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Reactivity of acetylenic ω -keto-esters towards transition metal complexes : synthesis of polycyclic motives of natural products

Christian Schäfer

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ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES

UMR 7177

THÈSE présentée par
Christian SCHÄFER
soutenue le : **21 janvier 2013**

pour obtenir le grade de : **Docteur de l'université de Strasbourg**

Discipline / Spécialité : **Chimie organique**

**Réactivité des ω -céto-esters acétyléniques
vis-à-vis de complexes de métaux de transition:
application à la synthèse de squelettes carbonés
originaux.**

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We absolutely must leave room for doubt
or there is no progress and no learning.
There is no learning without having to pose
a question.
And a question requires doubt.

(Richard Feynman)

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Glossary

$[\alpha]_D^{20}$ specific rotation at 20 °C and 589 nm

Boc *tert*-butyloxycarbonyl

DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE 1,2-dichloroethane

DCM dichloromethane

DIBAL-H diisobutylaluminiumhydride

DMAP 4-(dimethylamino)-pyridine

Et Ethyl

INAS intramolecular nucleophilic acyl substitution

IPr 1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-ylidene

***i*Pr** *isopropyl*

LAH lithium aluminium hydride

LiHMDS lithium bis(trimethylsilyl)amide

LUMO lowest unoccupied molecular orbital

Me Methyl

NBS *N*-bromosuccinimide

NCS *N*-chlorosuccinimide

NHC *N*-heterocyclic carbene

NIS *N*-iodosuccinimide

NMR nuclear magnetic resonance

PE petroleum ether

- PMP** *para*-methoxyphenyl
- PTSA** *para*-toluenesulfonic acid
- rt** room temperatur
- TBAF** tetra-*n*-butylammonium fluoride
- TBS** *tert*-butyldimethylsilyl
- t*Bu** *tert*-butyl
- Tf** CF₃SO₂⁻
- TfOH** trifluoromethanesulfonic acid
- thexyl** dimethyl-(2,3-dimethyl-2-butyl)silyl
- THF** tetrahydrofuran
- TIPS** triisopropylsilyl
- TLC** thin layer chromatography
- TMS** trimethylsilyl
- triflimide** trifluoromethanesulfonimide
- Triton B** benzyl trimethylammonium hydroxide
- Ts** Tosyl
- p*TsOH** *para*-toluenesulfonic acid

1. General Introduction

Life on earth is essentially built on organic molecules. Macromolecular assemblies such as proteins, carbohydrates and lipids regulate cellular processes, form tissues and serve as energy resource. Small organic molecules have often been observed to function as signal transmitters (e.g. hormones), activators (e.g. ATP) or inhibitors (e.g. toxins) in cellular systems via interaction with proteins. These cellular regulatory functions of small organic molecules are recurrently used in drug development where structures of natural bioactive molecules are mimicked to obtain desired biological effects.

One of the major tasks in organic chemistry is the development and application of strategies for the synthesis of such small but complex organic molecules. An important intermediate step towards the total synthesis of organic compounds consists in obtaining their carbon skeleton, which often constitute recurrent structural motifs in several bioactive molecules.

In my thesis, I have concentrated on the development of new methodologies for the synthesis of such carbon skeletons, in particular of polycyclic nature, that can serve as starting material for the synthesis of bioactive organic molecules. We aimed at obtaining polycyclic compounds by using monocyclic acetylenic ω -ketoesters **1** (Figure 1.1) as substrates.

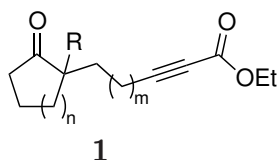
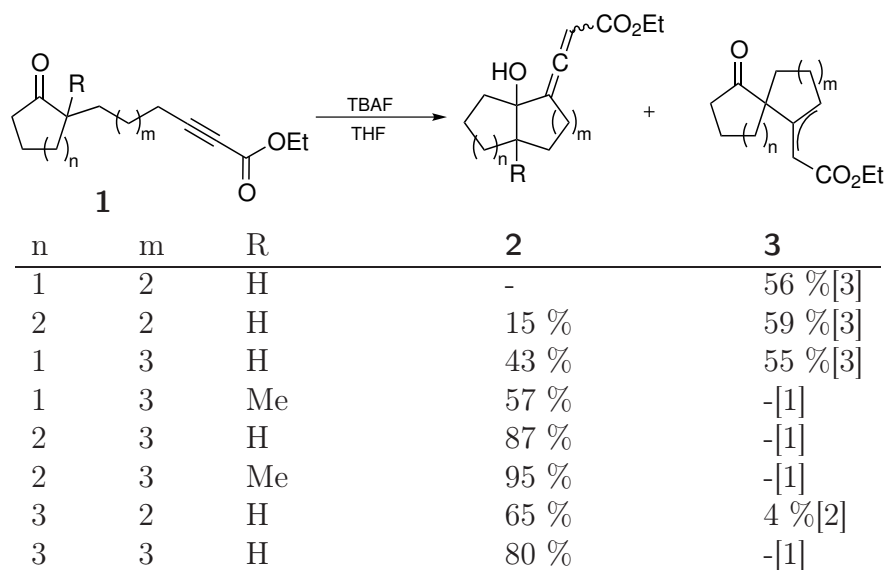
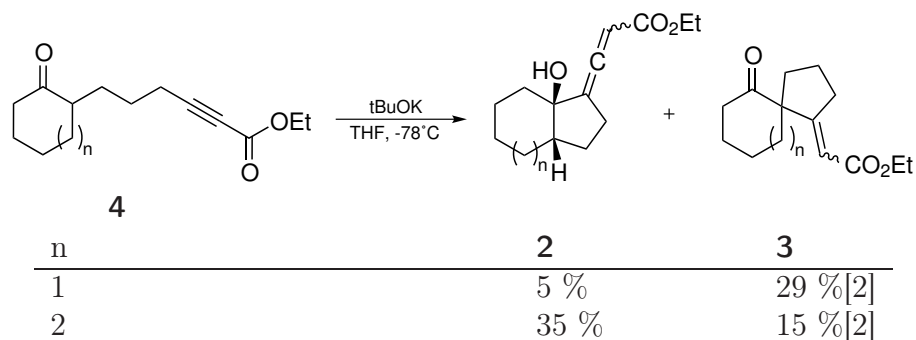


Figure 1.1.: Acetylenic ω -ketoesters of interest in our laboratory.

The reactivity of this type of compound toward a base has already been studied in detail. When acetylenic ω -ketoesters **1** are treated with TBAF in THF a mixture of allenic derivate **2** and spiranic derivate **3** was obtained (Table 1.1).[1–3] Both the allenic compound **2** and the spiro compound **3** were obtained as a mixture of stereoisomers. The yield of the reaction as well as the distribution of the different products was strongly dependent on the substrate used, i.e. the ring size and the chain length of the tether between the ring and the triple bond were crucial.

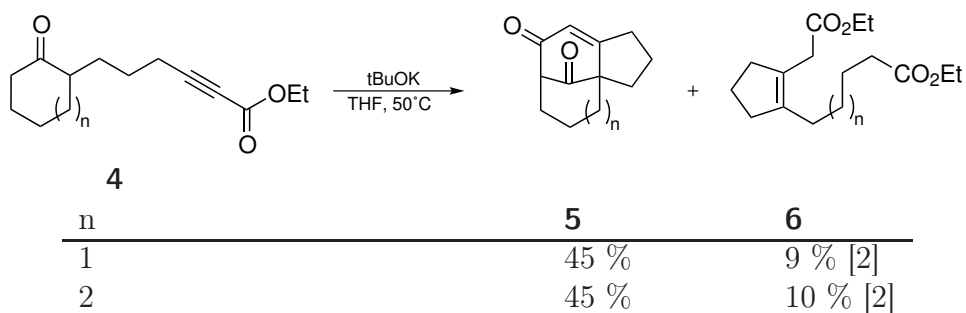
Table 1.1.: Reaction of acetylenic ω -ketoesters with TBAF.

When acetylenic ω -ketoesters with a 3-carbon-atom tether **4** are treated with *t*BuOK at low temperature (-78 °C) the same products as for the TBAF reaction could be obtained. It has to be noted that in this case for the spiranic compound only the exo-double bond is formed (Table 1.2).[2]

Table 1.2.: Reaction of acetylenic ω -ketoesters with *t*BuOK at low temperature.

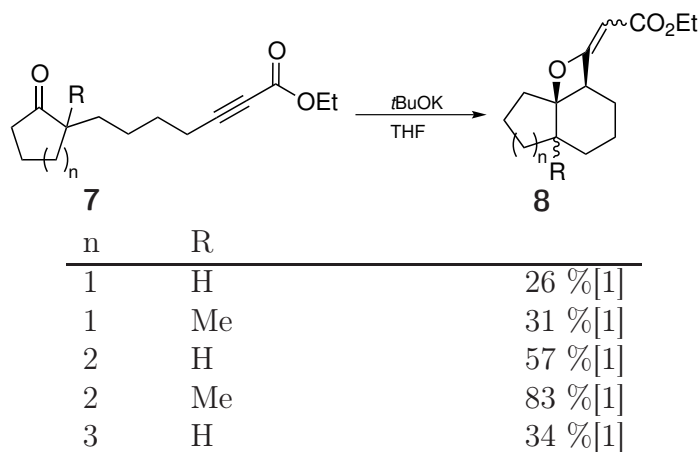
The same reaction performed at 50 °C instead of -78 °C yielded bridged compounds **5** together with the diester **6** (Table 1.3).[2]

Table 1.3.: Reaction of acetylenic ω -ketoesters with *t*BuOK at high temperature.

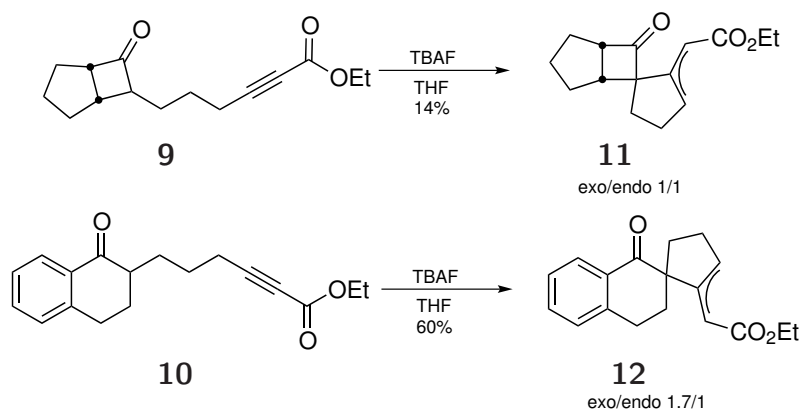


Changing from a 3-carbon to a 4-carbon tether, oxetanes **8** were obtained with *t*BuOK as base (Table 1.4).[1]

Table 1.4.: Reaction of acetylenic ω -ketoesters **7** with *t*BuOK .

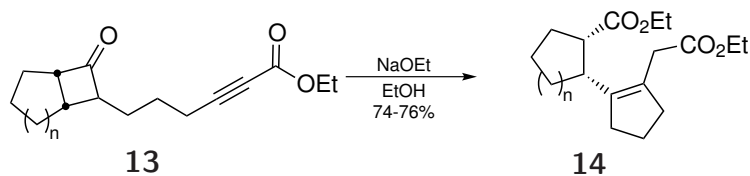


Moreover, the reactivity of bicyclic acetylenic ω -ketoesters **9** and **10** was different from monocyclic acetylenic ω -ketoesters. When they were treated with TBAF only the spiranic products **11** and **12** were obtained (Scheme 1.1).[4] The formation of the allenic derivatives was not observed.



Scheme 1.1: Reactivity of bicyclic acetylenic ω -ketoesters towards TBAF.

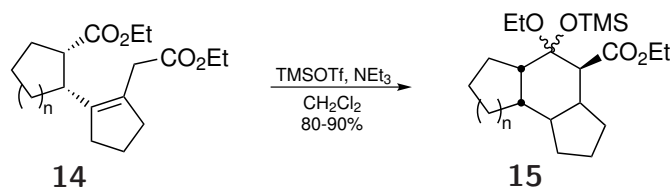
The reactivity of bicyclic starting materials is even more diverging when NaOEt is used as base. In this case neither the allenic nor the spiranic derivative were obtained. Instead, bicyclic diester **14** was obtained via an anionic cascade reaction (Scheme 1.2).[5]



Scheme 1.2: Reactivity of bicyclic acetylenic ω -ketoesters towards NaOEt.

It has been shown that the reaction passes through a spiranic intermediate of type **11**. The strained 4-membered ring is then opened by the attack of ethanolate on the keto-group.

The diesters obtained can be used for further cyclization reactions. When treated with TMSOTf, they undergo Dieckmann cyclization to give tricyclic compounds **15** (Scheme 1.3).[5]



Scheme 1.3: Dieckmann cyclization of diester **14**.

The objective of my work during my PhD consisted in further explore the reactivity of those acetylenic ω -ketoesters. We set our focus on the exploration of the reactivity of acetylenic ω -ketoesters towards transition metals and we also investigated the reactivity of the compounds obtained during these studies.

In the first part of my PhD thesis, special attention was drawn on the reactivity of acetylenic ω -ketoesters towards low valent titanium complexes. Intramolecular reductive coupling of acetylenic ω -ketoesters in the presence of (η^2 -propene)titanium was successfully performed to provide hydroxy-esters in a diastereoselective manner. Subsequent lactonization afforded angularly fused unsaturated tricyclic lactones which represent relevant substructures of numerous bioactive compounds.

In the second part of my work, we concentrated on the reactivity of ω -keto alkynes in cycloisomerization reactions catalyzed by gold(I)- and silver(I)-complexes. The cycloisomerization of alkynyl silyl enol ethers proceeds well under mild conditions to yield mono- or bicyclic spirocompounds through 5-*exo*-dig reactions. Trapping the reaction intermediates with an iodide source, such as *N*-iodosuccinimide (NIS), afforded the alkenyl iodide derivatives.

Finally, we used the compounds obtained to synthesize the core structure of a large panel of diterpenes. This natural products containing a tricyclic spiranic skeleton are highly bioactive and therefore interesting target molecules.

All our results will be described in the following three parts:

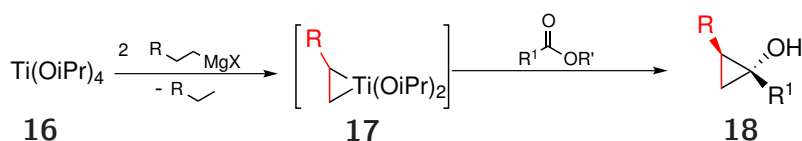
- I Reactivity of acetylenic ω -ketoesters with low-valent titanium complexes
- II Noble metal catalyzed cycloisomerizations of ω -ketoalkynes and acetylenic ω -ketoesters
- III Reactivity of spirocyclic γ -methylene ketones

Part I.

Reactivity of acetylenic ω -ketoesters with low-valent titanium complexes

2. The Kulinkovich reaction: original findings and mechanism

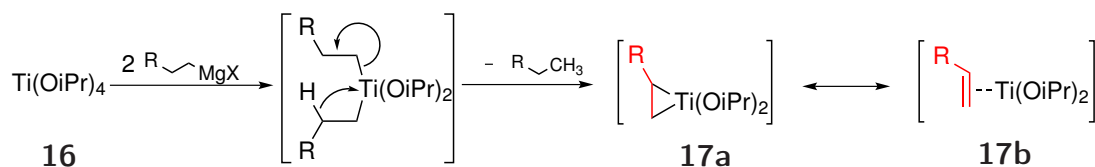
In 1989 Kulinkovich *et al.* described a new methodology for the preparation of cyclopropanols from esters and low valent titanium complexes (Scheme 2.1).[6, 7]



Scheme 2.1: General scheme for the Kulinkovich reaction.

The low valent titanium complex **17** is thereby generated *in situ* from Ti(OiPr)_4 **16** and a Grignard reagent. This reaction sequence is now referred to the Kulinkovich reaction.

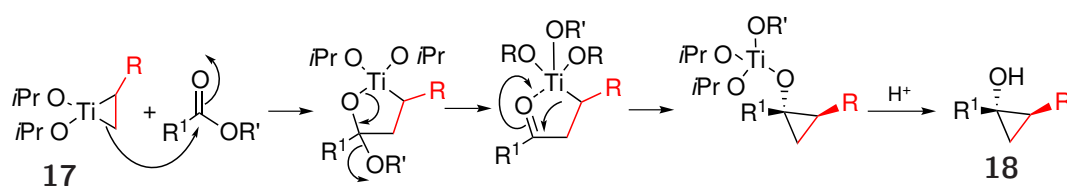
The generally accepted reaction mechanism initially involves two successive stages of transmetalation of the committed Grignard reagent, leading to dialkyldiisopropoxytitanium complex. This complex undergoes a dismutation to give an alkane molecule and titanacyclopropane **17**. **17** can be described in two mesomeric forms **17a** and **17b** (Scheme 2.2).



Scheme 2.2: Formation of complex **17**.

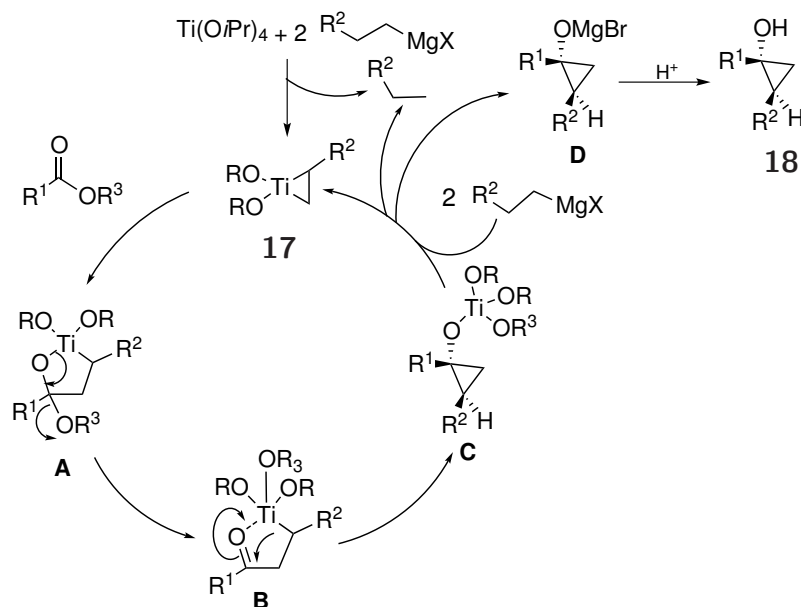
The structure of **17** has not yet been completely elucidated. The Ti(IV) metallacyclopropane **17a** limiting structure is supported by experiments showing the 1,2-dianionic character of this species[8, 9] whereas Ti(II)-ethylene limiting structure **17b** is supported by experiments showing the capacity to undergo ligand exchange reactions.[10–12] Although it was not possible to obtain X-ray structures for compounds of type **17**, Bercaw *et al.* were able to obtain the X-ray structure of the related complex $(\eta^5\text{-C}_5\text{Me}_5)_2\text{Ti}(\eta^2\text{-ethylene})$. [13] The obtained bond lengths and angles suggest a structure lying between the limiting structures **17a** and **17b**. On account of this, the structure which explains best the performed transformations is often chosen for representation.

Once the titanacyclopropane **17** is formed, it attacks the ester-functionality to form an oxatitanacyclopentane intermediate which rearranges to give a ketone complex. Lastly, the insertion of the carbonyl group in the residual carbon titanium bond forms the cyclopropane ring and a titanium alcoholate which is then hydrolysed during the work-up procedure to finally yield the cyclopropanol **18**. (Scheme 2.3). It should be noted that the attack of the Ti-complex occurs at the less hindered carbon-atom and that the cyclopropanols are obtained with a *cis*-relationship between the two R-groups. This *cis*-relationship is determined by a strong agostic interaction between the titanium and the hydrogen in α -position in the cyclopropane-forming transition state which counterbalances the steric repulsion between R and R¹.^[14]



Scheme 2.3: Mechanism of the Kulinkovich reaction.

The Kulinkovich reaction can be catalytic in titanium.^[15–17] The catalytic cycle is initiated by the formation of the titanacyclopropane **17** as described in Scheme 2.2. In the next step the ester group is attacked via a 1,2-insertion reaction of the ester



Scheme 2.4: Catalytic cycle for the Kulinkovich reaction.

carbonyl group in the titanacyclopropane to form oxatitanacyclopentane intermediate **A**. Elimination of an alkoxy-group leads to intermediate **B**. This intermediate undergoes intramolecular 1,2-insertion to form the cyclopropane ring of titanium alcoholate

C. **C** plays a similar role as $\text{Ti}(\text{O}i\text{Pr})_4$ and reacts with two molecules of Grignard reagent to close the catalytic cycle and forms magnesium alcoholate **D** which leads to cyclopropanol **18** after work-up.[14–17] Thus the amount of $\text{Ti}(\text{O}i\text{Pr})_4$ can be lowered to 5-10 mol%.

3. Modifications of the Kulinkovich reaction

3.1. Influence of the Grignard reagent

The Grignard reagents used in Kulinkovich type reactions can in principle be divided into two categories: cyclic and acyclic ones. Both can be used for the formation of cyclopropanols, cyclic grignard reagent yield in the formation of *cis*-fused bicyclic cyclopropanols.[18] It has been shown that titanacyclopropanes derived from cyclic Grignard reagent perform better in ligand exchange reactions with alkenes (see Section 3.3) than those derived from acyclic Grignard reagents.[10, 19] In ligand exchange reactions with triple bonds (Section 3.4) titanacyclopropane **19** derived from *i*PrMgBr proved to be especially useful. [20, 21]

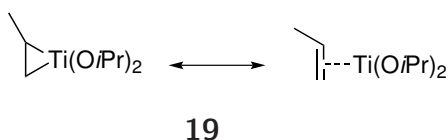


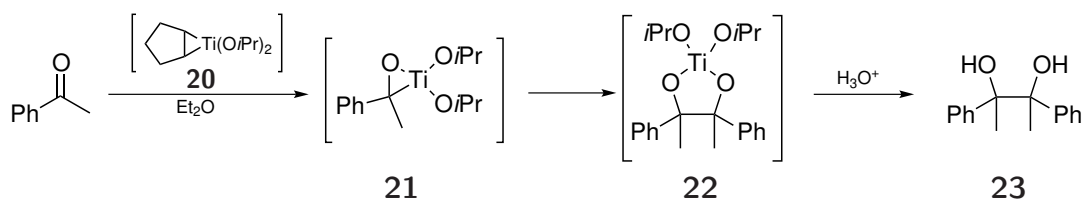
Figure 3.1.: Titanacyclopropane **19** derived from *i*PrMgBr.

3.2. Reaction without ligand exchange

3.2.1. Reaction with aldehydes and ketones

The reactivity of aldehydes as substrates is not much investigated and there are little examples in literature. It has been shown that aldehydes react under the Kulinkovich conditions to form primary alcohols via a Meerwein-Ponndorf-Verley type reduction, as well as Tishchenko-type esters and pinacol-coupling products.[22] The latter are probably formed by a ligand exchange reaction of the titanacyclopropane formed with the carbonyl group of the aldehyde followed by 1,2-insertion of a second molecule of aldehyde.

When benzophenone reacts with titanacyclopropane **20** formed from $\text{Ti}(\text{O}i\text{Pr})_4$ and *cyclo*-pentylmagnesium chloride, the corresponding pinacol-coupling product is obtained. The mechanism of this formation is thought to be similar to the one described above with the aldehyde (Scheme 3.1).[23]

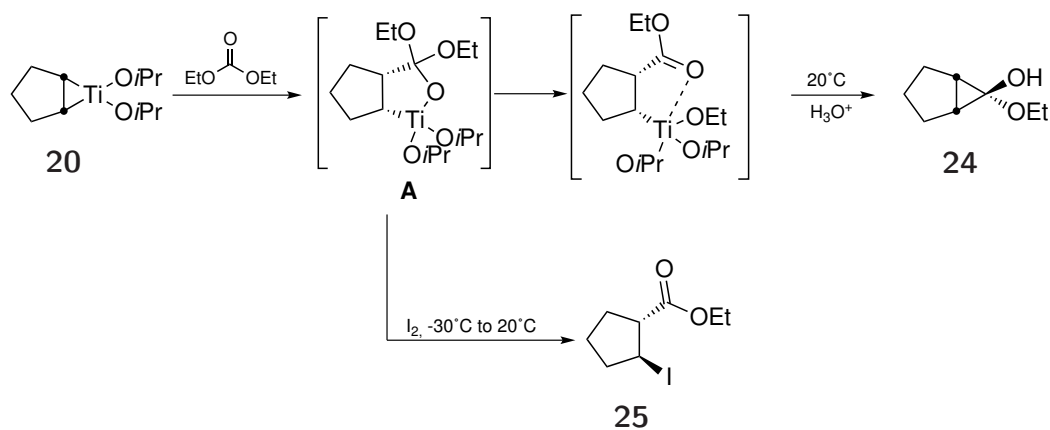


Scheme 3.1: Pinacol-type coupling of benzophenone mediated $(\eta^2\text{-C}_5\text{H}_8)\text{Ti}(\text{O}i\text{Pr})_2$ **20**.

Preformed $(\eta^2\text{-C}_5\text{H}_8)\text{Ti}(\text{O}i\text{Pr})_2$ **20** reacts first in a ligand exchange reaction with the carbonyl group of the ketone to form intermediate **21**. The latter undergoes an 1,2-insertion with a second ketone molecule to give intermediate **22** which yields the pinacol product **23** after hydrolysis.

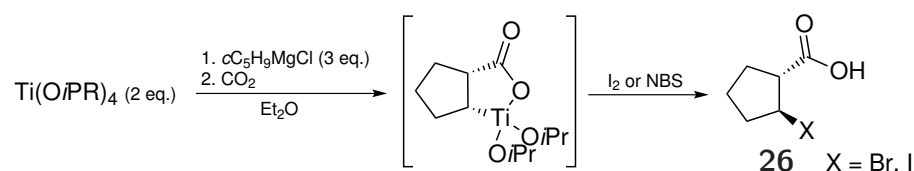
3.2.2. Reaction with carbonates and carbon dioxide

When preformed $(\eta^2\text{-C}_5\text{H}_8)\text{Ti}(\text{O}i\text{Pr})_2$ **20** reacts with diethyl carbonate, the hemiacetal **24** can be formed when the reaction is performed at room temperature and an acidic work-up is done.[9] Using the same starting materials, but performing the reaction at low temperature, the intermediate **A** is stable enough to be quenched by the addition of iodine to yield β -iodo-ester **25** (Scheme 3.2).



Scheme 3.2: Reaction of **20** with diethyl carbonate and subsequent functionalization.

Using the same methodology **20** can react with carbon dioxide and an electrophile such as NBS or I_2 to form β -halogenated acids **26** (Scheme 3.3).[9, 23] Again, the reactions proceed with a complete *trans*-selectivity. This was explained by an $\text{S}_{\text{E}}2$ (back) mechanism in the halogenolysis of the $\text{C}sp_3\text{-Ti}$ bond.[9]

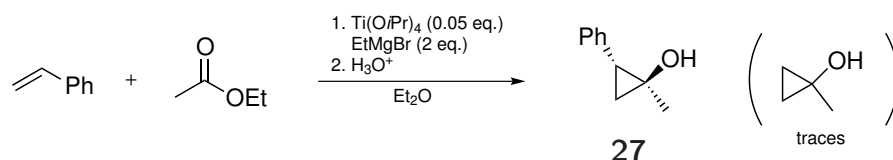


Scheme 3.3: Formation of β -halogen-acids by reaction of **20** and CO_2 .

3.3. Ligand exchange reactions with alkenes

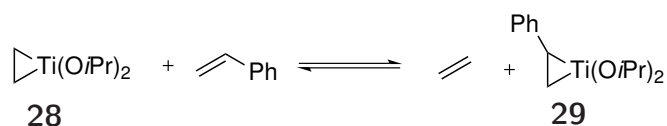
3.3.1. Intermolecular reactions

The group of Kulinkovich showed in 1993 that when the reaction of EtOAc with $\text{Ti}(\text{O}i\text{Pr})_4/\text{EtMgBr}$ is performed in the presence of styrene, (*E*)-1-methyl-2-phenylcyclopropanol **27** is obtained as the major product (Scheme 3.4).[24]



Scheme 3.4: Reaction of $\text{Ti}(\text{O}i\text{Pr})_4/\text{EtMgBr}$ with EtOAc in the presence of styrene.

This outcome could be explained by a ligand exchange reaction between the initially formed complex **28** and styrene to form ethylene and complex **29** (Scheme 3.5). The latter one will then react with EtOAc to form **27**.



Scheme 3.5: Ligand exchange reaction between **28** and styrene.

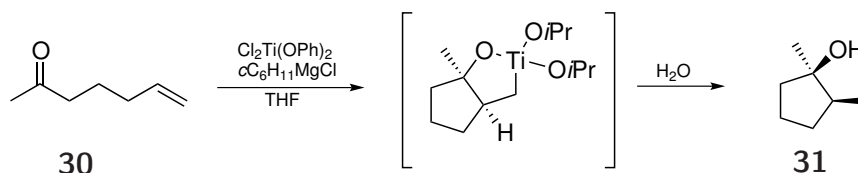
This ligand exchange reaction is more likely to take place when titanacyclopropanes from cyclic Grignard reagents are used.[10, 19] In regard to the alkene used, the reaction is limited to monosubstituted alkenes. As the ligand exchange reaction is an equilibrium reaction, the equilibrium is in general shifted towards the titanacyclopropane with minimized steric interactions.

The finding that titanacyclopropanes can undergo ligand exchange reactions was an important improvement as this ligand exchange reaction allows the use of functionalized titanacyclopropanes which usually involves a complicated and sometimes difficult to achieve synthesis of the corresponding Grignard reagent. The ligand exchange reaction equally offers the possibility to perform intramolecular Kulinkovich reactions.[25]

3.3.2. Intramolecular reactions

Reaction with ketones

When ketones with a tethered alkene function of type **30** are submitted to *cyclo*-hexyl-magnesium chloride and $\text{Cl}_2\text{Ti}(\text{OPh})_2$ one can obtain *cis*-cyclopentanol **31** after hydrolysis (Scheme 3.6).[25]



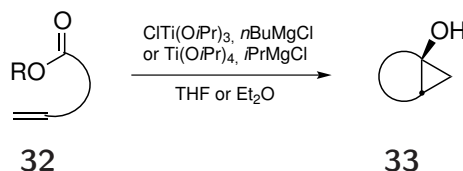
Scheme 3.6: Formation of *cis*-cyclopentanol using Ti-mediated ketone-alkene-coupling.

If a chiral center is installed in the α -position of the ketone, the corresponding cyclopentanol can be obtained with medium to high diastereoselectivities.[25, 26]

It has also been shown that the intermediate can be trapped by other electrophiles than H^+ . Thus the Ti-carbon bond of the formed bicyclic intermediate can be functionalized to form the iodide substituted cyclopentanol.[26]

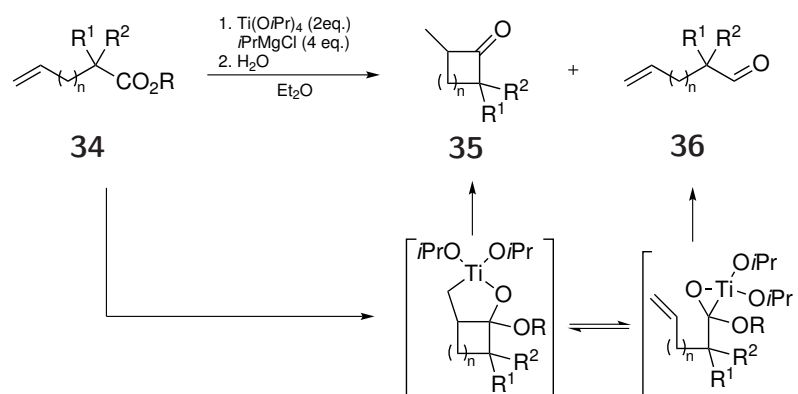
Reaction with esters and carbonates

It has been shown that intramolecular versions of the Kulinkovich reaction are possible when the alkene moiety is connected via a tether to an ester group.[27, 28] After ligand exchange of the initially formed titanacyclopropane with the alkene **32** an intramolecular attack can take place to yield bicyclic cyclopropanols **33** (Scheme 3.7).



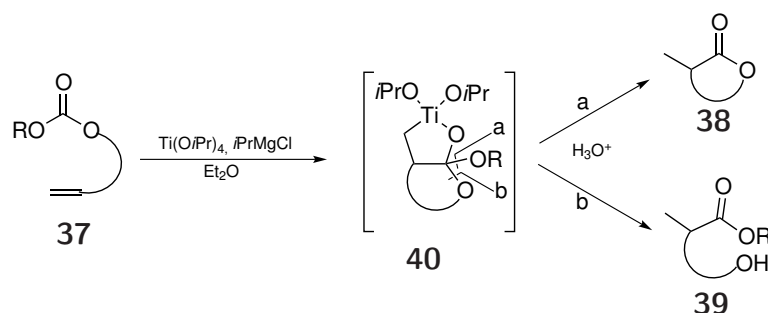
Scheme 3.7: Reaction of alkene tethered to ester groups.

This synthetic route allows the obtention of [n.1.0] ($n = 3 - 5$) skeletons. The formation of larger ring systems is unfavoured[27] and smaller ring systems tend to form cyclic ketone **35** or acyclic aldehydes **36**,[29] both produced by the lack of the second 1,2-insertion reaction (Scheme 3.8).



Scheme 3.8: Formation of ketone **35** and aldehyde **36**.

When alkene substituted carbonates **37** are used as substrates, an intramolecular nucleophilic acyl substitution (INAS) was performed yielding lactones **38** or carboxylic esters **39**.^[21, 30]

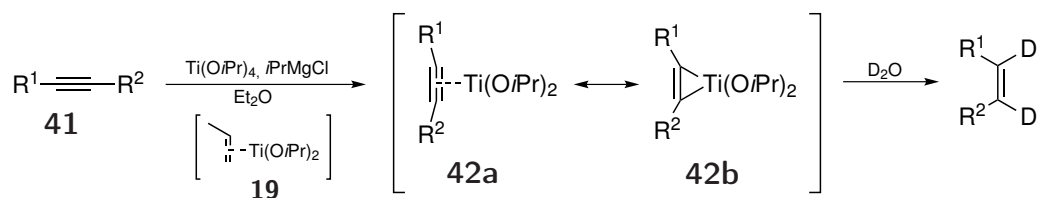


Scheme 3.9: INAS reaction of alkene tethered carbonates.

The outcome of the reaction depends on whether carbon-oxygen bond **a** or **b** is cleaved in intermediate **40** (Scheme 3.9).^[21]

3.4. Ligand exchange with alkynes

The first example of ligand exchange reaction of titanacyclopentanes with the triple bond of an alkyne has been reported in 1995 by Sato and coworkers (Scheme 3.10).^[31]



Scheme 3.10: Ligand exchange reaction of an alkyne with titanacyclopentene **19**.

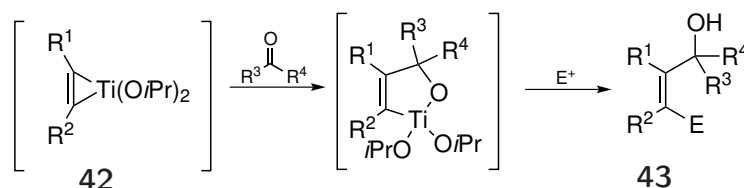
As it is the case for titanacyclopropanes, the newly formed titanacyclopropenes can be described in two mesomeric forms represented by the limiting structures **42a** and **42b**.

The structure of the related compounds $\text{Cp}_2\text{Ti}(\eta^2\text{-alkyne})$ and $\text{Cp}_2^*\text{Ti}(\eta^2\text{-alkyne})$ has been studied by spectroscopy and X-ray analysis and is in good agreement with the proposed limiting structures **42** with a more pronounced contribution of cyclic structure **42b**. [32–36] The X-ray structures show that the substituents in the titanacyclopropene are already in a (*Z*)-like conformation. Thus the deuteration of titanacyclopropenes **42** yields pure (*Z*)-bis-deuterated alkenes. [31]

3.4.1. Intermolecular reactions

Reaction of titanacyclopropenes with aldehydes and ketones

Titanacyclopropene **42** can react with a large variety of reagents [19] amongst others aldehydes and ketones. First a cyclic intermediate is formed which can then be trapped by the addition of a second electrophile to obtain allylic alcohols **43** (Scheme 3.11). [31]



Scheme 3.11: Synthesis of allylic alcohols **43** with **42**.

H_3O^+ as well as I_2 can be used as second electrophile. The reaction tolerates a variety of functional groups on both the alkyne moiety and the aldehyde/ketone.

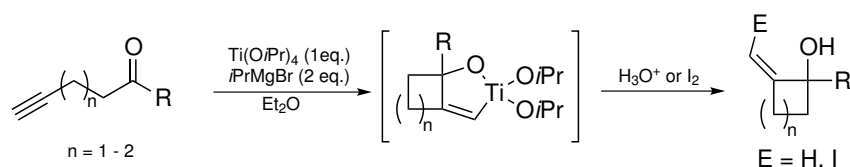
As in most reactions performed unsymmetrical substituted alkynes are used as substrate, the regioselectivity of the reaction could not be neglected. The regioselective outcome of the reaction is dependent on the nature of the group with which the titanacyclopropene reacts as well as the nature of the substituents on the triple bond. There are substituents directing the attack in α -position, others are more β -directing. In addition intermolecular complexation of attacking molecule can have an impact on the regioselectivity.

Thus the combination of different substituent effects (+M/-M, +I/-I) with the molecule attacked results in a complex combination of factors which are difficult to predict but can supply helpful information to understand the outcome of a reaction. [19]

3.4.2. Intramolecular reactions

Reaction of titanacyclopropenes with ketones

Further, the group of Marek showed that starting from alk-1-yn-5-ones or alk-1-yn-6-ones, cyclobutanols or cyclopentanols can be obtained via an intramolecular process (Scheme 3.12).[37]

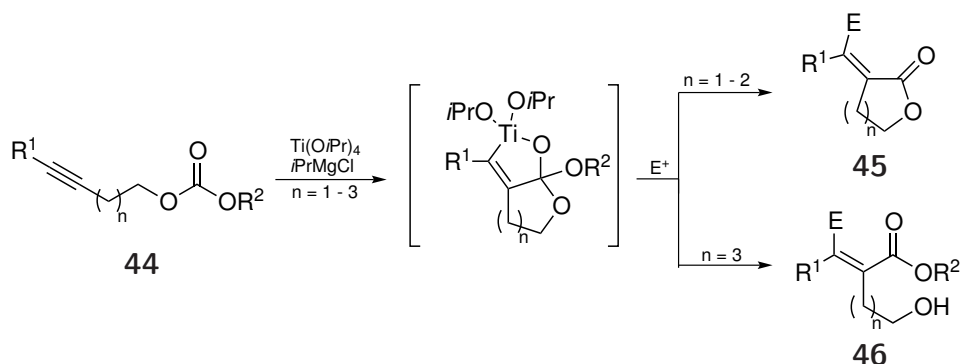


Scheme 3.12: Synthesis of cyclic allylic alcohols.

The mechanism involves a ligand exchange reaction of the titanacyclopropane with alkyne followed by intramolecular 1,2-insertion of the carbonyl group. The resulting Ti-carbon bond is then transformed into C-H or C-I by addition of the proper electrophile.

Reaction of carbonates and esters

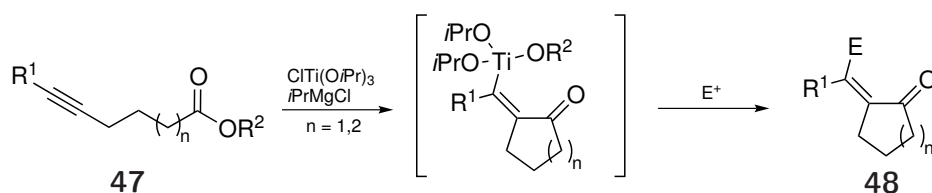
When alkynes tethered to carbonates and esters are submitted to $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgCl}$, the product of an INAS reaction can be obtained. After ligand exchange reaction the titanacyclopropane undergoes 1,2-insertion onto the carbonate group to form a bicyclic intermediate (Scheme 3.13).[21, 38]



Scheme 3.13: INAS reaction of alkyne-carbonates **44**.

Depending on the tether length between the alkyne and the carbonate, two type of products can be obtained: α , β -unsaturated lactones **45** or unsaturated alcohols **46**. When additional substituents are added to the tether the formation of lactones is favored through the Thorpe-Ingold-effect.[21, 29] The carbon-titanium bond in the intermediate can be used for further functionalization of the product by adding an appropriate electrophile as trapping reagent.

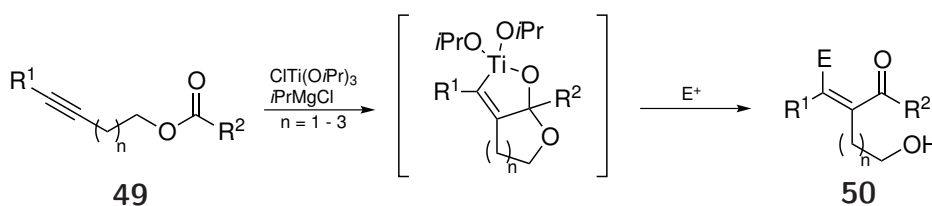
It is also possible to perform intramolecular reaction between a titanacyclopentene and an ester.[21, 29] Starting from esters **47**, this process yields via a INAS-type reaction the α , β -unsaturated cyclic ketones **48** (Scheme 3.14).



Scheme 3.14: Synthesis of α , β -unsaturated cyclic ketones **48**.

The intermediate formed during the reaction can be trapped using a variety of electrophiles such as H_2O , I_2 and aldehydes. When aldehydes are used as trapping reagent the corresponding alcohols are obtained (see page 17).

Under similar conditions, internal esters **49** can be transformed into unsaturated keto-alcohols **50** (Scheme 3.15).

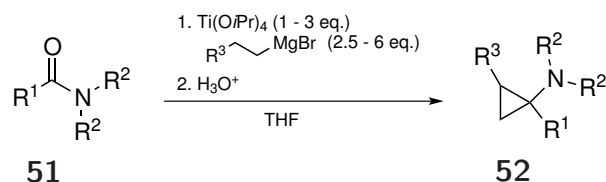


Scheme 3.15: INAS-reaction of internal esters.

As it is the case for the formation of α , β -unsaturated cyclic ketones **48**, many electrophiles can be used as trapping reagent. Hence this methodology allows the one-pot synthesis of multifunctionalized compound starting from easy accessible starting materials.

3.5. Synthesis of substituted cyclopropyl-amines: Findings of de Meijere

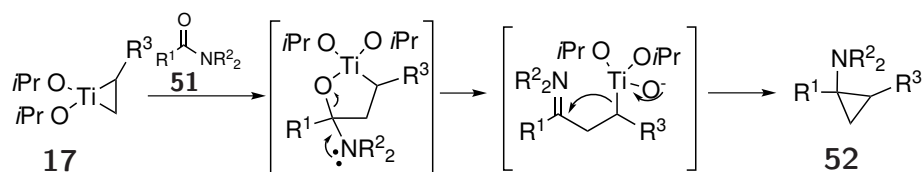
In 1996, the group of de Meijere reported an important modification to the Kulinkovich reaction.[39] They showed that the reaction conditions of the Kulinkovich reaction could be applied to amides **51** as substrates conducting to cyclopropylamines **52** (Scheme 3.16). In contrast to the original procedure with esters, a excess of Grignard reagent and Ti(OiPr)_4 has to be used.



Scheme 3.16: Synthesis of cyclopropylamines from amides.

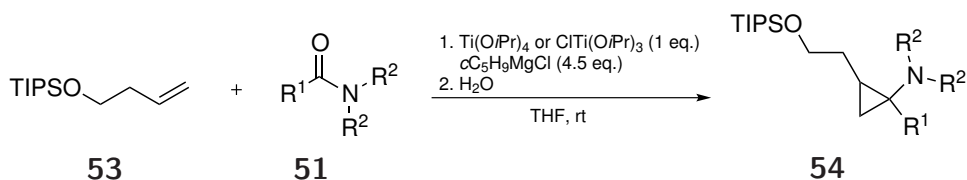
This reaction is one of the most general and versatile method for the preparation of cyclopropylamines[19] albeit the fact that diastereoselectivity is low except for some cases.[40]

The low diastereoselectivity of the reaction can be explained by the acyclic nature of the intermediate formed during the reaction (Scheme 3.17).[41]



Scheme 3.17: Mechanism for the synthesis of cyclopropylamines from amides.

As demonstrated by Cha *et al.* this reaction can also be performed with ligand exchange on the titanium (Scheme 3.18).[10, 42] As for the synthesis of cyclopropylamines without ligand exchange the diastereoselectivity is modest and substrate dependent.

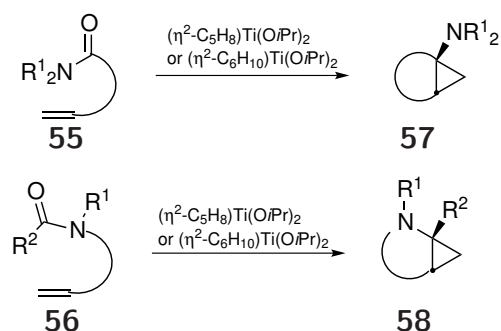


Scheme 3.18: Synthesis of cyclopropylamines with alkene ligand exchange.

Using this methodology only tertiary amines can be obtained. neither primary nor secondary amides are tolerated as starting materials.[43]

3.5.1. Modifications by Cha

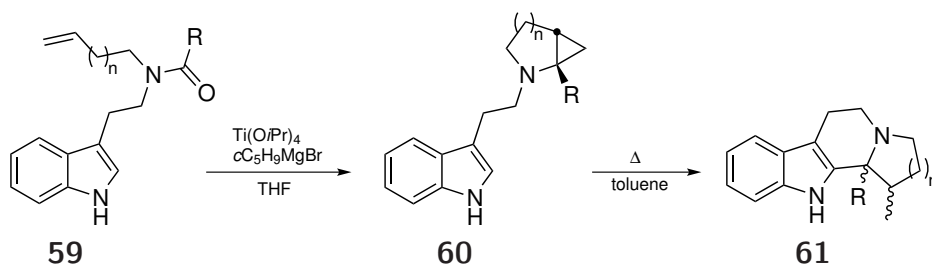
The group of Cha showed that bicyclic amines can be obtained through an intramolecular reaction when the alkene is tethered to an amide. Two types of substrates can be used generating either a product with an exocyclic amine function (**57**) or the amine function incorporated in the ring (**58**) starting from *N,N*-dialkylalkenamides **55** or *N*-alkenylalkanamides **56** respectively (Scheme 3.19).[43]



Scheme 3.19: Synthesis of bicyclic cyclopropylamines.

3.5.2. Application by Six

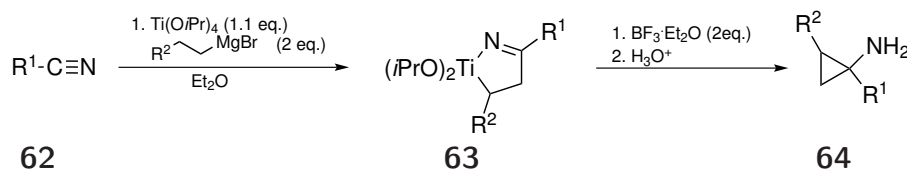
In the group of Six, this methodology was used for the synthesis of indole substituted aminocyclopropanes **60**. The products obtained can undergo intramolecular aromatic substitution to furnish interesting tetracyclic compounds **61** containing a 1,2,3,4-tetrahydro-2-carboline structure.[44, 45]



Scheme 3.20: Synthesis of bicyclic cyclopropylamines.

3.6. Synthesis of free cyclopropyl-amines: Findings by Smyzoniak

To obtain primary cyclopropylamines a procedure was established in the group of Smyzoniak, using nitriles as substrate.[46]



Scheme 3.21: Synthesis of primary cyclopropylamines from nitriles.

As for the synthesis of tertiary amines, the primary amines are obtained with low

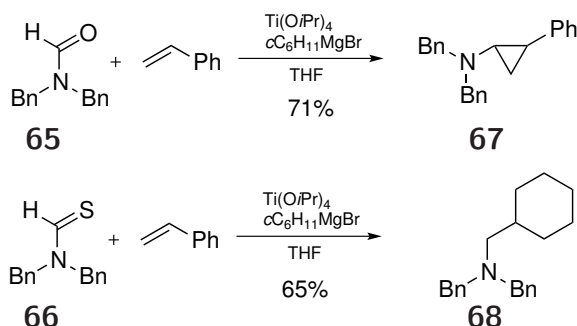
diastereoselectivities.

It has to be noted that the addition of a Lewis acid is necessary for the cyclopropane formation as the azatitanacycle intermediate **63** formed seems to be rather stable and needs to be activated to undergo the second 1,2-insertion reaction.[46]

3.7. Kulinkovich-type reactions of thioamides: Recent findings by Six

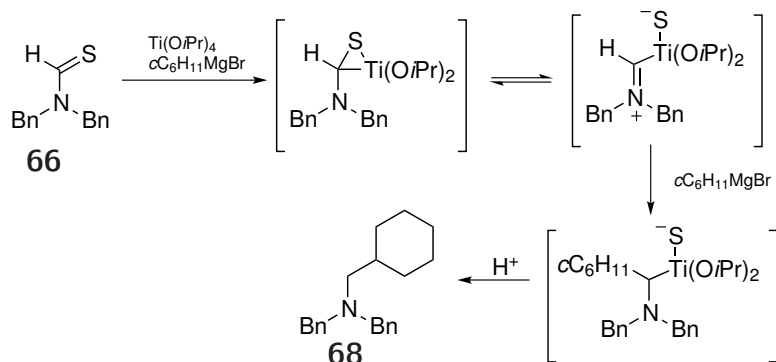
Recently, Six and co-workers studied the behavior of thioamides under Kulinkovich type conditions.[47] They noticed a drastically different behavior in comparison with carboxylic amides.

The reactions of **65** and **66** in the presence of styrene are clearly divergent. While the carboxylic amide **65** undergoes an intermolecular Kulinkovich-de Meijere reaction to afford compound **67**, from **66**, only the cyclohexane-substituted tertiary amine **68** is formed.



Scheme 3.22: Reaction of thioamides under Kulinkovich conditions.

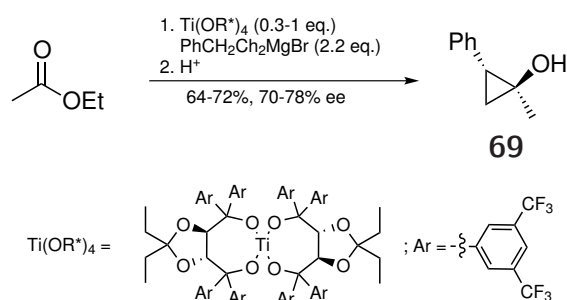
The authors postulated a thia-titanacyclopropane intermediate that can open to form an iminium which will be attacked by the Grignard reagent to form the amine **68** (Scheme 3.23).



Scheme 3.23: Proposed mechanism for the formation of **68**.

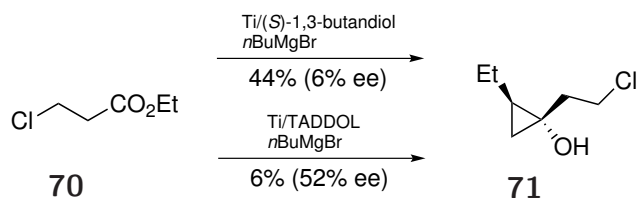
3.8. Enantioselective modifications of the Kulinkovich reaction

There are few examples known in the literature for the synthesis of enantiomeric enriched cyclopropanols by the use of a chiral titanium complex. Corey *et al.* showed that the use of Taddol-derived ligands on the titanium led to the formation of enantiomeric enriched products **69** with good yields and good enantioselectivities (Scheme 3.24).[48]



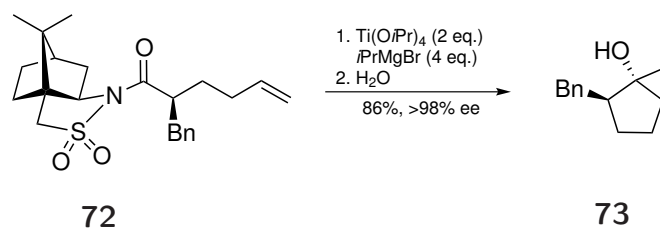
Scheme 3.24: Enantioselective catalytic synthesis of cyclopropanols using a chiral Ti-complex.

Similar attempts of Kulinkovich *et al.* on other substrates were not productive as products were obtained either with modest enantioselectivities and low yield or modest yield and low enantioselectivities (Scheme 3.25).[49]



Scheme 3.25: Attempts for enantioselective transformations by Kulinkovich *et al.*

A more frequently used methodology to obtain enantiomeric enriched cyclopropanols was to start from chiral substrates.[50, 51] When for example (-)-2,10-camphorsultam was used as chiral auxiliary, the corresponding products could be obtained in good yields and high enantioselectivities depending on the substrate.[51]

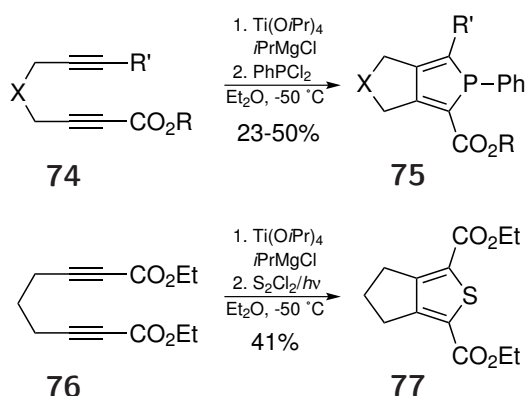


Scheme 3.26: Enantioselective catalytic synthesis of cyclopropanols using a chiral auxiliary.

4. Results

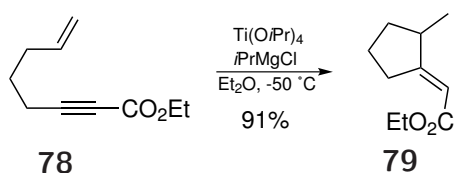
Objective

With the objective to broaden the scope of use of our acetylenic ω -ketoesters, we started investigating their reactivity under the conditions of the Kulinkovich reaction. The reactivity of Sato's reagent ($(\eta^2$ -propene)Ti(O*i*Pr₄) with a variety of acetylenic compounds has intensively been studied (see above and [19, 21, 52–57]). Still there is less work done on the studies of activated alkynes [58–64] and only the work of Matano and Sato deals with intramolecular reactivity (Scheme 4.1, Scheme 4.2).[58, 59, 63, 64]



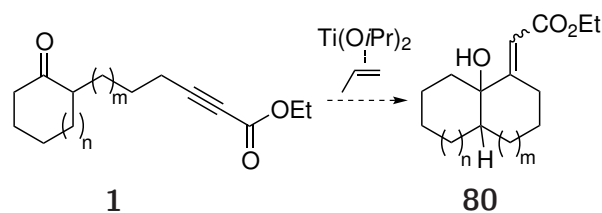
Scheme 4.1: Work of Matano *et al.* on the use of activated alkynes using $(\eta^2$ -propene)Ti(O*i*Pr₄).

To the best of our knowledge there is only one study involving 7-en-2-ynonates **78** (Scheme 4.2).[63, 64]



Scheme 4.2: Work of Sato *et al.* using 7-en-2-ynonates as substrates.

Our aim was to investigate the reactivity of acetylenic ω -ketoesters **1** towards $(\eta^2$ -propene)Ti(O*i*Pr₄) in order to obtain bicyclic γ -hydroxy α,β -unsaturated esters **80** through this procedure (Scheme 4.3).



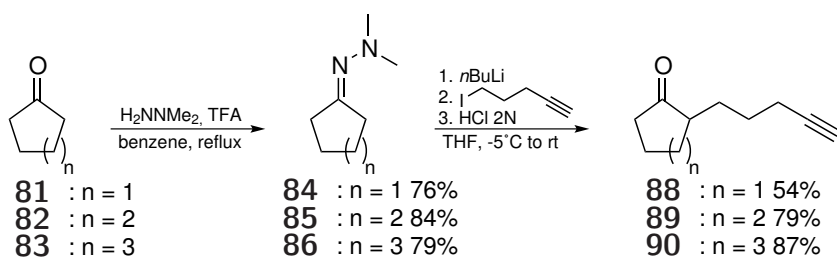
Scheme 4.3: Synthetic plan for the synthesis of compounds **80**.

4.1. Synthesis of the starting materials

We first had to synthesize the acetylenic ω -ketoesters as starting material. To achieve this, we followed a procedure established in our laboratory.[2, 3]

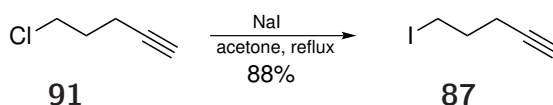
4.1.1. Synthesis of acetylenic ω -ketoesters bearing a 3-carbon tether

Starting from commercially available cyclic ketones **81-83** the corresponding hydrazones **84-86** were synthesized in good yields (Scheme 4.4).



Scheme 4.4: Synthesis of keto-alkynes **88-90**.

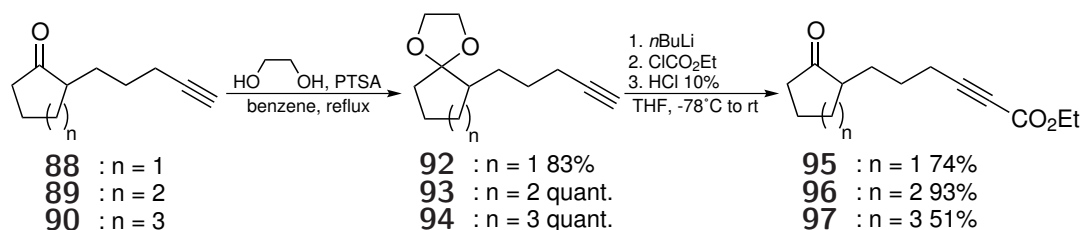
The resulting hydrazones were then alkylated using *n*BuLi and 5-iodopentyne **87** as alkylating agent. Thus the α -substituted ketones **88-90** were obtained. 5-iodopentyne **87** could be synthesized from commercially available 5-chloropentyne **91** via a classical Finkelstein reaction (Scheme 4.5).



Scheme 4.5: Synthesis of 5-iodopentyne **87**.

To install the ester group on the alkyne function of the molecule, the carbonyl group had to be protected. Reaction of keto-alkynes **88-90** with ethylene glycol yielded the desired products **92-94** with the keto group protected as dioxolan in high yields (Scheme 4.6). In the last step of the synthesis the ester group was installed and the keto-group was deprotected under acidic conditions. Thus the acetylenic ω -ketoesters

95-97 were obtained in 4 steps starting from commercially available materials with a reasonable overall yield of 25-62 %.



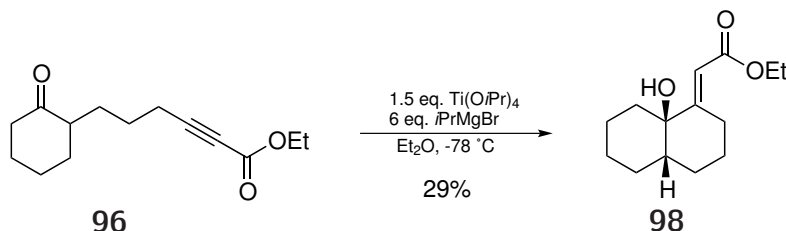
Scheme 4.6: Synthesis of acetylenic ω -ketoesters **95-97**.

4.2. Applying Kulinkovich reaction conditions to acetylenic ω -ketoesters

4.2.1. Preliminary assay

We started our investigation using the acetylenic ω -ketoester **96** derived from cyclohexanone and bearing a 3-carbon tether as model substrate.

When the reaction was performed with 1.5 eq. $\text{Ti}(\text{O}i\text{Pr})_4$, 6 eq. $i\text{PrMgBr}$ in Et_2O as solvent at -78°C the desired product **98** was obtained in 29% yield as a single diastereoisomer (Scheme 4.7).

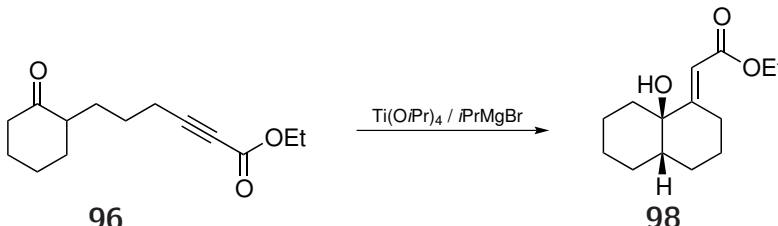


Scheme 4.7: First reaction using **96** for the synthesis of bicyclic γ -hydroxy α,β -unsaturated esters **98**.

although the desired product was only obtained in low yield, we were pleased to find that the reaction proceeded as expected and a single diastereoisomer was obtained. We therefore decided to go on and optimize the reaction conditions.

4.2.2. Optimizing the reaction conditions

To improve the yield of the reaction, we started to modify different parameters such as the amount of the reagents used as well as the temperature and the solvent of the reaction. The results of this optimization experiments are summarized in Table 4.1.

Table 4.1.: Variation of the reaction conditions for the formation of **98**.


Entry	solvent	Ti(O <i>i</i> Pr) ₄ [eq.]	<i>i</i> PrMgBr [eq.]	T [°C]	Yield
1	Et ₂ O	1.5	6+3+3	-78	29%
2	Et ₂ O	1.5	6	-78 to -30	60%
3	Et ₂ O	1.5	6 ^[a]	-78 to -30	12%
4	CH ₂ Cl ₂	1.5	6	-78 to -30	53%
5	THF	1.5	6	-78 to -30	9%
6	Et ₂ O	2	6	-30	84%

[a] cyclohexyl magnesiumbromide was used instead of *i*PrMgBr.

When the amount of Grignard reagent used was increased (entry 1) the yield was not enhanced. Raising the reaction temperature during the reaction to -30 °C yielded in a significant improvement of the yield up to 60 % (entry 2). No amelioration has been obtained when the solvent was varied. When CH₂Cl₂ was used as solvent (entry 4) slightly lower yields in comparison to Et₂O were observed. Replacing Et₂O by THF however resulted in dramatic drop of the yield to 9 % (entry 5). Equally low yields were obtained when the Grignard reagent was changed to *c*HexMgBr (entry 3). A significant enhancement of the yield was observed when the amount of Ti(O*i*Pr)₄ was raised to 2 eq. (entry 6).

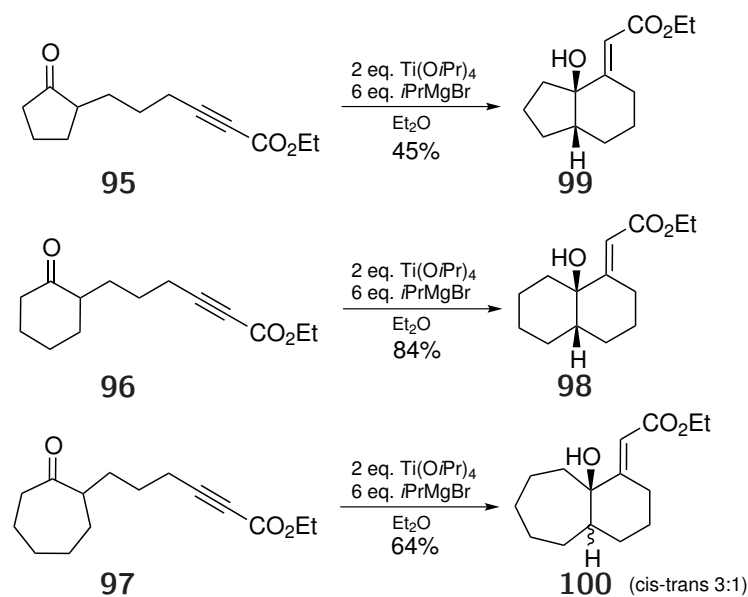
When the reaction was performed with 2 eq. Ti(O*i*Pr)₄ and 6 eq. *i*PrMgBr in Et₂O at -30 °C the desired product **98** was obtained with 84 % yield.

4.3. Reaction scope

Once these optimized conditions have been found, we decided to use them to broaden the scope of the discovered transformation. To do so, different acetylenic ω -ketoesters were synthesized and used as starting materials. We started our investigations by varying the ring size of the starting ketone.

4.3.1. Reaction of acetylenic ω -ketoesters bearing a 3-carbon spacer

The synthesis of the acetylenic ω -ketoesters **95-97** is described in Section 4.1. When acetylenic ω -ketoesters **95-97** were submitted to the reaction conditions, the corresponding bicyclic γ -hydroxy α,β -unsaturated esters **98-100** were obtained (Scheme 4.8).



Scheme 4.8: Synthesis of bicyclic γ -hydroxy α,β -unsaturated esters **98-100** starting from acetylenic ω -ketoesters bearing a 3-carbon tether.

The highest yield was obtained for the reaction of substrate **96** with a 6-membered ring. A slight decrease of the yield was observed when **97** was used as substrate. With the 5-membered ring substrate **95** only 45 % of **99** were obtained. Compounds **98** and **99** were obtained as single diastereoisomers. This was not the case with **100** bearing a 7-6-ring system which was obtained as a 3 : 1 mixture of *cis*- and *trans*-ring junction. In the case of compounds **95** and **96** steric hindrance in the ring-closing transition state favor the formation of the *cis*-configured compound. Figure 4.1 illustrates the transition states forming *cis*-configured **96** (I) and *trans*-configured **96** (II). Transition state II shows a steric interaction between the ester-group and the axial hydrogen atom in α -position to the ketone. 7-membered ring systems are known to be more flexible than the corresponding 5- and 6-membered ring systems.[65] Thus, **97** may adopt multiple conformations allowing the approach of the titanacyclopropene from both sides of the ketone.



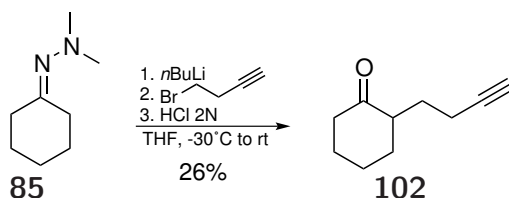
Figure 4.1.: Intermediates leading to the *cis*- and *trans*-configured (II) **96**. E = CO₂Et

4.3.2. Reaction of acetylenic ω -ketoesters bearing a 2-carbon spacer

In addition to the starting materials bearing a 3-carbon tether we decided to use compounds bearing a 2-carbon tether as starting materials.

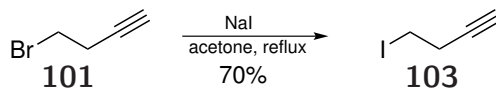
Synthesis of the starting materials

To synthesize the starting materials with a 2-carbon tether we applied the same synthetic strategy as for the 3-carbon tether, starting with commercially available cyclic ketones. After transformation into the corresponding hydrazones the alkyl chain is installed. Using commercially available 4-bromobutyne **101** as alkylating reagent we obtained the desired product **102** with a promising but unsatisfactory yield of 26 % using hydrazone **85** derived from cyclohexanone as substrate (Scheme 4.9).



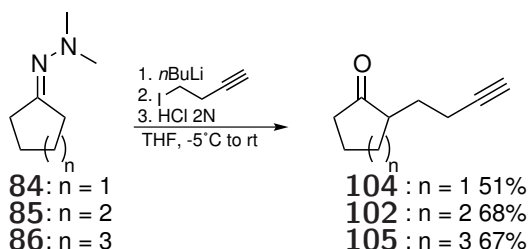
Scheme 4.9: Synthesis of keto-alkyne **102** using 4-bromobutyne as alkylating reagent.

In order to increase the yield of the alkylation reaction we decided to transform the bromo-compound **101** into the iodo-compound **103**. This was achieved by treating the former with NaI in refluxing acetone (Scheme 4.10).



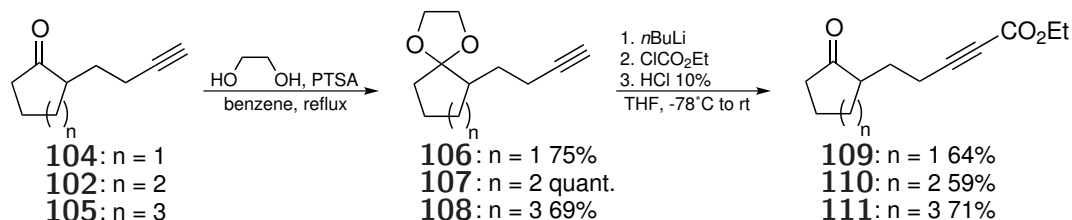
Scheme 4.10: Synthesis of 4-iodobutyne **103**.

The use of iodobutyne instead of bromobutyne allowed us to increase the yield of **102** from 26 % to 68 %. Using the same methodology, the 5- and 7-membered ring analogues **104** and **105** could be synthesized (Scheme 4.11).



Scheme 4.11: Synthesis of keto-alkynes **102**, **104** and **105**.

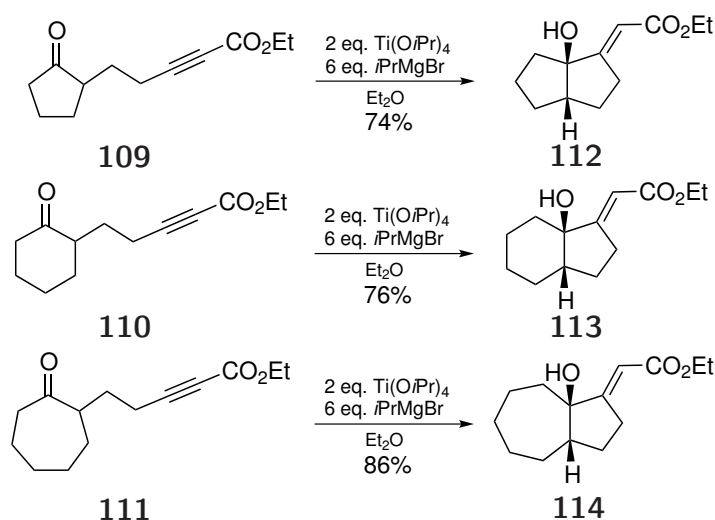
The acetylenic ω -ketoesters were then obtained using the same reaction sequence as described for the 3-carbon tethered molecules. First the keto-group was protected as dioxolan, then the ester moiety was installed and the keto-function deprotected (Scheme 4.12). Thus acetylenic ω -ketoesters **109-111** were obtained in good yields.



Scheme 4.12: Synthesis of acetylenic ω -ketoesters **109-111**.

Reaction with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$

Once the acetylenic ω -ketoesters **109-111** were obtained, we submitted them to the optimized carbometallation reaction conditions. The results are shown in Scheme 4.13. For all three examined substrates the corresponding bicyclic products **112-114** were isolated in good yields and as single isomers.

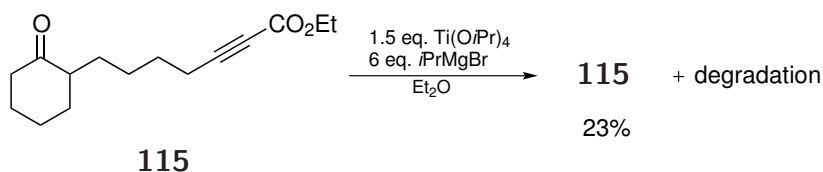


Scheme 4.13: Synthesis of bicyclic γ -hydroxy α,β -unsaturated esters **112-114** starting from acetylenic ω -ketoesters bearing a 2-carbon tether.

In contrast to substrates **95-97**, with the shorter tether in substrates **109-111** less conformations are allowed and so the formation of the *cis*-configured molecules are favored.

4.3.3. Reaction of acetylenic ω -ketoesters bearing a 4-carbon spacer

We then attempted to synthesize a 6-7-membered ring system starting from acetylenic ω -ketoesters bearing a 4-carbon tether. For this purpose, acetylenic ω -ketoester **115** was used as starting material.¹ Unfortunately, when submitting **115** to our reaction conditions we were only able to recover the starting material in 23 % yield, no bicyclic compound could be identified (Scheme 4.14).



Scheme 4.14: Reaction of acetylenic ω -ketoester **115** under Kulinkovich conditions.

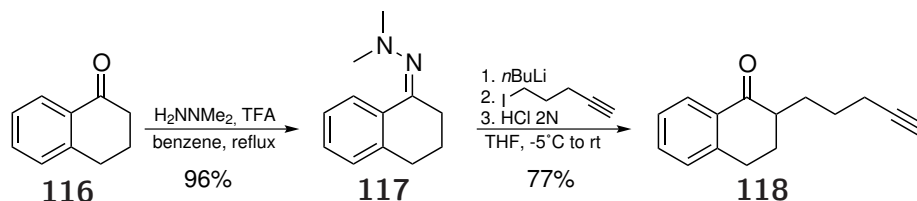
The lack of reactivity for this substrate may be explained by a higher flexibility of the tether and are in agreement with previous findings in our group[66] and the general finding that 7-membered rings are not as easily formed as their 5- or 6-membered analogues.[67]

4.3.4. Reaction of bicyclic acetylenic ω -ketoesters

We also wanted to examine the reactivity of bicyclic acetylenic ω -ketoesters under our reaction conditions.

Synthesis of the starting material

We decided to synthesize an acetylenic ω -ketoester derived from tetralone **116** as test substrate. Following the same procedure as described above (see Scheme 4.4) the hydrazone **117** was obtained with 96% yield. Alkylation of the latter yielded the ketoalkyne **118** with 77% yield (Scheme 4.15).

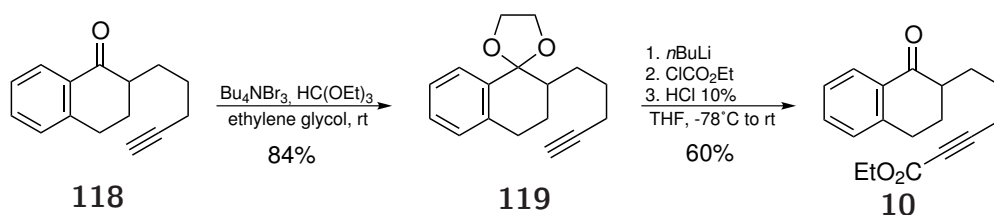


Scheme 4.15: Synthesis of acetylenic ω -ketoester **118**.

It has been shown previously in our laboratory that protection of **118** as dioxolan

¹The acetylenic ω -ketoester **115** bearing a 4-carbon tether was synthesised by A. Klein during her PhD thesis.[66]

119 does not work under the conditions used before.[68] Instead of that a procedure presented by Patel *et al.* furnished the desired product.[69] Using this procedure we were able to obtain **119** with 84% yield (Scheme 4.16).

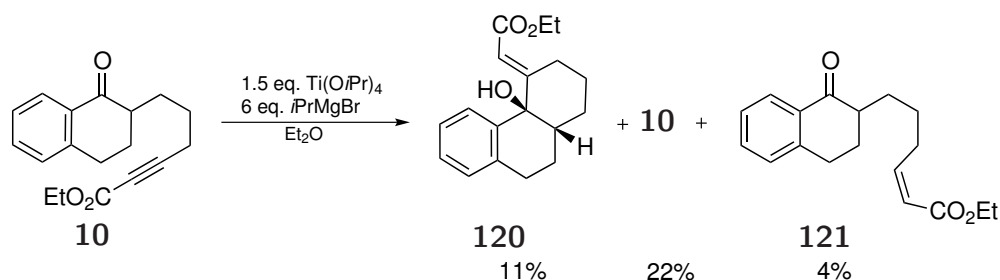


Scheme 4.16: Synthesis of acetylenic ω -ketoester **10**.

Transformation of the protected keto-alkyne into the corresponding ester **10** yielded the desired product with 60% yield.

Reaction with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$

When performing the reaction with acetylenic ω -ketoester derived from tetralone **10** we had to note that it was not a suitable substrate. The desired product **120** was formed only in 11 % yield together with 22 % of the starting material and 4 % of the partially reduced compound **121** (Scheme 4.17).



Scheme 4.17: Reaction of acetylenic ω -ketoester **10** under Kulinkovich conditions.

The decreased reactivity of **10** in comparison to its analogue **96** may be explained by a more rigid conformation of the starting material which makes the attack of the titanacyclopropene more difficult (Figure 4.2) and a different electronic configuration due to the conjugation of the carbonyl with the aromatic system. Additionally it can not be excluded that the reactivity of the titanium intermediate is changed through complexation by the aromatic system.

The formation of the reduced compound **121** can be explained as follows. In a first step, **10** undergoes ligand exchange reaction with the titanium reagent to form **122**. If this species is still present when the reaction mixture is hydrolyzed, **122** would yield **121**.^[31]

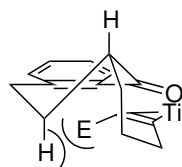
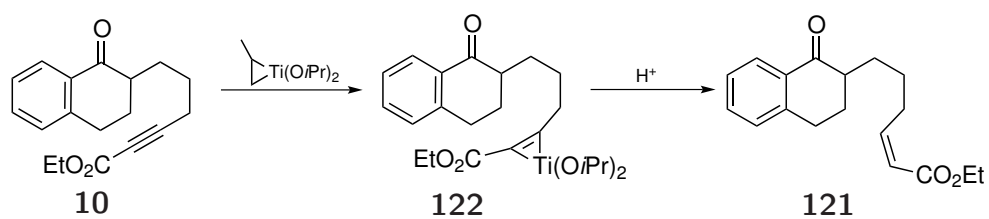


Figure 4.2.: Steric interactions in the transition state for the formation of compound **120**.



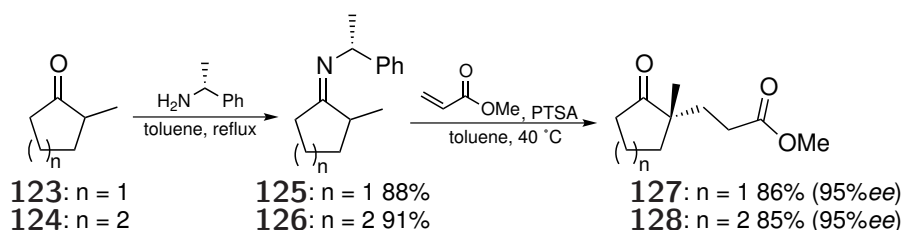
Scheme 4.18: Proposal for the formation of **121**.

5. Synthesis of enantiomerically enriched γ -hydroxy α,β -unsaturated esters

Having developed a method permitting the efficient synthesis of γ -hydroxy α,β -unsaturated esters, we envisaged the synthesis of enantiomerically enriched γ -hydroxy α,β -unsaturated esters. As the use of chiral titanium complexes proved to be very substrate dependent,[48, 49] we decided to focus on the more promising strategy using a defined chiral center already present in the starting material.

5.1. Synthesis of the starting material

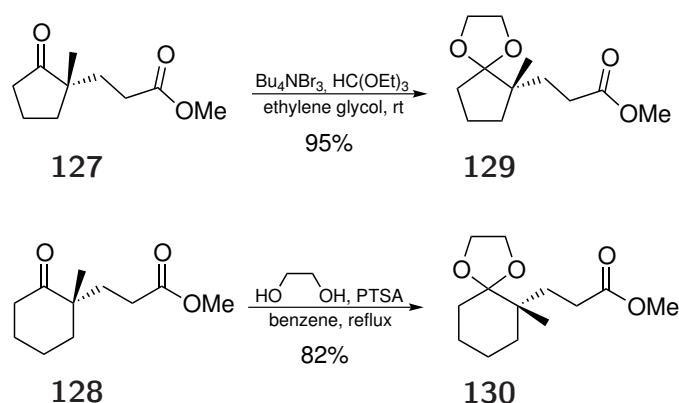
We first had to synthesize the starting materials. To do this, we followed a procedure which has already been used in the laboratory.[70, 71] Starting from α -methylated ketones **123** and **124** we prepared the chiral imines **125** and **126** in high yield. Using these chiral imines the group of d'Angelo showed that it was possible to perform enantioselective alkylations.[72] With the conditions described, we were able to obtain the alkylated products **127** and **128** in high yield and high enantioselectivities (Scheme 5.1).



Scheme 5.1: Synthesis and alkylation of enantiomerically enriched imines **125** and **126**.

The enantiomeric excess of the obtained compounds is high (95 %*ee*). Optical rotation values are in good accordance with those of the literature.[66]

To be able to perform further manipulations on the ester function of **127** and **128** we decided to protect the keto function as a dioxolan. Whereas compound **128** was best protected using standard conditions (ethylene glycol, PTSA), it proved that for the five-membered ring compound **127** the conditions of Patel *et al.*[69] were more favorable (Scheme 5.2).

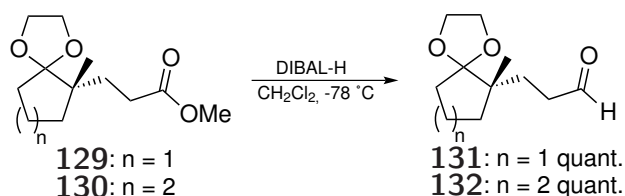


Scheme 5.2: Protection of esters **127** and **128** using different conditions.

Hence, the protected esters **129** and **130** were obtained in good yields and served as common intermediate for the synthesis of the compounds bearing a 2-carbon and those bearing a 3-carbon tether between the ring and the triple bond.

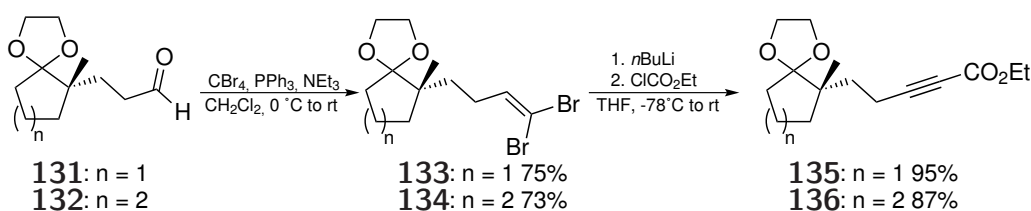
Enantiomerically enriched acetylenic ω -ketoesters bearing a 2-carbon tether

The synthesis starts with the reduction of the ester moiety of **129** and **130** to the aldehyde. This was achieved using DIBAL-H as a selective reducing agent. Working at low temperatures allowed the synthesis of aldehydes **131** and **132** in quantitative yield (Scheme 5.3).



