Aziridines and their asymmetric conversion to bioactive compounds

Approaches to terpestacin, oseltamivir and analogues

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Dissertation presented to obtain the degree of Doctor in Chemistry

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“No one can pass through life, any more than he can pass through a bit of country, without leaving tracks behind, and those tracks may often be helpful to those coming after him in finding their way.”

Robert Stephenson Smyth Baden-Powell

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Abbreviations

$[\alpha]_D$ specific rotation

δ chemical shift

λ wavelength

abs absorbance

Ac acetyl (CH_3CO-)

AcOEt Ethyl acetate

Alk alkyl

Anal. elemental analysis

Ar aryl

asym asymmetric

ATR attenuated total reflectance

A.U. absorbance units

Bn benzyl ($C_6H_5CH_2$-)

Boc *tert*-butyloxycarbonyl ($(CH_3)_3COCO$-)

b.p. boiling point

br broad

Bu butyl (C_4H_9-)

c concentration

CAL-B *Candida antarctica* lipase B

calcd calculated

cat. catalytic

Cbz carboxybenzyl ($C_6H_5CH_2OCO$-)

COSY correlation spectroscopy

C_q quaternary carbon

d doublet

dba dibenzylideneacetone

DBU 1,8-diazabicycloundec-7-ene

DCM dichloromethane (CH_2Cl_2)

decomp. Decomposition

DFT density functional theory

DIPE diisopropyl ether

DIPEA diisopropylethylamine

DMAP 4-dimethylaminopyridine

DMF dimethylformamide

DPPB 1,4-bis(diphenylphosphino)butane

d.r. diastereomeric ratio

E electrophile

e.e. enantiomeric excess

epox epoxidation

eq. equivalent

ESI electron spray ionization

Et ethyl (C_2H_5-)

FTIR Fourier transform infrared spectroscopy

G Gibbs energy

h hour

Hal halogen

Hex Hexane

HMBC Heteronuclear Multiple-Bond Correlation

HMQC Heteronuclear Multiple-Quantum Correlation

HPLC high performance (pressure) liquid chromatography

HRMS high resolution mass spectrometry

IR infrared

IT ion trap

J coupling constant

KEX potassium ethyl xanthate (xanthogenate)

LDA lithium diisopropyl amide ($(((CH_3)_2CH)_2NLi$)

lit. literature

m multiplet or mass

M generic metal or molecular ion

***m*-CPBA** *meta*-chloroperoxybenzoic acid

Me methyl (CH_3-)

min minutes

m.p. melting point

Ms mesyl or methyl sulfonyl (CH_3SO_2-)

MS mass spectrometry

MW microwaves

n normal

NA neuraminidase

NMR nuclear magnetic resonance

Ns nitrobenzenesulfonyl ($NO_2C_6H_4SO_2$-)

Nu nucleophile

o ortho

[O] oxidation

o.o.p. out of plane

p pentet (quintet)

p para

Ph phenyl (C_6H_5-)

ppm parts per million

Py pyridine (C_5H_5N)

q quartet

R generic group

Ref reference

r.t. room temperature

s singlet

sex sextet

st stretching

t time or triplet

T temperature

TBAF tetrabutylammonium fluoride (Bu_4NF)

TBDPS *tert*-butyldiphenylsilyl (*t*$BuPh_2Si$-)

TBS *tert*-butyldimethylsilyl (*t*$BuMe_2Si$-)

Tf Triflyl or trifluoromethanesulfonyl (CF_3SO_2-)

THF tetrahydrofuran

TIPS triisopropylsilyl ($((CH_3)_2CH)_3Si$-)

TLC thin layer chromatography

TMS trimethylsilyl (Me_3Si-) or tetramethylsylane ($SiMe_4$)

TOF time of flight

Ts tosyl or toluenesulfonyl ($CH_3C_6H_4SO_2$-)

V volume

w weight

X generic good leaving group

z charge

Abstract

This work is mainly focused in the development of new synthetic methodologies. A new method for the preparation of optically active aziridines was developed, as well as their transformation into influenza antiviral drugs oseltamivir (Tamiflu) and tamiphosphor. Other important chemical transformations useful for organic synthesis were also studied.

In the first part of this work a new method for the asymmetric synthesis of cyclic 4-hydroxy-acylazyridines is described. It is based on a very efficient enzymic resolution procedure using novozym 435 (solid-supported *Candida Antarctica* Lipase B). The optically active aziridines were obtained in high yields (up to 50%) and enantiomeric excesses (up to 99%). These very important chiral building blocks were used as substrates in the syntheses described in this work.

Approaches to the synthesis of terpestacin, a bioactive natural product, are also described. The three designed strategies failed, however interesting chemistry was discovered and new molecules were prepared that may be used in the synthesis of other products. In one of these molecules it was possible to observe by NMR aziridine invertomers, a special type of conformers. To our knowledge alkyl aziridine invertomers have not been previously observed at room temperature and this equilibrium was studied by DFT calculations.

Novel formal syntheses of the antiviral drugs oseltamivir and tamiphosphor were also developed. Using the enzymatic resolution procedure, an almost enantiomerically pure aziridine was prepared and used as starting material for subsequent conversion to oseltamivir and tamiphosphor diethyl ester in 10 or 12 additional steps and 22% or 19% overall yield, respectively, is described. The preparation of a new sulfur analogue of oseltamivir was also

attempted. Although it was not successful, two reactions were discovered and the study of their scope is described in the last two chapters.

An efficient method for the α-chlorination of ketones under basic conditions is described using methyl chlorosulfate. It is a very clean reaction and the products are obtained in quantitative yield. Its use in the α-chlorination of carbonyl group of other functional groups was also studied, and was equally useful for the preparation of α-chloroesters or amides and 4-chloro dicarbonyl compounds. Methyl chlorosulfate is described for the first time as an electrophilic chlorine source. Some aldol and Claisen condensation reactions that also occur during the chlorination of some substrates were also studied.

Lastly, a method for the transformation of 2-oxo *S*-carbonyl or thiocarbonyl into 2-oxo (thio)carbonyl compounds, by a base promoted sulfur abstraction rearrangement is described. It is a very clean reaction and products are obtained in good yield (close to 90%) in just 30 minutes. This method is particularly efficient for the introduction of thiocarbonyl containing groups whereas for the introduction of acid derivatives it is less efficient. This constitutes an alternative synthetic strategy for the generation of a new carbon-carbon bond and the preparation of β-dicarbonyl compounds.

Keywords: organic synthesis; asymmetric synthesis; aziridines; oseltamivir; tamiphoshphor; terpestacin; aziridine invertomers; chlorination; sulfur abstraction.

Resumo

O principal objetivo deste trabalho foi o desenvolvimento de novas metodologias de síntese orgânica. Foi desenvolvido um novo método para a preparação de aziridinas opticamente ativas, assim como a sua conversão em oseltamivir e tamiphosphor, dois antivirais da gripe. Também foram estudadas outras transformações químicas com igual importância e interesse para a síntese orgânica.

Inicialmente, foi desenvolvido um novo método para a síntese assimétrica de 4-hidroxi-acilaziridinas cíclicas. Este método tem por base um procedimento de resolução enzimática, usando novozym 435 (lípase B de *Candida Antarctica* em suporte sólido). As aziridinas opticamente ativas foram produzidas com elevado rendimento (até 50%) e excesso enantiomérico (até 99%). Estes importantes *building blocks* foram usados como substratos nas sínteses desenvolvidas neste trabalho.

Estão descritas tentativas de síntese de terpestacin, um produto natural com atividade biológica. As três estratégias concebidas não tiveram sucesso, contudo foram preparadas moléculas com interesse que podem ser usadas na síntese de outros produtos. Numa destas moléculas, foi possível observar por RMN invertómeros da aziridina, um tipo especial de confórmeros. Dentro do nosso conhecimento, invertómeros de alquilaziridinas nunca foram observados à temperatura ambiente. Este equilíbrio foi estudado usando ferramentas de química computacional.

Uma nova síntese dos antivirais oseltamivir e tamiphosphor foi desenvolvida. Utilizando o novo método de resolução enzimática, uma aziridina foi preparada praticamente enantiomericamente pura e usada como material de

partida. A sua conversão em oseltamivir e éster dietílico de tamiphosphor foi conseguida em 10 ou 12 passos e 22% ou 19% de rendimento, respetivamente. Também foram feitas tentativas de usar esta metodologia na preparação de um análogo de oseltamivir com enxofre. Apesar de não se o ter conseguido com sucesso, duas reações foram descobertas e o estudo do seu escopo está descrito nos dois últimos capítulos.

Está também descrito um novo método para a α-cloração de cetonas em meio básico usando clorosulfato de metilo. É uma reação bastante limpa, em que os produtos são obtidos praticamente puros e com rendimento quantitativo. O seu uso na cloração de outros grupos funcionais foi também explorado e é igualmente útil na preparação de α-cloroésteres ou amidas e compostos 4-clorodicarbonílicos. O clorosulfato de metilo é pela primeira vez descrito como uma fonte eletrofílica de cloro. Foram também estudadas reações de aldol e condensação de Claisen que ocorrem durante a cloração de alguns substratos.

Por último, está descrito um método para a transformação de compostos 2-oxo-*S*-carbonílicos ou tiocarbonílicos em 2-oxo(tio)carbonílicos, através de um rearranjo com extrusão de enxofre em meio básico. É uma reação consideravelmente limpa e os produtos são obtidos com bom rendimento (cerca de 90%) em apenas 30 minutos. Este método é particularmente eficiente na introdução de um tiocarbonilo, ao passo que a introdução de derivados de ácido não é tão eficiente. É também uma estratégia sintética alternativa para a criação de uma nova ligação carbono-carbono e preparação de compostos β-dicarbonílicos.

Palavras-chave: síntese orgânica; síntese assimétrica; aziridinas; oseltamivir; tamiphosphor; terpestacin; invertómeros de aziridina; cloração; extrusão de enxofre

Chapter 1

General Introduction

Organic synthesis

Organic compounds are needed in different fields of Science (biology, materials, pharmacy, etc.) as well as in our daily lives (drugs, food additives, dyes, polymers and other materials, etc.). Hence organic synthesis plays a central role in the development of Science and in the improvement of our quality of life, providing not only new molecules with potential social applications but also environmental implications such as more economical or clean processes.

The focus of the research of a synthetic chemist can vary. It can be focused on the product, when a new compound that has not been previously synthetized is the target. Although the new compound may have a purpose, structure elucidation, particularly the stereochemistry, of new isolated natural products is also an important topic. In this case, the main goal of the work is to provide the desired compound in a reasonably amount in the shortest possible time, regardless of the method used. Alternatively, the objective may be the development of an improved method for the preparation of an already known molecule for large scale production. Contrary to the first case, the development of a new method should consider several factors: global yield, number of steps, time economy, safety, costs, available raw materials, impact on the environment, etc…

The development of a new synthetic methodology implies the design of a synthetic transformation and its execution in the laboratory. The successful design of a new synthetic methodology relies on a good knowledge of chemistry: chemical transformations, functional group reactivities, reaction mechanisms, stereochemistry, protecting groups, etc… On the other hand, its execution requires also practical skills such as the design and setting up of ~~e~~xperiments;

execution of unit operations; purification and drying of reagents, solvents and products and characterization and structure determination of products. *It can be hard to find or train someone to have both the knowledge and the required skills.*

Recently, *Nature* published[1] a comment on chemical synthesis and its importance. A point discussed was the fact that students with skills in chemical synthesis can find jobs in the pharmaceutical industry more easily. However, synthetic methods developed in the laboratory are often impracticable in industry, therefore the specific synthetic skills are not *per se* the most valued. Pharmaceutical industry is more interested in other skills developed by these students such as the capacity to solve problems rapidly, cope with disappointing results, perseverance and a broad knowledge of chemistry. In conclusion, students engaged in chemical synthesis (including organic synthesis) seem to be more prepared for the job market.

In general, synthetic strategies comprise several steps to transform the starting material into the final product. In each step, a different reaction or transformation occurs. The development of new and improved reactions is essential for the improvement of organic synthesis. The reactions described in the literature are the tools available for a chemist to shape the molecules into the desired structure. The more tools available, the greater the number of molecules it is possible to prepare. Although some groups are focused exclusively on either developing new reactions or new synthetic strategies, both are intrinsically connected. During the development of a new reaction, its application in a complex synthesis demonstrates its scope or perhaps its limitations. On the other hand, while developing a new synthesis sometimes a chemist must develop a new method for a specific transformation.

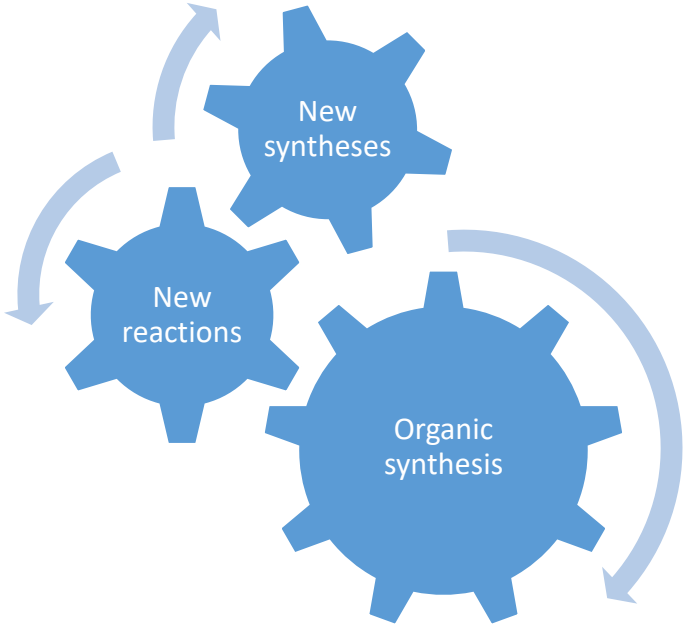


Figure 1.

Strategies for optically active molecules synthesis

Most molecules have an asymmetric structure in a way that their mirror image is not superposable, this property is called chirality and these two different structures are called enantiomers. Most organic compounds in nature occur as only one enantiomer, for example aminoacids, nucleic acids and sugars. Therefore, different enantiomers of the same molecule interact in a different way with biomolecules and hence may produce different effects when administrated. Most chiral drugs are commercialized as a single enantiomer and for reasons of efficiency need to be produced selectively that way. The synthesis of just one enantiomer of a molecule constitutes a challenge for synthetic chemists.

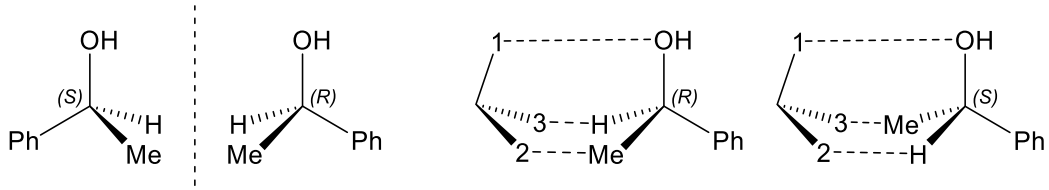


Figure 2 - Comparison of the structures of the two enantiomers (*R* and *S*) of 2-phenylethanol.

For the synthesis of a optically active compound different strategies may be followed. One strategy is to use a chiral enantiomerically pure starting material. Some compounds are commercially available as single enantiomers at an affordable cost. In general, they are extracted from an abundant natural source or produced by fermentation, some examples are simple acids (e.g. tartaric acid), the amino acids or sugars. This set of chiral available molecules is called the chiral pool. Some of the compounds produced by the other strategies that will be presented but are commercially available may be considered as being part of the chiral pool too.

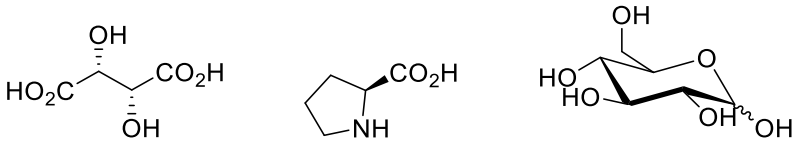
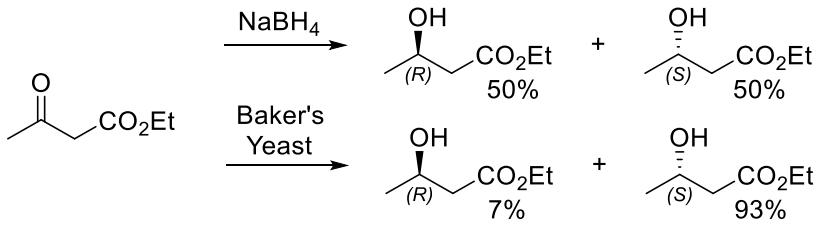


Figure 3 - Examples of chiral molecules from the chirality pool.

When the starting material used is not optically active, selective formation or isolation of one enantiomer is always dependent on the formation of a diastereomeric species, at least transiently. Diastereomers are a different type of stereoisomers and unlike enantiomers have different physical properties.

Other strategy is the use of an enantioselective reaction. In some reactions, a symmetric molecule is transformed into an asymmetric one, typical

conditions lead to the formation of two enantiomers in the same amount (racemate). However, if a chiral reagent or catalyst is used, one enantiomer may be produced in a selective way. Chiral catalysts containing a metal are commonly used, but more recently a new field emerged, the organocatalysis, using non-metal catalyst. Enzymes are also used as they are extremely selective and, in some cases, whole cells or microorganisms are used (e.g. pig liver cells or baker's yeast). These reagents normally are dependent upon the formation of a loose chiral intermediate that then reacts in a diastereoselective way. The catalyst then leaves to transform another molecule and the optically enriched product remains.

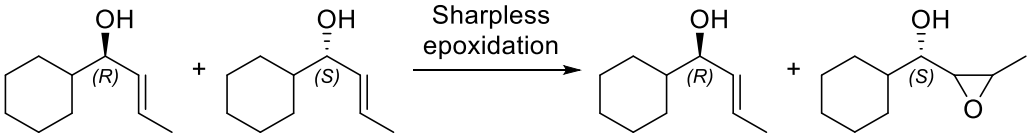


Scheme 1 - Example of a symmetric and asymmetric reaction[2] catalyzed by an enzyme.

The use of chiral auxiliaries is also a possible strategy. It consists in the use of a chiral-non-racemic reagent that will be covalently connected to a symmetric molecule transforming it into an asymmetric one. Further diastereoselective reaction(s) and removal of the chiral auxiliary render predominantly one enantiomer, the unaffected chiral auxiliary may be recovered and reused.

The last strategy that can be used is the resolution of a racemate, it consists in the separation of two enantiomers present in a mixture. Enantiomers cannot be separated by common purification techniques as both have the same physical properties, however some approaches can be used. One is the

derivatization of the racemate with a chiral reagent transforming the enantiomers into diastereomers and their further separation, it is commonly called diastereomeric resolution. As in the case of chiral auxiliaries the derivatization reagents may be recovered and reused. Other approach is a reaction with a chiral reagent or catalyst (kinetic resolution) and one enantiomer will react faster than the other. Is possible to stop the reaction at a point where one enantiomer has almost reacted completely and the other not, the product can then be separated from the unreacted enantiomer. The most used catalysts are the same for asymmetric reactions. One common approach also used is the formation of a salt with a chiral acid or base. This way is possible to recrystallize selectively one diastereomer and then convert the salt into the required acid or base.



Scheme 2 - Example of a kinetic resolution[3].

When the asymmetric strategy used is a resolution procedure, it should be considered that half of the material is lost. There is the idea that a resolution should be done as soon as possible in the synthesis, otherwise an impurity (the undesired enantiomer) will be carried through the synthesis. This will lead to an unnecessary use of solvents, reagents and other resources. On the other hand, a resolution carried earlier in a synthesis will result in more costs than one carried later, because a larger amount of chiral reagent or catalyst needs to be used. It should be noted that in many cases the asymmetric step in the synthesis is the one that requires more costs. In conclusion, the cost of the other steps and of

the resolution should be balanced, and probably a very early resolution will be as bad option as a very late one.

The first impression can be that a resolution is a bad option when compared with the other strategies, since it implies a decrease in 50% of the final yield of the product. It is a fair argument but not that straightforward, since each strategy has its pros and cons. For example, a compound from the chiral pool may be expensive or unavailable in large amounts when compared to a simpler raw material, that other strategies may constitute a better alternative. Alternatively, the cost or efficiency of an asymmetric reaction may be so bad that a resolution may be a better alternative. Several aspects need to be considered in order to choose the best alternative for the purposes of the synthetic chemist. While in some cases time efficiency may be more important than costs, in others, raw material availability may be an essential feature.

Aziridines

Aziridines are an important class of organic compounds, basically they are a fully saturated three-member ring containing one nitrogen and two carbon atoms. This moiety is present in natural products, molecules having biological activity and even in products of industrial interest. **Figure 4** illustrates some examples of natural bioactive molecules baring an aziridine ring. They play an important role in organic synthesis and methods for their preparation[4] and new application are still being developed[5].

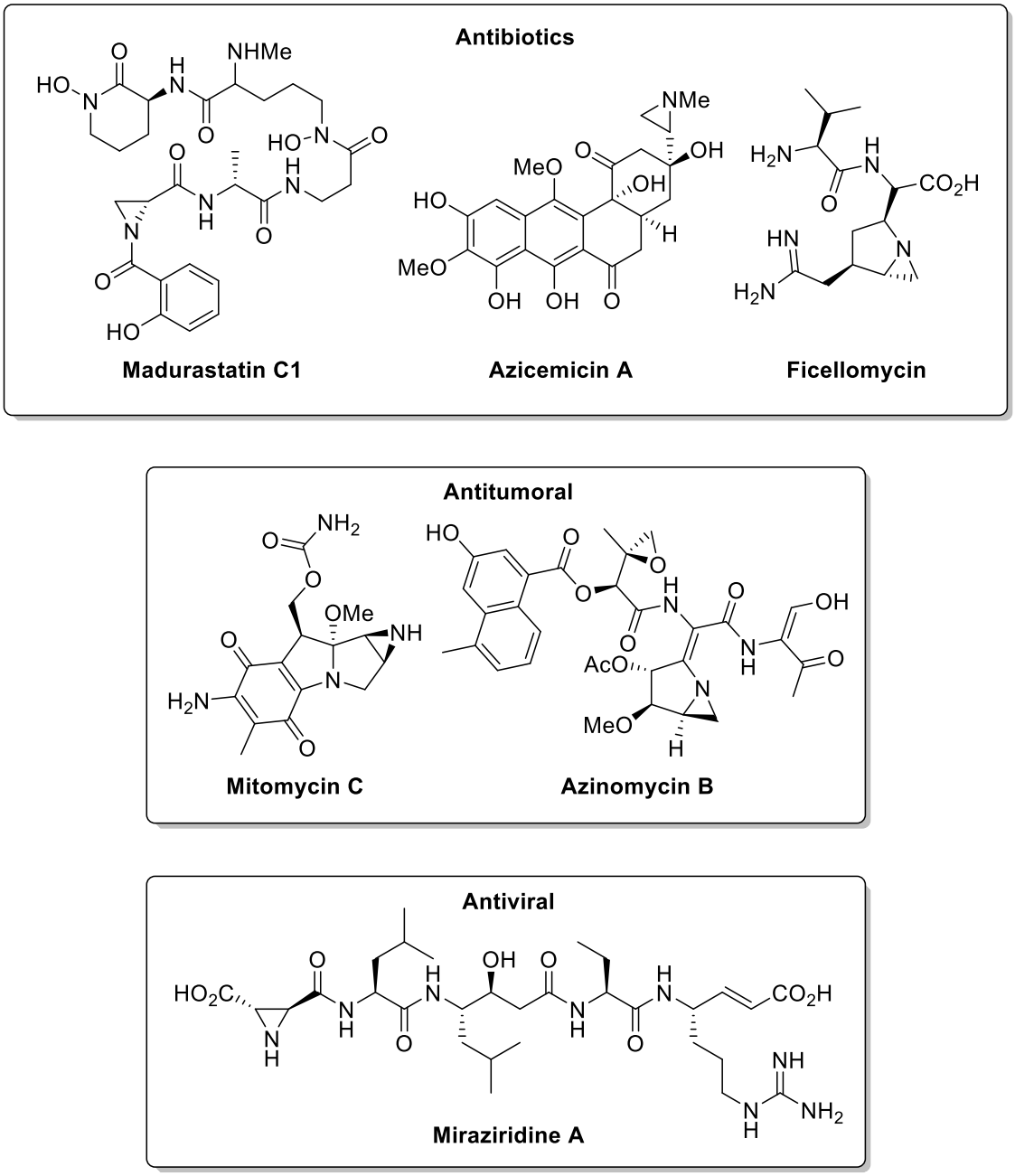
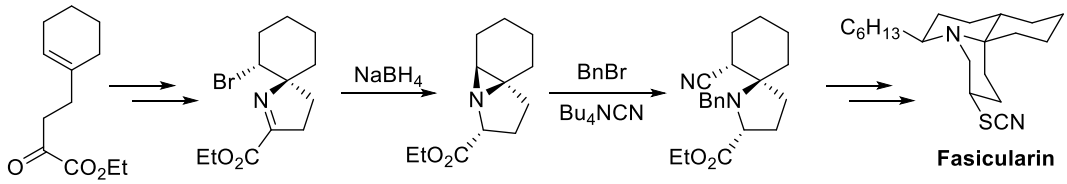
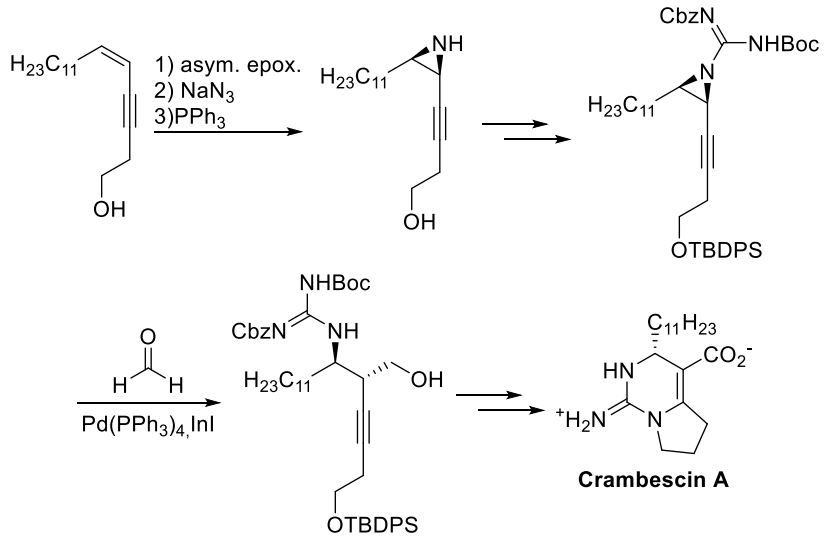


Figure 4 - Examples of bioactive natural products containing aziridines.

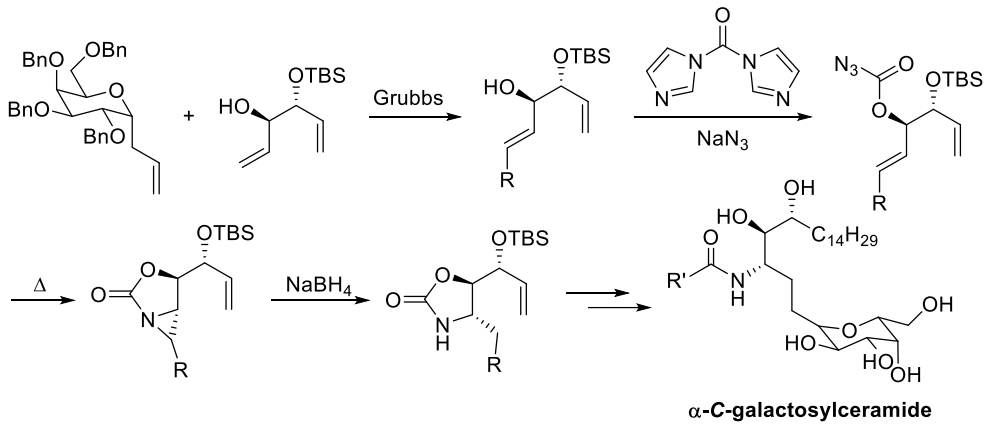
Aziridines are very versatile regarding its synthesis and reactions, therefore they are frequently used as a strategy to introduce a nitrogen atom into a molecule. Since the aziridine ring is very rigid, they often play an important role as intermediates orienting the stereochemical outcome of subsequent ring opening reactions. The following schemes illustrate examples of recent syntheses using aziridines: fasicularin[6], crambescin A[7], α-C-galactosylceramide[8] and SGRM modulators[9].



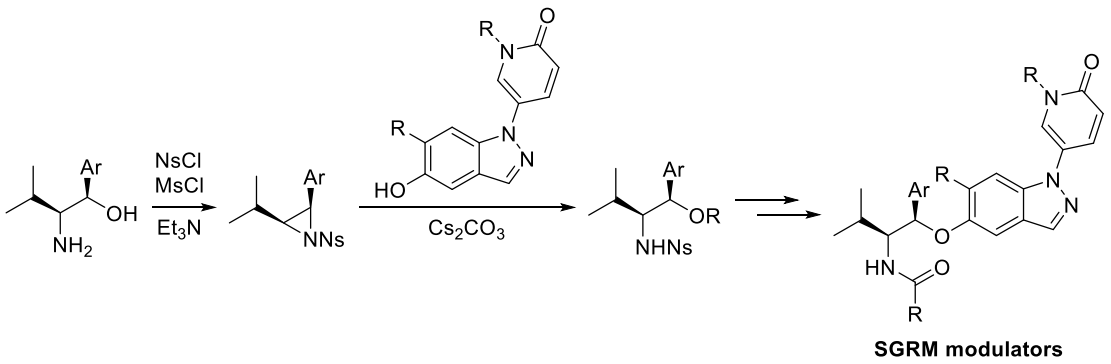
Scheme 3 - Synthesis of fasicularin.



Scheme 4 - Synthesis of crambescin A.



Scheme 5 - Synthesis of α-C-galactosylceramide.

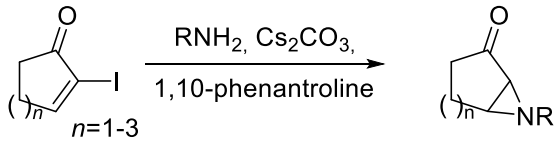


Scheme 6 - Synthesis of SGRM modulators.

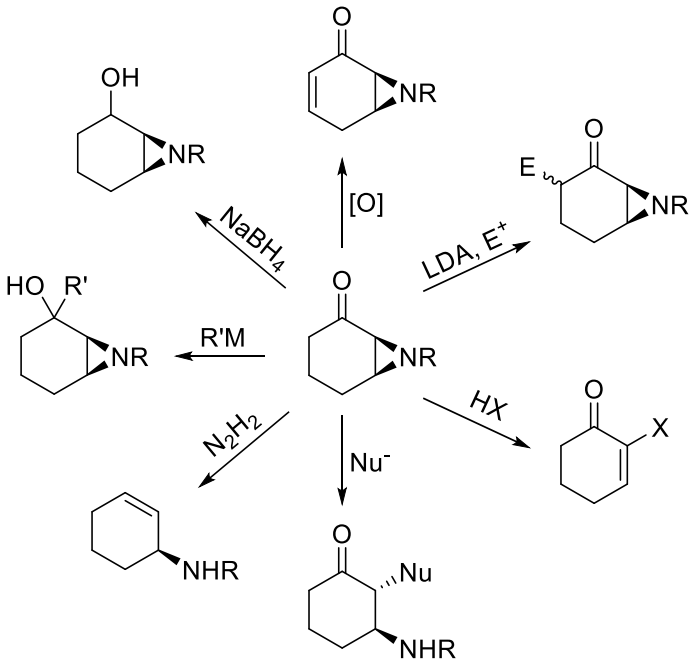
Cyclic acylaziridines (azabicyclo[x.1.0]alkane-2-ones)

In our group a Grabriel-Cromwell[10] like method for the synthesis of acylaziridines has been studied[11]. It consists of the reaction of iodoenones with a primary amine under basic conditions (**Scheme 7**). It is particularly useful with cyclic substrates leading to the formation of the bicyclic compounds azabicyclo[x.1.0]alkane-2-ones**.** Since this discovery, its synthetic potential has been exploited and new applications for this reaction have been developed. **Scheme 8** illustrates some applications for these compounds. As in the case of acyl epoxides they are particularly rich, since reactions can occur both at the

aziridine or ketone carbonyl. One particularly interesting transformation is the reaction with hydrazine to form an allylic amine, which we called the aza-Wharton reaction after the discoverer of the epoxide analogue and was recently published[12].



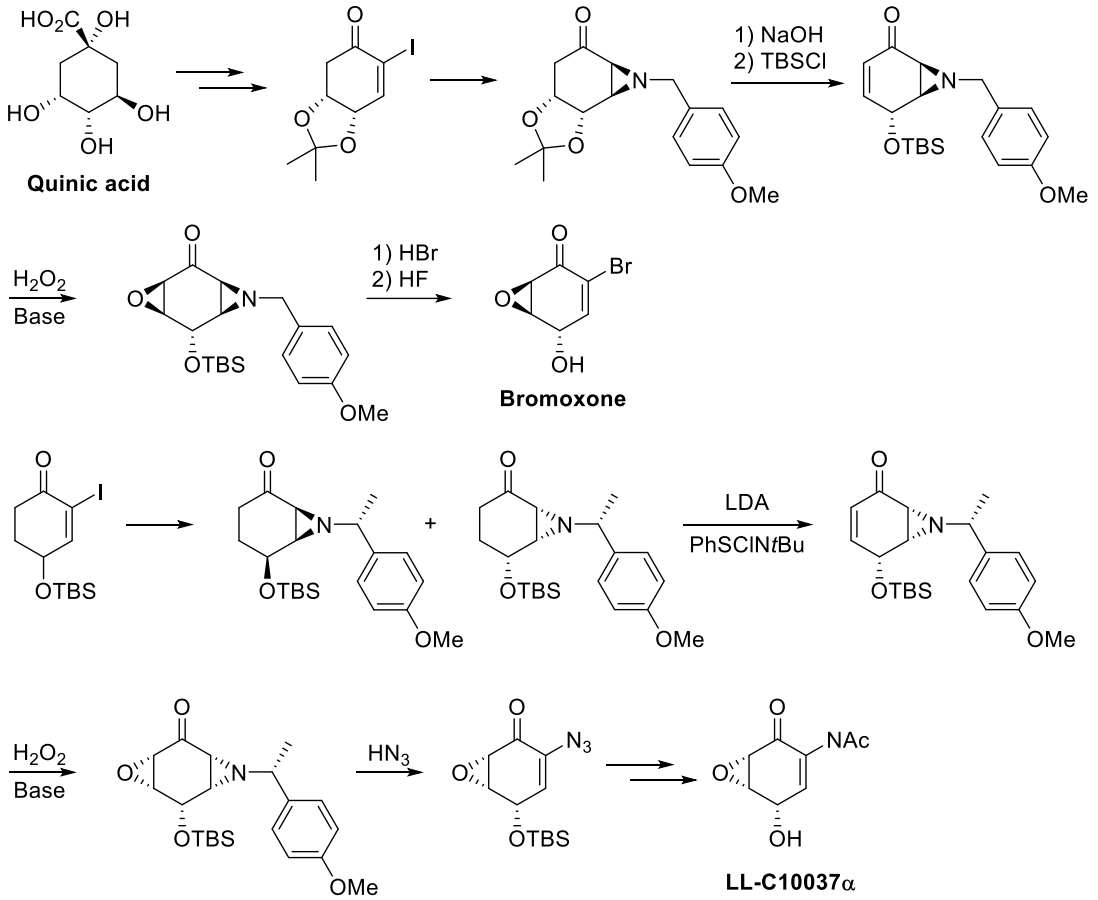
Scheme 7 - Aziridination of cyclic iodoenones.



Scheme 8 - Synthetic applications of cyclic acylaziridines.

This aziridination method was used in the synthesis of two natural products: bromoxone[13] and LL-C10037α[14] (**Scheme 9**). In the case of bromoxone an enantiomerically pure iodoenone prepared from quinic acid was used. In the case of LL-C10037α a racemic iodoenone was resolved with a chiral amine,

demonstrating the usefulness of this reaction as a possible strategy for resolution. In both cases, it should be noted the stereoselectivity of both the aziridination and the epoxidation, in which the aziridine orientates the formation of the epoxide.

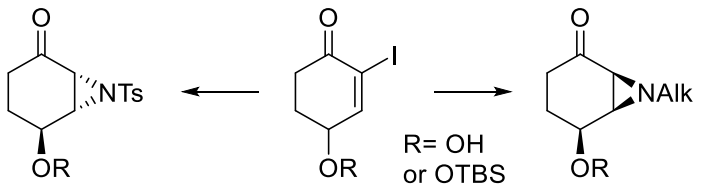


Scheme 9 - Synthesis of bromoxone and LL-C10037α.

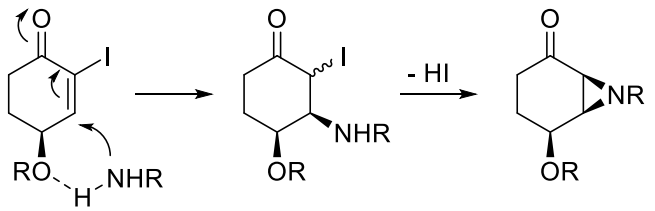
Objectives

Cyclic acyl aziridines are particularly useful for the design of synthetic strategies as demonstrated. In the presented syntheses, besides the stereoselectivity of the aziridination, the aziridine is used as protecting, orienting and diastereomeric resolving group. We have previously described[12,14] the

stereoselective aziridination of cyclic 4-hydroxyiodohexenones and respective TBS derivatives (**Scheme 10**). The *trans* aziridine would be the expected product, by Michael addition occurring at the least hindered side of the enone double bond. However, using alkyl amines, the *cis* aziridine is formed instead. We believe this is due to hydrogen bonding between the amine and the oxygen atom (**Scheme 11**) and a similar selectivity has previously been observed in the 1,4-additions of thiols to similar systems[15]. In the case of tosylamide the proton attached to the nitrogen atom is much more acidic therefore a nitrogen anion may be formed by reaction with cesium carbonate, hence in the absence of hydrogen bonding the expected *trans* aziridine is formed.



Scheme 10 - Stereoselective aziridination of cyclic 4-hydroxyiodohexenones.



Scheme 11 - Proposed mechanism for the formation of *cis* 5-hydroxyazabicyclo[4.1.0]heptane-2-ones.

Taking advantage of the synthetic potential of these compounds, the objective of this work was to develop new strategies for the asymmetric synthesis of bioactive compounds: terpestacin, oseltamivir and analogues.

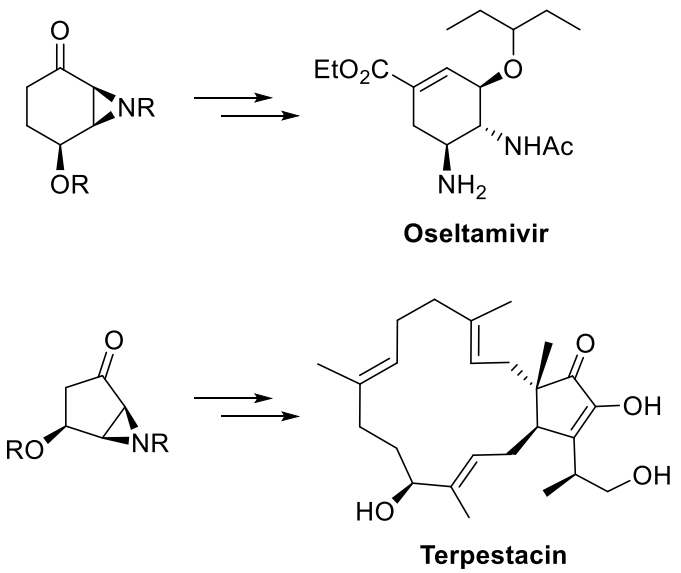


Figure 5 – Proposed synthesis of oseltamivir and terpestacin.

Chapter 2

Asymmetric synthesis of cyclic 4-hydroxyacylaziridines *via* enzymic resolution

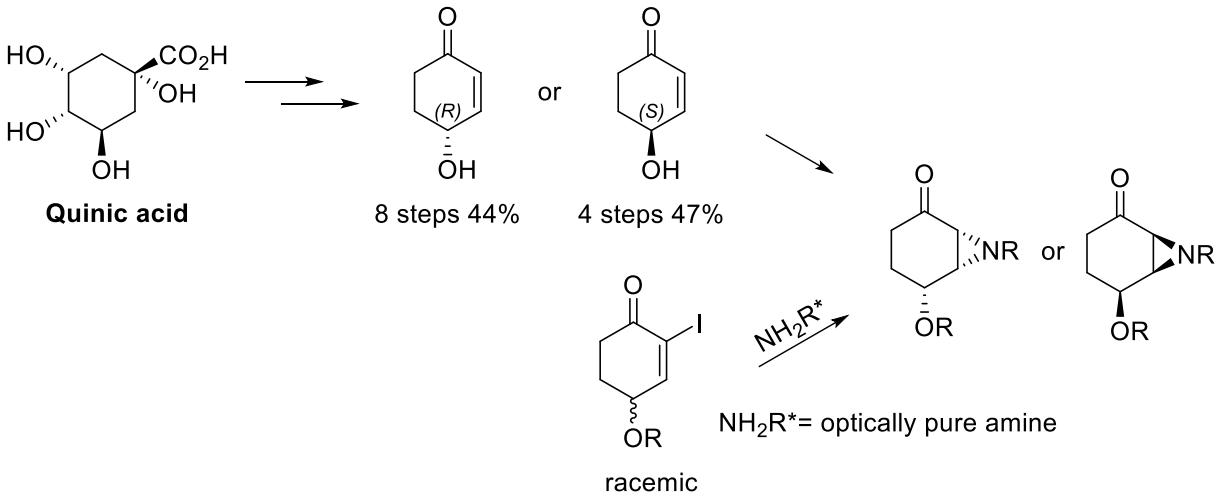
Abstract

A method for the preparation of optically active cyclic 4-hydroxy-acylazyridines ((x+1)-hydroxyazabicyclo[x.1.0]alkane-2-ones) is described. It is based on the stereoselective aziridination of protected racemic 4-hydroxycycloenones followed by enzymic resolution with Novozym 435 (CAL-B). The described method is simple, reproducible, scalable and chiral hydroxyaziridines are obtained in good yield (up to 50%) and enantiomeric excess (up to 99%). A stereoselective nucleophilic substitution of the acetyl group of an acetylated five-membered ring substrate (4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate) is also described.

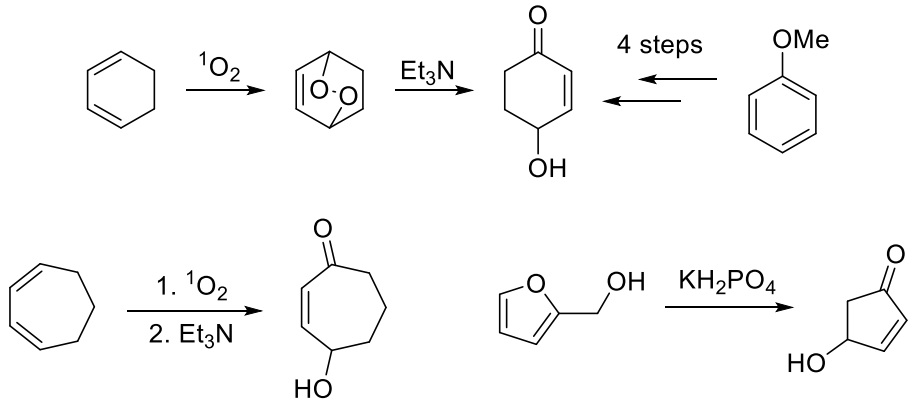
Introduction

For the development of new asymmetric syntheses of bioactive molecules and their analogues, the first task to be undertaken should be the synthesis of the optically active cyclic 4-hydroxyacylaziridines. The previous approaches used quinic acid as starting material from the chiral pool or an optically active amine during aziridination for the purpose of resolution (**Scheme 12**).[14] The first approach is very time consuming since 8 steps are needed to convert quinic acid into (*R*)-4-hydoxy-cyclohexenone and 4 steps into (*S*)-4-hydoxy-cyclohexenone.[16] The second approach involves the separation of two diastereomers by chromatography, although practicable it needs very good chromatographic skills and some work in order to find the right conditions, since the difference in R_f of the two diastereomers is normally small. Alternative published methods[15,17] for the preparation of optically active 4-hydroxycycloenones are time consuming, expensive or involve derivatization prior to resolution. In contrast, the preparation[15,18,19] of racemic enones is expedient and inexpensive (**Scheme 13**).

In addition, 4-hydroxycycloenones are volatile and unstable, therefore a method for the resolution of cyclic 4-hydroxyacylaziridines ((x+1)-hydroxyazabicyclo[x.1.0]alkane-2-ones) would be a good alternative for an asymmetric route for these compounds.



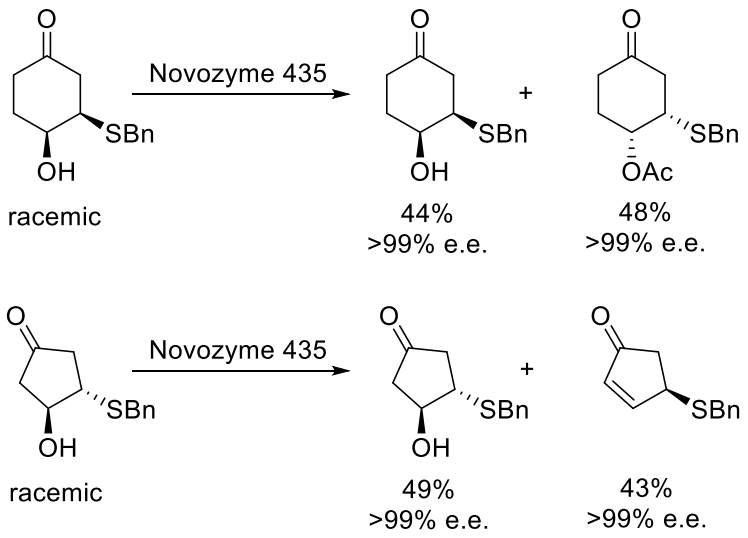
Scheme 12 - Previous synthetic strategies for the preparation of optically active cyclic 4-hydroxyacylaziridines.



Scheme 13 - Asymmetric routes to 4-hydroxycycloenones.

In a method reported for the enantioselective synthesis of 4-hydroxycycloenones, a procedure for the enzymic resolution of 3-thiobenzyl-4-

hydroxy cyclic enones was used (**Scheme 14**). This procedure is very efficient, having high yields (>43%) and enantiomeric excesses (>99%). The enzyme used Novozym 435 is the lipase CAL-B on a solid support and has the advantages of being commercially available, affordable, easy to handle and compatible with organic solvents. Due to structure similarity, the procedure was expected to work as well in cyclic 4-hydroxyacylaziridines and appeared to constitute a good option for their resolution.

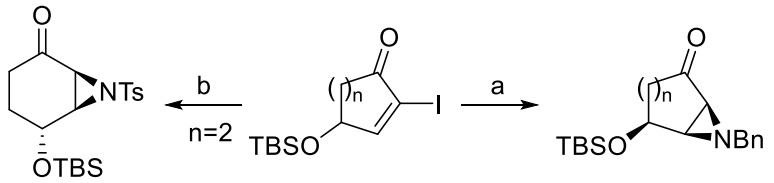


Scheme 14 - Enzymic resolution of 3-thiobenzyl-4-hydroxy cycloketones.

Preparation of racemic cyclic 4-hydroxyacylaziridines

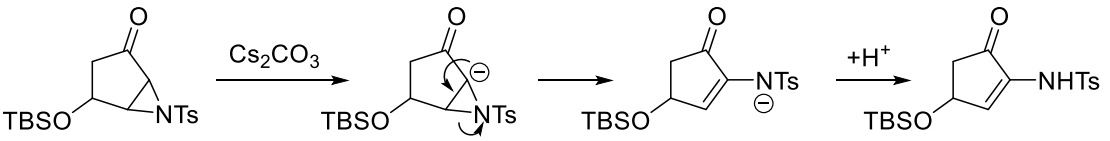
Stereoselective aziridinations of TBS-protected 4-hydroxy-cycloiodoenones **1** (**scheme 3**) have been discussed in the previous chapter. *Cis* aziridines **2a-c** have been prepared using benzylamine as well as *trans* tosyl aziridine **2d**. In the case of **1c** (n=3) no selectivity was observed using tosylamide

and for **1b** (n=1) aziridination is not possible, as the only product formed is **4**. Product **4** is probably formed by basic rearrangement of aziridine **3** (**Scheme 16**).



2d (85%) **1a-c** **2a** (n=2, 83%), **2b** (n=1, 82%), **2c** (n=3, 68%)

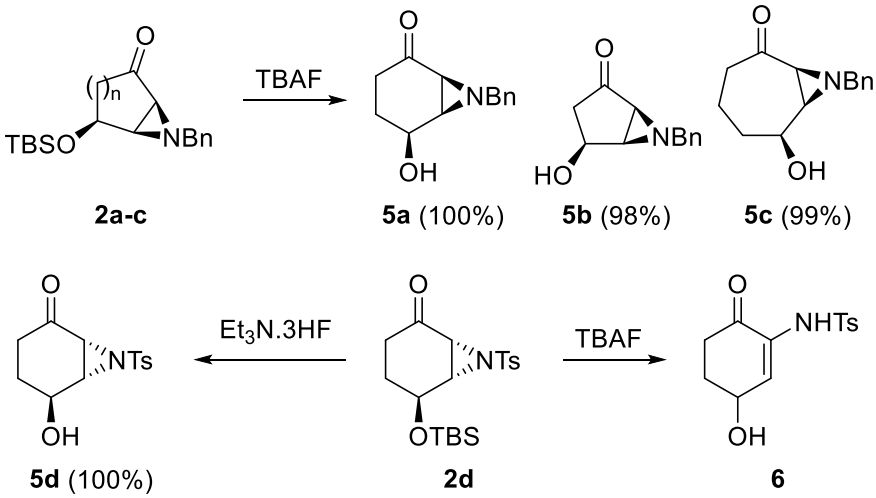
Scheme 15 - Stereoselective aziridination of 4-((tert-butyldimethylsilyl)oxy)-2-iodocycloenones. Reaction conditions: a) $BnNH_2$, Cs_2CO_3, 1,10-Phenanthroline, Toluene; b) $TsNH_2$, Cs_2CO_3, Toluene.



3 **4**

Scheme 16 - Proposed mechanism for the formation of product **4**.

Hydroxyaziridines **5a-c** were obtained by TBS group removal of **2a-c** with TBAF in excellent yields (**Scheme 17**). Deprotection of tosylaziridine **2d** with TBAF resulted in the formation of **6**. Since fluoride is also a base it may have promoted the same rearrangement as in **Scheme 16**. Deprotection was possible with the less basic reagent triethylamine trihydrofluoride.

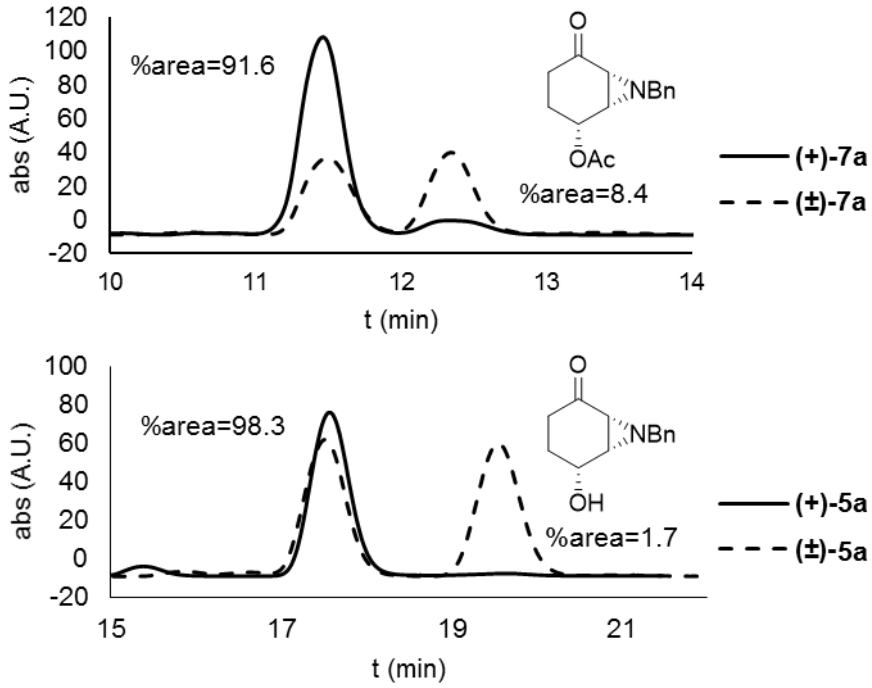


Scheme 17 - TBS deprotection of aziridines **2**.

Enzymic resolution

Aziridine **5a** was used to optimize a resolution protocol, the same conditions[15] were applied and products analyzed by chiral HPLC. The method worked very well and (-)-**5a** was obtained in good yield (48%) and enantiomeric excess (>99%). In the other hand acetate (+)-**7a** was obtained with only 83% of enantiomeric excess and shorter conversions were not leading to a higher enantiomeric excess as expected. In addition, HPLC analyses were not reproducible and very dependent on the analyte concentration. The acetate group of (+)-**7a** was removed with potassium carbonate in methanol leading to the formation of (+)-**5a** in quantitative yield. The HPLC analysis of (+)-**5a** afforded a reproducibly higher enantiomeric excess. **Graphic 1** shows the chromatograms of a sample before and after the acetate hydrolysis. Although we do not have an explanation for this, the HPLC analysis of acetate (+)-**7a** was leading to inaccurate values of enantiomeric excess. Another interesting feature of this protocol is that 4, 8 or 16 hours of reaction time leads to the same conversion and enantiomeric excess. The lipase reaches a point where it stops catalyzing the acetylation and

this might be explained by a very high-energy transition state for the acylation of the unreacted enantiomer.

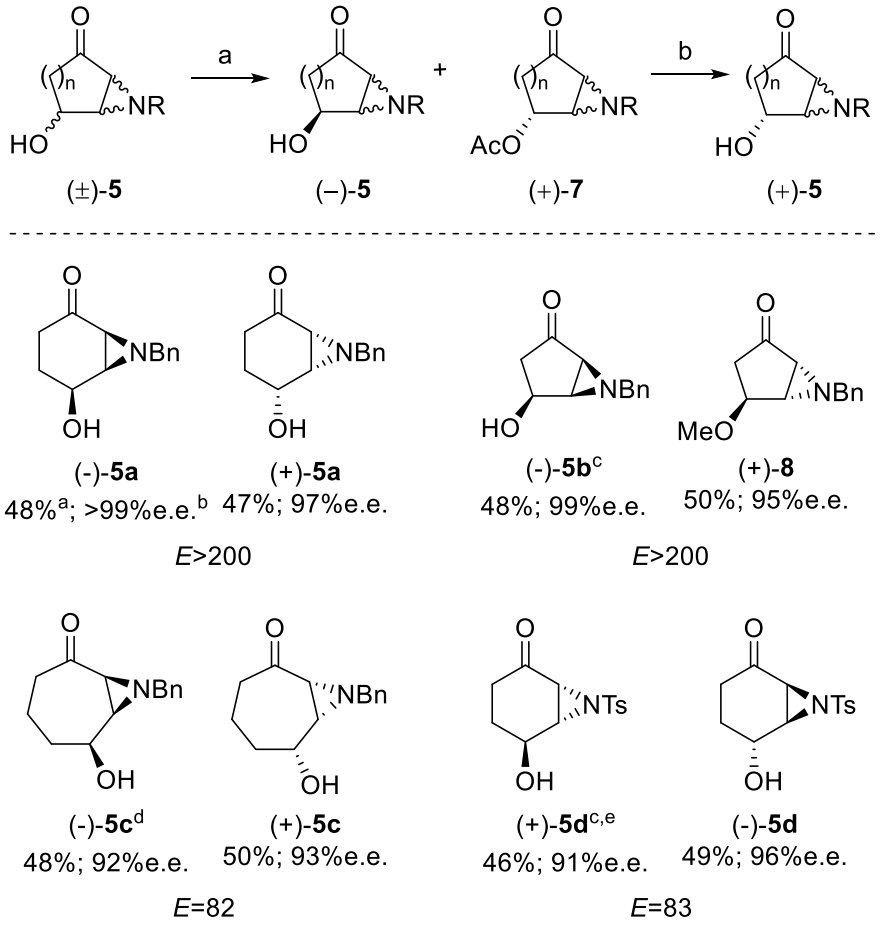


Graphic 1 - Chiral HPLC analysis of resolved acetoxyaziridine (+)-**7a** and hydroxyaziridine (+)-**5a** after acetate hydrolysis.
Elution conditions: AD-H column; 95:5 hexane:isopropanol; 1.0ml.min^{-1}; 237nm.

The results of the lipase-catalyzed resolution of aziridines **5a-d** are summarized in **Table 1**, all the acetates were analyzed after methanolysis. It is interesting to notice that lipase substrate selectivity was only dependent on the stereochemistry of the hydroxyl group and not on the aziridine. While **5a** was an oil, **5b** and **5d** were solids only partially soluble in the solvent, diisopropyl ether, and probably for this reason the conversions of these compounds using the conditions applied to racemic **5a** were lower (35%). This problem was solved by using a larger amount of solvent while maintaining the proportion of diisopropyl

ether/vinyl acetate and resulted in higher conversions (**Table 1**). In the case of substrates **5c** and **5d** at the point where the reaction stopped the conversions were only about 40%. Increasing the amount of enzyme used lead to higher conversions. We also found that the addition of all of the enzyme in one portion at the beginning or in several smaller portions during the esterification, did not affect the final outcome.

Table 1 - Enzymatic resolution of cyclic 4-hydroxy-acylazyridines.



Reaction conditions: a) Novozym 435 (25 mg), vinyl acetate (5 eq.), Diisopropyl ether (1 mL); b) K_2CO_3, MeOH. [a] All yields refer to isolated products starting from 50 mg of aziridine. [b] All enantiomeric excesses were determined by chiral HPLC. [c] 10 eq. of vinyl acetate and 2mL of DIPE were used. [d] 75 mg of lipase was used. [e] 50 mg of lipase was used.

Methanolysis of acetate **7b** was not possible under the same basic conditions, to form the corresponding alcohol, instead the methyl ether **8** was formed. The presence of a methyl group at 3.35 ppm on the ^{1}H NMR spectrum (**Figure 6**) is indicative that the structure of compound **8** contains a methoxy group. The NMR signal of H-4 of *cis* aziridines **2b**, **5b** and **7b** is a triplet of doublets while for aziridine **8** is a doublet, therefore it is possible to conclude formation of **8** occurred with inversion of configuration.

