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Synthesis of thioenol ether functionalized cyclooctyne and its orthogonal cycloaddition sequence

Tesi di laurea sperimentale

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Abstract

In this work, the synthesis of a new bifunctionalized cyclooctyne for a possible layer by layer surface functionalization is presented. The main objective is to find a more stable molecule than the literature known methyl enol ether substituted cyclooctyne. Accordingly, the two target functionalities are an internal alkyne group and a vinyl methyl sulfide group. The synthesis was achieved in 9 steps and consists first of all in the preparation of an aldehyde starting from 1,5-cyclooctadiene with a cyclopropanation reaction followed by a reduction and the SWERN oxidation to an aldehyde. The new functionality was introduced by exploiting the WITTIG reaction. For the alkyne group a bromination followed by a double elimination gave good results. The reactivity of the new molecule was tested using a sequential application of SPAAC and iEDDA reactions, comparing it with the cyclooctyne functionalized with a methyl enol ether. Concerning the comparison of both compounds the sulfur ether is significantly slower and therefore more stable. It will be tested in the future for surface functionalization from the KOERT group.

Summary

1 Introduction

1.1 Diels-Alder Cycloadditions

Since its discovery by Professor OTTO DIELS and his student KURT ALDER in 1928[1] the DIELS-ALDER cycloaddition has become a pillar in modern organic synthesis. The reactions are one of the most efficient methods in organic synthesis to form multiple bonds simultaneously. The importance of this reaction was recognised by the Nobel Prize in 1950.[2] Its popularity is given by its simplicity, short reaction time, usually additive free conditions and it gives the possibility to form heterocycles. Therefore, they are often used for the synthesis of natural products and biologically active molecules.[3]

The DIELS-ALDER [4+2]-cycloaddition occurs between a conjugated diene (e.g. 1,2,4,5-tetrazines) and a dienophile (alkene or alkyne) to form a six membered ring by the interaction of 4π-electrons of the diene and the 2π-electrons of the dienophile.[4] The interaction is governed by the energy gap between the HOMO and LUMO of the reactants. In particular, a pair of diene/dienophile with a small energy gap has a good overlap of the two orbitals in the transition state so the reaction goes faster. The presence, on the reagents, of electron-withdrawing (EWG) groups lowers both HOMO and LUMO energy, whereas electron-donating groups (EDG) raise both orbitals energy. So, by tuning the cycloaddends with different functional groups it is possible to manipulate the HOMO-LUMO energy gap and consequently reactivity.[4] In a normal electron demand DIELS-ALDER reaction an electron-rich diene with a high energy HOMO reacts with an electron-poor dienophile with a low energy LUMO.

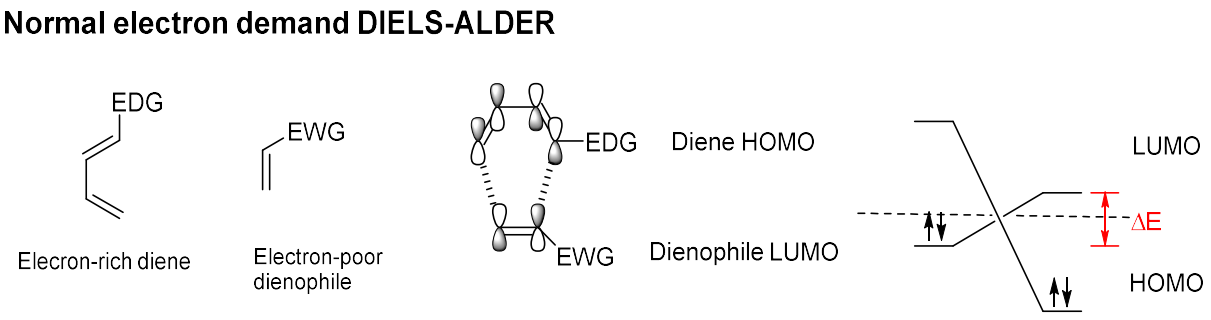


Fig. 1: Normal electron demand DIELS-ALDER orbital interactions.

Steric effects must also be considered, the diene must be able to take up the s-*cis* conformation, in order to have right spatial arrangement of the atoms to overlap its orbitals with the dienophile, for the formation of the ring.[5] In addition sterically demanding substituents raise the distortion energy in the transition state and a high degree of strain reduces the activation energy, making reactions faster.[6]

In contrast, in an inverse electron demand DIELS-ALDER reaction (iEDDA) an electron-rich dienophile reacts with an electron-poor diene, the interaction is $HOMO_{dienophile}$-$LUMO_{diene}$.

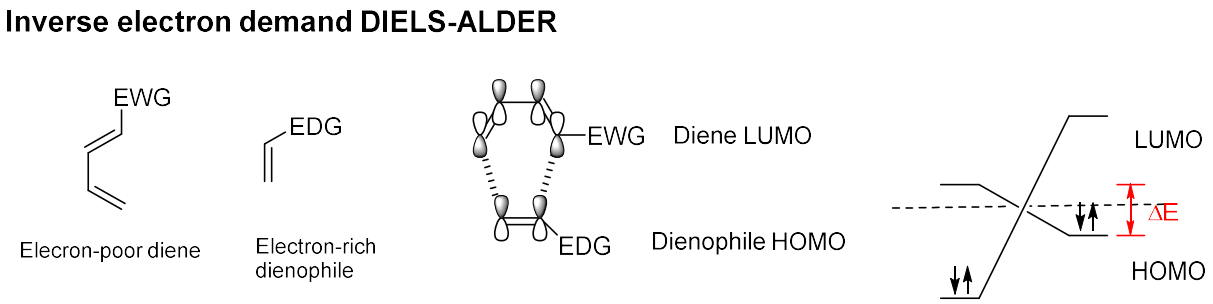
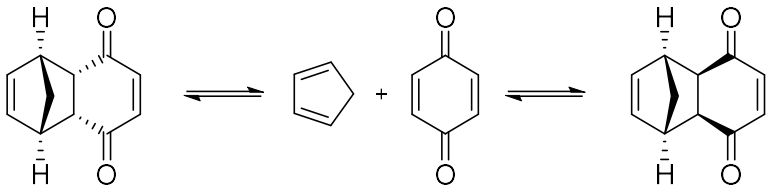


Fig. 2: Inverse electron demand DIELS-ALDER orbital interactions.

Like in the normal DIELS-ALDER reaction the selectivity of iEDDA follows that the *endo* product is always the favoured over the *exo*, even if it is the more sterically hindered because the EWG and EDG group are on the same side of the new six membered ring.[7]



3-endo **1** **2** ***3-exo***

Scheme 1: *Endo* and *exo* products of normal DA cycloaddition.

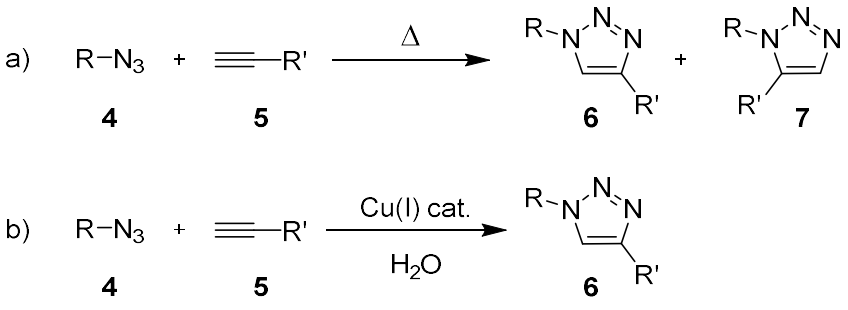
This happens because in the *endo* transition state the electron donating group is positioned over the diene so an interaction between π orbitals of diene and dienophile take place which lower the energy of this particular transition state.[5] In DIELS-ALDER reactions the *endo* product is the kinetic product while the *exo* is the thermodynamic

one. At high temperatures, the products are in equilibrium with its starting materials so the *exo* product tends to be the major one.

These reactions feature a tolerance of a diverse range of functional groups and it is a powerful and atom-economical tool for the stereoselective construction of functionalized five and six membered rings (triazoles, diazines).[8]

1.2 Click chemistry

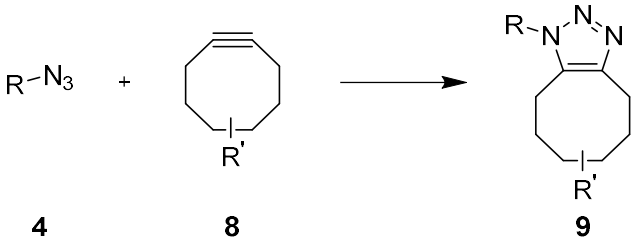
After the introduction by SHARPLESS *et al.* in 2001[9] of the concepts of "click chemistry" inverse electron demand DIELS-ALDER reactions have gained importance in the last years. "Click chemistry" is a term used to describe reactions that combine high yield, mild reaction conditions, rapid conversion, high selectivity and functional group tolerance.[10] Additionally, click chemistry occurs in one pot and allow easy isolation of the desired products without using complicated separations methods.[11] The iEEDA reactions have been used in a variety of processes in both material science (synthesis of polymers, nanoparticles, hydrogels) and biomedical applications (drug synthesis, biolabeling, imaging) thanks to their bioorthogonal chemistry.[10] Bioorthogonal chemistry uses chemical transformations that can occur in presence of all type of biomolecules and even living cells, between two reactive groups that react only with themselves[12], that implies in an aqueous media and fast reaction rates at ~37 °C. Of all the bioorthogonal click reaction the most widely applied is the Cu(I)-catalysed [3+2] azido-alkyne cycloaddition (CuAAC) between an azide and an alkyne that selectively gives 1,2,3-triazoles.



Scheme 2: Alkyne-azide cycloadditions: a) Non-catalyzed termal cycloaddition (Huisgen reaction); b) Copper catalyzed cycloaddition (CuAAC).

The non catalized [3+2] cycloaddition between azide and alkyne, first reported by A. MICHAEL in 1893[12] was then studied and developed by HUISGEN in the middle of the 20th century[13], henceforth the reaction is known as HUISGEN reaction. It gives both 1,4- and 1,5- substituted products (**6**, **7**) and despite the formation of the triazole ring, the lack of regioselectivity and the need of elevated temperatures (>100 °C) and pressure, limited its utility.[14] The copper-catalyzed version gives only the 1,4-isomer furthermore it occurs in a variety of solvents, wide temperature range and pH values.[14] However, the wide use of CuAAC chemistry has been hindered by the potential toxicity induced by copper catalyst even at low concentration levels. The necessity of it displays a major limitation for applications in living systems, one of the major area of applications of the reaction.

To bypass this issue, a strain promoted azide-alkyne cycloaddition (SPAAC) was developed by BERTOZZI and coworkers in 2004.[15] This cycloaddition proceeds, with mild reaction conditions, in absence of a catalyst due to the high degree of ring strain on the cyclooctyne ring **5**. The absence of metal catalysts makes these reactions suitable for *in vivo* applications of biorthogonal click chemistry.