Scheme 5.3: Reduction of esters **129** and **130** using DIBAL-H.

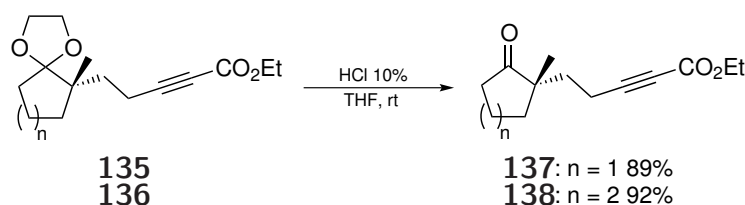
The aldehydes could be transformed into acetylenic esters **135** and **136** using the Corey-Fuchs reaction.^[73] This reaction sequence allows the formation of substituted and unsubstituted triple bonds starting from aldehydes and via a homologous dibromo compound as intermediate (Scheme 5.4). Using ethylchloroformate (ClCO₂Et) to trap the carbanion formed by reaction of *n*BuLi with the dibromo compounds **133** and **134** afforded protected acetylenic ω -ketoesters **135** and **136** in good yields.



Scheme 5.4: Synthesis of protected esters **135** and **136** using a Corey-Fuchs procedure.

It proved to be better to perform the deprotection of the dioxolan in a separate reaction. Indeed yields of the two-step procedure were considerably higher compared to a one-pot procedure. This was surprising as the one-pot procedure worked well for the synthesis of racemic acetylenic ω -ketoesters (see Chapter 4.1).

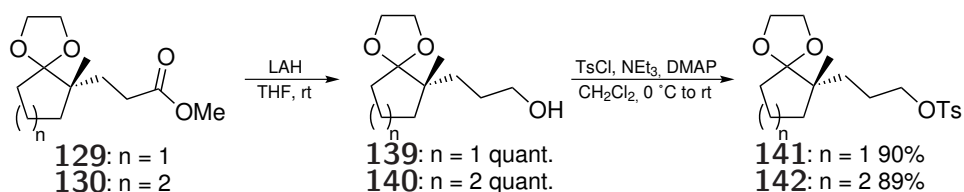
The unprotected acetylenic ω -ketoesters **137** and **138** were finally obtained by deprotection of **135** and **136** under acidic conditions (Scheme 5.5).



Scheme 5.5: Deprotection of esters **135** and **136** to yield **137** and **138**.

Enantiomerically enriched acetylenic ω -ketoesters bearing a 3-carbon tether¹

The synthesis of enantiomerically enriched acetylenic ω -ketoesters bearing a 3-carbon tether uses the same protected esters **129** and **130** already used for the synthesis of the 2-carbon tether. This time, the ester function was reduced to alcohols **139** and **140** using LAH. The alcohols **139** and **140** were obtained in quantitative yield and transformed in the corresponding tosylates **141** and **142** (Scheme 5.6).

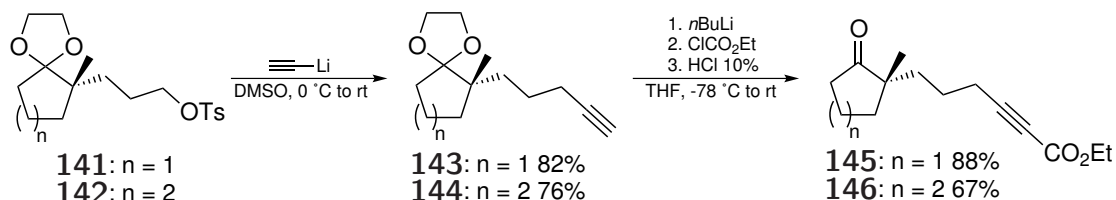


Scheme 5.6: Transformation of esters **129** and **130** into tosylates **141** and **142**.

Once the alcohol function was transformed into a leaving group, we performed a

¹The synthesis of compounds **145**[70] and **146**[71] has already been described.

substitution reaction to introduce the triple bond. Lithium-acetylide ethylenediamine complex was used as nucleophile. Compounds **143** and **144** were obtained in good yields. In the last step of the synthesis the ester moiety was attached to the triple bond using *n*BuLi/*C*lCO₂Et (Scheme 5.7). As for the racemic substrates deprotection of the keto-group under acidic conditions could be performed as a one-pot procedure with the introduction of the ester function.

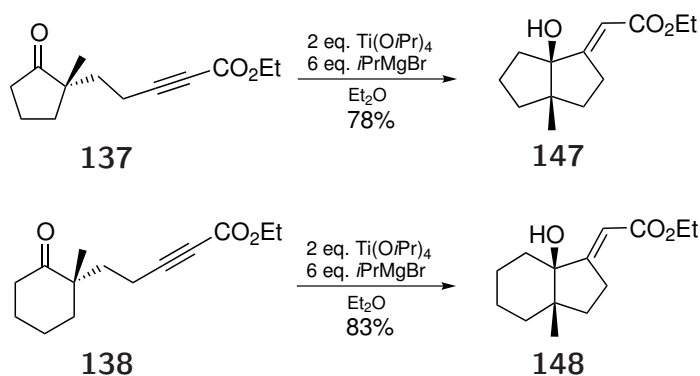


Scheme 5.7: Synthesis of acetylenic ω -ketoesters **145** and **146**.

In this way, the acetylenic ω -ketoesters **145** and **146** were obtained in 7 steps in good overall yield (47% and 29% respectively).

5.2. Reaction of enantiomerically enriched acetylenic ω -ketoesters with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$

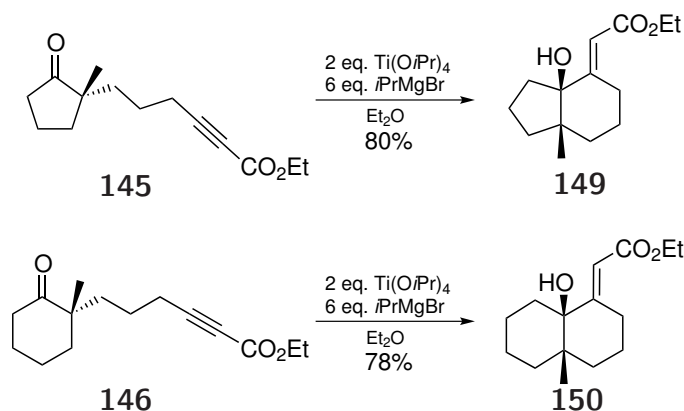
With the enantiomerically enriched acetylenic ω -ketoesters in hand, we tested whether we can submit them to the optimal reaction conditions developed previously in order to obtain the corresponding enantiomerically enriched bicyclic γ -hydroxy α,β -unsaturated esters. When acetylenic ω -ketoesters **137** and **138** were used as substrates the corresponding bicyclic γ -hydroxy α,β -unsaturated esters **147** and **148** were obtained in high yield (Scheme 5.8).



Scheme 5.8: Synthesis of bicyclic γ -hydroxy α,β -unsaturated esters **147** and **148** starting from enantiomerically enriched acetylenic ω -ketoesters bearing a 2-carbon tether.

As for the reaction of the racemic substrates, compounds **147** and **148** were obtained with complete selectivity concerning the ring junction. Thus the enantiomeric excess of the starting materials (95 %*ee*) was transferred to the products.

When acetylenic ω -ketoesters **145** and **146** were submitted to the reaction conditions similar results were obtained. The bicyclic γ -hydroxy α,β -unsaturated esters **149** and **150** were obtained in high yield and complete stereoselectivity (Scheme 5.9).



Scheme 5.9: Synthesis of bicyclic γ -hydroxy α,β -unsaturated esters **149** and **150** starting from enantiomerically enriched acetylenic ω -ketoesters bearing a 3-carbon tether.

We were pleased to obtain the crystal structure for two of the products (compound **149** and **150**, Figure 5.1). These structures clearly indicate the *cis*-configuration of the ring junction as well as the *E*-configuration of the double bond.

These results prompted us to go for the assumption that for racemic compounds the configuration of the ring junction is *cis* and for the double *E* as well.

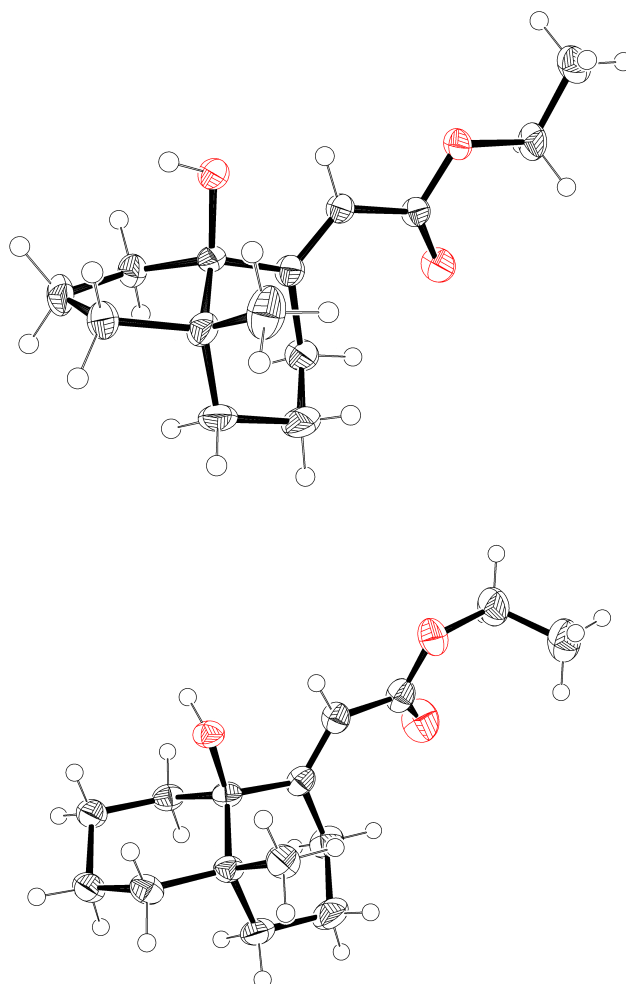
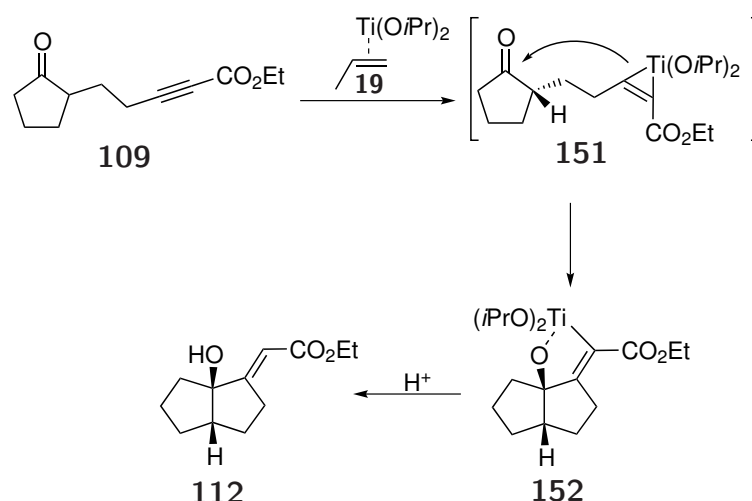


Figure 5.1.: X-ray structure of compound **149** (up) and **150** (down). Ortep view at the 30% probability level.

6. Proposed mechanism and *in situ* trapping of reaction intermediates

6.1. Proposed mechanism

A proposal of the reaction mechanism for the formation of bicyclic γ -hydroxy α,β -unsaturated esters is shown in Scheme 6.1.



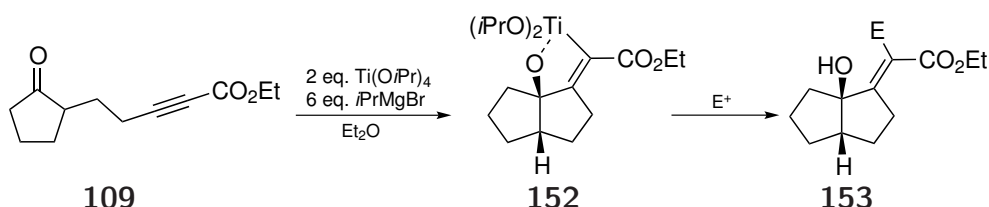
Scheme 6.1: Proposed mechanism for Ti-mediated formation of bicyclic γ -hydroxy α,β -unsaturated esters.

In a first step, the acetylenic ω -ketoester **109** undergoes ligand exchange reaction with Sato's reagent **19** formed *in situ* from $\text{Ti}(\text{O}i\text{Pr})_4$ and $i\text{PrMgBr}$ to form the titanacyclopropene **151**.^[21, 29, 37] This intermediate undergoes an intramolecular 1,2-insertion reaction with the keto-group to form **152**.^[21, 37] The final product **112** is then formed from **151** through hydrolysis during the work-up procedure.

The stereochemistry of the ring junction is thereby determined during the 1,2-insertion step (**151** to **152**). Molecular models suggest that the 1,2-insertion is more likely to happen on the *syn*-side of the ketone. The *E* configuration of the double bond is determined by the *Z*-like conformation of the titanacyclopropene **151**.^[31]

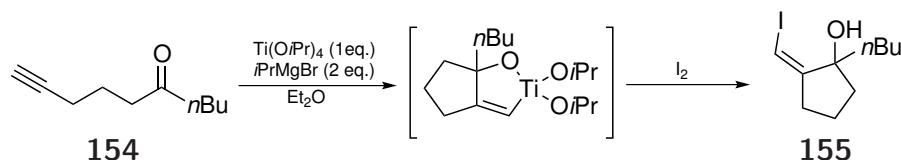
6.2. *In situ* trapping of reaction intermediates

It is known in the literature that reaction intermediates containing a C–Ti-bond can be trapped by the addition of external electrophiles.[21, 23, 26, 31, 37, 74–76] With regard to the intermediate **152**, we thought that it should be possible to use this method to prove the existence of metallacycle **152**. This would not only allow to get more information about the mechanism, but also to obtain more functionalized compounds **153** (Scheme 6.2).



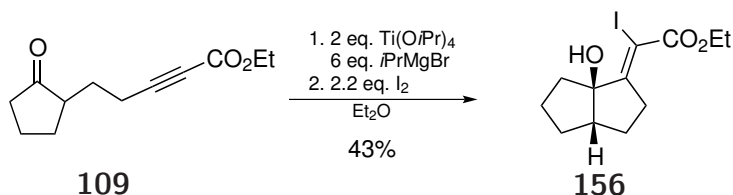
Scheme 6.2: Trapping of intermediate **152** with an electrophile.

Amongst others,[21, 26, 31] Marek *et al.* showed that iodine can insert in C–Ti-bonds in order to synthesize vinyl iodide **155** as illustrated in Scheme 6.3.[37]



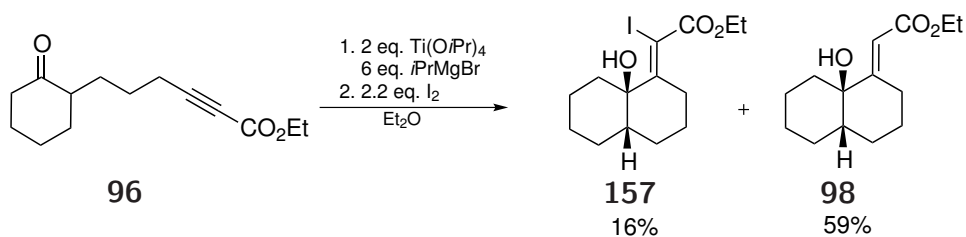
Scheme 6.3: Synthesis of vinyl iodide **155** by Marek *et al.*

We tried to apply this approach to our substrates and trap **152** using I_2 as electrophile (Scheme 6.4). When iodine was added to the reaction mixture after all the starting material **109** was consumed, we were able to isolate the desired compound **156** in 43 % yield (Scheme 6.4).



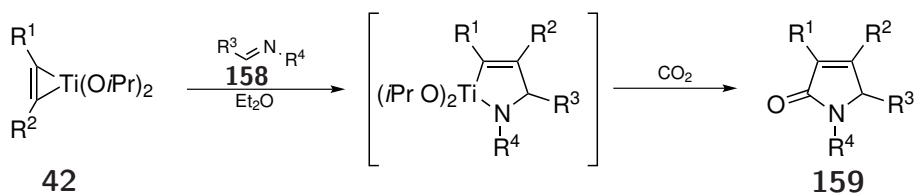
Scheme 6.4: Formation of bicyclic vinyl iodide **156** from **109**.

We then explored the expansion of this method to other substrates. Using acetylenic ω -ketoester **96** derived from cyclohexanone and bearing a 3-membered tether as substrate we could synthesize iodinated compound **157** in 16 % yield, together with 59 % of the not substituted compound **98** (Scheme 6.5).



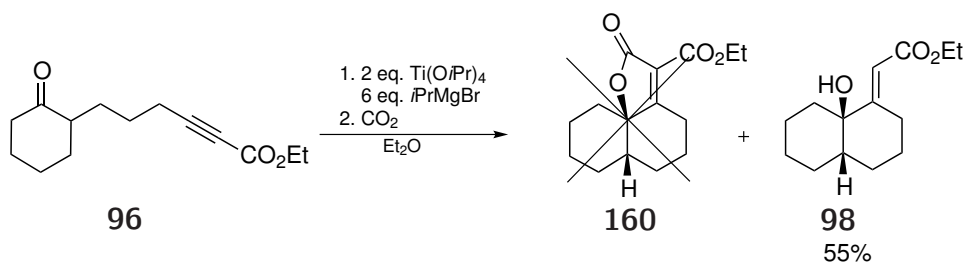
Scheme 6.5: Reaction of **96** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$ and I_2 .

We also attempted to trap the intermediate with a carbon electrophile. As shown in the work of Sato[76] and Six[23, 75] carbon dioxide can react with the intermediates containing C–Ti-bonds. Sato used this method to obtain α,β -unsaturated lactams **159** (Scheme 6.6).



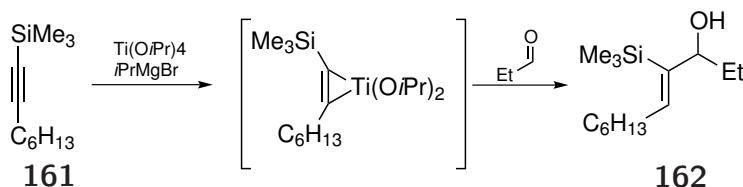
Scheme 6.6: Formation of α,β -unsaturated lactams by Sato *et al.*

Inspired by this work we decided to apply this strategy to our substrates in order to obtain tricyclic lactones like **160**. To do so, we bubbled CO_2 through the reaction mixture after consumption of the starting material **96**. Unfortunately, we were not able to isolate the tricyclic compound **160**, just the known bicyclic compound **98** was isolated in 55% yield.



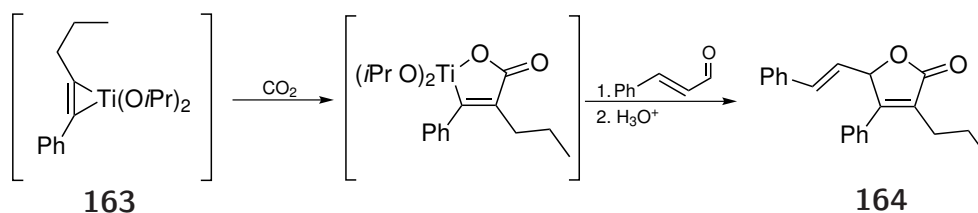
Scheme 6.7: Reaction of **96** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$ and CO_2 .

As there was no reactivity with CO_2 as carbon electrophile we decided to use a more electrophilic species like an aldehyde. The feasibility of this reaction has been demonstrated by Sato *et al.* who synthesized allylic alcohols with this methodology (Scheme 6.8).



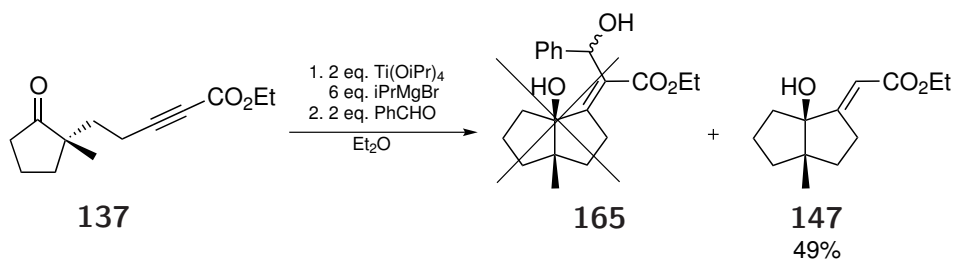
Scheme 6.8: Synthesis of allylic alcohol by Sato *et al.*

Six used a combination of CO_2 and aldehyde trapping for an elegant synthesis of α,β -unsaturated lactones from alkynes. The titanacyclopentadiene **163** reacts first with CO_2 , the aldehyde then inserts into the second Ti–C-bond. The hydroxy acid formed could not be isolated and undergoes direct lactonization to form **164** (Scheme 6.9).



Scheme 6.9: Synthesis of α,β -unsaturated lactones by Six.

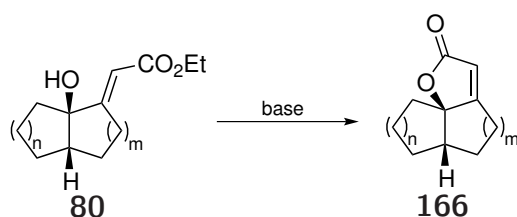
We then tried to perform a similar reaction with our substrates. Methylated acetylenic ω -ketoester **137** was used as starting material and benzaldehyde as electrophile. Unfortunately, we had to state that this approach has been neither successful. Only the known bicyclic compound **147** was obtained in 49 % yield and the desired compound **165** was not observed (Scheme 6.10). A possible explanation is that the intermediate titanacycle is not reactive enough to undergo the insertion reaction with the aldehyde.



Scheme 6.10: Reaction of **137** with Ti(OiPr)_4 /*iPrMgBr* and PhCHO .

7. Synthesis of tricyclic lactones

Once we had obtained a series of γ -hydroxy α,β -unsaturated esters we thought that it should also be possible to obtain the corresponding lactones. We imagined that the treatment of the hydroxy-esters with a suitable base could lead to tricyclic unsaturated butyrolactones of type **166** (Scheme 7.1).



Scheme 7.1: Lactonization of **80**.

The lactones we wanted to synthesize by this method represent the carbon skeleton of different natural products like the alliacol family and arteannuin B. Representative structures are shown in Figure 7.1.

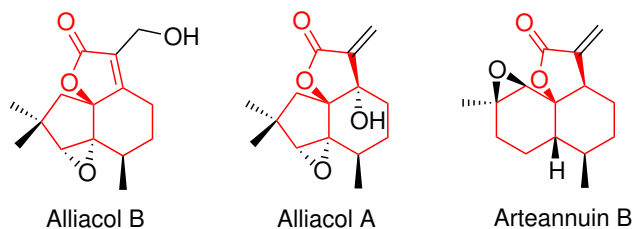
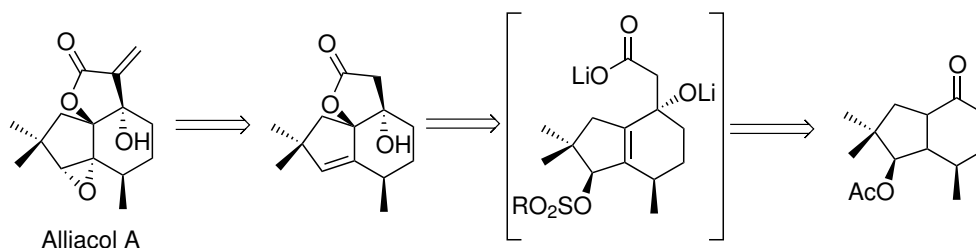


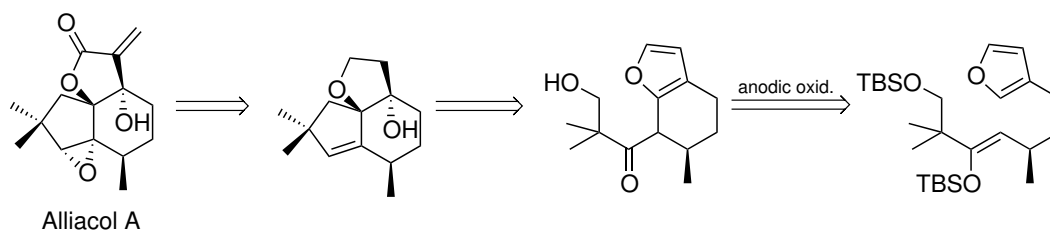
Figure 7.1.: Natural products containing tricyclic lactones.

The products of the alliacol family were isolated from the fungus *Marasmius alliacus*[77, 78]. It has been shown that these molecules display a moderate antimicrobial activity and have antitumoral properties.[78] The first syntheses have been achieved in 1988 by Landsbury[79]. They used the double addition of dilithium carboxylates as a key step in their synthesis (Scheme 7.2).



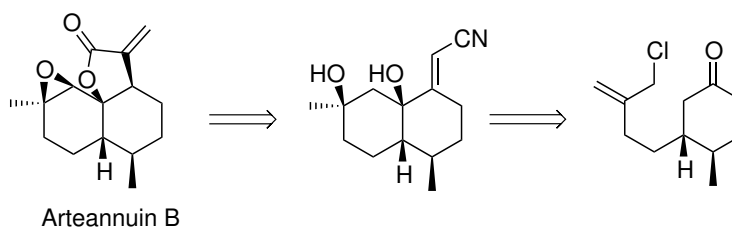
Scheme 7.2: Racemic synthesis of Alliacol A by Lansbury.

In 2004 the first asymmetric synthesis of (-)-alliacol A has been described by Moeller.[80] They used an anodic oxidation as key step to form the tricyclic system (Scheme 7.3).



Scheme 7.3: Enantiomeric synthesis of Alliacol A by Moeller.

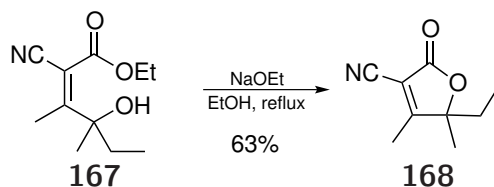
Arteannuin B was isolated in 1977 from the plant *Artemisia annua L.*[81] which is used in traditional chinese medicine since a long time. It was shown that several products extracted from the plant, including Arteannuin B, show significant antitumoral behavior.[82] The first synthesis of this compound was achieved by Lansbury.[83] They used an intramolecular alkoxyhydride reduction of the unsaturated nitrile followed by hydrolysis for the formation of the lactone (Scheme 7.4). The decaline system was constructed through intramolecular enolate alkylation.



Scheme 7.4: First synthesis of Arteannuin B by Lansbury.

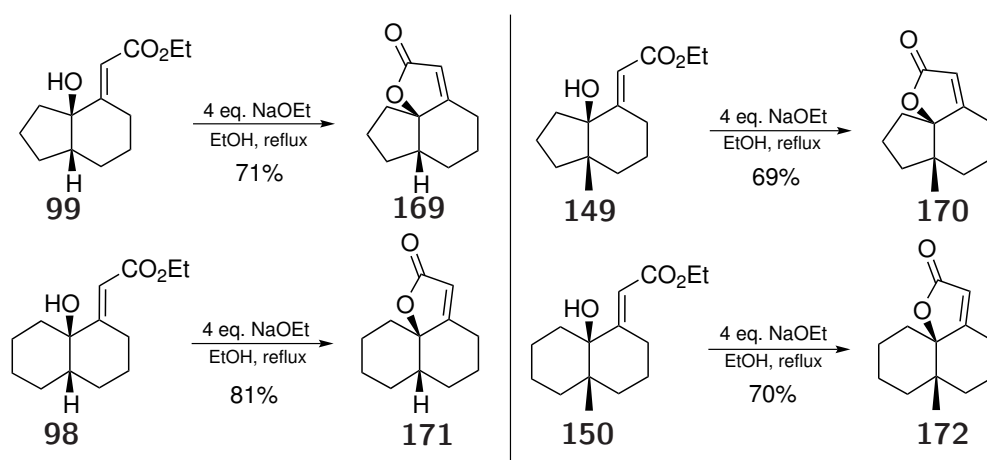
7.1. Lactonization reactions

In search of a suitable base for our lactonization reaction we became aware of the work of Villemin *et al.* They showed that the transformation of **167** into lactone **168** can be achieved easily using sodium ethoxide (NaOEt) as base (Scheme 7.5).[84]



Scheme 7.5: Lactonization performed by Villemin *et al.*

We were pleased to find that the use of NaOEt was a good choice for our substrate too. Substrates bearing a 5-6- (**99** and **149**) or 6-6-membered ring system (**98** and **150**) could be transformed into the desired lactones in good yields. Thus, the tricyclic lactones bearing a 5-6-5-ring system **169** and **170** as well as the tricyclic lactones **171** and **172** with a 6-6-5 membered ring system could be obtained (Scheme 7.6).



Scheme 7.6: Lactonization reaction of γ -hydroxy α,β -unsaturated esters with a 5-6- and a 6-6-membered ring system.

We were glad to obtain a X-ray structure for product **172** (Figure 7.2). This allowed us to confirm the structure for the obtained lactones.

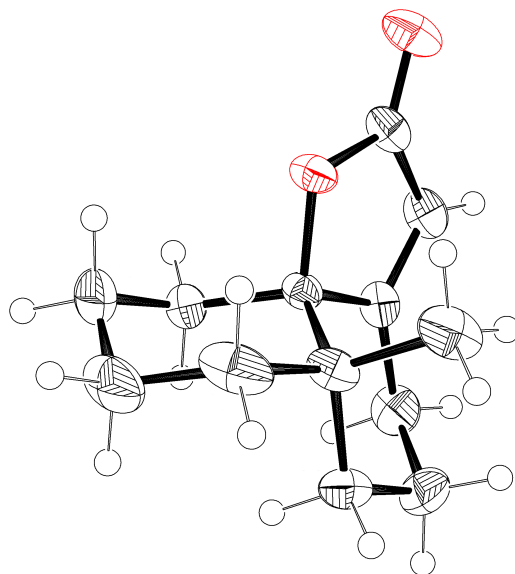
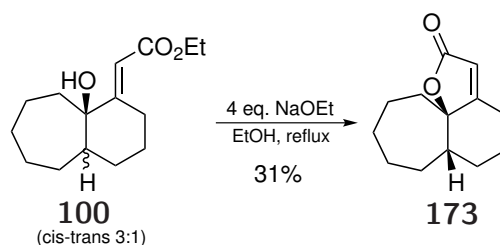


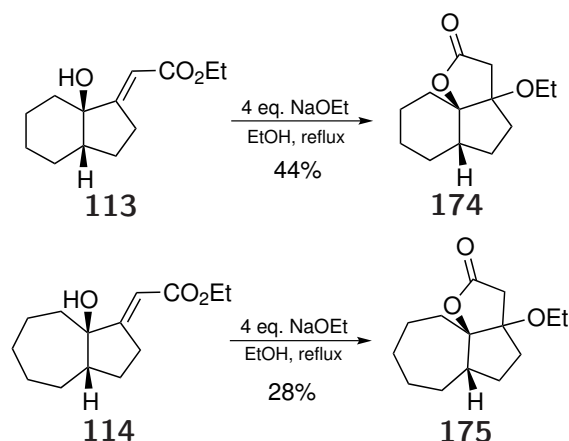
Figure 7.2.: X-ray structure of compound **172**. Ortep view at the 30% probability level..

When the 7-6-membered ring substrate **100** was submitted to these conditions we obtained the lactone **173** in only 31 % yield (Scheme 7.7). This relatively low yield may be due to the fact that the starting material was used as *cis-trans*-mixture. As confirmed by NMR-spectroscopy, only the *cis*-configured starting material undergoes lactonization to yield *cis*-configured lactone **173**.



Scheme 7.7: Lactonization reaction of γ -hydroxy α,β -unsaturated esters with a 7-6-membered ring system.

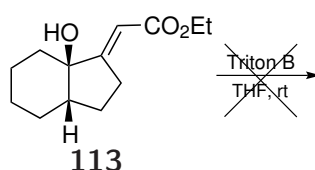
Performing the same lactonization reactions with substrates **112-114** and **147-148** possessing a 5-5-, 6-5-, 7-5-membered ring system different results were obtained. For the substrates **113** and **114**, the formation of saturated lactones **174** and **175** is observed (Scheme 7.8). Other substrates bearing a [n.3.0]bicyclic system only led to degradation of the starting material. It should be noted that the products **174** and **175** are only obtained after prolonged reaction times (48h in contrast to 14h).



Scheme 7.8: Lactonization reaction of γ -hydroxy α,β -unsaturated esters with a 6-5- and 7-5-membered ring system.

The formation of **174** and **175** can be explained by an 1,4-addition of ethanolate on the unsaturated system, probably prior to lactonization.

When **113** was treated with Triton B as non-nucleophilic base, no reaction was observed (Scheme 7.9).

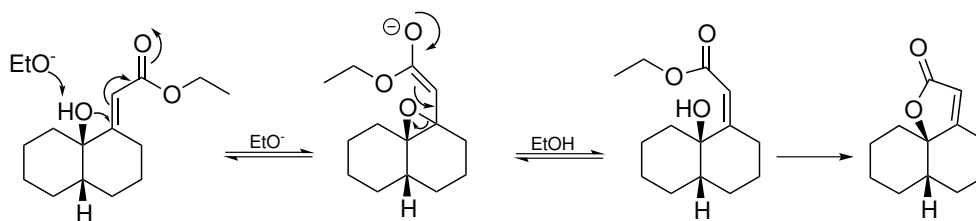


Scheme 7.9: Lactonization reaction of γ -hydroxy α,β -unsaturated esters with a 7-6-membered ring system.

7.2. Proposed mechanism

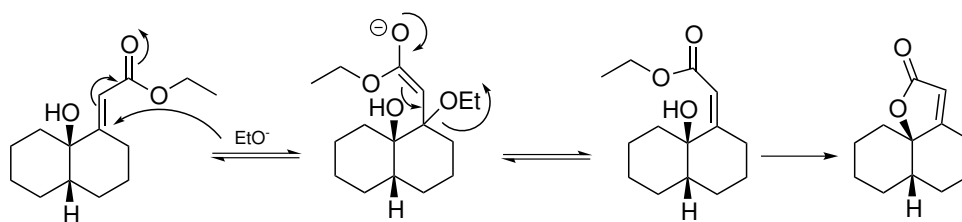
The crystal structures obtained for γ -hydroxy α,β -unsaturated esters **149** and **150** (Figure 5.1) show that the configuration of the double bond is *E*. The structure obtained for lactone **172** (Figure 7.2) shows that the configuration of the double bond has changed from *E* to *Z*. So there has to be an inversion of the double bond configuration during the lactonization reaction.

There are in principle three possibilities for the inversion which can be imagined. First, one can imagine an intramolecular epoxide formation-opening sequence after deprotonation of the alcohol function by the base (Scheme 7.10).



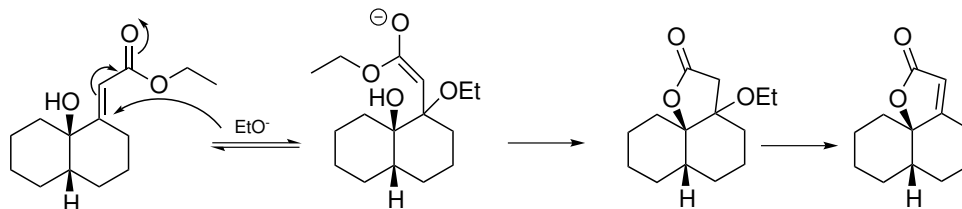
Scheme 7.10: Inversion of the double bond via an epoxide-intermediate.

A second possibility is a Michael-retro-Michael sequence. 1,4-addition of ethanolate would yield the formation of a tetraedric intermediate. Subsequent bond rotation and ethanolate elimination would furnish the *Z*-configured double bond (Scheme 7.11).



Scheme 7.11: Inversion of the double bond via a Michael-retro-Michael sequence.

Another possibility is that the lactonization takes place directly after the Michael addition of the ethanolate. Once the lactonization has occurred, retro-Michael reaction gives the unsaturated lactone (Scheme 7.12).



Scheme 7.12: Inversion of the double bond via a Michael-retro-Michael sequence.

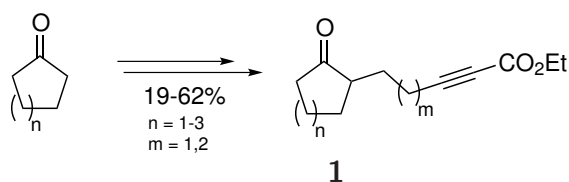
With the results obtained for the lactonization of the [n.3.0]bicyclic substrates, this latter reaction pathway seems to be the most probable. This is supported by the findings of products **174** and **175** where ethanolate has added in 1,4-fashion to the α,β -unsaturated ester.

The reaction with Triton B also indicates that the reaction proceeds via a Michael-retro-Michael sequence. Triton B should be able to deprotonate the alcohol function in γ -hydroxy α,β -unsaturated esters to initiate the epoxide sequence. In contrast, an isomerization via the Michael-retro-Michael sequence seems to be less likely with Triton B.

8. Summary

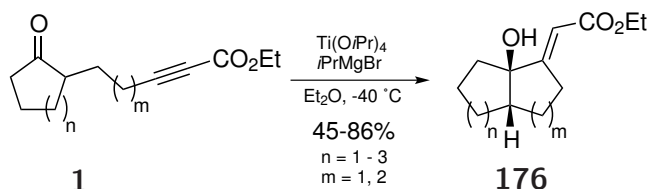
During our work we could show that acetylenic ω -ketoesters are suitable substrates for reactions under Kulinkovich conditions. The reaction with a low valent titanium reagent enlarges the reaction scope of acetylenic ω -ketoesters.

Acetylenic ω -ketoesters can be synthesized in 4 steps from commercially available cyclic ketones in overall yields of 19-62 %.



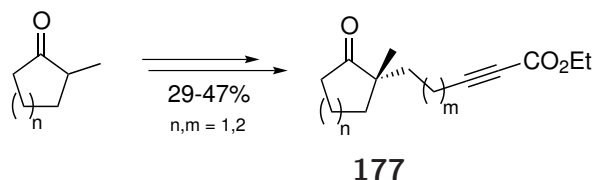
Scheme 8.1: Synthesis of acetylenic ω -ketoesters **1**.

The reaction of acetylenic ω -ketoesters **1** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$ yields bicyclic compounds **176** in high yields and complete selectivity concerning the ring junction and the configuration of the double bond. Compounds **176** were obtained with a *cis* ring junction and a *E* double bond.



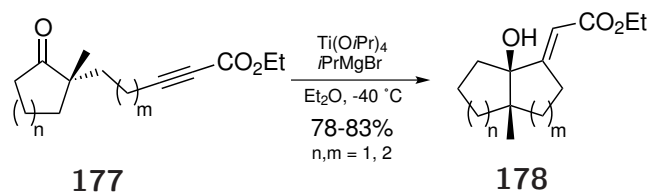
Scheme 8.2: Reaction of acetylenic ω -ketoesters **1** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$.

The reaction scope was enlarged to enantiomerically enriched acetylenic ω -ketoesters **177**. These compounds are accessible via the asymmetric alkylation of α -methyl ketones and subsequent side chain transformation.



Scheme 8.3: Synthesis of enantiomerically enriched acetylenic ω -ketoesters **177**.

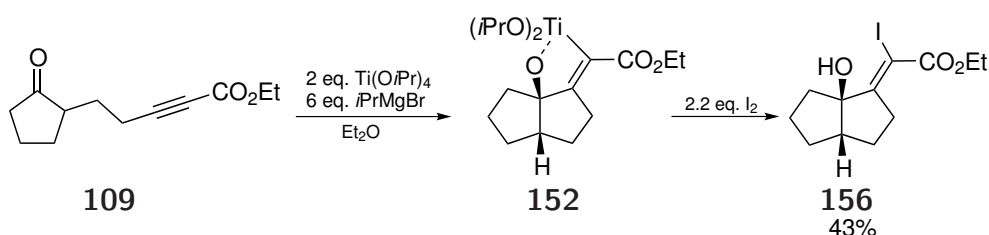
The reaction of the enantiomerically enriched substrates equally yields in the formation of a single compound **178** without racemization.



Scheme 8.4: Reaction of enantiomerically enriched acetylenic ω -ketoesters **177** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$.

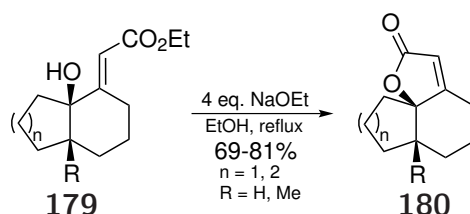
The structure of the bicyclic compounds was unambiguously proven by the crystal structures of compounds **149** and **150** confirming the *cis* ring junction and the *E* double bond.

During the reaction a ligand exchange reaction between the titanium reagent employed and the alkyne occurs, followed by an insertion reaction to form a titanacycle as intermediate. This intermediate can be trapped by the addition of iodine as shown for the example of compound **156** which is formed in 43 % yield.



Scheme 8.5: Formation of bicyclic vinyl iodide **156** from **109**.

The obtained hydroxy-esters can be employed in lactonization reactions. Submitting compounds **179** to NaOEt in refluxing ethanol yields in the formation of tricyclic lactones **180** with good yields. The structure of the lactones was confirmed by X-ray crystallography of compound **172**. Experimental results suggest that the necessary double bond inversion is obtained through a Michael-retro-Michael-sequence prior to lactonization.



Scheme 8.6: Formation of tricyclic lactones **180**.

Finally, it can be stated that starting from readily available acetylenic ω -ketoesters we were able to synthesize tricyclic lactones with complete diastereoselectivity and without racemization if enantiomerically enriched starting materials are employed. The tricyclic lactones obtained represent the core skeleton of a group of bioactive natural products as shown by representative examples below.

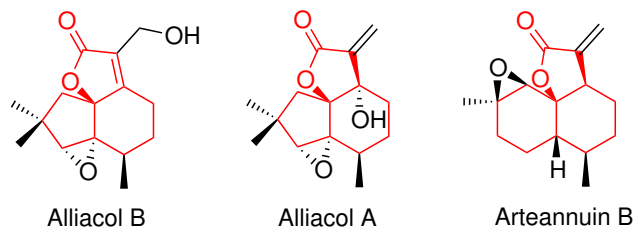


Figure 8.1.: Natural products containing tricyclic lactones.

Part II.

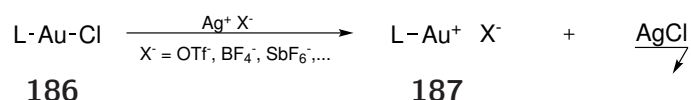
Noble metal catalyzed
cycloisomerizations of ω -keto
alkynes and acetylenic ω -ketoesters

this relativistic effects, which have to be considered for heavy elements, the energy of the frontier orbitals changes. In the case of gold, the 6s-orbitals is contracted and thus its energy lowered.[89] As this is the LUMO, lowering its energy yields in an increase of Lewis acidity. As a consequence of the contraction of the 6s-orbital, the 5d-orbitals are subjected to an expansion and a rise in energy occurs. This offers the possibility of "back-donation" from the metal to the ligand[90] which can stabilize cationic reaction intermediates. This diffusion of the 5d-orbitals makes the gold-ion a soft acid according to the HSAB concept[91] which has a preference to coordinate to soft bases like multiple bonds. This preference to coordinate multiple bonds has been quantified by calculations of Yamamoto which show that the heat of formation of gold multiple bond complexes is higher than that of gold-heteroatom complexes.[92]

9.1. Gold-complexes and their synthesis

In addition to simple gold salts like AuCl or AuCl₃ a large array of gold-complexes showing higher reactivity and selectivity has been synthesized and applied in catalysis.

Most gold complexes are synthesized from gold chlorides and thus obtained with a chloride as a counterion. While Au(III)-chloride-complexes can be used directly, Au(I)-chloride-complexes need to be activated to be effective catalysts. This is achieved by exchanging the chloride into a less coordinating counterion and generating a more cationic gold-center. This activation is often done *in situ* by the addition of a silver salt with a low coordinating counterion as for example TfO⁻, BF₄⁻ or SbF₆⁻ (Scheme 9.3). The catalytic active species **187** is formed together with AgCl, which precipitates.



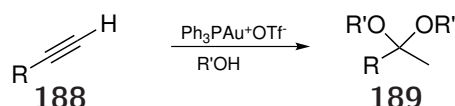
Scheme 9.3: Activation of Au-complexes by addition of silver salts.

A drawback of this method is that most of the silver salts commonly used are hygroscopic and light sensitive and hence not easy to handle. In addition to this practical point of view it has been shown recently that the silver salt formed is not innocent in the reaction. Shi *et al.* showed that the silver salts not only play a "supporting role" but have large impact on some transformations which do not proceed under silver-free gold-catalysis.[93] To circumvent these problems, two classes of air and moisture stable gold complexes have been developed. Gagosz *et al.* proposed the use of bistriflimidate ion as counterion[94, 95] whereas Echavarren *et al.* used the SbF₆⁻ counterion and a stabilizing nitrile group.[96]

9.2. Addition of O-nucleophiles to activated alkynes

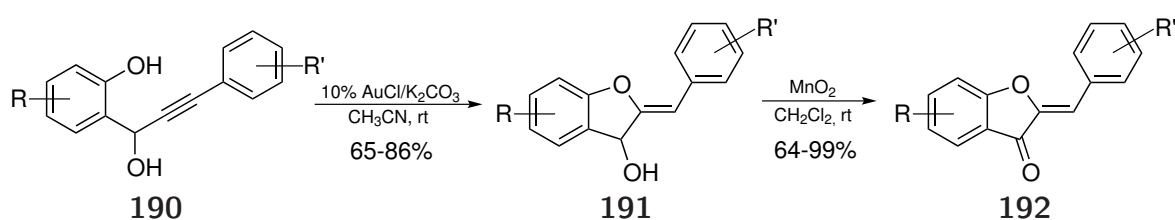
A large variety of oxygen nucleophiles have been described for the addition to alkynes activated by triple bonds, amongst others water, alcohols, carbonyl compounds etc. As a detailed study would go beyond the scope of this work, only a selection of examples is given.

Pioneering work on the addition of alcohols to alkynes activated by gold(I)-complexes has been done by Teles *et al.* They showed the effective formation of acetals **189** starting from alkynes (Scheme 9.4).[88]



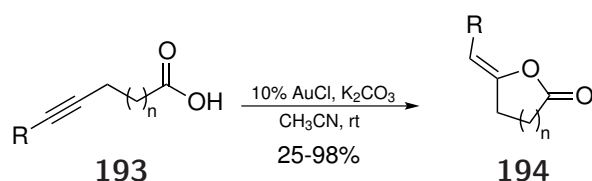
Scheme 9.4: Addition of alcohols to alkynes activated by gold(I)-complexes.

Pale *et al.* investigated the intramolecular addition of a hydroxy group to an alkyne. When compounds **190** were treated with $\text{Ph}_3\text{PAuOTf}/\text{K}_2\text{CO}_3$ the cyclized products **191** were obtained in good yields (Scheme 9.5). Compounds **191** could be transformed into the corresponding aurones **192** by MnO_2 oxidation.[97]



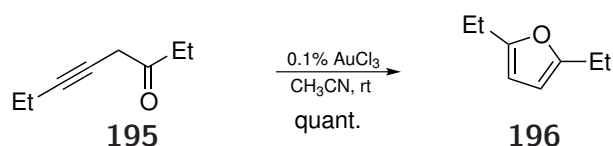
Scheme 9.5: Formation of aurone precursors **191** by Pale *et al.*

The same group also described the intramolecular cyclization of carboxylic acids onto alkynes under Au(I) catalysis.[98] Cyclic lactones **194** are formed in good yields when ω -acetylenic acids are treated with 10 % AuCl in the presence of a base (Scheme 9.6).



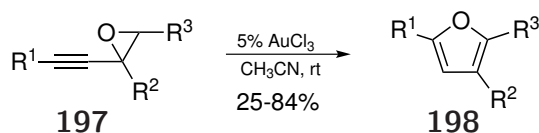
Scheme 9.6: Formation of lactones by intramolecular addition of carboxylic acids to alkynes.

Hashmi *et al.* showed that propargylic ketones can be used in gold catalysis.[99] Ketone **195** was successfully transformed into furan **196** under mild conditions in quantitative yield (Scheme 9.7).



Scheme 9.7: Formation of furan **196** through cyclization of ketone **195**.

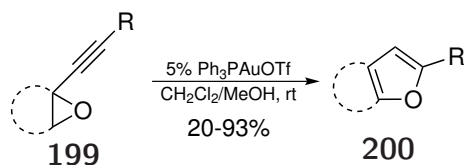
Another possibility for the synthesis of furans uses alkynyl epoxides as substrates. Hashmi *et al.* used AuCl_3 as catalyst for the transformation of epoxides **197** into furans **198** (Scheme 9.8).[100]



Scheme 9.8: Formation of furans **198** from epoxides.

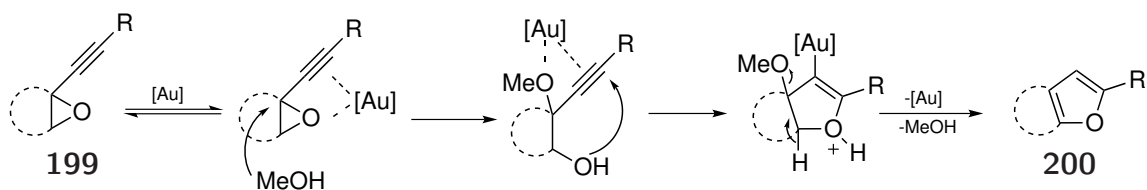
The proposed mechanism involved an activation of the triple bond by the gold-complex, followed by attack of the epoxide to form the 5-membered heterocycle which gives the furan after aromatization and demetalation.

Pale *et al.* started from similar substrates **199** using a gold(I)-catalyst. Furans **200** are obtained in good yields (Scheme 9.9).



Scheme 9.9: Formation of furans **200** by Pale *et al.*

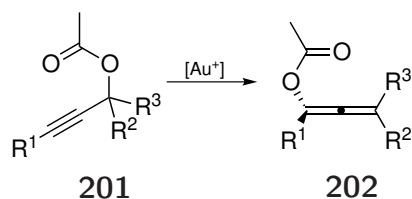
A revised mechanism is proposed for this transformation based on observed reaction intermediates. Concomitant activation of the triple bond and the epoxide by the catalyst, followed by epoxide opening through MeOH, led to the formation of an alcohol which undergoes cyclization to the triple bond. MeOH elimination and demetalation furnished the furans **200** (Scheme 9.10).[101]



Scheme 9.10: Revised mechanism for the formation of furans **200** by Pale *et al.*

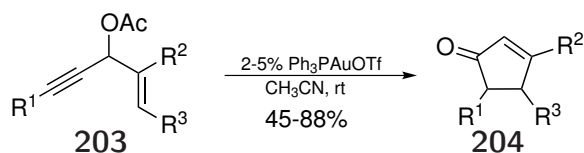
When propargylic esters like **201** are submitted to gold(I)-complexes the isomerization into allenes **202** can be observed (Scheme 9.11).[102] During this isomerization

the ester group migrates along the molecule. The allene can thereby be formed via a 1,2- or a 1,3-migration.



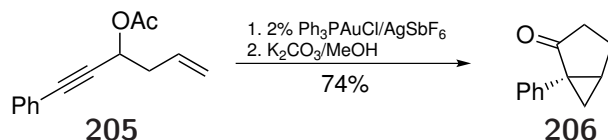
Scheme 9.11: Isomerization of propargylic esters into allenes.

When the reaction is performed in the presence of a suitable nucleophile, the gold intermediate can be trapped. With alkenes as nucleophiles cyclopentanones can be formed.[103, 104] Toste *et al.* showed that when the ester is in allylic position to the double bond, α,β -unsaturated cyclopentanones **204** are obtained (Scheme 9.12).[104]



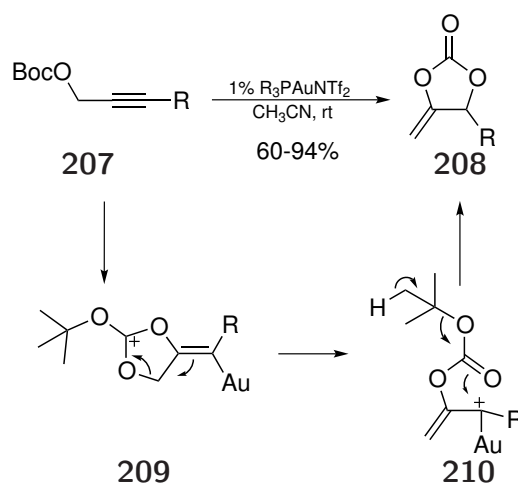
Scheme 9.12: Formation of α,β -unsaturated cyclopentanones **204** by Toste *et al.*

When homoallylic ester **205** is used as substrate, Fürstner *et al.* showed that bicyclic cyclopentanones **206** are obtained under gold(I)-catalysis.[103]



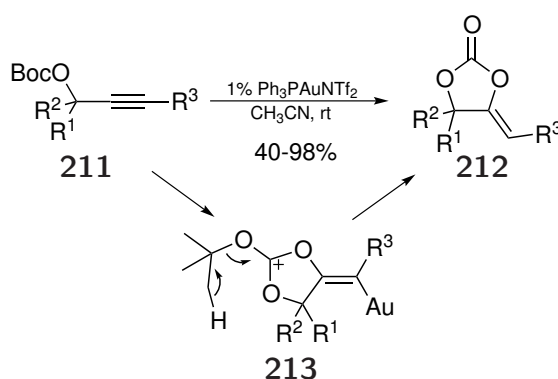
Scheme 9.13: Formation of bicyclic cyclopentanones **206** by Fürstner *et al.*

Gagosz *et al.* showed that this type of rearrangement is not limited to esters but also proceeds with carbonates.[105] When Boc-protected propargylic alcohols **207** are treated with gold(I), the 1,3-dioxolan-2-ones **208** are obtained. The reaction pathway depends on the nature of the alkyne substituent. Gold(I) activation of the alkyl-substituted triple bond in compound **207** promotes the formation of a stabilized cationic gold species **209** which undergoes ring opening to afford stabilized allylic cation **210**. Cyclization followed by fragmentation of the *tert*-butyl group and protodemetalation provides cyclic carbonate **208** (Scheme 9.14).



Scheme 9.14: Formation of 1,3-dioxolan-2-ones **208**.

When the triple bond is a terminal one or substituted by electron-withdrawing substituents (**211**), compounds **212** are obtained (Scheme 9.15). In this case, fragmentation of the *tert*-butyl group in stabilized cationic gold species **213** followed by demetallation furnishes cyclic carbonate **212**.

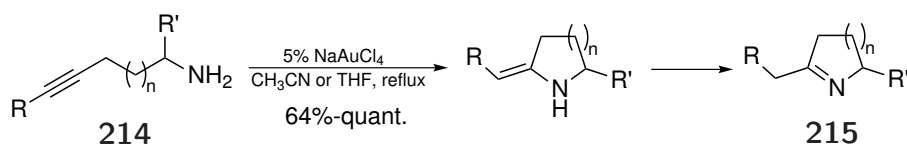


Scheme 9.15: Formation of 1,3-dioxolan-2-ones **212**.

9.3. Addition of N-nucleophiles to activated alkynes

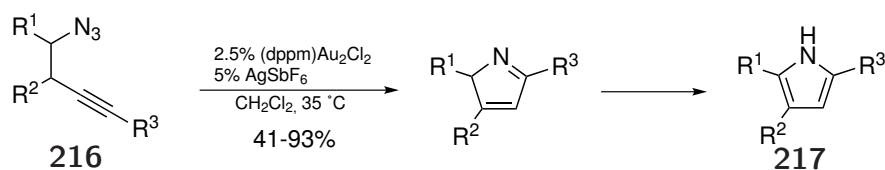
As for the reaction of oxygen-nucleophiles, a large variety of nitrogen-centered nucleophiles are capable of adding to activated triple bonds. Some examples are given in the following section.

The group of Utimoto could show that using a simple gold(III)-catalyst, the intramolecular addition of amines to triple bonds is possible. The product formed undergoes *in situ* double bond isomerization to form dihydropyrroles/tetrahydropyridines **215** (Scheme 9.16).[106, 107]



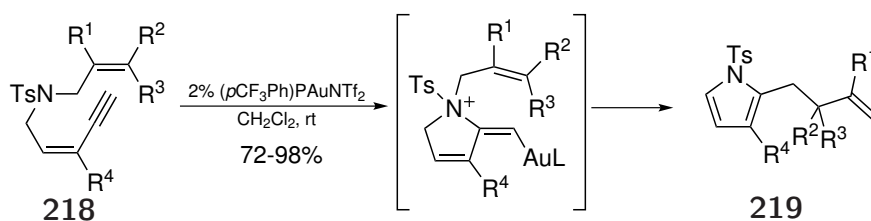
Scheme 9.16: Formation of dihydropyrroles/tetrahydropyridines **215** by Utimoto *et al.*

Toste *et al.* showed that azides **216** can be used as substrates to form pyrroles **217** under gold(I)-catalysis.[108] The reaction proceeds under loss of nitrogen and *in situ* isomerization of the primarily formed 2H-pyrroles into 1H-pyrroles **217** (Scheme 9.17).



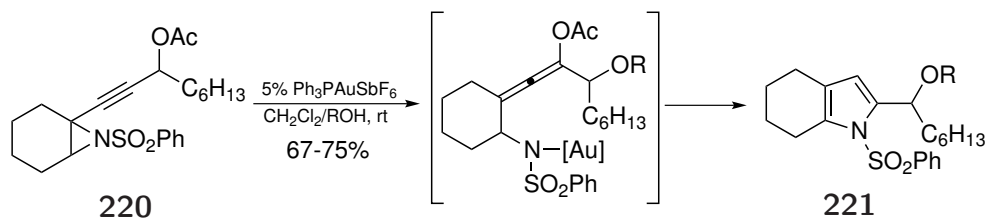
Scheme 9.17: Formation of pyrroles **217** by Toste *et al.*

The group of Gagosz developed a method for the synthesis of functionalized pyrroles from tertiary amines. During this transformation, the starting material **218** undergoes a gold(I)-catalyzed cyclisation followed by an aza-Claisen-type rearrangement to form pyrroles **219**. [109]



Scheme 9.18: Formation of pyrroles **219** by Gagosz *et al.*

Pale *et al.* used aziridine **220** for the synthesis of substituted pyrroles **221**. [110] The mechanism of the reaction is thought to pass through a 1,2-acyl-migration with aziridine opening followed by a nucleophilic substitution to give the allenic intermediate. After cyclization and elimination of AcOH, the substituted pyrrole **221** is formed (Scheme 9.19).



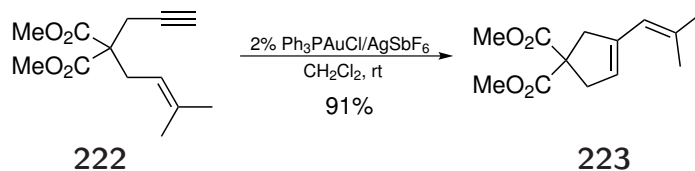
Scheme 9.19: Formation of substituted pyrroles **221** by Pale *et al.*

9.4. Skeletal rearrangement and addition of C-nucleophiles to activated alkynes

What is true for heteroatom-nucleophiles in gold chemistry also applies to carbon nucleophiles. A large variety of different nucleophiles can be used. In the following section, a selection of reactions will be discussed.

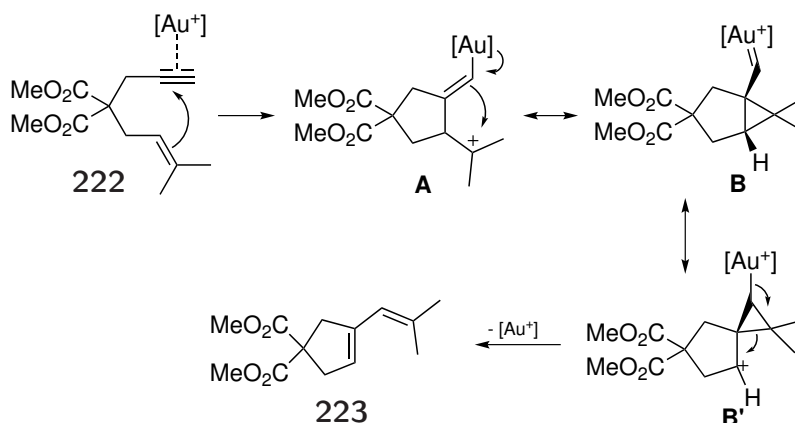
9.4.1. Enyne rearrangements

When unsaturated carbon-carbon bonds are used as nucleophiles in intramolecular reaction with activated alkynes, one obtains the product of a cycloisomerization reaction. Enynes with different spacers between the alkyne and the alkene can be used. An example from the group of Echavarren using an 1,6-enyne is shown in Scheme 9.20.[111] Compound **222** can be transformed into diene **223** under mild conditions in high yield.



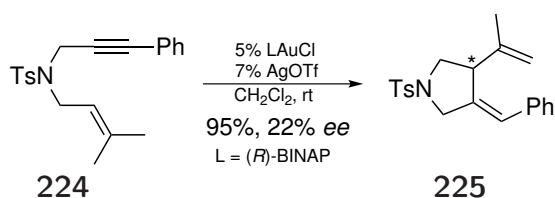
Scheme 9.20: 1,6-enyne rearrangement to form diene **223**.

The mechanism of the reaction is described in Scheme 9.21. First, cyclic intermediate **A** is formed through attack of the alkene to the activated alkyne. Facilitated by the "back-donation" ability of gold[90] the carbene-like intermediate **B** can be formed. Rearrangement via its canonical form **B'** and demetalation give finally compound **223**.



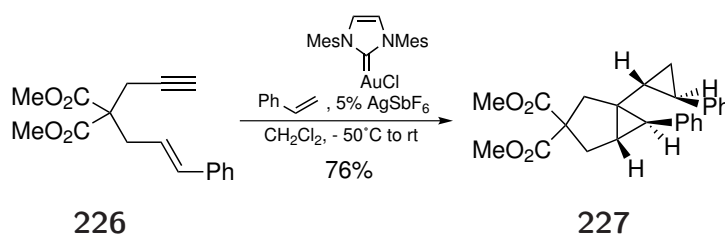
Scheme 9.21: Proposed mechanism for 1,6-enyne rearrangement to form diene **223**.

The group of Chung showed that such cycloisomerizations can be performed when heteroatoms are incorporated in the carbon chain as illustrated with compound **224**. When the reaction is performed with a chiral ligand, the diene **225** can be obtained with low enantiomeric excess (Scheme 9.22).^[112]



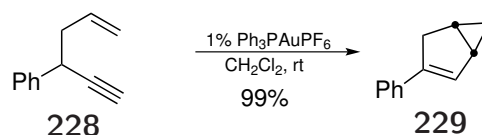
Scheme 9.22: Enantiomeric 1,6-enyne rearrangement to form diene **225**.

Echavarren *et al.* showed that the carbene-like intermediates of the 1,6-enyne rearrangement (**B** in Scheme 9.20) can be trapped when for example styrene is added to the reaction mixture. The gold-carbene intermediate undergoes cyclopropanation reaction with styrene to form compound **227** (Scheme 9.23).^[113]



Scheme 9.23: 1,6-enyne rearrangement with trapping of the intermediate by styrene.

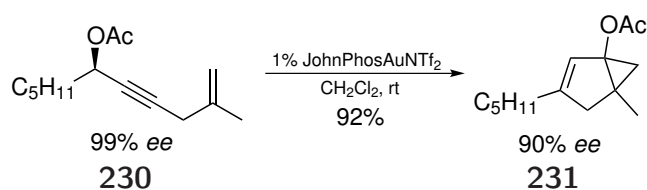
Bicyclo[3.1.0]hexenes can equally be obtained from the rearrangement of 1,5-enynes as demonstrated for example by Toste *et al.* by the synthesis of **229** in quantitative yield (Scheme 9.24).^[114]



Scheme 9.24: Formation of bicyclo[3.1.0]hexenes through 1,5-enyne rearrangement.

Gagosz could show that this type of reaction is strongly substrate dependent. Different products like bicyclohexenes, cyclopentenenes, cyclohexadienes or enals can be obtained depending on the substitution of the enyne.[115]

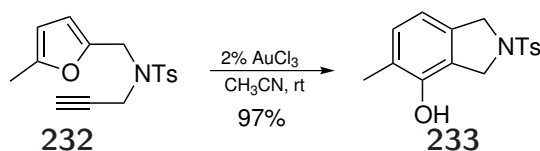
The group of Gagosz demonstrated equally that 1,4-enynes can also be used as substrates for the synthesis of bicyclo[3.1.0]hexenes.[116] In the first step of the reaction the acetate group of **230** undergoes a 1,3-migration to form an allenic intermediate which then undergoes cycloisomerization to give bicyclo[3.1.0]hexene **231**.



Scheme 9.25: Formation of bicyclo[3.1.0]hexenes starting from 1,4-enyne **230**.

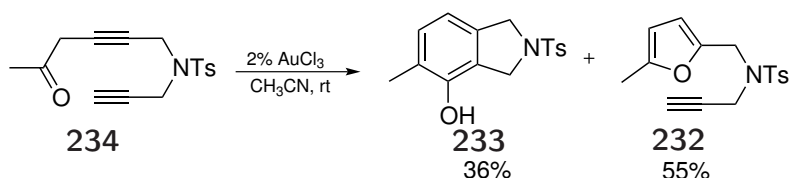
The use of enantiomeric pure substrate showed that the reaction is stereoselective as the stereochemical information was nearly completely transferred to the product.

The group of Hashmi demonstrated the use of furans as nucleophiles in enyne cycloisomerizations.[117] Furan **232** can be transformed into the phenol **233** under gold(III)-catalysis (Scheme 9.26).



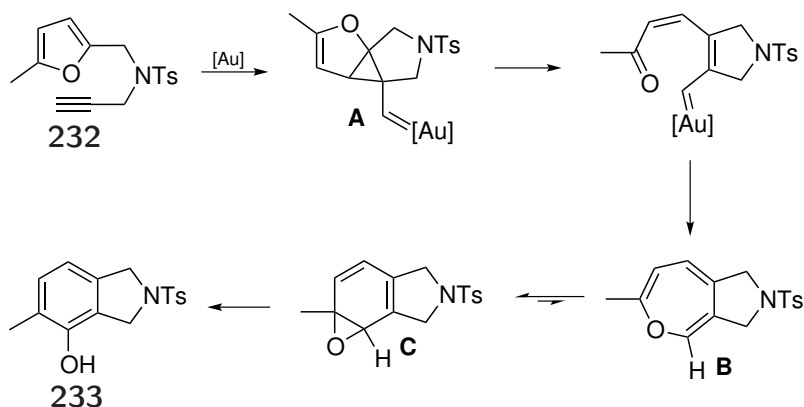
Scheme 9.26: Formation of phenols starting from furans.

The furans applied for the synthesis of phenols can themselves be obtained via gold-catalysis (see Section 9.2). Thus, starting with diynes, the one-pot formation of phenols can be achieved. With diyne **234** as starting material, the furan **232** is formed first, which reacts *in situ* to the phenol **233**. The reaction to the phenol is not complete and furan **232** was obtained as byproduct (Scheme 9.27).



Scheme 9.27: One-pot synthesis of phenol **233** starting from diyne **234**.

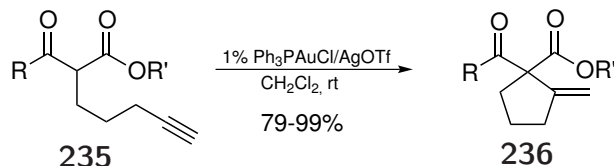
The mechanism of the transformation is thought to be the following. First intermediate **A** (Scheme 9.28) is formed through attack of the furan to the activated triple bond.[118, 119] Intermediate **A** forms **C** via **B**. The existence of **C** has been proven at low temperature.[120] Rearomatisation yields then the phenol **233**.



Scheme 9.28: Mechanistic proposal for formation of phenols starting from furans.

9.4.2. Gold-catalyzed Conia-ene reactions

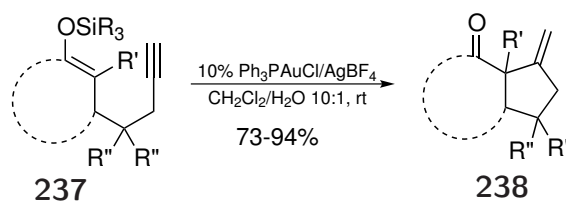
The thermal cyclization of ketones onto alkynes (Conia-ene-reaction) generates α -vinyl ketones without prior deprotonation of the substrate.[121] However, the high temperatures needed for this reaction limits its use to simple substrates.[122] Thus catalytic methods have been developed. Amongst others, gold-catalysis has been used to perform Conia-ene-type reactions. Toste *et al.* demonstrated that β -keto-esters **235** can be used for the synthesis of cyclized products **236** (Scheme 9.29).[123]



Scheme 9.29: Gold(I)-catalyzed Conia-ene-type reaction by Toste *et al.*

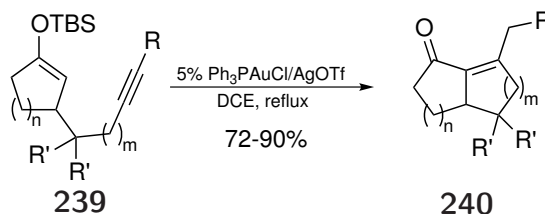
The authors state that this methodology is limited to substrates bearing a 1,3-dicarbonyl function. In order to synthesize vinylketones bearing only one carbonyl function silyl

enol ethers **237** were used as substrates. This allowed the synthesis of compounds **238** in high yields (Scheme 9.30).[124]



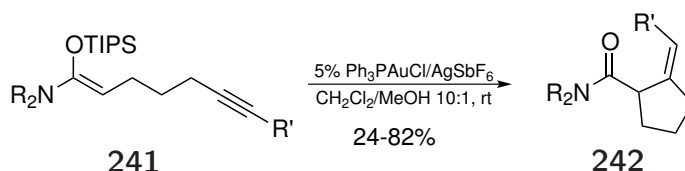
Scheme 9.30: Synthesis of cyclic vinyl ketones from silyl enol ethers by Toste *et al.*

A proton source in the reaction mixture is necessary for the reaction to perform desilylation and form the ketone functional group. Lee and Lee showed that when the substrate possesses an α -hydrogen to the ketone functional group, the reaction is possible in aprotic reaction media although higher temperatures are needed. Silyl enols **239** have been successfully transferred into bicyclic α,β -unsaturated ketones **240** (Scheme 9.31).[125]



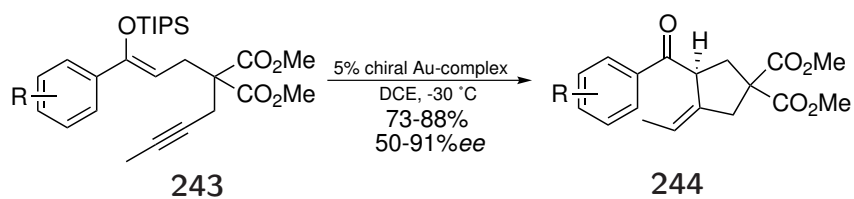
Scheme 9.31: Synthesis of bicyclic α,β -unsaturated ketones by Lee and Lee.

Shen *et al.* showed that it is possible to synthesize α -vinyl amides **242** from silyl ketene amides **241** using this methodology (Scheme 9.32).[126]



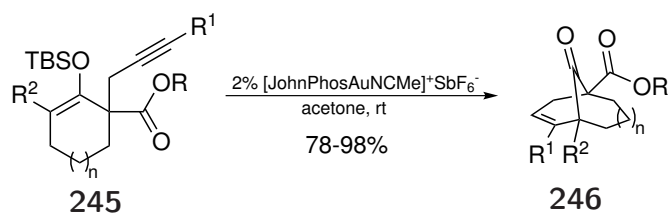
Scheme 9.32: Synthesis of α -vinyl amides by Shen *et al.*

Recently Toste *et al.* developed an enantioselective transformation of alkynyl-silyl-enol ethers.[127] The use of a chiral gold-complex in the transformation of silyl enol ethers **243** led to compounds **244** with good yields and high enantioselectivities (Scheme 9.33).



Scheme 9.33: Enantiomeric synthesis of cyclic vinyl ketones from silyl enol ethers by Toste *et al.*

The group of Barriault showed that the use of α -disubstituted silyl enol ethers **245** as substrates led to bridged compounds of type **246**.^[128] The reaction proceeds preferentially via a 6-*endo* cyclization, the product of the 5-*exo* cyclization was not observed.



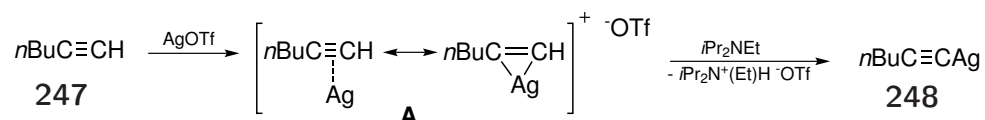
Scheme 9.34: Synthesis of bridged compounds by Barriault *et al.*

10. Introduction to silver catalyzed reactions

As is the case in gold chemistry, silver chemistry has a long history.[129] It has mainly been used for anion metathesis and oxidation reactions. With the recent advances in gold catalysis, silver has widely been used to generate more reactive species. In addition to its use as co-catalyst in many reactions, silver salts and complexes can be used as sole catalyst in various transformations. The focus of this chapter will be set on silver-catalyzed transformations involving alkynes.

10.1. C_{sp}-H functionalization

When silver salts react with terminal alkynes like **247**, the formation of silver acetylides **248** can be observed. The mechanism of this reaction has been elucidated by Pale *et al.*[130] The silver salt coordinates in a first step to the alkyne to form intermediate **A**, which can then be deprotonated by a base to form the silver acetylide (Scheme 10.1).

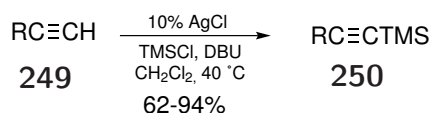


Scheme 10.1: Formation of silver acetylides.

This activation can be used for the functionalization of terminal alkynes under silver-catalysis.

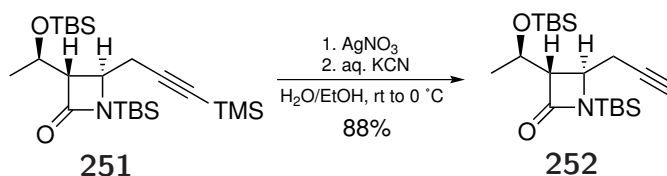
10.1.1. Functionalization of terminal alkynes

Using the ability of silver salts to activate alkynes, the protection of terminal alkynes with a TMS-group can be achieved under mild conditions as demonstrated by Yamaguchi *et al.*[131] They showed that the transformation of terminal alkynes **249** into TMS-protected alkynes **250** can be performed with a catalytic amount of AgCl using DBU as base (Scheme 10.2).



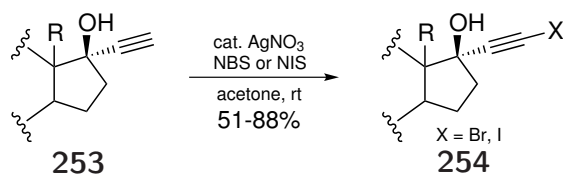
Scheme 10.2: Protection of terminal alkynes with a TMS group under silver catalysis.

Silver salts can equally be used for the deprotection of TMS-alkynes. This mild method allows the deprotection of TMS-alkynes in the presence of other silyl protecting groups as demonstrated by Ikegame *et al.*[132] They removed the TMS-group efficiently from the alkyne function of **251** to form **252** without touching the TBS-groups on nitrogen and oxygen (Scheme 10.3).



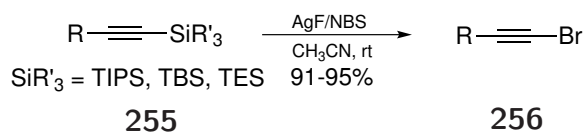
Scheme 10.3: Deprotection of TMS-alkynes under silver catalysis.

Silver salts are also used for the halogenation of terminal triple bonds. This was first demonstrated by Hofmeister *et al.* who performed bromination and iodination of 17 α -ethynyl steroids **253** under silver-catalysis (Scheme 10.4).[133]



Scheme 10.4: Halogenation of alkynes under silver catalysis.

When AgF is used instead of AgNO₃, the transformation of silyl-protected alkynes **255** into halogenated alkynes **256** can be performed in one step (Scheme 10.5).[134, 135]



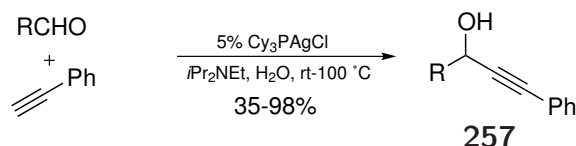
Scheme 10.5: Deprotection and bromination of alkynes under silver catalysis.

10.1.2. Addition of silver acetylides to carbonyl compounds

The silver acetylides obtained by the reaction of a terminal alkyne with a silver salt can be used for addition reactions to carbonyl compounds.

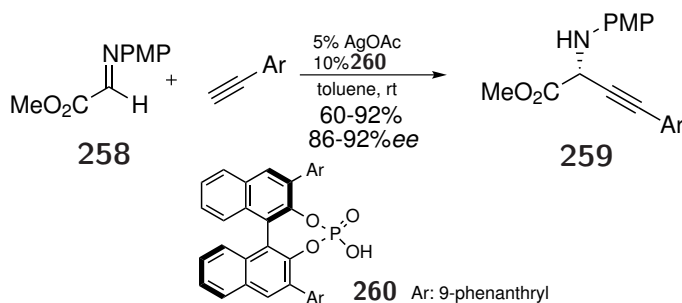
Addition to aldehydes and imines

When an aldehyde is treated with phenylacetylene in the presence of a silver-phosphine-complex and a base, the propargylic alcohols **257** resulting from the attack of the alkyne on the aldehyde can be obtained in high yields (Scheme 10.6).[136]



Scheme 10.6: Silver(I)-catalyzed formation of propargylic alcohols.

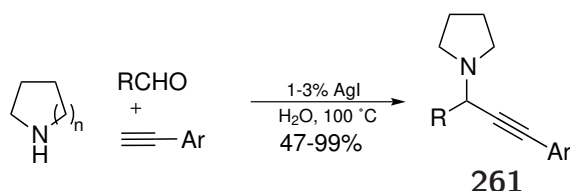
The reaction can equally be performed with imines instead of aldehydes. An enantioselective version of this reaction was presented by Rueping *et al.* Starting from PMP-substituted imine **258**, the amines **259** can be obtained in high yields and high enantioselectivities.[137] Enantioselectivity is obtained through a chiral ion-pair between the imine and **260**.



Scheme 10.7: Enantioselective formation of propargylic amines **259**.

Silver catalyzed A³-coupling

The group of Li also demonstrated the first use of silver as catalyst in aldehyde-alkyne-amine couplings (A³-couplings).[138] This reaction allows the efficient synthesis of propargyl amine derivatives. They showed that a cyclic amine, an aromatic alkyne and an aldehyde could be efficiently coupled in water to give propargylic amine **261** in high yields (Scheme 10.8).



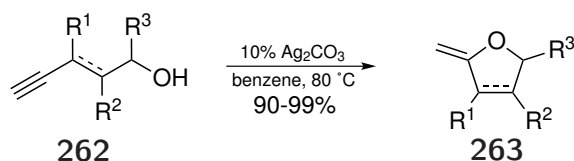
Scheme 10.8: Silver(I)-catalyzed A³-coupling by Li *et al.*

When the same reaction is performed in the presence of a phosphine, the addition of the silver acetylide to the aldehyde predominates over the A³-coupling (see Scheme 10.6).

10.2. Addition of O-nucleophiles to alkynes

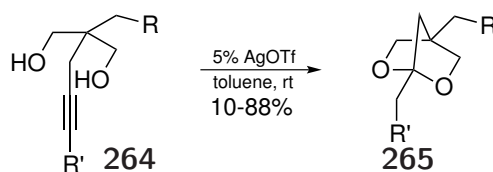
Silver salts can also be used to activate alkynes for the attack of nucleophiles. Representative examples for the attack of oxygen-nucleophiles are given below.

When alkynes with a tethered alcohol such as **262** are treated with Ag₂CO₃, the oxolane-derivatives **263** can be obtained in high yields (Scheme 10.9).[139, 140] The use of silver salts with basic counterion proved to be essential to obtain high yields for the transformation.



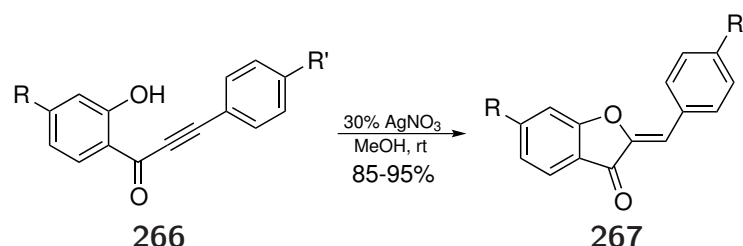
Scheme 10.9: Formation of oxolane derivatives **263** by Pale *et al.*

A double addition of two hydroxy-groups onto a triple bond was achieved by Oh *et al.*[141] Starting from diol **264**, they obtained the bridged ketals **265** in good yield in most of the cases (Scheme 10.10).



Scheme 10.10: Double OH-addition to alkynes to yield bridged ketals **265** by Oh *et al.*

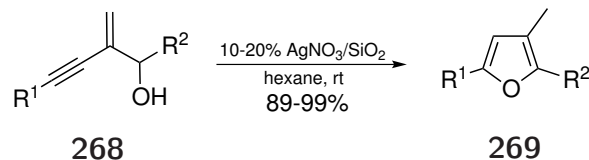
It is also possible to use phenols as nucleophiles. Jong *et al.* showed that the synthesis of aurones **267** can be achieved using **266** as starting material (Scheme 10.11).[142]



Scheme 10.11: Formation of aurones **267** by Jong *et al.*

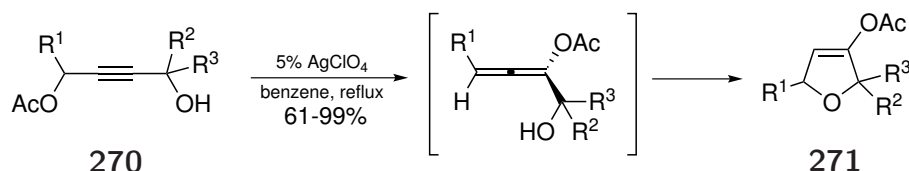
In contrast to gold-catalysis, the formation of flavones was only detected in trace amounts.

