd, *J* = 17.5, 1.2 Hz, 1H), 5.12 (dd, *J* = 11.3, 1.4 Hz, 1H), 4.64 (s, 2H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 154.07 (C_q), 152.85 (C_q), 125.21 (+), 112.02 (-), 108.98 (+), 108.89 (+), 58.45 (-), 26.03 (+), 18.58 (C_q), -5.04 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2956, 2929, 2885, 2858, 1687, 1642, 1526, 1472, 1463, 1370, 1254, 1190, 1077, 1036, 1017, 1006, 980, 939, 988, 833,775, 723, 671, 650; MS (EI): m/z (%) = 75.1 (19), 107.1 (100) [$M^+\Delta C_6H_{15}OSi$], 181.1 (93) [$M^+\Delta C_4H_9$], 238.2 (5) [M^+];

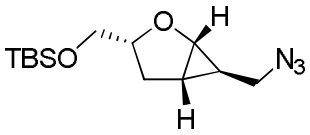
169: mp = 79 °C; R_f = 0.27 (PE/EA 5:1); $[\alpha]_D^{20}$ = - 47.7 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.16 (dt, *J* = 2.3, 1.1 Hz, 1H), 4.53 (dd, *J* = 6.0, 1.2 Hz, 1H), 4.08 (m, 2H), 3.58 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.48 (dd, *J* = 14.4, 7.9 Hz, 2H), 2.20 (ddd, *J* = 5.6, 2.7, 2.6 Hz, 1H), 0.87 (s, 9H), 0.81 (tdd, *J* = 7.7, 2.8, 1.2, 1H), 0.04 (d, 3H), 0.04 (d, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 168.52 (C_q), 158.25 (C_q), 134.12 (+), 132.32 (C_q), 123.43 (+), 102.21 (+), 64.56 (+), 58.57 (-), 37.99 (-), 26.50 (+), 25.98 (+), 20.08 (+), 18.50 (C_q), -5.21 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2929, 2857, 1772, 1714, 1468, 1433, 1387, 1355, 1268, 1175, 1136, 1115, 1084, 1016, 962, 944, 838, 780, 719, 619, 529; MS (EI):

m/z (%) = 73.1 (62), 107.0 (18), 160 (26) [$C_6H_9NO_2$], 181.0 (100), 225.1 (83) [$M^+\Delta C_6H_9NO_2$], 253.0 (25), 328.0 (26) [$M^+\Delta C_4H_9$], 385.1 (<1) [M^+]; HRMS (EI): calcd for $C_{11}H_{35}N_3O_4Si$ [$M^{+\bullet}$] 385.1709, found 385.1707.

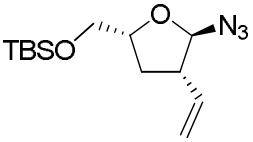
(*R*)-*tert*-butyldimethyl((4-vinyl-2,3-dihydrofuran-2-yl)methoxy)silane (153), (((1*S*,3*R*,5*S*,6*R*)-6-(azidomethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(*tert*-butyl)dimethylsilane (175), (((2*R*,4*S*,5*R*)-5-azido-4-vinyltetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (176a), (((2*R*,4*S*,5*S*)-5-azido-4-vinyltetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (176b)



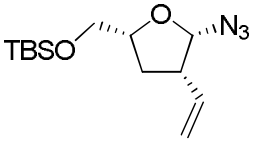
153



175



176a



176b

Method A: To a solution of alcohol **116** (86 mg, 0.33 mmol) and PPh_3 (175 mg, 0.67 mmol, 2.0 equiv) in anhydrous THF (3.5 mL), DIAD (143 mg, 0.67 mmol, 2.0 equiv) and DPPA (187 mg, 0.67 mmol, 2.0 equiv) were added dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 0.5 h at the same temperature. The mixture was allowed to warm to room temperature and the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (PE/EA 19:1 to 5:1) to afford compound **153** (4.0 mg, 0.02 mmol, 5%), compound **176a** (35 mg, 0.12 mmol, 37%), compound **176b** (18 mg, 0.06 mmol, 19%) and compound **175** (19 mg, 0.07 mmol, 21%) as colorless oils.

Method B: Alcohol **116** (84 mg, 0.33 mmol) was dissolved in a 9:1 mixture of anhydrous toluene and anhydrous DMF (1.4 mL) under a nitrogen atmosphere. DPPA (183 mg, 0.65 mmol, 2.0 equiv) and DBU (99 mg, 0.66 mmol, 2.0 equiv) was added. The reaction was stirred for 1 h at 50 °C. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (PE/EA 50:1, then 19:1) to afford compound **153** (4.0 mg,

0.02 mmol, 5%), compound **176a** (31 mg, 0.10 mmol, 32%), compound **176b** (27 mg, 0.09 mmol, 27%) and compound **175** (11 mg, 0.04 mmol, 12%) as colorless oils.

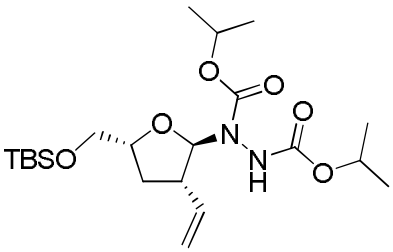
153: for analytical data see page 111.

176a: R_f = 0.50 (PE/EA 19:1); $[\alpha]_D^{20}$ = - 80.0 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.77 (ddd, *J* = 17.2, 10.2, 8.1 Hz, 1H), 5.19 - 5.09 (m, 1H), 5.16 (d, *J* = 4.3, 1H) 5.12 - 5.04 (m, 1H), 4.28 (ddt, *J* = 8.6, 6.7, 4.4 Hz, 1H), 3.73 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.68 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.72 (qd, *J* = 8.0, 4.1 Hz, 1H), 2.20 (ddd, *J* = 12.7, 7.9, 6.7 Hz, 1H), 1.71 (dt, *J* = 12.6, 8.2 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 137.39 (+), 116.73 (-), 96.83 (+), 80.58 (+), 64.91 (-), 50.12 (+), 33.02 (-), 26.06 (+), 18.52 (C_q), -5.14 (+), -5.17 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2929, 2857, 2103, 1472, 1462, 1254, 1233, 1139, 1096, 1073, 837, 779; MS (ESI): m/z (%) = 256.2 [$MH^+\Delta N_2$] (100); HRMS (ESI): calcd for $C_{13}H_{26}NO_2Si$ [$MH^+\Delta N_2$] 256.1727, found 256.1730.

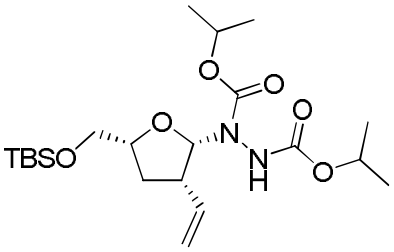
176b: R_f = 0.38 (PE/EA 19:1); $[\alpha]_D^{20}$ = + 161.4 (DCM, c = 0.5); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 5.75 (ddd, *J* = 17.4, 10.4, 7.6 Hz, 1H), 5.38 (d, *J* = 5.3 Hz, 1H), 5.19 - 5.15 (m, 1H), 5.15 - 5.11 (m, 1H), 4.22 (td, *J* = 10.7, 5.7 Hz, 1H), 3.75 (dd, *J* = 10.7, 5.6 Hz, 1H), 3.68 (dd, *J* = 10.7, 4.9 Hz, 1H), 2.89 (td, *J* = 12.5, 7.1 Hz, 1H), 2.15 - 2.01 (m, 1H), 1.74 (td, *J* = 12.4, 10.1 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 134.51 (+), 117.83 (-), 94.22 (+), 81.96 (+), 66.47 (-), 48.99 (+), 31.88 (-), 26.03 (+), 18.52 (C_q), -5.21 (+), -5.23 (-); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2929, 2857, 2111, 1472, 1463, 1250, 1130, 1085, 1060, 1030,994, 920,837, 777, 679; MS (ESI): m/z (%) = 241.2 (100) [$MH^+\Delta N_3H$], 256.2 (32) [$MH^+\Delta N_2$], 306.2 (13) [MNa^+]; HRMS (ESI): calcd for $C_{13}H_{26}NO_2Si$ [$MH^+\Delta N_2$] 256.1727, found 256.1733.

175: R_f = 0.55 (PE/EA 5:1); $[\alpha]_D^{20}$ = + 44.1 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.48 (ddd, *J* = 8.7, 8.2, 4.5 Hz, 1H), 3.77 (dd, *J* = 6.3, 1.1 Hz, 1H), 3.54 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.48 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.14 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.87 (dd, *J* = 13.2, 8.1 Hz, 1H), 2.28 (ddd, *J* = 12.8, 8.4, 7.2 Hz, 1H), 1.80 (ddd, *J* = 12.9, 7.5, 1.5 Hz, 1H), 1.62 - 1.49 (m, 1H), 1.36 - 1.18 (m, 1H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 87.78 (+), 65.73 (-), 64.39 (+), 51.22 (-), 31.18 (-), 30.42 (+), 26.09 (+), 23.17 (+), 18.55 (C_q), -5.17 (+), -5.22 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 2929, 2857, 2089, 1472, 1462, 1253, 1173, 1128, 1094, 1060, 1007, 990, 886, 834, 776, 670; MS (ESI): m/z (%) = 283.1 (50) [M^+], 292.1 (82), 301.1 (58) [MNH_4^+], 315.1 (72), 333.0 (62), 456.1 (100); HRMS (ESI): calcd for $C_{13}H_{26}N_3O_2Si$ 284.1789 [MH^+], found 284.1794.

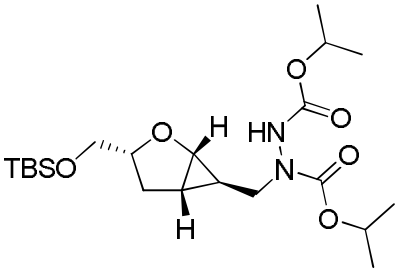
diisopropyl 1-((2*R*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)hydrazine-1,2-dicarboxylate (184a), diisopropyl 1-((2*S*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)hydrazine-1,2-dicarboxylate (184b), diisopropyl 1-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methyl)hydrazine-1,2-dicarboxylate (185)



184a



184b



185

To a solution of alcohol **116** (79 mg, 0.31 mmol) and PPh_3 (240 mg, 0.92 mmol, 3.0 equiv) in anhydrous THF (6 mL) at 0 °C under a nitrogen atmosphere was added DIAD (197 mg, 0.92 mmol, 3.0 equiv). The reaction mixture was stirred for 3 h at 0 °C, then warmed to room temperature and further stirred for 17 h. The solvent was removed under reduced pressure. Purification by column chromatography (PE/EA 9:1) afforded compound **153** (7 mg, 0.03 mmol, 9%), an epimeric mixture of compounds **184a** and **184b** (75 mg, 0.17 mmol, 54%, *dr* = 7:3) and **185** (44 mg, 0.10 mmol, 32%) as colorless oils.

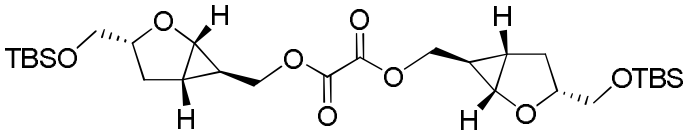
153: for analytical data see page 111.

184a: R_f = 0.26 (PE/EA 5:1); $[\alpha]_D^{20}$ = - 4.8 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 6.30 (s, 0.7H), 6.15 (s, 0.3H), 5.87 (ddd, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.68 (br s, 1H), 5.26 - 5.11 (m, 1H), 5.13 - 5.06 (m, 1H), 4.95 (sept, *J* = 6.3 Hz, 2H), 4.18 (td, *J* = 9.7, 4.5 Hz, 1H), 3.62 (d, *J* = 3.1 Hz, 2H), 2.95 (br s, 1H), 2.13 (ddd, *J* = 12.7, 7.3, 5.9 Hz, 1H), 1.76 (m, 1H), 1.36 - 1.14 (m, 12H), 0.89 (s, 9H), 0.06 (s, 3H) 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 156.32 (C_q), 155.27 (C_q), 136.34 (+), 116.78 (-), 91.12 (+), 79.56 (+), 70.68 (+), 69.86 (+), 65.70 (-), 44.83 (+), 33.53 (-), 26.05 (+), 22.10 (+), 22.02 (+), 18.48 (C_q), -5.14 (+), -5.22 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3289 (br), 2979, 2930, 2858, 1721, 1470, 1407, 1373, 1291, 1252, 1233, 1181, 1106, 1038, 1005, 990, 915, 834, 776, 667; MS (ESI): m/z (%) = 445.1 (100) [MH^+], 889.6 (75) [$2MH^+$]; HRMS (ESI): calcd for $C_{21}H_{44}N_2O_6Si$ [MH_4^+] 462.2994, found 462.3004.

184b: R_f = 0.25 (PE/EA 5:1); analytically pure sample could not be separated from **184a**.

185: R_f = 0.17 (PE/EA 5:1); $[\alpha]_D^{20}$ = - 15.4 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 6.50 (br s, 3/4H), 6.27 (br s, 1/4H), 4.94 (sept, *J* = 6.5 Hz, 2H), 4.54 - 4.38 (m, 1H), 3.79 (d, *J* = 5.9 Hz, 1H), 3.49 (d, *J* = 4.9 Hz, 2H), 3.18 (br s, 2H), 2.33 - 2.16 (m, 1H), 1.70 (dd, *J* = 12.2, 8.3 Hz, 1H), 1.54 - 1.42 (m, 1H), 1.31 - 1.14 (m, 12 H), 1.23 - 1.13 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H).^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 155.87 ($2C_q$), 88.02 (+), 70.19 (+), 69.80 (+), 66.02 (-), 64.85 (+), 49.53 (-), 31.56 (-), 30.53 (+), 26.09 (+), 22.62 (+), 22.19 (+), 22.11 (+), 18.54 (C_q), -5.17 (+), -5.20 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3289 (br), 2977, 2927, 2858, 1708, 1508, 1469, 1405, 1385, 1253, 1223, 1179, 1107, 1033, 1013, 938, 835, 776, 668; MS (ESI): m/z (%) = 445.1 (100) [MH^+], 462.1 (50) [MNH_4^+], 889.6 (60) [$2MH^+$]; HRMS (ESI): calcd for $C_{21}H_{41}N_2O_6Si$ [MH^+] 445.2728, found 445.2741.

bis(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methyl) oxalate (190)

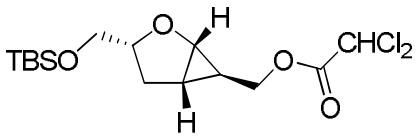


A solution of oxalyl chloride (39 mg, 0.31 mmol, 1.5 equiv) in anhydrous DCM (0.5 ml) was added dropwise to a stirred solution of alcohol **116** (53 mg, 0.21 mmol) in anhydrous DCM (2 ml), containing NEt_3 (62 mg, 0.62 mmol, 3.0 equiv) at 0 °C. After 0.5 h the reaction mixture was quenched with water (3 mL) and extracted with EA (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (PE/EA 9:1) to give compound **190** (50 mg, 0.18 mmol, 86%) as a colorless oil.

R_f = 0.31 (PE/EA 3:1); $[\alpha]_D^{20}$ = + 24.2 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 4.48 (ddd, *J* = 12.9, 8.4, 4.7 Hz, 2H), 4.06 (dd, *J* = 11.8, 7.7 Hz, 2H), 3.97 (dd, *J* = 11.8, 7.9 Hz, 2H), 3.86 (dd, *J* = 6.3, 0.9 Hz, 2H), 3.49 (dd, *J* = 4.7, 1.1 Hz, 4H), 2.28 (ddd, *J* = 12.9, 8.4, 7.2 Hz, 2H), 1.77 (ddd, *J* = 12.9, 7.5, 1.3 Hz, 2H), 1.69 - 1.58 (m, 2H), 1.39 (tdd, *J* = 7.8, 3.9, 1.0 Hz, 2H),

0.88 (s, 18H), 0.04 (s, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 157.94 (C_q), 87.81 (+), 66.73 (-), 65.90 (-), 64.55 (+), 31.23 (-), 30.12 (+), 26.08 (+), 23.08 (+), 18.54 (C_q), -5.18 (+), -5.22 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 2929, 2857, 1768, 1743, 1472, 1463, 1414, 1389, 1361, 1313, 1253, 1161, 1135, 1096, 1005, 939, 916, 835, 776, 670; MS (ESI): m/z (%) = 588.3 (40) [MNH_4^+], 593.3 (100) [MNa^+]; HRMS (ESI): calcd for $C_{28}H_{50}NaNO_8Si_2$ [MNa^+] 593.2936, found 593.2919.

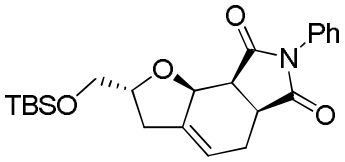
((1*S*,3*R*,5*S*,6*R*)-3-((tert-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methyl 2,2-dichloroacetate (191)



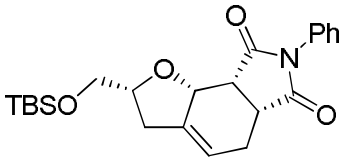
Dichloroacetyl chloride (36.5 mg, 0.25 mmol, 2.2 equiv) in anhydrous DCM (0.5 ml) was added dropwise to a stirred solution of alcohol **116** (29.1 mg, 0.11 mmol) in anhydrous DCM (1.4 ml) containing NEt_3 (25 mg, 0.25 mmol, 2.2 equiv) at room temperature under a nitrogen atmosphere. Further NEt_3 (13 mg, 0.13 mmol, 1.1 equiv) was added after 30 min and the reaction was stirred for additional 1 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (PE/EA 5:1) to afford compound **191** (39 mg, 0.11 mmol, 94%) as a colorless oil.

R_f = 0.42 (PE/EA 5:1); $[\alpha]_D^{20}$ = + 18.0 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 5.94 (s, 1H), 4.49 (ddt, *J* = 8.7, 7.6, 4.4 Hz, 1H), 4.03 (dd, *J* = 10.4, 6.5 Hz, 1H), 3.97 (dd, *J* = 10.4, 6.5 Hz, 1H), 3.85 (dd, *J* = 6.3, 1.0 Hz, 1H), 3.54 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.47 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.28 (ddd, *J* = 12.9, 8.5, 7.2 Hz, 1H), 1.80 (ddd, *J* = 12.9, 7.4, 1.4 Hz, 1H), 1.68 - 1.56 (m, 1H), 1.40 (tdd, *J* = 7.8, 3.9, 1.1 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 164.82 (C_q), 87.73 (+), 67.23 (-), 65.70 (-), 64.44 (+), 64.40 (+), 31.00 (-), 29.81 (+), 26.09 (+), 22.93 (+), 18.55 (C_q), -5.17 (+), -5.23 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2929, 2886, 2857, 1765, 1749, 1472, 1463, 1300, 1279, 1255, 1163, 1137, 1097, 1006, 962, 838, 816, 778, 670; MS (ESI): m/z (%) = 241.2 (95), 280.3 (100), 369.1 [MH^+] (30), 386.1 [MNH_4^+] (98); HRMS (ESI): calcd for $C_{15}H_{27}Cl_2O_4Si$ [MH^+] 369.1050, found 369.1040.

(2*R*,5a*S*,8a*S*,8b*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)-7-phenyl-5,5a,8a,8b-tetrahydro-2*H*-furo[2,3-*e*]isoindole-6,8(3*H*,7*H*)-dione (206a) and (2*R*,5a*R*,8a*R*,8b*R*)-2-((*tert*-butyl-dimethylsilyloxy)methyl)-7-phenyl-5,5a,8a,8b-tetrahydro-2*H*-furo[2,3-*e*]isoindole-6,8(3*H*,7*H*)-dione (206b)



206a



206b

To a solution of diene ***ent*-153** (68 mg, 0.28 mmol) in DCM (1 mL) was added *N*-phenyl maleimide (54 mg, 0.31 mmol, 1.1 equiv) and stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EA acetate 2:1) to afford both **206a** and **206b** as a colorless solid. Crystallizations from ether/*n*-pentane gave a crystalline solid of compound **206a** (82 mg, 0.20 mmol, 70%) and compound **206b** (15 mg, 0.04 mmol, 13%).

206a: mp = 142 °C; R_f = 0.48 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 47.7 (DCM, c = 1.0); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.52 - 7.29 (m, 3H), 7.20 (dt, *J* = 3.5, 2.1 Hz, 2H), 5.85 - 5.64 (m, 1H), 4.72 - 4.54 (m, 1H), 4.24 (qd, *J* = 7.2, 4.3 Hz, 1H), 3.74 (qd, *J* = 10.7, 4.0 Hz, 2H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.22 (ddd, *J* = 8.6, 6.7, 1.6 Hz, 1H), 2.87 (ddd, *J* = 15.3, 7.3, 1.7 Hz, 1H), 2.73 - 2.45 (m, 2H), 2.29 - 2.05 (m, 1H), 0.96 - 0.75 (m, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 178.68 (C_q), 174.89 (C_q), 143.87 (C_q), 132.08 (C_q), 129.20 (+), 128.65 (+), 126.49 (+), 115.65 (+), 80.71 (+), 76.16 (+), 65.37 (-), 43.80 (+), 39.45 (+), 31.98 (-), 25.96 (+), 24.79 (-), 18.36 (C_q), -5.21 (+), -5.33 (+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2950, 2928, 2855, 1706, 1499, 1472, 1386, 1254, 1205, 1185, 1098, 1074, 1008, 973, 878, 835, 775, 756, 692, 624, 570; MS (ESI): m/z (%) = 414.0 (100) [MH^+], 431.0 (53) [MNH_4^+], 827.4 (20) [$2MH^+$]; HRMS (ESI): calcd for $C_{23}H_{32}NO_4Si$ [MH^+] 414.2095, found 414.2105.

206b: R_f = 0.39 (PE/EA 1:1); $[\alpha]_D^{20}$ = + 5.1 (DCM, c = 0.5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 7.48 - 7.31 (m, 3H), 7.24 - 7.16 (m, 2H), 5.81 - 5.71 (m, 1H), 4.50 - 4.42 (m, 1H), 4.20 - 4.09 (m, 1H), 3.83 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.68 (t, *J* = 8.8 Hz, 1H), 3.50 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.28

- 3.19 (m, 1H), 2.91 (ddd, *J* = 15.6, 7.3, 1.7 Hz, 1H), 2.77 - 2.65 (m, 1H), 2.34 (m, 1H), 2.26 - 2.14 (m, 1H), 0.86 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 178.39 (C_q), 173.72 (C_q), 142.15 (C_q), 132.17 (C_q), 129.21 (+), 128.61 (+), 126.51 (+), 116.63 (+), 80.48 (+), 75.39 (+), 65.50 (-), 43.66 (+), 40.16 (+), 33.52 (-), 26.03 (+), 24.35 (-), 18.46 (C_q), -5.21 (+), -5.26(+); IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2929, 2856, 1712, 1499, 1471, 1380, 1253, 1181, 1098, 837, 778, 754, 692; MS (ESI): m/z (%) = 414.0 (100) [MH^+], 431.0 (30) [MNH_4^+], 827.4 (5) [$2MH^+$], 844.6 (25) [$2MNH_4^+$]; HRMS (ESI): calcd for $C_{23}H_{32}NO_4Si$ [MH^+] 414.2095, found 414.2099.

Pharmacological methods

Materials

Histamine dihydrochloride was purchased from Alfa Aesar GmbH & Co. KG (Karlsruhe, Germany). [^{3}H]N^{α}-methylhistamine and [^{3}H]histamine were from PerkinElmer Life Sciences (Boston, MA). Guanosine diphosphate (GDP) was from Sigma-Aldrich Chemie GmbH (Munich, Germany), unlabeled GTPγS was from Roche (Mannheim, Germany). [^{35}S]GTPγS was from PerkinElmer Life Sciences (Boston, MA) or Hartmann Analytic GmbH (Braunschweig, Germany). GF/C filters were from Whatman (Gaithersburg, USA). For liquid scintillation counting was used: PerkinElmer MicroBeta^2 2450 MicroplateCounter (Massachusetts, USA), Brandel Harvester MWXRT-96TI, Brandel (Gaithersburg, USA). Scintillation cocktail RotiszintTM eco plus was from Carl Roth GmbH & Co KG (Karlsruhe, Germany).

[^{35}S]GTPγS binding assay[220,221]

[^{35}S]GTPγS binding assays were performed as previously described for the H_3R[222,223] and H_4R.[224] H_3R assays: Sf9 insect cell membranes coexpressing the hH_3R, mammalian $G\alpha_{i2}$ and $G\beta_1\gamma_2$ were employed, H_4R assays: Sf9 insect cell membranes coexpressing the hH_4R, mammalian $G\alpha_{i2}$ and $G\beta_1\gamma_2$ were employed.

The respective membranes were thawed, sedimented by a 10 min centrifugation at 4 °C and 13000 g. Membranes were resuspended in binding buffer (12.5 mM $MgCl_2$, 1 mM EDTA, and 75 mM Tris/HCl, pH 7.4). Each assay tube contained Sf9 membranes expressing the respective HR subtype (15 – 30 µg protein/tube), 1 µM GDP, 0.05% (w/v) bovine serum albumin, 0.2 nM [^{35}S]GTPγS and the investigated ligands (dissolved in millipore water or in a mixture (v/v) of 80% millipore water and 20% DMSO) at various concentrations in binding buffer (total volume 250 µL). All H_4R assays additionally contained 100 mM NaCl. For the determination of K_B values (antagonist mode of the [^{35}S]GTPγS binding assay) histamine was added to the reaction mixtures (final concentrations: $H_{3/4}R$: 100 nM). Incubations were conducted for 90 min at 25 °C and shaking at 250 rpm. Bound [^{35}S]GTPγS was separated from free [^{35}S]GTPγS by filtration through GF/C filters, followed by three washes with 2 ml of binding buffer (4 °C) using a Brandel Harvester. Filter-bound radioactivity was determined after an equilibration phase of at least 12 h by liquid scintillation counting. The experimental conditions chosen ensured that no more than 10% of the total amount of [^{35}S]GTPγS added

was bound to filters. Non-specific binding was determined in the presence of 10 µM unlabeled GTPγS.

Radioligand binding assay[225,226]

For the binding experiments the Sf9 insect cell membranes described above were employed. The respective membranes were thawed and sedimented by centrifugation at 4 °C and 13000 g for 10 min. Membranes were resuspended in binding buffer (12.5 mM $MgCl_2$, 1 mM EDTA and 75 mM Tris/HCl, pH 7.4). Each well (total volume 250 µL) contained 50 µg (hH_3R) or 120 µg (hH_4R) of membrane protein. Competition binding experiments were performed in the presence 3 nM [^{3}H]N^{α}-methylhistamine (hH_3R) or 15 nM [^{3}H]histamine (hH_3R and hH_4R) and increasing concentrations of unlabeled ligands. Incubations were conducted for 60 min at 25 °C and shaking at 250 rpm. Bound radioligand was separated from free radioligand by filtration through 0.3% polyethyleneimine-pretreated (PEI) GF/C filters, followed by three washes with 2 mL of cold binding buffer (4 °C) using a Brandel Harvester. Filter-bound radioactivity was determined after an equilibration phase of at least 12 h by liquid scintillation counting.

Data analysis and pharmacological parameters

All data are presented as mean of N independent experiments ± SEM. Agonist potencies were given as EC_{50} values (molar concentration of the agonist causing 50% of the maximal response). Maximal responses (intrinsic activities) were expressed as α-values. The α-value of histamine was set to 1.00; α-values of other compounds were referred to this value.

IC_{50} values were converted to K_i and K_B values using the Cheng-Prussoff equation.[227] pK_i values were analyzed by nonlinear regression and best fit to one-site (monophasic) competition isotherms. pEC_{50} and pK_B values from the functional [^{35}S]GTPγS were analyzed by nonlinear regression and best fit to sigmoidal dose-response curves (GraphPad Prism 5.0 software, San Diego, CA).

F. Appendix

HPLC purity data

Table 10. HPLC purity data of the synthezised target compounds.[a]

no.	t_R (min)	k'	purity (%)	no.	t_R (min)	k'	purity (%)
55a	3.30	0.42	98	**55b**	3.31	0.42	94
55c	3.29	0.41	> 99	**55d**	3.30	0.42	> 99
54a[b]	4.20 8.34	0.80 2.58	> 99	**54b**[b]	4.20 8.35	0.80 2.58	> 99
54c[b]	4.22 8.26	0.81 2.55	> 99	**54d**[b]	4.22 8.29	0.81 2.56	> 99
57a	4.34	0.86	93	**57b**	4.23	0.82	91
56a[b]	4.27 11.38	0.83 3.88	> 99	**56b**[b]	4.16 11.33	0.79 3.86	95

[a] Eurosphere-100 C18, 250 × 4.0 mm, 5 µm; Knauer, Berlin, Germany; t_0 = 2.33 min; gradient mode: MeCN (0.1% TFA)/water (0.1% TFA): 0 min: 10/90, 20 min: 90/10, 30 min: 90/10; [b] two t_R values due two partial protonation of the cyanoguanidines.

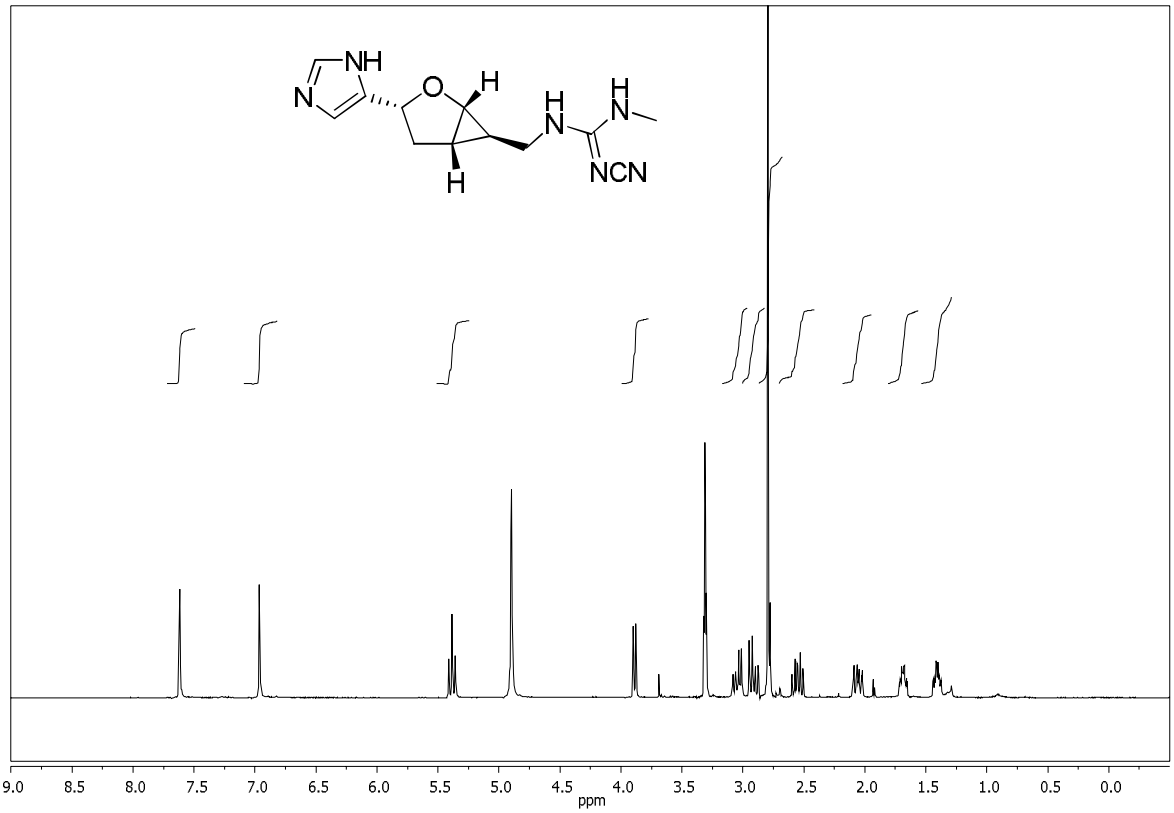
NMR Spectra

^{1}H- and ^{13}C-NMR spectra of the synthezised compounds.

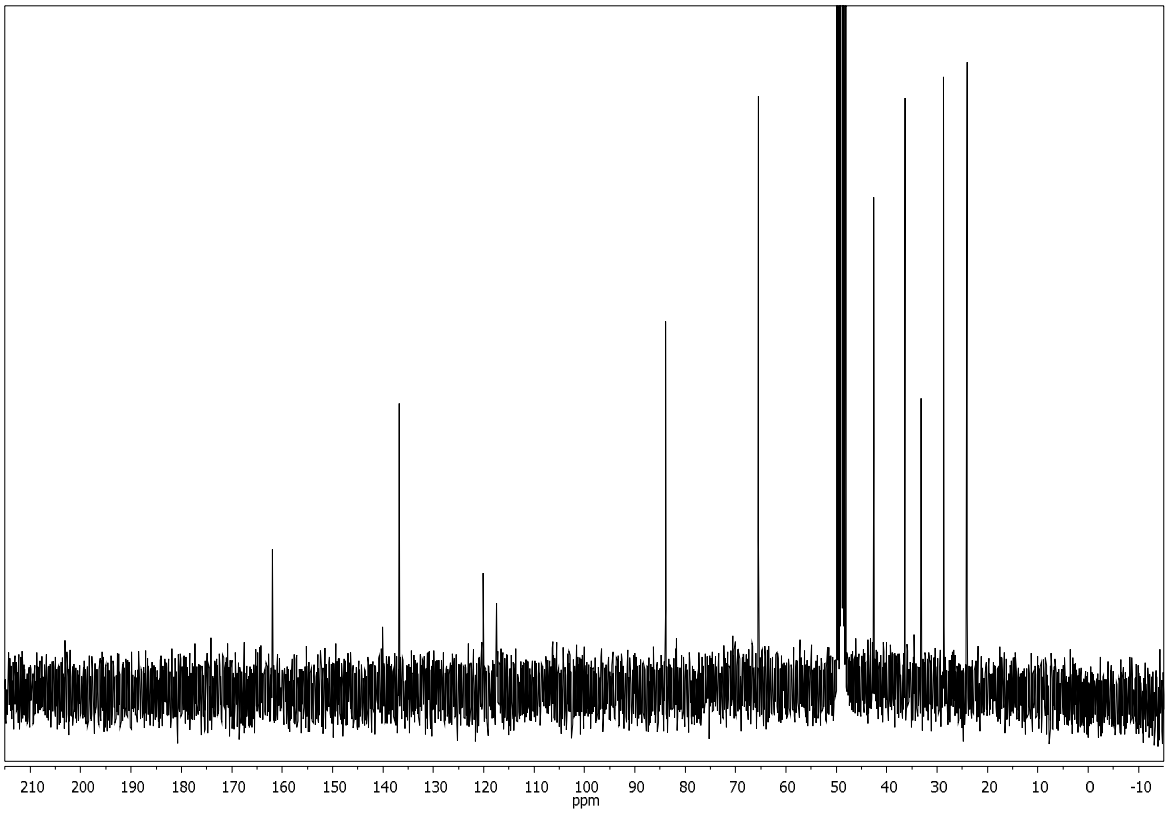
NMR frequencies and used solvents are stated for the respective spectra.

1-(((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-2-cyano-3-methylguanidine (54a)

^{1}H-NMR (300 MHz, MeOD)

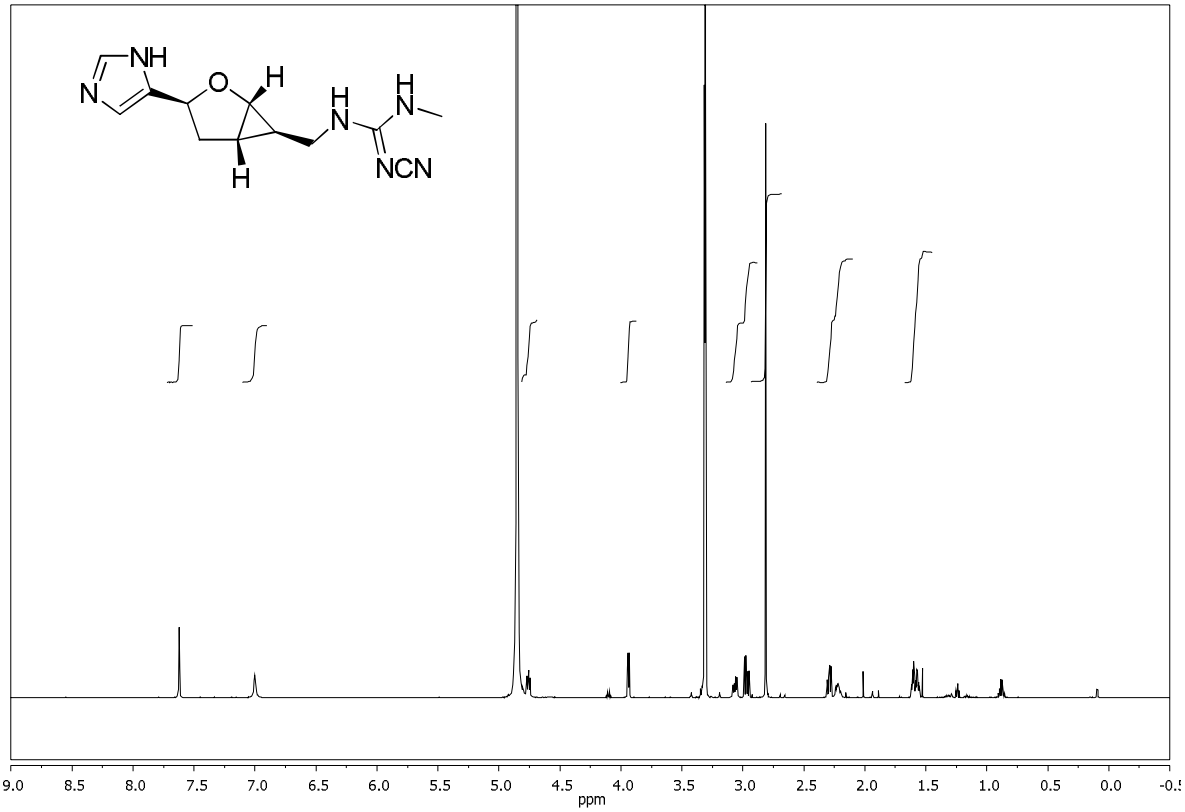


^{13}C-NMR (75 MHz, MeOD)

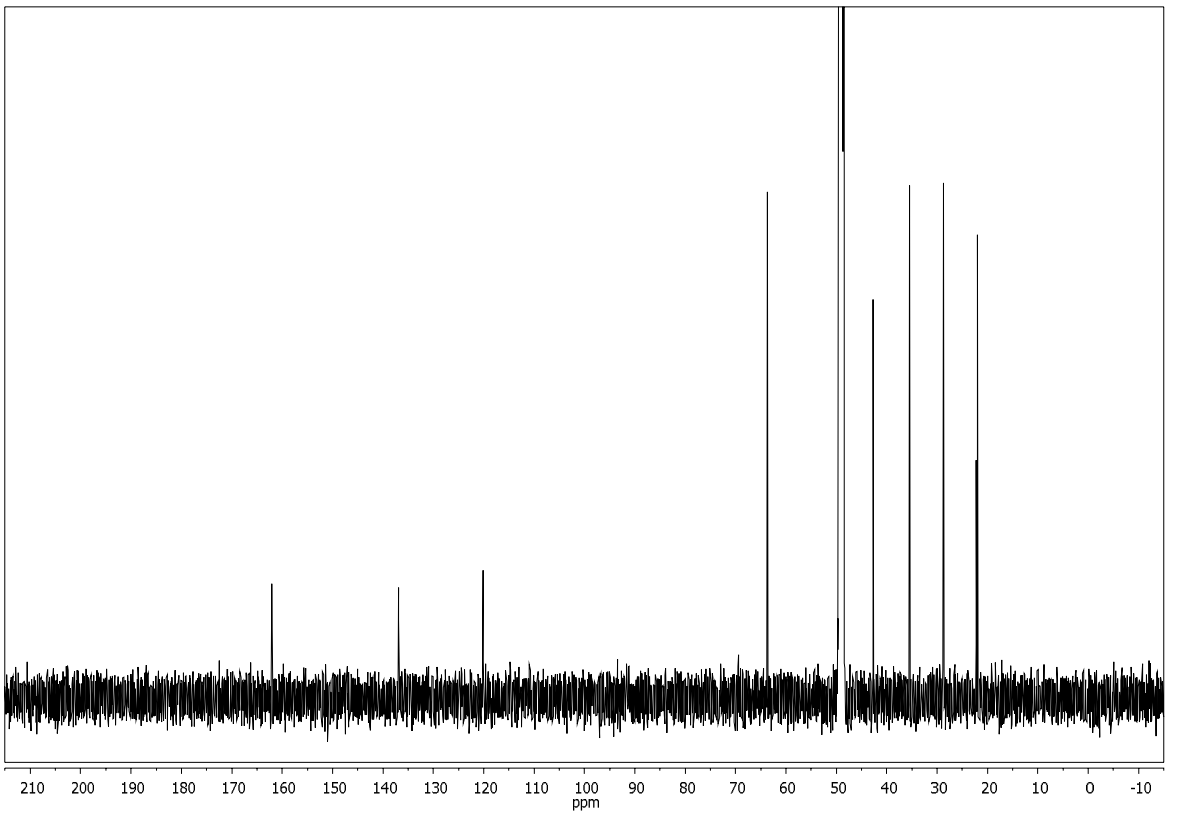


1-(((1*S*,3*S*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-2-cyano-3-methylguanidine (54c)

^{1}H-NMR (600 MHz, MeOD)

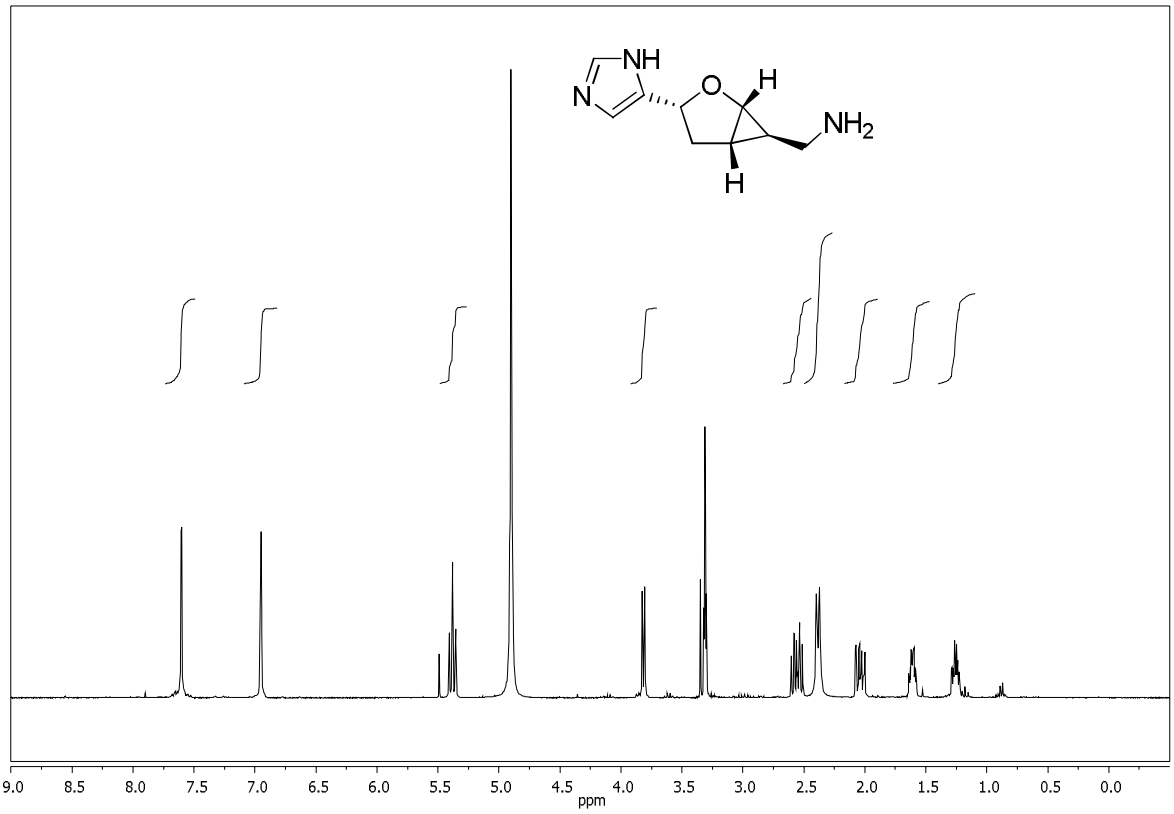


^{13}C-NMR (150 MHz, MeOD)

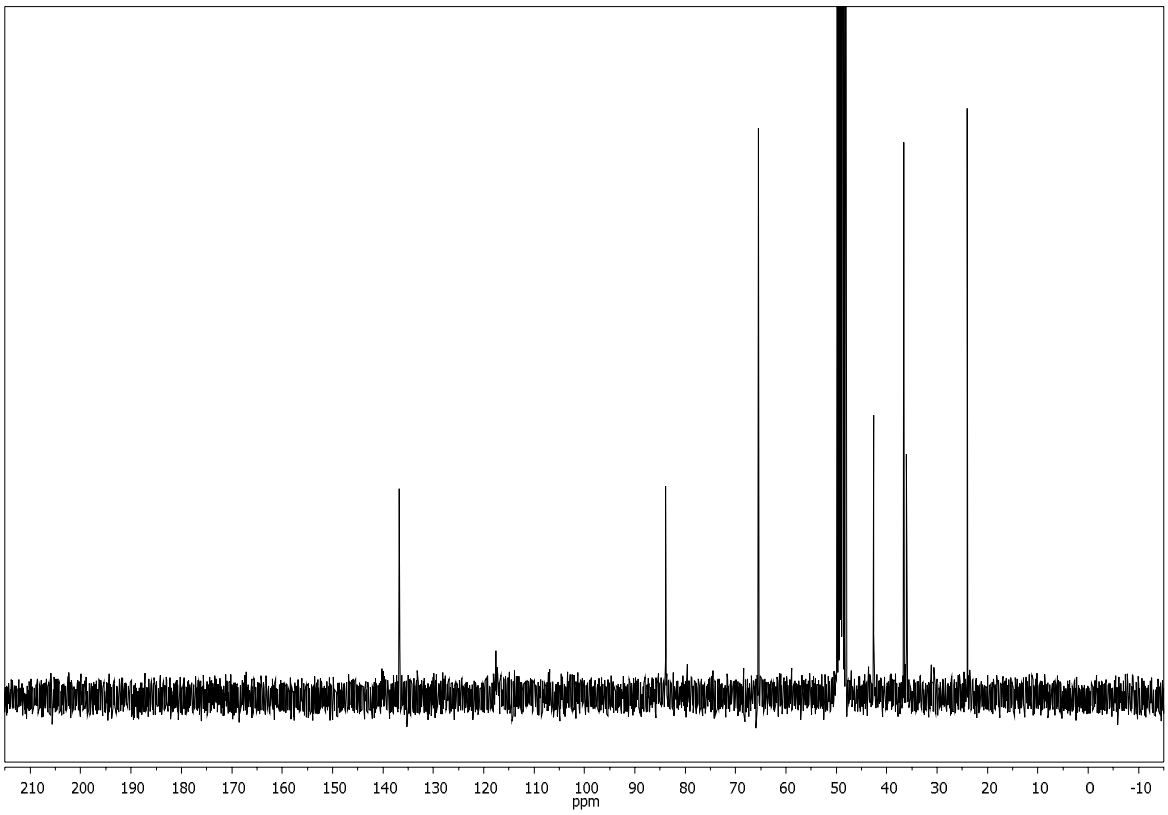


((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (55a)

^{1}H-NMR (300 MHz, MeOD)

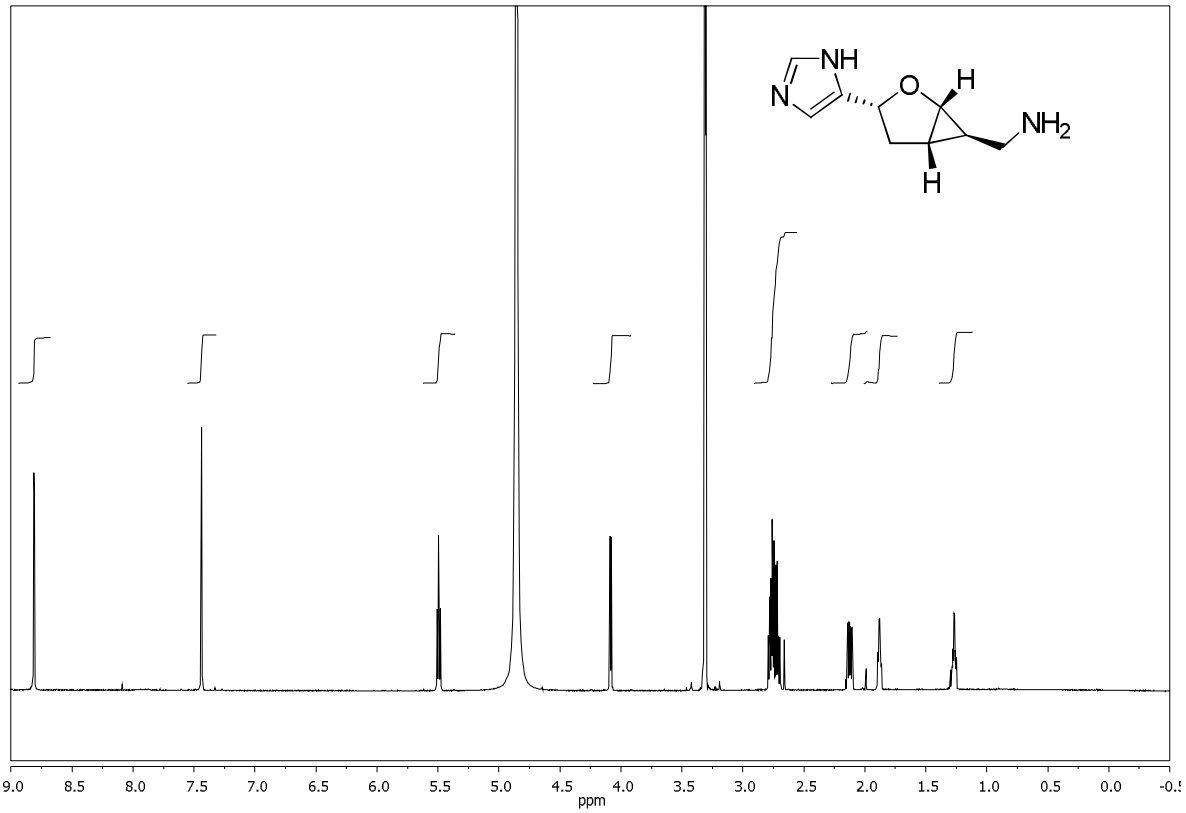


^{13}C-NMR (75 MHz, MeOD)