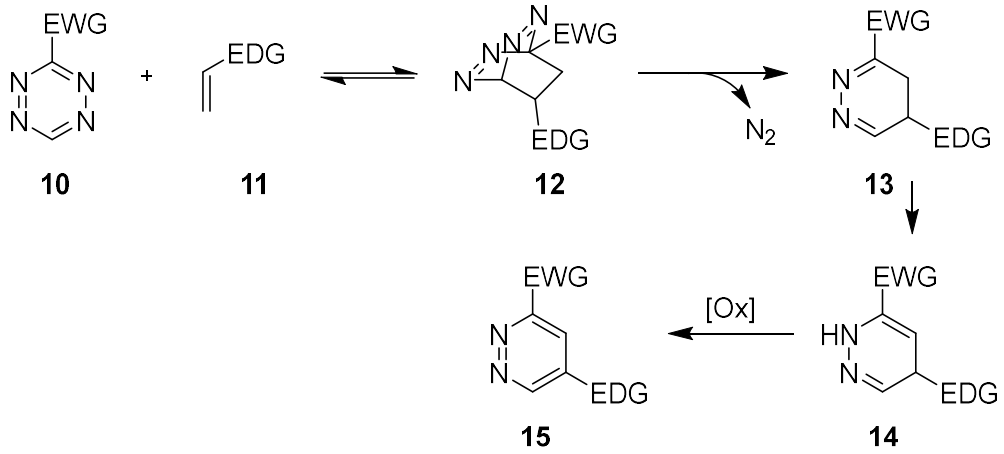
4 **8** **9**

Scheme 3: Strain promoted azide-alkyne cycloaddition (SPAAC).

The stability of the resulting products, the commercial access of starting materials and its ease of operation have put SPAAC in additional areas aside biorthogonal chemistry such as polymers and nanoparticles functionalization, genetic encoding, controlled drug release and many more.[16]

Another possibility is the [4+2] cycloaddition of 1,2,4,5-tetrazines **10** and olefins **11** has recently gained importance as metal-free click chemistry to give 1,2-diazines **15** for biorthogonal applications (Scheme 4). These catalyst-free, irreversible reactions have been shown to be fast at room temperature, selective and high yielding.[17] Due to the irreversible elimination of nitrogen this reaction enables the production of stable

compounds. In addition, it is possible to regulate the reaction rate by chemically manipulating the electron deficiency of the tetrazine 3,6 position substituents.[12]



Scheme 4: 1,2,3,4-Tetrazine (iEDDA) reaction with olefins.

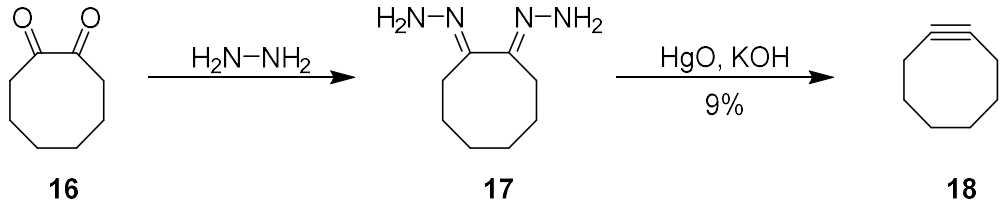
1.3 Cyclooctynes synthesis

Cyclooctyne is the smallest cycloalkyne stable enough to be isolated and stored at room temperature.[18] By virtue of its cyclic structure the sp-hybridized carbons of the triple bond do not present the ideal linear geometry so, the acetylene bond has an angle of 163°. This generate a ring strain of 18 kcal/mol[19] which makes cyclooctynes very reactive compounds. The first reported successful preparation of cyclooctyne was from BLOMQUIST *et al*. in 1953.[20] A range of different synthetic procedures is known to obtain cyclooctynes.

The synthesis can be classified in two main ways:

i) Oxidative decomposition

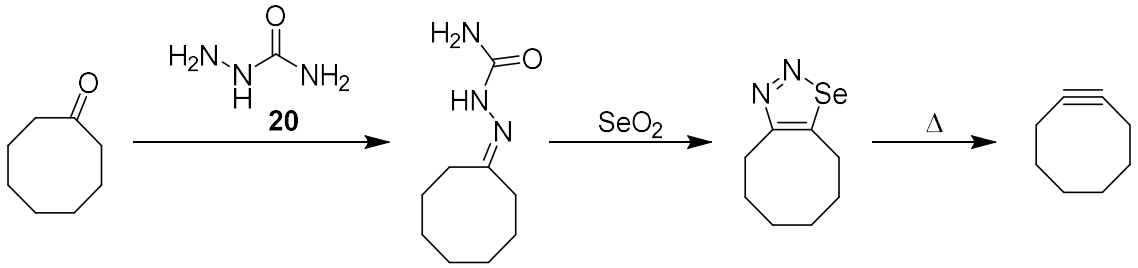
The first synthetic reports involved starting from vicinal diketone **16** (Scheme 5), a condensation reaction with hydrazine to form bis-hydrazones **17** and then a base catalyzed oxidative decomposition to give cyclooctyne. As oxidant, HgO or $Pb(OAc)_2$ are both suitable.[16] However, due to the harsh conditions this method gives a low yield, around 9% and generates a lot of tetrazine and triazole by-products which are difficult to separate. For these reasons, this method resulted of little importance for the synthesis of cyclooctyne derivates.



16 17 18

Scheme 5: Cyclooctyne synthesis from Blomquist *et al.* in 1953.[16]

Another direct procedure to get cyclooctynes is from cyclooctanone **19** (Scheme 6). Introduced by MEIER AND MENZEL in 1971 consist first in the reaction of cyclooctanone with semicarbazide acetate **20** to form semicarbazone **21** then oxidized to 1,2,3-selendiazole with SeO_2. Heating of the selendiazole at 170-220 °C leads to the elimination of N_2 and Se with formation of the cyclooctyne in moderate yields (34%).[21]



19 21 22 18

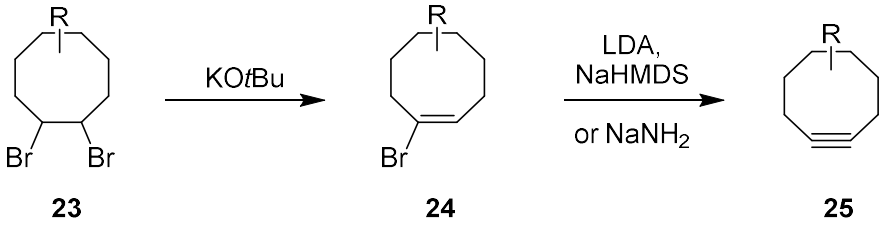
Scheme 6: Oxidative cyclooctyne synthesis from MEIER and MENZEL.[19]

ii) Dehydrohalogenation

A different way to obtain cyclooctyne was published by WITTIG and DORSCH in 1968[22], it starts with 1,2-dibromocyclooctane **23**, easily obtainable from cyclooctene treatment with elemental halogen. This method permits the generation of cyclooctyne **3** after a double dehydrohalogenation. They were able to eliminate the (*E*)-vinyl bromide using molten sodium amide ($NaNH_2$) at 200 °C with 17% yield.[22]

The most often applied and reliable procedure to obtain cyclooctyne is still based on the double dehydrohalogenation of vicinal dihalogenide, even if now it is usually done in two steps and with much milder conditions (Scheme 7). Starting from 1,2-dibromocyclooctane **23** the first E2 *anti* elimination proceeds under mild basic conditions with KO*t*Bu[10] forming the (*E*)-vinyl bromide **24**. To convert **24** in alkyne **25** a *syn* elimination must be carried out, which is harder and slower than the

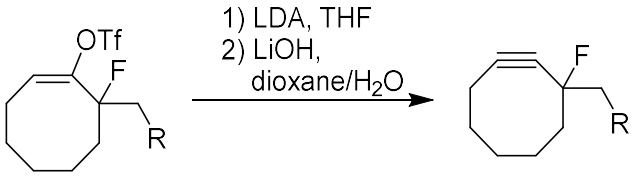
corresponding *anti* elimination.[23] So, superbases are necessary such as LDA or NaHMDS at low temperatures.[24]



23 **24** **25**

Scheme 7: Double dehydrohalogenation synthesis of cyclooctyne (**25**).

Lastly in 2006 BERTOZZI *et al.* developed a synthesis for functionalized cyclooctynes starting from (*Z*)-vinyl triflate **26** (Scheme 8).[25] The elimination to cyclooctyne can be performed with LDA at -78 °C. The difference here is that a triflate anion is a better leaving group than a bromide ion so it is possible to generate the triple bond more easily, with milder reaction conditions.

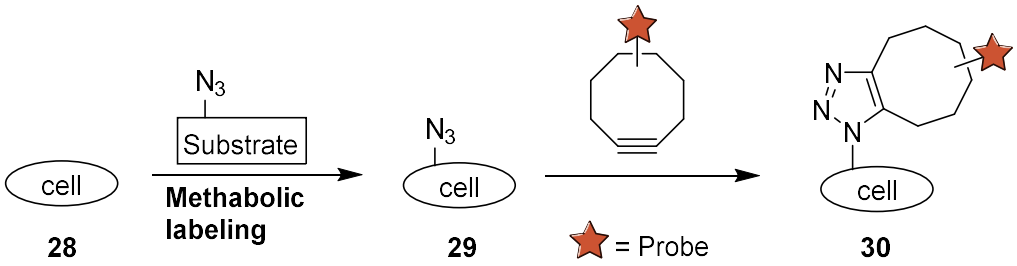


26 **27**

Scheme 8: BERTOZZI *et al.* cyclooctyne synthesis.[24]

1.4 Applications of Cyclooctyne

As mentioned above cyclooctynes enable copper free click reactions (SPAAC), BERTOZZI *et al.* were the first, in 2004 to show that they are suitable compounds for the labelling and modification of biomolecules and living organisms.[14] The targeted covalent labelling of biomolecules is a powerful tool for analysing molecular events in cells. Cyclooctynes react selectively with azides without the need for a metal catalyst, which can be integrated into living systems by feeding azide functionalized metabolic substrates.[26] The azide is an optimal chemical reporter because it is inert to cell environment and adds only a small perturbation to the systems.[27]



Scheme 9: Azide labelled molecules reaction with cyclooctyne probes.[27]

By exploiting the click reaction between azide and functionalized cyclooctynes it is possible to label biomolecules in living animals[29], live cell surface fluorescence imaging[28,30], and many more applications.

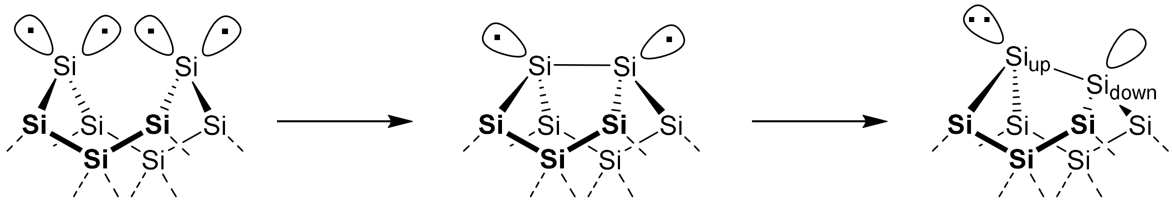
The chemistry of cyclooctynes is also interesting for material science, for example it was used for *in situ* crosslinking of azide-terminated photodegradable polymers[31] and hydrogels[32,33]. It is possible to functionalize polymers[34] and Au-nanoparticles[35], realized by implementing cyclooctynes at the interface and then with a strain promoted azide-alkyne cycloaddiction the desired functionality is set on the surface.

Since this concept has only been studied for approximately 15 years, it can be expected that the possible applications will increase in the coming years. Currently, the KOERT research group is working to whether cyclooctynes are suitable for the targeted functionalization of silicon surfaces.

1.5 Cyclooctynes on Si(001) surface

Semiconductor materials are and will be in the foreseeable future the key elements of modern electronics. They can be found in microelectronic components, sensors, lasers, photovoltaic and many more applications. Elemental semiconductors are elements of the VI group such as silicon, germanium and carbon.[36] With the adsorption of organic molecules it is possible to introduce functionalities to the surface that allow to design and create semiconductors with different properties like molecular recognition or biocompatibility.[37]

As opposed to metal conductors where valence electrons are not bound to individual atoms, silicon semiconductors have covalent bonds between atomic pairs. This means that atoms on the surface do not have binding partners and each of them is left with two dangling bonds. The silicon undergoes reconstruction to minimize the surface energy, and that leads to the formation of dimers arranged in rows.[38] This transformation is driven by the reduction of the number of dangling bonds from two to one for each surface atom (Scheme 10). In addition, the energy is reduced by an asymmetrical shift of the dimers in Si_{up} with both electrons on its orbital and Si_{down} with its empty orbital.[39]



Scheme 10: Representation of the surface reconstruction of Si(001).