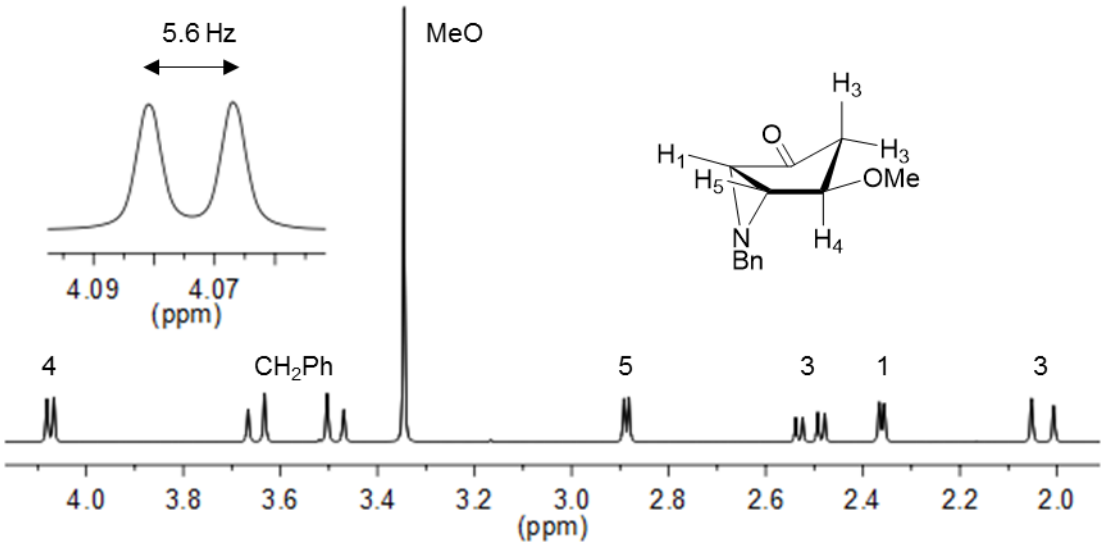
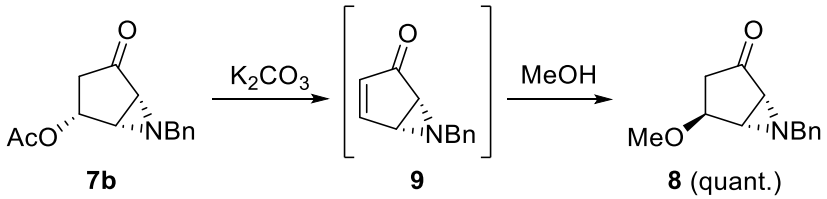


Figure 6 - Partial ^{1}H NMR spectrum of aziridine **8**.

A plausible explanation for the formation of **8** involves elimination of acetate followed by stereoselective methanol addition (**Scheme 18**). The high stereoselectivity of the reaction is noteworthy, methanol addition occurred exclusively at the side of the enone system at the opposite face to the aziridine nitrogen atom. This result is most certainly due to steric hindrance of the aziridine ring.



Scheme 18 - Acetate elimination and methanol addition of **7b**.

Conclusion

The described enzymic resolution method allows the preparation of chiral cyclic 4-hydroxy-acylaziridines, useful molecules for organic chemistry as they can be transformed into functionalized cycloalkane products. It is an affordable, reproducible and scalable method, therefore having the potential to be used in multistep syntheses, as it will be demonstrated in the next two chapters.

Chapter 3

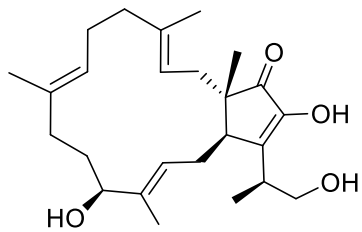
Terpestacin synthesis preliminary attempts

Abstract

Three strategies for the synthesis of natural product terpestacin were designed. Although those strategies failed, interesting molecules were prepared that may be useful as intermediates in other syntheses. Aziridine invertomers were observed by NMR in one of these molecules and this equilibrium was studied by DFT calculations.

Introduction

Terpestacin is a fungal secondary metabolite. It is a sesterterpene that was first isolated from *Arthrinium sp.* in 1993 and described as an inhibitor of the formation of syncytia by HIV-infected T cells.[20] After its initial discovery, it was also isolated from other species of fungi[21] and reported to have other biological activities such as the inhibition of angiogenesis[22] and syncytia formation in other viruses[23]. Therefore, it is a promising lead for the development of new anticancer and antiviral drugs.

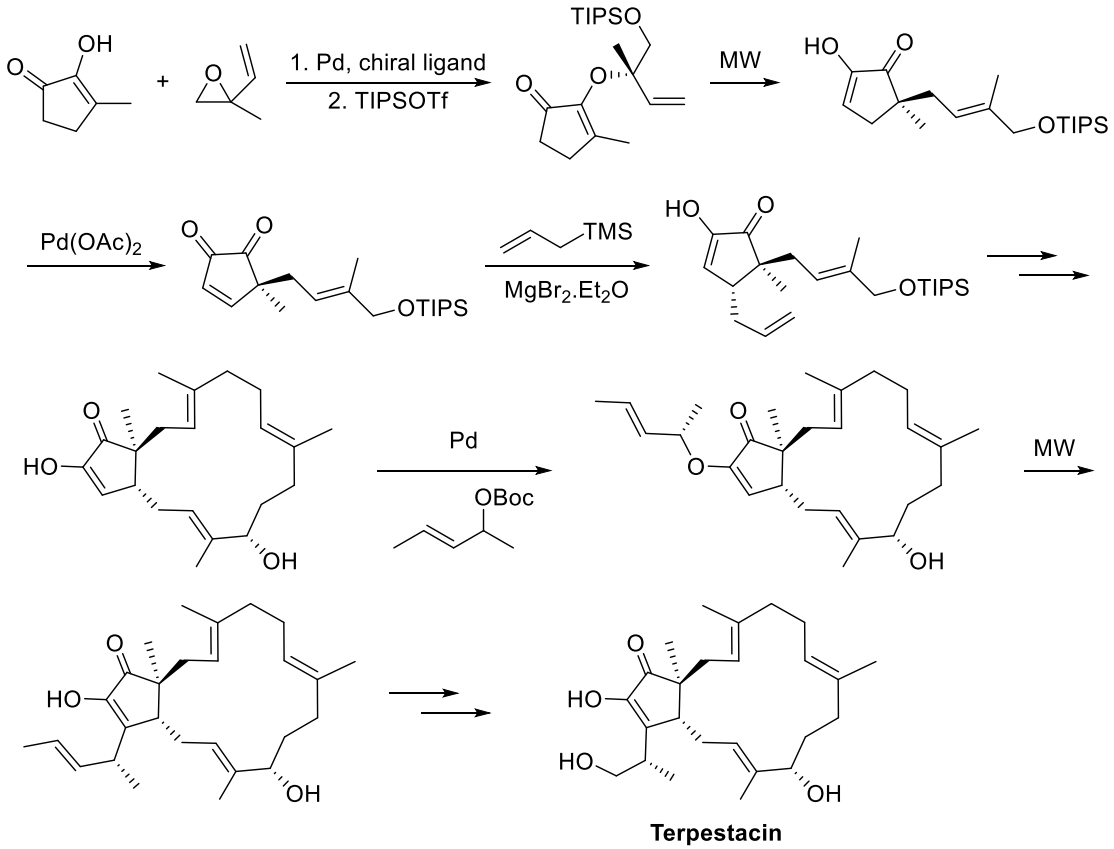


Terpestacin

Figure 7 - Terpestacin structure.

Due to its importance as a lead for drug development and its structural complexity, terpestacin has been a target for synthetic chemists and several syntheses have been developed[24]. All reported syntheses can be divided into two different parts, a) the synthesis of the cyclopentadione ring and b) of the macrocycle ring. Even though both tasks are very challenging, the construction

of the cyclopentadione ring requires the most stereocontrol. One of the more expedient routes was developed by Trost and coworkers[24f,24g] and is illustrated in **Scheme 19**.

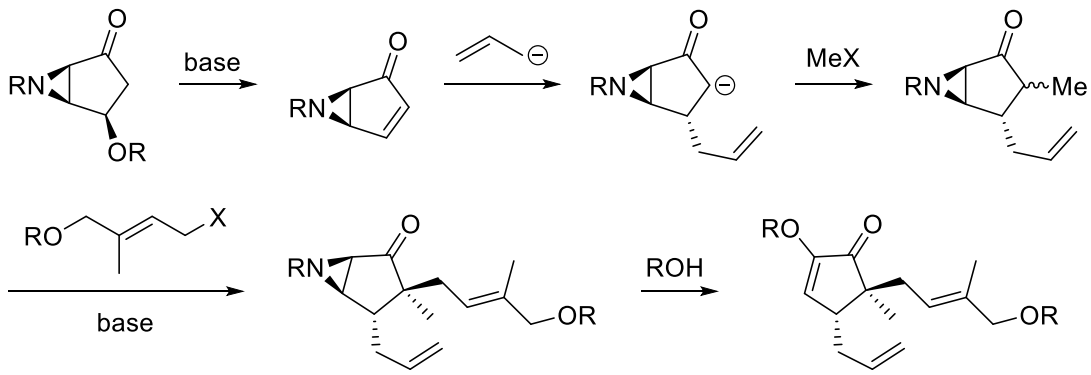


Scheme 19 - Trost synthesis of terpestacin.

Based on the Trost synthesis, a synthetic strategy for a key intermediate was designed (**Scheme 20**). The starting material is one of the 4-hydroxyacylaziridines described in the previous chapter. In this strategy, the aziridine ring orients the introduction of the several groups in the cyclopentanone ring. The described allyl group Michael addition is expected to form *trans* product due to aziridine steric hindrance. This allyl group would orient the ketone alkylation and the second substituted allyl group would be formed

trans to first one. Although the presented strategy is based on the macrocyclization approach developed by Trost, other described strategies or a new one could be used depending on the groups introduced. This strategy would constitute a new asymmetric approach for terpestacin.

terpestacin is a considerable complex structure and its synthesis involves several steps, and like other complex natural products efficient processes are needed for its production to be viable. Probably, terpestacin won't be a good candidate for a new commercial drug, however its structure can be used as a lead for the design of new drugs. For the design of new analogues efficient synthetic tools are needed, therefore development of new and efficient synthetic strategies for terpestacin are still useful. In this part of the work, the objective was to develop a new synthetic strategy for terpestacin and eventually other analogues.

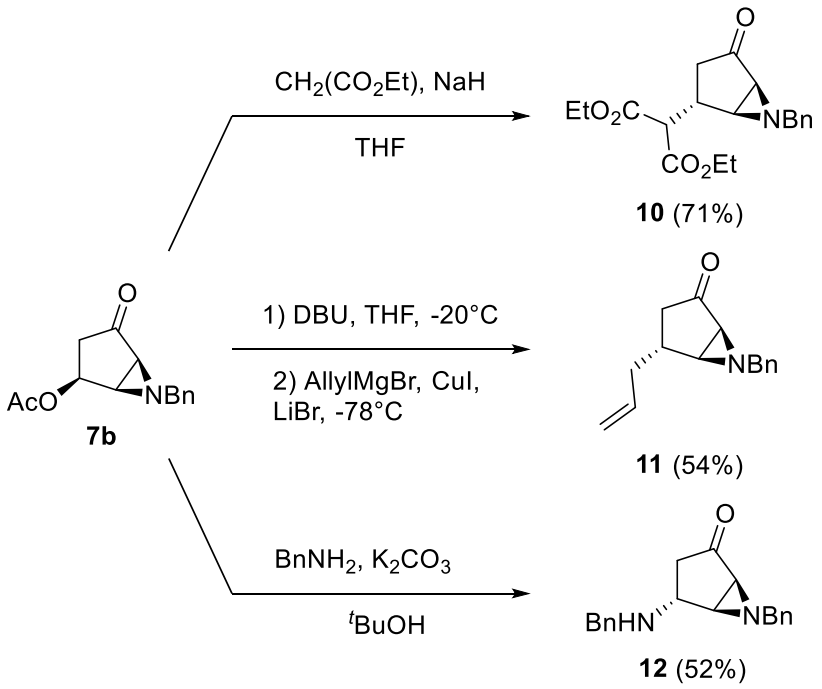


Scheme 20 - Proposed synthetic strategy for Trost intermediate.

1st attempt

Aziridine **7b** underwent beta elimination and stereoselective methanol 1,4-addition as described in the previous chapter. The addition of other C and N nucleophiles was also tested (**Scheme 21**) and the *trans* products **10-12** were

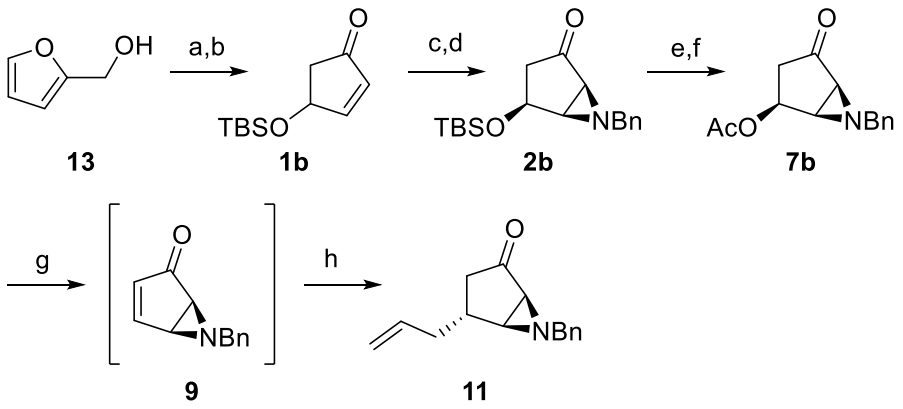
exclusively obtained, albeit in moderate yield. Again, the aziridine ring seems to orientate very efficiently the addition of nucleophiles in this system.



Scheme 21 - Aziridine **7b** elimination of acetate and addition of different nucleophiles.

Aziridine **11** was one of the intermediates of the proposed synthetic route (**Scheme 20**), its complete synthesis is described in **Scheme 22**. We opted to start with racemic **7b** for an initial development of the methodology, however it can be obtained in optically enriched form by resolution as described in the previous chapter. The starting material, furfuryl alcohol **13** is inexpensive and commercially available, its transformation into 4-hydroxycyclopent-2-enone has been described[15]. Stereoselective aziridination and the preparation of **2b** has already been discussed in the previous chapter. α,β-Unsaturated ketone **9** can be obtained by treating **7b** with a base, however it is a very reactive species that quickly degrades upon isolation. Nevertheless, it was possible to identify its

structure by ^{1}H NMR (**Figure 8**). The two signals at 7.6 and 5.9 ppm are consistent with the presence of a enone system, while the ones at 3.0 and 2.7 are produced by the unreacted aziridine moiety.



Scheme 22 - Synthesis of **11.**
Reaction conditions: a) KH_2PO_4, H_2O, reflux, 48h, 40%; b) TBSCl, DIPEA, DMAP (cat.), DCM, r.t., 16h, 92%; c) I_2, DMAP (cat.), Et_2O:Py 1:1, r.t., 1h, 99%; d) $BnNH_2$, Cs_2CO_3, 1,10-Phenanthroline, Toluene, r.t., 4h, 83%; e) TBAF, THF, r.t., 30 min, 98%; f) Ac_2O, Et_3N, DCM, r.t., 5h, 93%; g) DBU, THF, -20°C, 30 min; h) AllylMgBr, CuI, LiBr, THF, -78°C, 30min, 54%.

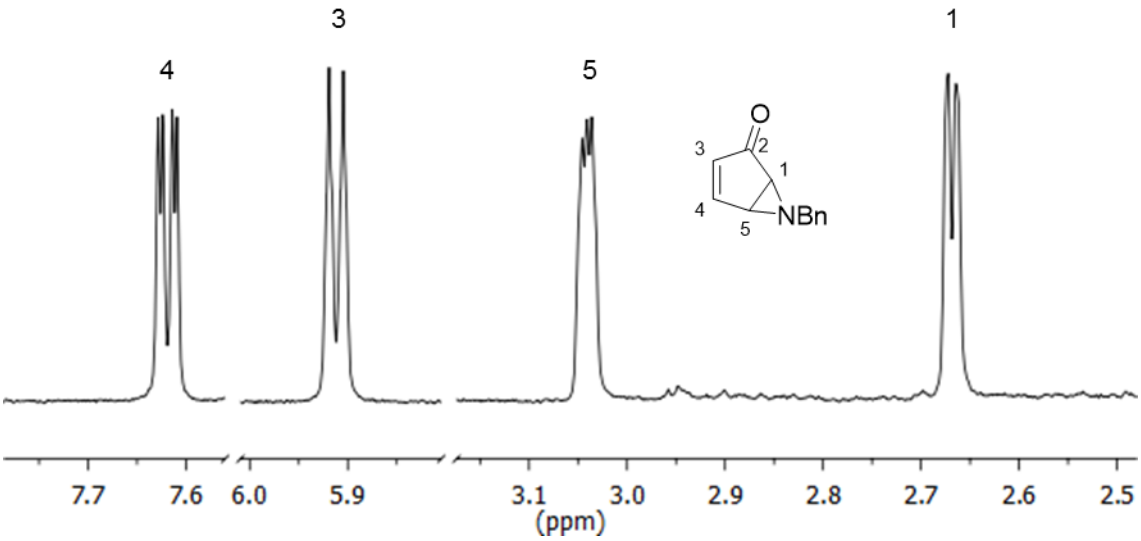
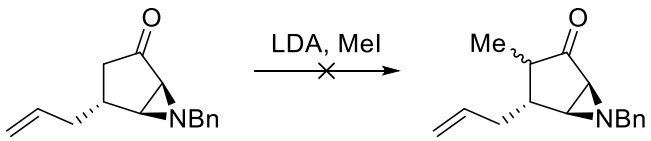


Figure 8 - Partial ^{1}H NMR spectrum of compound **9**.

The enolate of **11** was formed with LDA and reacted with methyl iodide. Unfortunately, even at room temperature no reaction occurred and only initial compound **11** was recovered. Probably **11** is too crowded and methylation is not possible. Hence this was a dead end to this route.



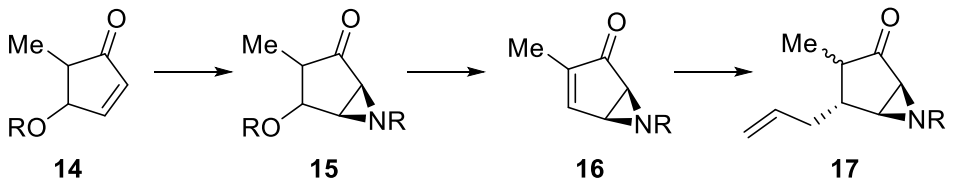
11 **13**

Scheme 23 - Unsuccessful reaction of lithium enolate of **11** with methyl iodide.

2nd attempt

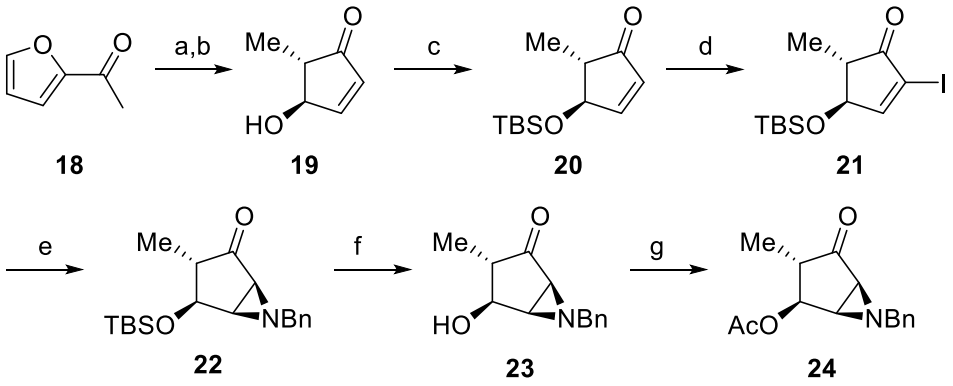
An alternative strategy for the synthesis of compound **13** (**17** R=Bn) was planned, where the methyl group was already in the cyclopentanone ring before aziridination and allyl group addition (**Scheme 24**). As before, *trans* product **17**

was expected to be formed and the alkylation of its enolate was considered to be possible using a more reactive allylic electrophile.



Scheme 24 - Strategy for the synthesis of **17**.

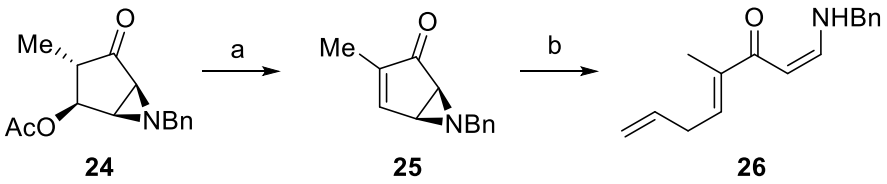
5-Methyl-4-hydroxy-cyclopentenone **19** (**Scheme 25**) was prepared starting from methylfurylketone **18**.[25] Ketone **18** was reduced to the respective alcohol that underwent a Piancatelli rearrangement[26] to form the enone **19**. Steric hindrance of a methyl *trans* to the protected hydroxyl group should favor the *cis*-selectivity of **21** aziridination. Indeed, **22** was exclusively obtained and further elaboration produced the desired compound **24.**



Scheme 25 - Synthesis of **24**.

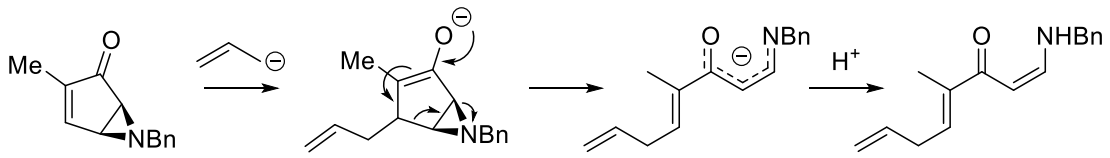
Reaction conditions: a) $NaBH_4$, EtOH, r.t., 1h, 98%; b) $ZnCl_2$, HCl, Dioxane/H_2O, reflux, 24h, 90%; c) TBSCl, DIPEA, DMAP (cat.), DCM, r.t., 16h, 66%; d) I_2, DMAP (cat.), Et_2O:Py 1:1, r.t., 30 min, 56%; e) $BnNH_2$, Cs_2CO_3, 1,10-Phenanthroline, Toluene, r.t., 3h, 70%; f) TBAF, THF, r.t., 30 min, 93%; g) Ac_2O, Et_3N, DCM, r.t., 3h, 73%.

Treatment of **24** with a base generated the expected α,β-unsaturated ketone **25** (**Scheme 26**), it was much more stable than **9** and could be isolated. The addition of the allyl group occurred, however, the expected product **17** was not formed, instead **26** was obtained. A possible mechanism for this transformation is proposed in **Scheme 27**, where Michael addition of the allyl group takes place but the enolate formed collapses opening both rings to form the unsaturated linear enaminone **26**.



24 **25** **26**

Scheme 26 - Formation of **26**.
Reaction conditions: a) DBU, THF, -20°C, 30 min; b) AllylMgBr, CuI, LiBr, THF, -78°C, 30min, 20%.



25 **26**

Scheme 27 - Proposed mechanism for the formation of **26**.

The ^{1}H spectrum of **26** (**Figure 9**) contains several signals at low field (5-7 ppm), consistent with a structure containing multiple unsaturations. There is also a signal at very low field (10.3 ppm) that corresponds to the NH of the enamine group. 2D experiments (COSY, HMQC and HMBC) were essential for the determination of the presented structure and attribution of signals. The stereochemistry of the double bond between carbon 4 and 5 was determined by a NOESY experiment, in which it was possible to observe a correlation signal between the methyl group and proton 6, as well as between protons 5 and 2.

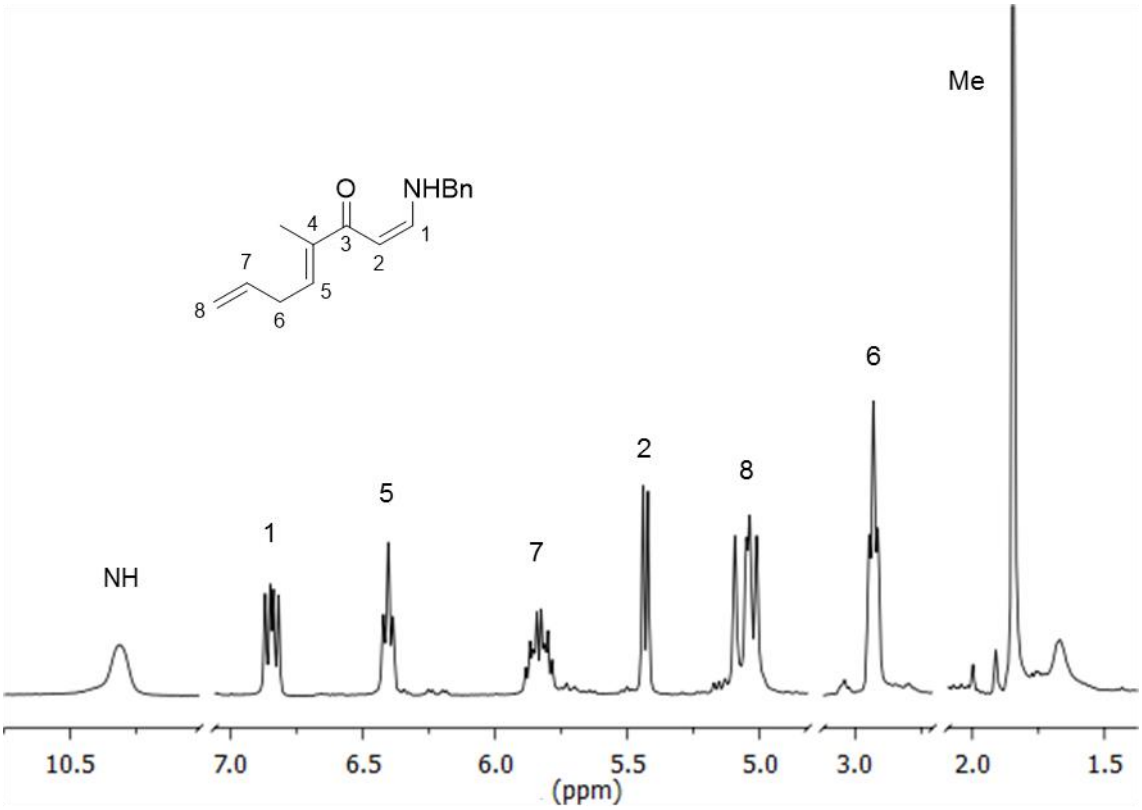
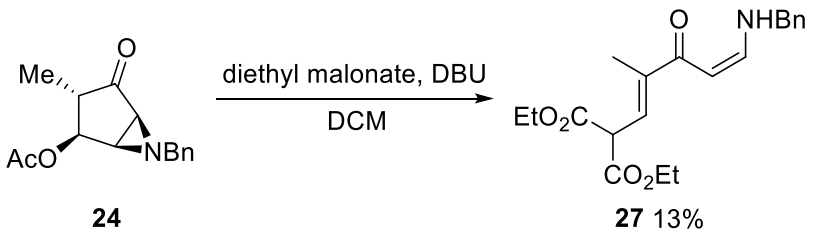


Figure 9 - Partial ^{1}H NMR of compound **26**.

For the formation of **26** was used an organometallic reagent (allylcuprate). Suspecting that the organocuprate was responsible for this reaction we decided to use a different nucleophile to check if the same rearrangement still occurred. Indeed, using diethyl malonate and an organic base (DBU) a similar product **27** was also obtained (**Scheme 28**). Treatment of **24** with a base in methanol resulted in the formation of enone **25** and the addition of methanol was not observed. It seems to be a very crowded system and probably the preparation of a compound with structure **17** would not be possible, so this was a dead end for this strategy. Although the rearrangement that produces **26** and **27** is interesting, it has few synthetic applications since all the chiral information of the starting material was lost.

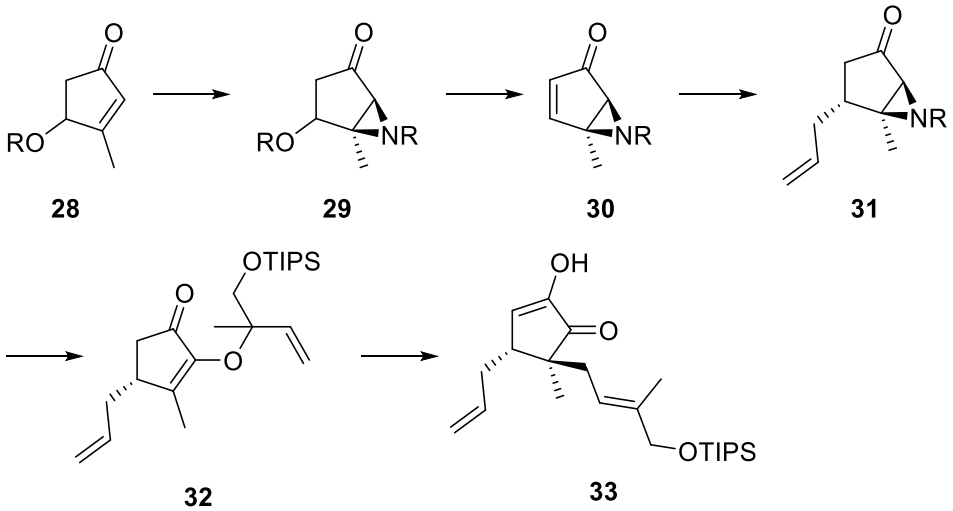


24 **27** 13%

Scheme 28 - Formation of **27**.

3rd attempt

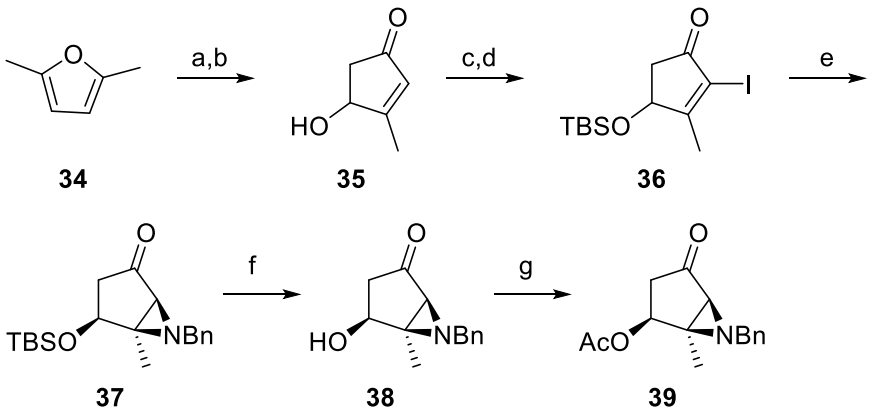
A new synthetic strategy for Trost intermediate **33** was designed, starting from a substrate with a methyl group in a different position (**Scheme 29**). While the simple allyl group would still be introduced by Michael addition, the substituted allyl group would be introduced by Claisen rearrangement and not by alkylation as initially planned.



Scheme 29 - synthetic strategy for Trost intermediate **33**.

Preparation of 3-methyl-4-hydroxy-cyclopentenone **35** has been described[27] starting from 2,5-dimethylfuran **34** (**Scheme 30**). The aziridination of **36** was less stereoselective when compared with previous substrates, a mixture

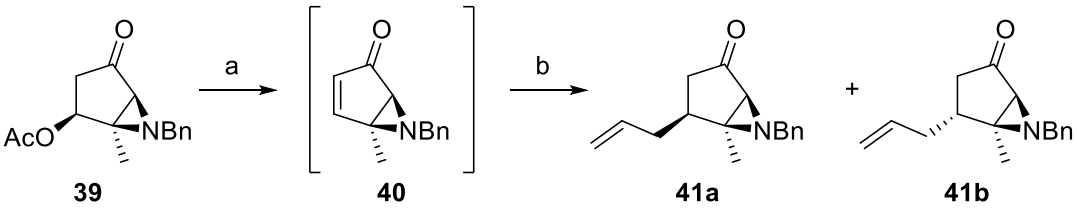
of 3:1 *cis*:*trans* was obtained whereas only one diastereoisomer is normally observed. However, a mixture of dichloromethane and toluene was used because the reaction was very slow in just toluene. We had previously observed with other substrates that, although the reaction is faster in dichloromethane, it is more selective in toluene. Further investigation of the right conditions for the aziridination of **36** for optimization of yield and selectivity is required. Further elaboration produced the desired compound **39**.



Scheme 30 - Synthesis of **39**.
Reaction conditions: a) m-CPBA, DCM, r.t., 30 min, 94%, b) Na_2CO_3, H_2O, reflux, 2h, 70%; c) TBSCl, DIPEA, DMAP (cat.), DCM, r.t., 16h, 55%; d) I_2, DMAP (cat.), Et_2O:Py 1:1, r.t., 16h, 80%; e) $BnNH_2$, Cs_2CO_3, 1,10-Phenanthroline, Toluene/DCM, r.t., 24h, 61% (28% trans); f) TBAF, THF, r.t., 30 min, 100%; g) Ac_2O, Et_3N, DCM, r.t., 16h, 91%.

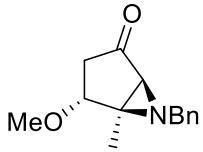
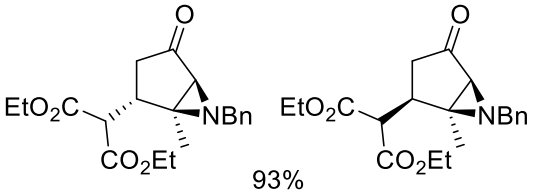
Treating **39** with a base generates α,β-unsaturated ketone **40** and further Michael addition of allylcuprate produced the expected product **41** (**Scheme 31**). However, no selectivity was observed and **41** was obtained as a 1:1 mixture of diastereomers in only 30% yield. The diastereomer of **41** obtained is not important for the planned strategy, as the aziridine chiral information is lost in its opening, but a good selectivity is essential. **Table 2** summarizes other conditions tried for the Michael addition. Maintaining the allylcuprate as reagent

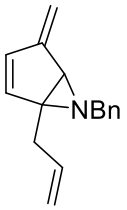
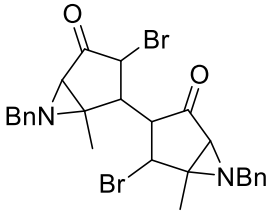
but using isolated **40** leads to a little improvement on the selectivity (6:4) but the yield was still low (34%). The use of other nucleophiles resulted in a much better selectivity (**42** and **43**). We tried to substitute lithium bromide with hexamethylphosphoramide (HMPA), but the allylcuprate was not formed and, instead of 1,4-addition, 1,2-addition occurred and **44** was formed (**Scheme 32**). We also tried to use allyltrimethylsilane instead of an organometallic reagent but the desired product **41** was not obtained.

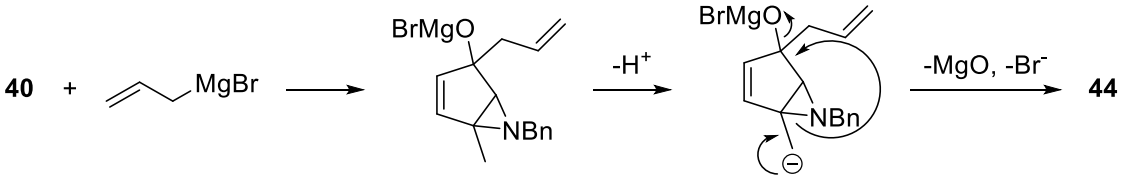


Scheme 31 - Formation of **41**.
Reaction conditions: a) DBU, THF, -20°C, 30 min; b) allylMgBr, CuI, LiBr, THF, -78°C, 30 min, 30% (d.r.=1:1 RMN).

Table 2 - Several Michael addition conditions.

initial	conditions	product
40	allylMgBr, CuI, LiBr, THF, -78°C	**41** 34% (d.r.=6:4, **a**:**b**)
39	K_2CO_3, MeOH, r.t.	 **42** (90%)
39	diethyl malonate, DBU, DCM, r.t.	 **43a** 93% d.r.=9:1, **a**:**b** **43b**

39	1) DBU, THF 2) allylMgBr, CuI, HMPA, THF, -78°C	 **44** 36%
39	1) DBU, THF 2) allylTMS, $MgBr_2.Et_2O$, -78°C	 **45** 16%
39	DBU, CsF, allylTMS, THF, r.t.	**40**
39	1) DBU, THF 2) allylTMS, $TiCl_4$	Complex mixture



Scheme 32 - Proposed mechanism for the formation of **44**.

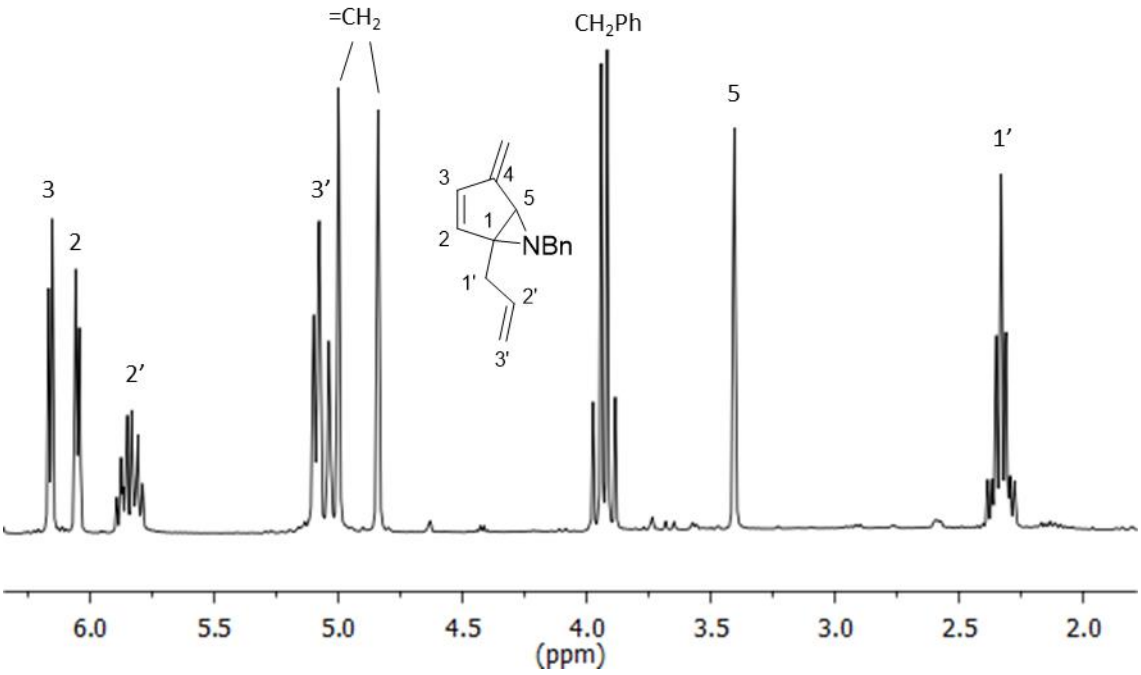


Figure 10 - Partial ^{1}H NMR spectrum of compound **44**.

From the ^{1}H NMR (**Figure 10**) it is possible to conclude that compound **44** contains unsaturations other than the allyl group. Signals at 6.2 and 6.1 ppm are consistent with the cyclopentene double bond. Also, signals at 5.0 and 4.8 indicate the presence of a methylene group, as by HMQC is possible to conclude both protons are bonded to the same carbon. Carbon 4 generates a signal at 155 ppm in the ^{13}C NMR spectrum and was possible to conclude by HMBC it is connected to the methylene group and carbons 3 and 5. A second quaternary carbon is also present at 80 ppm, which corresponds to carbon 1. By HMBC was possible to conclude it is connected to carbons 1', 2 and 5. By FTIR spectroscopy the absence of a carbonyl groups in this molecule is also evident, supporting the presented structure.

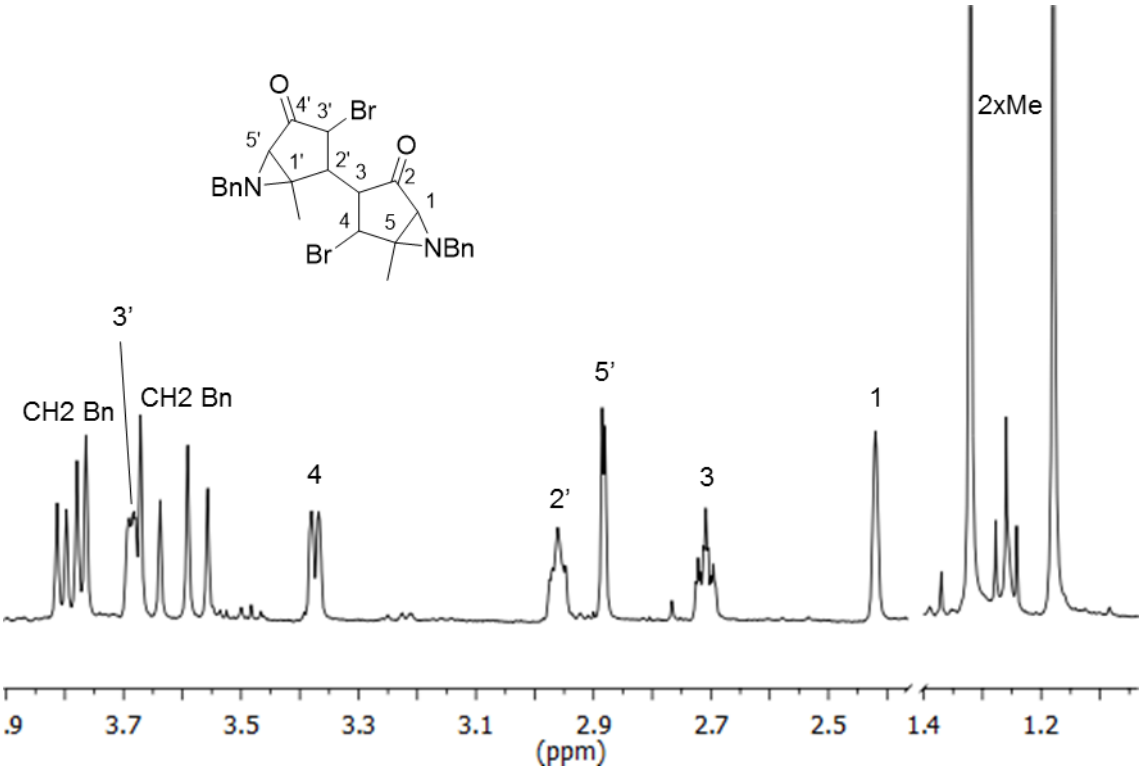
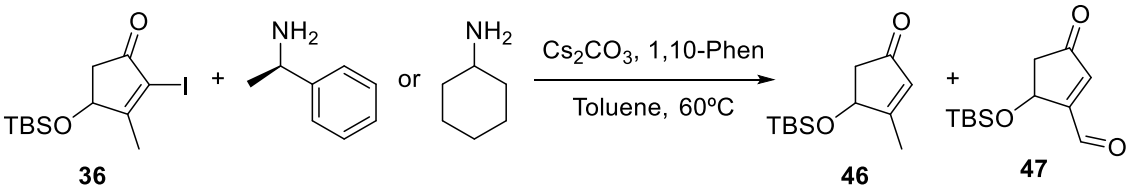


Figure 11 - Partial ^{1}H spectrum of compound **45**.

From the ^{1}H and ^{13}C NMR spectra of compound **45** (**Figure 11**) it is possible to understand it is the result of some type of dimerization of **40**, as it contains two signals of each moiety of the structure (e.g. Bn and Me). Analyzing COSY and HMQC experiments it was possible to conclude carbons 2' and 3 were bonded to each other. From the chemical shifts, we have hypothesized carbons 3' and 4' were connected to a bromine atom, what was consistent with chemical shift, but further mass spectrometry analysis is needed for confirmation.

The use of a bulkier group in the aziridine could be a strategy to improve the selectivity of the Michael addition. The aziridination was carried using methylbenzylamine and cyclohexylamine, however the expected aziridines were not observed. Instead, a disproportionation seems to take place, and **46** and **47** were isolated (**Scheme 33**).



Scheme 33 - Attempted aziridination of iodoenone 36.

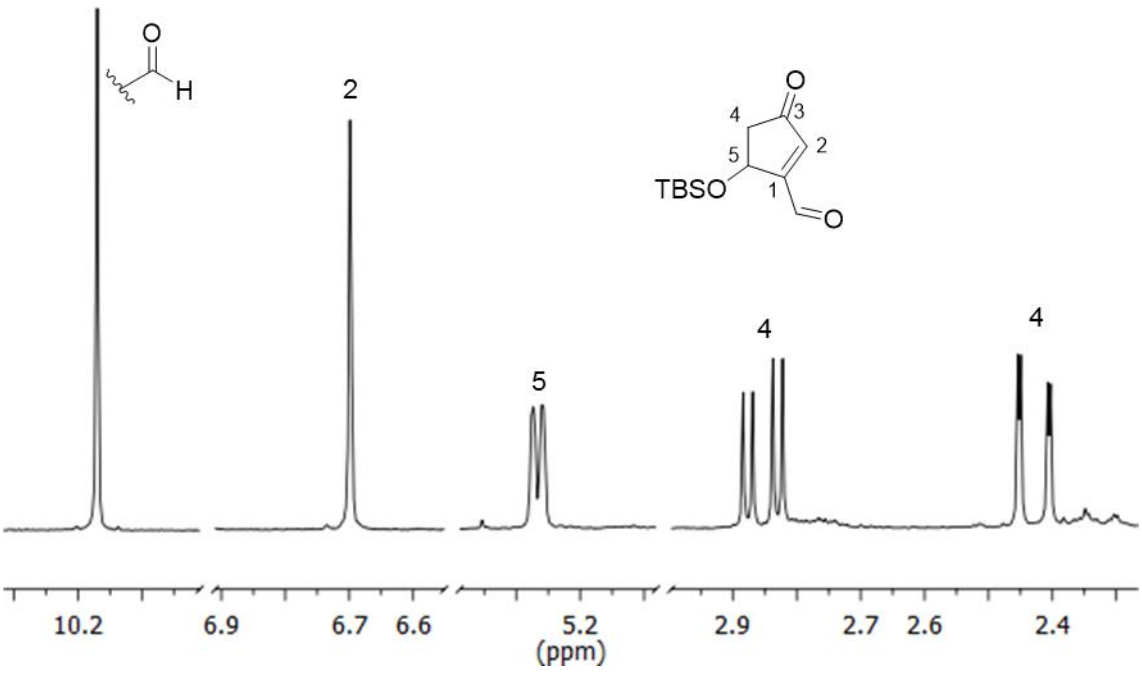


Figure 12 - Partial ^{1}H spectrum of compound **47**.

^{1}H spectrum of compound **47** (**Figure 12**) contains a signal at low field (10.2 ppm), which corresponds to an aldehyde group. The rest of the

spectroscopic data is consistent with the proposed structure and signals were assigned with the help of 2D NMR experiments.

Three of the steps of this route were not very efficient: TBS-protection, aziridination and Michael addition of the allyl group. Hence, this route was abandoned, as it was becoming much less efficient when compared to other described syntheses.

Aziridine invertomers

An interesting feature about aziridine **40** is that two species can be observed in both ^{1}H and ^{13}C NMR spectra, having the same type of signals but with different chemical shifts (**Figure 13**). It is unexpected as its structure cannot have diastereomers, therefore they must be conformers of the same molecule. The only part of the molecule flexible enough to have different conformations is the aziridine ring (**Figure 14**). Although invertomers of aziridines have already been described[28], we had never observed them for other compounds, not even for the very similar aziridines **25** and **9**. We decided to investigate deeper this effect by DFT calculations.

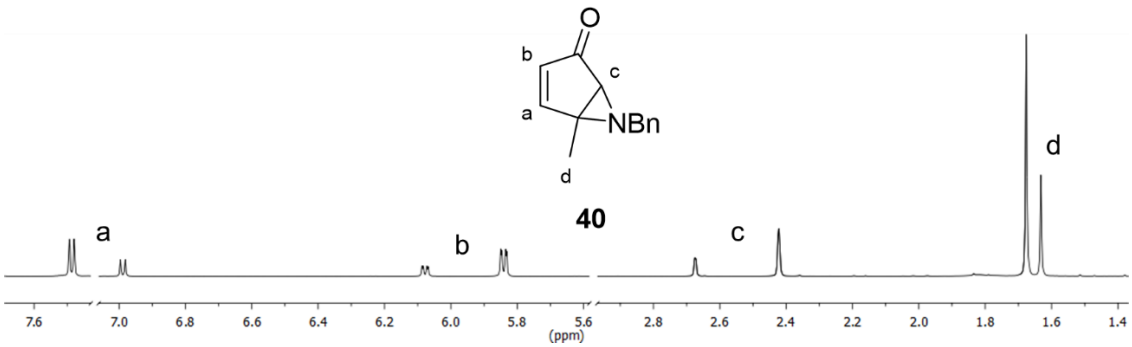
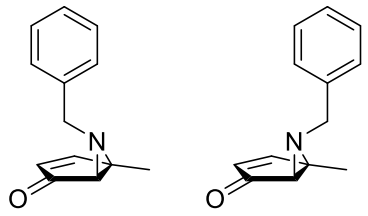


Figure 13 - Partial ^{1}H NMR spectrum of aziridine **40**.



***endo*-40** ***exo*-40**

Figure 14 - Invertomers (conformers) *endo* and *exo* of aziridine **40**.

The structures of both invertomers of **40** (**Figure 15**) and of the transition state between them were calculated along with their respective energies, using Gaussian 9. For the optimization of the structures the method/basis set used was PBE1PBE/6-311g** and to calculate the energy of the optimized structure MP2/6-311g**. For two species in equilibrium to be observed by NMR, the energy barrier between them should be in the range of 8-14 Kcal/mol. Hence, the calculated value of 18,4 Kcal/mol (**Graphic 2**) indicates that the observed species may be the invertomers. The calculated difference in energy 1,4 Kcal/mol corresponds to a ratio *endo* to *exo* of 9:1. The proportion, determined by integration of the ^{1}H NMR, of 7:3 is not very far from the predicted value. Unexpectedly the more stable structure was the *endo*-invertomer. Empirically,

due to steric effects, the expected more stable structure would be the *exo*, also in previous[12] X-ray structures of similar aziridines the *exo* structure was always obtained.

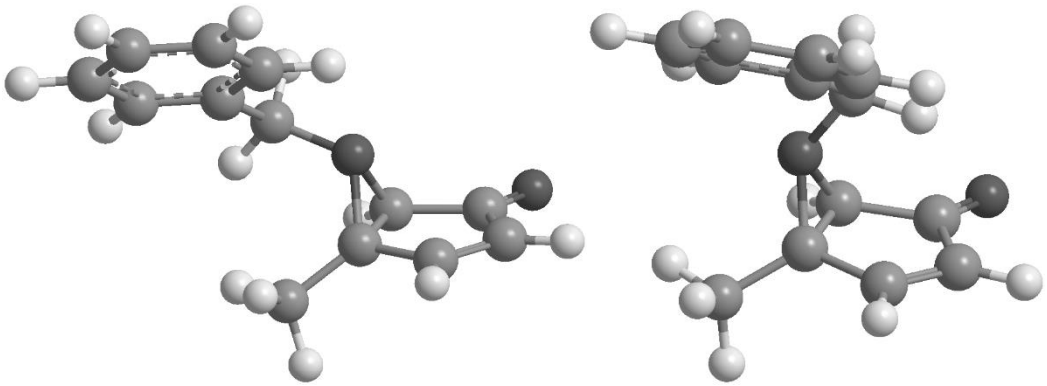
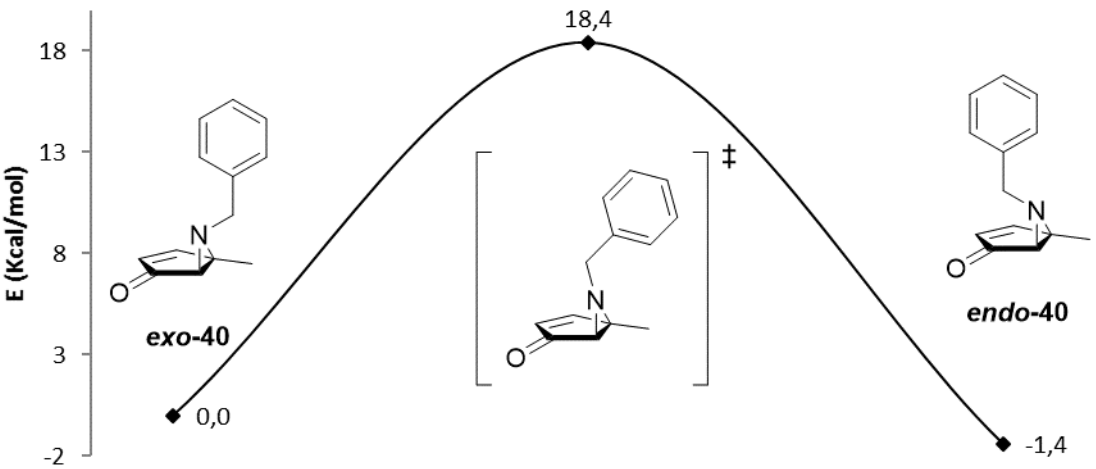


Figure 15 - Optimized structures of *exo*-**40** (left) and *endo*-**40** (right) (PBE1PBE/6-311g**).



Graphic 2 - Calculated Gibbs energies of the aziridines *endo*- and *exo*-**40** and the transition state (MP2/6-311g**).

These calculations are in accordance with the assumption that the species observed in the NMR spectra of **25** are invertomers, however, it appears that this effect has never been observed in similar compounds. To get a deeper understanding, the same calculations were also performed for different substrates (**Figure 16**), and the results are summarized in **Table 3**. The first interesting observation is that for compounds that do not contain the double bond or the methyl group (**9**, **48** and **50**) the *exo* structure is the more stable and not the *endo*, but not for the compound without the carbonyl group at position 2 (**49**). This indicates that the methyl group and the double bond was facilitating this effect, while the carbonyl seems to be irrelevant. Compared with **9**, the aziridine **40** nitrogen atom is pushed closer to the double bond by the methyl group. Due to this proximity, the repulsion between the lone pair of electrons of the nitrogen atom and the π electrons of the double bond is higher (**Figure 17**). Therefore, the *exo* structure of **40** is destabilized. The calculations were also carried out with other compounds (**51**-**53**) and it was possible to predict that the alkyl group at the nitrogen (**51**) and at position 5 (**52**) do not significantly change the difference in energy of *exo* and *endo*, but a second alkyl group at position 1 (**53**) greatly increases this difference.

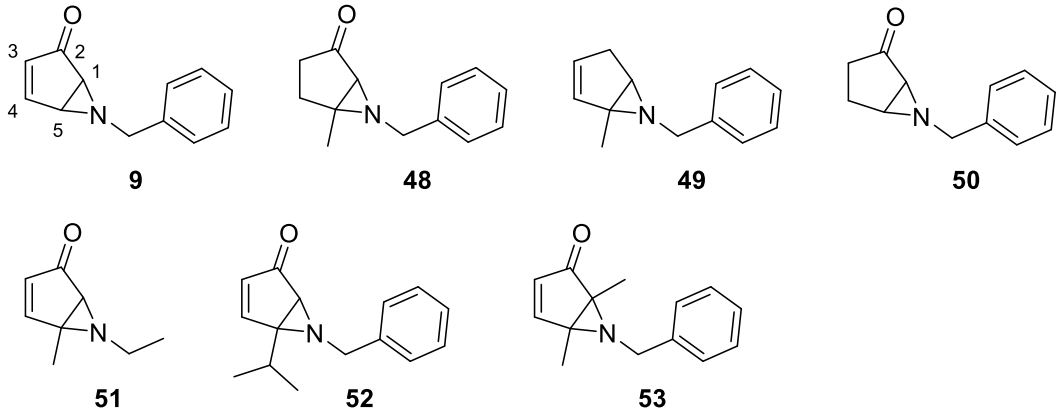


Figure 16 - Structures of the compounds **9** and **48-53**.

Table 3 - Calculated values of $\Delta G^{\ddagger}$ and ΔG(exo - endo) for compounds **9**, **40** and **48-53**.

compound	**$\Delta G^{\ddagger}$** (Kcal/mol)	**ΔG(*exo* - *endo*)** (Kcal/mol)
40	18.4	1.4
9	20.2	-0.8
48	17.2	-1.7
49	18.4	2.2
50	18.7	-4.1
51	17.2	1.8
52	18.1	1.8
53	17.3	4.0

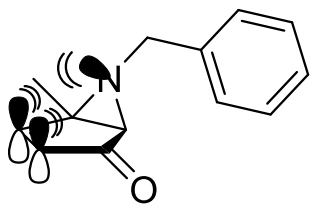


Figure 17 - Illustration of the repulsion between the lone pair of electrons of the nitrogen and the π electrons of the double bond in **exo-40**.

From these results, we deduced that in similar aziridines previously prepared the *endo*- invertomer was much less stable than the *exo*- and thus had never been observed. In the case of aziridine **40**, the *endo* invertomer is destabilized by electronic repulsion forces and the *exo* could be observed by NMR.

Conclusion

The initial goal of developing a new synthetic route for terpestacin was not achieved, as the three designed strategies were not successful. However, several aziridines were prepared, which may be interesting intermediates for the synthesis of other products of interest. It is also interesting to observe how little changes in a molecule, such as the introduction of a methyl group, can change its reactivity completely. Finally, for the first time we have observed aziridine invertomers and their equilibrium was studied by DFT calculation

Chapter 4

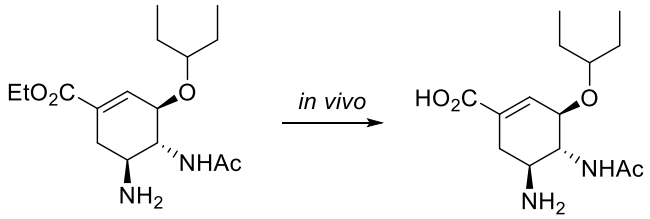
Oseltamivir and tamiphosphor syntheses

Abstract

A new method for the synthesis of the influenza antiviral drugs oseltamivir and tamiphosphor was developed. A chiral aziridine produced by the enzymic method described in the chapter 1 was used as starting material. Its conversion to oseltamivir and tamiphosphor diethyl ester in 10 or 12 additional steps and 22% or 19% yield, respectively, is described. An attempt to synthesize a sulfonate analogue is also described.

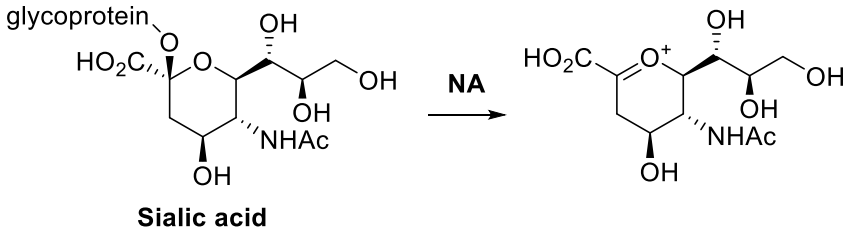
Introduction

Influenza is still a considerable threat to human health. New strains of the virus continue to appear, in some cases turning into deadly global pandemics (e.g. H1N1 2009). The most common treatment for these infections is oseltamivir[29] administration. This drug is commercialized by Roche under the name Tamiflu®, as a phosphate salt. It is a prodrug hydrolyzed *in vivo* to the corresponding acid (**Scheme 34**). This species is a potent inhibitor of influenza neuraminidase (NA), because it is structurally similar to NA natural substrate, a sialic acid (**Scheme 35**). During infection, influenza virus recognizes sialic acid present on glycoproteins on host cell surface and after removing it infects the cell. When administrated, oseltamivir acts by preventing new cells of an infected patient from being infected.