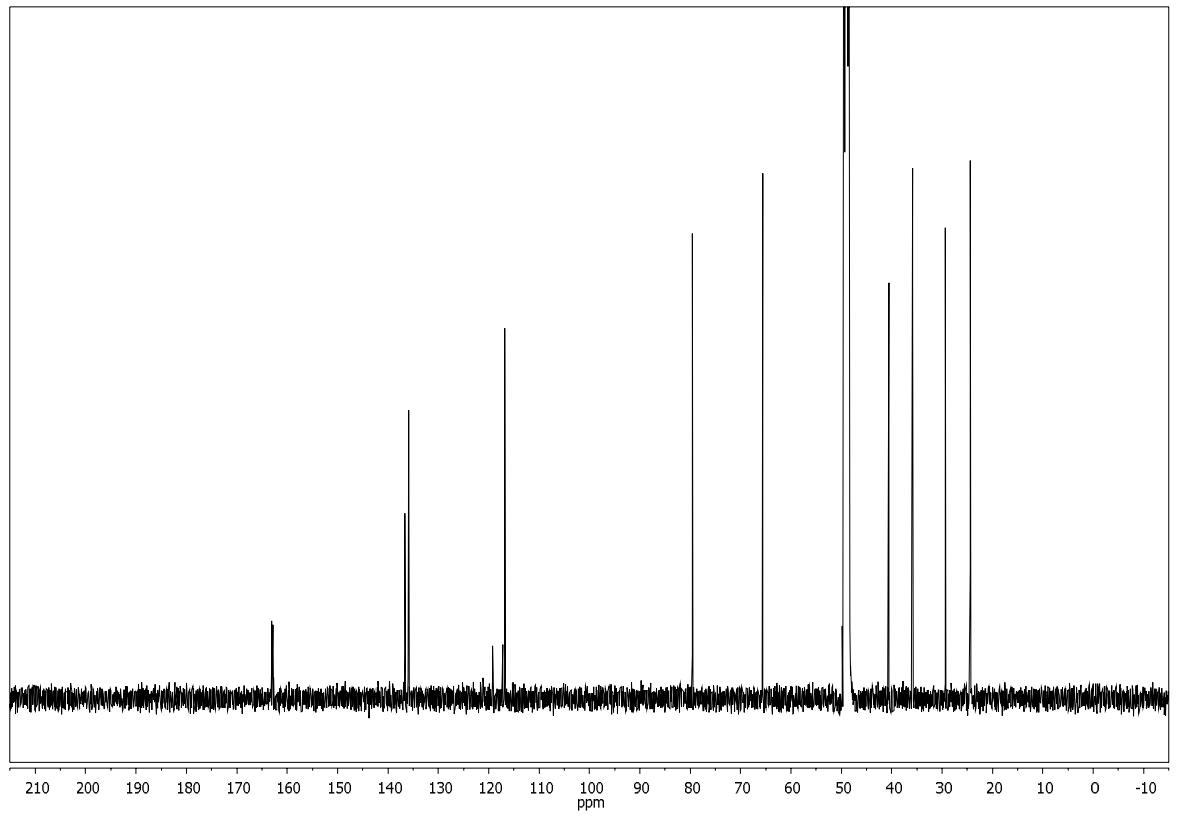


((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine • 2 TFA (55a•2TFA)

^{1}H-NMR (600 MHz, MeOD)



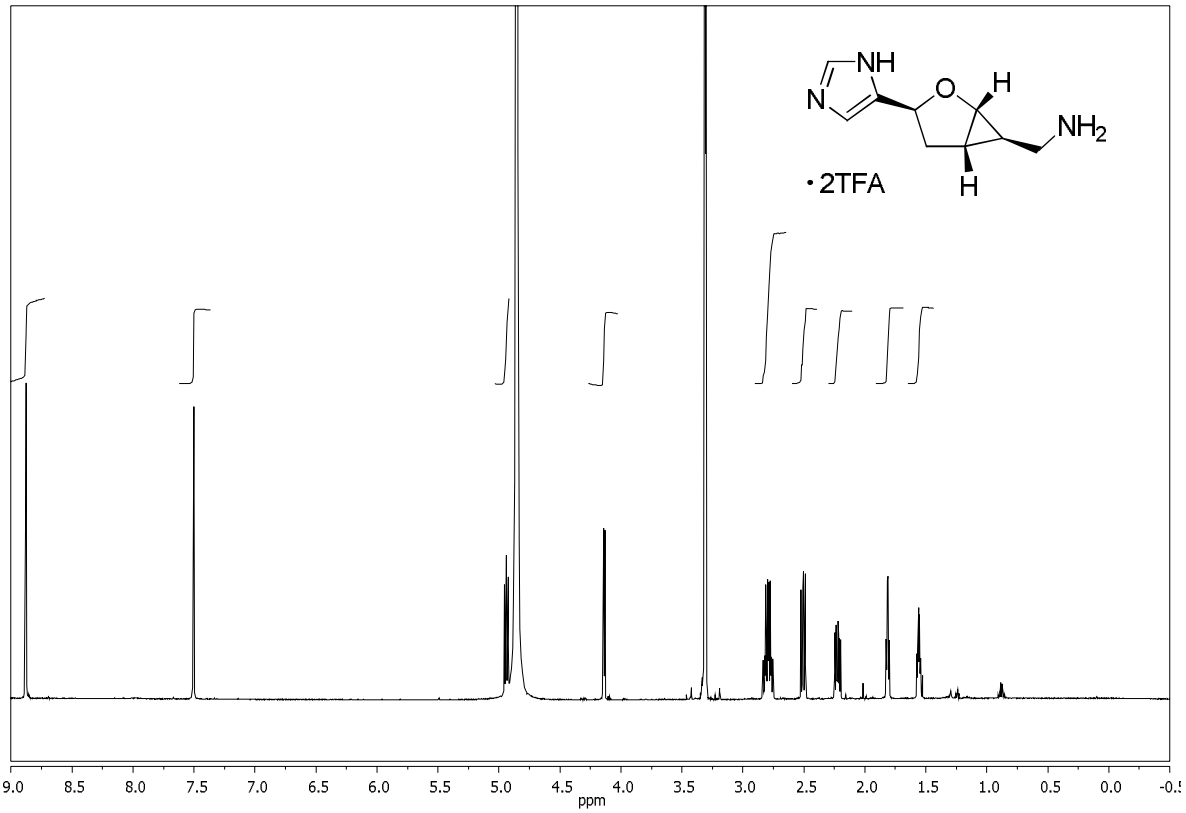
^{13}C-NMR (150 MHz, MeOD)



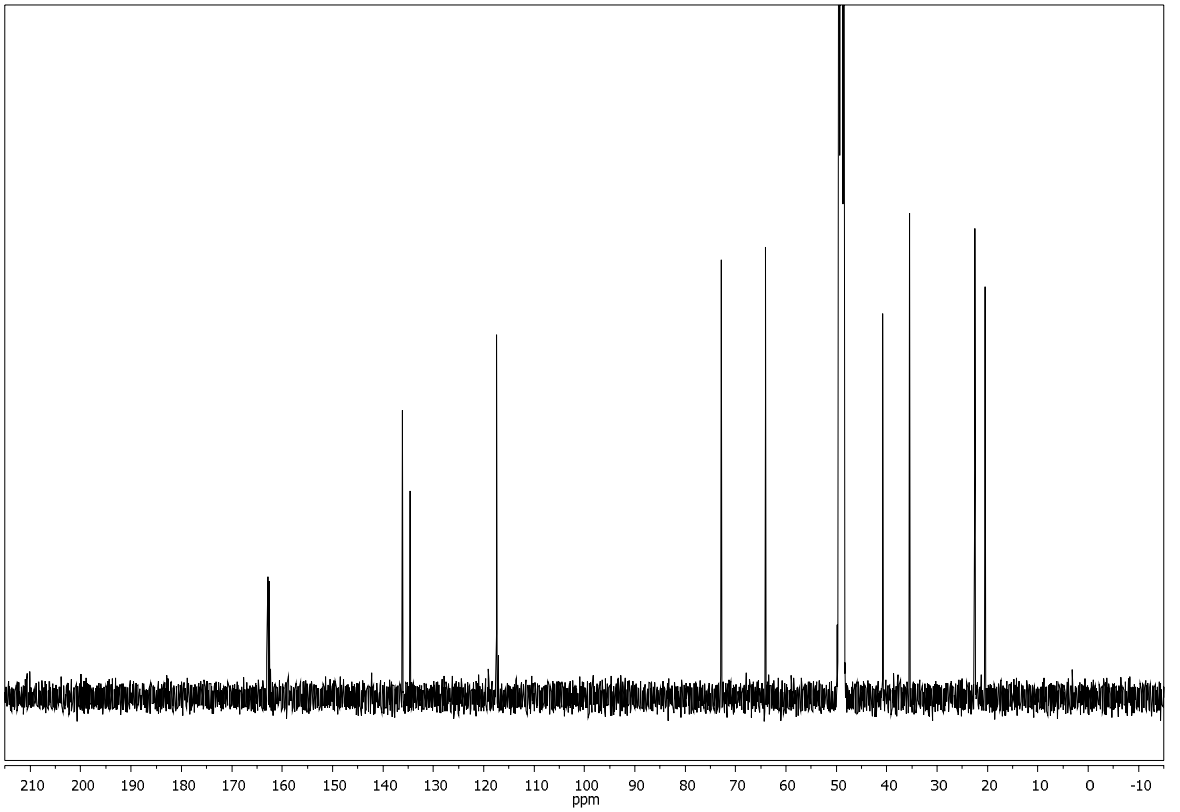
((1*S*,3*S*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine • 2 TFA

(55c• 2 TFA)

^{1}H-NMR (600 MHz, MeOD)

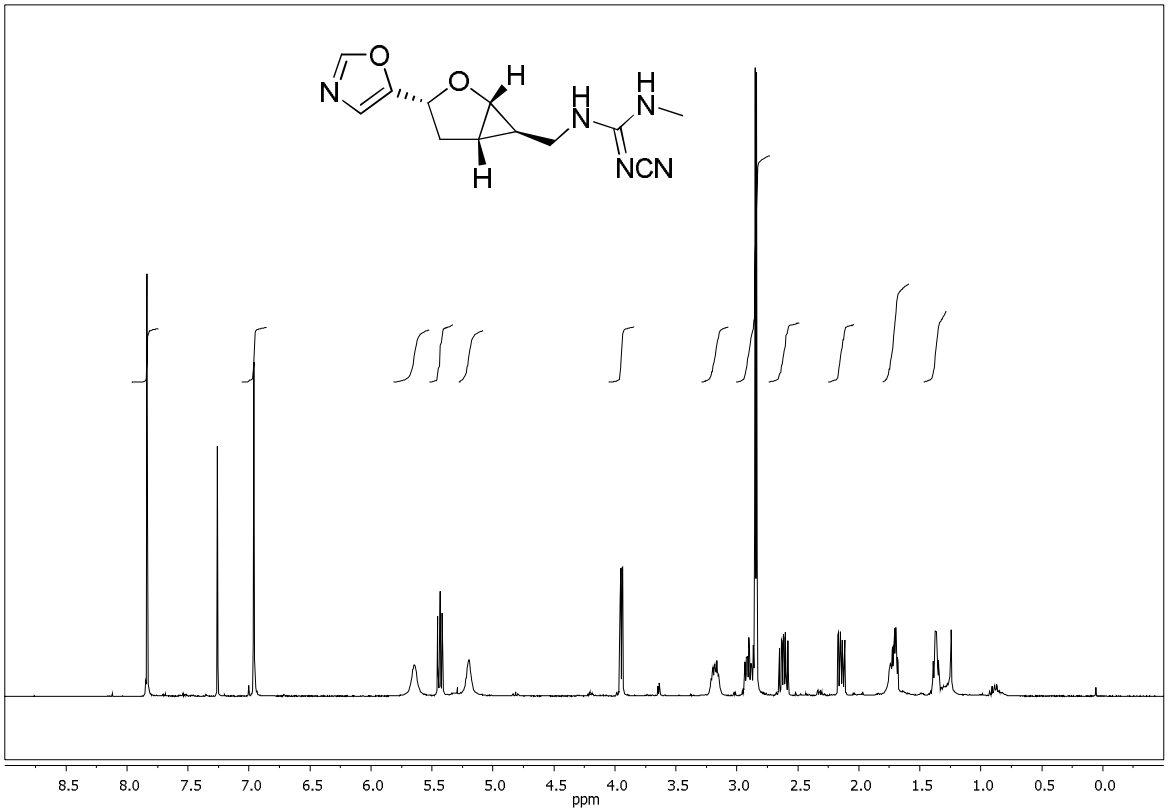


^{13}C-NMR (150 MHz, MeOD)

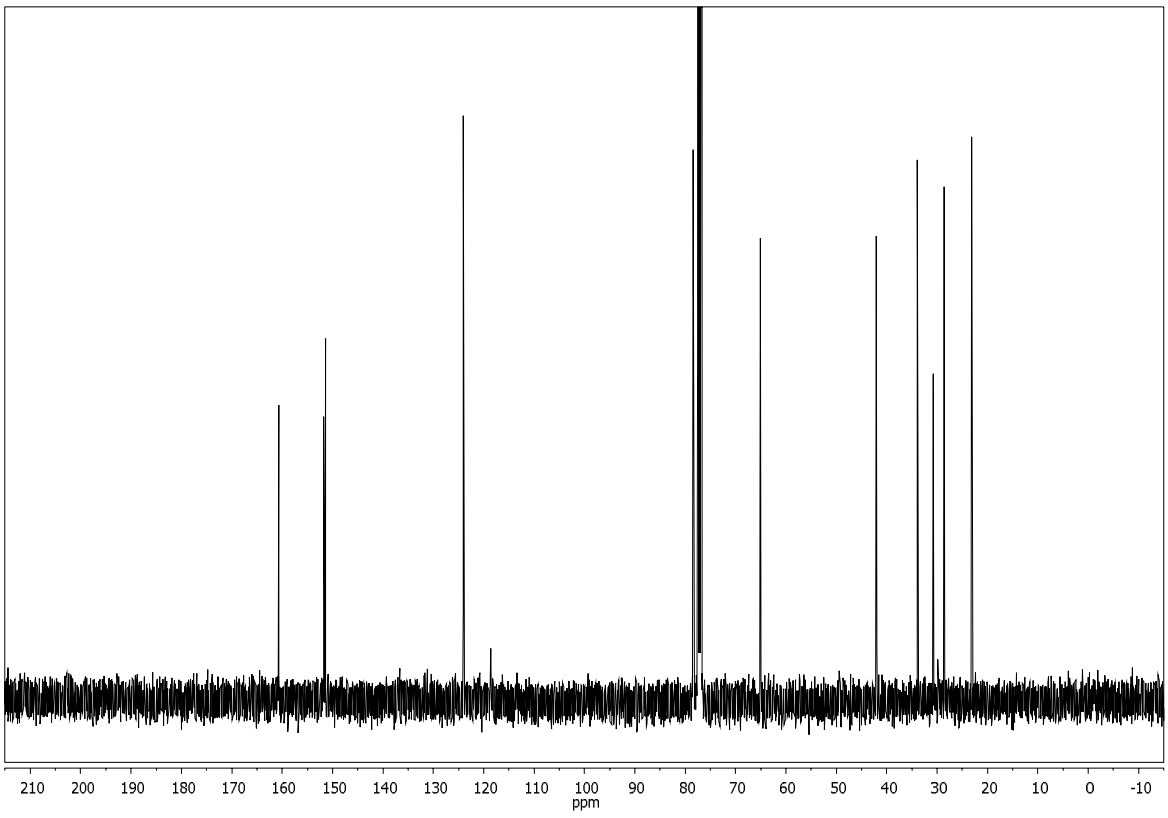


2-cyano-1-methyl-3-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl) guanidine (56a)

^{1}H-NMR (400 MHz, $CDCl_3$)

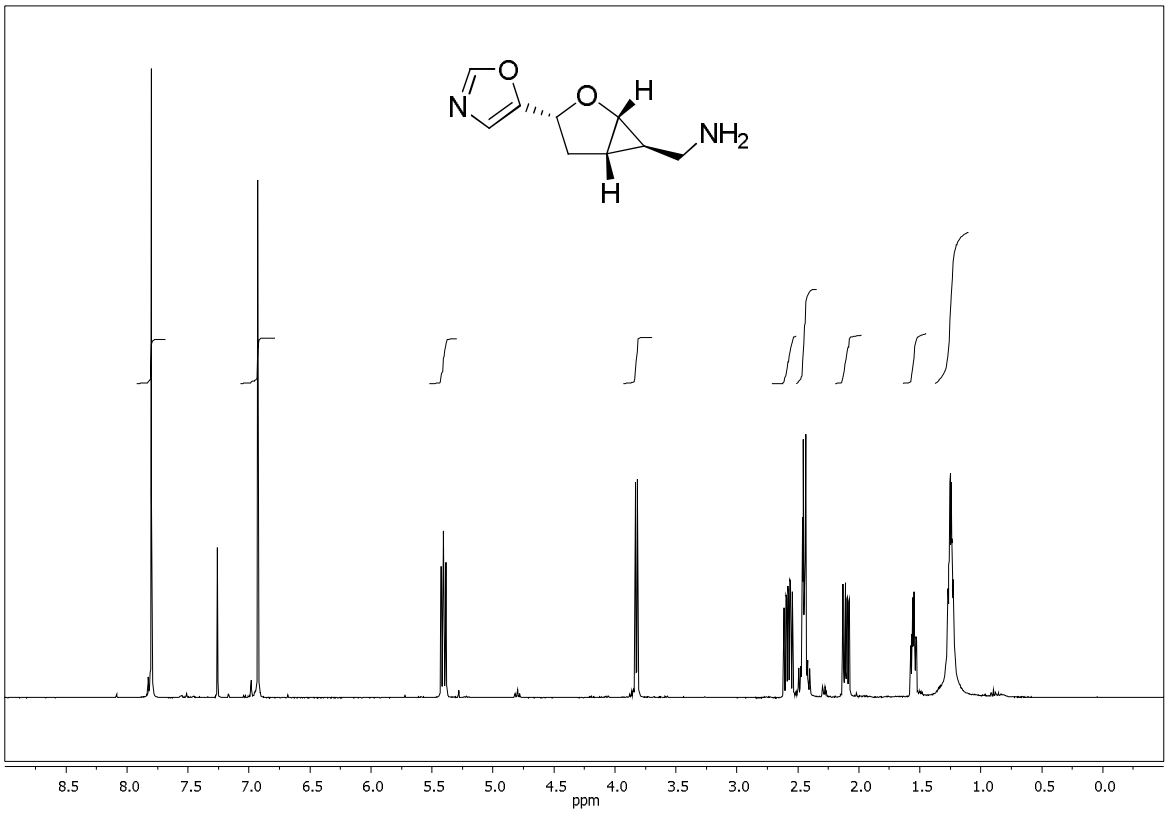


^{13}C-NMR (100 MHz, $CDCl_3$)

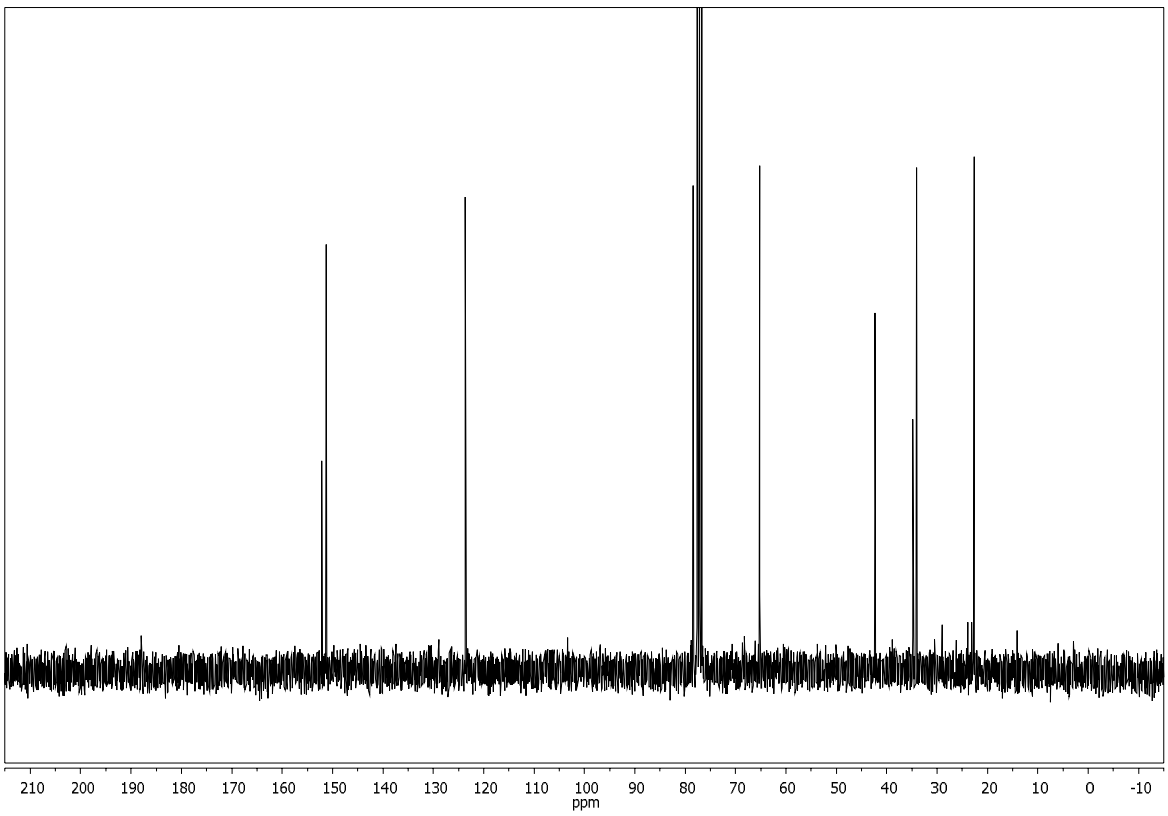


((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (57a)

^{1}H-NMR (400 MHz, $CDCl_3$)

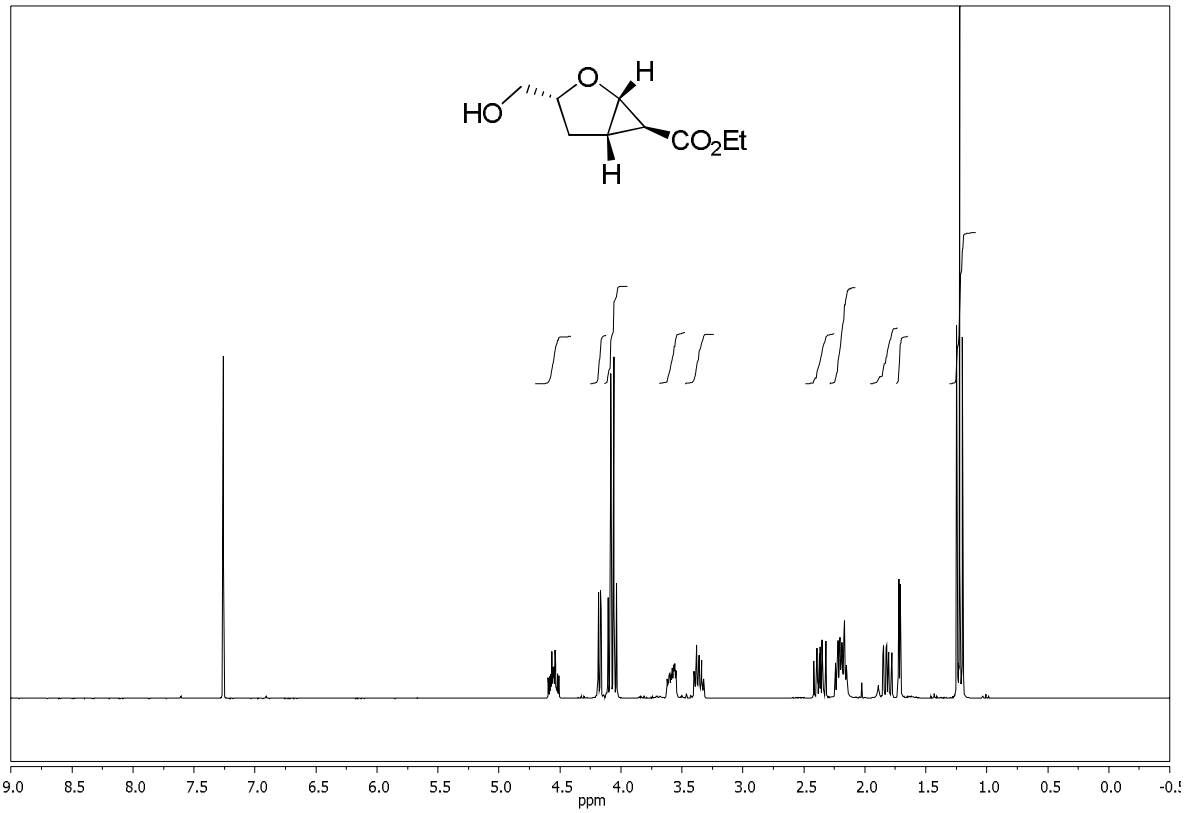


^{13}C-NMR (75 MHz, $CDCl_3$)

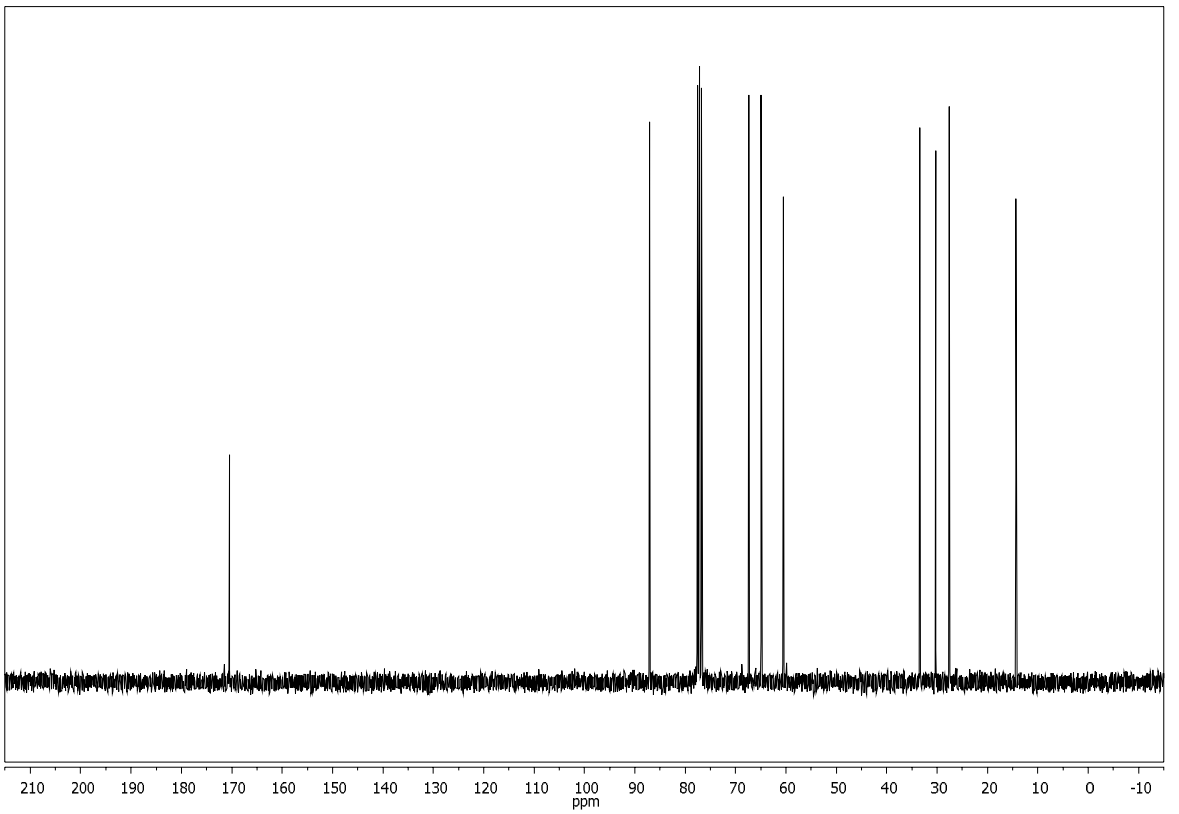


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (79)

^{1}H-NMR (300 MHz, $CDCl_3$)

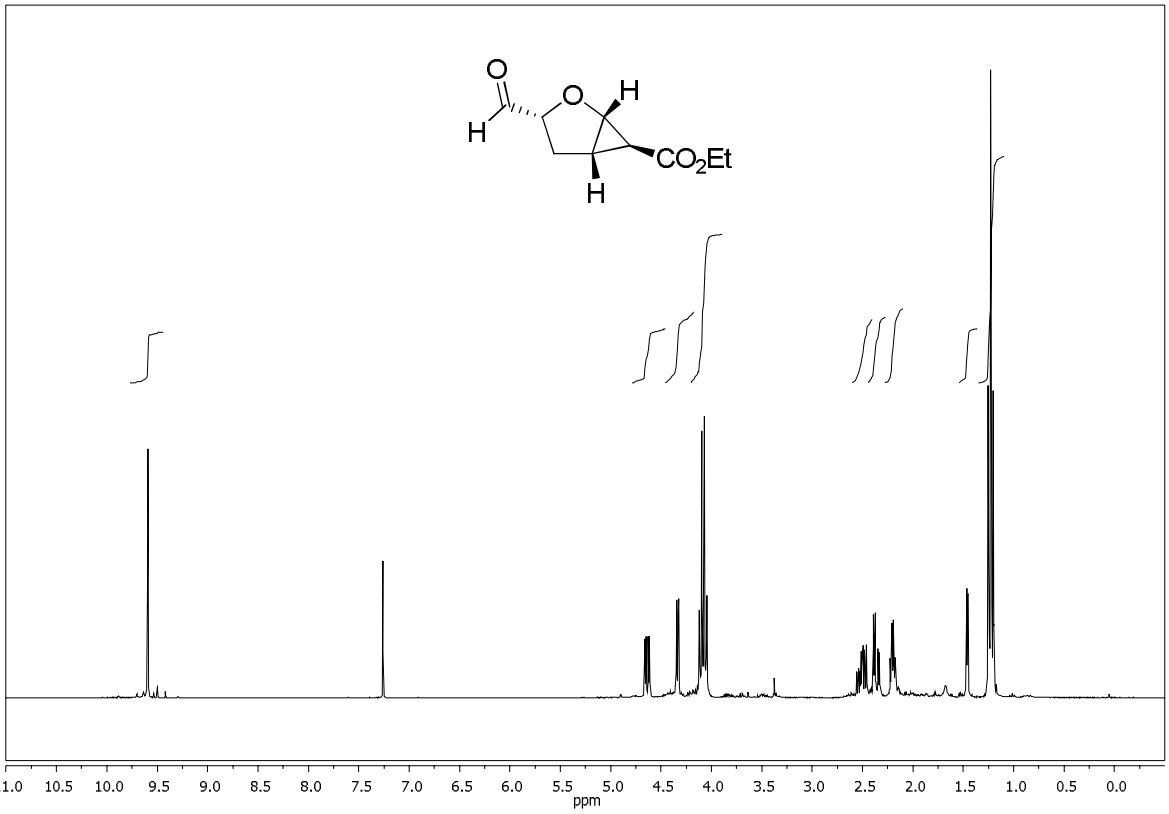


^{13}C-NMR (75 MHz, $CDCl_3$)

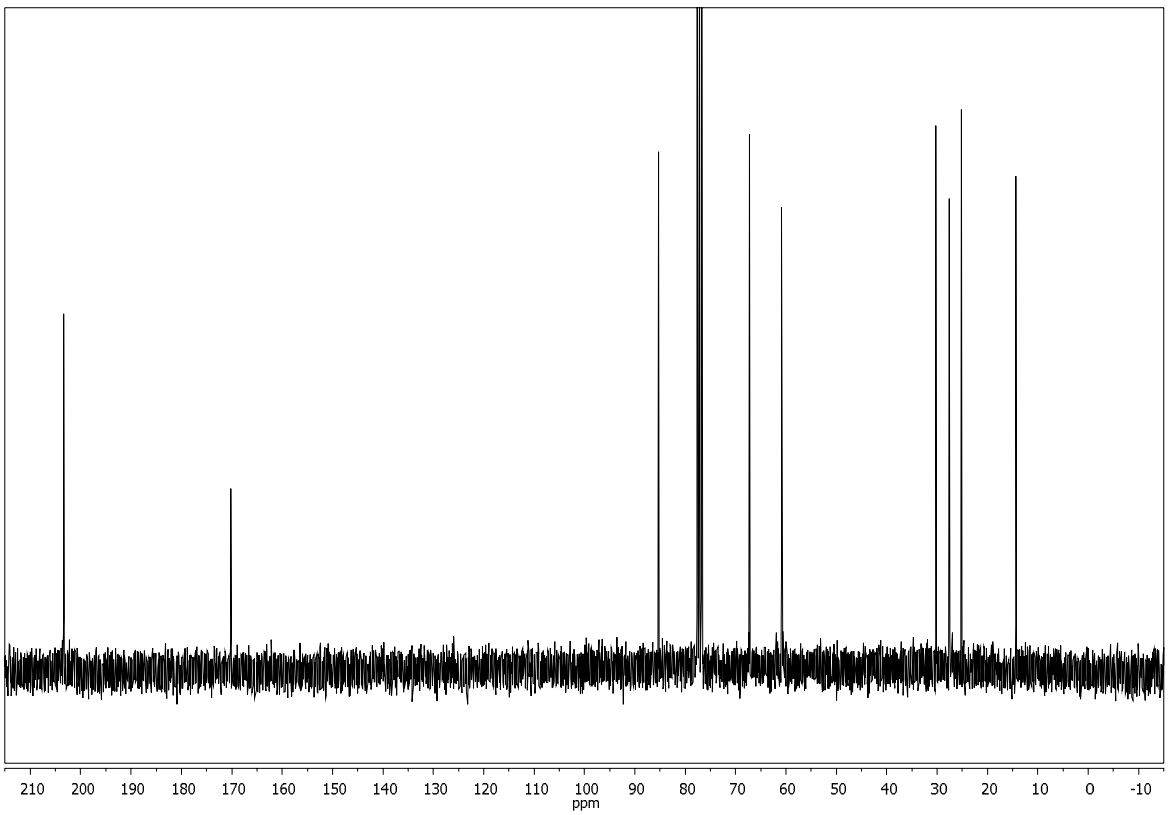


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-formyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (83)

^{1}H-NMR (300 MHz, $CDCl_3$)

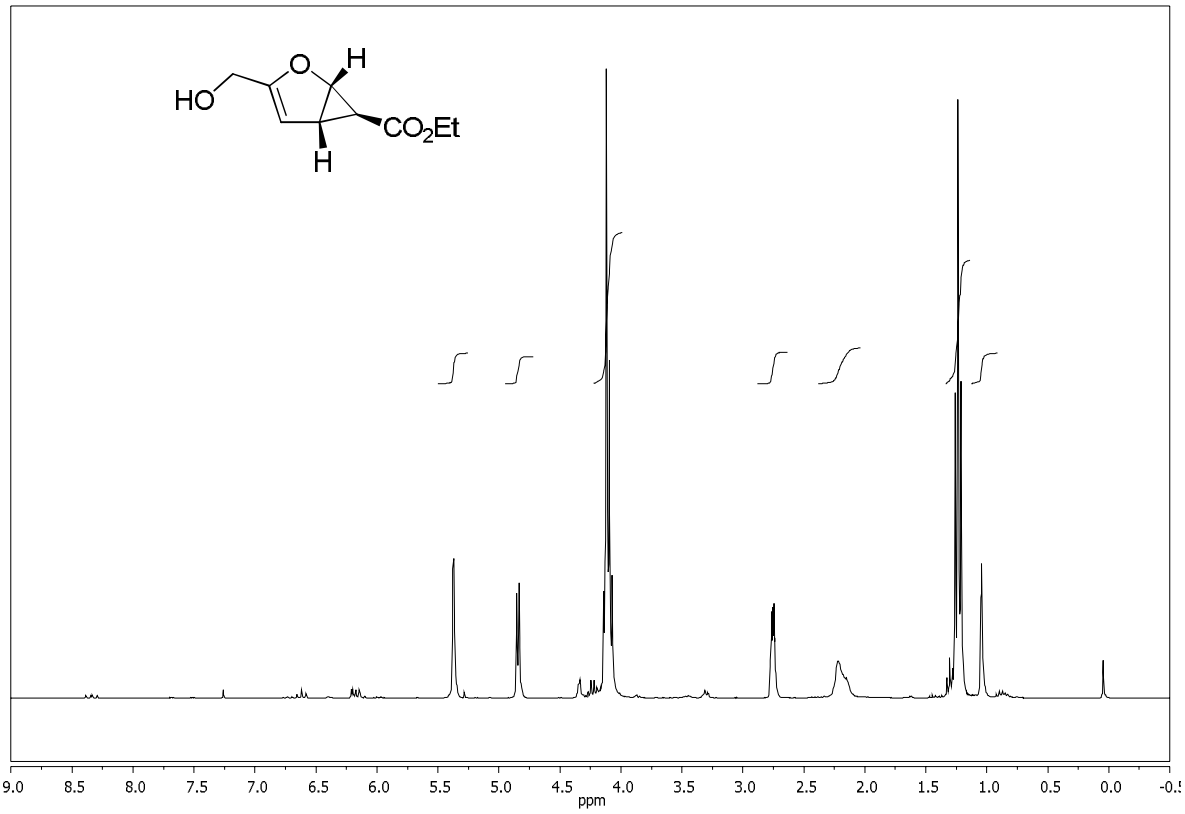


^{13}C-NMR (75 MHz, $CDCl_3$)

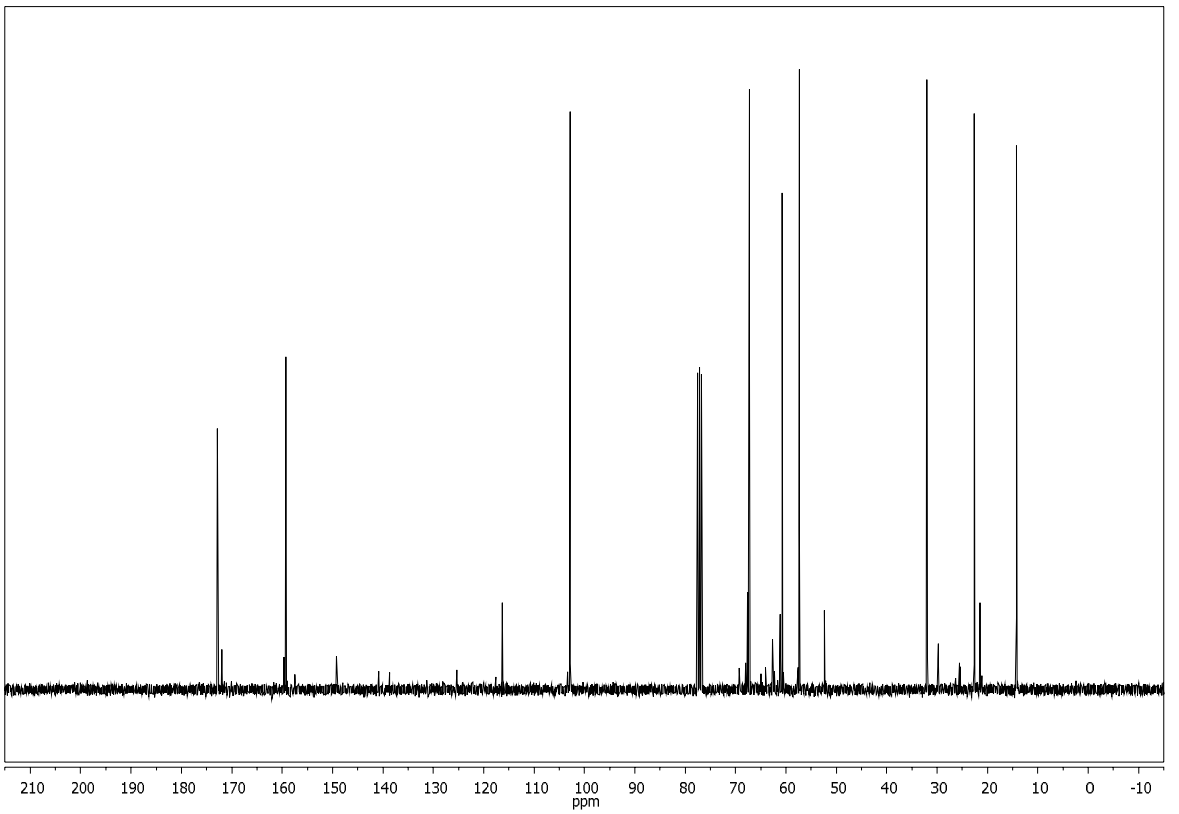


(1*S*,5*S*,6*S*)-ethyl 3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (98)

^{1}H-NMR (300 MHz, $CDCl_3$)

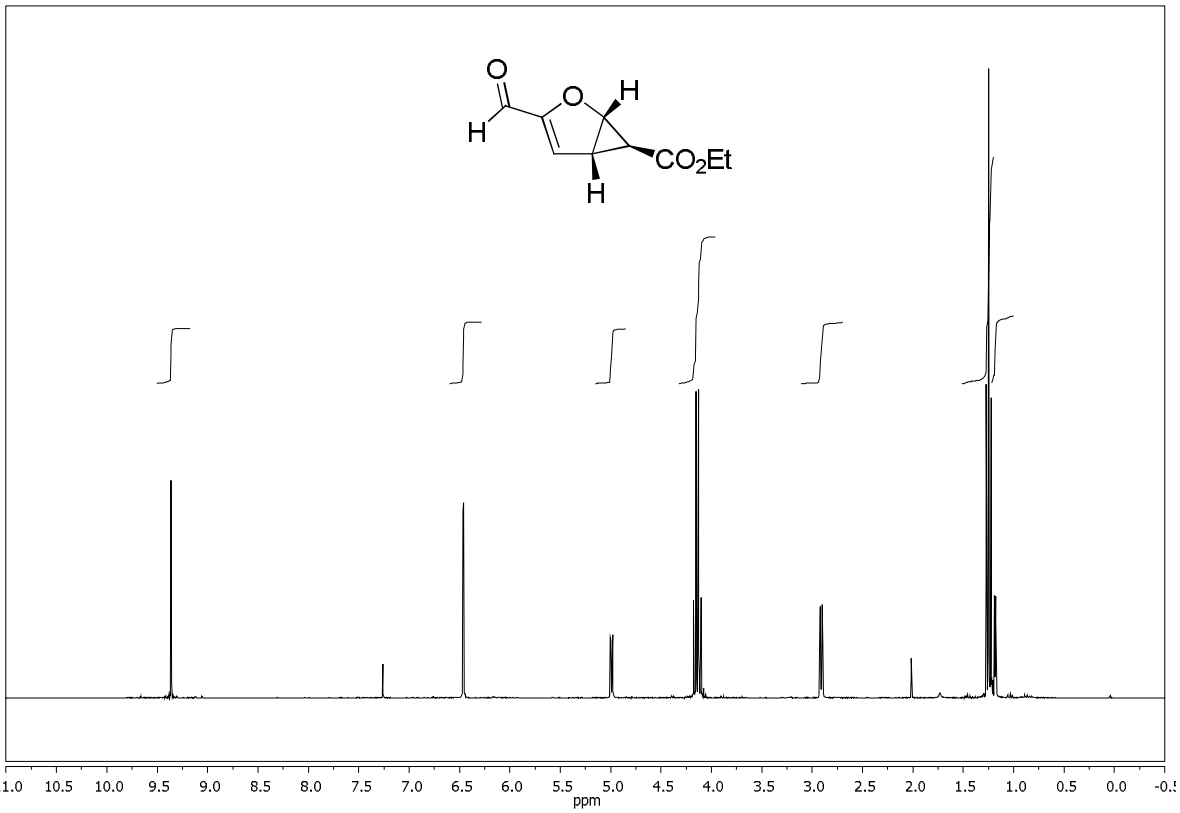


^{13}C-NMR (75 MHz, $CDCl_3$)

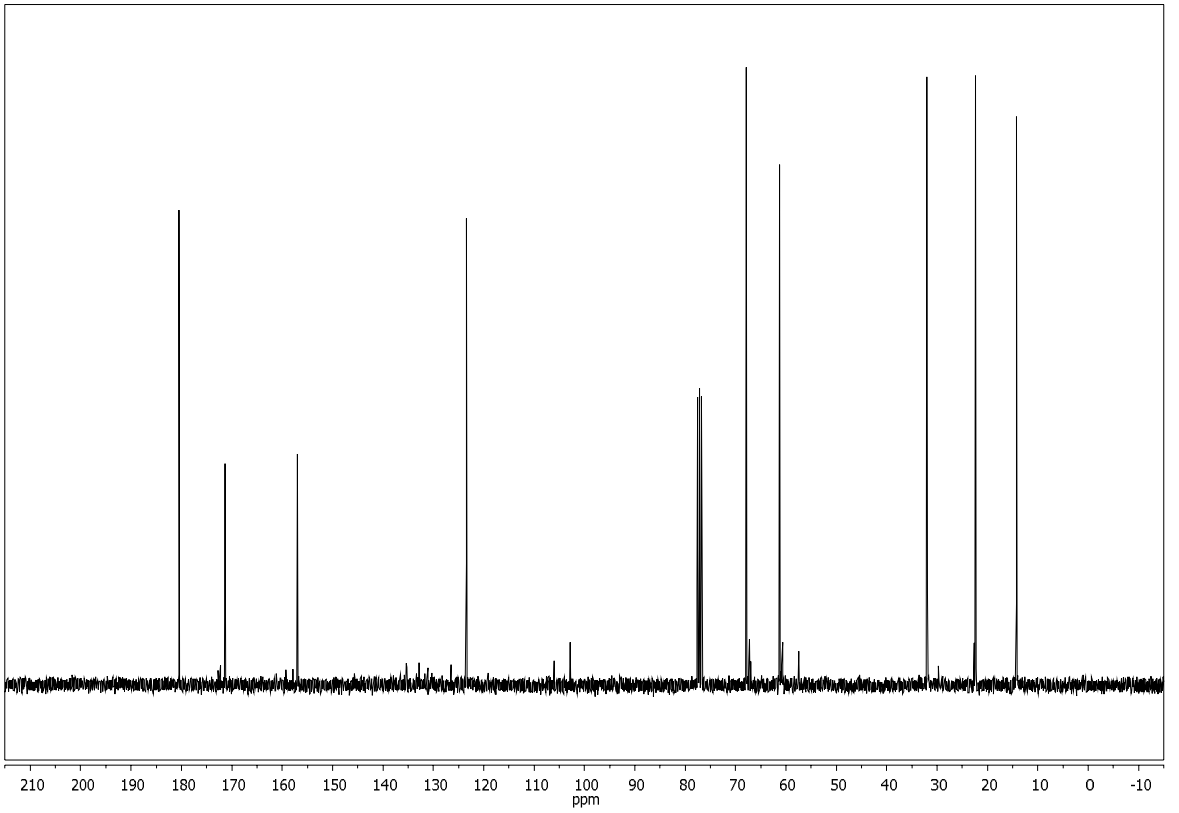


(1*S*,5*S*,6*S*)-ethyl 3-formyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (99)

^{1}H-NMR (300 MHz, $CDCl_3$)

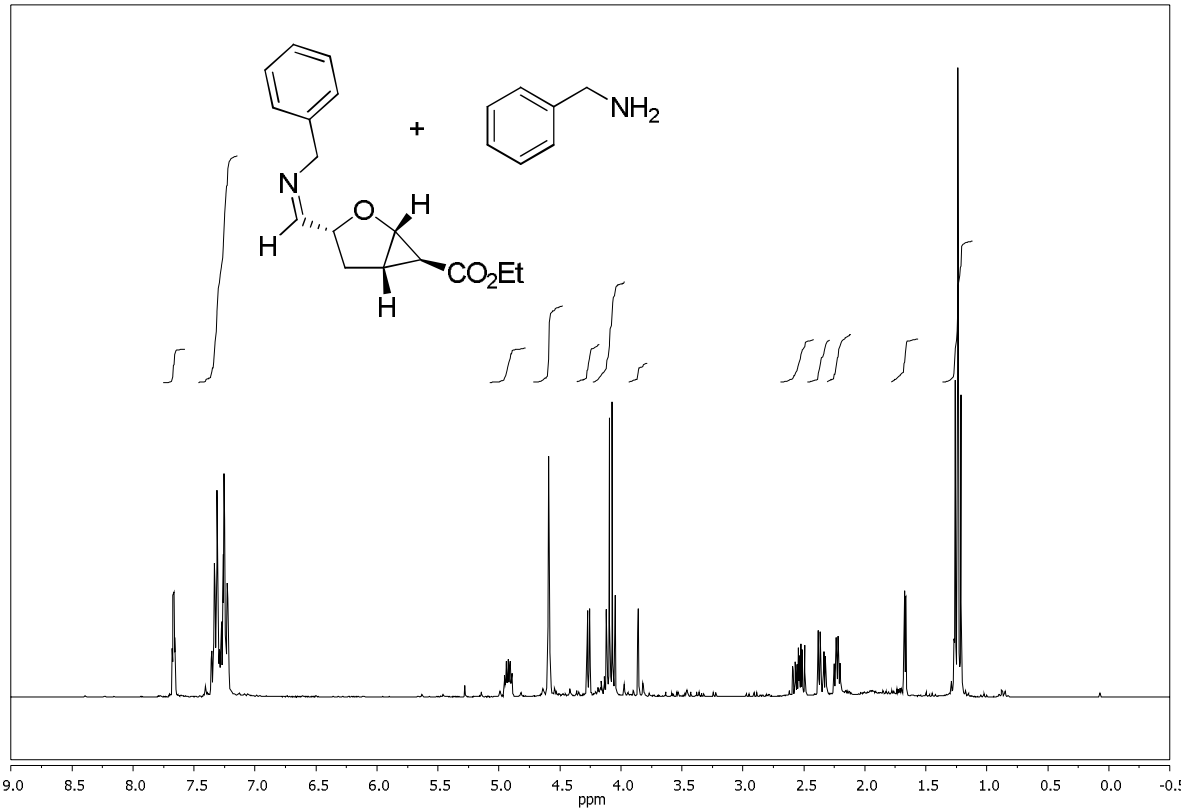


^{13}C-NMR (75 MHz, $CDCl_3$)