Each dimer consists in a σ-bond and a partial π-bond. With an energy of 2-8 kcal/mol, the π interaction is weak (olefin interaction is around 64 kcal/mol) so the dimer can stay in a non-symmetric configuration.[40] Even after the reconstruction, the silicon surface is still reactive due to the partial π-bond character that is sufficient to do pericyclic reactions with organic molecules.[41] On Si(001) cyclooctynes reacts directly with the strained triple bond in a [2+2] cycloaddition.[42] There are four possible modes of adsorption in competition: on top (two σ bonds with one dimer), bridge (two σ bonds with Si atoms from different dimers), pedestal (four σ bonds over two different dimers)

and sublayer (one σ-bond with a dimer and one with a Si from the lower layer) (Fig. 3).[43]

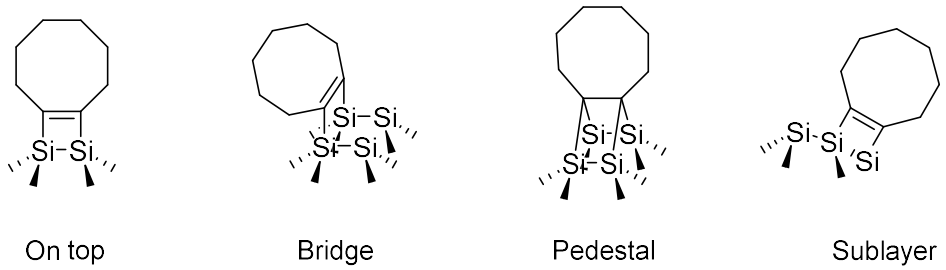


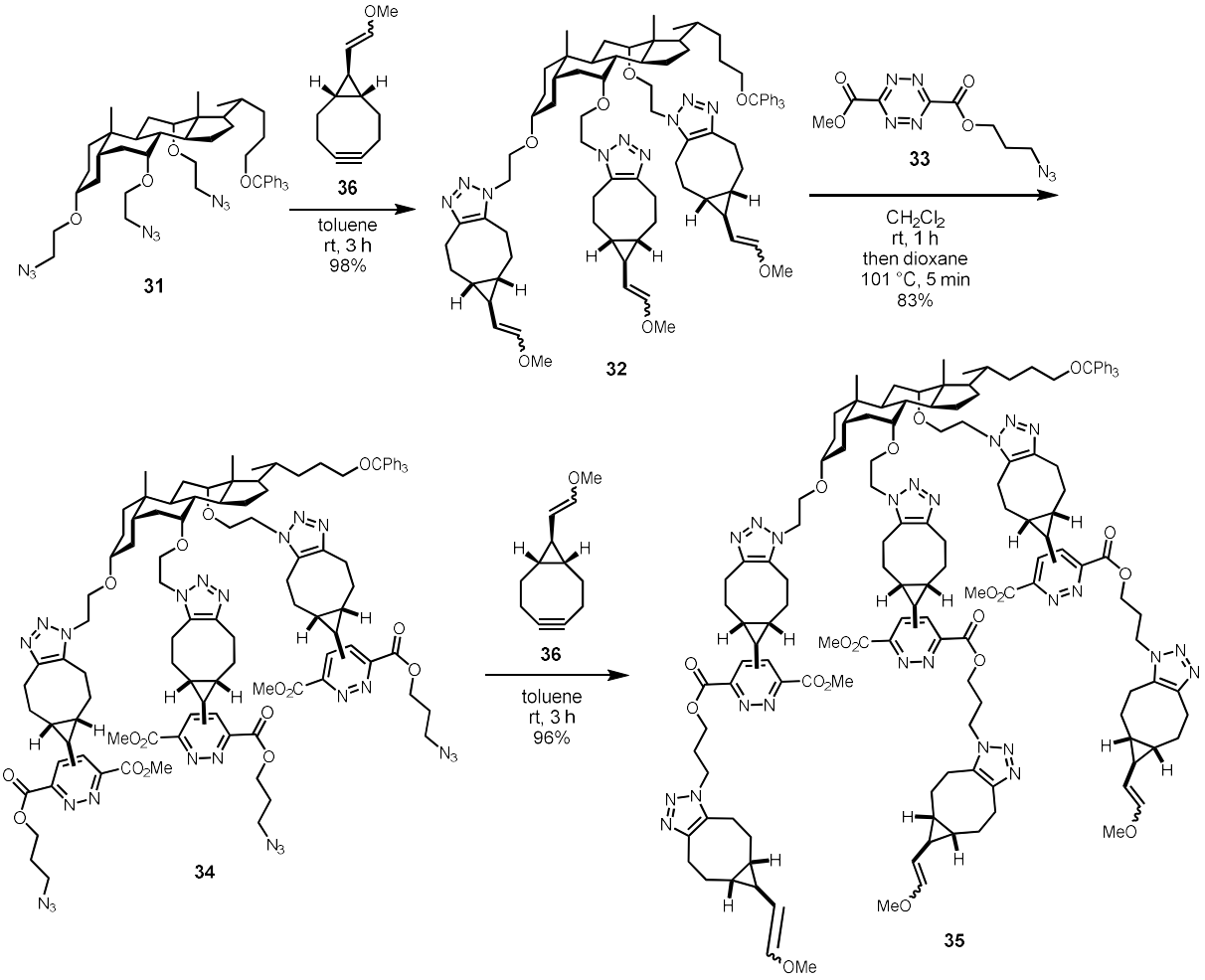
Fig. 3: Four adsorpion ways of cyclooctyne on Si(001) surface.

The on top mode is the thermodynamically most stable while the pedestal is the most unstable configuration. The sublayer has never been observed experimentally.[43,44] Bifunctionalized cyclooctynes reacts selectively via the strained triple bond due to its direct adsorption mechanism, instead of a metastable intermediate forming with most functional groups. The other group remains intact[42,45] and can act as a bridge to connect the semiconductor surface with the many possibilities of organic chemistry. This opens the possibility of using bifunctionalized cyclooctynes for multilayer synthesis.

1.6 Layer by Layer approach

The layer by layer approach allows to create multilayer thin films with controlled thickness and composition by applying monolayers to the substrate one by one. This concept was introduced by DECHER *et al.* in 1991[46], depositing polyelectrolytes on a charged surface by alternating cationic and anionic layers. The stability of the films obtained in this way is limited so different ways have been developed in order to link layers with covalent bonds.[47] In 2010 DINOLFO *et al.* were the first to use copper(I) catalized azide-alkyne cycloaddition (CuAAC) to grow a thin film on a surface.[48] However the click reaction used was not chemoselective and only symmetrical building blocks were used. A previous work from the KOERT group combined the different reactivities of alkene/cyclooctyne and azide/tetrazine to make a chemoselective layer by layer synthesis.[10] As a substrate a cholic acid derived triazide **31** was used, due to its rigid structure (Scheme 11). First the SPAAC reaction allowed to connect the triple

bond of the cycloalkyne with the azide to give the triazole ring. Afterwards, the iEDDA reaction was carried to place the second layer. Both work without additive and at room temperature.



Scheme 11: Layer by layer synthesis alternating SPAAC and iEDDA cycloadditions.[10]

By alternating these two steps it allows to get a chemoselective layer deposition on an azide functionalized substrate.

2 Aim of the thesis

In this thesis we try to synthesize a new bifunctionalized cyclooctyne with a different electron donating group from the already known methyl enol ether substituted for layer by layer assembly on Si(001).[10]

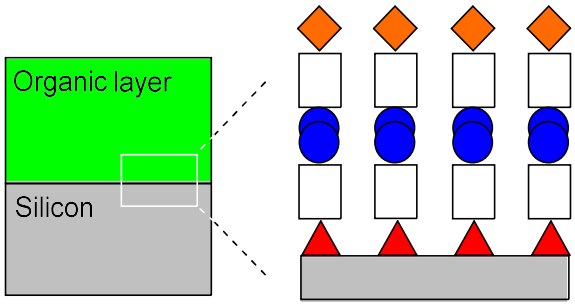
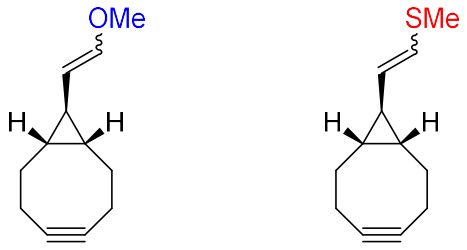


Fig. 4: Organic interface formation on silicon.

The methyl enol ether **36** previously adsorbed on silicon dangling bonds via chemical vapour deposition by KOERT group, with the idea of making a multilayer structure, was not very stable. Even though it was to a large extent still intact on the silica surface there was decomposition to aldehyde, even at 80 °C. In particular, the purpose of this work is the preparation of the methyl vinyl sulfide **37** and to test firstly if it tolerates cyclooctyne and secondly its reactivity towards a tetrazine. By the principle of stability/reactivity the more stable the reactant the less reactive it will be. So, the new molecule should be more stable than the already known bifunctional cyclooctyne **36** and at the same time it should not take too long to react.

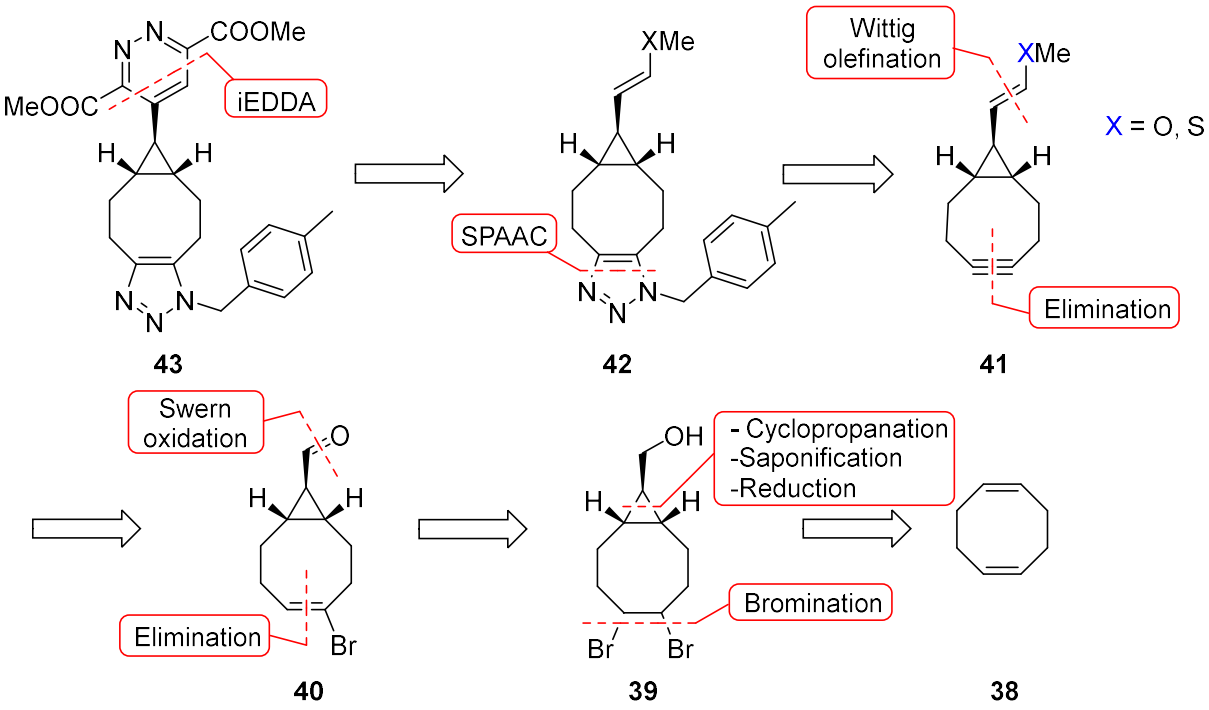


36 **37**

Fig. 5: Cyclooctynes: **36** known molecule; **37** aim of the work.