Osetalmivir

Scheme 34 – Oseltamivir *in vivo* hydrolysis.

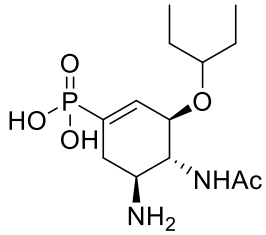


Scheme 35 – Influenza Neuraminidase (NA) activity.

After its discovery, oseltamivir became an important target for synthetic chemists and a great number of syntheses have been developed by Roche and others[30]. In 2009, during the H1N1 pandemic, Tamiflu was the only effective treatment against the virus. This event turned even more the attention of chemists toward oseltamivir and new syntheses continued to be reported[31]. An important factor in any synthesis is control of the relative stereochemistry of the required product. More recently an efficient oseltamivir synthetic methodology comprising an asymmetric Michael addition[32], based on the Hayashi[31a] route has been reported. Notably Hayashi and co-workers have reported a time-efficient one-pot methodology for the production of oseltamivir.[33]

Fang et al.[30k] developed a strategy to produce a new phosphorus analogue he called tamiphosphor. Tamiphosphor has a phosphonate group instead of the carboxylate and it has been shown to be more potent than oseltamivir. Further studies[34] demonstrated that tamiphosphor was active against oseltamivir resistant strains of influenza virus, however poor bioavailability was a problem. In a recent paper[35], in which Fang describes an improvement on the first synthesis, the importance of tamiphosphor was highlighted. Besides this synthetic route there is only one reported alternative[36],

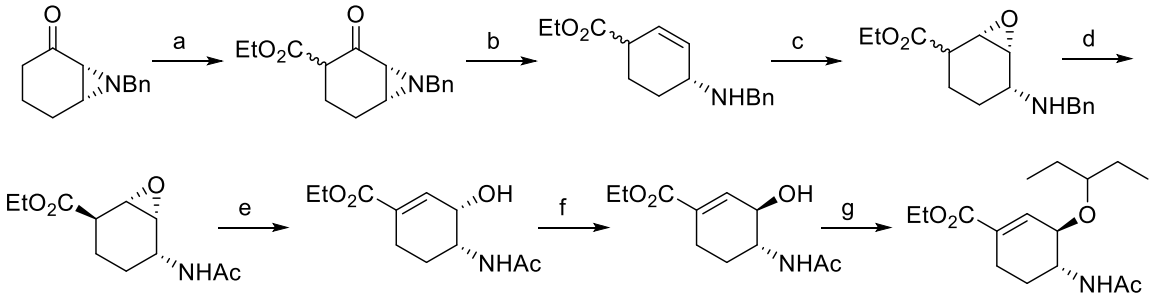
also described by Fang, and a method[31j] to convert oseltamivir into tamiphosphor.



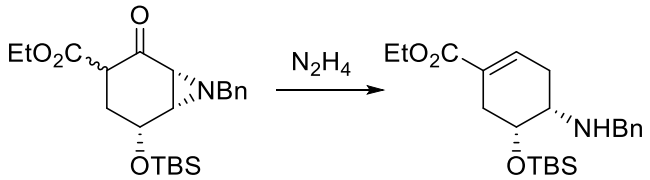
tamiphosphor

Figure 18 - Tamiphosphor structure.

Previously we had developed a synthesis of an oseltamivir analogue (**Scheme 36**) based on the aza-Wharton reaction.[37] This synthesis was a model for the development of a new synthetic route to oseltamivir, however it failed with a more substituted substrate (**Scheme 37**). During aza-Wharton reaction a double bond migration occurred forming an undesired α,β-unsaturated ester. The 5-OTBS analogue seems to significantly change reactivity of the molecule and the outcome of the reactions, probably by imposing different conformational strains on the cyclohexane ring. Thus, we decided to design a new strategy, this time using the required hydroxylated starting material and not a simpler model.

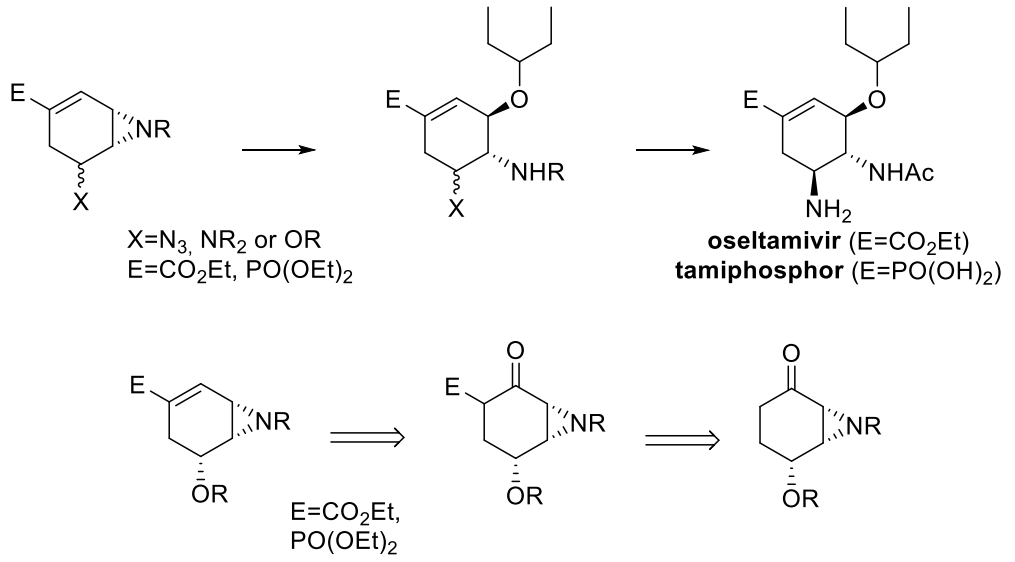


Scheme 36 – Synthesis of an oseltamivir analogue based upon an aza-Wharton reaction. Reaction conditions: a) LDA, EtOCOCN, THF, -78ºC 1h (77%); b) $N_2H_4.H_2O$; AcOH, MeOH, r.t. 15h (61%); c) CF_3CO_2H, CF_3CO_3H, CH_2Cl_2, r.t. 30 min (87%); d) H_2, Pd(C), THF, AcOH, 4h; Ac_2O, Py, r.t. 30 min (61%); e) K_2CO_3, EtOH, r.t. 4h (100%); f) DIAD, PPh_3, p-nitrobenzoic acid, THF, 0ºC 20 min; K_2CO_3, EtOH, r.t. 30 min. (87%); g) $CCl_3C(NH)OCHEt_2$, TfOH, CH_2Cl_2, r.t. 24h (20%).



Scheme 37 - Aza-Wharton reaction/double bond migration.

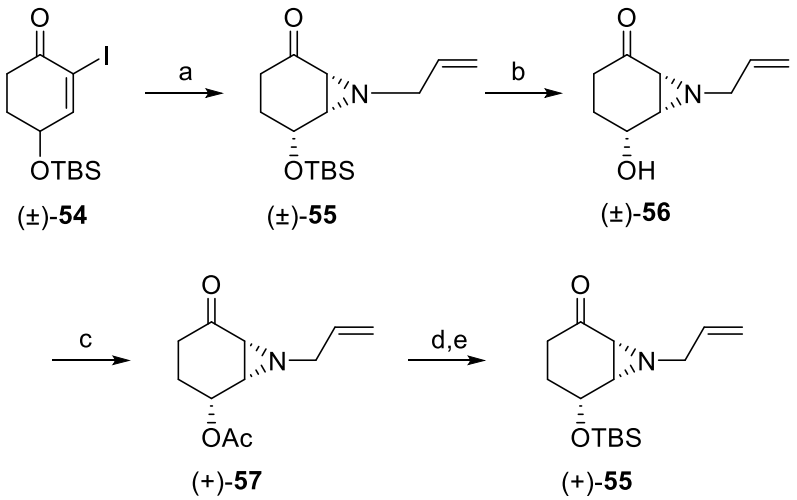
A considerable number of the recorded synthetic routes to oseltamivir use an aziridine as intermediate that can be opened with 3-pentanol producing a *trans*-α-hydroxyamine (**Scheme 38**). For this work, we designed a synthetic plan to produce this intermediate aziridine from one of the 4-hydroxyacylaziridines described in the chapter 2. Thus, we expected to develop a new versatile and concise synthesis to oseltamivir, tamiphosphor and other analogues.



Scheme 38 - Plan for the synthesis of oseltamivir and tamiphosphor.

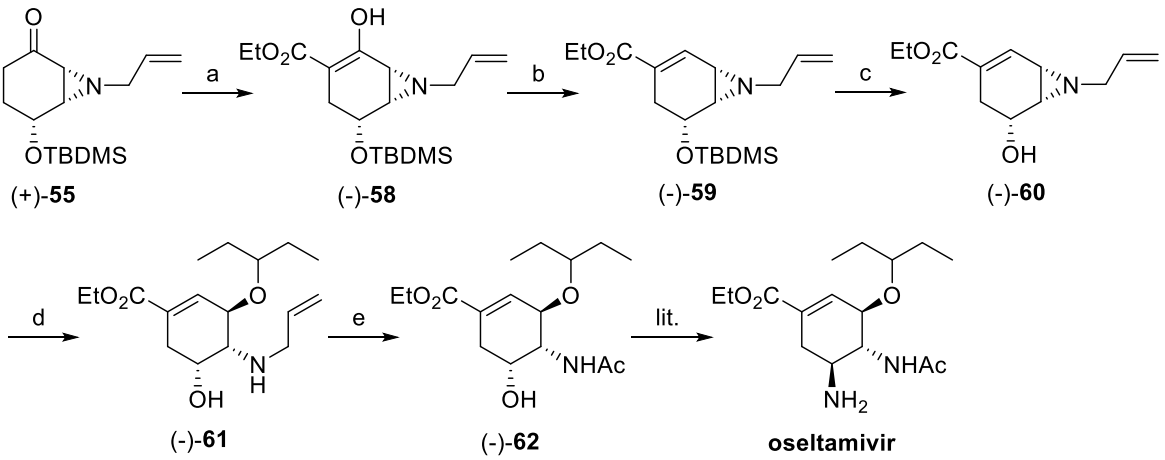
Oseltamivir synthesis

Optically active aziridine **55** was prepared using the methodology described in chapter 2 (**Scheme 39**). We opted to change the alkyl group in the aziridine from benzyl to allyl, because removal of benzyl group by hydrogenolysis could be a problem in the presence of the double bond. In chapter 2 all resolutions were carried on a small scale (50 mg), 1.4 grams of aziridine **56** were resolved maintaining the excellent yields and e.e., thus demonstrating the scope of this methodology and its ability to be scaled-up. A TBS group had to be introduced using DBU as base, because the reaction of **56** using DIPEA and DMAP as base resulted only in the recovery of starting material. The use of more reactive reagents such as imidazole and/or TBSOTf, resulted in degradation of the aziridine **56**.



Scheme 39 - Synthesis of aziridine (+)-**55**.
Reagents and conditions: a) Allylamine, Cs_2CO_3, 1,10-Phenantroline, Toluene, r.t., 4h, 88%; b) TBAF, THF, r.t., 30 min, 100%; c). Novozym 435, vinyl acetate, DIPE, r.t., 4h, 49%, e.e.>99%; d) K_2CO_3 (cat.), MeOH, r.t., 99%; e) TBSCl, DBU, DCM, r.t., 1h, 95%.

The ethoxycarbonyl group was introduced successfully by acylation of the lithium enolate of **55** affording β-ketoester **58** (80% yield) as a mixture of two diastereoisomers in equilibrium with the respective enol (**Scheme 40**). Subsequent one-pot reduction, mesylation and elimination produced **59** ($[\propto]_D^{20^\circ C}$= -70 (c= 0.7; DCM)), however the yield (50%) was not good but represents a three-step transformation. In the first step, the reduction of the ketone carbonyl, four different diastereoisomers were formed. Although all of these diastereoisomers converge to the same final product each of them seems to have a different reactivity with methanesulfonyl chloride and the resulting methanesulfonates also having different rates of elimination.



Scheme 40 - Synthesis of oseltamivir.

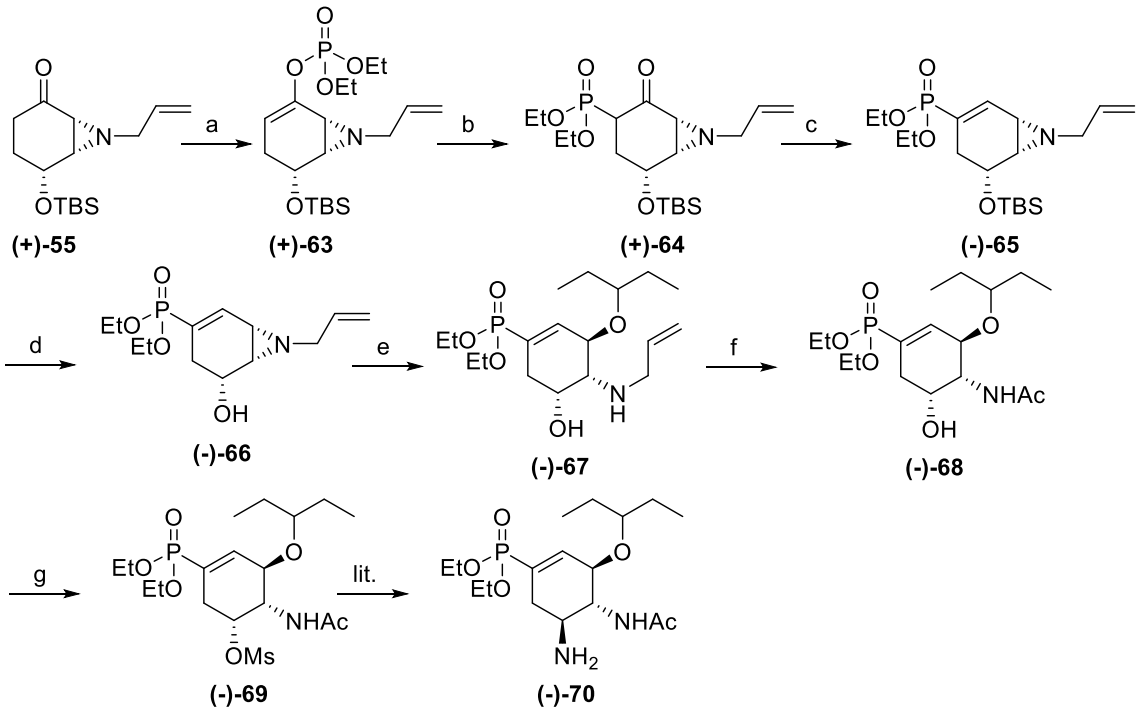
Reagents and conditions: a) EtOCOCN, LDA, THF, -78°C, 1h, 80%; b) 1. $NaBH_4$, EtOH, 0°C, 1h; 2. MsCl, Py, r.t, 1h; 3. K_2CO_3, EtOH, r.t., 1h, 50% (3 steps); c) TBAF, THF, r.t., 1h, 100%; d) $BF_3.Et_2O$, 3-pentanol, 70°C, 30 min, 90%; e) 1. thiosalicylic acid, $Pd(dba)_2$/DPPB (cat.), THF, 60°C, 30 min; 2. Ac_2O, Py, r.t., 15 min, 83%.

Opening of the aziridine **60** with 3-pentanol was accomplished by Lewis acid catalysis (90% yield). A palladium catalyst in the presence of thiosalicylic acid was used for the removal of the allyl group **61**[38] followed by acetylation of the product without isolation of the intermediate amine afforded **62** ($[\propto]_D^{20^\circ C}$= -100 (c=1.7; AcOEt); lit[39]: $[\propto]_D^{25^\circ C}$= -104 (c=3.0; AcOEt)) in a good yield (83%). Its transformation into oseltamivir has already been described.[31f]

Tamiphosphor synthesis

A similar strategy was used for the synthesis of the diethyl ester of tamiphosphor **70** (**Scheme 41**). The enol phosphate **63** (87% yield, $[\propto]_D^{20^\circ C}$= +45 (c=1.1; DCM)), was obtained by reacting the enolate of ketone **55** with diethyl cyanophosphonate and the required phosphonate **64** was generated (91% yield) by subsequent treatment with a strong base.[40] As in the case of ketoester **58**, phosphonate **64** was present in three forms and phosphorous coupling with

adjacent protons and carbon atoms was evident in the respective NMR spectra (**Figure 19**).



Scheme 41 - Synthesis of tamiphosphor diethyl phosphonate **70**.

Reagents and conditions: a) $(EtO)_2POCN$, LDA, THF, -78°C, 1h, 87%; b) LDA, THF, -78°C, 30 min, 91%; c) 1. $NaBH_4$, EtOH, -78°C, 1h; 2. MsCl, Et_3N, DCM, r.t, 3h; 3. DBU, DCM, r.t., 1h 47%; d) TBAF, THF, r.t., 1h, 100%; e) $BF_3.Et_2O$, 3-pentanol, 70°C, 30 min, 100%; f) 1. 1,3-dimethylbarbituric acid, $Pd(dba)_2$/DPPB (cat.), THF, 60°C, 30 min; 2. Ac_2O, Et_3N, r.t., 1 h; 3. K_2CO_3, EtOH, 70%; g) MsCl, Et_3N, DCM, r.t., 1h, 99%.

By lowering the temperature of the borohydride reduction of **64** from 0°C to -78°C the global yield of **65** increased from 28 to 47%. In our opinion, the yield increased due to a higher selectivity during the reduction. As before, four diastereoisomers were formed in this step, each one having a different reactivity. Hence the global yield could be higher if the diastereoisomer or diastereoisomers more suitable for mesylation/elimination are formed in a larger quantity. The use of K-selectride, a more hindered reducing agent, was tested, however only

ketophosphonate **64** was recovered. For the elimination step 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), a stronger homogeneous base had to be used instead of potassium carbonate. This was expected since the proton α to a phosphonate ester is less acidic than that α to a carboxylate ester.

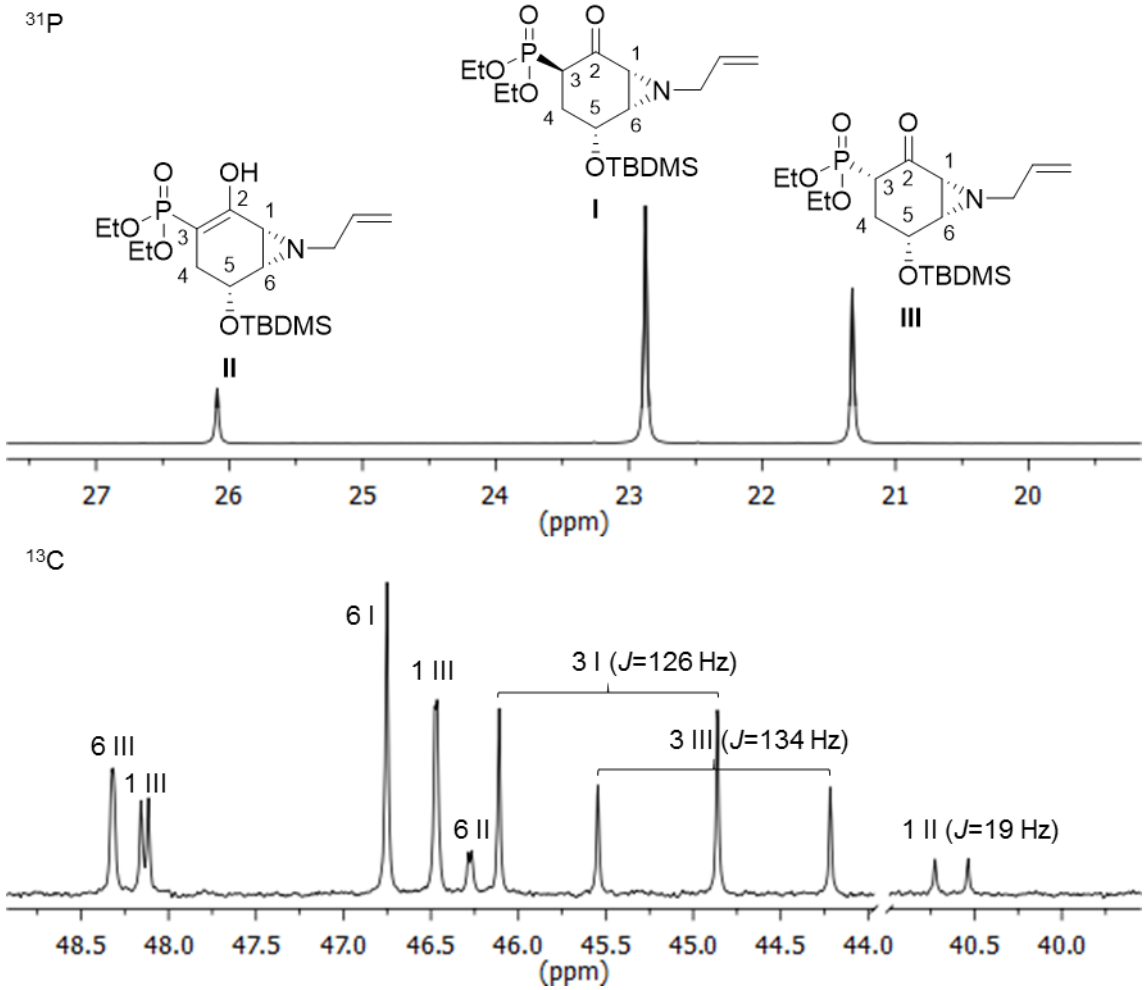


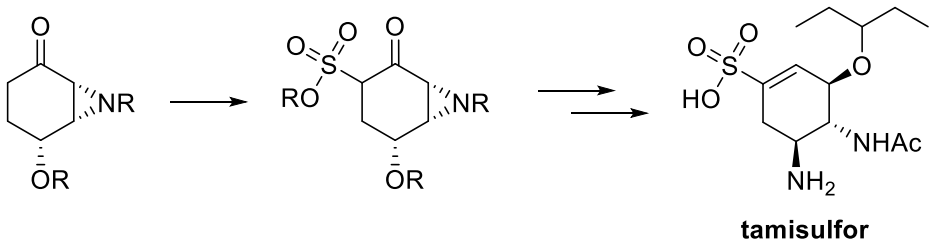
Figure 19 - Partial ^{13}C and ^{31}P spectrum of compound **64**.

Some alterations were made in the deprotection/acetylation of allylamine **67** to form acetamide **68** (77% yield). 1,3-Dimethylbarbituric acid was used instead of thiosalicylic acid because during chromatographic purification the latter co-eluted with product **68**. Also, selective acetylation of the amine was

not possible, so an additional hydrolysis of the acetate ester, also formed, had to be carried out. The conversion of mesylate **69** ($[\propto]_D^{20°C}$= -110 (c=1.2; AcOEt); lit[35]: $[\propto]_D^{22°C}$= -102.5 (c=0.4; AcOEt)) into tamiphosphor diethyl ester **70** and subsequent conversion into tamiphosphor has already been described[35].

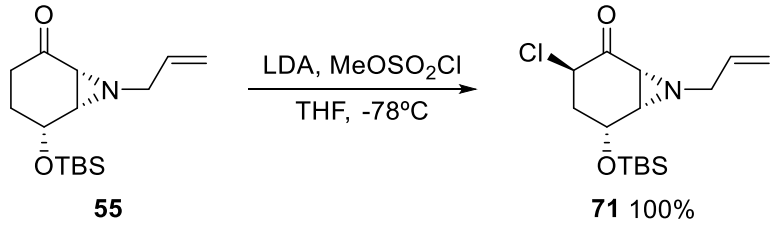
Tamisulfur

As in the case of tamiphosphor, where the substitution of the carboxylate group by a phosphonate group rendered a more potent analogue, a sulfonate group could also act as a bioisoster. The new target became the sulfonate analogue of oseltamivir, which we called tamisulfur (**Scheme 42**).



Scheme 42 - Synthetic plan to tamisulfor.

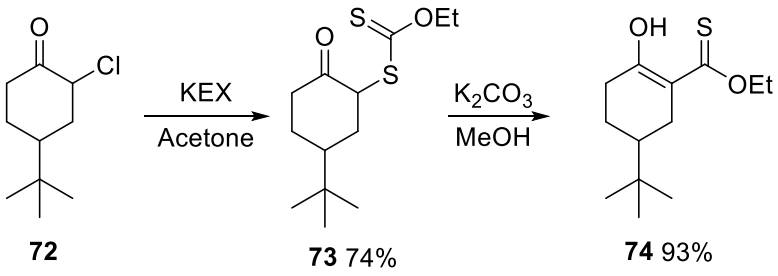
Initial plans involved the direct inclusion of a sulfonate group by reacting the lithium enolate of aziridine **55** with methyl chlorosulfate. However, the product of this reaction was the chloroketone **71** in quantitative yield (**Scheme 43**). This type of chlorination had already been described using tosyl chloride.[41] This was a very efficient alfa-chlorination method and was thus further studied, the results are presented in the next chapter.



55 **71** 100%

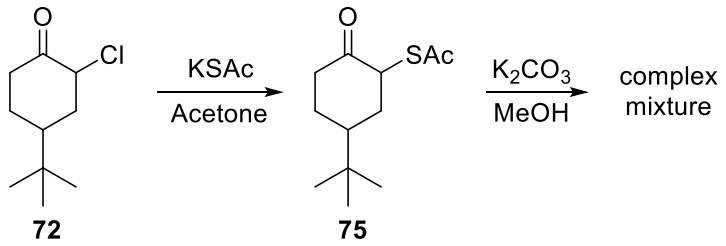
Scheme 43 - Reaction of lithium enolate of **55** with methyl chlorosulfate.

Since the direct introduction of the sulfonate group did not occur, an alternative strategy could involve the substitution of the chlorine atom by a thio group, which could then be further oxidized. To develop this approach, we used 4-(*tert*-butyl)-2-chlorocyclohexanone **72** as a model. Chloride displacement with potassium ethyl xanthate (KEX) produced **73** in 74% yield (**Scheme 44**). Basic hydrolysis of **73**, using potassium carbonate in methanol did not generate the respective thiol, instead thionoester **74** was formed in 93% yield. This type of sulfur abstraction process is known[42] and was also further studied and the results are presented in the next chapters. Thioacetate **75** was prepared also by chloride displacement (**Scheme 45**). Further hydrolysis produced a complex mixture, although the thiol may have been formed, it is probably very reactive and formed other products.



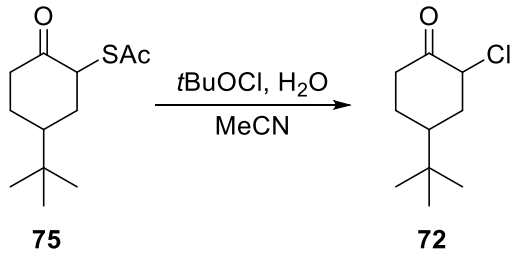
72 **73** 74% **74** 93%

Scheme 44 - Xanthate **73** preparation and conversion into thionoester **74**.

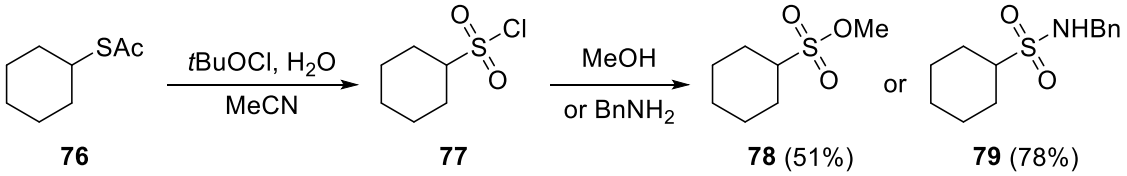


Scheme 45 - Thioacetate **75** preparation and hydrolysis.

Since thiol preparation seemed to be a difficult task, we decided to oxidize thioacetate **75** directly (**Scheme 46**). We opted to use tertbutylhypochlorite[43] as oxidizing reagent, but surprisingly the chloroketone **72** was obtained. To check if the carbonyl has any influence, cyclohexyl thioacetate **76** was also oxidized under the same conditions (**Scheme 47**). The oxidation occurred and methyl sulfonate **78** (51%) and benzyl sulfonamide **79** (78%) were obtained without isolating chlorosulfonate **77**. Indeed the carbonyl group has an influence, 2-oxocycloakanesulfunyl chlorides **80** are known to rearrange spontaneously to form the respective chlorides **81** (**Scheme 48**).[44]

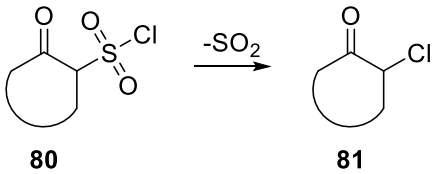


Scheme 46 - oxidation of thioacetate **75**.



76 **77** **78** (51%) **79** (78%)

Scheme 47 - Oxidation of cyclohexyl thioacetate **76.**



80 **81**

Scheme 48 - Spontaneous conversion of 2-oxocycloalkanesulfonylchlorides into 2-chlorocycloalkanones.

Unable to develop a strategy to introduce the sulfonate group in aziridine **55**, the synthesis of tamisulfor was abandoned. Nevertheless, the α-chlorination of ketones and the sulfur abstraction of α-xanthyl ketones appeared to be interesting subjects for further study and the results of this are presented in the next chapters.

Conclusion

A new versatile synthesis of the anti-influenza drugs oseltamivir and tamiphosphor was developed. The early formation of an aziridine moiety is a key step, not used in previous syntheses. Also, the resolution of intermediate **55** constitutes an efficient asymmetric approach, with almost quantitative yield and very high enantiomeric excess. Its conversion into oseltamivir was achieved in 10 steps and 22% yield and into tamiphosphor diethyl phosphonate in 12 steps and 19% yield. Work to find the optimum conditions for the reduction/mesylation/ elimination step is required to improve the global yield of the synthesis. To this end some studies were carried out in an attempt to increase the selectivity of the reduction. An expedient asymmetric route for the synthesis of the key

intermediate (*R*)-4-hydroxyxyclohexenone would also render a more efficient process. Nevertheless, the development of a notable strategy for the asymmetric synthesis of two small but highly functionalized molecules of some economic importance was achieved.

Chapter 5

Alpha-chlorination of carbonyls under basic conditions using methyl chlorosulfate

Abstract

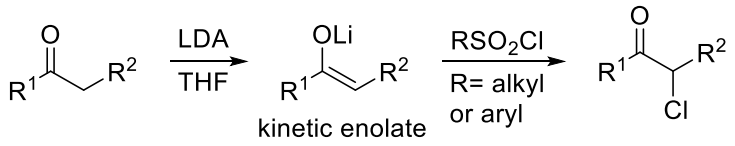
Methyl chlorosulfate is described for the first time as an electrophilic chlorine source. An efficient method for the α-chlorination of ketones under basic conditions using methyl chlorosulfate is described. Its applicability for the chlorination of other functional groups have been studied and is equally useful for the synthesis of α-chloroesters and amides. Aldol and Claisen condensation reactions that occur during the chlorination of some substrates were also studied.

Introduction

Halogenation of the alpha position of carbonyl containing compounds is a classical method for the introduction of several functional groups in organic chemistry. It is widely used in synthesis both in academia and in industry, and is particularly useful in heterocycle generation.[45] New methods for the halogenation of carbonylic compounds are still being developed[46], as the search for more efficient, selective, economical or greener solutions that are essential for improved industrial processes. While the use of acid catalyzed methods has been extensively explored, basic methods have been less studied since polyhalogenation can be difficult to avoid.

Brummond and Gesenberg[41] described the chlorination of the lithium enolates of ketones using chlorosulfonates as chlorinating reagents (**Scheme 49**). It constitutes a good alternative for the chlorination of acid sensitive molecules and/or selective chlorination at the more acidic carbon atom. This strategy has been used with tosyl, benzenesulfonyl, mesyl and triflyl chlorides.[47] It is a very useful method but there is still space for reaction yield improvement since one of the problems involves the purification of the product having reagent-derived

contaminants. In our experience, the chromatographic purification of this type of compound leads to the loss of product as they degrade by several processes. Hence the development of cleaner methods without the need for purification would lead to improved yields.

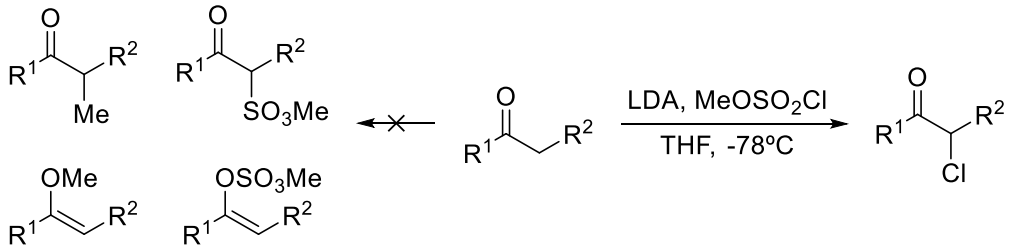


Scheme 49 - Chlorination of a ketone lithium enolate with alkyl and arylsulfonyl chlorides.

In this chapter, we report the use of methyl chlorosulfate as an improved chlorinating reagent for ketones under basic conditions. Its use in the chlorination of other functional groups was also studied. To our knowledge this is the first report of the use of an alkyl chlorosulfate for chlorination.

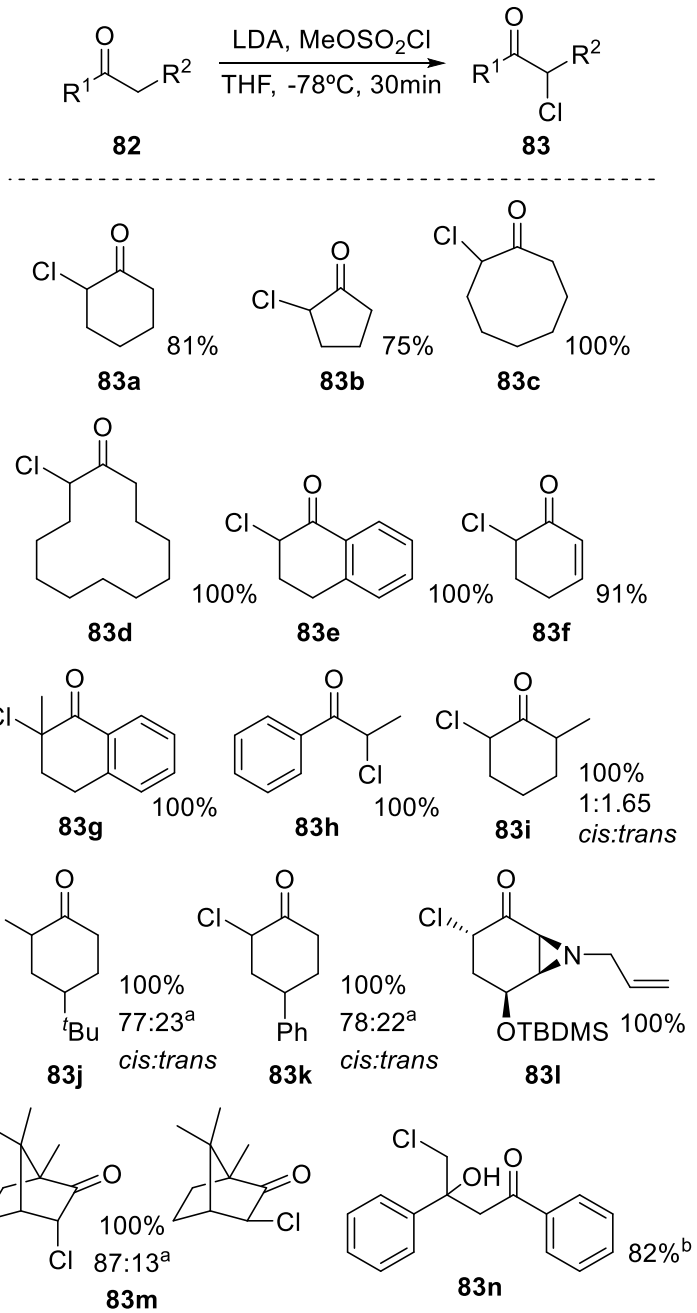
Preparation of α-chloroketones

Methyl chlorosulfate can be readily prepared[48] by reacting methanol with sulfuryl chloride and has been used as a sulfating[49] and methylating[50] reagent. Its reaction with camphor is described[51] as producing methyl camphor-3-sulfonate under neutral conditions. Consequently, it would be expected that the reaction of ketones with methyl chlorosulfate under basic conditions would form the respective methyl α-sulfonates, however we found that the α-chloroketones are formed instead (**Scheme 50**), as reported in the previous chapter. This transformation was not completely predictable because, unlike chlorosulfonates, alkyl chlorosulfates have never been described as an electrophilic chlorine source.



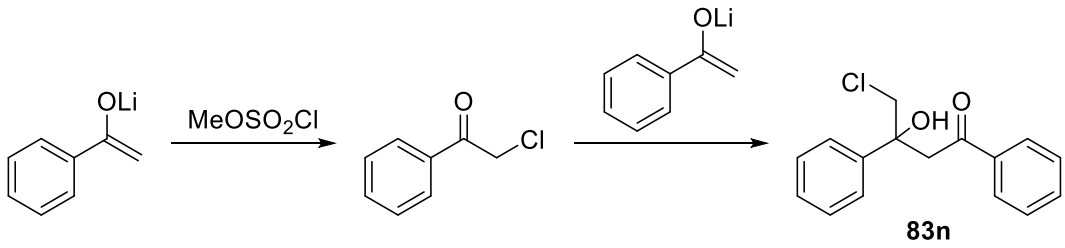
Scheme 50 - Reaction of ketones with methyl chlorosulfate under basic conditions and possible sulfated and methylated products.

A range of ketones was submitted to the chlorination conditions (**Scheme 51**), and the products were always obtained in quantitative yields with exception of some small volatile molecules (**83a**, **83b** and **83f**). It is a relatively clean reaction and there was normally no need for further purification after work-up. Preparation of **83f** had already been described by Brummond and Gesenberg[41] with tosyl chloride, it is the only reported route to these compounds, since other chlorination methods resulted in the chlorination of carbon 2 instead of 6. The reaction worked very well with a tertiary ketone and **83g** was formed in quantitative yield, containing a quaternary carbon. Chlorination of 1-methylcyclohexanone was regioselective, as expected, and only the product (**83i**) from reaction of the kinetic enolate was obtained. The chlorination of the highly functionalized ketone **82l** (**55**) has already been reported in the previous chapter and this result shows the versatility of this method for molecules having reactive functional groups. The aziridine ring is very sensitive to acidic conditions and it would probably be difficult to perform this transformation using classical methods. The stereoselectivity obtained for **83l** is also interesting, as it was obtained as a single diastereomer while other asymmetric substrates (**83i-k** and **83m**) were obtained as mixtures. Contrary to previous reports for neutral conditions[51], reaction with camphor resulted in the chlorination products **83m**.



Scheme 51 - Results of α-chlorination of ketones.
[a] Diastereomeric ratio calculated by ^{1}H NMR. [b] yield after chromatographic purification.

The method was applied to acetophenone and **83n** was obtained as the major product. Initially chlorination of acetophenone occurs but then addition of acetophenone lithium enolate to the formed 2-chloroacetophenone apparently occurs faster than the chlorination (**Scheme 52**). Methyl ketones seems to be a substrate limitation of this method. This limitation was observed by Brummond and Gesenberg[41] but only decomposition of the starting material was reported. The chlorine atom seems to have an important role in the aldol reaction as it occurs only in poor yield with acetophenone (**Table 7**). This is predictable since the carbonyl of the chloroacetophenone is more electrophilic and the alkoxide of **83n** more stable. **83n** chloride intramolecular substitution with subsequent formation of an epoxide would be expected, however it has not been observed under the reaction conditions.



Scheme 52 - Formation of **83n** by addition of acetophenone lithium enolate with 2-chloroacetophenone.

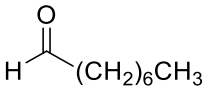
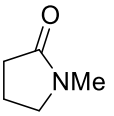
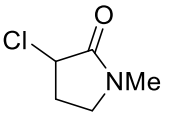
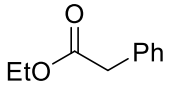
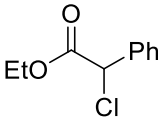
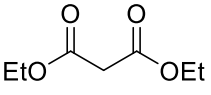
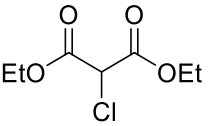
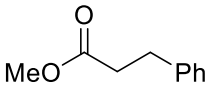
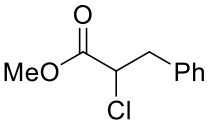
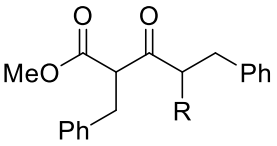
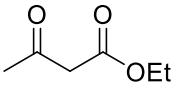
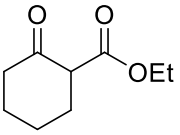
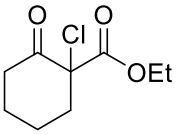
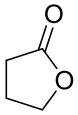
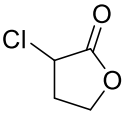
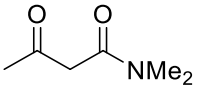
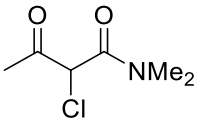
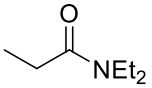
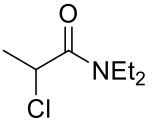
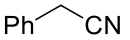
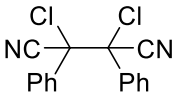
Chlorination of substrates containing different functional groups

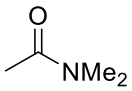
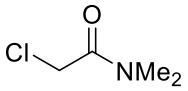
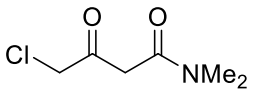
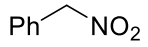
Other substrates have been subjected to the same conditions (**Table 4**). Aldehyde **84a** and nitro compound **84m** apparently didn't react and all the starting material was recovered. Some esters have also been tested (**84b-d**), in the case of esters **84b** and **84d** the reaction took place but it was not complete and some starting material was recovered. More equivalents of base and reagent were used in an attempt to increase the conversion of **84b** but no difference was

observed. This limitation is probably due to the higher acidity of chloroester **85b** compared to the respective ester **85b**, the proton exchange being faster than the chlorination. For the less hindered ester **84c** Claisen condensation products were formed, as in the case of methyl ketone **82n**. Amides were also tested (**84d-f**) and chloroamides **85e** and **85g** were produced in good yield. In the case of less hindered amide **84f** Claisen condensation product **86k** was the main product obtained. The chlorination of 1,3-dicarbonyl compounds (**84h-k**) resulted in low conversions (14-66%) and in the case of ethyl acetoacetate **84i** no reaction occurred at all.

Applying the same conditions to benzylnitrile (phenylacetonitrile) **84l**, product **85l** and starting material were obtained as major products. Using two equivalents of base and methyl chlorosulfate lead to complete conversion of **84l** and a higher yield of **85l**. By ^{1}H and ^{13}C NMR is only possible to detect a phenyl group and a quaternary carbon, however the signals have different chemical shifts than the ones described for dichlorobenzylnitrile, the expected product. By mass spectrometry (EI-B) was not possible to detect the molecular ion, only a fragment with half of the mass (m/z=150.0114). We believe **85l** has the presented structure because the chemical shift of the quaternary carbon (68.2 ppm) is that expected and its formation had already been reported during chlorination of **84l** using thionyl chloride under acid conditions.[52] It is interesting to note that formation of **85l** was stereoselective and only one diastereomer was obtained.

Table 4 - Chlorination of different functional groups.

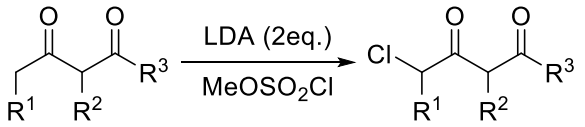
substrate	product	substrate	product
 **84a**	No reaction (only SM recovered).	 **84g**	 **85g** 80%
 **84b**	 **85b** 92% (8% SM)	 **84h**	 **85h** 66% (34% SM)
 **84c**	 **85c** 36%[a]  R=Cl **85c'** 30%[a] R=H **85c''** 17%[a]	 **84i**	No reaction (only SM recovered).
		 **84j**	 **85j** 14% (86% SM)
 **84d**	 **85d** 85% (15% SM)	 **84k**	 **85k** 48% (48% SM)
 **84e**	 **85e** 100%	 **84l**	 **85l** 66%[a,b]

 **84f**	 **85f** 16%  **86k** 83%	 **84m**	No reaction (only SM recovered).

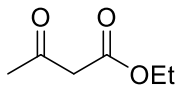
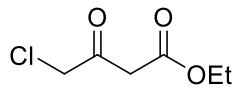
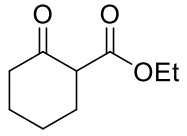
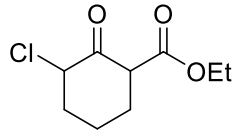
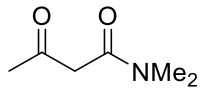
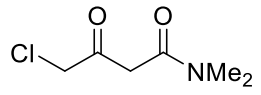
[a] Yield after purification by chromatography. [b] Two equivalents of LDA and $MeOSO_2Cl$ were used.

The lithium dianion of 3-keto esters and amide **84i-k** was generated and further chlorinated (**Table 5**). In all cases 4-chlorination occurred and products **86i-k** were obtained in good yield.

Table 5 - 4-chlorination of 1,3-dicarbonyl compounds.



84 **86**

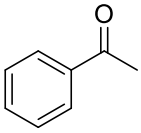
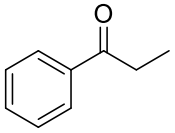
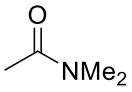
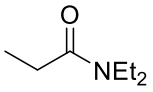
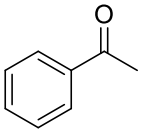
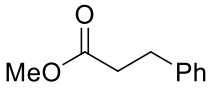
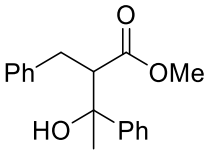
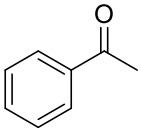
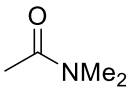
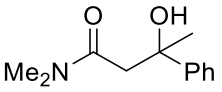
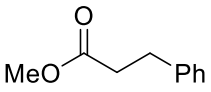
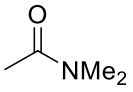
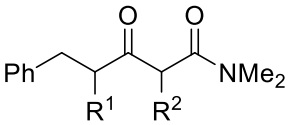
substrate	product
 **84i**	 **86i** (100%)
 **84j**	 **86j** (100%)
 **84k**	 **86k** (77%)

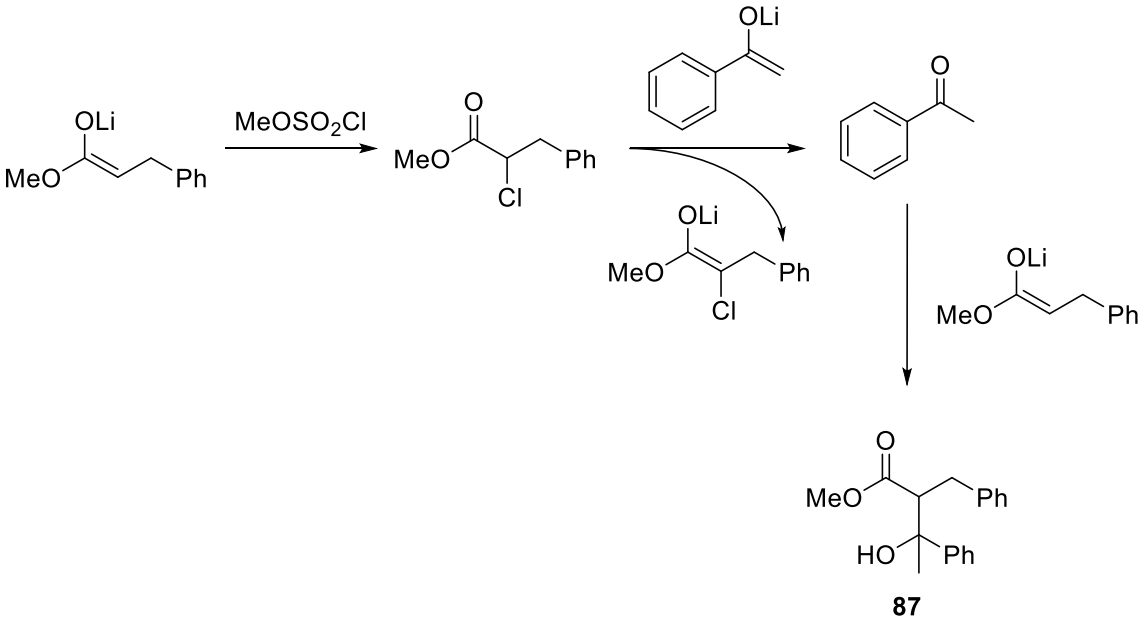
Chlorination of mixtures of compounds

Given that chlorination of less hindered substrates (**82n**, **84c** and **84f**) resulted in aldol reactions, we decided to investigate the chlorination of mixtures containing those compounds (**Table 6**). The objective was to understand the synthetic usefulness of this reaction for the preparation of different γ-chloro-carbonyl derivatives such as **83n**, **85c'** and **86k**. In mixtures containing the same functional groups (**entry 1-2**) cross reaction products were not observed, only the same products obtained using single compounds. Using a mixture of acetophenone **82n** with ester **84c** and dimethyl acetamide **84f** (**entry 3-4**) aldol reaction occurred and products **87** and **88** were isolated. The respective chlorination products (chloroacetophenone, **85c** and **85f**) were also detected by NMR. Surprisingly, products **87** and **88** do not contain chlorine, they are the result of a simple aldol reaction of the substrates. We propose that initial chlorination occurs but acetophenone is reprotonated and reacts with the ester or amide lithium enolate (**Scheme 53**). To support this mechanism, we have reacted the lithium enolate of **84c** and **84f** with acetophenone (**Table 7**). While in the case of **84f** product **88** was formed, for **84c** only starting materials were recovered in the presence of **85c''** and product **87** was not observed. In light of this result, we reacted the lithium enolates of **82n** and **84c** together with chloroester **85c** and surprisingly product **87** was produced. It is very interesting and unexpected how direct aldol reaction of **82n** and **84c** doesn't occur in the conditions used, however producing both enolates and reacting with a chloroester led to the aldol reaction to take place (**Scheme 54**). This reaction can be an alternative to the Reformatsky reaction for the synthesis of tertiary 3-hydroxyesters like **87**.

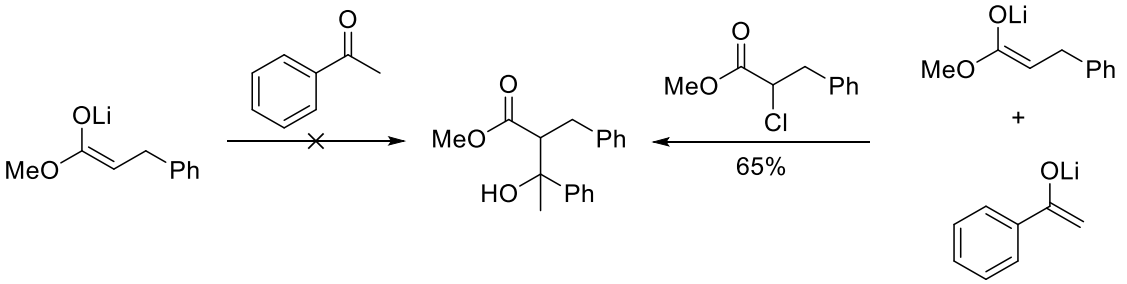
The reaction with the mixture of **84c** and **84f** (**entry 5**) produced two cross reaction products **89** and **90**. Contrary to the results obtained with other two mixtures, chlorine was present in these products, obtained in low yields. The presence of the amide **3c** and **3f** seems to enhance a mutual chlorination, since products **4c** and **4f** were obtained in a better yield compared to the reaction with the single compounds.

Table 6 - Chlorination of equimolar mixtures of different substrates.

Entry	Substrates		Products
1	 **82n**	 **82h**	Cross reaction products not observed
2	 **84f**	 **84e**	Cross reaction products not observed
3	 **82n**	 **84c**	 **87** 62% (d.r.=2:1)
4	 **82n**	 **84f**	 **88** 62%
5	 **84c**	 **84f**	 R^1=Cl, R^2=H **89** 18% R^1=H, R^2=Cl **90** 4% **85c** 54% **85f** 49%

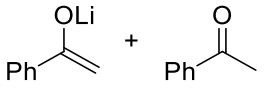
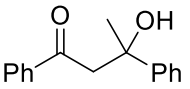
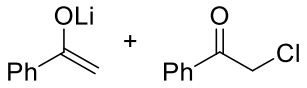
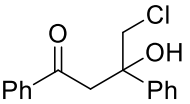
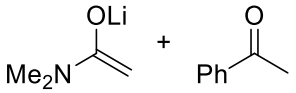
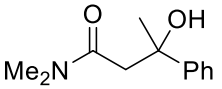
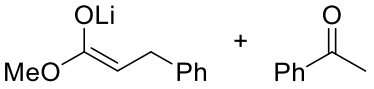
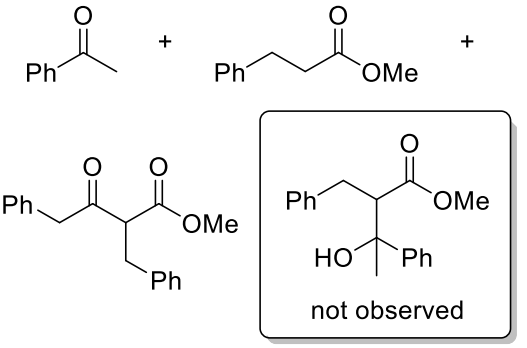
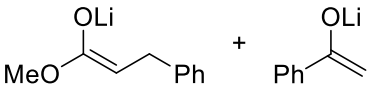
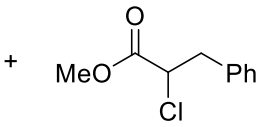
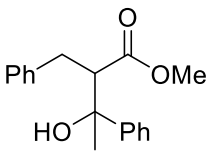


Scheme 53 - Proposed mechanism for the formation of **87** and **88** (**87** is used as example).



Scheme 54 - Reaction of lithium enolate of **84c** with acetophenone and of both enolates with chloroester **85c**.

Table 7 - Additional aldol experiments results.

reagents	products
	 11% (89% initial)
	 60%[a]
	 77%[a]
	 not observed
 	 65%[a] (d.r.= 2:1)

All reactions were carried in THF at -78°C for 30 min. [a] Yield after purification by chromatography.

Conclusion

A method for the basic α-chlorination of ketones and other functional groups is described. It is useful for acid sensitive substrates or selective chlorination of the less substituted carbon, since most of the methods available are acid catalyzed. To our knowledge, this is the first time an alkyl chlorosulfate has been described as a chlorinating reagent. Methyl chlorosulfate is an inexpensive and easily preparable reagent and found to have a better performance when compared to alkyl and aryl chlorosulfonates. Also, the reaction is very clean and affords quantitative yields and for all these reasons it is a very practical procedure. It works particularly well with ketones but can also be applied to esters and amides. It is useful in the preparation 4-chloro-1,3-dicarbonyl compounds *via* chlorination of the lithium dianion. Finally, the aldol and Claisen condensation of different molecules was also studied. Applying these conditions to less hindered ketones, esters and amides results in a one-pot chlorination and aldol or Claisen condensation process. On the other hand, using a mixture of a ketone with an ester or amide results in a simple aldol reaction.

Chapter 6

Sulfur abstraction under basic conditions (method for the synthesis of beta-diketones, beta-ketothiones and esters)

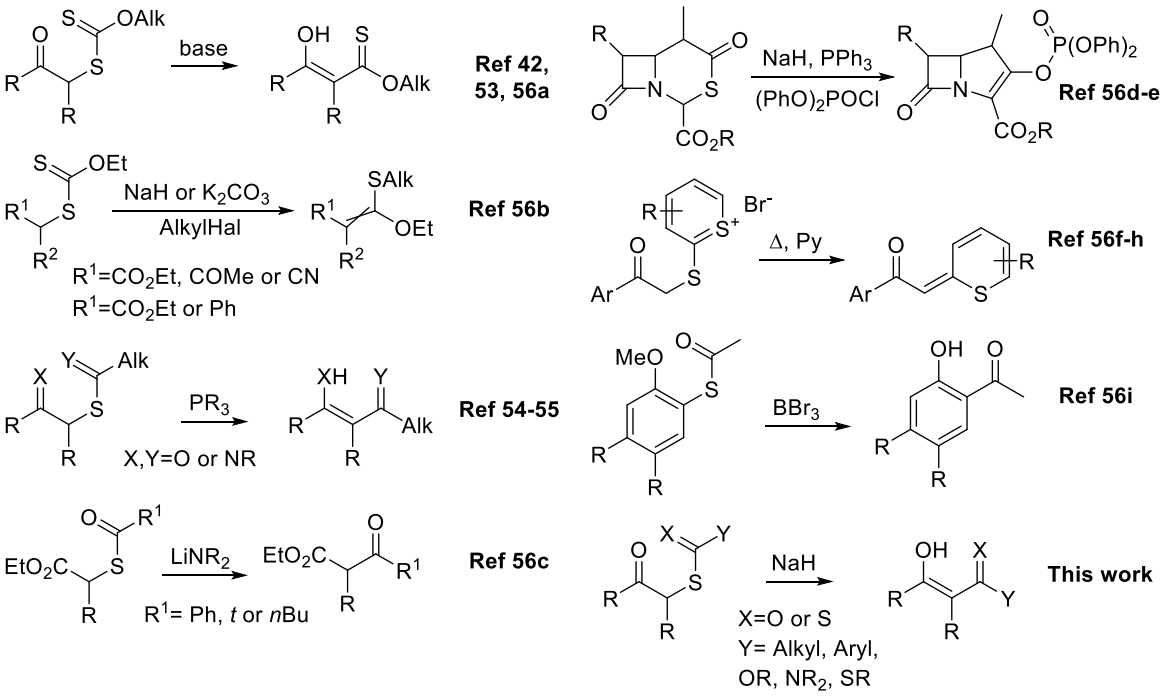
Abstract

A method for the transformation of 2-oxo *S*-carbonyl or thiocarbonyl into 2-oxo (thio)carbonyl compounds by a base promoted sulfur abstraction rearrangement is described. It is a very clean reaction and products are obtained in good yield (around 90%) in just 30 minutes. This method is particularly efficient for the introduction of thiocarbonyl containing groups, whereas for the introduction of acid derivatives it is less efficient. This method constitutes an alternative synthetic strategy for the generation of a new carbon-carbon bond and preparation of β-dicarbonyl compounds.

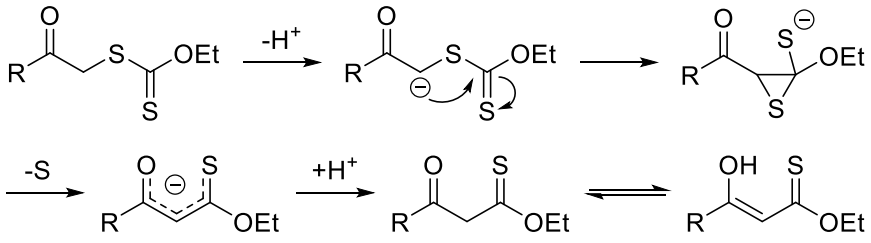
Introduction

Rearrangement reactions, although in some cases unpredictable, are important transformations in organic chemistry and particularly useful in synthesis when a new carbon-carbon bond is formed. The sulfur abstraction reaction of β-oxo thioacyl compounds is one example, where two carbons connected by a sulfur atom become directly connected.