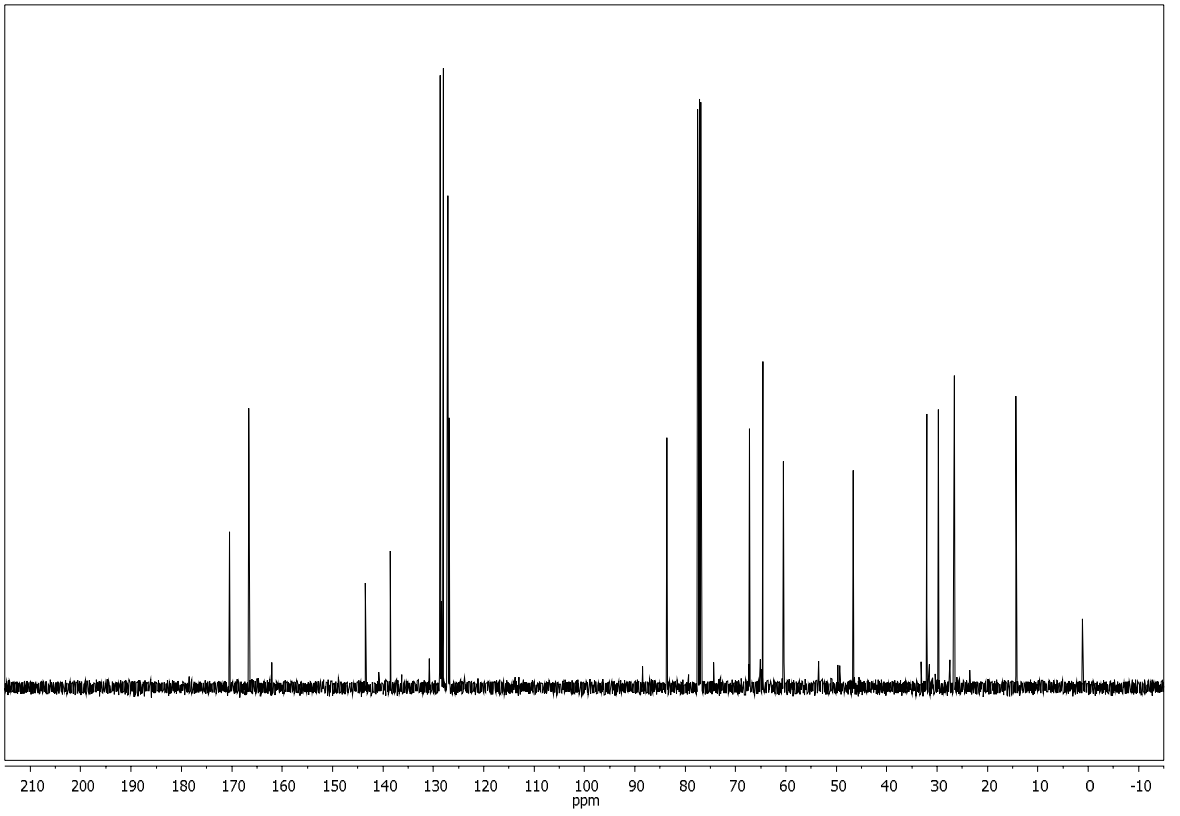


(1S,3R,5S,6S)-ethyl 3-((benzylimino)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (102) + benzylamine

^{1}H-NMR (300 MHz, $CDCl_3$)

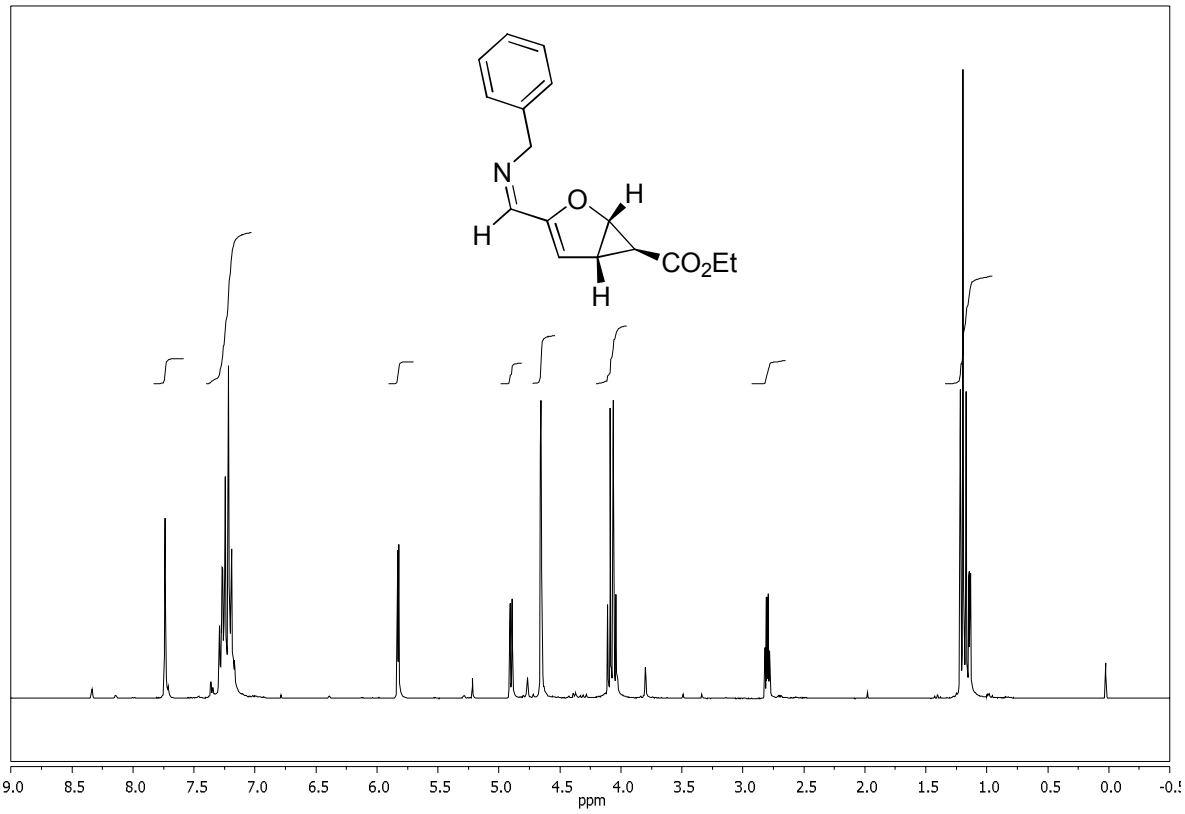


^{13}C-NMR (100 MHz, $CDCl_3$)

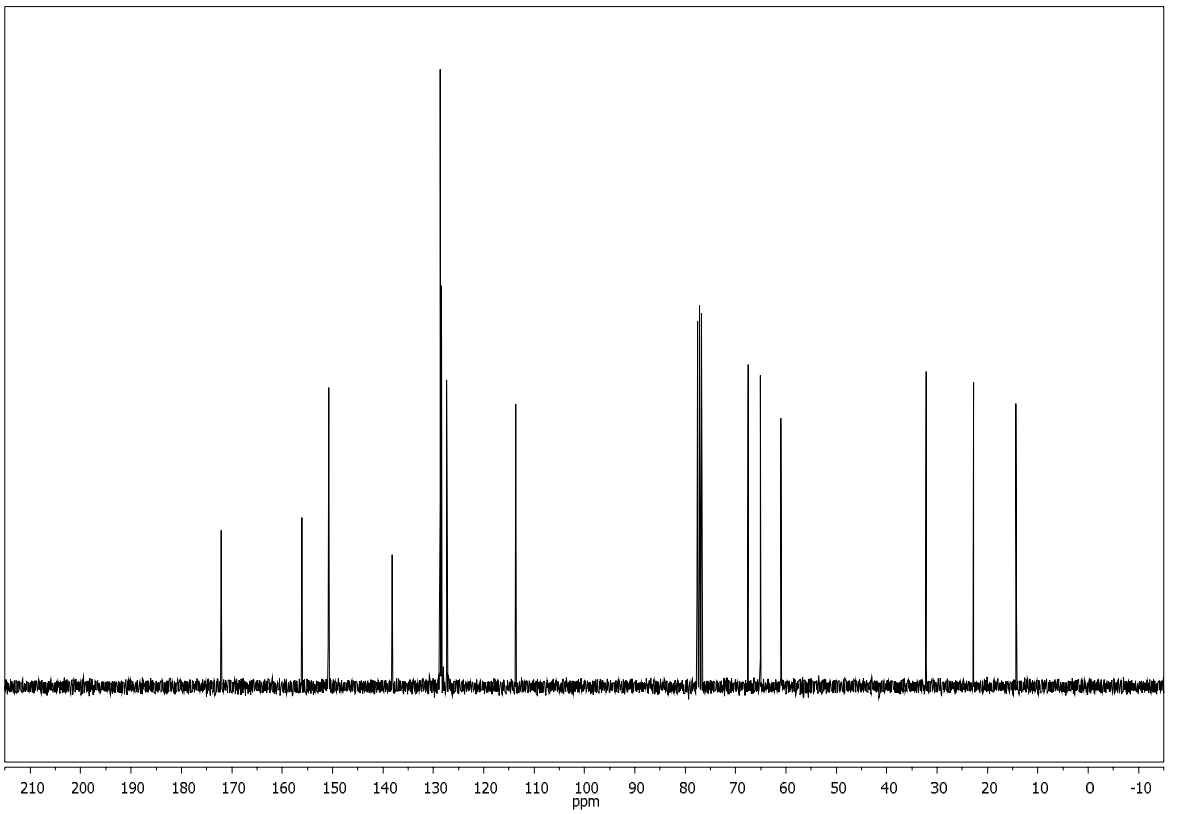


(1S,5S,6S)-ethyl 3-((benzylimino)methyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (104)

^{1}H-NMR (300 MHz, $CDCl_3$)

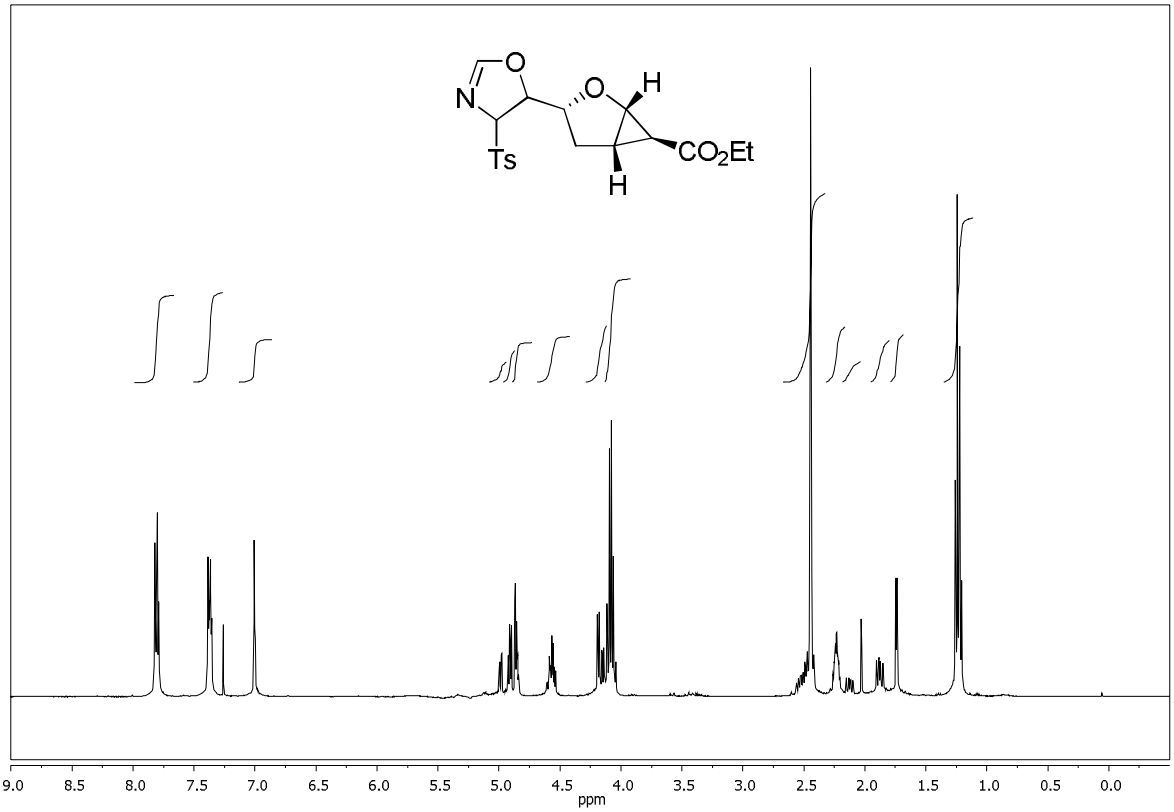


^{13}C-NMR (75 MHz, $CDCl_3$)

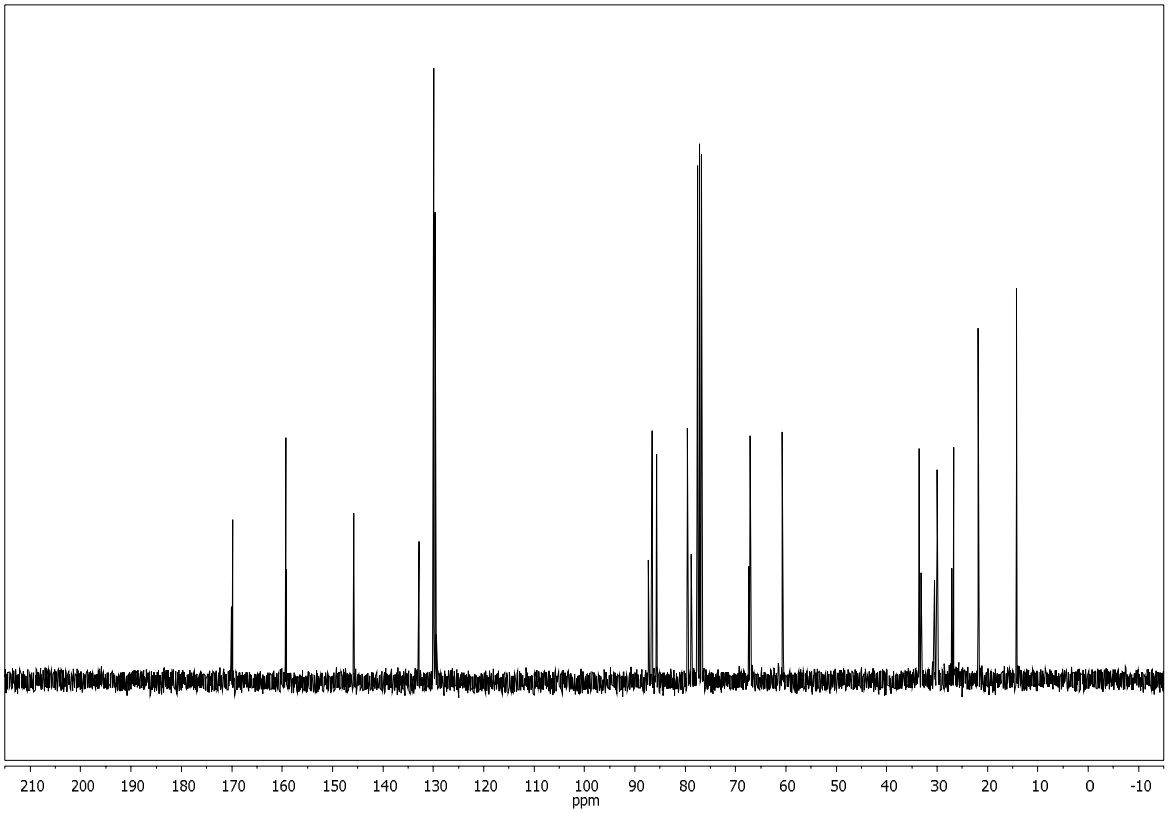


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-(4-tosyl-4,5-dihydrooxazol-5-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (106)

^{1}H-NMR (400 MHz, $CDCl_3$)

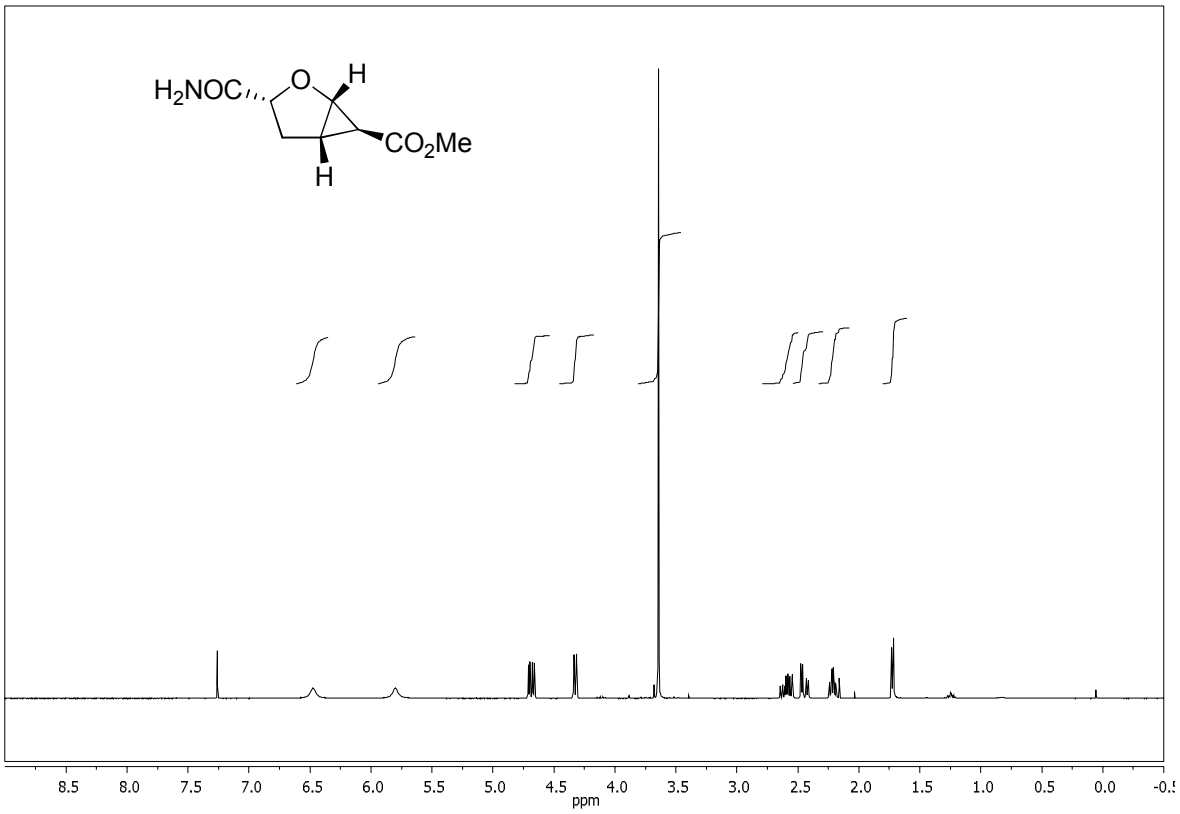


^{13}C-NMR (75 MHz, $CDCl_3$)

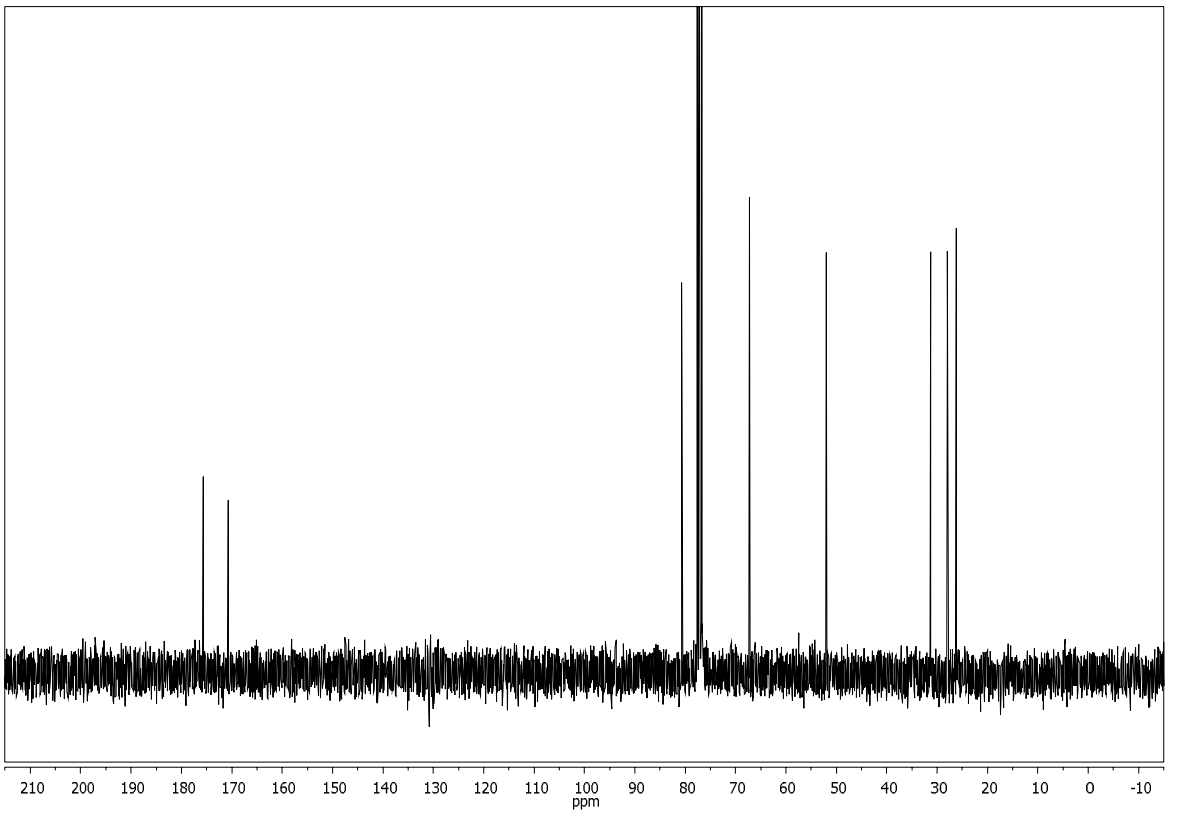


(1*S*,3*R*,5*S*,6*S*)-methyl 3-carbamoyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (108)

^{1}H-NMR (300 MHz, $CDCl_3$)

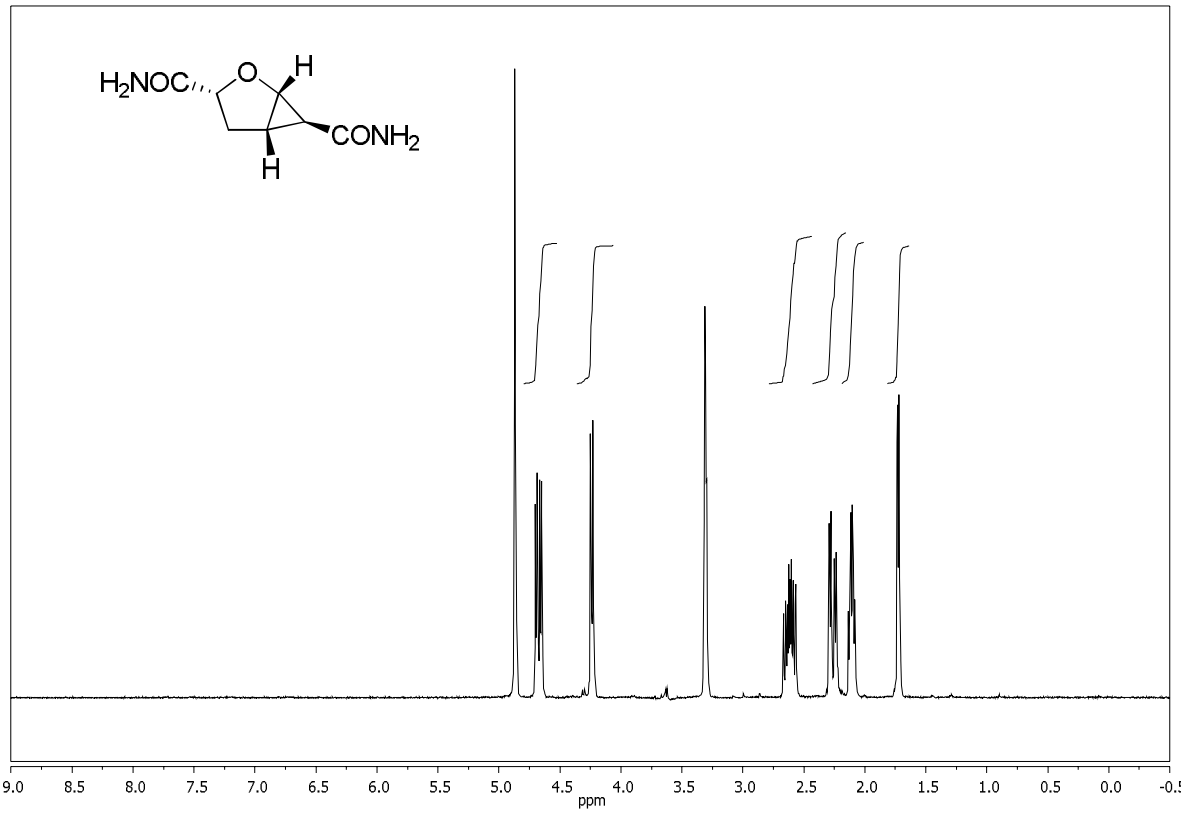


^{13}C-NMR (75 MHz, $CDCl_3$)

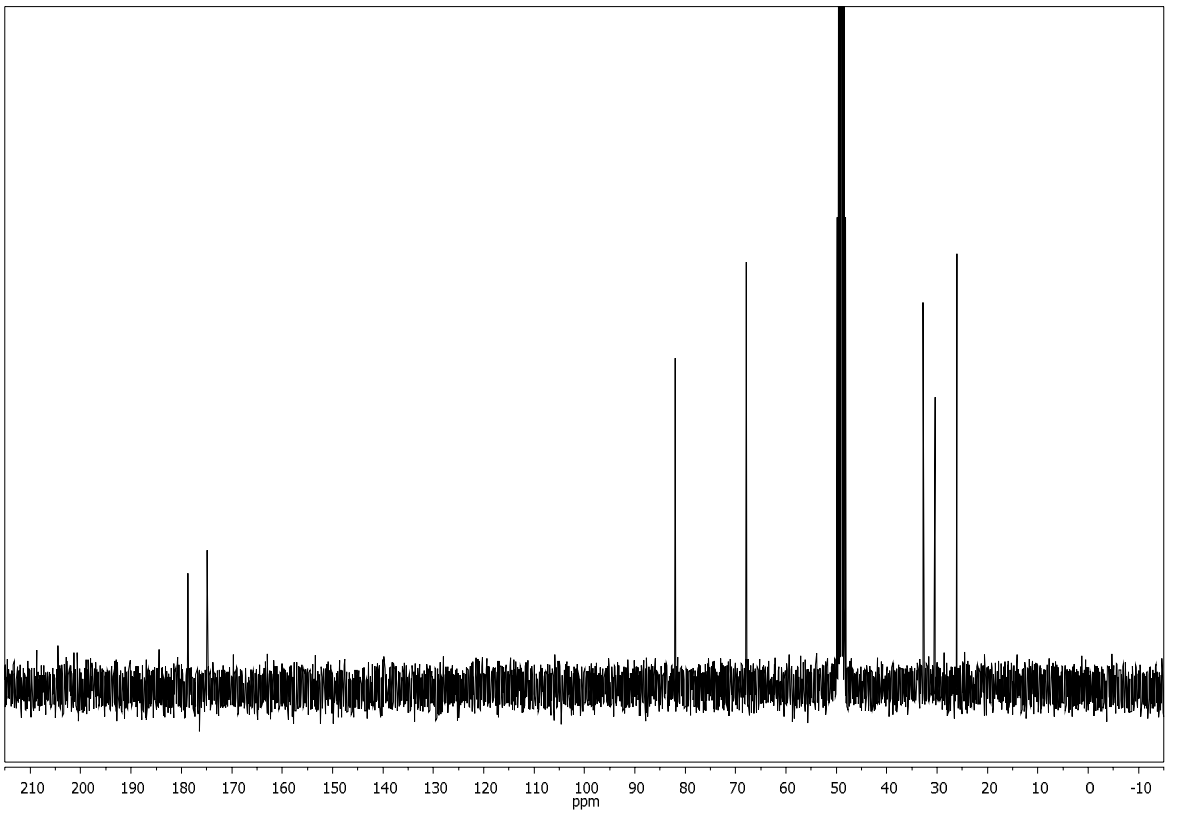


(1*S*,3*R*,5*S*,6*S*)-2-oxabicyclo[3.1.0]hexane-3,6-dicarboxamide (109)

^{1}H-NMR (300 MHz, MeOD)

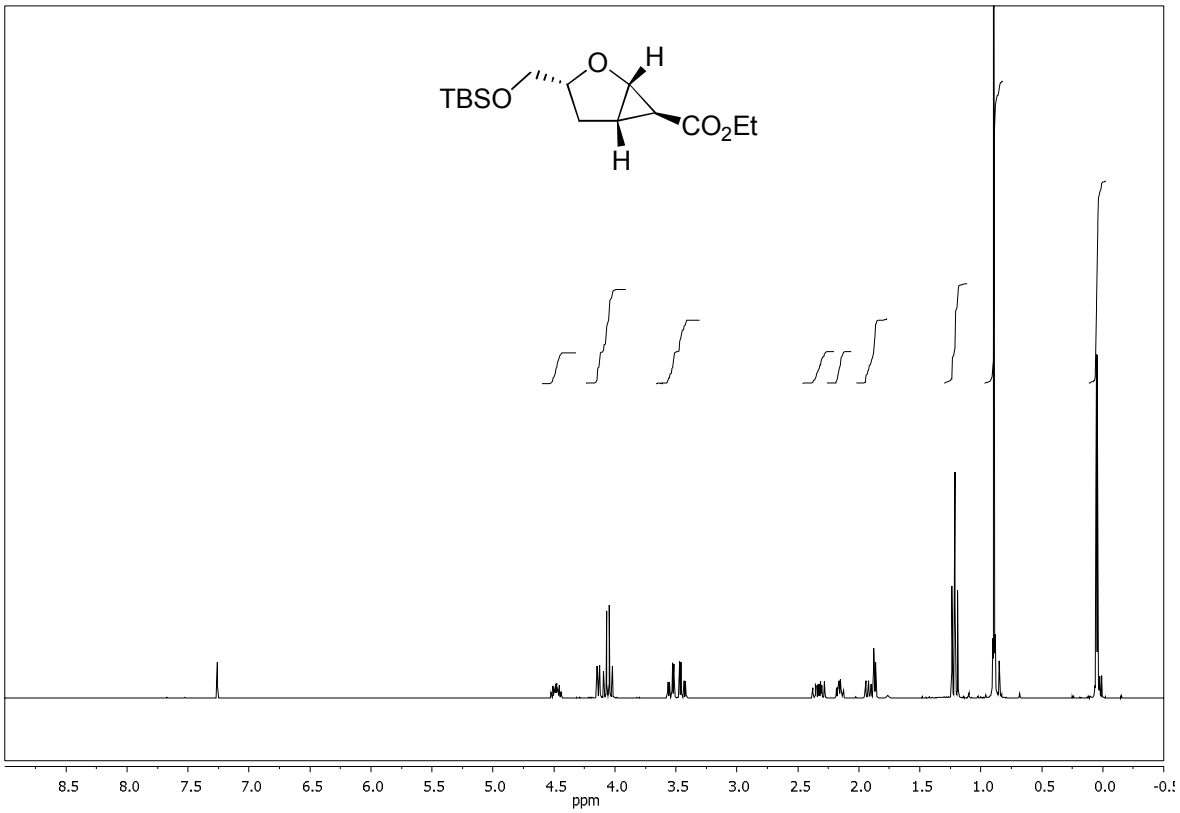


^{13}C-NMR (75 MHz, $CDCl_3$)

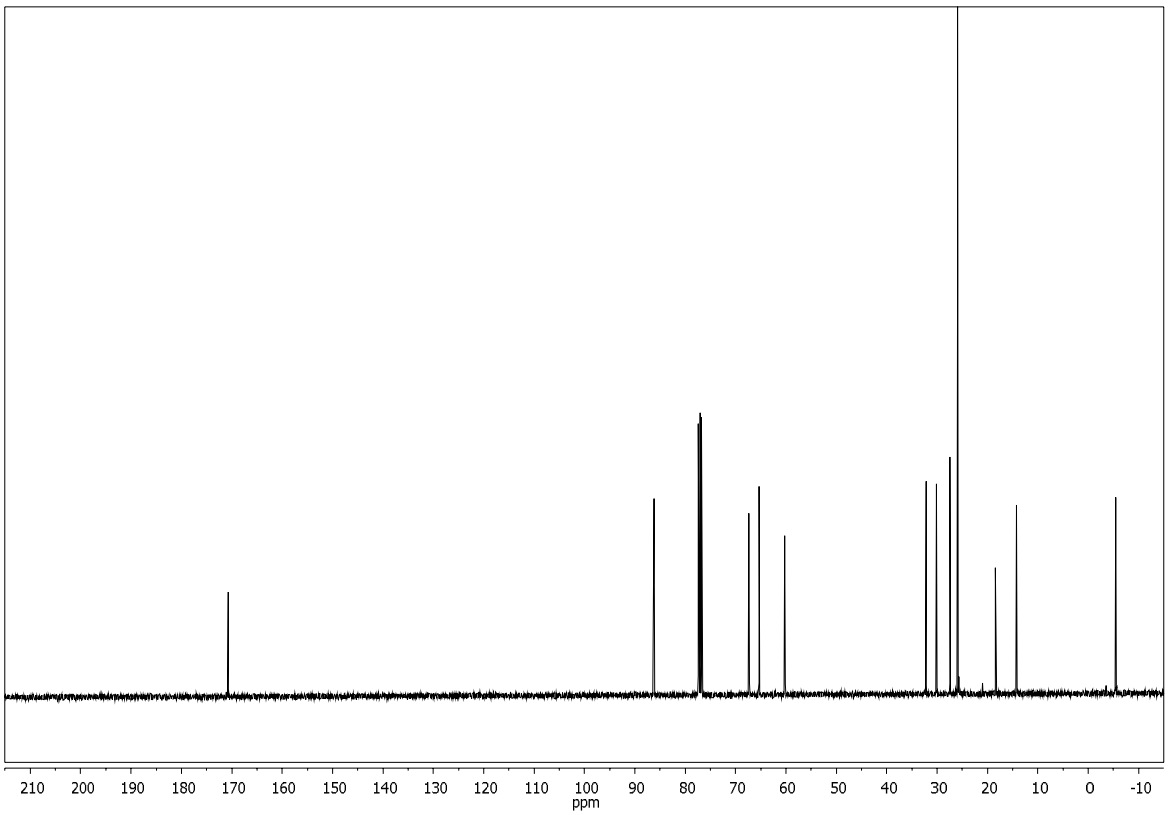


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (110)

^{1}H-NMR (300 MHz, $CDCl_3$)

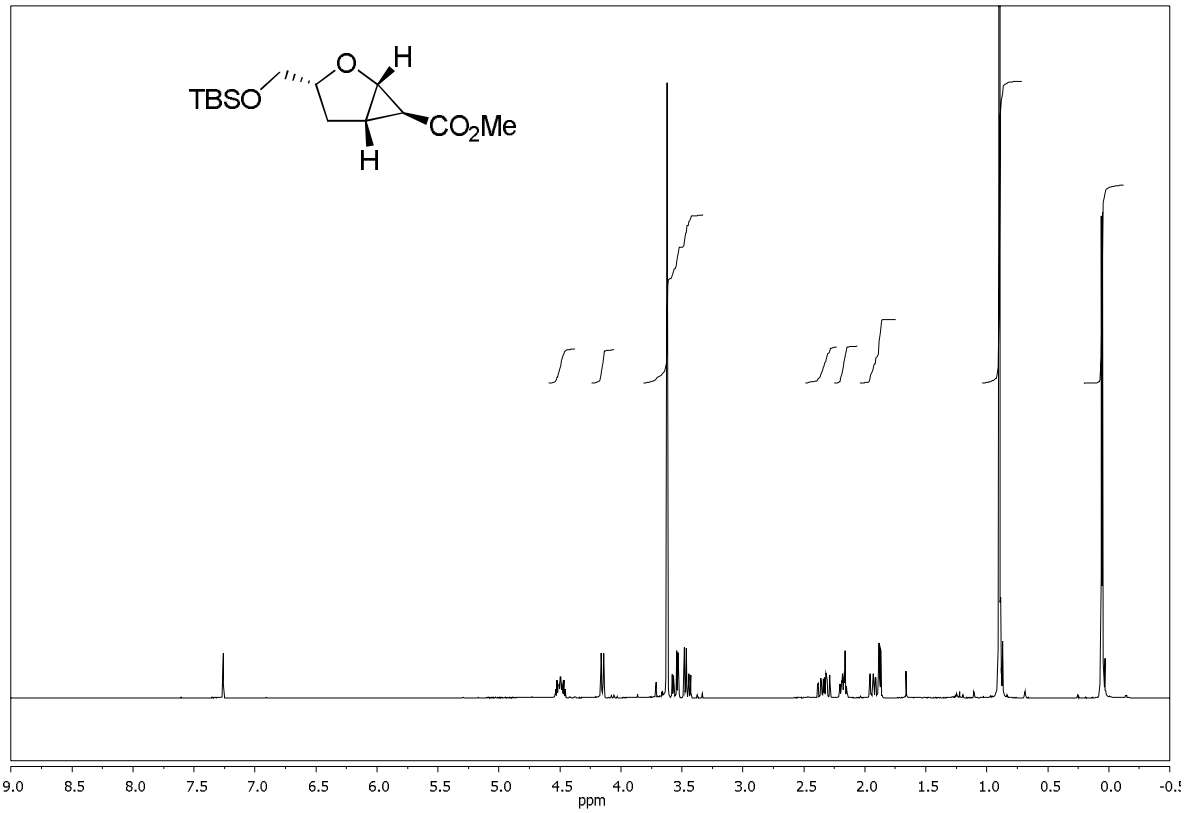


^{13}C-NMR (100 MHz, $CDCl_3$)

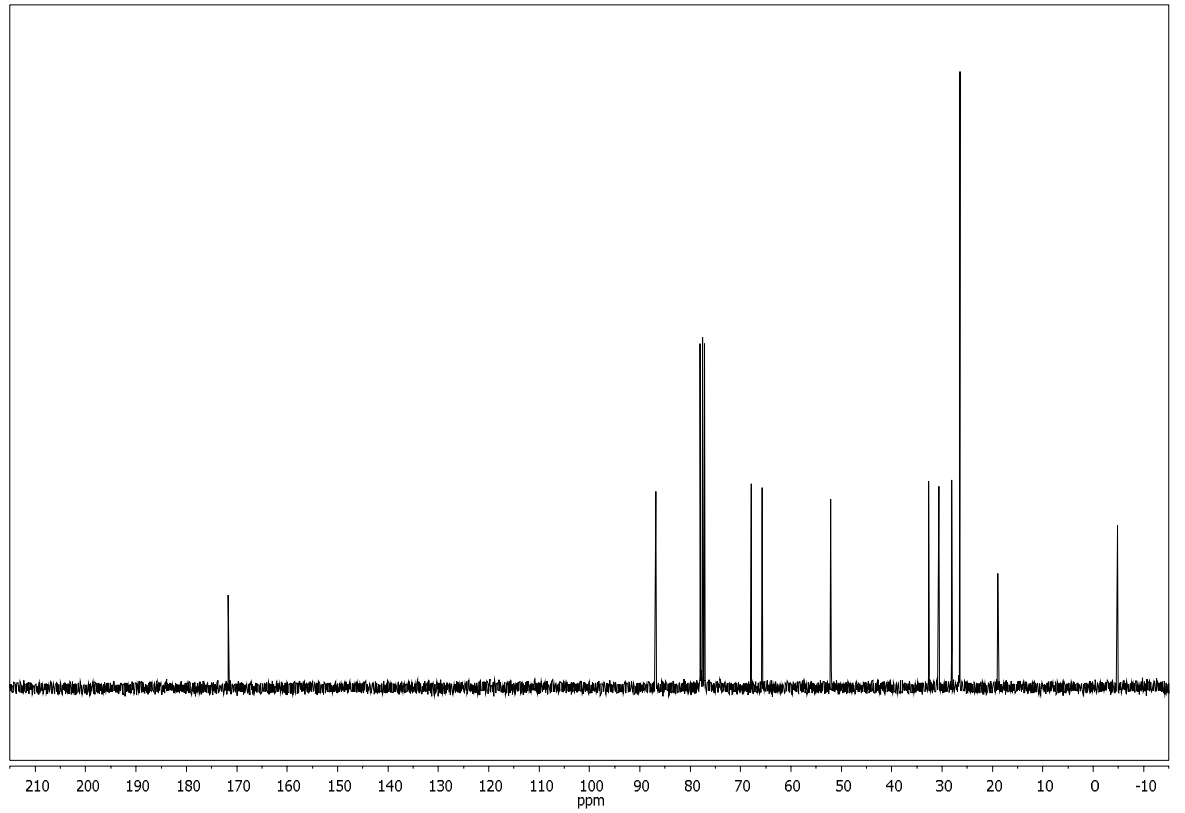


(1*S*,3*R*,5*S*,6*S*)-methyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (111)

^{1}H-NMR (300 MHz, $CDCl_3$)

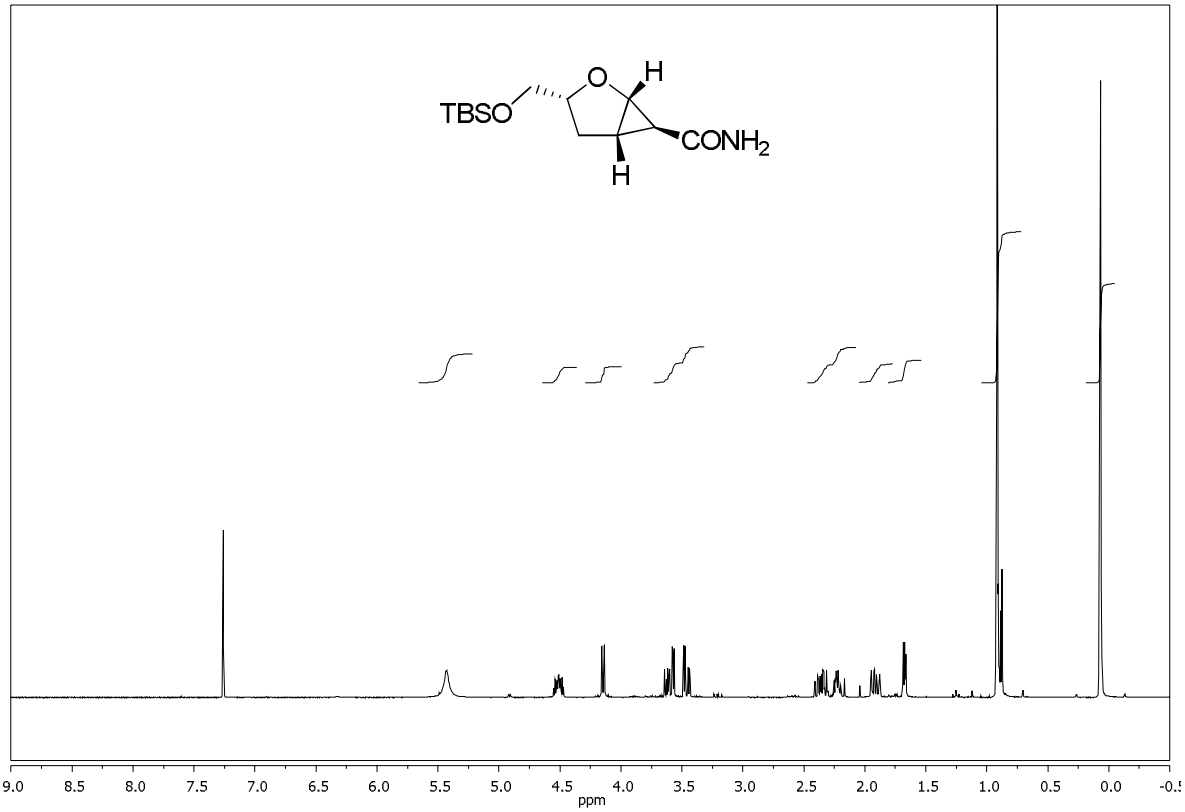


^{13}C-NMR (75 MHz, $CDCl_3$)

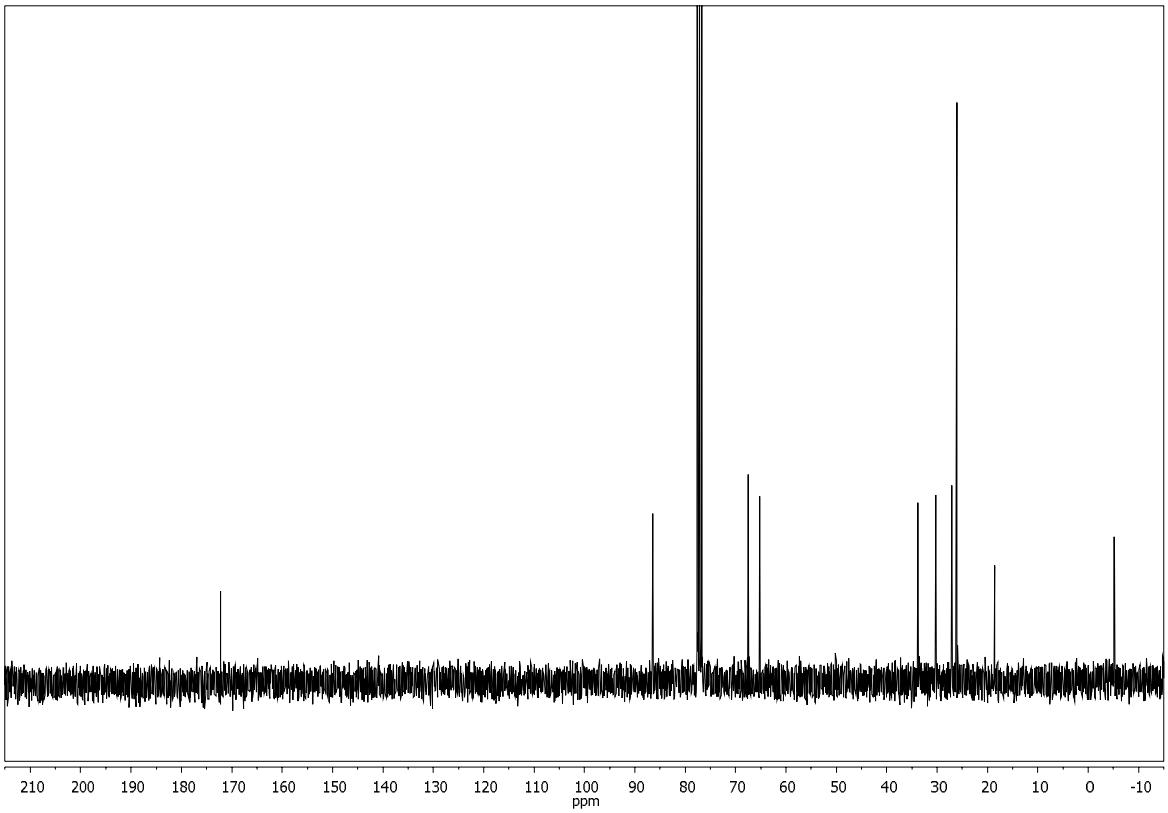


(1*S*,3*R*,5*S*,6*S*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxamide (112)

^{1}H-NMR (300 MHz, $CDCl_3$)

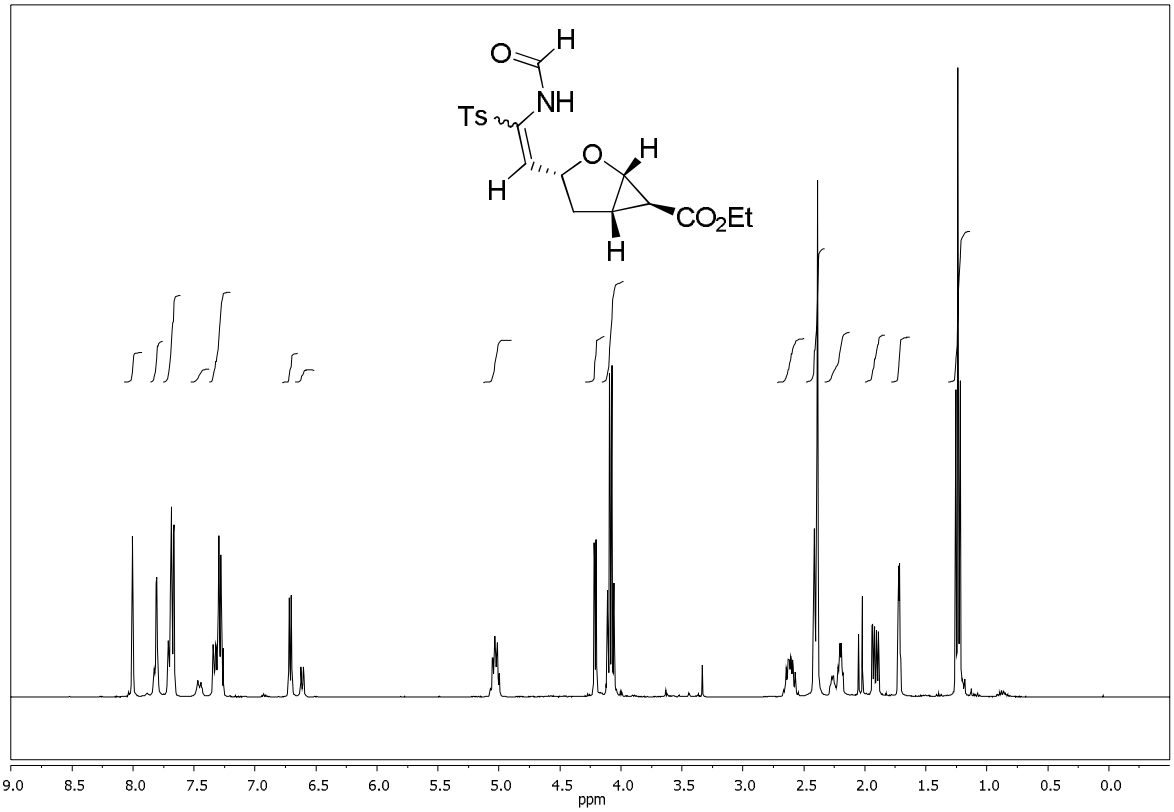


^{13}C-NMR (75 MHz, $CDCl_3$)