- Synthesis plan

The synthesis plan for compound **37** foresees a bromination followed by double HBr eliminations to generate the triple bond at the bottom (**41**); For the upper part, a cyclopropanation with ethyl 2-diazoacetate **45** followed by reduction and then oxidation to aldehyde **40**. Lastly, the WITTIG reaction is used to introduce the new functionality (Scheme 12). Then we present a sequential combination of two orthogonal reactions: SPAAC and IEDDA. The former reaction is used on the alkyne, the more reactive group, to deactivate it and to simulate the interaction with the silicon surface, a triazole ring is formed (**42**). The latter is used to test the stability and reactivity of the new compound, specifically the reaction with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate was used.

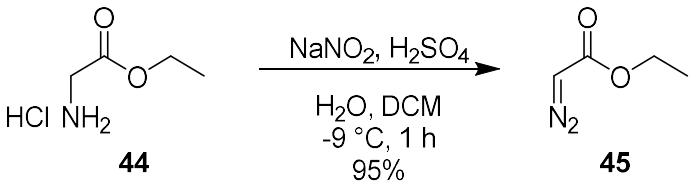


Scheme 12: Synthesis plan of functionalized cyclooctynes.

3 Results and discussion

3.1 Synthesis of *exo*-bicyclus alcohol

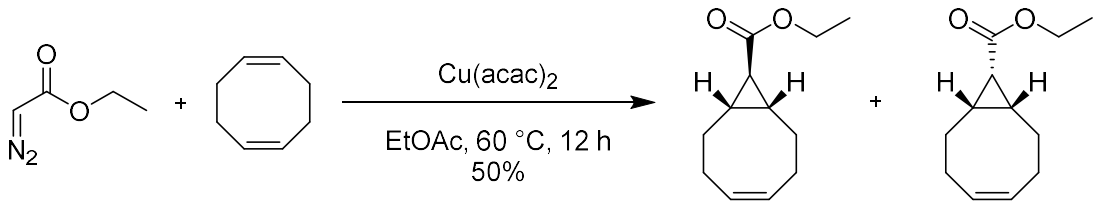
Starting from the commercially available glycine ethyl ester hydrochloride (**44**), the ethyl diazoacetate (**45**), necessary for the cyclopropanation reaction was synthesized following the procedure from MEZZETTI (Scheme 13).[49] This step involves the reaction of the primary amine with nitrosyl cation, generated *in situ* from sodium nitrite and sulfuric acid. The reaction has to be conducted at low temperature to avoid the formation of byproducts due to the diazo compound instability. Product **45** was obtained with a 95% yield working on 20.0 g scale.



44 **45**

Scheme 13: Ethyl diazoacetate (**45**) synthesis.

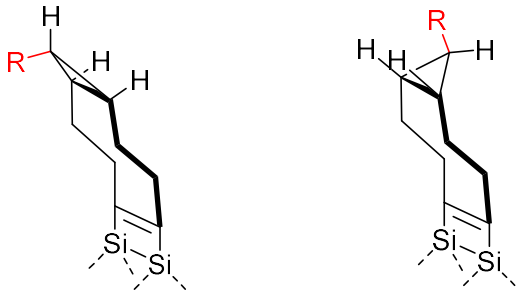
Having the diazo compound in hand, the next step was the cyclopropanation of 1,5-cyclooctadiene (**46**) (Scheme 14). Ester **47** was made following a modified procedure from FILIPPOV.[50] For this reaction it is possible to use different rhodium catalysts, but the copper catalysed variant was selected because $Cu(acac)_2$ it is significantly cheaper (about 100 times less than the Rh catalysts) and brings similar results. This reaction requires a large excess of cyclooctadiene to statistically oppose the double cyclopropanation. A mixture of both *exo/endo* diastereoisomers was obtained with 50% yield on 15.0 g scale.



45 **46** *exo*-**47** *endo*-**47**

Scheme 14: Cu catalized synthesis of bicyclo **47**.

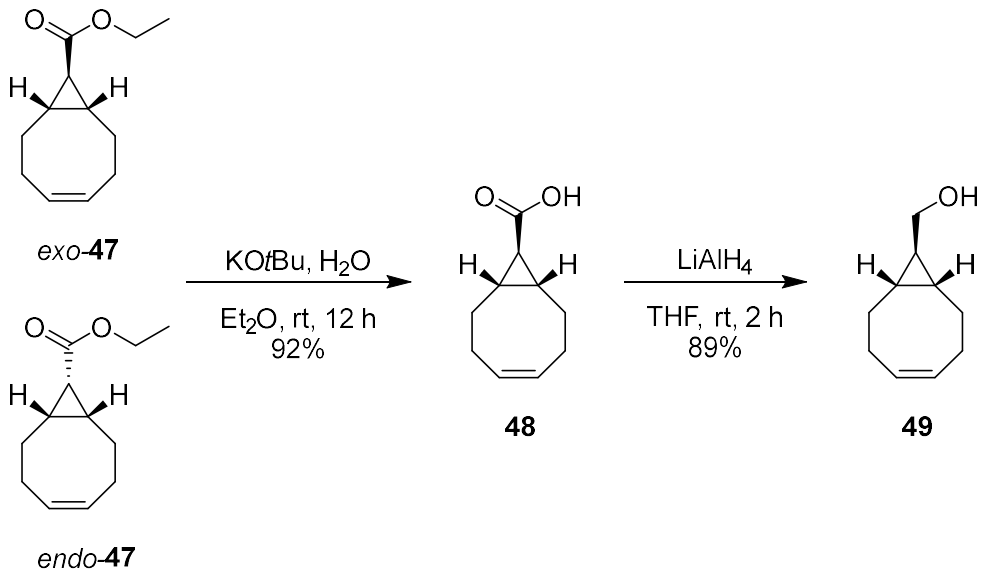
Only the *exo* diastereoisomer is useful for the preparation of compound **37**, since in its most stable chair configuration[43] it has the better lateral orientation when adsorbed on silica dangling bonds. On the contrary, the *endo* diastereoisomer would look back to the alkyne and it will not be possible to apply the layer by layer approach (Fig. 6).



endo ***exo***

Fig. 6: Orientation of *endo* and *exo* diastereoisomers adsorbed on Si(001).

Following the protocol from Fox[51], the *exo/endo* mixture of **47** was directly saponificated with KO*t*Bu since the *exo* isomer furnished the corresponding *exo* carboxylic acid **48** whereas the *endo* diastereoisomer epimerizing in the reaction conditions (room temperature for 12 h). In this way it was possible to avoid a long and difficult column chromatography and obtain an almost quantitative yield (92%) in the desired, thermodynamic more stable *exo* compound.



exo-**47** **48** **49**

endo-**47**

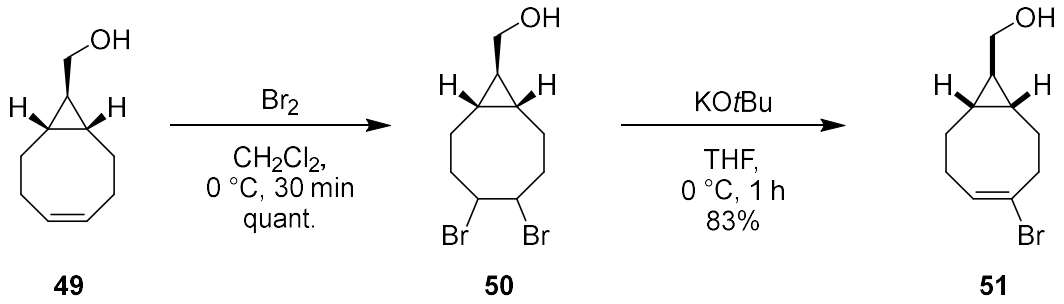
Scheme 14: Saponification under epimerizing conditions and reduction steps.[51]

Subsequent reduction with $LiAlH_4$ gave the corresponding alcohol **49**. In order to carry out the reaction in grams scale without any problems, first a suspension of $LiAlH_4$ was prepared at 0 °C then the ester **48** was added dropwise to it, to prevent the reaction from generating too much heat.

3.2 Synthesis of (*E*)-Vinyl bromide

Similarly, to the synthesis of cyclooctynes described before (Section 1.2), the next step plan of the synthesis consists in obtaining the (*E*)-Vinyl bromide.

The first reaction was the bromination on the double bond in **49** using Br_2, following the protocol from VAN DELFT (Scheme 16).[52] This simple reaction works well giving dibromo cyclooctane **50** in quantitative yield. The subsequent β-dehydroalogenation was conducted with KO*t*Bu at 0 °C. After a reaction time of 30 minutes, only one of the two bromides were eliminated to give the racemic mixture of alkenyl bromide **51** in good yield.

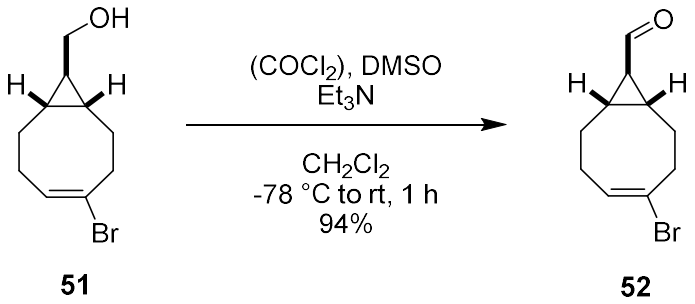


Scheme 16: Synthesis of (*E*)-Vinyl bromide (**51**).

3.3 Synthesis of Methyl Enol Ether 36 and Methyl Vinyl Sulfide 37

Following the protocol previously used by KOERT group[10] to introduce the new functionality, two sequential reactions were performed on the hydroxyl group of compound **51**. Firstly, the SWERN oxidation to obtain aldehyde **52** and then a WITTIG reaction to obtain the desired functionality.

The SWERN oxidation is carried at –78 °C in very mild conditions using oxalyl chloride, DMSO and Et_3N (Scheme 17). The oxidation perfectly tolerates the vinyl bromide to give aldehyde **52** in 94% yield, avoiding the formation of the carboxylic acid that could be generated by a second oxidation on the aldehyde. Compound **52** is a relatively unstable molecule due to the aldehyde functionality so it should be used quickly after the synthesis.