When β -alkynyl allylic alcohols **268** are used as substrates, Marshall and co-workers described the formation of substituted furans **269** (Scheme 10.12).[143]



Scheme 10.12: Formation of furans **269** by Marshall and co-workers.

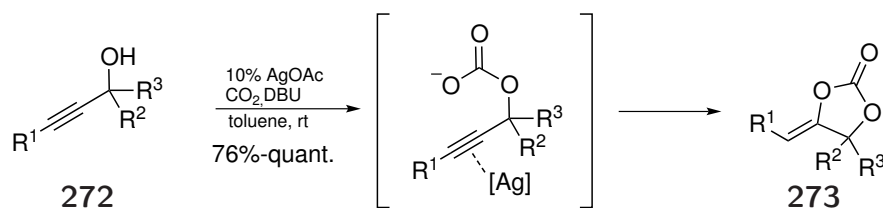
The group of Hiyama described an efficient synthesis for 2,5-dihydrofurans. Starting from monoacetylated alkyne-diols **270**, the synthesis of compounds **271** proceeds in good yields under silver-catalysis (Scheme 10.13).[144]



Scheme 10.13: Formation of dihydrofurans **271** by Hiyama *et al.*

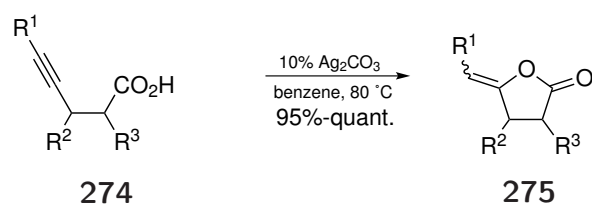
In the first step of the reaction a 1,3-migration of the acetate takes place to form the allene intermediate which then undergoes cyclization to form 2,5-dihydrofurans **271**.

The formation of cyclic carbonates was described by Yamada *et al.* starting from propargylic alcohols. In the presence of carbon dioxide and a base, propargylic alcohols **272** form first the carbonates, which then undergoes the cyclization to afford cyclic carbonates **273** in high yield (Scheme 10.14).[145]



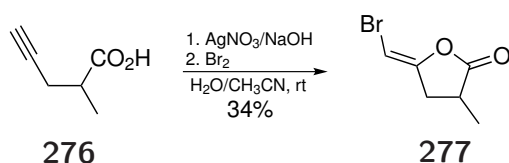
Scheme 10.14: Formation of cyclic carbonates **273**.

When carboxylic acids are used as substrates, one can obtain lactones through silver catalyzed cyclizations. Pale and co-workers described the transformation of homo-propargylic acids **274** into lactones **275** in high yield (Scheme 10.15).[139, 146]



Scheme 10.15: Formation of lactones **194** under silver catalysis.

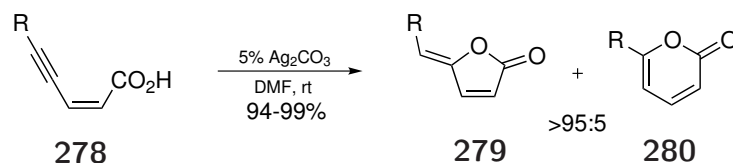
The group of Katzenellenbogen showed that it is possible to trap the silver-vinyl intermediates of such cyclization reaction with bromine. Using stoichiometric amounts of AgNO_3 , they obtained **277** from homopropargylic acid **276** (Scheme 10.16).[147]



Scheme 10.16: Formation of bromo-lactone **277** through Ag-mediated cyclization of **276**.

The authors explain the unusual formation of the *Z*-configured compound **277** via a [2+2] or [4+2] reaction between the alkyne and a silver carboxylate formed *in situ*. Taking into account the ability of Ag-salts to catalyze the formation of 1-halogeno-1-alkynes,[148] it may be possible that **277** is formed through Ag-catalyzed bromination of the alkyne followed by Ag-catalyzed cyclization of the carboxylate onto the bromoalkyne.

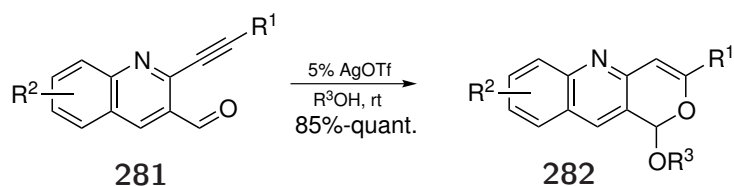
The formation of unsaturated lactones was one of the first examples of silver catalysis.[149] Unfortunately this reaction showed only a low *exo*- and *endo*-selectivity and mixtures of 5- and 6-membered lactones were formed. Negishi *et al.* improved the reaction by changing the silver salt from AgNO_3 to Ag_2CO_3 . [150] Thus, they were able to transform acids **278** into lactones **279** and **280** with ratios higher than 95:5 (Scheme 10.17).



Scheme 10.17: Synthesis of unsaturated lactones **279** and **280**.

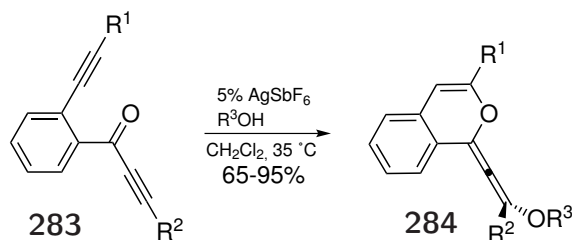
Less examples are known using aldehydes and ketones as nucleophiles in silver-catalyzed additions to triple bonds. Belmont and co-workers showed that aldehydes can be used as nucleophiles in the synthesis of furoquinolines and pyranoquinolines.[151] Aldehydes like **281** can be transformed into pyranoquinolines **282** under AgOTf -catalysis (Scheme 10.18). The oxonium-ion formed intermediately is trapped by the addition of

an alcohol. The cyclization mode changes from 5-*exo*-dig to 6-*endo*-dig when Ag₂O is used as the catalyst. Consequently, the corresponding furoquinolines can be obtained.



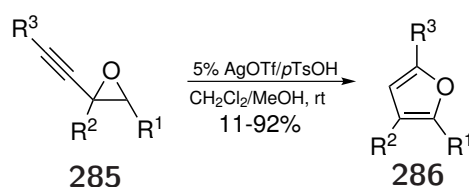
Scheme 10.18: Silver(I)-catalyzed addition of an aldehyde to an alkyne to form pyranoquinoline **282**.

A similar reaction with a ketone was obtained by Yamamoto *et al.* Reacting **283** with AgSbF₆ in the presence of an alcohol yielded in the formation of 1-allenyl isochromene **284** (Scheme 10.19).[152] The oxonium-ion which is formed first is then trapped through the 1,4-attack of the alcohol on the second triple bond to form the allene **284**.



Scheme 10.19: Silver(I)-catalyzed addition of an aldehyde to an alkyne to form isochromene **284**.

Pale *et al.* showed that epoxides can be used to form furans under silver catalysis. Starting with epoxides **285**, the synthesis of furans **286** was possible using an AgOTf/*p*TsOH co-catalyzed system (Scheme 10.20).[101, 153]

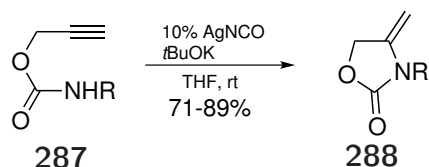


Scheme 10.20: Formation of furans **286** by Pale *et al.*

As under gold-catalysis, the authors propose the epoxide opening by methanol as first step, followed by cyclization of the generated alcohol onto the alkyne.

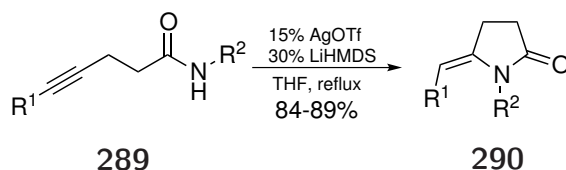
10.3. Addition of N-nucleophiles to alkynes

One of the first examples of a silver catalyzed addition of a N-nucleophile to an alkyne was reported by Tamaru and co-workers. They describe the synthesis of oxazolidinones **288** from *O*-propargylcarbamates **287** (Scheme 10.21).[154]



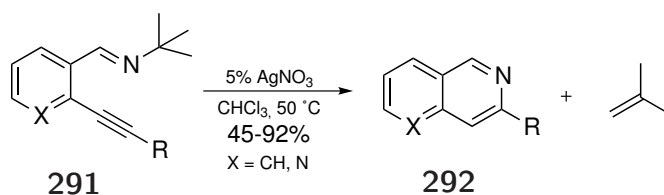
Scheme 10.21: Synthesis of oxazolidinones **288** *O*-propargylcarbamates.

The group of Nagasaka showed that butyrolactam derivatives **290** can be synthesized by the reaction of alkyne tethered amides **289** under silver-catalysis in the presence of a base (Scheme 10.22).[155]



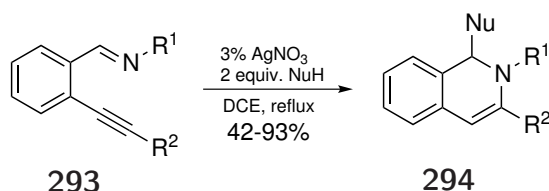
Scheme 10.22: Synthesis of butyrolactams **290** by Nagasaka *et al.*

When imines are used as nucleophiles in silver-catalyzed reaction, two types of substrates can be obtained. Larock *et al.* used *tert*-butyl substituted imines **291** to form aromatic compounds **292** (Scheme 10.23).[156] The iminium-ion formed intermediately fragments with loss of isobutene to form **292**.



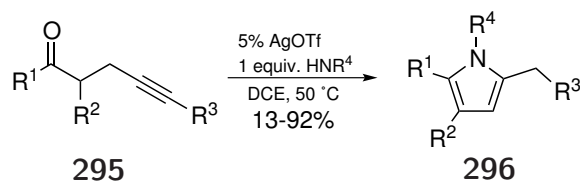
Scheme 10.23: Reaction of an imine with an alkyne under Ag-catalysis.

When the reaction is performed in the presence of a nucleophile, the iminium is trapped through the addition of the nucleophile and compounds **294** are formed (Scheme 10.24).[157]



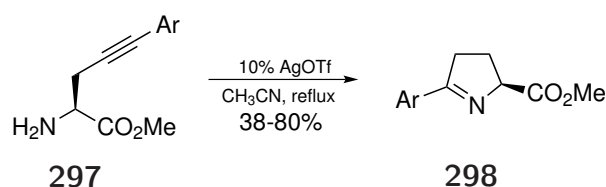
Scheme 10.24: Reaction of an imine with an alkyne under Ag-catalysis and subsequent trapping with a nucleophile.

The group of Dake showed that imines formed *in situ* from ketones **295** and an amine can be used as substrates leading to the formation of pyrroles **296** (Scheme 10.25).[158]



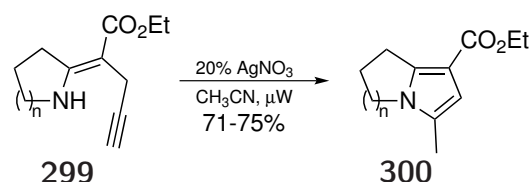
Scheme 10.25: Synthesis of pyrroles by Dake *et al.*

Rutjes *et al.* showed that homopropargylic amines derived from glycine **297** can be used to form pyrrolines **298**. [159] These pyrrolines served as precursors to 5-substituted proline analogs.



Scheme 10.26: Synthesis of substituted pyrrolines **298** as precursors for proline derivatives.

Dovey and co-workers developed the synthesis of pyrroles containing a bridgehead nitrogen. Starting from cyclic secondary amines **299** they obtained pyrroles **300** using a microwave assisted silver-catalysis (Scheme 10.27).[160, 161]

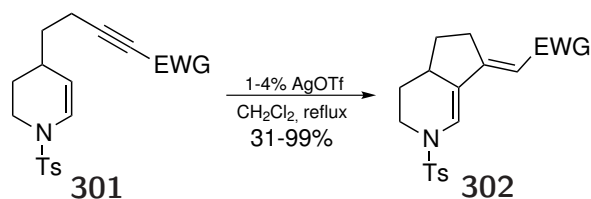


Scheme 10.27: Synthesis of pyrroles **300** containing a bridgehead nitrogen.

10.4. Addition of C-nucleophiles to alkynes

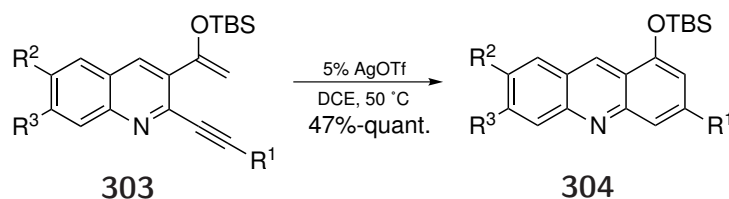
Although silver complexes are used for a variety of C–C-bond forming reactions,[148, 162–166] there are few examples for the addition of carbon nucleophiles onto alkynes.

Dake and co-workers showed that enamines such as **301** can attack the alkyne after activation through a silver complex. Thus dienes **302** are formed with the *E*-configured double bond as the major isomer (Scheme 10.28).[167] The diene can be isolated or used directly for Diels-Alder reactions in a one-pot-procedure.



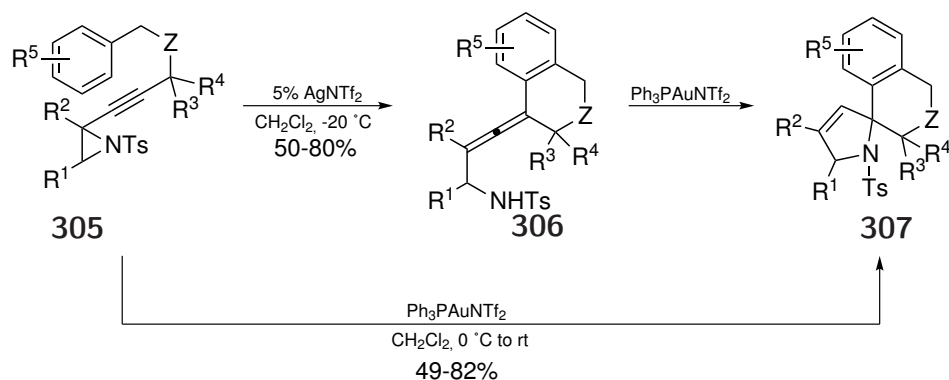
Scheme 10.28: Cyclization of an enamine onto an alkyne to form diene **302**.

The group of Belmont used enols as substrates for the addition to alkynes. When TBS-enol **303** was reacted with AgOTf, the acridine derivatives **304** can be obtained (Scheme 10.29).[168]



Scheme 10.29: Synthesis of acridines **304** by Belmont *et al.*

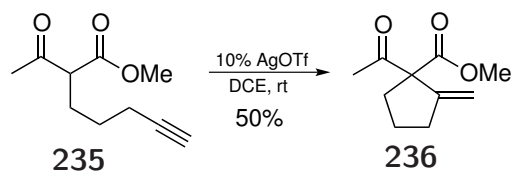
Recently, Pale and co-workers showed that the aromatic ring in **305** can add under silver-catalysis to the alkyne function to form the allene **306** after aziridine opening (Scheme 10.30).[169] Interestingly, the synthesis of **306** can be performed selectively using silver catalysis. When the reaction is performed under gold-catalysis, **306** is formed as intermediate that undergoes a second cyclization to give pyrrole **307**.



Scheme 10.30: Formation of allenes **306** and pyrrols **307** by Pale *et al.*

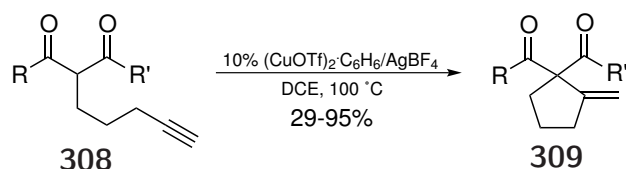
10.5. Silver-catalyzed Conia-ene reactions

During their studies on gold-catalyzed Conia-ene reactions, Toste *et al.* found that the reaction can also be catalyzed by AgOTf albeit with a lower yield compared to gold-catalysis (Scheme 10.31).[123]



Scheme 10.31: Silver(I)-catalyzed Conia-ene-type reaction by Toste *et al.*

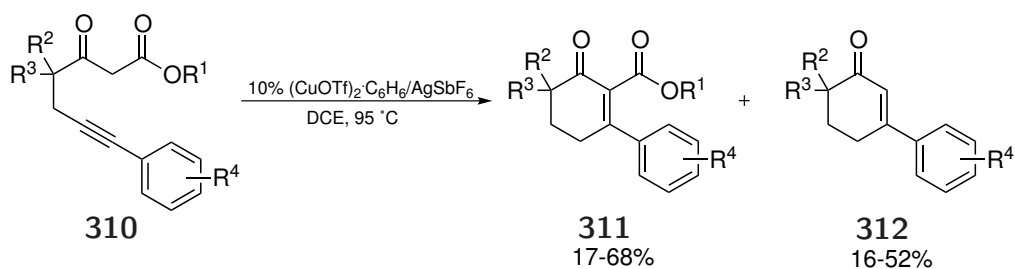
The group of Li showed that similar starting materials such as **308** can be transformed into cyclic ketons **309** in higher yield using copper/silver-cocatalysis (Scheme 10.32).[170]



Scheme 10.32: Silver(I)-catalyzed Conia-ene-type reaction by Li *et al.*

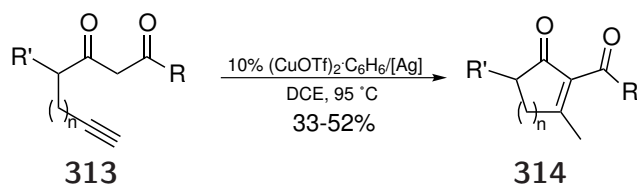
The authors state that none of the metals alone can efficiently catalyze the reaction and therefore both metals must be implicated in the reaction mechanism. One metal will coordinate to the carbonyl-functions facilitating the enol-formation while the other metal coordinates and activates the triple bond. No indication is given regarding which metal is performing which task.

The same group showed that when linear substrates like **310** are used, one can obtain a mixture of compounds **311** together with the corresponding decarboxylated compounds **312** (Scheme 10.33).[171] The cyclization occurs through a 6-*endo*-dig mode.



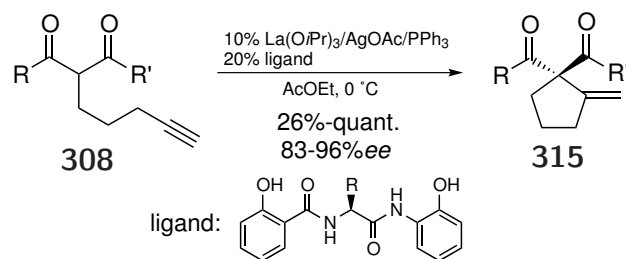
Scheme 10.33: Silver(I)-catalyzed Conia-ene-type reaction of linear substrates by Li *et al.*

When terminal alkynes such as **313** are used as substrates, one obtains the product of a 5-*exo*-dig cyclization followed by isomerization of the double bond (**314**, Scheme 10.34).[171]



Scheme 10.34: Silver(I)-catalyzed Conia-ene-type reaction of terminal linear substrates by Li *et al.*

Shibasaki *et al.* developed an asymmetric Conia-ene cyclization starting from 1,3-dicarbonyl compounds **308**. Using a silver/lanthan co-catalyzed system with a peptide derived ligand. They were able to obtain compounds **315** with good yields and high enantioselectivities (Scheme 10.35).[172]



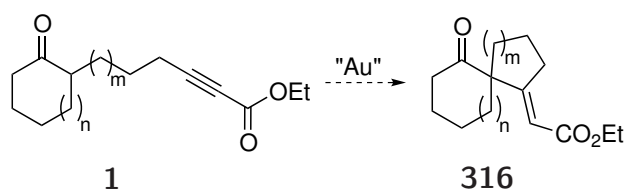
Scheme 10.35: Silver(I)-catalyzed asymmetric Conia-ene-type reaction by Shibasaki *et al.*

11. Gold(I) catalyzed cycloisomerization of ω -keto alkynes

Objective

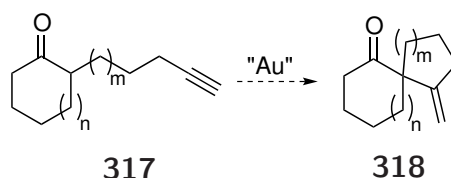
Having shown that acetylenic ω -ketoesters are good substrates for the cyclization with low valent titanium complexes to yield bicyclic allylic alcohols, we wanted to investigate their reactivity under gold catalysis. To the best of our knowledge, the reactivity of alkynoates under gold catalysis is less investigated and acetylenic ω -ketoesters like **1** are not documented. This should hopefully allow us to synthesize spirocyclic compounds **316** in a selective fashion. These molecules have already been obtained by treatment of acetylenic ω -ketoesters under basic conditions (see Chapter 1 Table 1.1, Table 1.2 and Scheme 1.1). Moreover, under these conditions mixtures of products were always obtained (*exo/endo* position and E/Z configuration of the double bond) and yields were not very high.

Keeping in mind the affinity of gold complexes for triple bonds, we were confident to obtain spirocyclic products **316** in a selective fashion and high yield (Scheme 11.1).



Scheme 11.1: Synthesis of **316** from **1** using gold catalysis.

To prove the feasibility of our strategy, we decided to simplify our substrates and use ω -keto alkynes **317** as substrates instead of acetylenic ω -ketoesters (Scheme 11.2).



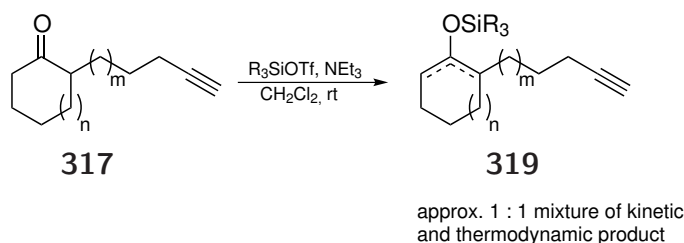
Scheme 11.2: Synthesis of **318** from **317** using gold catalysis.

11.1. Cycloisomerizations using phosphine-gold complexes

We began our investigations on gold(I)-catalyzed cycloisomerization reaction by using the conditions of Lee and Lee,^[125] which consist in the use of the catalytic system $\text{PPh}_3\text{AuCl}/\text{AgOTf}$ and silyl enol ethers as substrate.

11.1.1. Synthesis of silyl-enol ethers

As the cycloisomerization reaction we envisaged uses silyl enol ethers as substrate, we first had to transform the ω -keto alkynes into the corresponding silyl-enol-ethers **319**. This reaction was performed with the appropriate silyl triflate in the presence of NEt_3 . The yield of the reaction is in general quantitative and the products are obtained as an approximate equal mixture of kinetic and thermodynamic enol ethers where possible (Scheme 11.3).

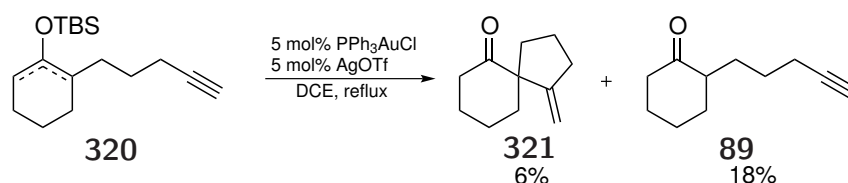


Scheme 11.3: Synthesis of TBS enol ethers **319** from ω -keto alkyne **317**.

11.1.2. TBS-enol ethers as substrates

Unsubstituted ring systems

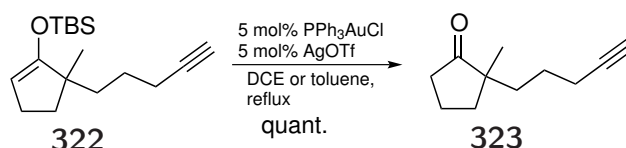
As our first substrate, we chose TBS enol ether **320** which was obtained from ω -keto alkyne **89** by reaction with $\text{TBSOTf}/\text{NEt}_3$. Treatment of **320** with $\text{PPh}_3\text{AuCl}/\text{AgOTf}$ in refluxing DCE lead to the formation of cycloisomerization product **321** in 6 % yield, together with 18 % yield of desilylated material **89** (Scheme 11.4).



Scheme 11.4: Reaction of TBS-enol ether **320** with $\text{PPh}_3\text{AuCl}/\text{AgOTf}$.

2,2-disubstituted ω -keto alkynes

We then tested whether we can synthesize bridged compounds starting from 2,2-disubstituted ω -keto alkynes. Enol ether **322** was synthesized from **323** and employed in the reaction. Neither with DCE nor with toluene as solvent a bridged compound was obtained. Under both conditions, only desilylation of the starting material was observed (Scheme 11.5).



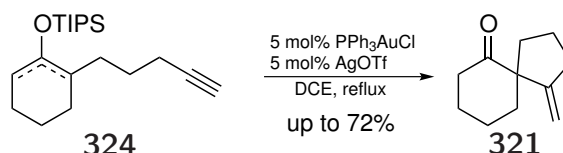
Scheme 11.5: Reaction of TBS-enol ether **322** with $\text{PPh}_3\text{AuCl}/\text{AgOTf}$.

11.1.3. TIPS-enol ethers as substrates

Having found that with the TBS-enol ether mainly desilylation of the starting material occurs, we decided to change the silyl-group of the enol ether involved in the reaction. We opted for a triisopropylsilyl (TIPS) group, which should be more stable than the TBS-group.[173]

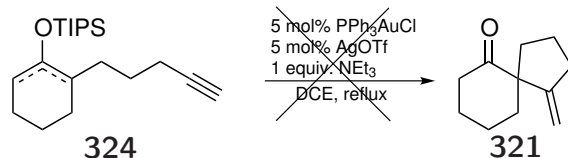
Unsubstituted ring systems

Silyl enol ethers **324** and **325** were synthesized similarly to **320** and **322**. When we submitted **324** to the reaction conditions, we were happy to find that desilylation no longer occurred and **321** was obtained in yields up to 72 % (Scheme 11.6). Unfortunately, the yield of the reaction was not reproducible.



Scheme 11.6: Reaction of TIPS-enol ether **324** with $\text{PPh}_3\text{AuCl}/\text{AgOTf}$.

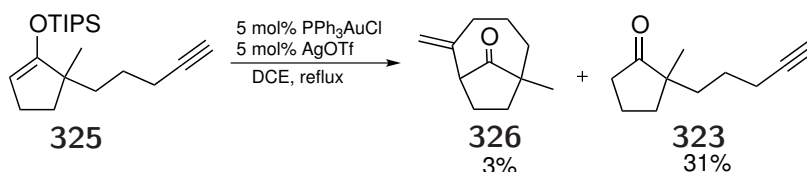
We assumed that the varying yield of the reaction might be due to a different degree of desilylation of the starting material. This may be the result of varying amounts of TfOH in the reaction mixture, formed through hydrolysis of AgOTf. When the reaction was performed in the presence of NEt_3 to avoid free TfOH, no conversion was observed and the starting material was recovered.



Scheme 11.7: Reaction of TIPS-enol ether **324** with $\text{PPh}_3\text{AuCl}/\text{AgOTf}$ in the presence of NEt_3 .

2,2-disubstituted ω -keto alkynes

2,2-Disubstituted ω -keto alkynes were also tested with a TIPS-group. TIPS-enol ether **325** was synthesized and submitted to the previously used conditions. The desired bridged compound **326** was obtained, although with a low yield of 3 %, together with 31 % of desilylated material (Scheme 11.8).



Scheme 11.8: Reaction of TIPS-enol ether **325** with $\text{PPh}_3\text{AuCl}/\text{AgOTf}$.

Given that no satisfying results were obtained with the catalytic system $\text{PPh}_3\text{AuCl}/\text{AgOTf}$, we decided to change the nature of the catalyst.

11.2. Cycloisomerizations using NHC-gold complexes

As new catalytic system we chose the *N*-heterocyclic carbene (NHC) gold complex 1,3-Bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride **327** (IPrAuCl , Figure 11.1) together with AgOTf as co-catalyst.

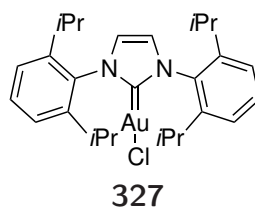
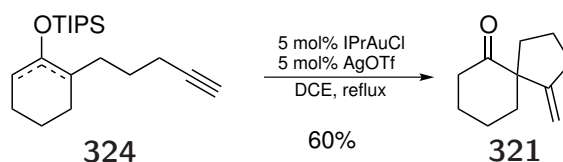


Figure 11.1.: Structure of NHC-gold complex **327**.

11.2.1. TIPS-enol ethers as substrates

Unsubstituted ring systems

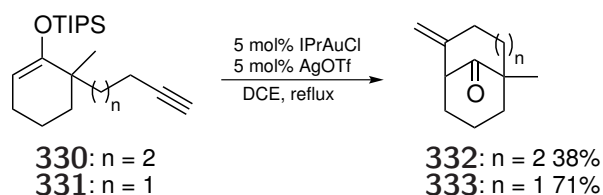
When TIPS-enol ether **324** was reacted with the new catalytic system, we were pleased to find that we could obtain the desired spirocyclic compound **321** in 60 % yield (Scheme 11.9).



Scheme 11.9: Reaction of TIPS-enol ether **324** with IPrAuCl/AgOTf.

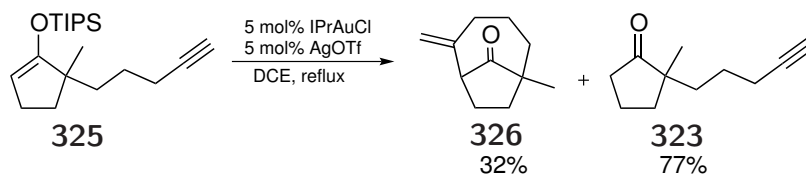
2,2-disubstituted ω -keto alkynes

We then applied these reaction conditions to 2,2-disubstituted ω -keto alkynes. First, ω -keto alkynes **328** and **329** with a 6-membered ring and a 3- respectively 2-carbon tether were transformed into the corresponding TIPS enol-ethers **330** and **331**. The reaction of **330** with the NHC-gold-complex gave the desired bridged compound **332** in 38 % yield. Shortening the tether from 3 to 2 carbon atoms, a 6-membered ring is formed instead of a 7-membered ring. This increased the yield of the reaction up to 71 % (Scheme 11.10).



Scheme 11.10: Reaction of TIPS-enol ethers **331** and **330** with IPrAuCl/AgOTf.

With the 5-membered ring substrate **325**, the desired product **326** was obtained in 32 % yield together with 77 % of the desilylated starting material (Scheme 11.11).



Scheme 11.11: Reaction of TIPS-enol ether **325** with IPrAuCl/AgOTf.

The yield obtained in the reaction of **325** illustrates that the reaction conditions used still caused some problems. When TIPS-enol ethers were used for the reaction, we encountered an unseparable side product in many cases.

After careful investigations of the reaction process and the NMR-spectra, we concluded that the impurity in the product is a byproduct of TIPS-group. Figure 11.2 shows for example the $^1\text{H-NMR}$ -spectra of compound **321**. The peaks of the impurity at 1.05 and 1.44 ppm are marked by arrows and match with the peaks expected for a TIPS-group.¹ Still, the exact nature of the side product could not be elucidated. Without any knowledge of the exact structure and mass of the side product, no exact statement to the reaction yield was possible.

To circumvent this problem, we sought for another silyl-group which will be stable enough to prevent desilylation.

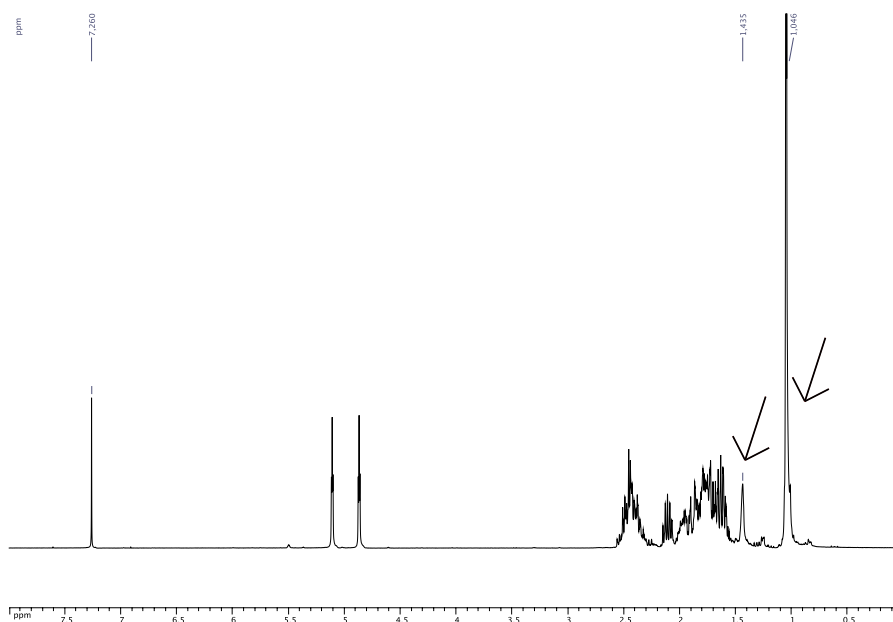
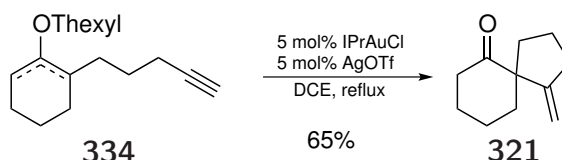


Figure 11.2.: $^1\text{H-NMR}$ -spectra of compound **321** with impurity.

¹TIPSOTf: $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.16 (d, $J = 7.3$ Hz, 18H), 1.38 (septet, $J = 7.3$ Hz, 3H).

11.2.2. Thexyl-enol ethers as substrates

The dimethyl-(2,3-dimethyl-2-butyl)silyl-group (thexyl-group) has a related structure to the TBS-group but showed a higher stability in desilylation experiments.[174] We hence thought that the thexyl-group might be an good alternative to the TIPS group for the formation of silyl enol ethers. Thexyl-enol ether **334** could be synthesized from **89** using ThexylOTf/ NEt_3 . **334** was then submitted to the cyclization reaction conditions. We were pleased to find that the desired spirocyclic compound **321** was obtained with an improved yield of 65 % and no side-product was observed (Scheme 11.12).



Scheme 11.12: Reaction of Thexyl-enol ether **334** with IPrAuCl/AgOTf.

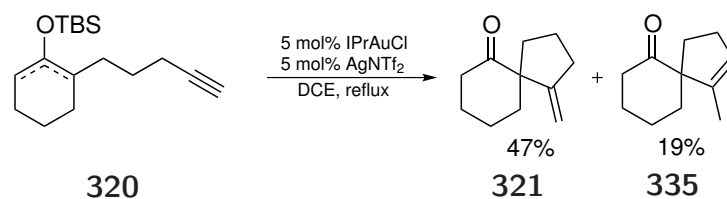
However, we were not satisfied with the use of the thexyl silyl enol ether in the reaction. The thexyl group in silylated compounds is less common than the TIPS or TBS groups and moreover more difficult to obtain.² In addition, the presence of the thexyl group is less favorable with regard to atom economy than the TBS group.

11.3. Cycloisomerizations using AgNTf_2 as cocatalyst

In order to be able to use TBS silyl enol ethers in the reaction we had to eliminate the source of acid in the reaction. AgNTf_2 is much less hygroscopic than other silver salts commonly used in catalysis.[94, 95, 175] The less pronounced hygroscopy causes not only a higher stability of the compound, but also less free acid is introduced into the reaction mixture. With this preconditions in hand, we decided to replace the cocatalyst AgOTf by AgNTf_2 .

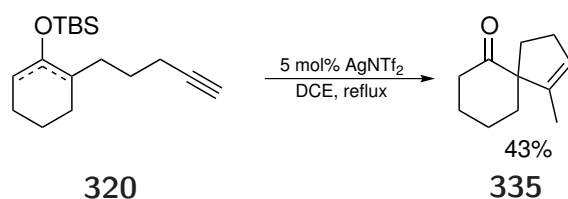
Submitting the TBS-enol ether **320** to this new reaction conditions (IPrAuCl/ AgNTf_2) furnished a mixture of two compounds. Careful investigations of the mixture revealed that the product is composed of the two isomeric products **321** and **335** (Scheme 11.13). While **321** has an exocyclic double bond, in **335** the double bond migrated into an endocyclic position. The two products were obtained in 2.5 : 1 ratio as determined by $^1\text{H-NMR}$ -spectroscopy and an overall yield of 66 %.

²At the date of manuscript preparation ThexylOTf was not commercially available.



Scheme 11.13: Reaction of TBS-enol ether **320** with IPrAuCl/AgNTf₂.

We then decided to cross-check the reactivity of our catalytic system, answering the question whether the cycloisomerization requires the presence of the gold catalyst or not. Thus the reaction was performed in the absence of gold-complex **327** only with AgNTf₂ as catalyst (Scheme 11.14). We were surprised to find that the gold-complex is not necessary for the reaction and the *endo*-spirocyclic compound **335** was obtained in 43 % yield.



Scheme 11.14: Reaction of TBS-enol ether **320** with AgNTf₂ alone.

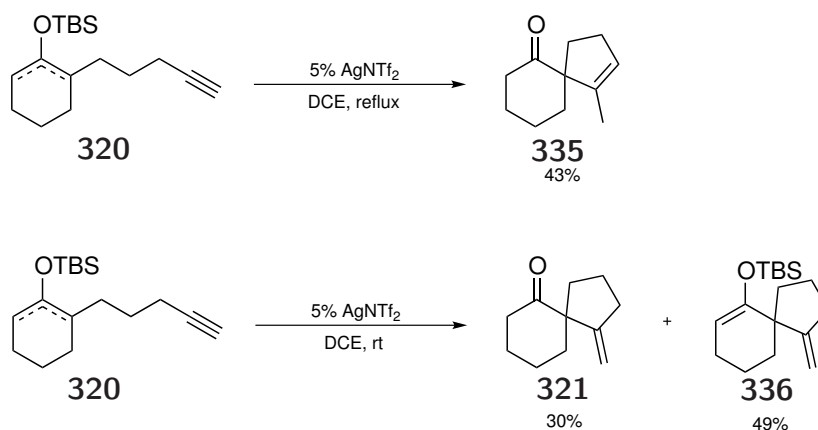
Encouraged by this result and the finding that similar gold catalysed reactions have recently been published,[176, 177] we decided to continue our research on silver-catalyzed cycloisomerizations.

12. Silver(I) catalyzed cycloisomerization reactions

Having found that the cycloisomerization of silyl enol ethers derived from ω -keto alkynes can be performed without a gold catalyst and only in the presence of a simple silver salt we decided to further investigate this reaction.

12.1. Optimizing the reaction conditions

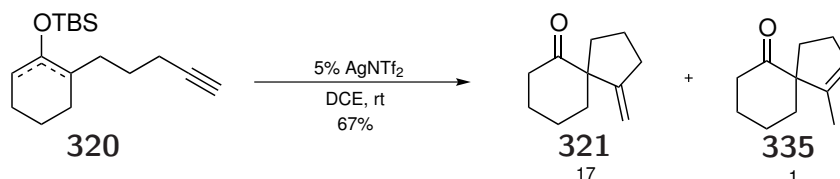
We started our investigations on silver catalyzed cycloisomerizations by optimizing the conditions for the reaction of TBS-enol ether **320** obtained from ω -keto alkyne **89**. Our initial attempt consisted of treating TBS-silyl enol ether **320** with AgNTf₂ in refluxing DCE (84 °C), yielding spirocyclic compound **335** in 43 % yield. When lowering the reaction temperature for the reaction of **320** with AgNTf₂ to room temperature, two products were isolated. One was the spirocyclic product **321** with the *exo*-double bond. The second product isolated could be identified as the corresponding silyl-enol ether **336** (Scheme 12.1). **321** could be isolated in 30 % yield, **336** in 49 % yield



Scheme 12.1: Reaction of **320** at high and room temperature.

The discovery of this product led us to change the conditions for the work-up of the reaction. While up to this point the work-up consisted in a simple filtration of the reaction mixture through Celite, we decided to perform an acidic work-up to transform

silyl-enol ether **320** into ketone **321**. Treatment of the reaction mixture with 10 % HCl after consumption of the starting material afforded the desired spirocyclic ketone in 67 % yield as a 17 : 1 mixture of *exo*- and *endo*-isomer **321** and **335** (Scheme 12.2).



Scheme 12.2: Reaction of **320** with AgNTf₂ and subsequent acidic work-up.

We then investigated the influence of the solvent and the catalyst on the outcome of the reaction. Therefore a variety of solvents and catalyst were screened. The results of these reactions are summarized in Table 12.1.

Table 12.1.: Optimization of the reaction conditions for Ag(I)-catalyzed cycloisomerizations.

Entry	Solvent	[Ag]	Yield	321/335/89
1	DCE	AgNTf ₂	67 %	17/1/0
2	CH ₂ Cl ₂	AgNTf ₂	78 %	16/1/0
3	THF	AgNTf ₂	81 %	20/1/20
4	acetone	AgNTf ₂	quant.	0/0/100
5	toluene	AgNTf ₂	76 %	9/1/0
6	CH ₃ CN	AgNTf ₂	72 %	1/5/54
7	DCE/MeOH (10:1)	AgNTf ₂	quant.	0/0/100
8	toluene ^[a]	AgNTf ₂	68 %	1/38/8
9	DCE	HNTf ₂	quant.	0/0/100
10	DCE	Ag ₂ CO ₃	quant.	0/0/100
11	DCE	-	- ^[b]	-

[a] Toluene was not distilled before use. [b] Starting material was recovered.

We first started our investigation by checking the influence of different solvents on the reaction outcome. We were especially interested in the product yield and distribution of the different products, i.e. the ratio of the two cyclized products (**321** and **335**) and the desilylated compound **89**.

The desired compounds **321** and **335** were isolated in 78 % respectively 76 % yield

when the reaction was carried out using dry CH_2Cl_2 or dry toluene as solvent (entries 2 and 5). With DCE as solvent (entry 1) the two spirocyclic products were formed as well, but the yield was about 10 % lower. In all three cases no desilylated product was found. Other solvents yielded to partial (THF, CH_3CN , entries 3 and 6) or complete desilylation (acetone, entry 4).

Toste *et al.* stated that for the completion of the catalytic cycle in gold(I) catalyzed reactions of silyl enol ethers, the addition of an external proton source is necessary.[124] We decided to check whether this could further improve the yield of our reaction. To this issue two experiments were performed. First, the reaction was performed using a 10 : 1 mixture of DCE and methanol (entry 7). This solvent system was proposed by Toste *et al.* for their gold catalyzed reactions.[124] Then the reaction was performed in commercial toluene which was not further treated in any way (entry 8). Neither of these experiments led to an improvement in yields or selectivities in comparison to dry CH_2Cl_2 or dry toluene as solvent. The DCE/MEOH mixture led to complete desilylation of the starting material whereas in the "wet" toluene reaction the yield was lower than using dry toluene (68 % to 76 %) and the desilylated compound was formed as byproduct. In addition, the *exo-endo* ratio was inverted from 9 : 1 in dry toluene to 1 : 38 in commercial toluene. These experiments showed that an external proton source is not only unnecessary but detrimental to the yield and product distribution.

In a last set of experiments, we tested the influence of the catalyst on the reaction. We could show that neither triflimide (HNTf_2) alone (entry 9) nor Ag_2CO_3 (entry 10) can catalyze the reaction. In both cases, only the desilylated starting material was obtained. When the reaction was performed without any catalyst (entry 11), no conversion could be observed. Thus the possibility of a thermal reaction was ruled out.

In summary we found that the reaction is best performed using dry CH_2Cl_2 or dry toluene as solvent.

12.2. Reaction scope

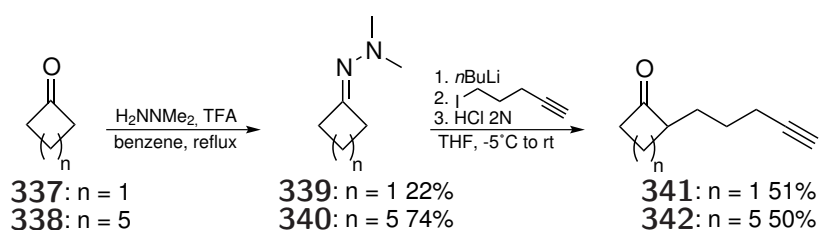
Having found this optimal reaction conditions, we went on to explore the reaction scope of the cycloisomerization reaction. A series of starting materials was submitted to the conditions found. As dry CH_2Cl_2 and dry toluene gave nearly the same yield of the desired cycloisomerization product, we decided to use both solvents for our reactions.

12.2.1. Unsubstituted ring systems as substrates

We started our study by checking the effect of different ring sizes in the starting material. To do so, we first had to synthesize the corresponding starting materials.

Synthesis of the starting materials

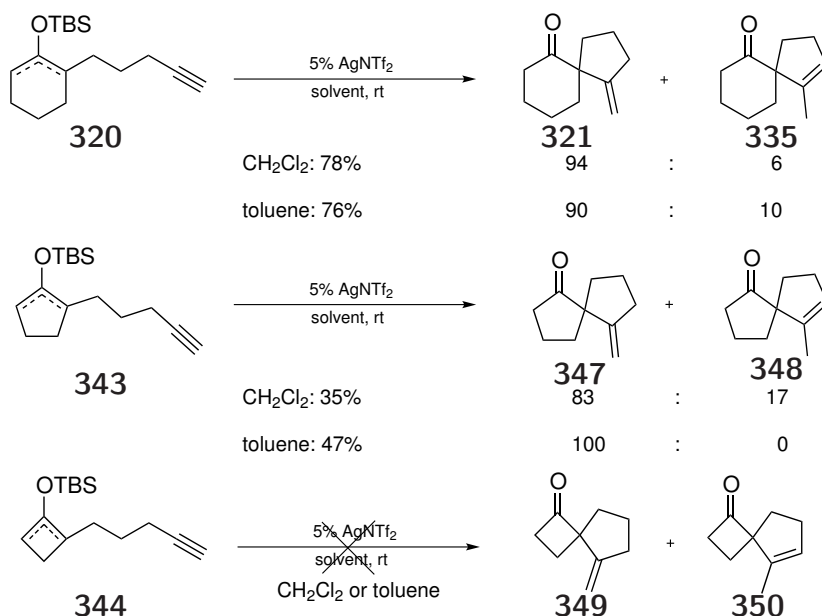
The synthesis of compounds **88-90** with a 5- to 7-membered ring system is already described in Section 4.1 as these products were intermediates for the synthesis of acetylenic ω -ketoesters used in titanium mediated reactions. To synthesize the ω -keto alkynes **341** and **342** with a 4- and 8-membered ring respectively, the same reaction sequence as used for **88-90** was used. Albeit, the yields obtained were lower compared to the 5-, 6- and 7-membered ring system (Scheme 12.3).



Scheme 12.3: Synthesis of ω -keto alkynes **341** and **342**.

Reaction with AgNTf₂

After transformation into the corresponding silyl enol ethers **320** and **343-346**, ω -keto alkynes **88-90**, **341** and **342** with 4- to 8-membered ring were tested under the reaction conditions previously determined. The results for the 4- to 6-membered ring substrates are summarised in Scheme 12.4.

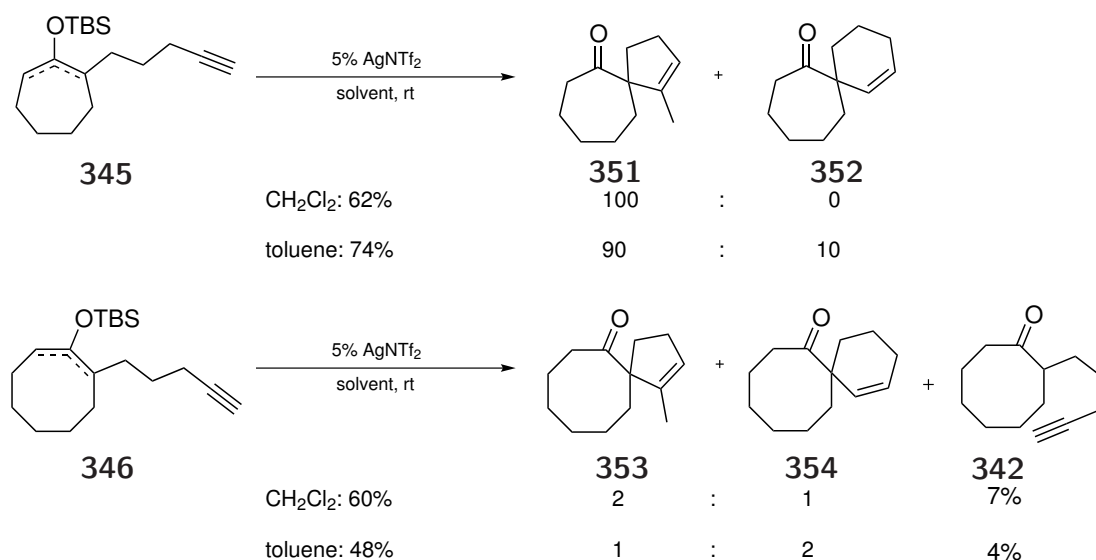


Scheme 12.4: Cyclization of TBS enol ethers **320**, **344** and **343**.

Starting from the 6-membered ring enol ether **320** the desired compounds could be synthesized in good yield, whereas the conversion of the 5-membered ring substrate **343** gave only a modest yield of the spirocyclic products. When the ring size is further decreased to a 4-membered ring, no cyclized product was observed. The formation of desilylated compound **341** was not observed either.

When the *exo* to *endo* ratio of the obtained products was analyzed, we found that for the 5- and 6-membered ring (products **347/348** and **321/335**) the *exo*-compound was the major product.

The situation changed when TBS-enol-ethers with bigger rings **345** and **346** (7- and 8-membered ring) were submitted to the reaction conditions. In both cases the compound with an exocyclic double bond was no longer obtained. Instead the product with a [n.5] spirocyclic ring system was obtained. In case of the 7-membered ring, compound **352** was the minor compound with respect to **351** when toluene is used as solvent. CH₂Cl₂ as solvent led to the exclusive formation of **351**. Increasing the ring size to a 8-membered ring, a mixture of compounds **353** and **354** was obtained together with small amounts of desilylated compound **342** for both solvents (Scheme 12.5). In CH₂Cl₂ **354** was the minor compound (**353** : **354** 2 : 1). This ratio was inverted when toluene was used as solvent.



Scheme 12.5: Cyclization of TBS enol ethers **345** and **346**.

The formation of compounds **352** and **354** with the spiro[n.5] motive can be explained by a different cyclization mode as for the formation of spiro[n.4] motive. The spiro[n.4] motive is formed through a 5-*exo*-dig cyclization, compounds **352** and **354** are formed through a 6-*endo*-dig cyclization.[178] While for radical cyclizations it is generally accepted that 5-*exo*-trig cyclizations are preferred over the competing 6-*endo*-trig cyclizations in radical chemistry,[179] this is not the case for other cyclization reactions. The groups of Toste[180] and Echavarren[96, 111] found that in gold catalysis, the reaction outcome (5-*exo* vs. 6-*endo*) is strongly depending on the substrate and that

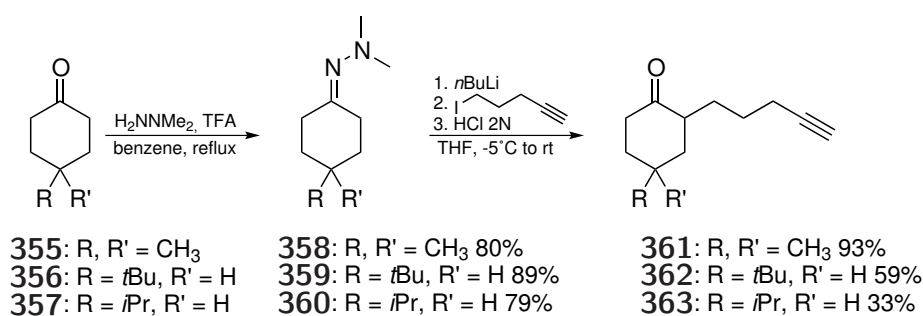
steric interactions in the transition state play an important role. A general prognosis is therefore not possible and each case has to be investigated individually. It is therefore not surprising that in our case, the 6-*endo*-compounds are formed with the large 7 and 8-membered ring substrates which can adopt more different conformations than the corresponding 5- or 6-membered rings.[65]

12.2.2. Substituted ring systems

We then envisaged the synthesis of substituted substrates. We chose symmetric substituted starting materials to avoid regioselectivity problems during the synthesis.

Synthesis of the starting materials

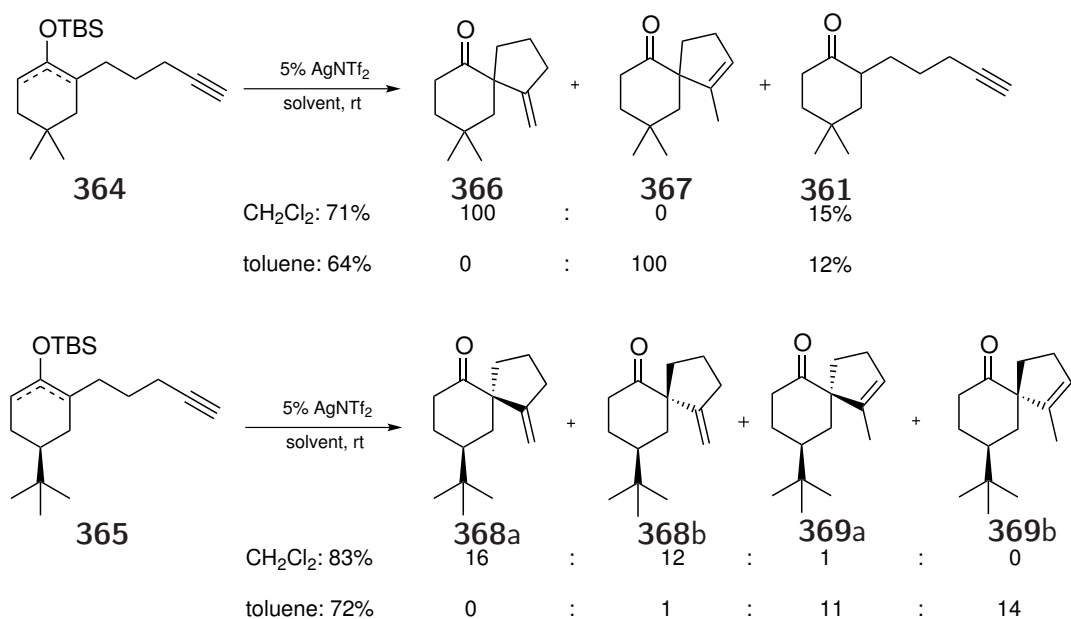
Commercially available ketones bearing a 4,4-dimethyl (**355**), a 4-*tert*-butyl (**356**) and a 4-*iso*-propyl (**357**) substitution were chosen as substrates. Transformation into the hydrazones and subsequent alkylation gave the ω -keto alkynes **361-363** in good yields (Scheme 12.6).



Scheme 12.6: Synthesis of ω -keto alkynes **361** - **363**.

Reaction with AgNTf₂

After transformation of the 4-substituted ω -keto alkynes **361** and **362** into the corresponding TBS-enol ethers **364** and **365**, we submitted them to our reaction conditions (Scheme 12.7).



Scheme 12.7: Cyclization of TBS enol ether **364** and **365**.

Both compounds yielded in the formation of the *exo*- and *endo*-cyclic spirocyclic compounds **366/367** and **368/369**. Interestingly, the product distribution (*exo* vs. *endo*) was solvent dependent for this substrates. In CH₂Cl₂ the *exo*-compounds were formed exclusively (**366**) or with a large excess (**368**). The inverse situation was observed when toluene was used as solvent.

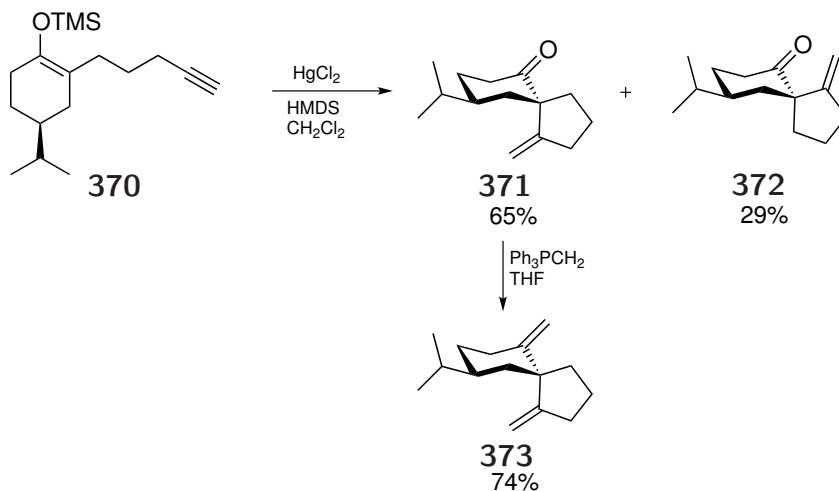
It should be noted that ω -keto alkyne **362** and thus enol ether **365** were used in it's racemic form.¹ Thus compounds **368** and **369** were obtained as mixture of diastereoisomers. When the reaction was performed in CH₂Cl₂, the ratio of the two *exo*-diastereoisomers **368** was 16 : 12. For the *endo* compound **369**, only one diastereoisomer was formed. With toluene as solvent, a 14 : 11 ratio for the two diastereoisomers of the *endo* compound **369** was obtained. This time, only one diastereoisomer of the *exo* compound **368** was formed. Interestingly, the single *endo* diastereoisomer of the reaction in CH₂Cl₂ represents the minor of the two *endo* isomers in the reaction with toluene. The same also applies to the inverse case. The single *exo* diastereoisomer of the toluene reaction is the minor of the two *exo* isomers in the reaction with CH₂Cl₂.

12.2.3. 4-*i*Pr-substituted substrate: Formal total synthesis of (\pm)-Erythrodiene

The 4-*i*Pr-substituted ω -keto alkyne **363** served as substrate for the formal total synthesis of the sesquiterpene Erythrodiene. This molecule has been isolated by the group of Fenical in 1993.[181] Shortly after, the group of Forsyth published the racemic synthesis of this compound,[182] followed by an enantioselective synthesis.[183] For

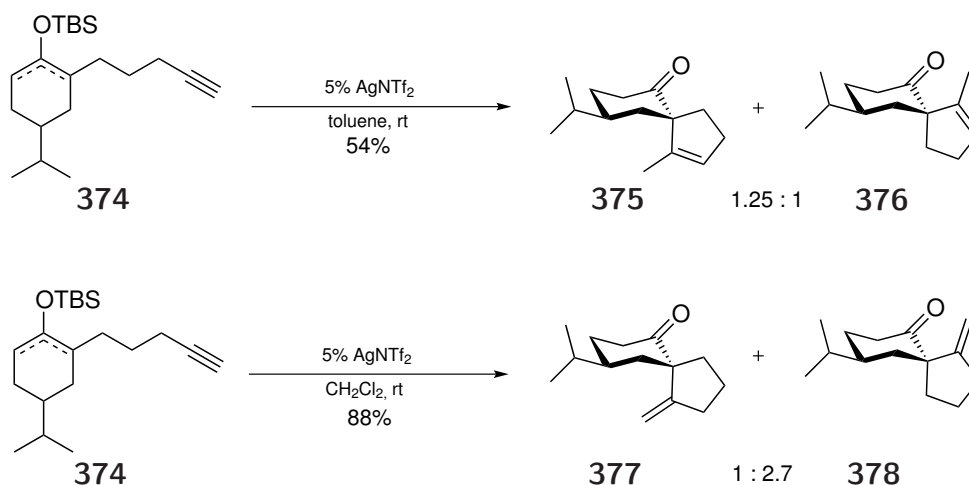
¹For better understanding only one of the enantiomers is shown. The attribution of the diastereoisomers has been done arbitrarily to clarify the results obtained.

both synthesis, they used a carbomecuration reaction as key step (Scheme 12.8). Starting from enantiomerically enriched silyl enol ether **370**, they obtained compounds **371** and **372** with the alkenyl moiety in axial respectively equatorial position (65 % and 29 % yield). **371** was then converted by a Wittig reaction into (-)-Erythrodiene **373** in 74 % yield.



Scheme 12.8: Total synthesis of (-)-Erythrodiene by Forsyth *et al.*

We proposed to replace the carbomecuration step of their synthesis by our silver-catalyzed cyclization. To do so, racemic ω -keto alkyne **363** was transformed into TBS-enol ether **374**. We then submitted **374** to our reaction conditions. The results obtained for the reaction in CH_2Cl_2 and toluene are shown in Scheme 12.9.



Scheme 12.9: Reaction of **374** with AgNTf_2 to form the (\pm)-Erythrodiene precursor **377**.

In both solvents, the spirocyclic products were obtained. Similar to the reaction of *t*Bu-substituted compound **365**, we observed a change in *exo*-/*endo*-selectivity when changing the solvent. When toluene was used we observed the exclusive formation

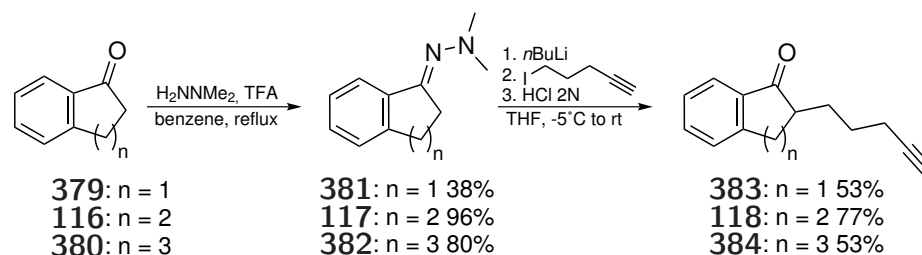
of compounds **375** and **376** with an endocyclic double bond. The ratio of the two diastereoisomers was determined to 1.25 : 1. When the reaction was performed in CH₂Cl₂ we obtained a mixture of the diastereomeric compounds **377** and **378** with an exocyclic double bond. Products **375** and **376** with the endocyclic double bond were not observed. **377** and **378** were obtained in a 1 : 2.7 ratio. Spectral data for compound **377** and **378** were in agreement with those obtained by Forsyth *et al.*[183] Compound **377** is a direct precursor of Erythrodiene **373** (see Scheme 12.8), thus a formal total synthesis of (±)-Erythrodiene was achieved.

12.2.4. Bicyclic ring systems with a condensed aromatic ring

After having successfully applied our strategy to substituted ring systems, we decided to extend our strategy to bicyclic compounds. We first concentrated on cyclic ketones condensed to an aromatic ring.

Synthesis of the starting material

Using our established strategy for the synthesis of ω-keto alkynes, aromatic substrates **118**, **383** and **384** were synthesized in two steps from the corresponding commercial ketones (Scheme 12.10).

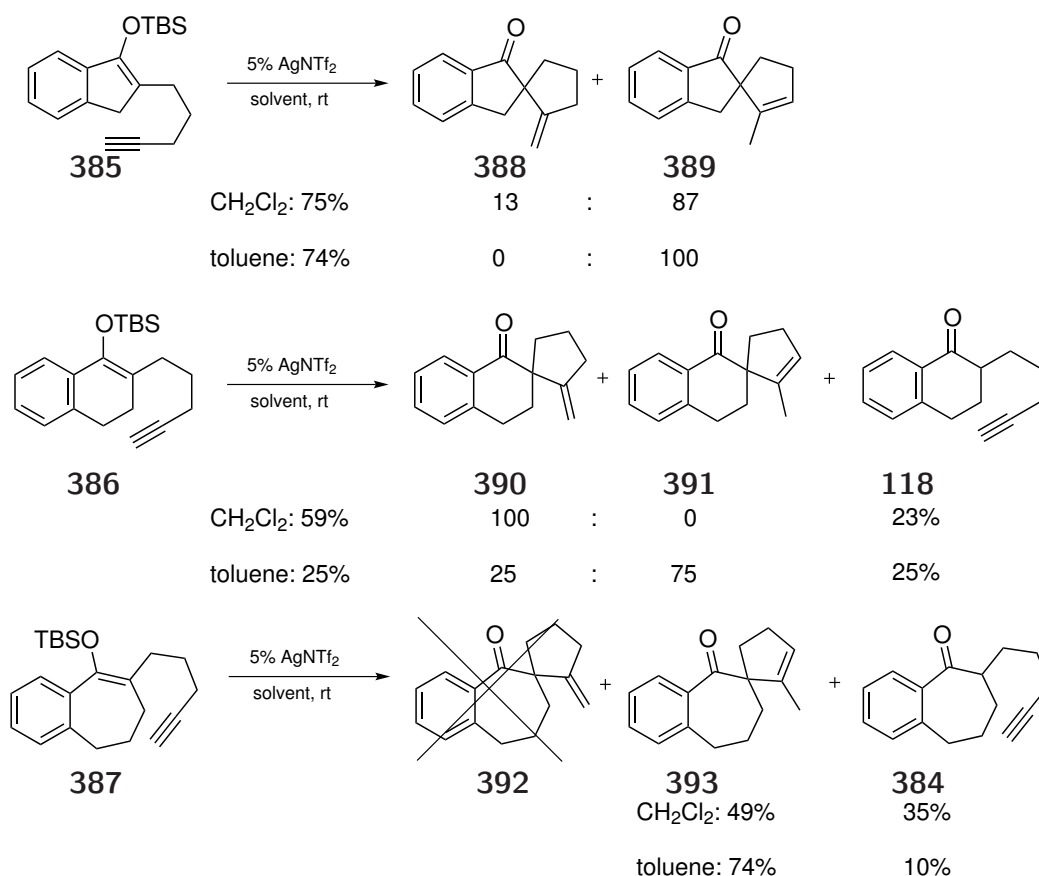


Scheme 12.10: Synthesis of ω-keto alkynes **118**, **383** and **384**.

Reaction with AgNTf₂

After transformation of the ω-keto alkynes **118**, **383** and **384** into the corresponding TBS-enol-ethers **385** - **387**, the latter were used as starting materials in silver-catalyzed cycloisomerization reactions.

When performing the reaction in the presence of a catalytic amount of AgNTf₂, we observed the formation of the desired tricyclic compounds (Scheme 12.11) even though ratio of *exo*- and *endo*-product differs between the substrates.



Scheme 12.11: Cyclization of TBS enol ethers **385** - **387**.

In the case of the indanone derivative **385** the reaction could be performed with a good yield and without observation of the desilylated ketone. Compound **388** with the exocyclic double bond was the minor compound when CH₂Cl₂ was used and was not formed using toluene.

Compound **386** derived from tetralone behaved differently, as the ratio of regioisomers (*exo/endo*) was again solvent dependent. **390** is formed exclusively in CH₂Cl₂. On the contrary, in toluene, **391** is the major compound. In both solvents the yield of the reaction is modest and a significant amount of desilylated starting material was isolated.

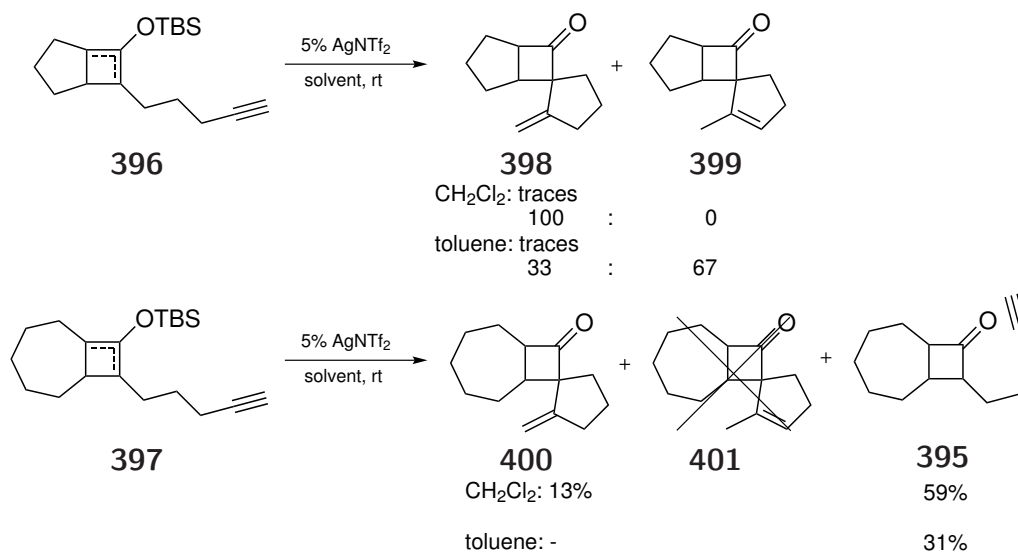
When suberone derivative **387** was used as substrate a similar behavior to the indanone derivative **385** was observed. The *exo* compound **392** was never observed, but we isolated compound **393** with an endocyclic double bond in both solvents. The yield obtained with toluene as solvent is good, although some desilylated material was isolated. With CH₂Cl₂ as solvent, a high amount (35 %) of desilylated material was formed, consequently the yield of tricyclic **393** was modest.

12.2.5. Bicyclic ring systems with a condensed saturated ring

We then attempted the formation of a saturated tricyclic spirocyclic compound. To do so, we used ω -keto alkynes **394** with a bicyclo[3.2.0] and **395** with a bicyclo[5.2.0] system originally synthesized for other projects in our group.[5]

Reaction with AgNTf₂

Unfortunately, when submitting the enol ethers **396** and **397** to our reaction conditions we detected only small amounts of the desired products (Scheme 12.12).



Scheme 12.12: Cyclization of TBS enol ethers **396** and **397**.

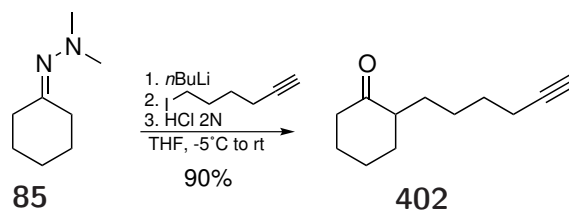
With **396** bearing a bicyclo[3.2.0]heptane ring system both solvents led only to trace amounts of the desired products **398** and **399**. Nevertheless, we were able to determine the ratio of *exo*- and *endo*-product for both reactions. While in CH₂Cl₂ *exo*-compound **398** is formed exclusively, the use of toluene led to the formation of a 1 : 2 mixture of **398** and **399**.

The situation is similar for **397** with a bicyclo[5.2.0]nonane system. CH₂Cl₂ as solvents led to the sole formation of *exo*-compound **400** with 13 %, *endo*-product **401** was not observed. Compound **400** was accompanied by 59 % of the desilylated material. When toluene was used as solvent, no tricyclic product was observed, only the desilylated material was recovered in 31 % yield.

12.2.6. Varying the spacer chain length

In addition to varying the substitution pattern of the tested substrates, we also wanted to change the spacer length between the two reactive sites, the carbonyl and the alkyne. For this purpose ketones **102** with a 2-carbon spacer and **402** with a 4-carbon spacer were used as substrates. The synthesis of **102** is described in Section 4.1, **402** was

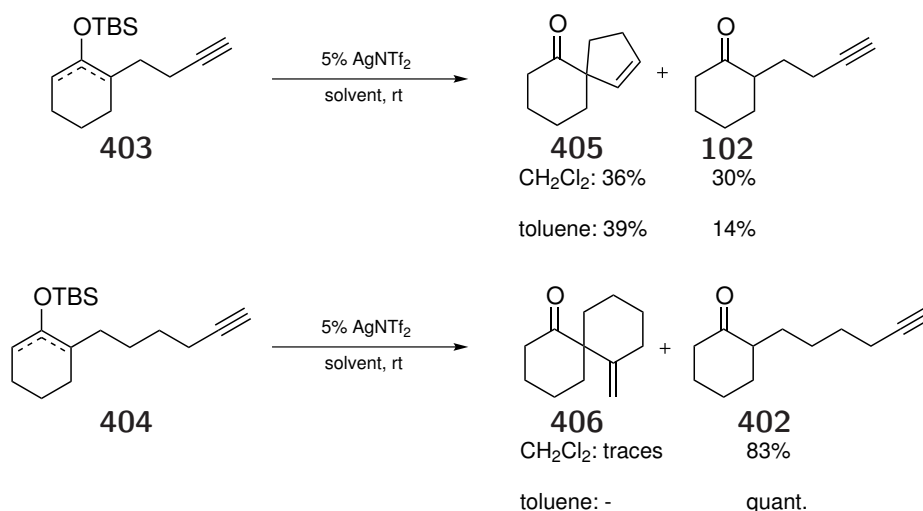
synthesized using the same strategy using 6-iodohexyne as alkylating agent.[66] Thus the ω -keto alkyne **402** was isolated in 90 % yield (Scheme 12.13).



Scheme 12.13: Synthesis of ω -keto alkyne **402**.

Reaction with AgNTf₂

Starting from ketones **102** and **402** the enol ethers **403** with a 2-carbon spacer and **404** with a 4-carbon spacer were synthesized. The results obtained for their reaction with AgNTf₂ are shown in Scheme 12.14.



Scheme 12.14: Reaction of TBS enol ethers **403** and **404** with AgNTf₂.

When **403** is used as substrate, only the product **405** resulting from a 5-*endo*-dig cyclization was isolated. This is not very surprising as the other possible cyclization mode is 4-*exo*-dig, which is disfavored due to geometric reasons.[178]

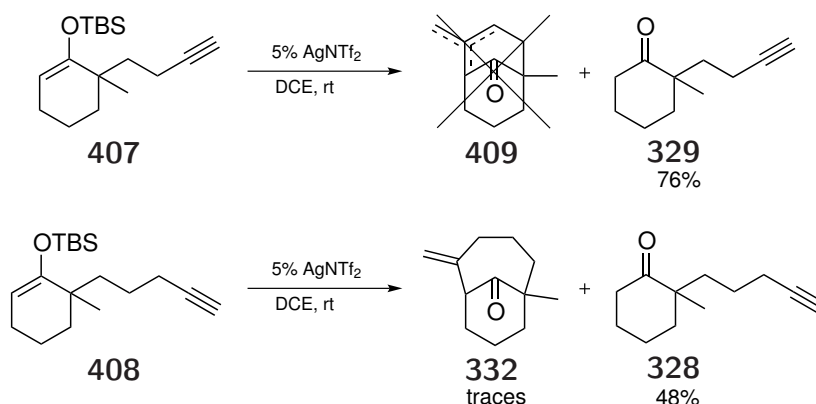
With substrate **404**, we observed complete desilylation in toluene. Using CH₂Cl₂, we were able to identify **406** resulting from a 6-*exo*-dig cyclization in trace amounts together with 83 % of desilylated material.

12.2.7. Reaction of 2-methylated substrates

We then wanted to explore whether our silver catalyzed reaction can be used to synthesize bridged compounds. Thus, we used ω -keto alkynes **328** and **329** as test substrates.

Reaction with AgNTf₂

After formation of TBS-enol ethers **407** and **408** the latter were submitted to our reaction conditions (Scheme 12.15).



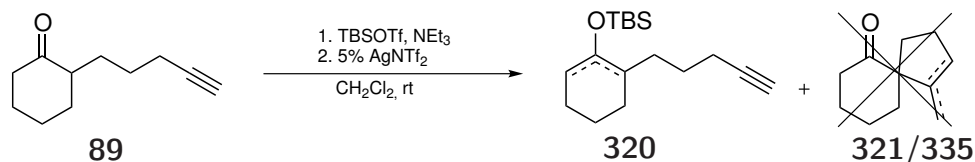
Scheme 12.15: Reaction of 2-methylated TBS enol ethers with AgNTf₂.

To our disappointment none of the three possible bridged compounds **409** could be isolated when a 2-carbon tether was used. Only the desilylated material was recovered in 76 % yield. When a 3-carbon tether was used, the bridged compound **332** was obtained in trace amounts together with 48 % of desilylated starting material.

12.2.8. One-pot formation of spiro compounds

We also envisaged the possibility of a one-pot-reaction for the formation of spiro-compounds starting from ω -keto alkynes without isolation of the silyl enol ethers. Again, ω -keto-alkyne **89** was chosen as test substrate.

We initiated the reaction by reacting **89** with TBSOTf/NEt₃ in CH₂Cl₂ and the reaction was monitored by TLC. As soon as the starting material was consumed, AgNTf₂ was added to the reaction mixture. Continued monitoring of the reaction by TLC showed that there was no further evolution, even after prolonged reaction times. The reaction stopped at the stage of enol ether **320**. None of the spirocyclic products **321** or **335** were formed. This is probably due to the fact that the salts formed during the enol ether formation and excess NEt₃ are inhibiting the catalyst by complexation of the metal center. Catalyst poisoning by amines has already been described in the literature.[184]



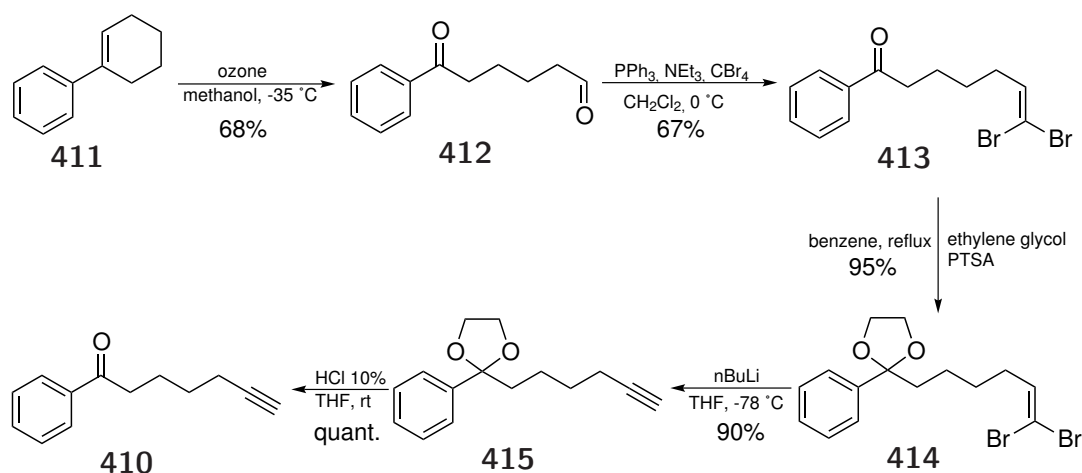
Scheme 12.16: One-pot reaction for the formation of spiro compounds.

12.2.9. Reaction of open chain substrates

The group of Toste described recently the cyclization of non-cyclic silyl enol ether on alkynes using gold and palladium catalysis.[127] We wanted to test whether we can perform a similar reaction with our silver catalytic system, starting from ω -keto alkyne **410**.

Synthesis of the starting material

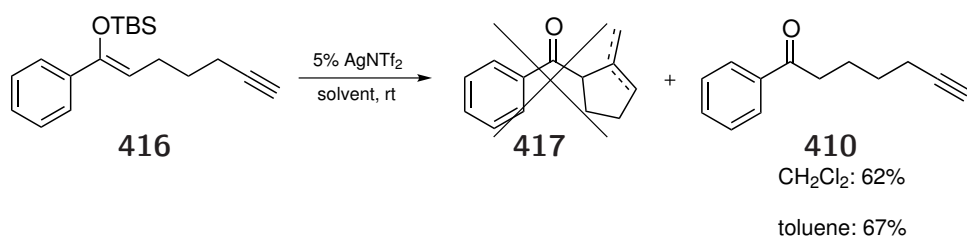
The acyclic ω -keto alkyne **410** used as test substrate was synthesized as follows. Starting from cyclic alkene **411**, ozonolysis of the double bond furnished the linear keto-aldehyde **412**. Maintenance of the reaction temperature and short reaction times were crucial for the ozonolysis in order to prevent degradation of the product. The aldehyde was then transformed into a triple bond using the Corey-Fuchs-procedure.[73] The aldehyde reacted selectively in the presence of the ketone in the first step of the Corey-Fuchs reaction. The carbonyl function of dibromo compound **413** was then protected as dioxolan (**414**) to allow the transformation of the dibromoalkene into the triple bond. Reaction of compound **414** with *n*BuLi gave in high yield the alkyne **415**. In a last step, the carbonyl group was deprotected under acidic conditions. **410** was synthesized in 5 steps from **411** with 39 % overall yield.



Scheme 12.17: Synthesis of the open chain ω -keto alkyne **410**.