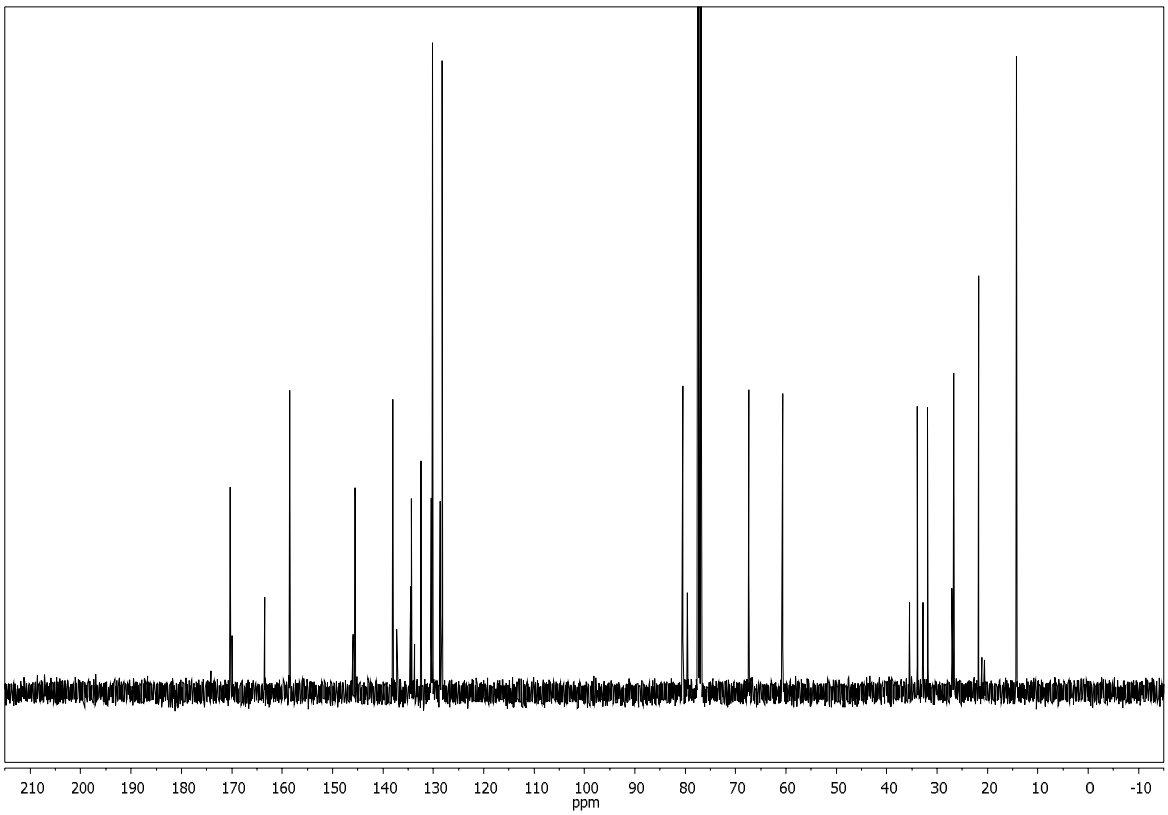


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((*E*/*Z*)-2-formamido-2-tosylvinyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (113)

^{1}H-NMR (400 MHz, $CDCl_3$)

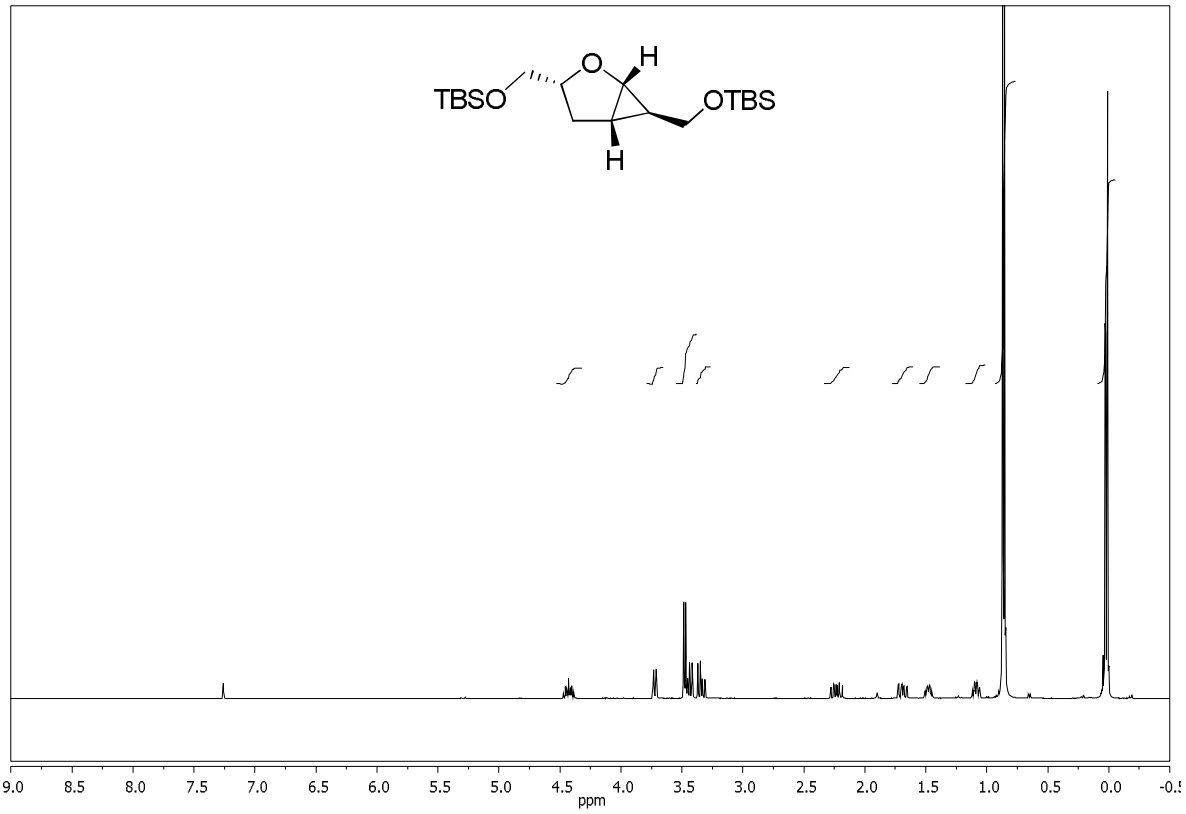


^{13}C-NMR (100 MHz, $CDCl_3$)

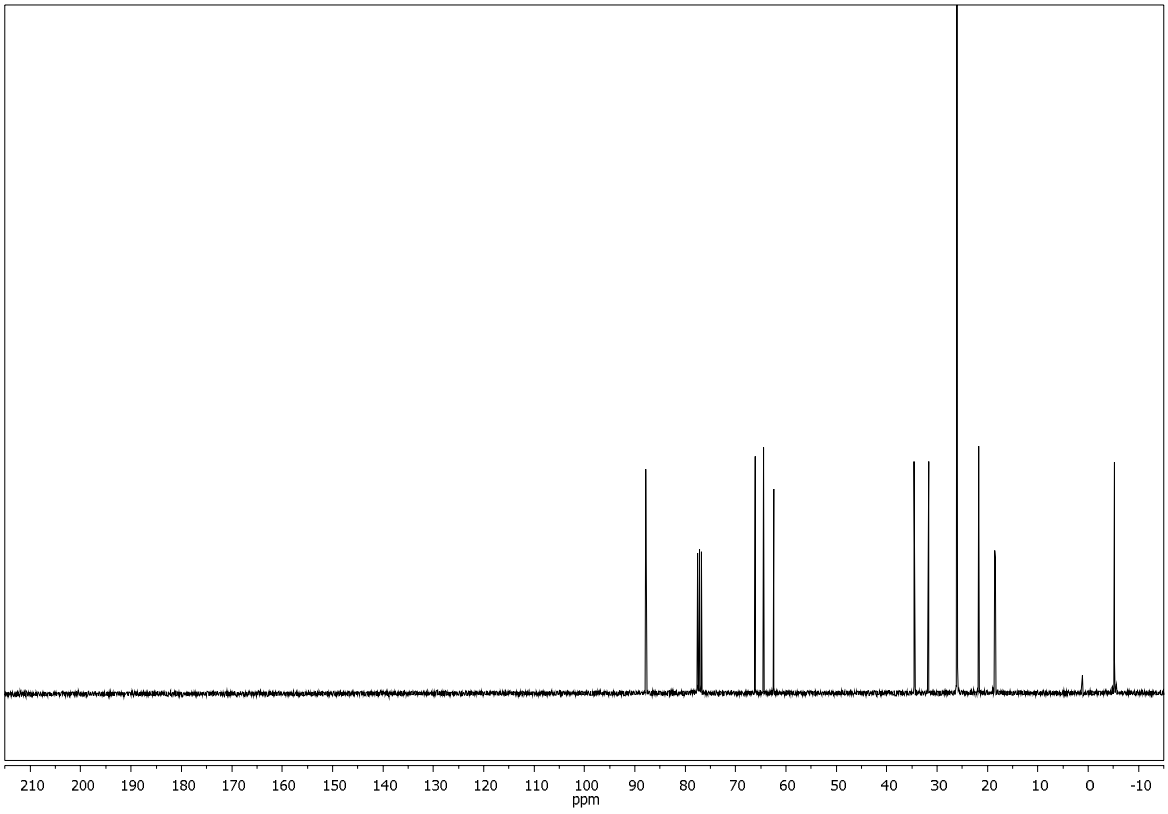


(1*S*,3*R*,5*S*,6*R*)-2-oxabicyclo[3.1.0]hexane-3,6-diylbis(methylene)bis(oxy)bis(*tert*-butyl-dimethylsilane) (115)

^{1}H-NMR (300 MHz, $CDCl_3$)

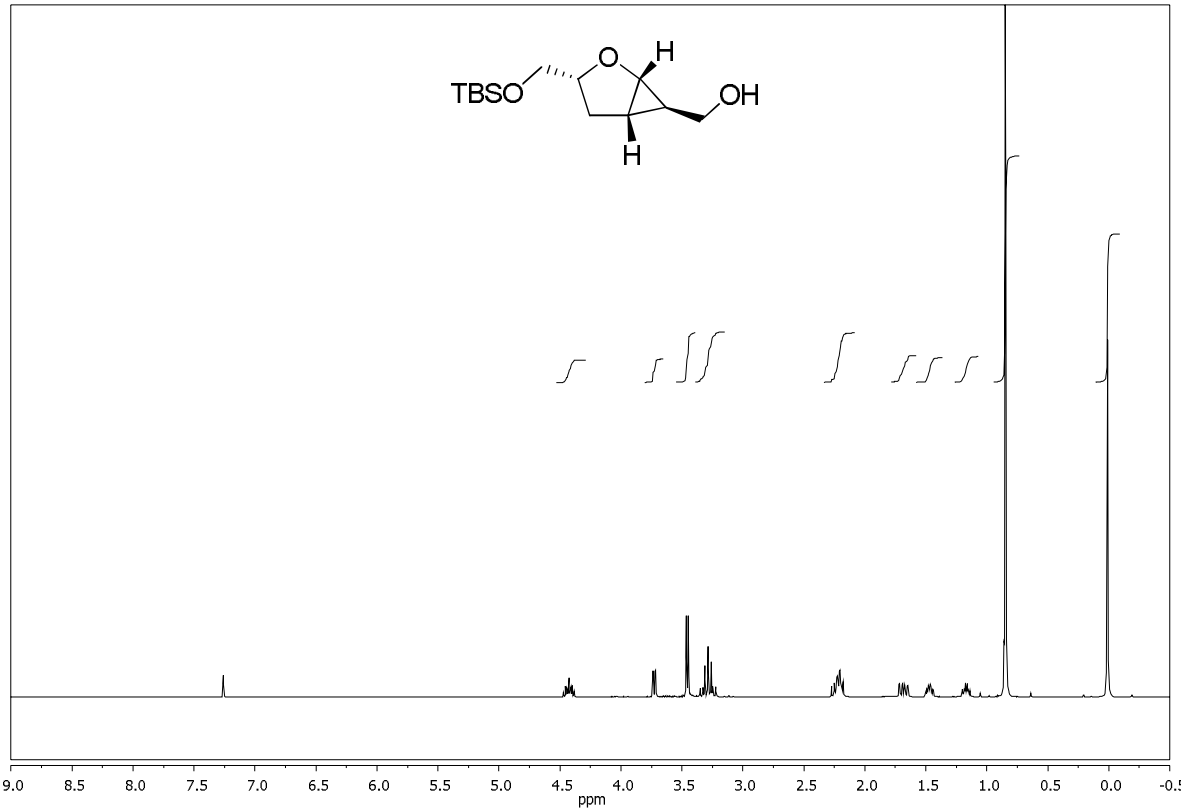


^{13}C-NMR (75 MHz, $CDCl_3$)

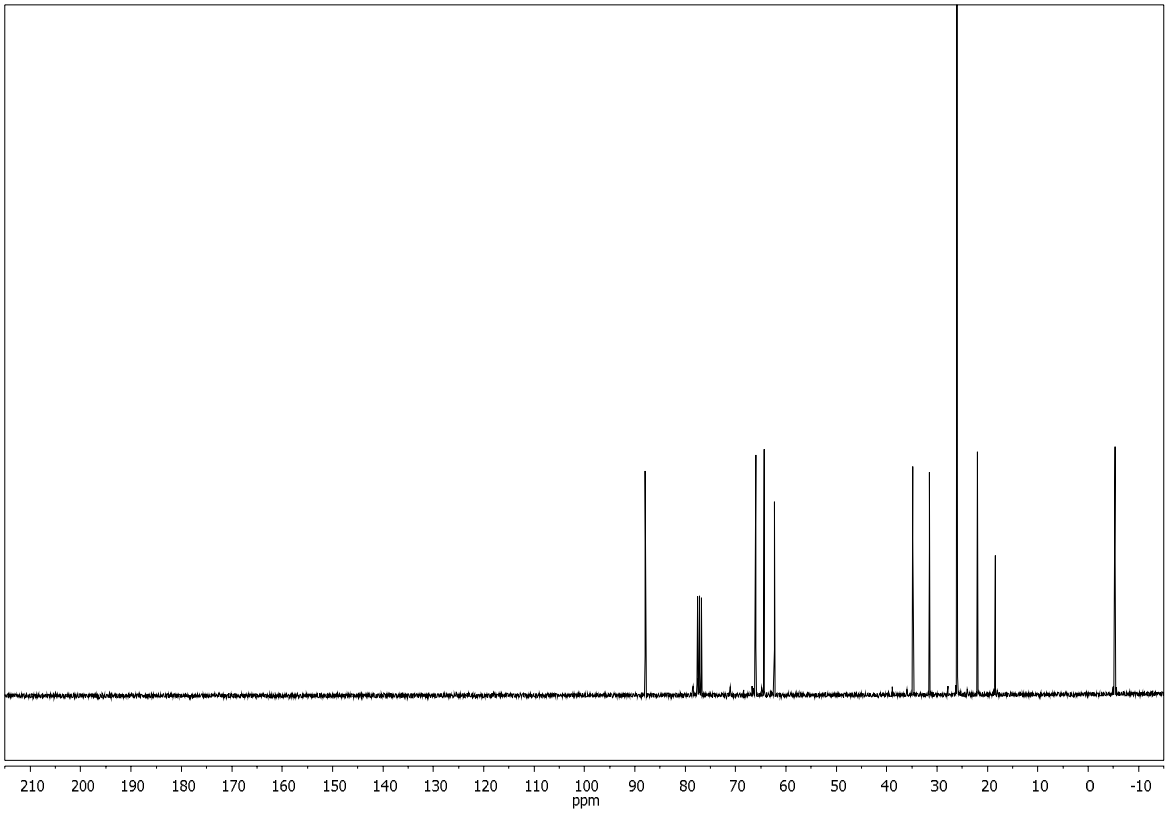


((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methanol (116)

^{1}H-NMR (300 MHz, $CDCl_3$)

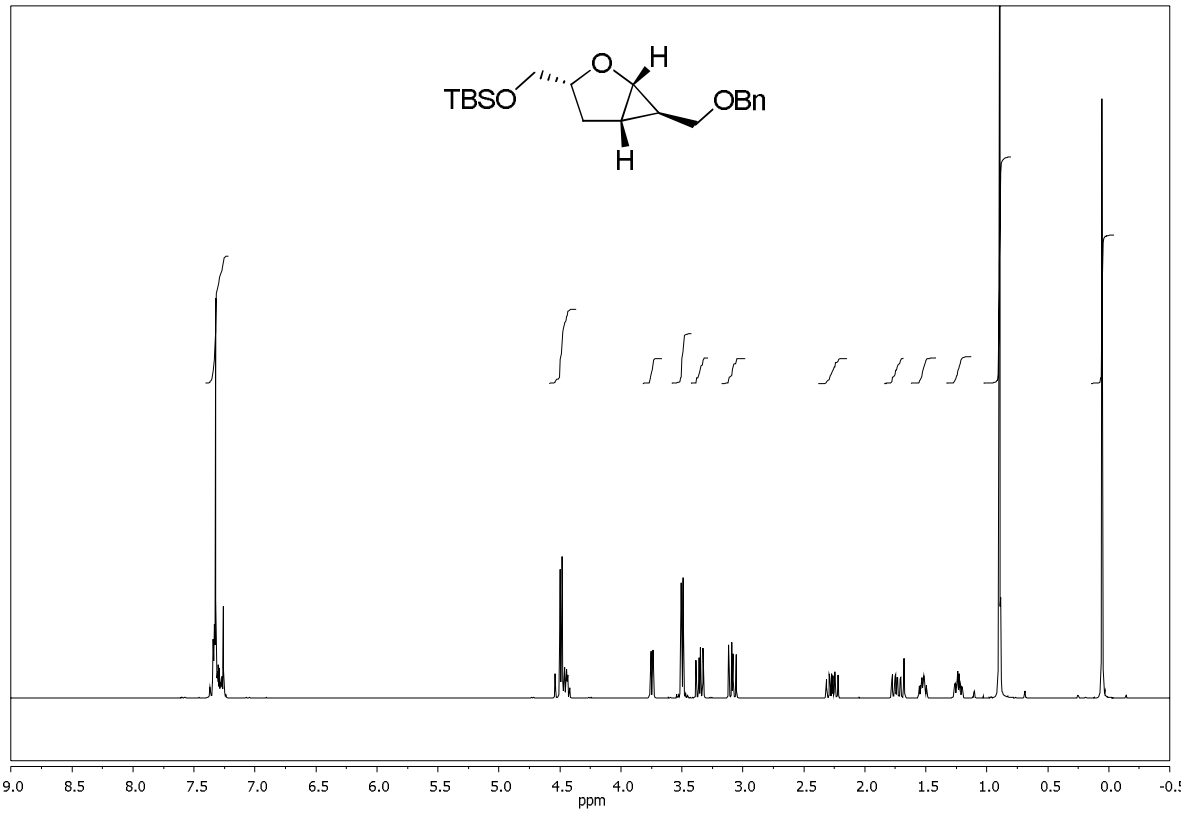


^{13}C-NMR (75 MHz, $CDCl_3$)

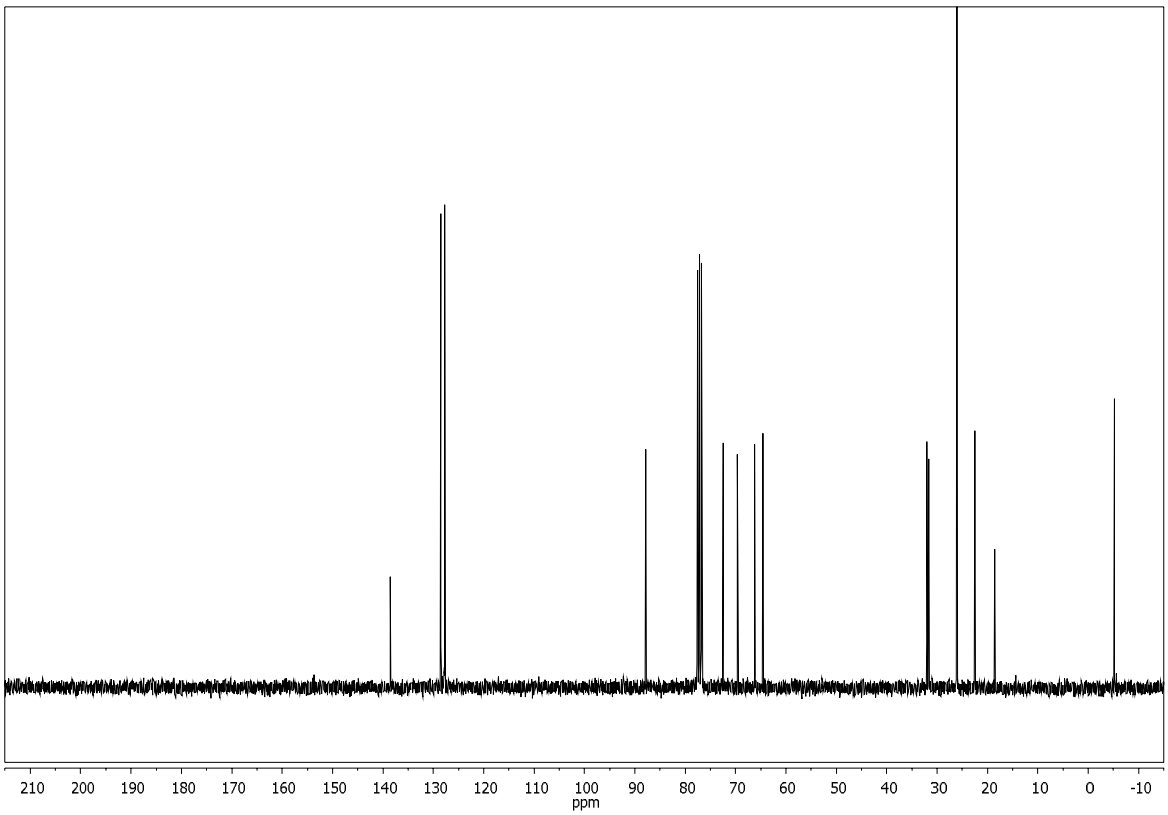


(((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(*tert*-butyl)-dimethylsilane (117)

^{1}H-NMR (300 MHz, $CDCl_3$)

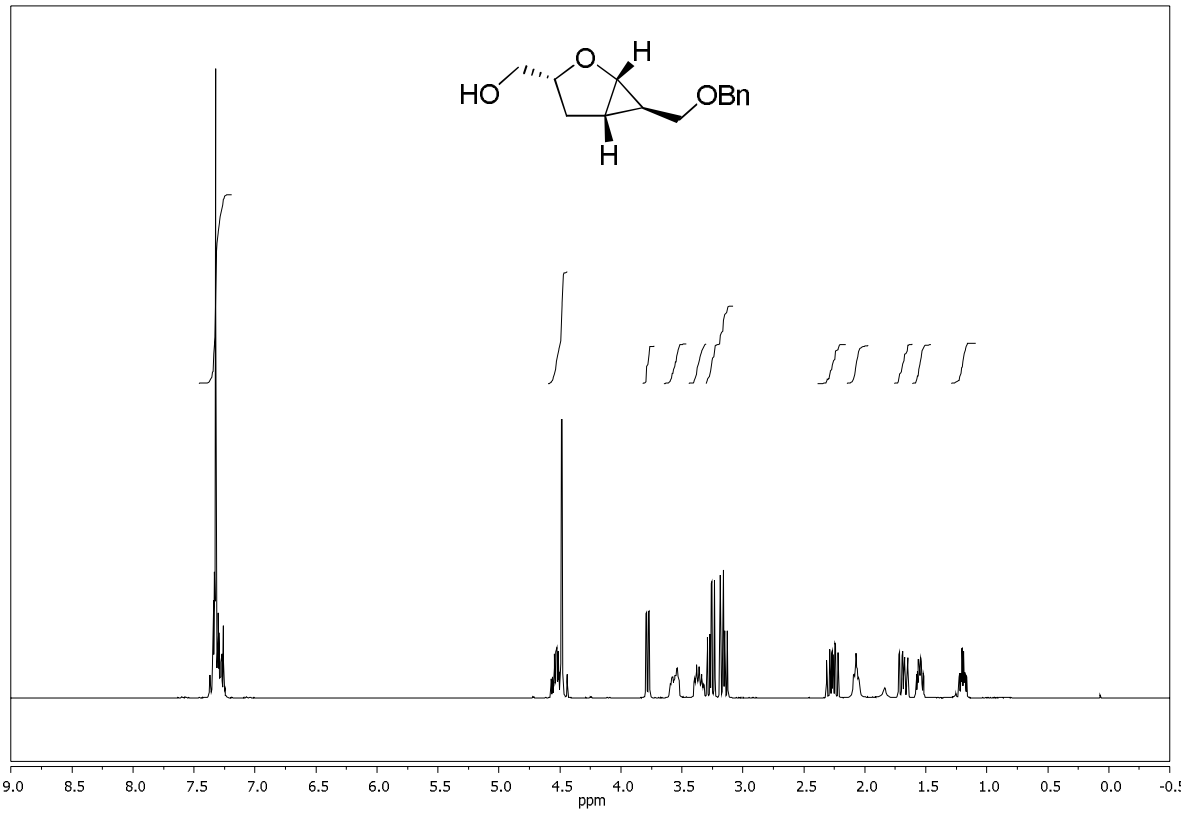


^{13}C-NMR (75 MHz, $CDCl_3$)

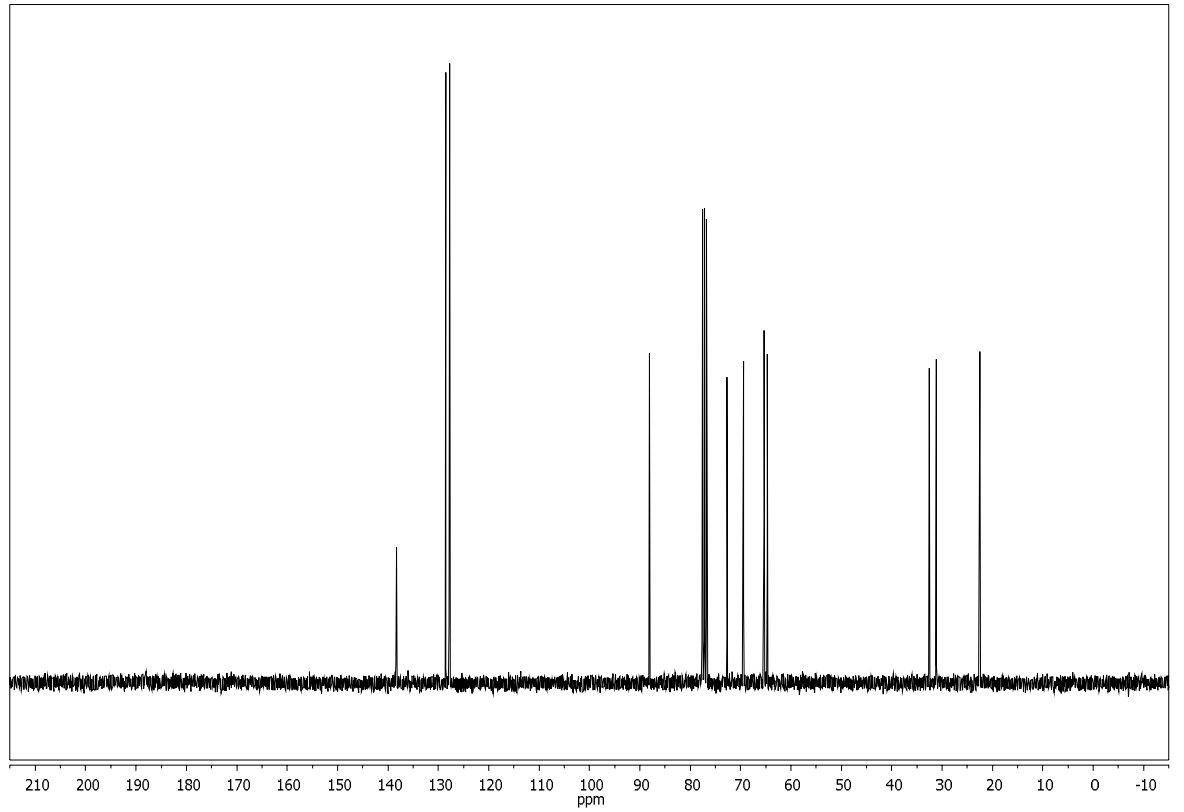


(1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (118)

^{1}H-NMR (300 MHz, $CDCl_3$)

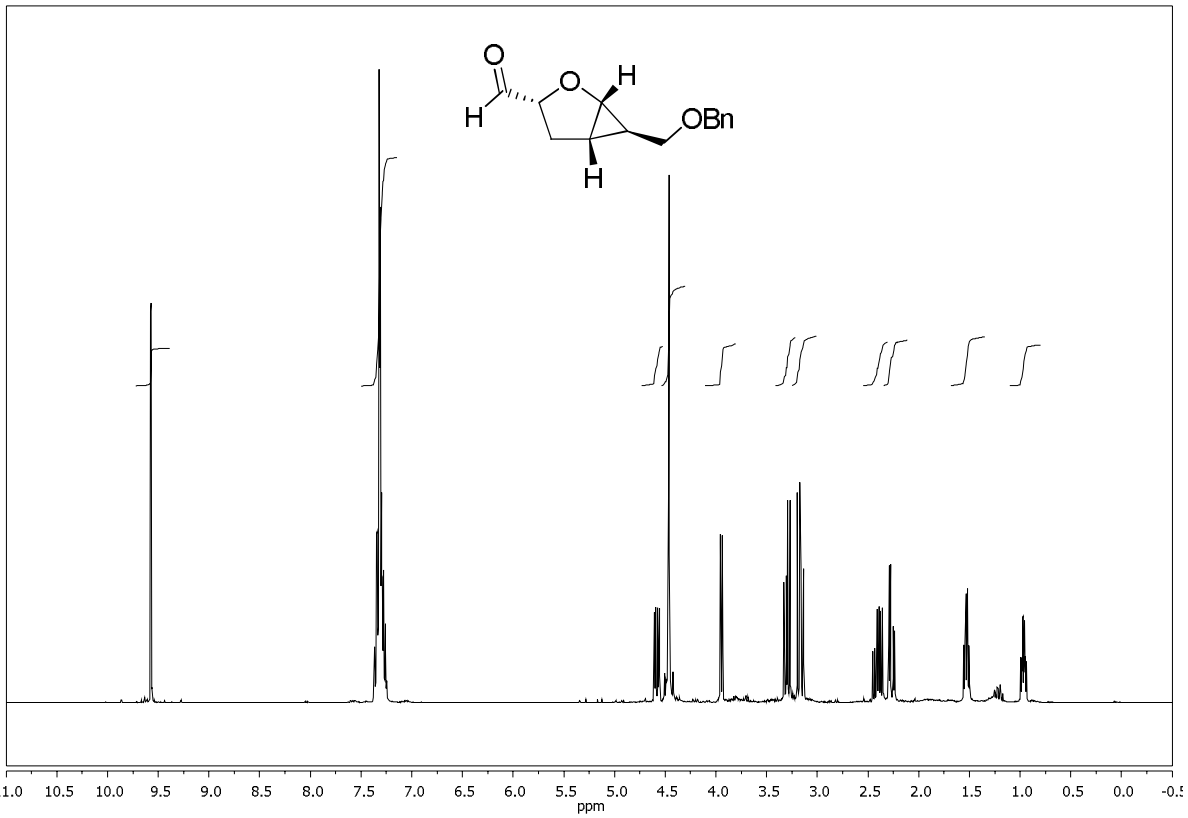


^{13}C-NMR (75 MHz, $CDCl_3$)

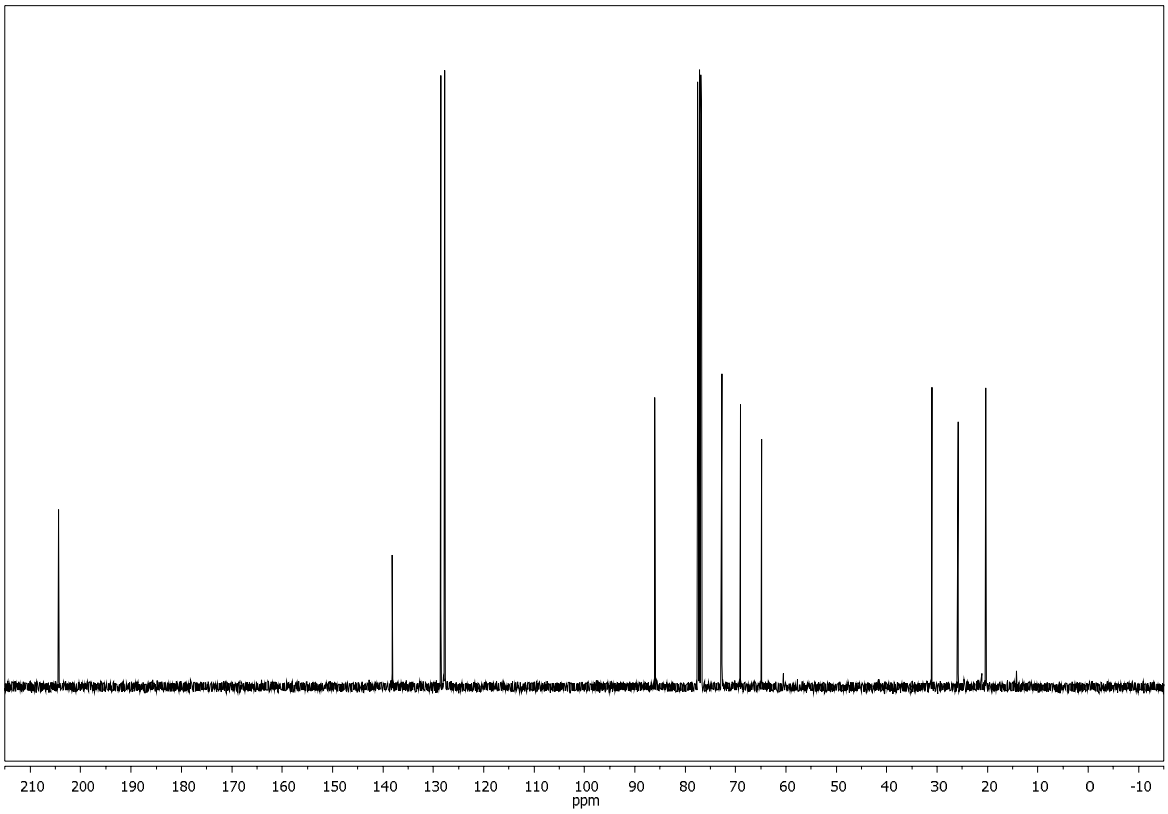


(1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexane-3-carbaldehyde (119)

^{1}H-NMR (300 MHz, $CDCl_3$)

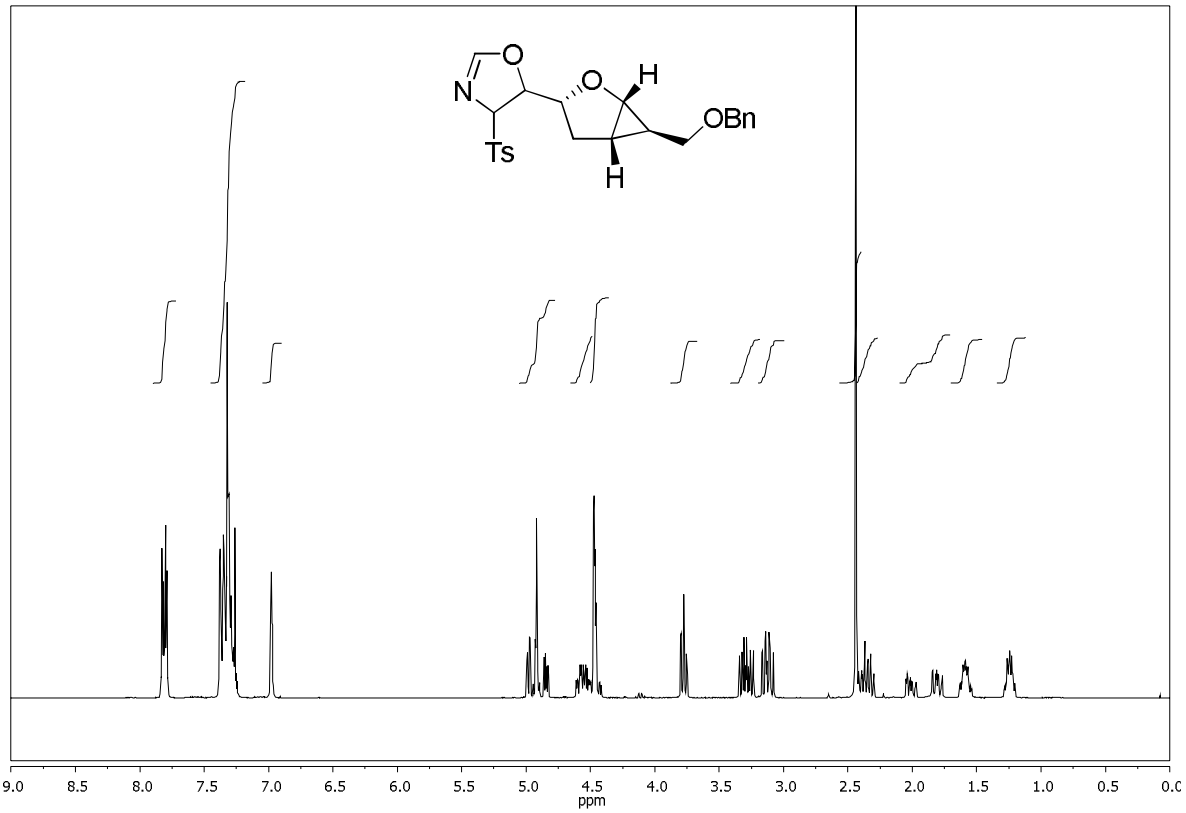


^{13}C-NMR (100 MHz, $CDCl_3$)

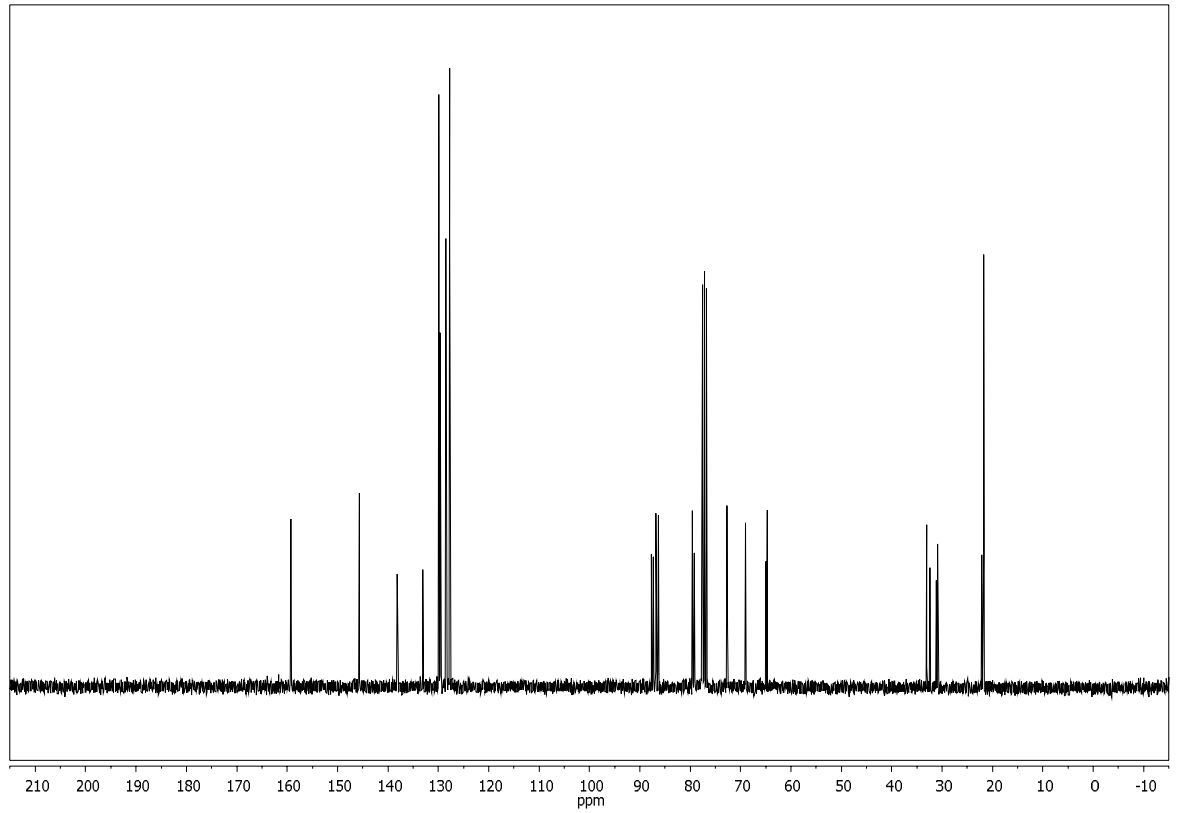


5-((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-4-tosyl-4,5-dihydrooxazole (120)

^{1}H-NMR (300 MHz, $CDCl_3$)

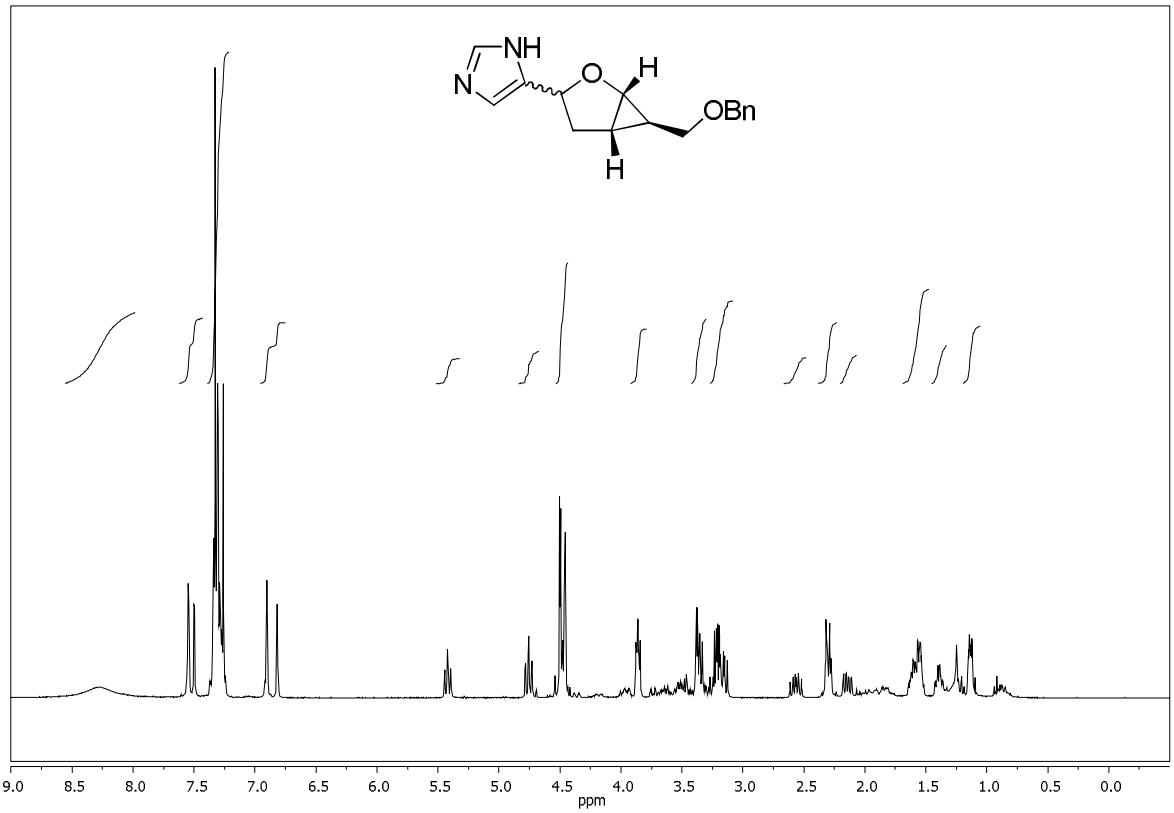


^{13}C-NMR (75 MHz, $CDCl_3$)

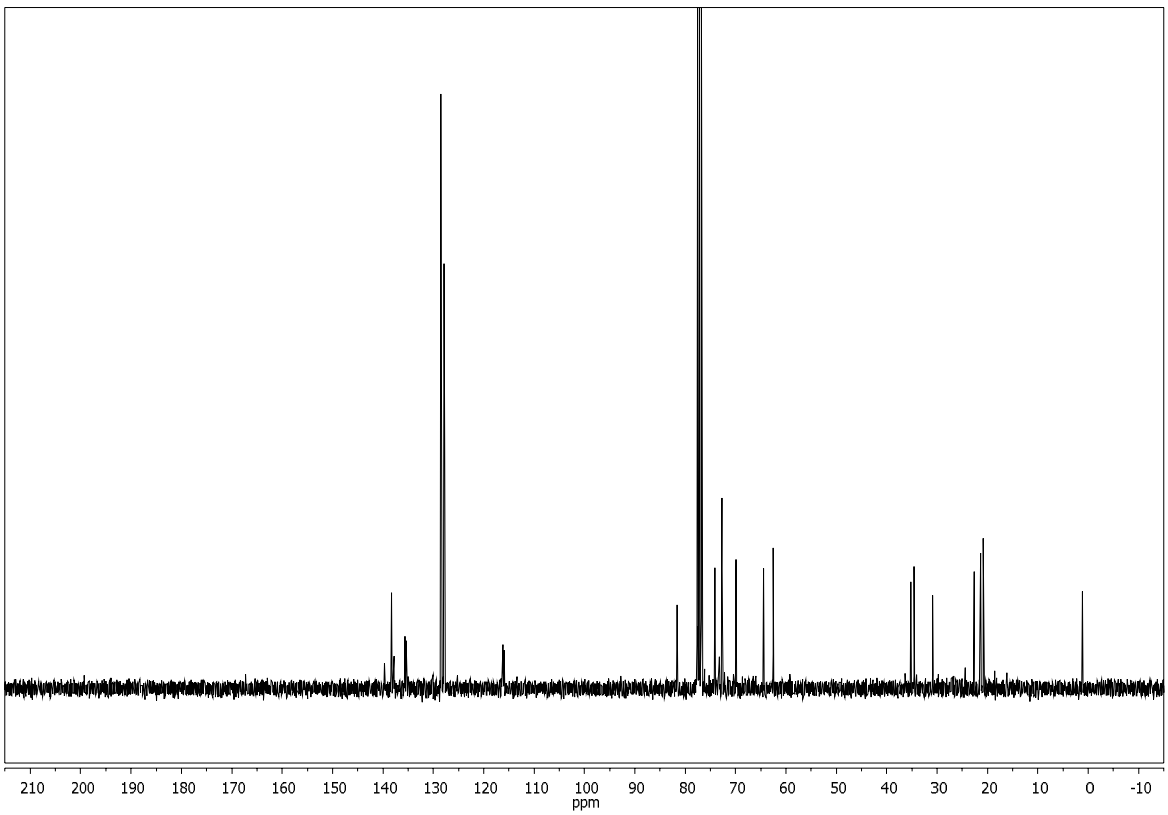


5-((1*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole (121)

^{1}H-NMR (300 MHz, $CDCl_3$)

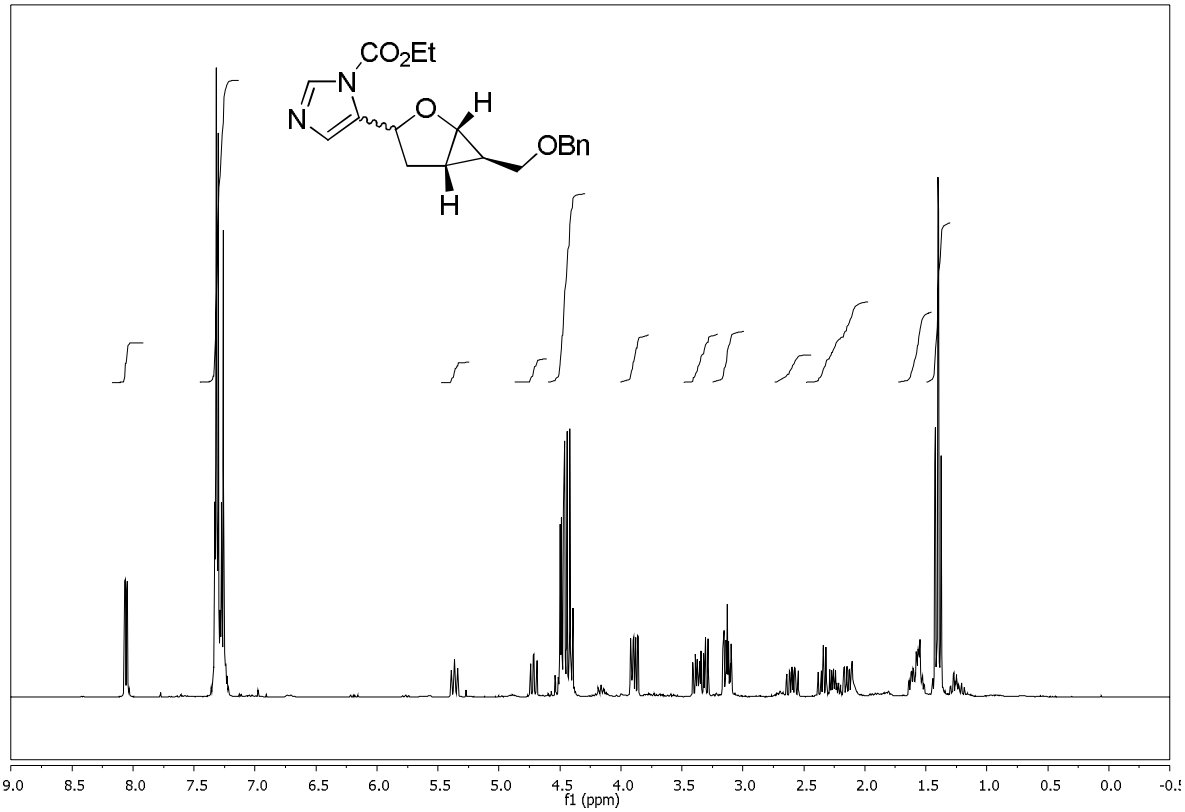


^{13}C-NMR (75 MHz, $CDCl_3$)