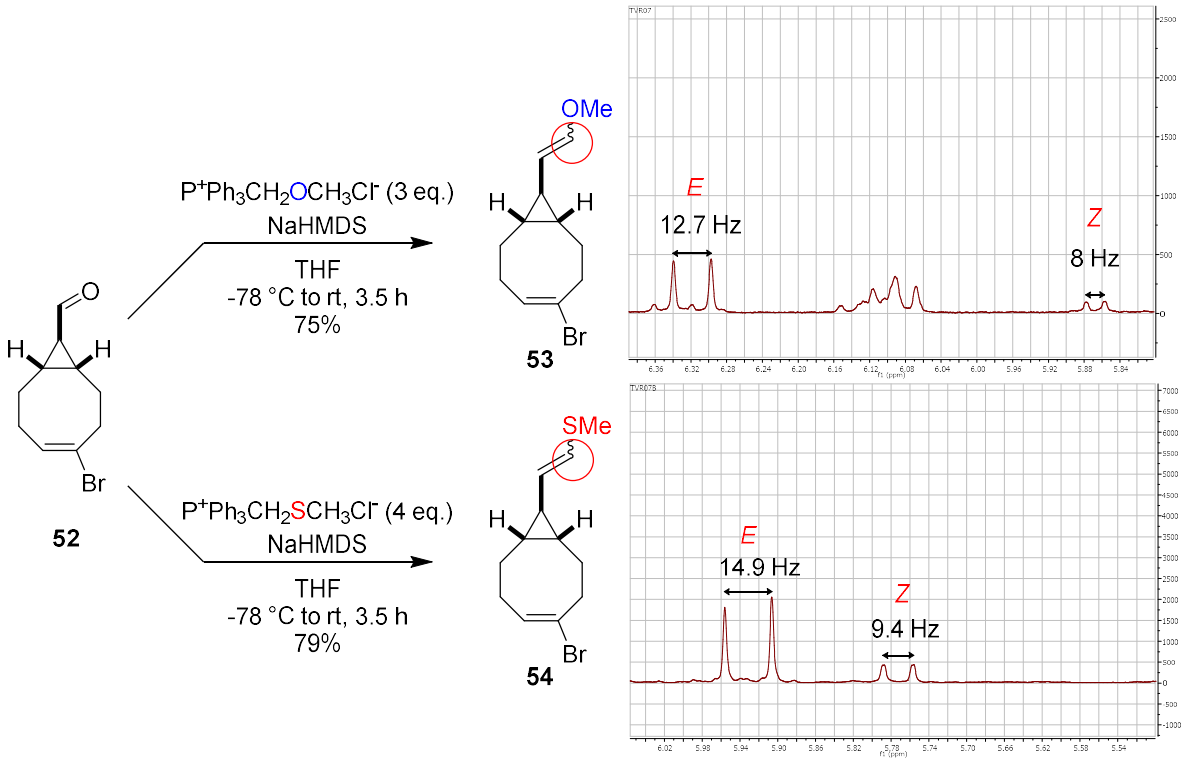


51 **52**

Scheme 17: SWERN oxidation step.

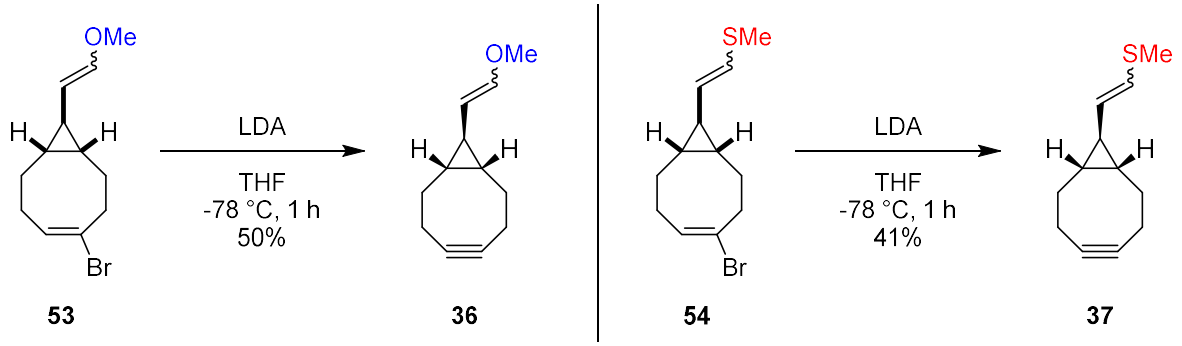
The WITTIG olefination was selected to create a new C-C double bonds starting from aldehyde **52**. The methyl enol ether **53** and the methyl vinyl sulfide **54** were obtained using the appropriate WITTIG reagents (Scheme 18). The required triphenyl phosphonium ylide was generated by adding NaHMDS to a suspension of the corresponding WITTIG salts at –78 °C and then aldehyde **52** was slowly added to the reaction mixture. For the methyl vinyl sulfide **54**, 4 equivalents of WITTIG salts were used, whereas 3 equivalents were enough for the preparation of methyl enol ether **53**. During the workup of the reaction the oil was taken in acetone and then CuCl was added because it forms an insoluble complex with the triphenylphosphine oxide (Ph_3PO), co-product of the reaction. In both cases the alkenes were obtained in good yields.

Scheme 18 shows sections of the ^{1}H-NMR spectra of molecule **53** and **54**, in particular the –C*H*OMe peaks at 6.35 ppm (J = 12.7 Hz), 5.89 ppm (J = 5.8 Hz) and –C*H*SMe at 5.93 ppm (J = 14.9 Hz), 5.77 ppm (J = 9.4 Hz). An approximately *E/Z* 3/1 selectivity was achieved using these ylides. The methyl peaks are at 3.60 (*Z*), 3.47 (*E*) ppm for compound **53** and 2.28 (*Z*), 2.20 (*E*) for molecule **54** as it is expected due to the lower electronegativity of sulfur compared to oxygen.



Scheme 18: WITTIG reaction (left); *E/Z* selectivity (right).

The last step of the synthesis of the target molecule of this work was a second HBr elimination (Scheme 19). This reaction requires a stronger base than the one used in the previous β-dehydrohalogenation since it is a *syn* elimination and it gives a strained triple bond, therefore the use of cryogenic temperature is required. It is possible to use different superbases (NaHMDS, $NaNH_2$, LDA, etc.): for our purpose LDA was added slowly to a solution of (*E*)-Vinyl bromide **53** and **54** at low temperatures to give only the *exo* diastereoisomer of alkyne **36** and **37** in moderate yields. Both products are not very stable due to the strained triple bond, so it is better to use them in few days after the synthesis.



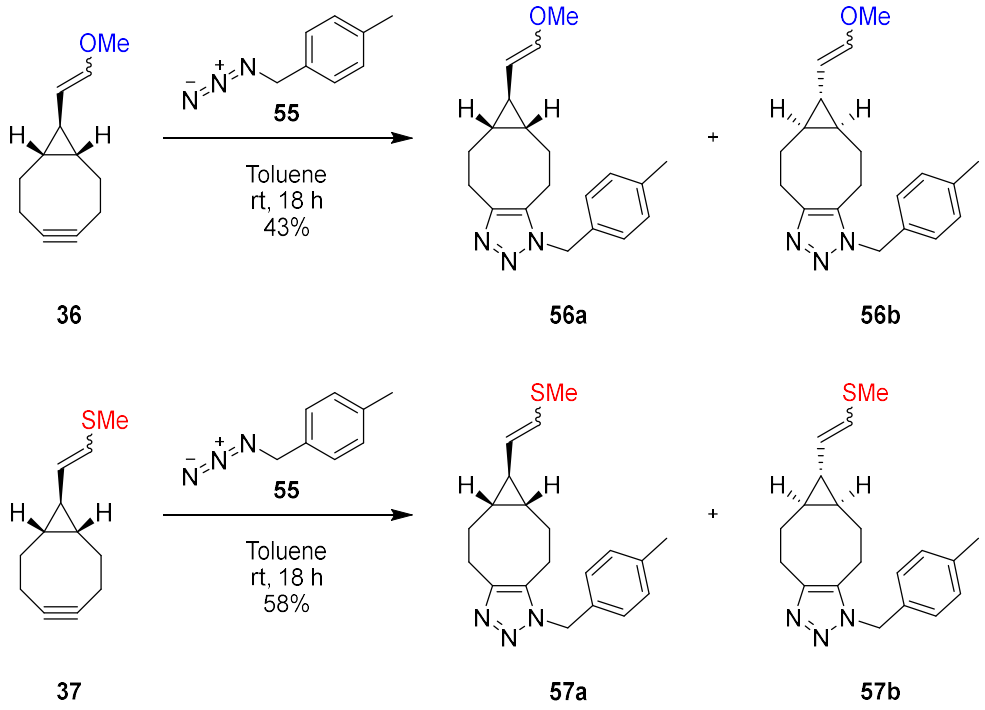
53 **36** **54** **37**

Scheme 19: HBr elimination: methyl enol ether **53** (left); methyl sulfide **54** (right).

3.4 SPAAC and iEDDA reactions

With our target molecule **37** in hand, we compared its reactivity towards 1,2,4,5-tetrazine to the already known methyl enol ether **36**. A sequential combination of SPAAC and iEDDA is used.

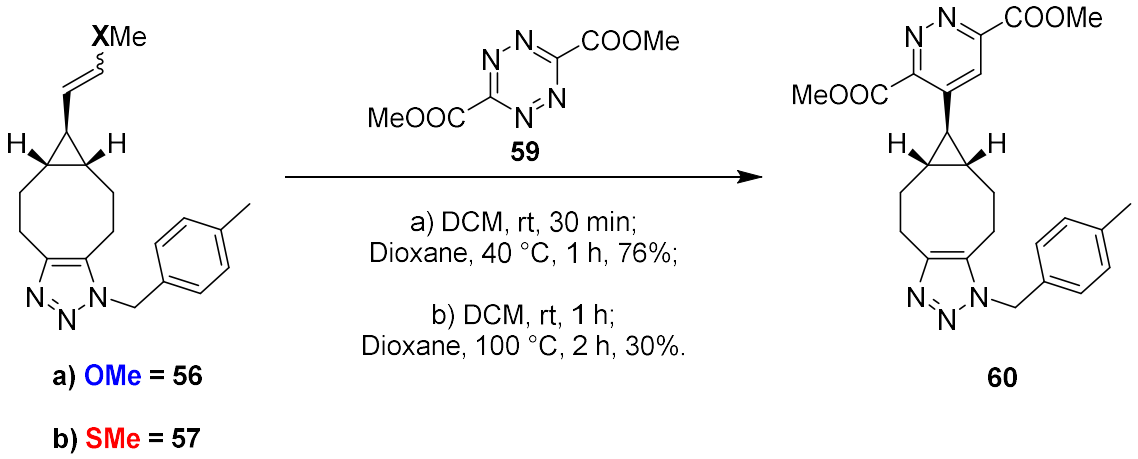
The SPAAC reaction with 1-(azidomethyl)-4-methylbenzene (**55**), was used to simulate the attack of both compounds on a solid substrate and at the same time to remove the strained triple bond, which is more reactive than the vinyl group, before doing the next step (Scheme 20). The reaction works at room temperature without the need of any additive. It led to the formation of the triazole ring products (**56**, **57**) as a mixture of diastereoisomers after 18 hours, in moderate yield. This shows that the presence of a different substituent at the exocyclic double bond of the two reagents, does not influence the rate of the SPAAC reaction.



Scheme 20: SPAAC reactions: methyl enol ether **36** (left); methyl sulfide **37** (right).

To compare of the reactivity of **37** and **36**, the iEDDA reaction with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**59**) was exploited (Scheme 21): compounds **56** and **57** (obtained by **36** and **37** respectively) were reacted in the same starting conditions and the reaction time to afford complete conversion was checked.

Indeed, a small excess of tetrazine was slowly added to a solution of the alkene in DCM at room temperature. This reaction was monitored by TLC, but also by the disappearance of the strong red colour due to the presence in solution of tetrazine. The disappearance of the red colour implied the reaction with the alkene group to form the pyridazine ring (Fig. 7). To complete the reactions, dioxane was added and the mixture was heated at different temperatures for the two molecules (Scheme 21).



Scheme 21: iEDDA reaction: a) methyl enol ether; b) methyl vinyl sulfide.