This rearrangement (**Scheme 55**) was first reported by Lightner and Djerassi[53] in 1963 with the conversion of a steroid β-oxo xanthate into a β-oxo thionoester under basic conditions, the mechanism is illustrated in **Scheme 56**. Later, Eshenmoser[54] described the use of a tertiary phosphine as an alternative reagent, acting as a thiophile. This method has been extensively used with β-oxo thioimidates and is known as Eschenmoser sulfide contraction.[55] Besides the Eschenmoser reaction this rearrangement has been little used despite its synthetic potential, examples described in the literature[42,56] are summarized in **Scheme 55**.



Scheme 55 - Examples of sulfur abstraction reactions.



Scheme 56 - Mechanism of sulfur abstraction of a α-dithiocarbonate (or xanthate) ketone.

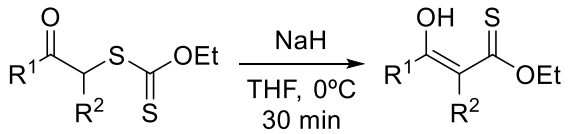
In this chapter, we explored the potential of this reaction for the introduction of different groups via sulfur abstraction. We opted to use a base promoted method since the use of phosphines normally produces a great mass of byproducts. This rearrangement constitutes a clean and green method for the introduction of different carbonyl and thiocarbonyl containing groups.

Reaction with β-oxo xanthates

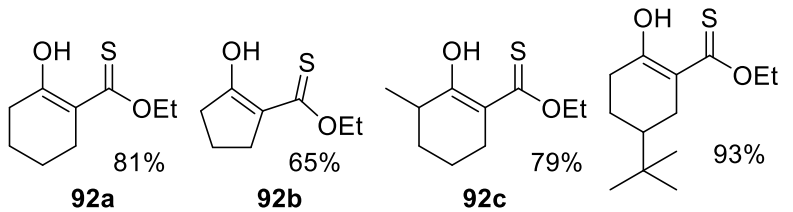
β-oxo xanthates or α-xanthyl ketones can be readily prepared by reacting the α-halo ketones with the respective xanthate salt. With the commercially available ethyl potassium xanthate a series of cyclic β-oxo ethyl xanthates was prepared and reacted with sodium hydride to promote the rearrangement (**Table 8**). It is a very clean and fast reaction; however, it is sensitive to the quality of sodium hydride used and a degraded sodium hydride (probably containing NaOH) leads to complex mixtures of products. Two simple substrates, *S*-(2-oxocyclohexyl) and *S*-(2-oxocyclopentyl) *O*-ethyl xanthates (**91a** and **91b**), were used and the respective β-oxo thionoesters **92a** and **92c** were obtained in moderate yields. Other substituted cyclohexanones were also used and the respective thionoesters **92c-f** were always obtained with good yields. A possible explanation for the lower yield of **92b** could be its higher volatility and loss during solvent evaporation since it has a low molecular weight. A highly functionalized optically active thionoester **92g** was also prepared in good yield, demonstrating the compatibility of this transformation with different functional groups.

Although the thionoesters (**92a-g**) were mainly present in the enol form, in the ^{1}H and ^{13}C NMR spectra (**Figure 20**) it was possible to detect also the keto-form. The enol produced a characteristic signal in the ^{1}H NMR spectrum at low field (13-15 ppm). In the ^{13}C NMR spectrum a signal at low field (>205 ppm) was characteristic of thiocarbonyl groups.

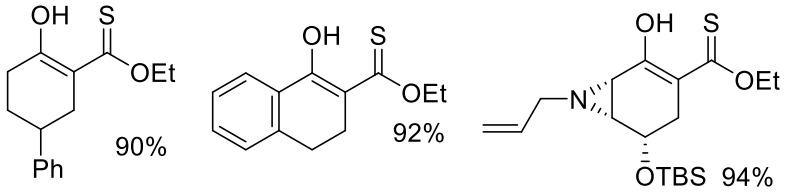
Table 8 - Cyclic β-oxo thionoesters synthesis via sulfur abstraction of the respective β-oxo xanthates.



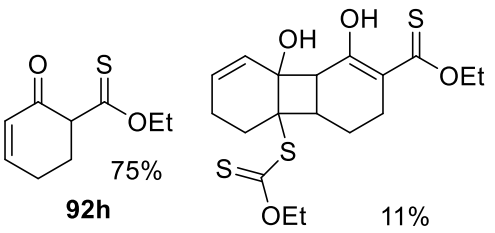
91 **92**



92a **92b** **92c** **92d**



92e **92f** **92g**



92h **92h'**

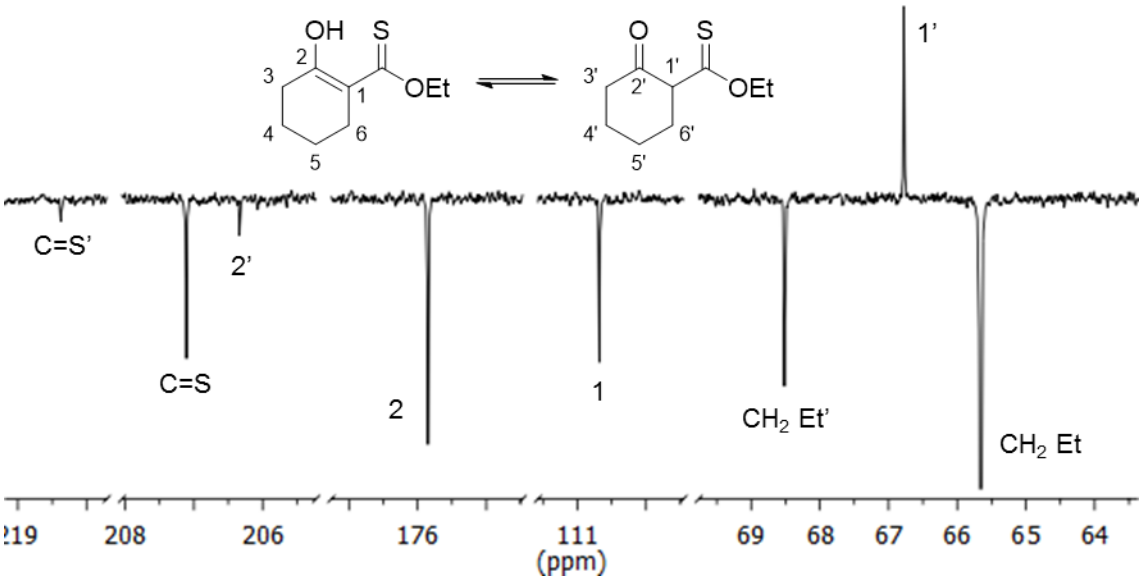
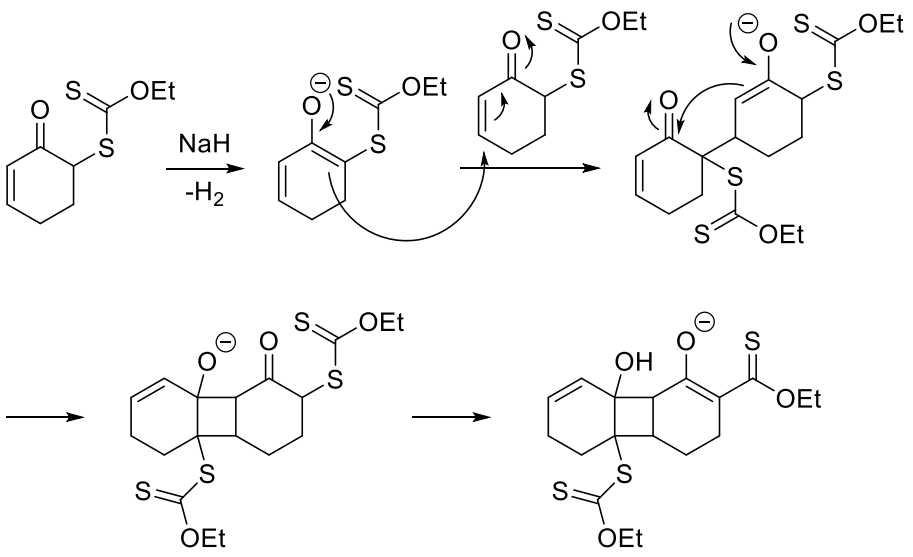


Figure 20 - Partial ^{13}C APT NMR spectrum of compound **92a**.

S-(2-oxocyclohex-3-en-1-yl) *O*-ethyl xanthate **91h** was prepared starting from 6-chloro-2-cyclohexenone, although Michael addition of the xanthate occurs we found that chloride substitution is also possible using two equivalents of xanthate. Using a sodium bicarbonate solution in the work-up instead of water, the xanthate group added to the enone eliminates and **91h** is obtained. In the rearrangement of **91h** the expected product **92h** is obtained, however a secondary product **92h'** is also produced. The product **92h'**, containing two cyclohexane rings fused by a cyclobutane, is produced by a tandem Michael-Dieckmann reaction (**Scheme 57**). During an attempt to avoid **92h'** formation, the reaction was carried at a lower temperature (-20°C), however the opposite effect was observed and the yield of **92h'** increased to 40%. Although it was not investigated, carrying out the reaction at an even lower temperature could lead to the exclusive formation of **92h'**.



Scheme 57 - Proposed mechanism for the formation of compound **92h'**.

In the ^{1}H and ^{13}C NMR spectrum of compound **92h'** (**Figure 21**) it was possible to observe two different ethyl groups, which indicated that it was the result of the dimerization of **91h**. Two different signals (224 and 207 ppm) for thiocarbonyl groups were also present in the ^{13}C spectrum. These differences in chemical shift and the presence of the enol group in the ^{1}H spectrum were an indication that one of the groups was the expected 2-oxo-thionoester, while the other one seemed to be a xanthate. It was also possible to observe a double bond, however the chemical shifts (5.9 and 5.6 ppm for ^{1}H; 129 and 128 ppm for ^{13}C) are not consistent with conjugation with a carbonyl as expected. With the help of 2D experiments the presented structure have been determined; however it was not possible to determine the relative stereochemistry of the cyclobutane ring, further X-Ray structure determination is required.

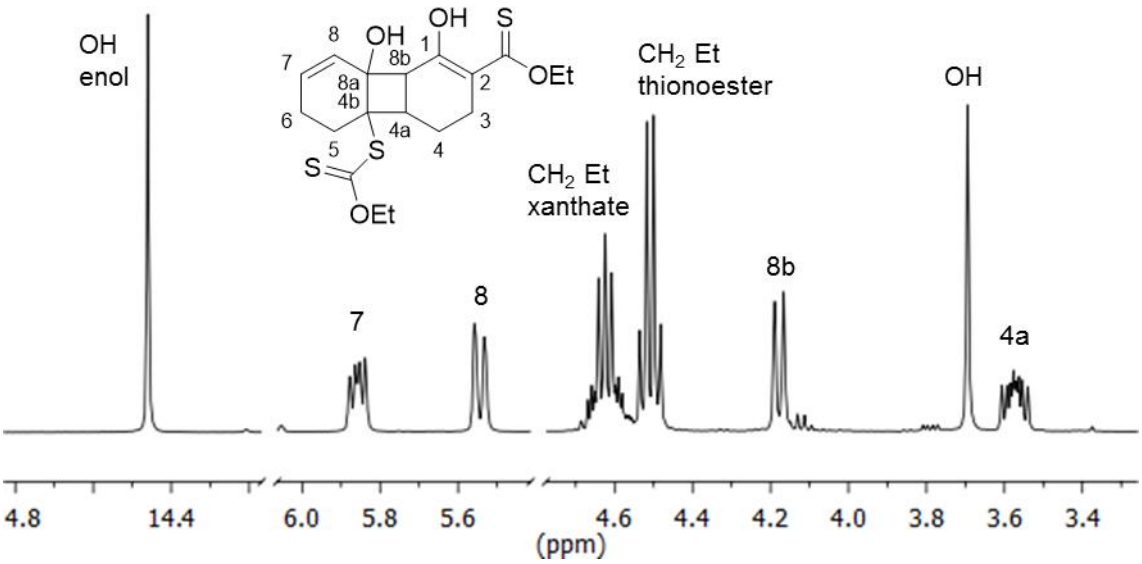


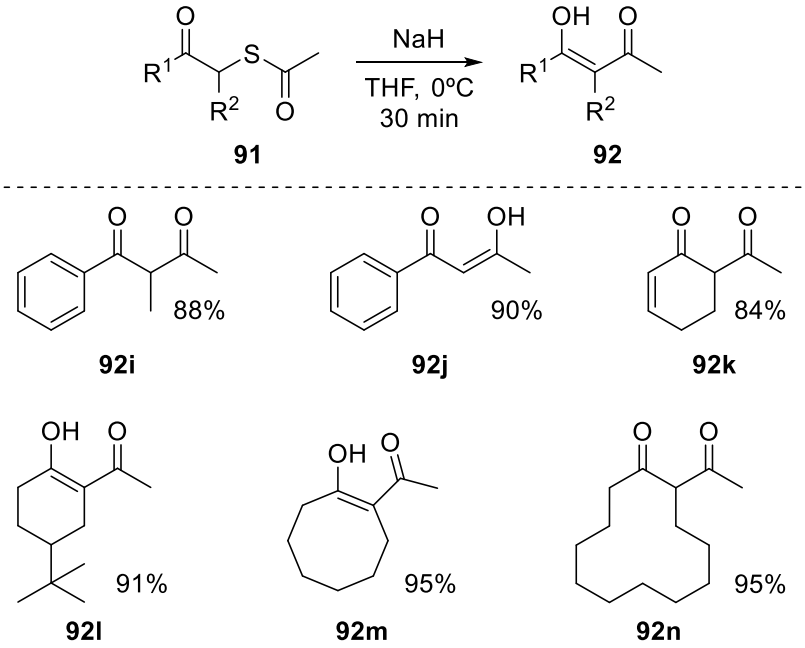
Figure 21 - Partial ^{1}H spectrum of compound **92h'**.

Reaction with β-oxo thioacetates

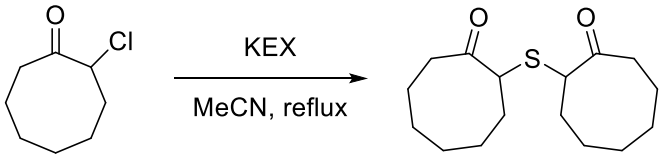
As for β-oxo xanthates, β-oxo thioacetates are easily prepared by halogen substitution using commercially available potassium thioacetate. A series of β-oxo thioacetates was also prepared and submitted to the same conditions (**Table 9**). Two linear substrates were tested and the respective β-diketones **92i** and **92j** were obtained in good yield. 3-acetylthio-4-*tert*butylcyclohexanone **91l** was tested for comparison with the structurally similar ethyl xanthate **91d**, **92l** was obtained almost in the same yield as **92d**. Thioacetate **91k** was prepared in the same way as **91h**. Upon reaction with sodium hydride **92k** was obtained in good yield and the Michael addition that produced **92h'** was not observed. 2-acetylthiocyclooctanone **91m** and cyclododecanone **91n** were prepared by chlorine substitution, however the reaction had to be carried at 70°C for 70 hours. For these 2-chloro substituted cycloketones containing a larger cycle, chlorine displacement seems to be more difficult and their substitution with ethyl

xanthate was not possible (**Scheme 58**). The respective β-diketones (**92m** and **92n**) were however obtained in good yields.

Table 9 - β-diketones synthesis via sulfur abstraction of the respective β-oxo thioacetates.



As presented in **Scheme 58**, reaction of chloroketone **83c** with potassium ethyl xanthate resulted in thioether **93**. The expected 2-oxo xanthate was probably formed but was hydrolyzed to the corresponding thiol and reacted with the chloroketone **83c**. By NMR it was possible to conclude that compound **93** was an alpha substituted cylcooctanone and a molecular ion (m/z: 283) was consistent with the presented structure. By NMR it was possible to observe the two diastereoisomers of **93** in a 6:4 ratio.



83c **93** (53%)

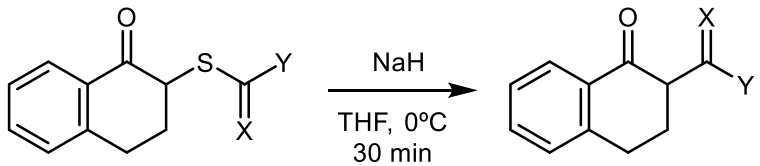
Scheme 58 - Reaction of 2-chlorocyclooctanone **83c** with potassium ethyl xanthate.

Reaction with different functional groups

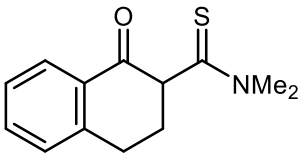
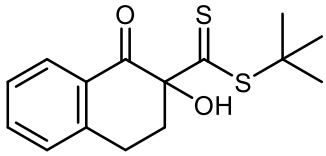
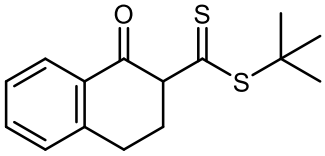
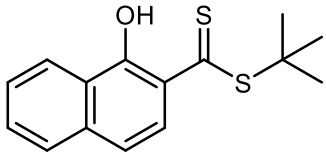
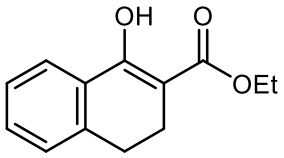
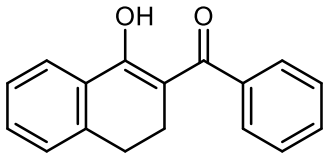
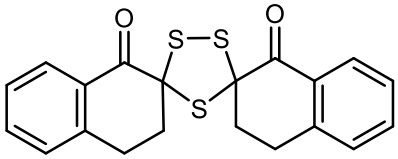
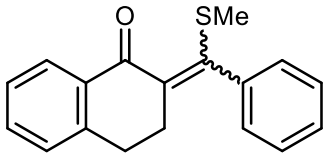
Tetralone was used as a model to study the reaction with different carbonyl and thiocarbonyl containing groups at the sulfur atom (**Table 10**). Compounds **91o** and **91p** were prepared by halogen substitution using the right salt. Reaction of dithiocarbamate **91o** produced thioamide **92o** in good yield, however the reaction had to be carried at 60°C and therefore solvent was changed to DMF. The sodium enolate of **91o** is formed at lower temperatures, as can be observed by hydrogen releasing, however the sulfur abstraction only occurred when the temperature was raised to 60°C. Dithioester **92p** was also obtained in good yield.

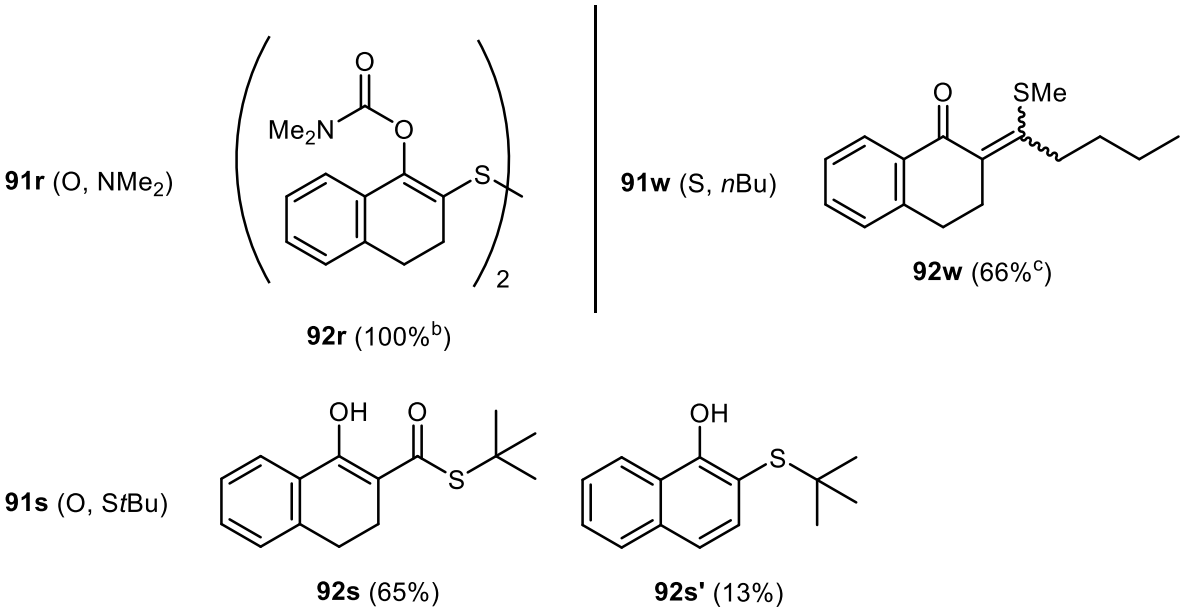
Compounds **91q-t** were obtained by thiocarbonyl oxidation of compounds **91f**, **91o** and **91p** (**Scheme 59**). Reaction of monothiocarbonate **91q** afforded ester **92q** in a moderate yield and a secondary product **92q'** was also formed. The trithiolane **92q'** was probably formed by reaction of thioketone **94** with sulfur released from the rearrangement (**Scheme 60**).[57] Two diastereomers of **92q'** are possible but only one was observed. In the ^{13}C NMR of compound **92q'** a quaternary carbon was observed at 83.9 ppm, which corresponds to the carbon alpha to the carbonyl group. Mass spectrometry ($[M+Na]^+$ $C_{20}H_{16}NaO_2S_3$ m/z: 407.0199) was essential for the determination of the proposed structure, having a trithiolane ring since it contained 3 sulfur atoms and 2 tetralone rings.

Table 10 - Basic rearrangement of different 2-S-carbonyl and thiocarbonyl tetralone derivatives.

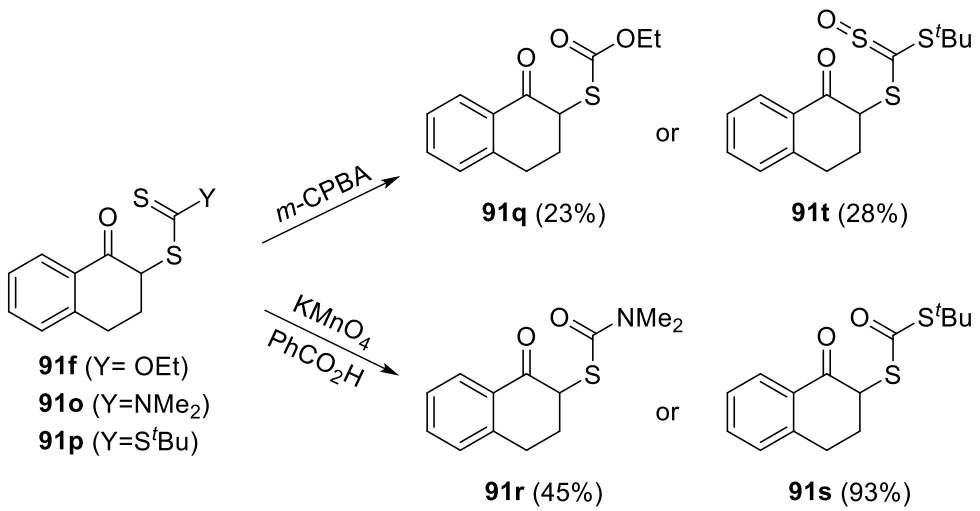


91 **92**

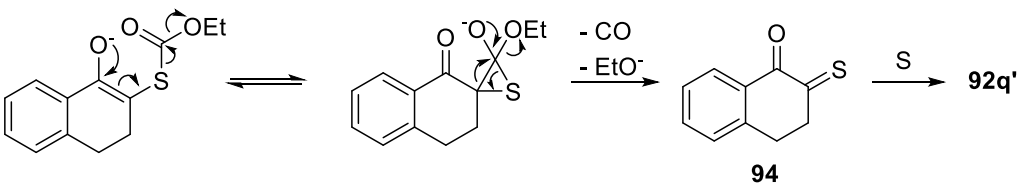
91 (X, Y)	**92**	**91** (X, Y)	**92**
91o (S, NMe2)	 **92o** (91%[a])		 **92t** (78%)
91p (S, S*t*Bu)	 **92p** (85%)	**91t** (S=O, S*t*Bu)	 **92t'** (10%)
91q (O, OEt)	 **92q** (71%)	**91u** (O, Ph)	 **92u** (100%)
	 **92q'** (21%)	**91v** (S, Ph)	 **92v** (70%[c])



[a] Reaction was carried in DMF at 60°C. [b] Reaction was carried in DMF at 80°C. [c] After 30 min, MeI was added.



Scheme 59 - Oxidation of compounds **91f**, **91o** and **91p**.



Scheme 60 - Proposed mechanism for the formation of trithiolane **92q'**.

Basic rearrangement of monothiocarbamate **91r** resulted in a quantitative yield of **92r**, as for dithiocarbamate **91o** any reaction only occurs at a higher temperature (80°C). Instead of sulfur abstraction the carbamate group migrated from the sulfur to the oxygen atom, further dimerization resulted in **92r**. In the ^{13}C NMR spectrum is possible to observe four quaternary unsaturated carbons and the absence of a ketone carbonyl group, leading to the conclusion that **92r** was an enol derivative of tetralone. A signal at 1721 cm^{-1} in the FTIR spectrum was consistent with the presence of a carbamate carbonyl, which could also be observed in the ^{13}C NMR spectrum. Once again mass spectrometry was essential for the determination of the proposed structure.

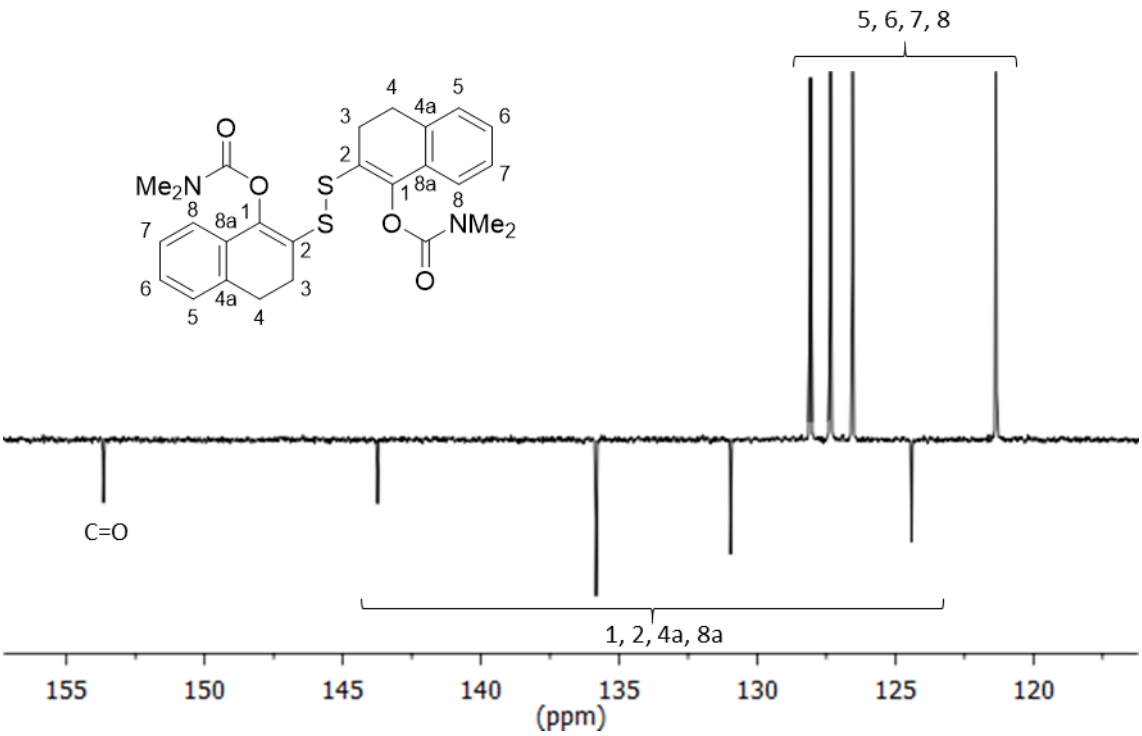


Figure 22 - Partial ^{13}C NMR spectrum of compound **92r**.

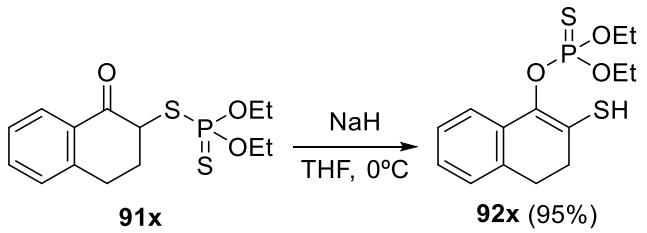
Oxidation of trithiocarbonate **91p** using permanganate resulted in dithiocarbonate **91s** while using *m*-CPBA, sulfine **91t** was obtained (**Scheme 59**). Spectroscopic data for these two compounds was very similar, only by mass spectroscopy could they be distinguished. Although reaction of **91s** produced the expected product **92s**, a secondary product was also formed. The formation of **92s'** could be due to sulfur and CO elimination or direct elimination of carbonyl sulfide, further aromatization is possible in the presence of sulfur. During the rearrangement of **91t** both sulfur abstraction and oxygen migration occurred resulting in the formation of **92t** as well as aromatic secondary product **92t'**.

Compounds **91q-s** seem to be less suitable for the rearrangement when compared to the respective thiocarbonyl analogues **91f**, **91o** and **91p.** Their basic

rearrangement resulted in the formation of secondary products (**92s'** and **92q'**) or sulfur abstraction didn't occur at all in the case of **91t**. According to the proposed mechanism (**Scheme 56**) an episulfide intermediate needs to be formed for the sulfur abstraction to occur, in the case of carbonyl derivatives an alkoxide is formed instead of a thiolate. Thus, this episulfide intermediate is probably less stable for carbonyl derivatives explaining the lower efficiency of the sulfur abstraction.

Considering the good results of thioacetates **91i-n** rearrangement, monothiobenzoate **91u** and dithioesters **92v** and **92w** were prepared by substitution of 2-bromotetralone with the right salt and submitted to the same conditions. Reaction of **91u** resulted in the expected product **92u** in quantitative yield. Rearrangement of dithioesters **91v** and **91w** produced the expected thioketones, however these products were very unstable and degradation was observed upon air exposure or chromatographic purification. For an easy isolation of the products they were methylated with iodomethane in a one-pot procedure and **91v** and **91w** were obtained as a mixture of two diastereoisomers. Other methylation (*O* and *C*) products were observed in the NMR of the crude, what may explain the lower yields of **91v** and **91w**.

A dithiophosphate derivative **91x** (**Scheme 61**) was also prepared and submitted to basic conditions to understand if the sulfur abstraction was also possible in a phosphorous analogue. However only migration of the thiophosphate from the sulfur to the oxygen occurred and **92x** was obtained. As in the case of **92r**, by ^{13}C NMR was possible to conclude **92x** is an enol derivative of tetralone. A thiol proton could also be observed in the ^{1}H NMR spectrum at 3.62 ppm.



91x **92x** (95%)

Scheme 61 - Basic rearrangement of 2-diethyldithiophosphate tetralone **91x**.

Conclusion

The basic sulfur abstraction of 2-oxo (thio)carbonyl compounds is a useful synthetic strategy for the preparation of β-dicarbonyl compounds that comprises the generation of a new carbon-carbon bond. Although synthetic applications described in the literature are almost all restricted to the Eschenmoser method, a broader range of substrates has here been demonstrated. It is a very clean reaction and the products are obtained in good yields. It is particularly useful for the introduction of a thiocarbonyl containing group: thioketone, thionoester, thioamide and dithioester. In addition to its potential for new synthetic routes design, the β-dicarbonyl compounds produced are useful as ligands in metal complexes especially when containing a thiocarbonyl group. Although the generation of acid derivative group (ester, amide and thioester) seem to be a limitation of this method, products and by products obtained have been isolated and identified.

Conclusion

The aim of this work was to develop new synthetic applications for cyclic acyl aziridines (azabicyclo[x.1.0]alkane-2-ones), particularly in the preparation of oseltamivir, terpestacin and analogues. While for oseltamivir a new synthesis is described, for terpestacin all the synthetic strategies designed failed. As part of this project, a new asymmetric synthesis of the studied cyclic acyl aziridines based on an enzymic resolution methodology was also developed. Other transformations with great synthetic potential were also studied.

The described preparation of optically active cyclic 4-hydroxyacylaziridines is very efficient. Both enantiomers can be produced in high yield and enantiomeric excess. It is easily scalable maintaining the efficiency, as demonstrated in the oseltamivir synthesis. The main disadvantage of this strategy is the need to introduce the TBS group for the aziridination that is subsequently removed for the resolution process. The direct halogenation of the cyclic 4-hydroxyenones would render a more efficient process. Further work may be done for the development of a new halogenation methodology, since the conditions used are not compatible with the unprotected hydroxyl group. Nevertheless, a very efficient process for the preparation of useful building blocks for organic chemistry is described. These small chiral molecules were used as starting materials in the synthetic strategies developed.

The synthetic strategies designed for terpestacin did not work out as planned and its synthesis was not achieved as initially proposed. Nevertheless, some interesting molecules were prepared and may be used in the synthesis of other products. It is interesting to observe how small changes in the structure of a molecule, such as the introduction of a methyl group, can change completely the outcome of a reaction. Although the initial idea was that the aziridine ring

could orient the introduction of the functional groups, it seems to impose such a steric hindrance that render it a very unstable system. The observation of aziridine invertomers was also interesting and to our knowledge they have never been detected at room temperature in alkyl aziridines. Computational chemistry tools were essential for the study of this effect.

The new synthesis of oseltamivir was achieved as initially proposed. Many syntheses are described in the literature, for example the recent one-pot method of Hayashi[33]. The early formation of the aziridine and the enzymic resolution are the most distinguishable features of the developed synthesis. The process could still be improved, especially the reduction/mesylation/elimination. Contrary to other described syntheses of oseltamivir, the one reported in this thesis employed simple and reproducible reactions and also relatively inexpensive and readily available reagents. For those reasons, it is a methodology easy to reproduce and scale up, even by less experienced synthetic chemists. Probably, this synthesis is not the most viable for industrial production of oseltamivir, however it is very versatile and can be used for the synthesis of different analogues. The synthesis of tamiphosphor illustrates this potential and similarly other molecules containing different acid bioisosters could be produced. The α-chloroketone prepared could also be useful in this task, as different groups could be introduced by chlorine displacement. Resuming, this methodology has a great potential to be used in the medicinal chemistry of antiviral drugs.

The last two chapters of this work were focused on the study of two reactions that are particularly useful for organic synthesis. The first one, the basic chlorination of ketones with methyl chlorosulfate was not easily predicted, since α-sulfonates were the expected products under the reaction conditions. It is a

very clean and efficient reaction, and the reagent used was easily prepared and inexpensive. Although this type of reaction has been described using alkyl sulfonyl chlorides (chlorosulfonates), the use of methyl chlorosulfate rendered a much more efficient reaction. Moreover, this was the first time a chlorosulfate has been described as an electrophilic chlorine source to our knowledge. The α-halogenation of carbonyl containing compounds is a classical strategy for the functionalization of organic molecules. The methodology herein described is one of the few examples described for this transformation under basic conditions, hence being compatible with a variety of functional groups and very useful.

The second reaction was the basic sulfur abstraction of 2-oxocarbonyl and thiocarbonyl compounds and is also a very efficient and clean reaction. In this reaction, a new carbon-carbon bond is formed, one of the most important tasks in organic chemistry. Therefore, this transformation has great synthetic potential. The products obtained, 1,3-dicarbonyl compounds, are very useful as metal ligands. The reported methodology can be used for the design of new metal complexes, that have different applications (*e.g.* catalysis). The work presented in this two last chapters deviated a little from what was initially proposed. Although the two reactions studied have great potential, reports of their use in organic synthesis are scarce, therefore we decided to investigate them deeper to understand their scope and limitations.

With this work, we hope to have contributed to our organic chemistry knowledge with new synthetic methodologies. The developed synthesis of oseltamivir and tamiphosphor may provide a contribution to medicinal chemistry, making available new routes for different molecules with potential

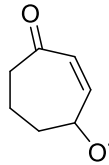
antiviral activity. All the described transformations and strategies are tools available to synthetic chemists for the preparation of compounds of interest.

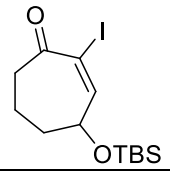
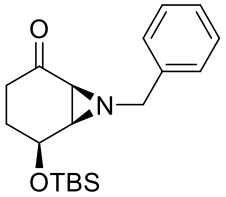
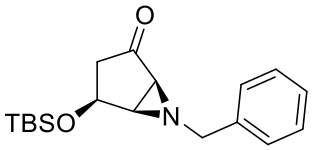
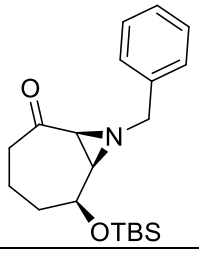
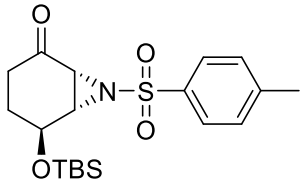
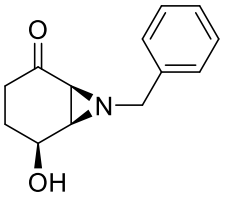
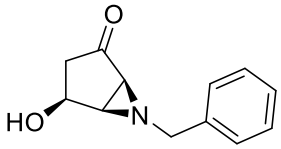
Experimental

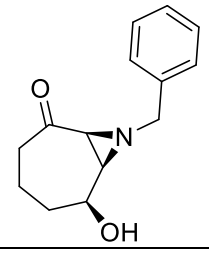
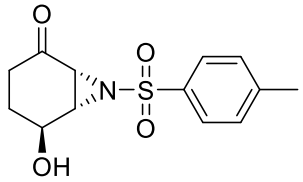
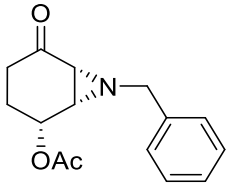
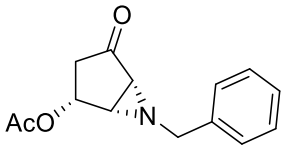
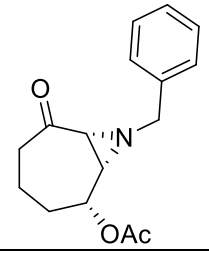
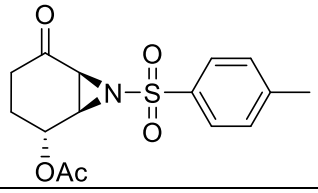
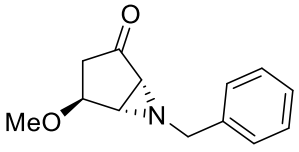
General

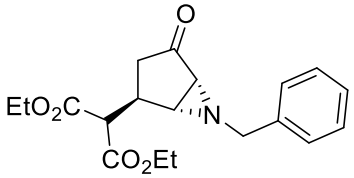
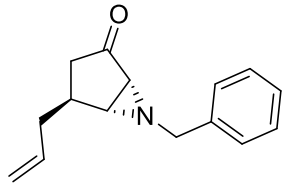
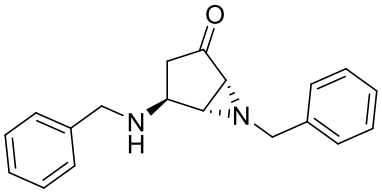
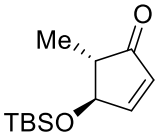
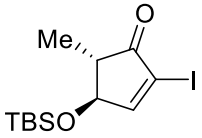
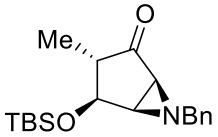
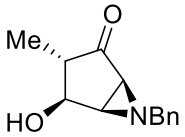
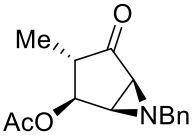
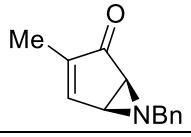
All chemicals used were of reagent grade. All solvents were dried where necessary by established methods.[58] Flash chromatography was performed on Kieselgel 60, particle size 0.032–0.063 mm. Preparative TLC employed silica gel Merck 60 GF_{254}. Analytical TLC: Aluminum-backed silica gel Merck 60 F_{254}. Infrared (IR) spectra were obtained using a commercial ATR-FTIR spectrophotometer and are in cm^{-1}. Specific rotations were measured using an automatic polarimeter and are reported as follows: $[\propto]_D^T$ (c= g/100mL; solvent). Melting points were determined with a capillary apparatus and are uncorrected. HRMS was recorded on a commercial apparatus (ESI Source). NMR spectra were obtained at commercial instrument 400 MHz (^{1}H NMR), 101 MHz (^{13}C NMR) and 162 MHz (^{31}P NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million relative to TMS (^{1}H and ^{13}C) or phosphoric acid (^{31}P) and coupling constants in hertz. The chemical shift assignments of all compounds were carried out with the help of 2D NMR experiments as COSY, HMQC and HMBC. Chiral HPLC analysis was carried out by using a Chiralpak® AD-H or IB (250 x 4.6 mm) column in a Waters system: 515 pump and 2485 dual λ absorbance detector. All calculations were performed with Gaussian 09w, the vibrational frequencies were computed to check whether each optimized structure is an energy minimum or a transition state and to calculate thermal corrections at 298 K.

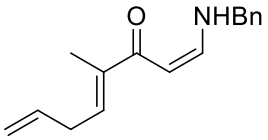
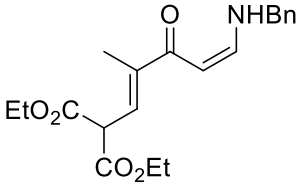
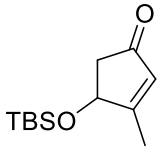
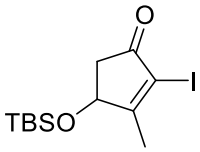
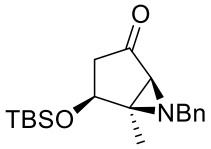
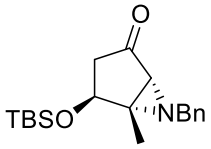
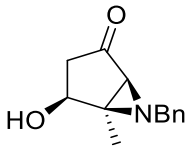
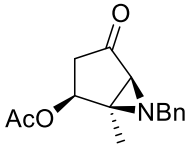
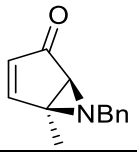
Graphic index of compounds

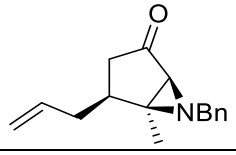
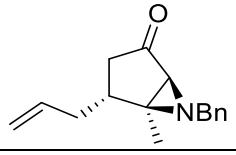
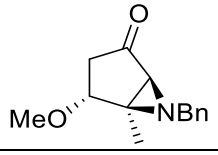
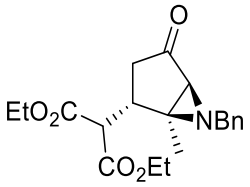
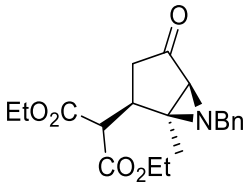
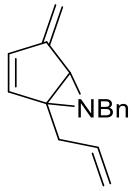
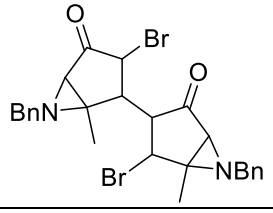
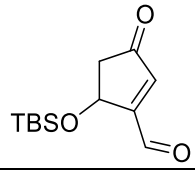
structure	name and number	page
	**4-[(*tert*-Butyldimethylsilyl)oxy]cyclohept-2-en-1-one**	128

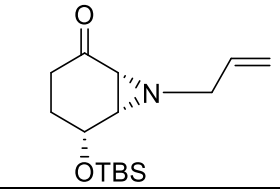
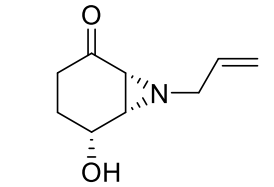
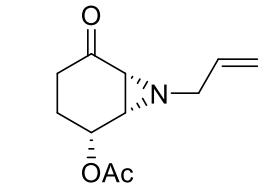
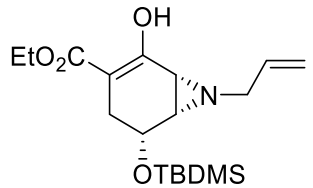
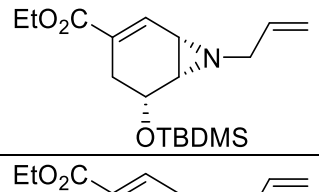
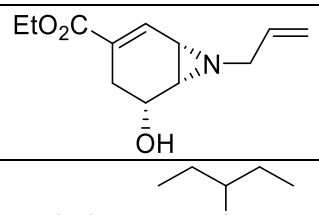
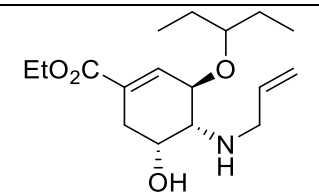
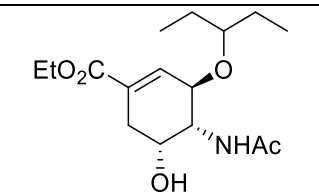
	**4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodocyclohept-2-en-1-one 1c**	129
	**(±)-(1S,5S,6R)-7-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-7-azabicyclo[4.1.0]heptan-2-one 2a**	130
	**(±)-(1S,4S,5R)-6-Benzyl-4-[(tert-butyldimethylsilyl)oxy]-6-azabicyclo[3.1.0]hexan-2-one 2b**	131
	**(±)-(1S,6S,7R)-8-Benzyl-6-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[5.1.0]octan-2-one 2c**	131
	**(±)-(1R,5S,6S)-5-[(tert-Butyldimethylsilyl)oxy]-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]heptan-2-one 2d**	132
	**(-)-(1S,5S,6R)-7-benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one 5a**	133, 134
	**(-)-(1S,4S,5R)-6-Benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one 5b**	133, 134

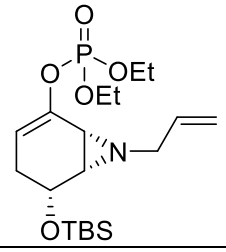
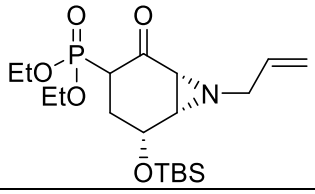
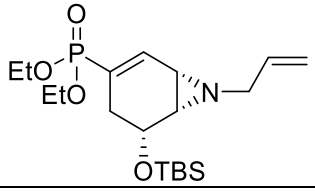
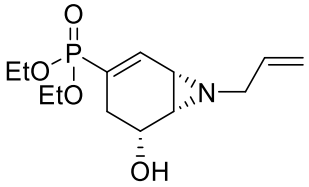
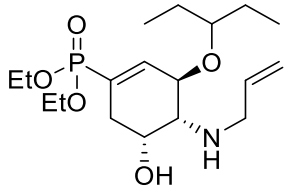
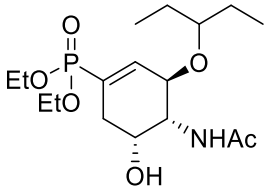
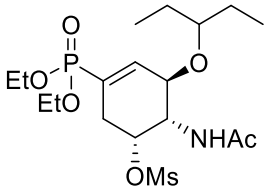
	**(-)-(1S,6S,7R)-8-Benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one 5c**	133, 135
	**(+)-(1R,5S,6S)-5-Hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one 5d**	133, 136
	**(+)-(1S,2R,6R)-7-Benzyl-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate 7a**	134
	**(+)-(1S,2R,5R)-6-Benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 7b**	135
	**(+)-(1S,2R,7R)-8-Benzyl-6-oxo-8-azabicyclo[5.1.0]octan-2-yl acetate 7c**	136
	**(-)-(1R,2R,6S)-7-(4-Methylbenzenesulfonyl)-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate 7d**	137
	**(+)-(1R,4S,5S)-6-Benzyl-4-methoxy-6-azabicyclo[3.1.0]hexan-2-one 8**	138

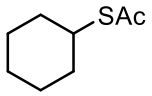
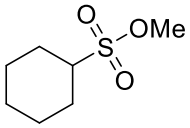
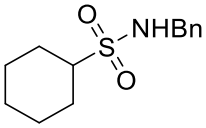
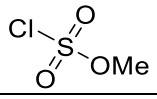
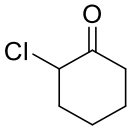
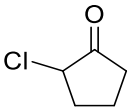
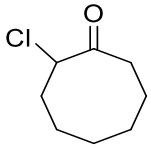
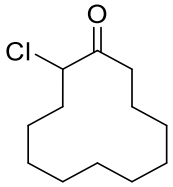
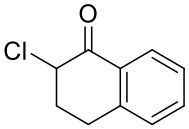
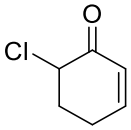
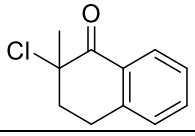
	**(±)-1,3-Diethyl 2-[(1R,2R,5R)-6-benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 10**	138
	**(±)-(1R,4S,5R)-6-Benzyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 11**	139
	**(±)-(1R,4S,5R)-6-Benzyl-4-(benzylamino)-6-azabicyclo[3.1.0]hexan-2-one 12**	140
	**(±)-(4R,5S)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-methylcyclopent-2-en-1-one 2059**	140
	**(±)-(4S,5S)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-5-methylcyclopent-2-en-1-one 21**	141
	**(±)-(1S,3S,4S,5R)-6-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-6-azabicyclo[3.1.0]hexan-2-one 22**	142
	**(±)-(1S,3S,4S,5R)-6-Benzyl-4-hydroxy-3-methyl-6-azabicyclo[3.1.0]hexan-2-one 23**	142
	**(±)-(1R,2S,3S,5S)-6-Benzyl-3-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 24**	143
	**6-Benzyl-3-methyl-6-azabicyclo[3.1.0]hex-3-en-2-one 25**	144

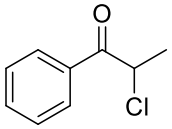
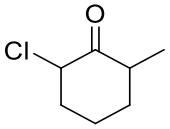
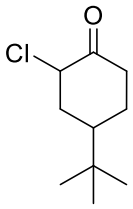
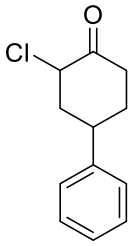
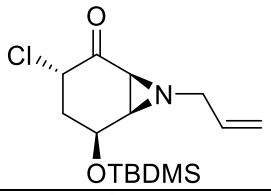
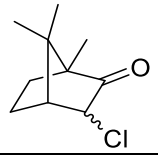
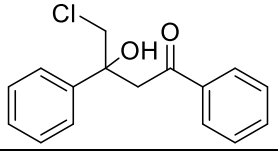
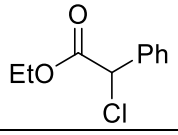
	**(4E)-1-(Benzylamino)-4-methylocta-1,4,7-trien-3-one 26**	144
	**1,3-Diethyl 2-[(1E)-5-(benzylamino)-2-methyl-3-oxopenta-1,4-dien-1-yl]propanedioate 27**	145
	**4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylcyclopent-2-en-1-one60**	146
	**4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-3-methylcyclopent-2-en-1-one 3660**	146
	**(±)-(1S,4S,5R)-6-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 37**	146
	**(±)-(1R,4S,5S)-6-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 37'**	147
	**(±)-(1S,4S,5R)-6-Benzyl-4-hydroxy-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 38**	147
	**(±)-(1R,2S,5S)-6-Benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 39**	148
	**6-Benzyl-5-methyl-6-azabicyclo[3.1.0]hex-3-en-2-one 40**	149

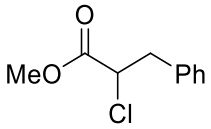
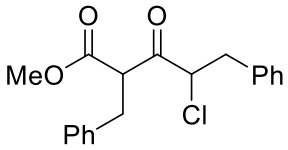
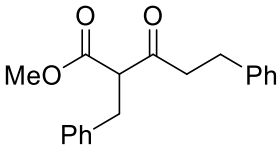
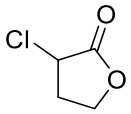
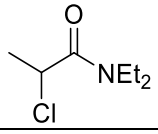
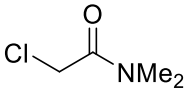
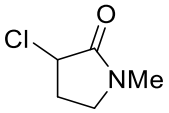
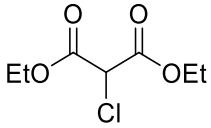
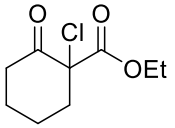
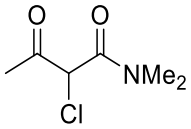
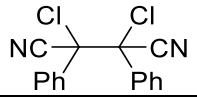
	**(±)-(1S,4S,5S)-6-Benzyl-5-methyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 41a**	150
	**(±)-(1S,4R,5S)-6-Benzyl-5-methyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 41b**	150
	**(±)-(1S,4R,5R)-6-Benzyl-4-methoxy-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 42**	151
	**1,3-Diethyl 2-[(1S,2S,5S)-6-benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 43a**	152
	**1,3-Diethyl 2-[(1S,2R,5S)-6-benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 43a**	152
	**6-Benzyl-4-methylidene-1-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hex-2-ene 44**	152
	**6-Benzyl-3-{6-benzyl-3-bromo-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl}-4-bromo-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 45**	153
	**5-[(*tert*-Butyldimethylsilyl)oxy]-3-oxocyclopent-1-ene-1-carbaldehyde 47**	154

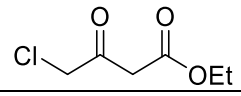
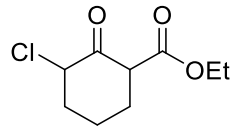
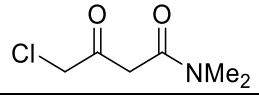
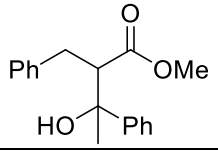
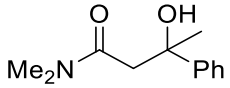
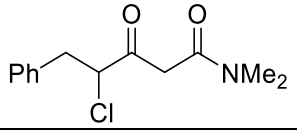
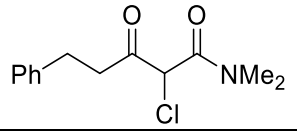
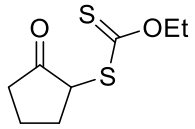
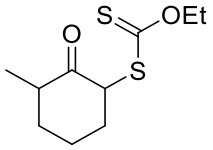
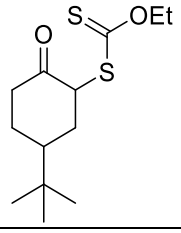
	**(+)-(1R,5R,6S)-5-[(*tert*-Butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 55**	155, 157
	**(+)-(1R,5R,6S)-5-Hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 56**	155, 156
	**(+)-(1S,2R,6R)-5-Oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-yl acetate 57**	156
	**Ethyl (-)-(1R,5R,6S)-5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 58**	158
	**Ethyl (-)-(1S,5R,6S)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 59**	159
	**Ethyl (-)-(1S,5R,6S)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 60**	160
	**Ethyl (-)-(3R,4R,5R)-5-hydroxy-3-(pentan-3-yloxy)-4-[(prop-2-en-1-yl)amino]cyclohex-1-ene-1-carboxylate 61**	161
	**Ethyl (-)-(3R,4R,5R)-4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate 62**	162

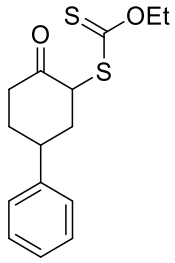
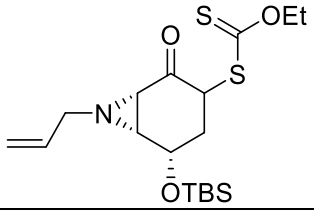
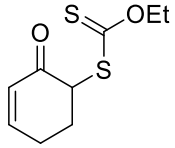
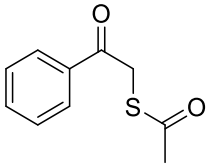
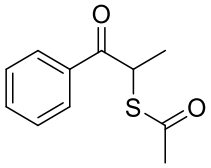
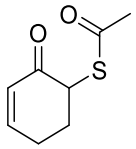
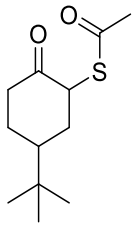
	**(+)-(1R,5R,6S)-5-[(*tert*-Butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-2-yl diethyl phosphate 63**	163
	**Diethyl (+)-[(1R,5R,6S)-5-[(*tert*-butyldimethylsilyl)oxy]-2-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-3-yl]phosphonate 64**	164
	**Diethyl (-)-[(1S,5R,6S)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-3-yl]phosphonate 65**	166
	**Diethyl (-)-[(1S,5R,6S)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-3-yl]phosphonate 66**	167
	**Diethyl (-)-[(3R,4R,5R)-5-hydroxy-3-(pentan-3-yloxy)-4-[(prop-2-en-1-yl)amino]cyclohex-1-en-1-yl]phosphonate 67**	168
	**Diethyl (-)-[(3R,4R,5R)-4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-en-1-yl]phosphonate 68**	169
	**(-)-(1R,5R,6S)-3-(Diethoxyphosphoryl)-6-acetamido-5-(pentan-3-yloxy)cyclohex-3-en-1-yl methanesulfonate 69**	170

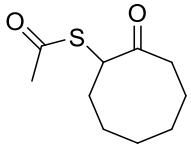
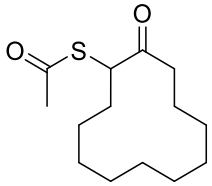
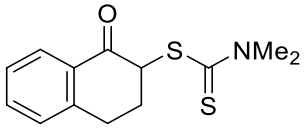
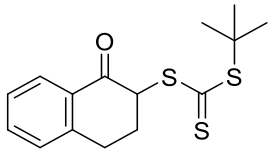
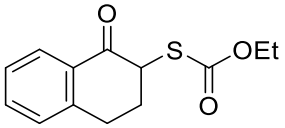
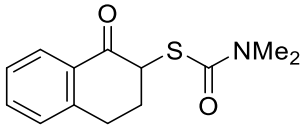
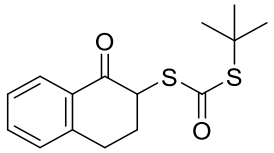
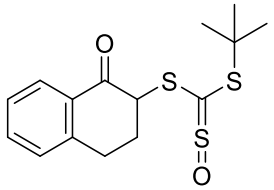
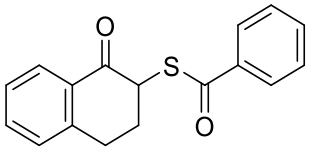
	1-(Cyclohexylsulfanyl)ethan-1-one 7661	171
	**Methyl cyclohexanesulfonate 78**	171
	***N*-Benzylcyclohexanesulfonamide 79**	172
	**Methyl chloranesulfonate**[48]	172
	**2-Chlorocyclohexan-1-one 83a63**	173
	**2-Chlorocyclopentan-1-one 83b44**	173
	**2-Chlorocyclooctan-1-one 83c41**	173
	**2-Chlorocyclododecan-1-one 83d41**	173
	**2-Chloro-1,2,3,4-tetrahydronaphthalen-1-one 83e63**	174
	**6-Chlorocyclohex-2-en-1-one 83f64**	174
	**2-Chloro-2-methyl-1,2,3,4-tetrahydronaphthalen-1-one 83g65**	174