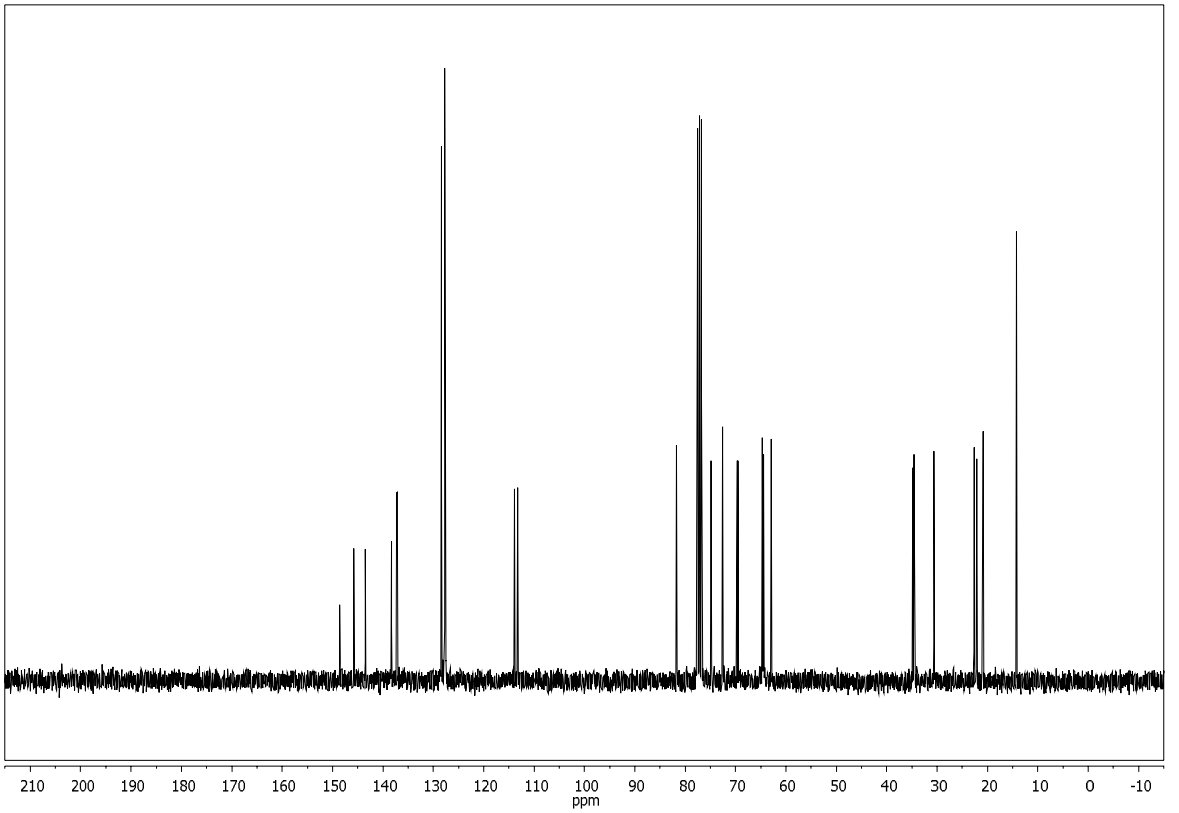


ethyl 5-((1*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (131)

^{1}H-NMR (300 MHz, $CDCl_3$)

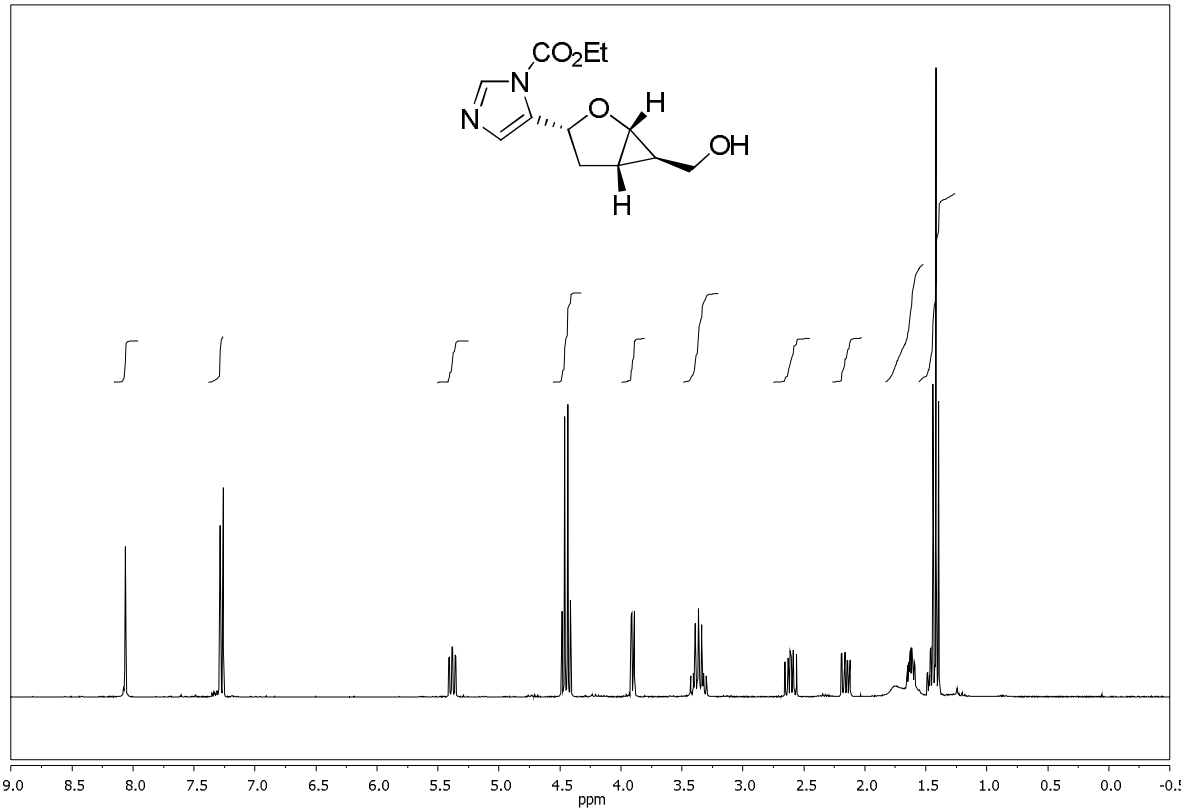


^{13}C-NMR (75 MHz, $CDCl_3$)

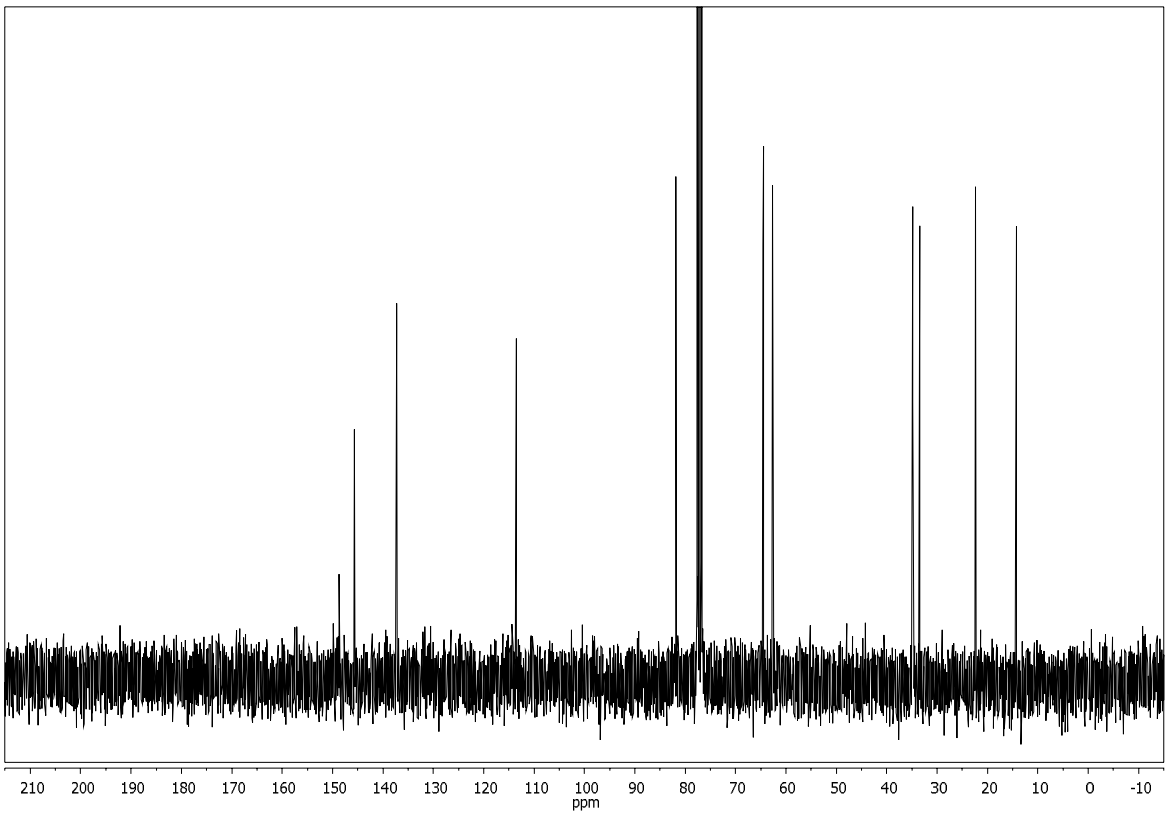


ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (132a)

^{1}H-NMR (300 MHz, $CDCl_3$)

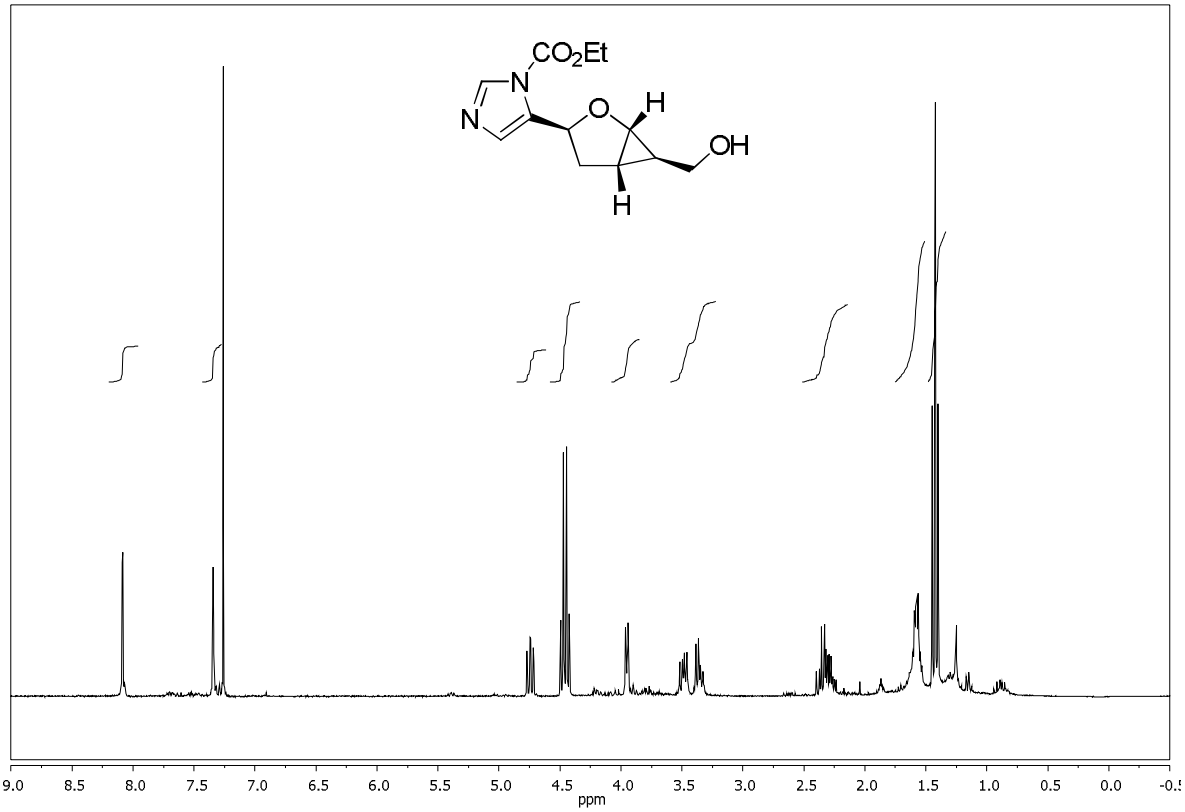


^{13}C-NMR (75 MHz, $CDCl_3$)

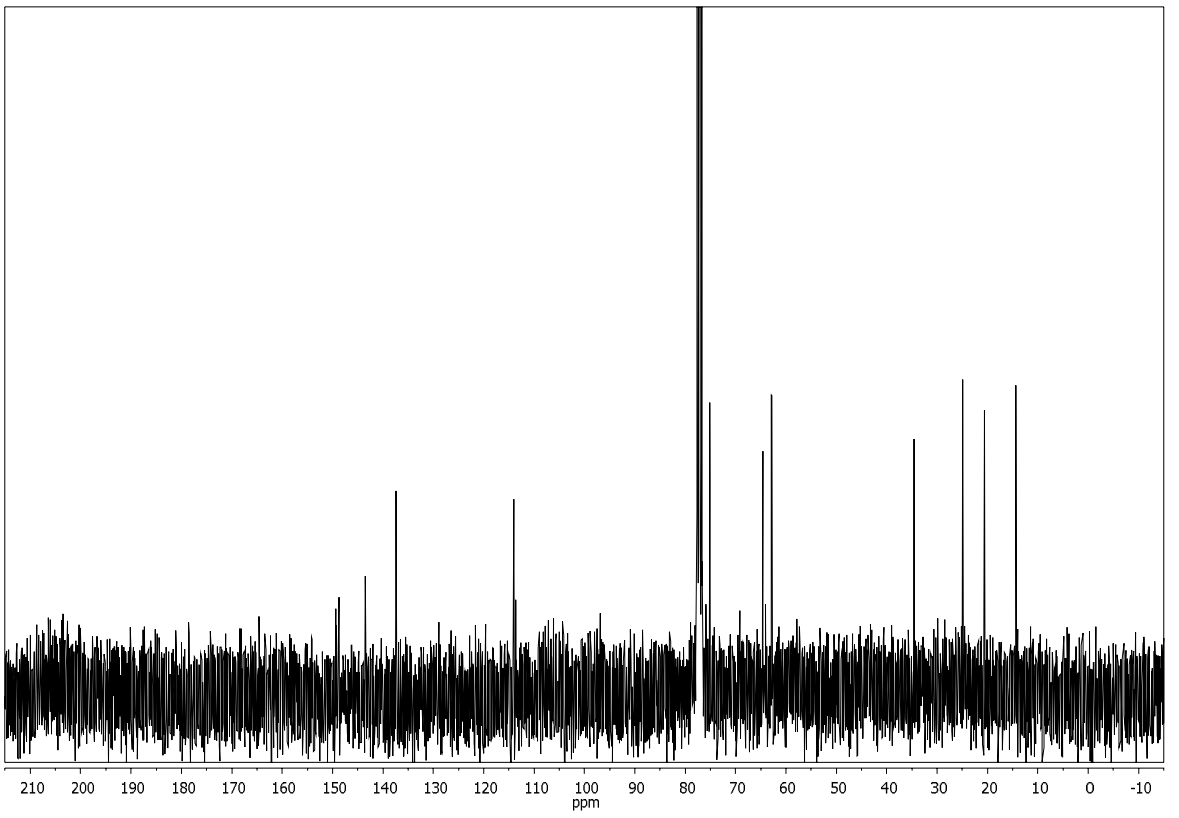


ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (132b)

^{1}H-NMR (300 MHz, $CDCl_3$)

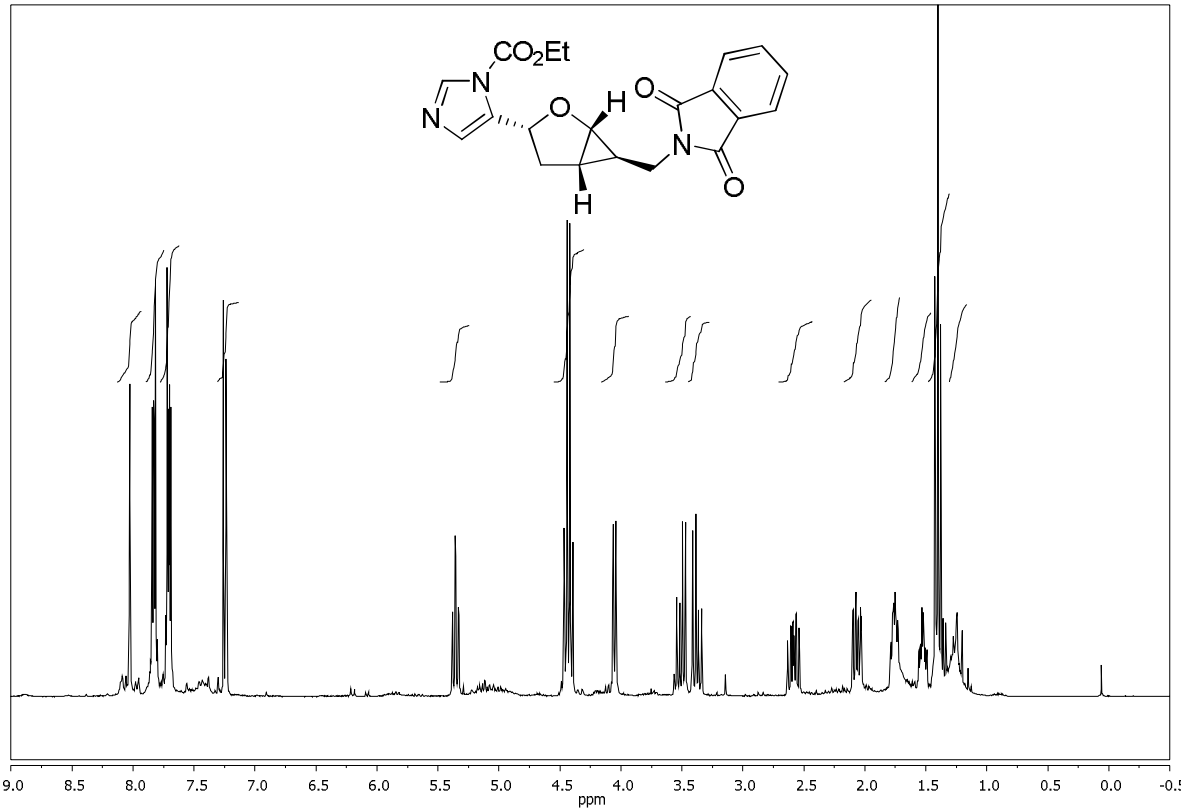


^{13}C-NMR (75 MHz, $CDCl_3$)

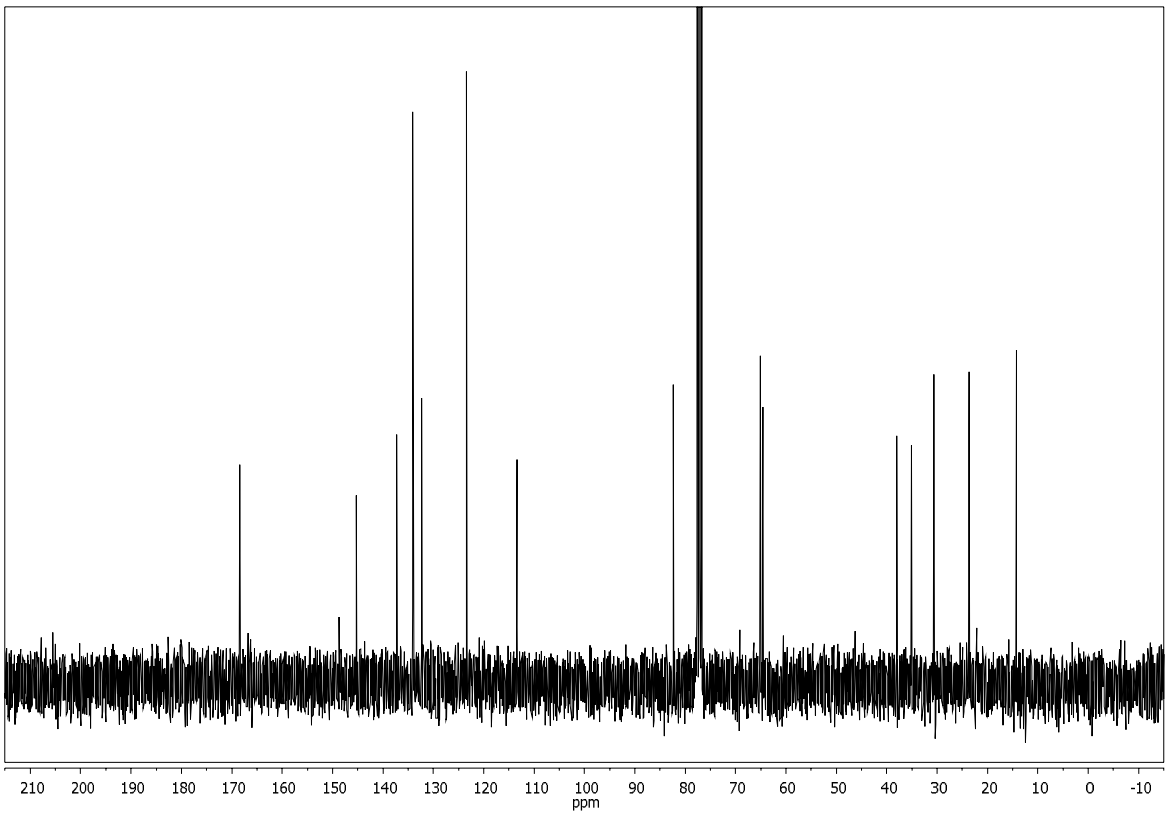


ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (133)

^{1}H-NMR (300 MHz, $CDCl_3$)

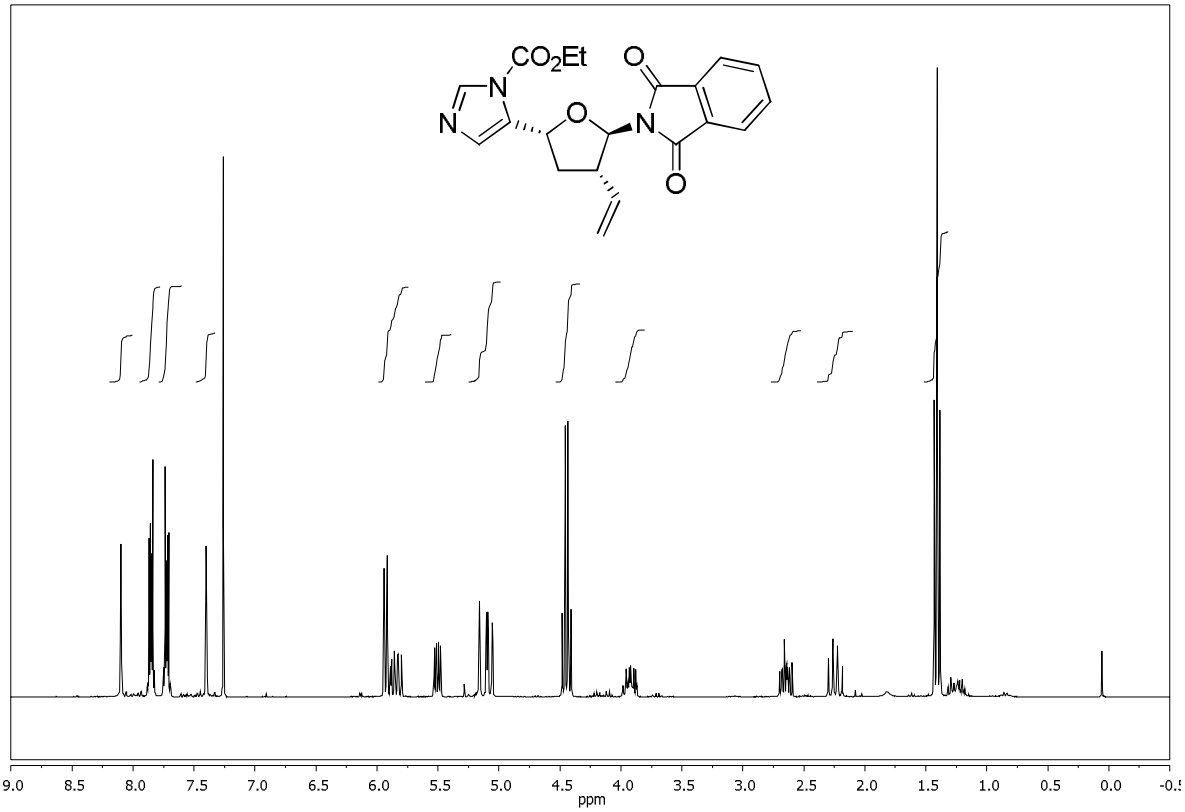


^{13}C-NMR (75 MHz, $CDCl_3$)

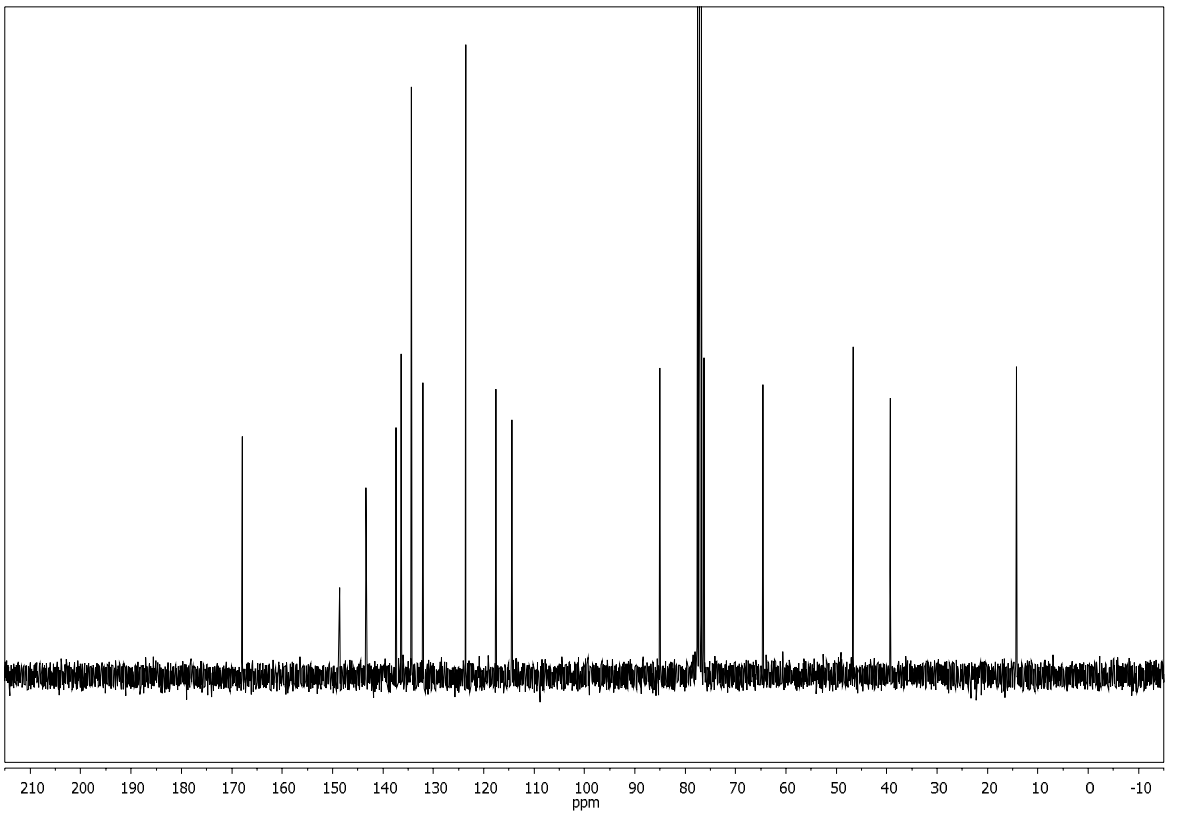


ethyl 5-((2*R*,4*S*,5*R*)-5-(1,3-dioxoisoindolin-2-yl)-4-vinyltetrahydrofuran-2-yl)-1*H*-imidazole-1-carboxylate (135a)

^{1}H-NMR (300 MHz, $CDCl_3$)

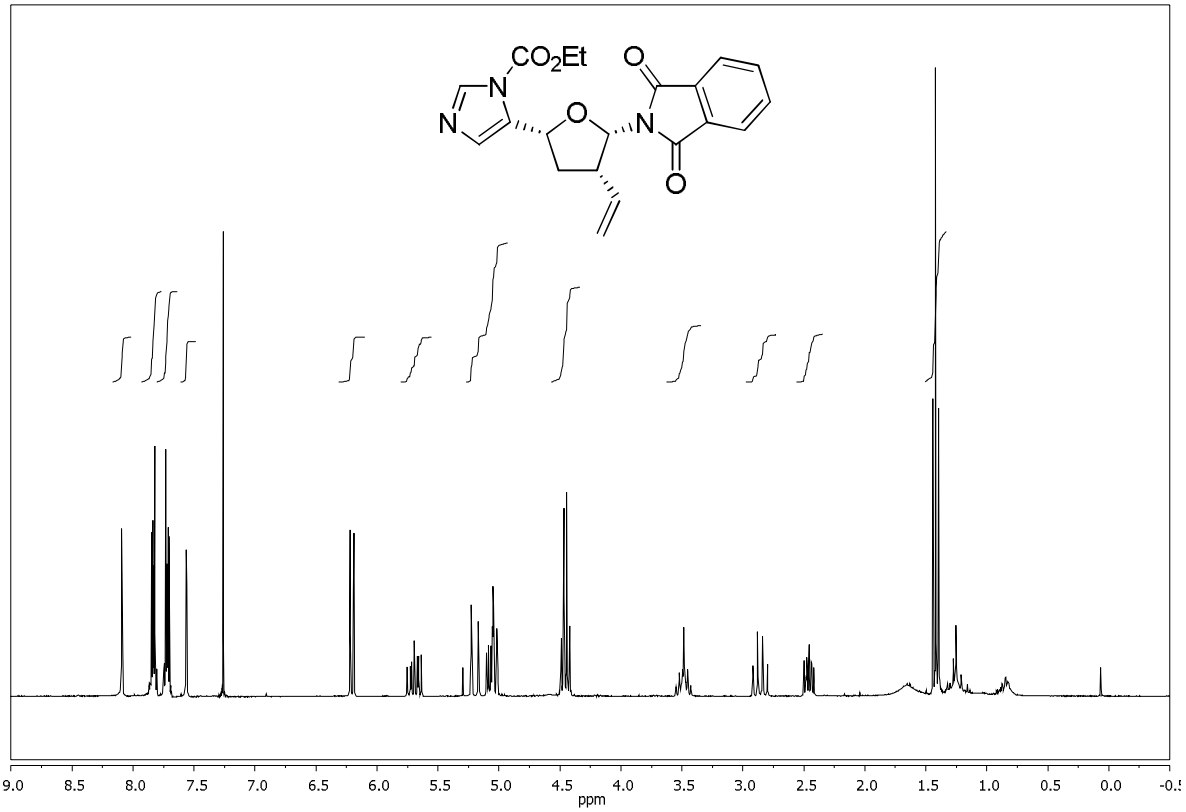


^{13}C-NMR (75 MHz, $CDCl_3$)

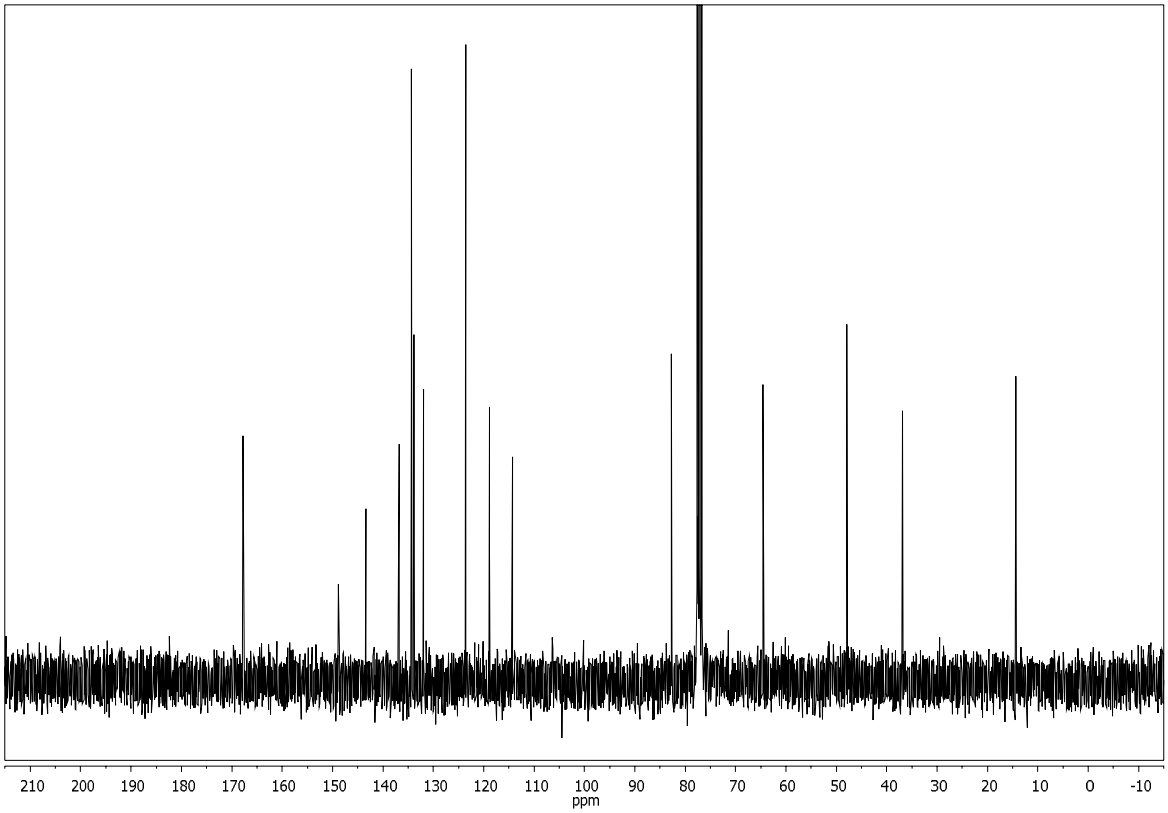


ethyl 5-((2*R*,4*S*,5*S*)-5-(1,3-dioxoisoindolin-2-yl)-4-vinyltetrahydrofuran-2-yl)-1*H*-imidazole-1-carboxylate (135b)

^{1}H-NMR (300 MHz, $CDCl_3$)

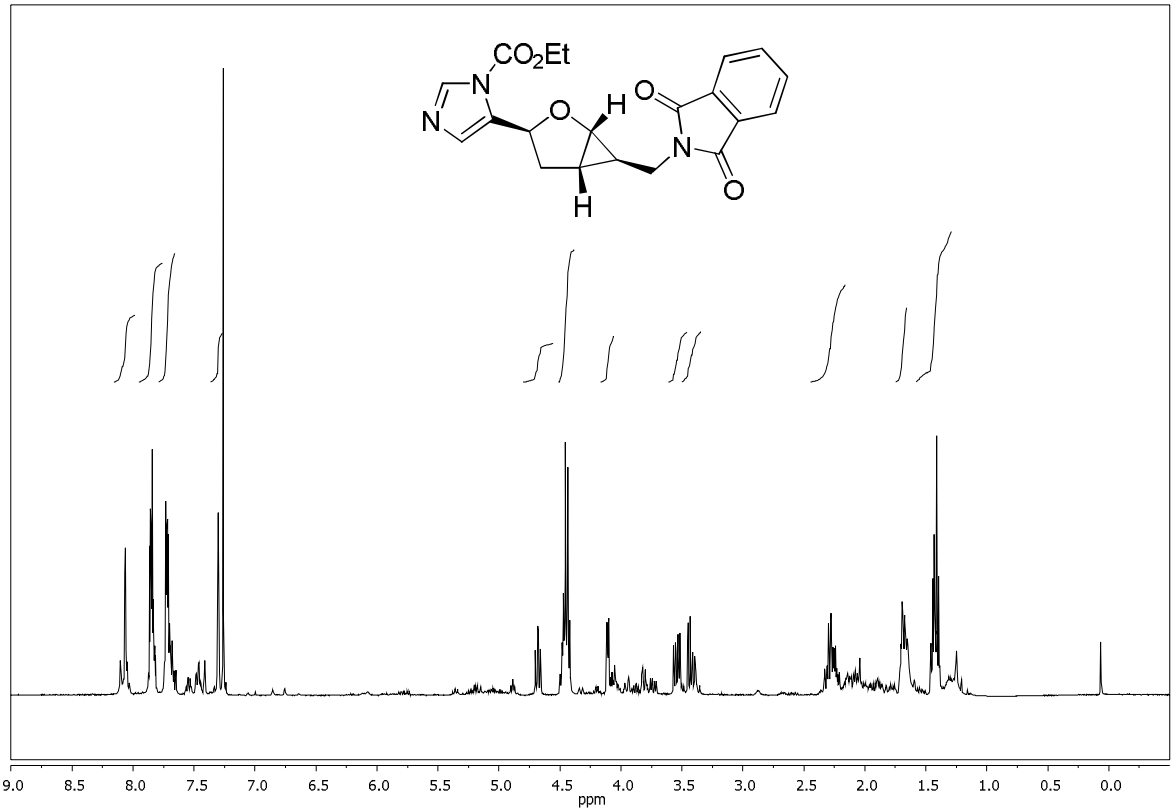


^{13}C-NMR (75 MHz, $CDCl_3$)

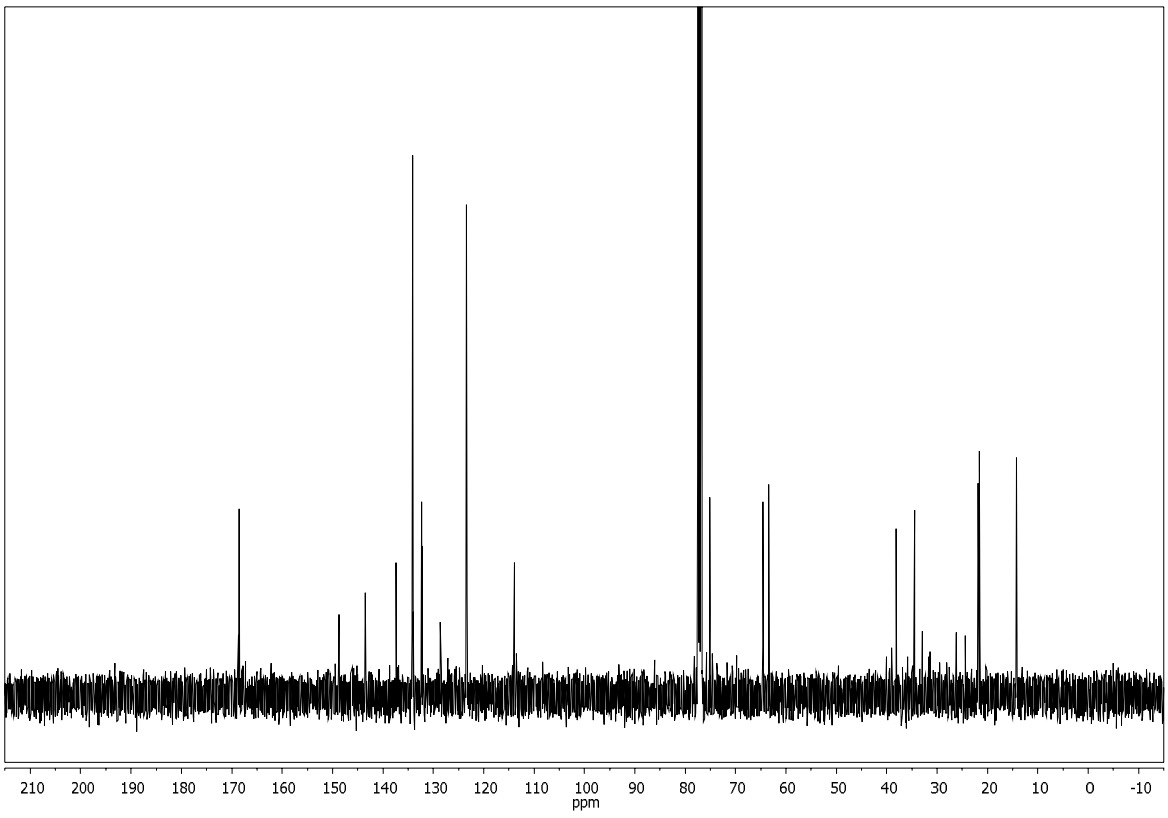


ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (137)

^{1}H-NMR (400 MHz, $CDCl_3$)

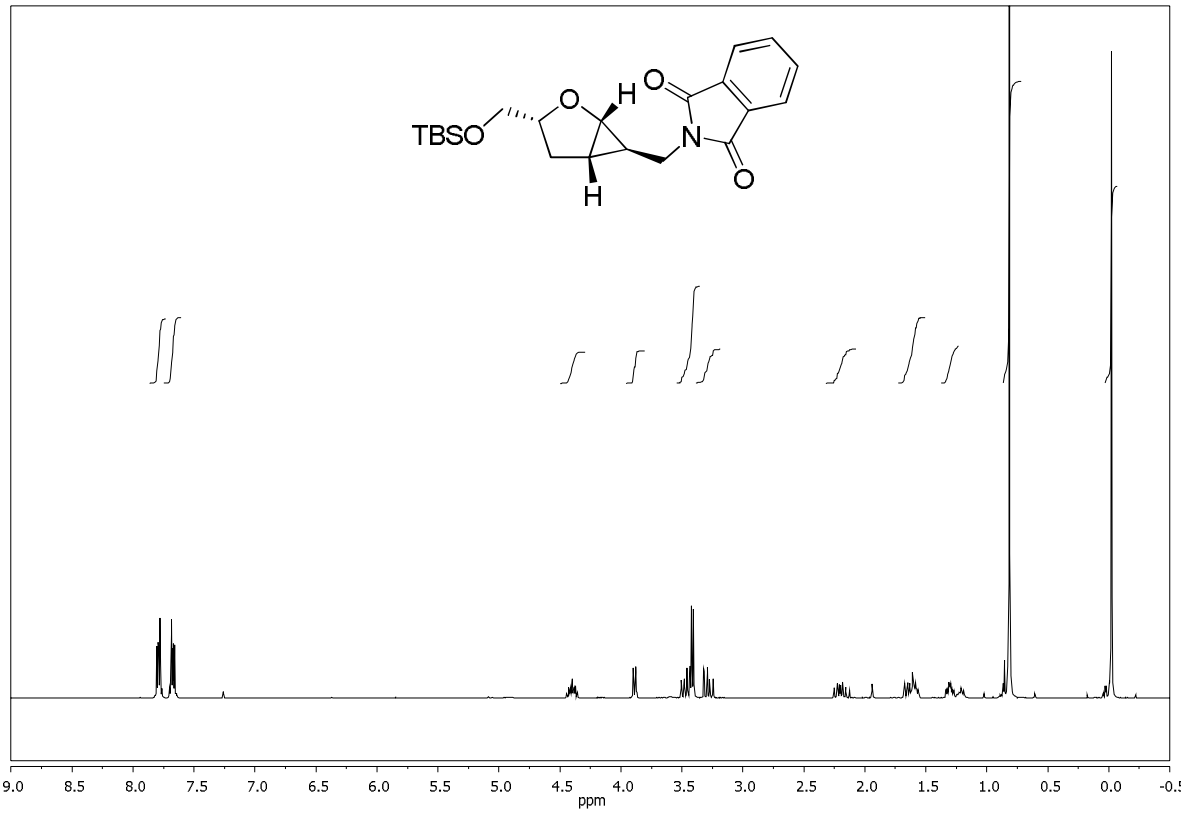


^{13}C-NMR (100 MHz, $CDCl_3$)

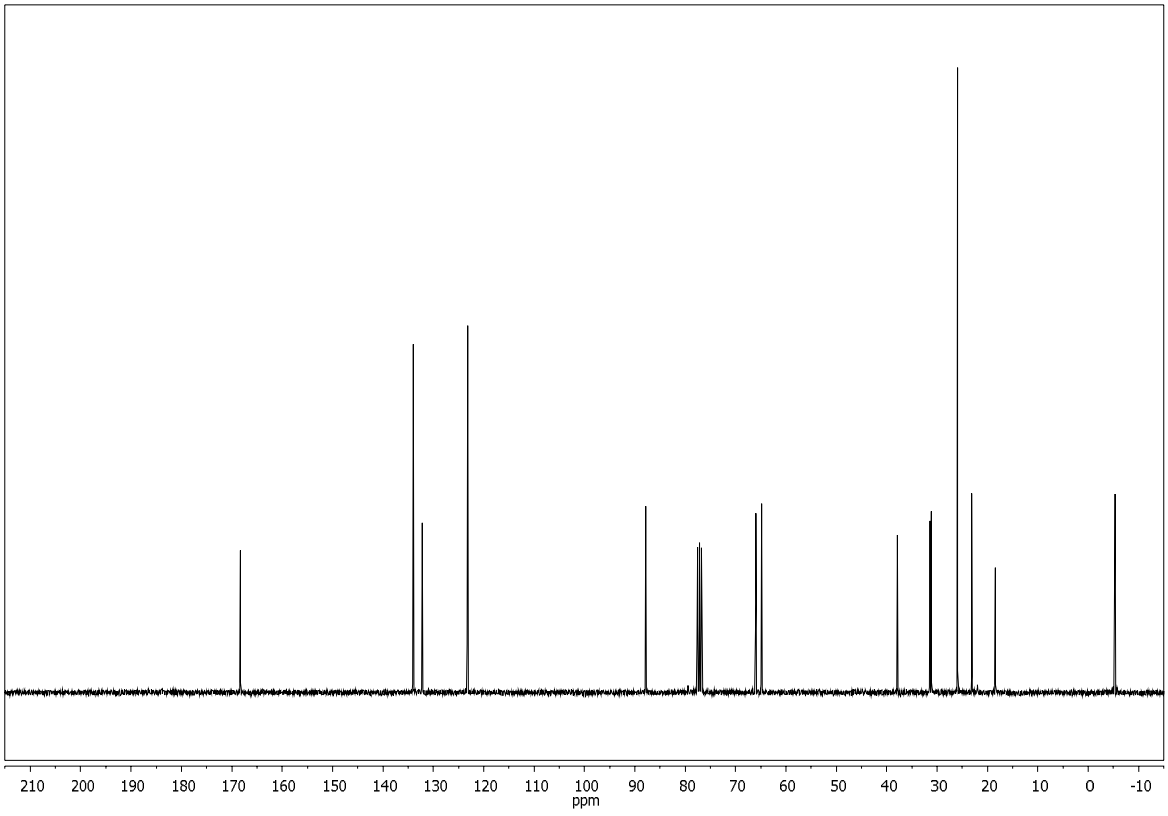


2-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (138)

^{1}H-NMR (300 MHz, $CDCl_3$)

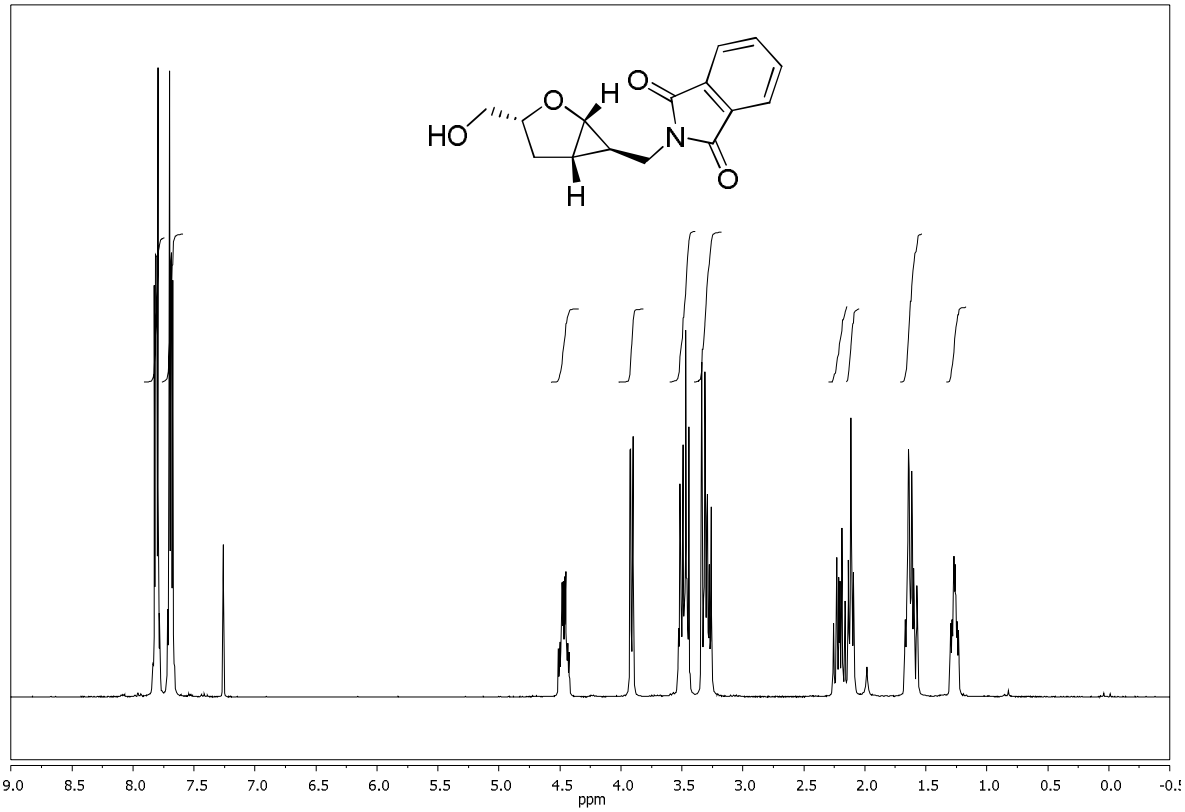


^{13}C-NMR (75 MHz, $CDCl_3$)