Reaction with AgNTf₂

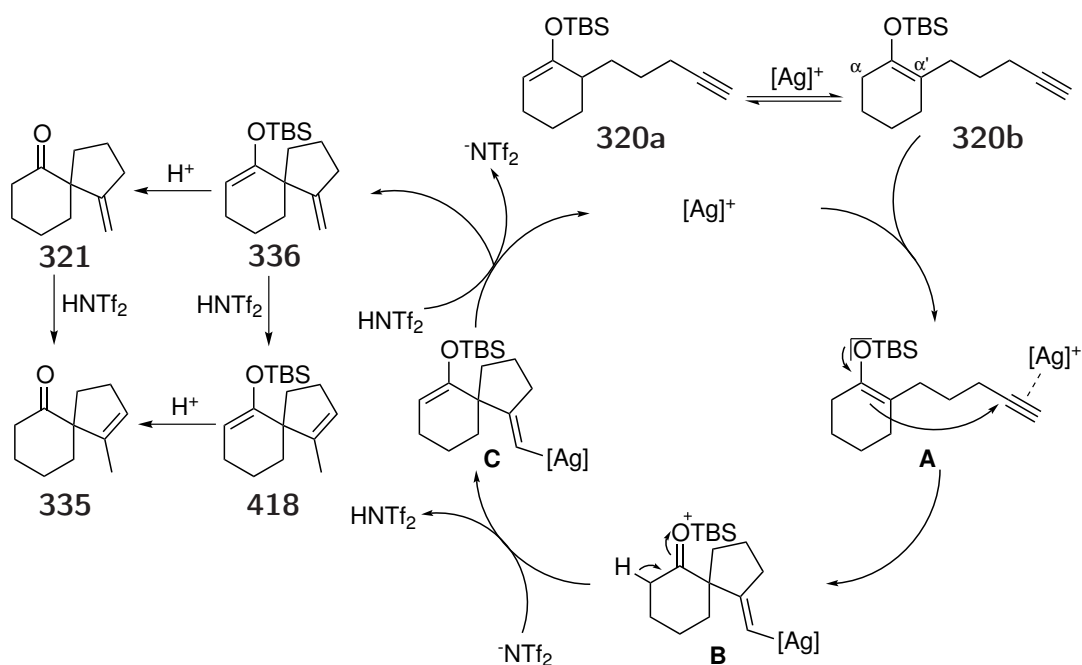
TBS-enol ether **416** was then synthesized from **410**. Unfortunately, we were not able to isolate any cycloisomerization product **417** when reacting **416** with AgNTf₂ in CH₂Cl₂ or toluene (Scheme 12.18). In both reactions, the only isolable product was the desilylated starting material. This result was surprising with regard to the results obtained by Toste *et al.* who showed that similar substrates can be transformed using gold-catalysis.[127]



Scheme 12.18: Reaction of open chain substrate **416** with AgNTf₂.

12.3. Proposed mechanism

The proposed mechanism for AgNTf₂-catalyzed reactions is shown in Scheme 12.19. For this discussion the mixture of TBS-enol-ether **320a** and **320b** is chosen as a representative substrate.



Scheme 12.19: Proposed mechanism for the AgNTf₂-catalyzed cycloisomerization.

The TBS-enol-ether **320** was employed as a 2 : 1 mixture of kinetic isomer **320a** and thermodynamic isomer **320b** in the reaction (see Section 11.1.1). The fact that no bridged compound is formed in the reaction shows that the cyclization occurs exclusively on the α'-carbon of **320b** and not on the α-carbon. As the thermodynamic silyl-enol ether **320b** represents only 33 % of the starting material, the yield of 78 % of spirocyclic products can not be explained without an isomerization of **320a** into **320b** probably catalyzed by AgNTf₂ (see Section 12.3.1).

The catalytic cycle is initiated by complexation of silver(I) to the triple bond of **320b**

to form intermediate **A**. Once the triple bond is activated through the complexation, an ene-yne cyclisomerization forms intermediate **B**.^[125, 168] Attack on the triple bond occurred anti to the silver complex,^[123, 185] thus an *E*-double bond is formed. Deprotonation of intermediate **B** at the α -position of the ketone yields in the formation of intermediate **C**. Subsequent protodemetalation of **C** led to the regeneration of the silver catalyst and the formation of compound **336**.

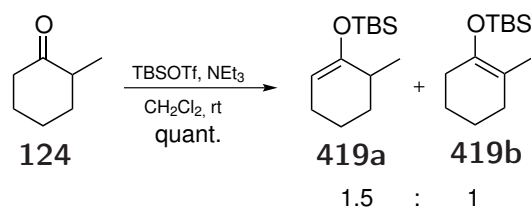
Desilylation of **336** led to the formation of compound **321** with the exocyclic double bond. For the formation of **335** there are two possible explanations: **335** can be formed through double bond isomerization of *exo*-product **321**. One can also postulate that isomerization occurs before desilylation. **336** would yield silylated *endo*-compound **418**, which after desilylation gives **335**. Isomerization of the *exo*- into the *endo*-double bond is probably promoted by small amounts of HNTf₂ present in the reaction (see below).

Substrates **385-387** with a fused aromatic ring possess no α -proton in intermediate **B**. We assume therefore that for these substrates, desilylation occurs directly from intermediate **B**, followed by protodemetalation.

The formation of the desilylated compounds in some of the reactions may be explained in two ways. First, that desilylation occurs during the reaction by trace amounts of acid present in the reaction mixture. A second explanation is that the desilylation occurs during the work-up procedure when unreacted starting material is still present in the reaction mixture.

12.3.1. Isomerization of silyl-enol-ethers with AgNTf₂

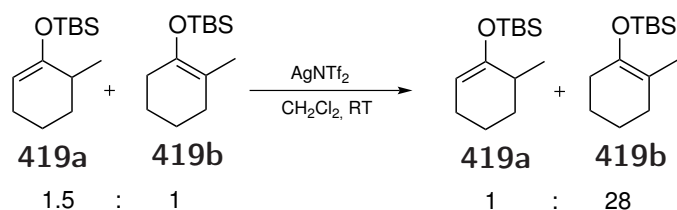
To establish whether under the reaction conditions of the cyclization reaction the isomerization of the TBS-enolether **320a** into **320b** can take place a control experiment was performed. Therefore methylcyclohexanone **124** was transformed into the corresponding TBS-enol ether (Scheme 12.20).



Scheme 12.20: Synthesis of TBS enol ethers **419a** and **419b**.

The enol ether was obtained as a 1.5 : 1 mixture of the kinetic product **419a** and the thermodynamic product **419b** (determined by ¹H-NMR spectroscopy).

This mixture was then submitted to the reaction conditions of the cyclization reaction (5% AgNTf₂, CH₂Cl₂, room temperature, Scheme 12.21). ¹H-NMR-analysis of the crude reaction mixture showed that an isomerization takes place as the ratio **419a** : **419b** changed to 1 : 28.



Scheme 12.21: Isomerization reaction with TBS enol ethers **419a** and **419b**.

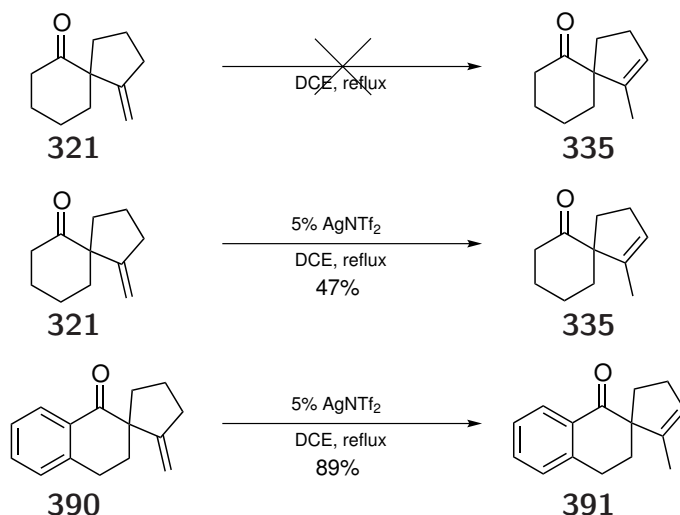
We hence think that it is reasonable to presume that under the conditions of the cyclization reaction, the kinetic TBS-enol ether is transformed into the thermodynamic one which then undergoes cycloisomerization.

12.3.2. *Exo* to *endo* isomerization of double bonds

To probe the isomerization of the double from the *exo*- into the thermodynamic more stable *endo*-position, we performed several experiments. During these experiments we also wanted to establish whether the isomerization is promoted by AgNTf₂ or HNTf₂ present in the reaction mixture in small amounts or if it is a thermal reaction not requiring any promoter.

When compound **321** was heated to reflux in dry DCE, no reaction was observed and the starting material was recovered in nearly quantitative yield. Performing the same reaction in the presence of 5 mol% of AgNTf₂, the *endo*-compound **335** was isolated in 47 % yield.

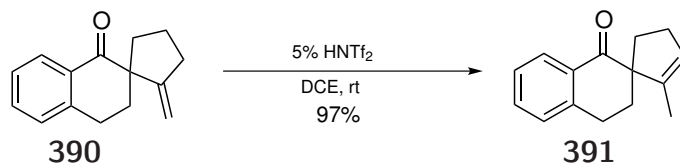
The yield of the reaction is significantly higher when the substrate was changed to tetralone derived spirocyclic compound **390**. Isomerized compound **391** could be isolated this time in 89 % yield.



Scheme 12.22: Isomerization of *exo*-double bond into *endo*-double bond with AgNTf₂.

These results showed that the isomerization is not a thermal reaction but needs a

promoter. We then tested whether the isomerization is catalyzed by the silver salt or by trace amounts of HNTf_2 present in the reaction mixture. To do so, compound **390** was treated with a catalytic amount of HNTf_2 in DCE at room temperature (Scheme 12.23). We were able to isolate the isomerization the product **391** in nearly quantitative yield.

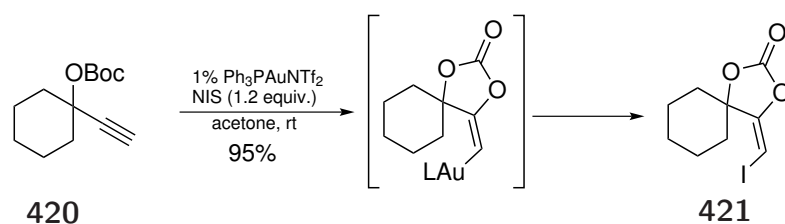


Scheme 12.23: Isomerization of *exo*-double bond into *endo*-double bond with HNTf_2 .

This results led to the conclusion that the migration of the double bond from *exo*- into *endo*-position is catalyzed by trace amounts of HNTf_2 which are present in the reaction mixture.

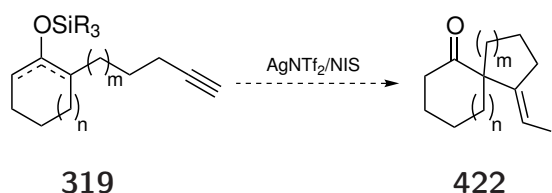
13. Trapping of a reaction intermediate: Synthesis of alkenyl iodides

Having in mind that during the catalytic cycle the demetalation of an alkenyl-silver intermediate occurs (see Scheme 12.19, page 104), we wondered whether we can perform other demetalation reactions than protodemetalation. It has been shown that in alkenyl-gold species, the Au-C(sp²)-bond can be transformed into a C-I bond by addition of a source for I⁺. [105, 185–188] *N*-iodosuccinimide (NIS) is often used for this purpose. For example, Gagosz *et al.* showed that the reaction intermediate in the reaction of **420** with gold(I) can be trapped with NIS to form the alkenyl iodide **421** in high yield (Scheme 13.1). [185]



Scheme 13.1: Trapping of alkenyl-gold-intermediates with NIS by Gagosz *et al.*

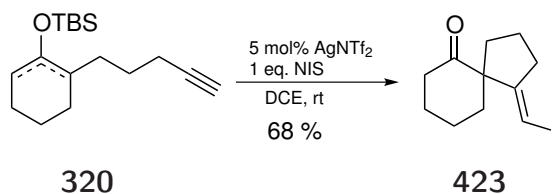
In analogy to this reactions, we wanted to perform an iododemetalation reaction from the alkenyl-silver intermediate to form spirocyclic alkenyl iodides **422** (Scheme 13.2).



Scheme 13.2: Synthetic plan for the formation of alkenyl iodide **422**.

13.1. Preliminary assay

In a first test assay, TBS-enol ether **320** was treated with 5 mol% AgNTf₂ and 1 equivalent NIS in DCE as solvent. We were pleased to find that the reaction worked and the desired alkenyl iodide was isolated in 68 % yield (Scheme 13.3).

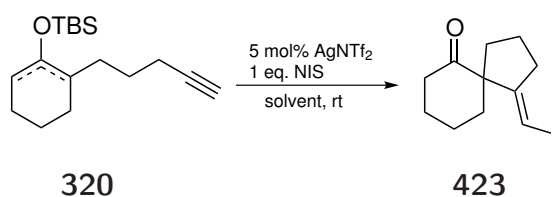


Scheme 13.3: Reaction of **320** with AgNTf₂/NIS in DCE.

13.2. Finding optimal reaction conditions

To find the optimal reaction conditions for this transformation, we tested different solvents in order to maximize the reaction yield (Table 13.1).

Table 13.1.: Screening different solvents for the formation of alkenyl iodide **422**.



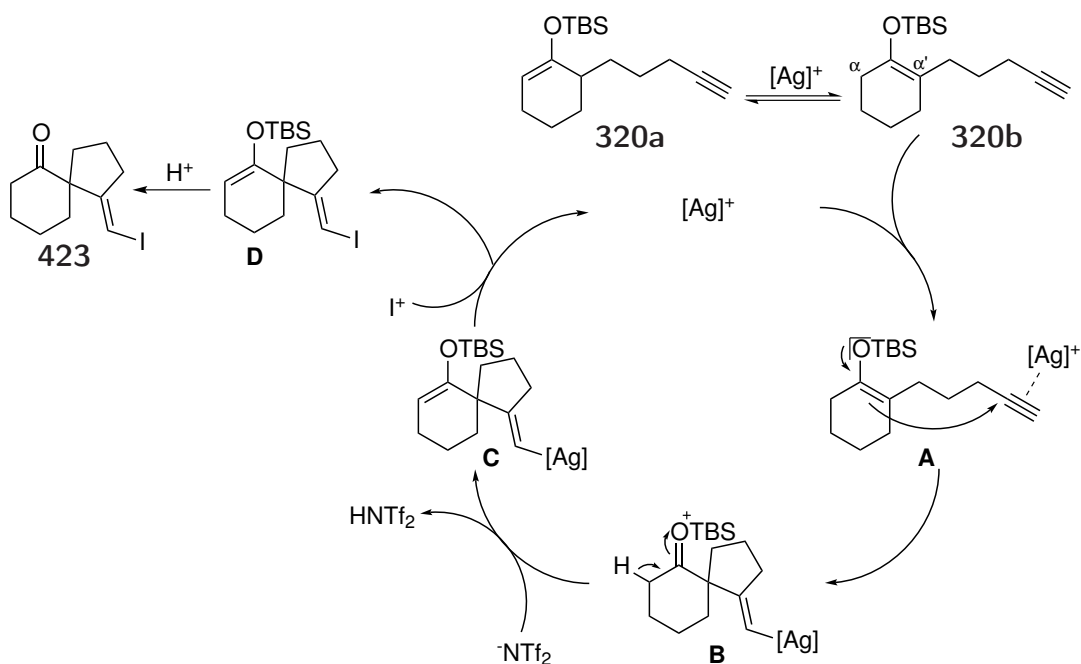
Entry	Solvent	Yield
1	DCE	68 %
2	CH ₂ Cl ₂	31 %
3	toluene	traces
4	acetone	- ^a

[a] Degradation of the starting material was observed.

Our preliminary assay showed that with DCE as solvent, the desired product was isolated in 68 % yield. When changing to CH₂Cl₂, which gave better yields in cycloisomerization reactions without NIS, the yield of the reaction dropped to 31 %. Toluene as solvent proved to be even more disappointing as the desired compound was only obtained in trace amounts together with desilylated starting material and an unidentified side-product. Gagosz *et al.* showed that acetone is superior to CH₂Cl₂ in demetalation reaction of gold-alkenyl species.[185] When acetone was used as solvent in our system, it turned out that this is not the case. Only degradation of the starting material was observed for this reaction. We therefore chose DCE as solvent for further investigations.

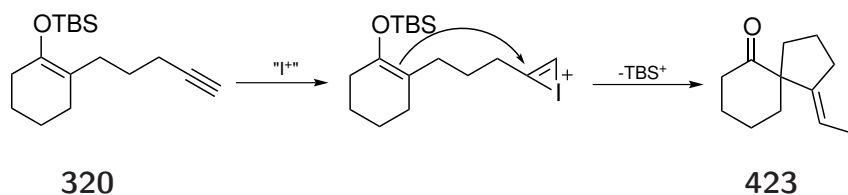
13.3. Mechanistic investigations

Alkenyl iodide **423** was obtained as a single isomer. According to the reaction mechanism presented in Scheme 13.4, the alkenyl-silver species is formed through *anti*-attack of the enol on the activated triple bond (**A** to **B**).^[123, 185] Thus the alkenyl-silver species **B** will have an *E*-configuration of the double bond. The demetalation process is stereoselective and does not change the configuration of the double bond,^[185] so the double bond configuration remains *E* after iodo-demetalation (**C** to **D**).



Scheme 13.4: Proposed mechanism for the AgNTf₂-catalyzed formation of alkenyl iodides.

One can imagine another mechanism for the formation of **423**, namely the formation of an iodonium ion through attack of I⁺ to the triple bond and subsequent attack of the enol ether (Scheme 13.5).



Scheme 13.5: Plausible mechanism for the formation of alkenyl iodide **423**.

To find out whether the reaction proceeds via this mechanism or the iodo-demetalation of an alkenyl-silver species, a control experiment was performed. If the iodonium mechanism is valid, the spirocyclic product should be formed even if the reaction is run without the silver catalyst. This was not the case when **320** was reacted with NIS in

DCE. The only product observed was the α -iodo ketone **424** (Scheme 13.6). These findings are in agreement with those of Sreedhar *et al.* who published the α -halogenation of ketones using *N*-halosuccinimides.[189]



Scheme 13.6: Reaction of **320** with NIS in the absence of AgNTf_2 .

We therefore think that alkenyl iodide **423** is formed through iododemetalation of the alkenyl-silver species formed during the reaction.

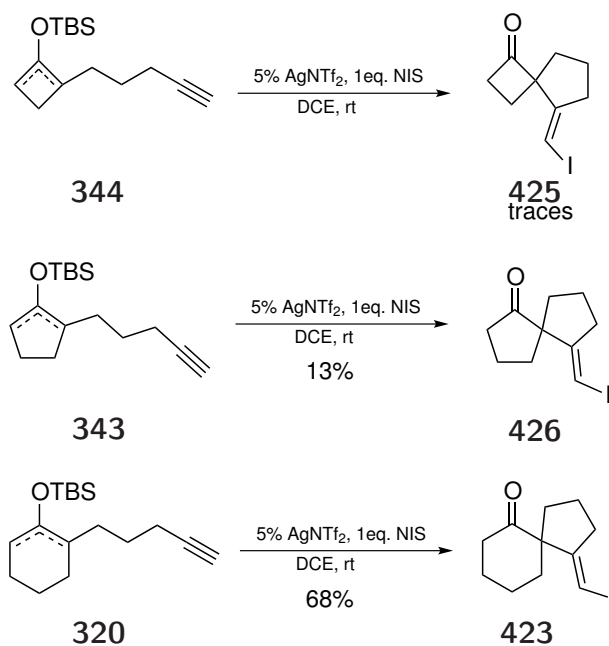
13.4. Reaction scope

Once we had found the optimal reaction conditions for the formation of spirocyclic alkenyl iodides we decided to submit a series of ω -keto alkynes to these conditions.

13.4.1. Unsubstituted ring systems

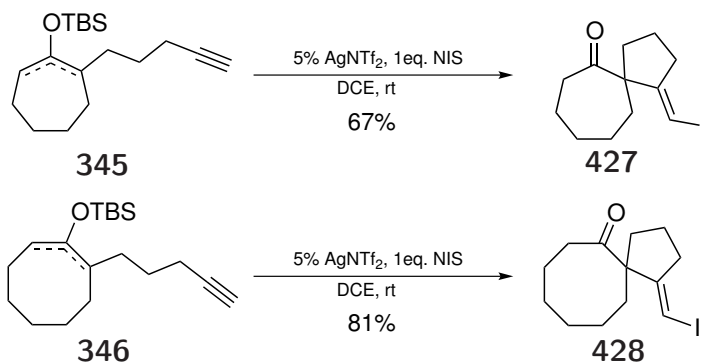
We began our investigations on the reaction scope by using enol ethers derived from ω -keto alkynes with an unsubstituted ring system. The results are summarized in Scheme 13.7 and Scheme 13.8. When the 6-membered ring compound **320** was used as substrate, the desired alkenyl-iodide **423** was isolated in a good yield of 68 %. Yield dropped dramatically when 5-membered ring compound **343** was used: **426** was obtained in only 13 % yield. As for cycloisomerization reactions without NIS (Section 12.2.1), this trend is continued when the 4-membered ring system is employed as substrate. Enol ether **344** gave the alkenyl iodide **425** with a 4-5-spirocyclic system only in trace amounts.

Compounds **423** and **426** were obtained as single isomers, no *exo-endo* double bond isomerization was observed.



Scheme 13.7: Cyclization of TBS enol ethers **320**, **344** and **343** in the presence of NIS.

An interesting observation was made when the enol ethers **345** (7-membered ring) and **346** (8-membered ring) were submitted to the reaction conditions.



Scheme 13.8: Cyclization of TBS enol ethers **345** and **346** in the presence of NIS.

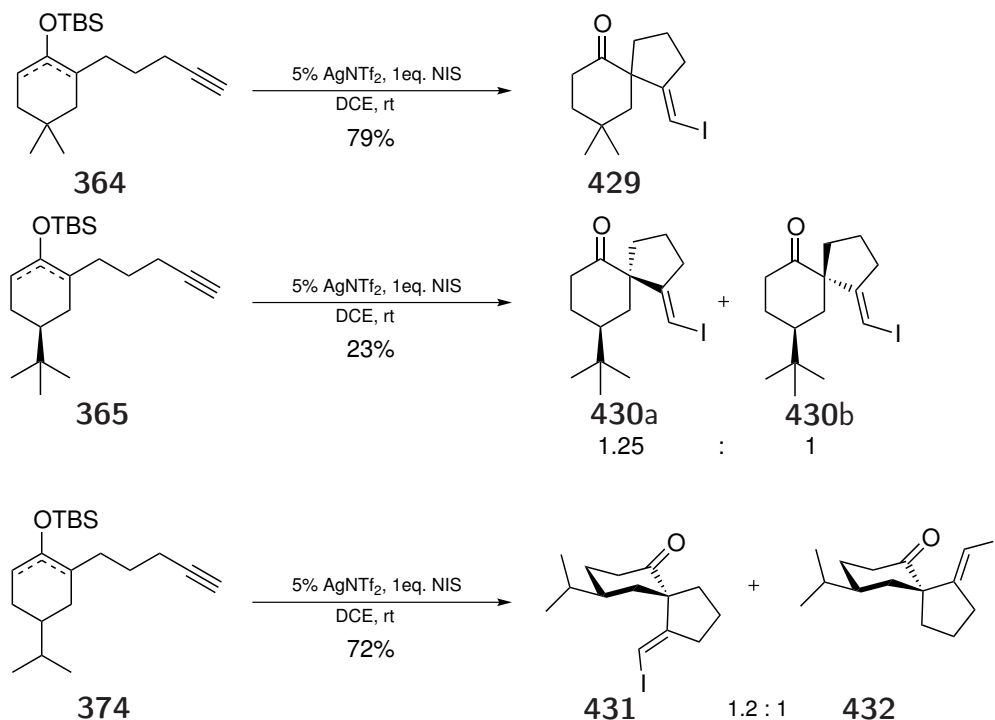
The spirocyclic iodides **427** and **428** were obtained in good yields and as single isomers. Both products contain the [n.4]-spirocyclic motive with an exocyclic double bond. The [n.5]-motive, obtained without NIS, was not observed. The addition of NIS inhibits not only the double bond isomerization but also makes the 5-*exo*-dig cyclization mode preferred over the 6-*endo*-dig cyclization.

13.4.2. Substituted ring systems

We then extended the strategy to substrates bearing a substituent on the ring system to generate the corresponding alkenyl iodides.

Substrates **364** with a 4,4-dimethyl substitution and **374** with a 4-*i*Pr substituent gave the corresponding spirocyclic alkenyl iodides **429** and **431/432** in high yield (Scheme 13.9). The ratio of the two diastereoisomers **431** and **432** was 1.2 : 1.

Likewise, when compound **365** with a 4-*t*Bu substituent was used as starting material a mixture of diastereoisomers of alkenyl iodide **430** in a 1.25 : 1 ratio was obtained.¹ Owing to the formation of an unidentified byproduct, the yield was low (23 %) in this case.



Scheme 13.9: Cyclization of TBS enol ethers **364**, **365** and **374** in the presence of NIS.

13.4.3. Bicyclic ring systems

After having synthesized alkenyl-iodides bearing a substituent on the ring system, we turned our attention towards the reaction of bicyclic substrates with AgNTf₂ in the presence of NIS. When condensed aromatic substrates **385-387** (Table 13.2, entry 1-3) were submitted to the reaction conditions, the corresponding alkenyl-iodides **433-435** were formed in high yields and as single isomers. Again, no isomerization of the double bond could be observed.

To our surprise, compound **396**, which gave only trace amounts of product in the reaction without NIS, was a suitable substrate for the reaction with NIS. Alkenyl-iodide **436** bearing a 5-4-5 ring system is formed in 54 % yield.

¹For better understanding only one of the enantiomers is shown. The attribution of the diastereoisomers has been done arbitrarily to clarify the results obtained.

Table 13.2.: Cyclization of bicyclic TBS enol ethers in the presence of NIS.

Entry	Starting material	Product	Yield
1	 385	 433	78 %
2	 386	 434	80 %
3	 387	 435	73 %
4	 396	 436	54 %

We were pleased to find that **436** provided suitable crystals to obtain a X-ray analysis (Figure 13.1). The X-ray structure confirms the *E* configuration of the double bond, thereby giving evidence for the proposed reaction mechanism.

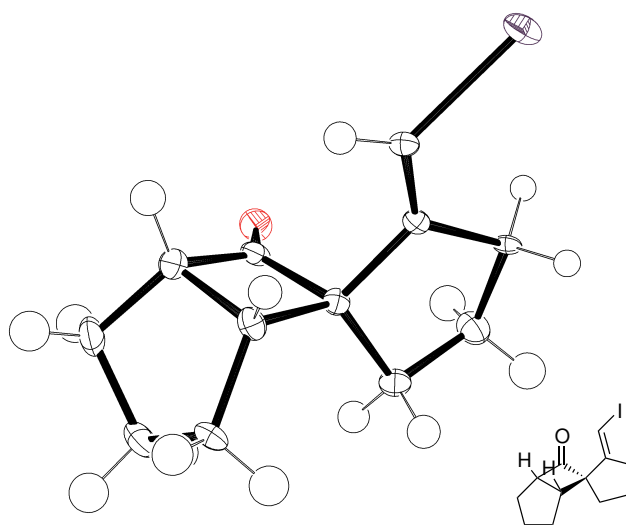
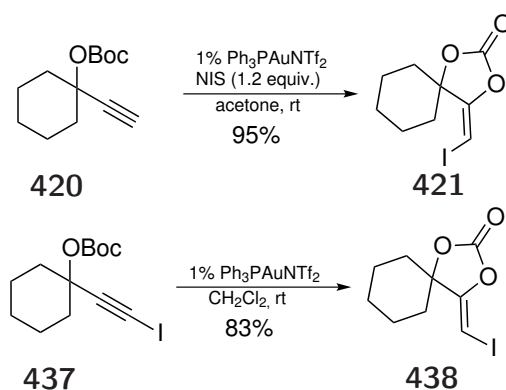


Figure 13.1.: X-ray structure of compound **436**. Ortep view at the 30% probability level.

13.5. Studies towards the synthesis of *Z*-alkenyl-iodides

The cycloisomerization reactions with NIS addition described above yielded in the formation of *E* configured double bonds. The *E*-configuration is due to the iododemetalation of the alkenyl-silver species during the reaction. It should therefore be possible to obtain the corresponding *Z*-alkenyl-iodides when iodine-substituted alkynes are used as substrate. Indeed Gagosz *et al.* showed that *E*- and *Z*-configured double bonds can be obtained depending on the fact whether the halogen atom is already present in the starting material or added during the reaction.[185]



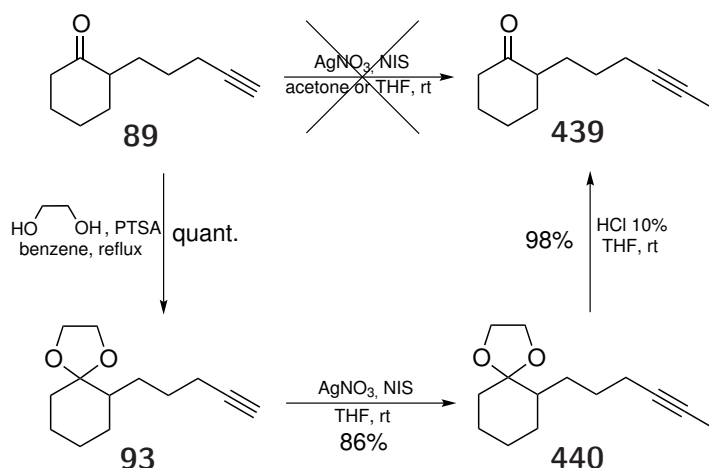
Scheme 13.10: Synthesis of *E*- and *Z*-alkenyl iodide **421** and **438**.

Treating terminal alkyne **420** with NIS under gold-catalysis yielded in the formation of *E*-configured compound **421**. The *Z*-configured isomer **438** was obtained when iodoalkyne **437** was used as starting material using the same catalyst (Scheme 13.10).

13.5.1. Synthesis of the starting material

To do so, we first had to synthesize the iodine substituted starting material. Once again the 6-membered ring substrate was chosen as test-substrate. The functionalization of an alkyne function with a halogen atom is known in the literature and can be performed using catalytic amounts of AgNO_3 and NXS (X = halogen).[133, 190–192]

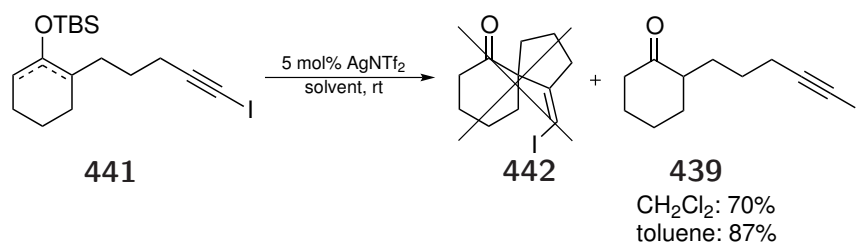
When **89** was treated with AgNO_3 and NIS in THF or acetone, the desired product **439** could not be isolated, even after prolonged reaction times (Scheme 13.11). As NIS is known to perform α -iodation of ketones,[189] we decided to protect the carbonyl function in order to avoid this problem. Thus the formation of **440** proceeded smoothly. Deprotection of **440** under acidic conditions yielded nearly quantitatively compound **439**.



Scheme 13.11: Formation of alkyne-iodide **439**.

13.5.2. Reaction with AgNTf_2

After transformation of **439** into enol ether **441**, the cycloisomerization reaction was performed (Scheme 13.12). Unfortunately, the cyclised product **442** was not obtained. In both solvents tested, the desilylated starting material **439** was recovered in good yields.

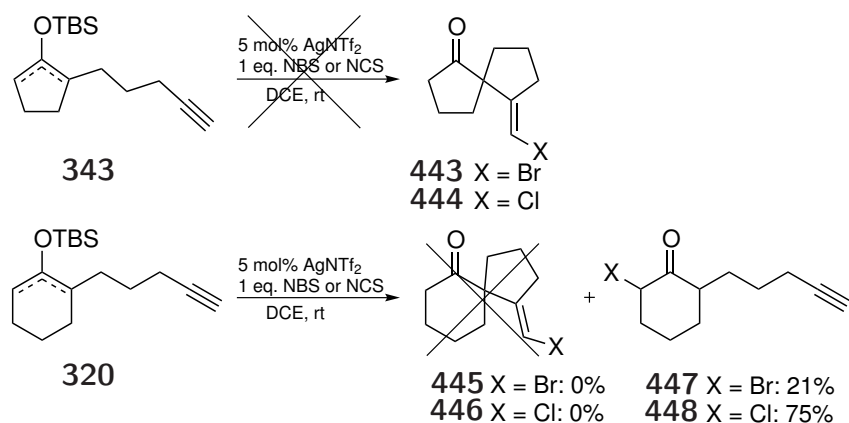


Scheme 13.12: Reaction of TBS enol ether **441** in the presence of NIS.

13.6. Attempts to introduce other functional groups than iodides

After having achieved the transformation of ω -keto alkynes into spirocyclic alkenyl iodides, we envisaged the synthesis of compounds with another functionalization than iodide.

To do so, we used enol ethers **343** and **320** as substrates to perform some test reactions. *N*-halosuccinimides were chosen as source for electrophiles. The results obtained are summarized in Scheme 13.13.



Scheme 13.13: Attempts to introduce chloride and bromide functionalization.

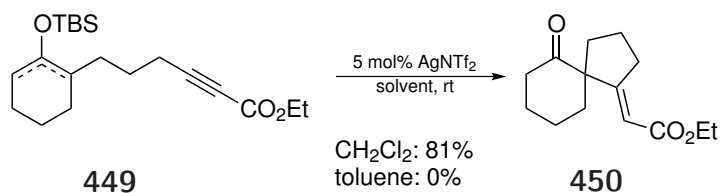
When compound **343** was treated with 5 mol% AgNTf₂ in the presence of *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS), none of the products **443** and **444** could be obtained. Both reaction led to degradation of the starting material. Changing the ring size to a 6-membered ring, unfortunately does not led to the formation of spirocyclic products **445** and **446**. Instead of that, the formation of α -halogenated compounds **447** and **448** was observed in 21 and 75 % yield.

14. Reactivity of acetylenic ω -ketoesters towards AgNTf₂

Having shown that AgNTf₂ can successfully be used for the cycloisomerization of ω -keto alkynes and for the formation of alkenyl iodides, we wondered if a similar silver-catalyzed pathway could account for activated alkynes.

14.1. Reactivity of **96**

We started our investigations on the reactivity of acetylenic ω -ketoesters with compound **96** as test substrate. Transformation into the corresponding TBS-enol ether **449** proceeded smoothly and in quantitative yield. The enol ether obtained was then submitted to the reaction conditions established for the cycloisomerization of ω -keto alkynes (Scheme 14.1).



Scheme 14.1: Reaction of TBS enol ether **449** with AgNTf₂.

With toluene as solvent no cyclized product could be obtained and the desilylated starting material was isolated in 68 % yield instead. To our delight, subjecting alkyonate **449** to the silver catalyzed cycloisomerization condition in CH₂Cl₂ afforded spiroester **450** in 81 % yield. NMR-spectra indicated that the product was obtained with the *E*-configured double bond. This was unambiguously confirmed by the X-ray structure obtained for the compound (Figure 14.1). To our knowledge this was the first selective synthesis of the spiroester **450**.^[1–3]

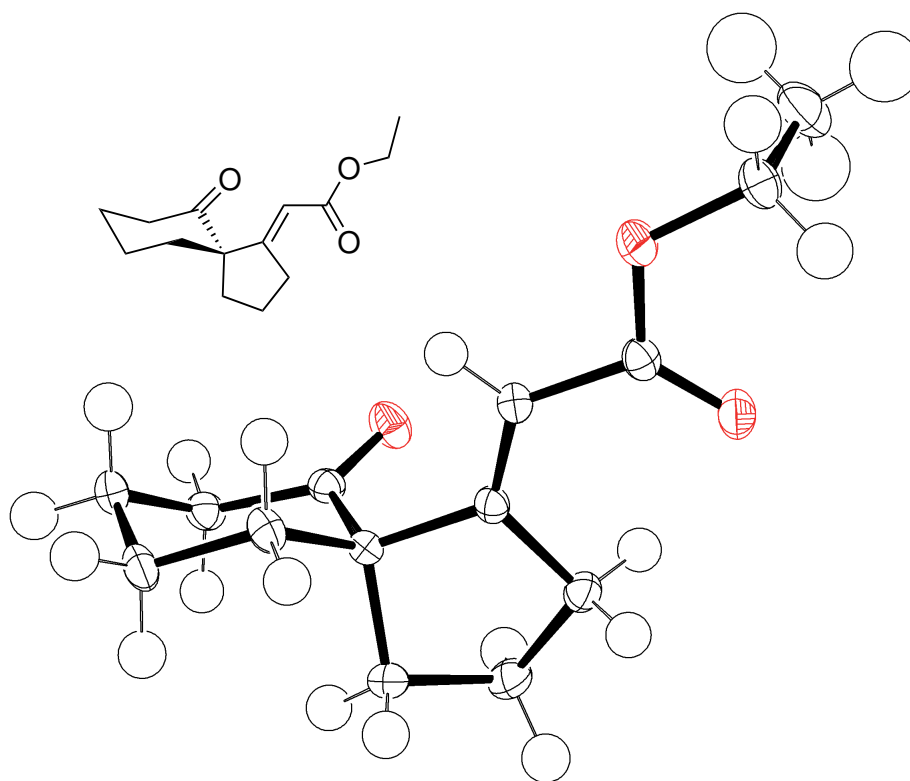
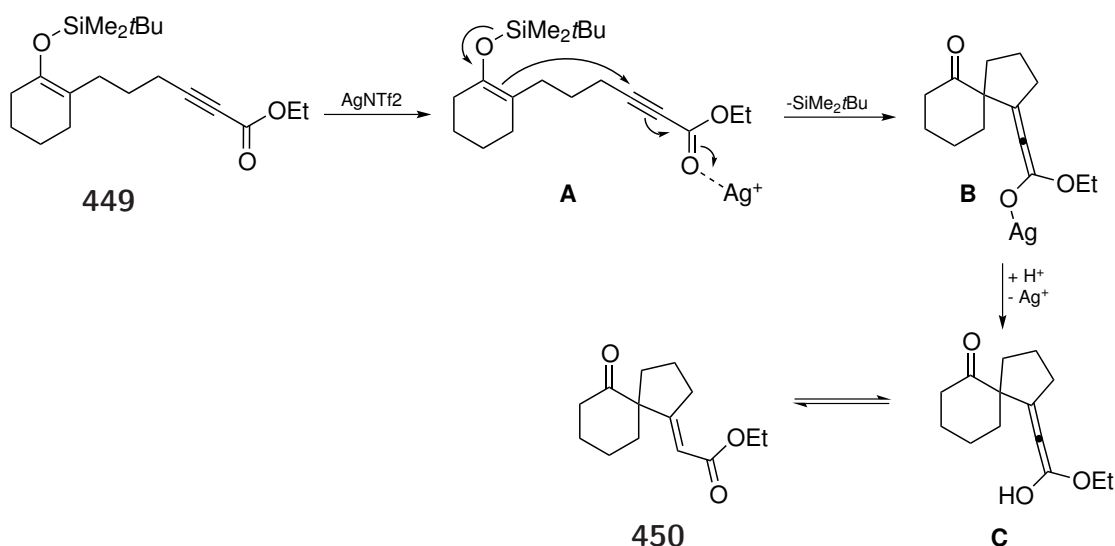


Figure 14.1.: X-ray structure of compound **450**. Ortep view at the 30% probability level.

The finding that the *E*-configured compound **450** was formed exclusively and not the *Z*-configured compound was surprising. If the reaction follows the same mechanism as described above (i.e. activation of the triple bond by the Ag-catalyst followed by *anti* attack of the enol) the reaction should furnish a *Z* double bond.

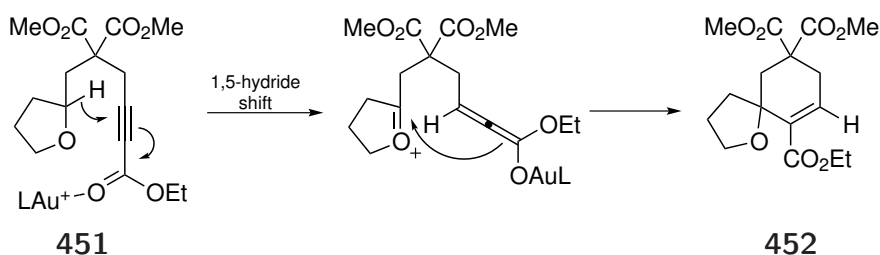
14.2. Mechanistic considerations

A possible explanation for the formation of *E*-configured product is shown in Scheme 14.2. Instead of complexation onto the triple bond, the Ag(I)-catalyst can complex to the carbonyl-group of the ester moiety (**A**). Subsequent Michael-addition would furnish intermediate **B**. Protonation of **B** leads to **C** which upon isomerization gives ester **450** with the *E*-configured double bond.



Scheme 14.2: Possible mechanism for the formation of **450**.

An analog possible reaction pathway for the cycloisomerization of ester-substituted alkynes was proposed by Gagosz *et al.*[193] They proposed an initial coordination of the cationic gold(I) complex to the carbonyl group of the ester **451** inducing a hydride transfer leading to the formation of the cyclisomerized products **452** after nucleophilic addition of the gold allenolate moiety onto the oxonium intermediate (Scheme 14.3).

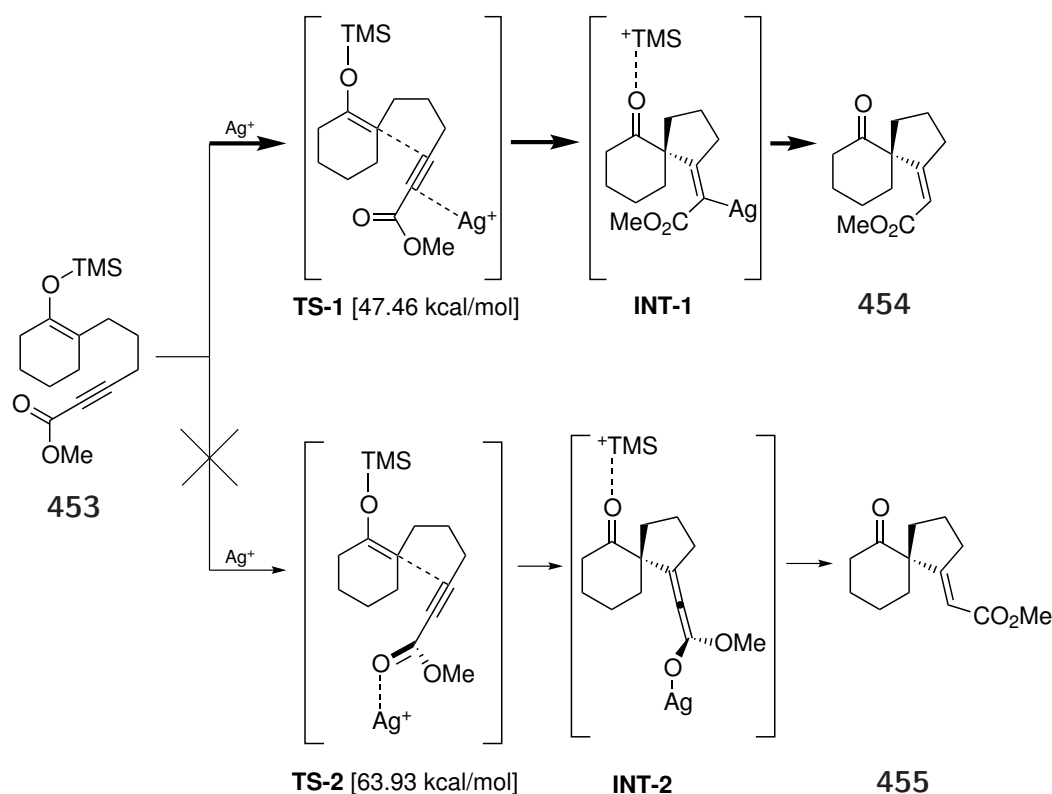


Scheme 14.3: Mechanistic explanation for the formation of compound **452** via an allene intermediate.

To gain some insights into the complexation mechanism, computational studies have been achieved.¹ Semi-empirical calculations have been performed with the simplified substrate **453** at PM6 level (Scheme 14.4).

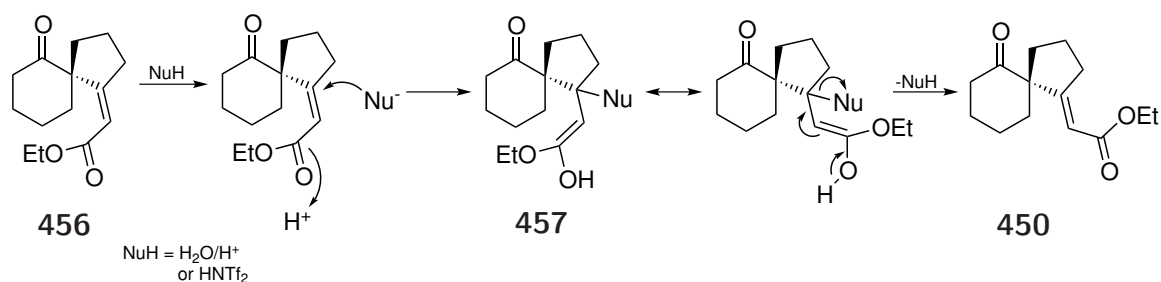
The computational studies showed that the transition state **1** (**TS-1**) where the silver complexes the triple bond is 16.47 kcal/mol more stable than **TS-2** where the silver is complexed to the carbonyl-group. **TS-1** leads to intermediate **1** (**INT-1**) which gives *Z* configured compound **454**. **TS-2** in contrast leads to **INT-2** and **455** after hydrolysis.

¹Calculations have been performed in the group of Prof. Isamu Shiina at Tokyo University of Science (Japan) by Keisuke Ono.



Scheme 14.4: Possible mechanism for the formation of **450**.

Thus the formation of the *Z*-configured compound **456** is energetically more favorable. The experimentally found formation of the *E*-compound **450** by cycloisomerization of **449** can then be explained through an isomerization of the double bond via a Michael-retro-Michael mechanism (Scheme 14.5). Under acidic conditions the 1,4-addition of a nucleophile to the unsaturated ester is possible to form the intermediate **457**. Bond rotation around the former double bond and retro-Michael reaction would then lead to *E*-configured compound **450**. This isomerization can happen during the reaction with HNTf_2 as nucleophile or during the work-up procedure with $\text{H}_2\text{O}/\text{H}^+$ or HNTf_2 as nucleophile.

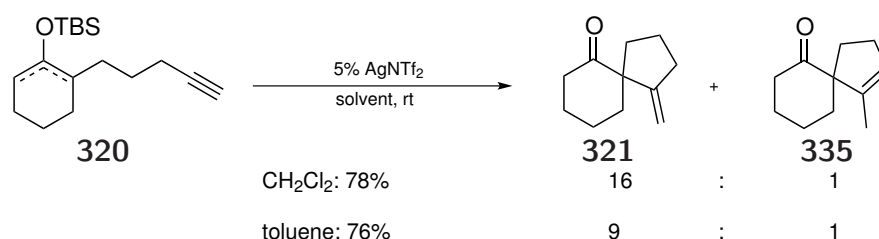


Scheme 14.5: Possible mechanism for the isomerization of **456** to **450**.

15. Summary

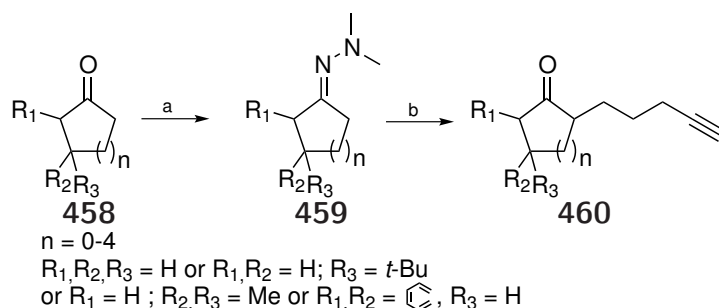
During our work on noble metal catalyzed cycloisomerization reactions we could show that not only gold(I) complexes are suitable catalysts but also the simple silver(I) salt AgNTf₂ can be used for the cycloisomerization of ω -keto alkynes.

We started our investigation using the ω -keto alkyne **89** as substrate. Optimization of the reaction conditions for the cycloisomerization of TBS-enol ether **320** showed that the reaction is best performed using dry CH₂Cl₂ or toluene as solvent. The yield of the reaction was high and the products were obtained with satisfying product distribution (Scheme 15.1).



Scheme 15.1: Cyclization of TBS enol ethers **320**.

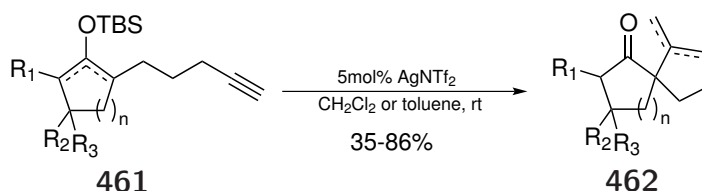
With this conditions in hand we proceeded to the synthesis of a panel of ω -keto alkynes with different ring size and substitution pattern. These compounds can be obtained in two steps from the commercially available ketones (Scheme 15.2).



Scheme 15.2: Synthesis of ω -keto alkynes with different ring size and substitution pattern.

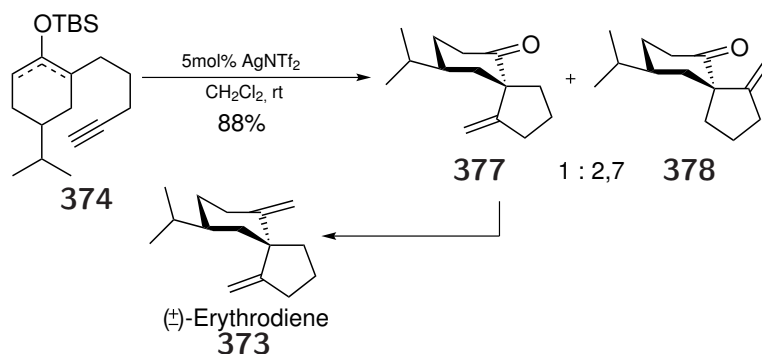
a) Me₂NNH₂, trifluoroacetic acid, benzene, reflux ; b) *n*-BuLi, I(CH₂)₃CCH, THF, -30 °C then HCl 10 %, rt.

We were pleased to find that for most of the substrates the cycloisomerization works well and products are obtained in good yields (Scheme 15.3). It turned out that the *exo*-/*endo*-selectivity is substrate and solvent dependent.



Scheme 15.3: Cycloisomerization reaction of TBS-enol ethers **461** with AgNTf₂.

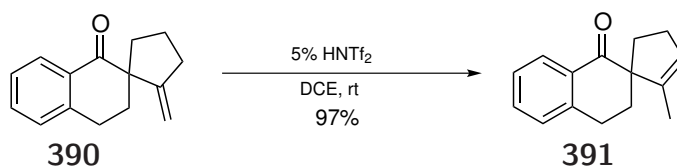
The developed method has then been used to complete the formal total synthesis of the natural product Erythrodiene **373** in its racemic form.



Scheme 15.4: Formal total synthesis of (±)-Erythrodiene.

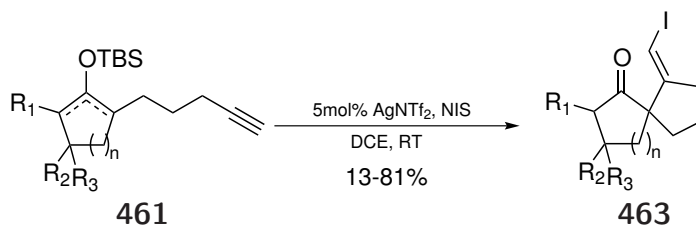
The mechanistic investigation undertaken revealed that AgNTf₂ not only promotes the cycloisomerization reaction but is also able to perform the isomerization of a kinetic enol ether into the thermodynamic silyl enol ether and thus allows the use of both silyl enol ethers as substrates for the cycloisomerization reaction.

It has also been shown that the *endo*-compounds are probably formed by isomerization of the *exo*-compound under acidic conditions.



Scheme 15.5: Isomerization of *exo*-double bond into *endo*-double bond with AgNTf₂.

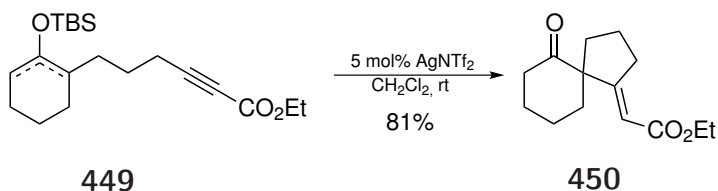
We were also able to show that the proposed alkenyl-silver intermediate can be trapped with an electrophile. Performing the reaction in the presence of NIS as electrophile yields in the formation of the corresponding alkenyl iodides **463**.



Scheme 15.6: Synthesis of alkenyl iodides **463**.

Under these conditions only one isomer with an *E*-configured double bond was obtained. The structure and double bond configuration of the alkenyl iodides was unambiguously proven by X-ray crystallography. The structure of the alkenyl iodides is in agreement with the proposed mechanism for the cycloisomerization reaction.

Furthermore, we could show that the conditions of the cycloisomerization reaction are applicable to activated alkynes. The transformation **449** under AgNTf₂ catalysis gave *E*-configured spiroester **450** in high yield. The structure of **450** was proven by X-ray crystallography.



Scheme 15.7: Reaction of TBS enol ether **449** with AgNTf₂.

Computational studies showed that the reaction proceeds via the same mechanism as for terminal alkynes, followed by double bond isomerization, probably via a Michael-retro-Michael mechanism.

Part III.

Reactivity of spirocyclic γ -methylene ketones

16. Synthesis of the tricyclic core of natural products

A large group of bioactive natural diterpenoids possesses a quaternary carbon incorporated within a spirocyclic system that is part of a more complex ring system. Some examples are shown in Figure 16.1. A 6-6-5-fused ring system is present in Salviatriene B, Colombiasin A and Elisabethin A. Aberrarone possesses a 6-5-5-fused ring system whereas Elisapterosin B has a 6-6-5- and a 6-5-5-fused ring system at the same time.

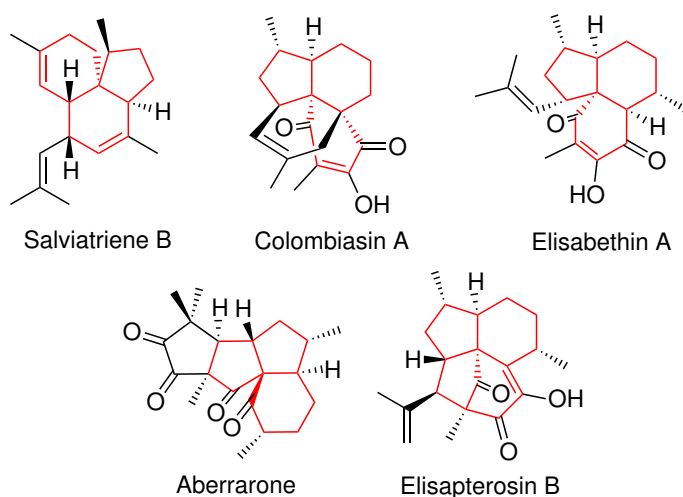
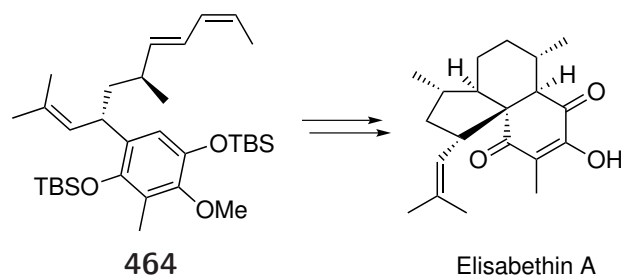


Figure 16.1.: Structure of selected natural products containing a 6-6-5- or 6-5-5-fused ring system.

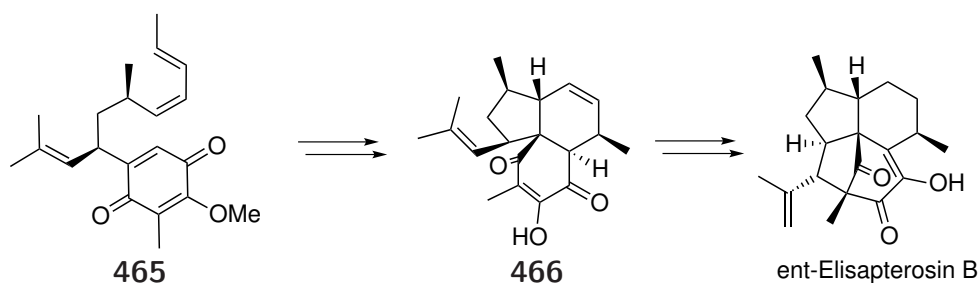
Salviatriene B was isolated from *Salvia sclarea*. Extracts from this plant showed activity against a range of different biological targets.[194] Colombiasin A, Elisabethin A, Aberrarone and Elisapterosin B were isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae*. [195–198]

Elisabethin A, isolated in 1998,[196] was synthesized by Mulzer and co-worker in 2003.[199] The compound showed significant in vitro cell cancer cytotoxicity. The synthesis of Mulzer employed an intramolecular Diels-Alder reaction of **464** as a key step for the formation of the tricyclic skeleton (Scheme 16.1).



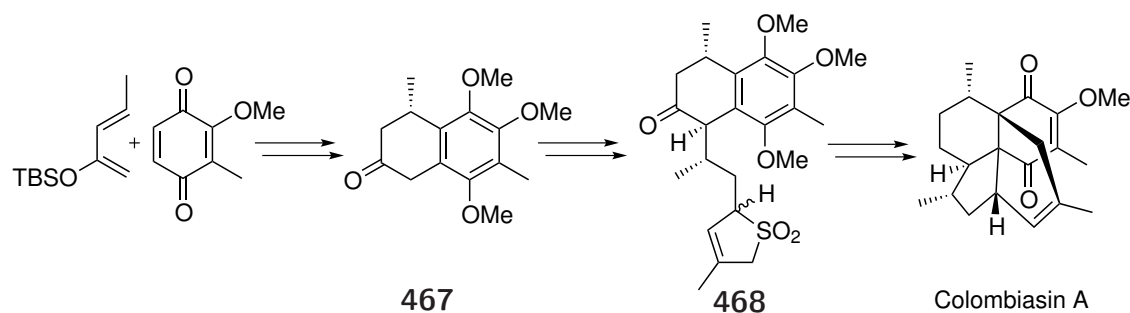
Scheme 16.1: Synthesis of Elisabethin A by Mulzer *et al.*

For Elisapterosin B, isolated in 2000,[198] no biological activity has been found until today. But it seems not unlikely that there is one regarding the high activity of the other members of its family. The synthesis of *ent*-Elisapterosin B has been achieved by Rawal *et al.* in 2003 (Scheme 16.2). They first synthesized the Elisabethin precursor **466** through intramolecular Diels-Alder reaction of **465**. An oxidative cyclization furnished then *ent*-Elisapterosin B.



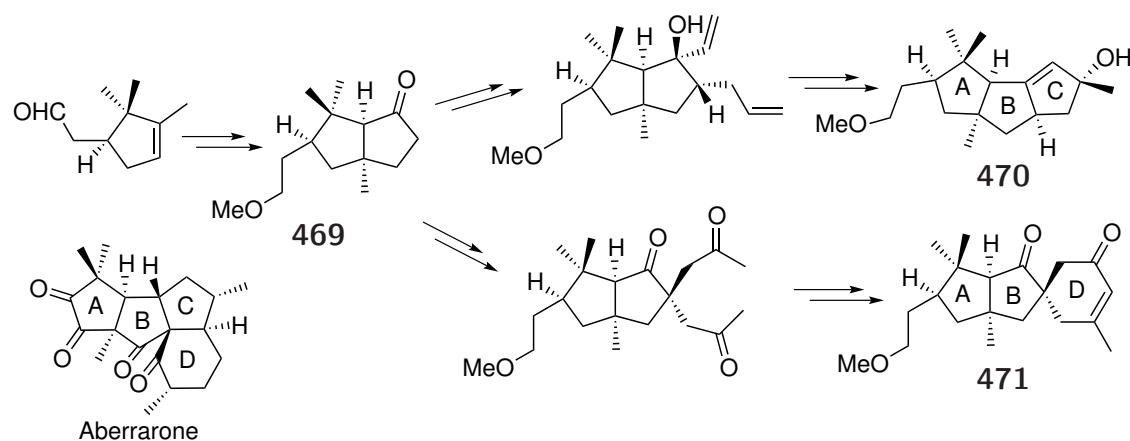
Scheme 16.2: Synthesis of *ent*-Elisapterosin B A by Rawal *et al.*

Colombiasin A, isolated in 2000, showed activity against a tuberculosis bacterium strain[195] and antimalarial activity.[197] A total synthesis of this compound has been achieved by Nicolaou *et al.*[200, 201] The synthesis of a diastereoisomer was described by Harrowven and co-workers.[202] Nicolaou *et al.* used two Diels-Alder-reactions as key steps in their enantioselective synthesis. First, compound **467** was synthesized using an asymmetric Diels-Alder reaction. After transformation of **467** into **468** the latter was used in a thermal Diels-Alder reaction after extraction of SO₂ to yield finally (-)-Colombiasin A (Scheme 16.3).



Scheme 16.3: Synthesis of (-)-Colombiasin A by Nicolaou *et al.*

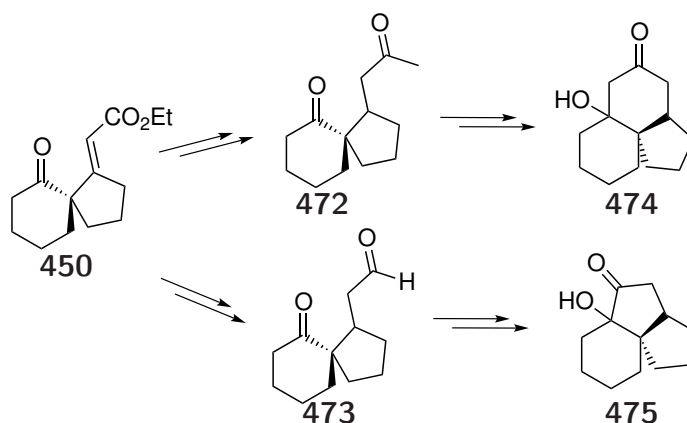
Aberrarone was one of the last compounds isolated from *P. elisabethae* and possesses a unique carbon skeleton.[197] As Colombiasin A, Aberrarone showed high activity against a common etiologic malaria agent. Until now no total synthesis of this compound is known even though Srikrishna and co-worker published the synthesis of two parts of the carbon skeleton.[203] Starting from chiral (*S*)-campholenaldehyde, they synthesized the intermediate **469** which served for the synthesis of the ABC and ABD ring system. Alkylation and ring closing in α -position of the ketone led to the Aberrarone subsystems **470** and **471** (Scheme 16.4).



Scheme 16.4: Synthesis of Aberrarone tricyclic cores by Srikrishna *et al.*

Objective

Having obtained the spiroester **450**, our aim was to explore the possibility of using this molecule as a starting material for the synthesis of the tricyclic core of natural products described above. The two ring systems (6-6-5 and 6-5-5) should be accessible via two approaches using the ketone **472** on the one side and aldehyde **473** on the other side as substrates for the formation of **474** and **475** respectively (Scheme 16.5). For a better understanding, only one of the enantiomers for the spirocyclic compounds is presented throughout this chapter.

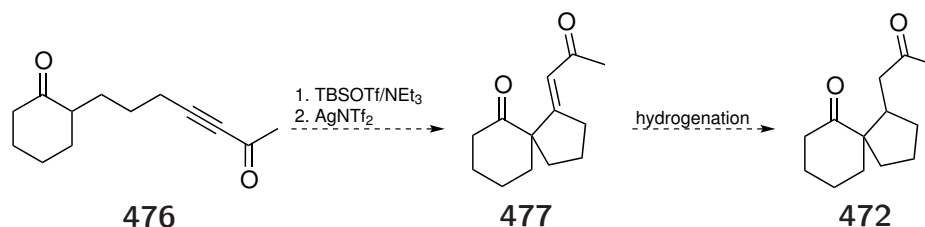


Scheme 16.5: Envisaged synthesis of tricyclic compounds **474** and **475**.

While **474** should be available through intramolecular aldol reaction of **472** a NHC-catalyzed cyclization[204] of **473** should give **475**.

16.1. Synthesis of ketone **472** through silver catalyzed cycloisomerization

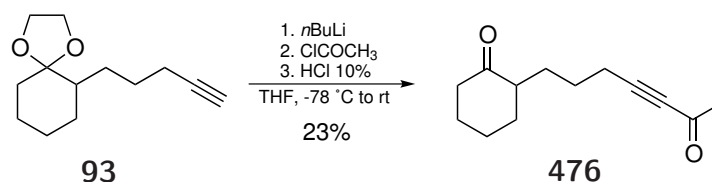
In a first attempt we tried to synthesize ketone **472** via direct Ag(I)-catalyzed cyclization of the acetylenic ketone **476** followed by the reduction of the double bond of compound **477**.



Scheme 16.6: Synthetic plan for the synthesis of **472**.

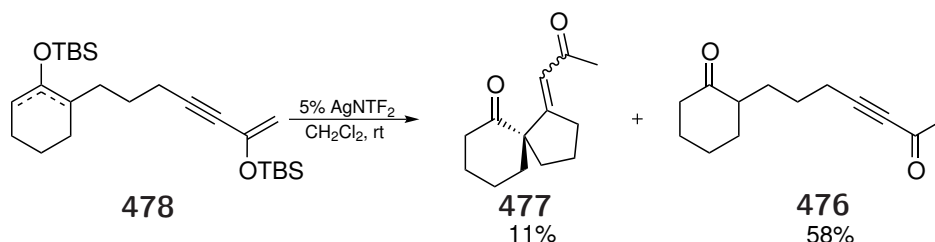
16.1.1. Synthesis of the starting material

First, we had to synthesize the desired starting material **476**. To do so, we used the protected ω -keto alkyne **93** as substrate and a similar strategy as for the synthesis of acetylenic ω -ketoesters was applied. The alkyne was deprotonated with *n*BuLi and subsequently treated with acetyl chloride to give **476** (Scheme 16.7). Unfortunately, we obtained only a low yield of 23%. This low yield may be due to the fact that the pK_a of the formed ketone **478** is lower than the pK_a of the alkyne **478**. This allows the protonation of the alkyne by the ketone and thus the neutralization of the reactive species.

Scheme 16.7: Synthesis of **476** from **93**.

16.1.2. Reaction with AgNTf₂

With ketone **476** in hand, we tested its behavior under the cycloisomerization conditions. Therefore, we first had to transform **476** into the corresponding silyl-enol ether. As **476** possesses two carbonyl functions, we decided to transform both of them into silyl-enol ethers. The bis-silyl-enol ether **478** was obtained in quantitative yield and submitted to the conditions of the cycloisomerization reaction (Scheme 16.8).

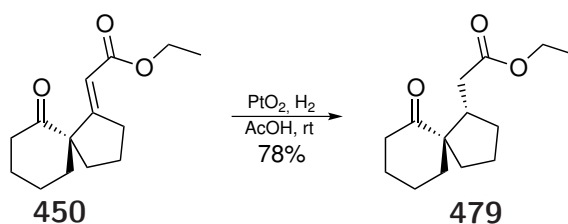
Scheme 16.8: Reaction of **478** with AgNTf₂.

The desired product **477** was obtained in a low yield of 11 %, together with 58 % of the deprotected starting material. The configuration of the double bond could not be definitely established, but was thought to be *E* in analogy to the ester-substituted compound **450**.

16.2. Synthesis of ketone **472** from ester **450**

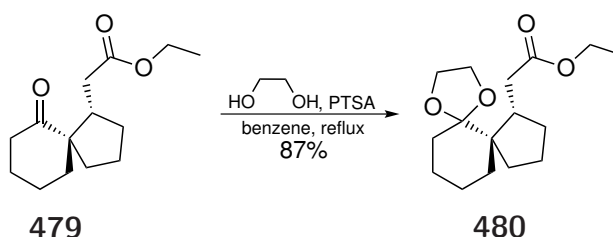
As both the formation of alkynyl ketone **476** and its cycloisomerization gave only low yields, we decided to pursue another strategy for the synthesis of spirocyclic ketone **472**. Starting from spirocyclic ester **450**, the ketone should be accessible through appropriate side chain transformations.

In the first step of the synthesis of ketone **472**, the α , β -unsaturated spirocyclic ester **450** was hydrogenated with PtO₂ (Adam's catalyst)[205, 206] to yield saturated spirocyclic ester **479** in 78 % yield. Molecular modelling shows that the access to one of the faces of the double bond is less sterically hindered and thus reduction appears preferentially via this side. Evidence for this was furnished by the X-ray structure obtained for one of the tricyclic compounds (Figure 16.2 p. 134). The structure allowed the determination of the relative stereochemistry as shown for **479**.



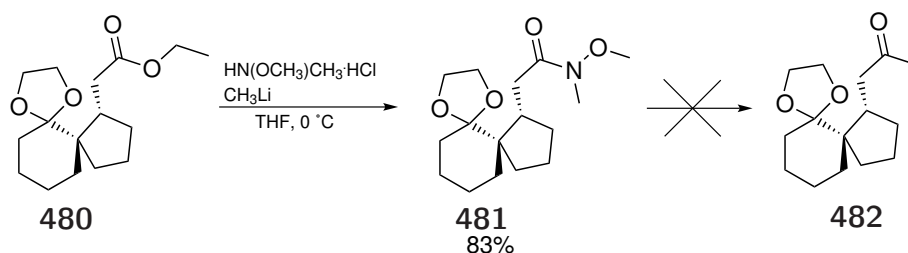
Scheme 16.9: Reduction of **450** to **479**.

To be able to work on the ester-function, we decided to protect the ketone functional group. Protection as dioxolane using standard conditions worked well and gave protected ketone **480** with 87 % yield (Scheme 16.10).



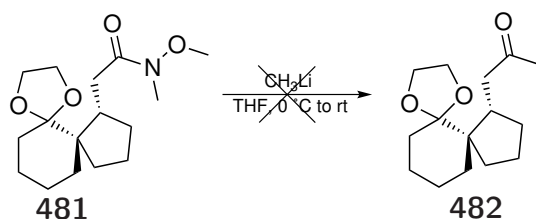
Scheme 16.10: Protection of saturated spirocyclic ester **450**.

Our goal was then to transform the latter into the corresponding methyl ketone. To do so, we first chose to use the Weinreb ketone synthesis.[207] A one pot synthesis without isolation of the corresponding amide was envisaged.[208] Thus the ester **480** was treated with *N,O*-dimethylhydroxylamine and an excess methyl lithium in THF at 0 °C. Amide **481** should be formed as intermediate and transformed directly in the ketone **482**. Unfortunately the reaction stopped at the stage of the amide **481** which was isolated in 83 % yield (Scheme 16.11).



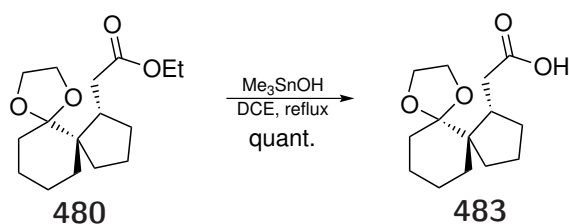
Scheme 16.11: Attempt to transform **480** into ketone **482**.

We then tried to transform amide **481** in a separate reaction into ketone **482**. When **481** was treated with MeLi in THF at 0 °C no reaction was observed. Warming the reaction to room temperature led only to degradation of the starting material and the ketone **482** was not obtained (Scheme 16.12).



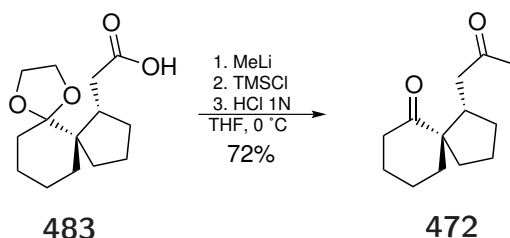
Scheme 16.12: Attempt to transform the amide **481** into ketone **482**.

We then decided to change the strategy and transform **480** into the corresponding acid **483** which could be further transformed into the ketone **482**. To achieve the acidification of the ester, we chose a method described by Nicolaou *et al.*[209] This method using Me_3SnOH proved to be a mild method for the hydrolysis of esters and has been successfully applied to the hydrolysis of esters in the presence of a dioxolane protecting group in our laboratory.[210] When submitting the ester **480** to the reaction conditions, we were pleased to find that the acid **483** was obtained in quantitative yield (Scheme 16.13).



Scheme 16.13: Transformation of ester **480** into acid **483**.

The next step consisted of the transformation of the acid **483** into the ketone **472**. We chose a method described by Rubottom for this transformation.[211] Reacting the acid **483** with MeLi in THF at 0°C and treating the crude reaction mixture with TMSCl yielded the ketone **472** in 72 % after acidic work-up (Scheme 16.14).

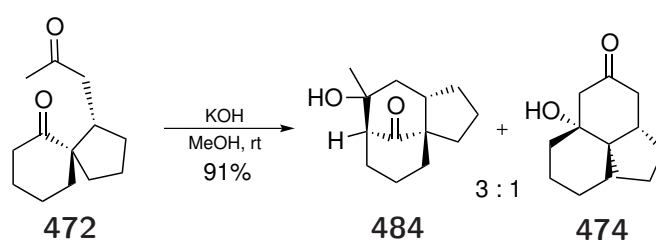


Scheme 16.14: Transformation of acid **483** into ketone **472**.

16.3. Cyclization of ketone 472

16.3.1. Cyclization of ketone 472 under basic conditions

Once we had obtained the ketone **472** we explored the possibility to cyclize this compound and obtain the tricyclic compound **474**. In a first attempt we submitted **472** to basic conditions to perform an aldol-reaction. Performing the reaction with KOH led to an unseparable mixture of two products, the bridged compound **484** together with the desired tricyclic compound **474** (Scheme 16.15) as a 3 : 1 mixture in favor of the bridged compound **484** (determined by NMR-spectroscopy) in 91 % overall yield.



Scheme 16.15: Reaction of ketone **472** with KOH/MeOH.

We were able to obtain a crystal structure for compound **474** (Figure 16.2) thus providing evidence for the structure of compound **474**.

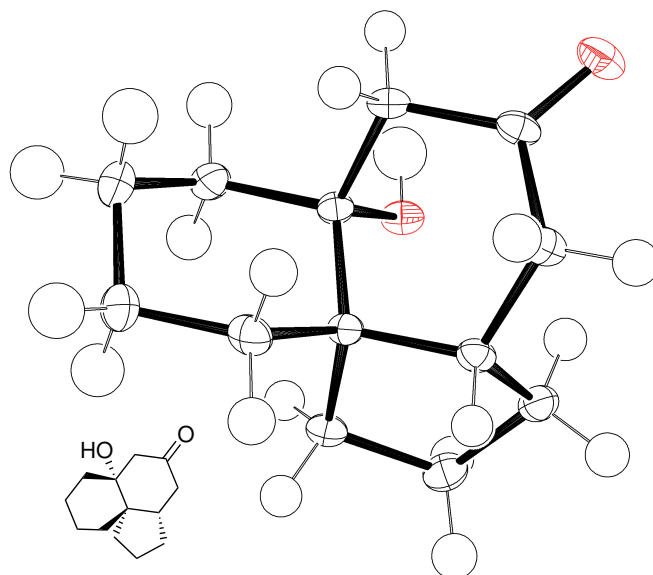
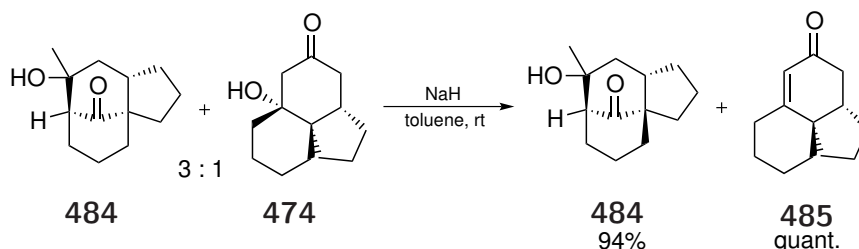


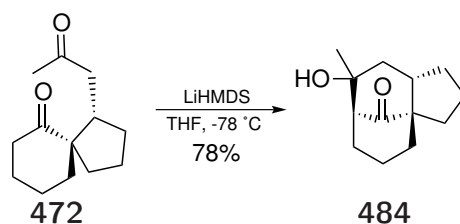
Figure 16.2.: X-ray structure of compound **474**. Ortep view at the 30% probability level.

We then decided to perform an elimination reaction on the obtained mixture. Submitting the mixture of **484** and **474** to NaH in toluene at room temperature for 2 h led to eliminated product **485** in quantitative yield, together with unchanged tricyclic compound **484**, allowing this time the isolation of compound **485** (Scheme 16.16).



Scheme 16.16: Elimination reaction to form compound **485**.

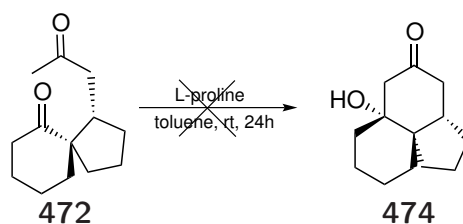
To increase the amount of the tricyclic product **474**, we decided to change the reaction conditions. In general, the deprotonation of a terminal methyl ketone is preferred over the deprotonation of the cyclic ketone when the reaction is performed at low temperature and a sterically hindered base is used.[67] To our surprise, when reacting ketone **472** with LiHMDS in THF at $-78\text{ }^{\circ}\text{C}$, we exclusively obtained the bridged compound **484** in 78 % yield (Scheme 16.17).



Scheme 16.17: Reaction of ketone **472** with LiHMDS.

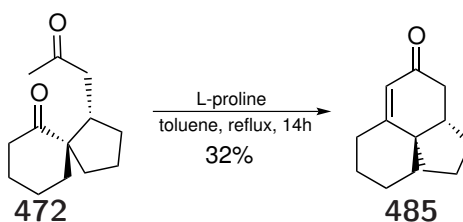
16.3.2. Cyclization of ketone 472 using organocatalysis

Having obtained these results under basic conditions, we decided to explore the possibility to use organocatalysis to favour the formation of tricyclic compound **474**. In a first attempt, we employed **472** in a proline-catalyzed reaction.[212] Performing the reaction at room temperature did not lead to the formation of any product, even after prolonged reaction times (24h, Scheme 16.18).



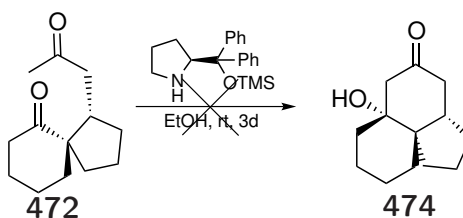
Scheme 16.18: Reaction of ketone **472** using L-proline as organocatalyst.

When the reaction is heated to reflux in toluene, compound **485** was formed in 32 % yield. Elimination occurs directly after cyclization and the formation of **474** was not observed.



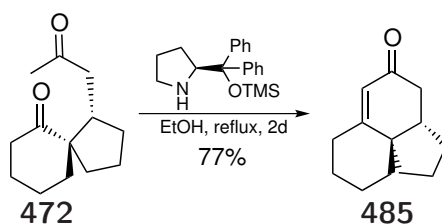
Scheme 16.19: Reaction of ketone **472** using L-proline as organocatalyst at high temperature.

With regard to low yield and the fact that only the elimination product **485** was obtained, we decided to change the catalyst and use a diphenylprolinol silyl ether instead of proline.[213] When the reaction was performed at room temperature no reaction occurred (Scheme 16.20).



Scheme 16.20: Reaction of ketone **472** using a diphenylprolinol silyl ether as organocatalyst.

Changing the reaction conditions and heating the reaction to reflux in ethanol yielded in the formation of elimination product **485** in 77 % yield (Scheme 16.21). In contrast to the reaction using proline as catalyst the formation of **474** was observed by TLC at the beginning of the reaction. A careful optimization of the reaction conditions could maybe lead to the formation of **474** without further elimination and thus the possibility of an enantioselective catalysis would be given.

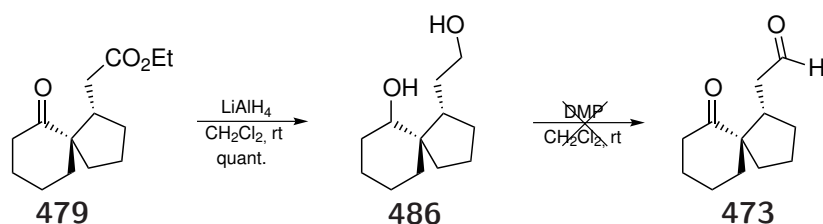


Scheme 16.21: Reaction of ketone **472** using a diphenylprolinol silyl ether as organocatalyst at high temperature.

Having obtained the synthesis of the 6-6-5-fused tricyclic compound **485**, we turned our attention towards the synthesis of the 6-5-5-fused tricyclic system.

16.4. Synthesis of aldehyde **473** from ester **450**

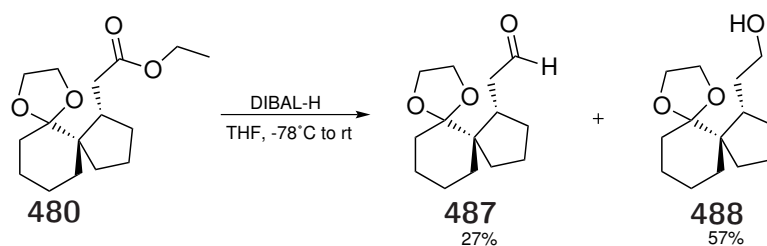
To use aldehyde **473** as starting material, we first had to achieve its synthesis. As for the ketone **472**, reduction of the double bond to obtain the saturated ester **479** was the first step for the synthesis of the requisite aldehyde **473**. In a first attempt, we thought of a subsequent reaction sequence involving the complete reduction of the unsaturated ester **479** to the diol **486** and selective reoxidation to the aldehyde. Ester **479** was reduced to the diol **486** using LiAlH_4 in quantitative yield. Unfortunately oxidation of the diol to the aldehyde using Dess-Martin-reagent failed (Scheme 16.22).



Scheme 16.22: Complete reduction of **479** and failed oxidation to aldehyde **473**.

We therefore decided to protect the ketone functionality of **479** to perform the reduction of the ester functionality selectively. After protection of the ester **479** as dioxolane, we thought that it should be possible to perform a selective reduction of the ester function to the aldehyde using DIBAL-H. This methodology worked well for the selective reduction of chiral ester **129** and **130** to chiral aldehydes **131** and **132** (Section 5.1).

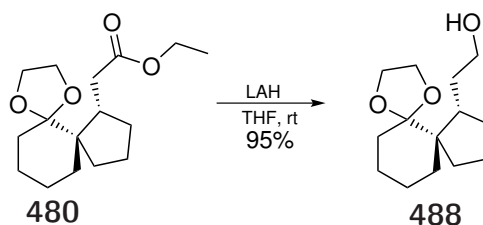
Unfortunately, when performing the reaction at low temperature, no evolution could be observed by TLC. When warming the reaction mixture slowly to room temperature, both the aldehyde **487** and the corresponding alcohol **488** were obtained (Scheme 16.23).