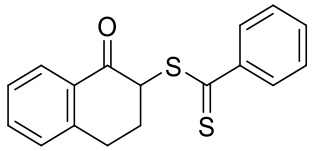
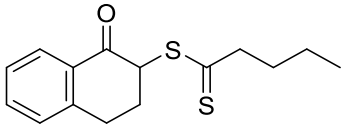
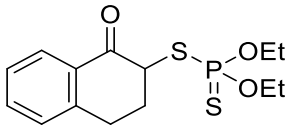
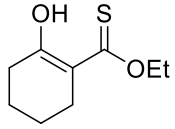
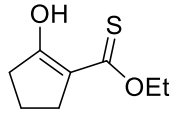
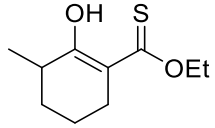
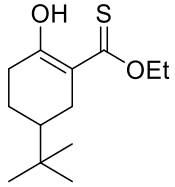
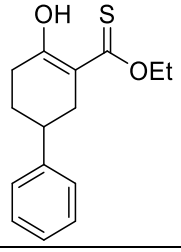
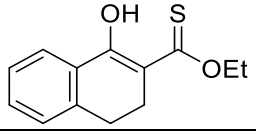
	**2-Chloro-1-phenylpropan-1-one 83h46h**	174
	**2-Chloro-6-methylcyclohexan-1-one 83i66**	174
	**4-*tert*-Butyl-2-chlorocyclohexan-1-one 83j47h**	174
	**2-Chloro-4-phenylcyclohexan-1-one 83k63**	174
	**(1S,3S,5S,6R)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-chloro-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 83l**	175
	**3-Chloro-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 83m67**	175
	**4-Chloro-3-hydroxy-1,3-diphenylbutan-1-one 83n68**	175
	**Ethyl 2-chloro-2-phenylacetate 85b**	176

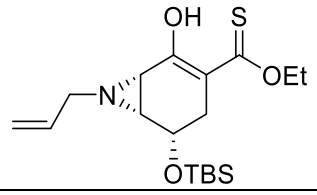
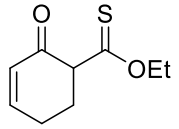
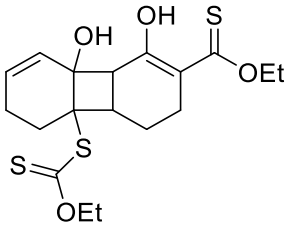
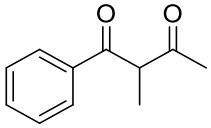
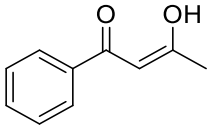
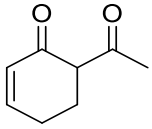
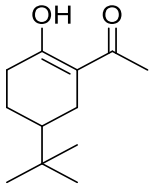
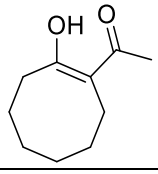
	**methyl 2-chloro-3-phenylpropanoate 85c**	176
	**Methyl 2-benzyl-4-chloro-3-oxo-5-phenylpentanoate 85c'**	176
	**methyl 2-benzyl-3-oxo-5-phenylpentanoate 85c''**	176
	**3-chlorooxolan-2-one 85d**	177
	**2-Chloro-*N*,*N*-diethylpropanamide 85e**	177
	**2-chloro-*N*,*N*-dimethylacetamide 85f**	177, 182
	**3-chloro-1-methylpyrrolidin-2-one 85g**	177
	**1,3-diethyl 2-chloropropanedioate 85h**	178
	**Ethyl 1-chloro-2-oxocycloHex-1-carboxylate 85j**	178
	**2-chloro-*N*,*N*-dimethyl-3-oxobutanamide 85k**	178
	**2,3-Dichloro-2,3-diphenylbutanedinitrile 85l**	178

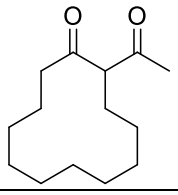
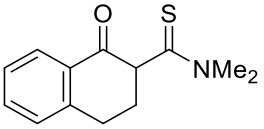
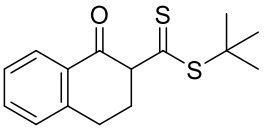
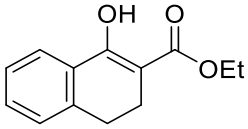
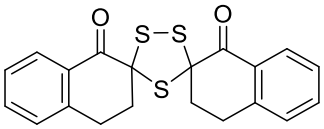
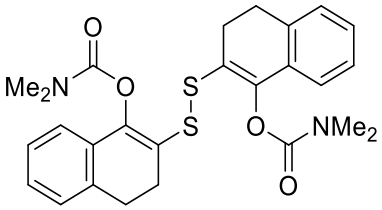
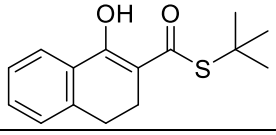
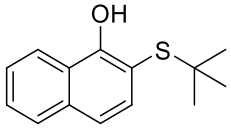
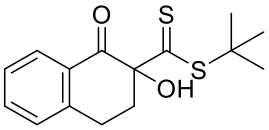
	**Ethyl 4-chloro-3-oxobutanoate 86i[77]**	179
	**Ethyl 3-chloro-2-oxocycloHex-1-carboxylate 86j**	179
	**4-Chloro-*N*,*N*-dimethyl-3-oxobutanamide 86k**	180
	**2-Benzyl-3-hydroxy-3-phenylbutanoate 87**	180
	**3-hydroxy-*N*,*N*-dimethyl-3-phenylbutanamide 88**	181
	**4-Chloro-*N*,*N*-dimethyl-3-oxo-5-phenylpentanamide 89**	182
	**2-Chloro-*N*,*N*-dimethyl-3-oxo-5-phenylpentanamidethe 90**	182
	**Ethyl [(2-oxocyclopentyl)sulfanyl]methanethioate 91b**	183
	**Ethyl [(3-methyl-2-oxocyclohexyl)sulfanyl]methanethioate 91c**	183
	**Ethyl [(5-*tert*-butyl-2-oxocyclohexyl)sulfanyl]methanethioate 91d**	184

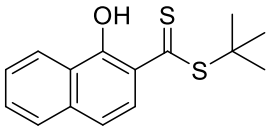
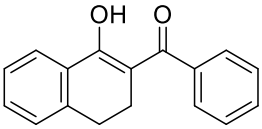
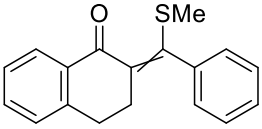
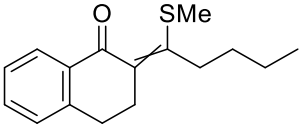
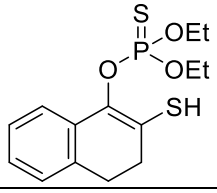
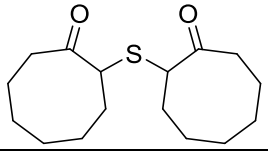
	**Ethyl [(2-oxo-5-phenylcyclohexyl)sulfanyl]methanethioate 91e**	184
	**Ethyl {[(1S,5S,6R)-5-[(*tert*-butyldimethylsilyl)oxy]-2-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-3-yl]sulfanyl}methanethioate 91g**	185
	**Ethyl [(2-oxocyclohex-3-en-1-yl)sulfanyl]methanethioate 91h**	186
	**2-(Acetylsulfanyl)-1-phenylpropan-1-one 91i**[80]	186
	**2-(Acetylsulfanyl)-1-phenylethan-1-one 91j**[80-81]	186
	**6-(Acetylsulfanyl)cyclohex-2-en-1-one 91k**	187
	**2-(Acetylsulfanyl)-4-*tert*-butylcyclohexan-1-one 91l**	187

	**2-(Acetylsulfanyl)cyclooctan-1-one 91m**	188
	**2-(Acetylsulfanyl)cyclododecan-1-one 91n**	188
	***N*,*N*-Dimethyl-1-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]methanethioamide 91o**	189
	**2-{[(*tert*-Butylsulfanyl)methanethioyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91p**	189
	**Ethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]formate 91q**	190
	***N*,*N*-Dimethyl-1-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]formamide 91r**	190
	**2-{[(*tert*-Butylsulfanyl)carbonyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91s**	191
	**2-{[(*tert*-Butylsulfanyl)(oxo-lambda4-sulfanylidene)methyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91t**	192
	**2-(Benzoylsulfanyl)-1,2,3,4-tetrahydronaphthalen-1-one 91u**	193

	**1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl benzenecarbodithioate 91v**	193
	**1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl pentanedithioate 91w**	194
	***O*,*O*-Diethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]phosphonothioate 91x**	195
	**Ethyl 2-hydroxy-5-phenylcyclohex-1-ene-1-carbothioate 92a**	196
	**Ethyl 2-hydroxycyclopent-1-ene-1-carbothioate 92b[86]**	196
	**Ethyl 2-hydroxy-3-methylcyclohex-1-ene-1-carbothioate 92c**	197
	**Ethyl 5-*tert*-butyl-2-hydroxycyclohex-1-ene-1-carbothioate 92d**	197
	**Ethyl 2-hydroxy-5-phenylcyclohex-1-ene-1-carbothioate 92e**	198
	**Ethyl 1-hydroxy-3,4-dihydronaphthalene-2-carbothioate 92f[85]**	198

	**Ethyl (1*S*,5*S*,6*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carbothioate 92g**	199
	**Ethyl 2-oxocyclohex-3-ene-1-carbothioate 92h**	200
	**Ethyl 4b-[(ethoxymethanethioyl)sulfanyl]-1,8a-dihydroxy-3,4,4a,4b,5,6,8a,8b-octahydrobiphenylene-2-carbothioate 92h'**	200
	**2-methyl-1-phenylbutane-1,3-dione 92i**	201
	**3-hydroxy-1-phenylbut-2-en-1-one 92j**	201
	**6-Acetylcyclohex-2-en-1-one 92k**	201
	**1-(5-*tert*-butyl-2-hydroxycyclohex-1-en-1-yl)ethan-1-one 92l**	202
	**1-(2-hydroxycyclooct-1-en-1-yl)ethan-1-one 92m**	202

	**2-Acetylcyclododecan-1-one 92n[92]**	202
	***N*,*N*-Dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbothioamide 92o**	203
	**2-(*tert*-Butylsulfanylcarbothioyl)-1,2,3,4-tetrahydronaphthalen-1-one 92p**	203
	**Ethyl 1-hydroxy-3,4-dihydronaphthalene-2-carboxylate 92q**	204
	**3,3'',4,4''-Tetrahydro-1H,1''H-dispiro[naphthalene-2,2'-[1,3,5]trithiolane-4',2''-naphthalene]-1,1''-dione 92q'**	204
	**2-({1-[(Dimethylcarbamoyl)oxy]-3,4-dihydronaphthalen-2-yl}disulfanyl)-3,4-dihydronaphthalen-1-yl N,N-dimethylcarbamate 92r**	205
	**(*tert*-Butylsulfanyl)(1-hydroxy-3,4-dihydronaphthalen-2-yl)methanone 92s**	205
	**2-(*tert*-Butylsulfanyl)naphthalen-1-ol 92s'**	206
	**2-(*tert*-Butylsulfanylcarbothioyl)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one 92t**	207

	**2-(*tert*-Butylsulfanylcarbothioyl)naphthalen-1-ol 92t'**	207
	**2-benzoyl-3,4-dihydronaphthalen-1-ol 92u**	207
	**2-[(Methylsulfanyl)(phenyl)methylidene]-1,2,3,4-tetrahydronaphthalen-1-one 92v**	208
	**2-[1-(Methylsulfanyl)pentylidene]-1,2,3,4-tetrahydronaphthalen-1-one 92w**	208
	**Ethyl 2-sulfanyl-3,4-dihydronaphthalen-1-yl ethoxy(sulfanylidene)phosphonite 92x**	209
	**2-[(2-Oxocyclooctyl)sulfanyl]cyclooctan-1-one 93**	210

Synthesis experiments

4-[(*tert*-Butyldimethylsilyl)oxy]cyclohept-2-en-1-one

To a stirred solution of 4-hydroxycyclohept-2-en-1-one[19] (1.0 g, 7.9 mmol) in dry DCM (16 mL) under argon was added diisopropylamine (2.8 mL, 2.5 eq.), *tert*-butyldimethylsilylchloride (2.4 g, 2 eq.) and DMAP (cat.) at 0°C. After 16 hours of stirring at room temperature the reaction was quenched with water (20mL) and the mixture was extracted with DCM (3x 10mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness.

Purification by flash column chromatography, eluted with Hex:AcOEt (95:5), afforded 1.6 g (84%) of the pure title compound as colorless oil.

^{1}H NMR δ: 6.50 (1H, ddd, $J_{3,2}$=12.5, $J_{3,4}$=3.2, $J_{3,5}$=1.0, H-3); 5.91 (1H, ddd, $J_{2,3}$=12.5, $J_{2,4}$=2.0, $J_{2,7}$=0.8, H-2); 4.56-4.51 (1H, m, H-4); 2.65-2.58 (1H, m, H-7); 2.56-2.49 (1H, m, H-7); 2.12-2.04 (1H, m, H-5); 1.89-1.78 (3H, m, H-5, H-6), 0.91 (9H, s, ^{t}Bu TBS); 0.11 (3H, s, Me TBS); 0.10 (3H, s, Me TBS). ^{13}C NMR δ: 203.5 (C-1); 150.6 (C-3); 129.4 (C-2); 71.0 (C-4); 43.0 (C-7); 35.4 (C-5); 25.8 (3xMe ^{t}Bu); 18.3 (C-6); 18.1 (C_q ^{t}Bu); -4.6 (Me TBS); -4.7 (Me TBS). FTIR(Neat): 1674 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{25}O_2Si$ 241.1618; Found 241.1612.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodocyclohept-2-en-1-one 1c

To a stirred solution of 4-[(*tert*-butyldimethylsilyl)oxy]cyclohept-2-en-1-one (1.0 g, 4.2 mmol) in a 1:1 THF:water mixture (17 mL) was added K_2CO_3 (1.15 g, 2 eq.), iodine (2.1 g, 2 eq.) and DMAP (100 mg, 20 mol%). After 24 hours of stirring at 60°C the reaction was diluted with ethyl ether (20mL) and washed with a sodium thiosulfate solution 20%(w/V) (20mL) and water (20mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness, affording 699 mg (46%) of the pure compound **1c** as colorless oil.

^{1}H NMR δ: 7.48 (1H, d, $J_{3,4}$=3.7, H-3); 4.51 (1H, dt, $J_{4,5}$=8.5, $J_{4,3}$=$J_{4,5}$=4.1, H-4); 2.81 (1H, dt, ^{2}J=15.2, $J_{7,6}$=5.1, H-7); 2.57 (1H, ddd, ^{2}J=15.0, $J_{7,6}$=10.1, $J_{7,6}$=4.8, H-7); 2.05-1.95 (1H, m, H-5); 1.87-1.76 (3H, m, H-5, H-6), 0.90 (9H, s, ^{t}Bu TBS); 0.10 (3H, s, Me TBS); 0.09 (3H, s, Me TBS). ^{13}C NMR δ: 197.9 (C-1); 159.4 (C-3); 103.3 (C-2); 72.0 (C-4); 39.7 (C-7); 34.0 (C-5); 25.7 (3xMe ^{t}Bu); 18.09 (C-6); 18.06 (C_q ^{t}Bu); -4.79 (Me TBS); -4.83 (Me TBS). FTIR(Neat): 1682 (C=O st). HRMS (ESI-TOF) m/z: $[M-TBS+H]^+$ Calcd for $C_7H_{10}IO_2$ 252.9720; Found 252.9714.

General procedure for the preparation of TBS-protected *cis*-hydroxybenzylaziridines (±)-2

In a flask under argon a mixture of iodoenone (1.35 mmol), anhydrous cesium carbonate (480 mg, 1.1eq.), 1,10-phenanthroline (240 mg, 1.0 eq.), benzylamine (220 µL, 1.5 eq.) and dry toluene (10 mL) was stirred at room temperature. After complete reaction (TLC, around 4 hours), the reaction mixture was diluted with DCM (10 mL) and washed with water (10 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:AcOEt 9:1) afforded the pure aziridine **2**.

(±)-(1*S*,5*S*,6*R*)-7-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-7-azabicyclo[4.1.0]heptan-2-one 2a

Using the general procedure 700 mg of compound **2a** were obtained as colorless oil in 82% yield.

^{1}H NMR δ: 7.41 (2H, d, ^3J=7.6, Ar(*o*)), 7.31 (2H, t, ^3J=7.4, Ar(*m*)), 7.25 (2H, t, ^3J =8.0 Hz, Ar(*p*)), 4.12 (1H, ddd, $J_{5,4}$=10.4, $J_{5,4}$=5.2, $J_{5,6}$=1.8, H-5), 3.91 (1H, d, ^2J=14.0, CH_2 Bn), 3.35 (1H, d, ^2J=14.0, CH_2 Bn), 2.45 (1H, ddd, ^2J=18.4, $J_{3,4}$=5.6, $J_{3,4}$=2.0, H-3), 2.32 (1H, br d, $J_{6,1}$=6.4,H-6), 2.29-2.21 (1H, m, H-4), 2.19 (1H, d, $J_{1,6}$=6.0, H-1), 2.08 (1H, ddd, ^2J=18.8, $J_{3,4}$=12.4, $J_{3,4}$=6.4, H-3), 1.67-1.60 (1H, m, H-4), 0.87 (9H, s, ^{t}Bu TBS), 0.08 (3H, s, Me TBS), 0.05 (3H, s, Me TBS). ^{13}C NMR δ: 205.7 (C-2), 138.1 (Ar C_q), 128.3 (Ar(*m*)), 127.5 (Ar(*o*)), 127.1 (Ar(*p*)), 67.9 (C-5), 62.8 (CH_2 Bn), 48.2 (C-6), 46.9 (C-1), 35.3 (C-3), 25.9 (C-4), 25.7 (3xMe ^{t}Bu), 18.1 (C_q ^{t}Bu), -4.66 (Me TBS), -4.72 (Me TBS). FTIR (Neat): 1711 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{30}NO_2Si$ 332.2040; Found 332.2038.

(±)-(1*S*,4*S*,5*R*)-6-Benzyl-4-[(tert-butyldimethylsilyl)oxy]-6-azabicyclo[3.1.0]hexan-2-one 2b

Using the general procedure 780 mg of compound **2b** were obtained as colorless oil in 83% yield.

^{1}H NMR δ: 7.46 (2H, d, ^3J=7.2, Ar(*o*)), 7.32 (2H, t, ^3J=7.3, Ar(*m*)), 7.26 (2H, t, ^3J =7.3 Hz, Ar(*p*)), 4.39 (1H, td, $J_{4,3}$=8.0, $J_{4,5}$=3.1, H-4), 3.95 (1H, d, ^2J=14.2, CH_2 Bn), 3.26 (1H, d, ^2J=14.2, CH_2 Bn), 2.76 (1H, t, $J_{5,4}$= $J_{5,1}$=3.7, H-5), 2.49 (1H, dd, ^2J=16.8, $J_{3,4}$=8.0, H-3), 2.37 (1H, d, $J_{1,5}$=4.2, H-1), 2.22 (1H, ddd, ^2J=16.8, $J_{3,4}$=8.0, H-3), 0.90 (9H, s, ^{t}Bu TBS), 0.07 (3H, s, Me TBS), 0.06 (3H, s, Me TBS). ^{13}C NMR δ: 205.7 (C-2), 137.9 (Ar C_q), 128.4 (Ar(*m*)), 127.3 (Ar(*o*)), 127.1 (Ar(*p*)), 68.3 (C-4), 60.8 (CH_2 Bn), 50.3 (C-5), 48.6 (C-1), 41.6 (C-3), 25.8 (3xMe ^{t}Bu), 18.1 (C_q ^{t}Bu), -4.7 (Me TBS), -4.8 (Me TBS). FTIR (Neat): 1741 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{28}NO_2Si$ 318.1884; Found 318.1884.

(±)-(1*S*,6*S*,7*R*)-8-Benzyl-6-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[5.1.0]octan-2-one 2c

Using the general procedure 580 mg of compound were obtained as colorless oil in 68% yield.

^{1}H NMR δ: 7.39 (2H, d, ^3J=7.4, Ar(*o*)), 7.31 (2H, t, ^3J=7.4, Ar(*m*)), 7.25 (2H, d, ^3J =7.2 Hz, Ar(*p*)), 3.85 (1H, dd, $J_{6,5}$=10.8, $J_{6,5}$=3.2, H-6), 3.63 (1H, d, ^2J=13.8, CH_2 Bn), 3.55 (1H, d, ^2J=13.8, CH_2 Bn), 2.83 (1H, ddd, ^2J=13.8, $J_{3,4}$=10.9, $J_{3,4}$=3.1, H-3), 2.23-2.04 (4H, m, H-1, H-3, H-5, H-7), 1.85-1.78 (1H, m, H-4), 1.73-1.68 (1H, m, H-5), 1.17 (1H, q, *J*=13.7, H-4), 0.86 (9H, s, ^{t}Bu TBS), 0.06 (3H, s, Me TBS), 0.05 (3H, s, Me TBS). ^{13}C NMR δ: 211.7 (C-2), 138.2 (Ar C_q), 128.3 (Ar(*m*)), 127.8 (Ar(*o*)), 127.1 (Ar(*p*)), 72.6 (C-6), 64.0 (CH_2 Bn), 51.2, 48.2 (C-1, C-7), 41.4 (C-3), 34.3 (C-5), 25.7 (3xMe ^{t}Bu), 22.9 (C-4); 18.0 (C_q ^{t}Bu), -4.7 (Me TBS), -4.8 (Me TBS). FTIR (Neat):

1696 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{32}NO_2Si$ 346.2197; Found 346.2202.

(±)-(1R,5S,6S)-5-[(tert-Butyldimethylsilyl)oxy]-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]heptan-2-one 2d

The general procedure was followed except that 1,10-phenanthroline was not added and 3 eq. of tosylamide was used instead of the normal 1.5 eq. 386 mg (85% yield) of the pure product **2d** was obtained as a white solid.

^{1}H NMR δ: 7.80 (2H, d, ^2J=8.0, Ar(*o*)); 7.36 (2H, d, ^2J=8.0, Ar(*m*)); 4.38 (1H, q, $J_{5,4}$=$J_{5,6}$=3.1, H-5); 3.34 (1H, ddd, $J_{6,1}$=6.4; $J_{6,5}$=2.8; J=1.2, H-6); 3.17 (1H, d, $J_{1,6}$=6.4, H-1); 2.45 (3H, s, Me Ts); 2.38 (1H, ddd, ^2J=18.2; $J_{3,4}$=12.2, $J_{3,4}$=6.2, H-3); 2.20 (1H, ddd, ^2J=18.4, $J_{3,4}$=5.2, $J_{3,4}$=3.2, H-3); 2.07−1.99 (1H, m, H-4); 1.71−1.63 (1H, m, H-4); 0.89 (9H, s, *t*Bu TBS); 0.13 (3H, s, Me TBS); 0.09 (3H, s, Me TBS). ^{13}C NMR δ:200.8 (C-2); 145.2 (Ar C−SO_2 Ts); 134.0 (Ar(*p*)); 129.9 (Ar(*m*)); 127.9 (Ar(*o*)); 63.6 (C-5); 43.7 (C-1); 43.5 (C-6); 31.9 (C-3); 25.6 (3 × Me *t*Bu); 35.4 (C-4); 21.6 (Me Ts); 17.9 (C_q *t*Bu); −4.8 (Me TBS); −4.9 (Me TBS). FTIR (Neat): 1722 (C=O st); 1163 (SO_2 st). M.p. = 98.5−99 °C. Anal. Calcd for $C_{19}H_{29}NO_4SSi$: C 57.69; H 7.39; N 3.54; S 8.11. Found: C 57.90; H 7.54; N 3.58; S 7.90.

General procedure for the preparation of *cis*-hydroxybenzylaziridines 5

To a stirred solution of TBS-protected aziridine **2** (1.26 mmol) in dry tetrahydrofuran (5mL) under argon was added tetrabutylammonium fluoride (2.3 mL, 1 M in THF, 1.8 eq.). After 30 minutes, the reaction mixture was diluted with DCM (5 mL) and washed with water (5 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:AcOEt 1:1) afforded the pure aziridine **5** with a yield greater than 98%.

(±)-(1*S*,5*S*,6*R*)-7-Benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one 5a

Using the general procedure 430 mg of compound **5a** were obtained as colorless oil in quantitative yield.

(±)-(1*S*,4*S*,5*R*)-6-Benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one 5b

Using the general procedure 380 mg of compound **5b** were obtained as white solid (m.p.=90-91°C) in 98% yield.

(±)-(1*S*,6*S*,7*R*)-8-Benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one 5c

Using the general procedure 360 mg of compound **5c** were obtained as colorless oil in 99% yield.

(±)-(1*R*,5*S*,6*S*)-5-Hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one 5d

A procedure similar to the general was used, but 10 eq. of triethylamine trihydrofluoride were used instead of 1.8 eq. of tetrabutylammonium fluoride and the reaction took 16h to be complete. 180 mg of compound **5d** were obtained as a white solid (m.p. = 121-122°C) in quantitative yield.

General procedure for the resolution

A mixture of racemic hydroxyaziridine **5** (50 mg), vinyl acetate (5 eq.), novozym 435 and diisopropyl ether (1mL) was agitated (700 r.p.m.) in a closed tube at 24°C. After the resolution was completed the solid-supported enzyme was removed by decantation and the organic solution was evaporated to dryness. Purification by flash column chromatography, eluted with Hex/AcOEt (1:1), afforded (-)-hydroxyaziridine **5** and (+)-acetoxyaziridine **7**.

(-)-(1*S*,5*S*,6*R*)-7-benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one 5a

Using the general procedure, with 25 mg of novozym 435 and the resolution took 4h to be complete, 24 mg (48%) of **(-)-5a** (>99% e.e, HPLC) as a white solid and 28 mg (47%) of **(+)-7a** (97% e.e., HPLC) as an oil. HPLC conditions: AD-H; 95:5 Hex:isopropanol; 1.0ml.min^{-1}; 237nm.

^{1}H NMR δ: 7.37-7.27 (5H, m, Ar), 4.11-4.05 (1H, m, H-5), 3.77 (1H, d, ^{2}J=13.2, CH_2 Bn), 3.40 (1H, d, ^{2}J=13.2, CH_2 Bn), 2.57-2.46 (2H, m, H-3, H-6), 2.31 (1H, br t, J=8.6, OH), 2.07-1.94 (2H, m, H-3, H-4), 1.85-1.73 (1H, m, H-4). ^{13}C NMR δ: 206.0 (C-2), 137.8 (Ar C_q), 128.7 (Ar(*m*)), 128.0 (Ar(*o*)), 127.7 (Ar(*p*)), 64.8 (C-5), 63.3 (CH_2 Bn), 48.0, 47.7 (C-1, C-6), 34.9 (C-3), 29.2 (C-4). $[\propto]_D^{20^oC}$= -81 (c=1.1; CH_2Cl_2). M.p. = 78-79°C. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1176; Found 218.1171.

(+)-(1*S*,2*R*,6*R*)-7-Benzyl-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate 7a

^{1}H NMR δ: 7.34-7.25 (5H, m, Ar), 5.08 (1H, ddd, $J_{2,3}$=10.1, $J_{2,3}$=5.2, $J_{2,1}$=2.3, H-2), 3.96 (1H, d, ^{2}J=13.2, CH_2 Bn), 3.21 (1H, d, ^{2}J=13.4, CH_2 Bn), 2.56 (1H, dm, $J_{1,6}$=6.0, H-1), 2.52 (1H, ddd, ^{2}J=17.3, $J_{4,3}$=4.3, $J_{4,3}$=3.3, H-4), 2.29 (1H, d, $J_{6,1}$=6.1, H-6), 2.26-2.04 (2H, m, H-3, H-4), 1.88 (3H, s, CH_3 Ac), 1.82-1.75 (1H, m, H-3). ^{13}C NMR δ: 206.0 (C-5), 170.7 (C=O Ac), 137.7 (Ar C_q), 128.3 (Ar(*m*)), 128.0 (Ar(*o*)), 127.3 (Ar(*p*)), 69.0 (C-2), 62.9 (CH_2 Bn), 46.9 (C-6), 43.7 (C-1), 34.8 (C-4), 22.8 (C-3), 20.8 (CH_3 Ac). $[\propto]_D^{20^oC}$= -185 (c=1.0; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1279.

(-)-(1*S*,4*S*,5R)-6-Benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one 5b

Using the general procedure, with 25 mg of novozym 435, the quantity of diisopropyl ether and vinyl acetate used was 2 mL and 10 eq., respectively, and

the resolution took 16h to be complete, 24 mg (48%) **(-)-5b** (99% e.e, HPLC) as a white solid and 30 mg (50%) **(+)-7b** (95% e.e., HPLC) as an oil. HPLC conditions: AD-H; 95:5 Hex:isopropanol; 1.0ml.min^{-1}; 237nm.

^{1}H NMR δ: 7.37-7.27 (5H, m, Ar), 4.33 (1H, td, $J_{4,3}$=8.1, $J_{4,5}$=3.3, H-4), 3.65 (1H, d, ^{2}J=13.4, CH_2 Bn), 3.47 (1H, d, ^{2}J=13.4, CH_2 Bn), 2.95 (1H, t, $J_{5,1}$=$J_{5,4}$=3.8, H-5), 2.47 (1H, d, $J_{1,5}$=4.2, H-1), 2.45-2.30(1H, br s, OH), 2.38 (1H, dd, ^{2}J=17.8, $J_{3,4}$=8.4, H-3), 2.22 (1H, dd, ^{2}J=17.8, $J_{3,4}$=7.0, H-3). ^{13}C NMR δ: 206.8 (C-2), 137.6 (Ar C_q), 128.7 (Ar(*m*)), 127.9 (Ar(*o*)), 127.8 (Ar(*p*)), 67.5 (C-4), 61.3 (CH_2 Bn), 50.1, 49.6 (C-1, C-5), 42.2 (C-3). FTIR (Neat): 3260 (OH st), 1731 (C=O st). $[\propto]_D^{20^oC}$= -36 (c=1.0; CH_2Cl_2). M.p. = 115.5-117.5°C (decomp.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}NO_2$ 204.1019; Found 204.1020.

(+)-(1*S*,2*R*,5*R*)-6-Benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 7b

^{1}H NMR δ: 7.37-7.26 (5H, m, Ar), 5.15 (1H, td, $J_{2,3}$=8.1, $J_{2,1}$=3.2, H-2), 3.84 (1H, d, ^{2}J=13.5, CH_2 Bn), 3.31 (1H, d, ^{2}J=13.6, CH_2 Bn), 3.08 (1H, t, $J_{1,2}$=$J_{1,5}$=3.7, H-1), 2.49 (1H, dd, ^{2}J=17.5, $J_{3,2}$=7.8, H-3), 2.48 (1H, d, $J_{5,1}$=4.0, H-5), 2.40 (1H, dd, ^{2}J=17.6, $J_{3,2}$=6.8, H-3), 1.97 (3H, s, CH_3 Ac). ^{13}C NMR δ: 205.4 (C-2), 170.8 (C=O Ac), 137.6 (Ar C_q), 128.5 (Ar(*m*)), 127.8 (Ar(*o*)), 127.5 (Ar(*p*)), 69.4 (C-2), 60.9 (CH_2 Bn), 48.7 (C-5), 46.5 (C-1), 38.2 (C-3), 20.7 (CH_3 Ac). FTIR (Neat): 1732 (C=O st). $[\propto]_D^{20^oC}$= +120 (c=0.7; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}NO_3$ 246.1125; Found 246.1123.

(-)-(1*S*,6*S*,7*R*)-8-Benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one 5c

Using the general procedure, with 75 mg of novozym 435 and the resolution took 24h to be complete, 24 mg (48%) **(-)-5c** as an oil and 30 mg (50%)

(+)-7c (93% e.e., HPLC) as an oil. HPLC conditions: IB; 98:2 Hex:isopropanol (0.1% diethylamine); 2.0ml.min^{-1}; 237nm.

^{1}H NMR δ: 7.36-7.26 (5H, m, Ar), 3.83 (1H, dd, $J_{6,5}$=10.7, $J_{6,5}$=2.4, H-6), 3.71 (1H, d, ^{2}J=13.3, CH_2 Bn), 3.43 (1H, d, ^{2}J=13.3, CH_2 Bn), 2.80 (1H, ddd, ^{2}J=13.9, $J_{3,4}$=10.9, $J_{3,4}$=3.0, H-3), 2.33 (1H, br d, $J_{1,7}$=7.3, H-1); 2.29 (1H, br d, $J_{7,1}$=7.6, H-7); 2.24-2.19 (1H, m, H-3), 1.98-1.78 (4H, m, H-4, H-5, OH), 1.24-1.13 (1H, m, H-4). ^{13}C NMR δ: 210.8 (C-2), 138.3 (Ar C_q), 128.6 (Ar(*m*)), 128.0 (Ar(*o*)), 127.6 (Ar(*p*)), 71.6 (C-6), 64.1 (CH_2 Bn), 49.6, 49.2 (C-1, C-7), 41.5 (C-3), 34.2 (C-5), 22.3 (C-4). FTIR (Neat): 3420 (O-H st); 1687 (C=O st). $[\propto]_D^{20^oC}$= -110 (c=0.8; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1332; Found 232.1330.

(+)-(1*S*,2*R*,7*R*)-8-Benzyl-6-oxo-8-azabicyclo[5.1.0]octan-2-yl acetate 7c

^{1}H NMR δ: 7.34-7.26 (5H, m, Ar), 4.96 (1H, dd, $J_{2,3}$=11.4, $J_{2,3}$=3.2, H-2), 3.71 (1H, d, ^{2}J=13.4, CH_2 Bn), 3.44 (1H, d, ^{2}J=13.4, CH_2 Bn), 2.81 (1H, ddd, $J_{5,4}$=13.8, ^{2}J=11.2, $J_{5,4}$=2.9, H-5), 2.32 (1H, d, $J_{7,1}$=7.4, H-7); 2.27 (1H, d, $J_{1,7}$=7.7, H-1); 2.24 (1H, dd, ^{2}J=11.1, $J_{5,4}$=5.4, H-5), 2.07 (1H, q, ^{2}J=$J_{3,2}$= $J_{3,4}$=11.9, H-3), 1.94 (3H, s, CH_3 Ac), 1.89-1.76 (2H, m,H-3, H-4), 1.22 (1H, q, ^{2}J=$J_{4,3}$=$J_{4,5}$=13.8, H-4). ^{13}C NMR δ: 210.3 (C-6), 170.3 (C=O Ac), 137.8 (Ar C_q), 128.4 (Ar(*m*)), 128.0 (Ar(*o*)), 127.4 (Ar(*p*)), 73.8 (C-2), 63.9 (CH_2 Bn), 48.6 (C-7), 46.7 (C-1), 41.3 (C-5), 30.2 (C-3), 21.9 (C-4), 21.1 (CH_3 Ac). FTIR (Neat): 1730, 1693 (C=O st). $[\propto]_D^{20^oC}$= +167 (c=0.6; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{20}NO_3$ 274.1438; Found 274.1436.

(+)-(1*R*,5*S*,6*S*)-5-Hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one 5d

Using the general procedure, with 50 mg of novozym 435, the quantity of diisopropyl ether and vinyl acetate used was 2 mL and 10 eq., respectively, and the resolution took 24h to be complete, 23 mg (46%) **(+)-5d** (91% e.e, HPLC) as

a white solid and 28 mg (49%) **(-)-7d** (96% e.e., HPLC) as an oil. HPLC conditions: AD-H; 80:20 Hex:isopropanol; 1.0ml.min^{-1}; 254nm.

^{1}H NMR δ: 7.81 (2H, d, ^{3}J=8.2, Ar(*o*)), 7.36 (2H, d, ^{3}J=8.0, Ar(*m*)), 4.46 (1H, q, $J_{5,4}$=$J_{5,6}$=2.9, H-5), 3.44 (1H, dm, $J_{6,1}$=6.4, H-6), 3.19 (1H, d, $J_{1,6}$=6.4, H-1), 2.46 (3H, s, CH_3 Ts), 2.41 (1H, ddd, ^{2}J=18.3, $J_{3,4}$=12.1, $J_{3,4}$=6.3, H-3), 2.26 (1H, ddd, ^{2}J=18.3, $J_{3,4}$=5.4, $J_{3,4}$=3.5, H-3), 2.13-2.04 (1H, m, H-4), 1.85 (1H, br s, OH), 1.82-1.75 (1H, m, H-4). ^{13}C NMR δ: 201.0 (C-2), 145.5 (Ar C-SO_2 Ts), 133.6 (Ar(*p*)), 130.1 (Ar(*m*)), 128.1 (Ar(*o*)), 62.8 (C-5), 43.6 (C-1), 43.4 (C-6), 31.8 (C-3), 25.2 (C-4), 21,7 (CH_3 Ts). FTIR (Neat): 1701 (C=O st). $[\propto]_D^{20^oC}$= +13 (c=1.0; CH_2Cl_2). M.p. = 114-116°C. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_4S$ 282.0795; Found 282.0796.

(-)-(1*R*,2*R*,6*S*)-7-(4-Methylbenzenesulfonyl)-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate 7d

^{1}H NMR δ: 7.82 (2H, d, ^{3}J=8.2, Ar(*o*)), 7.37 (2H, d, ^{3}J=8.2, Ar(*m*)), 5.34 (1H, q, $J_{2,3}$=$J_{2,1}$=3.0, H-2), 3.49 (1H, dm, $J_{1,6}$=6.3, H-1), 3.25 (1H, d, $J_{6,1}$=6.3, H-6), 2.46 (3H, s, CH_3 Ts), 2.34-2.30 (2H, m, H-4), 2.17-2.04 (1H, m, H-3), 2.10 (3H, s, CH_3 Ac), 1.89-1.82 (1H, m, H-3). ^{13}C NMR δ: 199.7 (C-5), 170.0 (C=O Ac), 145.6 (Ar C-SO_2 Ts), 133.7 (Ar(*p*)), 130.1 (Ar(*m*)), 128.1 (Ar(*o*)), 65.3 (C-2), 43.0 (C-6), 41.1 (C-1), 32.1 (C-4), 22.4 (C-3), 21,7 (CH_3 Ts), 20,9 (CH_3 Ac). FTIR (Neat): 1743, 1722 (C=O st). $[\propto]_D^{20^oC}$= -11 (c=0.8; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_5S$ 324.0900; Found 324.0897.

General procedure for the hydrolysis of acetoxyaziridines

To a stirred solution of acetoxyaziridine (approx. 30 mg, 0.12 mmol) in methanol (1 mL) was added potassium carbonate (1.6 mg, 10 mol%). After 1 hour, ammonium chloride (2 mg) was added. The salts were then filtered and the

solution evaporated to dryness affording the hydroxyaziridine **5** in quantitative yield.

(+)-(1R,4S,5S)-6-Benzyl-4-methoxy-6-azabicyclo[3.1.0]hexan-2-one 8

A procedure similar to the general was used, but 2 eq. of potassium carbonate were used instead of 10 mol%. 44 mg of compound **8** were obtained as colorless oil with quantitative yield. HPLC conditions: AD-H; 95:5 Hex:isopropanol; 1.0ml.min^{-1}; 237nm.

^{1}H NMR δ: 7.37-7.26 (5H, m, Ar), 4.07 (1H, $J_{4,5}$=5.6, d, H-4), 3.65 (1H, d, ^{2}J=13.6, CH_2 Bn), 3.49 (1H, d, ^{2}J=13.8, CH_2 Bn), 3.35 (3H, s, OMe), 2.89 (1H, d, $J_{5,1}$=3.9, H-5), 2.41 (1H, dd, ^{2}J=18.2, $J_{3,4}$=5.6, H-3), 2.36 (1H, d, $J_{1,5}$=3.9, H-1), 2.03 (1H, d, ^{2}J=18.2, H-3). ^{13}C NMR δ: 209.4 (C-2), 137.7 (Ar C_q), 128.6 (Ar(*m*)), 127.7 (Ar(*o*)), 127.5 (Ar(*p*)), 77.4 (C-4), 61.3 (CH_2 Bn), 56.5 (OMe), 48.9 (C-5), 46.0 (C-1), 40.3 (C-3). FTIR (Neat): 1744 (C=O st). $[\propto]_D^{20^oC}$ = +35 (c=0.6; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1176; Found 218.1176.

(±)-1,3-Diethyl 2-[(1*R*,2*R*,5*R*)-6-benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 10

To a stirred solution of **(±)-8** (40 mg, 0.16 mmol) and diethyl malonate (50µL, 2eq.) in dry THF (1 mL) under argon was added sodium hydride (8 mg, 2eq.) at 0°C. After 1 hour of stirring at room temperature, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 2:1) afforded 40 mg (71%) of pure compound **10** as colorless oil.

^{1}H NMR δ: 7.38-7.25 (5H, m, Ar), 4.26-4.13 (4H, m, 2xCH_2 Et), 3.63 (1H, d, ^{2}J=13.7, CH_2 Bn), 3.48 (1H, d, ^{2}J=13.7, CH_2 Bn), 3.44 (1H, d, $J_{2,2'}$=6.9, H-2), 3.11 (1H, ddd, $J_{2',3'}$=8.3, $J_{2',2}$=7.2, J=1.1, H-2'), 2.77 (1H, d, $J_{1',5'}$=3.9, H-1'), 2.62 (1H, dd, ^{2}J=18.5, $J_{3',2'}$=8.7, H-3'), 2.31 (1H, d, $J_{5',1'}$=3.9, H-5'), 1.96 (1H, d, ^{2}J=18.5, H-3'), 1.25 (6H, t, ^{3}J=7.1, 2xCH_3 Et). ^{13}C NMR δ: 209.5 (C-4'), 167.84, 167.81 (C-1, C-3), 137.8 (Ar C_q), 128.5 (Ar(*m*)), 127.7 (Ar(*o*)), 127.4 (Ar(*p*)), 61.9, 61.8 (2xCH_2 Et), 61.4 (CH_2 Bn), 54.2 (C-2), 48.3 (C-1'), 47.0 (C-5'), 38.0 (C-3'), 35.9 (C-2'), 14.0 (2xCH_3 Et). FTIR (Neat): 1743, 1728 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{24}NO_5$ 346.1649; Found 346.1649.

(±)-(1*R*,4*S*,5*R*)-6-Benzyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 11

To a stirred solution of **(±)-8** (60 mg, 0.25 mmol) in dry THF (0.5 mL) under argon was added DBU (55 µL, 1.5eq.) at -20°C. After 30 min of stirring at this temperature, this solution was added to a mixture of allyl magnesium bromide (1M in Et_2O, 2.8 eq., 690 µL), CuI (3.2 eq., 150 mg), LiBr (3.2eq., 70 mg) and dry THF 1mL at -78°C. After 30 minutes of stirring at this temperature, reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 8:2) afforded 30 mg (54%) of pure compound **11** as colorless oil.

^{1}H NMR δ: 7.40 (2H, d, ^{3}J=7.3, Ar(*o*)), 7.32 (2H, t, ^{3}J=7.5, Ar(*m*)), 7.25 (1H, d, ^{3}J=7.2, Ar(*p*)), 5.88 (1H, ddt, $J_{2',3'}$=18.1, $J_{2',3'}$=9.3, $J_{2',1'}$=6.9, H-2'), 5.10-5.04 (2H, m, H-3'); 3.59 (1H, d, ^{2}J=13.8, CH_2 Bn), 3.47 (1H, d, ^{2}J=13.8, CH_2 Bn), 2.62 (1H, d, $J_{1,5}$=4.0, H-1), 2.58-2.48 (2H, m, H-3, H-4), 2.24 (1H, d, $J_{5,1}$=4.0, H-5), 2.16 (1H, dt, ^{2}J=13.7, $J_{1',2'}$=$J_{1',4}$=6.8, H-1'), 2.05 (1H, dt, ^{2}J=14.4, $J_{1',2'}$=$J_{1',4}$=7.1, H-1'), 1.74 (1H, d,

^{2}J=16.8, H-3). ^{13}C NMR δ: 211.5 (C-2), 138.3 (Ar C_q), 134.9 (C-2'), 128.5 (Ar(*m*)), 127.6 (Ar(*o*)), 127.3 (Ar(*p*)), 117.6 (C-3'), 61.5 (CH_2 Bn), 50.8 (C-1), 46.6 (C-5), 39.3 (C-3), 37.6 (C-1'), 35.7 (C-4). FTIR (Neat): 1741 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO$ 228.1383; Found 228.1383.

(±)-(1*R*,4*S*,5*R*)-6-Benzyl-4-(benzylamino)-6-azabicyclo[3.1.0]hexan-2-one 12

To a stirred solution of (±)-**8** (60 mg, 0.25 mmol) and benzylamine (55 µL, 2 eq.) in dry *tert*-butanol (1 mL) was added potassium carbonate (70 mg, 2 eq.) at room temperature. After 1.5 hours of stirring at this temperature, reaction mixture was quenched with water and extracted with AcOEt (3x5 mL). The combined organic layers were dried with sodium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with AcOEt) afforded 47 mg (52%) of pure compound **12** as fluorescent greenish yellow oil.

^{1}H NMR δ: 7.36-7.24 (10H, m, Ar), 3.83 (1H, d, ^{2}J=13.1, CH_2 Bn amine), 3.79 (1H, d, ^{2}J=13.0, CH_2 Bn amine), 3.62 (1H, d, ^{2}J=13.8, CH_2 Bn aziridine), 3.59 (1H, d, $J_{4,3}$=6.6, H-4), 3.46 (1H, d, ^{2}J=13.7, CH_2 Bn aziridine), 2.76 (1H, d, $^{2}J_{5,1}$=4.0, H-5), 2.59 (1H, dd, ^{2}J=18.0, $J_{3,4}$=6.5, H-3), 2.32 (1H, d, $J_{1,5}$=3.9, H-1), 1.89 (1H, d, ^{2}J=18.0, H-3), 1.50 (1H, S, NH). ^{13}C NMR δ: 210.5 (C-2), 139.6, 137.9 (2xAr C_q), 128.59, 128.55, 128.2, 127.7, 127.4, 127.3 (6xAr), 61.4 (CH_2 Bn aziridine), 55.1 (C-4), 51.4 (CH_2 Bn amine), 50.6 (C-5), 46.2 (C-1), 41.4 (C-3). FTIR (Neat): 1739 (C=O st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{21}N_2O$ 293.1648; Found 293.1646.

(±)-(4*R*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-methylcyclopent-2-en-1-one 20[59]

To a stirred solution of (±)-(4R,5S)-4-hydroxy-5-methylcyclopent-2-en-1-one **19**[25] (210 mg, 1.9 mmol) in dry DCM (4 mL) under argon was added diisopropylamine (810 µL, 2.5 eq.), *tert*-butyldimethylsilylchloride (560 mg, 2 eq.)

and DMAP (cat.) at 0ºC. After 16 hours of stirring at room temperature, the reaction was quenched with water (5mL) and the mixture was extracted with DCM (3x 5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex:AcOEt (95:5), afforded 280 mg (66%) of the pure compound as colorless oil.

(±)-(4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-5-methylcyclopent-2-en-1-one 21

To a stirred solution of **20** (270 mg, 1.2 mmol) in Et_2O:Py 1:1 (2mL) under argon was added iodine (600mg, 2 eq.) at 0 ºC. After 30 min of stirring at room temperature, the reaction mixture was diluted with Et_2O (5mL) and washed with a sodium thiosulfate solution 20%(w/V) (5mL), HCl 2M (2x5mL) and water (5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex:AcOEt (95:5) afforded 235 mg (56%) of the pure compound **21** as colorless oil.

^{1}H NMR δ: 7.74 (1H, d, $J_{3,4}$=2.3, H-3); 4.48 (1H, t, $J_{4,3}$=$J_{4,5}$=2.4, H-4); 2.36 (1H, qd, $J_{5,Me}$=7.4, $J_{5,4}$=2.4, H-5); 1.28 (3H, d, $J_{Me,5}$=7.5, Me); 0.92 (9H, s, ^{t}Bu TBS); 0.15 (3H, s, Me TBS); 0.14 (3H, s, Me TBS). ^{13}C NMR δ: 202.1 (C-1); 167.5 (C-3); 103.6 (C-2); 79.4 (C-4); 48.8 (C-5); 25.7 (3xMe ^{t}Bu); 18.0 (C_q ^{t}Bu); 12.9 (Me); -4.63 (Me TBS); -4.65 (Me TBS). FTIR(NEAT): 1731 (C=O st); 1259 (Si-Me bend); 1105 (Si-O-C st); 837 (Si-O-C bend); 778 (alkene C-H o.o.p. bend).

(±)-(1*S*,3*S*,4*S*,5*R*)-6-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-6-azabicyclo[3.1.0]hexan-2-one 22

To a stirred solution of **21** (230 mg, 0.65 mmol) in dry Toluene (3 mL) under argon was added anhydrous cesium carbonate (230 mg, 1.1eq.), 1,10-phenantroline (120 mg, 1.0 eq.) and benzylamine (110 µL, 1.5 eq.) at room temperature. After stirring at the same temperature for 3 hours, reaction mixture was quenched with water (5mL) and extracted with DCM (3x5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:AcOEt 95:5) afforded 152 mg (70%) of pure compound **22** as colorless oil.

^{1}H NMR δ: 7.41 (2H, d, ^{3}J=7.2, Ar(*o*)); 7.32 (2H, t, ^{3}J=7.3, Ar(*m*)); 7.25 (1H, t, ^{3}J =7.3 Hz, Ar(*p*)); 3.86 (1H, d, ^{2}J=13.9, CH_2 Bn); 3.82 (1H, dd, $J_{4,5}$=8.0, $J_{4,3}$=3.0, H-4); 3.27 (1H, d, ^{2}J=13.9, CH_2 Bn); 2.66 (1H, dd, $J_{5,1}$=4.3, $J_{5,4}$=3.2, H-5); 2.54 (1H, p, $J_{3,4}$= $J_{3,Me}$=7.2, H-3), 2.39 (1H, d, $J_{1,5}$=4.4, H-1); 1.01 (3H, d, $J_{Me,3}$=7.1, H-3); 0.89 (9H, s, ^{t}Bu TBS), 0.08 (3H, s, Me TBS), 0.03 (3H, s, Me TBS). ^{13}C NMR δ: 208.7 (C-2); 137.9 (Ar C_q); 128.4 (Ar(*m*)); 127.6 (Ar(*o*)); 127.2 (Ar(*p*)); 75.9 (C-4); 61.2 (CH_2 Bn); 49.1 (C-5); 48.1 (C-1); 45.5 (C-3); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 10.3 (Me); -4.3 (Me TBS); -4.7 (Me TBS). FTIR (Neat): 1743 (C=O st); 1107 (Si-O-C st); 837 (Si-O-C bend).

(±)-(1*S*,3*S*,4*S*,5*R*)-6-Benzyl-4-hydroxy-3-methyl-6-azabicyclo[3.1.0]hexan-2-one 23

To a stirred solution of **22** (140 mg, 0.42 mmol) in dry THF (2mL) under argon was added TBAF (760 µL, 1 M in THF, 1.8 eq.) at room temperature. After 15 minutes, the reaction mixture was diluted with DCM (5 mL) and washed with water (5 mL). The organic layer was dried with magnesium sulfate and

evaporated to dryness. Purification by chromatography (preparative plate eluted with Hex:AcOEt 1:2) afforded 85 mg (93%) of pure compound **23** as white solid.

^{1}H NMR δ: 7.35-7.26 (5H, m, Ar); 3.80-3.76 (1H, m, H-4); 3.63 (1H, d, ^{2}J=13.4, CH_2 Bn); 3.48 (1H, d, ^{2}J=13.4, CH_2 Bn); 2.90 (1H, t, $J_{5,1}$=$J_{5,4}$=3.3, H-5); 2.50 (1H, d, $J_{1,5}$=4.2, H-1); 2.29 (1H, p, $J_{3,4}$= $J_{3,Me}$=7.2, H-3); 2.02 (1H, br s, OH); 1.07 (3H, d, $J_{Me,3}$=7.2, H-3). ^{13}C NMR δ: 208.3 (C-2); 137.7 (Ar C_q); 128.7 (Ar(*m*)); 127.9 (Ar(*o*)); 127.7 (Ar(*p*)); 75.5 (C-4); 61.4 (CH_2 Bn); 49.1 (C-1); 48.4 (C-5); 45.5 (C-3); 10.7 (Me). FTIR (Neat): 3420 (O-H st); 1737 (C=O st). M.p.=111.5°C.

(±)-(1*R*,2*S*,3*S*,5*S*)-6-Benzyl-3-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 24

To a stirred solution of **23** (70 mg, 0.32 mmol) in dry DCM (1mL) under argon was added triethylamine (110 µL, 2.5 eq.) and acetic anhydride (60 µL, 2 eq.) at room temperature. After 3 hours, the reaction mixture was quenched with water (5 mL) and extracted with DCM (3x5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative plate eluted with Hex:AcOEt 2:1) afforded 61 mg (73%) of pure compound **24** as white solid.

^{1}H NMR δ: 7.37-7.27 (5H, m, Ar); 4.74 (1H, dd, $J_{2,3}$=8.0, $J_{2,1}$=3.1, H-2); 3.81 (1H, d, ^{2}J=13.5, CH_2 Bn); 3.28 (1H, d, ^{2}J=13.5, CH_2 Bn); 3.05 (1H, t, $J_{1,2}$=$J_{1,5}$=3.7, H-1); 2.62 (1H, p, $J_{3,2}$=$J_{3,Me}$=7.4, H-3); 2.51 (1H, d, $J_{5,1}$=4.4, H-5); 2.00 (3H, s, CH_3 Ac); 1.05 (3H, s, Me). ^{13}C NMR δ: 207.2 (C-4); 171.1 (C=O Ac); 137.7 (Ar C_q); 128.5 (Ar(*m*)); 127.7 (Ar(*o*)); 127.4 (Ar(*p*)); 76.8 (C-2); 61.0 (CH_2 Bn); 48.4 (C-5); 45.3 (C-1); 31.7 (C-3); 20.8 (CH_3 Ac); 10.8 (Me). FTIR (Neat): 1731 (C=O st); 1228 (C-O-C st); 1028 (C-O-C st). M.p.=37.5-38°C.

6-Benzyl-3-methyl-6-azabicyclo[3.1.0]hex-3-en-2-one 25

To a stirred solution of **24** (40 mg, 0.15 mmol) in methanol (1mL) was added potassium carbonate (42 mg, 2 eq.). After 2 hours, ammonium chloride (40 mg) was added. The salts were then filtered and the solution evaporated to dryness. Purification by chromatography (preparative plate eluted with Hex:AcOEt 1:1) afforded 10 mg (33%) of pure compound **25** as colorless oil.

^{1}H NMR δ: 7.37-7.28 (5H, m, Ar); 7.24 (1H, p, $J_{4,3}$= $J_{4,Me}$=1.6, H-4); 3.64 (1H, d, ^{2}J=13.6, CH_2 Bn); 3.53 (1H, d, ^{2}J=13.6, CH_2 Bn); 2.93 (1H, dd, $J_{5,1}$=4.1, $J_{5,4}$=2.0, H-5); 2.65 (1H, d, $J_{1,5}$=4.1, H-1); 1.70 (3H, d, $J_{Me,4}$=1.5, H-3). ^{13}C NMR δ: 201.9 (C-2); 151.3 (C-4); 142.2 (C-3); 137.6 (Ar C_q); 128.6 (Ar(*m*)); 127.9 (Ar(*o*)); 127.5 (Ar(*p*)); 62.2 (CH_2 Bn); 43.9 (C-1); 42.2 (C-5); 10.4 (Me). FTIR (Neat): 1710 (C=O st).

(4*E*)-1-(Benzylamino)-4-methylocta-1,4,7-trien-3-one 26

To a stirred solution of **24** (54 mg, 0.21 mmol) in dry THF (0.5 mL) under argon was added DBU (37 µL, 1.2eq.) at -20°C. After 30 min of stirring at this temperature, this solution was added to a mixture of allyl magnesium bromide (1M in Et_2O, 2.8 eq., 582 µL), CuI (3.2 eq., 127 mg), LiBr (3.2eq., 58 mg) and dry THF (1mL) at -78°C. After 30 minutes of stirring at this temperature, reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 8:2) afforded 10 mg (20%) of pure compound **26** as yellow oil.

^{1}H NMR δ: 10.31 (1H, br s, NH); 7.36-7.25 (5H, m, Ar); 6.84 (1H, dd, *J*=12.5, $J_{1,2}$=7.7, H-1); 6.40 (1H, t, $J_{5,6}$=7.7, H-5); 5.83 (1H, ddt, $J_{7,8}$=16.5, $J_{7,8}$=10.5, $J_{7,6}$=6.1,

H-7); 5.43 (1H, d, $J_{2,1}$=7.6, H-2); 5.07 (1H, d, $J_{8,7}$=17.5, H-8); 5.02 (1H, d, $J_{8,7}$=10.3, H-8); 4.39 (2H, d, *J*=6.0, CH_2 Bn); 2.93 (2H, t, $J_{6,5}$=$J_{6,7}$=6.5, H-6); 1.85 (3H, s, Me). ^{13}C NMR δ: 193.0 (C-3); 153.0 (C-1); 138.0 (C-4, Ar C_q); 132.7 (C-5); 128.8 (Ar(*m*)); 127.7 (Ar(*p*)); 127.2 (Ar(*o*)); 115.6 (C-8); 90.5 (C-2); 52.6 (CH_2 Bn); 32.9 (C-6); 12.2 (Me). FTIR (Neat): 3300 (N-H st); 1628 (C=O st); 1549 (N-H bend); 1485 (C=C st); 1278 (C-N st).

1,3-Diethyl 2-[(1*E*)-5-(benzylamino)-2-methyl-3-oxopenta-1,4-dien-1-yl]propanedioate 27

To a stirred solution of **24** (40 mg, 0.15 mmol) in dry DCM (1 mL) was added DBU (25 µL, 1.1eq.) and diethyl malonate (47 µL, 2eq.) at 0°C. After 1 hour of stirring at room temperature, reaction mixture was quenched with water (10 mL) and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with DCM:AcOEt 98:2) afforded 7 mg (13%) of pure compound **27** as yellow oil.

^{1}H NMR δ: 10.35 (1H, br s, NH); 7.37-7.25 (5H, m, Ar); 6.90 (1H, dd, *J*=12.7, $J_{5,4}$=7.6, H-5); 6.56 (1H, d, $J_{1,CH\ malonate}$=9.4, H-1); 5.48 (1H, d, $J_{4,5}$=7.6, H-4); 4.41 (2H, d, *J*=6.1, CH_2 Bn); 4.35 (1H, d, $J_{CH\ malonate,1}$=9.4, CH malonate); 4.21 (4H, q, ^{3}J=7.1, 2xCH_2 Et) 1.91 (3H, s, Me); 1.27 (6H, t, ^{3}J=7.1, 2xCH_3 Et). ^{13}C NMR δ: 191.9 (C-3); 167.6 (C=O malonate); 153.6 (C-5); 141.8 (C-2); 137.8 (Ar C_q); 128.8 (Ar(*m*)); 127.8 (Ar(*p*)); 127.2 (Ar(*o*)); 125.2 (C-1); 90.7 (C-4); 61.9 (CH_2 Et); 52.7 (CH_2 Bn); 52.1 (CH malonate); 14.0 (CH_3 Et) 12.9 (Me). FTIR (Neat): 1730 (C=O st); 1628 (C=O st) 1279, 1217 (C-O-C st, C-N st); 1028 (C-O-C st).