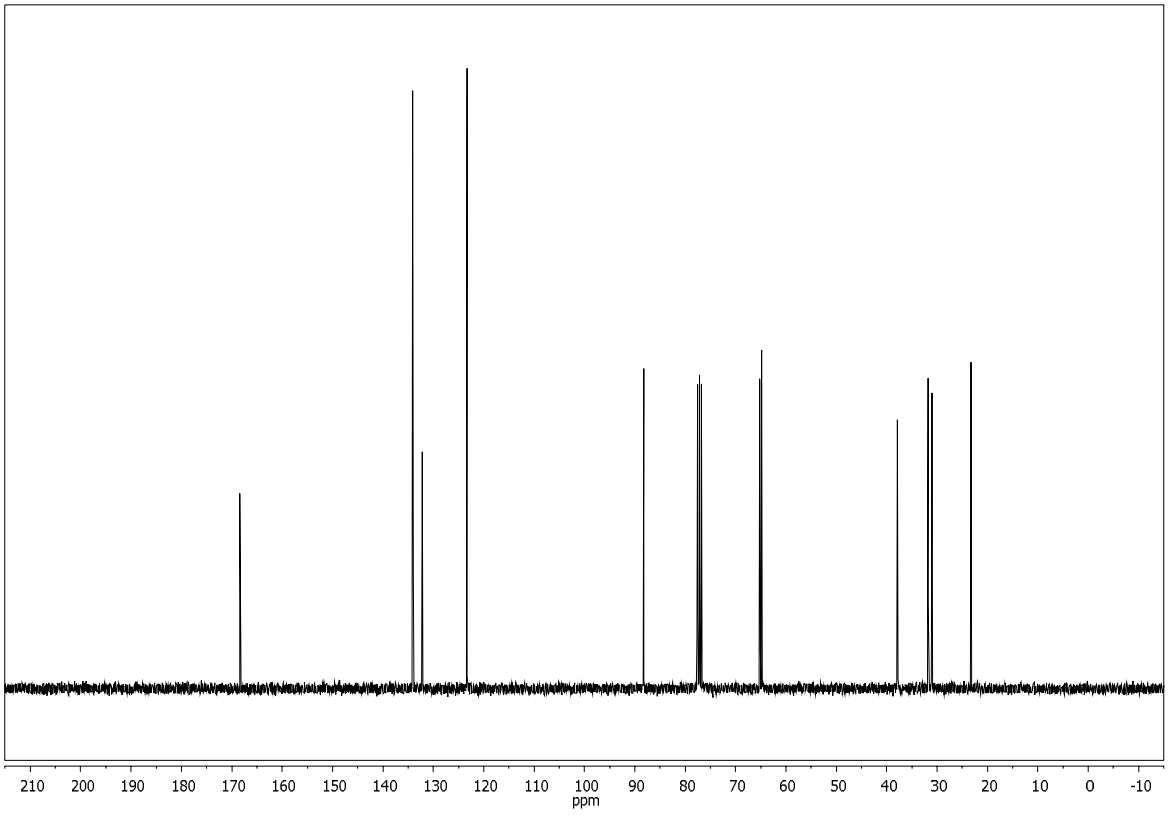


2-(((1*S*,3*R*,5*S*,6*R*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (139)

^{1}H-NMR (300 MHz, $CDCl_3$)

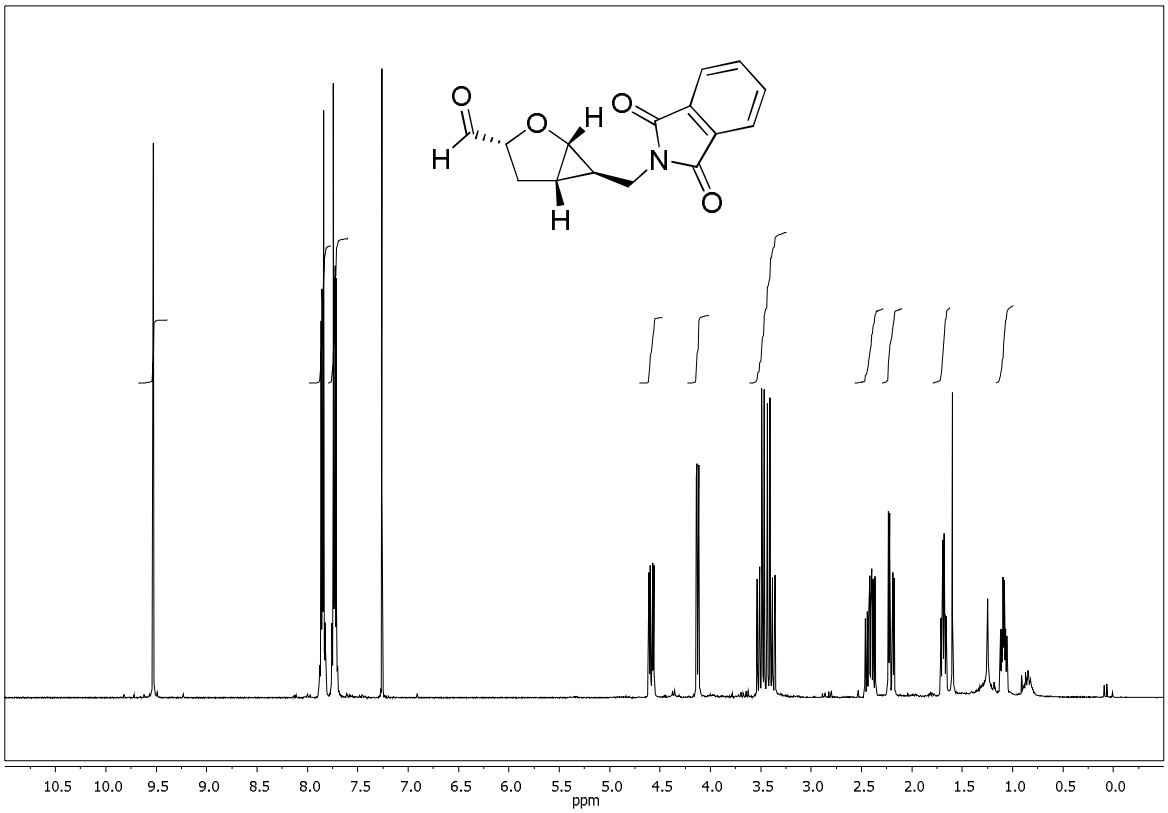


^{13}C-NMR (75 MHz, $CDCl_3$)

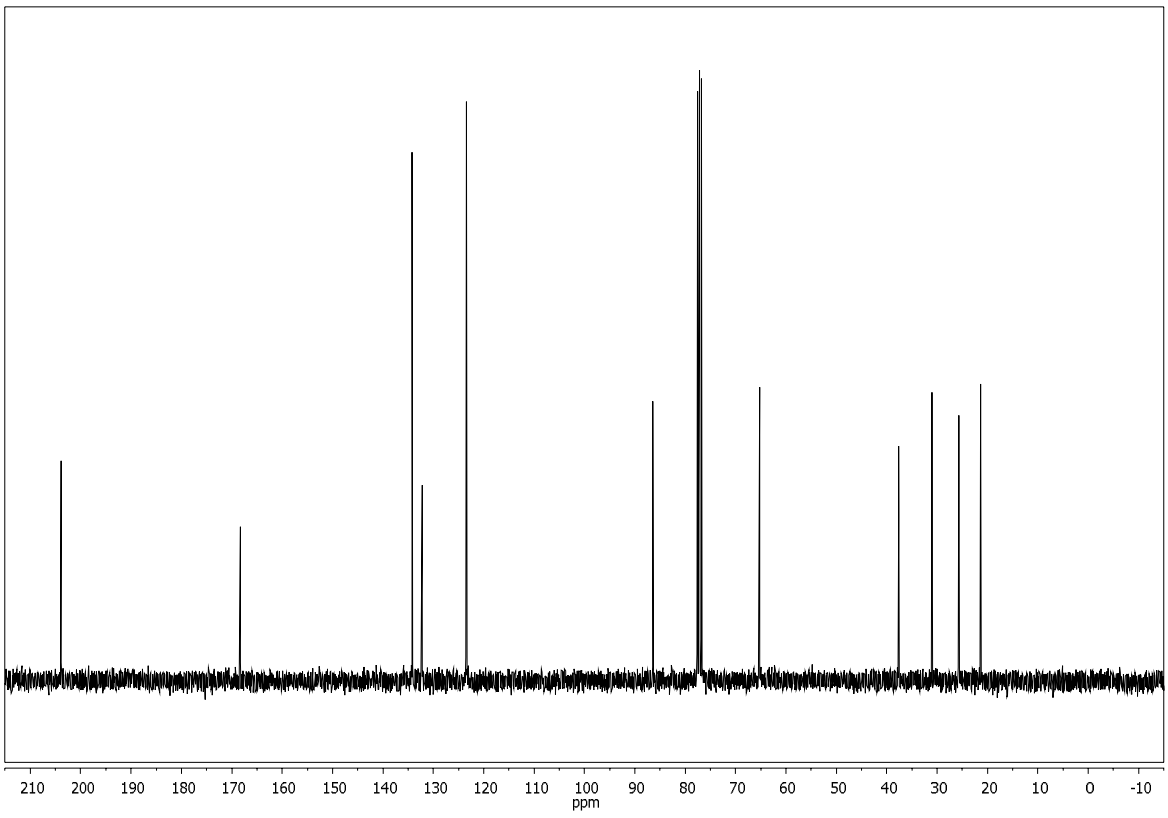


(1*S*,3*R*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexane-3-carbaldehyde (140)

^{1}H-NMR (300 MHz, $CDCl_3$)

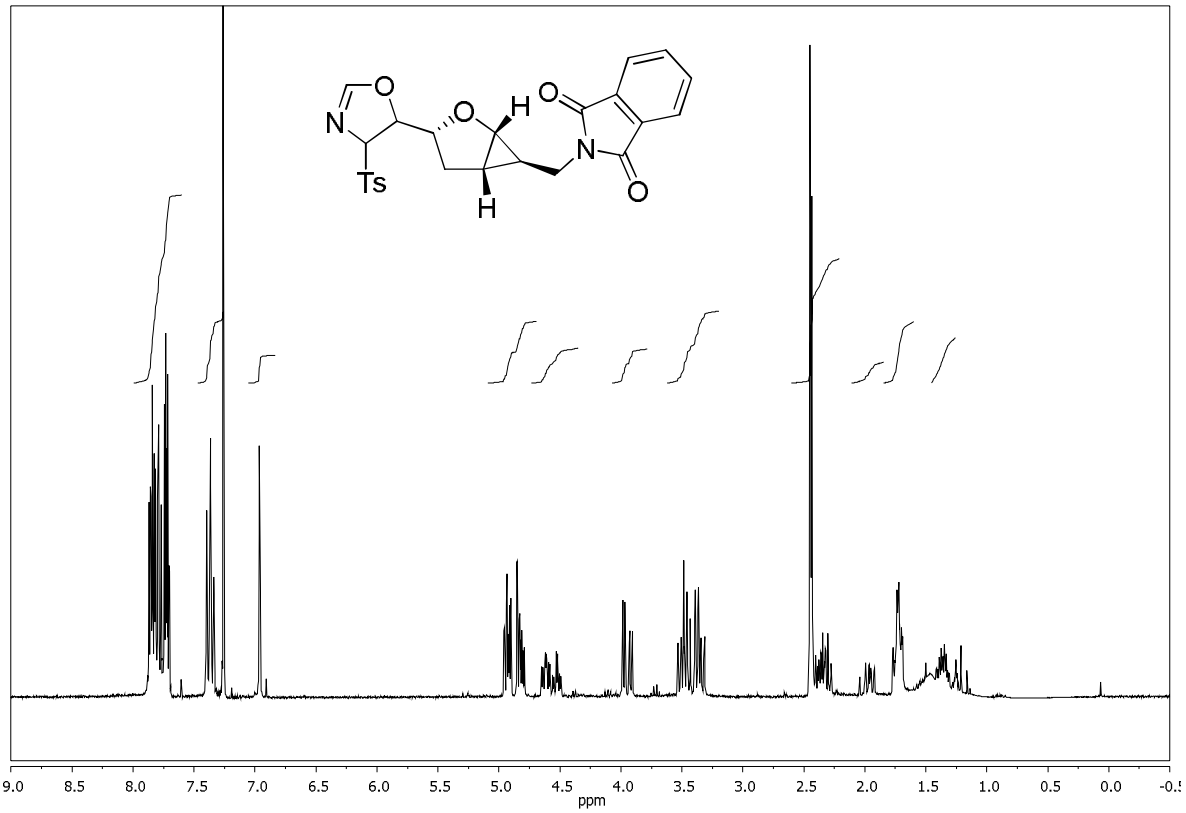


^{13}C-NMR (75 MHz, $CDCl_3$)

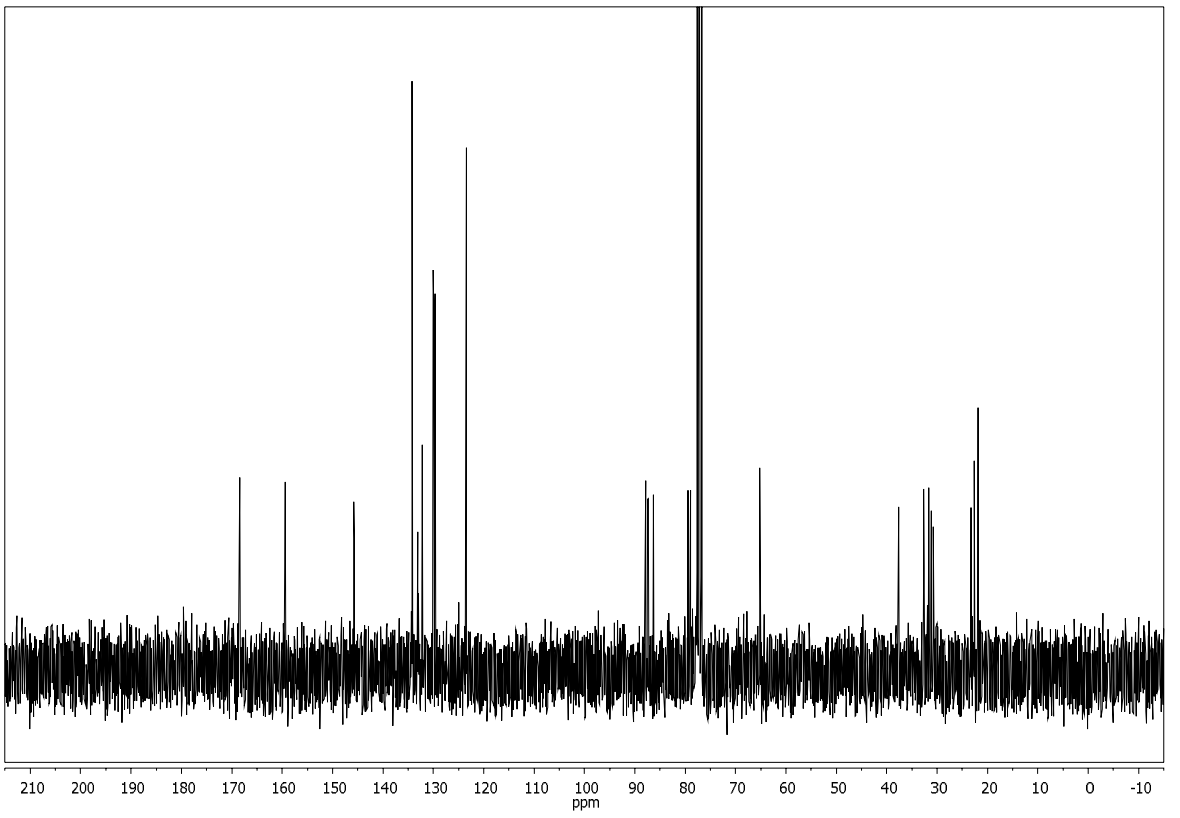


2-(((1*S*,3*R*,5*S*,6*R*)-3-(4-tosyl-4,5-dihydrooxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (141)

^{1}H-NMR (400 MHz, $CDCl_3$)

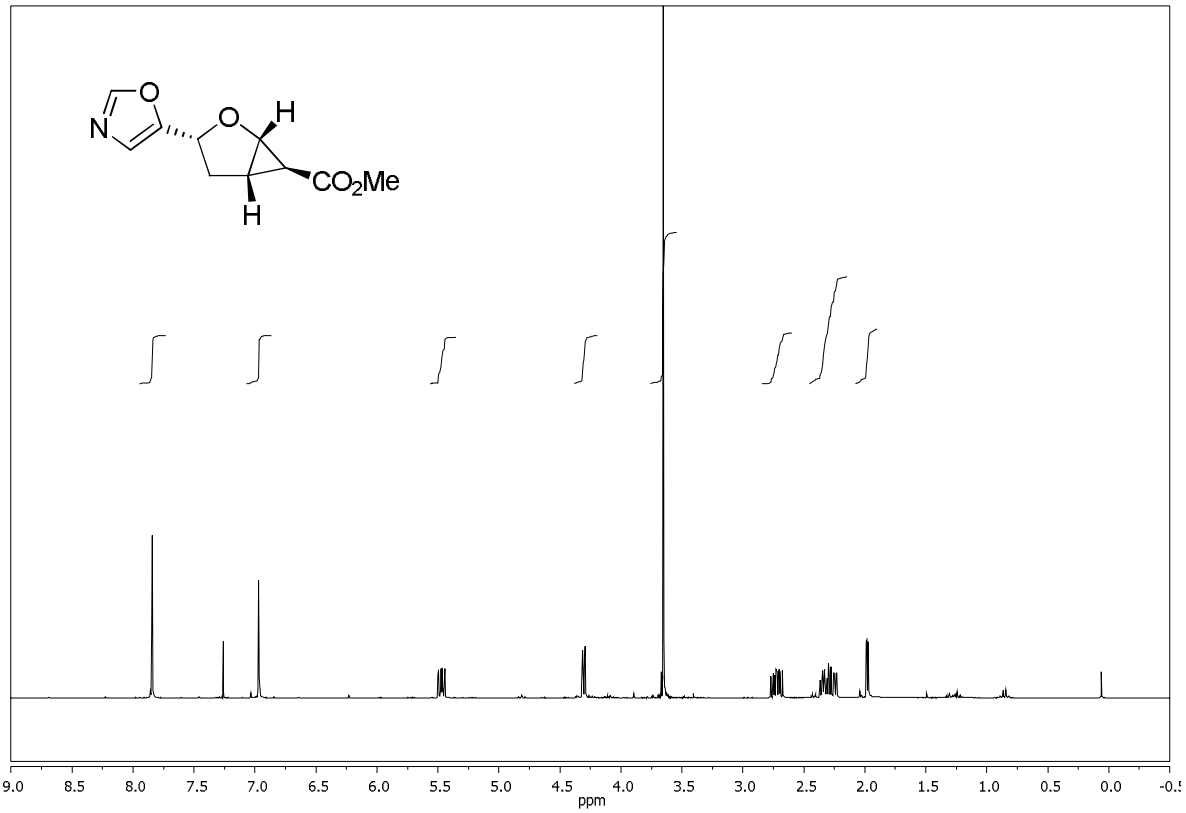


^{13}C-NMR (75 MHz, $CDCl_3$)

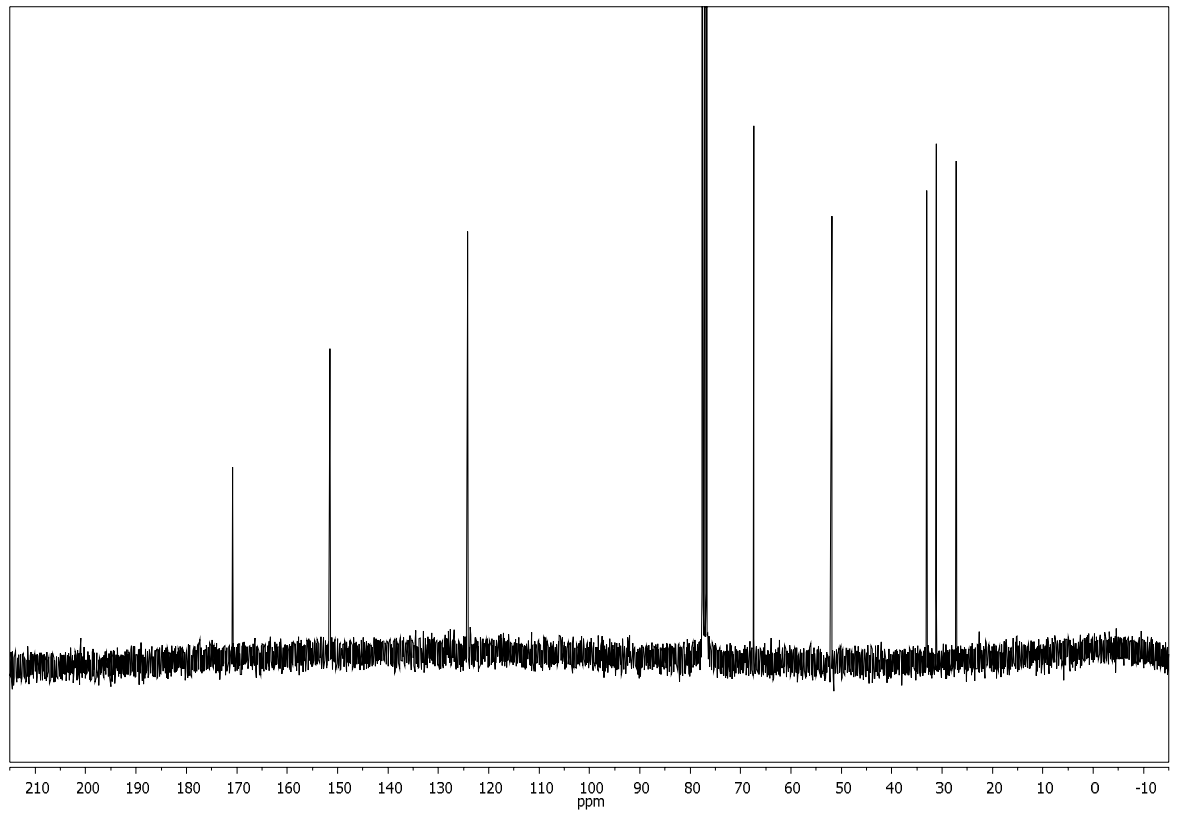


(1*S*,3*R*,5*S*,6*S*)-methyl 3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (142)

^{1}H-NMR (300 MHz, $CDCl_3$)

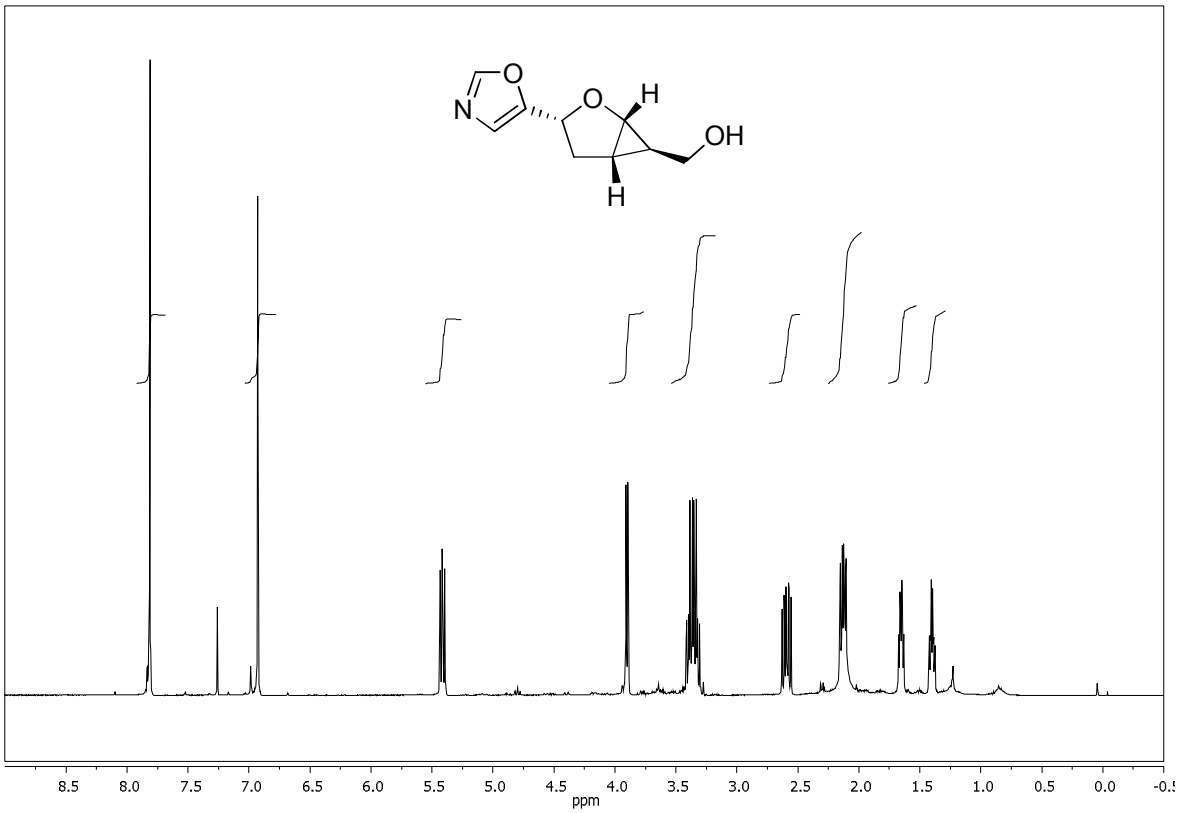


^{13}C-NMR (75 MHz, $CDCl_3$)

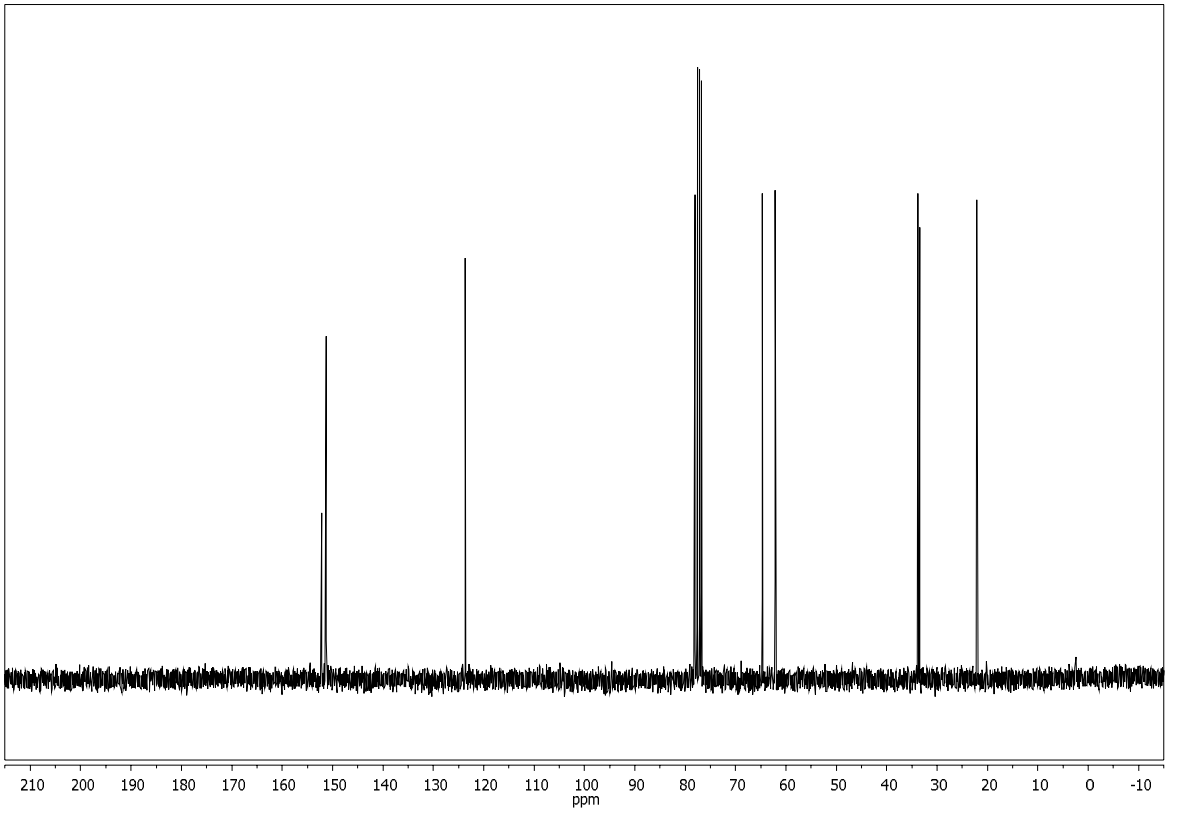


((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanol (143)

^{1}H-NMR (400 MHz, $CDCl_3$)

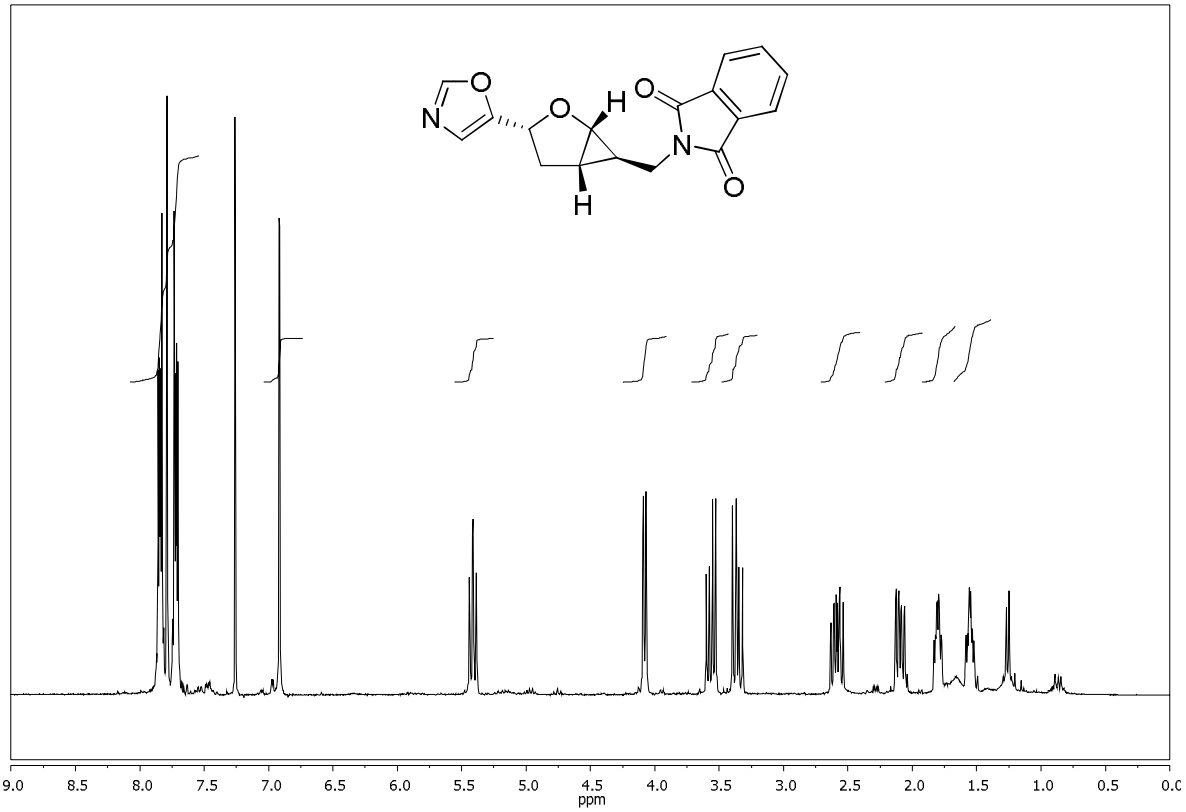


^{13}C-NMR (75 MHz, $CDCl_3$)

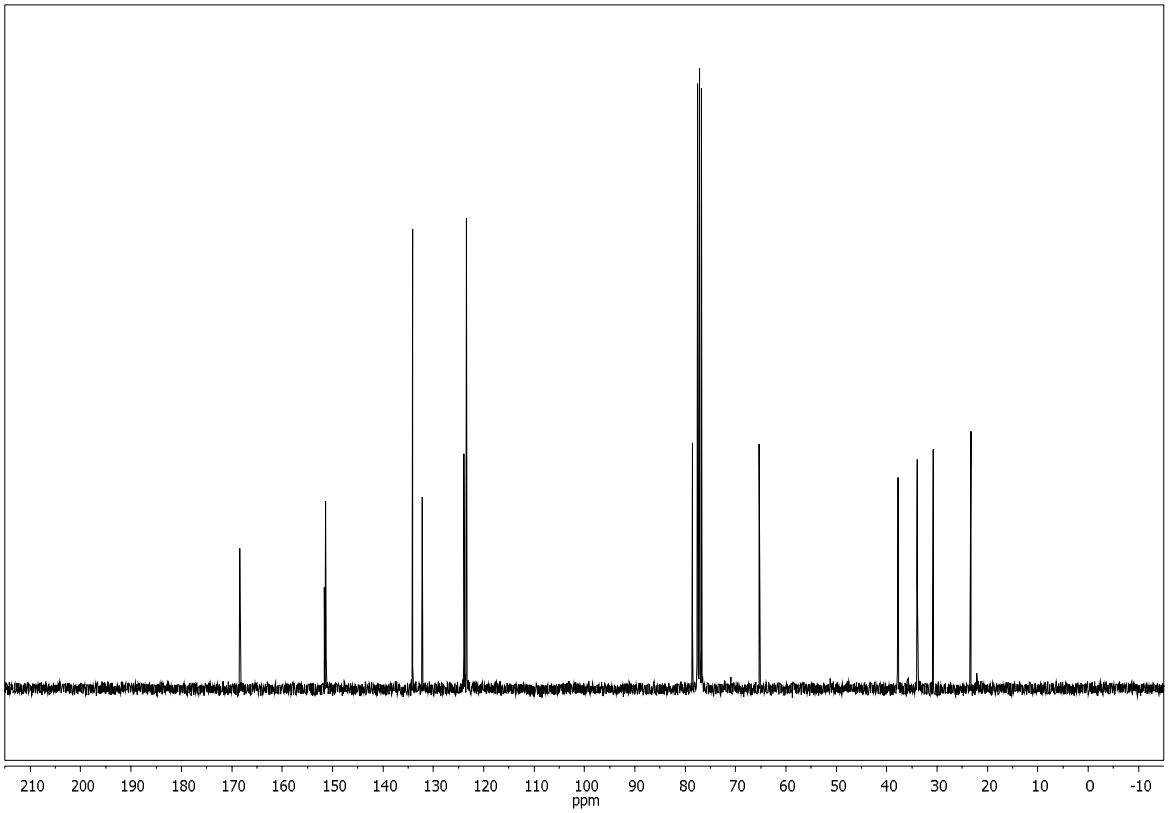


2-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (144)

^{1}H-NMR (300 MHz, $CDCl_3$)

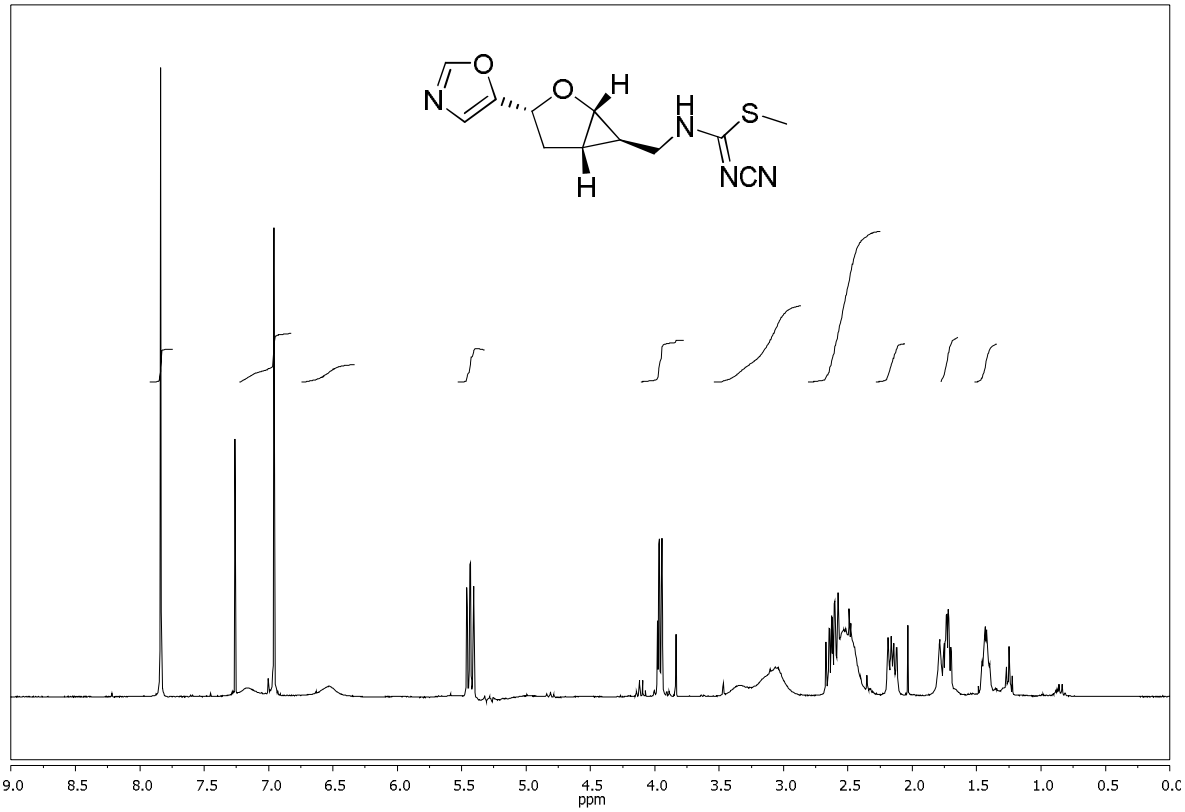


^{13}C-NMR (75 MHz, $CDCl_3$)

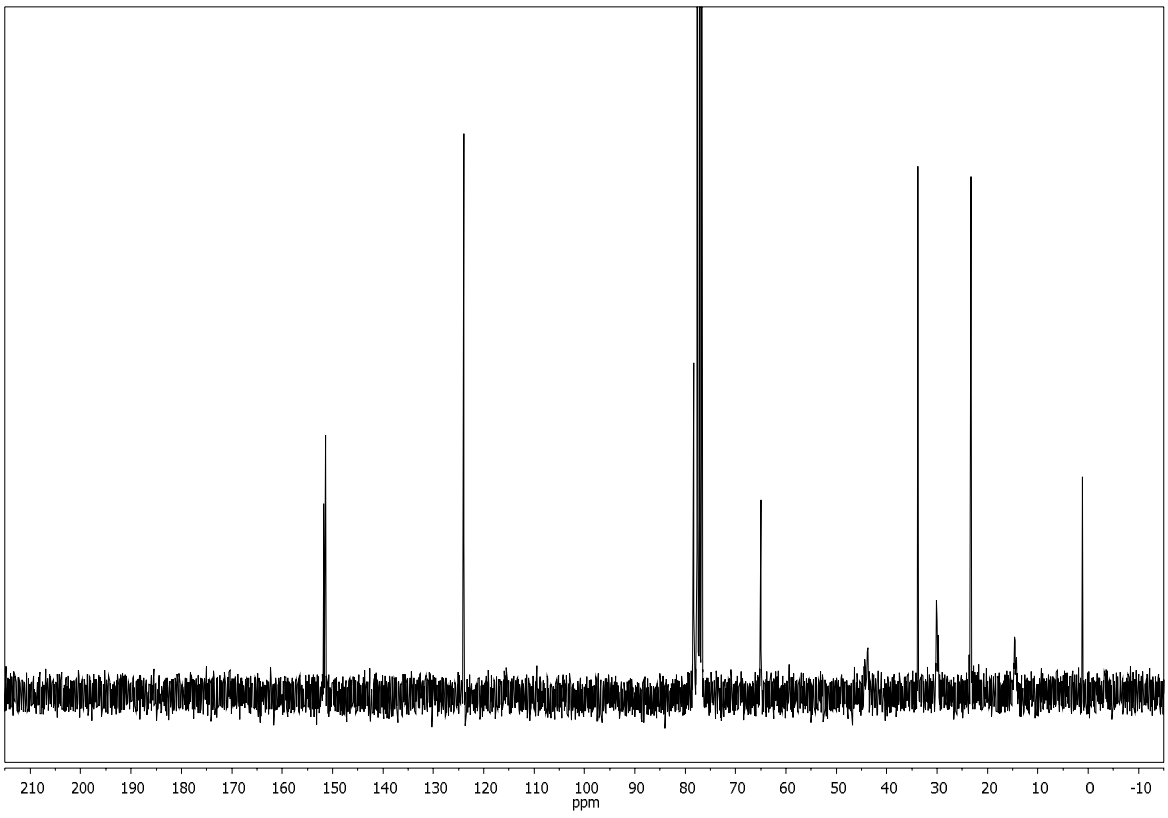


methyl *N*'-cyano-*N*-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)carbamimidothioate (145)

^{1}H-NMR (300 MHz, $CDCl_3$)

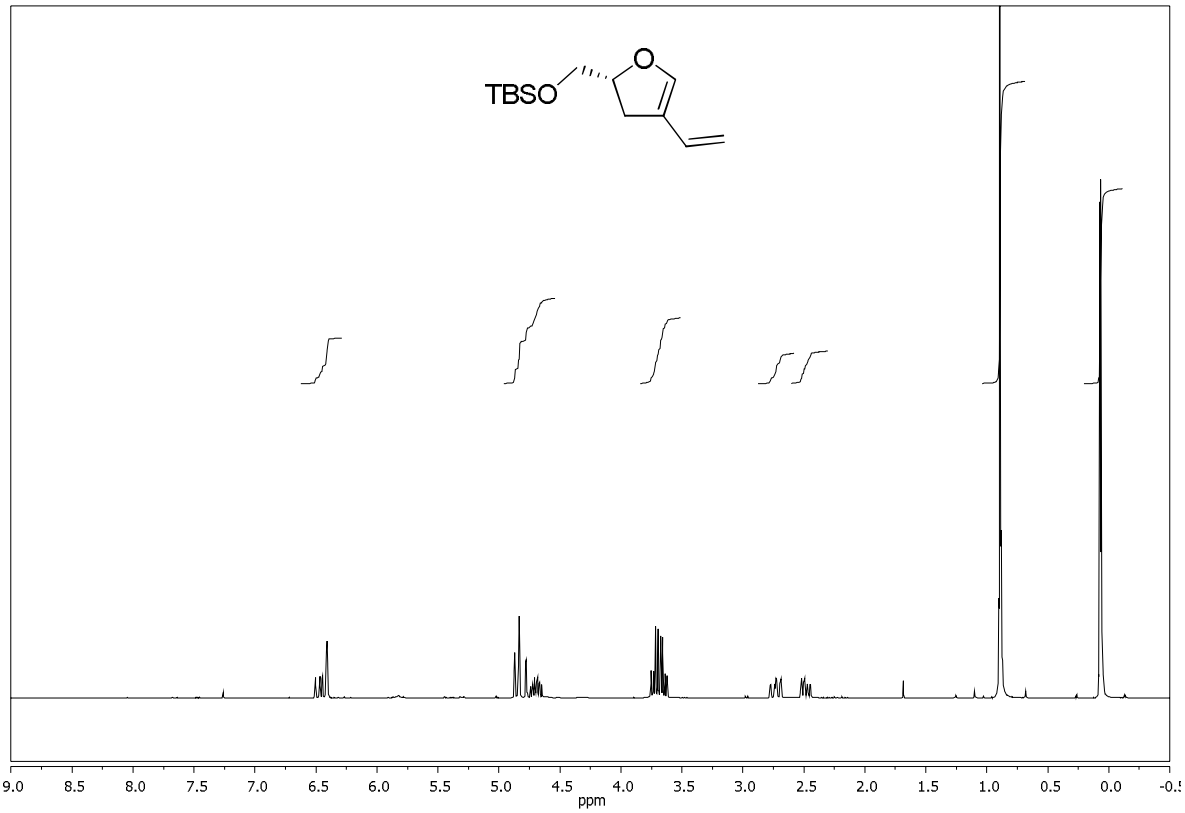


^{13}C-NMR (75 MHz, $CDCl_3$)

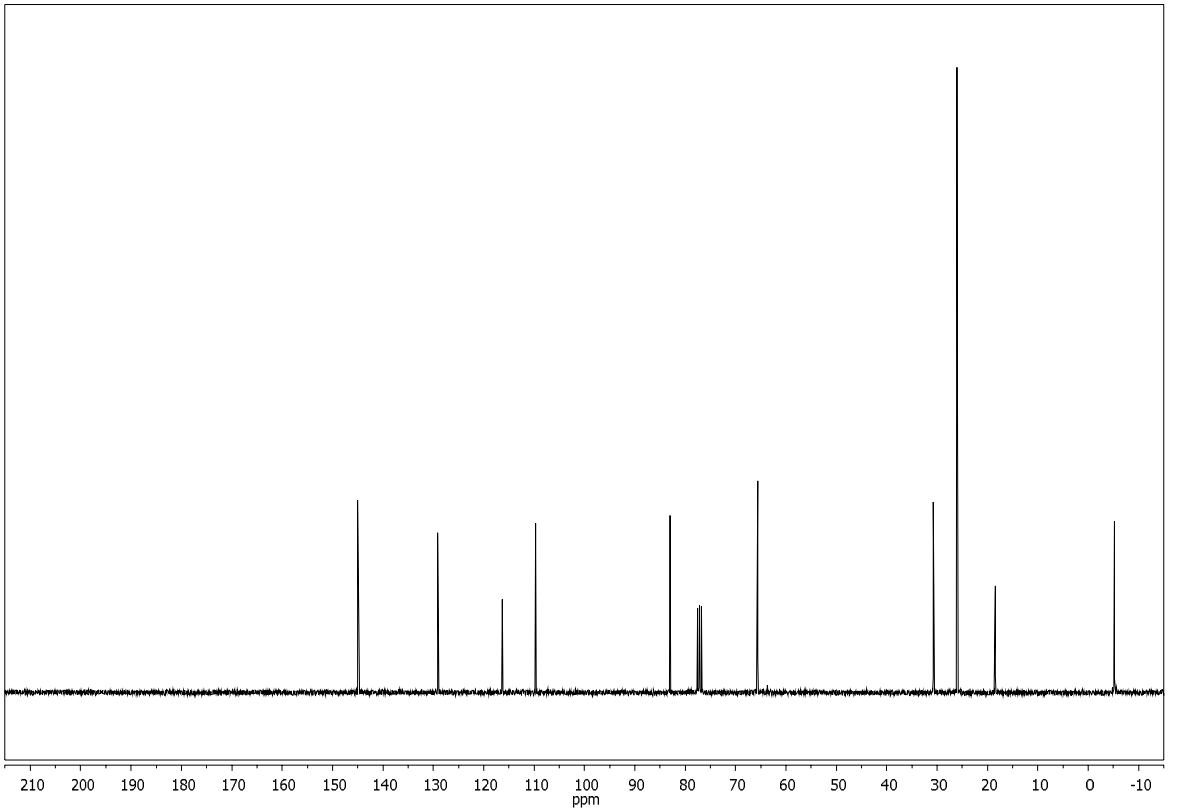


(*R*)-*tert*-butyldimethyl((4-vinyl-2,3-dihydrofuran-2-yl)methoxy)silane (153)

^{1}H-NMR (300 MHz, $CDCl_3$)

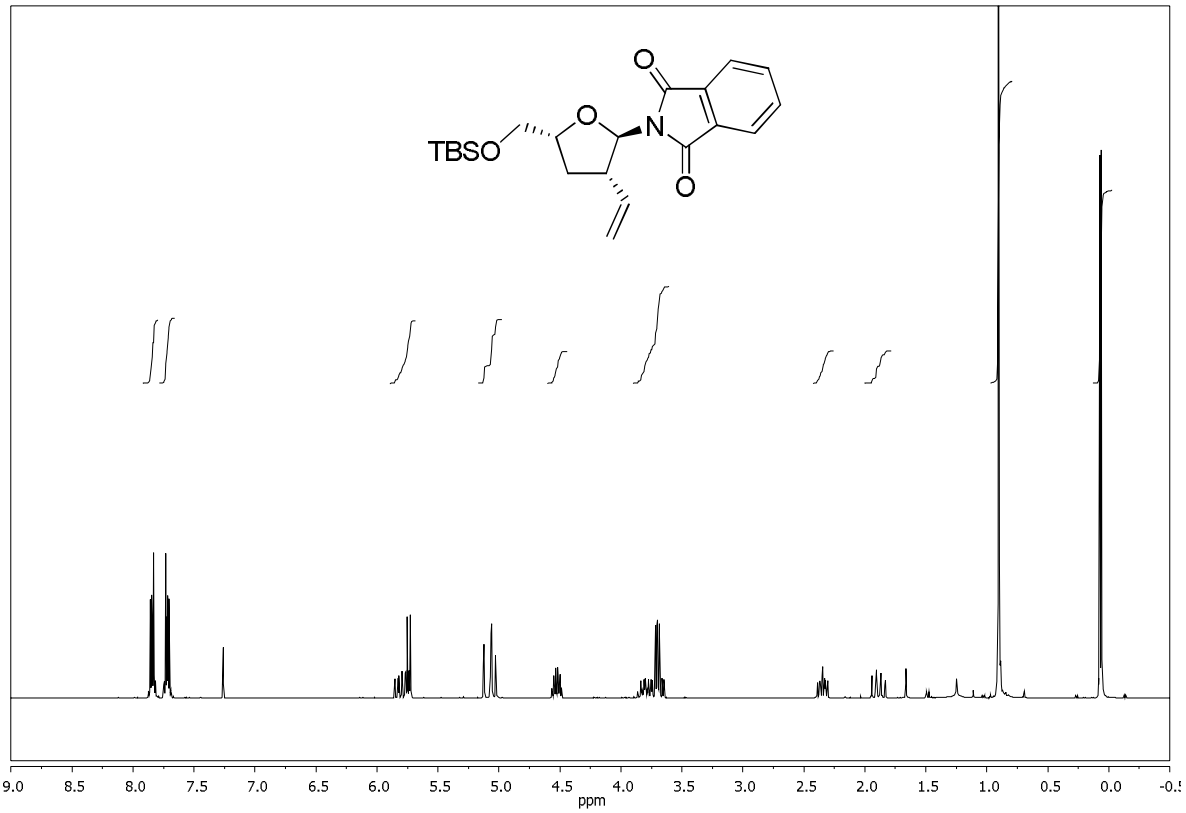


^{13}C-NMR (75 MHz, $CDCl_3$)