Scheme 16.23: Reduction of ester **480** with DIBAL-H.

Even prolonged reaction times at $-78\text{ }^{\circ}\text{C}$ did not increase the conversion of the ester into the aldehyde. To force the reaction towards complete reduction to the alcohol **488** by addition of excess DIBAL-H failed as well.

As it was obvious that using DIBAL-H did not give a selective reduction of the ester, we decided to perform a complete reduction of the ester functionality using LAH as reducing reagent. This time, the reduction of ester **480** to alcohol **488** proceeded in high yield (Scheme 16.24).

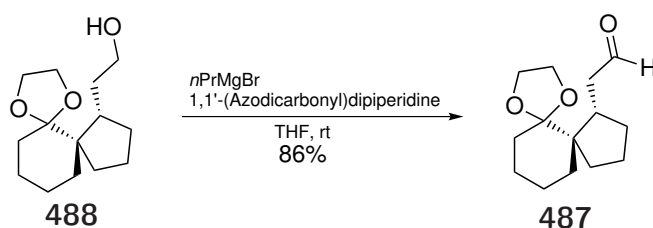


Scheme 16.24: Reduction of ester **480** with LAH.

For the following oxidation, a methodology had to be chosen which ensures that no overoxidation of the aldehyde to the corresponding acid takes place. In addition, we had to make sure that the chosen methodology is compatible with the dioxolan protecting group.

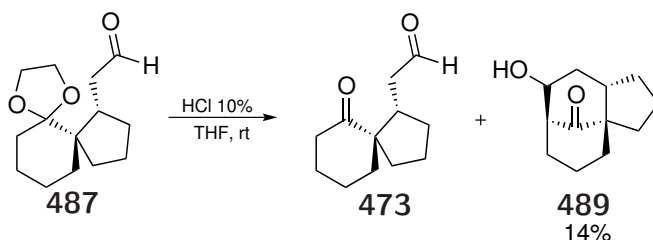
First, we tried to oxidize the alcohol to the aldehyde under Swern-conditions.[214, 215] Unfortunately, the latter led only to a mixture of various unseparable and unidentified products.

During former work in the group it was shown that an oxidation of alcohols to aldehydes proceeds smoothly under mild conditions using reaction conditions first shown by Mukaiyama *et al.*[216] Using this reaction we were able to obtain the desired aldehyde **487** with a good yield (Scheme 16.25).



Scheme 16.25: Oxidation of alcohol **488** to aldehyde **487**.

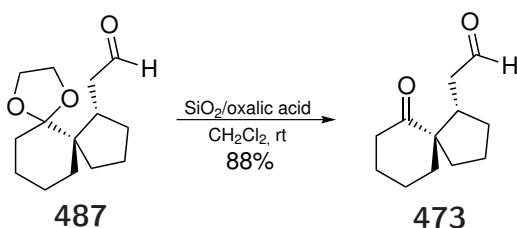
Once the protected aldehyde was obtained, we had to remove the protecting dioxolane to obtain the desired keto-aldehyde **473**. Using a standard protocol developed in our laboratory for the deprotection of dioxolanes (10% HCl in THF), we obtained aldehyde **473** as a mixture containing various impurities together with the bridged molecule **489** in 14 % yield (Scheme 16.26). Compound **489** is probably formed by an aldol-reaction of **473** in the acidic reaction mixture.



Scheme 16.26: Deprotection of protected ketone **487** with HCl 10%.

Although we obtained this interesting bridged tricyclic molecule **489**, we were displeased by the fact we did not obtain aldehyde **473** as pure compound nor was the tricyclic product **489** acquired in good selectivity and good yield. To circumvent this problem, we thought of another possibility to remove the dioxolane group without promoting the aldol reaction.

This deprotection could be obtained using the conditions of Conia *et al.*[217] Submitting the protected ketone to wet silica gel in DCM yielded selectively the desired keto-aldehyde **473** with good yield (Scheme 16.27). Under this conditions the formation of tricyclic product **489** was not detected.

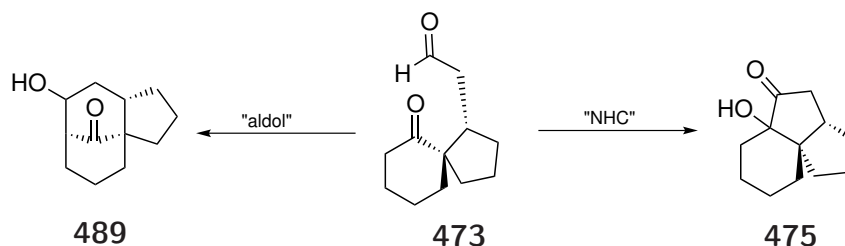


Scheme 16.27: Deprotection of protected ketone **487** with SiO₂/oxalic acid.

16.5. Cyclization of 473: Synthesis of tricyclic products 489 and 475

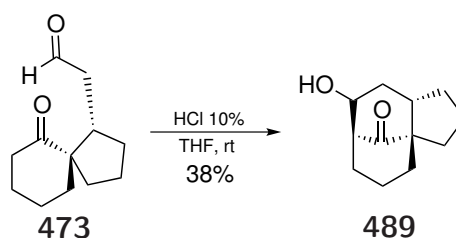
16.5.1. Cyclization of 473 under acidic conditions

Once the keto-aldehyde **473** was obtained, we tested different possibilities to cyclize this molecule. In addition to the bridged molecule **489**, we had to synthesize the tricyclic molecule **475** (Scheme 16.28).



Scheme 16.28: Accessible tricyclic molecule starting from keto-aldehyde **473**.

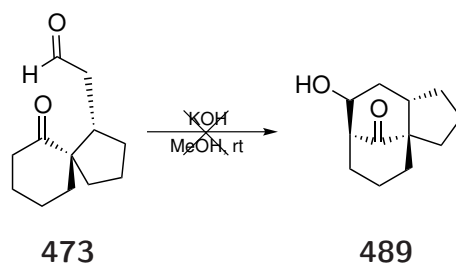
The bridged compound **489** has already been obtained during the deprotection procedure using HCl 10 % (Scheme 16.26). In order to obtain the bridged compound in a higher yield and as a single product, we treated aldehyde **473** with HCl 10 % in THF. This reaction yielded in the formation of tricyclic bridged compound **489** in 38 % yield (Scheme 16.29).



Scheme 16.29: Aldol reaction of **473** under acidic conditions.

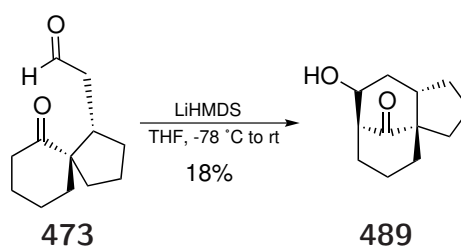
16.5.2. Cyclization of 473 under basic conditions

As we did not improve the yield in comparison to the direct approach from protected keto-aldehyde **487**, we decided to change the conditions for the aldol reaction and treated compound **473** under basic conditions (KOH in MeOH). Unfortunately, the aldol product was not obtained; instead the starting material was recovered in 69 % yield (Scheme 16.30).



Scheme 16.30: Aldol reaction of **473** under basic conditions (KOH/MeOH).

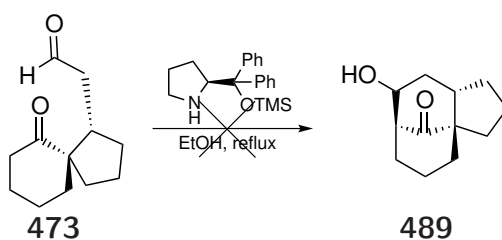
We submitted the aldehyde **473** to a strong and sterically hindered base. When performing the reaction of **473** with LiHMDS at $-78\text{ }^{\circ}\text{C}$ no reaction could be observed, warming the reaction mixture slowly to room temperature led to tricyclic alcohol **489** but only in a low yield of 18 % (Scheme 16.31).



Scheme 16.31: Aldol reaction of **473** under basic conditions (LiHMDS).

16.5.3. Cyclization of **473** using organocatalysis

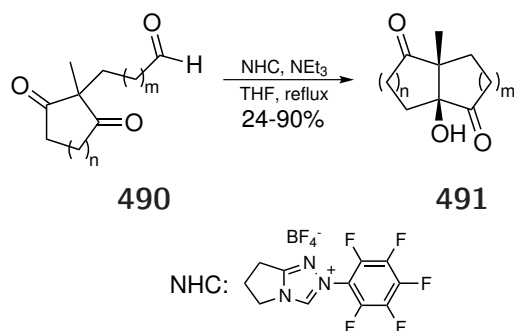
As the Hayashi-catalyst worked well for the formation of tricyclic compound **485**, we decided to test its capability for the formation of tricyclic compound **489**. When the reaction was performed under these conditions, we observed no evolution. The starting material was fully recovered (Scheme 16.32).



Scheme 16.32: Attempt to cyclize **473** using organocatalysis.

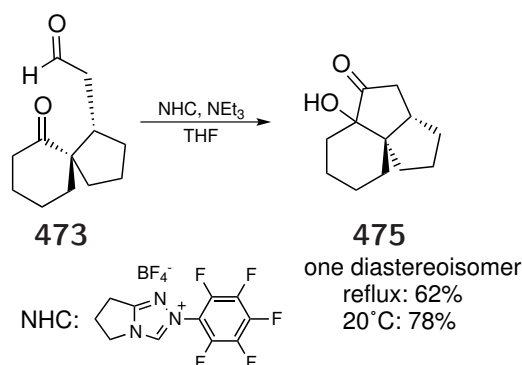
16.5.4. Cyclization of 473 using NHC-catalysis

Having obtained the bridged compound, we envisaged the synthesis of compound **475** via a NHC based strategy. Ema *et al.* showed that using catalytic quantities of *N*-heterocyclic carbenes it is possible to perform intramolecular bezoin condensation (Scheme 16.33).[204]



Scheme 16.33: Cyclization of aldehydes using a NHC-catalyst.

Taking up their conditions (THF, reflux) yielded in the formation of the desired compound **475** in 62 % yield (Scheme 16.34). In order to improve the yield of the reaction, we decided to lower the reaction temperature. Performing the reaction at room temperature provided tricyclic compound **475** in an increased yield of 78 %.

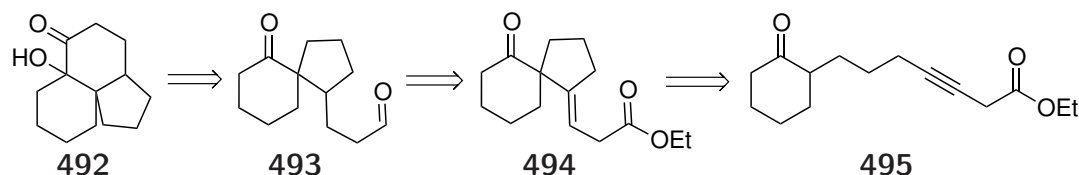


Scheme 16.34: Cyclization of **473** using a NHC-catalyst.

The use of the NHC-catalyst provided an efficient synthesis of the tricyclic compound **475**.

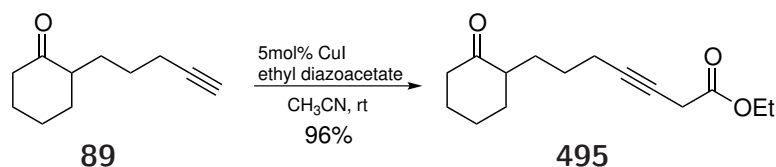
16.6. Synthesis of tricyclic compound **492** via a NHC-catalysis based strategy

Thus we reasoned that this method could be also a good way to access the 6-6-5-tricyclic system. The tricyclic compound **492** could be synthesized from keto-aldehyde **493**. The latter should be accessible from **495** via AgNTf₂-catalyzed reaction and subsequent transformation of the ester into the aldehyde (Scheme 16.35).



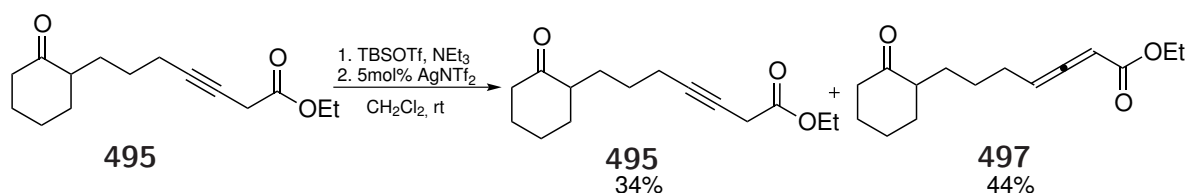
Scheme 16.35: Retrosynthetic analysis of tricyclic compound **492**.

We therefore had to synthesize the propargylic ester **495**. This was achieved using a method described by the group of Fu.[218] They showed that the synthesis of propargylic esters can be achieved through the reaction of a terminal acetylene with ethyl diazoacetate under copper(I)-catalysis. Applying this conditions to ketoalkyne **89** we were pleased to obtain the desired compound **495** 96 % yield (Scheme 16.36).



Scheme 16.36: Synthesis of propargylic ester **495**.

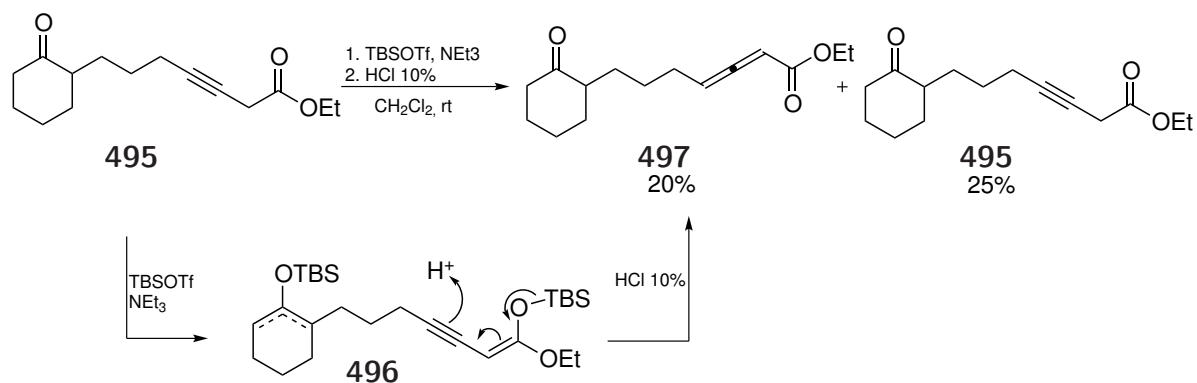
Having obtained the propargylic ester **495**, we submitted it to the reaction sequence for the cyclization. Formation of the the TBS-enol-ether **496** and subsequent reaction did not yield the desired spirocyclic compound **494**. Instead of that, the allene **497** was obtained in 44 % yield together with 34 % of the starting material (Scheme 16.37).



Scheme 16.37: Reaction of propargylic ester **495** with AgNTf₂.

Apparently, allene **497** was formed during the desilylation procedure. This has been shown by the reaction of compound **495** with TBSOTf/NEt₃ and direct desilylation

with HCl 10 % (Scheme 16.38). Indeed, in this case we obtained allene **497** in 20 % yield, together with 25 % of the starting material (Scheme 16.38).



Scheme 16.38: Protection/deprotection of propargylic ester **495**.

It thus seems reasonable to conclude that the cyclization of **496** will not occur and that this intermediate will evolve towards the formation of allene **497** during the work-up procedure.

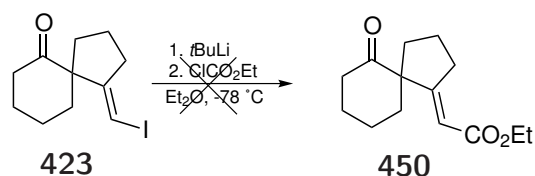
17. Reactivity of alkenyl iodides

We also investigated the reactivity of the alkenyl iodides obtained by AgNTf₂-catalysed cycloisomerization reactions.

Having obtained various spirocyclic iodides we envisioned that these molecules could be utilized to access more highly functionalized compounds in good yields and with good selectivities.

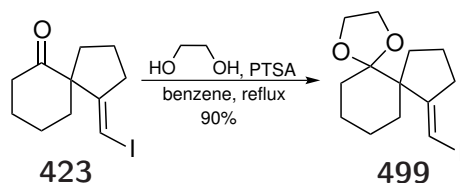
17.1. Halogen-metal exchange of alkenyl-iodides

First, we performed a halogen metal exchange of alkenyl-iodide **423** in the presence of *t*BuLi according to a recently described procedure.[219] Trapping of the vinyl-lithium formed with ClCO₂Et should give the known compound **498**. Unfortunately, when the reaction was performed only degradation of the starting material was observed (Scheme 17.1).



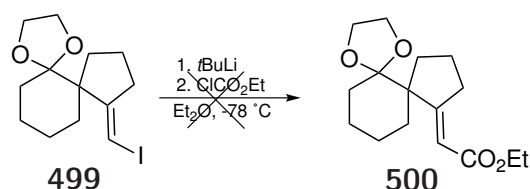
Scheme 17.1: Metal-halogen exchange of **423** with *t*BuLi and trapping with ClCO₂Et.

We assumed that the keto-function of **423** could cause difficulties in the reaction and decided to protect it as dioxolane. The protection using standard conditions (ethylene glycol, PTSA) proceeded smoothly and gave the protected alkenyl-iodide **499** in 90 % yield (Scheme 17.2).



Scheme 17.2: Protection of **423** as dioxolane.

The protected compound **499** was then submitted to the reaction conditions of the metal-exchange. To our disappointment **500** could not be isolated. Again only degradation was detected.

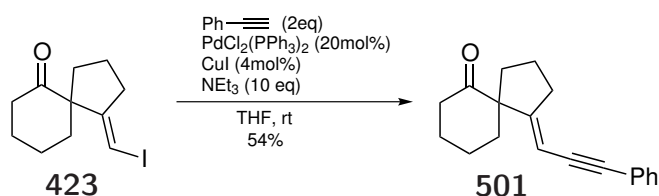


Scheme 17.3: Metal-halogen exchange of **499** with *t*BuLi and trapping with ClCO₂Et.

17.2. Sonogashira reactions

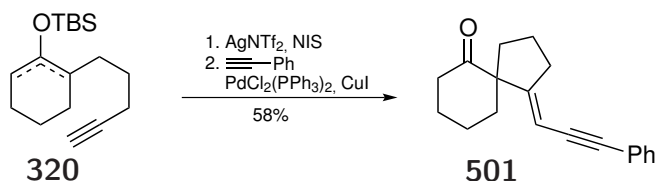
Palladium coupling chemistry is a very useful and extensively used tool in organic chemistry, honored by the Nobel Prize in Chemistry 2010.[220] Alkenyl-iodides can be used as substrates for these coupling reactions. We therefore choose alkenyl iodide **423** as substrate and tested its behavior towards Sonogashira reactions[221] with phenylacetylene. This reaction has already been used by Gagosz and co-workers to show the reactivity of alkenyl iodides.[185]

To our delight, the reaction worked well and we obtained the desired product **501** using standard conditions in 54 % yield (Scheme 17.4).



Scheme 17.4: Sonogashira coupling between alkenyl iodide **423** and phenylacetylene.

We then envisaged a one pot procedure for this reaction. Thus the TBS-enol-ether **320** was first treated with 5 mol% AgNTf₂ and 1 eq. NIS in DCE. The reaction was monitored by TLC and after the cyclization reaction was completed, the solvent was evaporated. The resulting slime was dissolved in THF and the reagents for the coupling reaction were added. This approach allowed the isolation of coupled product **501** with 58 % yield (Scheme 17.5).



Scheme 17.5: One-pot-Sonogashira coupling between ω -keto alkyne **320** and phenylacetylene.

Thus, palladium coupling chemistry allowed us to obtain functionalized spirocyclic compounds in two steps starting from easily obtained ω -ketoalkynes.

18. Summary

In this last part of the work we could show that the products obtained via silver-catalyzed cycloisomerization reactions can be used as substrates in the synthesis of complex molecules such as for examples the carbon skeleton of natural products of which some examples are shown below.

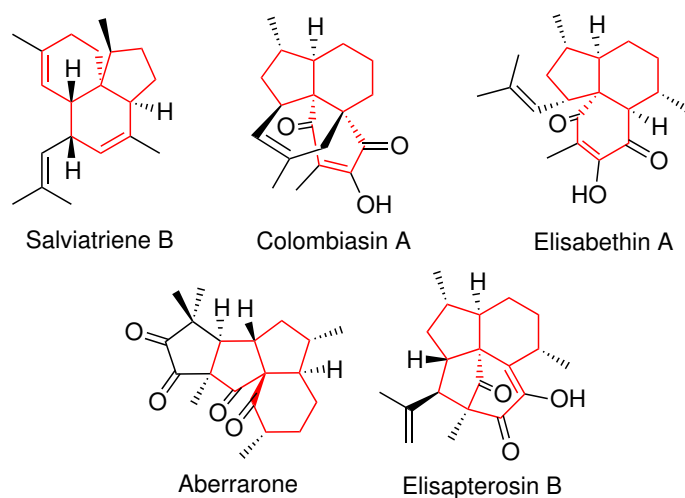
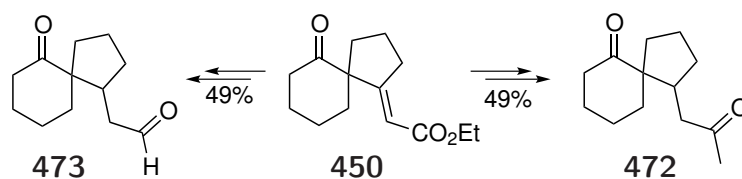


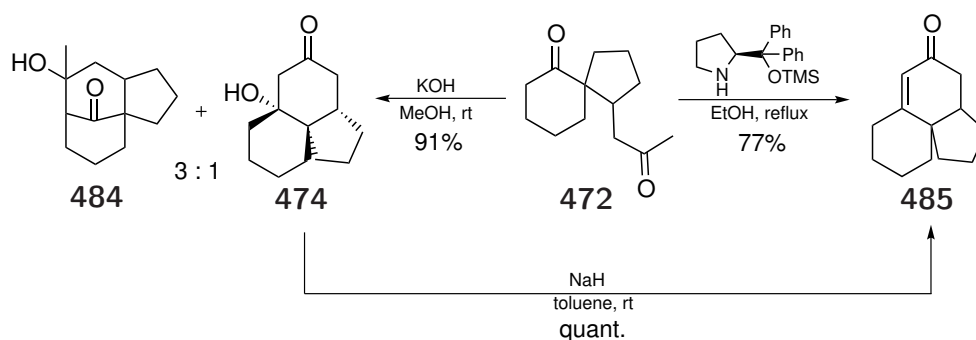
Figure 18.1.: Structure of selected natural products containing a 6-6-5- or 6-5-5-fused ring system.

Starting from spirocyclic ester **450**, the synthesis of ketone **472** and aldehyde **473** have been achieved in good yields.



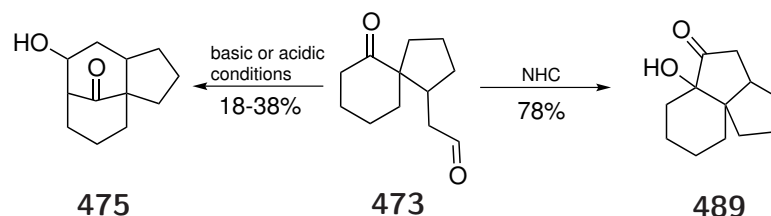
Scheme 18.1: Synthesis of ketone **472** and aldehyde **473**.

We then could show that ketone **472** could be transformed into a mixture of tricyclic **474** and bridged compound **484** under basic conditions. The former could be transformed into α,β -unsaturated tricyclic compound **485** using NaH. **485** is also accessible via an organocatalyzed reaction of **450**.



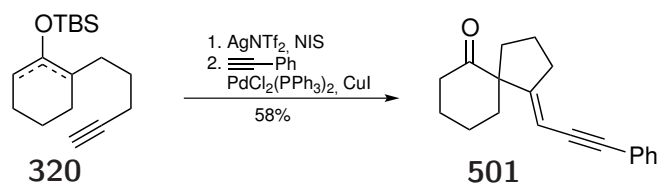
Scheme 18.2: Transformation of ketone **472** into tricyclic compounds **474**, **484** and **485**.

When aldehyde **473** was used as substrate the bridged compound **489** was obtained under basic or acidic conditions. The tricyclic compound **475** with a 6-5-5-tricyclic system was accessible from aldehyde **473** via an NHC-catalyzed reaction.



Scheme 18.3: Cyclization of aldehyde **473** using different conditions.

In addition to the synthesis of tricyclic molecules, we were able to show that the alkenyl-iodides accessible through AgNTf₂-catalyzed cycloisomerizations can be used to obtain complex molecules. The Sonogashira-coupling of alkenyl-iodide **423** can be performed as a one-pot reaction starting from TBS-enol ether **320** leading to the formation of the coupled product **501** in reasonable yield.

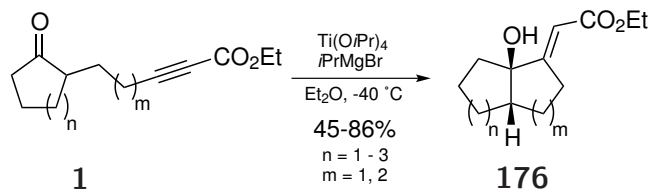


Scheme 18.4: One-pot-Sonogashira coupling between ω -keto alkyne **320** and phenylacetylene.

19. General conclusion

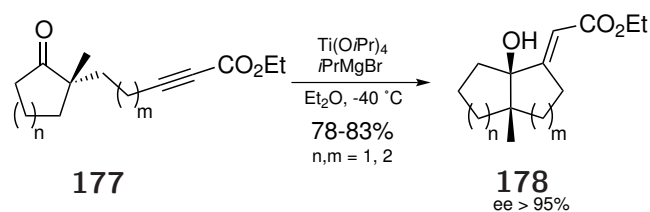
The work presented in this manuscript is part of the ongoing research on the reactivity of acetylenic ω -ketoesters in our group. We explored the reactivity of acetylenic ω -ketoesters toward different metal complexes and used the compounds obtained by these reactions for the synthesis of the core structures of various natural products.

In the first part of our work, we developed the synthesis of bicyclic α,β -unsaturated- γ -hydroxy esters from acetylenic ω -ketoesters as starting materials using a low valent titanium complex as reagent. The reactivity of low valent titanium complexes has first been described by Kulinkovich for the synthesis of cyclopropanols from esters and alkenes.[222] The group of Sato showed that, in addition to alkenes, alkynes can be used as substrates via a ligand exchange reactions[31] and that the titanacyclopropane derived from isopropyl magnesium bromide is especially useful for this purpose. We applied this strategy to acetylenic ω -ketoesters. Treating them with a $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$ mixture led to the formation of bicyclic α,β -unsaturated- γ -hydroxy esters in good yields and with total stereoselectivity concerning the ring junction (*cis*) and the double bond configuration (*E*).



Scheme 19.1: Reaction of acetylenic ω -ketoesters **1** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$.

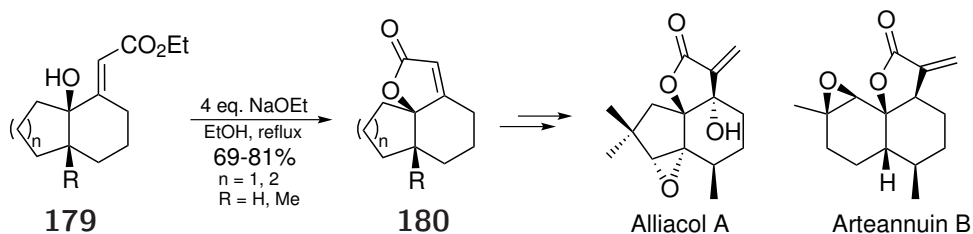
Enantiomerically enriched bicyclic α,β -unsaturated- γ -hydroxy esters can be formed by the method when enantiomerically enriched acetylenic ω -ketoesters are used as substrates.



Scheme 19.2: Reaction of enantiomerically enriched acetylenic ω -ketoesters **177** with $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$.

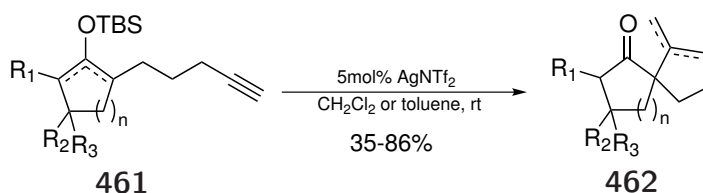
This reaction allows the synthesis of enantiomerically enriched functionalized bicyclic compounds from easily accessible starting materials.

Furthermore, the compounds obtained can be used for the formation of tricyclic unsaturated lactones that are found as core substructure in various natural products, such as those of the alliacol family.



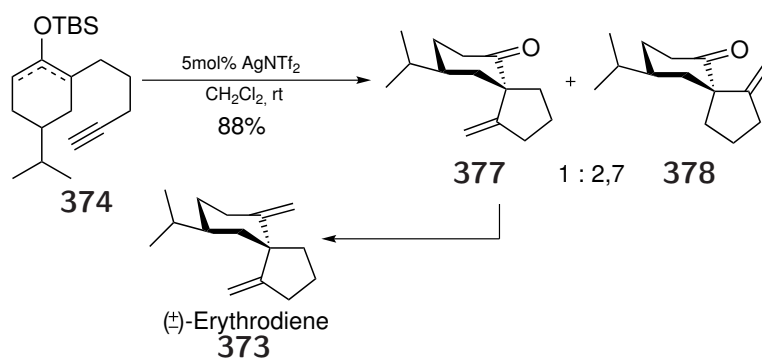
Scheme 19.3: Formation of tricyclic lactones **180**.

In the second part of our work, we explored the reactivity of ω -keto alkynes and acetylenic ω -ketoesters in noble metal catalyzed reactions. Noble metal catalyzed reactions gained large interest over the recent few years. Especially gold-catalyzed reactions involving the activation of multiple bonds towards nucleophilic addition is a highly investigated field. We were interested in the possibility to use noble metal complexes as catalyst for the transformation of acetylenic ω -ketoesters into spirocyclic compounds. While our attempts using gold(I)-complexes were not very fruitful, we demonstrated that silver(I)-salts can just as well perform cycloisomerization reactions of ω -keto alkynes.



Scheme 19.4: Cycloisomerization reaction of TBS-enol ethers **461** with AgNTf_2 .

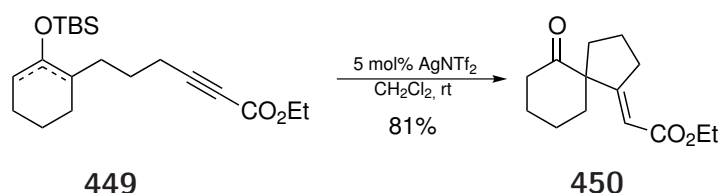
The spirocyclization reaction could be applied to a large panel of substrates, as illustrated by the formal total synthesis of (\pm)-erythrodiene.



Scheme 19.5: Formal total synthesis of (±)-Erythrodiene.

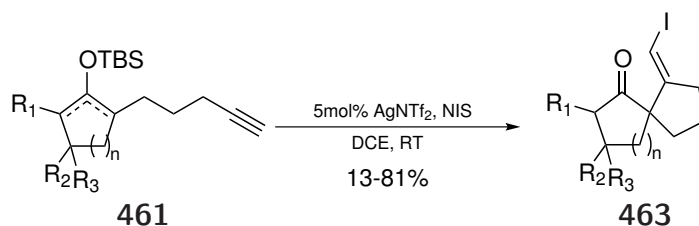
As the silver-salt not only served as catalyst for the cycloisomerization but equally catalyses the isomerization of a kinetic into the corresponding thermodynamic silyl enol ether, a mixture of both silyl enol ethers can be used as substrate for the reaction.

This reaction can be applied to activated alkynes like acetylenic ω -ketoesters as illustrated by the transformation of **449** into spirocyclic ester **450**.



Scheme 19.6: Reaction of TBS enol ether **449** with AgNTf_2 .

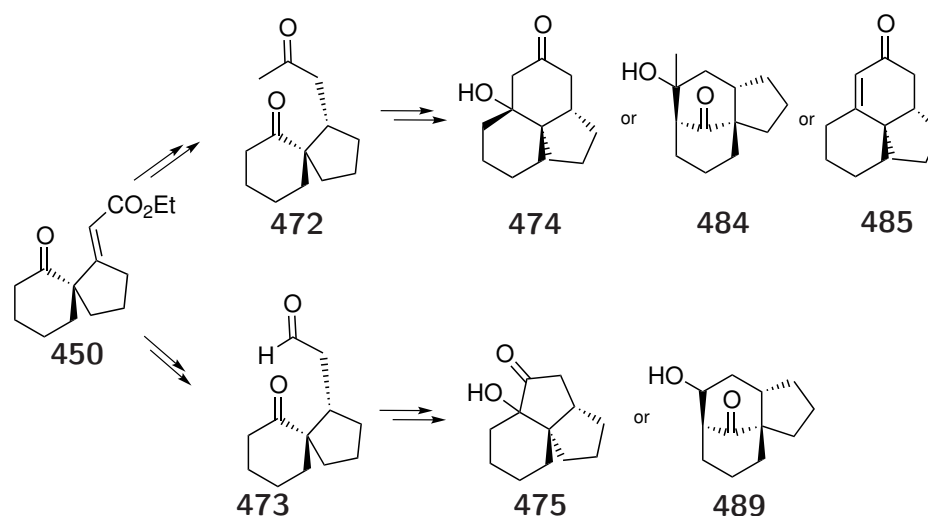
In order to obtain more functionalized spirocyclic compounds, we synthesized spirocyclic alkenyl iodides by trapping the formed alkenyl silver intermediate with a source of electrophilic iodine like NIS.



Scheme 19.7: Synthesis of alkenyl iodides **463**.

Thus we could show that using a simple silver(I) salt as catalyst, the synthesis of functionalized spirocyclic compounds can be easily achieved from readily available starting materials.

In the last part of the work we explored the reactivity of the obtained spirocyclic compounds in natural product synthesis. Starting from spirocyclic ester **450** we were able to synthesize several tricyclic compounds containing a 6-5-5- or 6-6-5-fused ring system.



Scheme 19.8: Synthesis of tricyclic compounds **474**, **475**, **484**, **485** and **489**.

These compounds are of high interest as they represent the core skeleton of various natural products like .

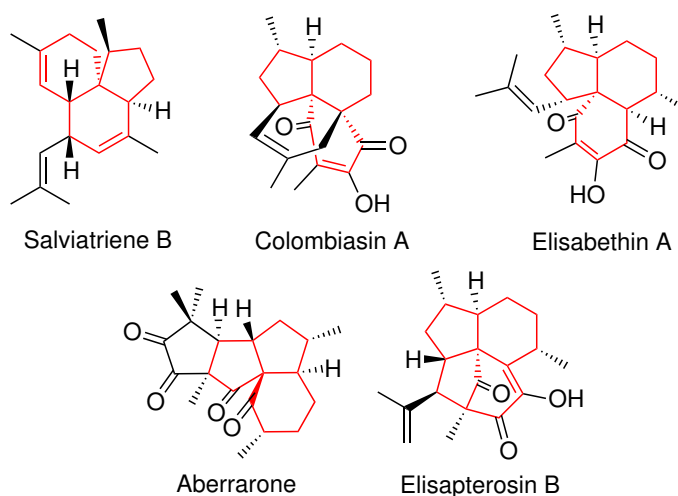
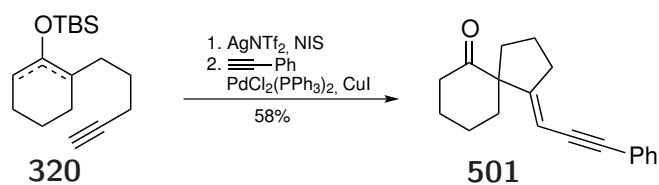


Figure 19.1.: Structure of selected natural products containing a 6-6-5- et 6-5-5-fused ring system.

The alkenyl iodides obtained can be used as substrates for palladium catalyzed coupling reactions. This was demonstrated by the Sonogashira-coupling of **423** with phenylacetylene. The reaction can be performed in two separate steps or as a one-pot procedure.

During this work we were able to show that ω -keto alkynes and acetylenic ω -ketoesters



Scheme 19.9: One-pot-Sonogashira coupling between ω -keto alkyne **320** and phenylacetylene.

are highly valuable substrates for the selective synthesis of complex carbon skeletons found in natural products. These reactions proceed under smooth conditions and with high selectivity and thus broaden the scope of application of this easily available starting materials for organic synthesis.

Part IV.

Experimental section

20. General remarks

When dry reaction conditions were needed the reactions were performed in flamed glassware under Ar atmosphere.

Commercial reagents were distilled from appropriate reagents prior to use.[223] Et₂O and THF were distilled from Na/benzophenone, CH₂Cl₂ was distilled from P₂O₅ or dried using a Dry Solvent Station GT S100. 1,2-dichloroethane was distilled from CaH₂, toluene was distilled from Na.

Ozonolysis reactions were performed using a Fisher 502 ozone generator and an ozone flow rate of 0.1 mol/h.

NMR spectra were recorded by the "Service Commun de RMN" of the "Institut de Chimie" using a Bruker AV-300 or AV-400 or AV-500 spectrometer with the solvent residual peak as internal standard.[224]

The multiplicity of the signals is described as follows: s = singlet, d = duplet, t = triplet, q = quartet, qu = quintet, sex = sextet and m = multiplet.

High resolution mass spectrometry (HRMS) data were recorded by the "Service Commun de Spectrométrie de Masse" of the "Institut de Chimie" on a microTOF spectrometer equipped with an orthogonal electrospray (ESI) interface.

Optical rotation was measured using a Perkin Elmer 341 Polarimeter.

Infrared spectra were recorded on Bruker-ALPHA spectrophotometer.

X-ray structures were recorded by the "Service Commun de rayons X" of the "Institut de Chimie" using an Enraf-Nonius-CAD4 or KappaCCD diffractometer.

Thin layer chromatography (TLC) was performed using Merck TLC Silica gel 60 F254 glass plates. UV light (254 nm) and vanillin or phosphomolybdic acid followed by heating with a heat gun were used to reveal the TLCs.

Merck Geduran[®] (40-63 μm) silica gel was used for column chromatography.

Flash chromatography was performed using a Biotage Isolera One system.

21. Synthesis of ω -keto alkynes

21.1. Synthesis of *N,N*-dimethylhydrazones

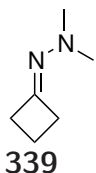
Typical procedure for the preparation of *N,N*-dimethylhydrazones GP A

The cycloalkanone was dissolved in benzene (0.7 M), *N,N*-dimethylhydrazine (1.2 eq.) and trifluoroacetic acid (cat.) were added. The reaction mixture was heated to reflux in a Dean-Stark for 16h.

The reaction mixture was cooled to room temperature, diluted with Et₂O and H₂O was added. The aqueous phase was extracted 3× with Et₂O. The combined organic phases were washed with a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by distillation under reduced pressure.

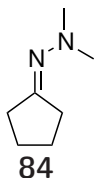
2-Cyclobutylidene-1,1-dimethylhydrazine **339**



Yield: 22 %
colourless oil
C₆H₁₂N₂
MW 112.17 g/mol

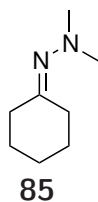
Characterization data for compound **339** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 186.

2-Cyclopentylidene-1,1-dimethylhydrazine **84**



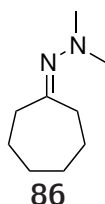
Yield: 76 %
colourless oil;
C₇H₁₄N₂
MW 126.20 g/mol

Characterization data for compound **84** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 186.

2-Cyclohexylidene-1,1-dimethylhydrazine **85**

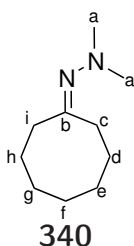
Yield: 84 %
 colourless oil;
 $C_8H_{16}N_2$
 MW 140.23 g/mol

Characterization data for compound **85** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 187.

2-Cycloheptylidene-1,1-dimethylhydrazine **86**

Yield: 79 %
 colourless oil
 $C_9H_{18}N_2$
 MW 154.25 g/mol

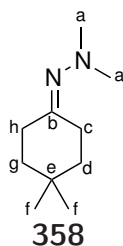
Characterization data for compound **86** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 187.

2-Cyclooctylidene-1,1-dimethylhydrazine **340**

Yield: 74 %
 colourless oil;
 $C_{10}H_{20}N_2$
 MW 168.28 g/mol
 b.p. 86 °C (10 mbar)

1H -NMR (300 MHz, $CDCl_3$) δ 1.32 - 1.45 (m, 2H), 1.45 - 1.56 (m, 4H), 1.69 - 1.83 (m, 4H), 2.27 - 2.36 (m, 2H), 2.40 (s, 6H. H_a), 2.44 - 2.53 (m, 2H) ppm;
 ^{13}C -NMR(75 MHz, $CDCl_3$) δ 24.2, 25.2, 26.8, 27.4, 27.8, 29.9, 35.3, 47.1 ($2 \times C_a$), 176.2 (C_b) ppm;
IR (neat) 2924, 2852, 1466, 1445, 967 cm^{-1} .

2-(4,4-Dimethylcyclohexylidene)-1,1-dimethylhydrazine 358

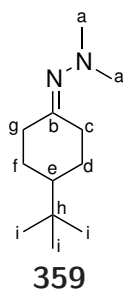


Yield: 80 %
 colourless oil
 $C_{10}H_{20}N_2$
 MW 168.28 g/mol
 b.p. 55 °C (0.1 Torr)

1H -NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 3H, H_a), 0.99 (s, 3H, H_a), 1.42 (t, $J = 6.7$ Hz, 2H, H_g), 1.48 (t, $J = 6.7$ Hz, 2H, H_d), 2.25 (t, $J = 6.3$ Hz, 2H, H_h), 2.42 (s, 3H, H_f), 2.43 (s, 3H, H_f), 2.51 (t, $J = 6.6$ Hz, 2H, H_c) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 27.2 (C_c), 27.9 (C_f), 30.5 (C_e), 32.0 (C_h), 39.0 (C_d or g), 39.7 (C_d or g), 47.6 (C_a), 170.1 (C_b) ppm;

IR (neat) 2950, 2850, 1635, 1466, 1152, 976 cm^{-1} .

2-(4-(*tert*-Butyl)cyclohexylidene)-1,1-dimethylhydrazine 359

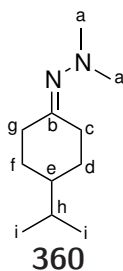
Yield: 89 %
 yellow oil
 $C_{12}H_{24}N_2$
 MW 196.33 g/mol
 b.p. 53 °C (5.3×10^{-2} Torr)

1H -NMR (300 MHz, C_6D_6) δ 0.73 (s, 9H, H_i), 0.91 - 1.12 (m, 3H), 1.46 (ddd, $J = 13.7, 12.5, 5.3$ Hz, 1H), 1.59 - 1.72 (m, 2H), 1.91 (ddd, $J = 13.8, 12.9, 4.9$ Hz, 1H), 2.47 (s, 6H, H_a), 2.61 (d, $J = 15.1$ Hz, 1H), 3.45 (d, $J = 13.3$ Hz, 1H) ppm;

^{13}C -NMR(75 MHz, C_6D_6) δ 27.5, 27.7 ($3 \times C_i$), 28.1, 28.3, 32.4 (C_h), 35.8 (C_g), 47.8 ($2 \times C_a$), 47.9 (C_e), 168.6 (C_b) ppm;

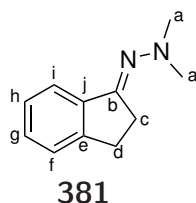
IR (neat) 2948, 2864, 1718, 1638, 1467, 1366, 994 cm^{-1} .

2-(4-Isopropylcyclohexylidene)-1,1-dimethylhydrazine 360



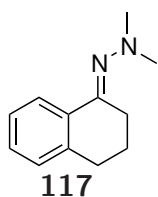
Yield: 79 %
 slightly yellow oil
 $C_{11}H_{22}N_2$
 MW 182.31 g/mol
 b.p. 52 °C (4.7×10^{-2} Torr)

¹H-NMR (300 MHz, C₆D₆) δ 0.74 (dd, J = 6.7, 1.4 Hz, 6H, H_i), 0.89 - 1.14 (m, 3H), 1.16 - 1.33 (m, 1H), 1.42 - 1.65 (m, 3H), 1.84 - 2.01 (m, 1H, H_h), 2.47 (s, 6H, H_a), 2.59 (d, J = 13.5 Hz, 1H), 3.38 (d, J = 13.7 Hz, 1H) ppm;
¹³C-NMR(75 MHz, C₆D₆) δ 19.9 (C_i), 20.0 (C_i), 27.8 (C_c), 29.6 (C_d or f), 30.3 (C_d or f), 32.4 (C_h), 35.5 (C_g), 43.7(C_e), 47.8 (2 × C_a), 168.6 (C_b) ppm;
IR (neat) 2950, 2855, 1636, 1466, 1442, 965 cm⁻¹.

(*E*)-2-(2,3-Dihydro-1*H*-inden-1-ylidene)-1,1-dimethylhydrazine 381

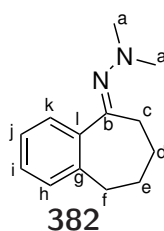
Yield: 38 %
 yellow oil
 C₁₁H₁₄N₂
 MW 174.24 g/mol
 b.p. 52 °C (4.7×10⁻² Torr)

¹H-NMR (300 MHz, CDCl₃) δ 2.67 (s, 6H, H_a), 2.87 - 2.98 (m, 2H, H_c), 3.01 - 3.10 (m, 2H, H_d), 7.19 - 7.42 (m, 3H, H_{f-h}), 7.77 (d, J = 7.6 Hz, 1H, H_i) ppm;
IR (neat) 2951, 2853, 1464, 970, 755 cm⁻¹.

(*E*)-2-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-1,1-dimethylhydrazine 117

Yield: 96 %
 slightly yellow oil
 C₁₂H₁₆N₂
 MW 188.27 g/mol

Characterization data for compound **117** are in good agreement with those found in the PhD thesis of T. Welsch[68] on page 204.

(*E*)-1,1-Dimethyl-2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)hydrazine 382

Yield: 80 %
 yellow oil
 C₁₃H₁₈N₂
 MW 202.30 g/mol
 b.p. 125 °C (8.2×10⁻² Torr)

¹H-NMR (300 MHz, C₆D₆) δ 1.40 - 1.54 (m, 4H, H_d and e), 2.47 - 2.54 (m, 2H, H_f), 2.55 (s, 6H, H_a), 2.65 - 2.72 (m, 2H, C_c), 6.87 - 6.93 (m, 1H, H_i), 7.08 - 7.13 (m, 2H, H_h and j), 7.87 - 7.94 (m, 1H, H_k) ppm;
¹³C-NMR(75 MHz, C₆D₆) δ 23.3 (C_e), 26.9 (C_c or d), 29.4 (C_c or d), 32.9 (C_f), 47.8 (2

$\times C_a$), 126.6 (C_k), 128.8, 129.0, 129.1, 129.5 (C_l), 139.3 (C_g), 169.1 (C_b) ppm;
IR (neat) 2930, 2852, 1449, 1431, 982, 764 cm^{-1} .

21.2. Synthesis of ω -keto alkynes

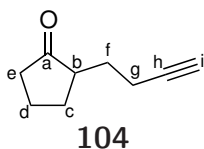
Typical procedure for the alkylation of hydrazines GP B

The hydrazone was dissolved in THF (0.25 M) and cooled to $-5\text{ }^\circ\text{C}$. *n*BuLi (1.05 eq., 1.43 M in hexanes) was added dropwise. The reaction mixture was stirred for 1 h at this temperature. The iodoalkyne (4-iodobutyne or 5-iodopentyne or 6-iodohexyne, 1.2 eq., dissolved in little THF) was added dropwise. The reaction mixture was warmed slowly to room temperature and stirred for 6h.

The reaction mixture was hydrolysed with 75 ml of a 2 N solution of HCl and stirred for 4h. The aqueous phase was extracted $3\times$ with EtOAc. The combined organic phases were washed with a saturated aqueous solution of NaHCO_3 , a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$, a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by distillation under reduced pressure or by column chromatography (PE:EtOAc 100:0 to 95:5)

2-(But-3-yn-1-yl)cyclopentanone **104**



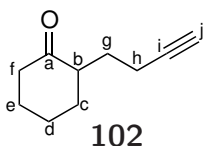
Yield: 51 %
 colourless oil
 $\text{C}_9\text{H}_{12}\text{O}$
 MW 136.19 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.36 - 1.56 (m, 2H), 1.67 - 1.85 (m, 1H), 1.92 (t, $J = 2.6$ Hz, 1H, H_i), 1.93 - 2.04 (m, 2H), 2.05 - 2.40 (m, 6H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 16.8 (C_g), 20.8 (C_g), 28.5 (C_c or f), 29.6 (C_c or f), 38.1 (C_e), 48.1 (C_b), 69.0 (C_i), 83.7 (C_h), 220.7 (C_a) ppm;

IR (neat) 3290 ($\equiv\text{C-H}$), 2958, 2866, 1731 (C=O), 630 cm^{-1} .

2-(But-3-yn-1-yl)cyclohexanone **102**

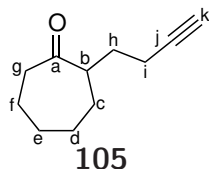


Yield: 68 %
 colourless oil
 $\text{C}_{10}\text{H}_{14}\text{O}$
 MW 150.22 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.23 - 1.40 (m, 2H), 1.51 - 1.74 (m, 2H), 1.79 - 1.87 (m, 1H), 1.89 (t, $J = 2.6$ Hz, 1H, H_j), 1.92 - 2.02 (m, 1H), 2.02 - 2.15 (m, 2H), 2.21 (td, $J = 7.0, 2.5$ Hz), 2.26 - 2.35 (m, 2H), 2.38 - 2.52 (m, 1H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 16.2 (C_h), 25.2 (C_d), 28.1 (C_e or g), 28.2 (C_e or g), 34.1 (C_c), 42.3 (C_f), 49.1 (C_b), 68.7 (C_j), 84.2 (C_i), 212.7 (C_a) ppm;
IR (neat) 3291 ($\equiv\text{C-H}$), 2933, 2862, 1705 (C=O), 629 cm^{-1} .

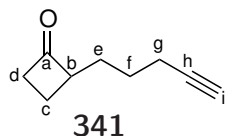
2-(But-3-yn-1-yl)cycloheptanone 105



Yield: 67 %
 colourless oil
 $\text{C}_{11}\text{H}_{16}\text{O}$
 MW 164.24 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.17 - 1.39 (m, 3H), 1.39 - 1.54 (m, 2H), 1.54 - 1.71 (m, 1H), 1.72 - 1.89 (m, 4H), 1.91 (t, $J = 2.6$ Hz, 1H, H_k), 2.16 (td, $J = 7.1, 2.7$ Hz, 2H, H_i), 2.44 (q, $J = 4.9$ Hz, 2H), 2.65 - 2.77 (m, 1H) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 16.4 (C_i), 24.2 (C_f), 28.8, 29.3, 30.5, 31.4, 43.2 (C_g), 50.4(C_b), 68.9 (C_k), 83.9 (C_j), 215.5 (C_a) ppm;
IR (neat) 3291 ($\equiv\text{C-H}$), 2926, 2854, 1698 (C=O), 627 cm^{-1} .

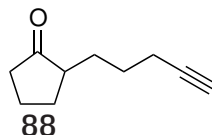
2-(Pent-4-yn-1-yl)cyclobutanone 341



Yield: 51 %
 colourless oil
 $\text{C}_9\text{H}_{12}\text{O}$
 MW 136.19 g/mol

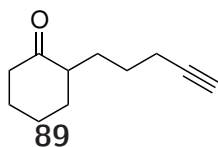
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.46 - 1.72 (m, 4H), 1.72 - 1.87 (m, 1H), 1.94 (t, $J = 2.6$ Hz, 1H, H_i), 2.09 - 2.34 (m, 3H), 2.83 - 3.12 (m, 2H), 3.20 - 3.37 (m, 1H) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 17.0 (C_c), 18.4 (C_g), 26.1(C_f), 28.7 (C_e), 44.7 (C_d), 60.1 (C_b), 68.8 (C_i), 84.0 (C_h), 211.8 (C_a) ppm;
IR (neat) 3288 ($\equiv\text{C-H}$), 2933, 1772 (C=O), 1086, 633 cm^{-1} .

2-(Pent-4-yn-1-yl)cyclopentanone 88



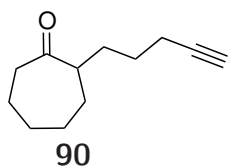
Yield: 54 %
 colourless oil
 $\text{C}_{10}\text{H}_{14}\text{O}$
 MW 150.22 g/mol

Characterization data for compound **88** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 190.

2-(Pent-4-yn-1-yl)cyclohexanone **89**

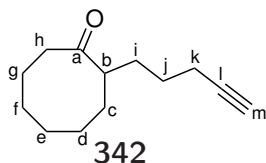
Yield: 79 %
 colourless oil
 $C_{11}H_{16}O$
 MW 164.24 g/mol

Characterization data for compound **89** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 190.

2-(Pent-4-yn-1-yl)cycloheptanone **90**

Yield: 87 %
 colourless oil
 $C_{12}H_{18}O$
 MW 178.27 g/mol

Characterization data for compound **90** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 191.

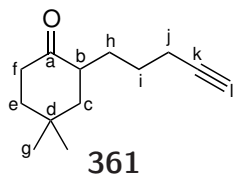
2-(Pent-4-yn-1-yl)cyclooctanone **342**

Yield: 50 %
 colourless oil
 $C_{13}H_{20}O$
 MW 192.30 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.15 - 1.31 (m, 1H), 1.32 - 1.52 (m, 5H), 1.52 - 1.74 (m, 4H), 1.74 - 1.87 (m, 2H), 1.88 - 2.05 (m, 1H), 1.93 (t, $J = 2.6$ Hz, 1H, H_m), 2.10 - 2.21 (m, 3H), 2.29 (ddd, $J = 13.6, 6.9, 3.5$ Hz, 1H), 2.42 (ddd, $J = 13.4, 11.3, 3.7$ Hz, 1H), 2.50 - 2.64 (m, 1H) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.6 (C_k), 24.9, 25.7, 25.9, 26.5, 27.5, 31.7, 32.9, 42.1 (C_h), 50.3 (C_b), 68.6 (C_m), 84.2 (C_l), 220.0 (C_a) ppm;

IR (neat) 3290 ($\equiv C-H$), 2925, 2855, 1696 ($C=O$), 1446, 626 cm^{-1} .

4,4-Dimethyl-2-(pent-4-yn-1-yl)cyclohexanone **361**

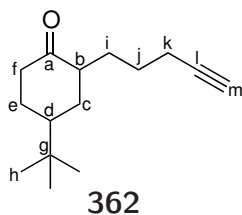
Yield: 93 %
 light yellow oil
 $C_{13}H_{20}O$
 MW 192.30 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.00 (s, 3H, H_g), 1.20 (s, 3H, H_g), 1.43 - 1.59 (m, 2H), 1.61 (d, $J = 4.5$ Hz, 1H), 1.63 - 1.71 (m, 2H), 1.71 - 1.77 (m, 1H), 1.77 - 1.82 (m, 1H), 1.82 - 1.89 (m, 1H), 1.93 (t, $J = 2.7$ Hz, 1H, H_l), 2.12 - 2.22 (m, 2H), 2.23 - 2.27 (m, 1H), 2.34 - 2.52 (m, 2H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 18.8 (C_j), 24.7 (C_g), 26.3 (C_i), 28.6 (C_h), 31.0 (C_d), 31.6 (C_g), 38.6 (C_f), 40.2 (C_e), 45.7 (C_b), 46.9 (C_c), 68.5 (C_l), 84.5 (C_k), 213.5 (C_a) ppm;

IR (neat) 3295 ($\equiv\text{C-H}$), 2952, 2925, 2865, 1709 (C=O), 626 cm^{-1} .

4-(*tert*-Butyl)-2-(pent-4-yn-1-yl)cyclohexanone 362

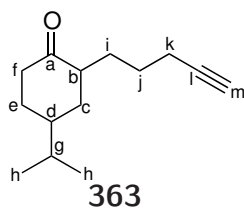


Yield: 59 %
light yellow oil;
 $\text{C}_{15}\text{H}_{24}\text{O}$
MW 220.35 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.89 (s, 9H, H_h), 1.13 (q, $J = 12.8$ Hz, 1H), 1.21 - 1.33 (m, 1H), 1.41 (qd, $J = 12.7, 4.7$ Hz, 1H), 1.45 - 1.64 (m, 3H), 1.77 - 1.90 (m, 1H), 1.93 (t, $J = 2.7$ Hz, 1H, H_m), 2.01 - 2.22 (m, 4H), 2.22 - 2.42 (m, 3H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 18.7 (C_k), 26.3, 27.7 (C_h), 28.8 (2C), 32.5 (C_g), 35.2, 41.7 (C_f), 47.2 (C_d), 49.4 (C_b), 68.3 (C_m), 84.5 (C_l), 213.1 (C_a) ppm.

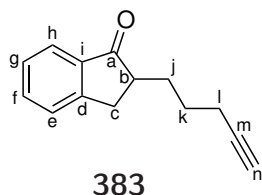
4-Isopropyl-2-(pent-4-yn-1-yl)cyclohexanone 363



Yield: 33 %
colourless oil
 $\text{C}_{14}\text{H}_{22}\text{O}$
MW 206.32 g/mol

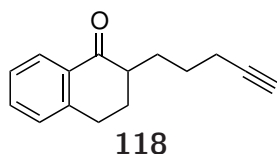
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.89 (d, $J = 6.7$ Hz, 6H, H_h), 1.11 (q, $J = 12.5$ Hz, 1H), 1.19 - 1.33 (m, 1H), 1.33 - 1.47 (m, 1H), 1.47 - 1.69 (m, 4H), 1.76 - 1.89 (m, 1H), 1.89 - 1.94 (m, 1H, H_m), 1.95 - 2.11 (m, 2H), 2.11 - 2.21 (m, 2H), 2.22 - 2.41 (m, 3H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 18.8 (C_k), 20.0 (C_h), 20.1 (C_h), 26.3 (C_j), 28.7 (C_i), 30.8 (C_e), 32.2 (C_g), 37.3 (C_c), 41.7 (C_f), 43.2 (C_d), 49.4 (C_b), 68.4 (C_m), 84.5 (C_l), 213.2 (C_a) ppm.

2-(Pent-4-yn-1-yl)-2,3-dihydro-1H-inden-1-one **383**

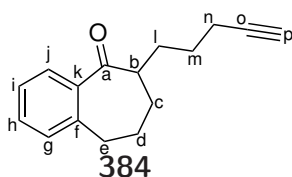
Yield: 53 %
light yellow oil
 $C_{14}H_{14}O$
MW 198.26 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.51 - 1.77 (m, 3H), 1.95 (t, $J = 2.7$ Hz, 1H, H_n), 1.98 - 2.11 (m, 1H), 2.20 - 2.30 (m, 4H), 2.68 (dddd, $J = 8.8, 7.9, 4.5, 4.0$ Hz, 1H, H_b), 2.83 (ABX-system, $J_{AB} = 17.2, J_{AX} = 4.0$ Hz, 1H, H_c), 3.35 (ABX-system, $J_{AB} = 17.2, J_{BX} = 7.9$ Hz, 1H, H_c), 7.36 (dd, $J = 7.7, 7.4$ Hz, 1H, H_g), 7.46 (d, $J = 7.7$ Hz, 1H, H_e), 7.58 (dd, $J = 7.7, 7.4$ Hz, 1H, H_f), 7.75 (d, $J = 7.7$ Hz, 1H, H_h) ppm;
 ^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.6 (C_l), 26.5 (C_i or k), 30.7 (C_i or k), 33.0 (C_c), 47.1 (C_b), 68.8 (C_n), 84.1 (C_m), 124.0 (C_g), 126.7 (C_e or h), 127.5 (C_e or h), 134.8 (C_f), 136.8 (C_i), 153.7 (C_d), 208.6 (C_a) ppm.

2-(Pent-4-yn-1-yl)-3,4-dihydronaphthalen-1(2H)-one **118**

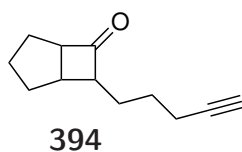
Yield: 77 %
yellow oil
 $C_{15}H_{16}O$
MW 212.29 g/mol

Characterization data for compound **118** are in good agreement with those found in the PhD thesis of T. Welsch[68] on page 205.

6-(Pent-4-yn-1-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one **384**

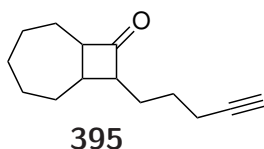
Yield: 53 %
light yellow oil
 $C_{16}H_{18}O$
MW 260.30 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.38 - 1.75 (m, 5H), 1.76 - 1.91 (m, 1H), 1.93 (t, $J = 2.6$ Hz, 1H, H_p), 1.94 - 2.03 (m, 1H), 2.05 - 2.14 (m, 1H), 2.19 (td, $J = 6.9, 2.5$ Hz, 2H), 2.80 - 3.09 (m, 3H), 7.21 (d, $J = 7.4$ Hz, 1H, H_g), 7.27 (td, $J = 7.7, 1.2$ Hz, 1H, H_i), 7.37 (td, $J = 7.4, 1.7$ Hz, 1H, H_h), 7.63 (dd, $J = 7.6, 1.6$ Hz, 1H, H_j) ppm;
 ^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.7 (C_n), 25.6 (C_d or m), 26.5 (C_d or m), 30.4 (C_c or l), 30.6 (C_c or l), 33.8 (C_e), 49.6 (C_b), 68.5 (C_p), 84.4 (C_o), 126.5 (C_i), 128.3 (C_g or j), 130.0 (C_g or j), 131.3 (C_h), 140.3 (C_k), 142.1 (C_f), 207.2 (C_a) ppm.

7-(Pent-4-yn-1-yl)bicyclo[3.2.0]heptan-6-one 394

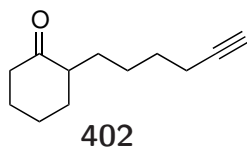
Yield: 86 %
 light yellow oil
 $C_{12}H_{16}O$
 MW 176.26 g/mol

Characterization data for compound **394** are in good agreement with those found in the PhD thesis of V. Rietsch[225] on page 122.

9-(Pent-4-yn-1-yl)bicyclo[5.2.0]nonan-8-one 395

Yield: 64 %
 colourless oil
 $C_{14}H_{20}O$
 MW 204.31 g/mol

Characterization data for compound **395** are in good agreement with those found in the PhD thesis of V. Rietsch[225] on page 126.

2-(Hex-5-yn-1-yl)cyclohexanone 402

Yield: 90 %
 colourless oil
 $C_{12}H_{18}O$
 MW 178.27 g/mol

Characterization data for compound **402** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 189.

21.3. Synthesis of α -methylated ω -keto alkynes

General procedure for the transformation of dibromoalkenes into terminal alkynes GP C

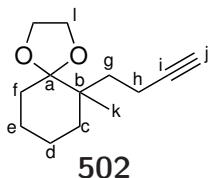
According to the literature[226] the dibromoalkene (2.91 mmol, 1 equiv.) was dissolved in dry THF (0.1 M) and cooled to $-78\text{ }^{\circ}\text{C}$. *n*BuLi (1.6 M in hexanes, 2.4 equiv.) was added dropwise and the reaction mixture is stirred for 15 min at $-78\text{ }^{\circ}\text{C}$. The reaction mixture is then warmed to room temperature and stirred for 3h.

The reaction mixture was hydrolyzed with 15 mL of a saturated aqueous solution of NH_4Cl and stirred for 15 min at room temperature. After dilution with 20 mL H_2O , the aqueous phase is extracted $3 \times 30\text{ mL}$ Et_2O . The combined organic phases are washed with 50 mL of a saturated aqueous solution of NaCl, dried over anhydrous

Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product is obtained by column chromatography (PE:EtOAc 98:2 to 95:5).

2-(But-3-yn-1-yl)-2-methylcyclohexanone 502



Yield: 84 %
 colourless oil
 $\text{C}_{13}\text{H}_{20}\text{O}_2$
 MW 208.30 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.92 (s, 3H, H_k), 1.35 - 1.46 (m, 4H), 1.47 - 1.63 (m, 5H), 1.67 - 1.80 (m, 2H), 1.92 (t, $J = 2.7$ Hz, 1H, H_j), 2.09 - 2.20 (m, 2H), 3.84 - 3.96 (m, 4H, H_k) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 13.5 (C_h), 19.3 (C_k), 20.9 (C_d or e), 23.7 (C_d or e), 30.6, 34.4, 34.6, 41.2 (C_b), 64.8 (C_l), 65.1 (C_l), 67.8 (C_j), 86.0 (C_i), 112.8 (C_a) ppm;

IR (neat) 3298 ($\equiv\text{C-H}$), 2931, 2864, 1449, 1087, 625 cm^{-1} .

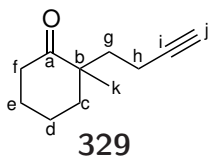
General procedure for the deprotection of dioxolans GP D

The protected ketone (9.70 mmol, 1 equiv.) was dissolved in THF (0.1 M) and 10 % HCl (30 mL) was added. The reaction mixture was stirred at room temperature for 4h.

The aqueous phase was extracted with 3×50 mL Et_2O . The combined organic phases were washed with 50 mL of a saturated aqueous solution of NaHCO_3 , 50 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2).

2-(But-3-yn-1-yl)-2-methylcyclohexanone 329

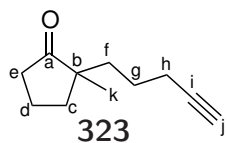


Yield: 75 %
 colourless oil
 $\text{C}_{11}\text{H}_{16}\text{O}$
 MW 164.24 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.06 (s, 3H, H_k), 1.50 - 1.90 (m, 7H), 1.93 (t, $J = 2.7$ Hz, 1H, H_j), 1.93 - 2.07 (m, 2H), 2.17 (dddd, $J = 16.6, 11.1, 5.8, 2.7$ Hz, 1H), 2.30 - 2.46 (m, 2H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 13.6 (C_h), 21.1 (C_d or e), 22.4 (C_k), 27.6 (C_d or e), 36.7, 38.9, 39.3, 48.4 (C_b), 68.6 (C_j), 84.5 (C_i), 215.2 (C_a) ppm.

2-Methyl-2-(pent-4-yn-1-yl)cyclopentanone 323

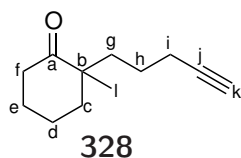


Yield: 70 %
 colourless oil
 $C_{11}H_{16}O$
 MW 164.24 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H, H_k), 1.29 - 1.61 (m, 4H), 1.65 - 1.78 (m, 1H), 1.79 - 1.91 (m, 3H), 1.92 (t, $J = 2.6$ Hz, 1H, H_j), 2.14 (td, $J = 6.8, 2.7$ Hz, 2H), 2.15 - 2.28 (m, 2H) ppm;

^{13}C -NMR (75 MHz, $CDCl_3$) δ 18.8 ($C_{d \text{ or } h}$), 19.0 ($C_{d \text{ or } h}$), 21.8 (C_k), 23.6 (C_g), 35.8, 35.9, 37.7, 48.1 (C_b), 68.7 (C_j), 84.2 (C_i), 223.4 (C_a) ppm.

2-Methyl-2-(pent-4-yn-1-yl)cyclohexanone 328



Yield: quant.
 colourless oil
 $C_{12}H_{18}O$
 MW 178.27 g/mol

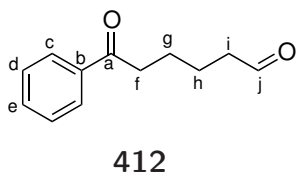
1H -NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H, H_l), 1.17 - 1.37 (m, 1H), 1.40 - 1.62 (m, 3H), 1.63 - 1.83 (m, 5H), 1.83 - 1.92 (m, 1H), 1.94 (t, $J = 2.7$ Hz, 1H, H_k), 2.17 (td, $J = 6.8, 2.5$ Hz, 2H), 2.27 - 2.48 (m, 2H) ppm;

21.4. Synthesis of acyclic ω -keto alkyne 410

Synthesis of 6-Oxo-6-phenylhexanal 412

1-Phenyl-1cyclohexen (756mg, 4.78 mmol, 1 equiv.) was dissolved in 20 mL dry MeOH and cooled to -35 °C. O_3 is bubbled through the solution for 30 min. The reaction mixture is degassed with Ar for 10 min. 2 mL Me_2S are added and the reaction mixture is slowly warmed to room temperature. After stirring for 30 min, the reaction mixture was concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE/EtOAc 98:2 to 8:2).



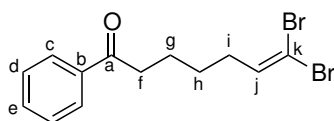
Yield: 74 %
 colourless oil
 $C_{12}H_{14}O_2$
 MW 190.24 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.63 - 1.85 (m, 4H, $H_{g,h}$), 2.25 (td, $J = 6.9, 1.6$ Hz,

2H, H_i), 3.00 (t, J = 6.9 Hz, 2H, H_f), 7.39 - 7.50 (m, 2H, H_d), 7.51 - 7.59 (m, 1H, H_e), 7.89 - 7.99 (m, 2H, H_b), 9.77 (t, J = 1.6 Hz, 1H, H_j) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 21.8 (C_g or h), 23.7 (C_g or h), 38.2 (C_f or i), 43.9 (C_f or i), 128.1 (2C, C_c or d), 128.7 (2C, C_c or d), 133.2 (C_e), 137.0 (C_b), 199.8 (C_a), 202.3 (C_j) ppm.

Synthesis of 7,7-Dibromo-1-phenylhept-6-en-1-one 413

Compound 413 is prepared according to GP H (p. 182).



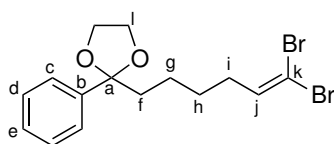
413

Yield: 67 %
 light yellow oil
 C₁₃H₁₄Br₂O
 MW 346.06 g/mol

¹H-NMR (300 MHz, CDCl₃) δ 1.52 (qu, J = 7.6 Hz, 2H, H_h), 1.78 (qu, J = 7.2 Hz, 2H, H_g), 2.15 (q, J = 7.4 Hz, 2H, H_i), 2.98 (t, J = 7.2 Hz, 2H, H_f), 6.40 (t, J = 7.3 Hz, 1H, H_j), 7.41 - 7.50 (m, 2H, H_d), 7.56 (tt, J = 7.4, 1.4 Hz, 1H, H_e), 7.92 - 7.98 (m, 2H, H_c) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 23.7 (C_g or i), 27.5 (C_g or i), 33.0 (C_h), 38.2 (C_f), 89.1 (C_k), 128.1.2 (2C, C), 128.7 (2C, C), 133.1 (C_e), 137.1 (C_b), 138.4 (C_j), 200.0 (C_a) ppm.

Synthesis of 2-(6,6-Dibromohex-5-en-1-yl)-2-phenyl-1,3-dioxolane 414

Compound 414 is prepared according to GP E (p. 173).



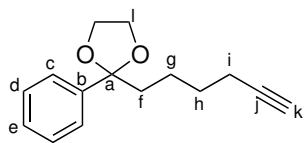
414

Yield: 95 %
 slightly yellow oil
 C₁₅H₁₈Br₂O₂
 MW 390.11 g/mol

¹H-NMR (300 MHz, CDCl₃) δ 1.32 - 1.46 (m, 4H, H_{g,h}), 1.86 - 1.95 (m, 2H, H_f), 1.98 - 2.11 (m, 2H, H_i), 3.70 - 3.82 (m, 2H, H_i), 3.94 - 4.08 (m, 2H, H_i), 6.34 (t, J = 7.2 Hz, 1H, H_j), 7.28 - 7.38 (m, 3H), 7.41 - 7.48 (m, 2H) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 23.3 (C_g), 27.9 (C_i), 33.1 (C_h), 40.3 (C_f), 64.6 (2C, C_l), 88.8 (C_k), 110.4 (C_a), 125.8 (2C, C_c), 127.9 (C_e), 128.2 (2C, C_d), 138.7 (C_j), 142.6 (C_b) ppm.

Synthesis of 2-(Hex-5-yn-1-yl)-2-phenyl-1,3-dioxolane 415

Compound **415** is prepared according to GP C (p. 167).

**415**

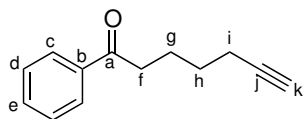
Yield: 90 %
 colourless oil
 $C_{15}H_{18}O_2$
 MW 230.30 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.38 - 1.58 (m, 4H, $H_{g,h}$), 1.86 - 1.95 (m, 2H, H_f), 1.91 (t, $J = 2.6$ Hz, 1H, H_k), 2.14 (td, $J = 6.8, 2.6$ Hz, 2H, H_i), 3.73 - 3.80 (m, 2H, H_l), 3.97 - 4.05 (m, 2H, H_l), 7.27 - 7.38 (m, 3H), 7.41 - 7.48 (m, 2H) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.5 (C_g), 23.0 (C_i), 28.7 (C_h), 40.1 (C_f), 64.6 (2C, C_l), 68.3(C_k), 84.6 (C_j), 110.5 (C_a), 125.8 (2C, C_c), 127.9 (C_e), 128.2 (2C, C_d), 142.7 (C_b) ppm.

Synthesis of 1-Phenylhept-6-yn-1-one 410

Compound **410** is prepared according to GP D (p. 168).

**410**

Yield: quant.
 colourless oil
 $C_{13}H_{14}O$
 MW 186.25 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.63 (qu, $J = 7.2$ Hz, 2H, $H_{g \text{ or } h}$), 1.87 (qu, $J = 7.6$ Hz, 2H, $H_{g \text{ or } h}$), 1.95 (t, $J = 2.6$ Hz, 1H, H_k), 2.25 (td, $J = 7.1, 2.7$ Hz, 2H, H_i), 3.00 (t, $J = 7.3$ Hz, 2H, H_f), 7.45 (t, $J = 7.1$ Hz, 2H, H_d), 7.55 (tt, $J = 7.4, 1.4$ Hz, 1H, H_e), 7.96 (dd, $J = 8.0, 1.3$ Hz, 2H, H_c) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.4 (C_i), 23.5 (C_g), 28.2 (C_h), 38.1 (C_f), 68.7 (C_k), 84.3 (C_j), 128.2 (2C, $C_c \text{ or } d$), 128.7 (2C, $C_c \text{ or } d$), 133.1 (C_e), 137.1 (C_b), 200.0 (C_a) ppm;

IR (neat) 3296 ($\equiv C-H$), 2936, 2865, 1682 (C=O), 1223, 689 cm^{-1} .

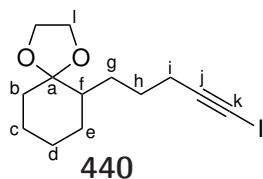
21.5. Synthesis of iodo-alkyne 439**Synthesis of 6-(5-Iodopent-4-yn-1-yl)-1,4-dioxaspiro[4.5]decane 440**

The alkyne **93** (100 mg, 0.480 mmol, 1 equiv.) was dissolved in 5 mL dry THF. $AgNO_3$ (16 mg, 0.096 mmol, 0.2 equiv.) and NIS (135 mg, 0.600 mmol, 1.25 equiv.) were added and the reaction mixture was stirred at room temperature for 2.5 h.

The reaction mixture was hydrolysed with 5 mL H_2O . The aqueous phase was extracted with 3×8 mL EtOAc. The combined organic phases were washed with 6 mL

of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2).



Yield: 86 %
 colourless oil
 $\text{C}_{13}\text{H}_{19}\text{IO}_2$
 MW 334.19 g/mol

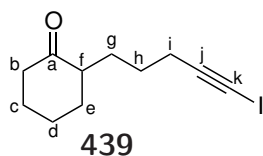
$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.05 - 1.35 (m, 4H), 1.36 - 1.54 (m, 3H), 1.54 - 1.66 (m, 4H), 1.67 - 1.80 (m, 2H), 2.23 - 2.28 (m, 2H), 3.83 - 3.96 (m, 4H, H_k) ppm;

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ -7.1 (C_k), 21.3, 23.9, 24.6, 26.8, 27.7, 29.2, 34.8 (C_b), 44.3 (C_f), 64.7 (C_l), 64.8 (C_l), 94.9 (C_j), 110.8 (C_a) ppm;

IR (neat) 2930, 2860, 1086, 922 cm^{-1} .

Synthesis of 2-(5-Iodopent-4-yn-1-yl)cyclohexanone

Compound **439** was synthesized according to GP D (p. 168).



Yield: 98 %
 colourless oil
 $\text{C}_{11}\text{H}_{15}\text{IO}_2$
 MW 290.14 g/mol

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.08 - 1.41 (m, 2H), 1.42 - 1.55 (m, 2H), 1.57 - 1.71 (m, 2H), 1.73 - 1.90 (m, 2H), 1.94 - 2.14 (m, 2H), 2.19 - 2.41 (m, 3H), 2.33 (t, $J = 6.3$ Hz, 2H, H_i) ppm;

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ -6.8 (C_k), 21.1 (C_i), 25.0, 26.2, 28.1, 28.8, 34.1, 42.1 (C_b), 50.3 (C_f), 94.5 (C_j), 213.1 (C_a) ppm;

IR (neat) 2930, 2859, 1698 ($\text{C}=\text{O}$), 1447, 1128 cm^{-1} .

22. Synthesis of acetylenic ω -ketoesters

22.1. Protection of cycloalkanons: Synthesis of 1,3-dioxolans

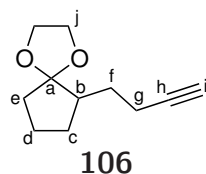
General procedure for the protection of ketones as dioxolan GP E

The ketone (34.52 mmol, 1 equiv.) is dissolved in benzene (0.1 M). Ethylene glykol (51.78 mmol, 1.5 equiv.) and PTSA (cat.) are added and the reaction mixture was heated to reflux in a Dean-Stark for 16h.

The reaction mixture was cooled to room temperature and hydrolyzed with 40 mL of a saturated aqueous solution of NaHCO_3 . The aqueous phase was extracted with 3×80 mL Et_2O . The combined organic phases were washed with 40 mL of a saturated aqueous solution of NaCl , dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2).

6-(But-3-yn-1-yl)-1,4-dioxaspiro[4.4]nonane 106

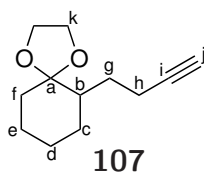


Yield: 75 %
colourless oil
 $\text{C}_{11}\text{H}_{16}\text{O}_2$
MW 180.24 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.16 - 1.36 (m, 1H), 1.36 - 1.52 (m, 1H), 1.53 - 1.69 (m, 2H), 1.69 - 1.82 (m, 3H), 1.84 - 1.97 (m, 1H), 1.92 (t, $J = 2.6$ Hz, 1H, H_i), 1.97 - 2.13 (m, 1H), 2.13 - 2.31 (m, 2H), 3.79 - 3.96 (m, 4H, H_j) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 17.3 (C_d or g), 20.7 (C_d or g), 28.1 (C_c or f), 29.2 (C_c or f), 35.8 (C_e), 45.2 (C_b), 64.6 (C_j), 64.7 (C_j), 68.3 (C_i), 84.8 (C_h), 118.2 (C_a) ppm;

IR (neat) 3291 ($\equiv\text{C-H}$), 2951, 2876, 1030, 627 cm^{-1} .

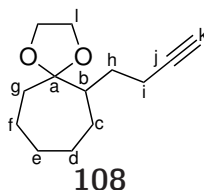
6-(But-3-yn-1-yl)-1,4-dioxaspiro[4.5]decane **107**

Yield: quant.
colourless oil
 $C_{12}H_{18}O_2$
MW 194.27 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.15 - 1.38 (m, 4H), 1.38 - 1.53 (m, 1H), 1.55 - 1.70 (m, 3H), 1.70 - 1.80 (m, 2H), 1.80 - 1.90 (m, 1H), 1.92 (t, $J = 2.6$ Hz, 1H, H_j), 2.06 - 2.32 (m, 2H), 3.85 - 3.99 (m, 4H, H_k) ppm;

^{13}C -NMR (75 MHz, $CDCl_3$) δ 16.7 (C_h), 23.9 (C_c or e), 24.6 (C_c or e), 27.5 (C_d or g), 29.0 (C_d or g), 34.7 (C_f), 43.6 (C_b), 64.7 (C_k), 64.9 (C_k), 68.2 (C_j), 85.0 (C_i), 110.8 (C_a) ppm;

IR (neat) 3310 ($\equiv C-H$), 2929, 2856, 1087, 923, 625 cm^{-1} .

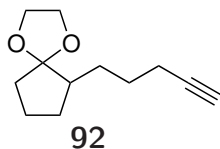
6-(But-3-yn-1-yl)-1,4-dioxaspiro[4.6]undecane **108**

Yield: 69 %
colourless oil
 $C_{13}H_{20}O_2$
MW 208.30 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.29 - 1.50 (m, 5H), 1.50 - 1.65 (m, 2H), 1.65 - 1.88 (m, 6H), 1.93 (t, $J = 2.7$ Hz, 1H, H_k), 2.14 (dddd, $J = 16.8, 8.4, 7.7, 2.7$ Hz, 1H), 2.29 (dddd, $J = 17.0, 8.4, 5.6, 2.8$ Hz, 1H), 3.80 - 3.99 (m, 4H, H_l) ppm;

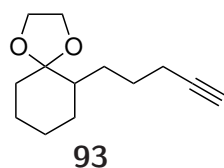
^{13}C -NMR (75 MHz, $CDCl_3$) δ 17.0 (C_i), 21.7 (C_c or f), 26.9, 28.7 (2C), 37.0 (C_g), 46.4 (C_b), 64.0 (C_l), 65.0 (C_l), 68.3 (C_k), 84.9 (C_j), 114.1 (C_a) ppm;

IR (neat) 3293 ($\equiv C-H$), 2927, 2863, 1046, 624 cm^{-1} .