4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylcyclopent-2-en-1-one[60]

To a stirred solution of 4-Hydroxy-3-methylcyclopent-2-enone **35**[27] (600 mg, 5.4 mmol) in dry DCM (20 mL) under argon was added diisopropylamine (2.3 mL, 2.5 eq.), *tert*-butyldimethylsilylchloride (1.7 g, 2 eq.) and DMAP (cat.) at 0ºC. After 16 hours of stirring at room temperature, the reaction was quenched with water (20mL) and the mixture was extracted with DCM (3x 10mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex:AcOEt (9:1), afforded 669 mg (66%) of the pure title compound as colorless oil.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-3-methylcyclopent-2-en-1-one 36[60]

To a stirred solution of 4-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclopent-2-en-1-one (1g, 4.4 mmol) in Et_2O:Py 1:1 (10mL) under argon was added iodine (4.5 g, 2 eq.) at 0°C. After 16 hours of stirring at room temperature, the reaction mixture was diluted with Et_2O (20mL) and washed with a sodium thiosulfate solution 20%(w/V) (10mL), HCl 2M (2x10mL) and water (10mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness, affording 1.25 g (80%) of the pure compound **36** as colorless oil.

(±)-(1*S*,4*S*,5*R*)-6-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 37

To a stirred solution of **36** (600 mg, 1.7 mmol) in dry Toluene (7 mL) and dry DCM (5mL) under argon was added anhydrous cesium carbonate (660 mg, 1.1eq.), 1,10-phenantroline (306 mg, 1.0 eq.) and benzylamine (280 µL, 1.5 eq.) at room temperature. After stirring at the same temperature for 24 hours, reaction mixture was quenched with water (20mL) and extracted with DCM (3x10

mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:AcOEt 9:1) afforded 344 mg (61%) of **37** as colorless oil and 109 mg (28%) of (±)-(1*R*,4*S*,5*S*)-6-benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-6-azabicyclo[3.1.0]hexan-2-one **37'** as white solid.

^{1}H NMR δ: 7.51 (2H, d, ^{3}J=7.5, Ar(*o*)); 7.31 (2H, t, ^{3}J=7.5, Ar(*m*)); 7.23 (1H, t, ^{3}J =7.3 Hz, Ar(*p*)); 4.20 (1H, t, $J_{4,3}$=7.9, H-4); 4.12 (1H, d, ^{2}J=15.2, CH_2 Bn); 3.55 (1H, d, ^{2}J=15.2, CH_2 Bn); 2.61 (1H, dd, ^{2}J=16.3, $J_{3,4}$=8.1, H-3); 2.22 (1H, dd, ^{2}J=16.3, $J_{3,4}$=7.7, H-3); 2.17 (1H, s, H-1); 1.48 (3H, s, Me); 0.94 (9H, s, ^{t}Bu TBS); 0.10 (3H, s, Me TBS), 0.08 (3H, s, Me TBS). ^{13}C NMR δ: 207.9 (C-2); 138.9 (Ar C_q); 128.3 (Ar(*m*)); 126.8 (Ar(*o*)); 126.7 (Ar(*p*)); 73.4 (C-4); 54.2 (CH_2 Bn); 53.4 (C-1); 53.1 (C-5); 42.6 (C-3); 25.7 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 10.7 (Me); -4.5 (Me TBS); -5.0 (Me TBS). FTIR (Neat): 1746 (C=O st); 1106 (Si-O-C st); 830 (Si-O-C bend).

(±)-(1*R*,4*S*,5*S*)-6-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 37'

^{1}H NMR δ: 7.34-7.23 (5H, m, Ar); 4.29 (1H, d, $J_{4,3}$=5.6, H-4); 3.77 (1H, d, ^{2}J=14.3, CH_2 Bn); 3.67 (1H, d, ^{2}J=14.3, CH_2 Bn); 2.78 (1H, dd, ^{2}J=17.5, $J_{3,4}$=5.6, H-3); 2.13 (1H, s, H-1); 1.85 (1H, d, ^{2}J=17.5, H-3); 1.52 (3H, s, Me); 0.89 (9H, s, ^{t}Bu TBS); 0.09 (3H, s, Me TBS), 0.06 (3H, s, Me TBS). ^{13}C NMR δ: 211.3 (C-2); 138.8 (Ar C_q); 128.5 (Ar(*m*)); 127.3 (Ar(*o*)); 127.1 (Ar(*p*)); 72.8 (C-4); 55.2 (CH_2 Bn); 54.9 (C-5); 52.4 (C-1); 45.8 (C-3); 25.7 (3xMe ^{t}Bu); 18.0 (C_q ^{t}Bu); 8.4 (Me); -4.6 (Me TBS); -5.0 (Me TBS). FTIR (Neat): 1746 (C=O st); 1074 (Si-O-C st); 837 (Si-O-C bend). M.p.=65°C.

(±)-(1*S*,4*S*,5*R*)-6-Benzyl-4-hydroxy-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 38

To a stirred solution of **37** (400 mg, 1.2 mmol) in dry THF (2mL) under argon was added TBAF (2.2 mL, 1 M in THF, 1.8 eq.) at room temperature. After

30 minutes, reaction mixture was quenched with water (10mL) and extracted with DCM (3x5 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:AcOEt 1:1) afforded 267 mg (100%) of pure compound **38** as colorless oil.

^{1}H NMR δ: 7.36-7.26 (5H, m, Ar); 4.12 (1H, dt, $J_{4,OH}$=10.7, $J_{4,3}$=7.6, H-4); 3.72 (2H, s, CH_2 Bn); 2.44 (1H, dd, ^{2}J=17.8, $J_{3,4}$=8.3, H-3); 2.29 (1H, dd, ^{2}J=17.8, $J_{3,4}$=6.7, H-3); 2.28 (1H, s, H-1); 2.09 (1H, d, $J_{OH,4}$=11.0, OH); 1.65 (3H, s, Me). ^{13}C NMR δ: 207.7 (C-2); 138.5 (Ar C_q); 128.7 (Ar(*m*)); 127.6 (Ar(*o*)); 127.4 (Ar(*p*)); 72.8 (C-4); 55.1 (C-1); 55.2 (CH_2 Bn); 53.5 (C-5); 43.3 (C-3); 10.9 (Me). FTIR (Neat): 3420 (O-H st); 1735 (C=O st).

(±)-(1*R*,2*S*,5*S*)-6-Benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 39

To a stirred solution of **38** (170 mg, 0.78 mmol) in dry DCM (3mL) under argon was added triethylamine (270 µL, 2.5 eq.) and acetic anhydride (150 µL, 2 eq.) at room temperature. After 16 hours, the reaction mixture was quenched with water (5 mL) and extracted with DCM (3x5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative plate eluted with Hex:AcOEt 2:1) afforded 184 mg (91%) of pure compound as colorless oil.

^{1}H NMR δ: 7.43 (2H, d, ^{3}J=7.4, Ar(*o*)); 7.33 (2H, t, ^{3}J=7.4, Ar(*m*)); 7.26 (1H, t, ^{3}J =7.3 Hz, Ar(*p*)); 5.15 (1H, t, $J_{2,3}$=8.0, H-2); 3.90 (1H, d, ^{2}J=14.6, CH_2 Bn); 3.72 (1H, d, ^{2}J=14.6, CH_2 Bn); 2.52 (2H, d, $J_{3,2}$=8.0, H-3); 2.24 (1H, s, H-5); 2.12 (3H, s, CH_3 Ac); 1.53 (3H, s, Me). ^{13}C NMR δ: 206.2 (C-4); 170.9 (C=O Ac); 138.5 (Ar C_q); 128.3 (Ar(*m*)); 127.2 (Ar(*o*)); 127.1 (Ar(*p*)); 74.1 (C-2); 54.7 (CH_2 Bn); 53.6 (C-5); 50.4 (C-

1); 39.8 (C-3); 20.9 (CH_3 Ac); 11.1 (Me). FTIR (Neat): 1736 (C=O st); 1232 (C-O-C st).

6-Benzyl-5-methyl-6-azabicyclo[3.1.0]hex-3-en-2-one 40

To a stirred solution of **39** (30 mg, 0.12 mmol) in dry DCM (1 mL) under argon was added DBU (26 µL, 1.5eq.) at 0°C. After 30 min of stirring at room temperature, reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness, affording 24 mg (100%) of pure compound **40** as yellow oil.

^{1}H NMR δ: 7.49 (0.7H, d, $J_{4,3}$=5.8, H-4); 7.33-7.22 (5H, m, Ar); 6.99 (0.3H, d, $J_{4',3'}$=5.8, H-4'); 6.08 (0.3H, dd, $J_{3',4'}$=5.8, $J_{3',1'}$=1.6, H-3'); 5.84 (0.7H, dd, $J_{3,4}$=5.8, $J_{3,1}$=1.4, H-3); 4.00 (0.3H, d, ^2J=14.0, CH_2 Bn'); 3.74 (0.7H, d, ^2J=14.3, CH_2 Bn); 3.71 (0.3H, d, ^2J=14.5, CH_2 Bn'); 3.68 (0.7H, d, ^2J=14.2, CH_2 Bn); 2.67 (0.3H, d, $J_{1',3'}$=1.4, H-1'); 2.42 (0.7H, s, H-1); 1.68 (2.1H, s, Me); 1.63 (0.9H, s, Me'). ^{13}C NMR δ: 202.8 (C-2); 201.4 (C-2'); 163.6 (C-4); 155.1 (C-4'); 139.0 (Ar C_q'); 138.1 (Ar C_q); 131.80 (C-3); 131.75 (C-3'); 128.5 (Ar(*m*)); 127.9 (Ar(*o*)'); 127.5 (Ar(*o*)'); 127.18 (Ar(*p*)); 127.17 (Ar(*p*)'); 57.0 (CH_2 Bn); 51.2 (C-5'); 49.4 (CH_2 Bn'); 49.1 (C-1); 48.9 (C-5); 46.6 (C-1'); 17.6 (Me); 9.5 (Me'). FTIR (Neat): 1712 (C=O st).

6-Benzyl-5-methyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 41

To a stirred solution of allyl magnesium bromide (1M in Et_2O, 2.8 eq., 340 µL), CuI (3.2 eq., 73 mg), LiBr (3.2 eq., 33 mg) in dry THF (0.5mL) at -78°C was added a solution of **40** (24 mg, 0.12 mmol) in dry THF (0.5mL). After 30 minutes of stirring at this temperature, reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The

combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 8:2) afforded 10 mg (34%) of product as a mixture of two diastereomers (d.r.=6:4, **41a**:**41b**). The diastereomers **41a** and **41b** were further separated by chromatography (preparative TLC eluted with DCM).

(±)-(1*S*,4*S*,5*S*)-6-Benzyl-5-methyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 41a

^{1}H NMR δ: 7.37-7.24 (5H, m, Ar); 5.37 (1H, ddt, $J_{2',3'}$=17.1, $J_{2',3'}$=10.2, $J_{2',1'}$=6.8, H-2'); 4.97 (1H, d, $J_{3',2'}$=17.2, H-3'); 4.95 (1H, d, $J_{3',2'}$=9.9, H-3'); 3.75 (1H, d, ^{2}J=14.0, CH_2 Bn); 3.66 (1H, d, ^{2}J=14.0, CH_2 Bn); 2.40-2.33 (1H, m, H-1'); 2.23-2.07 (4H, m, H-3, H-4, H-1'); 2.05 (1H, s, H-1); 1.53 (3H, s, Me). ^{13}C NMR δ: 212.0 (C-2); 138.9 (Ar C_q); 136.7 (C-2'); 128.4 (Ar(*m*)); 127.8 (Ar(*o*)); 127.1 (Ar(*p*)); 116.1 (C-3'); 55.5 (CH_2 Bn); 54.0 (C-1); 52.1 (C-5); 42.6 (C-4); 40.1 (C-3); 34.6 (C-1'); 12.4 (Me). FTIR (Neat): 1740 (C=O st).

(±)-(1*S*,4*R*,5*S*)-6-Benzyl-5-methyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 41b

^{1}H NMR δ: 7.36-7.30 (4H, m, Ar(*o*,*m*)); 7.27-7.23 (1H, m, Ar(*p*)); 5.69 (1H, m, H-2'); 5.13-5.02 (2H, m, H-3'); 3.78 (1H, d, ^{2}J=14.4, CH_2 Bn); 3.73 (1H, d, ^{2}J=14.5, CH_2 Bn); 2.64 (1H, dd, ^{2}J=17.4, $J_{3,4}$=8.2, H-3); 2.48 (1H, td, $J_{4,3}$= $J_{4,1'}$=8.9, $J_{4,1'}$=3.8, H-4); 2.42-2.36 (1H, m, H-1'); 2.06 (1H, s, H-1); 1.99 (1H, dt, ^{2}J=17.3, $J_{1',4}$= $J_{1',2'}$=7.4, H-1'); 1.85 (1H, d, ^{2}J=17.4, H-3); 1.49 (3H, s, Me). ^{13}C NMR δ: 212.8 (C-2); 139.0 (Ar C_q); 135.0 (C-2'); 128.4 (Ar(*m*)); 127.3 (Ar(*o*)); 127.0 (Ar(*p*)); 117.8 (C-3'); 55.1 (CH_2 Bn); 52.8 (C-1); 52.7 (C-5); 40.8 (C-4); 39.5 (C-3); 36.3 (C-1'); 9.8 (Me). FTIR (Neat): 1741 (C=O st).

(±)-(1*S*,4*R*,5*R*)-6-Benzyl-4-methoxy-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 42

To a stirred solution of **39** (30 mg, 0.12 mmol) in methanol (1mL) was added potassium carbonate (32 mg, 2 eq.). After 20 minutes, ammonium chloride (40 mg) was added. The salts were then filtered and the solution evaporated to dryness, affording 24 mg (90%) of compound **42** as colorless oil.

^{1}H NMR δ: 7.35-7.23 (5H, m, Ar); 3.86 (1H, d, $J_{4,3}$=5.5, H-4); 3.74 (2H, s, CH_2 Bn); 3.31 (3H, s, OMe); 2.61 (1H, dd, ^{2}J=17.7, $J_{3,4}$=5.5, H-3); 2.15 (1H, s, H-1); 2.05 (1H, d, ^{2}J=17.7, H-3); 1.55 (3H, s, Me). ^{13}C NMR δ: 210.8 (C-2); 138.7 (Ar C_q); 128.5 (Ar(*m*)); 127.3 (Ar(*o*)); 127.1 (Ar(*p*)); 81.2 (C-4); 56.9 (OMe); 54.9 (CH_2 Bn); 53.2 (C-5); 51.9 (C-1); 40.2 (C-3); 8.1 (Me). FTIR (Neat): 1744 (C=O st); 1115, 1089 (C-O-C st); 731, 696 (Ar C-H o.o.p bend).

1,3-Diethyl 2-{6-benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl}propanedioate 43

To a stirred solution of **39** (28 mg, 0.11 mmol) in dry DCM (1 mL) was added DBU (24 µL, 1.5eq.) and diethyl malonate (33 µL, 2eq.) at 0°C. After 3 hours of stirring at room temperature, reaction mixture was quenched with water (10 mL) and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 2:1) afforded 36 mg (93%) of product as a mixture of two diastereomers (d.r.=9:1, **43a**:**43b**). The diastereomers **43a** and **43b** were further separated by chromatography (preparative TLC eluted with DCM:AcOEt 95:5).

1,3-Diethyl 2-[(1*S*,2*S*,5*S*)-6-benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 43a

^{1}H NMR δ: 7.33-7.32 (4H, m, Ar(*o*,*m*)); 7.28-7.23 (1H, m, Ar(*p*)); 4.20 (4H, q, ^{3}J=7.1, 2xCH_2 Et); 3.82 (1H, d, ^{2}J=14.4, CH_2 Bn); 3.70 (1H, d, ^{2}J=14.4, CH_2 Bn); 3.69 (1H, d, $J_{CH\ malonate,2}$=4.0, CH malonate); 3.00 (1H, dd, $J_{2,3}$=8.8, $J_{2,CH\ malonate}$=2.8, H-2); 2.68 (1H, dd, ^{2}J=18.1, $J_{3,2}$=9.3, H-3); 2.16 (1H, d, ^{2}J=18.1, H-3); 2.15 (1H, s, H-5); 1.45 (3H, s, Me); 1.264 (3H, t, ^{3}J=7.1, CH_3 Et); 1.257 (3H, t, ^{3}J=7.1, CH_3 Et). ^{13}C NMR δ: 210.5 (C-4); 168.6, 168.0 (2xC=O malonate); 138.8 (Ar C_q); 128.8 (Ar(*m*)); 127.3 (Ar(*o*)); 127.1 (Ar(*p*)); 61.9, 61.7 (2xCH_2 Et); 55.1 (CH_2 Bn); 53.3 (C-5); 52.6 (CH malonate); 50.3 (C-1); 41.2 (C-2); 37.9 (C-3); 14.0, 13.9 (2xCH_3 Et); 9.7 (Me). FTIR (Neat): 1728 (C=O st).

1,3-Diethyl 2-[(1*S*,2*R*,5*S*)-6-benzyl-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 43a

^{1}H NMR δ: 7.34-7.23 (5H, m, Ar); 4.21-4.07 (4H, m, 2xCH_2 Et); 3.88 (1H, d, ^{2}J=14.0, CH_2 Bn); 3.71 (1H, d, $J_{CH\ malonate,2}$=7.6, CH malonate); 3.44 (1H, d, ^{2}J=14.1, CH_2 Bn); 2.90 (1H, q, $J_{2,3}$=$J_{2,CH\ malonate}$=8.5, H-2); 2.40 (1H, dd, ^{2}J=17.8, $J_{3,2}$=8.8, H-3); 2.31 (1H, dd, ^{2}J=17.8, $J_{3,2}$=8.8, H-3); 2.05 (1H, s, H-5); 1.56 (3H, s, Me); 1.23 (6H, t, ^{3}J=7.1, 2xCH_3 Et). ^{13}C NMR δ: 210.0 (C-4); 168.6, 168.2 (2xC=O malonate); 138.5 (Ar C_q); 128.4 (Ar(*m*)); 127.6 (Ar(*o*)); 127.2 (Ar(*p*)); 61.60, 61.57 (2xCH_2 Et); 55.1 (CH_2 Bn); 54.3 (C-5); 52.8 (CH malonate); 50.1 (C-1); 42.0 (C-2); 38.3 (C-3); 14.00, 13.98 (2xCH_3 Et); 12.7 (Me). FTIR (Neat): 1728 (C=O st).

6-Benzyl-4-methylidene-1-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hex-2-ene 44

To a stirred solution of **39** (32 mg, 0.12 mmol) in dry THF (0.5 mL) under argon was added DBU (28 µL, 1.5eq.) at 0°C. After 30 min of stirring at this temperature, this solution was added to a mixture of allyl magnesium bromide

(1M in Et_2O, 2.8 eq., 340 µL), CuI (3.2 eq., 75 mg), HMPA (5eq., 110 µL) and dry THF (0.5mL) at -78°C. After 30 minutes of stirring at this temperature, reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 8:2) afforded 10 mg (36%) of pure compound **44** as yellow oil.

^{1}H NMR δ: 7.42-7.26 (5H, m, Ar); 6.16 (1H, d, $J_{3,2}$=5.7, H-3); 6.05 (1H, d, $J_{2,3}$=5.7, H-2); 5.84 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.1, $J_{2',1'}$=7.2, H-2'); 5.09 (1H, d, $J_{3',2'}$=8.9, H-3');5.06 (1H, d, $J_{3',2'}$=16.8, H-3'); 5.00 (1H, s, =CH_2); 4.84 (1H, s, =CH_2); 3.96 (1H, d, ^2J=13.1, CH_2 Bn); 3.90 (1H, d, ^2J=13.1, CH_2 Bn); 3.40 (1H, s, H-5); 2.36 (1H, dd, ^2J=13.9, $J_{1',2'}$=7.6, H-1'); 2.30 (1H, dd, ^2J=14.1, $J_{1',2'}$=7.5, H-1'). ^{13}C NMR δ: 154.8 (C-4); 143.1 (C-2); 139.6 (Ar C_q); 134.1 (C-2'); 132.9 (C-3); 128.6 (Ar(*m*)); 128.4 (Ar(*o*)); 127.4 (Ar(*p*)); 117.9 (C-3'); 106.5 (=CH_2); 80.2 (C-1); 63.9 (C-5); 53.7 (CH_2 Bn); 44.9 (C-1').

6-Benzyl-3-{6-benzyl-3-bromo-1-methyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl}-4-bromo-5-methyl-6-azabicyclo[3.1.0]hexan-2-one 45

To a stirred solution of **39** (30 mg, 0.12 mmol) in dry DCM (0.5 mL) under argon was added DBU (26 µL, 1.5eq.) at 0°C. After 30 min of stirring at this temperature, this solution was added to a mixture of magnesium bromide ethyl etherate (3 eq., 90 mg) and dry DCM (0.5 mL) at -78°C. After 30 minutes of stirring at this temperature, allyltrimethylsilane (10 eq., 188 µL) was added. After 4 hours of stirring at room temperature, reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and extracted with DCM (3x5 mL). The combined organic layers were dried with magnesium sulfate and evaporated to

dryness. Purification by chromatography (preparative TLC eluted with Hex:AcOEt 2:1) afforded 5 mg (16%) of pure compound **45** as yellow oil.

^{1}H NMR δ: 7.36-7.22 (10H, m, Ar); 3.80 (1H, d, ^{2}J=13.6, CH_2 Bn); 3.78 (1H, d, ^{2}J=13.4, CH_2 Bn); 3.69-3.68 (1H, m, H-3'); 3.65 (1H, d, ^{2}J=13.4, CH_2 Bn); 3.57 (1H, d, ^{2}J=13.4, CH_2 Bn); 3.37 (1H, d, $J_{4,3}$=4.9, H-4); 2.97-2.95 (1H, m, H-2'); 2.88 (1H d, $J_{5',3'}$=1.9, H-5'); 2.71 (1H, tt, $J_{3,4}$=$J_{3,2'}$=5.2, $J_{3,1}$=$J_{3,3'}$=1.6, H-3); 2.42 (1H, s, H-1); 1.32 (3H, s, Me); 1.18 (3H, s, Me). ^{13}C NMR δ: 206.2, 202.5 (C-2, C-4'); 137.6, 137.5 (Ar C_q); 128.6 (Ar(*m*)); 128.5, 128.4 (Ar(*o*)); 127.7, 127.2 (Ar(*p*)); 80.1 (C-3'); 75.4 (C-5); 70.4 (C-5'); 68.7 (C-4); 67.8 (C-1); 57.8 (CH_2 Bn); 55.2 (C-2'); 49.7 (C-3); 48.6 (CH_2 Bn); 47.9 (C-1'); 20.7, 18.5 (Me). FTIR (Neat): 1733 (C=O st); 734, 699 (Ar C-H o.o.p bend).

5-[(*tert*-Butyldimethylsilyl)oxy]-3-oxocyclopent-1-ene-1-carbaldehyde 47

To a stirred solution of **36** (50 mg, 0.14 mmol) in dry Toluene (1 mL) under argon was added anhydrous cesium carbonate (51 mg, 1.1eq.), 1,10-phenantroline (26 mg, 1.0 eq.) and cyclohexylamine (23 µL, 1.5 eq.) at room temperature. After stirring at 60°C for 24 hours, reaction mixture was quenched with water (10mL) and extracted with DCM (3x5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by chromatography (preparative plate eluted with Hex:AcOEt 9:1) afforded 7 mg (22%) of 4-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclopent-2-en-1-one as colorless oil and 2 mg (6%) of **47**.

^{1}H NMR δ: 10.15 (1H, s, aldehyde); 6.70 (1H, s, H-2); 5.27 (1H, d, $J_{5,4}$=5.3, H-4); 2.85 (1H, dd, ^{2}J=18.7, $J_{4,5}$=6.1, H-4); 2.43 (1H, dd, ^{2}J=18.7, $J_{4,5}$=1.8, H-4); 0.88 (9H, s, ^{t}Bu TBS); 0.17 (3H, s, Me TBS); 0.16 (3H, s, Me TBS). ^{13}C NMR δ: 204.4 (C-3);

189.2 (aldehyde); 166.5 (C-1); 140.2 (C-2); 67.7 (C-5); 46.3 (C-4); 25.6 (3xMe ^{t}Bu); 18.0 (C_q ^{t}Bu); -5.0 (Me TBS); -5.1 (Me TBS).

(±)-(1*R*,5*R*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 55

In a flask under argon a mixture of racemic 4-((tert-butyldimethylsilyl)oxy)-2-iodocyclohex-2-en-1-one[16b] (1.1 g, 3.1 mmol), anhydrous cesium carbonate (1.2 g, 1.1 eq.), anhydrous 1,10-phenantroline (590 mg, 1.0 eq.), allylamine (370 µL, 1.5 eq.) and dry toluene (7 mL) was stirred at room temperature. After 4 hours, the reaction mixture was diluted with DCM (10 mL) and washed with water (10 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex/AcOEt (9:1), afforded 770 mg (88%) of the pure compound **55** as a colorless oil.

(±)-(1*R*,5*R*,6*S*)-5-Hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 56

To a stirred solution of **(±)-55** (1.9 g, 6.75 mmol) in dry tetrahydrofuran (30 mL) under argon was added tetrabutylammonium fluoride (12.2 mL, 1 M in THF, 1.8 eq.). After 30 minutes, the reaction mixture was diluted with DCM (30 mL) and washed with water (30 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex/AcOEt (1:1), afforded 1.15 g (100%) of the pure compound **56** as colorless oil.

(+)-(1*S*,2*R*,6*R*)-5-Oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-yl acetate 57

A mixture of **(±)-56** (1.36 g, 2.9 mmol), vinyl acetate (1.3 mL, 5 eq.), novozym 435 (680 mg) and diisopropyl ether (30mL) was agitated (700 r.p.m.) in a closed tube for 4 hours at 24°C. The solid-supported enzyme was then removed by decantation and the organic solution was evaporated to dryness. Purification by flash column chromatography, eluting with Hex/AcOEt (1:1), afforded 829 mg of **(+)-57** (49%) and 685 mg of **(-)-56** (50%, >99% e.e. HPLC), both as colorless oils.

^{1}H RMN δ: 5.87 (1H, ddt, $J_{2',3'}$=17.3, $J_{2',3'}$=10.6, $J_{2',1'}$=5.4, H-2'); 5.29 (1H, dq, $J_{3',2'}$=17.3, ^{2}J=$J_{3',1'}$=1.5, H-3'); 5.16 (1H, dq, $J_{3',2'}$=10.6, ^{2}J=$J_{3',1'}$=1.3, H-3'); 5.12 (1H, ddd, $J_{2,3}$=9.9, $J_{2,3}$=5.3, $J_{2,1}$=2.3, H-2); 3.19 (1H, dd, ^{2}J=14.2, $J_{1',2'}$=5.4, H-2'); 2.86 (1H, dd, ^{2}J=14.2, $J_{1',2'}$=5.6, H-2'); 2.53-2.44 (2H, m, H-1, H-4); 2.28-2.06 (3H, m, H-3, H-4, H-6); 2.11 (3H, s, CH_3 Ac); 1.85-1.75 (1H, m, H-3). ^{13}C RMN δ: 204.4 (C-5); 170.8 (C=O Ac); 134.0 (C-2'); 117.0 (C-3'); 69.2 (C-2); 61.6 (C-1'); 46.5 (C-6); 43.9 (C-1); 34.8 (C-4); 22.8 (C-3); 21.1 (CH_3 Ac). IR: 1736, 1706 (C=O st); 1235 (C-O-C st); 1027 (C-O-C st). $[\propto]_D^{20^oC}$= +184 (c=1.3; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{17}NO_3$ 210.1125; Found 210.1120.

(+)-(1*R*,5*R*,6*S*)-5-Hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 56

To a stirred solution of **(+)-57** (540 mg, 2.58 mmol) in methanol (5 mL) was added potassium carbonate (37 mg, 10 mol%). After 1 hour, ammonium chloride (40 mg) was added. The salts were then filtered and the solution evaporated to dryness. 425 mg of alcohol **56** (99%,>99% e.e. HPLC) were obtained as a colorless oil. HPLC conditions: AD-H; 95:5 Hex:isopropanol; 1.0ml.min^{-1}; 210nm.

^{1}H RMN δ: 5.91 (1H, ddt, $J_{2',3'}$=17.0, $J_{2',3'}$=10.4, $J_{2',1'}$=5.9, H-1'); 5.26 (1H, dq, $J_{3',2'}$=17.2, ^{2}J=$J_{3',1'}$=1.5, H-3'); 5.19 (1H, dq, $J_{3',2'}$=10.3, ^{2}J=$J_{3',1'}$=1.2, H-3'); 4.17-4.14 (1H, m, H-5); 3.11 (1H, dd, ^{2}J=13.8, $J_{1',2'}$=5.8, H-1'); 2.99 (1H, dd, ^{2}J=13.8, $J_{1',2'}$=5.9, H-1'); 2.56-2.47 (2H, m, H-3, H-6);2.45 (1H, s br, OH); 2.19 (1H, d, $J_{1,6}$=5.9, H-1); 2.09-1.96 (2H, m, H-3, H-4); 1.86-1.77 (1H, m, H-4). ^{13}C RMN δ: 206.2 (C-2); 133.9 (C-2'); 117.9 (C-3'); 64.5 (C-5); 62.1 (C-1'); 48.1 (C-6); 47.4 (C-1); 33.8 (C-3); 29.7 (C-4). IR: 3400 (OH st); 1694 (C=O st); 1054 (C-O st); 924 (CH bend).$[\propto]_D^{20^oC}$= +126 (c=0.8; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{14}NO_2$ 168.1019; Found 168.1015.

(+)-(1*R*,5*R*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 55

To a stirred solution of **(+)-56** (50 mg, 0.30 mmol) in dry DCM (1 mL) under argon was added DBU (54 µL, 1.2 eq.) and *tert*-butyldimethylsilyl chloride (50 mg, 1.1 eq.) at 0ºC. After 1 hour, the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL). The mixture was then extracted with DCM (3x5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex/AcOEt (95:5), afforded 80 mg (95%) of the pure compound **55** as colorless oil.

^{1}H RMN δ: 5.88 (1H, ddt, $J_{2',3'}$=17.1, $J_{2',3'}$=10.5, $J_{2',1'}$=5.3, H-2'); 5.37 (1H, dq, $J_{3',2'}$=17.3, ^{2}J=$J_{3',1'}$=1.6, H-3'); 5.14 (1H, dq, $J_{3',2'}$=10.5, ^{2}J=$J_{3',1'}$=1.5, H-3'); 4.10 (1H, ddd, $J_{5,4}$=10.4, $J_{5,4}$=5.0, $J_{5,6}$=1.8, H-5); 3.25 (1H, ddt, ^{2}J=14.5, $J_{1',2'}$=5.3, $J_{1',3'}$=1.5, H-1'); 2.82 (1H, ddt, ^{2}J=14.5, $J_{1',2'}$=5.1, $J_{1',3'}$=1.5, H-1'); 2.42 (1H, ddd, ^{2}J=18.2, $J_{3,4}$=5.0, $J_{3,4}$=2.5, H-3), 2.21-2.00 (4H, m, H-1, H-3, H-4, H-6); 1.66-1.59 (1H, m, H-4); 0.92 (9H, s, ^{t}Bu TBS); 0.11 (3H, s, Me TBS); 0.10 (3H, s, Me TBS). ^{13}C RMN δ: 205.8 (C-

2); 134.1 (C-2'); 116.8 (C-3'); 67.7 (C-5); 61.8 (C-1'); 47.6, 46.8 (C-1, C-6); 35.4 (C-3); 25.9 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); -4.58 (Me TBS); -4.63 (Me TBS). IR: 1712 (C=O st), 1095 (Si-O st), 838 (Si-O-C bend). $[\propto]_D^{20^oC}$= +147 (c=0.8; DCM). Anal. Calcd for $C_{15}H_{27}NO_2Si$: C 64.01; H 9.67; N 4.98. Found: C 64.21; H 9.46; N 4.81.

Ethyl (-)-(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 58

To a solution of diisopropylamine (350 µL, 1.6 eq.) in THF (2.5 mL) under argon at 0°C was added *n*-butyllithium (1.46 mL, 1.6 M in Hexanes, 1.5 eq.) drop by drop, and the reaction mixture was stirred at this temperature for 15 minutes, then cooled at –78 °C and a solution of **(+)-55** (440 mg, 1.56 mmol) in THF (2.5 mL) was slowly added. Stirring at –78 °C was continued for further 30 minutes and ethyl cyanoformate (150 µL, 1.2 eq.) was then added. The reaction mixture was stirred at –78 °C for 1 hour. The reaction was quenched with saturated ammonium chloride aqueous solution (5mL). The mixture was then extracted with DCM (3 x 5 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. Purification by flash column chromatography, eluted with Hex/AcOEt (95:5), afforded 440 mg (80%) of the pure compound **58** as a colorless oil.

Although the two ketone tautomers can be observed in the ^{1}H and ^{13}C NMR spectra, only the enol is described.

^{1}H RMN δ: 12.30 (1H, s, OH); 5.80 (1H, ddt, $J_{2',1'}$=17.2, $J_{2',1'}$=10.5, $J_{2',3'}$=5.2, H-2'); 5.37 (1H, dq, $J_{3',2'}$=17.3, ^{2}J=$J_{3',1'}$=1.6, H-3'); 5.14 (1H, dq, $J_{3',2'}$=10.4, ^{2}J=$J_{3',1'}$=1.5, H-3'); 4.26-4.11 (2H, m, CH_2 Et); 3.97 (1H, ddd, $J_{5,4}$=9.6, $J_{5,4}$=6.4, $J_{5,6}$=2.4, H-5); 3.29 (1H, dd, ^{2}J=14.5, $J_{1',2'}$=5.2, H-1'); 2.74 (1H, dd, ^{2}J=14.5, $J_{1',2'}$=5.2, H-1'); 2.44 (1H,

ddd, ^{2}J=14.9, $J_{4,5}$=6.6, J=1.5, H-4); 2.20-2.11 (2H, m, H-4, H-6); 2.07 (1H, d, $J_{1,6}$=6.5, H-1); 1.27 (3H, t, ^{3}J=7.1, CH_3 Et); 0.91 (9H, s, ^{t}Bu TBS); 0.11 (6H, s, 2x Me TBS). ^{13}C RMN δ: 201.5 (C-2); 169.3 (C=O CO_2Et); 134.2 (C-2'); 116.7 (C-3'); 101.6 (C-3); 67.2 (C-5); 61.5 (C-1'); 60.5 (CH_2 Et); 47.4 (C-6), 39.8 (C-1); 27.2 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 14.3 (CH_3 Et); -4.59 (Me TBS); -4.63 (Me TBS). IR: 1651 (C=O st); 1277, 1254, 1229 (C-O-C st, C-O st); 1090 (Si-O st), 837 (Si-O-C bend). $[\propto]_D^{20^oC}$= -29 (c=0.7; DCM). Anal. Calcd for $C_{18}H_{31}NO_4Si$: C 61.15; H 8.84; N 3.96. Found: C 61.35; H 8.40; N 3.77.

Ethyl (-)-(1*S*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 59

To a stirred solution of **58** (400 mg, 1.13 mmol) in ethanol abs. (3.5 mL) at 0ºC was added sodium borohydride (43 mg, 1 eq.) portionwise. After 1 hour, the reaction was quenched with a saturated ammonium chloride aqueous solution (3.5mL) and the mixture was extracted with DCM (2x 5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The obtained crude (400 mg) was dissolved in dry pyridine (3.5 mL) under argon and mesyl chloride (175 µL, 2 eq.) was added at 0ºC. After 1 hour of stirring at room temperature the reaction mixture was diluted with DCM (5 mL) and washed with water (5mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. The obtained crude (515 mg) was dissolved in ethanol abs. (3.5 mL) and potassium carbonate (310 mg, 2 eq.) was added. After 1 hour, ammonium chloride (310 mg) was added. The salts were then filtered and the solution evaporated to dryness. Purification by flash column chromatography, eluted with Hex/AcOEt (9:1), afforded 190 mg (50%) of the pure compound **59** as colorless oil.

^{1}H RMN δ: 7.12 (1H, dd, $J_{2,1}$=4.6, $J_{2,4}$=3.3, H-2); 5.88 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.3, H-2'); 5.35 (1H, dq, $J_{3',2'}$=17.2, ^{2}J=$J_{3',1'}$=1.7, H-3'); 5.11 (1H, dq, $J_{3',2'}$=10.5, ^{2}J=$J_{3',1'}$=1.4, H-3'); 4.17 (2H, q, ^{3}J=7.1, CH_2 Et); 4.00 (1H, ddd, $J_{5,4}$=9.4, $J_{5,4}$=6.8, $J_{5,6}$=2.3, H-5); 3.21 (1H, ddt, ^{2}J=14.4, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'); 2.77 (1H, ddt, ^{2}J=14.5, $J_{1',2'}$=5.1, $J_{1',3'}$=1.5, H-1'); 2.67 (1H, dd, ^{2}J=16.5, $J_{4,5}$=6.5, H-4); 2.20 (1H, ddd, ^{2}J=16.4, $J_{4,5}$=9.7, $J_{4,2}$=3.1, H-4); 2.08 (1H, dt, $J_{6,1}$=6.3, $J_{6,5}$= $J_{6,4}$=2.0, H-6); 2.00 (1H, dd, $J_{1,6}$=6.1, $J_{1,2}$=4.9, H-1); 1.27 (3H, t, ^{3}J=7.1, CH_3 Et); 0.92 (9H, s, ^{t}Bu TBS); 0.11 (6H, s, 2x Me TBS). ^{13}C RMN δ: 166.3 (C=O CO_2Et); 135.8 (C-2); 134.6 (C-2'); 130.7 (C-3); 116.5 (C-3'); 67.1 (C-5); 61.9 (C-1'); 60.5 (CH_2 Et); 47.6 (C-6), 37.1 (C-1); 30.5 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 14.3 (CH_3 Et); -4.56 (Me TBS); -4.61 (Me TBS). IR: 1712 (C=O st); 1250 (C-O-C st); 1070 (Si-O st), 836 (Si-O-C bend). $[\propto]_D^{20^oC}$= -70 (c=0.7; DCM). Anal. Calcd for $C_{18}H_{31}NO_3Si$: C 64.05; H 9.26; N 4.15. Found: C 64.08; H 9.37; N 4.21.

Ethyl (-)-(1*S*,5*R*,6*S*)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 60

To a stirred solution of **59** (100 mg, 0.296 mmol) in dry tetrahydrofuran (3 mL) under argon was added tetrabutylammonium fluoride (530 µL, 1 M in THF, 1.8 eq.). After 1 hour, the reaction mixture was diluted with DCM (3 mL) and washed with water (3 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex/AcOEt (1:1), afforded 66 mg (100%) of the pure compound **60** as white solid.

^{1}H RMN δ: 7.14 (1H, dd, $J_{2,1}$=4.6, $J_{2,4}$=3.3, H-2); 5.92 (1H, ddt, $J_{2',3'}$=16.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.8, H-2'); 5.26 (1H, dq, $J_{3',2'}$=17.2, ^{2}J=$J_{3',1'}$=1.6, H-3'); 5.16 (1H, dq, $J_{3',2'}$=10.4, ^{2}J=$J_{3',1'}$=1.2, H-3'); 4.18 (2H, q, ^{3}J=7.1, CH_2 Et); 4.00 (1H, tdd, $J_{5,4}$=$J_{5,OH}$=8.8, $J_{5,4}$=6.6,

$J_{5,6}$=2.3, H-5); 3.06 (1H, dd, ^2J=13.9, $J_{1',2'}$=5.4, H-1'); 2.95 (1H, dd, ^2J=14.0, $J_{1',2'}$=5.7, H-1'); 2.86 (1H, ddd, ^2J=16.4, $J_{4,5}$=6.6, $J_{4,6}$=1.3, H-4); 2.30 (1H, dt, $J_{6,1}$=6.3, $J_{6,5}$=$J_{6,4}$=2.0, H-6); 2.14-2.04 (2H, m, H-1, H-4); 1.66 (1H, d, $J_{OH,5}$=8.6, OH); 1.27 (3H, t, ^3J=7.1, CH_3 Et). ^{13}C RMN δ: 166.1 (C=O CO_2Et); 135.5 (C-2); 134.7 (C-2'); 130.5 (C-3); 117.2 (C-3'); 66.1 (C-5); 62.1 (C-1'); 60.7 (CH_2 Et); 46.7 (C-6); 37.9 (C-1); 30.5 (C-4); 14.2 (CH_3 Et). IR: 3400 (OH st); 1705 (C=O st); 1242 (C-O-C st, C-O st); 1036 (C-O-C st). $[\propto]_D^{20^oC}$= -140 (c=0.7; DCM). M.p. = 82ºC. Anal. Calcd for $C_{12}H_{17}NO_3$: C 64.55; H 7.67; N 6.27. Found: C 64.67; H 7.87; N 6.50.

Ethyl (-)-(3*R*,4*R*,5*R*)-5-hydroxy-3-(pentan-3-yloxy)-4-[(prop-2-en-1-yl)amino]cyclohex-1-ene-1-carboxylate 61

To a stirred solution of **60** (120 mg, 0.54 mmol) in 3-pentanol (3.5 mL) under argon was added boron trifluoride diethyl etherate (100 µL, 1.5 eq.). After 30 minutes of stirring at 70ºC the reaction was quenched with a saturated sodium bicarbonate aqueous solution (5mL) and the mixture was extracted with AcOEt (3x5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with AcOEt, afforded 150 mg (90%) of the pure compound **61** as white solid.

^{1}H RMN δ: 6.86 (1H, q, $J_{2,3}$=$J_{2,6}$=1.9, H-2); 5.90 (1H, dddd, $J_{2',3'}$=16.8, $J_{2',3'}$=10.3, $J_{2',1'}$=6.3, $J_{2',1'}$=5.4, H-2'); 5.22 (1H, dq, $J_{3',2'}$=17.2, ^2J=$J_{3',1'}$=1.5, H-3'); 5.12 (1H, dq, $J_{3',2'}$=10.3, ^2J=$J_{3',1'}$=1.4, H-3'); 4.20 (2H, q, ^3J=7.1, CH_2 Et); 4.17-4.14 (1H, m, H-5); 4.03 (1H, dq, $J_{3,4}$=8.1, $J_{3,2}$= $J_{3,6}$=2.2, H-3); 3.39-3.32 (2H, m, H-1', CH pentyl); 3.23 (1H, ddt, ^2J=14.2, $J_{1',2'}$=6.4, $J_{1',3'}$=1.2, H-1'); 2.72 (1H, dd, $J_{4,3}$=8.1, $J_{4,5}$=2.5, H-4); 2.58 (1H, ddt, ^2J=18.8, $J_{6,5}$=3.1, $J_{6,2}$=$J_{6,3}$=1.6, H-6); 2.48 (1H, ddt, ^2J=18.9, $J_{6,5}$=4.9, $J_{6,2}$=$J_{6,3}$=2.6, H-6); 2.40 (2H, s br, OH, NH); 1.64-1.44 (4H, m, CH_2 pentyl); 1.28 (3H, t, ^3J=7.1, CH_3 Et); 0.94 (3H, t, ^3J=7.4, CH_3 pentyl); 0.92 (3H, t, ^3J=7.5, CH_3 pentyl).

^{13}C RMN δ: 166.6 (C=O CO_2Et); 136.4 (C-2'); 136.3 (C-2); 128.5 (C-1); 116.1 (C-3'); 81.0 (CH pentyl); 73.2 (C-3); 63.8 (C-5); 60.8 (C-4); 60.6 (CH_2 Et); 49.3 (C-1'); 29.9 (C-6); 26.5, 25.6 (2xCH_2 pentyl); 14.2 (CH_3 Et); 9.7, 9.5 (2xCH_3 pentyl). IR: 3400 (OH st, NH st); 1715 (C=O st); 1251 (C-O-C st); 1054 (C-O-C st). $[\propto]_D^{20^oC}$= -123 (c=1.0; DCM). M.p. = 95-95.5ºC. Anal. Calcd for $C_{12}H_{17}NO_3$: C 65.57; H 9.39; N 4.50. Found: C 65.83; H 9.61; N 4.75.

Ethyl (-)-(3*R*,4*R*,5*R*)-4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate 62

In a flask under argon a mixture of bis(dibenzylideneacetone)palladium(0) (26 mg, 10 mol%), 1,4-Bis(diphenylphosphino)butane (20 mg, 10 mol%) and dry tetrahydrofuran (1 mL) was stirred at room temperature for 15 minutes. This mixture was then added to a stirred solution of 61 (140 mg, 0.45 mmol) in tetrahydrofuran (1 mL) under argon followed by addition of thiosalicylic acid (143 mg, 2 eq.). After 30 minutes of stirring at 60ºC the reaction was cooled to 0ºC and pyridine (180 µL, 5 eq.) and acetic anhydride (47 µL, 1.1 eq.) were added. After additional 15 minutes of stirring at room temperature the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL) and the mixture was extracted with AcOEt (3x 2mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with AcOEt, afforded 117 mg (83%) of the pure compound **62** as white solid.

^{1}H RMN δ: 6.84 (1H, dt, $J_{2,3}$=3.3, $J_{2,6}$=1.8, H-2); 5.93 (1H, d, $J_{NH,4}$=7.0, NH); 4.30 (1H, td, $J_{5,6}$=4.9, $J_{5,4}$=2.3, H-5); 4.25-4.21 (1H, m, H-3); 4.21 (2H, q, ^3J=7.1, CH_2 Et); 3.90 (1H, td, $J_{4,3}$=$J_{4,NH}$=7.2, $J_{4,5}$=2.3, H-4); 3.40 (1H, p, ^3J=5.8, CH pentyl); 2.69 (1H, ddt, ^2J=18.5, $J_{6,5}$=4.3, $J_{6,2}$=$J_{6,3}$=2.1, H-6); 2.43 (1H, ddt, ^2J=18.5, $J_{6,5}$=5.3,

$J_{6,2}$=$J_{6,3}$=1.3, H-6); 2.04 (3H, s, CH_3 Ac); 1.58-1.48 (4H, m, 2xCH_2 pentyl); 1.29 (3H, t, ^3J=7.1, CH_3 Et); 0.92 (6H, t, ^3J=7.4, 2xCH_3 pentyl). ^{13}C RMN δ: 171.7 (C=O Ac); 166.5 (C=O CO_2Et); 136.0 (C-2); 129.3 (C-1); 81.9 (CH pentyl); 72.6 (C-3); 67.1 (C-5); 60.9 (CH_2 Et); 55.1 (C-4); 31.5 (C-6); 26.3, 26.0 (2xCH_2 pentyl); 23.5 (CH_3 Ac); 14.2 (CH_3 Et); 9.6, 9.5 (2xCH_3 pentyl). IR: 3300 (OH st, NH st); 1714 (C=O st ester); 1651 (C=O st amide); 1545 (Amide II); 1250 (C-O-C st); 1092, 1054 (C-O-C st). $[\propto]_D^{20^oC}$= -100 (c=1.7; AcOEt) [lit[39]: $[\propto]_D^{25^oC}$= -104 (c=3.0; AcOEt)]. M.p. = 132ºC (lit[39]: 131.9-132.2ºC).

(+)-(1*R*,5*R*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-2-yl diethyl phosphate 63

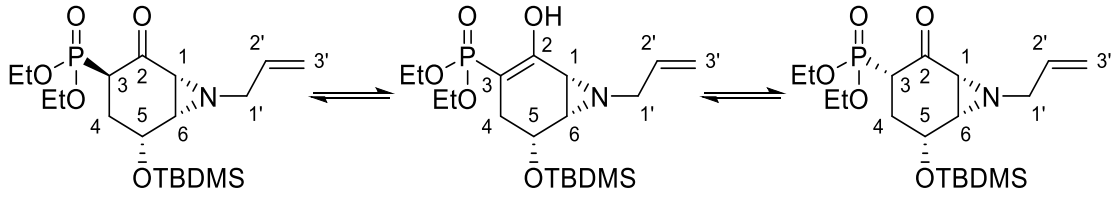
To a solution of diisopropylamine (600 µL, 1.6 eq.) in THF (5 mL) under argon at 0°C was added *n*-butyllithium (2.5 mL, 1.6 M in Hexanes, 1.5 eq.) drop by drop, and the reaction mixture was stirred at this temperature for 15 minutes, then cooled at –78 °C and a solution of **(+)-55** (750 mg, 2.7 mmol) in THF (5 mL) was slowly added. Stirring at –78 °C was continued for further 30 minutes and diethyl cyanophosphonate (480 µL, 1.2 eq.) was then added. The reaction mixture was stirred at –78 °C for 1 hour. The reaction was quenched with saturated ammonium chloride aqueous solution (10mL). The mixture was then extracted with DCM (3 x 10 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. Purification by flash column chromatography, eluted with Hex:AcOEt (2:1), afforded 962 mg (80%) of the pure compound **63** as colorless oil.

^{1}H RMN δ: 5.89 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.3, H-2'); 5.37 (1H, dq, $J_{3',2'}$=17.3, ^2J=$J_{3',1'}$=1.7, H-3'); 5.29-5.23 (1H, m, H-3); 5.11 (1H, dq, $J_{3',2'}$=10.5, ^2J=$J_{3',1'}$=1.5, H-3'); 4.22-4.13 (4H, m, 2xCH_2 Et); 4.04 (1H, t, J=8.0, H-5); 3.25 (1H,

ddt, ^{2}J=14.5, $J_{1',2'}$=5.2, $J_{1',3'}$=1.5, H-1'); 2.69 (1H, ddt, ^{2}J=14.6, $J_{1',2'}$=5.2, $J_{1',3'}$=1.4, H-1'); 2.23-2.03 (4H, m, H-1, H-4, H-6); 1.37 (3H, td, ^{3}J=7.1, $^{4}J_{H,P}$=1.0, CH_3 Et); 1.36 (3H, td, ^{3}J=7.1, $^{4}J_{H,P}$=1.0, CH_3 Et); 0.91 (9H, s, ^{t}Bu TBS); 0.09 (3H, s, Me TBS); 0.07 (3H, s, Me TBS). ^{13}C RMN δ: 145.5 (d, $^{2}J_{C,P}$=9, C-2); 134.6 (C-2'); 116.4 (C-3'); 107.6 (d, $^{3}J_{C,P}$=5, C-3); 66.6 (C-5); 64.44 (d, $^{2}J_{C,P}$=6, CH_2 Et); 64.38 (d, $^{2}J_{C,P}$=6, CH_2 Et); 61.5 (C-1'); 46.7 (C-6), 39.1 (d, $^{3}J_{C,P}$=6, C-1); 29.3 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 16.1 (d, $^{3}J_{C,P}$=7, CH_3 Et); -4.63 (Me TBS); -4.66 (Me TBS). ^{31}P RMN δ: -6.2. IR (Neat): 1033 (P-O-C st). $[\propto]_D^{20^oC}$= +45 (c=1.1; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{37}NO_5PSi$ 418.2173; Found 418.2177.

Diethyl (+)-[(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-3-yl]phosphonate 64

To a solution of diisopropylamine (875 µL, 2.4 eq.) in THF (5 mL) under argon at 0°C was added *n*-butyllithium (3.6 mL, 1.6 M in Hexanes, 2.2 eq.) drop by drop, and the reaction mixture was stirred at this temperature for 15 minutes, then cooled at –78 °C and a solution of **63** (1.1 g, 2.6 mmol) in THF (5 mL) was slowly added. After 30 minutes of stirring at this temperature the reaction was quenched with saturated ammonium chloride aqueous solution (10mL). The mixture was then extracted with DCM (3 x 10 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. Purification by flash column chromatography, eluted with Hex:AcOEt (2:1), afforded 996 mg (91%) of the pure compound **64** as colorless oil.



64(I) **64(II)** **64(III)**

^{1}H NMR δ: 10.92 (0.1H, s, OH II), 5.93-5.81 (1H, m, H-2'); 5.40-5.34 (1H, m, H-3'); 5.29-5.23 (1H, m, H-3); 5.13 (1H, d, $J_{3',2'}$=10.5, H-3'); 4.56-4.51 (0.5H, m, H-5 I); 4.3-3.9 (4.5H, m, 2xCH_2 Et, H-5); 3.31-3.12 (1H, m, H-1'); 2.99-2.69 (1.9H, m, H-3, H-1'); 2.54 (0.4H, p, $^{2}J=^{3}J_{H,P}=J_{4,3}=J_{4,2}$=12.4, H-4 II); 2.39-1.85 (3.6H, H-1, H-4, H-6); 1.36-1.31 (3H, m, CH_3 Et); 0.926, 0.914, 0.910 (9H, s, ^{t}Bu TBS); 0.13, 0.103, 0.095 (6H, s, Me TBS).^{13}C NMR δ: 200.2 (d, $^{2}J_{C,P}$=7, C-2 III); 199.7 (d, $^{2}J_{C,P}$=5, C-2 I); 168.0 (d, $^{2}J_{C,P}$=7, C-2 II); 134.4 (II), 134.0 (I), 133.8 (III) (C-2'); 116.9 (I), 116.8 (III), 116.5 (II) (C-3'); 84.5 (d, $^{1}J_{C,P}$=183, C-3 II); 67.5 (d, $^{3}J_{C,P}$=4, C-5 II); 67.5 (d, $^{3}J_{C,P}$=11, C-5 II); 67.4 (d, $^{3}J_{C,P}$=18, C-5 III); 65.1 (d, $^{3}J_{C,P}$=1, C-5 I); 63.0 (d, $^{2}J_{C,P}$=7), 62.6 (d, $^{2}J_{C,P}$=6), 62.4 (d, $^{2}J_{C,P}$=7), 61.7 (d, $^{2}J_{C,P}$=4) (CH_2 Et); 61.9 (I), 61.5 (II), 61.2 (III) (C-1'); 48.3 (d, $^{4}J_{C,P}$=1, C-6 III); 48.1 (d, $^{3}J_{C,P}$=4, C-1 III); 46.8 (C-6 I); 46.5 (d, $^{3}J_{C,P}$=1, C-1 III); 46.3 (d, $^{4}J_{C,P}$=2, C-6 III); 45.5 (d, $^{1}J_{C,P}$=126, C-3 I); 44.9 (d, $^{1}J_{C,P}$=134, C-3 III); 40.6 (d, $^{3}J_{C,P}$=19, C-1 II); 27.5 (d, $^{3}J_{C,P}$=5, C-4 II); 27.4 (d, $^{3}J_{C,P}$=3, C-4 III); 27.0 (d, $^{3}J_{C,P}$=6, C-4 I); 25.8, 25.7 (3xMe ^{t}Bu); 18.14 (II), 18,10 (I), 18.0 (III) (C_q ^{t}Bu); 16.43, 16.37, 16.34, 16.28, 16.21, 16.19, 16.14 (CH_3 Et); -4.65, -4.67, -4.73 (Me TBS). ^{31}P NMR δ: 26.1; 22.9; 21.4. FTIR (Neat): 1705 (C=O st); 1253 (P=O st; Si-C st); 1094, 1052, 1026 (P-O-C st, Si-O-C st); 838 (Si-O-C bend); 774 (P-O-C st). $[\propto]_D^{20^oC}$= +71 (c=1.2; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{37}NO_5PSi$ 418.2173; Found 418.2169.

Diethyl (-)-[(1*S*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-3-yl]phosphonate 65

To a stirred solution of **64** (750 mg, 1.8 mmol) in ethanol abs. (7 mL) under argon at -78ºC was added sodium borohydride (68 mg, 1 eq.) portionwise. After 1 hour, the reaction was quenched with a saturated ammonium chloride aqueous solution (7mL) and the mixture was extracted with DCM (3x 10mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The obtained crude (750 mg) was dissolved in dry DCM (7 mL) under argon and triethylamine (920 µL, 3 eq.) and mesyl chloride (280 µL, 2 eq.) were added at 0ºC. After 3 hours of stirring at room temperature, the reaction mixture was quenched with water (10mL) and then extracted with DCM (3x 10mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. The obtained crude (1.2 g) was dissolved in dry DCM (7 mL) under argon and DBU (400 µL, 1.5 eq.) was added at 0ºC. After 1 hour of stirring at room temperature the reaction was treated using the same procedure above. Purification by flash column chromatography, eluted with Hex:AcOEt (1:2), afforded 339 mg (47%) of the pure compound **65** as colorless oil.

^{1}H RMN δ: 6.91 (1H, ddd, $^{3}J_{H,P}$=20.0, $J_{2,1}$=4.3, $J_{2,5}$=3.2, H-2); 5.87 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.4, $J_{2',1'}$=5.2, H-2'); 5.33 (1H, dq, $J_{3',2'}$=17.2, ^{2}J=$J_{3',1'}$=1.7, H-3'); 5.11 (1H, dq, $J_{3',2'}$=10.5, ^{2}J=$J_{3',1'}$=1.5, H-3'); 4.10-3.95 (5H, m, H-5, 2xCH_2 Et); 3.10 (1H, ddt, ^{2}J=14.6, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'); 2.85 (1H, ddt, ^{2}J=14.6, $J_{1',2'}$=5.0, $J_{1',3'}$=1.6, H-1'); 2.38-2.20 (2H, m, H-4); 2.04 (1H, dt, $J_{6,1}$=6.3, $^{5}J_{H,P}$=$J_{6,5}$=1.8, H-6); 1.98 (1H, dt, $^{4}J_{H,P}$=10.9, $J_{1,6}$=$J_{1,2}$=4.8, H-1); 1.31 (3H, t, ^{3}J=7.0, CH_3 Et); 1.30 (3H, t, ^{3}J=7.0, CH_3 Et); 0.92 (9H, s, ^{t}Bu TBS); 0.11 (3H, s, Me TBS); 0.10 (3H, s, Me TBS). ^{13}C RMN δ: 140.0 (d, $^{2}J_{C,P}$=10, C-2); 134.7 (C-2'); 128.3 (d, $^{1}J_{C,P}$=184, C-3); 116.3 (C-

3'); 66.6 (d, $^{3}J_{C,P}$=12, C-5); 61.9 (C-1'); 61.8 (d, $^{2}J_{C,P}$=5, CH_2 Et); 61.6 (d, $^{2}J_{C,P}$=5; CH_2 Et); 46.7 (d, $^{4}J_{C,P}$=2, C-6), 37.8 (d, $^{3}J_{C,P}$=24, C-1); 30.9 (d, $^{2}J_{C,P}$=8, C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 16.3 (d, $^{3}J_{C,P}$=6, CH_3 Et); -4.6 (2xMe TBS). ^{31}P RMN δ: 18.2. IR (Neat): 1250 (P=O st; Si-C st); 1090, 1069, 1054, 1026, 965 (P-O-C st, Si-O-C st); 837 (Si-O-C bend); 777 (P-O-C st). $[\propto]_D^{20^oC}$= -1 (c=1.0; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{37}NO_4PSi$ 402.2224; Found 402.2230.