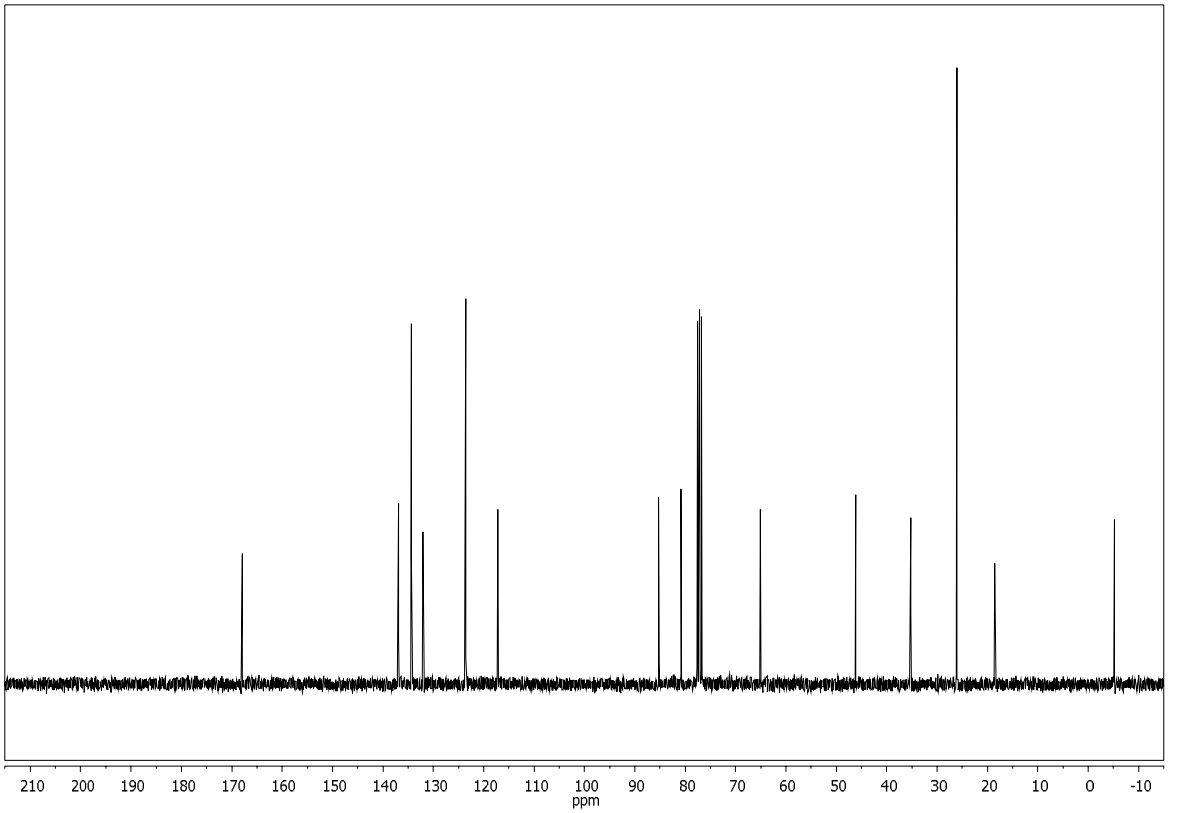


2-((2*R*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)-isoindoline-1,3-dione (154a)

^{1}H-NMR (300 MHz, $CDCl_3$)

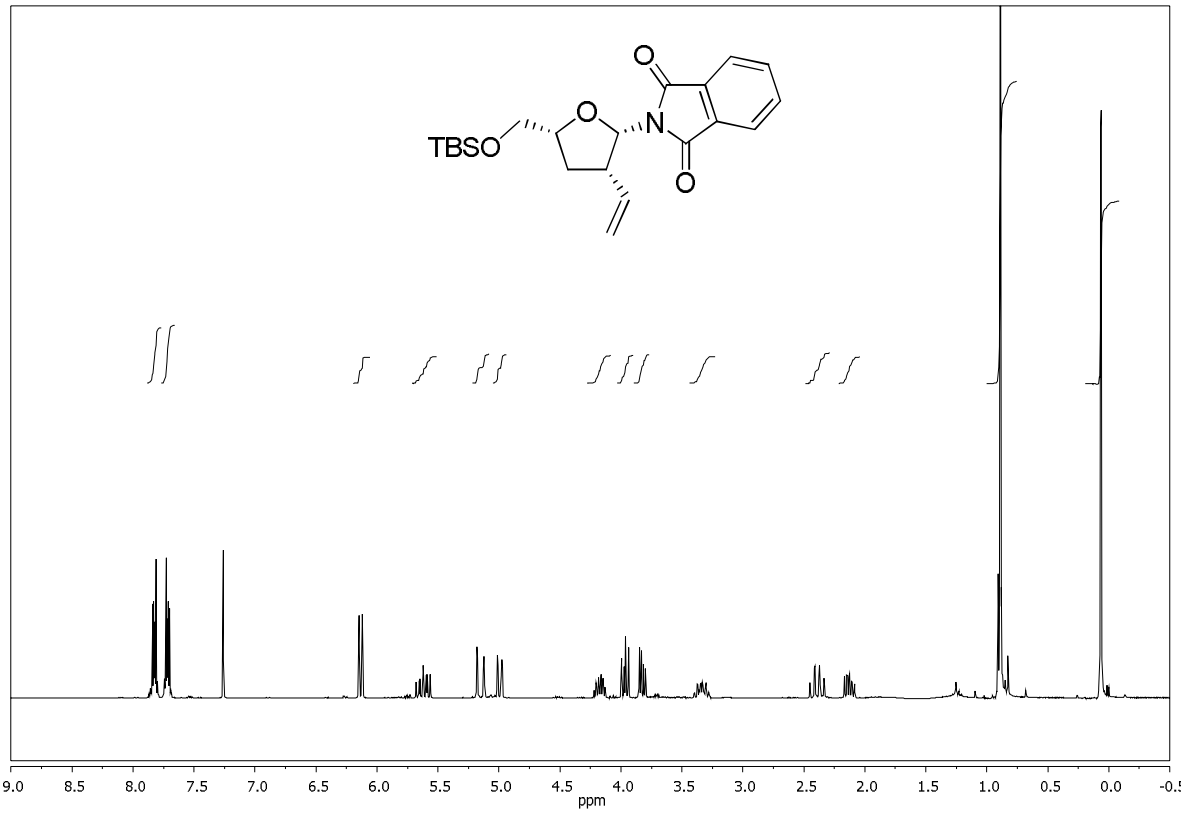


^{13}C-NMR (75 MHz, $CDCl_3$)

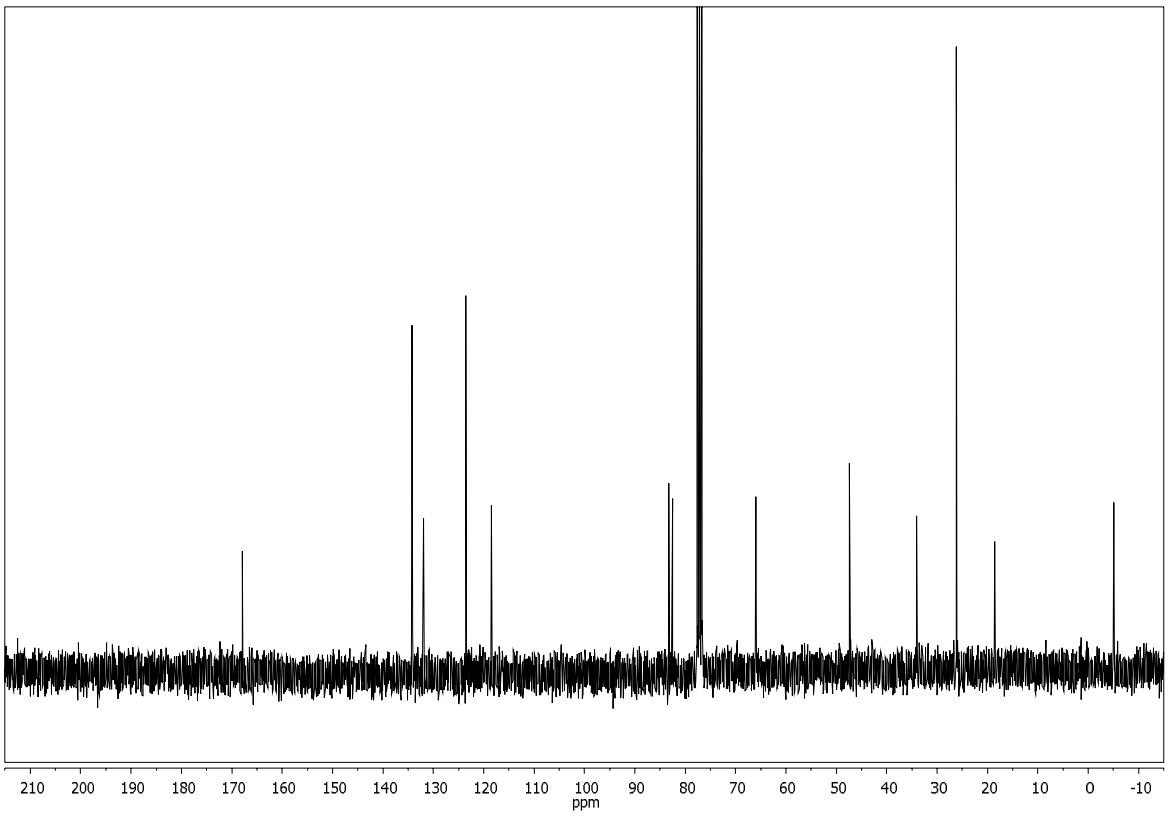


2-((2*S*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)-isoindoline-1,3-dione (154b)

^{1}H-NMR (300 MHz, $CDCl_3$)

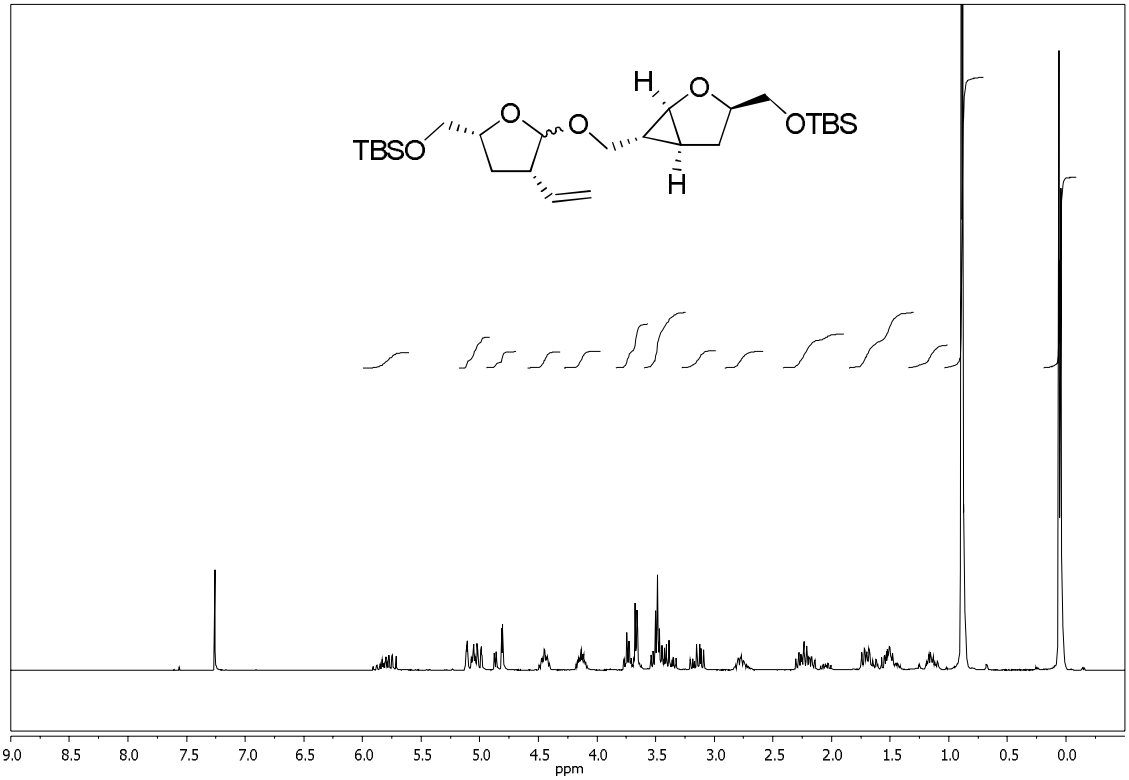


^{13}C-NMR (75 MHz, $CDCl_3$)

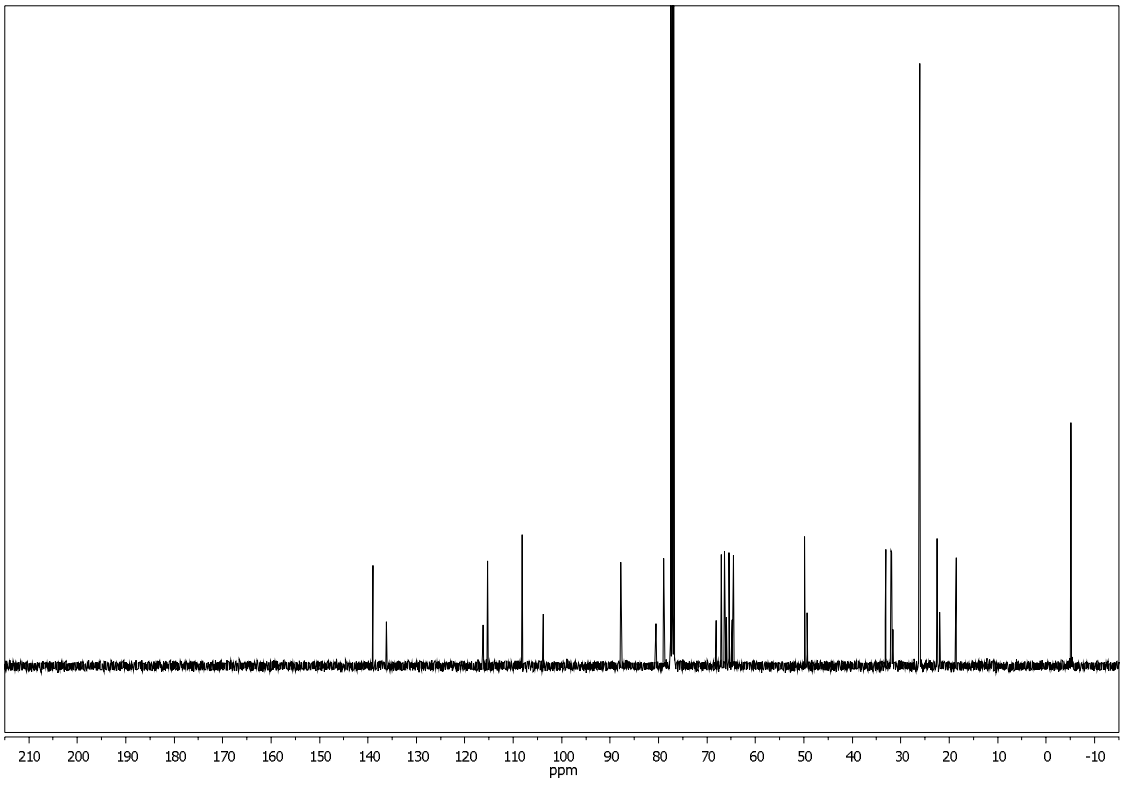


***tert*-butyl(((2*R*,4*S*)-5-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo-[3.1.0]hexan-6-yl)methoxy)-4-vinyltetrahydrofuran-2-yl)methoxy)dimethylsilane (165)**

^{1}H-NMR (300 MHz, $CDCl_3$)

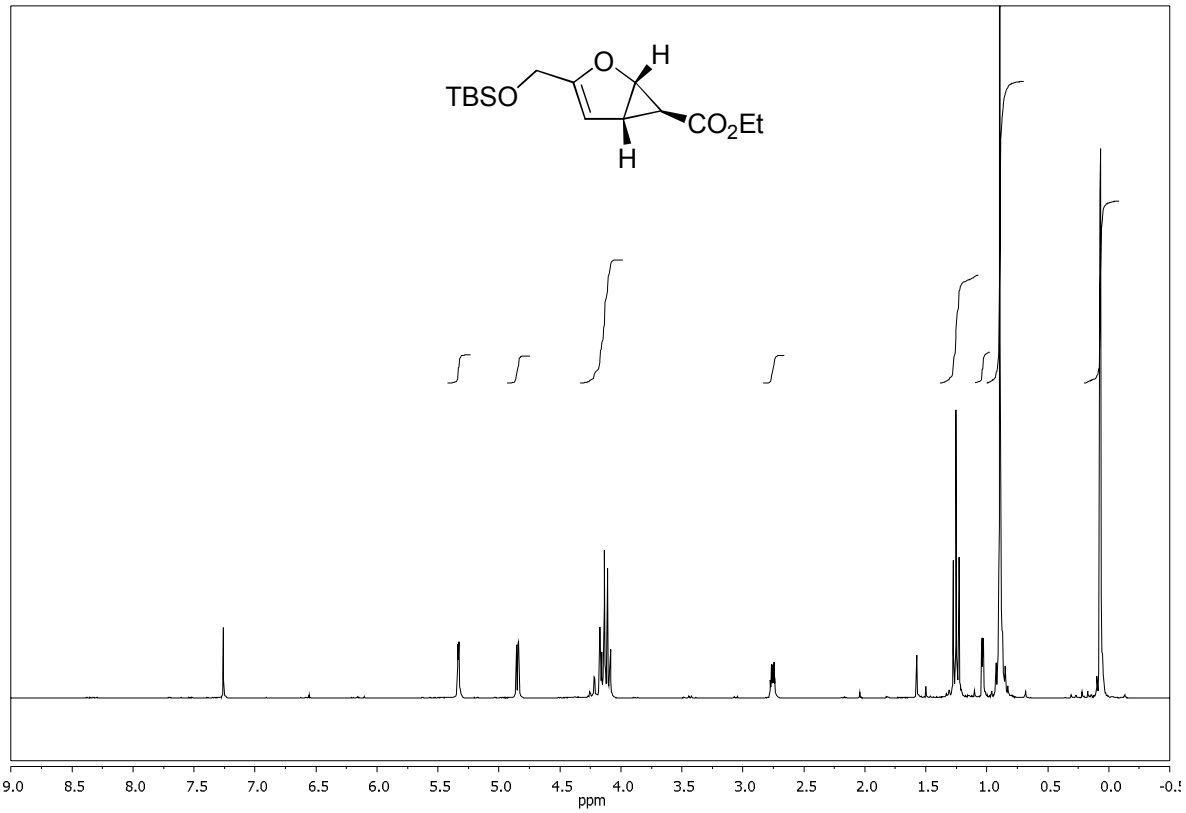


^{13}C-NMR (100 MHz, $CDCl_3$)

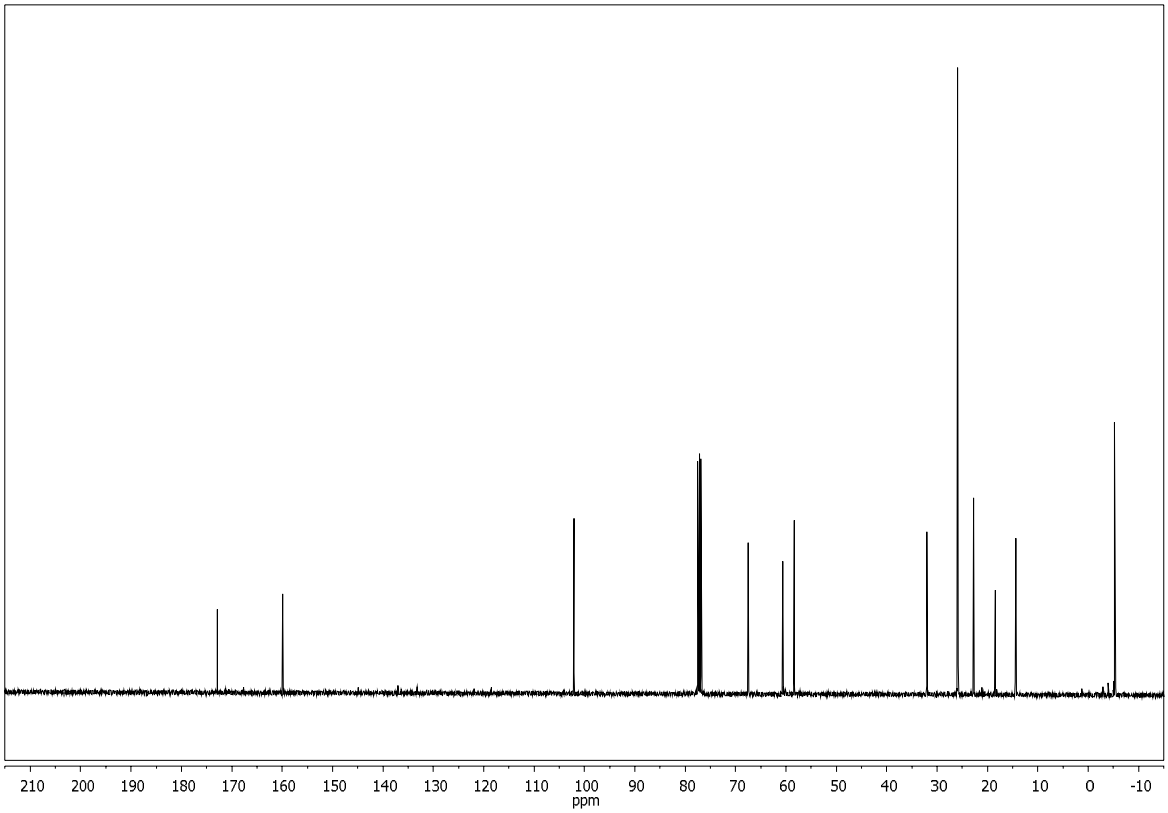


(1*S*,5*S*,6*S*)-ethyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (166)

^{1}H-NMR (300 MHz, $CDCl_3$)

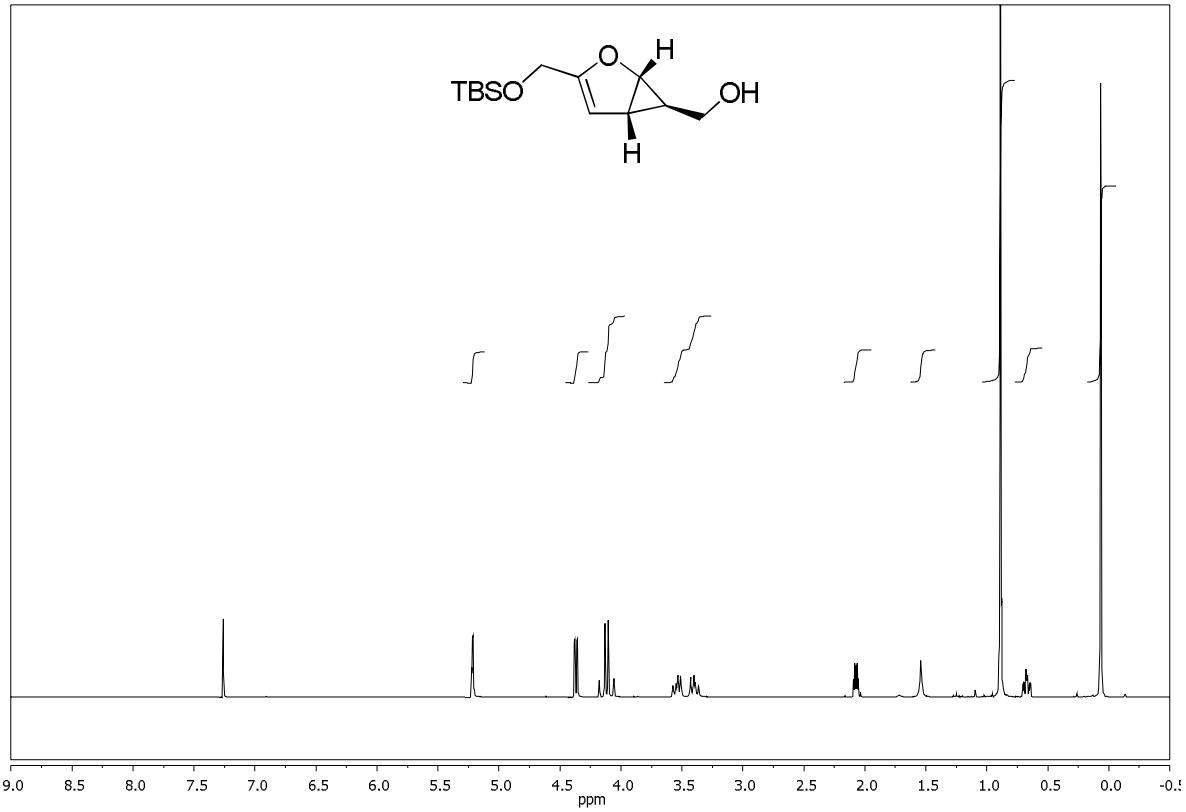


^{13}C-NMR (100 MHz, $CDCl_3$)

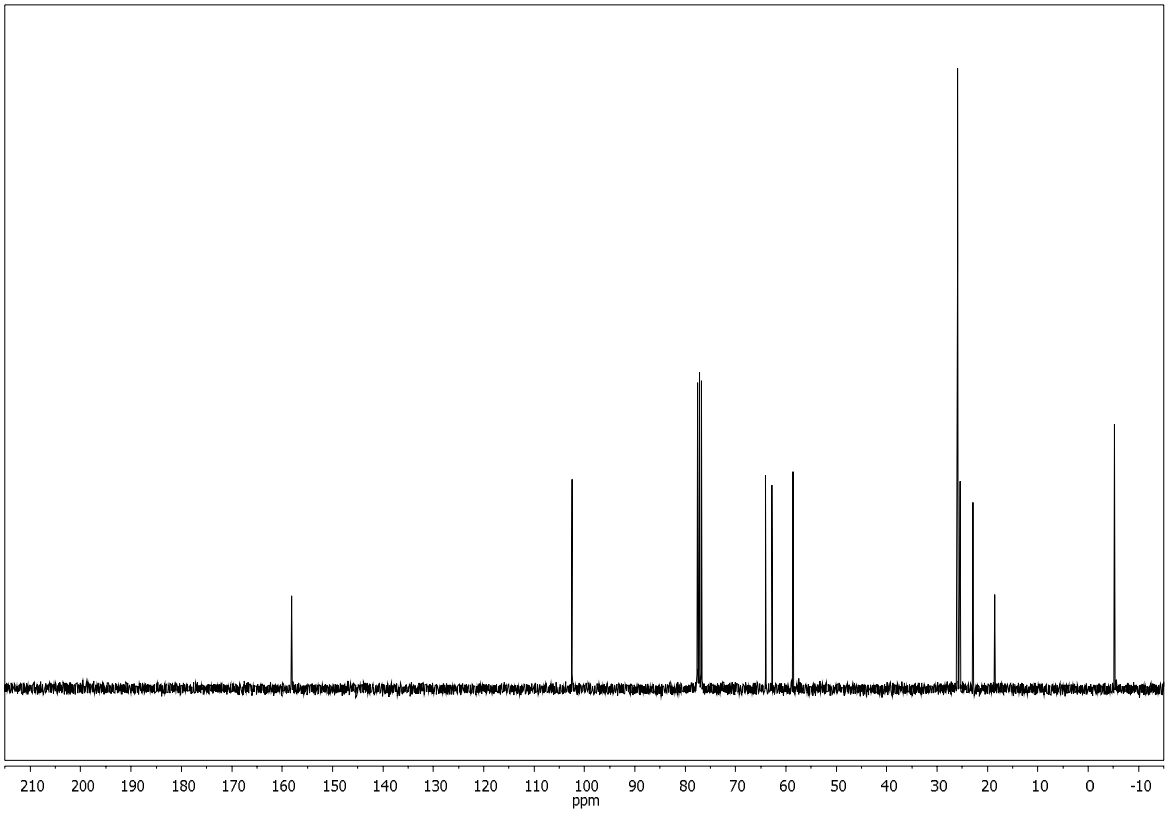


((1*S*,5*R*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hex-3-en-6-yl)-methanol (167)

^{1}H-NMR (300 MHz, $CDCl_3$)

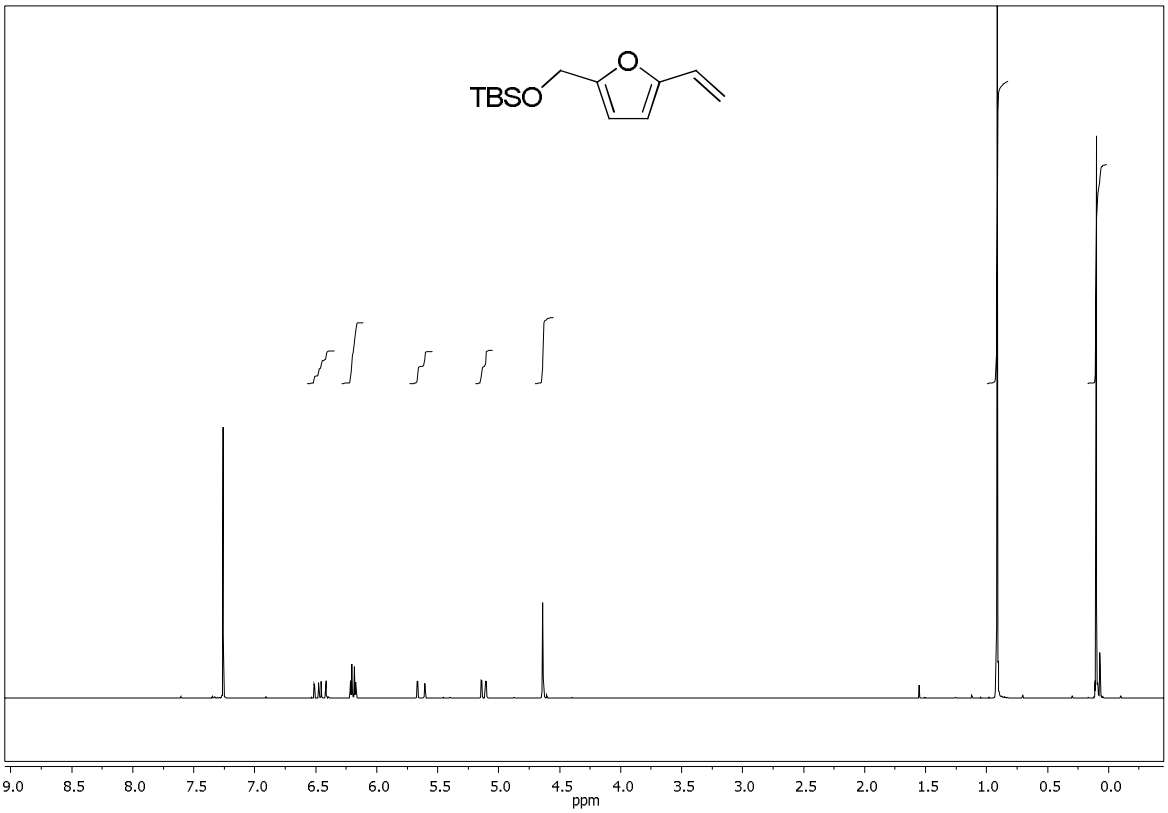


^{13}C-NMR (75 MHz, $CDCl_3$)

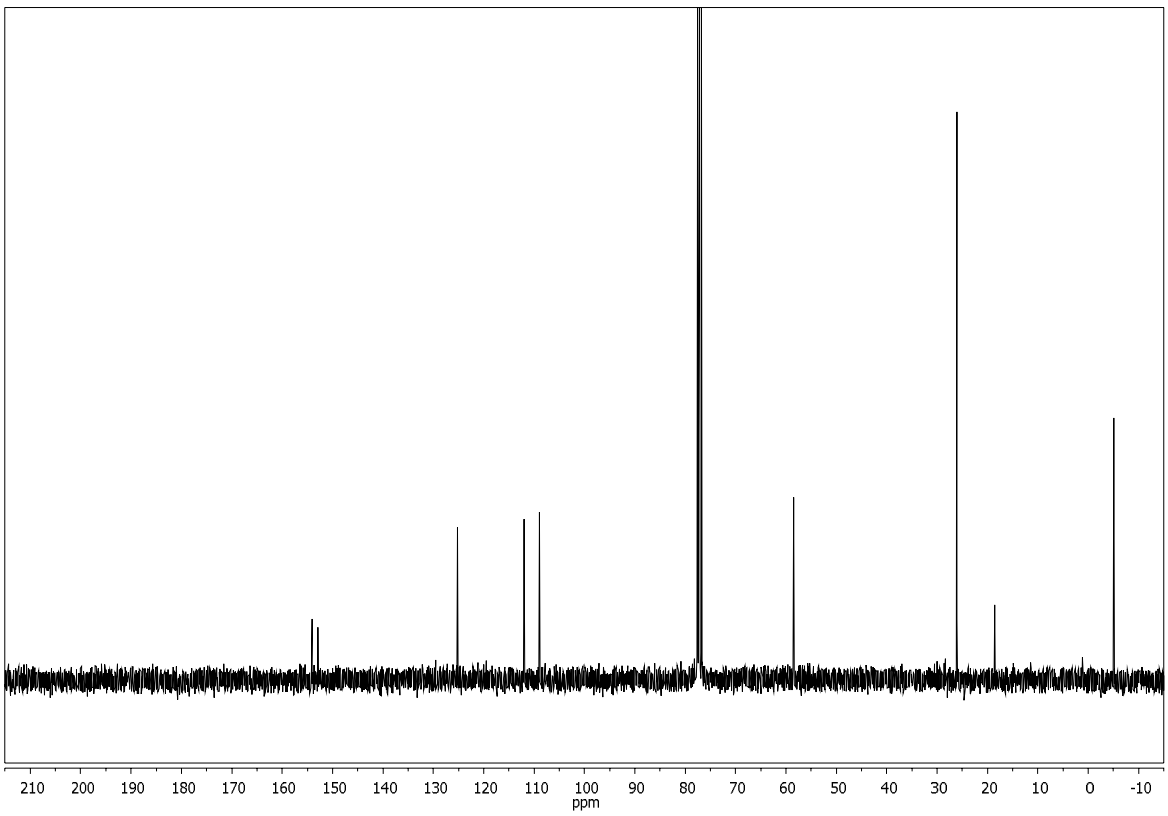


tert-butyldimethyl((5-vinylfuran-2-yl)methoxy)silane (168)

^{1}H-NMR (300 MHz, $CDCl_3$)

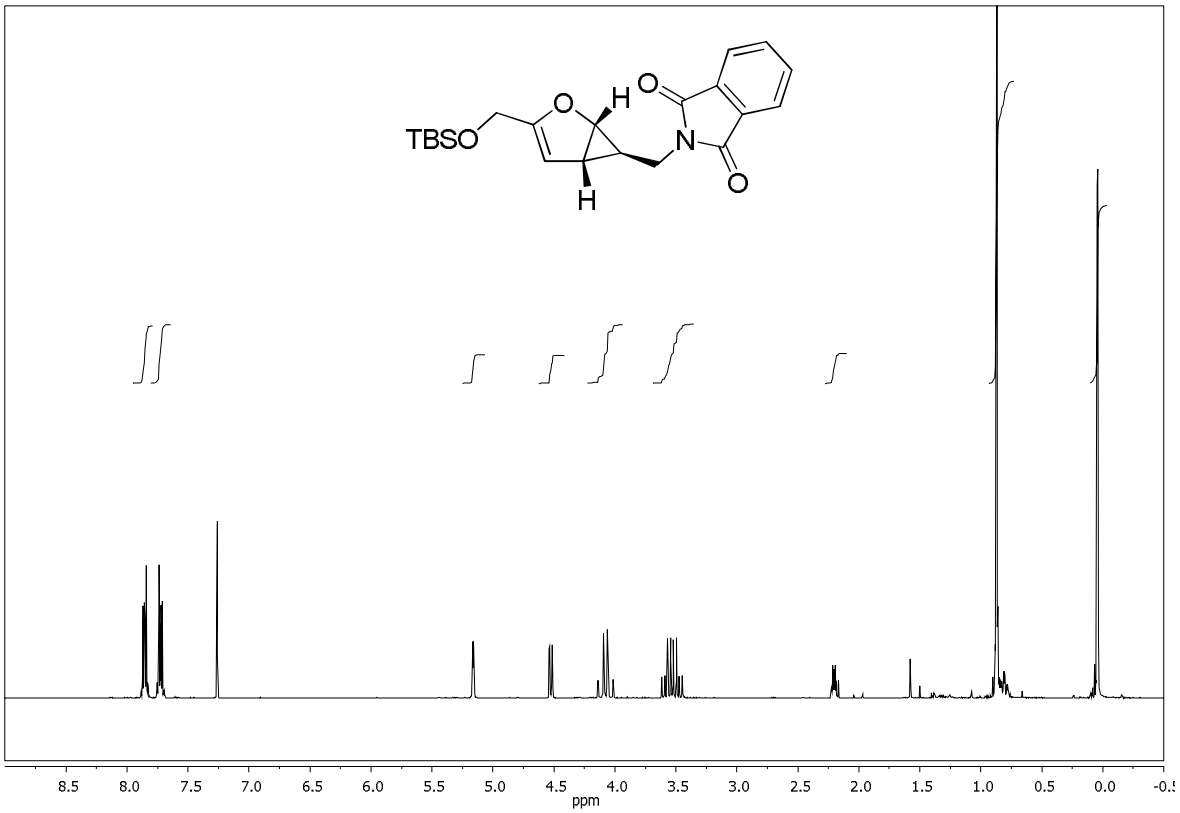


^{13}C-NMR (75 MHz, $CDCl_3$)

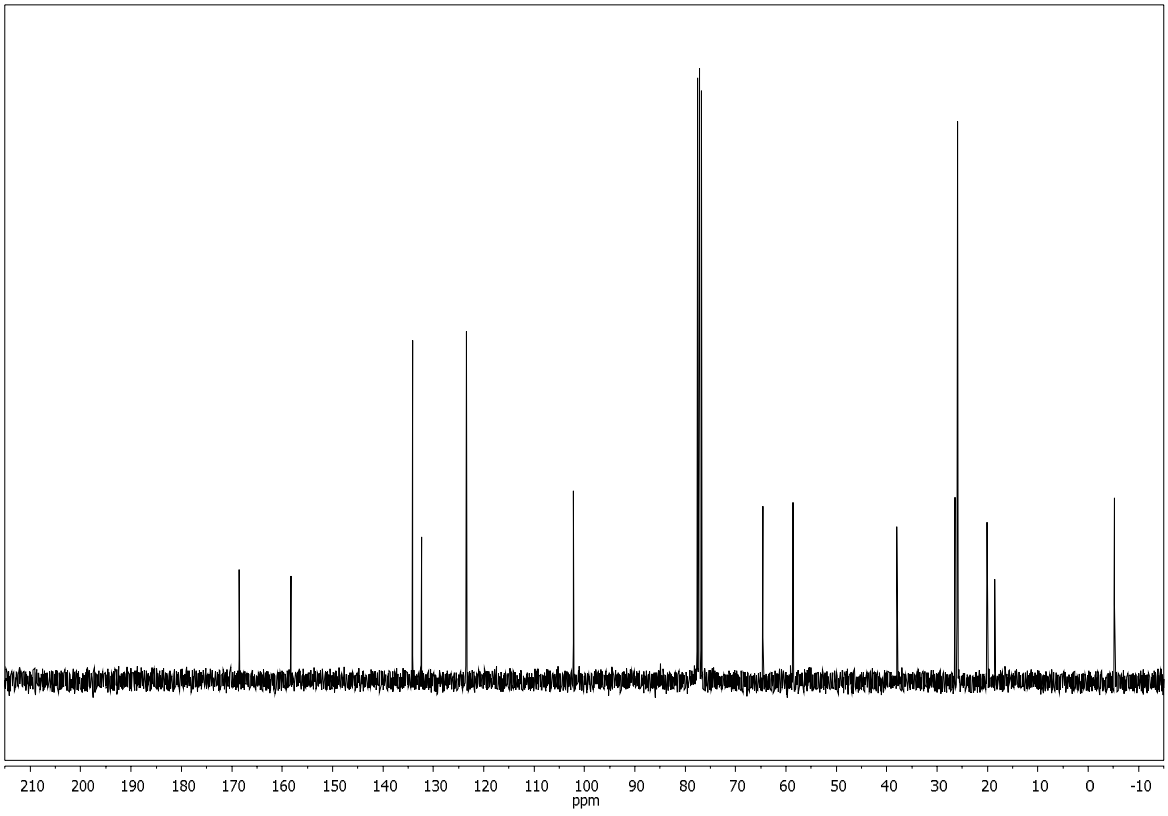


2-(((1*S*,5*R*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hex-3-en-6-yl)-methyl)isoindoline-1,3-dione (169)

^{1}H-NMR (300 MHz, $CDCl_3$)

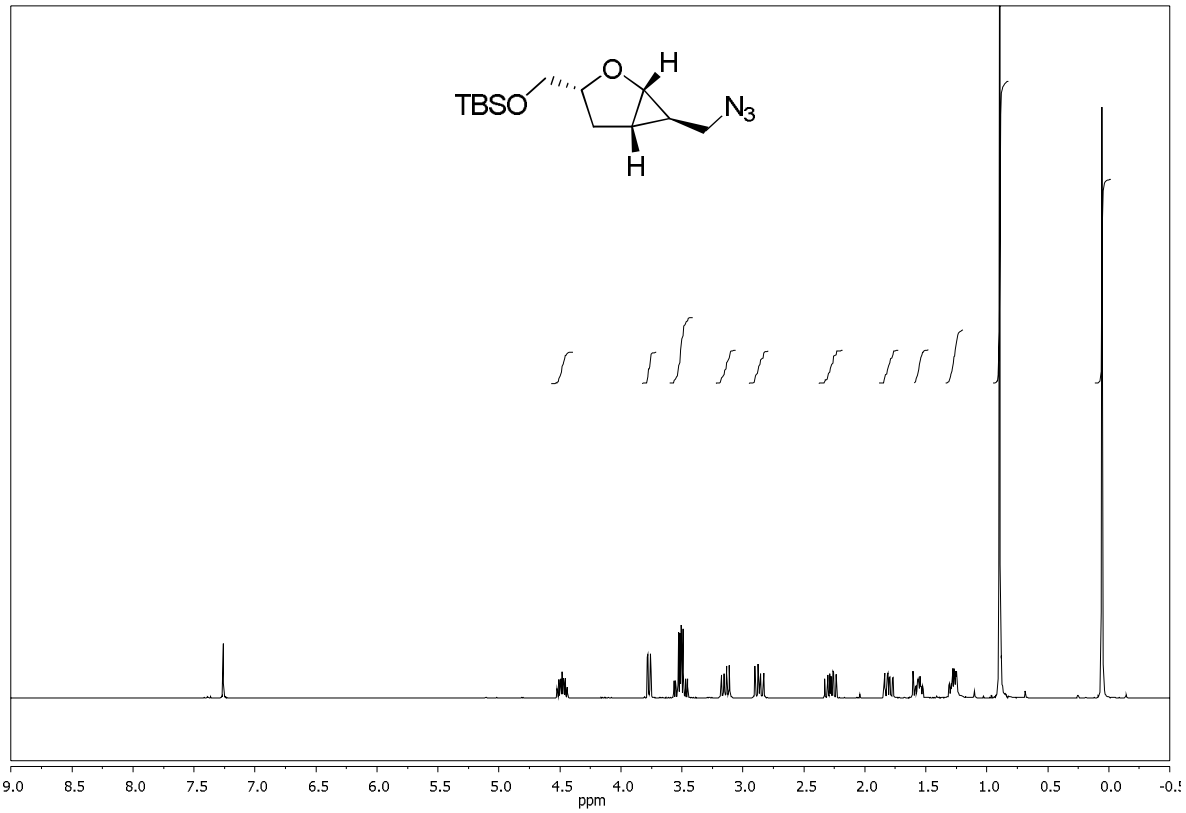


^{13}C-NMR (75 MHz, $CDCl_3$)

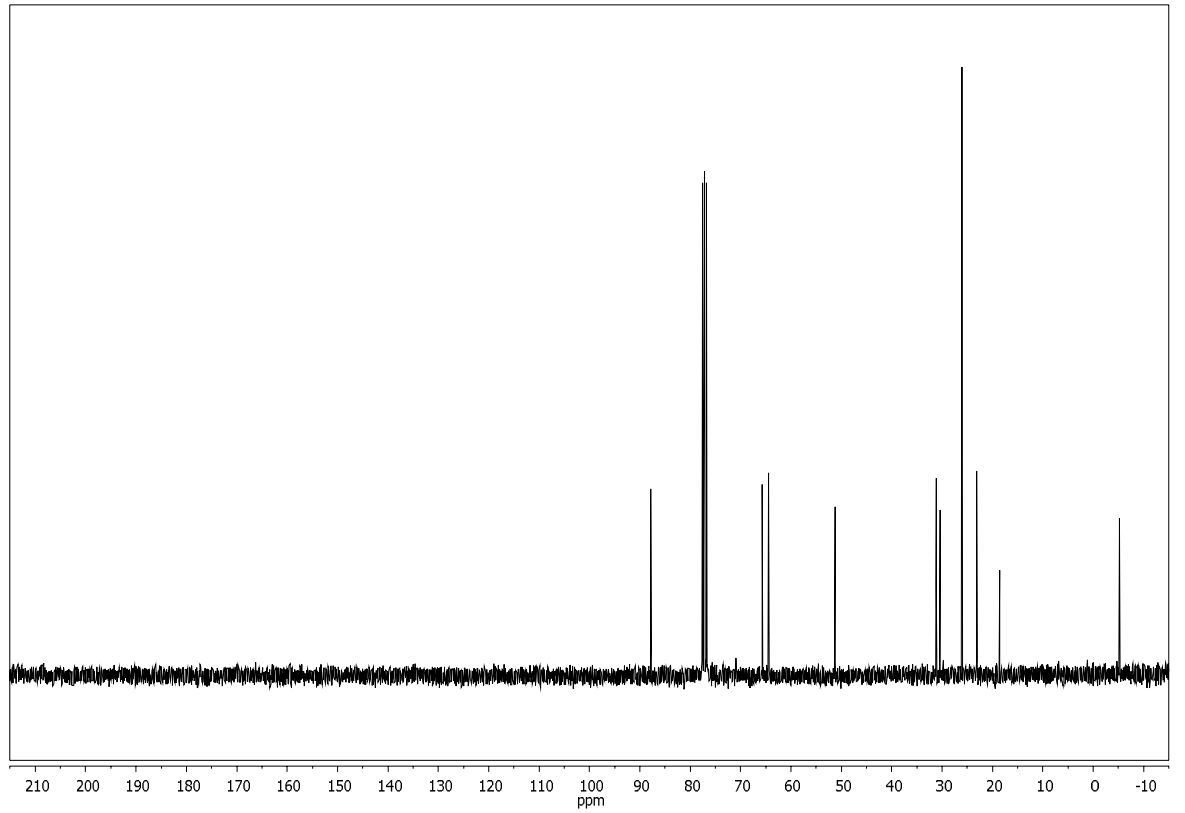


(((1*S*,3*R*,5*S*,6*R*)-6-(azidomethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(*tert*-butyl)dimethylsilane (175)

^{1}H-NMR (300 MHz, $CDCl_3$)

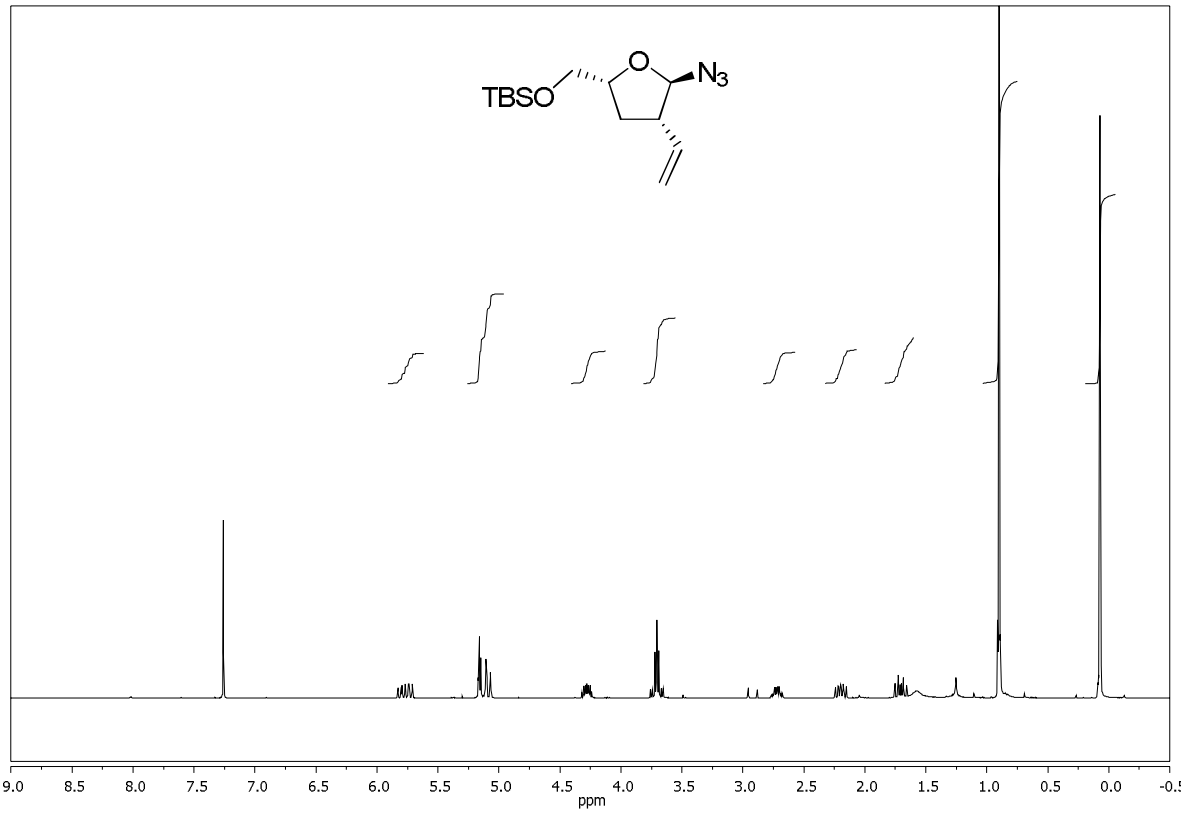


^{13}C-NMR (75 MHz, $CDCl_3$)