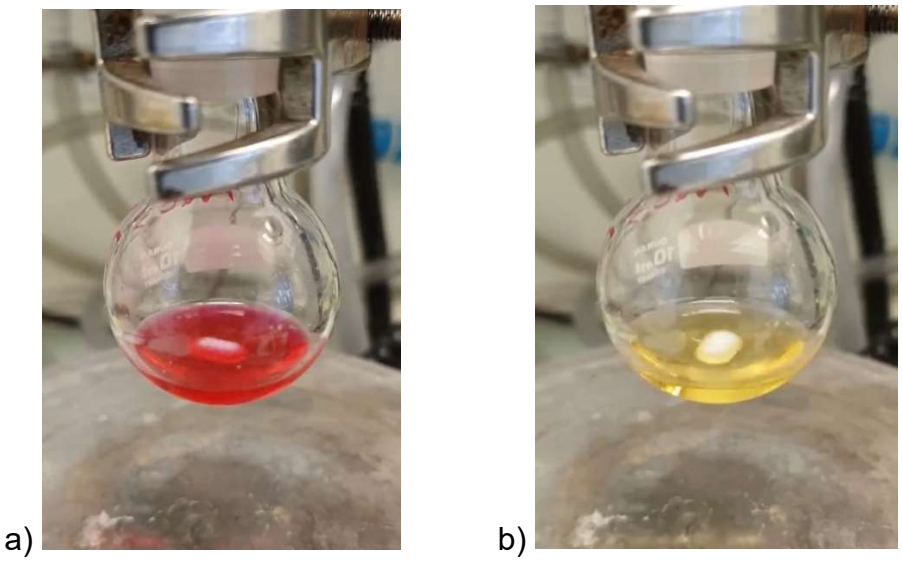


Fig. 7: Colour difference a) before and b) after the reaction.

In the case of methyl enol ether **56**, tetrazine **59** was completely reacted in 30 minutes in DCM at room temperature (change of colour from red to yellow). Heating in dioxane at 40 °C for 1 h furnished product **60** with 76% yield.

On the contrary, methyl vinyl sulfide **57** did not react with tetrazine **59** in DCM even after one hour. Dioxane was added and the mixture was heated at 100 °C (reflux) to increase the reaction rate, but product **60** was obtained only in 30% yield after 2 h.

In Fig. 8 it is shown the ^{1}H-NMR spectrum of compound **56** before the reaction with 1,2,4,5-tetrazine-3,6-dicarboxylate **59** (up) and after being recovered at the end of the reaction (bottom). As can be seen, the *E* stereoisomer reacts faster than the *Z,* as the signal corresponding to the *E* isomer decreases more than the corresponding signal of the *Z* isomer: starting from a 2:1 *E/Z* mixture of **56**, it was possible to recover a 1:2 mixture.

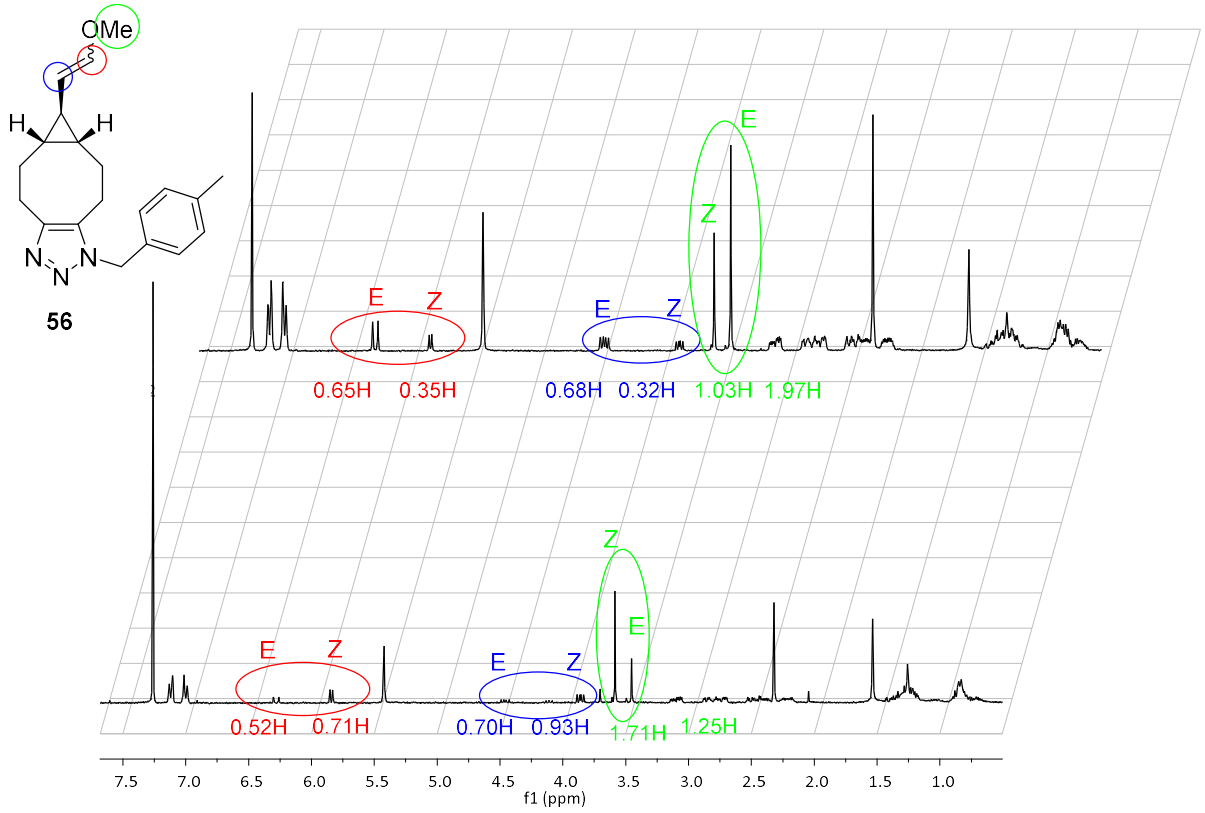
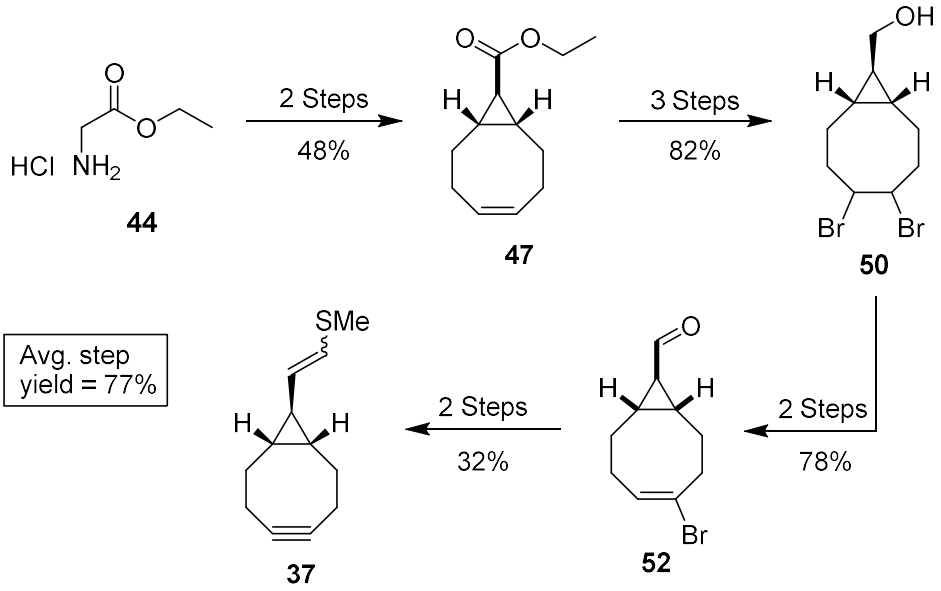


Fig. 8: ^{1}H-NMR (300 MHz) of the diastereoisomeric mixture of **56** before (up) and after (bottom) the reaction with tetrazine **59**.

4 Conclusions

The synthesis of methyl vinyl sulfide **37** starting from ethyl 2-diazoacetate **44** was achieved in 9 steps with an overall yield of 10% and an average step yield of 77%. It involves the generation of an aldehyde **52** with SWERN oxidation, conversion of the aldehyde using WITTIG reaction, and a double β-dehydrohalogenation to get the triple bond (Scheme 22).



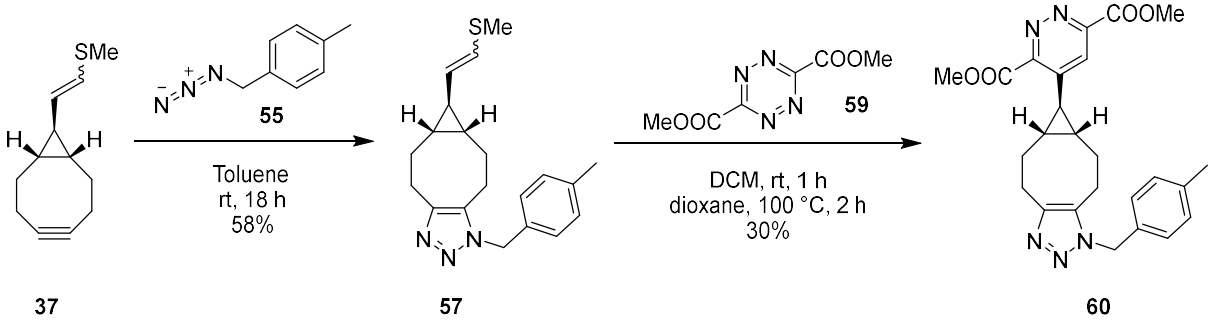
Scheme 22: Synthesis of methyl sulfide **37** over 9 steps with an overall yield of 10%.

The second elimination of HBr to cyclooctyne is a critical step of the synthesis with a yield of 41%, a different approach, like the one described in chapter 1.2 could give better results and it will be tried to improve the yield.

With the aim of developing a more stable molecule for layer by layer surface functionalization, a SPAAC followed by and iEDDA reaction was studied, obtaining compound **60** with an overall yield of 17% (Scheme 23). However, the main objective was to evaluate the reactivity and stability of compound **37** versus the corresponding methyl enol ether **36**. The SPAAC reaction gave similar results between the two strained triple bonds, indicating that the reactivity of the triple bond is not strongly influenced by substituents on the opposite side of the cyclooctyne. However, the iEDDA reaction of methyl vinyl sulfide **57** did not work at room temperature but it needed to be heated to reflux in order to proceed. This observation, combined with the

fact that **57** has not decomposed at a temperature of 100 °C while the methyl enol ether already decomposes to the respective aldehyde at 80 °C shows that the new molecule **37** is less reactive and more stable.

The need to use high temperatures for the reaction of methyl vinyl sulfide **57** with 1,2,4,5-tetrazines could be a limitation for the vapor phase deposition on a highly reactive surface such as Si(001), but it is in any case a positive result and it will be tested in the upcoming future by the KOERT group to see if an application on solid surface/semiconductor is tolerable by it.



Scheme 23: SPAAC and iEDDA reaction steps.

5 Esperimental section

5.1 General methods

NMR: ^{1}H-NMR spectra were recorded on AV II (300 MHz) spectrometer from BRUKER at 300 K. ^{13}C-NMR were performed with the same probe head at 75 MHz. Chemical shifts (δ) are reported in ppm. $CDCl_3$ was used as solvent (^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm). Multiplicity is explained in brackets as follow: “s”, singlet; “d”, doublet; “t”, triplet; “q”, quadruplet; “m”, multiplet.

TL-/Column chromatography: R_f values were determined through TLC, silica covered aluminium cards (thickness 0.2 mm on glass) F_{254} by MERCK. Chromatographic purifications were performed using silica gel (particles diameter 0.04 – 0.063 mm) by MERCK.