6-(Pent-4-yn-1-yl)-1,4-dioxaspiro[4.4]nonane **92**

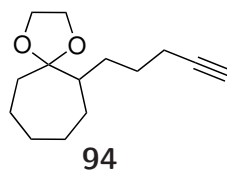
Yield: 83 %
colourless oil
 $C_{12}H_{18}O_2$
MW 194.27 g/mol

Characterization data for compound **92** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 194.

6-(Pent-4-yn-1-yl)-1,4-dioxaspiro[4.5]decane 93

Yield: quant.
colourless oil
 $C_{13}H_{20}O_2$
MW 208.30 g/mol

Characterization data for compound **93** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 194.

6-(Pent-4-yn-1-yl)-1,4-dioxaspiro[4.6]undecane 94

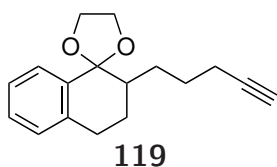
Yield: quant.
colourless oil
 $C_{14}H_{22}O_2$
MW 222.32 g/mol

Characterization data for compound **94** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 195.

General procedure for the protection of ketones as dioxolan using Patel's conditions[69] GP F

The ketone (1 equiv.) was dissolved in ethylene glykol (6 equiv.) and triethyl orthoformate (1.5 equiv.) and Bu_4NBr_3 (0.03 equiv.) were added. The reaction mixture was heated to 60 °C for 16h.

After cooling to room temperature, the reaction mixture was poured on a saturated aqueous solution of $NaHCO_3$. The aqueous phase is extracted 3× with ETOAc. The combined organic phases are washed with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15mbar).

2'-(Pent-4-yn-1-yl)-3',4'-dihydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalene] 119

Yield: 84 %
light yellow oil
 $C_{17}H_{20}O_2$
MW 256.34 g/mol

Characterization data for compound **119** are in good agreement with those found in the PhD thesis of T. Welsch[68] on page 206.

22.2. Esterification of terminal alkynes

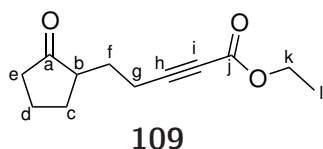
General procedure for the esterification of alkynes GP G

The alkyne (33.49 mmol, 1 equiv.) was dissolved in dry THF (0.15 M) and cooled to $-78\text{ }^{\circ}\text{C}$. $n\text{BuLi}$ was added dropwise. The reaction mixture was stirred for 1h at $-78\text{ }^{\circ}\text{C}$, then warmed to room temperature and stirred for 45 min. After cooling to $-78\text{ }^{\circ}\text{C}$ again, ClCO_2Et was added dropwise. The reaction mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$ then warmed to room temperature and stirred for 5h.

The reaction mixture was hydrolyzed with 150 mL 10 % HCl and stirred for 16h at room temperature. The aqueous phase is extracted $3 \times 100\text{ mL Et}_2\text{O}$. The combined organic phases were washed with 150 mL of a saturated aqueous solution of NaHCO_3 , 100 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2 to 9:1).

Ethyl 5-(2-oxocyclopentyl)pent-2-ynoate 109



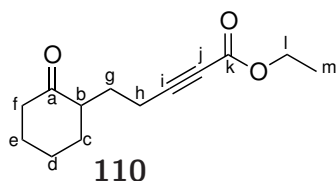
Yield: 64 %
 colourless oil
 $\text{C}_{12}\text{H}_{16}\text{O}_3$
 MW 208.25 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.27 (t, $J = 7.1\text{ Hz}$, 3H, H_l), 1.42 - 1.59 (m, 2H), 1.69 - 1.87 (m, 1H), 1.93 - 2.08 (m, 2H), 2.08 - 2.39 (m, 4H), 2.39 - 2.55 (m, 2H), 4.18 (q, $J = 7.1\text{ Hz}$, 2H, H_k) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.1 (C_l), 17.0 (C_g), 20.7 (C_d), 27.7 (C_c or f), 29.6 (C_c or f), 38.0 (C_e), 48.0 (C_b), 61.9 (C_k), 73.8 (C_i), 88.3 (C_h), 153.8 (C_j), 220.2 (C_a) ppm;

IR (neat) 2961, 2874, 2233 ($\text{C}\equiv\text{C}$), 1734 ($\text{C}=\text{O}$), 1703 ($\text{C}=\text{O}$), 1244, 1068, 751 cm^{-1} .

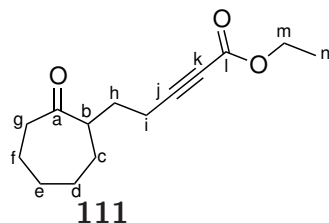
Ethyl 5-(2-oxocyclohexyl)pent-2-ynoate 110



Yield: 59 %
 colourless oil
 $\text{C}_{13}\text{H}_{18}\text{O}_3$
 MW 222.28 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.29 (t, $J = 7.2\text{ Hz}$, 3H, H_m), 1.31 - 1.48 (m, 2H), 1.57 - 1.79 (m, 2H), 1.81 - 1.92 (m, 1H), 1.97 - 2.16 (m, 3H), 2.24 - 2.51 (m, 5H), 4.20 (q, $J = 7.2\text{ Hz}$, 2H, H_l) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.2 (C_m), 16.6 (C_h), 25.3 (C_d), 27.6 (C_e or g), 28.2 (C_e or g), 34.4 (C_c), 42.4 (C_f), 49.2 (C_b), 61.9 (C_l), 73.6 (C_j), 89.0 (C_i), 153.9 (C_k),

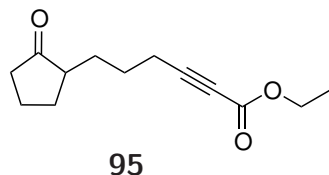
212.4 (C_a) ppm;**IR** (neat) 2934, 2862, 2232 ($C\equiv C$), 1703 ($C=O$), 1244, 1067, 752 cm^{-1} .**Ethyl 5-(2-oxocycloheptyl)pent-2-ynoate 111**

Yield: 71 %
 colourless oil
 $C_{14}H_{20}O_3$
 MW 236.31 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.20 - 1.35 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H, H_n), 1.36 - 1.58 (m, 2H), 1.58 - 1.71 (m, 1H), 1.71 - 1.89 (m, 4H), 1.96 (ddt, $J = 13.6, 8.4, 6.8$ Hz, 1H), 2.31 (td, $J = 7.1, 1.5$ Hz, 2H), 2.39 - 2.54 (m, 2H), 2.61 - 2.73 (m, 1H), 4.17 (q, $J = 7.2$ Hz, 2H, H_m) ppm;

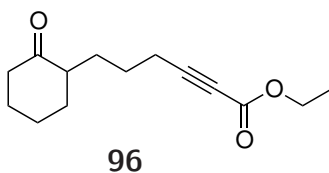
^{13}C -NMR(75 MHz, $CDCl_3$) δ 14.1 (C_n), 16.6 (C_i), 24.0 (C_f), 28.8, 29.2, 29.6, 31.5, 43.2 (C_g), 50.3 (C_b), 61.9 (C_m), 73.7 (C_k), 88.6 (C_j), 153.8 (C_l), 215.0 (C_a) ppm;

IR (neat) 2927, 2855, 2233 ($C\equiv C$), 1699 ($C=O$), 1244, 1069, 751 cm^{-1} .

Ethyl 6-(2-oxocyclopentyl)hex-2-ynoate 95

Yield: 74 %
 colourless oil
 $C_{13}H_{18}O_3$
 MW 222.28 g/mol

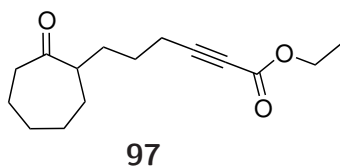
Characterization data for compound **95** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 202.

Ethyl 6-(2-oxocyclohexyl)hex-2-ynoate 96

Yield: 93 %
 colourless oil
 $C_{14}H_{20}O_3$
 MW 236.31 g/mol

Characterization data for compound **96** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 202.

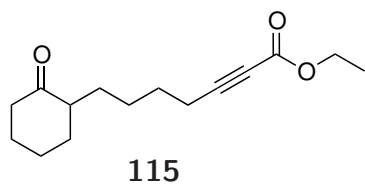
Ethyl 6-(2-oxocycloheptyl)hex-2-ynoate 97



Yield: 51 %
colourless oil
 $C_{15}H_{22}O_3$
MW 250.33 g/mol

Characterization data for compound **97** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 203.

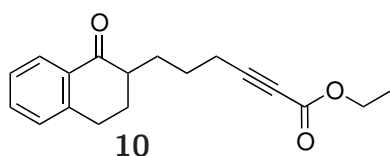
Ethyl 7-(2-oxocyclohexyl)hept-2-ynoate 115



Yield: 78 %
colourless oil
 $C_{16}H_{24}O_3$
MW 250.33 g/mol

Characterization data for compound **115** are in good agreement with those found in the PhD thesis of A. Klein[66] on page 203.

Ethyl 6-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hex-2-ynoate 10



Yield: 60 %
light yellow oil
 $C_{18}H_{20}O_3$
MW 284.35 g/mol

Characterization data for compound **10** are in good agreement with those found in the PhD thesis of T. Welsch[68] on page 207.

23. Synthesis of enantiomerically enriched acetylenic ω -ketoesters

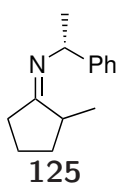
23.1. Synthesis of chiral imines **125** and **126**

The α -methylated cycloalkanone (1 equiv.) was dissolved in toluene (2.5 M) and *S*-(-)- α -methylbenzylamine (1.05 equiv.) was added. The reaction mixture was heated to reflux in a Dean-Stark for 16h.

The reaction mixture is cooled to room temperature and concentrated in vacuum (15 mbar).

The pure product was obtained by distillation under reduced pressure.

(1*R*,*Z*)-*N*-(2-Methylcyclopentylidene)-1-phenylethanamine **125**

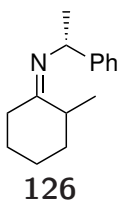


125

Yield: 88 %
colourless oil
 $C_{14}H_{19}N$
MW 201.31 g/mol
b.p. 72 °C (6.4×10^{-3} Torr)

Characterization data for compound **125** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 193.

(1*R*,*Z*)-*N*-(2-Methylcyclohexylidene)-1-phenylethanamine **126**



126

Yield: 91 %
colourless oil
 $C_{15}H_{21}N$
MW 215.33 g/mol
b.p. 86 °C (4.6×10^{-2} Torr)

Characterization data for compound **126** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 194.

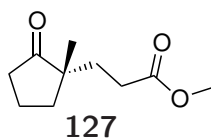
23.2. Alkylation of enantiomerically enriched imines

The enantiomerically enriched imine (**125/126**, 62.17 mmol, 1 equiv.) was dissolved in dry toluene (5 M) and PTSA (cat.) was added. The reaction mixture was cooled to 0 °C and freshly distilled methyl acrylate (186.51 mmol, 3 equiv.) was added slowly via syringe. The reaction mixture was stirred for 10 min at 0 °C, then warmed slowly to 40 °C and held at this temperature for 16h.

The reaction mixture was cooled to 0 °C and hydrolyzed with 5 mL H₂O and 15 mL acetic acid. After stirring for 2h at 0 °C, 20 mL H₂O and 15 mL of a saturated aqueous solution of NaCl were added. The aqueous phase was extracted 5× 30 mL Et₂O. The combined organic phases were washed with 30 mL HCl 10 %, 30 mL H₂O and 30 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product is obtained by distillation under reduced pressure or column chromatography (PE:EtOAc 98:2 to 9:1)

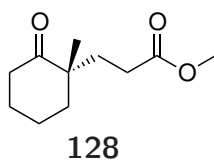
(S)-Methyl 3-(1-methyl-2-oxocyclopentyl)propanoate **127**



Yield: 86 %
 colourless oil
 C₁₀H₁₆O₃
 MW 184.23 g/mol
 $[\alpha]_D^{20} = -42.4$ (c = 1, CHCl₃)

Characterization data for compound **127** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 195.

(S)-Methyl 3-(1-methyl-2-oxocyclohexyl)propanoate **128**



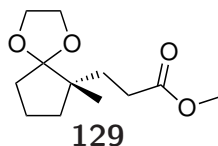
Yield: 85 %
 colourless oil
 C₁₁H₁₈O₃
 MW 198.26 g/mol
 b.p. 69 °C (1.2×10⁻² Torr)
 $[\alpha]_D^{20} = -29.2$ (c = 1, EtOH)

Characterization data for compound **128** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 195.

23.3. Synthesis of enantiomerically enriched dioxolans **129** and **130**

Enantiomerically enriched dioxolans were synthesized according to the general procedures E (p. 173, **129**) and F (p. 175, **130**).

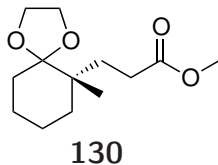
(*S*)-Methyl 3-(6-methyl-1,4-dioxaspiro[4.4]nonan-6-yl)propanoate **129**



Yield: 95 %
 colourless oil
 $C_{12}H_{20}O_4$
 MW 228.28 g/mol
 $[\alpha]_D^{20} = +2.1$ ($c = 1$, $CHCl_3$)

Characterization data for compound **129** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 196.

(*S*)-Methyl 3-(6-methyl-1,4-dioxaspiro[4.5]decan-6-yl)propanoate **130**



Yield: 82 %
 colourless oil
 $C_{13}H_{22}O_4$
 MW 242.31 g/mol
 $[\alpha]_D^{20} = -4.8$ ($c = 1$, $CHCl_3$)

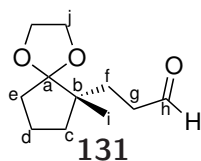
Characterization data for compound **130** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 197.

23.4. Preparation of enantiomerically enriched aldehydes **131** and **132**

The protected keto-ester (**127/128**, 2.27 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (0.1 M) and cooled to $-78\text{ }^\circ\text{C}$. DIBAL-H (1 M in toluene, 3.40 mmol, 1.5 equiv.) was added dropwise under vigorous stirring. The reaction mixture was stirred at this temperature for 45 min.

The reaction mixture was hydrolysed with 5 mL methanol and warmed to rt. 10 mL H_2O were added. The reaction mixture was stirred for 30 min. The aqueous phase was extracted 3×10 mL Et_2O . The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

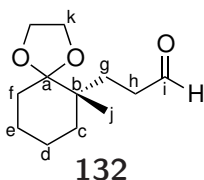
The aldehydes were used without further purification.

(S)-3-(6-Methyl-1,4-dioxaspiro[4.4]nonan-6-yl)propanal 131

Yield: quant.
 colourless oil
 $C_{11}H_{18}O_3$
 MW 198.26 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H, H_j), 1.43 - 1.68 (m, 6H), 1.77 - 1.89 (m, 2H), 2.41 (td, $J = 7.9, 2.1$ Hz, 1H, H_g), 2.46 (td, $J = 8.2, 2.0$ Hz, 1H, H_g), 3.86 - 3.98 (m, 4H, H_i), 9.80 (t, $J = 1.9$ Hz, 1H, H_h) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.0 (C_d), 20.3 (C_i), 27.4 (C_f), 33.5 (C_c or e), 35.8 (C_c or e), 40.1 (C_g), 41.8 (C_b), 64.6 (C_j), 64.8 (C_j), 138.0 (C_a), 203.4 (C_h) ppm.

(S)-3-(6-Methyl-1,4-dioxaspiro[4.5]decan-6-yl)propanal 132

Yield: quant.
 colourless oil
 $C_{12}H_{20}O_3$
 MW 212.29 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H, H_j), 1.31 - 1.43 (m, 4H), 1.43 - 1.62 (m, 5H), 1.68 - 1.80 (m, 1H), 2.34 - 2.43 (m, 2H, H_h), 3.81 - 3.95 (m, 4H, H_k), 9.74 (t, $J = 1.9$ Hz, 1H, H_i) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 19.5 (C_j), 21.0 (C_e or g), 23.6 (C_e or g), 27.1 (C_e), 30.5 (C_c or f), 34.3 (C_c or f), 39.3 (C_h), 40.7 (C_b), 64.7 (C_k), 65.0 (C_k), 113.1 (C_a), 203.5 (C_i) ppm;

IR (neat) 3439, 2930, 2864, 1724 (C=O), 1089 cm^{-1} .

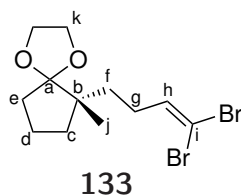
23.5. Synthesis of dibromoalkenes 133 and 134**General procedure for the formation of dibromoalkenes GP H**

CBr_4 (4.54 mmol, 2 equiv.) was dissolved in 30 mL dry CH_2Cl_2 and cooled to 0 °C. PPh_3 (9.05 mmol, 4 equiv., 1 M in dry CH_2Cl_2) was added dropwise. NEt_3 (27.23 mmol, 12 equiv.) was added. The aldehyde (**131/132**, 2.27 mmol, 1 equiv., 0.5 M in dry CH_2Cl_2) was added dropwise. The reaction mixture was stirred for 2 h at room temperature.

The reaction mixture was hydrolyzed with 40 mL of a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted 3 \times 20 mL CH_2Cl_2 . The combined organic layers were washed with 15 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2 to 95:5).

(S)-6-(4,4-Dibromobut-3-en-1-yl)-6-methyl-1,4-dioxaspiro[4.4]nonane 133



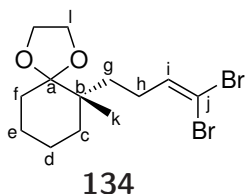
Yield: 75 %
slightly yellow oil
 $C_{12}H_{18}Br_2O_2$
MW 354.08 g/mol
 $[\alpha]_D^{20} = -39.2$ (c = 1, $CHCl_3$)

1H -NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H, H_j), 1.41 - 1.56 (m, 3H), 1.58 - 1.72 (m, 3H), 1.74 - 1.92 (m, 2H), 1.95 - 2.22 (m, 2H), 3.85 - 3.95 (m, 4H, H_k), 6.39 (t, J = 7.3 Hz, 1H, H_h) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 18.1 (C_d), 20.2 (C_j), 29.0, 33.1, 33.5, 35.5, 45.8 (C_b), 64.7 (C_k), 64.9 (C_k), 88.4 (C_i), 119.6 (C_a), 139.6 (C_h) ppm;

IR (neat) 2959, 2870, 1731($C=C$) cm^{-1}

(S)-6-(4,4-Dibromobut-3-en-1-yl)-6-methyl-1,4-dioxaspiro[4.5]decane 134



Yield: 73 %
light yellow oil
 $C_{12}H_{18}Br_2O_2$
MW 354.08 g/mol
 $[\alpha]_D^{20} = -11.5$ (c = 1, $CHCl_3$)

1H -NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3H, H_k), 1.35 - 1.46 (m, 4H), 1.47 - 1.62 (m, 6H), 1.96 - 2.09 (m, 2H), 3.86 - 3.97 (m, 4H, H_l), 6.38 (t, J = 7.3 Hz, 1H, H_i) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 19.5 (C_k), 21.0, 23.7, 28.0, 30.6, 32.8, 34.5, 41.2 (C_b), 64.9 (C_l), 65.1 (C_l), 88.3 (C_j), 112.8 (C_a), 139.7 (C_i) ppm;

IR (neat) 2930, 2863, 1706 ($C=C$), 1453 cm^{-1}

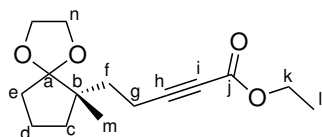
23.6. Synthesis of the enantiomerically enriched protected acetylenic ω -ketoesters 135 and 136

The protected dibromoalkene (**133/134**, 5.23 mmol, 1 equiv.) was dissolved in 65 mL dry THF and cooled to $-78^\circ C$. $nBuLi$ (1.6 M in hexanes, 11.50 mmol, 2.2 equiv.) was added dropwise and the reaction mixture was stirred for 45 min at $-78^\circ C$. Ethyl chloroformate (11.50 mmol, 2.2 equiv.) was added slowly. The reaction mixture was stirred for 30 min at $-78^\circ C$, then warmed to room temperature and stirred for 3 h. The reaction mixture was hydrolyzed with 45 mL of a saturated aqueous solution of NH_4Cl . The aqueous phase was extracted 3×90 mL Et_2O . The combined organic layers were washed with 110 mL of a saturated aqueous solution of $NaCl$, dried over

anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE to PE:EtOAc 98:2).

(S)-Ethyl 5-(6-methyl-1,4-dioxaspiro[4.4]nonan-6-yl)pent-2-ynoate 135



135

Yield: 95 %

colourless oil

$\text{C}_{15}\text{H}_{22}\text{O}_4$

MW 266.33 g/mol

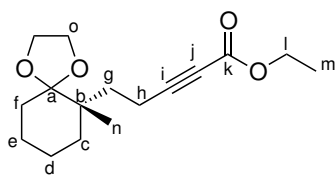
$[\alpha]_D^{20} = -7.3$ ($c = 1$, CHCl_3)

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.95 (s, 3H, H_m), 1.29 (t, $J = 7.2$ Hz, 3H, H_l), 1.42 - 1.53 (m, 1H), 1.54 - 1.67 (m, 3H), 1.71 (t, $J = 8.4$ Hz, 2H), 1.75 - 1.87 (m, 2H), 2.32 (dtd, $J = 23.8, 17.4, 8.8$ Hz, 2H), 3.81 - 3.97 (m, 4H), 4.20 (q, $J = 7.2$ Hz, 2H, H_k) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.2 (C_l), 14.7 (C_d or g), 18.0 (C_d or g), 20.0 (C_m), 33.4, 33.5, 35.6, 45.5 (C_b), 61.9 (C_k), 64.6 (C_n), 64.9 (C_n), 72.9 (C_i), 90.6 (C_h), 119.4 (C_a), 154.1 (C_j) ppm;

IR (neat) 2963, 2877, 2861, 2231 ($\text{C}\equiv\text{C}$), 1705 ($\text{C}=\text{O}$), 1245, 1065, 751 cm^{-1}

(S)-Ethyl 5-(6-methyl-1,4-dioxaspiro[4.5]decan-6-yl)pent-2-ynoate 136



136

Yield: 87 %

slightly yellow oil

$\text{C}_{16}\text{H}_{24}\text{O}_4$

MW 280.36 g/mol

$[\alpha]_D^{20} = -12.1$ ($c = 1$, CHCl_3)

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.91 (s, 3H, H_m), 1.28 (t, $J = 7.1$ Hz, 3H, H_l), 1.40 ("s", 4H), 1.46 - 1.60 (m, 4H), 1.66 - 1.87 (m, 2H), 2.30 (ddd, $J = 10.4, 6.5, 3.6$ Hz, 2H, H_h), 3.84 - 3.96 (m, 4H, H_o), 4.19 (q, $J = 7.1$ Hz, 2H, H_l) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 13.9 (C_h), 14.2 (C_m), 19.4 (C_n), 20.9 (C_d), 23.6 (C_e), 30.6, 33.6, 34.8, 41.1 (C_b), 61.9 (C_l), 64.8 (C_o), 65.1 (C_o), 72.9 (C_j), 90.8 (C_i), 112.7 (C_a), 154.1 (C_k) ppm;

IR (neat) 2932, 2866, 2231 ($\text{C}\equiv\text{C}$), 1706 ($\text{C}=\text{O}$) cm^{-1}

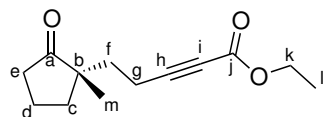
23.7. Synthesis of enantiomerically enriched acetylenic ω -ketoesters **137** and **138**

The protected acetylenic ω -ketoester (**135/136**, 1.15 mmol, 1 equiv.) was dissolved in 10 mL Et₂O and 5 mL of 10 % HCl were added. The reaction mixture was stirred at room temperature for 17h.

The aqueous phase was extracted 3× 10 mL Et₂O. The combined organic layer was consecutively washed with 5 mL of a saturated aqueous solution of NaHCO₃, 10 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE to PE:EtOAc 98:2 to 95:5).

(S)-Ethyl 5-(1-methyl-2-oxocyclopentyl)pent-2-ynoate **137**

**137**

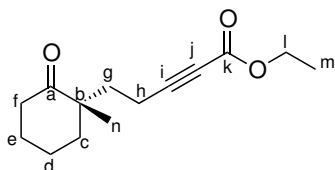
Yield: 89 %
 colourless oil
 C₁₃H₁₈O₃
 MW 222.28 g/mol
 $[\alpha]_D^{20} = -45.6$ (c = 1, CHCl₃)

¹H-NMR (300 MHz, C₆D₆) δ 1.01 (s, 3H, H_m), 1.29 (t, J = 7.1 Hz, 3H, H_l), 1.64 - 1.82 (m, 3H), 1.85 - 1.97 (m, 3H), 2.14 - 2.45 (m, 4H), 4.20 (q, J = 7.1 Hz, 2H, H_k) ppm;

¹³C-NMR(75 MHz, C₆D₆) δ 14.2 (C_l), 14.4 (C_g), 18.8 (C_d), 21.4 (C_m), 34.5, 36.0, 37.6, 47.9 (C_b), 62.0 (C_k), 73.6 (C_i), 88.9 (C_h), 153.9 (C_j), 222.3 (C_a) ppm;

IR (neat) 2963, 2873, 2232 (C≡C), 1733 (C=O), 1704, 1245, 1069, 752 cm⁻¹

(S)-Ethyl 5-(1-methyl-2-oxocyclohexyl)pent-2-ynoate **138**

**138**

Yield: 92 %
 colourless oil
 C₁₄H₂₀O₃
 MW 236.31 g/mol
 $[\alpha]_D^{20} = -40.4$ (c = 1, CHCl₃)

¹H-NMR (300 MHz, CDCl₃) δ 1.07 (s, 3H, H_n), 1.27 (t, J = 7.1 Hz, 3H, H_m), 1.53 - 1.66 (m, 1H), 1.67 - 1.86 (m, 6H), 1.95 (ddd, J = 13.8, 10.6, 5.3 Hz, 1H), 2.17 (dq, J = 17.2, 5.3 Hz, 1H), 2.29 (dd, J = 10.8, 6.0 Hz, 1H), 2.32 - 2.41 (m, 2H), 4.18 (q, J = 7.1, 2H, H_l) ppm;

¹³C-NMR(75 MHz, CDCl₃) δ 14.0 (C_h), 14.1 (C_m), 21.1, 22.4 (C_n), 27.5, 35.8, 38.8, 39.1, 48.2 (C_b), 61.9 (C_l), 73.4 (C_j), 89.1 (C_i), 153.8 (C_k), 214.8 (C_a) ppm;

IR (neat) 2936, 2866, 2232 (C \equiv C), 1701 (C=O), 1245, 1069, 752 cm⁻¹

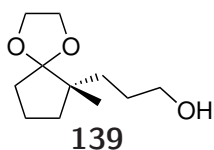
23.8. Synthesis of enantiomerically enriched alcohols **139** and **140**

The protected keto-ester (**127/128**, 50.11 mmol, 1 equiv.) was dissolved in dry THF (0.15 M). The LAH was added in small portions and the reaction mixture was stirred at room temperature for 20 min.

The reaction mixture was hydrolyzed with 50 mL EtOAc, 50 mL Et₂O and 50 mL H₂O. The reaction mixture was diluted with 150 mL Et₂O and filtered through a pad of celite. The aqueous phase is extracted 2 \times 150 mL Et₂O. The combined organic phases are washed with 200 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The crude product was used without purification.

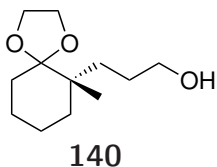
(S)-3-(6-Methyl-1,4-dioxaspiro[4.4]nonan-6-yl)propan-1-ol **139**



Yield: quant.
colourless oil
C₁₁H₂₀O₃
MW 200.27 g/mol
[α]_D²⁰ = +7.4 (c = 1, CHCl₃)

Characterization data for compound **139** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 197.

(S)-3-(6-Methyl-1,4-dioxaspiro[4.5]decan-6-yl)propan-1-ol **140**



Yield: quant.
colourless oil
C₁₂H₂₂O₃
MW 214.30 g/mol

Characterization data for compound **140** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 198.

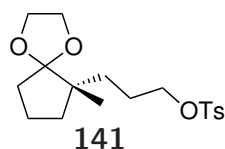
23.9. Synthesis of enantiomerically enriched tosylates **141** and **142**

The alcohol (**139/140**, 47.52 mmol, 1 equiv.) was dissolved in dry CH₂Cl₂ (0.15 M) and cooled to 0 °C. The NEt₃ (71.27 mmol, 1.5 equiv.) was added, followed by DMAP (cat.) and TsCl (57.02 mmol, 1.2 equiv., in small portions). The reaction mixture was slowly warmed to room temperature and was stirred for 16h.

The reaction mixture was hydrolyzed with 180 mL of a saturated aqueous solution of NH₄Cl. The aqueous phase is extracted 3× 60 mL Et₂O. The combined organic phases are washed with 150 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2 to 9:1).

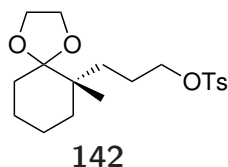
(S)-3-(6-Methyl-1,4-dioxaspiro[4.4]nonan-6-yl)propyl 4-methylbenzenesulfonate **141**



Yield: 90 %
 colourless oil
 C₁₈H₂₆O₅S
 MW 354.46 g/mol
 [α]_D²⁰ = -11.9 (c = 1, CHCl₃)

Characterization data for compound **141** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 199.

(S)-3-(6-Methyl-1,4-dioxaspiro[4.5]decan-6-yl)propyl 4-methylbenzenesulfonate **142**



Yield: 89 %
 colourless oil
 C₁₉H₂₈O₅S
 MW 368.49 g/mol

Characterization data for compound **142** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 200.

23.10. Synthesis of enantiomerically enriched alkynes **143** and **144**

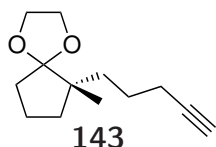
Lithium acetylide ethylene diamine complex (55.25 mmol, 1.3 equiv.) was cooled to 0 °C and the tosylate (**141/142**, 42.50 mmol, 1 equiv.) in the minimum dry DMSO needed was added dropwise. The reaction mixture was slowly warmed to room temperature

and was stirred for 1.5 h.

The reaction mixture was hydrolyzed with 100 mL of a saturated aqueous solution of NH_4Cl . The aqueous phase is extracted 3×150 mL Et_2O . The combined organic phases are washed with 200 mL of a saturated aqueous solution of NaCl , dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 98:2).

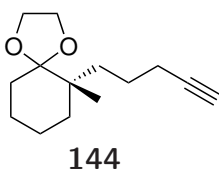
(R)-6-Methyl-6-(pent-4-yn-1-yl)-1,4-dioxaspiro[4.4]nonane 143



Yield: 82 %
 colourless oil
 $\text{C}_{13}\text{H}_{20}\text{O}_2$
 MW 208.30 g/mol
 $[\alpha]_D^{20} = +3.7$ ($c = 1$, CHCl_3)

Characterization data for compound **143** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 200.

(S)-6-Methyl-6-(pent-4-yn-1-yl)-1,4-dioxaspiro[4.5]decane 144



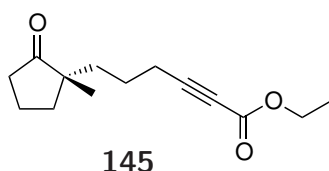
Yield: 76 %
 colourless oil
 $\text{C}_{14}\text{H}_{22}\text{O}_2$
 MW 222.33 g/mol

Characterization data for compound **144** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 201.

23.11. Synthesis of enantiomerically enriched acetylenic ω -ketoesters 145 and 146

The acetylenic ω -ketoesters are synthesized according to the GP G (p. 176).

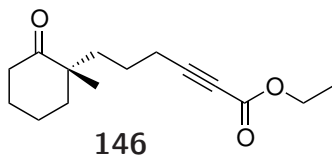
(R)-Ethyl 6-(1-methyl-2-oxocyclopentyl)hex-2-ynoate 145



Yield: 88 %
 colourless oil
 $\text{C}_{14}\text{H}_{20}\text{O}_3$
 MW 208.30 g/mol
 $[\alpha]_D^{20} = -47.7$ ($c = 1$, CHCl_3)

Characterization data for compound **145** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 202.

(S)-Ethyl 6-(1-methyl-2-oxocyclohexyl)hex-2-ynoate 146



Yield: 67 %
colourless oil
 $C_{15}H_{22}O_3$
MW 250.33 g/mol

Characterization data for compound **146** are in good agreement with those found in the PhD thesis of M.-P. Ballet[227] on page 203.

24. Ti-mediated reductive cyclization reactions

24.1. Synthesis of bicyclic γ -hydroxy α,β -unsaturated esters

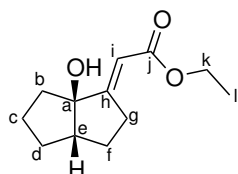
General procedure for the formation of bicyclic γ -hydroxy α,β -unsaturated esters GP I

The starting material (0.6 mmol, 1 equiv.) was dissolved in 10 mL of dry Et₂O and cooled to -30 °C. Ti(OiPr)₄ (1.2 mmol, 2 equiv.) was added under vigorous stirring. Then iPrMgBr (3.6 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred at -30 °C for 2h.

The reaction mixture was hydrolysed with 10 mL of 10% HCl at -30 °C, warmed to rt and stirred for 30 min. The aqueous phase was extracted 2× 25 mL of Et₂O and 2× 25 mL of EtOAc. The combined organic layers were consecutively washed with 25 mL of a saturated aqueous solution of NaHCO₃, 15 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 95:5).

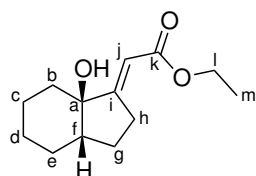
(*E*)-Ethyl 2-(6a-hydroxyhexahydropentalen-1(2*H*)-ylidene)acetate 112



112

Yield: 74 %
colourless oil
C₁₂H₁₈O₃
MW 210.27 g/mol

¹H-NMR (300 MHz, CDCl₃) δ 1.26 (t, J = 7.2 Hz, 3H, H_l), 1.28 - 1.39 (m, 1H), 1.43 - 1.55 (m, 2H), 1.70 - 1.83 (m, 3H), 1.83 - 1.92 (m, 1H), 1.92 - 2.12 (m, 2H), 2.25 (qd, J = 8.1, 3.5 Hz, 1H), 2.86 (dddd, J = 19.4, 8.5, 5.2, 2.6 Hz, 1H), 2.99 (dtd, J = 19.4, 8.4, 2.6 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H, H_k), 5.94 (t, J = 2.5 Hz, 1H, H_i) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 14.4 (C_l), 24.8, 29.2, 30.6, 31.0, 40.2 (C_b or f), 51.8 (C_e), 59.9 (C_k), 91.8 (C_a), 112.2 (C_i), 167.3 (C_j), 171.6 (C_h) ppm;
IR (neat) 3436 (OH), 2954, 2871, 1692 (C=O), 1657 cm⁻¹;
HRMS Cal. for [M+Na]⁺: C₁₂H₁₈O₃: 233.1148 Found: 233.1164.

(E)-Ethyl 2-(7a-hydroxyoctahydro-1*H*-inden-1-ylidene)acetate 113**113**

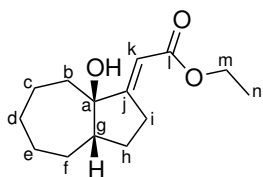
Yield: 76 %
 colourless oil
 $C_{13}H_{20}O_3$
 MW 224.30 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.1$ Hz, 3H, H_m), 1.30 - 1.52 (m, 5H), 1.52 - 1.72 (m, 4H), 1.72 - 1.96 (m, 3H), 2.81 - 2.91 (m, 2H, H_h), 4.14 (q, $J = 7.1$ Hz, 2H, H_l), 5.84 (t, $J = 2.7$ Hz, 1H, H_j) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 14.4 (C_m), 21.7 (C_c or h), 22.3 (C_c or h), 25.2 (C_d or e), 25.4 (C_d or e), 28.7 (C_b or h), 33.3 (C_b or h), 45.2 (C_f), 59.9 (C_l), 80.2 (C_a), 111.5 (C_j), 167.3 (C_k), 171.4 (C_i) ppm;

IR (neat) 3451 (OH), 2928, 2859, 1692 (C=O), 1657 cm^{-1}

HRMS Cal. For $[M+Na]^+$: $C_{13}H_{20}O_3$: 247.1305 Found: 247.1316.

(E)-Ethyl 2-(8a-hydroxyoctahydroazulen-1(2*H*)-ylidene)acetate 114**114**

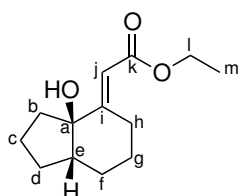
Yield: 86 %
 colourless oil
 $C_{14}H_{22}O_3$
 MW 238.32 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.23 - 1.40 (m, 2H), 1.27 (t, $J = 7.1$ Hz, 3H, H_n), 1.40 - 1.54 (m, 2H), 1.54 - 1.69 (m, 4H), 1.69 - 1.92 (m, 4H), 1.94 - 2.10 (m, 2H), 2.73 - 2.89 (m, 1H, H_i), 2.90 - 3.05 (m, 1H, H_i), 4.15 (q, $J = 7.1$ Hz, 2H, H_m), 5.86 (t, $J = 2.6$ Hz, 1H, H_k) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 14.5 (C_n), 22.6, 27.4, 30.3, 30.3, 30.7, 30.9, 38.1, 51.3 (C_g), 60.0 (C_m), 84.6 (C_a), 113.0 (C_k), 167.4 (C_l), 173.5 (C_j) ppm;

IR (neat) 3467 (OH), 2923, 2853, 1694 (C=O) cm^{-1} ;

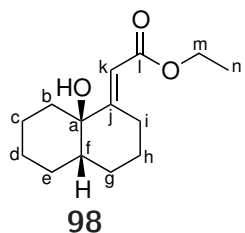
HRMS Cal. For $[M+Na]^+$: $C_{14}H_{22}O_3$: 261.1461 Found: 261.1453.

(E)-Ethyl 2-(3a-hydroxyhexahydro-1*H*-inden-4(2*H*)-ylidene)acetate 99**99**

Yield: 45 %
 light yellow oil
 $C_{13}H_{20}O_3$
 MW 224.30 g/mol

¹H-NMR (300 MHz, C₆D₆) δ 0.83 (td, J = 12.3, 3.3 Hz, 1H), 1.05 (t, J = 7.2 Hz, 3H, H_m), 1.14 - 1.35 (m, 4H), 1.35 - 1.48 (m, 1H), 1.48 - 1.66 (m, 3H), 1.70 - 1.84 (m, 3H), 1.99 - 2.13 (m, 1H), 4.06 (q, J = 7.2 Hz, 2H, H_l), 4.28 (dq, J = 14.7, 3.0 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H, H_j) ppm;
¹³C-NMR(75 MHz, C₆D₆) δ 14.5 (C_m), 21.3 (C_c), 26.6, 27.0, 30.9 (2×C), 37.1 (C_b), 52.0 (C_e), 59.6 (C_l), 83.8 (C_a), 113.4 (C_j), 164.8 (C_i), 167.0 (C_k) ppm;
IR (neat) 3508 (OH), 2930, 2861, 1710 (C=O) cm⁻¹.

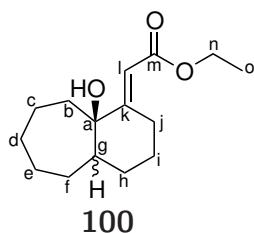
(E)-Ethyl 2-(8a-hydroxyoctahydronaphthalen-1(2H)-ylidene)acetate 98



Yield: 84 %
 colourless oil
 C₁₄H₂₂O₃
 MW 238.32 g/mol

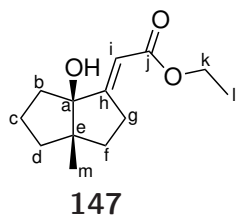
¹H-NMR (300 MHz, CDCl₃) δ 1.27 (t, J = 7.1 Hz, 3H, H_n), 1.32 - 1.41 (m, 2H), 1.42 - 1.65 (m, 7H), 1.55 - 1.92 (m, 3H), 1.92 - 2.04 (m, 2H), 2.04 - 2.14 (m, 1H), 3.79 (d, J = 13.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H, H_m), 6.13 (d, J = 1.5 Hz, 1H, H_k) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 14.3 (C_n), 20.2, 21.8, 26.3, 26.9, 27.2, 28.3, 32.4 (C_b), 44.8 (C_f), 59.7 (C_m), 75.1 (C_a), 111.7 (C_k), 166.7 (C_j), 167.5 (C_l) ppm;
IR (neat) 3480 (OH), 2929, 2863, 1713 (C=O) cm⁻¹;
HRMS Cal. For [M+Na]⁺: C₁₄H₂₂O₃: 261.1461 Found: 261.1480.

(E)-Ethyl 2-(9a-hydroxydecahydro-1H-benzo[7]annulen-1-ylidene)acetate 100



Yield: 63 %
 colourless oil
 C₁₅H₂₄O₃
 MW 252.35 g/mol

¹H-NMR (300 MHz, CDCl₃) δ 1.26 (t, J = 7.1 Hz, 3H, H_o), 1.32 - 1.56 (m, 6H), 1.56 - 1.68 (m, 5H), 1.71 - 1.90 (m, 3H), 1.91 - 1.98 (m, 1H), 1.98 - 2.12 (m, 2H), 3.81 (ddd, J = 14.1, 3.8, 3.4 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H, H_n), 6.10 (d, J = 1.3 Hz, 1H, H_l) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 14.4 (C_o), 21.2, 22.2, 26.7, 27.1, 27.5, 27.5, 28.8, 38.2 (C_b), 49.1 (C_g), 59.8 (C_n), 78.1 (C_a), 110.7 (C_l), 167.8 (C_k or m), 168.3 (C_k or m) ppm;
IR (neat) 3486 (OH), 2923, 2860, 1695 (C=O), 1639 cm⁻¹
HRMS Cal. For [M+Na]⁺: C₁₅H₂₄O₃: 275.1618 Found: 275.1620.

(E)-Ethyl 2-((3a*S*,6a*R*)-6a-hydroxy-3a-methylhexahydropentalen-1(2*H*)-ylidene)acetate 147

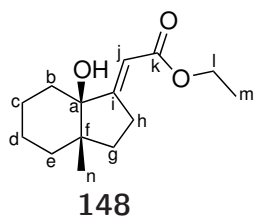
Yield: 78 %
 colourless oil
 $C_{13}H_{20}O_3$
 MW 224.30 g/mol
 $[\alpha]_D^{20} = 13.2$ ($c = 1$, $CHCl_3$)

1H -NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3H, H_m), 1.27 (t, $J = 7.1$ Hz, 3H, H_l), 1.47 - 1.64 (m, 3H), 1.64 - 1.76 (m, 3H), 1.76 - 1.97 (m, 3H), 2.78 (dddd, $J = 20.1, 8.3, 4.6, 2.5$ Hz, 1H), 2.96 (dtd, $J = 20.1, 9.0, 2.7$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H, H_k), 5.95 (t, $J = 2.6$ Hz, 1H, H_i) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 14.5 (C_l), 19.7 (C_m), 22.3, 28.1, 35.0, 37.5, 40.2, 52.3 (C_e), 59.9 (C_k), 91.7 (C_a), 112.4 (C_i), 167.2 (C_j), 171.6 (C_h) ppm;

IR (neat) 3476 (OH), 2951, 2871, 1693 (C=O), 1657 cm^{-1} ;

HRMS Cal. For $[M+Na]^+$: $C_{13}H_{20}O_3$: 247.1305 Found: 247.1294.

(E)-Ethyl 2-((3a*S*,7a*R*)-7a-hydroxy-3a-methyloctahydro-1*H*-inden-1-ylidene)-acetate 148

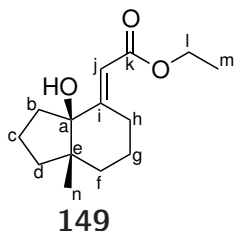
Yield: 83 %
 colourless oil
 $C_{14}H_{22}O_3$
 MW 238.32 g/mol
 $[\alpha]_D^{20} = -19.5$ ($c = 1.960$, $CHCl_3$)

1H -NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H, H_n), 1.28 (t, $J = 7.1$ Hz, 3H, H_m), 1.37 - 1.64 (m, 10H), 1.83 (ddd, $J = 12.9, 9.1, 7.7$ Hz, 1H), 2.76 (dddd, $J = 20.6, 9.5, 4.1, 2.6$ Hz, 1H), 2.95 (dddd, $J = 20.6, 9.7, 7.4, 2.6$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H, H_l), 5.87 ("t", $J = 2.6$ Hz, 1H, H_i) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 14.5 (C_m), 21.5, 22.0 (C_n), 22.3, 26.9, 32.0, 32.8, 33.9, 43.1 (C_f), 59.9 (C_l), 81.8 (C_a), 111.9 (C_j), 167.2 (C_k), 172.0 (C_i) ppm;

IR (neat) 3484 (OH), 2930, 2863, 1693 (C=O) cm^{-1} ;

HRMS Cal. For $[M+Na]^+$: $C_{14}H_{22}O_3$: 261.1461 Found: 261.1458.

(E)-Ethyl 2-((3a*R*,7a*R*)-3a-hydroxy-7a-methylhexahydro-1*H*-inden-4(2*H*)-ylidene)acetate 149

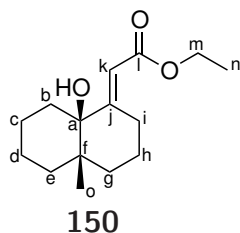
Yield: 80 %
 colourless oil
 $C_{14}H_{22}O_3$
 MW 238.32 g/mol
 $[\alpha]_D^{20} = 46.3$ ($c = 1.031$, $CHCl_3$)

1H -NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3H, H_n), 1.28 (t, $J = 7.2$ Hz, 3H, H_m), 1.33 - 1.46 (m, 2H), 1.46 - 1.63 (m, 4H), 1.63 - 1.74 (m, 1H), 1.78 - 1.92 (m, 3H), 1.92 - 2.06 (m, 1H), 2.24 - 2.40 (m, 1H), 3.86 - 3.96 (m, 1H), 4.16 (q, $J = 7.2$ Hz, 2H, H_l), 6.14 (d, $J = 1.9$ Hz, 1H, H_j) ppm;

^{13}C -NMR (75 MHz, $CDCl_3$) δ 14.5 (C_m), 18.5 (C_n), 20.3 (C_c or g), 23.4 (C_c or g), 26.8 (C_h), 36.4, 38.4, 39.2, 50.4 (C_e), 59.8 (C_l), 85.7 (C_a), 113.4 (C_j), 163.9 (C_i), 167.2 (C_k) ppm;

IR (neat) 3522 (OH), 2935, 1692 (C=O), 1633, 1373 cm^{-1}

HRMS Cal. For $[M+Na]^+$: $C_{14}H_{22}O_3$: 261.1461 Found: 261.1474.

(E)-Ethyl 2-((4a*S*,8a*R*)-8a-hydroxy-4a-methyloctahydronaphthalen-1(2*H*)-ylidene)acetate 150

Yield: 78 %
 colourless oil
 $C_{15}H_{24}O_3$
 MW 252.35 g/mol
 $[\alpha]_D^{20} = +39.24$ ($c = 0.576$, $CHCl_3$)

1H -NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H, H_o), 1.07 - 1.25 (m, 2H), 1.27 (t, $J = 7.1$ Hz, 3H, H_n), 1.45 - 1.77 (m, 9H), 1.93 - 2.21 (m, 3H), 3.90 (d, $J = 14.3$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H, H_m), 6.11 (d, $J = 1.8$ Hz, 1H, H_k) ppm;

^{13}C -NMR (75 MHz, $CDCl_3$) δ 14.4 (C_n), 21.0, 21.5, 22.3, 22.7 (C_o), 26.6, 33.6, 34.0, 35.9, 39.7 (C_f), 59.8 (C_m), 77.4 (C_a), 112.4 (C_k), 166.3 (C_j), 167.5 (C_l) ppm;

IR (neat) 3516 (OH), 2926, 2864, 1696 (C=O), 1638 cm^{-1} ;

HRMS Cal. For $[M+Na]^+$: $C_{15}H_{24}O_3$: 275.1618 Found: 275.1611.

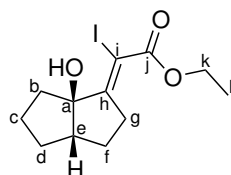
24.2. Procedure for the preparation of bicyclic γ -hydroxy α iodo α,β -unsaturated ester

The starting material (0.23 mmol, 1 equiv.) was dissolved in 5 mL of dry Et₂O and cooled to -30 °C. Ti(O*i*Pr)₄ (0.46 mmol, 2 equiv.) was added under vigorous stirring. Then *i*PrMgBr (1.38 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred at -30 °C for 2 h. After cooling to -78 °C, a solution of I₂ (0.51 mmole, 2.2 equiv.) in 2 mL of dry Et₂O was added quickly. After warming to rt, the reaction mixture was stirred for 25 min.

The reaction mixture was hydrolysed with 5 mL of 1 N HCl. The aqueous phase was extracted with 2 × 7 mL of Et₂O and 2 × 7 mL of EtOAc. The combined organic layers were consecutively washed with 7 mL of a saturated aqueous solution of NaHCO₃, 7 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 95:5).

(*Z*)-Ethyl 2-(6a-hydroxyhexahydropentalen-1(2*H*)-ylidene)-2-iodoacetate **156**



156

Yield: 43 %
colourless solid
C₁₂H₁₇IO₃
MW 364.22 g/mol

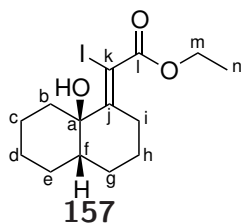
¹H-NMR (300 MHz, CDCl₃) δ 1.16 - 1.31 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H, H_l), 1.40 - 1.56 (m, 1H), 1.69 - 2.09 (m, 6H), 2.20 - 2.37 (m, 1H), 2.43 - 2.56 (m, 1H), 2.91 (ddd, *J* = 18.7, 9.5 7.9 Hz, 1H), 3.02 (ddd, *J* = 18.7, 7.6, 4.6 Hz, 1H), 4.23 (q, *J* = 7.1Hz, 2H, H_k) ppm;

¹³C-NMR(75 MHz, CDCl₃) δ 14.2 (C_l), 25.0, 28.6, 29.9, 37.7, 38.9, 53.9 (C_e), 62.4 (C_k), 81.2 (C_i), 93.6 (C_a), 164.4 (C_h), 169.0 (C_j) ppm;

IR(neat) 3545 (OH), 2959, 2872, 1711 (C=O), 1234 cm⁻¹;

HRMS Cal. For [M+Na]⁺: C₁₂H₁₇IO₃: 359.0115 Found: 359.0074.

(*Z*)-Ethyl 2-(8a-hydroxyoctahydronaphthalen-1(2*H*)-ylidene)-2-iodoacetate **157**



157

Yield: 16 %
light yellow oil
C₁₄H₂₁IO₃
MW 364.22 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.19 - 1.37 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H, H_n), 1.37 - 1.51 (m, 3H), 1.51 - 1.92 (m, 9H), 1.95 - 2.23 (m, 2H), 2.61 (d, $J = 15.6$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H, H_m) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.0 (C_n), 20.0, 21.4, 25.7, 27.3, 28.5, 31.1, 32.7, 43.6 (C_f), 62.1 (C_m), 73.1 (C_a or k), 75.7 (C_a or k), 150.7 (C_j), 168.1 (C_l) ppm.

24.3. Synthesis of tricyclic α,β -unsaturated lactons

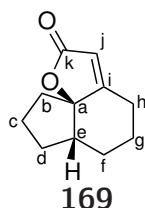
General procedure for the formation of tricyclic α,β -unsaturated lactons GP J

A solution of sodium (4 equiv.) in dry EtOH (10 mL) was added to a solution of the bicyclic γ -hydroxy α,β -unsaturated esters (0.5 mmol, 1 equiv.) in 6 mL of dry EtOH. The resulting mixture was heated to reflux for 16 h.

After cooling to room temperature the solvent was removed. The resulting slime was dissolved in 15 mL of Et_2O and treated with 8 mL of a saturated aqueous solution of NH_4Cl . The aqueous phase was extracted 3×15 mL of Et_2O . The combined organic layers were washed with 20 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE:EtOAc 95:5).

5,6,6a,7,8,9-Hexahydroindeno[3a,4-b]furan-2(4H)-one 169



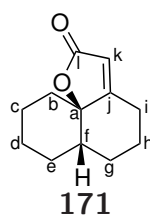
Yield: 71 %
light yellow oil
 $\text{C}_{11}\text{H}_{14}\text{O}_2$
MW 178.23 g/mol

$^1\text{H-NMR}$ (300 MHz, C_6D_6) δ 0.47 (qd, $J = 13.8, 3.6$ Hz, 1H), 0.77 (qt, $J = 13.2, 3.8$ Hz, 1H), 0.97 - 1.04 (m, 1H), 1.05 - 1.17 (m, 1H), 1.22 - 1.34 (m, 1H), 1.35 - 1.64 (m, 5H), 1.70 - 1.86 (m, 1H), 1.92 - 2.09 (m, 2H), 5.40 (d, $J = 1.8$ Hz, 1H, H_j) ppm;

$^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ 22.3, 26.7, 27.9, 29.7, 30.8, 33.5, 51.1 (C_e), 95.6 (C_a), 113.7 (C_j), 171.3 (C_i or k), 171.4 (C_i or k) ppm;

IR (neat) 2937, 1740 ($\text{C}=\text{O}$), 1221 cm^{-1} .

4,5,6,6a,7,8,9,10-Octahydro-2H-naphtho[8a,1-b]furan-2-one 171



Yield: 81 %
light yellow oil
 $\text{C}_{12}\text{H}_{16}\text{O}_2$
MW 192.25 g/mol

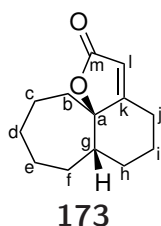
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.25 - 1.39 (m, 2H), 1.39 - 1.57 (m, 4H), 1.62 - 1.82 (m, 4H), 1.82 - 1.96 (m, 2H), 1.96 - 2.08 (m, 1H), 2.21 (tdd, $J = 13.5, 5.7, 1.8$ Hz, 1H), 2.69 (tdd, $J = 13.5, 4.2, 2.1$ Hz, 1H), 5.59 (d, $J = 1.8$ Hz, 1H, H_k) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 19.6, 22.1, 27.2, 27.4, 27.4 (C_f), 30.0, 43.9 (C_f), 88.2 (C_a), 111.9 (C_k), 173.0 (C_j or l), 176.4 (C_j or l) ppm;

IR 2941, 2865, 1760 (C=O), 1219 cm^{-1} ;

HRMS Cal. For $[\text{M}+\text{Na}]^+$: $\text{C}_{12}\text{H}_{16}\text{O}_2$: 215.1043 Found: 215.1043.

4,5,6,6a,7,8,9,10-Octahydro-2H-naphtho[8a,1-b]furan-2-one 173



173

Yield: 31 %

light yellow oil

$\text{C}_{13}\text{H}_{18}\text{O}_2$

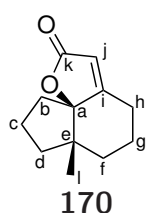
MW 206.28 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.34 (qt, $J = 12.9, 4.3$ Hz, 1H), 1.37 - 1.46 (m, 2H), 1.46 - 1.52 (m, 2H), 1.54 - 1.65 (m, 3H), 1.65 - 1.74 (m, 2H), 1.76 - 1.97 (m, 3H), 1.96 - 2.15 (m, 2H), 2.19 (tdd, $J = 13.1, 5.5, 1.9$ Hz, 1H), 2.71 (ddt, $J = 13.3, 4.3, 1.9$ Hz, 1H), 5.54 (d, $J = 1.8$ Hz, 1H, H_l) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 21.4, 22.0, 27.5, 27.5, 28.0, 28.9, 30.1, 33.5, 48.3 (C_g), 91.2 (C_a), 110.9 (C_l), 173.2 (C_k or m), 177.8 (C_k or m) ppm;

IR 2924, 2861, 1742 (C=O), 1443, 1227, 934 cm^{-1} .

(6a*R*,9a*R*)-6a-Methyl-5,6,6a,7,8,9-hexahydroindeno[3a,4-b]furan-2(4*H*)-one 170



170

Yield: 69 %

colourless solid

$\text{C}_{12}\text{H}_{16}\text{O}_2$

MW 192.25 g/mol

$[\alpha]_D^{20} = -102.1$ ($c = 1, \text{CHCl}_3$)

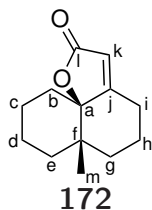
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.85 (s, 3H, H_l), 1.35 - 1.75 (m, 4H), 1.78 - 2.05 (m, 5H), 2.19 - 2.39 (m, 2H), 2.72 (ddt, $J = 13.8, 4.3, 1.5$ Hz, 1H), 5.71 (d, $J = 1.9$ Hz, 1H, H_j) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 17.2 (C_l), 20.7, 24.1, 26.8, 34.8, 35.2, 39.5, 51.4 (C_e), 98.0 (C_a), 113.6 (C_j), 171.8 (C_i or k), 172.9 (C_i or k) ppm;

IR (neat) 2939, 2860, 1731 (C=O), 1262 cm^{-1}

HRMS Cal. For $[\text{M}+\text{Na}]^+$: $\text{C}_{12}\text{H}_{16}\text{O}_2$: 215.1043 Found: 215.1032.

(6a*S*,10a*R*)-6a-Methyl-4,5,6,6a,7,8,9,10-octahydro-2*H*-naphtho[8a,1-b]furan-2-one
172



Yield: 70 %
 colourless solid
 $C_{13}H_{18}O_2$
 MW 206.28 g/mol
 $[\alpha]_D^{20} = -40.17$ ($c = 0.605$, $CHCl_3$)

1H -NMR (300 MHz, C_6D_6) δ 0.61 (s, 3H, H_j), 0.84 - 1.27 (m, 6H), 1.28 - 1.43 (m, 4H), 1.43 - 1.69 (m, 3H), 1.93 (ddt, $J = 13.9, 4.6, 1.8$ Hz, 1H), 5.35 (d, $J = 2.0$ Hz, 1H, H_j) ppm;

^{13}C -NMR(75 MHz, C_6D_6) δ 20.8 (C_m), 21.2, 22.2, 22.6, 25.9, 32.3 (2C), 36.5, 39.6 (C_f), 88.6 (C_a), 113.4 (C_k), 172.0 (C_j or l), 172.7 (C_j or l) ppm;

IR (neat) 2927, 2864, 1731 (C=O), 1235 cm^{-1}

HRMS Cal. For $[M+Na]^+$: $C_{13}H_{18}O_2$: 229.1199 Found: 229.1205.

25. Ag(I)-catalyzed cycloisomerization reactions

25.1. Synthesis of TBS-enol ethers

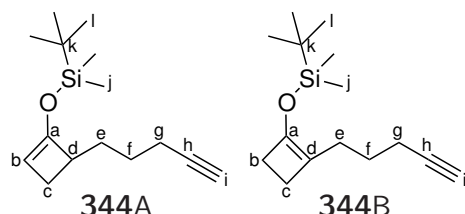
General procedure for the preparation of TBS-enol ethers GP K

The ketone (2.1 mmol, 1 equiv.) was dissolved in 15 mL CH₂Cl₂. NEt₃ (5.25 mmol, 2.5 equiv.) was added and the reaction mixture was stirred at room temperature for 15 min. Then TBSOTf (2.52 mmol, 1.2 equiv.) was added dropwise and the reaction mixture stirred for 2 h.

The reaction mixture was treated with 4 mL NEt₃ and stirred for 15 min. 10 mL cold H₂O are added. The aqueous phase was extracted with 2 × 10 mL CH₂Cl₂ and 2 × 10 mL Et₂O. The combined organic phases were washed with 12 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE/NEt₃ 100:1).

tert-Butyldimethyl((2-(pent-4-yn-1-yl)cyclobut-1-en-1-yl)oxy)silane / *tert*-Butyldimethyl((4-(pent-4-yn-1-yl)cyclobut-1-en-1-yl)oxy)silane **344**



Yield: 73 %
colourless oil
C₁₅H₂₆OSi
MW 250.45 g/mol
344A:344B 3:1

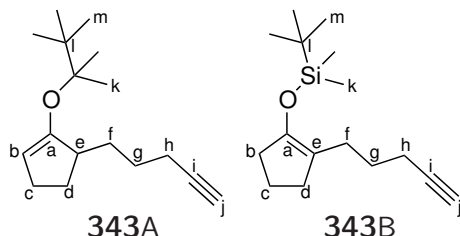
Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

¹H-NMR (400 MHz, CDCl₃) δ 0.09 (s, H_j(A) or H_j(B)), 0.13 (s, H_j(A) or H_j(B)), 0.14 (s, H_j(A) or H_j(B)), 0.95 (s, H_l(A) or H_l(B)), 0.96 (s, H_l(A) or H_l(B)), 1.45 - 1.58 (m), 1.62 (t, J = 7.3 Hz), 1.66 - 1.75 (m), 1.77 (dt, J = 5.0, 2.7 Hz), 1.86 - 1.90 (m, H_i(A) and H_i(B)), 1.99 (td, J = 6.7, 2.8 Hz), 2.03 - 2.12 (m), 2.16 (ddd, J = 10.3, 4.4, 0.7 Hz), 2.41 - 2.46 (m), 2.74 - 2.83 (m), 4.56 (t, J = 0.9 Hz, 1H, H_b(A)) ppm;

¹³C-NMR (100 MHz, CDCl₃) δ -4.8 (C_j(A) or C_j(B)), -4.6 (C_j(A) or C_j(B)), -2.7 (C_j(A) or C_j(B)), 18.6, 18.8, 22.2, 25.8 (C₁(A) or C₁(B)), 26.0 (C₁(A) or C₁(B)), 26.1,

30.1 (C_k(A) or C_k(B)), 31.9, 32.4, 46.7 (C_d(A)), 68.9 (C_i(A) or C_i(B)), 84.4 (C_h(A) or C_h(B)), 100.3 (C_b(A)), 116.5 (C_d(B)), 153.1 (C_a(A) or C_a(B)) ppm.

***tert*-Butyldimethyl((5-(pent-4-yn-1-yl)cyclopent-1-en-1-yl)oxy)silane / *tert*-Butyldimethyl((2-(pent-4-yn-1-yl)cyclopent-1-en-1-yl)oxy)silane 343**



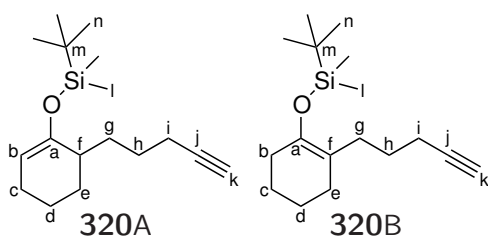
Yield: quant.
colourless oil
C₁₆H₂₈OSi
MW 264.48 g/mol
343A:343B 1:1

Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

¹H-NMR (300 MHz, CDCl₃) δ 0.09 (s, H_k(A) or H_k(B)), 0.14 (s, H_k(A) or H_k(B)), 0.15 (s, H_k(A) or H_k(B)), 0.99 (s, H_m(A) or H_m(B)), 1.00 (s, H_m(A) or H_m(B)), 1.23 - 1.50 (m), 1.50 - 1.75 (m), 1.57 (t, J = 7.8 Hz), 1.79 (t, J = 2.7 Hz, H_j(A) or H_j(B)), 1.80 (t, J = 2.6 Hz, H_j(A) or H_j(B)), 1.82 - 1.94 (m), 2.00 (td, J = 6.9, 2.9 Hz), 2.06 (td, J = 7.3, 2.9 Hz), 2.07 - 2.14 (m), 2.15 - 2.29 (m), 2.37 - 2.54 (m), 4.59 (q, J = 2.1 Hz, 1H, H_b(A)) ppm;

¹³C-NMR (75 MHz, CDCl₃) δ -4.7 (C_k(A) or C_k(B)), -4.6 (C_k(A) or C_k(B)), -3.8 (C_k(A) or C_k(B)), -2.7 (C_k(A) or C_k(B)), 18.3, 18.7, 19.0, 20.2, 26.0 (C_m(A) or C_m(B)), 26.5, 27.3, 27.4, 28.3, 31.2, 32.8, 34.2, 44.8 (C_e(A)), 68.9 (C_j(A) or C_j(B)), 84.5 (C_i(A) or C_i(B)), 84.7 (C_i(A) or C_i(B)), 101.0 (C_b(A)), 115.6 (C_e(B)), 147.6 (C_a(B)), 158.2 (C_a(A)) ppm.

***tert*-Butyldimethyl((6-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)silane / *tert*-Butyldimethyl((2-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)silane 320**



Yield: quant.
colourless oil
C₁₇H₃₀OSi
MW 278.50 g/mol
320A:320B 2:1

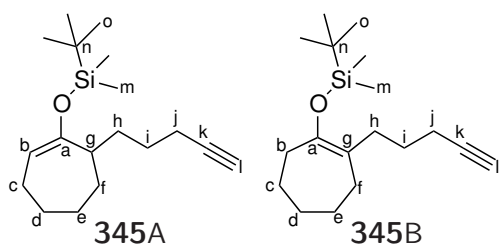
Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

¹H-NMR (300 MHz, CDCl₃) δ 0.10 (s, H_l(A) or H_l(B)), 0.15 (s, H_l(A) or H_l(B)), 0.16 (s, H_l(A) or H_l(B)), 1.00 (s, H_n(A) or H_n(B)), 1.25 - 1.70 (m), 1.80 (t, J = 2.7 Hz, H_k(A) or H_k(B)), 1.81 (t, J = 2.8 Hz, H_k(A) or H_k(B)), 1.83 - 2.07 (m), 2.02 (td,

$J = 6.8, 2.7$ Hz), 2.11 (td, $J = 7.3, 2.7$ Hz), 2.21 (t, $J = 8.0$ Hz), 4.88 (td, $J = 3.9, 1.3$ Hz, 1H, $H_b(A)$) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ -4.7 ($C_1(A)$ or $C_1(B)$), -4.6 ($C_1(A)$ or $C_1(B)$), -3.9 ($C_1(A)$ or $C_1(B)$), 18.0 ($C_m(A)$ or $C_m(B)$), 18.1 ($C_m(A)$ or $C_m(B)$), 18.4, 18.5, 20.3, 23.0, 23.6, 24.1, 25.7 ($C_n(A)$ or $C_m(B)$), 25.8 ($C_n(A)$ or $C_m(B)$), 26.1, 27.0, 27.6, 27.8, 29.6, 30.4, 31.5, 38.5 ($C_f(A)$), 68.5 ($C_k(A)$ or $C_k(B)$), 68.6 ($C_k(A)$ or $C_k(B)$), 84.1 ($C_j(A)$ or $C_j(B)$), 84.4 ($C_j(A)$ or $C_j(B)$), 103.2 ($C_b(A)$), 114.0 ($C_f(B)$), 143.6 ($C_a(B)$), 153.2 ($C_a(A)$) ppm.

***tert*-Butyldimethyl((7-(pent-4-yn-1-yl)cyclohept-1-en-1-yl)oxy)silane / *tert*-Butyldimethyl((2-(pent-4-yn-1-yl)cyclohept-1-en-1-yl)oxy)silane 345**



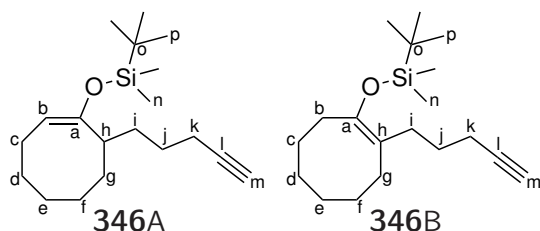
Yield: quant.
colourless oil
 $\text{C}_{18}\text{H}_{32}\text{OSi}$
MW 292.53 g/mol
345A:345B 2:1

Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

$^1\text{H-NMR}$ (400 MHz, C_6D_6) δ 0.15 (s, $H_m(A)$ or $H_m(B)$), 0.16 (s, $H_m(A)$ or $H_m(B)$), 0.99 (s, $H_o(A)$ or $H_o(B)$), 1.36 - 1.69 (m), 1.79 (t, $J = 2.7$ Hz, $H_1(A)$ or $H_1(B)$), 1.81 - 1.96 (m), 1.97 - 2.02 (m), 2.04 (td, $J = 6.9, 2.7$ Hz), 2.13 (td, $J = 7.4, 3.3$ Hz), 2.24 (qd, $J = 7.1, 3.2$ Hz), 5.02 (dd, $J = 7.5, 6.0$ Hz, 1H, $H_b(A)$) ppm;

$^{13}\text{C-NMR}$ (100 MHz, C_6D_6) δ -4.3 ($C_m(A)$ or $C_m(B)$), -4.2 ($C_m(A)$ or $C_m(B)$), 18.3 ($C_n(A)$ or $C_n(B)$), 18.9, 24.4, 26.1 ($C_o(A)$ or $C_o(B)$), 26.7, 27.2, 28.4, 29.5, 31.0, 45.0 ($C_g(A)$), 68.9 ($C_1(A)$ or $C_1(B)$), 84.5 ($C_k(A)$ or $C_k(B)$), 106.7 ($C_b(A)$), 158.6 ($C_a(A)$ or $C_a(B)$) ppm.

***(E)*-*tert*-Butyldimethyl((8-(pent-4-yn-1-yl)cyclooct-1-en-1-yl)oxy)silane / *(Z)*-*tert*-Butyldimethyl((2-(pent-4-yn-1-yl)cyclooct-1-en-1-yl)oxy)silane 346**



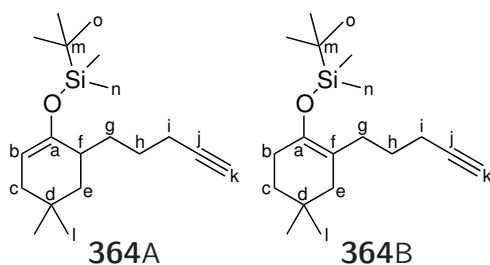
Yield: quant.
colourless oil
 $\text{C}_{18}\text{H}_{32}\text{OSi}$
MW 292.53 g/mol
346A:346B 2.5:1

Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

$^1\text{H-NMR}$ (300 MHz, C_6D_6) δ 0.16 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.96 (s, $\text{H}_p(\text{A})$ or $\text{H}_p(\text{B})$), 1.11 - 1.26 (m), 1.26 - 1.39 (m), 1.39 - 1.58 (m), 1.59 - 1.77 (m), 1.80 (t, $J = 2.6$ Hz, $\text{H}_1(\text{A})$ and $\text{H}_1(\text{B})$), 1.89 - 2.04 (m), 2.09 (td, $J = 7.1, 2.5$ Hz), 2.50 - 2.63 (m), 4.79 (t, $J = 8.2$ Hz, 1H, $\text{H}_b(\text{A})$) ppm;

$^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ -4.5 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -4.1 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), 18.4 ($\text{C}_o(\text{A})$ or $\text{C}_o(\text{B})$), 19.0, 26.0 ($\text{C}_p(\text{A})$ or $\text{C}_p(\text{B})$), 26.3, 26.6, 27.3, 28.1, 31.6, 32.7, 35.3, 37.6 ($\text{C}_h(\text{A})$), 68.9 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 84.6 ($\text{C}_1(\text{A})$ or $\text{C}_1(\text{B})$), 105.0 ($\text{C}_b(\text{A})$), 153.6 ($\text{C}_a(\text{A})$ or $\text{C}_a(\text{B})$) ppm.

tert*-Butyl((4,4-dimethyl-6-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane / *tert*-Butyl((4,4-dimethyl-2-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane **364*



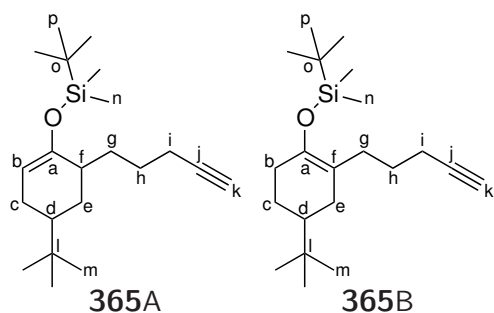
Yield: quant.
light yellow oil
 $\text{C}_{19}\text{H}_{34}\text{OSi}$
MW 306.56 g/mol
364A:364B 3:1

Due to the fact that both compounds and their diastereoisomers were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

$^1\text{H-NMR}$ (300 MHz, C_6D_6) δ 0.06 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.14 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.16 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.87 (s, $\text{H}_1(\text{A})$ or $\text{H}_1(\text{B})$), 0.90 (s, $\text{H}_1(\text{A})$ or $\text{H}_1(\text{B})$), 0.92 (s, $\text{H}_1(\text{A})$ or $\text{H}_1(\text{B})$), 0.95 (s, $\text{H}_1(\text{A})$ or $\text{H}_1(\text{B})$), 1.00 (s, $\text{H}_o(\text{A})$ or $\text{H}_o(\text{B})$), 1.11 (d, $J = 12.6$ Hz), 1.23 - 1.71 (m), 1.81 (t, $J = 2.6$ Hz, $\text{H}_k(\text{A})$ or $\text{H}_k(\text{B})$), 1.82 (t, $J = 2.4$ Hz, $\text{H}_k(\text{A})$ or $\text{H}_k(\text{B})$), 1.88 - 2.08 (m), 2.05 (td, $J = 6.5, 3.0$ Hz), 2.09 - 2.22 (m), 2.13 (td, $J = 7.5, 2.6$ Hz), 4.79 - 4.85 (m, 1H, $\text{H}_b(\text{A})$) ppm;

$^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ -4.5 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -4.0 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -3.5 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -2.7 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), 18.4 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 18.5 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 18.9, 19.2, 25.2 ($\text{C}_1(\text{A})$ or $\text{C}_1(\text{B})$), 25.6, 26.0 ($\text{C}_1(\text{A})$ or $\text{C}_1(\text{B})$), 26.1 ($\text{C}_o(\text{A})$ or $\text{C}_o(\text{B})$), 26.2 ($\text{C}_o(\text{A})$ or $\text{C}_o(\text{B})$), 27.3, 28.1 ($\text{C}_1(\text{A})$ or $\text{C}_1(\text{B})$), 28.5, 29.2 ($\text{C}_d(\text{A})$ or $\text{C}_d(\text{B})$), 29.6 ($\text{C}_d(\text{A})$ or $\text{C}_d(\text{B})$), 30.0, 31.7, 31.8 ($\text{C}_1(\text{A})$ or $\text{C}_1(\text{B})$), 36.5, 36.7 ($\text{C}_f(\text{A})$), 38.5, 42.3, 42.7, 69.0 ($\text{C}_k(\text{A})$ or $\text{C}_k(\text{B})$), 84.5 ($\text{C}_j(\text{A})$ or $\text{C}_j(\text{B})$), 102.8 ($\text{C}_b(\text{A})$), 113.1 ($\text{C}_f(\text{B})$), 142.8 ($\text{C}_a(\text{B})$), 152.1 ($\text{C}_a(\text{A})$) ppm.

tert-Butyl((4-(*tert*-butyl)-2-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane / *tert*-Butyl((4-(*tert*-butyl)-6-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane **365**



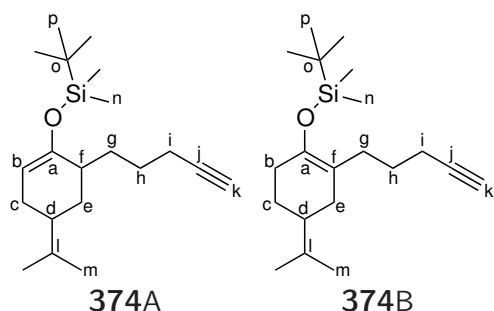
Yield: quant.
colourless oil
 $C_{21}H_{38}OSi$
MW 334.61 g/mol
365A:365B 2:1

Due to the fact that both compounds and their diastereoisomers were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

1H -NMR (300 MHz, C_6D_6) δ 0.17 (s, $H_n(A)$ or $H_n(B)$), 0.19 (s, $H_n(A)$ or $H_n(B)$), 0.83 (s, $H_m(A)$ or $H_m(B)$), 0.84 (s, $H_m(A)$ or $H_m(B)$), 1.20 (s, $H_p(A)$ and $H_p(B)$), 1.11 - 1.32 (m), 1.36 - 1.52 (m), 1.53 - 1.71 (m), 1.71 - 1.87 (m), 1.81 (t, $J = 2.7$ Hz, $H_k(A)$ or $H_k(B)$), 1.82 (t, $J = 2.8$ Hz, $H_k(A)$ or $H_k(B)$), 1.87 - 1.98 (m), 2.00 - 2.10 (m), 2.10 - 2.26 (m), 2.28 - 2.40 (m), 4.90 (t, $J = 2.1$ Hz, 1H, $H_b(A)$), 4.92 (t, $J = 2.1$ Hz, 1H, $H_b(A)$) ppm;

^{13}C -NMR(75 MHz, C_6D_6) δ -4.5 ($C_n(A)$ or $C_n(B)$), -4.1 ($C_n(A)$ or $C_n(B)$), -3.6 ($C_n(A)$ or $C_n(B)$), -3.3 ($C_n(A)$ or $C_n(B)$), -2.7 ($C_n(A)$ or $C_n(B)$), 18.5, 19.0, 19.3, 25.2, 25.6, 26.1 ($C_p(A)$ or $C_p(B)$), 26.2 ($C_p(A)$ or $C_p(B)$), 27.5 ($C_m(A)$ or $C_m(B)$), 29.7, 30.3, 31.2, 31.9, 32.1, 32.2, 40.3 ($C_f(A)$), 44.6 ($C_d(A)$ or $C_d(B)$), 44.8 ($C_d(A)$ or $C_d(B)$), 69.0 ($C_k(A)$ or $C_k(B)$), 84.6 ($C_j(A)$ or $C_j(B)$), 84.7 ($C_j(A)$ or $C_j(B)$), 103.8 ($C_b(A)$), 114.1 ($C_f(B)$), 153.1 ($C_a(A)$ or $C_a(B)$) ppm.

tert-Butyl((4-isopropyl-6-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane / *tert*-Butyl((4-isopropyl-2-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane **374**



Yield: quant.
colourless oil
 $C_{20}H_{36}OSi$
MW 320.58 g/mol
374A:374B 2:1

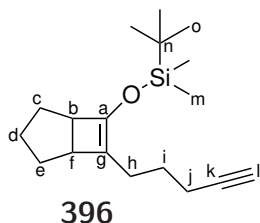
Due to the fact that both compounds and their diastereoisomers were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination

of the proton/carbon number for each peak.

$^1\text{H-NMR}$ (300 MHz, C_6D_6) δ 0.12 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.17 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.18 (s, $\text{H}_n(\text{A})$ or $\text{H}_n(\text{B})$), 0.84 (d, $J = 6.6$ Hz, $\text{H}_m(\text{A})$ or $\text{H}_m(\text{B})$), 0.86 (d, $J = 7.0$ Hz, $\text{H}_m(\text{A})$ or $\text{H}_m(\text{B})$), 1.01 (s, $\text{H}_p(\text{A})$ and $\text{H}_p(\text{B})$), 1.10 - 1.30 (m), 1.31 - 1.49 (m), 1.51 - 1.66 (m), 1.67 - 1.79 (m), 1.81 (t, $J = 2.6$ Hz, $\text{H}_k(\text{A})$ or $\text{H}_k(\text{B})$), 1.82 (t, $J = 2.5$ Hz, $\text{H}_k(\text{A})$ or $\text{H}_k(\text{B})$), 1.83 - 1.99 (m), 2.00 - 2.09 (m), 2.10 - 2.25 (m), 2.14 (td, $J = 7.3$, 2.6 Hz), 2.27 - 2.40 (m), 4.90 (t, $J = 2.2$ Hz, 1H, $\text{H}_b(\text{A})$ or $\text{H}_b(\text{B})$), 4.92 (t, $J = 2.1$ Hz, 1H, $\text{H}_b(\text{A})$ or $\text{H}_b(\text{B})$) ppm;

$^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ -4.5 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -4.1 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -3.6 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -3.3 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), -2.7 ($\text{C}_n(\text{A})$ or $\text{C}_n(\text{B})$), 18.5, 18.9, 19.2, 19.8 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 20.2 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 20.2 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 20.3 ($\text{C}_m(\text{A})$ or $\text{C}_m(\text{B})$), 25.5, 26.1 ($\text{C}_p(\text{A})$ or $\text{C}_p(\text{B})$), 26.2 ($\text{C}_p(\text{A})$ or $\text{C}_p(\text{B})$), 27.2, 27.4, 28.0, 30.2, 31.2, 32.0, 32.0, 32.3 ($\text{C}_l(\text{A})$ or $\text{C}_l(\text{B})$), 32.7 ($\text{C}_l(\text{A})$ or $\text{C}_l(\text{B})$), 33.6, 39.8 ($\text{C}_f(\text{A})$), 40.7 ($\text{C}_d(\text{A})$ or $\text{C}_d(\text{B})$), 40.9 ($\text{C}_d(\text{A})$ or $\text{C}_d(\text{B})$), 69.0 ($\text{C}_k(\text{A})$ or $\text{C}_k(\text{B})$), 84.6 ($\text{C}_j(\text{A})$ or $\text{C}_j(\text{B})$), 84.8 ($\text{C}_j(\text{A})$ or $\text{C}_j(\text{B})$), 103.7 ($\text{C}_b(\text{A})$), 113.9 ($\text{C}_f(\text{B})$), 153.1 ($\text{C}_a(\text{A})$ or $\text{C}_a(\text{B})$) ppm.

***tert*-Butyldimethyl((7-(pent-4-yn-1-yl)bicyclo[3.2.0]hept-6-en-6-yl)oxy)-silane 396**

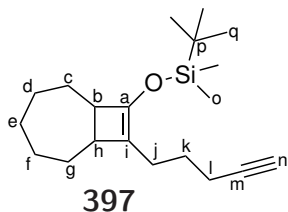


Yield: quant.
colourless oil
 $\text{C}_{18}\text{H}_{30}\text{OSi}$
MW 290.52 g/mol

$^1\text{H-NMR}$ (400 MHz, C_6D_6) δ 0.13 (s, 6H, H_m), 0.97 (s, 9H, H_o), 1.02 - 1.14 (m, 2H), 1.47 - 1.56 (m, 1H), 1.56 - 1.69 (m, 3H), 1.69 - 1.77 (m, 2H), 1.78 (t, $J = 2.7$ Hz, 1H, H_l), 1.89 - 1.99 (m, 1H), 2.04 - 2.14 (m, 3H), 2.61 (dd, $J = 6.6$, 3.4 Hz, 1H, H_b or f), 3.07 (d, $J = 7.2$ Hz, 1H, H_b or f) ppm;

$^{13}\text{C-NMR}$ (100 MHz, C_6D_6) δ -3.9 (C_m), -3.8 (C_m), 18.3 (C_n), 18.7, 23.5, 24.5, 24.9, 25.8, 25.9 (3C, C_q), 27.0, 39.9 (C_b), 50.0 (C_f), 69.0 (C_l), 84.4 (C_k), 116.8 (C_g), 142.0 (C_a) ppm.