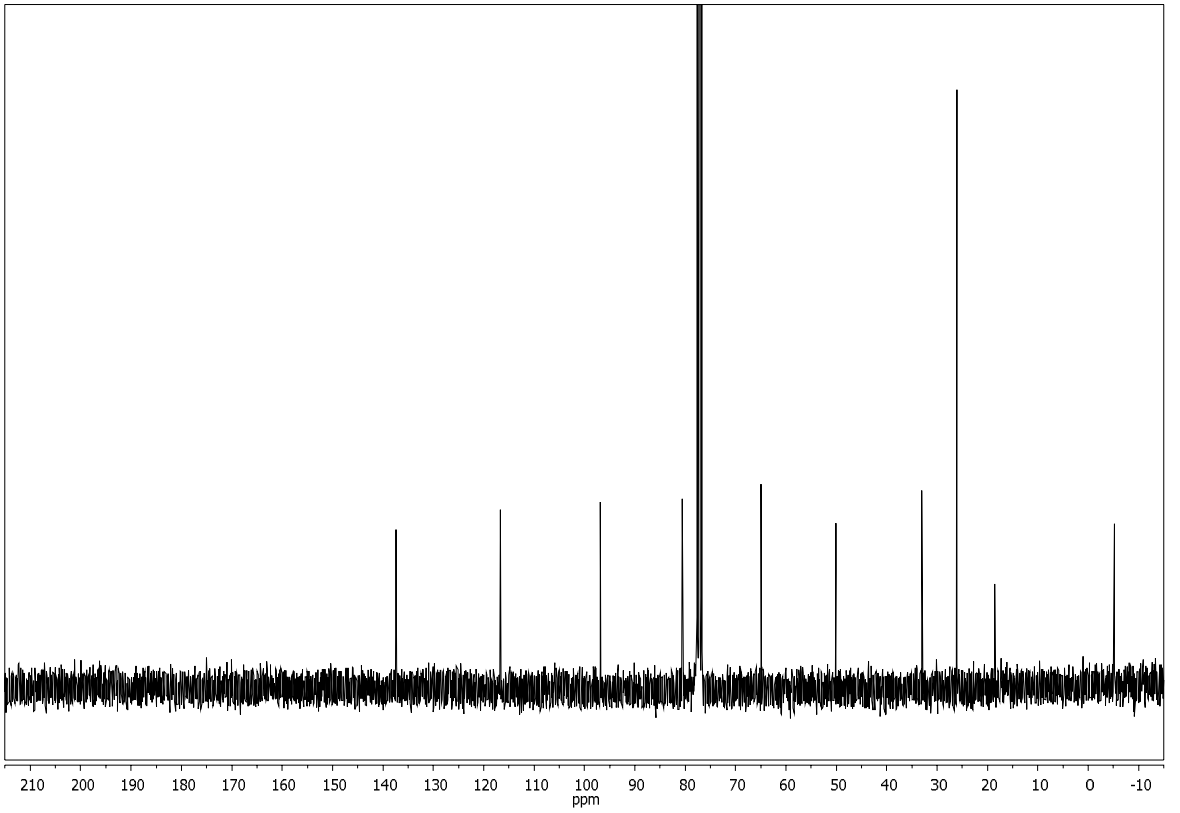


(((2*R*,4*S*,5*R*)-5-azido-4-vinyltetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (176a)

^{1}H-NMR (400 MHz, $CDCl_3$)

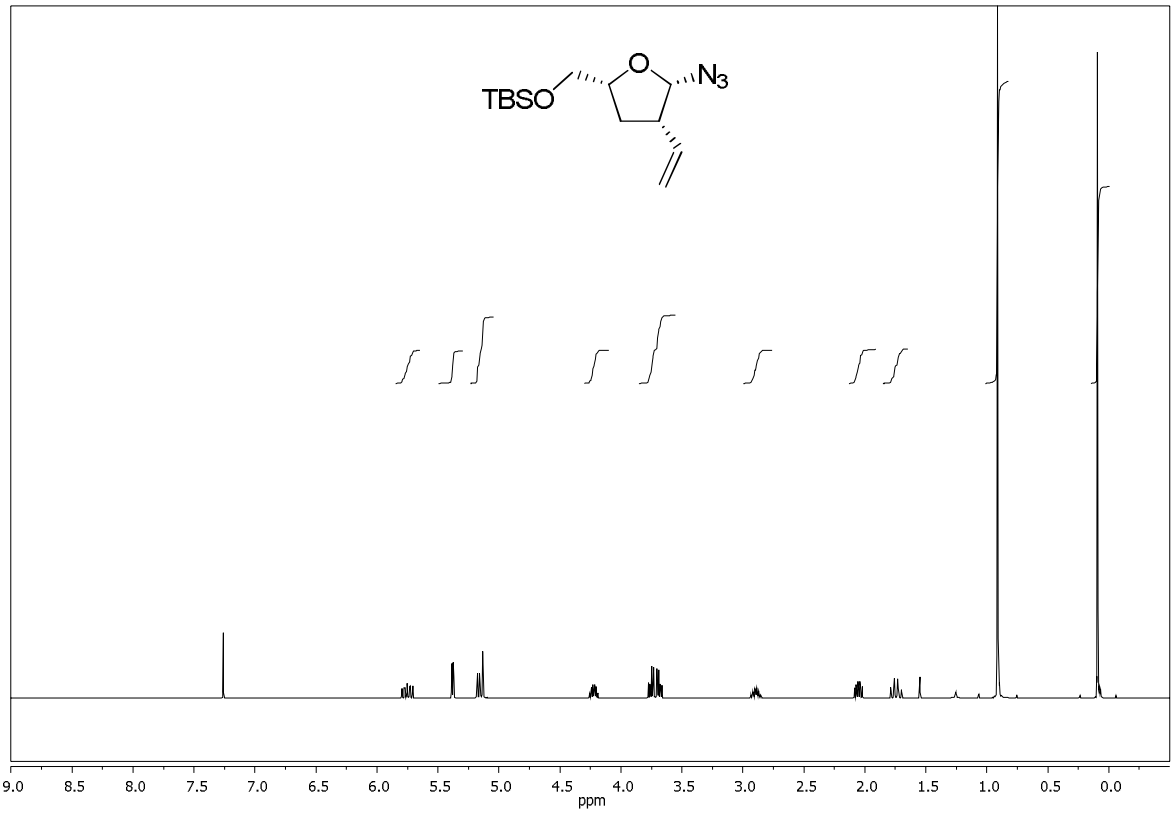


^{13}C-NMR (75 MHz, $CDCl_3$)

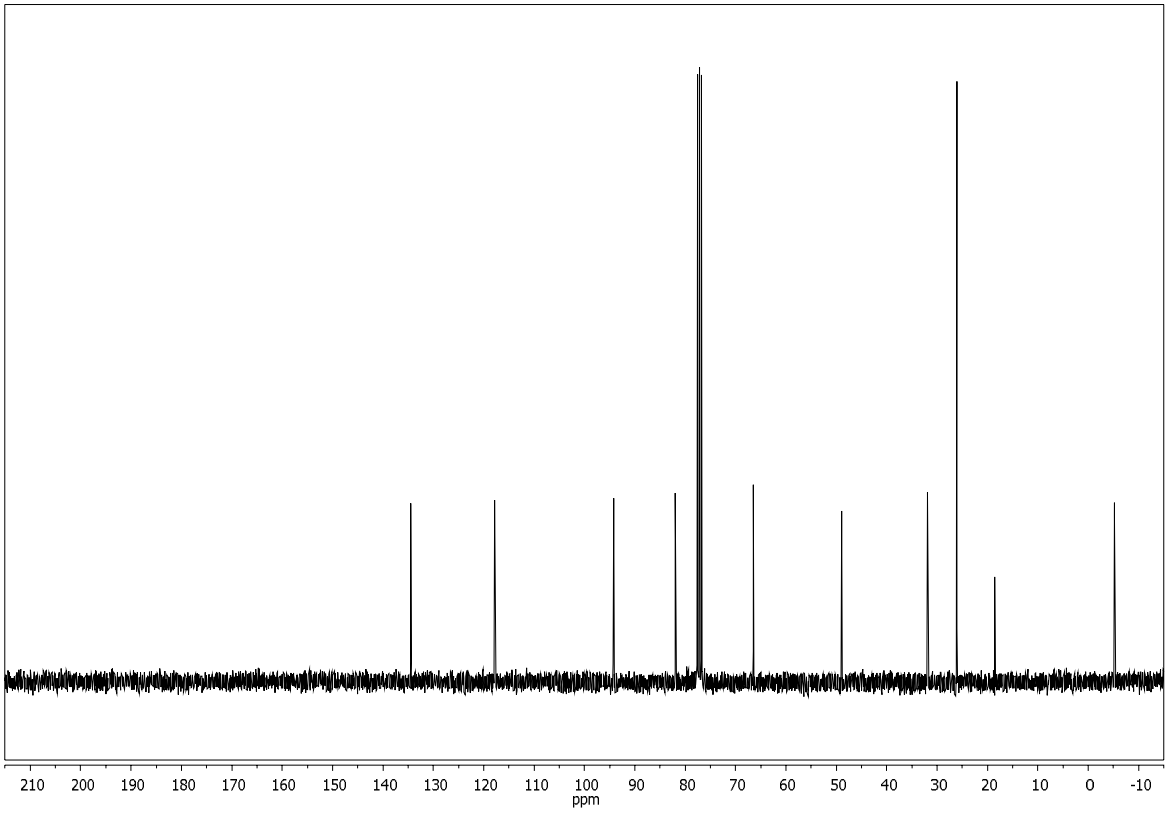


(((2*R*,4*S*,5*S*)-5-azido-4-vinyltetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (176b)

^{1}H-NMR (400 MHz, $CDCl_3$)

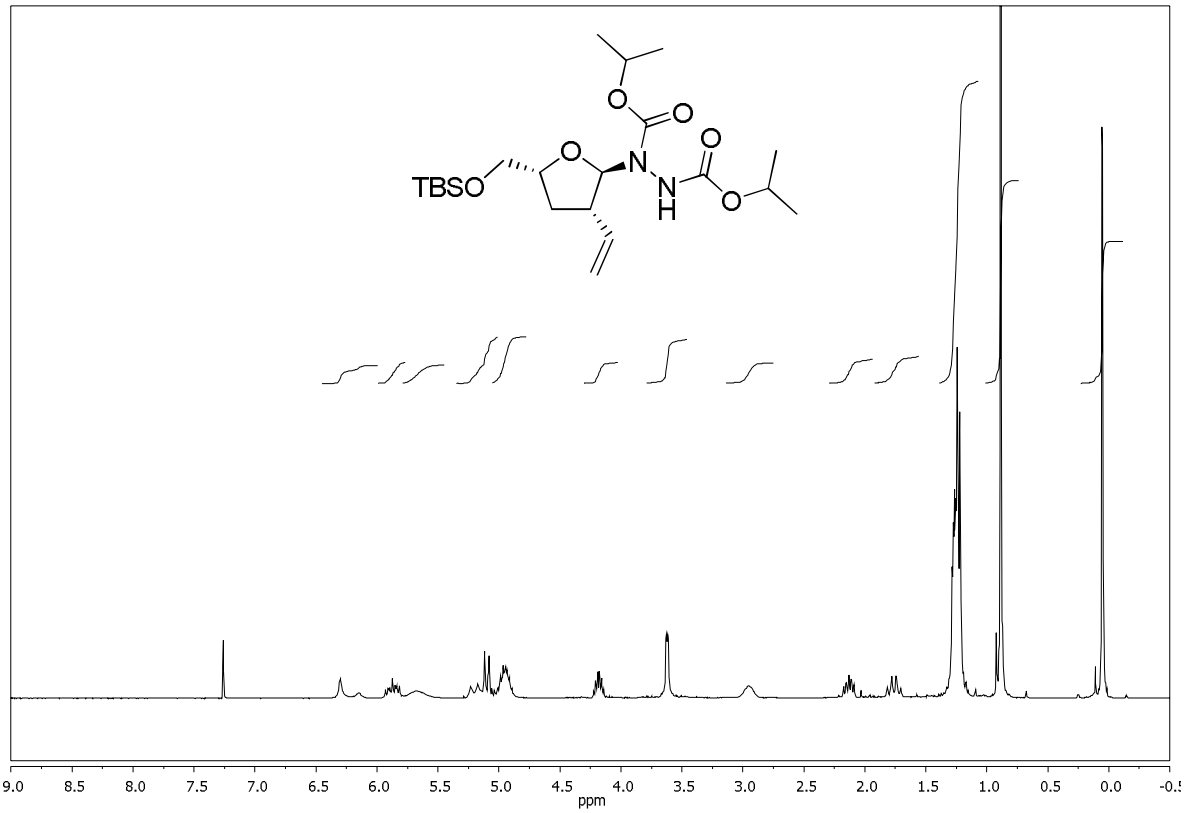


^{13}C-NMR (75 MHz, $CDCl_3$)

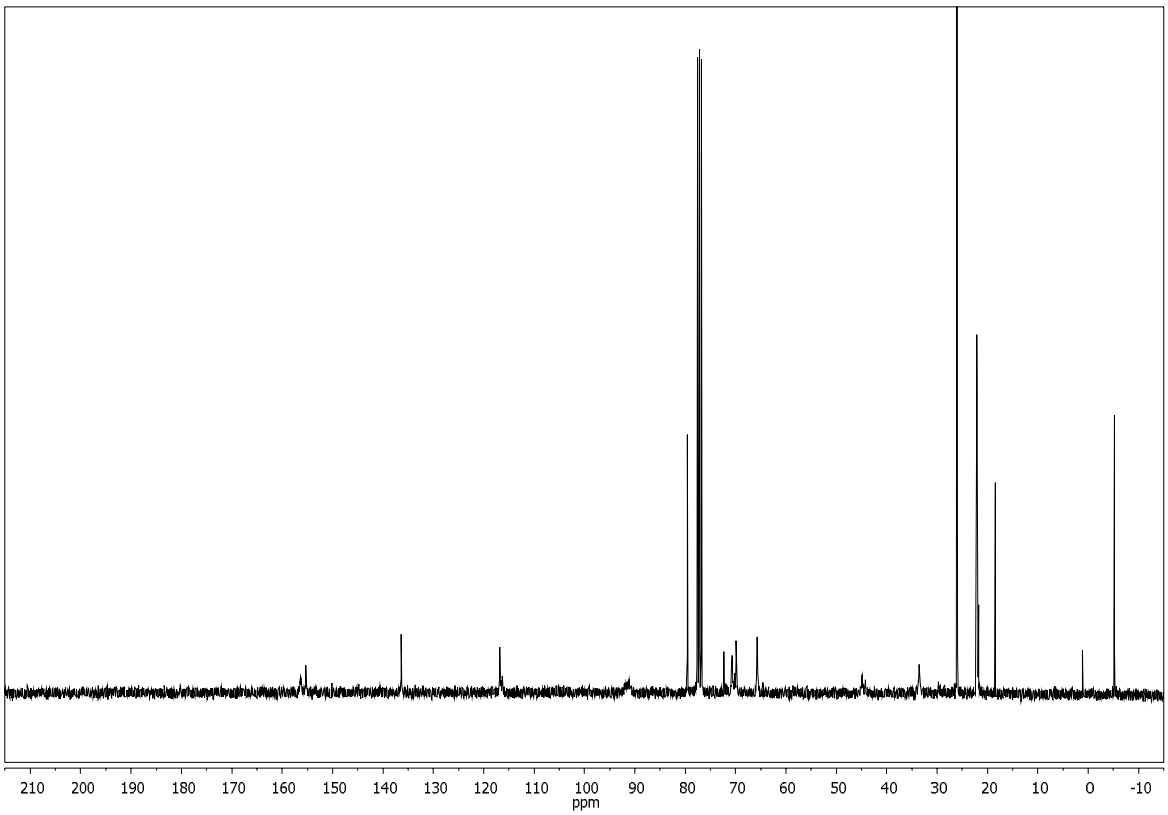


diisopropyl 1-((2*R*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)hydrazine-1,2-dicarboxylate (184a)

^{1}H-NMR (300 MHz, $CDCl_3$)

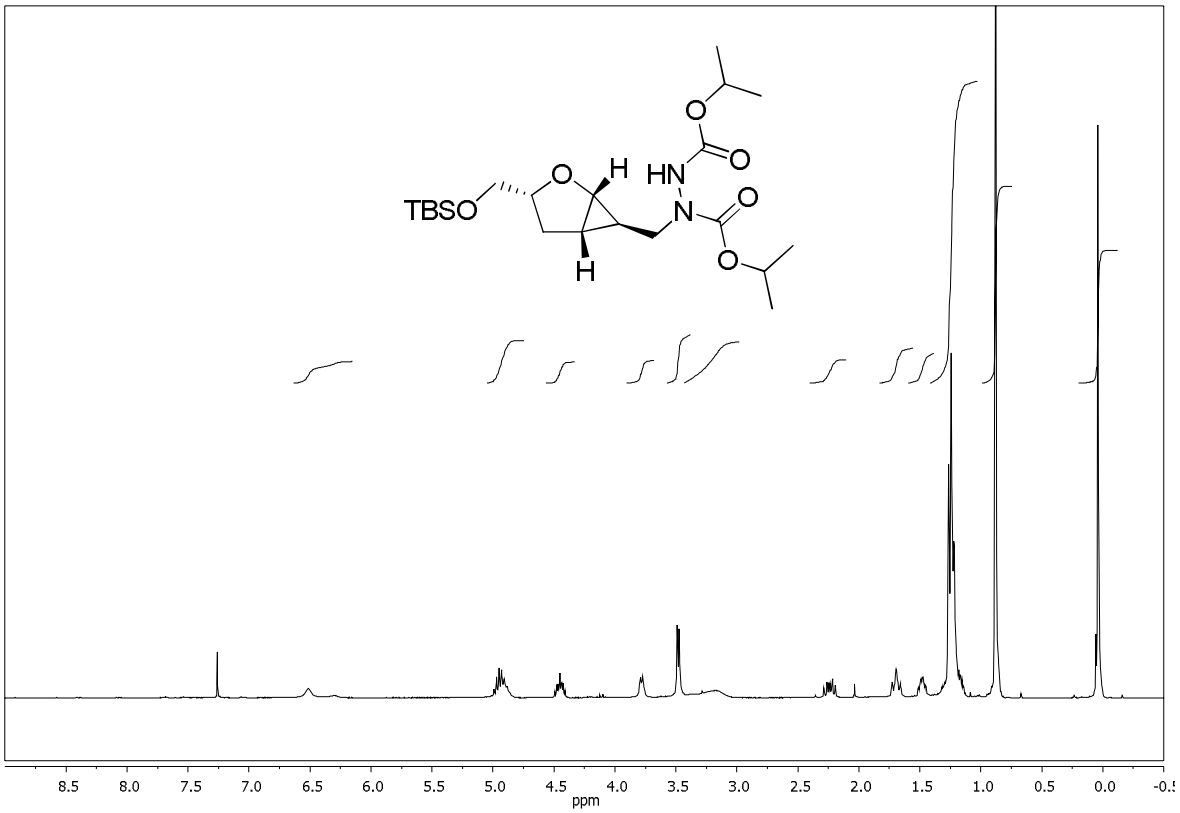


^{13}C-NMR (75 MHz, $CDCl_3$)

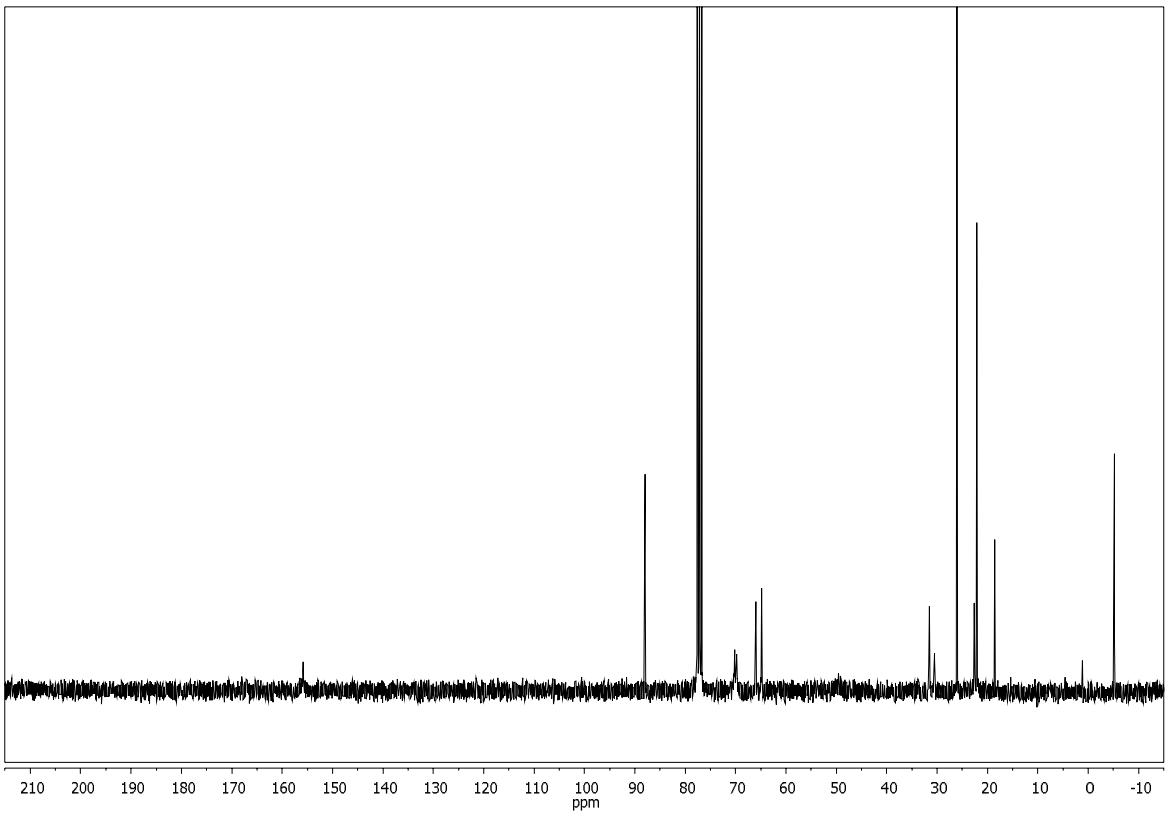


diisopropyl 1-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]-hexan-6-yl)methyl)hydrazine-1,2-dicarboxylate (185)

^{1}H-NMR (300 MHz, $CDCl_3$)

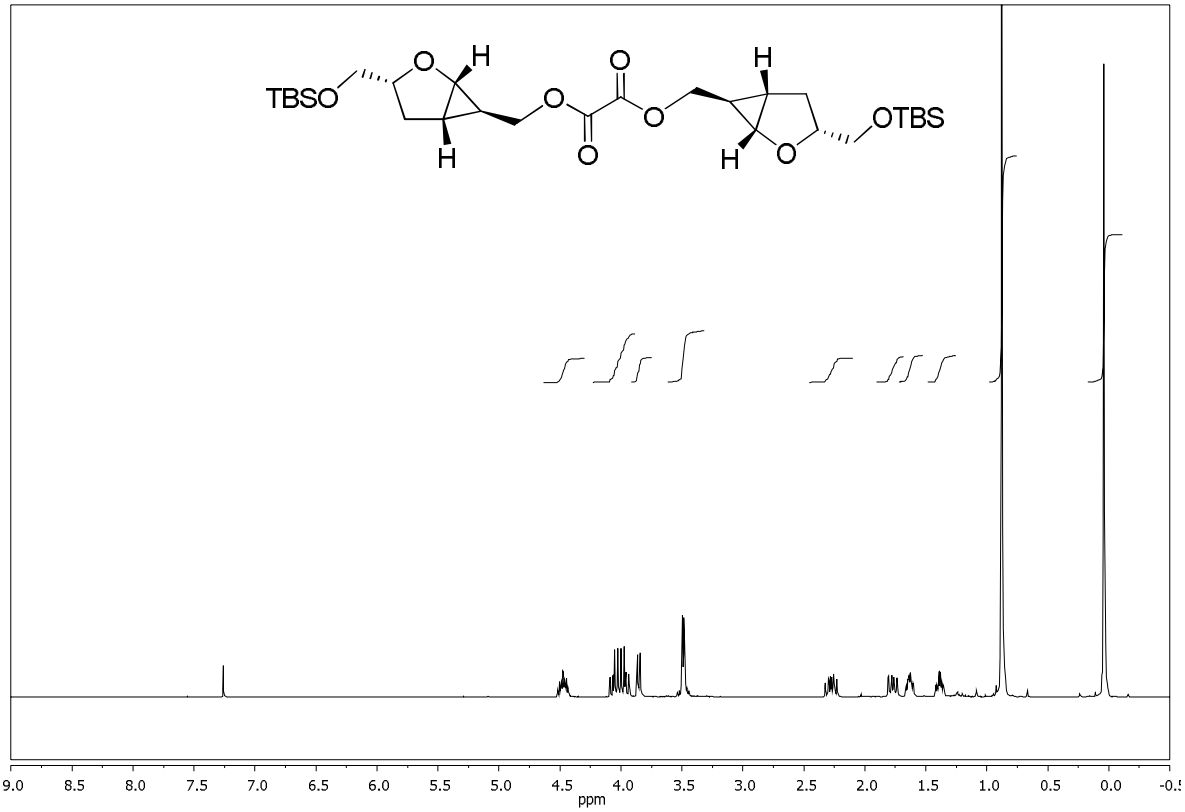


^{13}C-NMR (75 MHz, $CDCl_3$)

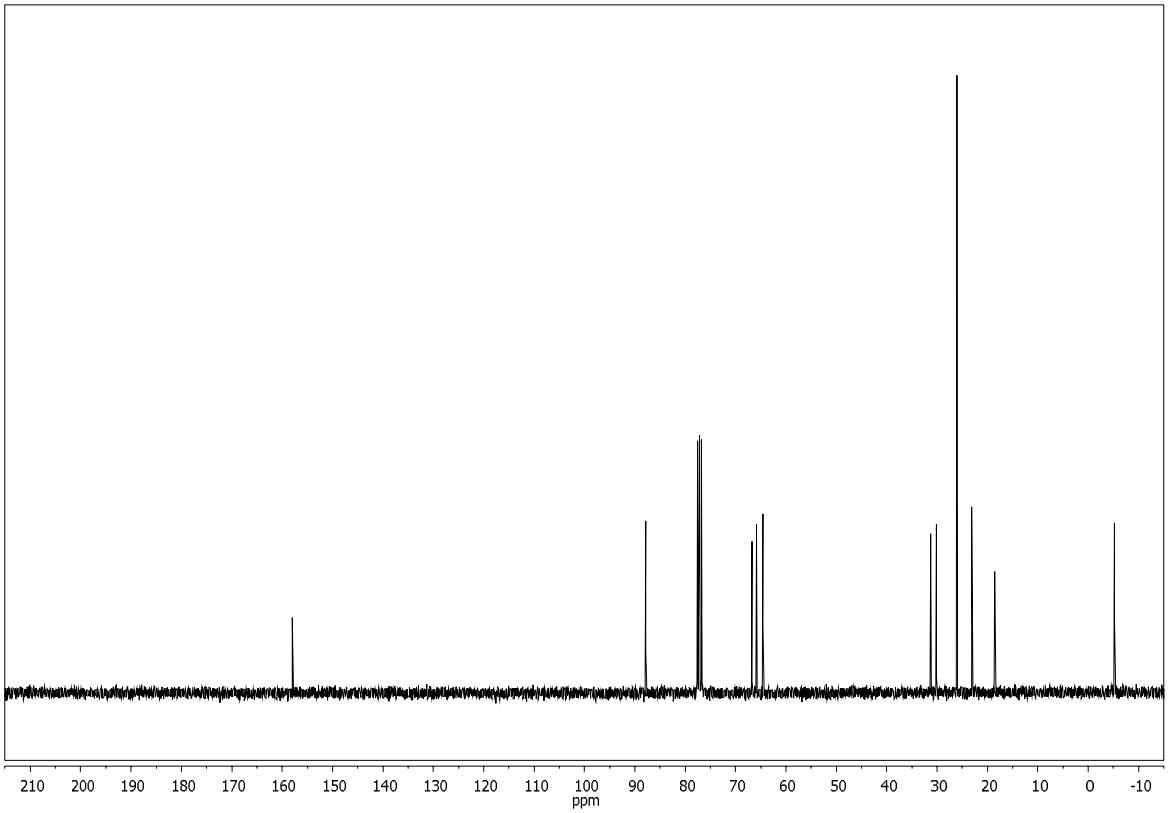


bis(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl) oxalate (190)

^{1}H-NMR (300 MHz, $CDCl_3$)

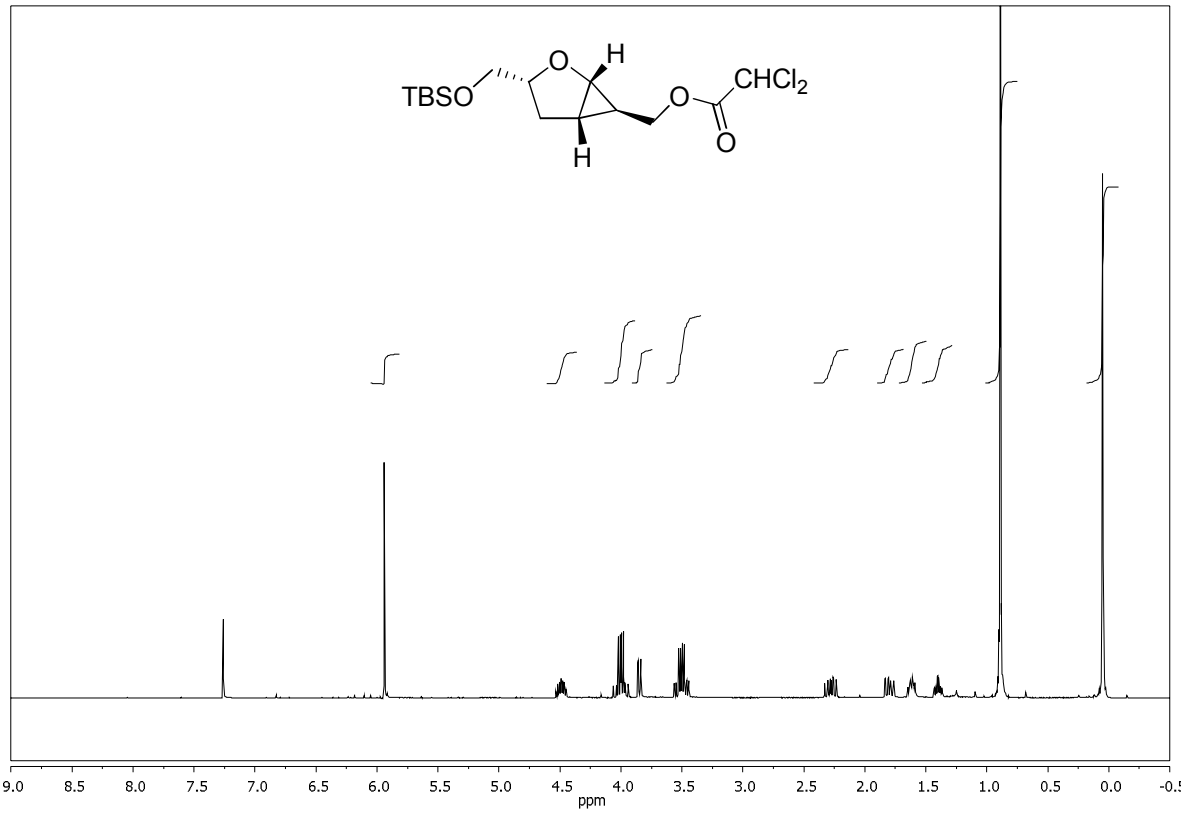


^{13}C-NMR (75 MHz, $CDCl_3$)

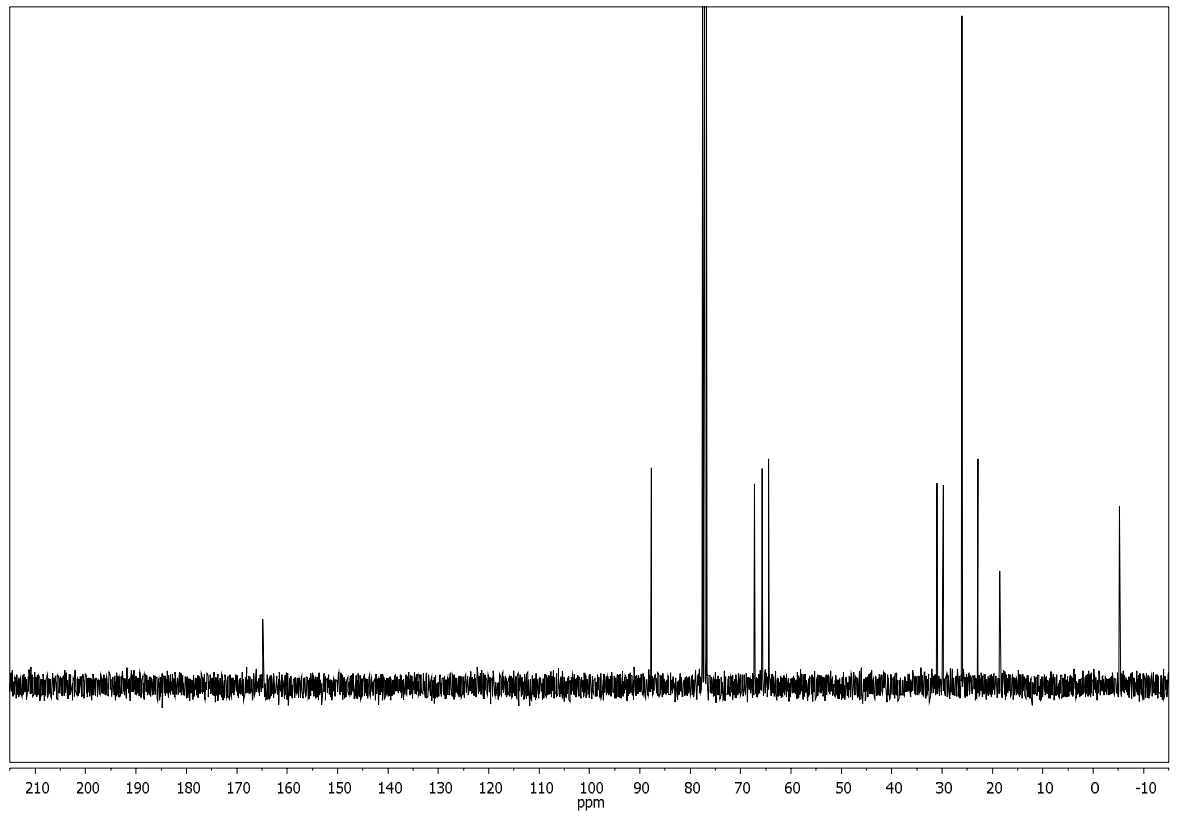


((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl 2,2-dichloroacetate (191)

^{1}H-NMR (300 MHz, $CDCl_3$)

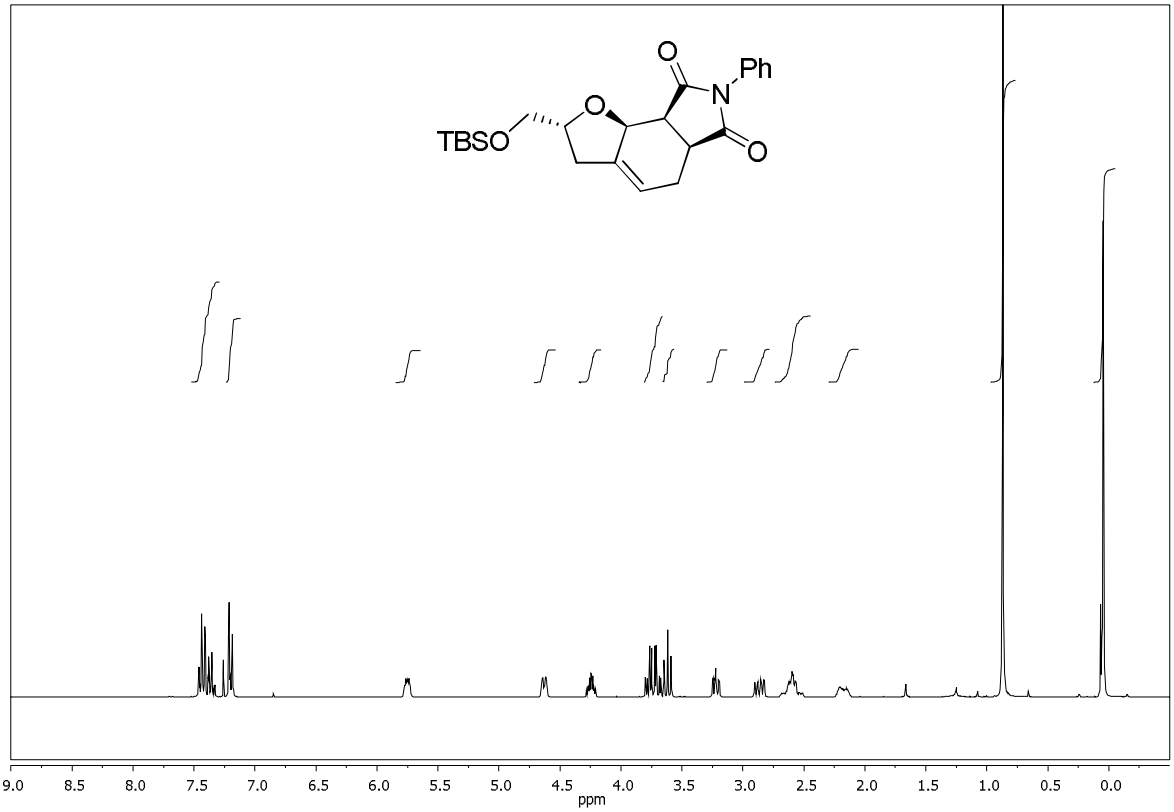


^{13}C-NMR (75 MHz, $CDCl_3$)

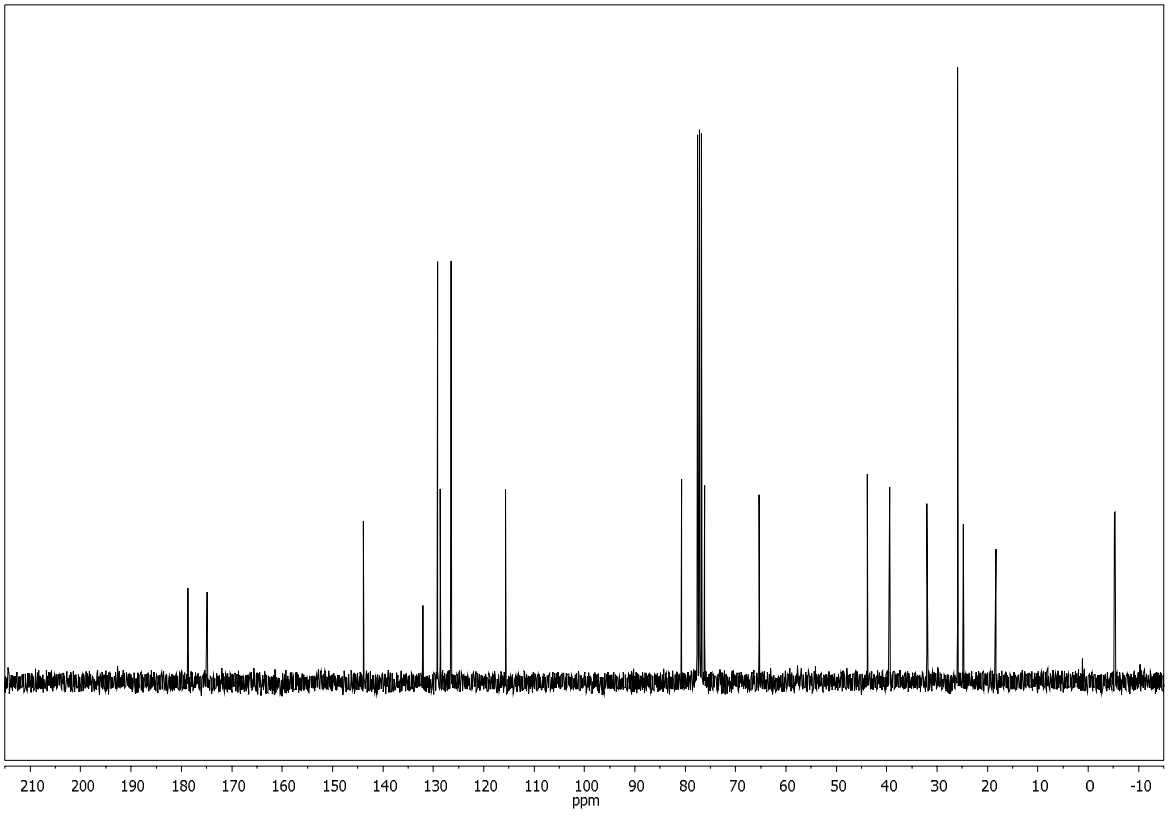


(2*R*,5a*S*,8a*S*,8b*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)-7-phenyl-5,5a,8a,8b-tetrahydro-2*H*-furo[2,3-*e*]isoindole-6,8(3*H*,7*H*)-dione (206a)

^{1}H-NMR (300 MHz, $CDCl_3$)

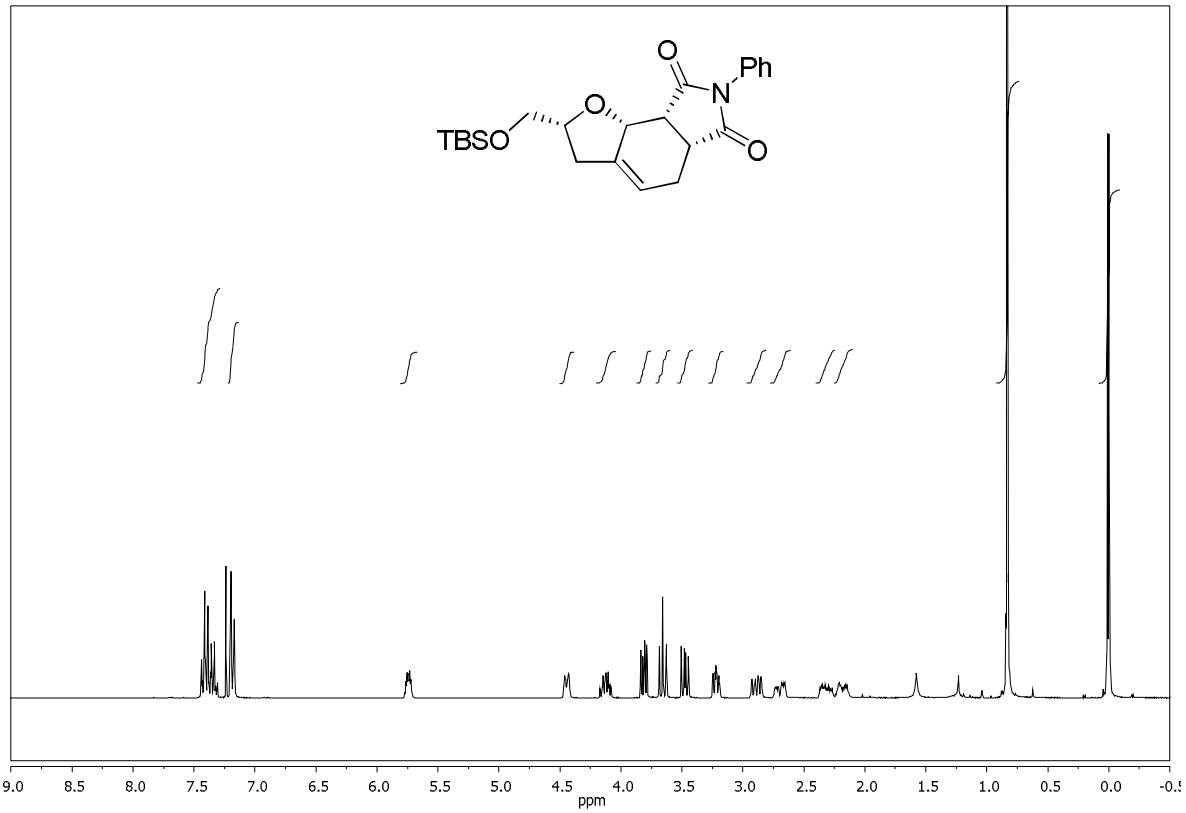


^{13}C-NMR (75 MHz, $CDCl_3$)



(2*R*,5a*R*,8a*R*,8b*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)-7-phenyl-5,5a,8a,8b-tetrahydro-2*H*-furo[2,3-*e*]isoindole-6,8(3*H*,7*H*)-dione (206b)

^{1}H-NMR (300 MHz, $CDCl_3$)



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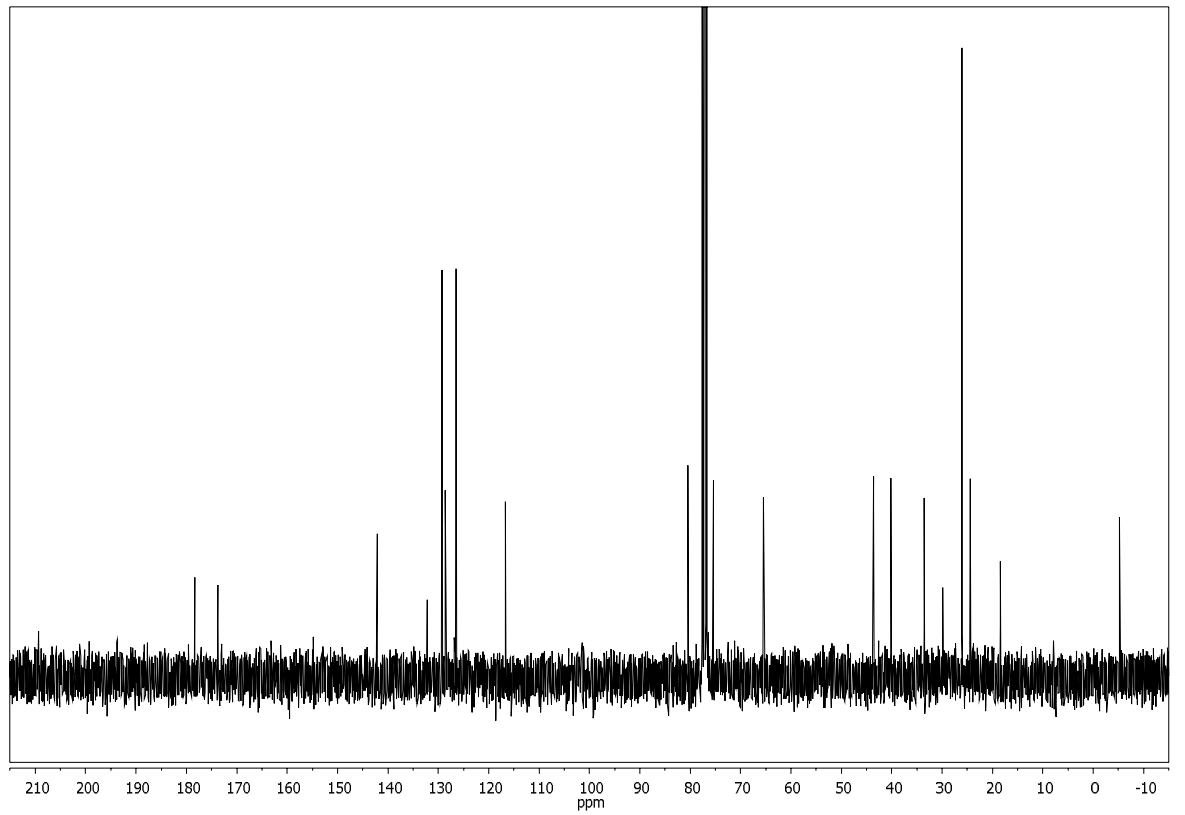

List of publications

- **New tetrahydrofuran based histamine H_3 receptor ligands**
  J. Bodensteiner, P. Baumeister, A. Buschauer, O. Reiser
  Manuscript in preparation

Poster presentations and scientific meetings

- 5th Summerschool "Medicinal Chemistry" GRK 760, Regensburg, Germany, **2010**
  poster presentation: "*New tetrahydrofuran based compounds as potential histamine H_3 and H_4 receptor ligands"*, J. Bodensteiner, A. Buschauer, O. Reiser

- 2nd INDIGO Conference, Donaustauf, Germany, **2010**

- EFS-COST High-Level Research Conference on Natural Products Chemistry, Biology and Medicine II, Acquafredda di Maratea, Italy, **2009**
  poster presentation: "*New tetrahydrofuran based compounds as potential histamine H_4 receptor ligands"*, J. Bodensteiner, C.A. Kashamalla, A. Buschauer, O. Reiser

- International COST Action Workshop – BM0806 – WG4, BioMedChem on Histamine H_4 Receptor – New Compounds for Translational Steps, Frankfurt/Main, Germany, **2009.**

Curriculum Vitae

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Education

10/2008 – 07/2012	**PhD thesis** at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser: "Synthesis and pharmacological characterization of new tetrahydrofuran based compounds as histamine receptor ligands"
02/2011 – 05/2011	**Research project** at the Institute of Life Sciences, Hyderabad, India under supervision of Prof. Dr. Javed Iqbal
10/2008 – 09/2011	associated member of the **Research Training Group** (Graduiertenkolleg 760) "Medicinal Chemistry: Molecular Recognition – Ligand Receptor Interactions", DFG scholarship
09/2008	**Graduation**: Diplom Chemiker (diploma in chemistry, equivalent to Master of Science)
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10/2003 – 09/2008	**Studies in Chemistry**, University of Regensburg, Germany
10/2002 - 07/2003	**Teacher training course** in Biology and Chemistry, University of Regensburg, Germany
09/1993 - 06/2002	**Abitur** (A-levels, High school Certificate equivalent) Kepler-Gymnasium, Weiden i. d. Opf.
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Appendix

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I. Declaration

Herewith I declare that I have made this existing work single-handed. I have only used the stated utilities.

Regensburg, 22nd June 2012

Julian Bodensteiner