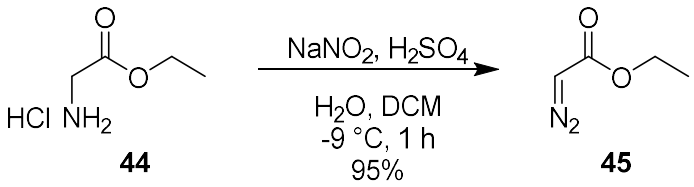
Mass spectrometry: Measurements were recorded with a LTQ-FT mass spectrometer from THERMO FISHER SCIENTIFIC (ESI & APCI) and with a MAT95 from FINNIGAN (EI). Measurements were performed by the mass department of Philipps-Universität Marburg.

IR spectroscopy: The IR spectra were measured in pure substance on a FT-IR spectrometer Alpha from BRUKER. All wave numbers are given ν in cm^{-1}, intensities are given as s (strong), m (medium), w (weak).

Abbreviations

acac	Acetylacetone
APCI	Atmospheric pressure chemical ionization
COD	1,5-Cyclooctadiene
d	Doublet (NMR)
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
g	Grams
HMDS	Bis(trimethylsilyl)amine
IR	Infrared
LDA	Lithium diisopropylamide
M	Molecular mass
m	Multiplet (NMR)
m/z	Mass/charge
MTBE	Methyl tert-butyl ether
NMR	Nuclear magnetic resonance
q	Quadruplet (NMR)
R*f*	Retention factor
s	Singlet (NMR)
t	Triplet (NMR)
TLC	Thin layer chromatography
THF	Tetrahydrofuran
% (w/w)	Mass fraction

Ethyl 2-diazoacetate (45)



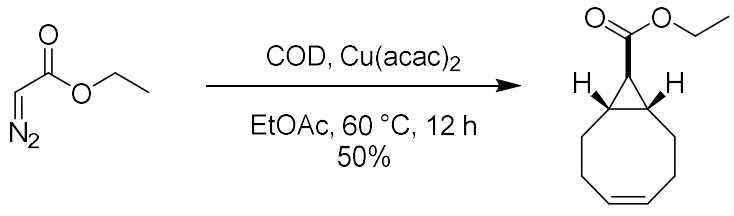
44 **45**

Ethyl 2-aminoacetate hydrochloride (**44**, 20.0 g, 143 mmol, 1.00 equiv.) was dissolved in H_2O (40.0 mL) and CH_2Cl_2 (80.0 mL). The solution was cooled down to -5 °C and a solution of $NaNO_2$ (11.9 g, 172 mmol, 1.20 equiv.) in H_2O (20.0 mL) at 0 °C was added. The mixture was cooled to -9 °C and a 5% (w/w) H_2SO_4 solution (13.6 g) was slowly added. After stirring for 60 minutes between -9 °C and +1 °C the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 40.0 mL). The organic layers were washed with a 5% $NaHCO_3$ solution (120 mL) and the water phase was extracted with CH_2Cl_2 (2 x 40.0 mL). The combined organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give product **45** (15.6 g, 137 mmol, 95%) as yellow oil.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 4.72 (s, 1H, N_2CH), 4.22 (q, 2H, OCH_2CH_3), 1.27 (t, 3H, OCH_2CH_3).

The analytical data are in accordance to literature.[50]

Ethyl 2-((1*R*,8*S*,9*r*,*Z*)-bicyclo[6.1.0]non-4-en-9-yl)acetate (47)



45 **47**

A solution of Ethyl 2-diazoacetate (**45**, 15.6 g, 137 mmol, 1.00 equiv.) in EtOAc (35.0 mL) was added over 30 min at 60 °C to a solution of $Cu(acac)_2$ (1.79 g, 6.85 mmol, 0.05 equiv.) and COD (119 g, 1096 mmol, 8.00 equiv.) in EtOAc (110 mL). After stirring for 12 h at the same temperature the solvent was removed under reduced pressure.

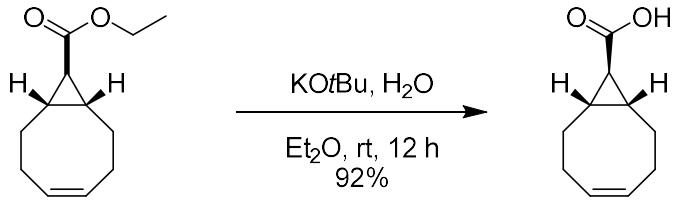
Column chromatography on silica gel using *n*-pentane/MTBE (100:0 then 30:1) gave the *exo*/*endo* mixture of the ester (**47**, 13.4 g, 69.1 mmol, 50%) as pale oil.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 5.67 – 5.58 (m, 2H, 2 x C*H*$_{alkene}$), 4.17 – 4.04 (m, 2H, OC*H*$_2$CH$_3$), 2.58 – 2.45 (m, 1H, C*H*$_{aliph.}$), 2.35 – 1.98 (m, 5H, C*H*$_{aliph.}$), 1.76 – 1.90 (m, 1H, C*H*$_{aliph.}$),1.35 – 1.60 (m, 4H, C*H*$_{aliph.}$), 1.21 (t, 3H, OCH$_2$C*H*$_3$).

^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 174.58 (*C*$_{endo}$OCH2CH3), 172.43 (*C*$_{exo}$OCH2CH3), 130.08 (*C*$_{alkene,\ endo}$), 129.62 (*C*$_{alkene,\ exo}$), 60.39 (O*C*H$_{2,\ endo}$), 59.86 (O*C*H$_{2,\ exo}$), 28.43 (*C*$_{aliph.}$), 28.05 (*C*$_{aliph.}$), 27.88 (*C*$_{aliph.}$), 27.24 (*C*$_{aliph.}$), 26.82 (*C*$_{aliph.}$), 24.33 (*C*$_{aliph.}$), 22.83 (*C*$_{aliph.}$), 21.42 (*C*$_{aliph.}$), 14.56 (OCH$_2$*C*H$_{3,\ endo}$), 14.45 (OCH$_2$*C*H$_{3,\ exo}$).

The analytical data are in accordance to literature.[55]

(1*R*,8*S*,9*r*,*Z*)-bicyclo[6.1.0]non-4-ene-9-carboxylic acid (48)



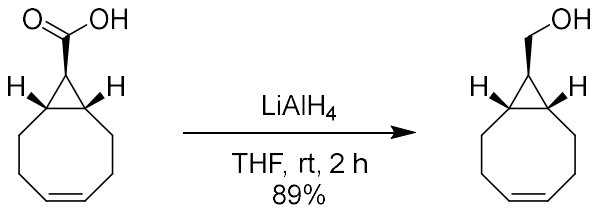
47 **48**

To a solution of the *exo/endo* mixture of the ester (**47**, 13.4 g, 69.1 mmol, 1.00 equiv.) in Et$_2$O (270 mL) was added H$_2$O (1.52 mL, 82.3 mmol, 1.22 equiv.) and KO*t*Bu (23.3 g, 206 mmol, 3.00 equiv.) at room temperature. The suspension was stirred at the same temperature for 12 h. A 3 M solution of NaOH (500 mL) was added and the layers were separated, the organic layer was extracted with NaOH 3 M (2 x 200 mL). To the combined aqueous layers at 0 °C concentrated HCl was added slowly until pH = 2. The resulting precipitate was dissolved in EtOAc (300 mL), layers were separated, and the aqueous layer was extracted with EtOAc (2 x 200 mL). The solvent was removed under reduced pressure to give the *exo* carboxylic acid (**48**, 10.6 g, 63.6 mmol, 92%).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 11.00 (s, 1H, COO*H*), 5.64 (m, 2H, 2 x C*H*$_{alkene}$), 2.38 – 2.26 (m, 2H, C*H*$_{aliph.}$), 2.25 – 2.14 (m, 2H, C*H*$_{aliph.}$), 2.14 – 2.02 (m, 2H, C*H*$_{aliph.}$), 1.70 – 1.57 (m, 2H, C*H*$_{aliph.}$), 1.57 – 1.43 (m, 2H, C*H*$_{aliph.}$), 1.22 – 1.15 (t, 1H, C*H*$_{aliph.}$).

The analytical data are in accordance to literature.[53]

((1*R*,8*S*,9*r*,*Z*)-bicyclo[6.1.0]non-4-en-9-yl)methanol (49)



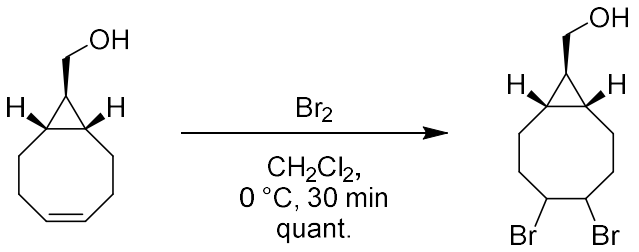
48 **49**

To a suspension of $LiAlH_4$ (0.69 g, 18.1 mmol, 3.00 equiv.) in THF (5.00 mL) at 0 °C was added dropwise a solution of the *exo* acid (**48**, 1.00 g, 6.02 mmol, 1.00 equiv.) in THF (2.50 mL) and it was allowed to warm to rt. The mixture was stirred for 2 h at the same temperature then it was cooled to 0 °C. Water was added until gas generation stopped. MTBE (6.00 mL) was added, layers were separated and the aqueous one was extracted with MTBE (2 x 6.00 mL). The combined organic layers were washed with NaCl (1 x 10.0 mL) and then dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the *exo* alcohol (**49**, 0.82 g, 5.38 mmol, 89%).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 4.85 (m, 1H, C*H*$_{alkene}$), 3.52 (d, 2H, C*H*$_2$OH), 2.74 – 2.66 (m, 1H, C*H*$_{alkene}$), 2.64 – 2.57 (m, 1H, C*H*$_{aliph.}$), 2.32 – 2.19 (m, 1H, C*H*$_{aliph.}$), 2.15 – 2.00 (m, 4H, C*H*$_{aliph.}$), 1.49 (s, 1H, O*H*), 1.45 – 1.30 (m, 2H, C*H*$_{aliph.}$), 0.97 – 0.84 (m, 2H, C*H*$_{aliph.}$), 0.72 – 0.63 (m, 1H, C*H*$_{aliph.}$).

The analytical data are in accordance to literature.[51]

((1*R*,8*S*,9*r*)-4,5-dibromobicyclo[6.1.0]nonan-9-yl)methanol (50)



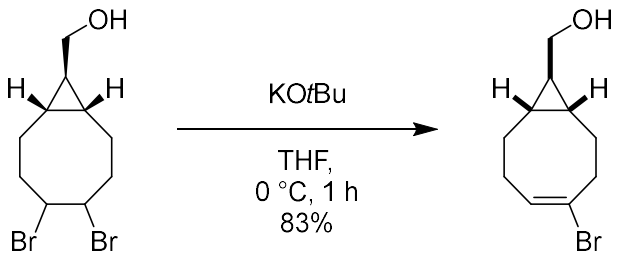
49 **50**

The olefin (**49**, 1.52 g, 9.16 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (25.0 mL) and cooled to 0 °C. A solution of Br_2 (0.61 mL, 11.9 mmol, 1.30 equiv.) in CH_2Cl_2 (2.50 mL) was added dropwise and the solution was stirred for 30 min at the same temperature. A 10 % (w/w) aqueous solution of $Na_2S_2O_3$ (2.00 mL) was added to quench the excess of bromine. Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 7.50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the dibromide (**50**, 2.86 g, 9.16 mmol, quant.) as solid.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ =5.69 (m, 2H, BrC*H*), 3.47 (d, 2H, CH_2OH), 2.35 – 2.23 (m, 2H, C$H_{aliph.}$), 2.22 – 2.12 (m, 2H, C$H_{aliph.}$), 2.11 – 2.00 (m, 2H, C$H_{aliph.}$), 1.48 – 1.35 (m, 3H, C$H_{aliph.}$, O*H*), 0.84 – 0.71 (m, 2H, C$H_{aliph.}$), 0.70 – 0.61 (m, 1H, C$H_{aliph.}$).