***tert*-Butyldimethyl((9-(pent-4-yn-1-yl)bicyclo[5.2.0]non-8-en-8-yl)oxy)-silane 397**



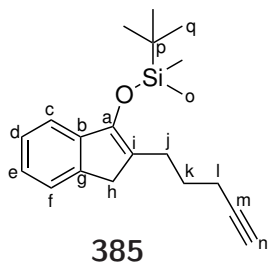
Yield: 50 %
colourless oil
 $\text{C}_{20}\text{H}_{34}\text{OSi}$
MW 318.57 g/mol

$^1\text{H-NMR}$ (300 MHz, C_6D_6) δ 0.16 (s, 6H, H_o), 0.95 (s, 9H, H_q), 1.05 - 1.28 (m, 3H),

1.28 - 1.41 (m, 2H), 1.41 - 1.59 (m, 2H), 1.59 - 1.92 (m, 6H), 1.79 (t, $J = 2.7$ Hz, 1H, H_k), 1.92 - 2.09 (m, 2H), 2.03 (td, $J = 7.0, 2.8$ Hz, 1H), 2.09 - 2.18 (m, 1H), 2.18 - 2.38 (m, 1H) ppm;

$^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ -3.9 (C_o), -3.7 (C_o), 18.3 (C_p), 19.0, 25.9 (3C, C_q), 27.0, 27.5, 28.2, 31.1, 31.3, 31.4, 36.5, 43.4 (C_b), 51.0 (C_h), 69.0 (C_n), 84.5 (C_m), 121.0 (C_i), 143.7 (C_a) ppm.

***tert*-Butyldimethyl((2-(pent-4-yn-1-yl)-1H-inden-3-yl)oxy)silane 385**

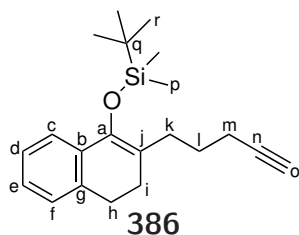


Yield: quant.
orange oil
 $\text{C}_{20}\text{H}_{28}\text{OSi}$
MW 312.52 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.19 (s, 6H, H_o), 1.07 (s, 9H, H_q), 1.77 (qu, $J = 7.3$ Hz, 2H, H_k), 1.97 (t, $J = 2.7$ Hz, 1H, H_n), 2.24 (td, $J = 7.2, 2.7$ Hz, 2H, H_l), 2.52 (t, $J = 7.9$ Hz, 2H, H_j), 3.20 (s, 2H, H_h), 7.13 (dt, $J = 7.3, 4.3$ Hz, 1H, H_e), 7.25 (d, $J = 4.5$ Hz, 2H, H_c and d), 7.33 (d, $J = 7.4$ Hz, 1H, H_f) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ -3.6 (2C, C_o), 18.5 (C_p), 18.6 (C_l), 26.1 (3C, C_q), 26.1 (C_j or k), 28.3 (C_j or k), 36.2 (C_h), 68.7 (C_n), 84.5 (C_m), 117.9, 123.3 (C_i), 123.6, 124.3, 126.1, 141.1 (C_b or g), 142.7 (C_b or g), 147.9 (C_a) ppm.

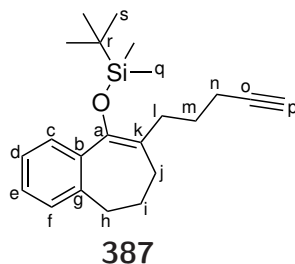
***tert*-Butyldimethyl((2-(pent-4-yn-1-yl)-3,4-dihydronaphthalen-1-yl)oxy)silane 386**



Yield: quant.
yellow oil
 $\text{C}_{21}\text{H}_{30}\text{OSi}$
MW 326.55 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.02 (s, 6H, H_p), 1.03 (s, 9H, H_r), 1.50 (qu, $J = 7.7$ Hz, 2H, H_l), 1.59 - 1.67 (m, 1H), 1.77 (q, $J = 2.3$ Hz, 1H, H_o), 1.97 (t, $J = 7.6$, 1H), 2.01 (td, $J = 7.0, 2.5$ Hz, 2H), 2.32 (td, $J = 7.6, 1.6$ Hz, 2H), 2.52 (t, $J = 7.8$ Hz, 2H), 6.92 - 7.04 (m, 2H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.43 - 7.52 (m, 1H) ppm;

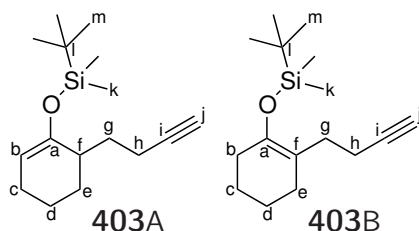
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ -3.6 (2C, C_p), 18.7 (C_q), 18.7 (C_m), 26.3 (3C, C_r), 26.6 (C_k or l), 27.4 (C_k or l), 28.8 (C_h or i), 30.5 (C_h or i), 69.0 (C_o), 84.5 (C_n), 120.2 (C_j), 122.7 (C_d), 126.2, 126.8, 127.0, 134.7 (C_b or g), 136.4 (C_b or g), 143.2 (C_a) ppm.

***tert*-Butyldimethyl((8-(pent-4-yn-1-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)-oxy)silane 387**

Yield: 99 %
 yellow oil
 $C_{22}H_{32}OSi$
 MW 340.57 g/mol

1H -NMR (300 MHz, C_6D_6) δ -0.11 (s, 6H, H_q), 1.02 (s, 9H, H_s), 1.59 - 1.72 (m, 4H), 1.83 (t, $J = 2.6$, 1H, H_p), 1.88 (qu, $J = 7.2$, 2H), 2.14 (td, $J = 7.3$, 2.7 Hz, 2H), 2.36 - 2.45 (m, 2H), 2.50 (t, $J = 7.1$ Hz, 2H), 7.00 - 7.14 (m, 3H), 7.52 (dd, $J = 7.5$, 1.4 Hz, 1H) ppm;

^{13}C -NMR (75 MHz, C_6D_6) δ -3.7 (2C, C_q), 18.5 (C_r), 19.2 (C_n), 26.2 (3C, C_s), 27.8, 28.4, 31.0, 32.9, 34.9, 69.2 (C_p), 84.7 (C_o), 120.8 (C_k), 126.2, 127.7, 127.8, 128.9, 140.2 (C_b or g), 140.2 (C_b or g), 144.0 (C_a) ppm.

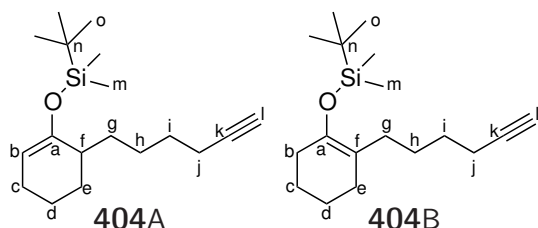
((6-(But-3-yn-1-yl)cyclohex-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane / ((2-(But-3-yn-1-yl)cyclohex-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane 403

Yield: quant.
 colourless oil
 $C_{16}H_{28}OSi$
 MW 264.48 g/mol
403A:403B 1.7:1

Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

1H -NMR (400 MHz, $CDCl_3$) δ 0.09 (s, H_k (A) or H_k (B)), 0.14 (s, H_k (A) or H_k (B)), 1.00 (s, H_m (A) or H_m (B)), 1.00 (s, H_m (A) or H_m (B)), 1.19 - 1.35 (m), 1.36 - 1.43 (m), 1.43 - 1.52 (m), 1.52 - 1.61 (m), 1.78 (t, $J = 2.5$ Hz, H_j (A) and H_j (B)), 1.79 (t, $J = 2.7$ Hz, H_j (A) and H_j (B)), 1.84 - 1.97 (m), 2.02 - 2.19 (m), 2.19 - 2.27 (m), 2.41 (t, $J = 7.7$ Hz), 4.86 (t, $J = 4.0$ Hz, 1H, H_b (A)) ppm;

^{13}C -NMR (100 MHz, $CDCl_3$) δ -4.3 (C_k (A) or C_k (B)), -4.2 (C_k (A) or C_k (B)), -3.5 (C_k (A) or C_k (B)), -2.7 (C_k (A) or C_k (B)), 16.4, 17.6, 18.4 (C_l (A) or C_l (B)), 18.4 (C_l (A) or C_l (B)), 20.6, 23.3, 23.9, 24.5, 26.1 (C_m (A) or C_m (B)), 26.1 (C_m (A) or C_m (B)), 28.0, 28.2, 30.2, 30.7, 31.7, 38.2 (C_f (A)), 68.6 (C_j (A) or C_j (B)), 68.9 (C_j (A) or C_j (B)), 84.5 (C_i (A) or C_i (B)), 84.9 (C_i (A) or C_i (B)), 104.0 (C_b (A)), 114.1 (C_f (B)), 153.2 (C_a (A) or C_a (B)) ppm.

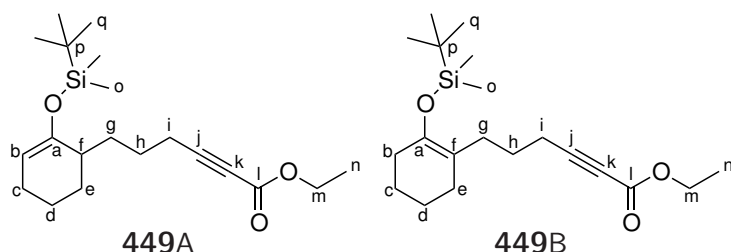
***tert*-Butyl((6-(hex-5-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane / *tert*-Butyl((2-(hex-5-yn-1-yl)cyclohex-1-en-1-yl)oxy)dimethylsilane 404**

Yield: quant.
 colourless oil
 $C_{18}H_{32}OSi$
 MW 292.53 g/mol
 404A:404B 1.4:1

Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

1H -NMR (400 MHz, $CDCl_3$) δ 0.15 (s, $H_m(A)$ or $H_m(B)$), 0.16 (s, $H_m(A)$ or $H_m(B)$), 1.00 (s, $H_o(A)$ or $H_o(B)$), 1.01 (s, $H_o(A)$ or $H_o(B)$), 1.20 - 1.57 (m), 1.58 - 1.69 (m), 1.78 (t, $J = 2.7$ Hz, $H_l(A)$ and $H_l(B)$), 1.88 - 2.10 (m), 2.10 - 2.18 (m), 4.88 (t, $J = 4.0$ Hz, 1H, $H_b(A)$) ppm;

^{13}C -NMR (100 MHz, $CDCl_3$) δ -4.6 ($C_m(A)$ or $C_m(B)$), -4.5 ($C_m(A)$ or $C_m(B)$), -3.8 ($C_m(A)$ or $C_m(B)$), -3.0 ($C_m(A)$ or $C_m(B)$), 18.1 ($C_n(A)$ or $C_n(B)$), 18.1 ($C_n(A)$ or $C_n(B)$), 18.4, 20.4, 23.2, 23.8, 24.3, 25.7 ($C_o(A)$ or $C_o(B)$), 25.8 ($C_o(A)$ or $C_o(B)$), 26.1, 27.9, 28.1, 28.6, 28.9, 29.7, 30.5, 31.8, 38.8 ($C_f(A)$), 68.5 ($C_1(A)$ and $C_1(B)$), 84.1 ($C_k(A)$ or $C_k(B)$), 84.3 ($C_k(A)$ or $C_k(B)$), 103.2 ($C_b(A)$), 114.7 ($C_f(B)$), 143.2 ($C_a(B)$), 153.5 ($C_a(A)$) ppm.

Ethyl 6-(2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)hex-2-ynoate / ethyl 6-(2-((*tert*-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)hex-2-ynoate 449

Yield: quant.
 colourless oil
 $C_{20}H_{34}O_3Si$
 MW 350.57 g/mol
 449A:449B 6:1

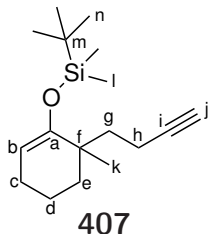
Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

1H -NMR (300 MHz, C_6D_6) δ 0.14 (s, $H_o(A)$ and $H_o(B)$), 0.15 (s, $H_k(o)$ and $H_o(B)$), 0.90 (t, $J = 7.1$ Hz, $H_n(A)$ and $H_n(B)$), 1.01 (s, $H_q(A)$ or $H_q(B)$), 1.17 - 1.37 (m), 1.37 - 1.58 (m), 1.72 - 1.83 (m), 1.87 (t, $J = 7.0$ Hz), 1.88 - 2.03 (m), 3.93 (t, $J = 7.1$ Hz, $H_m(A)$ and $H_m(B)$), 4.87 (t, $J = 3.2$ Hz, 1H, $H_b(A)$) ppm;

^{13}C -NMR (75 MHz, C_6D_6) δ -4.3 ($C_o(A)$ or $C_o(B)$), -4.2 ($C_o(A)$ or $C_o(B)$), -2.7 ($C_o(A)$ or $C_o(B)$), 14.0 ($C_n(A)$ or $C_n(B)$), 18.4, 18.9, 20.7, 24.5, 25.4, 26.0 ($C_q(A)$ or $C_q(B)$), 26.1 ($C_q(A)$ or $C_q(B)$), 28.4, 31.9, 38.8 ($C_f(A)$), 61.4 ($C_m(A)$ or $C_m(B)$), 88.7

(C_j(A) or C_j(B)), 103.7 (C_b(A)), 153.3 (C_a(A) or C_a(B)) ppm.

((6-(But-3-yn-1-yl)-6-methylcyclohex-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane 407

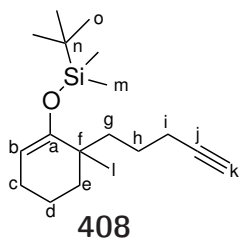


Yield: quant.
colourless oil
C₁₇H₃₀OSi
MW 278.50 g/mol

¹H-NMR (300 MHz, C₆D₆) δ 0.10 (s, 3H, H_l), 0.13 (s, 3H, H_l), 0.97 (s, H_n), 1.02 (s, 3H, H_k), 1.11 - 1.21 (m, 1H), 1.33 - 1.49 (m, 3H), 1.54 - 1.67 (m, 1H), 1.80 (t, J = 2.7 Hz, H_j), 1.82 - 1.90 (m, 2H), 1.94 - 2.07 (m, 1H), 2.16 (td, J = 8.2, 2.8 Hz), 4.71 (t, J = 4.0 Hz, 1H, H_b) ppm;

¹³C-NMR (75 MHz, C₆D₆) δ -4.7 (C_l), -4.1 (C_l), 14.3, 18.4 (C_m), 19.7, 24.9, 26.0 (4C, C_n and C_k), 34.9, 38.6 (C_f), 39.1, 68.4 (C_j), 85.3 (C_i), 102.5 (C_b), 155.1 (C_a) ppm.

***tert*-Butyldimethyl((6-methyl-6-(pent-4-yn-1-yl)cyclohex-1-en-1-yl)oxy)silane 408**



Yield: quant.
colourless oil
C₁₈H₃₂OSi
MW 292.53 g/mol

¹H-NMR (300 MHz, C₆D₆) δ 0.14 (s, 3H, H_m), 0.15 (s, 3H, H_m), 0.98 (s, H_o), 1.08 (s, 3H, H_l), 1.20 - 1.41 (m, 2H), 1.41 - 1.59 (m, 5H), 1.61 - 1.72 (m, 1H), 1.80 (t, J = 2.7 Hz, H_k), 1.88 - 1.98 (m, 2H), 1.99 - 2.08 (m, 2H), 4.74 (t, J = 3.9 Hz, 1H, H_b) ppm;

¹³C-NMR (75 MHz, C₆D₆) δ -4.7 (C_m), -4.0 (C_m), 18.5 (C_n), 19.5, 19.9, 24.0, 25.0, 26.1 (3C, C_n), 26.2 (C_l), 35.4, 38.4 (C_f), 39.3, 68.9 (C_k), 84.6 (C_i), 101.9 (C_b), 156.1 (C_a) ppm.

25.2. Synthesis of spirocyclic compounds

General procedure for the preparation of spirocyclic compounds GP L

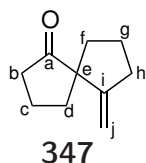
The TBS-enol ether (0.7 mmol, 1 equiv) was dissolved in 1.5 mL of dry CH₂Cl₂ (or toluene) at room temperature. AgNTf₂ (0.035 mmole, 0.05 equiv) in 1 mL of dry CH₂Cl₂ (or toluene) was added and the mixture was stirred at room temperature for

15 h.

The reaction mixture was diluted with 4 mL of CH₂Cl₂ (or Et₂O) and hydrolysed with 2 mL of 10% HCl and stirred for 45 min. The aqueous phase was extracted 3× 5 mL of CH₂Cl₂ (or Et₂O). The combined organic phases were washed with 6 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE/EtOAc 98:2).

6-Methylenespiro[4.4]nonan-1-one 347



Yield: 47 %
colourless oil
C₁₀H₁₄O
MW 150.22 g/mol

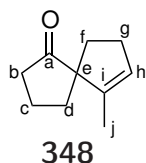
¹H-NMR (400 MHz, CDCl₃) δ 1.52 - 1.70 (m, 2H), 1.76 - 1.88 (m, 2H), 1.89 - 2.09 (m, 4H), 2.21 - 2.34 (m, 2H), 2.34 - 2.52 (m, 2H), 4.67 (t, J = 2.3 Hz, 1H, H_j), 4.95 (t, J = 2.1 Hz, 1H, H_j) ppm;

¹³C-NMR (100 MHz, CDCl₃) δ 19.6, 23.7, 34.2, 38.0, 38.2, 38.5, 60.1 (C_e), 106.3 (C_j), 156.6 (C_i), 221.7 (C_a) ppm;

IR (neat) 2936, 2853, 1731 (C=O), 1711 cm⁻¹;

HRMS Cal. for [M+Na]⁺: C₁₀H₁₄O: 173.0937 Found: 173.0945.

6-Methylspiro[4.4]non-6-en-1-one 348

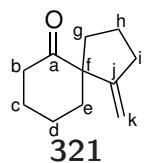


Yield: 6 %
yellow oil
C₁₀H₁₄O
MW 150.22 g/mol

¹H-NMR (400 MHz, CDCl₃) 1.52 - 1.70 (m, 2H), 1.76 - 1.88 (m, 3H), 1.89 - 2.09 (m, 4H), 2.21 - 2.34 (m, 2H), 2.34 - 2.52 (m, 2H), 5.58 (s, 1H, H_h) ppm;

¹³C-NMR (100 MHz, CDCl₃) δ 13.5 (C_j), 20.2, 30.3, 34.3, 36.8, 38.2, 64.7 (C_e), 129.0 (C_h), 140.5 (C_i), 223.0 (C_a) ppm.

1-Methylenespiro[4.5]decan-6-one 321

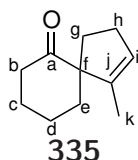


Yield: 78 %
colourless oil
C₁₁H₁₆O
MW 164.24 g/mol

¹H-NMR (300 MHz, CDCl₃) δ 1.53 - 1.71 (m, 3H), 1.71 - 1.81 (m, 3H), 1.81 - 1.92

(m, 2H), 1.92 - 2.04 (m, 1H), 2.11 (dt, $J = 12.0, 6.0$ Hz, 1H), 2.28 - 2.57 (m, 4H), 4.87 (t, $J = 2.3$ Hz, 1H, H_k), 5.10 (t, $J = 2.1$ Hz, 1H, H_k) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 22.5, 23.0, 27.3, 34.2, 38.4, 38.7, 39.4, 60.7 (C_f), 107.6 (C_k), 155.1 (C_j), 212.8 (C_a) ppm;
 IR (neat) 2934, 2862, 1702 (C=O), 1450, 1125, 878 cm^{-1}
 HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{11}\text{H}_{16}\text{O}$: 187.1093 Found: 187.1093.

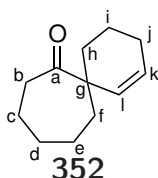
1-Methylspiro[4.5]dec-1-en-6-one 335



Yield: 47 %
 light yellow oil
 $\text{C}_{11}\text{H}_{16}\text{O}$
 MW 164.24 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.59 - 1.71 (m, 2H), 1.67 (q, $J = 1.9$ Hz, 3H, H_k), 1.72 - 1.93 (m, 3H), 1.94 - 2.07 (m, 1H), 1.98 (t, $J = 7.1$ Hz, 2H), 2.17 - 2.27 (m, 2H), 2.29 - 2.39 (m, 1H), 2.39 - 2.52 (m, 1H), 5.48 (q, $J = 1.8$ Hz, 1H, H_i) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 13.8 (C_k), 22.3, 26.6, 29.7, 35.9, 36.2, 40.0, 64.4 (C_f), 127.1 (C_i), 140.0 (C_j), 213.9 (C_a) ppm;
 IR (neat) 2926, 2853, 1702 (C=O), 1442, 1127, 580 cm^{-1} ;
 HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{11}\text{H}_{16}\text{O}$: 187.1093 Found: 187.1084.

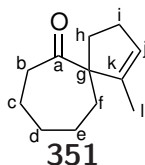
Spiro[5.6]dodec-1-en-7-one 352



Yield: 7 %
 yellow oil
 $\text{C}_{12}\text{H}_{18}\text{O}$
 MW 178.27 g/mol

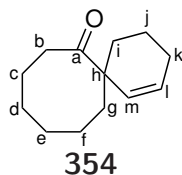
$^1\text{H-NMR}$ (400 MHz, CDCl_3) 1.35 - 1.62 (m, 4H), 1.68 (d, $J = 2.0$ Hz, 3H), 1.67 - 1.84 (m, 4H), 1.97 (dd, $J = 14.3, 10.0$ Hz, 1H), 2.12 - 2.35 (m, 2H), 2.41 (ddd, $J = 12.4, 8.1, 5.2$ Hz, 1H), 2.48 - 2.67 (m, 2H), 5.58 (dt, $J = 10.0, 2.3$ Hz, 1H, H_k or l), 5.82 (dt, $J = 10.0, 3.7$ Hz, 1H, H_k or l) ppm;
 $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 19.1, 24.4, 25.1, 26.9, 30.6, 31.6, 38.3, 40.0, 52.8 (C_g), 128.9 (C_k or l), 129.5 (C_k or l), 215.7 (C_a) ppm.

1-Methylspiro[4.6]undec-1-en-6-one 351



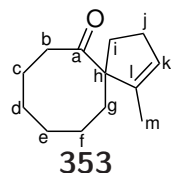
Yield: 67 %
 yellow oil
 $\text{C}_{12}\text{H}_{18}\text{O}$
 MW 178.27 g/mol

¹H-NMR (300 MHz, CDCl₃) δ 1.35 - 1.62 (m, 4H), 1.68 (d, J = 2.0 Hz, 3H, H_l), 1.67 - 1.84 (m, 4H), 1.97 (dd, J = 14.3, 10.0 Hz, 1H), 2.12 - 2.35 (m, 2H), 2.41 (ddd, J = 12.4, 8.1, 5.2 Hz, 1H), 2.48 - 2.67 (m, 2H), 5.41 (d, J = 1.5 Hz, 1H, H_j) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 14.3 (C_l), 26.3, 26.5, 29.8, 31.0, 35.2, 35.6, 43.2, 66.8 (C_g), 127.5 (C_j), 143.0 (C_k), 217.1 (C_a) ppm;
IR (neat) 2925, 2852, 1696 (C=O), 1441 cm⁻¹
HRMS Cal. for [M+Na]⁺: C₁₂H₁₈O: 201.1250 Found: 201.1240.

Spiro[5.7]tridec-1-en-7-one 354

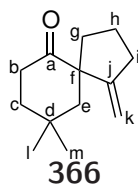
Yield: 32 %
 light yellow oil
 C₁₃H₂₀O
 MW 192.30 g/mol

¹H-NMR (300 MHz, CDCl₃) 1.27 - 1.74 (m, 5H), 1.76 (q, J = 1.76 Hz, 3H), 1.78 - 1.92 (m, 1H), 1.93 - 2.10 (m, 2H), 2.13 - 2.29 (m, 3H), 2.37 (tt, J = 7.6, 2.5 Hz, 1H), 2.42 - 2.59 (m, 4H), 2.79 (td, J = 11.2, 3.6 Hz, 1H), 5.63 (dt, J = 10.3, 2.1 Hz, 1H, H_l or m), 5.85 (dt, J = 10.3, 3.7 Hz, 1H, 1H, H_l or m) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 19.1, 24.5, 24.6, 25.2, 26.1, 30.2, 30.4, 35.4, 37.1, 51.6 (C_h), 128.5 (C_l or m), 129.8 (C_l or m), 218.7 (C_a) ppm.

1-Methylspiro[4.7]dodec-1-en-6-one 353

Yield: 38 %
 light yellow oil
 C₁₃H₂₀O
 MW 192.30 g/mol

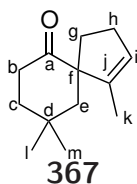
¹H-NMR (300 MHz, CDCl₃) δ 1.27 - 1.74 (m, 6H), 1.76 (q, J = 1.76 Hz, 3H, H_m), 1.78 - 1.92 (m, 1H), 1.93 - 2.10 (m, 2H), 2.13 - 2.29 (m, 3H), 2.37 (tt, J = 7.6, 2.5 Hz, 1H), 2.42 - 2.59 (m, 4H), 2.79 (td, J = 11.2, 3.6 Hz, 1H), 5.44 ("s", 1H, H_k) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 14.5 (C_m), 24.8, 25.9, 26.4, 30.3, 30.7, 32.8, 32.8, 39.4, 66.1 (C_h), 128.8 (C_k), 141.4 (C_l), 218.6 (C_a) ppm.

9,9-Dimethyl-1-methylenespiro[4.5]decan-6-one 366

Yield: 71 %
 light yellow oil
 C₁₃H₂₀O
 MW 192.30 g/mol

¹H-NMR (400 MHz, CDCl₃) δ 1.03 (s, 3H, H_l or m), 1.17 (s, 3H, H_l or m), 1.52 - 1.62 (m, 2H), 1.62 - 1.71 (m, 1H), 1.71 - 1.78 (m, 3H), 1.98 (d, J = 14.2 Hz, 1H), 2.18 - 2.26 (m, 1H), 2.26 - 2.34 (m, 2H), 2.43 - 2.53 (m, 1H), 2.65 (ddd, J = 15.7, 9.6, 8.5 Hz, 1H), 4.77 (t, J = 2.2 Hz, 1H, H_k), 5.09 (t, J = 2.2 Hz, 1H, H_k) ppm;
¹³C-NMR(100 MHz, CDCl₃) δ 23.4 (C_h), 26.9 (C_l or m), 30.8 (C_d), 32.7 (C_l or m), 33.3, 35.7, 38.6, 40.9, 51.4 (C_e), 59.7 (C_f), 107.3 (C_k), 156.9 (C_j), 214.3 (C_a) ppm;
IR (neat) 2952, 2926, 2867, 1702 (C=O), 883 cm⁻¹;
HRMS Cal. for [M+Na]⁺: C₁₃H₂₀O: 215.1406 Found: 215.1391.

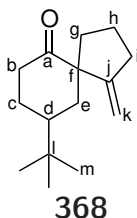
1,9,9-Trimethylspiro[4.5]dec-1-en-6-one 367



Yield: 64 %
 light yellow oil
 C₁₃H₂₀O
 MW 192.30 g/mol

¹H-NMR (400 MHz, CDCl₃) δ 1.01 (s, 3H, H_l or m), 1.20 (s, 3H, H_l or m), 1.48 (dd, J = 14.1, 2.9 Hz, 1H), 1.59 (s, 3H, H_k), 1.63 - 1.77 (m, 2H), 1.89 (d, J = 13.9 Hz, 1H), 1.98 - 2.14 (m, 2H), 2.16 - 2.30 (m, 3H), 2.65 (ddd, J = 15.9, 13.0, 5.9 Hz, 1H), 5.54 (s, 1H, H_i) ppm;
¹³C-NMR(100 MHz, CDCl₃) δ 14.0 (C_k), 26.4 (C_l or m), 30.3, 30.6 (C_d), 32.9 (C_l or m), 36.1, 38.6, 38.7, 47.8 (C_e), 63.4 (C_f), 127.7 (C_i), 142.2 (C_j), 214.6 (C_a) ppm;
IR (neat) 2951, 2920, 2852, 1703 (C=O) cm⁻¹;
HRMS Cal. for [M+Na]⁺: C₁₃H₂₀O: 215.1406 Found: 215.1389.

9-(tert-Butyl)-1-methylenespiro[4.5]decan-6-one 368



Yield:
 Diastereoisomer 1: 44 %
 Diastereoisomer 2: 46 %
 colourless oil
 C₁₅H₂₄O
 MW 220.35 g/mol

Diastereoisomer 1:

¹H-NMR (300 MHz, CDCl₃) δ 0.88 (s, 9H, H_m), 1.22 - 1.52 (m, 3H), 1.54 - 1.69 (m, 1H), 1.69 - 1.90 (m, 2H), 1.94 - 2.10 (m, 2H), 2.27 - 2.52 (m, 4H), 2.63 (ddd, J = 15.2, 13.5, 5.9 Hz, 1H), 5.02 (t, J = 2.0 Hz, 1H, H_k), 5.10 (t, J = 2.1 Hz, 1H, H_k) ppm;
¹³C-NMR(75 MHz, CDCl₃) δ 22.6, 27.2, 27.6 (3C, C_m), 32.5 (C_l), 34.6, 38.5, 39.5, 39.6, 42.6 (C_d), 60.0 (C_f), 107.9 (C_k), 156.1 (C_j), 212.5 (C_a) ppm;

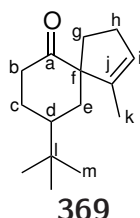
Diastereoisomer 2:

¹H-NMR (300 MHz, CDCl₃) δ 0.90 (s, 9H, H_m), 1.45 - 1.68 (m, 5H), 1.69 - 1.82 (m, 2H), 1.96 - 2.08 (m, 2H), 2.32 - 2.42 (m, 2H), 2.42 - 2.60 (m, 2H), 4.78 (t, J = 2.3 Hz,

1H, H_k), 5.11 (t, J = 2.2 Hz, 1H, H_k) ppm;

¹³C-NMR(75 MHz, CDCl₃) δ 23.1, 27.7 (3C, C_m), 28.9, 32.4 (C_l), 33.9, 38.8, 39.2, 39.9, 43.8 (C_d), 60.3 (C_f), 107.4 (C_k), 155.3 (C_j), 213.5 (C_a) ppm.

9-(*tert*-Butyl)-1-methylspiro[4.5]dec-1-en-6-one **369**



Yield:

Diastereoisomer 1: 29 %

Diastereoisomer 2: 40 %

yellow oil

C₁₅H₂₄O

MW 220.35 g/mol

Diastereoisomer 1:

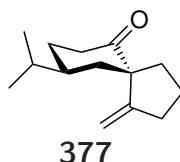
¹H-NMR (300 MHz, CDCl₃) δ 0.90 (s, 9H, H_m), 1.38 - 1.77 (m, 6H), 1.81 (q, J = 2.1 Hz, 3H, H_k), 1.93 - 2.01 (m, 2H), 2.16 - 2.41 (m, 2H), 2.41 - 2.60 (m, 1H), 5.48 (s, 1H, H_i) ppm;

¹³C-NMR(75 MHz, CDCl₃) δ 16.6 (C_k), 26.0, 27.4 (3C, C_m), 30.1, 32.7, 39.1, 39.1, 40.7, 44.0 (C_d), 62.7 (C_f), 129.6 (C_i), 142.4 (C_j), 214.7 (C_a) ppm;

Diastereoisomer 2:

¹H-NMR (300 MHz, CDCl₃) δ 0.90 (s, 9H, H_m), 1.03 - 1.32 (m, 1H), 1.64 (d, J = 2.0 Hz, 3H, H_k), 1.34 - 1.59 (m, 3H), 1.94 - 2.11 (m, 3H), 2.12 - 2.26 (m, 2H), 2.27 - 2.58 (m, 2H), 5.49 (s, 1H, H_i) ppm.

9-Isopropyl-1-methylenespiro[4.5]decan-6-one **377**



Yield: 24 %

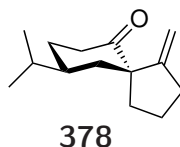
slightly yellow oil

C₁₄H₂₂O

MW 206.32 g/mol

Characterization data for compound **377** are in good agreement with those found in the literature.[183]

9-Isopropyl-1-methylenespiro[4.5]decan-6-one **378**



Yield: 64 %

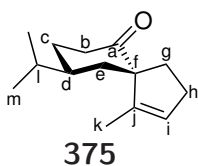
slightly yellow oil

C₁₄H₂₂O

MW 206.32 g/mol

Characterization data for compound **377** are in good agreement with those found in the literature.[183]

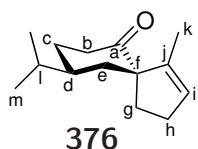
9-Isopropyl-1-methylspiro[4.5]dec-1-en-6-one 375



Yield: 30 %
 yellow oil
 $C_{14}H_{22}O$
 MW 206.32 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H, H_m), 0.91 (s, 3H, H_m), 1.43 - 1.57 (m, 2H), 1.58 - 1.63 (m, 1H) 1.79 (q, $J = 2.0$ Hz, 3H, H_k), 1.90 - 2.03 (m, 2H), 2.10 - 2.24 (m, 1H), 2.24 - 2.39 (m, 2H), 2.40 - 2.56 (m, 1H), 5.45 (d, $J = 1.7$ Hz, 1H, H_i) ppm;
 ^{13}C -NMR(75 MHz, $CDCl_3$) δ 16.5 (C_k), 20.0 (C_m), 20.1 (C_m), 28.4, 30.1, 32.4(C_l), 38.8, 40.2 (C_d), 40.5, 41.0, 62.7 (C_f), 129.5 (C_i), 142.3 (C_j), 214.2 (C_a) ppm.

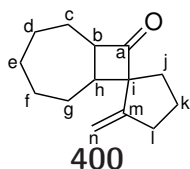
9-Isopropyl-1-methylspiro[4.5]dec-1-en-6-one 376



Yield: 24 %
 yellow oil
 $C_{14}H_{22}O$
 MW 206.32 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, H_m), 0.93 (s, 3H, H_m), 1.17 - 1.47 (m, 2H), 1.47 - 1.60 (m, 2H) 1.66 (q, $J = 1.9$ Hz, 3H, H_k), 1.91 - 2.03 (m, 3H), 2.13 - 2.27 (m, 2H), 2.27 - 2.41 (m, 2H), 2.49 (ddd, $J = 15.1, 13.4, 6.0$ Hz, 1H), 5.50 (d, $J = 1.7$ Hz, 1H, H_i) ppm;
 ^{13}C -NMR(75 MHz, $CDCl_3$) δ 13.6 (C_k), 20.0 (C_m), 20.1 (C_m), 29.4, 29.6, 32.3(C_l), 36.9, 39.2, 39.4, 39.7 (C_d), 63.9 (C_f), 127.1 (C_i), 142.0 (C_j), 214.4 (C_a) ppm.

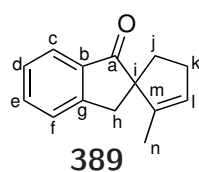
2'-Methylenespiro[bicyclo[5.2.0]nonane-8,1'-cyclopentan]-9-one 400



Yield: 13 %
 light yellow oil
 $C_{14}H_{20}O$
 MW 204.31 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 0.81 - 0.96 (m, 2H), 1.08 - 1.39 (m, 4H), 1.43 - 1.71 (m, 2H), 1.73 - 2.08 (m, 4H), 2.32 - 2.64 (m, 4H), 3.09 - 3.23 (m, 1H), 3.55 (dq, $J = 12.1, 5.8$ Hz, 1H), 4.93 (t, $J = 2.3$ Hz, 1H, H_n), 5.00 (t, $J = 2.1$ Hz, 1H, H_n) ppm.

2-Methylspiro[cyclopent[2]ene-1,2'-inden]-1'(3'H)-one 389



Yield: 74 % yellow oil

 $C_{14}H_{14}O$

MW 198.26 g/mol

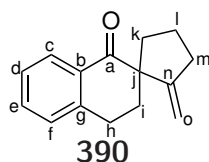
1H -NMR (400 MHz, $CDCl_3$) δ 1.44 (d, $J = 1.8$ Hz, 3H, H_n), 1.87 - 1.95 (m, 1H), 2.35 - 2.55 (m, 3H), 3.08 (d, $J = 17.5$ Hz, 1H, H_h), 3.22 (d, $J = 17.5$ Hz, 1H, H_h), 5.62 (d, $J = 1.7$ Hz, 1H, H_l), 7.36 (t, $J = 7.4$ Hz, 1H, H_d), 7.45 (d, $J = 7.7$ Hz, 1H, H_f), 7.79 (td, $J = 7.4, 1.0$ Hz, 1H, H_e), 7.76 (d, $J = 7.7$ Hz, 1H, H_c) ppm;

^{13}C -NMR(100 MHz, $CDCl_3$) δ 13.0 (C_n), 31.0, 37.7, 39.5, 64.8 (C_i), 124.1, 126.4, 127.5, 129.0, 135.0 (C_e), 136.7 (C_b), 141.3 (C_m), 153.4 (C_g), 210.6 (C_a) ppm;

IR (neat) 2930, 2851, 1705 ($C=O$), 729 cm^{-1}

HRMS Cal. for $[M+Na]^+$: $C_{14}H_{14}O$: 221.0937 Found: 221.0952.

2-Methylene-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-one 390



Yield: 58 %

yellow oil

 $C_{15}H_{16}O$

MW 212.29 g/mol

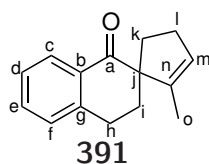
1H -NMR (400 MHz, $CDCl_3$) δ 1.66 - 1.88 (m, 3H), 1.98 (ddd, $J = 13.6, 6.9, 4.8$ Hz, 1H), 2.18 - 2.39 (m, 2H), 2.43 - 2.55 (m, 1H), 2.55 - 2.66 (m, 1H), 2.91 - 3.11 (m, 2H, H_h), 4.66 (t, $J = 2.4$ Hz, 1H, H_o), 5.02 (t, $J = 2.1$ Hz, 1H, H_o), 7.23 (d, $J = 7.7$ Hz, 1H, H_f), 7.30 (t, $J = 7.4$ Hz, 1H, H_d), 7.46 (td, $J = 7.5, 1.5$ Hz, 1H, H_e), 8.05 (dd, $J = 7.8, 1.5$ Hz, 1H, H_c) ppm;

^{13}C -NMR(100 MHz, $CDCl_3$) δ 23.0, 26.3, 34.1, 34.2, 36.7, 56.9 (C_j), 107.2 (C_o), 126.7, 128.2, 128.8, 132.3 (C_b), 133.2 (C_e), 143.3 (C_g), 155.4 (C_n), 200.6 (C_a) ppm;

IR (neat) 2929, 2855, 1679 ($C=O$), 1599, 1218, 831, 740 cm^{-1} ;

HRMS Cal. for $[M+Na]^+$: $C_{15}H_{16}O$: 235.1093 Found: 235.1085.

2-Methyl-3',4'-dihydro-1'H-spiro[cyclopent[2]ene-1,2'-naphthalen]-1'-one 391



Yield: 89 %

light yellow oil

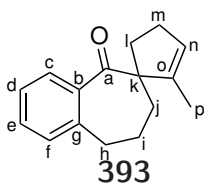
 $C_{15}H_{16}O$

MW 212.29 g/mol

1H -NMR (400 MHz, $CDCl_3$) δ 1.67 (q, $J = 2.0$ Hz, 3H, H_o), 1.88 (ddd, $J = 13.3, 4.6, 3.0$ Hz, 1H), 2.03 - 2.11 (m, 2H), 2.31 - 2.38 (m, 2H), 2.41 (dd, $J = 13.1, 4.6$ Hz, 1H), 2.94 (ddd, $J = 16.9, 4.6, 3.0$ Hz, 1H, H_h), 3.17 (ddd, $J = 16.9, 12.8, 4.6$ Hz, 1H,

H_h), 5.65 (q, $J = 1.9$ Hz, 1H, H_m), 7.25 (d, $J = 7.5$ Hz, 1H, H_f), 7.32 (t, $J = 7.6$ Hz, 1H, H_d), 7.47 (td, $J = 7.5, 1.5$ Hz, 1H, H_e), 8.08 (dd, $J = 8.0, 1.5$ Hz, 1H, H_c) ppm;
 $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 13.6 (C_o), 26.4, 29.8, 32.2, 33.8, 61.3 (C_j), 126.7, 128.0, 128.1, 128.6, 132.1 (C_b), 133.2 (C_e), 142.2 (C_g or n), 143.8 (C_g or n), 200.6 (C_a) ppm;
 IR (neat) 2924, 2851, 1676 ($\text{C}=\text{O}$), 1598, 1453, 1309, 1217, 901, 739 cm^{-1} ;
 HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{15}\text{H}_{16}\text{O}$: 235.1093 Found: 235.1102.

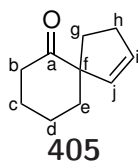
2'-Methyl-8,9-dihydrospiro[benzo[7]annulene-6,1'-cyclopent[2]en]-5(7H)-one
393



Yield: 70 %
 yellow oil
 $\text{C}_{15}\text{H}_{16}\text{O}$
 MW 212.29 g/mol

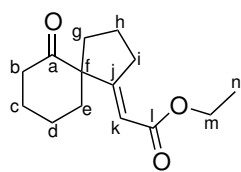
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.52 - 1.63 (m, 1H), 1.57 (d, $J = 1.7$ Hz, 3H, H_p), 1.76 - 1.92 (m, 1H), 1.93 - 2.09 (m, 3H), 2.22 - 2.39 (m, 2H), 2.40 - 2.54 (m, 1H), 2.68 - 2.89 (m, 2H, H_h), 5.48 (q, $J = 2.0$ Hz, 1H, H_n), 7.10 (d, $J = 7.2$ Hz, 1H), 7.22 - 7.30 (m, 1H), 7.36 (d, $J = 6.8$ Hz, 1H), 7.38 (dd, $J = 7.4, 7.2$ Hz, 1H) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 13.7 (C_p), 23.1 (C_i), 30.6, 31.1, 32.1, 32.9, 64.5 (C_k), 126.5, 126.9, 127.0, 128.4, 131.4, 137.7 (C_b), 141.7 (C_g or o), 144.7 (C_g or o), 215.4 (C_a) ppm;
 IR (neat) 2931, 2855, 1674 ($\text{C}=\text{O}$), 1598, 1446, 1248, 959, 755 cm^{-1} ;
 HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{16}\text{H}_{18}\text{O}$: 249.1250 Found: 249.1282.

Spiro[4.5]dec-1-en-6-one **405**



Yield: 39 %
 yellow oil
 $\text{C}_{10}\text{H}_{14}\text{O}$
 MW 150.22 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.66 - 1.93 (m, 6H), 2.27 - 2.49 (m, 6H), 5.75 - 5.84 (m, 2H, $H_{i,j}$) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 22.9, 27.6, 31.3, 32.4, 39.7, 40.1, 64.1 (C_f), 132.8 (C_i or j), 133.3 (C_i or j), 213.3 (C_a) ppm.

(E)-Ethyl 2-(6-oxospiro[4.5]decan-1-ylidene)acetate 450**450**

Yield: 81 %
 colourless solid
 $C_{14}H_{20}O_3$
 MW 236.31 g/mol

1H -NMR (400 MHz, $CDCl_3$) δ 1.27 (t, $J = 7.1$ Hz, 3H, H_n), 1.56 - 1.68 (m, 1H), 1.70 - 1.90 (m, 7H), 1.98 - 2.16 (m, 2H), 2.38 (dt, $J = 14.8, 3.8$ Hz, 1H), 2.49 - 2.62 (m, 1H), 2.91 (ddd, $J = 7.9, 6.5, 2.6$ Hz, 2H), 4.14 (qd, $J = 7.1, 1.3$ Hz, 2H, H_m), 5.68 (t, $J = 2.8$ Hz, 1H, H_k) ppm;

^{13}C -NMR(100 MHz, $CDCl_3$) δ 14.5 (C_n), 22.3, 23.0, 27.0, 33.2, 37.6, 38.3, 39.3, 59.8 (C_m), 63.6 (C_f), 114.5 (C_k), 166.9 ($C_{j \text{ or } 1}$), 168.8 ($C_{j \text{ or } 1}$), 211.3 (C_a) ppm;

IR (neat) 2936, 2865, 1703 (C=O), 1651, 1190, 1144 cm^{-1} ;

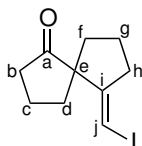
HRMS Cal. for $[M+Na]^+$: $C_{14}H_{20}O_3$: 259.1305 Found: 259.1332.

25.3. Synthesis of spirocyclic alkenyl iodides**Typical procedure for the preparation of spirocyclic alkenyl iodides GP M**

The TBS-enol ether (0.7 mmole, 1 equiv) was dissolved in 1.5 mL dry $ClCH_2CH_2Cl$ at rt. $AgNTf_2$ (0.035 mmol, 0.05 equiv) in 1 mL of dry $ClCH_2CH_2Cl$ was added, directly followed by addition of N-iodosuccinimide (0.7 mmol, 1 equiv). The mixture was stirred at rt for 15 h.

The reaction mixture was diluted with 4 mL of CH_2Cl_2 and hydrolysed with 2 mL of 10% HCl at rt and stirred for 45 min. The aqueous phase was extracted with 3×5 mL CH_2Cl_2 . The combined organic phases were washed with 6 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure product was obtained by column chromatography (PE/EtOAc 98:2).

(E)-6-(Iodomethylene)spiro[4.4]nonan-1-one 426**426**

Yield: 13 %
 yellow oil
 $C_{10}H_{13}IO$
 MW 276.11 g/mol

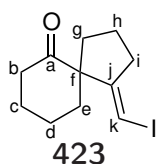
1H -NMR (400 MHz, $CDCl_3$) δ 1.70 - 1.81 (m, 2H), 1.84 - 2.01 (m, 4H), 2.01 - 2.14 (m, 2H), 2.26 - 2.37 (m, 2H), 2.39 - 2.48 (m, 2H), 5.86 (t, $J = 2.6$ Hz, 1H, H_k) ppm;

^{13}C -NMR(100 MHz, $CDCl_3$) δ 19.5, 22.6, 37.7, 38.1, 38.4, 39.1, 62.2 (C_e), 71.7 (C_j), 159.0 (C_i), 219.7 (C_a) ppm;

IR (neat) 2953, 2864, 1731 (C=O), 1150 cm^{-1} ;

HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{10}\text{H}_{13}\text{IO}$: 298.9903 Found: 298.9908.

(E)-1-(Iodomethylene)spiro[4.5]decan-6-one 423



Yield: 68 %

yellow oil

$\text{C}_{11}\text{H}_{15}\text{IO}$

MW 290.14 g/mol

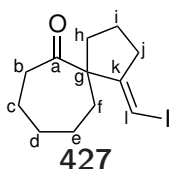
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.53 - 1.92 (m, 8H), 1.92 - 2.08 (m, 1H), 2.21 - 2.45 (m, 4H), 2.45 - 2.60 (m, 1H), 6.02 (t, $J = 2.6$ Hz, 1H, H_j) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 21.9, 22.5, 27.1, 38.4, 38.4, 39.3, 39.5, 63.2 (C_f), 73.4 (C_k), 157.3 (C_j), 211.1 (C_a) ppm;

IR (neat) 2932, 2861, 1702 (C=O), 1229, 1124 cm^{-1} ;

HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{11}\text{H}_{15}\text{IO}$: 313.0060 Found: 313.0048.

(E)-1-(Iodomethylene)spiro[4.6]undecan-6-one 427



Yield: 67 %

yellow oil

$\text{C}_{12}\text{H}_{17}\text{IO}$

MW 304.17 g/mol

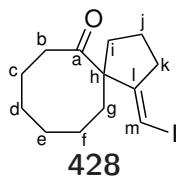
$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.22 - 1.36 (m, 1H), 1.42 - 1.56 (m, 2H), 1.56 - 1.73 (m, 2H), 1.73 - 1.82 (m, 3H), 1.82 - 1.96 (m, 3H), 2.36 - 2.44 (m, 2H), 2.44 - 2.54 (m, 2H), 2.70 (td, $J = 11.4, 2.7$ Hz, 1H), 6.10 (t, $J = 2.6$ Hz, 1H, H_i) ppm;

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 22.2, 25.8, 26.9, 30.6, 37.5, 38.7, 38.8, 41.6, 64.7 (C_g), 72.7 (C_l), 158.8 (C_k), 212.5 (C_a) ppm;

IR (neat) 2925, 2854, 1694 (C=O), 1141 cm^{-1} ;

HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{12}\text{H}_{17}\text{IO}$: 327.0216 Found: 327.0224.

(E)-1-(Iodomethylene)spiro[4.7]dodecan-6-one 428



Yield: 81 %

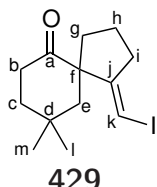
light yellow solid

$\text{C}_{13}\text{H}_{19}\text{IO}$

MW 318.19 g/mol

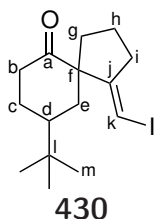
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.89 - 1.06 (m, 1H), 1.21 - 1.39 (m, 1H), 1.41 - 1.80 (m, 8H), 1.81 - 2.02 (m, 2H), 2.15 (ddd, $J = 11.6, 5.9, 3.3$ Hz, 1H), 2.34 (dd, $J = 6.5, 2.6$ Hz, 1H), 2.37 (dd, $J = 7.0, 2.6$ Hz, 1H), 2.41 - 2.57 (m, 2H), 2.87 (td, $J = 12.1, 3.5$ Hz, 1H), 6.24 (t, $J = 2.6$ Hz, 1H, H_m) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 22.2, 24.3, 25.6, 26.0, 30.4, 34.1, 35.5, 37.1, 38.2, 64.6 (C_h), 73.5 (C_m), 156.8 (C_l), 214.0 (C_a) ppm;
IR (neat) 2923, 2854, 1691 ($\text{C}=\text{O}$) cm^{-1} ;
HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{13}\text{H}_{19}\text{IO}$: 341.0373 Found: 341.0356.

(E)-1-(Iodomethylene)-9,9-dimethylspiro[4.5]decan-6-one 429

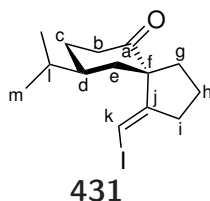
Yield: 79 %
 orange oil
 $\text{C}_{13}\text{H}_{19}\text{IO}$
 MW 318.19 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.01 (s, 3H, H_l or m), 1.16 (s, 3H, H_l or m), 1.52 - 1.66 (m, 2H), 1.66 - 1.76 (m, 3H), 1.77 - 1.89 (m, 1H), 1.96 (d, $J = 14.2$ Hz, 1H), 2.14 - 2.30 (m, 2H), 2.35 - 2.53 (m, 2H), 2.66 (ddd, $J = 15.7, 11.4, 7.2$ Hz, 1H), 5.93 (t, $J = 2.6$ Hz, 1H, H_k) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 22.2 (C_h), 26.7 (C_l or m), 30.8 (C_d), 32.7 (C_l or m), 35.5, 37.9, 38.6, 41.9, 50.9 (C_e), 61.9 (C_f), 73.2 (C_k), 158.9 (C_j), 212.3 (C_a) ppm;
IR (neat) 2952, 1701 ($\text{C}=\text{O}$), 1135 cm^{-1} ;
HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{13}\text{H}_{19}\text{IO}$: 341.0373 Found: 341.0389.

(E)-9-(tert-Butyl)-1-(iodomethylene)spiro[4.5]decan-6-one 430

Yield: 23 %
 orange oil
 $\text{C}_{15}\text{H}_{23}\text{IO}$
 MW 346.25 g/mol

The separation of the two diastereoisomers obtained was not possible. Therefore the spectral data for the compounds could not be determined.

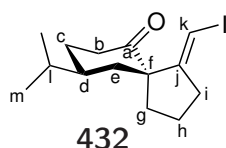
(E)-1-(Iodomethylene)-9-isopropylspiro[4.5]decan-6-one 431

Yield: 33 %
 orange oil
 $\text{C}_{14}\text{H}_{21}\text{IO}$
 MW 332.22 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.91 (d, $J = 6.8$ Hz, 6H, H_m), 1.36 - 1.67 (m, 6H),

1.68 - 1.95 (m, 3H), 1.95 - 2.08 (m, 1H), 2.16 - 2.27 (m, 1H), 2.27 - 2.46 (m, 2H), 2.56 (ddd, $J = 14.9, 13.6, 6.3$ Hz, 1H), 5.94 (t, $J = 2.6$ Hz, 1H, H_k) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 19.9 (C_m), 20.1 (C_m), 21.9 (C_h), 30.0, 32.2 (C_l), 38.2, 38.6, 39.8 (C_d), 40.3, 41.8, 62.7 (C_f), 73.5 (C_k), 157.4 (C_j), 211.8 (C_a) ppm.

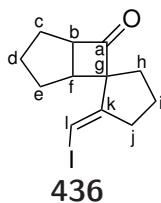
(*E*)-1-(Iodomethylene)-9-isopropylspiro[4.5]decan-6-one 432



Yield: 39 %
 orange oil
 $\text{C}_{14}\text{H}_{21}\text{IO}$
 MW 332.22 g/mol

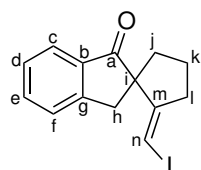
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 0.88 (d, $J = 4.8$ Hz, 3H, H_m), 0.90 (d, $J = 4.8$ Hz, 3H, H_m), 1.32 - 1.56 (m, 4H), 1.60 - 1.93 (m, 4H), 1.95 - 2.08 (m, 2H), 2.33 - 2.45 (m, 2H), 2.47 - 2.67 (m, 2H), 6.38 (t, $J = 2.6$ Hz, 1H, H_k) ppm;
 $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 19.7 (C_m), 20.2 (C_m), 22.0 (C_h), 29.0, 32.5 (C_l), 39.1, 39.2 (C_d), 39.3, 40.1, 41.6, 61.5 (C_f), 73.3 (C_k), 158.5 (C_j), 210.6 (C_a) ppm.

(*E*)-2'-(Iodomethylene)spiro[bicyclo[3.2.0]heptane-6,1'-cyclopentan]-7-one 436



Yield: 54 %
 yellow solid
 $\text{C}_{12}\text{H}_{15}\text{IO}$
 MW 302.15 g/mol

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.37 - 1.57 (m, 2H), 1.62 - 1.75 (m, 2H), 1.75 - 1.92 (m, 4H), 2.04 - 2.15 (m, 2H), 2.32 (qu.d, $J = 8.8, 2.7$ Hz, 1H), 2.39 - 2.49 (m, 1H), 2.79 (t, $J = 8.0$ Hz, 1H), 3.70 (t, $J = 8.0$ Hz, 1H, H_b), 6.12 (t, $J = 2.6$ Hz, 1H, H_i) ppm;
 $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 22.8, 26.7, 28.6, 29.3, 31.3, 37.9, 40.3 (C_f), 63.4 (C_b), 70.5 (C_l), 76.2 (C_g), 156.6 (C_k), 214.7 (C_a) ppm;
 IR (neat) 2950, 2865, 1761 (C=O), 1440, 732 cm^{-1} ;
 HRMS Cal. for $[\text{M}+\text{Na}]^+$: $\text{C}_{12}\text{H}_{15}\text{IO}$: 325.0060 Found: 325.0019.

(E)-2-(Iodomethylene)spiro[cyclopentane-1,2'-inden]-1'(3'H)-one 433**433**

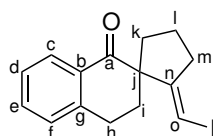
Yield: 78 %
 yellow oil
 $C_{14}H_{13}IO$
 MW 324.16 g/mol

1H -NMR (300 MHz, $CDCl_3$) δ 1.81 - 1.93 (m, 1H), 1.97 (dd, $J = 12.4, 6.7$ Hz, 1H), 2.11 - 2.25 (m, 1H), 2.39 (dt, $J = 12.0, 7.1$ Hz, 1H), 2.55 (td, $J = 7.4, 2.6$ Hz, 2H), 3.13 (d, $J = 17.2$ Hz, 1H, H_h), 3.28 (d, $J = 17.2$ Hz, 1H, H_h), 5.67 (t, $J = 2.6$ Hz, 1H, H_n), 7.40 (td, $J = 7.7, 0.6$ Hz, 1H, H_d), 7.45 (d, $J = 7.7$ Hz, 1H, H_f), 7.61 (td, $J = 7.4, 1.3$ Hz, 1H, H_e), 7.76 (d, $J = 7.6$ Hz, 1H, H_c) ppm;

^{13}C -NMR(75 MHz, $CDCl_3$) δ 23.3 (C_k), 38.3, 39.7, 43.0, 62.1 (C_i), 71.6 (C_n), 124.8, 126.5, 127.9, 135.2 (C_e), 136.0 (C_b), 152.5 (C_g), 159.6 (C_m), 206.9 (C_a) ppm;

IR (neat) 2949, 1704, 1605, 1462, 1276, 727 cm^{-1} ;

HRMS Cal. for $[M+Na]^+$: $C_{14}H_{13}IO$: 346.9903 Found: 346.9887.

(E)-2-(Iodomethylene)-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-one 434**434**

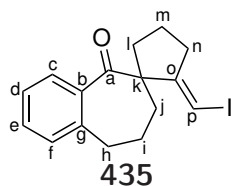
Yield: 80 %
 yellow oil
 $C_{15}H_{15}IO$
 MW 338.18 g/mol

1H -NMR (400 MHz, $CDCl_3$) δ 1.75 - 1.93 (m, 3H), 1.98 (dt, $J = 13.7, 5.8$ Hz, 1H), 2.29 (ddd, $J = 13.5, 7.2, 6.0$ Hz, 1H), 2.40 - 2.64 (m, 3H), 3.01 (t, $J = 6.3$ Hz, 2H, H_h), 5.82 (t, $J = 2.7$ Hz, 1H, H_o), 7.24 (d, $J = 7.9$ Hz, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.48 (td, $J = 7.4, 1.5$ Hz, 1H), 8.04 (dd, $J = 7.9, 1.6$ Hz, 1H, H_c) ppm;

^{13}C -NMR(100 MHz, $CDCl_3$) δ 21.7 (C_l), 26.2, 33.6, 37.7, 38.7, 59.3 (C_j), 72.6 (C_o), 127.0, 128.3, 128.9, 131.9 (C_b), 133.6 (C_e), 143.5 (C_g), 157.9 (C_n), 198.8 (C_a) ppm;

IR (neat) 2928, 2853, 1675 ($C=O$), 1598, 11218, 737 cm^{-1} ;

HRMS Cal. for $[M+Na]^+$: $C_{15}H_{15}IO$: 361.0060 Found: 361.0114.

(E)-2'-(Iodomethylene)-8,9-dihydrospiro[benzo[7]annulene-6,1'-cyclopentan]-5(7H)-one 435**435**

Yield: 73 %
 yellow oil
 $C_{16}H_{17}IO$
 MW 352.21 g/mol

¹H-NMR (400 MHz, CDCl₃) δ 1.69 - 1.85 (m, 3H), 1.85 - 2.02 (m, 5H), 2.37 - 2.58 (m, 3H), 2.72 - 2.81 (m, 2H, H_h), 5.83 (t, J = 2.6 Hz, 1H, H_p), 7.13 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 4.1 Hz, 2H), 7.38 (dt, J = 7.6, 4.1 Hz, 1H) ppm;

¹³C-NMR(100 MHz, CDCl₃) δ 22.8 (C_i or m), 22.9 (C_i or m), 32.3, 34.6, 36.7, 38.4, 62.5 (C_k), 72.8 (C_p), 127.0, 127.2, 128.6, 131.3, 137.1 (C_b), 141.2 (C_g), 161.0 (C_o), 211.9 (C_a) ppm;

IR (neat) 2934, 2860, 1677 (C=O), 1597, 1447, 1233, 750 cm⁻¹;

HRMS Cal. for [M+Na]⁺: C₁₆H₁₇IO: 375.0216 Found: 375.0202.

25.4. Isomerization of 2-Methylene-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-one **390**

To a solution of HNTf₂ (4 mg, 0.016 mmol, 0.05 equiv.) in 1 mL dry ClCH₂CH₂Cl was added **390** (67 mg, 0.316 mmol, 1 equiv.) in 1.5 mL of dry ClCH₂CH₂Cl. The reaction mixture was stirred at room temperature for 20 h.

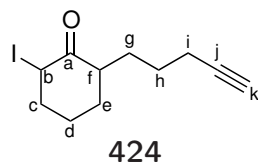
The reaction mixture was concentrated in vacuum (15 mbar) to yield 65 mg (97%) of **391** as yellow oil.

25.5. Synthesis of 2-Iodo-6-(pent-4-yn-1-yl)cyclohexanone **424**

To a solution of **89** (181 mg, 0.650 mmol, 1 equiv.) in 2 mL dry ClCH₂CH₂Cl was added NIS (146 mg, 0.650 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 20 h.

The reaction mixture was diluted with 4 mL of CH₂Cl₂ and hydrolyzed with 2 mL of 10% HCl at room temperature and stirred for 45 min. The aqueous phase was extracted with 3 × 5 mL of CH₂Cl₂. The combined organic phases were washed with 6 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure **424** was obtained by column chromatography (PE/EtOAc 98:2).



424

Yield: 33 %

orange oil

C₁₆H₁₇IO

MW 352.21 g/mol

¹H-NMR (400 MHz, CDCl₃) δ 1.28 - 1.39 (m, 2H), 1.49 - 1.59 (m, 2H), 1.74 - 1.93 (m, 3H), 1.94 (t, J = 2.6 Hz, 1H, H_k), 2.03 - 2.15 (m, 2H), 2.16 - 2.23 (m, 3H), 3.42 (sex, J = 6.3 Hz, 1H), 4.62 (ddd, J = 4.2, 2.6, 1.5 Hz, 1H, H_b) ppm;

¹³C-NMR(100 MHz, CDCl₃) δ 18.7 (C_i), 21.9 (C_d), 26.0, 28.5, 31.8 (C_b), 33.8, 37.1,

43.5 (C_f), 68.6 (C_k), 84.4 (C_j), 206.9 (C_a) ppm;

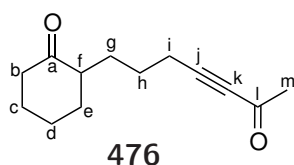
IR (neat) 3293 (C≡C), 2934, 2861, 1702 (C=O), 630 cm⁻¹.

26. Synthesis of tricyclic fused ring systems

26.1. Synthesis of ketone 477

Synthesis of 2-(6-Oxohept-4-yn-1-yl)cyclohexanone 476

Compound **476** was synthesized according to general procedure G (p. 176) with acetyl chloride used instead of ethyl chloroformate.



Yield: 23 %
colourless oil
 $C_{13}H_{18}O_2$
MW 206.28 g/mol

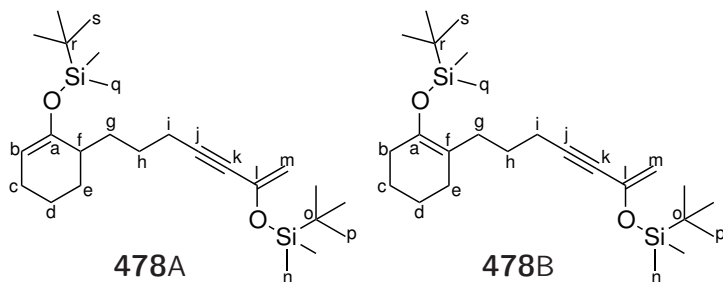
1H -NMR (300 MHz, $CDCl_3$) δ 1.22 - 1.46 (m, 2H), 1.47 - 1.73 (m, 4H), 1.76 - 1.91 (m, 2H), 1.96 - 2.15 (m, 2H), 2.21 - 2.43 (m, 5H), 2.29 (s, 3H, H_m) ppm;

^{13}C -NMR (75 MHz, $CDCl_3$) δ 19.3 (C_i), 25.1, 25.6, 28.1, 29.0, 32.9 (C_m), 34.2, 42.2 (C_b), 50.3 (C_f), 81.6 (C_j), 93.8 (C_k), 185.0 (C_l), 212.9 (C_a) ppm;

IR (neat) 2932, 2861, 2208, 1706, 1672, 1226 cm^{-1} .

tert-Butyl((7-(2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)hept-1-en-3-yn-2-yl)oxy)dimethylsilane / *tert*-Butyl((7-(2-((*tert*-butyldimethylsilyl)oxy)-cyclohex-1-en-1-yl)hept-1-en-3-yn-2-yl)oxy)dimethylsilane 478

Compound **476** was synthesized according to general procedure K (p. 199) with 2.5 equiv. TBSOTf and 4 equiv. NEt_3 .



Yield: quant.
colourless oil
 $C_{25}H_{46}O_2Si_2$
MW 434.80 g/mol
478A:478B 3:1

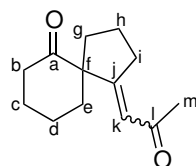
Due to the fact that both compounds were superposed, the spectra obtained could not be fully interpreted. This prevented also the determination of the proton/carbon number for each peak.

¹H-NMR (500 MHz, C₆D₆) δ 0.06 (s, H_n(A) or H_n(B) or H_q(a) or H_q(B)), 0.10 (s, H_n(A) or H_n(B) or H_q(a) or H_q(B)), 0.15 (s, H_n(A) or H_n(B) or H_q(a) or H_q(B)), 0.16 (s, H_n(A) or H_n(B) or H_q(a) or H_q(B)), 0.95 (s, H_p(A) or H_p(B) or H_s(A) or H_s(B)), 1.00 (s, H_p(A) or H_p(B) or H_s(A) or H_s(B)), 1.01 (s, H_p(A) or H_p(B) or H_s(A) or H_s(B)), 1.02 (s, H_p(A) or H_p(B) or H_s(A) or H_s(B)), 1.24 - 1.39 (m), 1.39 - 1.46 (m), 1.46 - 1.52 (m), 1.52 - 1.68 (m), 1.79 - 1.90 (m), 1.91 - 1.99 (m), 1.99 - 2.07 (m), 2.12 (t, J = 7.0 Hz), 2.16 - 2.26 (m), 4.77 (d, J = 14.7 Hz, 2H, H_m(A) or H_m(b)), 4.88 (td, J = 3.9, 1.2 Hz, 1H, H_b(A)) ppm;

¹³C-NMR (125 MHz, C₆D₆) δ -4.3 (C_n(A) or C_n(B) or C_q(A) or C_q(B)), -4.2 (C_n(A) or C_n(B) or C_q(A) or C_q(B)), -3.4 (C_n(A) or C_n(B) or C_q(A) or C_q(B)), -2.7 (C_n(A) or C_n(B) or C_q(A) or C_q(B)), 18.4 (C_o(A) or C_o(B) or C_r(A) or C_r(B)), 18.5 (C_o(A) or C_o(B) or C_r(A) or C_r(B)), 19.5, 19.7, 20.7, 23.4, 24.1, 24.6, 25.9 (C_p(A) or C_p(B) or C_s(A) or C_s(B)), 26.0 (C_p(A) or C_p(B) or C_s(A) or C_s(B)), 26.1 (C_p(A) or C_p(B) or C_s(A) or C_s(B)), 26.1 (C_p(A) or C_p(B) or C_s(A) or C_s(B)), 26.4, 27.3, 28.3, 28.5, 30.2, 30.8, 32.3, 38.9 (C_f(A)), 79.3 (C_k(A) and C_k(B)), 89.0 (C_j(A) or C_j(B)), 101.5 (C_m(A) or C_m(B)), 101.5 (C_m(A) or C_m(B)), 103.7 (C_b(A)), 114.4 (C_f(B)), 140.7 (C₁(A) or C₁(B)), 140.8 (C₁(A) or C₁(B)), 144.1 (C_a(B)), 153.6 (C_a(A)) ppm.

Synthesis of 1-(2-Oxopropylidene)spiro[4.5]decan-6-one 477

Compound **477** was synthesized according to general procedure L (p. 208).



477

Yield: 11 %
 colourless oil
 C₁₃H₁₈O₂
 MW 206.28 g/mol

¹H-NMR (500 MHz, CDCl₃) δ 1.52 - 1.69 (m, 2H), 1.70 - 1.81 (m, 4H), 1.81 - 1.90 (m, 2H), 2.00 - 2.13 (m, 2H), 2.21 (s, 3H, H_m), 2.25 - 2.34 (m, 1H), 2.34 - 2.41 (m, 1H), 2.52 - 2.62 (m, 1H), 2.88 (ddd, J = 7.9, 6.4, 2.6 Hz, 2H), 6.08 (t, J = 2.6 Hz, 1H, H_k) ppm;

¹³C-NMR(125 MHz, CDCl₃) δ 22.3, 23.2, 27.0, 31.8 (C_m), 33.9, 37.4, 38.5, 39.4, 63.8 (C_f), 121.9 (C_k), 167.6 (C_j), 198.3 (C₁), 211.4 (C_a) ppm.

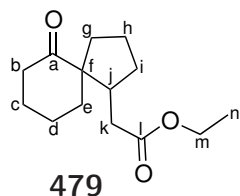
26.2. Synthesis of spirocyclic ketone 472

Synthesis of Ethyl 2-(6-oxospiro[4.5]decan-1-yl)acetate 479

A solution of **450** (250 mg, 1.06 mmol, 1 equiv.) in 5 mL dry AcOH was degassed with Ar for 10 min. The PtO₂ (4.8 mg, 0.02 mmol, 0.02 equiv.) was added and a balloon with H₂ was connected. The reaction mixture was stirred at room temperature for 16 h.

The reaction mixture was degassed with Ar for 20 min. After filtration through a pad

of celite, the reaction mixture was washed 2×10 ml H_2O . The aqueous phases were extracted 2×10 mL CH_2Cl_2 . The combined organic phases were washed with 20 mL of a saturated aqueous solution of NaHCO_3 , 20 mL of a saturated aqueous solution of NaCl , dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar). The pure **479** was obtained by column chromatography (PE/EtOAc 98:2).



Yield: 78 %
colourless oil
 $\text{C}_{14}\text{H}_{22}\text{O}_3$
MW 238.32 g/mol

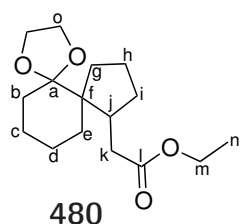
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.23 (t, $J = 7.2$ Hz, 3H, H_n), 1.36 - 1.47 (m, 1H), 1.47 - 1.57 (m, 1H), 1.57 - 1.66 (m, 3H), 1.66 - 2.02 (m, 6H), 2.08 - 2.30 (m, 4H), 2.35 - 2.53 (m, 2H), 4.10 (q, $J = 7.0$ Hz, 2H, H_m) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.4 (C_n), 21.4, 22.6, 26.7, 30.3, 35.4, 36.0, 38.2, 40.6, 44.4 (C_j), 59.5 (C_f), 60.4 (C_m), 173.8 (C_l), 214.0 (C_a) ppm;

IR (neat) 2935, 2868, 1731 (C=O), 1698, 1180, 1030 cm^{-1} .

Synthesis of protected spirocyclic ester **480**

Compound **480** was synthesized as described in general procedure GP E (p. 173).



Yield: 87 %
colourless oil
 $\text{C}_{16}\text{H}_{26}\text{O}_4$
MW 282.38 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.25 (t, $J = 7.0$ Hz, 3H, H_n), 1.31 - 1.59 (m, 4H), 1.60 - 1.77 (m, 2H), 1.78 - 1.92 (m, 2H), 2.07 - 2.17 (m, 1H), 2.23 (dd, $J = 14.6, 10.8$ Hz, 1H), 2.73 (dd, $J = 14.8, 3.8$ Hz, 1H), 3.83 - 4.01 (m, 4H, H_o), 4.11 (q, $J = 7.0$ Hz, 2H, H_m) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.5 (C_n), 22.1, 22.2, 23.3, 31.5, 32.3, 33.0, 36.9, 37.2, 44.6 (C_j), 51.5 (C_f), 60.0 (C_m), 63.0 (C_o), 63.8 (C_o), 113.4 (C_a), 174.7 (C_l) ppm.

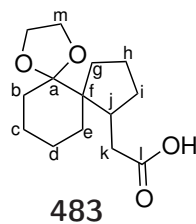
Synthesis of spirocyclic acid **483**

To a solution of **480** (243 mg, 0.860 mmol, 1 equiv.) in 5 mL dry $\text{ClCH}_2\text{CH}_2\text{Cl}$ was added Me_3SnOH (1167 mg, 6.45 mmol, 7.5 equiv.). The reaction mixture was heated to reflux for 20 h.

The reaction mixture was hydrolyzed with 5 mL 0.01 N aqueous solution of KHSO_4 . The organic phase is washed 5×5 mL 0.01 N aqueous solution of KHSO_4 . The aqueous

phases were extracted with 2×10 mL of EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure **483** was obtained by column chromatography (PE/EtOAc 98:2 to 8:2).



Yield: quant.
colourless oil
 $\text{C}_{14}\text{H}_{22}\text{O}_4$
MW 254.32 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.12 - 1.33 (m, 2H), 1.34 - 1.61 (m, 4H), 1.61 - 1.80 (m, 3H), 1.80 - 1.94 (m, 3H), 1.95 - 2.19 (m, 2H), 2.27 (dd, $J = 15.6, 10.4$ Hz, 2H), 2.65 (dd, $J = 9.1, 1.5$ Hz, 1H), 2.80 (dd, $J = 15.7, 4.7$ Hz, 1H), 3.57 - 3.77 (m, 2H, H_m), 3.87 - 4.04 (m, 2H, H_m) ppm;

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 22.2, 22.2, 23.2, 31.3, 32.6, 33.1, 36.9 (2C), 44.6 (C_j), 51.3 (C_f), 62.9 (C_m), 63.6 (C_m), 113.5 (C_a), 180.1 (C_l) ppm;

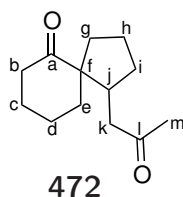
IR (neat) 2933, 2864, 1702 (C=O), 1095, 731 cm^{-1} .

Synthesis of 1-(2-Oxopropyl)spiro[4.5]decan-6-one 472

A solution of **483** (223 mg, 0.880 mmol, 1 equiv.) in 7 mL dry THF was cooled to 0 °C. MeLi (1.42 M, 2.47 mL, 3.51 mmol, 4 equiv.) was added fast. The reaction mixture was stirred at 0 °C for 1.5 h. Freshly distilled TMSCl (1905 mg, 17.54 mmol, 20 equiv.) was added and the reaction mixture was allowed to slowly warm to room temperature. The reaction mixture was heated to reflux for 20 h.

The reaction mixture was hydrolyzed with 7 mL 1 N HCl and stirred for 30 min. The aqueous phase was extracted with 3×10 mL of Et_2O . The combined organic phases were washed with 10 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure **472** was obtained by column chromatography (PE/EtOAc 98:2 to 95:5).



Yield: 72 %
colourless oil
 $\text{C}_{13}\text{H}_{20}\text{O}_2$
MW 208.30 g/mol

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 1.34 - 1.43 (m, 2H), 1.43 - 1.50 (m, 1H), 1.50 - 1.59 (m, 2H), 1.59 - 1.70 (m, 2H), 1.70 - 1.75 (m, 1H), 1.75 - 1.84 (m, 2H), 1.91 (dtd, $J = 12.6, 8.4, 5.5$ Hz, 1H), 2.05 (s, 3H, H_m), 2.06 - 2.18 (m, 3H), 2.28 (dd, $J = 17.7, 3.2$ Hz, 1H), 2.37 (ddd, $J = 14.9, 9.5, 5.8$ Hz, 1H), 2.67 (dd, $J = 17.7, 10.2$ Hz, 1H) ppm;

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 21.6, 22.6, 26.5, 30.5, 30.6 (C_m), 36.2, 38.1, 40.4, 42.9 (C_j), 44.6, 59.3 (C_f), 208.7 (C_a or l), 214.4 (C_a or l) ppm;

IR (neat) 2933, 2866, 1697 (C=O) cm^{-1} .

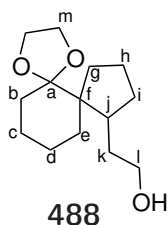
26.3. Synthesis of spirocyclic aldehyde 473

Synthesis of spirocyclic alcohol 488

To a solution of **480** (280 mg, 0.991 mmol, 1 equiv.) in 9 mL dry THF was added LiAlH_4 (45 mg, 1.19 mmol, 1.2 equiv.) in portions. The reaction mixture was stirred at room temperature for 45 min.

The reaction mixture was treated with 4 mL EtOAc, 4 mL Et_2O and 4 mL H_2O and filtered through a pad of celite. The organic phase was washed with 10 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure **488** was obtained by column chromatography (PE/EtOAc 9:1 to 8:2).



Yield: 95 %
 colourless oil
 $\text{C}_{14}\text{H}_{24}\text{O}_3$
 MW 240.34 g/mol

$^1\text{H-NMR}$ (500 MHz, C_6D_6) δ 1.29 - 1.39 (m, 2H), 1.40 - 1.51 (m, 7H), 1.51 - 1.59 (m, 3H), 1.66 - 1.73 (m, 2H), 1.73 - 1.85 (m, 4H), 1.97 - 2.07 (m, 1H), 2.19 (dtd, $J = 13.6, 7.8, 3.3$ Hz, 1H), 3.39 - 3.50 (m, 2H, H_m), 3.51 - 3.61 (m, 2H, H_m) ppm;

$^{13}\text{C-NMR}$ (125 MHz, C_6D_6) δ 22.7 (2C), 23.8, 32.1, 33.2, 34.3, 35.3, 37.9, 46.0 (C_j), 52.2 (C_f), 63.1 (2C, C_1 or m), 63.8 (C_1 or m), 113.8 (C_a) ppm;

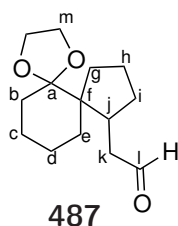
IR (neat) 3359 (OH), 2930, 2861, 1052, 948 cm^{-1} .

Synthesis of spirocyclic aldehyde 487

To a solution of *i*PrMgBr (0.4 M in THF, 1.5 mL, 0.699, 1.5 equiv.) was added dropwise **488** (112 mg, 0.466 mmol, 1 equiv.) in 2 mL dry THF. Then 1,1'-(azodicarbonyl)dipiperidine (141 mg, 0.559 mmol, 1.2 equiv.) in 3 mL dry THF was added. The reaction mixture was stirred at room temperature for 3 h.

The reaction mixture was hydrolyzed with 2 mL of a saturated aqueous solution of NaCl. The aqueous phase was extracted 3 \times 5 mL EtOAc. The organic phases were washed with 5 mL of a saturated aqueous solution of NaHCO_3 , 5 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure **487** was obtained by column chromatography (PE/EtOAc 98:2 to 95:5).



Yield: 86 %
 colourless oil
 $C_{14}H_{22}O_3$
 MW 238.32 g/mol

1H -NMR (500 MHz, C_6D_6) δ 1.20 - 1.52 (m, 11H), 1.56 - 1.82 (m, 4H), 1.82 - 1.94 (m, 1H), 2.01 (qu, $J = 7.3$ Hz, 1H), 2.16 (ddd, $J = 16.8, 8.8, 2.2$ Hz, 1H, H_k), 2.69 (ddd, $J = 16.7, 5.8, 2.0$ Hz, 1H, H_k), 3.31 - 3.49 (m, 4H, H_m), 9.56 (t, $J = 2.1$ Hz, 1H, H_l) ppm;

^{13}C -NMR(125 MHz, C_6D_6) δ 22.6, 22.8, 23.4, 31.4, 33.5, 33.6, 37.4, 46.9, 51.3 (C_f), 53.3 (C_j), 62.8 (2C, C_m), 63.1 (C_m), 113.2 (C_a), 201.8 (C_l) ppm;

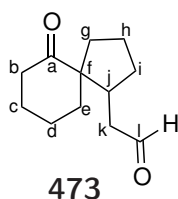
IR (neat) 2932, 2863, 1720 (C=O), 1088, 949 cm^{-1} .

Synthesis of 2-(6-Oxospiro[4.5]decan-1-yl)acetaldehyde **473**

Oxalic acid (10 % in H_2O , 70 mg) was added to a suspension of SiO_2 (700 mg) in CH_2Cl_2 . The protected aldehyde **487** (67 mg, 0.281 mmol, 1 equiv.) was added. The reaction mixture was stirred at room temperature for 3 h.

The reaction mixture was hydrolyzed with 2 mL of a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted 3×5 mL CH_2Cl_2 . The combined organic phases were washed with 5 mL of a saturated aqueous solution of $NaCl$, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

Compound **473** was used as obtained.



Yield: 88 %
 colourless oil
 $C_{12}H_{18}O_2$
 MW 194.27 g/mol

1H -NMR (500 MHz, C_6D_6) δ 1.02 - 1.13 (m, 2H), 1.13 - 1.23 (m, 2H), 1.23 - 1.33 (m, 2H), 1.33 - 1.49 (m, 4H), 1.49 - 1.61 (m, 1H), 1.78 - 1.98 (m, 3H), 2.00 - 2.25 (m, 2H), 2.50 (ddd, $J = 17.8, 9.7, 1.5$ Hz, 1H, H_k), 9.38 (s, 1H, H_l) ppm;

^{13}C -NMR(100 MHz, C_6D_6) δ 21.9 (C_d or h), 22.7 (C_d or h), 26.5, 30.8, 36.4, 38.1, 40.2, 42.2 (C_j), 45.4, 59.1 (C_f), 200.8 (C_l), 212.0 (C_a) ppm;

IR (neat) 2933, 2864, 1721 (C=O), 1697 cm^{-1} .