Diethyl (-)-[(1*S*,5*R*,6*S*)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-3-yl]phosphonate 66

To a stirred solution of **65** (330 mg, 0.82 mmol) in dry tetrahydrofuran (3 mL) under argon was added tetrabutylammonium fluoride (1.5 mL, 1 M in THF, 1.8 eq.). After 1 hour of stirring at room temperature the reaction mixture was quenched with water (5mL) and then extracted with AcOEt (3x 5mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with DCM/methanol (95:5), afforded 238 mg (100%) of the pure compound **66** as colorless oil.

^{1}H RMN δ: 6.93 (1H, dt, $^{3}J_{H,P}$=20.0, $J_{2,1}$=$J_{2,5}$=3.1, H-2); 5.90 (1H, ddt, $J_{2',3'}$=16.6, $J_{2',3'}$=11.0, $J_{2',1'}$=5.5, H-2'); 5.25 (1H, d, $J_{3',2'}$=17.2, H-3'); 5.15 (1H, d, $J_{3',2'}$=10.4, H-3'); 4.16-3.95 (5H, m, H-5, 2xCH_2 Et); 3.02 (1H, dd, ^{2}J=14.3, $J_{1',2'}$=3.5, H-1'); 2.96 (1H, dd, ^{2}J=14.2, $J_{1',2'}$=5.6, H-1'); 2.54 (1H, ddd, ^{2}J=16.3, $^{3}J_{H,P}$=11.1, $J_{4,5}$=5.7, H-4); 2.26 (1H, d, $J_{6,1}$=6.0, H-6); 2.16-1.96 (1H, m, H-1, H-4, OH); 1.31 (3H, t, ^{3}J=6.4, CH_3 Et); 1.30 (3H, t, ^{3}J=6.1, CH_3 Et). ^{13}C RMN δ: 139.6 (d, $^{2}J_{C,P}$=10, C-2); 134.8 (C-2'); 128.3 (d, $^{1}J_{C,P}$=185, C-3); 117.0 (C-3'); 65.7 (d, $^{3}J_{C,P}$=11, C-5); 62.0 (C-1'); 61.9 (d, $^{2}J_{C,P}$=6, CH_2 Et); 61.8 (d, $^{2}J_{C,P}$=6; CH_2 Et); 45.8 (C-6), 38.4 (d, $^{3}J_{C,P}$=23, C-1); 30.9 (d, $^{2}J_{C,P}$=8, C-4); 16.4 (d, $^{3}J_{C,P}$=6, CH_3 Et); 16.3 (d, $^{3}J_{C,P}$=6, CH_3 Et). ^{31}P RMN δ: 17.8. IR (Neat): 3370 (O-H st); 1227 (P=O st); 1021, 966 (P-O-C st, C-OH st). $[\propto]_D^{20^oC}$= -37

(c=0.5; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{23}NO_4P$ 288.1359; Found 288.1358.

Diethyl (-)-[(3*R*,4*R*,5*R*)-5-hydroxy-3-(pentan-3-yloxy)-4-[(prop-2-en-1-yl)amino]cyclohex-1-en-1-yl]phosphonate 67

To a stirred solution of **66** (150 mg, 0.52 mmol) in 3-pentanol (3.5 mL) under argon was added boron trifluoride diethyl etherate (100 µL, 1.5 eq.). After 30 minutes of stirring at 70ºC the reaction was quenched with a saturated sodium bicarbonate aqueous solution (5mL) and the mixture was extracted with AcOEt (3x 5mL). The combined organic phases were dried with sodium sulfate and evaporated to dryness, affording 200 mg (100%) of the pure compound **67** as colorless oil.

^{1}H RMN δ: 6.66 (1H, d, $^3J_{H,P}$=21.8, H-2); 5.93 (1H, dd, $J_{2',3'}$=16.7, $J_{2',3'}$=11.1, $J_{2',1'}$=5.6, H-2'); 5.27 (1H, d, $J_{3',2'}$=17.2, H-3'); 5.18 (1H, d, $J_{3',2'}$=10.0, H-3'); 4.22 (1H, br s, H-5); 4.12-4.03 (5H, m, H-3, 2xCH_2 Et); 3.47-3.33 (3H, m, H-1', CH pentyl); 2.79 (1H, br d, *J*=7.8, H-4); 2.51-2.38 (2H, m, H-6); 1.63-1.40 (4H, m, 2xCH_2 pentyl); 1.32 (6H, td, ^3J=7.1, $^4J_{H,P}$=3.0, 2xCH_3 Et); 0.92 (3H, t, ^3J=7.7, CH_3 pentyl); 0.91 (3H, t, ^3J=7.5, CH_3 pentyl). ^{13}C RMN δ: 139.9 (d, $^2J_{C,P}$=7, C-2); 135 (br, C-2'); 126.4 (d, $^1J_{C,P}$=181, C-1); 118 (br, C-3'); 80.8 (CH pentyl); 72.7 (d, $^3J_{C,P}$=21, C-3); 63.8 (d, $^3J_{C,P}$=12, C-5); 62.0 (d, $^2J_{C,P}$=5; CH_2 Et); 61.9 (d, $^2J_{C,P}$=6; CH_2 Et); 60.8 (C-4); 49.4 (H-1'); 30.0 (d, $^3J_{C,P}$=79, C-6); 26.4, 25.4 (2x CH_2 pentyl); 16.4 (d, $^3J_{C,P}$=6, 2xCH_3 Et); 9.7, 9.4 (2xCH_3 pentyl). ^{31}P RMN δ: 18.1. IR (Neat): 3370 (O-H st, NH st); 1226 (P=O st); 1091, 1052, 1024, 969 (P-O-C st, C-OH st, C-O-C st). $[\propto]_D^{20^oC}$ = -107 (c=0.9; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{35}NO_5P$ 376.2247; Found 376.2257.

Diethyl (-)-[(3*R*,4*R*,5*R*)-4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-en-1-yl]phosphonate 68

In a flask under argon a mixture of bis(dibenzylideneacetone)palladium(0) (11.5 mg, 10 mol%), 1,4-Bis(diphenylphosphino)butane (8.7 mg, 10 mol%) and dry tetrahydrofuran (0.5 mL) was stirred at room temperature for 15 minutes. This mixture was then added to a stirred solution of 67 (75 mg, 0.20 mmol) in tetrahydrofuran (0.5 mL) under argon followed by addition of 1,3-dimethylbarbituric acid (62 mg, 2 eq.). After 30 minutes of stirring at 60ºC the reaction was cooled to 0ºC and triethylamine (170 µL, 6 eq.) and acetic anhydride (80 µL, 4 eq.) were added. After additional 60 minutes of stirring at room temperature the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL) and the mixture was extracted with AcOEt (3x 2mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The obtained crude was dissolved in ethanol abs. (1 mL) and potassium *tert*-butoxide (4.4 mg, 20 mol%) was added. After 1 hour, ammonium chloride (5 mg) was added. The salts were then filtered and the solution evaporated to dryness. Purification by flash column chromatography, eluted with DCM:MeOH (93:7), afforded 53 mg (70%) of the pure compound **68** as colorless oil.

^{1}H RMN δ: 6.66-6.60 (1H, br s, NH); 6.58 (1H, d, $^{3}J_{H,P}$=22.0, H-2); 4.21 (1H, br s, H-5); 4.16 (1H, br d, *J*=6.5, H-3); 4.12-4.03 (4H, m, 2xCH_2 Et); 3.96 (1H, br t, *J*=7.5, H-4); 3.7 (1H, br s, OH); 3.35 (1H, p, ^{3}J=5.5,CH pentyl); 2.51 (1H, br d, ^{2}J=17.8, H-6); 2.36 (1H, dt, ^{2}J=18.0, *J*=4.6, H-6); 2.03 (3H, s, CH_3 Ac); 1.54-1.47 (4H, m, 2xCH_2 pentyl); 1.33 (6H, t, ^{3}J=7.1, 2xCH_3 Et); 0.90 (6H, t, ^{3}J=7.5, 2xCH_3 pentyl). ^{13}C RMN δ: 171,6 (C=O Ac); 140.2 (C-2); 126.5 (d, $^{1}J_{C,P}$=185, C-1); 82.0 (CH pentyl); 73.0 (d, $^{3}J_{C,P}$=21, C-3); 67.4 (d, $^{3}J_{C,P}$=12, C-5); 62.3 (d, $^{2}J_{C,P}$=6; CH_2 Et); 62.1 (d, $^{2}J_{C,P}$=6; CH_2

Et); 54.6 (C-4); 31.8 (d, $^{3}J_{C,P}$=9, C-6); 26.3, 25.8 (2xCH_2 pentyl); 23.3 (CH_3 Ac); 16.3 (d, $^{3}J_{C,P}$=6, 2xCH_3 Et); 9.54, 9.45 (2xCH_3 pentyl). ^{31}P RMN δ: 17.6. IR (Neat): 3300 (O-H st, NH st); 1652 (C=O st); 1553 (amide II); 1230 (P=O st); 1087, 1052, 1022, 965 (P-O-C st, C-OH st, C-O-C st). $[\propto]_D^{20^oC}$= -132 (c=0.7; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{32}NO_6P$ 378.2040; Found 378.2055.

(-)-(1*R*,5*R*,6*S*)-3-(Diethoxyphosphoryl)-6-acetamido-5-(pentan-3-yloxy)cyclohex-3-en-1-yl methanesulfonate 69

To a stirred solution of **68** (40 mg, 0.11 mmol) in dry DCM (1 mL) under argon was added triethylamine (30 µL, 2 eq.) and mesyl chloride (12 µL, 1.5 eq.) at 0^{o}C. After 1 hour of stirring at room temperature the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL) and the mixture was extracted with AcOEt (3x 2mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness, affording 48 mg (99%) of the pure compound **69** as a white solid.

^{1}H RMN δ: 6.67 (1H, d, $^{3}J_{H,P}$=21.6, H-4); 5.83 (1H, d, $J_{NH,6}$=8.1, NH); 5.24-5.20 (1H, m, H-1); 4.31 (1H, td, $J_{6,NH}$=$J_{6,5}$=8.2, $J_{6,1}$=2.2, H-6); 4.14-4.05 (4H, m, 2xCH_2 Et); 4.01 (1H, dm, *J*=8.2, H-5); 3.36 (1H, p, ^{3}J=5.4, CH pentyl); 3.05 (3H, s, CH_3 Ms); 2.77-2.61 (2H, m, H-2); 2.03 (3H, s, CH_3 Ac); 1.56-1.48 (4H, m, 2xCH_2 pentyl); 1.34 (6H, td, ^{3}J=7.1, $J_{H,P}$=0.7, 2xCH_3 Et); 0.91 (3H, t, ^{3}J=7.4, CH_3 pentyl); 0.90 (3H, t, ^{3}J=7.4, CH_3 pentyl). ^{13}C RMN δ: 170,7 (C=O Ac); 140.7 (d, $^{2}J_{C,P}$=7, C-4); 125.7 (d, $^{1}J_{C,P}$=184, C-3); 82.3 (CH pentyl); 78.1 (d, $^{3}J_{C,P}$=13, C-1); 72.7 (d, $^{3}J_{C,P}$=20, C-5); 62.4 (d, $^{2}J_{C,P}$=6; CH_2 Et); 62.2 (d, $^{2}J_{C,P}$=6; CH_2 Et); 51.6 (d, $^{4}J_{C,P}$=2, C-6); 38.6 (CH_3 Ms); 29.9 (d, $^{3}J_{C,P}$=10, C-2); 26.3, 25.8 (2xCH_2 pentyl); 23.2 (CH_3 Ac); 16.3 (d, $^{3}J_{C,P}$=6, 2xCH_3 Et); 9.43, 9.38 (2xCH_3 pentyl). ^{31}P RMN δ: 16.3. IR (Neat): 3276 (NH st); 1658 (C=O st); 1549(amide II); 1354 (O=S=O st); 1234 (P=O st); 1176 (O=S=O st); 1093, 1051,

1022, 970, 906 (P-O-C st, S-O-C st, C-O-C st). $[\propto]_D^{20^oC}$= -110 (c=1.2; AcOEt) [lit[35]: $[\propto]_D^{22^oC}$= -102.5 (c=0.4; AcOEt)]. M.p. = 106-108°C.

1-(Cyclohexylsulfanyl)ethan-1-one 76[61]

To a stirred solution of cyclohexyl 4-methylbenzene-1-sulfonate[62] (4,0 g, 15.7 mmol) in dry acetonitrile (60 mL) under argon was added potassium acetate (2.2 g, 1.2 eq.) at room temperature. The reaction mixture was stirred for 20 hours at 60°C. Afterwards, was quenched with water (60mL) and the mixture was extracted with Et_2O (3x 30mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex:AcOEt (98:2), afforded 492 mg (20%) of the pure compound as **76** yellow oil.

Methyl cyclohexanesulfonate 78

To a stirred solution of **76** (50 mg, 0.32 mmol) in dry acetonitrile (1 mL) under argon was added water (17 µL, 3 eq.) and *tert*-butyl hypochlorite (110 µL, 3 eq.) at 0°C. After 30 min of stirring at this temperature, diisopropylethylamine (220 µL, 4 eq.) and methanol (30 µL, 2 eq.) were added and the reaction mixture was allowed to stir for 3 hours at room temperature. Afterwards, was quenched with saturated sodium bicarbonate aqueous solution (5 mL) and the mixture was extracted with DCM (3x5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with Hex:AcOEt (9:1), afforded 29 mg (51%) of the pure compound **78** as colorless oil.

^{1}H NMR δ: 3.89 (3H, s, OMe); 3.04 (1H, tt, $J_{1,2}$=12.1, $J_{1,2}$=3.4, H-1); 2.21 (2H, d, ^2J=13.0, H-2); 1.91 (2H, d, ^2J=13.1, H-3); 1.72 (1H, d, ^2J=11.2, H-4); 1.59 (2H, qd,

^{2}J=$J_{2,1}$= $J_{2,3}$=12.4, $J_{2,3}$=2.9, H-2); 1.36-1.17 (3H, m, H-3, H-4). ^{13}C NMR δ: 59.5 (C-1); 55.0 (OMe); 26.4 (C-2); 25.0 (C-3); 24.9 (C-4). FTIR(Neat): 1338, 1162 (O=S=O st); 984 (S-O-C st).

N-Benzylcyclohexanesulfonamide 79

By means of the same procedure as for **78**, except that 5 eq. of benzylamine were used instead of diisopropylethylamine and methanol, 41 mg (78% yield) of the pure product **79** were obtained as white solid after purification by chromatography (preparative plate eluted with 6:4 Hex:EtOAc).

^{1}H NMR δ: 7.38-7.28 (5H, m, Ar); 4.39 (1H, br s, NH); 4.30 (2H, s, CH_2 Bn); 2.77 (1H, tt, $J_{1,2}$=12.1, $J_{1,2}$=3.3, H-1); 2.15 (2H, d, ^{2}J=12.8, H-2); 1.89-1.85 (2H, m, H-3); 1.70-1.66 (2H, m, H-4); 1.50 (2H, qd, ^{2}J=$J_{2,1}$= $J_{2,3}$=12.2, $J_{2,3}$=3.5, H-2); 1.27-1.14 (3H, m, H-3, H-4). ^{13}C NMR δ: 137.3 (Ar C_q); 128.8 (Ar(*m*)); 128.0 (Ar(*p*)); 127.9 (Ar(*o*)); 61.8 (C-1); 47.5 (CH_2 Bn); 26.4 (C-2); 25.2 (C-3); 25.1 (C-1). FTIR (Neat): 3266 (N-H st); 1312, 1135 (O=S=O st). M.p.=132°C.

Methyl chloranesulfonate[48]

An equimolar amount of methanol (5mL) was slowly added (30min) to sulfuryl chloride (10mL) under argon at 0ºC. After complete addition, the mixture was allowed to stir for 2h at room temperature with a continuous argon flux for partially releasing off dissolved hydrochloric acid. Title compound (6.7g, 41% yield) was distilled (b.p.=54-55°C) from the crude at reduced pressure (30 Torr). ^{1}H NMR δ: 4.20. ^{13}C NMR δ: 61.2.

α-chlorination of ketones

To a solution of diisopropylamine (170µL, 1.2 eq.) in dry THF (2 mL) in a flame dried round bottom flask under argon at 0°C was added *n*-butyllithium (690µL, 1.6 M in Hexanes, 1.1 eq.), and the reaction mixture was stirred at this temperature for 15 minutes. It was then cooled to –78 °C and a solution of ketone **82** (1 mmol) in THF (2 mL) was slowly added. Stirring at –78 °C was continued for further 30 minutes and methyl chlorosulfate (100µL, 1.1 eq.) was then added. After stirring at –78 °C for 30 minutes, the reaction was quenched with saturated ammonium chloride aqueous solution (5mL). The mixture was then extracted with DCM (3 x 5mL), the combined organic phases were dried with anhydrous magnesium sulfate and the solvent evaporated affording the desired α-chloroketone **83**.

2-Chlorocyclohexan-1-one 83a[63]

By means of the general procedure, 108 mg (81%) of product **83a** were obtained as colorless oil.

2-Chlorocyclopentan-1-one 83b[44]

By means of the general procedure, 89 mg (75%) of product **83b** were obtained as colorless oil.

2-Chlorocyclooctan-1-one 83c[41]

By means of the general procedure, 166 mg (quantitative yield) of product **83c** were obtained as colorless oil.

2-Chlorocyclododecan-1-one 83d[41]

By means of the general procedure, 222 mg (quantitative yield) of product **83d** were obtained as white solid.

2-Chloro-1,2,3,4-tetrahydronaphthalen-1-one 83e[63]

By means of the general procedure, 190 mg (quantitative yield) of product **83e** were obtained as white solid.

6-Chlorocyclohex-2-en-1-one 83f[64]

By means of the general procedure, 119 mg (91%) of product **83f** were obtained as colorless oil.

2-Chloro-2-methyl-1,2,3,4-tetrahydronaphthalen-1-one 83g[65]

By means of the general procedure, 146 mg (quantitative yield) of product **83g** were obtained as colorless oil.

2-Chloro-1-phenylpropan-1-one 83h[46h]

By means of the general procedure, 171 mg (quantitative yield) of product **83h** were obtained as colorless oil.

2-Chloro-6-methylcyclohexan-1-one 83i[66]

By means of the general procedure, 146 mg (quantitative yield) of product **83i** were obtained as colorless oil.

4-*tert*-Butyl-2-chlorocyclohexan-1-one 83j[47h]

By means of the general procedure, 189 mg (quantitative yield) of product **83j** (77:23 *cis*:*trans* RMN) were obtained as colorless oil.

2-Chloro-4-phenylcyclohexan-1-one 83k[63]

By means of the general procedure, 210 mg (quantitative yield) of product **83k** (78:22 *cis*:*trans* RMN) were obtained as colorless oil.

(1*S*,3*S*,5*S*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-chloro-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 83l

By means of the general procedure, 604 mg (quantitative yield) of product **83l** were obtained as colorless oil.

^{1}H NMR δ: 5.87 (1H, ddt, $J_{2',3'}$=17.1, $J_{2',3'}$=10.7, $J_{2',1'}$=5.4, H-2'); 5.32 (1H, dq, $J_{3',2'}$=17.2, ^2J=$J_{3',1'}$=1.6, H-3'); 5.15 (1H, dq, $J_{3',2'}$=10.5, ^2J=$J_{3',1'}$=1.4, H-3'); 4.44 (1H, ddd, $J_{5,4}$=8.7, $J_{5,4}$=5.5, $J_{5,6}$=2.9, H-5); 4.38 (1H, t, $J_{3,4}$=4.4, H-3); 3.24 (1H, ddt, ^2J=14.3, $J_{1',2'}$=5.5, $J_{1',3'}$=1.4, H-1'); 2.90 (1H, ddt, ^2J=14.3, $J_{1',2'}$=5.4, $J_{1',3'}$=1.3, H-1'); 2.50 (1H, ddd, ^2J=14.1, $J_{4,5}$=9.3, $J_{4,3}$=4.6, H-4), 2.28 (1H, dd, $J_{6,1}$=5.8, $J_{6,5}$=2.4, H-6), 2.22 (1H, d, $J_{1,6}$=5.9, H-1), 2.04 (1H, dtd, ^2J=14.3, $J_{4,3}$= $J_{4,5}$=4.8, $J_{4,6}$=0.6, H-4), 0.92 (9H, s, ^{t}Bu TBS); 0.13 (3H, s, Me TBS); 0.12 (3H, s, Me TBS). ^{13}C NMR δ: 198.0 (C-2); 133.8 (C-2'); 117.3 (C-3'); 64.0 (C-5); 62.0 (C-1'); 56.5 (C-3), 47.1 (C-6); 44.3 (C-1); 36.7 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); -4.65 (Me TBS); -4.73 (Me TBS). FTIR(Neat): 1729 (C=O st), 1254 (CHCl wag), 1097 (Si-O st), 836 (Si-O-C bend), 777 (C-Cl st). $[\propto]_D^{20^oC}$= -118 (c=1.0; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{27}ClNO_2Si$ 316.1494; Found 316.1495.

3-Chloro-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 83m[67]

By means of the general procedure, 190 mg (quantitative yield) of product **83m** (87:13 *exo*:*endo* RMN) were obtained as colorless oil.

4-Chloro-3-hydroxy-1,3-diphenylbutan-1-one 83n[68]

By means of the general procedure, 112 mg (quantitative yield) of product **83n** were obtained as colorless oil after chromatographic purification (preparative plate eluted with Hex:AcOEt 8:2).

Chlorination of different functional groups 84

Chlorination of ethyl 2-phenylacetate 84b

By means of the general procedure, 200 mg (100% yield) of a mixture of ethyl 2-chloro-2-phenylacetate **85b**[69] and **84b** (98:2 RMN) were obtained as colorless oil.

Chlorination of methyl 3-phenylpropanoate 84c

By means of the general procedure, 71 mg (36%) of methyl 2-chloro-3-phenylpropanoate **85c**[70], 50 mg (30%) of methyl 2-benzyl-4-chloro-3-oxo-5-phenylpentanoate **85c'** and 25 mg (17%) of methyl 2-benzyl-3-oxo-5-phenylpentanoate **85c''**[71] were obtained all as colorless oils after chromatographic purification (preparative plate eluted with Hex:AcOEt 9:1).

Methyl 2-benzyl-4-chloro-3-oxo-5-phenylpentanoate 85c'

^{1}H NMR δ: 12.99 (0.1H, s, OH''); 7.30-7.06 (9.8H, Ar); 6.87-6.85 (0.2H, Ar''); 4.80 (0.1H, t, $J_{4'',5''}$=7.5, H-4''); 4.61 (0.5H, t, $J_{4,5}$=7.1, H-4); 4.25 (0.4H, dd, $J_{4',5'}$=8.4, $J_{4',5'}$=5.9, H-4'); 4.19 (0.5H, t, $J_{2,CH2Bn}$=7.4, H-2); 4.07 (0.4H, t, $J_{2',CH2Bn'}$=7.6, H-2'); 3.69 (0.3H, s, OMe''); 3.67 (1.2H, s, OMe'); 3.56 (0.1H; ^2J=16.9, CH_2 Bn''); 3.46 (1.5H, s, OMe); 3.44 (0.1H, ^2J=17, CH_2 Bn''); 3.38 (0.1H, dd, ^2J=14, $J_{5'',4''}$=8, H-5''); 3.33 (0.5H, dd, ^2J=14.2, $J_{5,4}$=7.0, H-5); 3.22-3.14 (1.9H, m, CH_2 Bn, 5', CH_2 Bn', 5''); 3.07 (0.4H, ^2J=13.9, $J_{CH2Bn',2'}$=7.9, CH_2 Bn'); 2.95 (0.5H, dd, ^2J=14.1, $J_{5,4}$=7.3, H-5); 2.94 (0.4H, dd, ^2J=14.1, $J_{5',4'}$=8.6, H-5'). ^{13}C NMR δ: 199.0 (C-3'); 197.3 (C-3); 173.6 (C-1''); 169.6 (C-3''); 168.6 (C-1'); 168.5 (C-1); 139.6 (C_q Ar Bn''); 137.8 (C_q Ar Bn); 137.5 (C_q Ar Bn'); 136.5 (C_q Ar Ph''); 136.2 (C_q Ar Ph); 136.0 (C_q Ar Ph'); 129.5, 129.0, 128.53, 128.52 (Ar(*o*,*m*)); 129.42, 128.47, 127.6 (Ar(*o*,*m*)''); 129.37, 128.9, 128.8, 128.6 (Ar(*o*,*m*)'); 127.2, 127.0 (Ar(*p*)'); 127.1, 126.8 (Ar(*p*)); 127.1, 126.1 (Ar(*p*)''); 100.9 (C-2''); 63.1 (C-4''); 61.7 (C-4); 57.9 (C-2'); 57.6 (C-2); 56.3 (C-4'');

52.7 (OMe'); 52.6 (OMe); 52.2 (OMe''); 40.7 (C-5''); 39.2 (C-5'); 38.7 (C-5); 34.9 (CH_2 Bn'); 33.8 (CH_2 Bn); 30.6 (CH_2 Bn''). FTIR(NEAT): 1749, 1722 (C=O st), 696 (Ar C-H o.o.p. bend, C-Cl st). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{19}ClNaO_3$ 353.0915; Found 353.0914.

Chlorination of oxolan-2-one 84d

By means of the general procedure, 116 mg (100%) of a mixture of 3-chlorooxolan-2-one **85d**[72] and **84d** (85:15 RMN) were obtained as colorless oil.

Chlorination of *N,N*-diethylpropanamide 84e

By means of the general procedure, 166 mg (quantitative yield) of 2-chloro-*N*,*N*-diethylpropanamide **85h** were obtained as colorless oil.

2-Chloro-*N*,*N*-diethylpropanamide 85e

^{1}H NMR δ: 4.55 (1H, q, $J_{2,3}$=6.5, H-2); 3.54 (1H, p, *J*=7.3, CH_2 Et); 3.49 (1H, p, *J*=6.9, CH_2 Et); 3.32 (1H, qd, *J*=7.1, *J*=3.7, CH_2 Et); 3.28 (1H, qd, *J*=7.1, *J*=1.6, CH_2 Et); 1.67 (3H, d, $J_{3,2}$=6.5, H-3); 1.24 (3H, t, ^2J=7.2, CH_3 Et); 1.14 (3H, t, ^2J=7.1, CH_3 Et). ^{13}C NMR δ: 168.2 (C-1); 49.5 (C-2); 42.0, 40.8 (CH_2 Et); 21.2 (C-3); 14.7, 12.6 (CH_3 Et). FTIR(NEAT): 1651 (C=O st), 1462, 1434 (C-N st). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_7H_{15}ClNO$ 164.0837; Found 164.0838.

Chlorination of *N,N*-dimethylacetamide 84f

By means of the general procedure, 87 mg (99%) of a mixture of 2-chloro-*N*,*N*-dimethylacetamide **85f**[73] and 4-chloro-*N*,*N*-dimethyl-3-oxobutanamide **86k** (28:72 RMN) were obtained as yellow oil.

Chlorination of 1-methylpyrrolidin-2-one 84g

By means of the general procedure, 107 mg (80%) of 3-chloro-1-methylpyrrolidin-2-one **85g**[47a] were obtained as colorless oil.

Chlorination of 1,3-diethyl propanedioate 84h

By means of the general procedure, 181 mg (100%) of a mixture of 1,3-diethyl 2-chloropropanedioate **85h**[74] and **84h** (66:34 RMN) were obtained as colorless oil.

Chlorination of ethyl 2-oxocycloHex-1-carboxylate 84j

By means of the general procedure, 177 mg (100%) of a mixture of ethyl 1-chloro-2-oxocycloHex-1-carboxylate **85j**[75] and **84j** (14:86 RMN) were obtained as colorless oil.

Chlorination of *N*,*N*-dimethyl-3-oxobutanamide 84k

By means of the general procedure, 139 mg (96%) of a mixture of 2-chloro-*N*,*N*-dimethyl-3-oxobutanamide **85k**[76] and **84k** (50:50 RMN) were obtained as colorless oil.

Chlorination of 2-phenylacetonitrile 84l

The general procedure was followed except that were used 2.4 eq. of DIPA, 2.2 eq. of BuLi and 2.2 eq. of $MeOSO_2Cl$. After purification by chromatography (preparative plate eluted with Hex:AcOEt 95:5), 99 mg (66%) of 2,3-dichloro-2,3-diphenylbutanedinitrile **85l** were obtained as colorless oil.

2,3-Dichloro-2,3-diphenylbutanedinitrile 85l

^{1}H NMR δ: 7.86-7.81 (4H, m, Ar); 7.51-7.48 (6H, m, Ar). ^{13}C NMR δ: 137.34 (C_q Ar); 131.37 (Ar(*p*)); 129.18, 125.40 (Ar(*m*,*o*)); 115.16 (CN); 68.2 (C_q). FTIR(NEAT): 719 (Ar C-H o.o.p. bend, C-Cl st). HRMS (EI-B) m/z: $[1/2M]^+$ Calcd for C_8H_5ClN 150.0105; Found 150.0114.

Chlorination of lithium dianion of 1,3-dicarbonyl compounds

To a solution of diisopropylamine (340µL, 2.4 eq.) in dry THF (2 mL) in a flame dried round bottom flask under argon at 0°C was added *n*-butyllithium (1.4 mL, 1.6 M in Hexanes, 2.2 eq.), and the reaction mixture was stirred at this temperature for 15 minutes. At the same temperature, a solution of dicarbonyl compound **84** (1 mmol) in THF (2 mL) was slowly added. After 1 hour of stirring at 0 °C the solution was cooled to -78 °C and methyl chlorosulfate (110µL, 1.2 eq.) was then added. After stirring at –78 °C for 30 minutes, the reaction was quenched with saturated ammonium chloride aqueous solution (5mL). The mixture was then extracted with DCM (3 x 5mL), the combined organic phases were dried with anhydrous magnesium sulfate and the solvent evaporated affording the desired 4-chloro dicarbonyl compound **86**.

Ethyl 4-chloro-3-oxobutanoate 86i[77]

By means of the general procedure, 167 mg (100%) of product **86i** were obtained as yellow oil.

Ethyl 3-chloro-2-oxocycloHex-1-carboxylate 86j

By means of the general procedure, 209 mg (100%) of product **86j** were obtained as yellow oil.

Enol: ^{1}H NMR δ: 12.08 (1H, s, OH); 4.54 (1H, t, $J_{3,4}$=3.6, H-3); 4.28-4.20 (2H, m, CH_2 Et); 2.42 (1H, ddd, ^{2}J=16.6, $J_{6,5}$=5.3, $J_{6,5}$=2.9, H-6); 2.18 (1H, ddd, ^{2}J=16.8, $J_{6,5}$=11.0, $J_{6,5}$=5.8, H-6); 2.16-2.10 (1H, m, H-4); 2.03 (1H, tdd, ^{2}J= $J_{4,5}$=14.2, $J_{4,5}$=4.2, $J_{4,3}$=3.1, H-4); 1.95-1.83 (1H, m, H-5); 1.76-1.69 (1H, m, H-5); 1.31 (1H, t, ^{2}J=16.8, CH_2 Et). ^{13}C NMR δ: 172.3 (C-2); 165.9 (C=O ester); 100.4 (C-1); 60.9 (CH_2 Et); 54.5 (C-3); 31.9 (C-4); 22.3 (C-6); 17.3 (C-5); 14.2 (CH_2 Et). FTIR(NEAT): 1657 (C=O st); 1284,

1229, 1205, 1180 (C-O st, C-O-C st); 807 (Ar C-H o.o.p. bend, C-Cl st). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_9H_{13}ClNaO_3$ 227.0445; Found 227.0442.

4-Chloro-*N*,*N*-dimethyl-3-oxobutanamide 86k

By means of the general procedure, 126 mg (77%) of product **86k** were obtained as yellow oil.

^{1}H NMR δ: 15.07 (0.5H, s, OH'); 5.48 (0.5H, s, H-2'); 4.29 (1H, s, H-4); 4.02 (1H, s, H-4'); 3.71 (1H, s, H-2); 3.03 (1.5H, s, Me); 3.02 (3H, br s, Me'); 2.98 (1.5H, s, Me). ^{13}C NMR δ: 196.3 (C-3); 171.5 (C-1'); 170.7 C-3'); 166.0 (C-1); 87.6 (C-2'); 48.3 (C-4); 45.6 (C-2); 43.4 (C-4'); 37.8, 35.5 (Me). FTIR(NEAT): 3467 (O-H st); 1740 (C=O st ketone); 1635 (C=O st Amide). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_6H_{10}ClNNaO_2$ 186.0292; Found 186.0297.

Chlorination of equimolar mixtures of compounds

Chlorination of an equimolar mixture of 1-phenylethan-1-one 82n and methyl 3-phenylpropanoate 84c

The general procedure was followed except that a solution of 0.5 mmol of **82n** and 0.5 mmol of **84c** was used instead of 1 mmol of a single compound. After purification by chromatography (preparative plate eluted with Hex:AcOEt 8:2), 60 mg (42%) of methyl 2-benzyl-3-hydroxy-3-phenylbutanoate **87** and 29 mg (20%) of the other diastereoisomer **87'** were obtained both as white solids.

2-Benzyl-3-hydroxy-3-phenylbutanoate 87

^{1}H NMR δ: 7.43 (2H, d, ^3J=7.3, Ar(*o*) Ph); 7.31 (2H, t, ^3J=7.7, Ar(*m*) Ph); 7.28-7.17 (4H, m, Ar(*p*) Ph, Ar(*m,p*) Bn); 7.15 (2H, d, ^3J=7.9, Ar(*o*) Bn); 4.00 (1H, br s, OH); 3.06 (1H, dd, $J_{2,CH2Bn}$=9.8, $J_{2,CH2Bn}$=5.6, H-2); 3.13 (3H, s, OMe); 3.13-3.10 (2H, m, CH_2 Bn); 1.61 (3H, s, H-4). ^{13}C NMR δ: 175.9 (C-1); 147.1 (C_q Ar Ph); 139.0 (C_q Ar

Bn); 128.8 (Ar(*o*) Bn); 128.5 (Ar(*m*) Bn); 128.2 (Ar(*m*) Ph); 127.0 (Ar(*p*) Ph); 126.5 (Ar(*p*) Bn); 124.7 (Ar(*o*) Ph); 75.0 (C-3); 57.5 (C-2); 51.3 (OMe); 33.9 (CH_2 Bn); 27.1 (C-4). FTIR(NEAT): 3487 (O-H st); 1708 (C=O st); 1201, 1165 (C-O st, C-O-C st); 697 (Ar C-H o.o.p. bend). M.p.= 113 °C. Anal. Calcd for $C_{18}H_{20}O_3$: C 76.03; H 7.09. Found: C 76.21; H 7.35.

2-Benzyl-3-hydroxy-3-phenylbutanoate 87'

^{1}H NMR δ: 7.52 (2H, d, ^3J=7.4, Ar(*o*) Ph); 7.39 (2H, t, ^3J=7.7, Ar(*m*) Ph); 7.28 (1H, t, ^3J=7.3, Ar(*p*) Ph); 7.19 (2H, t, ^3J=7.2, Ar(*m*) Bn); 7.13 (1H, t, ^3J=7.2, Ar(*p*) Bn); 6.94 (2H, d, ^3J=7.0, Ar(*o*) Bn); 3.80 (1H, br s, OH); 3.52 (3H, s, OMe); 3.06 (1H, dd, $J_{2,CH2Bn}$=11.9, $J_{2,CH2Bn}$=3.5, H-2); 2.91 (1H, t, ^2J=$J_{CH2Bn,2}$=12.7, CH_2 Bn); 2.46 (1H, dd, ^2J=13.6, $J_{CH2Bn,2}$=3.5, CH_2 Bn); 1.55 (3H, s, H-4). ^{13}C NMR δ: 176.5 (C-1); 145.0 (C_q Ar Ph); 139.2 (C_q Ar Bn); 128.6 (Ar(*o*) Bn); 128.4, 128.3 (Ar(*m*)); 126.9 (Ar(*p*) Ph); 126.3 (Ar(*p*) Bn); 124.8 (Ar(*o*) Ph); 74.6 (C-3); 58.4 (C-2); 51.6 (OMe); 34.1 (CH_2 Bn); 30.3 (C-4). FTIR(NEAT): 3509 (O-H st); 1712 (C=O st); 1206, 1167 (C-O st, C-O-C st); 700 (Ar C-H o.o.p. bend). M.p.= 89 °C. Anal. Calcd for $C_{18}H_{20}O_3$: C 76.03; H 7.09. Found: C 75.78; H 7.33.

Chlorination of an equimolar mixture of 1-phenylethan-1-one 82n and *N,N*-dimethylacetamide 84i

The general procedure was followed except that a solution of 0.5 mmol of **82n** and 0.5 mmol of **84i** was used instead of 1 mmol of a single compound. After purification by chromatography (preparative plate eluted with AcOEt), 64 mg (62%) of 3-hydroxy-*N*,*N*-dimethyl-3-phenylbutanamide **88** were obtained as white solid (m.p.=87-88 °C, lit[78] 85-87°C).

Chlorination of an equimolar mixture of methyl 3-phenylpropanoate 84c and *N,N*-dimethylacetamide 84i

The general procedure was followed except that a solution of 0.5 mmol of **84c** and 0.5 mmol of **84i** was used instead of 1 mmol of a single compound. After purification by chromatography (preparative plate eluted with Hex:AcOEt 2:1), 54 mg (54%) of **85c**, 30 mg (49%) of **85f**, 23 mg (18 %) of 4-chloro-*N*,*N*-dimethyl-3-oxo-5-phenylpentanamide **89** (yellow oil) and 5 mg (4%) of 2-chloro-*N*,*N*-dimethyl-3-oxo-5-phenylpentanamidethe **90** (colorless oil) were obtained.

4-Chloro-*N*,*N*-dimethyl-3-oxo-5-phenylpentanamide 89

^{1}H NMR δ: 15.19 (0.5H, s, OH'); 7.32-7.15 (5H, m, Ar); 5.30 (0.5H, s, H-2'); 4.72 (0.5H, dd, $J_{4,5}$=8.6, $J_{4,5}$=5.5, H-4); 4.39 (0.5H, t, $J_{4',5'}$=7.2, H-4'); 3.85 (0.5H, d, ^{2}J=15.7, H-2); 3.63 (0.5H, d, ^{2}J=15.7, H-2); 3.42 (1H, dd, dd, *J*=14.1, *J*=6.3, H-5, H-5'); 3.20-3.02 (1H, m, H-5, H-5'); 2.95 (3H, br s, Me'); 2.93 (1.5H, s, Me); 2.92 (1.5H, s, Me). ^{13}C NMR δ: 198.3 (C-3); 172.4 (C-3'); 171.5 C-1'); 136.8 (C_q Ar); 136.3 (C_q Ar'); 129.5 (Ar(*m*)); 129.4 (Ar(*m*)'); 128.5 (Ar(*o*)); 128.4 (Ar(*o*)'); 127.1 (Ar(*p*)); 127.0 (Ar(*p*)'); 87.6 (C-2'); 62.5 (C-4); 61.3 (C-4'); 45.9 (C-2); 41.5 (C-5'); 38.9 (C-5'); 37.7, 35.4 (Me). FTIR(NEAT): 1634 (C=O); 700 (Ar C-H o.o.p. bend, C-Cl st). HRMS (ESI-TOF) m/z: $[M+Na]^{+}$ Calcd for $C_{13}H_{16}ClNNaO_2$ 276.0762; Found 276.0760.

2-Chloro-*N*,*N*-dimethyl-3-oxo-5-phenylpentanamidethe 90

^{1}H NMR δ: 7.28 (2H, t, *J*=7.6, Ar(*m*)); 7.21-7.18 (3H, m, Ar(*o,p*)); 4.93 (1H, s, H-2); 3.10-3.06 (2H, m, H-4); 2.99 (3H, s, Me); 2.97-2.93 (2H, m, H-5); 2.95 (3H, s, Me). ^{13}C NMR δ: 200.1 (C-3); 164.8 C-1); 140.4 (C_q Ar); 128.5, 128.4 (Ar(o,*m*)); 126.2 (Ar(*p*)); 60.0 (C-2); 40.6 (C-4); 37.7, 36.3 (Me); 29.6 (C-5). FTIR(NEAT): 1645 (C=O);

698 (Ar C-H o.o.p. bend, C-Cl st). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{16}ClNNaO_2$ 276.0762; Found 276.0761.

General procedure for the synthesis of 2-oxo-S-carbonyl or thiocarbonyl compounds 91

To a stirred solution of 2-chloroketone **83** (6.4mmol) in dry acetone (13mL) under argon atmosphere was added potassium ethyl xanthate, potassium thioacetate or other salt (1.2eq.). After reaction completion (followed by TLC, 2-8h), water was added (20mL) and extracted with DCM (3X10mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. Products **91** were purified by chromatography (flash column or preparative TLC).

Ethyl [(2-oxocyclopentyl)sulfanyl]methanethioate 91b

A described procedure[79] for the preparation of the compound **91b** was followed.

^{1}H NMR δ: 4.15 (2H, q, ^3J=7.1, CH_2 Et); 4.15 (1H, t, J=9.4, J=1.6, H-1); 2.66-2.59 (1H, m, H-5); 2.45 (1H, dm, ^2J=18.8, H-3); 2.30 (1H, dt, ^2J=18.8, $J_{3,4}$=9.5, H-3); 2.18-2.11 (1H, m, H-4); 2.08-1.89 (2H, m, H-4, H-5); 1.42 (3H, t, ^3J=7.1, CH_3 Et). ^{13}C NMR δ: 212.5, 212.4 (C-2, C=S); 70.6 (CH_2 Et); 55.0 (C-1)); 37.0 (C-3); 30.2 (C-5); 20.7 (C-4); 13.7 (CH_3 Et). FTIR (Neat): 1743 (C=O st), 1209 (C-O-C st), 1039 (C=S st).

Ethyl [(3-methyl-2-oxocyclohexyl)sulfanyl]methanethioate 91c

By means of the general procedure, 127 mg (55% yield) of product **91c** were obtained as colorless oil after purification by preparative TLC (eluted with 4:6 Hex:DCM).

^{1}H NMR δ: 4.65-4.55 (2.8H, m, CH_2 Et, H-1); 4.54 (0.2H, t, *J*=5.2, H-1'); 2.90-2.81 (0.2H, m, H-3'); 2.67-2.54 (1.6H, m, H-3, H-6); 2.36-2.00 (1.4H, m, H-4, H-4', H-6'); 1.99-1.70 (2.8H, m, H-5, H-5', H-6); 1.56-1.43 (1H, m, H-4, H-4'); 1.40 (3H, t, ^{3}J=7.1, CH_3 Et), 1.11 (0.6H, d, *J*=6.7, Me'), 1.09 (2.4H, d, *J*=6.5, Me'). ^{13}C NMR δ: 213.8 (211.2) (C=S); 206.5 (208.4) (C-2); 70.1 (70.4) (CH_2 Et); 60.6 (56.0) (C-1); 46.0 (42.8) (C-3); 36.7 (35.5) (C-4); 35.2 (33.5) (C-6); 25.8 (21.5) (C-5), 14.6 (15.1) (Me); 13.8 (13.6) (CH_3 Et). FTIR (Neat): 1712 (C=O st), 1209 (C-O-C st), 1046 (C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{16}NaO_2S_2$ 255.0484; Found 255.0480.

Ethyl [(5-*tert*-butyl-2-oxocyclohexyl)sulfanyl]methanethioate 91d

By means of the general procedure, 1.3g (74% yield) of product **91d** were obtained as colorless oil (74% yield) after purification by flash column chromatography (eluted with 95:5 Hex:EtOAc).

^{1}H NMR δ: 4.68-4.43 (3H, m, H-1, CH_2 Et); 2.78-1.96 (4H, m); 1.80-1.48 (3H, m); 1.41 (3H, t, ^{3}J=7.2, CH_3 Et); 0.94 (0.90) (9H, s, ^{t}Bu). ^{13}C NMR δ: 213.5 (210.5) (C=S); 205.2 (207.1) (C-2); 70.2 (70.5) (CH_2 Et); 60.0 (55.1) (C-1)); 47.7 (43.1) (C-5); 41.3 (38.2) (CH_2); 35.7 (33.2) (CH_2); 32.7 (32.4) (C_q ^{t}Bu); 28.3 (27.42) (CH_2); 27.6 (27.39) (3xCH_3 ^{t}Bu); 13.8 (13.6) (CH_3 Et). FTIR (Neat): 1717 (C=O st), 1216 (C-O-C st), 1052 (C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{22}NaO_2S_2$ 297.0953; Found 297.0949.

Ethyl [(2-oxo-5-phenylcyclohexyl)sulfanyl]methanethioate 91e

By means of the general procedure, 221 mg (75% yield) of product **91e** were obtained as colorless oil after purification by flash column chromatography (eluted with 95:5 Hex:EtOAc).

^{1}H NMR δ: 7.36-7.23 (5H, m, Ar); 4.79 (0.85H, dd, *J*=13.4, *J*=5.7, H-1); 4.67-4.58 (2H, m, CH_2 Et); 4.54 (0.15H, dt, *J*=4.7, *J*=1.6, H-1); 3.33-3.17 (1H, m, H-5); 2.93-1.97 (6H, m, H-3, H-4, H-6); 1.43 (1.40) (3H, t, ^{3}J=7.1, CH_3 Et). ^{13}C NMR δ: 213.3 (210.1) (C=S); 204.2 (205.7) (C-2); 143.3 (143.2) (C_q Ar); 128.8 (Ar(*m*)); 127.0 (126.9) (Ar(*p*)); 126.7 (126.8) (Ar(*o*)); 70.4 (70.6) (CH_2 Et); 59.7 (55.2) (C-1); 43.7 (38.8) (C-5); 41.5, 41.2, 34.4 (39.2, 38.4, 33.7) (C-3, C-4, C-6); 13.8 (13.6) (CH_3 Et). FTIR (Neat): 1716 (C=O st), 1220 (C-O-C st), 1049 (C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}NaO_2S_2$ 317.0640; Found 317.0644.

Ethyl {[(1S,5S,6R)-5-[(*tert*-butyldimethylsilyl)oxy]-2-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-3-yl]sulfanyl}methanethioate 91g

By means of the general procedure, 696 mg (84% yield) of product **91g** were obtained as colorless oil after purification by flash column chromatography (eluted with 95:5 Hex:EtOAc).

^{1}H NMR δ: 5.94-5.82 (1H, m, H-2'); 5.39-5.32 (1H, m, H-3'); 5.18-5.13 (1H, m, H-3'); 4.75 (0.3H, dd, $J_{3,4}$=6.8, $J_{3,4}$=5.0, H-3b); 4.71-4.60 (2H, m, CH_2 Et); 4.27-4.19 (1.7H, m, H-3a, H-5); 3.32 (0.7H, ddt, ^{2}J=14.4, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'a); 3.19 (0.3H, ddt, ^{2}J=14.4, $J_{1',2'}$=5.4, $J_{1',3'}$=1.4, H-1'b); 2.94 (0.3H, ddt, ^{2}J=14.4, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'b); 2.81 (0.7H, ddt, ^{2}J=14.4, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'a); 2.63 (0.3H, ddd, ^{2}J=14.0, $J_{4,5}$=8.7, $J_{4,3}$=6.9, H-4b); 2.36-2.17 (2.7H, m, H-1, H-4a, H-6); 2.11 (0.7H, dtd, ^{2}J=12.1, $J_{4,5}$=$J_{4,3}$=6.0, $J_{4,6}$=0.6, H-4a); 1.94 (0.3H, dtd, ^{2}J=13.9, $J_{4,5}$=$J_{4,3}$=5.3, $J_{4,6}$=0.6, H-4b); 1.42 (3H, t, ^{3}J=7.1, CH_3 Et); 0.92 (9H, s, ^{t}Bu TBS); 0.13 (2.1H, Me TBS a); 0.12 (2.1H, Me TBS a); 0.11 (0.9H, Me TBS b); 0.09 (0.9H, Me TBS b). ^{13}C NMR δ: 213.4 (211.2) (C=S); 199.1 (201.4) (C-2); 133.8 (133.9) (C-2'); 117.05 (117.14) (C-3'); 70.8 (70.5) (CH_2 Et); 67.6 (65.5) (C-5); 61.81 (61.75) (C-1'); 53.6 (51.4) (C-3); 46.8, 45.5 (49.1, 46.1) (C-1, C-6); 32.5 (36.0) (C-4); 25.7 (25.8)

(3x CH_3 ^tBu); 18.08 (18.11) (C_q ^tBu); 13.8 (13.7) (CH_3 Et); -4.60, -4.66, -4.71 (Me TBS). FTIR(NEAT): 1716 (C=O st); 1219 (C-O-C st); 1096 (Si-O st); 1049 (C=S st); 837 (Si-O-C bend); 777. $[\propto]_D^{20^oC}$= -125 (c=1.0; DCM). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{31}NNaO_3S_2Si$ 424.1407; Found 424.1414.

Ethyl [(2-oxocyclohex-3-en-1-yl)sulfanyl]methanethioate 91h

The general procedure was followed except that 2eq. of potassium ethyl xanthate were used instead of 1.2. After purification by flash column chromatography (eluted with 9:1 Hex:EtOAc), 158 mg (48% yield) of product **91h** were obtained as colorless oil.

^{1}H NMR δ: 7.02 (1H, dt, $J_{4,3}$=9.1, $J_{4,5}$=4.0, H-4); 6.12 (1H, d, $J_{3,4}$=10.1, H-4); 4.72-4.61 (3H, m, CH_2 Et, H-1); 2.62-2.45 (3H, m, H-5, H-6); 2.29-2.18 (1H, m, H-6); 1.42 (3H, t, ^3J=7.1, CH_3 Et). ^{13}C NMR δ: 211.9 (C=S); 193.4 (C-2); 150.4 (C-4); 129.1 (C-3); 70.4 (CH_2 Et); 56.1 (C-1); 29.7 (C-6); 25.9 (C-5); 13.8 (CH_3 Et). FTIR (Neat): 1679 (C=O st), 1210 (C-O-C st), 1042 (C=S st). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_9H_{12}NaO_2S_2$ 239.0171; Found 239.0176.

2-(Acetylsulfanyl)-1-phenylpropan-1-one 91i[80]

By means of the general procedure, 129 mg (62% yield) of product **91i** were obtained as colorless oil after purification by preparative TLC (eluted with 9:1 Hex:EtOAc).

2-(Acetylsulfanyl)-1-phenylethan-1-one 91j[80-81]

By means of the general procedure, 604 mg (96% yield) of product **91j** were obtained as white solid after purification by flash column chromatography (eluted with 9:1 Hex:EtOAc).

6-(Acetylsulfanyl)cyclohex-2-en-1-one 91k

By means of the same procedure as for **91h** (but with KSAc), 107 mg (53% yield) of the pure product **91k** were obtained as colorless oil after purification by flash column chromatography (eluted with 95:5 Hex:EtOAc).

^{1}H NMR δ: 7.02 (1H, dddd, $J_{3,2}$=10.0, $J_{3,4}$=4.7, $J_{3,4}$=3.5, $J_{3,5}$=0.9, H-3); 6.11 (1H, ddd, $J_{2,3}$=10.1, $J_{2,4}$=2.4, $J_{2,4}$=1.6, H-2); 4.35 (1H, dd, $J_{6,5}$=11.7, $J_{6,5}$=4.7, H-6); 2.61-2.44 (2H, m, H-4); 2.40-2.29 (1H, m, H-5); 2.39 (3H, s, CH_3 Ac); 2.15 (1H, dddd, ^{2}J=13.3, $J_{5,6}$=11.7, $J_{5,4}$=9.3, $J_{5,4}$=5.3, H-5). ^{13}C NMR δ: 194.14, 194.12 (C-1, C=O Ac); 150.5 (C-3); 129.2 (C-2); 49.7 (C-6); 30.6 (CH_3 Ac); 30.2 (C-5); 25.7 (C-4). FTIR (Neat): 1674 (C=O st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_8H_{10}NaO_2S$ 193.0294; Found 193.0293.

2-(Acetylsulfanyl)-4-*tert*-butylcyclohexan-1-one 91l

By means of the general procedure, 1.3g (88% yield) of product **91l** were obtained as white solid after purification by flash column chromatography (eluted with 95:5 Hex:EtOAc).

^{1}H NMR δ: 4.31 (1H, dd, $J_{2,3}$=13.3, $J_{2,3}$=5.8, H-2); 2.59 (1H, dt, ^{2}J=14.0, $J_{6,5}$=3.5, H-6); 2.39-2.32 (1H, m, H-3); 2.36 (3H, s, CH_3 Ac); 2.15 (1H, ddq, ^{2}J=12.7, $J_{5,6}$=6.2, $J_{5,4}$=$J_{5,6}$= $J_{5,3}$=3.1, H-5); 1.74 (1H, tt, $J_{4,5}$=$J_{4,3}$=12.1, $J_{4,5}$=$J_{4,3}$=2.8, H-4); 1.56 (1H, q, ^{2}J=$J_{3,4}$=$J_{3,2}$=12.4, H-3); 1.50 (1H, qd, ^{2}J=$J_{5,4}$=$J_{5,6}$=12.7, $J_{5,6}$=4.8, H-5); 0.92 (9H, s, ^{t}Bu). ^{13}C NMR δ: 205.5 (207.6) (C-1); 194.6 (192.5) (C=O Ac); 53.4 (49.6) (C-2); 47.5 (43.4) (C-4); 41.2 (38.7) (C-6); 36.2 (33.6) (C-3); 32.6 (32.4) (C_q ^{t}Bu); 30.6 (30.5) (CH_3 Ac); 28.1 (26.7) (C-5); 27.6 (27.4) (3XCH_3 ^{t}Bu). FTIR (Neat): 1721 (C=O st ketone), 1686 (C=O st thioacetate). M.p.=47-49°C. Anal. Calcd for $C_{12}H_{20}O_2S$: C 63.12; H 8.83; S 14.04. Found: C 62.85; H 8.53; S 13.90.

2-(Acetylsulfanyl)cyclooctan-1-one 91m

The general procedure was followed except that reaction temperature was 70°C (in a pressure tube), 2.0 eq. of potassium thioacetate were used and the reaction time was 70 hours. After purification by flash column chromatography (eluted with 95:5 Hex:EtOAc), 433mg (70% yield) of product **91m** were obtained as colorless.

^{1}H NMR δ: 4.50 (1H, dd, $J_{2,3}$=10.9, $J_{2,3}$=3.7, H-2); 2.77 (1H, ddd, ^{2}J=14.2, $J_{8,7}$=8.1, $J_{8,7}$=3.2, H-8); 2.41 (1H, ddd, ^{2}J=14.1, $J_{8,7}$=10.8, $J_{8,7}$=3.2, H-8); 2.31 (3H, s, CH_3 Ac); 2.17-2.07 (2H, m); 1.89-1.48 (7H, m); 1.19-1.09 (1H, m). ^{13}C NMR δ: 213.2 (C-1); 195.2 (C=O Ac); 51.3 (C-2); 42.2 (C-8); 30.1 (CH_3 Ac); 32.2, 27.6, 25.1, 24.8, 24.3 (5XCH_2). FTIR (Neat): 1708 (C=O st ketone), 1686 (C=O st thioacetate). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{16}NaO_2S$ 223.0763; Found 223.0761.

2-(Acetylsulfanyl)cyclododecan-1-one 91n

By means of the same procedure as for **91m**, 145 mg (57% yield) of the pure product **91n** were obtained as white solid after purification by flash column chromatography (eluted with 98:2 Hex:EtOAc).

^{1}H NMR δ: 4.55 (1H, dd, $J_{2,3}$=9.7, $J_{2,3}$=3.6, H-2); 2.81 (1H, ddd, ^{2}J=15.7, $J_{12,11}$=8.5, $J_{12,11}$=3.4, H-12); 2.35 (1H, ddd, ^{2}J=15.6, $J_{12,11}$=9.0, $J_{12,11}$=3.6, H-12); 2.35 (3H, s, CH_3 Ac); 2.09-2.00 (1H, m, H-3); 1.85-1.66 (3H, m); 1.45-1.17 (14H, m). ^{13}C NMR δ: 207.5 (C-1); 194.5 (C=O Ac); 50.0 (C-2); 38.5 (C-12); 30.3 (CH_3 Ac); 29.2 (C-3); 24.9, 24.8, 24.6, 24.3, 24.2, 23.0, 22.4, 22.2 (8XCH_2). FTIR (Neat): 1694 (C=O st). M.p.=65-66°C. Anal. Calcd for $C_{14}H_{24}O_2S$: C 65.58; H 9.44; S 12.50. Found: C 65.50; H 9.53; S 12.48.

N,*N*-Dimethyl-1-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]methanethioamide 91o

By means of the general procedure (using sodium dimethyl-dithiocarbamate hydrate), 1.3g (91% yield) of product **91o** were obtained as white solid after purification by flash column chromatography (eluted with 1:2 Hex:DCM).

^{1}H NMR δ: 8.07 (1H, dd, $J_{8,7}$=7.9, $J_{8,6}$=1.0, H-8); 7.50 (1H, td, $J_{6,5}$=$J_{6,7}$=7.5, $J_{6,8}$=1.3, H-6); 7.33 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.27 (1H, d, $J_{5,6}$=7.6, H-5); 5.37 (1H, dd, $J_{2,3}$=12.6, $J_{2,3}$=4.6, H-2); 3.58 (3H, s, Me); 3.44 (3H, s, Me); 3.28 (1H, ddd, ^{2}J=16.9, $J_{4,3}$=11.8, $J_{4,3}$=4.5, H-4); 3.06 (1H, dt, ^{2}J=16.9, $J_{4,3}$=4.0, H-4); 2.69 (1H, dq, ^{2}J=12.9, $J_{3,4}$=$J_{3,2}$=4.3, H-3); 2.32 (1H, qd, ^{2}J= $J_{3,4}$=$J_{3,2}$=12.4, $J_{3,4}$=4.3, H-3). ^{13}C NMR δ: 195.3, 193.5 (C-1, C=S); 143.7 (C-4a); 133.8 (C-6); 132.2 (C-8a); 128.8 (C-5); 127.9 (C-8); 126.8 (C-7); 60.0 (C-2); 45.9, 41.7 (2xMe); 31.5 (C-3); 29.7 (C-4). FTIR (Neat): 1682 (C=O st); 1497, 1375, 981 (N-C-S); 1145 (C=S st); 741 (Ar C-H o.o.p. bend). M.p.=149°C. Anal. Calcd for $C_{13}H_{15}NOS_2$: C 58.84; H 5.70; N 5.28; S 24.16. Found: C 59.09; H 5.98; N 5.50; S 23.90.

2-{[(*tert*-Butylsulfanyl)methanethioyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91p

A described procedure[82] for the preparation of compound **91p** was followed.

^{1}H NMR δ: 8.05 (1H, d, $J_{8,7}$=7.8, H-8); 7.51 (1H, t, $J_{6,5}$=$J_{6,7}$=7.5, H-6); 7.33 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.26 (1H, d, $J_{5,6}$=7.6, H-5); 5.25 (1H, dd, $J_{2,3}$=11.8, $J_{2,3}$=4.5, H-2); 3.20 (1H, ddd, ^{2}J=16.9, $J_{4,3}$=10.9, $J_{4,3}$=4.4, H-4); 3.07 (1H, dt, ^{2}J=16.9, $J_{4,3}$=4.4, H-4); 2.60 (1H, dq, ^{2}J=13.3, $J_{3,4}$=$J_{3,2}$=4.4, H-3); 2.30 (1H, qd, ^{2}J=$J_{3,4}$=$J_{3,2}$=11.9, $J_{3,4}$=4.4, H-3); 1.65 (9H, s, ^{t}Bu). ^{13}C NMR δ: 221.4 (C=S); 193.1 (C-1); 143.6 (C-4a);

134.0 (C-6); 132.1 (C-8a); 128.8 (C-5); 128.0 (C-8); 126.9 (C-7); 56.6 (C-2); 54.8 (C_q ^{t}Bu); 30.2 (C-3); 29.4 (3xCH_3 ^{t}Bu); 29.2 (C-4). FTIR (Neat): 1683 (C=O st); 1065 (C=S st); 804; 794; 740 (Ar C-H o.o.p. bend). M.p.=95-96°C (lit. 100-101°C).

Ethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]formate 91q

To a solution of **91f** (1g, 3.8 mmol) in DCM (15mL) was added m-CPBA (77%, 1.7g, 2eq.) at 0°C and the mixture was stirred for 30 min at room temperature. Afterward 20 mL of $NaHCO_3$ aqueous saturated solution were added and extracted with DCM (3x10mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. After purification by flash column chromatography (eluted with 95:5 Hex:EtOAc), 218 mg (23%) of pure product **91q** were obtained as yellowish white solid.

^{1}H NMR δ: 8.06 (1H, d, $J_{8,7}$=7.9, H-8); 7.50 (1H, t, $J_{6,5}$=$J_{6,7}$=7.5, H-6); 7.33 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.26 (1H, d, $J_{5,6}$=7.4, H-5); 4.38 (1H, dd, $J_{2,3}$=11.9, $J_{2,3}$=4.5, H-2); 4.34-4.27 (2H, m, CH_2 Et); 3.17 (1H, ddd, ^2J=16.9, $J_{4,3}$=10.8, $J_{4,3}$=4.5, H-4); 3.08 (1H, dt, ^2J=16.9, $J_{4,3}$=4.5, H-4); 2.60 (1H, dq, ^2J=13.3, $J_{3,4}$=$J_{3,2}$=4.5, H-3); 2.37 (1H, qd, ^2J= $J_{3,4}$=$J_{3,2}$=12.0, $J_{3,4}$=4.6, H-3); 1.32 (3H, t, ^2J=7.1; CH_2 Et). ^{13}C NMR δ: 193.1 (C-1); 169.7 (C=O thiocarbonate); 143.4 (C-4a); 133.9 (C-6); 131.8 (C-8a); 128.7 (C-5); 128.1 (C-8); 127.0 (C-7); 64.0 (CH_2 Et); 52.7 (C-2); 31.1 (C-3); 29.1 (C-4); 14.3 (CH_3 Et). FTIR (Neat): 1698 (C=O st); 1131 (C-O-C st); 738 (Ar C-H o.o.p. bend). M.p.=53°C. Anal. Calcd for $C_{13}H_{14}O_3S$: C 62.38; H 5.64; S 12.81. Found: C 62.60; H 5.85; S 12.60.

N,*N*-Dimethyl-1-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]formamide 91r

A described procedure for the oxidation of dithiocarbamates was used with some modifications.[83] To a solution of **91o** (950 mg, 3.6 mmol), benzoic acid

(1 eq., 440 mg) and benzyltriethylammonium chloride (10 mol%, 83 mg) in DCM (36 mL) was added a solution of $KMnO_4$ (3 eq., 1.7 g) in water (72 mL) and the reaction mixture was vigorously stirred for 5 hours. Afterward solid sodium metabisulfite was added until the reaction mixture color turned white which was then diluted with $NaHCO_3$ aqueous saturated solution (50 mL) and extracted with DCM (3X50 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. After purification by flash column chromatography (eluted with 95:5 DCM:EtOAc), 406 mg (45%) of pure product **91r** were obtained as yellowish white solid.

^{1}H NMR δ: 8.06 (1H, d, $J_{8,7}$=7.9, H-8); 7.48 (1H, t, $J_{6,5}$=$J_{6,7}$=7.5, H-6); 7.32 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.25 (1H, d, $J_{5,6}$=7.7, H-5); 4.54 (1H, dd, $J_{2,3}$=11.8, $J_{2,3}$=4.5, H-2); 3.17 (1H, ddd, ^2J=16.4, $J_{4,3}$=11.3, $J_{4,3}$=4.7, H-4); 3.09-3.03 (1H, m, H-4); 3.04 (6H, s, 2xMe); 2.55 (1H, dq, ^2J=13.2, $J_{3,4}$=$J_{3,2}$=4.4, H-3); 2.35 (1H, qd, ^2J=$J_{3,4}$=$J_{3,2}$=11.9, $J_{3,4}$=4.4, H-3). ^{13}C NMR δ: 194.2 (C-1); 166.6 (C=O monothiocarbamate); 143.6 (C-4a); 133.7 (C-6); 132.1 (C-8a); 128.7 (C-5); 128.0 (C-8); 126.8 (C-7); 52.4 (C-2); 36.8 (2xMe); 31.6 (C-3); 29.3 (C-4). FTIR (Neat): 1685 (C=O st ketone); 1648 (C=O st monothiocarbamate); 1365; 1100; 743 (Ar C-H o.o.p. bend). M.p.=95-96°C. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_2S$ 250.0896; Found 250.0891.

2-{[(*tert*-Butylsulfanyl)carbonyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91s

By means of the same procedure as for **91r** except the reaction time was 30 min, 947 mg (93% yield) of the pure product **91s** were obtained as colorless oil after purification by flash column chromatography (eluted with 2:1 Hex:DCM).

^{1}H NMR δ: 8.04 (1H, d, $J_{8,7}$=7.8, H-8); 7.49 (1H, td, $J_{6,5}$=$J_{6,7}$=7.6, $J_{6,8}$=0.9, H-6); 7.32 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.25 (1H, d, $J_{5,6}$=7.7, H-5); 4.59 (1H, dd, $J_{2,3}$=11.0, $J_{2,3}$=4.5, H-2); 3.14 (1H, ddd, ^{2}J=17.0, $J_{4,3}$=9.8, $J_{4,3}$=4.6, H-4); 3.06 (1H, dt, ^{2}J=17.0, $J_{4,3}$=5.0, H-4); 2.55 (1H, dq, ^{2}J=13.3, $J_{3,4}$=$J_{3,2}$=4.8, H-3); 2.31 (1H, dtd, ^{2}J=13.3, $J_{3,2}$=$J_{3,4}$=10.4, $J_{3,4}$=4.8, H-3); 1.51 (9H, s, ^{t}Bu). ^{13}C NMR δ: 193.0 (C-1); 187.8 (C=O dithiocarbonate); 143.5 (C-4a); 133.9 (C-6); 131.8 (C-8a); 128.7 (C-5); 128.1 (C-8); 126.9 (C-7); 51.55 (C_q ^{t}Bu); 51.46 (C-2); 30.9 (C-3); 30.3 (3xCH_3 ^{t}Bu); 28.8 (C-4). FTIR (Neat): 1686 (C=O st ketone); 1636 (C=O st dithiocarbonate); 853. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}O_3NaO_2S_2$ 317.0640; Found 317.0640.

2-{[(*tert*-Butylsulfanyl)(oxo-lambda4-sulfanylidene)methyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91t

By means of the same procedure as for **91q** but only 1 eq. of *m*-CPBA was used, 339 mg (28% yield) of the pure product **91t** were obtained as colorless oil after purification by flash column chromatography (eluted with DCM).

^{1}H NMR δ: 8.05 (1H, dd, $J_{8,7}$=7.9, $J_{8,6}$=1.0, H-8); 7.51 (1H, td, $J_{6,5}$=$J_{6,7}$=7.5, $J_{6,8}$=1.3, H-6); 7.34 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.26 (1H, d, $J_{5,6}$=7.7, H-5); 5.87 (1H, dd, $J_{2,3}$=11.5, $J_{2,3}$=4.6, H-2); 3.20 (1H, ddd, ^{2}J=17.0, $J_{4,3}$=10.5, $J_{4,3}$=4.5, H-4); 3.09 (1H, dt, ^{2}J=17.0, $J_{4,3}$=4.7, H-4); 2.62 (1H, dq, ^{2}J=13.1, $J_{3,4}$=$J_{3,2}$=4.7, H-3); 2.32 (1H, dddd, ^{2}J=13.1, $J_{3,2}$=11.4, $J_{3,4}$=10.7, $J_{3,4}$=4.6, H-3); 1.43 (9H, s, ^{t}Bu). ^{13}C NMR δ: 192.7 (C-1); 179.2 (C=S=O); 143.3 (C-4a); 134.1 (C-6); 131.4 (C-8a); 128.8 (C-5); 128.0 (C-8); 127.1 (C-7); 51.8 (C-2); 50.5 (C_q ^{t}Bu); 30.8 (3xCH_3 ^{t}Bu); 30.6 (C-3); 28.4 (C-4). FTIR (Neat): 1682 (C=O st); 1120; 740 (Ar C-H o.o.p. bend). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}NaO_2S_3$ 349.0361; Found 349.0361.

2-(Benzoylsulfanyl)-1,2,3,4-tetrahydronaphthalen-1-one 91u

By means of the general procedure (using potassium thiobenzoate), 712 mg (91% yield) of product **91u** were obtained as white solid after purification by flash column chromatography (eluted with 1:1 Hex:DCM).

^{1}H NMR δ: 8.09 (1H, d, $J_{8,7}$=7.8, H-8); 8.00 (2H, d, ^3J=7.6, Ar(*o*) Bz); 7.59 (1H, t, ^3J=7.4, Ar(*p*) Bz); 7.52 (1H, t, $J_{6,5}$=$J_{6,7}$=7.4, H-6); 7.46 (2H, t, ^3J=7.7, Ar(*m*) Bz); 7.34 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.28 (1H, d, $J_{5,6}$=7.7, H-5); 4.76 (1H, dd, $J_{2,3}$=11.6, $J_{2,3}$=4.6, H-2); 3.24 (1H, ddd, ^2J=16.9, $J_{4,3}$=10.7, $J_{4,3}$=4.4, H-4); 3.11 (1H, dt, ^2J=16.9, $J_{4,3}$=4.5, H-4); 2.59 (1H, dq, ^2J=13.2, $J_{3,4}$=$J_{3,2}$=4.6, H-3); 2.38 (1H, qd, ^2J= $J_{3,4}$=$J_{3,2}$=11.8, $J_{3,4}$=4.4, H-3). ^{13}C NMR δ: 193.5, 190.4 (C-1, C=O thioester); 143.6 (C-4a); 136.6 (Ar C_q Bz); 133.9 (C-6); 133.7 (Ar(*p*) Bz); 132.0 (C-8a); 128.8 (C-5); 128.7 (Ar(*m*) Bz); 128.1 (C-8); 127.5 (Ar(*o*) Bz); 127.0 (C-7); 50.9 (C-2); 31.0 (C-3); 29.2 (C-4). FTIR (Neat): 1686 (C=O st ketone); 1662 (C=O st thioester); 1207; 912, 687 (Ar C-H o.o.p. bend). M.p.=126°C. Anal. Calcd for $C_{17}H_{14}O_2S$: C 72.32; H 5.00; S 11.35. Found: C 72.12; H 5.32; S 11.51.

1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl benzenecarbodithioate 91v

By means of the general procedure (using sodium dithiobenzoate and 2-bromo-1-tetralone), 650 mg (72% yield) of product **91v** were obtained as pink solid after purification by flash column chromatography (eluted with 2:1 Hex:DCM).

^{1}H NMR δ: 8.09 (1H, dd, $J_{8,7}$=7.9, $J_{8,6}$=1.1, H-8); 8.04 (2H, d, ^3J=7.3, Ar(*o*) Bz); 7.56-7.51 (2H, m, H-6, Ar(*p*) Bz); 7.39 (2H, t, ^3J=7.9, Ar(*m*) Bz); 7.35 (1H, t, $J_{7,6}$=$J_{7,8}$=7.5, H-7); 7.29 (1H, d, $J_{5,6}$=7.7, H-5); 5.26 (1H, dd, $J_{2,3}$=12.3, $J_{2,3}$=4.6, H-2); 3.28 (1H, ddd, ^2J=16.9, $J_{4,3}$=11.5, $J_{4,3}$=4.4, H-4); 3.10 (1H, dt, ^2J=16.9, $J_{4,3}$=4.2, H-

4); 2.67 (1H, dq, ^{2}J=13.0, $J_{3,4}$=$J_{3,2}$=4.4, H-3); 2.35 (1H, qd, ^{2}J=$J_{3,4}$=$J_{3,2}$=12.3, $J_{3,4}$=4.3, H-3). ^{13}C NMR δ: 226.0 (C=S dithioester), 193.1 (C-1); 144.8 (Ar C_q Bz); 143.7 (C-4a); 134.1 (C-6); 132.7 (Ar(*p*) Bz); 132.1 (C-8a); 128.9 (C-5); 128.4 (Ar(*m*) Bz); 128.0 (C-8); 127.1 (Ar(*o*) Bz); 127.0 (C-7); 58.3 (C-2); 29.7 (C-3); 29.4 (C-4). FTIR (Neat): 1680 (C=O st); 1215; 1041; 759, 739, 683 (Ar C-H o.o.p. bend). M.p.=109°C. Anal. Calcd for $C_{17}H_{14}OS_2$: C 68.42; H 4.73; S 21.49. Found: C 68.10; H 4.94; S 21.40.

1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl pentanedithioate 91w

To a stirred solution of K_2CO_3 (1.2 eq., 370 mg) in dry acetone (5 mL) at 0°C under argon atmosphere was added dithiopentanoic acid (1.2 eq., 360 mg) dropwise. After 15 min 2-bromo-1-tetralone (500 mg, 2.2mmol) was added and stirring was continued at r.t. for 30min. Afterward H_2O (5 mL) was added and extracted with DCM (3x5mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. After purification by flash column chromatography (eluted with 2:1 Hex:DCM), 483 mg (78%) of pure product **91w** were obtained as yellow greenish solid.

^{1}H NMR δ: 8.06 (1H, d, $J_{8,7}$=7.9, H-8); 7.52 (1H, td, $J_{6,5}$=$J_{6,7}$=7.5, $J_{6,8}$=1.3, H-6); 7.33 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.27 (1H, d, $J_{5,6}$=7.7, H-5); 5.10 (1H, dd, $J_{2,3}$=12.4, $J_{2,3}$=4.6, H-2); 3.24 (1H, ddd, ^{2}J=16.9, $J_{4,3}$=11.6, $J_{4,3}$=4.4, H-4); 3.08 (2H, t, ^{3}J=7.6, H-2'); 3.06 (1H, dt, ^{2}J=17.0, $J_{4,3}$=4.1, H-4); 2.57 (1H, dq, ^{2}J=13.0, $J_{3,4}$=$J_{3,2}$=4.4, H-3); 2.26 (1H, qd, ^{2}J=$J_{3,4}$=$J_{3,2}$=12.3, $J_{3,4}$=4.3, H-3); 1.86 (2H, p, ^{3}J=7.6, H-3'); 1.42 (2H, sex, ^{3}J=7.4, H-4'); 0.94 (3H, t, ^{3}J=7.4, H-5'). ^{13}C NMR δ: 236.9 (C-1'); 193.1 (C-1); 143.6 (C-4a); 134.1 (C-6); 132.0 (C-8a); 128.8 (C-5); 127.9 (C-8); 126.9 (C-7); 57.5 (C-2); 51.7 (C-2'); 33.5 (C-3'); 29.5 (C-3); 29.4 (C-4); 22.0 (C-4'); 13.8 (C-5'). FTIR (Neat): 1684 (C=O st); 1304; 1218 (C=S st); 893; 740 (Ar C-H o.o.p. bend).

M.p.=85°C. Anal. Calcd for $C_{15}H_{18}OS_2$: C 64.71; H 6.52; S 23.03. Found: C 65.00; H 6.22; S 23.08.

O,*O*-Diethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]phosphonothioate 91x

To a stirred solution of K_2CO_3 (1.2 eq., 660 mg) in dry DMF (10 mL) at 0°C under argon atmosphere was added *O*,*O*-diethyl dithiophosphate (1.2 eq., 1.1mL) dropwise. After 15 min 2-bromo-1-tetralone (1.07g, 4.75mmol) was added and stirring was continued at r.t. for 2h. Afterward NH_4Cl aqueous saturated solution (20 mL) was added and extracted with DCM (3x10mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. After purification by flash column chromatography (eluted with 1:1 Hex:DCM), 1.13g (72%) of pure product **91x** were obtained as colorless oil.

^{1}H NMR δ: 8.04 (1H, d, $J_{8,7}$=7.9, H-8); 7.50 (1H, td, $J_{6,5}$=$J_{6,7}$=7.5, $J_{6,8}$=1.2, H-6); 7.33 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.25 (1H, d, $J_{5,6}$=7.7, H-5); 4.36-4.14 (5H, m, H-2, 2xCH_2 Et); 3.19-3.05 (2H, m, H-4); 2.64 (1H, ddt, ^2J=13.5, J=6.3, J=4.6, H-3); 2.37 (1H, tdd, ^2J=13.5, J=8.9, J=4.9, H-3); 1.40 (3H, t, ^3J=6.8, CH_3 Et); 1.39 (3H, t, ^3J=7.0, CH_3 Et). ^{13}C NMR δ: 192.9 (d, $^3J_{C,P}$=7, C-1); 143.3 (C-4a); 134.0 (C-6); 131.5 (C-8a); 128.8 (C-5); 128.1 (C-8); 127.0 (C-7); 64.6 (d, $^2J_{C,P}$=6, CH_2 Et); 64.3 (d, $^2J_{C,P}$=6, CH_2 Et); 55.0 (d, $^2J_{C,P}$=3, C-2); 31.7 (d, $^3J_{C,P}$=4, C-3); 28.1 (C-4); 15.9 (d, $^3J_{C,P}$=8, CH_3 Et); 15.8 (d, $^3J_{C,P}$=8, CH_3 Et). ^{31}P NMR δ: 93.0. FTIR (Neat): 1684 (C=O st); 1008, 957 (P-O-C st); 652 (P=S st). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}O_3PS_2$ 331.0586; Found 331.0588.

General procedure for the basic rearrangement of 2-oxo-carbonyl or thiocarbonyl compounds 91

To a stirred solution of **91** (0.5 mmol) in dry THF (2 mL) at 0°C under argon atmosphere was added NaH (1.6 eq., 13 mg). After 30 minutes of stirring at 0°C NH_4Cl aqueous saturated solution (5 mL) was added and extracted with Et_2O (3x5mL). The combined organic layers were dried with Na_2SO_4 and evaporated to dryness. Products were purified by chromatography (preparative TLC).

Basic rearrangement of ethyl [(2-oxocyclohexyl)sulfanyl]methanethioate 91a[79,84]

By means of the general procedure, 55 mg (81% yield) of ethyl 2-hydroxy-5-phenylcyclohex-1-ene-1-carbothioate **92a**[85] were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 95:5).

Basic rearrangement of ethyl [(2-oxocyclopentyl)sulfanyl]methanethioate 91b

By means of the general procedure, 44 mg (65% yield) of thionoester **92b** were obtained as yellow solid after purification by chromatography (preparative plate eluting with Hex:AcOEt 95:5).

Ethyl 2-hydroxycyclopent-1-ene-1-carbothioate 92b[86]

^{1}H NMR δ: 12.97 (1H, s, OH); 4.53 (2H, q, ^3J=7.1, CH_2 Et); 2.65 (4H, t, ^3J=7.6, H-3, H-5); 1.78 (2H, quint, ^3J=7.6, H-4); 1.40 (3H, t, ^3J=7.1, CH_3 Et). ^{13}C NMR δ: 205.3 (C=S); 181.3 (C-2); 111.9 (C-1); 65.3 (CH_2 Et); 34.8, 28.9 (C-3, C-5); 17.6 (C-4); 13.9 (CH_3 Et). FTIR (Neat): 1204 (C-O-C st, C=S st). M.p.=43-44°C (lit. 48°C).

Basic rearrangement of ethyl [(3-methyl-2-oxocyclohexyl)sulfanyl]methanethioate 91c

By means of the general procedure, 75 mg (79% yield) of thionoester **92c** were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 95:5).

Ethyl 2-hydroxy-3-methylcyclohex-1-ene-1-carbothioate 92c

^{1}H NMR δ: 14.30 (0.5H, s, OH I); 4.60-4.52 (1H, m, CH_2 Et II, III); 4.48 (1H, q, ^{3}J=7.1, CH_2 Et I); 3.82 (0.3H, dd, $J_{3,4}$=12.7, $J_{3,4}$=5.8, H-3 II); 3.63 (0.2H, t, $J_{3,4}$=4.9, H-3 III); 2.76-1.37 (10H, m); 1.25 (1.5H, d, $J_{Me,3}$=7.1, H-3 I); 1.08 (0.6H, d, $J_{Me,3}$=6.6, H-3 III); 1.25 (0.9H, d, $J_{Me,3}$=6.5, H-3 II). ^{13}C NMR δ: 218.8 (C=S II); 218.1 (C=S III); 209.1 (C-1 III); 207.7 (C-1 II); 207.3 (C=S I); 179.2 (C-2 I); 110.3 (C-1 I); 68.6 (CH_2 Et III); 68.4 (CH_2 Et II); 67.1 (C-1 III); 65.7 (CH_2 Et I); 65.2 (C-1 II); 46.0 (C-3 II); 43.9 (C-3 III); 35.1 (C-3 I); 36.5, 33.5, 24.5 (3xCH_2 II); 35.5, 32.4, 21.1 (3xCH_2 III); 30.2, 24.6, 19.9 (3xCH_2 I); 18.6 (Me I); 15.1 (Me III); 14.5 (Me II); 13.8 (CH_3 Et I); 13.54 (CH_3 Et II); 13.45 (CH_3 Et III). FTIR (Neat): 1206, 1175 (C-O-C st, C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{16}NaO_2S$ 223.0763; Found 223.0772.

Basic rearrangement of ethyl [(5-*tert*-butyl-2-oxocyclohexyl)sulfanyl]methanethioate 91d

By means of the general procedure, 69 mg (93% yield) of thionoester **92d** were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 95:5).

Ethyl 5-*tert*-butyl-2-hydroxycyclohex-1-ene-1-carbothioate 92d

^{1}H NMR δ: 14.12 (1H, s, OH); 4.51 (2H, q, ^{3}J=7.1, CH_2 Et); 2.61-2.55 (1H, m, H-6); 2.51-2.35 (2H, m, H-3); 2.03-1.94 (1H, m, H-6); 1.88-1.83 (1H, m, H-4); 1.42 (3H, t, ^{3}J=7.1, CH_3 Et); 1.27-1.20 (2H, m, H-4, H-5); 0.91 (9H, s, ^{t}Bu). ^{13}C NMR δ: 207.3 (C=S); 175.8 (C-2); 110.4 (C-1); 65.7 (CH_2 Et); 44.0 (C-5); 32.4 (C_q ^{t}Bu); 32.1 (C-3); 27.3 (3xCH_3 ^{t}Bu); 25.4 (C-6); 22.8 (C-4); 13.8 (CH_3 Et). FTIR (Neat): 1581 (C=C st), 1195 (C-O-C st, C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{22}NaO_2S$ 265.1233; Found 265.1232.

Basic rearrangement of ethyl [(2-oxo-5-phenylcyclohexyl)sulfanyl]methanethioate 91e

By means of the general procedure, 96 mg (90% yield) of thionoester **92e** were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 95:5).

Ethyl 2-hydroxy-5-phenylcyclohex-1-ene-1-carbothioate 92e

^{1}H NMR δ: 14.20 (1H, s, OH); 7.33 (2H, t, ^{3}J=7.5, Ar(*m*)); 7.25-7.21 (3H, m, Ar(*o*, *p*)); 4.48 (2H, q, ^{3}J=7.1, CH_2 Et); 2.88-2.72 (2H, m, H-5, H-6); 2.65-2.49 (2H, m, H-3); 2.36 (1H, dd, ^{2}J=15.7, $J_{6,5}$=10.9, H-6); 2.00 (1H, dtd, ^{2}J=13.3, J=5.4, J=2.3, H-4); 1.92 (1H, m, H-4); 1.35 (3H, t, ^{3}J=7.1, CH_3 Et). ^{13}C NMR δ: 207.1 (C=S); 175.2 (C-2); 145.7 (C_q Ar); 128.6 (Ar(*m*)); 126.9 (Ar(*p*)); 126.5 (Ar(*o*)); 110.1 (C-1); 65.9 (CH_2 Et); 40.2 (C-5); 32.3 (C-6); 31.4 (C-3); 28.3 (C-4); 13.8 (CH_3 Et). FTIR (Neat): 1577 (C=C st), 1206 (C-O-C st, C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd

Basic rearrangement of ethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]methanethioate 91f[87]

By means of the general procedure, 73 mg (92% yield) of thionoester **92f** were obtained as yellow solid after purification by chromatography (preparative plate eluting with Hex:AcOEt 95:5).

Ethyl 1-hydroxy-3,4-dihydronaphthalene-2-carbothioate 92f[85]

^{1}H NMR δ: 14.53 (0.9H, s, OH); 8.04 (1H, d, $J_{8',7'}$=7.8, H-8'); 7.93 (0.9H, dd, $J_{8,7}$=7.7, $J_{8,6}$=1.0, H-8); 7.48 (0.1H, td, $J_{6',5'}$=$J_{6',7'}$=7.5, $J_{6',8'}$=1.3; H-6'); 7.37-7.28 (1.9H, m, H-6, H-7, H-7'); 7.24 (0.1H, d, $J_{5',6'}$=7.5, H-5'); 7.17 (0.9H, d, $J_{5,6}$=7.3, H-5); 4.64-4.58 (0.2H, m, CH_2 Et'); 4.55 (1.8H, q, ^{2}J=7.1; CH_2 Et); 3.99 (0.1H, dd, $J_{2',3'}$=10.8, $J_{2',3'}$=4.7, H-2'); 3.10-2.89 (0.2H, m, H-4'); 2.81-2.72 (3.6H, m, H-3, H-4); 2.70-2.60 (0.1H, m, H-3'); 2.40 (0.1H, dq, ^{2}J=13.5, $J_{3,2}$=$J_{3,4}$=4.6, H-3); 1.32 (3H, t,

^{2}J=7.1; CH_2 Et). ^{13}C NMR δ: 218.7 (C=S'); 206.2 (C=S); 193.1 (C-1'); 168.0 (C-1); 143.6 (C-4a'); 140.3 (C-4a); 133.7 (C-6'); 132.2 (C-8a'); 131.1 (C-6); 130.9 (C-8a); 128.8 (C-5'); 127.8 (C-8'); 127.3 (C-5); 126.9 (C-7'); 126.7 (C-8); 125.5 (C-7); 109.8 (C-2); 68.6 (CH_2 Et'); 65.9 (CH_2 Et); 64.2 (C-2'); 29.4 (C-3'); 27.9 (C-4'); 27.7, 22.1 (C-3, C-4); 13.9 (CH_3 Et); 13.5 (CH_3 Et'). FTIR (Neat): 1190, 1153 (C-O-C st, C=S st). M.p.=73-74°C (lit. 69-70°C).

Basic rearrangement of ethyl {[(1S,5S,6R)-5-[(*tert*-butyldimethylsilyl)oxy]-2-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-3-yl]sulfanyl}methanethioate 91g

By means of the general procedure, 43 mg (94% yield) of thionoester **92g** were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

Ethyl (1*S*,5*S*,6*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carbothioate 92g

^{1}H NMR δ: 14.27 (1H, s, OH); 5.88 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.4, H-2'); 5.39 (1H, d, $J_{3',2'}$=17.3, H-3'); 5.14 (1H, d, $J_{3',2'}$=10.5, H-3'); 4.53-4.41 (2H, m, CH_2 Et); 3.95 (1H, dd, J=10.1, J=6.5, H-5); 3.30 (1H, dd, ^{2}J=14.6, $J_{1',2'}$=5.1 H-1'); 2.81-2.73 (2H, m, H-1', H-4); 2.24-2.18 (3H, m, H-1, H-4, H-6); 1.38 (3H, t, ^{3}J=7.1, CH_3 Et); 0.93 (9H, s, ^{t}Bu TBS); 0.11 (6H, 2xMe TBS). ^{13}C NMR δ: 206.1 (C=S); 172.8 (C-2); 134.1 (C-2'); 116.7 (C-3'); 106.6 (C-3); 67.3 (C-5); 65.9 (CH_2 Et); 61.5 (C-1'); 47.7, 41.5 (C-1, C-6); 27.9 (C-4); 25.8 (3x CH_3 ^{t}Bu); 18.1 (C_q ^{t}Bu); 13.7 (CH_3 Et); -4.6, -4.7 (2xMe TBS). FTIR(NEAT): 1214 (C=S, C-O-C st); 1092 (C-O-C st). $[\propto]_D^{20^oC}$= -282 (c=0.4; DCM). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{32}NO_3SSi$ 370.1867; Found 370.1862.

Basic rearrangement of ethyl [(2-oxocyclohex-3-en-1-yl)sulfanyl]methanethioate 91h

By means of the general procedure, 45 mg (75% yield) of **92h** and 7 mg (11% yield) of **92h'** were obtained after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1), both as yellow oils.

Ethyl 2-oxocyclohex-3-ene-1-carbothioate 92h

^{1}H NMR δ: 14.20 (0.4H, s, OH'); 6.98 (0.6H, dt, $J_{4,3}$=10.1, $J_{4,5}$=3.8, H-4); 6.52 (0.4H, dt, $J_{4',3'}$=9.8, $J_{4',5'}$=4.4, H-4'); 6.10 (1H, dt, $J_{3',4'}$=9.9, $J_{3',5'}$=2.0, H-4'); 6.06 (1H, dt, $J_{3,4}$=10.1, $J_{3,5}$=2.0, H-4); 4.63-4.53 (1.2H, m, CH_2 Et); 4.51 (0.8H, q, ^{3}J=7.1, CH_2 Et'); 3.79 (0.6H, dd, $J_{1,6}$=10.3, $J_{1,6}$=4.8, H-1); 2.62 (0.8H, t, $J_{6',5'}$=8.7, H-6'); 2.59-2.47 (1.2H, m, H-5, H-6); 2.45-2.35 (0.6H, m, H-5); 2.29-2.22 (1.4H, m, H-6, H-5'); 1.412 (1.2H, t, ^{3}J=7.1, CH_3 Et'); 1.406 (1.8H, t, ^{3}J=7.1, CH_3 Et). ^{13}C NMR δ: 218.4 (C=S); 205.2 (C=S'); 194.5 (C-2); 169.1 (C-2'); 150.2 (C-4); 141.6 (C-4'); 129.4 (C-3); 125.6 (C-3'); 107.4 (C-1'); 68.6 (CH_2 Et); 65.5 (CH_2 Et'); 63.1 (C-1); 28.6 (C-6); 24.7 (C-5); 23.9 (C-5'); 20.9 (C-6'); 13.9 (CH_3 Et'); 13.5 (CH_3 Et). FTIR (Neat): 1218 (C=S st C-O-C st). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}O_2S$ 185.0631; Found 185.0625.

Ethyl 4b-[(ethoxymethanethioyl)sulfanyl]-1,8a-dihydroxy-3,4,4a,4b,5,6,8a,8b-octahydrobiphenylene-2-carbothioate 92h'

^{1}H NMR δ: 14.46 (1H, s, OH enol); 5.86 (1H, dd, $J_{7,8}$=10.1, $J_{7,6}$=5.5, H-7); 5.55 (1H, d, $J_{8,7}$=10.1, H-8); 4.69-4.56 (2H, m, CH_2 Et xanthate); 4.51 (2H, q, ^{3}J=7.1, CH_2 Et thionoester); 4.18 (1H, d, $J_{8b,4a}$=9.2, H-8b); 3.69 (1H, s, OH); 3.57 (1H, ddd, $J_{4a,4}$=12.0, $J_{4a,8b}$=9.2, $J_{4a,4}$=5.5, H-4a); 2.70 (1H, dt, ^{2}J=16.3, $J_{3,4}$=3.8, H-3); 2.42-2.29 (2H, m, H-5, H-6); 2.22-2.02 (3H, m, H-3, H-5, H-6); 1.82-1.68 (2H, m, H-4); 1.46 (3H, t, ^{3}J=7.1, CH_3 Et xanthate); 1.43 (3H, t, ^{3}J=7.1, CH_3 Et thionoester). ^{13}C NMR δ:

224.1 (C=S xanthate); 207.2 (C=S thionoester); 172.4 (C-1); 129.3 (C-7); 128.3 (C-8); 112.9 (C-2); 81.8 (C-8a); 69.3 (CH_2 Et xanthate); 68.1 (C-4b); 66.4 (CH_2 Et thionoester); 51.8 (C-8b); 40.5 (C-4a); 29.1 (C-4); 27.3 (C-5); 24.1 (C-3); 22.7 (C-6); 13.7 (CH_3 Et xanthate); 13.6 (CH_3 Et thionoester). FTIR (Neat): 1211 (C-O-C st, C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}NaO_4S_3$ 423.0729; Found 423.0719.

Basic rearrangement of 2-(acetylsulfanyl)-1-phenylpropan-1-one 91i

By means of the general procedure, 55 mg (88% yield) of 2-methyl-1-phenylbutane-1,3-dione **92i**[88] were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 8:2).

Basic rearrangement of 2-(acetylsulfanyl)-1-phenylethan-1-one 91j

By means of the general procedure, 76 mg (90% yield) of 3-hydroxy-1-phenylbut-2-en-1-one **92j**[89] were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

Basic rearrangement of 6-(acetylsulfanyl)cyclohex-2-en-1-one 91k

By means of the general procedure, 27 mg (83% yield) of **92k** were obtained as yellow oil after purification by chromatography (preparative plate eluting with DCM).

6-Acetylcyclohex-2-en-1-one 92k

^{1}H NMR δ: 15.86 (1H, s, OH'); 7.02 (1H, dt, $J_{3,2}$=9.7, $J_{3,4}$=3.5, H-3); 6.68 (1H, dt, $J_{3',2'}$=9.9, $J_{3',4'}$=4.3, H-3'); 6.08-6.03 (2H, m, H-2, H-2'); 3.48 (1H, dd, $J_{6,5}$=8.3, $J_{6,5}$=5.1, H-6); 2.61-2.51 (1H, m, H-5); 2.52 (2H, t, $J_{5',4'}$=7.7, H-5'); 2.41-2.30 (4H, m, H-4, H-4'); 2.27 (3H, s, CH_3 Ac); 2.15-2.07 (1H, m, H-5); 2.10 (3H, s, CH_3 Ac). ^{13}C NMR δ: 205.0 (C=O Ac); 195.4 (C-1); 185.4, 183.4 (C-1', C=O Ac'); 151.4 (C-3);

145.3 (C-3'); 129.2, 127.8 (C-2, C-2'); 104.3 (C-6'); 60.2 (C-6); 30.0 (CH_3 Ac); 24.4 (CH_2); 24.3 (2XCH_2); 22.0 (C-5'); 21.5 (CH_3 Ac). FTIR (Neat): 1716, 1673 (C=O st). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_{11}O_2$ 139.0754; Found 139.0766.

Basic rearrangement of 2-(acetylsulfanyl)-4-*tert*-butylcyclohexan-1-one 91l

By means of the general procedure, 39 mg (91% yield) of 1-(5-*tert*-butyl-2-hydroxycyclohex-1-en-1-yl)ethan-1-one **92l**[90] were obtained as yellow oil.

Basic rearrangement of 2-(acetylsulfanyl)cyclooctan-1-one 91m

By means of the general procedure, 44 mg (95% yield) of 1-(2-hydroxycyclooct-1-en-1-yl)ethan-1-one **92m**[91] were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

Basic rearrangement of 2-(acetylsulfanyl)cyclododecan-1-one 91n

By means of the general procedure, 49 mg (95% yield) of 2-acetylcyclododecan-1-one **92n** were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

2-Acetylcyclododecan-1-one 92n[92]

^{1}H NMR δ: 3.82 (1H, dd, $J_{2,3}$=11.5, $J_{2,3}$=3.0, H-2); 2.63 (1H, ddd, ^2J=16.0, $J_{12,11}$=11.0, $J_{12,11}$=3.3, H-12); 2.41 (1H, ddd, ^2J=16.2, $J_{12,11}$=6.8, $J_{12,11}$=3.3, H-12); 2.38 (0.5H, t, $J_{12',11'}$=7.3, H-12'); 2.32 (0.5H, t, $J_{3',4'}$=7.1, H-3'); 2.25-2.18 (1H, m, H-3); 2.19 (0.75H, s, CH_3 Ac'); 2.15 (3H, s, CH_3 Ac); 2.0-1.2 (17H + 16X0.25H, m). ^{13}C NMR δ: 207.8, 204.7 (C-1, C=O Ac); 196.4, 190.4 (C-1', C=O Ac'); 110.2 (C-2'); 67.0 (C-2); 39.2 (C-12); 31.2 (C-12'); 28.66 (CH_3 Ac); 24.39 (CH_3 Ac'); 27.0, 25.4, 24.9, 24.44, 24.3, 24.2, 24.1 (9XCH_2); 28.71, 26.2, 25.8, 25.1, 24.6, 24.1, 23.43, 22.25 (CH_2'). FTIR (Neat): 1697 (C=O st).

Basic rearrangement of *N*,*N*-dimethyl-1-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]methanethioamide 91o

By means of the general procedure, except that the solvent used was DMF and the reaction temperature was 60°C, 40 mg (91% yield) of **92o** were obtained as white solid after purification by chromatography (preparative plate eluting with Hex:AcOEt 2:1).

N,*N*-Dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbothioamide 92o

^{1}H NMR δ: 8.03 (1H, d, $J_{8,7}$=7.9, H-8); 7.49 (1H, t, $J_{6,5}$=$J_{6,7}$=7.1, H-6); 7.31 (1H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.27 (1H, d, $J_{5,6}$=6.9, H-5); 4.14 (1H, dd, $J_{2,3}$=11.7, $J_{2,3}$=4.6, H-2); 3.58 (3H, s, Me); 3.35 (3H, s, Me); 3.17-3.02 (2H, m, H-4); 2.88 (1H, qd, ^{2}J= $J_{3,4}$=$J_{3,2}$=12.2, $J_{3,4}$=4.8, H-3); 2.35 (1H, dq, ^{2}J=13.4, $J_{3,4}$=$J_{3,2}$=4.2, H-3). ^{13}C NMR δ: 199.9 (C=S); 193.6 (C-1); 144.0 (C-4a); 133.8 (C-6); 132.2 (C-8a); 128.8 (C-5); 127.9 (C-8); 126.8 (C-7); 58.3 (C-2); 44.7, 42.1 (2xMe); 30.5 (C-3); 28.8 (C-4). FTIR (Neat): 1677 (C=O st); 1517; 1277. M.p.=104-106°C. Anal. Calcd for $C_{13}H_{15}NOS$: C 66.92; H 6.48; N 6.00; S 13.74. Found: C 66.90; H 6.80; N 6.27; S 13.92.

Basic rearrangement of 2-{[(*tert*-butylsulfanyl)methanethioyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91p

By means of the general procedure, 67 mg (95% yield) of **92p** were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 98:2).

2-(*tert*-Butylsulfanylcarbothioyl)-1,2,3,4-tetrahydronaphthalen-1-one 92p

^{1}H NMR δ: 16.21 (0.4H, s, OH'); 8.03 (0.6H, dd, $J_{8,7}$=7.8, $J_{8,6}$=0.8, H-8); 7.96 (0.4H, dd, $J_{8',7'}$=7.7, $J_{8',6'}$=0.8, H-8'); 7.47 (0.6H, td, $J_{6,5}$=$J_{6,7}$=7.5, $J_{6,8}$=1.3; H-6); 7.36 (0.4H, td, $J_{6',5'}$=$J_{6',7'}$=7.4, $J_{6',8'}$=1.4; H-6'); 7.32-7.28 (1H, m, H-7, H-7'); 7.23 (0.6H, d, $J_{5,6}$=7.7, H-5); 7.17 (0.4H, d, $J_{5',6'}$=7.4, H-5'); 4.21 (0.6H, dd, $J_{2,3}$=11.0, $J_{2,3}$=4.7, H-

2); 3.09 (0.6H, dt, ^{2}J=16.7, $J_{4,3}$=4.9, H-4); 3.02 (0.6H, ddd, ^{2}J=16.8, $J_{4,3}$=10.1, $J_{4,3}$=4.3, H-4); 2.95-2.91 (0.8H, m, H-3'); 2.83-2.73 (1.4H, m, H-3, H-4'); 2.36 (0.6H, dq, ^{2}J=13.8, $J_{3,2}$=$J_{3,4}$=4.6, H-3); 1.70 (3.6H, s, ^{t}Bu'); 1.63 (5.4H, s, ^{t}Bu). ^{13}C NMR δ: 234.4 (C=S); 216.3 (C=S'); 194.1 (C-1); 166.7 (C-1'); 143.6 (C-4a); 140.1 (C-4a'); 133.6 (C-6); 132.5 (C-8a); 131.4 (C-6'); 131.3 (C-8a'); 128.7 (C-5); 127.8 (C-8); 127.1 (C-5'); 126.90 (C-7'); 126.87 (C-7); 126.2 (C-8'); 117.5 (C-2'); 68.6 (C-2); 52.4 (C_q ^{t}Bu); 51.8 (C_q ^{t}Bu'); 31.3 (C-3); 29.3 (3xCH_3 ^{t}Bu'); 28.3 (C-4); 28.1 (3xCH_3 ^{t}Bu); 27.9 (C-4'); 26.0 (C-3'). FTIR (Neat): 1521 (C=C st); 1151 (C=S st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}NaOS_2$ 301.0691; Found 301.0690.

Basic rearrangement of Ethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]formate 91q

By means of the general procedure, 31 mg (71% yield) of ethyl 1-hydroxy-3,4-dihydronaphthalene-2-carboxylate **92q**[93] (yellow oil) and 8 mg (21% yield) of **92q'** (white solid) were obtained after purification by chromatography (preparative plate eluting with Hex:AcOEt 8:2).

3,3'',4,4''-Tetrahydro-1H,1''H-dispiro[naphthalene-2,2'-[1,3,5]trithiolane-4',2''-naphthalene]-1,1''-dione 92q'

^{1}H NMR δ: 8.14 (2H, d, $J_{8,7}$=7.7, H-8); 7.51 (2H, t, $J_{6,5}$=$J_{6,7}$=7.5, H-6); 7.36 (2H, t, $J_{7,6}$=$J_{7,8}$=7.6, H-7); 7.24 (2H, d, $J_{5,6}$=7.7, H-5); 3.28 (2H, ddd, ^{2}J=17.6; $J_{4,3}$=8.6; $J_{4,3}$=6.2, H-4); 3.18 (2H, dt, ^{2}J=17.5, $J_{4,3}$=4.8, H-4); 3.11-3.00 (4H, m, H-3). ^{13}C NMR δ: 187.4 (C-1); 142.2 (C-4a); 133.9 (C-6); 130.5 (C-8a); 129.1 (C-8); 128.6 (C-9); 127.3 (C-7); 83.9 (C-2); 34.7 (C-3); 29.4 (C-4). FTIR (Neat): 1679 (C=O st); 1286; 1212. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{16}NaO_2S_3$ 407.0205; Found 407.0199.

Basic rearrangement of *N*,*N*-dimethyl-1-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]formamide 91r

By means of the general procedure, except that the solvent used was DMF and the reaction temperature was 80°C, 70 mg (100%) of **92r** were obtained as yellow oil after purification by chromatography (preparative plate eluting with DCM).

2-({1-[(Dimethylcarbamoyl)oxy]-3,4-dihydronaphthalen-2-yl}disulfanyl)-3,4-dihydronaphthalen-1-yl N,N-dimethylcarbamate 92r

^{1}H NMR δ: 7.19-7.09 (8H, m, H-5, H-6, H-7, H-8); 3.17 (6H, s, Me); 3.03 (6H, s, Me); 2.94-2.89 (4H, m, H-4); 2.86-2.82 (4H, m, H-3). ^{13}C NMR δ: 153.7 (C=O); 143.7, 135.8, 131.0, 126.6 (C-1, C-2, C-4a, C-8a); 128.1, 127.3, 124.4, 121.4 (C-5, C-6, C-7, C-8); 37.0, 36.5 (2xMe); 28.3 (C-4); 26.5 (C-3). FTIR (Neat): 1721 (C=O st); 1156 (C-O-C st). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{28}NaN_2O_4S_2$ 519.1383; Found 519.1383.

Basic rearrangement of 2-{[(*tert*-butylsulfanyl)carbonyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91s

By means of the general procedure, 58 mg (65% yield) of **92s** (yellow oil) and 10 mg (13% yield) of **92s'** (yellow solid) were obtained after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

(*tert*-Butylsulfanyl)(1-hydroxy-3,4-dihydronaphthalen-2-yl)methanone 92s

^{1}H NMR δ: 13.72 (0.7H, s, OH); 8.03 (0.3H, d, $J_{8',7'}$=7.8, H-8'); 7.83 (0.7H, dd, $J_{8,7}$=7.5, $J_{8,6}$=1.0, H-8); 7.47 (0.3H, td, $J_{6',5'}$=$J_{6',7'}$=7.5, $J_{6',8'}$=1.1; H-6'); 7.34-7.26 (1.7H, m, H-6, H-7, H-7'); 7.23 (0.3H, d, $J_{5',6'}$=7.7, H-5'); 7.16 (0.7H, d, $J_{5,6}$=7.2, H-5); 3.67 (0.3H, dd, $J_{2',3'}$=9.0, $J_{2,3}$=4.8, H-2'); 3.10 (0.3H, ddd, ^{2}J=16.8, $J_{4',3'}$=6.9, $J_{4',3'}$=4.6, H-4'); 2.94 (0.3H, ddd, ^{2}J=16.8, $J_{4',3'}$=8.6, $J_{4',3'}$=4.6, H-4'); 2.82 (1.4H, t,

$J_{4,3}$=7.6, H-4); 2.57 (1.4H, t, $J_{3,4}$=7.7, H-3); 2.50 (0.3H, qd, ^2J= $J_{3',2'}$= $J_{3',4'}$=8.9, $J_{3',4'}$=4.5, H-3'); 2.34 (0.3H, ddt, ^2J=13.5, $J_{3',4'}$=7.0, $J_{3',4'}$=$J_{3',2'}$=4.8, H-3'); 1.56 (6.3H, s, ^{t}Bu); 1.49 (2.7H, s, ^{t}Bu'). ^{13}C NMR δ: 197.9 (C=O thioester); 197.3 (C-1'); 193.6 (C=O thioester'); 163.2 (C-1); 143.7 (C-4a'); 139.2 (C-4a); 133.9 (C-6'); 132.0 (C-8ª'); 130.8 (C-6); 130.1 (C-8a); 128.8 (C-5'); 127.7 (C-8'); 127.3 (C-5); 126.9 (C-7'); 126.7 (C-7); 125.0 (C-8); 106.5 (C-2'); 62.0 (C-2); 48.9 (C_q ^{t}Bu'); 48.2 (C_q ^{t}Bu); 30.1 (3xCH_3 ^{t}Bu); 29.8 (3xCH_3 ^{t}Bu'); 27.9 (C-4); 27.4 (C-3'); 27.0 (C-4'); 21.7 (C-3). FTIR (Neat): 1614, 1559 (C=O st, C=C st); 1154; 1006; 805. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{18}NaO_2S$ 285.0920; Found 285.0920.

2-(*tert*-Butylsulfanyl)naphthalen-1-ol 92s'

^{1}H NMR δ: 8.27-8.24 (1H, m, H-8); 7.76-7.74 (1H, m, H-5); 7.56 (1H, d, $J_{4,3}$=8.6, H-4); 7.52-7.47 (2H, m, H-6, H-7); 7.34 (1H, d, $J_{3,4}$=8.6, H-3); 7.02 (1H, br s, OH); 1.33 (9H, s, ^{t}Bu). ^{13}C NMR δ: 153.2 (C-1); 135.1 (C-4a); 130.0 (C-3); 127.52, 127.46 (C-5, C-7); 125.8 (C-6); 124.1 (C-8a); 122.8 (C-8); 120.3 (C-4); 115.1 (C-2); 49.1 (C_q ^{t}Bu); 30.0 (3xCH_3 ^{t}Bu). FTIR (Neat): 3445 (O-H st); 801 (Ar C-H o.o.p. bend). HRMS (ESI-TOF) m/z: [M - *t*Bu]$^+$ Calcd for $C_{10}H_7OS$ 175.0212; Found 175.0213.

Basic rearrangement of 2-{[(*tert*-butylsulfanyl)(oxo-lambda4-sulfanylidene)methyl]sulfanyl}-1,2,3,4-tetrahydronaphthalen-1-one 91t

By means of the general procedure, 49 mg (78% yield) of **92t** (yellow solid) and 2 mg (10% yield) of **92t'** (yellow oil) were obtained after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

2-(*tert*-Butylsulfanylcarbothioyl)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one 92t

^{1}H NMR δ: 8.03 (1H, d, $J_{8,7}$=7.8, H-8); 7.50 (1H, td, $J_{6,5}$=$J_{6,7}$=7.5, $J_{6,8}$=1.0; H-6); 7.34 (1H, td, $J_{7,6}$=$J_{7,8}$=7.5, H-7); 7.23 (1H, d, $J_{5,6}$=7.7, H-5); 4.95 (1H, s, OH); 3.15-3.03 (2H, m, H-4); 2.86 (1H, dt, ^2J=13.6, $J_{3,4}$=4.8, H-3); 2.30 (1H, ddd, ^2J=13.6, $J_{3,4}$=8.6, $J_{3,4}$=6.2, H-3); 1.60 (9H, s, ^{t}Bu). ^{13}C NMR δ: 238.3 (C=S); 196.6 (C-1); 143.7 (C-4a); 133.8 (C-6); 131.9 (C-8a); 128.8 (C-5); 127.8 (C-8); 126.9 (C-7); 86.3 (C-2); 52.4 (C_q ^{t}Bu); 36.8 (C-3); 28.2 (3xCH_3 ^{t}Bu); 26.2 (C-4). FTIR (Neat): 3446 (O-H st); 1686 (C=O st); 1290; 1081 (C=S st); 748 (Ar C-H o.o.p. bend). M.p.= 75-77°C. Anal. Calcd for $C_{15}H_{18}O_2S_2$: C 61.19; H 6.16; S 21.78. Found: C 60.90; H 6.41; S 21.60.

2-(*tert*-Butylsulfanylcarbothioyl)naphthalen-1-ol 92t'

^{1}H NMR δ: 14.16 (1H, s, OH); 8.51 (1H, d, $J_{8,7}$=8.4, H-8); 8.13 (1H, td, $J_{3,4}$=9.2, H-3); 7.71 (1H, d, $J_{5,6}$=8.1, H-5); 7.60 (1H, td, $J_{6,7}$=$J_{6,5}$=7.5, J=1.1, H-6); 7.51 (1H, td, $J_{7,6}$=$J_{7,8}$=7.7, J=1.0, H-7); 7.19 (1H, d, $J_{4,3}$=9.2, H-4); 1.75 (9H, s, ^{t}Bu). ^{13}C NMR δ: 225.4 (C=S); 159.4 (C-1); 136.4 (C-4a); 129.8 (C-6); 127.3 (C-5); 126.6 (C-8a); 126.0 (C-7); 125.2 (C-8); 122.7 (C-3); 121.5 (C-2); 117.8 (C-4); 53.0 (C_q ^{t}Bu); 28.9 (3xCH_3 ^{t}Bu). FTIR (Neat): 1623, 1562 (C=C st); 1187, 1145 (C-O st, C=S st); 962, 801, 748 (Ar C-H o.o.p. bend). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}OS_2$ 277.0715; Found 277.0715.

Basic rearrangement of 2-(benzoylsulfanyl)-1,2,3,4-tetrahydronaphthalen-1-one 91u

By means of the general procedure, 97 mg (95% yield) of 2-benzoyl-3,4-dihydronaphthalen-1-ol **92u**[94] were obtained as yellow oil after purification by chromatography (preparative plate eluting with Hex:AcOEt 9:1).

Basic rearrangement of 1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl benzenecarbodithioate 91v

The general procedure was followed except that after 30 min of reaction methyl iodide (1.5 eq.) was added at 0°C and the reaction mixture was allowed to stir at the same temperature for additional 30 min. The reaction mixture was treated as in the general procedure and after purification by chromatography (preparative plate eluting with 1:2 Hex:DCM), 66mg (70% yield) of **92v** were obtained as yellow solid.

2-[(Methylsulfanyl)(phenyl)methylidene]-1,2,3,4-tetrahydronaphthalen-1-one 92v

^{1}H NMR δ: 8.15 (1H, d, $J_{8,7}$=7.6, H-8); 7.48-7.32 (5H, m, 5, 7, Ar(*m,p*) Ph); 7.19-7.15 (3H, m, H-6, Ar(*o*) Bz); 2.82 (2H, t, $J_{4,3}$=6.5, H-4); 2.51 (2H, t, $J_{3,4}$=6.5, H-3); 1.75 (3H, s, Me). ^{13}C NMR δ: 187.0 (C-1); 156.2 (C-SMe); 142.6 (C-8a); 137.5 (Ar C_q Ph); 134.5 (C-4a); 132.5 (C-7); 128.9 (Ar(*o*) Ph); 128.0, 127.9, 127.8 (C-6, C-8, Ar(*m,p*) Ph); 127.6 (C-2); 126.9 (C-5); 30.0 (C-3); 29.4 (C-4); 16.8 (Me). FTIR (Neat): 1638, 1596, 1522, 1484 (C=O st, C=C st); 1303; 1240; 1218; 981, 888, 769, 743, 731, 701 (Ar C-H o.o.p. bend). M.p.=138°C. Anal. Calcd for $C_{18}H_{16}OS$: C 77.11; H 5.75; S 11.43. Found: C 77.20; H 5.98; S 11.40.

Basic rearrangement of 1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl pentanedithioate 91w

By means of the same procedure as for **91v**, 60 mg (66% yield) of **92w** were obtained as yellow oil after purification by chromatography (preparative plate eluting with 1:1 Hex:DCM).

2-[1-(Methylsulfanyl)pentylidene]-1,2,3,4-tetrahydronaphthalen-1-one 92w

^{1}H NMR δ: 8.08 (0.5H, dd, $J_{8,7}$=7.8, $J_{8,6}$=1.1, H-8); 8.05 (0.5H, dd, $J_{8,7}$=7.9, $J_{8,6}$=1.2, H-8); 7.40 (1H, td, $J_{6,5}$=$J_{6,7}$=7.4, $J_{6,8}$=1.3, H-6); 7.31 (0.5H, td, $J_{7,6}$=$J_{7,8}$=7.5,

$J_{7,5}$=0.8, H-7); 7.30 (0.5H, td, $J_{7,6}$=$J_{7,8}$=7.5, $J_{7,5}$=1.0, H-7); 7.19 (1H, d, $J_{5,6}$=7.5, H-5); 2.98-2.84 (5H, m, H-3, H-4, H-2'); 2.63 (1H, t, ^{3}J=8.0, H-2'); 2.39 (1.5H, s, Me); 2.35 (1.5H, s, Me); 1.64-143 (4H, m, H-3', H-4'); 0.979 (1.5H, t, ^{3}J=7.1, H-5'); 0.976 (1.5H, t, ^{3}J=7.3, H-5'). ^{13}C NMR δ: 186.5, 185.8 (C-1); 157.8, 157.7 (C-1'); 142.8, 142.2 (C-8a); 135.1, 134.7 (C-4a); 132.3, 132.1 (C-6); 128.1, 126.0 (C-2); 128.0, 127.9 (C-8); 127.8, 127.5 (C-5); 126.8, 126.7 (C-7); 32.0, 31.7 (C-3'); 31.2, 31.1 (C-2'); 29.7, 29.2, 29.0, 28.4 (C-3, C-4); 22.9, 22.7 (C-4'); 15.5, 14.0 (Me); 13.91, 13.89 (C-5'). FTIR (Neat): 1639, 1597, 1525 (C=O st, C=C st); 1296; 1224; 742 (Ar C-H o.o.p. bend). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}OS$ 261.1308; Found 261.1306.

Basic rearrangement of *O,O*-diethyl [(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)sulfanyl]phosphonothioate 91x

By means of the general procedure, 57 mg (95% yield) of **92x** were obtained as yellow oil (preparative plate eluting with Hex:AcOEt 9:1).

Ethyl 2-sulfanyl-3,4-dihydronaphthalen-1-yl ethoxy(sulfanylidene)phosphonite 92x

^{1}H NMR δ: 7.62 (1H, d, $J_{8,7}$=7.6, H-8); 7.21-7.08 (3H, m, H-5, H-6, H-7); 4.28-4.18 (4H, m, 2xCH_2 Et); 3.62 (1H, s, SH); 2.85 (2H, t, $J_{4,3}$=7.8, H-4); 2.57-2.52 (2H, m, H-3); 1.40 (6H, td, ^{3}J=7.1, $^{4}J_{H,P}$=0.8, 2xCH_3 Et). ^{13}C NMR δ: 140.0 (d, $^{2}J_{C,P}$=9, C-1); 134.7 (d, $^{4}J_{C,P}$=1, C-4a) 131.3 (d, $^{3}J_{C,P}$=2, C-8a); 126.99, 126.95, 126.3 (C-5, C-6, C-7); 121.6 (C-8); 118.9 (d, $^{3}J_{C,P}$=8, C-2); 65.3 (d, $^{2}J_{C,P}$=5, CH_2 Et); 31.4 (d, $^{4}J_{C,P}$=2, C-3); 28.1 (C-4); 15.9 (d, $^{3}J_{C,P}$=8, CH_3 Et). ^{31}P NMR δ: 63.8. FTIR (Neat): 1021, 969, 824 (P-O-C st). HRMS (ESI-TOF) m/z: $[M - H]^+$ Calcd for $C_{14}H_{18}O_3PS_2$ 329.0429; Found 329.0430.

2-[(2-Oxocyclooctyl)sulfanyl]cyclooctan-1-one 93

To a stirred solution of 2-chloroketone **83c** (160 mg, 1mmol) in dry acetonitrile (4mL) under argon atmosphere was added potassium ethyl xanthate (1.2 eq., 200mg) and the reaction mixture was refluxed for 24h. Afterwards water was added (10 mL) and extracted with DCM (3X5mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. After purification by chromatography (preparative TLC eluted with Hex:AcOEt 8:2) 75 mg (53%) of product as a mixture of two diastereomers (d.r.=6:4).

^{1}H NMR δ: 3.38 (0.4H, dd, $J_{2',3'}$=11.2, $J_{2',3'}$=3.7, H-2'); 3.20 (0.6H, dd, $J_{2,3}$=11.4, $J_{2,3}$=4.3, H-2); 2.75 (0.6H, td, ^2J=$J_{8,7}$=12.5, $J_{8,7}$=3.8, H-8); 2.62 (0.4H, ddd, ^2J=13.0, $J_{8',7'}$=10.4, $J_{8',7'}$=5.0, H-8'); 2.39 (0.6H, ddd, ^2J=12.7, $J_{8,7}$=5.7, $J_{8,7}$=3.7, H-8); 2.33 (0.4H, ddd, ^2J=13.1, $J_{8',7'}$=6.4, $J_{8',7'}$=4.1, H-8'); 2.1-1.1 (10H, m, 5xCH_2 ^{13}C NMR δ: 211.4 (212.7) (C-1); 52.2 (53.3) (C-1); 38.2 (38.7) (C-8); 29.4, 27.9, 26.9, 26.2, 24.49 (30.1, 27.6, 26.34, 26.31, 24.45) (5xCH_2). FTIR (Neat): 1686 (C=O st). MS (ESI-IT) m/z: 283 $[M + H]^+$.

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