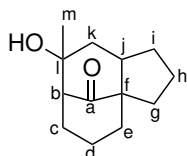
26.4. Synthesis of fused tricyclic compounds

Synthesis of 8-Hydroxy-8-methyldecahydro-3a,7-methanocyclopenta[8]-annulen-10-one **484**

The ketone **472** (50 mg, 0.240 mmol, 1 equiv.) was dissolved in 5 mL dry ETOH and (*S*)-2-(diphenyl(trimethylsilyl)oxy)methylpyrrolidine (8 mg, 0.024 mmol, 0.1 equiv.) was added. The reaction mixture was heated to reflux for 48 h.

The reaction mixture was concentrated in vacuum (15 mbar).

The pure **484** was obtained by column chromatography (PE/EtOAc 95:5).



484

Yield: 78 %
colourless oil
 $C_{13}H_{20}O_2$
MW 208.30 g/mol

¹H-NMR (500 MHz, $CDCl_3$) δ 1.02 - 1.12 (m, 1H), 1.24 (s, 3H, H_m), 1.36 - 1.55 (m, 5H), 1.66 - 1.88 (m, 5H), 2.03 (dd, $J = 14.7, 7.0$ Hz, 1H), 2.08 - 2.22 (m, 1H), 2.28 - 2.40 (m, 3H), 2.44 (t, $J = 7.9$ Hz, 1H) ppm;

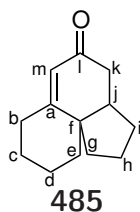
¹³C-NMR(125 MHz, $CDCl_3$) δ 20.4 ($C_{d \text{ or } h}$), 23.4 ($C_{d \text{ or } h}$), 30.8, 33.0, 33.9 (C_m), 34.1, 42.4, 42.7, 43.9 (C_j), 56.4 (C_f), 58.5 (C_b), 75.7 (C_l), 219.5 (C_a) ppm.

Synthesis of 2,3,3a,4,7,8,9,10-Octahydrocyclopenta[*d*]naphthalen-5(1*H*)-one **485**

The ketone **472** (50 mg, 0.240 mmol, 1 equiv.) was dissolved in 5 mL dry ETOH and (*S*)-2-(diphenyl(trimethylsilyl)oxy)methylpyrrolidine (8 mg, 0.024 mmol, 0.1 equiv.) was added. The reaction mixture was heated to reflux for 48 h.

The reaction mixture was concentrated in vacuum (15 mbar).

The pure **485** was obtained by column chromatography (PE/EtOAc 95:5).



485

Yield: 77 %
colourless oil
 $C_{13}H_{18}O$
MW 190.28 g/mol

¹H-NMR (500 MHz, $CDCl_3$) δ 1.30 - 1.41 (m, 2H), 1.47 (td, $J = 12.8, 4.7$ Hz, 1H), 1.55 - 1.73 (m, 5H), 1.75 - 1.87 (m, 2H), 1.87 - 1.95 (m, 2H), 2.05 (t, $J = 7.1$ Hz, 1H), 2.19 - 2.34 (m, 2H), 2.30 (dd, $J = 15.9, 7.1$ Hz, 1H), 2.40 (dd, $J = 16.0, 6.0$ Hz, 1H), 5.71 (d, $J = 1.5$ Hz, 1H, H_m) ppm;

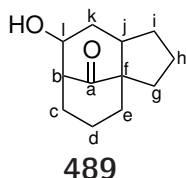
¹³C-NMR(125 MHz, $CDCl_3$) δ 23.0 ($C_{d \text{ or } h}$), 23.3 ($C_{d \text{ or } h}$), 28.3, 30.5, 34.4, 35.3, 38.7, 40.0, 45.6 (C_j), 48.0 (C_f), 122.7 (C_m), 169.3 (C_a), 200.0 (C_l) ppm.

Synthesis of 8-Hydroxydecahydro-3a,7-methanocyclopenta[8]annulen-10-one 489

The aldehyde **473** (142 mg, 0.731 mmol, 1 equiv.) was dissolved in 10 mL THF and 1 mL 10 % HCl were added. The reaction mixture was stirred at room temperature for 20 h.

The reaction mixture was extracted 3× 10 mL Et₂O. The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure **489** was obtained by column chromatography (PE/EtOAc 9:1 to 8:2).



Yield: 38 %
 colourless oil
 C₁₂H₁₈O₂
 MW 194.27 g/mol

¹H-NMR (300 MHz, C₆D₆) δ 0.78 - 1.00 (m, 2H), 1.01 - 1.19 (m, 2H), 1.20 - 1.38 (m, 4H), 1.40 - 1.74 (m, 6H), 1.74 - 1.86 (m, 1H), 2.43 - 2.52 (m, 3H), 2.59 (dt, J = 12.8, 7.1 Hz, 1H), 3.66 (s, 1H, OH) ppm;

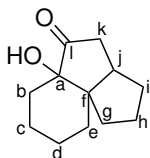
¹³C-NMR(125 MHz, C₆D₆) δ 19.3 (C_c or h), 24.3 (C_c or h), 33.6, 33.9, 35.0, 38.0, 41.8, 42.5 (C_j), 56.2 (C_f), 57.1 (C_b), 74.0 (C_l), 215.8 (C_a) ppm.

Synthesis of 5a-Hydroxyoctahydro-1H-cyclopenta[c]inden-5(5aH)-one 475

The aldehyde **473** (65 mg, 0.335 mmol, 1 equiv.) and 6,7-dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate (24 mg, 0.067 mmol, 0.2 equiv.) were dissolved in 1 mL dry THF. NEt₃ (0.01 mL, 0.067 mmol, 0.2 equiv.) was added and the reaction mixture was stirred at room temperature for 20 h.

The reaction mixture was diluted with 5 mL EtOAc and hydrolyzed with 4 mL of a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted 4× 5 mL EtOAc. The combined organic phases were washed with 5 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar).

The pure **475** was obtained by column chromatography (PE/EtOAc 9:1 to 8:2).



Yield: 78 %
 colourless oil
 C₁₂H₁₈O₂
 MW 194.27 g/mol

¹H-NMR (500 MHz, C₆D₆) δ 1.01 - 1.14 (m, 2H), 1.14 - 1.21 (m, 1H), 1.21 - 1.30 (m, 2H), 1.30 - 1.48 (m, 6H), 1.48 - 1.65 (m, 4H), 2.01 (dt, J = 11.0, 6.1 Hz, 1H), 2.29, (dd, J = 19.7, 10.8 Hz, 1H), 2.71 (s, 1H, OH) ppm;

$^{13}\text{C-NMR}$ (100 MHz, C_6D_6) δ 20.8, 22.7, 22.8, 30.9, 31.4, 33.6, 34.7, 37.3 (C_j), 39.2, 53.3 (C_f), 81.6 (C_a), 218.6 (C_l) ppm;
IR (neat) 3457 (OH), 2924, 2856, 1737 (C=O), 1147, 1039 cm^{-1} .

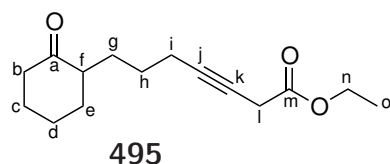
26.5. Synthesis of allene 497

Synthesis of Ethyl 7-(2-oxocyclohexyl)hept-3-ynoate 495

The alkyne **89** (503 mg, 3.063 mmol, 1 equiv.) was dissolved in 13 ml dry acetonitrile. Ethyl diazoacetate (411 mg, 3.063 mmol, 1 equiv.) and CuI (58.32 mg, 0.306 mmol, 0.1 equiv.) were added and the reaction mixture was stirred at room temperature for 20 h.

The reaction mixture filtered through a pad of celite and concentrated in vacuum (15 mbar).

The pure **495** was obtained by column chromatography (PE/EtOAc 98:2 to 95:5).



Yield: 96 %
 colourless oil
 $\text{C}_{15}\text{H}_{22}\text{O}_3$
 MW 250.33 g/mol

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.22 - 1.40 (m, 2H), 1.25 (t, $J = 7.2$ Hz, 3H, H_o), 1.49 (qu, $J = 7.5$ Hz, 2H), 1.58 - 1.74 (m, 2H), 1.75 - 1.90 (m, 2H), 1.95 - 2.14 (m, 2H), 2.14 - 2.23 (m, 3H), 2.23 - 2.42 (m, 3H), 3.21 (t, $J = 2.5$ Hz, 1H, H_l), 4.16 (q, $J = 7.2$ Hz, 2H, H_n) ppm;

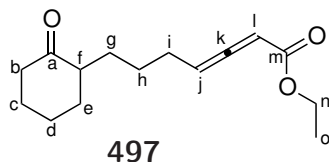
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 14.2 (C_o), 19.0 (C_i), 25.0, 26.2, 26.4, 28.1, 28.8, 34.1, 42.1 (C_b), 50.4 (C_f), 61.5 (C_n), 71.9 (C_j or C_k), 83.6 (C_j or C_k), 169.0 (C_m), 213.2 (C_a) ppm;
IR (neat) 2933, 2861, 1739 (C=O), 1706, 1178, 1028, 731 cm^{-1} .

Synthesis of ethyl 7-(2-Oxocyclohexyl)hepta-2,3-dienoate 497

The ester **495** (98 mg, 0.392 mmol, 1 equiv.) was dissolved in 4 ml dry CH_2Cl_2 . NEt_3 (99 mg, 0.979 mmol, 2.5 equiv.) was added and the reaction mixture was stirred for 15 min. TBSOTf (155 mg, 0.587 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 2 h.

The reaction mixture was hydrolyzed with 2 ml 10 % HCl and stirred for 1 h. The aqueous phase was extracted 3×5 mL CH_2Cl_2 . The combined organic phases were washed with 6 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure **497** was obtained by column chromatography (PE/EtOAc 98:2 to 9:1).



Yield: 45 %
 colourless oil
 $C_{15}H_{22}O_3$
 MW 250.33 g/mol

1H -NMR (500 MHz, $CDCl_3$) δ 0.85 - 0.92 (m, 1H), 0.98 (t, $J = 7.1$ Hz, 3H, H_o), 0.94 - 1.04 (m, 1H), 1.06 - 1.18 (m, 2H), 1.19 - 1.30 (m, 2H), 1.30 - 1.49 (m, 2H), 1.50 - 1.59 (m, 1H), 1.61 - 1.70 (m, 1H), 1.75 - 1.93 (m, 3H), 2.02 - 2.08 (m, 1H), 2.16 - 2.23 (m, 1H), 4.02 (q, $J = 7.1$ Hz, 2H, H_n), 5.30 (qd, $J = 6.8, 2.5$ Hz, 1H H_j or i), 5.66 (dq, $J = 6.3, 3.0$ Hz, 1H H_j or i) ppm;

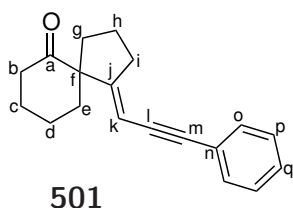
^{13}C -NMR(125 MHz, $CDCl_3$) δ 14.1 (C_o), 25.1, 25.1, 26.2, 26.8, 28.0, 29.2, 42.0 (C_b), 50.4 (C_f), 61.1 (C_n), 83.6 (C_l), 95.3 (C_j), 168.4 (C_m), 210.7 (C_a or k), 212.7 (C_a or k) ppm.

26.6. Synthesis of (*E*)-1-(3-Phenylprop-2-yn-1-ylidene)spiro[4.5]decan-6-one **501**

The TBS-enol **320** (206 mg, 0.740 mmol, 1 equiv.) was dissolved in 1.5 ml dry DCE. $AgNTf_2$ (14 mg, 0.037 mmol, 0.05 equiv.) and NIS (166 mg, 0.740 mmol, 1 equiv.) were added. The reaction mixture was stirred at room temperature for 18h. After concentration in vacuum (15 mbar) the resulting slime was dissolved in 5 mL dry THF. $PdCl_2(PPh_3)_2$ (104 mg, 0.148 mmol, 0.2 equiv.), CuI (6mg, 0.030 mmol, 0.04 equiv.), NEt_3 (748 mg, 7.397 mmol, 10 equiv.) and phenylacetylen (151 mg, 1.479 mmol, 2 equiv.) were added and the reaction mixture was stirred for 2 h.

The reaction mixture was hydrolyzed with 2 ml saturated aqueous solution of NH_4Cl . The aqueous phase was extracted 3 \times 5 mL Et_2O . The combined organic phases were washed with 6 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar).

The pure **501** was obtained by column chromatography (PE/ $EtOAc$ 98:2 to 95:5).



Yield: 58 %
 yellow oil
 $C_{19}H_{20}O$
 MW 264.36 g/mol

1H -NMR (500 MHz, $CDCl_3$) δ 0.85 - 0.92 (m, 1H), 0.98 (t, $J = 7.1$ Hz, 3H, H_o), 0.94 - 1.04 (m, 1H), 1.06 - 1.18 (m, 2H), 1.19 - 1.30 (m, 2H), 1.30 - 1.49 (m, 2H), 1.50 - 1.59 (m, 1H), 1.61 - 1.70 (m, 1H), 1.75 - 1.93 (m, 3H), 2.02 - 2.08 (m, 1H), 2.16 - 2.23 (m, 1H), 4.02 (q, $J = 7.1$ Hz, 2H, H_n), 5.30 (qd, $J = 6.8, 2.5$ Hz, 1H H_j or i), 5.66 (dq, $J = 6.3, 3.0$ Hz, 1H H_j or i) ppm;

^{13}C -NMR(125 MHz, $CDCl_3$) δ 22.4, 22.6, 27.0, 33.1, 38.5 (2C), 39.4, 61.7 (C_f), 87.6

(C_{l or m}), 94.1 (C_{l or m}), 103.4 (C_k), 124.0 (C_n), 127.9 (C_q), 128.4 (C_p), 131.4 (C_o), 161.6 (C_j, 211.8 (C_a) ppm.

Part V.
Appendices

A. Résumé en français

Réactivité des ω -céto-esters acétyléniques vis-à-vis de complexes de métaux de transition : application à la synthèse de squelettes carbonés originaux

Mon travail de thèse a consisté principalement en l'étude de la réactivité des ω -céto-esters acétyléniques vis à vis de complexe de métaux de transition.

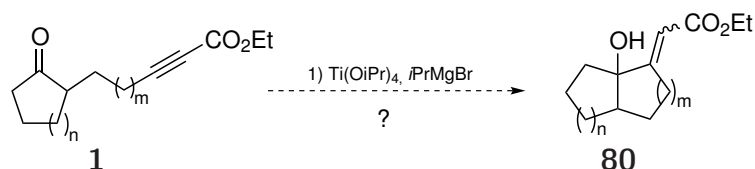
Dans une première partie, une réaction de carbométallation intramoléculaire en présence d'un complexe de titanacyclopropane a été entreprise au départ des ω -céto-esters acétyléniques. Il a été montré que cette réaction pouvait s'appliquer à divers substrats et une version asymétrique a été décrite. La lactonisation des hydroxy-esters bicycliques ainsi obtenus a ensuite été étudiée.

Dans une seconde partie, la réactivité d'alcynyl-cétone vis à vis de complexes d'or et d'argent a été explorée. Dans ce contexte, le bis-triflimidate d'argent s'est révélé être un catalyseur de choix pour effectuer des cycloisomérisations avec de bons rendements.

Enfin, la réactivité des espèces spiraniques issues de la catalyse à l'argent a été examinée, lors de réactions de couplage, en milieu basique, en présence de carbènes N-hétérocycliques et en organocatalyse.

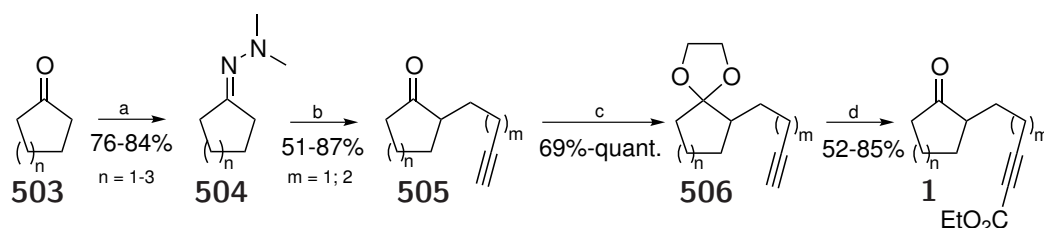
Réaction de carbométallation intramoléculaire au départ d' ω -cétoesters acétyléniques

Notre premier objectif a porté sur l'exploration de réactions de carbométallation intramoléculaire via des complexes de titane de basse valence au départ de cétones cycliques portant une chaîne ω -ynoate **1**. Cette stratégie s'appuie principalement sur la réaction de Kulinkovich.[222] La propension des titanacyclopropanes à subir des réactions d'échanges de ligands avec des oléfines,[31, 52] nous a incité à étudier leur réactivité vis à vis d' ω -cétoesters acétyléniques activés par des groupements électroattracteurs.



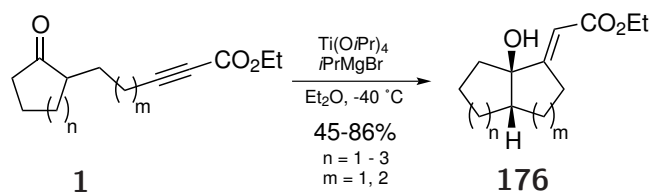
Scheme A.1: Synthèse proposée des composés **80**.

Dans ce but, et afin d'élargir le champ d'application de cette étude, une série d' ω -cétoesters acétyléniques comportant des cycloalcanones de tailles de cycle et de longueurs de chaînes variables ont tout d'abord été synthétisées.



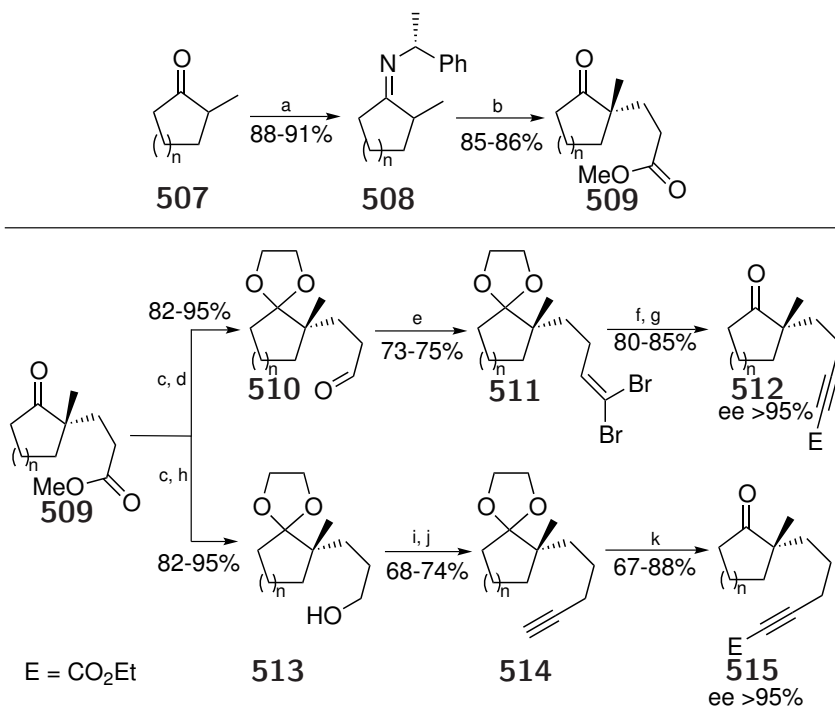
Scheme A.2: Synthèse des ω -cétoesters acétyléniques comportant des cycloalcanones de tailles de cycle et de longueurs de chaînes variables. a) Me_2NNH_2 , acide trifluoroacétique, benzène, reflux; b) $n\text{-BuLi}$, $\text{ICH}_2(\text{CH}_2)_m\text{CCH}$, THF, -30°C puis HCl 10 %, rt; c) éthylène glycol, APTS, benzène, reflux; d) $n\text{-BuLi}$, chloroformate d'éthyle, THF, -78°C , puis HCl 10 %.

Les cétones cycliques **1** portant une chaîne ynoate avec un bras espaceur de 2 et 3 atomes de carbones dérivant de la cyclopentanone, de la cyclohexanone et de la cycloheptanone ont été traités par le réactif de Sato, à savoir un mélange d'isopropoxyde de titane et de bromure d'isopropyle magnésium. Nous avons obtenu à l'issue de cette réaction les hydroxy esters bicycliques correspondants **176** avec une totale diastéréosélectivité.



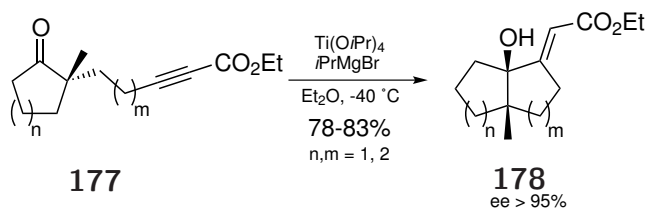
Scheme A.3: Réaction des ω -cétoesters acétyléniques **1** avec $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$.

Dans une deuxième temps, nous avons étendu cette réaction de carbométallation à des substrats de haute pureté énantiomérique (ee > 95 %). Pour ce faire, nous avons tout d'abord mis au point la synthèse des ω -ynoates de départ **512** et **515**.



Scheme A.4: Synthèse des ω -cétoesters acétyléniques énantiomériquement enrichis.a)
 (R)- α -Méthylebenzylamine, toluène, reflux; b) acrylate de méthyle, APTS, toluène, 40 °C; c) éthylène glycol, $n\text{-Bu}_4\text{Br}_3$, $\text{HC}(\text{OEt})_3$, rt; d) DIBAL-H, DCM, rt; e) CBr_4 , PPh_3 , NEt_3 , DCM, rt; f) $n\text{-BuLi}$, chloroformate d'éthyle, THF, -78 °C; g) HCl 10 %, THF, rt; h) LAH, THF, rt; i) TsCl , NEt_3 , DMAP, DCM, rt; j) lithium acetylide ethylene-diamine complex, DMSO, RT; k) $n\text{-BuLi}$, chloroformate d'éthyle, THF, -78 °C, puis HCl 10 %.

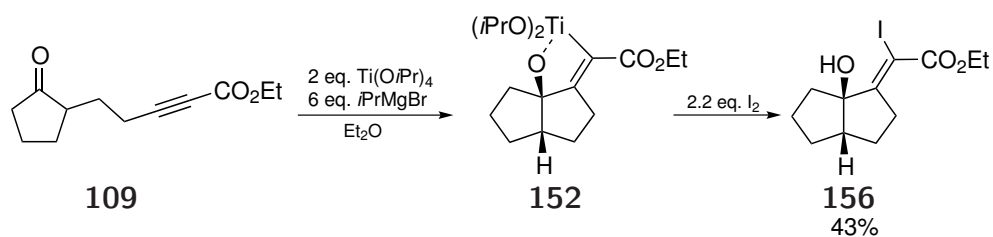
La cyclisation réductrice fonctionne très bien dans le cas des substrats énantiopurs **177** et les alcools allyliques correspondants **178** sont obtenus avec des rendements de l'ordre de 80 % et des excès énantiomériques supérieurs à 95 %.



Scheme A.5: Réaction des ω -cétoesters acétyléniques énantiomériquement enrichis **177** avec $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$.

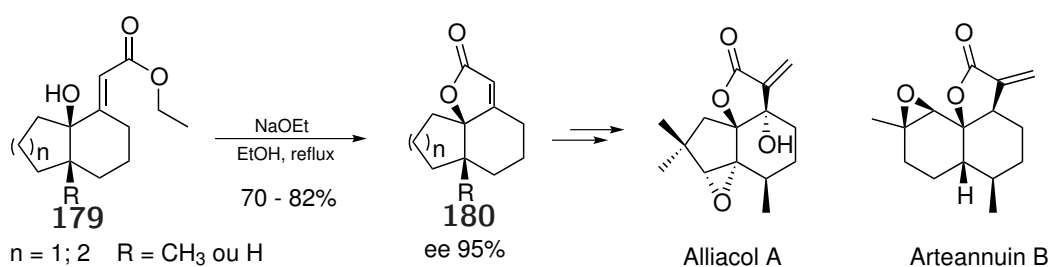
La structure des composés **178** obtenus a été prouvée par diffraction des rayons X.

Nous avons également synthétisé le composé α -iodé **156** en tenant compte de la possibilité de fonctionnaliser l'intermédiaire **152** avec de l'iode.



Scheme A.6: Formation du iodure vinylique **156** à partir de **109**.

Nous avons poursuivi ces travaux par la mise au point d'une réaction de lactonisation menant à des systèmes tricycliques **180** fort intéressants en vue de la synthèse de produits naturels comme par exemple l'Alliacol A ou l'Arteannuin B possédant respectivement des propriétés anticancéreuses et antipaludiques.



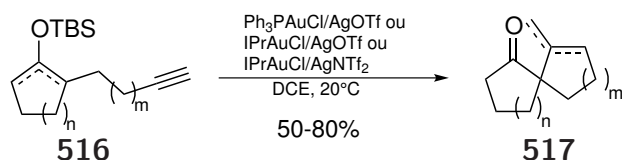
Scheme A.7: Réaction de lactonisation pour accéder à des systèmes tricycliques intéressants.

Réaction de cycloisomérisation d' ω -céto alcynes moyen de complexes d'Ag(I)

Après avoir exploré la réactivité des ω -cétoesters acétyléniques vis-à-vis de complexes de titane de basse valence, nous avons étudié leur comportement vis-à-vis d'autres métaux de transition, en particulier l'or et l'argent. Nous nous sommes tout d'abord intéressés aux espèces d'or au degré d'oxydation (I), étant donné leur capacité à activer de manière sélective des systèmes π tels que les alcynes.[125, 228]

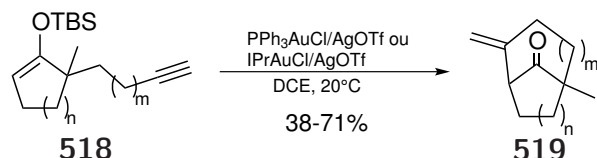
Ainsi, par analogie nous avons étudié la réaction de cycloisomérisation de nos ω -cétoesters acétyléniques avec des complexes d'or, tout d'abord au départ des alcynes vrais correspondants **516**.

De nombreuses cycloalcanones monocycliques, bicycliques, condensées à des cycles aromatiques ont été testées en présence de complexes d'Au(I) et de sels d'argents variés. De façon générale, les dérivés spiraniques correspondants **517** ont été obtenus avec des rendements allant de 50 à 80 %.



Scheme A.8: Réaction de cycloisomérisation des ω -cétoalcyne **516** avec différents catalyseurs d'or(I).

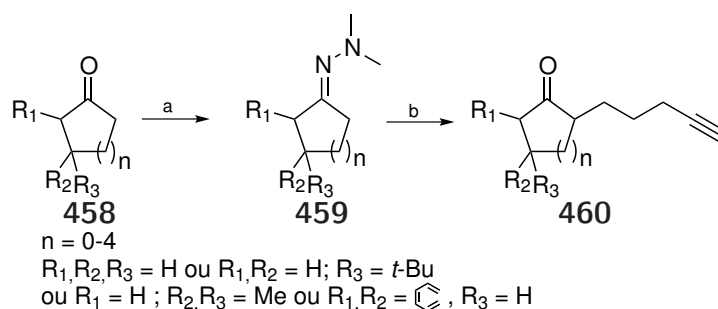
Lorsque la cycloalcanone est disubstituée en α (**518**), nous obtenons des composés pontés correspondants (**519**).



Scheme A.9: Réaction de cycloisomérisation des ω -cétoalcyne **518** avec différents catalyseurs d'or(I).

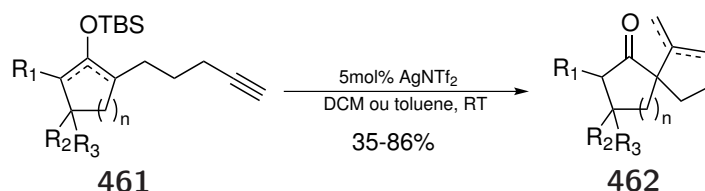
Toutefois, nous nous sommes rendus compte que l'utilisation de complexes d'Au(I) ne s'avérait pas indispensable à notre étude. En effet, nous avons montré que l'utilisation d'AgNTf₂ seule était suffisante pour effectuer nos cycloisomérisations de type 5-*exo*-dig sur nos substrats et que ce catalyseur simple d'utilisation et peu onéreux conduisait à d'excellents rendements en composés spiraniques.

Un large panel de substrats a ensuite été préparé pour montrer la versatilité de cette réaction de catalyse à l'argent.



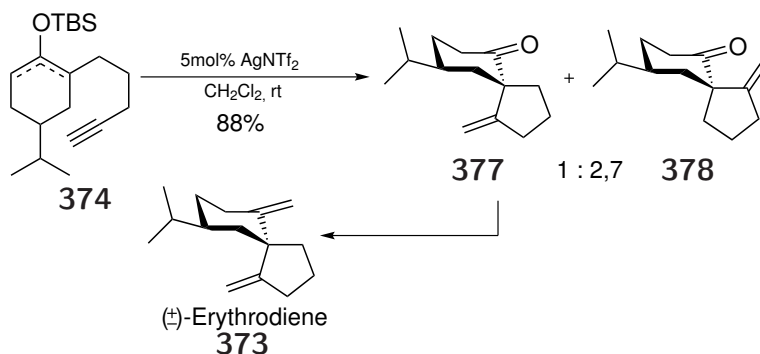
Scheme A.10: Synthèse des ω -cétoesters acétyléniques comportant des cycloalcanones de tailles de cycle et des substitutions variables. a) Me₂NNH₂, acide trifluoroacétique, benzène, reflux; b) *n*-BuLi, I(CH₂)₃CCH, THF, -30 °C puis HCl 10 %, rt.

Puis la réaction de cycloisomérisation a été optimisée et nous avons obtenu des rendements variant de 35 à 86 %, la sélectivité *exo* vs *endo* étant fonction du substrat mis en jeu.



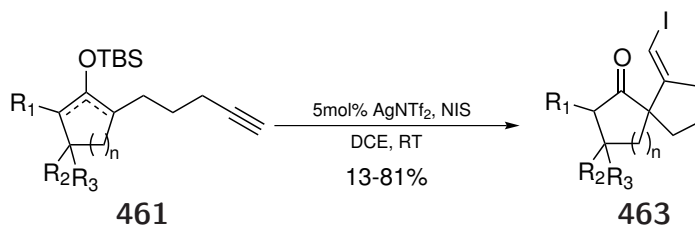
Scheme A.11: Réaction de cycloisomérisation des éthers d'enol **461** avec AgNTf_2 .

Une synthèse totale formelle de l'érythrodiène **373** utilisant cette nouvelle méthodologie a été également réalisé.



Scheme A.12: Synthèse formelle de (±)-Erythrodiène.

Dans le but de fonctionnaliser davantage les composés fournis au cours du processus de cycloisomérisation, nous avons tenté une fonctionnalisation « in situ » de la double liaison. Pour ce faire, nous avons traité nos substrats **461** avec un mélange 5 mol% AgNTf_2 en présence d'un équivalent de N-iodosuccinimide.

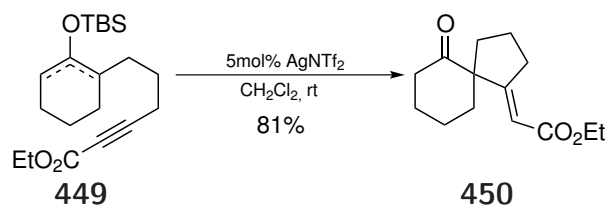


Scheme A.13: Synthèse des iodures vinyliques **463**.

Dans ces conditions nous avons pu synthétiser, les iodures vinyliques **463** correspondants avec de bons rendements. Les halo-alcènes spiraniques **463** ainsi obtenus constituent des intermédiaires de synthèse très intéressants pour la construction de squelettes carbonés originaux.

Par ailleurs, cette spirocyclisation catalysée par des sels d'argent est également compatible avec des acétyléniques activés. Ainsi par exemple, le traitement de l' ω -céto-esters acétylénique **449** par du bis-triflimidate d'argent nous a permis de synthétiser le composé spiranique fonctionnalisé **450** avec un rendement de 81 %. Ceci représente la

première synthèse sélective du composé **450**. Sa structure a été confirmée par diffraction des rayons X.



Scheme A.14: Synthèse des iodures vinyliques **463**.

Réactivité des dérivés spiraniques : accès à des squelettes carbonés originaux.

Un large panel de diterpènes bioactifs possède une architecture moléculaire comportant un carbone quaternaire issu d'un système spiranique. [194–198] Ainsi par exemple, un enchaînement 6-6-5 est présent dans la Colombiasin A, l'Elisabethin A et dans le Salvatriene B qui sont de nouveaux métabolites de plantes possédant d'intéressantes propriétés biologiques. D'un autre côté, les systèmes 6-5-5 se retrouvent dans l'Aberranone et les elisapteranes comme l'Elisapterosin B qui possède à la fois l'enchaînement 6-6-5 et 6-5-5.

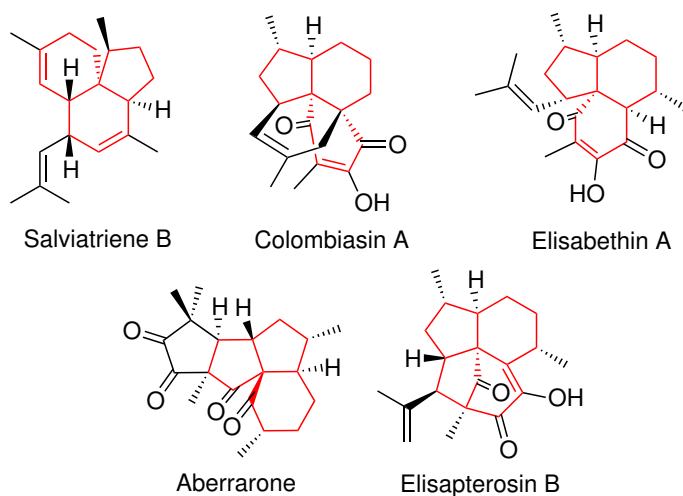
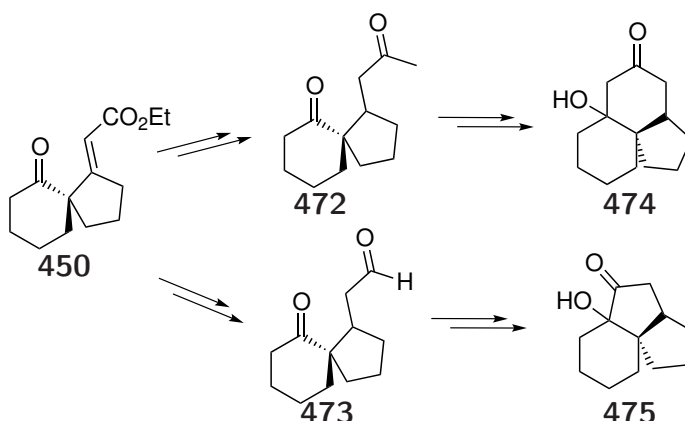


Figure A.1.: Structure de quelques produits naturels contenant des systèmes cycliques d'enchaînement 6-6-5- et 6-5-5.

Dans la troisième partie de notre travail, nous avons étudié la possibilité de modifier le spiro-ester fonctionnalisé **450** dans le but de construire des systèmes tricycliques existants dans ces composés naturels. Pour ce faire, deux approches ont été étudiées, l'une au départ de la méthyl-cétone spiranique **472** et l'autre au départ de l'aldéhyde spiranique **473**, ces substrats étant préparés au départ de l'ester spiranique **450**. Nous

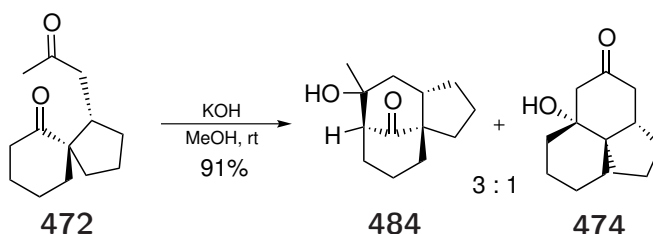
avons exploré la réactivité de ces deux composés en milieu basique, en présence de carbènes N-hétérocycliques ainsi qu'en organocatalyse.



Scheme A.15: Synthèse envisagée des composés tricyclique **474** et **475**.

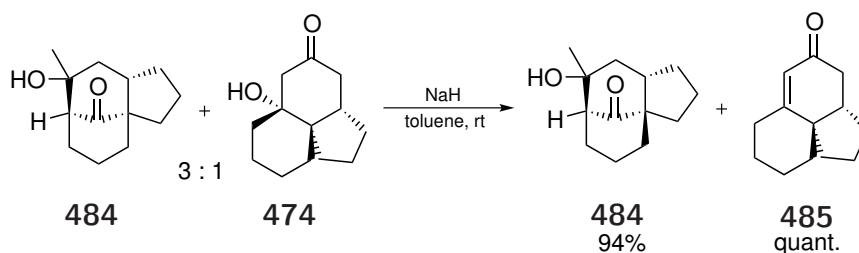
Au départ de la méthyl-cétone spiranique **472**

Au départ de la méthyl-cétone spiranique **472**, la stratégie consistait à effectuer une annélation de Robinson en milieu basique afin d'accéder au dérivé tricyclique **474** voulu. Nous obtenons à l'issue de cette réaction un mélange de céto-alcool ponté **484** accompagné du composé tricyclique **474** attendu mais de façon minoritaire (rapport 3/1).



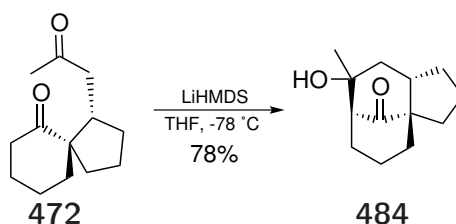
Scheme A.16: Réaction de la cétone **472** avec KOH/MeOH.

Cependant, une analyse par diffraction des RX nous a permis de confirmer la structure du dérivé tricyclique **474** et d'en déterminer ainsi sa configuration relative. La déshydratation du mélange (**474** et **484**) ainsi obtenu en présence d'hydruure de sodium a permis d'isoler la cétone tricyclique α,β insaturée **485**.



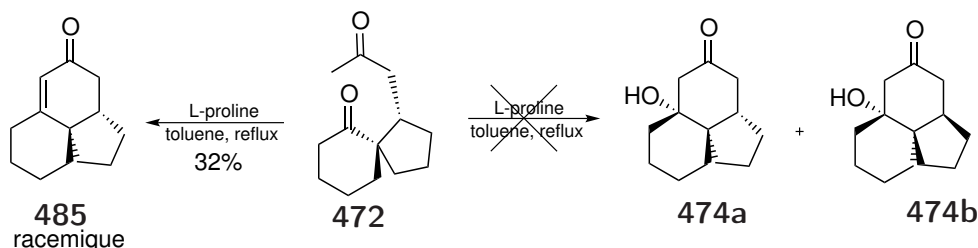
Scheme A.17: Réaction d'élimination pour former composé **485**.

Lorsque la méthyl-cétone **472** a été traitée par une base encombrée comme le LiHMDS, nous obtenons uniquement le céto-alcool ponté **484** avec un rendement de 78 %.



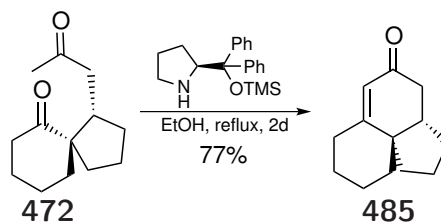
Scheme A.18: Réaction de la cétone **472** avec LiHMDS.

Dans le but d'accéder aux dérivés tricycliques énantiomériquement enrichis **474a** et **474b**, nous avons fait appel à une réaction organocatalysée par la L-proline.[212] Toutefois, dans ces conditions il ne nous a pas été possible d'isoler les céto-alcools tricycliques **474a** et **474b** optiquement purs correspondants mais uniquement un mélange racémique du dérivé tricyclique déshydraté **485**.



Scheme A.19: Réaction de la cétone **472** avec L-proline.

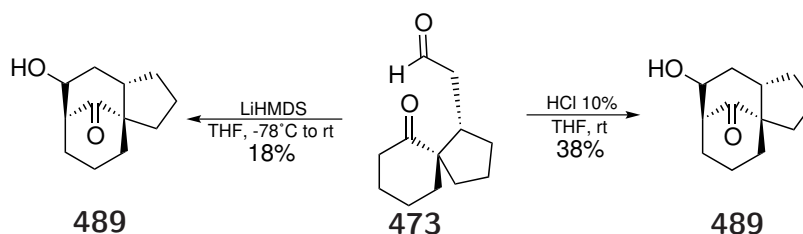
Il en est de même, lorsque cette réaction est effectuée en présence d'un catalyseur d'éther de diarylprolinol.[213] En revanche dans ce cas, le rendement observé a été plus que doublé.



Scheme A.20: Réaction de la cétone **472** avec l'éther silylé de diphénylprolinol comme organocatalyseur.

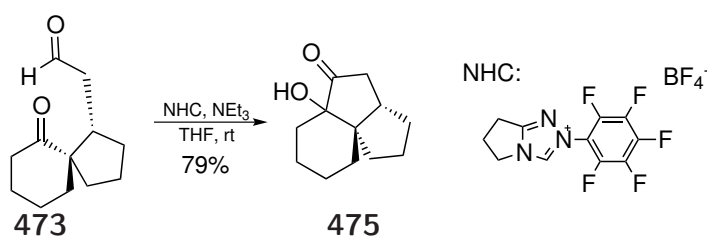
Au départ du spiro-aldéhyde **473**

L'étude de réactivité du spiro-aldéhyde **473** dans des conditions acides a montré que celui conduisait à la seule formation du dérivé ponté **489** accompagné de produits de dégradation. Dans des conditions basiques, le produit ponté **489** est également isolé avec un rendement plus modeste de 18 %.



Scheme A.21: Réaction de la l'aldéhyde **473** sous conditions acide et basique.

Toutefois, l'exploration de la réactivité de l'aldéhyde spiranique **473** en présence d'une quantité catalytique du carbène N-hétérocyclique,[204] s'est révélée plus fructueuse et a permis d'accéder au céto-alcool tricyclique **475** avec un rendement de 79 %.

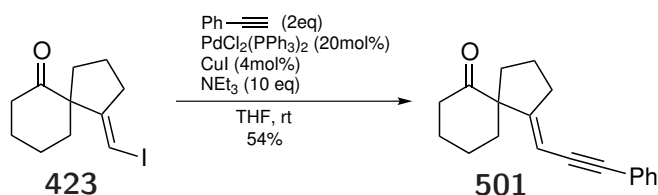


Scheme A.22: Réaction de la l'aldéhyde **473** avec un catalyseur du type NHC.

Réactivité des dérivés vinyl-iodés **463**.

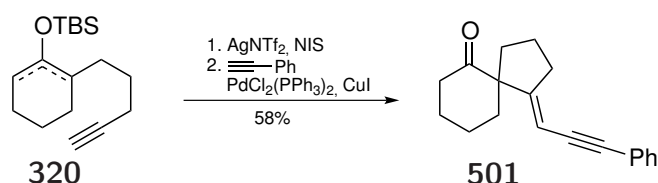
Nous avons également exploré la réactivité des dérivés vinyl-iodés préalablement synthétisés vis à vis d'un couplage pallado-catalysé de type Sonogashira. Ainsi, lorsque

le vinyl-iodé **423** est traité dans les conditions de Sonogashira en présence de phénylacétylène, nous obtenons le produit de couplage **501** avec un rendement de 54 %.



Scheme A.23: Réaction de Sonogashira du vinyl-iodé **423** et phénylacétylène.

Il a été également possible de réaliser cette synthèse en un seul pot au départ des énoxy-silanes **320**. Le dérivé ène-yne **501** est alors obtenu avec un rendement de 58 %.



Scheme A.24: Réaction de Sonogashira « one pot ».

Conclusion

Au départ d' ω -céto-ester acétyléniques, ce travail a permis d'accéder à des squelettes carbonés originaux, intermédiaires clés de produits naturels bioactifs.

Une cyclisation réductive intramoléculaire au départ d' ω -céto-ester acétylénique a conduit de façon diastéréoselective à des hydroxy-esters bicycliques, qui par traitement à l'éthanolate de sodium fournissent des lactones tricycliques insaturées. Ces derniers constituent des sous-structures très élaborées d'Alliacols.

La cycloisomérisation catalytique d'alcynyl-cétones en présence de bis-triflimidate d'argent permet d'accéder de manière efficace aux dérivés spiraniques correspondants. Le piégeage de l'espèce vinyl-argent généré lors de la réaction, avec le N-iodosuccinimide débouche sur la formation d'iodures vinyliques, intermédiaires clés pour la synthèse de produits naturels.

Enfin, l'étude de réactivité des dérivés spiraniques au départ de la spiro-cétone **472** ou du spiro-aldéhyde **473** a conduit à des squelettes carbonés originaux, notamment des sous-structures tricycliques d'elisabethanes et d'aberrarone présents dans les métabolites de plantes.

B. Communications and Publications

Oral communications

"Intramolecular Carbometalation of Acetylenic acetylenic ω -ketoesters mediated by low valent Titanium complexes"

10. 11. 2010, Journée des Doctorants en Chimie 2010
Université de Strasbourg

"Noble metal catalyzed cyclizations of ω -keto alkynes"

14. 05. 2012, Séminaire Jeunes Chercheurs,
Institut de Chimie, Université de Strasbourg

Poster communications

C. Schäfer, L. Miesch, M. Miesch,
Intramolecular Carbometalation of Acetylenic ω -ketoesters mediated by low valent Titanium complexes.

3rd EuChems Congress, Nürnberg, Germany, 29.08.2010 – 02.09.2010

Publications

C. Schäfer, M. Miesch, L. Miesch, Intramolecular reductive ketone-alkynoate coupling reaction promoted by (η^2 -propene)titanium, *Org. Biomol. Chem.* **2012**, *10*, 3253 – 3257.

C. Schäfer, M. Miesch, L. Miesch, A Silver-Catalyzed Spirocyclization of Alkynyl Silyl Enol Ethers, *Chem. Eur. J.* **2012**, *18* (26), 8028 – 8031.

Intramolecular reductive ketone–alkynoate coupling reaction promoted by (η^2 -propene)titanium†

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Intramolecular reductive coupling of cycloalkanones tethered to alkynoates in the presence of (η^2 -propene)titanium was successfully performed to provide hydroxy-esters in a diastereoselective manner. Subsequent lactonization afforded angularly fused unsaturated tricyclic lactones which represent relevant substructures of numerous bioactive compounds.

Introduction

Angularly fused 5-6-5 and 6-6-5 tricyclic fused lactones are relevant substructures for numerous bioactive compounds such as alliacolide,¹ alliacol A,² alliacol B³ and arteannuin B⁴ (Fig. 1).

The challenge associated with the synthesis of such tricyclic skeletons, combined with their pharmacological activities,³ has elicited considerable synthetic interest. As part of our studies of the reactivity of acetylenic ω -ketoesters,⁵ we planned an intramolecular ketone–alkynoate coupling reaction promoted by (η^2 -propene)Ti(O*i*Pr)₂ (Sato's reagent) for the construction of polycyclic skeletons (Scheme 1).

The generation of divalent dialkyltitanium complexes and their utilization in organic synthesis have attracted considerable interest over a number of years.⁶ Among these titanium complexes, the highly practical divalent (η^2 -propene)Ti(O*i*Pr)₂ reagent, was introduced as an equivalent of Ti(O*i*Pr)₂.⁷ Reactions of various acyclic alkynes with (η^2 -propene)Ti(O*i*Pr)₂ have been intensively investigated,^{6b,f,g,s} although the reaction with activated alkynes is less documented.⁹ Indeed to the best of our knowledge, only one preliminary study has been published by Sato *et al.* involving a titanium-mediated cyclization, starting from 2-en-7-ynoates for the preparation of bicyclic systems.¹⁰ Marek and coworkers reported an intramolecular cyclization, with a keto group at the γ - or δ -position affording four- and five-membered cycloalkanols.¹¹

Thus reaction of an alkyne with a titanium(II) species should generate (η^2 -alkynoate)Ti(O*i*Pr)₂ by ligand exchange of the coordinated propene in (η^2 -propene)Ti(O*i*Pr)₂. That is, *in situ*

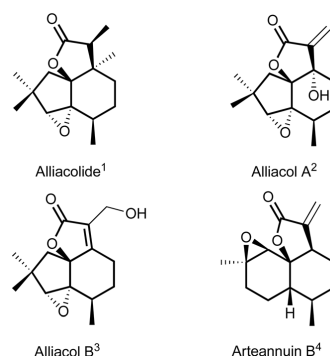
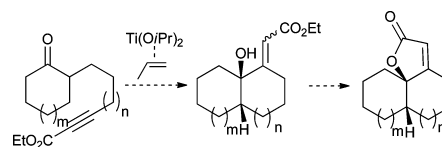


Fig. 1 Natural products containing tricyclic fused lactones.



Scheme 1

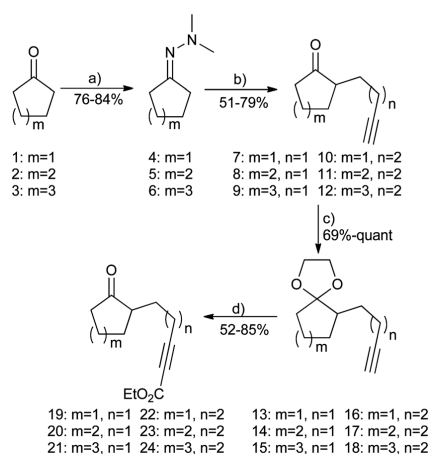
reductive coupling reaction of the carbonyl group with the alkynoate complex could proceed to provide an oxytitanacycle. The hydrolysis of the latter would afford a bicyclic compound that includes an allylic alcohol at the bridgehead carbon. Thus, we prepared various cycloalkanones bearing an ynoate side chain.

Results and discussion

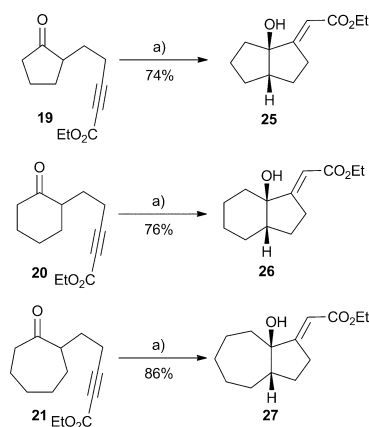
Acetylenic ω -ketoesters **19–24** were synthesized starting from the corresponding *N,N*-dimethylhydrazones according to our previously developed reaction sequence (Scheme 2).¹²

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization of compounds and crystallographic data. CCDC 784204–784206. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07049a



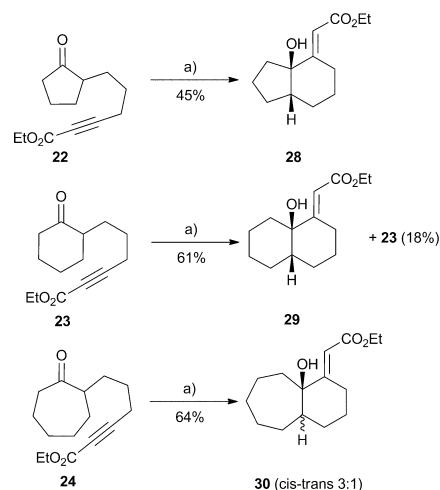
Scheme 2 Reagents and conditions: (a) H_2NNMe_2 , TFA, benzene, reflux; (b) (1) $n\text{BuLi}$, (2) $\text{I}(\text{CH}_2)_{n+1}\text{CCH}$, (3) 10% HCl, THF, -40°C to rt; (c) $\text{HOCH}_2\text{CH}_2\text{OH}$, PTSA, benzene, reflux; (d) (1) $n\text{BuLi}$, (2) ethyl chloroformate, (3) 10% HCl, -78°C to rt.



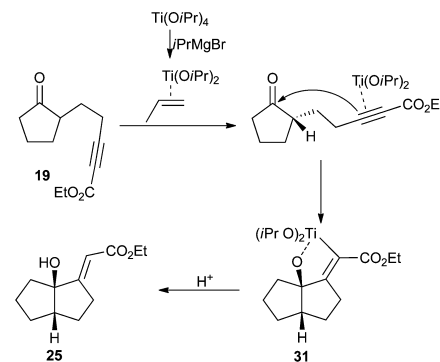
Scheme 3 Reagents and conditions: (a) 2 equiv. $\text{Ti}(\text{O}i\text{Pr})_4$, 6 equiv. $i\text{PrMgBr}$, Et_2O , -30°C , 2 h.

To examine the feasibility of our synthetic strategy, we first investigated the carbometallation reaction of cycloalkanones bearing 7-ynoates. Compounds **19–21** ($m = 1–3$, $n = 1$) were treated with $(\eta^2\text{-propene})\text{Ti}(\text{O}i\text{Pr})_2$, which was readily prepared by reacting $\text{Ti}(\text{O}i\text{Pr})_4$ with 2 equivalents of $i\text{PrMgBr}$. The reductive cyclization took place in a diastereoselective manner, providing exclusively *cis*-bicyclic ring systems bearing an *E*-substituted exocyclic electrophilic double bond (Scheme 3).

This reaction outlines an “umpolung” reaction of the ethoxy-carbonyl substituted alkynes, since the titanocyclopropene generated *in situ* creates a nucleophilic center β to the ester.¹³ Homologous 8-ynoates **22–24** underwent a similar *syn* selective



Scheme 4 Reagents and conditions: (a) 2 equiv. $\text{Ti}(\text{O}i\text{Pr})_4$, 6 equiv. $i\text{PrMgBr}$, Et_2O , -30°C , 2 h.



Scheme 5 Proposed mechanism.

cyclization to give bicyclic alcohols **28–30** in a stereoselective fashion in moderate to good yields (Scheme 4).¹⁴

Mechanistic investigations

A possible reaction mechanism of cyclization is shown in Scheme 5. First, coordination of the alkyne moiety of **19** to the titanium(IV) complex, followed by an intramolecular cyclization generates titanacycle **31** in a stereoselective fashion. Hydrolysis leads to the hydroxy *exo*-methylene ester compound **25**.

In order to probe the existence of a carbon–titanium bond as depicted in the oxatitanacycle **31**, iodine was added at the end of the reaction. The iodinolysis gave exclusively the *Z*-isomer of the corresponding alkenyl iodide **32** (Scheme 6).¹¹

Asymmetric version

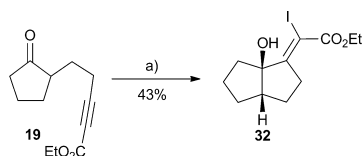
Because of the great importance of asymmetric synthesis and to broaden the scope of this cyclization, the optimal reaction conditions were extended to enantiomerically pure ynoates. Preparation of optically pure alkynoates **49** and **50** has already been described.¹⁵

The synthesis of compounds **43** and **44** was carried out as follows: after protection of the carbonyl group, of enantio-enriched ketoester derivatives **37** and **38**,¹⁵ the ester functions were reduced to aldehydes **39** and **40**. A modified Corey–Fuchs reaction involving the addition of ethyl chloroformate prior to aqueous work-up afforded acetylenic ω -keto esters **43** and **44** with good yields (Scheme 7).

Treatment of **43–44** and **49–50** with Sato's reagent provided various bicyclic compounds having two consecutive stereogenic centres including a tetrasubstituted carbon in a stereoselective fashion. The carbometallation reaction worked well and isolated yields were good (Scheme 8). The structure of compounds **53** and **54** were unambiguously confirmed by X-ray crystallographic analysis (Fig. 2) though providing evidence for the exclusive formation of *E*-alkenes.

Lactonization reactions

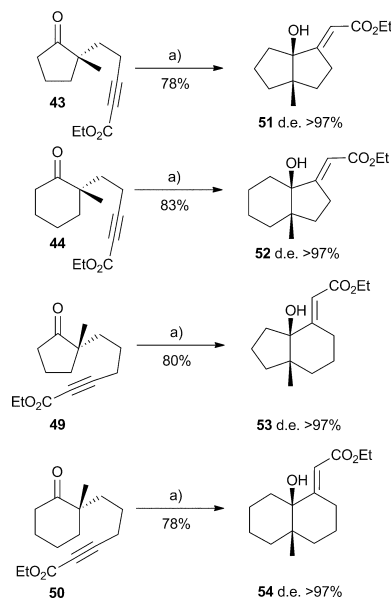
The bifunctional molecules obtained provided an opportunity to approach tricyclic unsaturated lactones. The lactonization



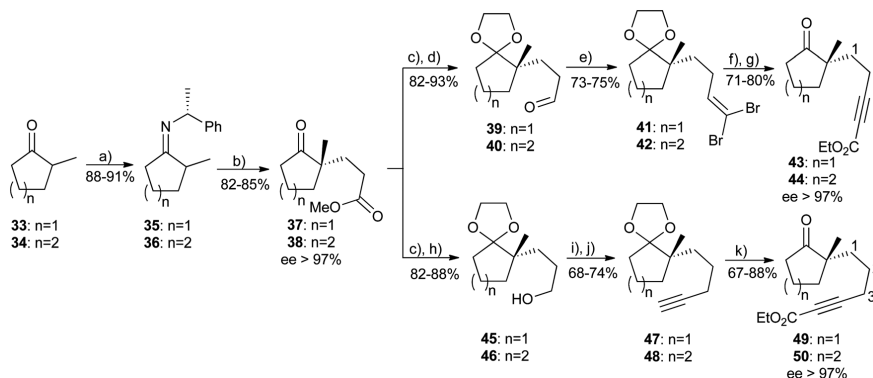
Scheme 6 Reagents and conditions: (a) (1) 2 equiv. $\text{Ti}(\text{O}i\text{Pr})_4$, 6 equiv. $i\text{PrMgBr}$, Et_2O , -30°C , 2 h, (2) I_2 , -78°C to 0°C , 25 min, (3) 1 N HCl.

reaction using sodium ethanolate in refluxing ethanol starting from bicyclic compounds (**25–27** and **51–52**) issued from ω -ketoesters bearing a two carbon tether remained fruitless. In contrast, bicyclic compounds (**28–29** and **53–54**) derived from a three carbon tether afforded the corresponding unsaturated lactones in high yields (Scheme 9).

Lactonization reactions were also performed with enantiomerically pure compounds affording the corresponding lactones in



Scheme 8 Reagents and conditions: (a) 2 equiv. $\text{Ti}(\text{O}i\text{Pr})_4$, 6 equiv. $i\text{PrMgBr}$, Et_2O , -30°C , 2 h.



Scheme 7 Reagents and conditions: (a) (*R*)- α -methylbenzylamine, toluene, reflux; (b) methyl acrylate, PTSA, toluene, 40°C ; (c) ethylene glycol, $n\text{Bu}_4\text{NBF}_4$, $\text{HC}(\text{OEt})_3$, rt; (d) DIBAL-H, DCM, rt; (e) CBr_4 , PPh_3 , NEt_3 , DCM, rt; (f) $n\text{BuLi}$, ethyl chloroformate, THF, -78°C ; (g) 10% HCl, THF, rt; (h) LAH, THF, rt; (i) TsCl , NEt_3 , DMAP, DCM, rt; (j) lithium acetylide–ethylenediamine complex, DMSO, 0°C to rt; (k) $n\text{BuLi}$, ethyl chloroformate, THF, -78°C to rt then 10% HCl, rt.

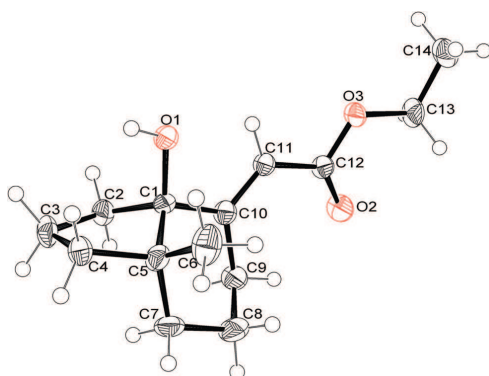


Fig. 2 ORTEP depiction of compounds **53** (top) and **54** (bottom) with thermal ellipsoids at the 50% probability level.¹⁶

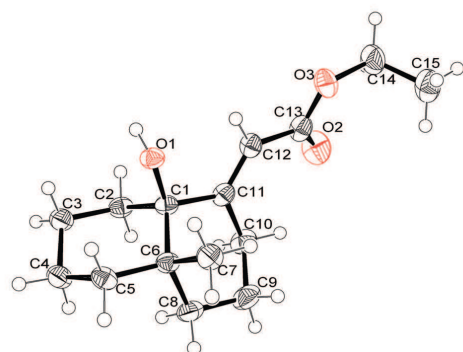
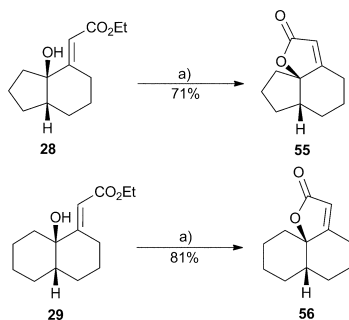


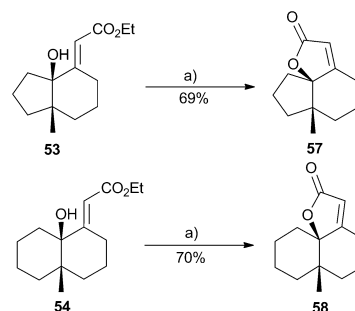
Fig. 2 ORTEP depiction of compounds **53** (top) and **54** (bottom) with thermal ellipsoids at the 50% probability level.¹⁶



Scheme 9 Lactonization reactions. Reagents and conditions: (a) 4 equiv. NaOEt, EtOH, reflux, 16 h.

good yields (Scheme 10). The structure of compound **58** was unambiguously confirmed by X-ray crystallographic analysis (Fig. 3).

Although the lactonization reaction was successful, the formation of the lactones stands in contrast with the stereochemistry



Scheme 10 Lactonization reactions: Asymmetric version. Reagents and conditions: (a) 4 equiv. NaOEt, EtOH, reflux, 16 h.

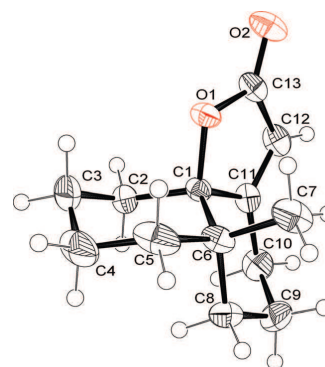


Fig. 3 ORTEP depiction of compound **58** with thermal ellipsoids at the 50% probability level.¹⁷

observed for the hydroxy-esters. Based on this precedence, we hypothesized a double bond isomerization prior to lactonization *via* a Michael retro-Michael addition of ethanolate on the allylic ester or the reversible formation of an epoxide by intramolecular Michael reaction.

Conclusions

In conclusion, (η^2 -propene)titanium promoted intramolecular reductive coupling reaction of cycloalkanones bearing activated alkynes provide bicyclic allylic alcohols in a stereoselective manner. This synthetically useful method was extended to various cycloalkanones bearing a 7-ynoate or 8-ynoate side chain. Although the lactonization reaction starting from m-5 bicyclic systems (compounds **25–27** and **51–52**) failed, unsaturated tricyclic lactones could be obtained starting from hydroxy-esters **28–29** and **53–54**. Thus the tricyclic compounds obtained are present in numerous bioactive natural products. Further studies on synthetic applications of this methodology are under investigation.

Experimental section

Typical procedure for the preparation of bicyclic γ -hydroxy α,β -unsaturated esters

The starting material (0.6 mmol, 1 equiv.) was dissolved in 10 mL of dry Et₂O and cooled to -30 °C. Ti(OiPr)₄ (1.2 mmol, 2 equiv.) was added under vigorous stirring. Then *i*PrMgBr (3.6 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred at -30 °C for 2 h, then hydrolysed with 10 mL of 10% HCl at -30 °C, warmed to rt and stirred for 30 min. The aqueous phase was extracted with 2 × 25 mL of Et₂O and 2 × 25 mL of EtOAc. The combined organic layers were consecutively washed with 25 mL of a saturated aqueous solution of NaHCO₃, 15 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar). The pure product was obtained by column chromatography (petroleum ether–EtOAc 95 : 5).

(E)-Ethyl-2-(4a*S*,8a*R*)-8a-hydroxy-4a-methyloctahydronaphthalen-1(2H)-ylidene)acetate 54. Yield: 78%; colourless oil; ¹H NMR (300 MHz, CDCl₃) δ 0.83 (s, 3H), 1.07–1.25 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.45–1.77 (m, 9H), 1.93–2.21 (m, 3H), 3.90 (d, *J* = 14.3 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 6.11 (d, *J* = 1.8 Hz, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 14.4, 21.0, 21.5, 22.3, 22.7, 26.6, 33.6, 34.0, 35.9, 39.7, 59.8, 77.4, 112.4, 166.3, 167.5 ppm; IR (neat) 3516, 2926, 2864, 1696, 1638 cm⁻¹; HRMS Cal for [M + Na]⁺: C₁₅H₂₄O₃; 275.1618 Found: 275.1611; [α]_D²⁰ = +39.24 (*c* = 0.576, CHCl₃).

Typical procedure for the preparation of tricyclic α,β -unsaturated lactons

A solution of sodium (4 equiv.) in dry EtOH (10 mL) was added to a solution of the bicyclic γ -hydroxy α,β -unsaturated esters (0.5 mmol, 1 equiv.) in 6 mL of dry EtOH. The resulting mixture was refluxed for 16 h. After cooling to rt the solvent was removed. The resulting slime was dissolved in 15 mL of Et₂O and treated with 8 mL of a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with 3 × 15 mL of Et₂O. The combined organic layers were washed with 20 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄ and concentrated in vacuum (15 mbar). The pure product was obtained by column chromatography (petroleum ether–EtOAc 95 : 5).

(6a*S*,10a*R*)-6a-Methyl-4,5,6,6a,7,8,9,10-octahydro-2H-naphtho[8a,1-b]furan-2-one 58. Yield: 70%; colourless solid; ¹H NMR (300 MHz, C₆D₆) δ 0.61 (s, 3H), 0.84–1.27 (m, 6H), 1.28–1.43 (m, 4H), 1.43–1.69 (m, 3H), 1.93 (dd, *J* = 13.9, 4.6, 1.8 Hz, 1H), 5.35 (d, *J* = 2.0 Hz, 1H) ppm; ¹³C NMR (75 MHz, C₆D₆) δ 20.8, 21.2, 22.2, 22.6, 25.9, 30.2, 32.3, 36.5, 39.6, 88.6, 113.4, 172.0, 172.7 ppm; IR (neat) 2927, 2864, 1731, 1235 cm⁻¹; HRMS Cal for [M + Na]⁺: C₁₃H₁₈O₂; 229.1199 Found: 229.1205; [α]_D²⁰ = -40.17 (*c* = 0.605, CHCl₃).

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- 17 CCDC-784205 contains the supplementary crystallographic data for compound **58**.

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A Silver-Catalyzed Spirocyclization of Alkynyl Silyl Enol Ethers

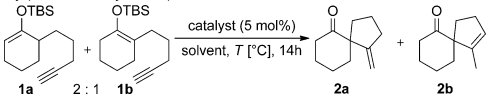
Christian Schäfer, Michel Miesch, and Laurence Miesch^{*,[a]}

Spiro compounds are of great interest because of their special conformational features and their structural implications on biological systems.^[1] The presence of the sterically constrained spiro structure in various natural products substantially promotes interest in the investigation of spiro compounds.^[2] The Conia-ene cyclization is one of the processes during which a quaternary center is formed by the pericyclic reaction of an enolizable carbonyl group with an alkyne. However, the need for high temperatures limits the synthetic utility of this reaction.^[3] On the other hand, transition-metal-catalyzed versions^[4] proceed under mild conditions at lower temperatures. Toste and co-workers have reported a phosphine-gold(I)-catalyzed version for the intramolecular addition of a β -ketoester to an unactivated alkyne.^[5] In a similar reaction, Davies and Dettly-Mambo demonstrated the cycloisomerization of unactivated ketones with alkynes under gold catalysis.^[6] In recent years, silver salts have gained increasing interest in homogeneous catalysis owing to their mildness and efficiency.^[7] More recent reviews discuss the current revolution in silver chemistry. Catalysis with silver salts has become widespread due to the σ and π Lewis acidic properties of silver(I) complexes,^[8] which lead to a variety of chemical transformations.^[9] Therefore, exploring new catalytic reactions with silver complexes is of great interest. For this reason, we focused on silver-catalyzed cycloisomerization to study the behavior of alkynyl silyl enol ethers.

Mainly used as cocatalysts in gold catalysis, silver salts, such as AgBF_4 , AgSbF_6 , and AgPF_6 , are very hygroscopic, causing difficulties in properly weighing the reagent and keeping the reaction medium nonacidic. In contrast, AgNTf_2 ($\text{Tf} = \text{triflyl}$)^[10] is known to be more stable and easier to handle than its congeners. Thus, this reagent proved to be an efficient catalyst for nucleophilic additions to alkynes.^[11] For this purpose, we envisaged the use of AgNTf_2 as a potentially valuable candidate for the cycloisomerization of silyl alkynyl enol ethers.

We began our investigation by examining the cyclization using various silver catalysts with different solvents for the reaction of compound **1** (Table 1). Interestingly, the use of AgNTf_2 alone led to spiro compounds **2a** and **2b** with the

Table 1. Screening of solvents and catalysts (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene).



Entry	Catalyst	Solvent	T [°C]	Yield [%] ^[b]	2a/2b
1	IPrAuCl/AgOTf	$\text{ClCH}_2\text{CH}_2\text{Cl}$	84	12 (63)	100:0
2	IPrAuCl/AgNTf ₂	$\text{ClCH}_2\text{CH}_2\text{Cl}$	84	66	2.5:1
3	AgNTf_2	$\text{ClCH}_2\text{CH}_2\text{Cl}$	20	67	17:1
4	AgNTf_2	CH_2Cl_2	20	78	16:1
5	AgNTf_2	THF	20	41 (40)	20:1
6	AgNTf_2	acetone	20	– ^[c]	–
7	AgNTf_2	toluene	20	76	9:1
8	AgNTf_2	CH_3CN	82	7 (65)	1:5
9	AgNTf_2	$\text{ClCH}_2\text{CH}_2\text{Cl}/\text{MeOH}$	20	– ^[c]	–
10	AgNTf_2	toluene ^[d]	20	56 (12)	1:38
11	AgNTf_2	$\text{ClCH}_2\text{CH}_2\text{Cl}$	20	– ^[c]	–
12	Ag_2CO_3	$\text{ClCH}_2\text{CH}_2\text{Cl}$	20	– ^[c]	–
13	–	$\text{ClCH}_2\text{CH}_2\text{Cl}$	20	– ^[d]	–

[a] Toluene was not distilled before use. [b] Yields in parentheses correspond to the deprotected starting material. [c] Only deprotection of the starting material occurred. [d] The starting material was recovered.

same yield as that observed under gold catalysis (Table 1, entry 3). Furthermore, the yield could be improved by using CH_2Cl_2 or toluene as the solvent (Table 1, entries 4 and 7). Control experiments revealed that silver carbonate or the corresponding free amine, that is, triflimide, could not catalyze the reaction of silyl alkynyl enol ethers to form spiro compounds, and no reaction occurred under metal-free conditions. Likewise, the unsilylated ketones could not be transformed into the spiro compounds.

Having found that Ag^I -catalyzed cycloisomerization favors the 5-*exo*-dig cyclization process, we evaluated the scope of the reaction by using various alkynyl cycloalkanes. The reaction proved to be quite general, although the yield is dependent upon both the substrate and the solvent (Table 2, entries 1, 2, 13–16, and 19). Interestingly, in most cases that use CH_2Cl_2 as the solvent, the *exo* regioisomer is favored, except for entries 6, 18, and 22 in Table 2, whereas the *endo* compound is obtained in toluene except for cyclo-

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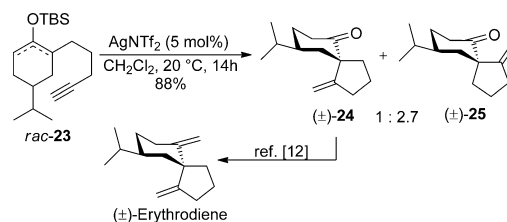
Supporting information for this article is available on the WWW
under <http://dx.doi.org/10.1002/chem.201200116>.

Table 2. Ag^I-catalyzed spirocyclization.

Entry ^[a]	Substrate	Solvent	Product	Yield [%] ^[a]	a/b
1		toluene		47	100:0
2		CH ₂ Cl ₂		35	5:1
3		toluene		76	9:1
4		CH ₂ Cl ₂		78	16:1
5		toluene		74	1:9 ^[b]
6		CH ₂ Cl ₂		62	0:100
7		toluene		48 (4)	1:2 ^[b]
8		CH ₂ Cl ₂		58 (9)	2:1 ^[b]
9		toluene		64 (12)	0:100
10		CH ₂ Cl ₂		71 (15)	100:0
11		toluene		72	1:25 ^[c]
12		CH ₂ Cl ₂		83	28 ^[c] :1
13		toluene		trace	1:2
14		CH ₂ Cl ₂		trace	100:0
15		toluene		0 (31)	–
16		CH ₂ Cl ₂		13 (59)	100:0
17		toluene		74	0:100
18		CH ₂ Cl ₂		75	1:7
19		toluene		25 (25)	1:3
20		CH ₂ Cl ₂		59 (23)	100:0
21		toluene		74 (10)	0:100
22		CH ₂ Cl ₂		49 (35)	0:100

[a] Yields in parentheses correspond to the deprotected starting material.
[b] The product of a 6-*endo* cyclization reaction is obtained instead of the 5-*exo* product. [c] Obtained as a mixture of diastereoisomers.

pentanone and cyclohexanone derivatives (Table 2, entries 1 and 3) for which the *exo* regioisomer is always the major product. Silyl alkyne enol ethers derived from larger rings furnished 6-*endo*-dig cyclization products (Table 2, entries 5, 7, 8).



Scheme 1. The formal total synthesis of (±)-erythrodiene (TBS=tert-butyl(dimethylsilyl)).

In this way, by starting from compound **23**, a mixture of spiroketones **24** and **25** was obtained (Scheme 1), the first of which was elaborated into spirobicyclic sesquiterpene (±)-erythrodiene by Huang and Forsyth.^[12]

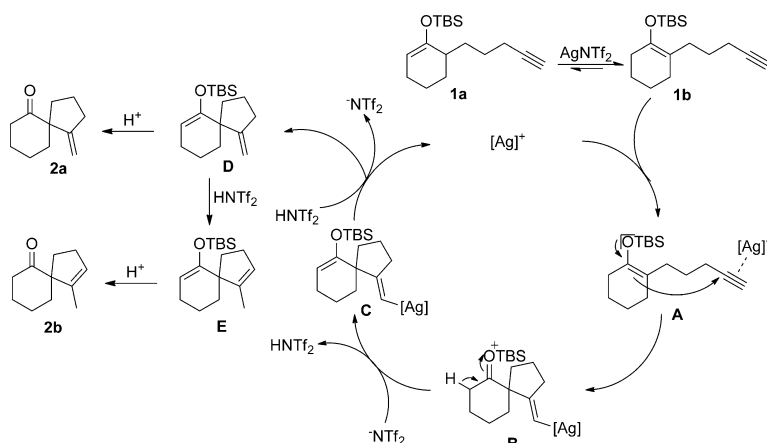
A tentative mechanism for this Ag-catalyzed cycloisomerization reaction is outlined in Scheme 2. Based on the fact that alkyne silyl enol ethers **1a** and **1b** are present as a 2:1 mixture, it seems that under silver catalysis isomerization from **1a** to **1b** takes place.^[13] Complexation of the silver salt to the alkyne moiety would initiate this process. After the complexation step, intermediate **A** could undergo an enyne cycloisomerization assisted by the alkyne activation^[14] and the presence of the oxygen atom to yield the intermediate silver complex **B**. Then, proton migration would give product **C**. Subsequent protonolysis of the alkenyl–silver species and hydrolysis of the silyl enol ether would afford either the 5-*exo*-dig isomer **2a**^[15] or further isomerization of *exo*-silyl enol ether **D** in the presence of HNTf₂ would lead (via **E**) to the *endo* product **2b**. The isomerization step has been proven by the treatment of **20a** with HNTf₂, which gave compound **20b** in 97% yield (Scheme 3).^[16]

To further highlight the potential of this new silver-catalyzed spirocyclization, we attempted to trap the newly formed alkenyl–silver intermediate prior to protonation with a source of electrophilic iodine.^[17] This type of transformation would be of high synthetic interest because it would lead to alkenyl iodides.^[18]

Thus, alkyne silyl enol ethers were treated in a one-pot reaction with AgNTf₂ (5 mol%), directly followed by addition of *N*-iodosuccinimide (NIS) in ClCH₂CH₂Cl, which provided exclusively the *E*-alkenyl iodide derivatives in good yields (Table 3).^[19] It should be noted that in this case no 6-*endo* compounds were isolated and the reaction of **1** with NIS alone led exclusively to the α -halogenated derivative of the desilylated starting material.^[16]

Although the silver-catalyzed cycloisomerization of bicyclo[3.2.0]alkanone **13** proved to be difficult, iodo-demetalation makes it possible to obtain alkenyl iodide derivative **31**. The X-ray crystal structure of tricyclic alkenyl iodide **31** (Figure 1) showed an *E*-configured *exo* double bond, thus, providing evidence for the iodo-demetalation of intermediate **C** with the NIS reagent.^[17]

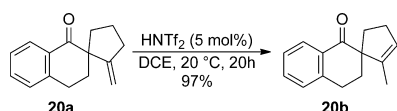
In light of this result, we considered the possibility that a similar silver-catalyzed pathway could account for activated alkynes. To our delight, subjecting alkyne **35** to the



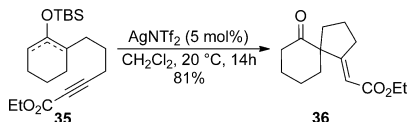
Scheme 2. Mechanistic proposal for the AgNTf_2 -mediated cyclization reactions.

silver-catalyzed cycloisomerization conditions afforded spiroester **36** in 81% yield (Scheme 4).

In summary, a silver(I)-catalyzed intramolecular addition reaction of silyl enol ethers to alkynes has been developed. The reaction allows the diastereoselective synthesis of a vari-



Scheme 3. Isomerization of compound **20a** into **20b** (DCE=dichloroethene).



Scheme 4. Spirocyclization of silyl enol ether **35**.

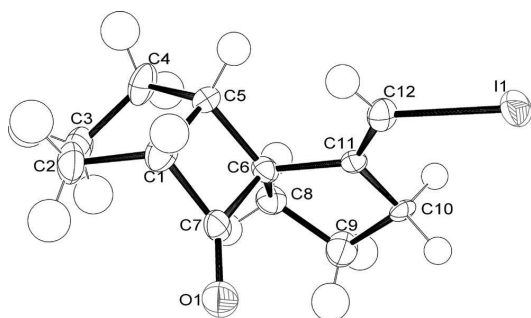


Figure 1. ORTEP diagram of tricyclic alkenyl iodide **31** with thermal ellipsoids at the 50% probability level.^[20]

ety of spiro compounds. Taken together, the silver catalysis and iodo trapping provides alkenyl iodides that are valuable synthons in organic synthesis and allows further functionalization by using Pd-catalyzed cross-coupling chemistry. Reactions with more complex substrates, as well as asymmetric versions of this reaction, are currently under investigation in our laboratory.

Table 3. Ag-catalyzed formation of alkenyl iodides.

Entry	Substrate	Product	Yield [%]
1			13
2			68
3			67
4			81
5			79
6			54
7			80
8			78
9			73

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Keywords: homogeneous catalysis • silver • spiro compounds • vinyl compounds

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Réactivité des ω -céto-esters acétyléniques vis-à-vis de complexes de métaux de transition: application à la synthèse de squelettes carbonés originaux.

Abstract:

In this work, the reactivity of acetylenic ω -ketoesters towards different metal complexes was investigated.

When acetylenic ω -ketoesters are submitted to $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$, the formation of fused bicyclic γ -hydroxy- α,β -unsaturated esters was observed. The products were obtained with absolute selectivity in regard to the ring junction formed (*cis*) and the configuration of the double bond (*E*) and could be transformed into the corresponding α,β -unsaturated lactones, substructures of various natural products.

When ω -ketoalkynes are used in $\text{Ag}(\text{I})$ -catalyzed cycloisomerization reactions, the formation of spirocyclic compounds was observed. By taking advantage of the reaction intermediates of this reaction, it was possible to isolate the corresponding spirocyclic alkenyl iodides. Performing cycloisomerization reactions with acetylenic ω -ketoesters, spirocyclic α,β -unsaturated esters are formed.

We could show that these products are valuable substrates for the formation of 6-5-5- and 6-6-5-fused tricyclic systems which represent the skeleton of a large group of natural products.

Résumé:

Les travaux décrits dans ce mémoire ont pour objet l'étude de la réactivité des ω -céto-esters acétyléniques vis-à-vis des métaux de transition. Lorsque ces composés sont traités avec un mélange $\text{Ti}(\text{O}i\text{Pr})_4/i\text{PrMgBr}$, la formation d'alcools allyliques bicycliques est observée avec une totale diastéréosélectivité par rapport à la jonction de cycle (*cis*) et une configuration (*E*) pour la double liaison. Il a été montré que ces produits peuvent être transformés en lactone α,β -insaturé, sous-structures de produits naturels.

La cycloisomérisation d'alcyne cétones catalysées par des sels d' $\text{Ag}(\text{I})$ conduit à la formation de composés spiraniques. En piégeant l'intermédiaire réactionnel, la synthèse des composés vinyl-iodés correspondants a été réalisée. Si la réaction de cycloisomérisation est effectuée avec des ω -céto-esters acétyléniques, des ester α,β -insaturés sont isolés. Les produits obtenus ont ensuite été utilisés comme substrats pour la formation de systèmes tricycliques 6-5-5 et 6-6-5. Ces enchaînements de cycles sont présents dans le squelette carboné d'une grande variété de produits naturels.