The analytical data are in accordance to literature[52].

((1*R*,8*S*,9*R*,*E*)-4-bromobicyclo[6.1.0]non-4-en-9-yl)methanol (51)



50 **51**

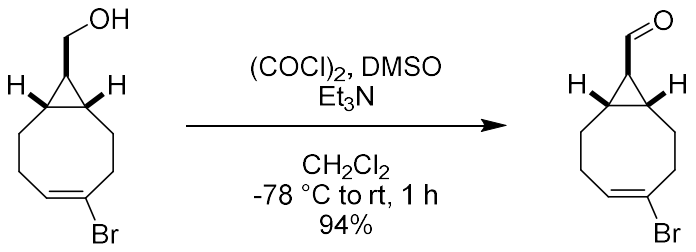
KO*t*Bu (1.22 g, 10.9 mmol, 2.20 equiv.) was added slowly over 10 min to a solution of dibromide (**50**, 1.54 g, 4.94 mmol, 1.00 equiv.) in THF (20.0 mL) at 0 °C. The solution was stirred for 1 h at the same temperature then a saturated, aqueous solution of NH_4Cl (15.0 mL) and CH_2Cl_2 (25.0 mL) were added. Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15.0 mL). Organic layers were dried over Na_2SO_4. Column chromatography using *n*-pentane/MTBE (3:1 then 1:1) gave vinyl bromide (**51**, 0.95 g, 4.10 mmol, 83%) as yellow oil.

TLC: R_f = 0.07 (*n*-pentane/MTBE; 5:1).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 6.10 (t, 1H, BrCC*H*), 3.49 (d, 2H, CH_2OH), 2.94 – 2.82 (m, 1H, C$H_{aliph.}$), 2.58 – 2.46 (m, 1H, C$H_{aliph.}$), 2.40 – 2.26 (m, 2H, C$H_{aliph.}$), 2.25 – 2.16 (m, 1H, C$H_{aliph.}$), 2.11 – 1.99 (m, 1H, C$H_{aliph.}$), 1.59 – 1.39 (m, 3H, C$H_{aliph.}$, O*H*), 0.91 – 0.83 (m, 1H, C$H_{aliph.}$), 0.82 – 0.75 (m, 1H, C$H_{aliph.}$), 0.73 – 0.67 (m, 1H, C$H_{aliph.}$).

The analytical data are in accordance to literature.[54]

(1*R*,8*S*,9*R*,*E*)-4-bromobicyclo[6.1.0]non-4-ene-9-carbaldehyde (52)



51 **52**

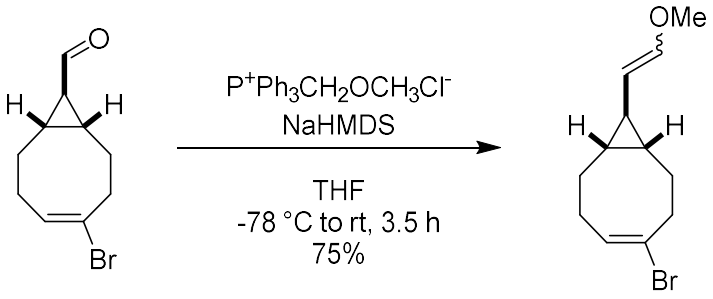
To a solution of oxalyl chloride (0.20 g, 0.87 mmol, 1.00 equiv.) in CH_2Cl_2 (8.00 mL) was added DMSO (0.22 mL, 3.14 mmol, 3.60 equiv.) in CH_2Cl_2 (0.60 mL), dropwise at -78 °C. The solution was stirred for 20 min at the same temperature. The alcohol (**51**, 0.20 g, 0.87 mmol, 1.00 equiv.) in CH_2Cl_2 (2.50 mL) was added and the solution was stirred for 1h at -78 °C. Et_3N (0.84 mL, 6.02 mmol, 6.90 equiv.) was added. The mixture was warmed up to room temperature over 1 h and a saturated, aqueous solution of NH_4Cl (10.0 mL) was added. Layers were separated and the aqueous one was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and filtration over a short plug of silica with *n*-pentane/MTBE (5:1) gave aldehyde (**52**, 0.19 g, 0.82 mmol, 94%).

TLC: R_f = 0.24 (*n*-pentane/MTBE; 5:1).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 9.06 (d, 1H, C*H*O), 6.11 (t, 1H, BrCC*H*), 2.98 – 2.85 (m, 1H, C$H_{aliph.}$), 2.60 – 2.47 (m, 1H, C$H_{aliph.}$), 2.43 – 2.31 (m, 2H, C$H_{aliph.}$), 2.28 – 2.21 (m, 1H, C$H_{aliph.}$), 2.16 – 2.08 (m, 1H, C$H_{aliph.}$), 1.80 – 1.73 (m, 1H, C$H_{aliph.}$), 1.73 – 1.60 (m, 3H, C$H_{aliph.}$), 1.55 – 1.48 (m, 1H, C$H_{aliph.}$).

The analytical data are in accordance to literature.[10]

(1*R*,4*E*,8*S*,9*R*)-4-bromo-9-(2-methoxyvinyl)bicyclo[6.1.0]non-4-ene (53)



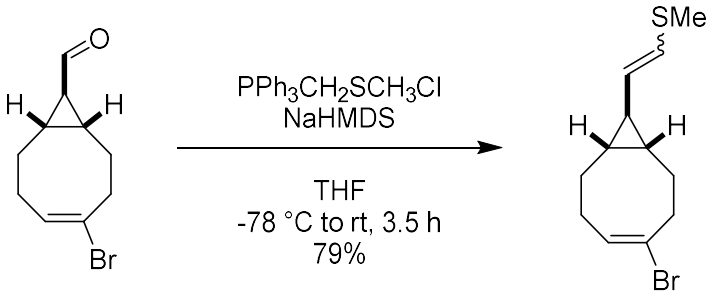
52 **53**

A 2 M NaHMDS in THF (1.55 mL, 7.64 mmol, 2.50 equiv.) was added dropwise to a suspension of $PPh_3CH_2OCH_3Cl$ (3.14 g, 9.17 mmol, 3.00 equiv.) in THF (35.0 mL) at -78 °C. The mixture was stirred for 20 minutes and aldehyde (**52**, 0.70 g, 3.06 mmol, 1.00 equiv.) in THF (3.50 mL) was added. The mixture was stirred for 2 h at -78 °C, gradually warmed to rt and stirred for 1.5 h. CH_2Cl_2 (40.0 mL) and a saturated aqueous solution of NH_4Cl (35.0 mL) was added, layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20.0 mL). Organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. To the obtained oil, acetone (20.0 mL) and CuCl (0.15 g, 1.53 mmol, 0.50 equiv.) were added. The mixture was filtered, and the solvent was removed under vacuum. The crude was purified by column chromatography using *n*-pentane/MTBE (9:1) as eluent. A mixture of *E/Z* (3:1) enol ether (**53**, 0.59 g, 2.30 mmol, 75%) was obtained as pale yellow oil.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 6.32 (d, 0.74H, CH_EOCH$_3$), 6.10 (t, 1H, *H*CCBr), 5.86 (d, 0.24H, CH_ZOCH$_3$), 4.50 (dd, 0.82H, CH_ECHOCH3), 3.90 (dd, 0.18H, CH_ZCHOCH3), 3.60 (s, 0.76H, OCH_{3Z}), 3.47 (s, 2.29H, OCH_{3E}), 2.92 – 2.81 (m, 1H, C$H_{aliph.}$), 2.57 – 2.46 (m, 1H, C$H_{aliph.}$), 2.40 – 2.28 (m, 2H, C$H_{aliph.}$), 2.27 – 2.20 (m, 1H, C$H_{aliph.}$), 2.08 – 2.00 (m, 1H, C$H_{aliph.}$), 1.52 – 1.35 (m, 2H, C$H_{aliph.}$), 1.25 (s, 0.34H, C$H_{aliph.}$), 0.91 – 0.77 (m, 2.66H, C$H_{aliph.}$).

The analytical data are in accordance to literature.[10]

(2-((1*R*,8*S*,9*R*,*E*)-4-bromobicyclo[6.1.0]non-4-en-9-yl)vinyl)(methyl)sulfane (54)



52 **54**

A 2 M NaHMDS in THF (0.42 mL, 2.07 mmol, 2.50 equiv.) was added dropwise to a suspension of $PPh_3CH_2SCH_3Cl$ (1.19 g, 3.32 mmol, 4.00 equiv.) in THF (10.0 mL) at -78 °C. The mixture was stirred for 20 minutes and aldehyde (**52**, 0.19 g, 0.83 mmol, 1.00 equiv.) in THF (1.00 mL) was added. The mixture was stirred for 2 h at -78 °C, gradually warmed to rt and stirred for 1.5 h. CH_2Cl_2 (12.0 mL) and a saturated aqueous solution of NH_4Cl (10.0 mL) were added, layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10.0 mL). Organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. To the obtained oil, acetone (8.00 mL) and CuCl (0.04 g, 0.42 mmol, 0.50 equiv.) were added. The mixture was filtered, and the solvent was removed under vacuum. The crude was purified by column chromatography using *n*-pentane/MTBE (9:1) as eluent. A mixture of *E/Z* (3:1) methyl vinyl sulfide (**54**, 0.18 g, 0.66 mmol, 79%) was obtained as yellow oil.

TLC: R_f = 0.80 (*n*-pentane/MTBE; 3:1).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 6.10 (t, 1H, *H*CCBr), 5.93 (d, 0.76H, CH_ESCH$_3$), 5.77 (d, 0.24H, CH_ZSCH$_3$), 5.18 – 5.02 (m, 1H, CH_ECHSCH3, CH_ZCHSCH3), 2.94 – 2.80 (m, 1H, C$H_{aliph.}$), 2.57 – 2.46 (m, 1H, C$H_{aliph.}$), 2.40 – 2.29 (m, 2H, C$H_{aliph.}$), 2.28 (s, 0.74H, SCH_{3Z}), 2.25 – 2.21 (m, 1H, C$H_{aliph.}$), 2.20 (s, 2.16H, SCH_{3E}), 2.09 – 1.98 (m, 1H, C$H_{aliph.}$), 1.6 – 1.37 (m, 2H, C$H_{aliph.}$), 1.08 – 1.02 (m, 1H, C$H_{aliph.}$), 1.01 – 0.97 (m, 1H, C$H_{aliph.}$), 0.97 – 0.88 (m, 1H, C$H_{aliph.}$).

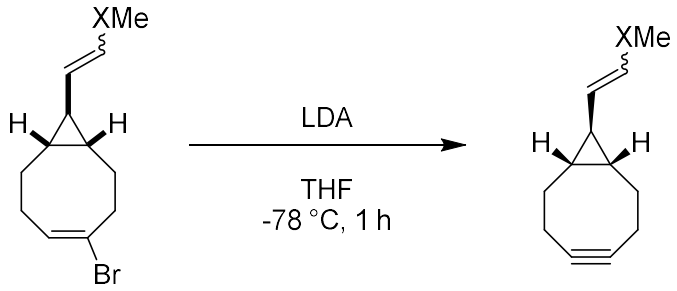
^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 131.48 (*C*H$_E$SCH$_3$), 131.29 (*C*H$_Z$SCH$_3$), 125.63 (H*C*CBr), 124.12 (HC*C*Br), 120.83 (*C*H$_E$CHSCH$_3$), 120.24 (*C*H$_Z$CHSCH$_3$), 37.78 (S*C*H$_{3,Z}$), 37.72 (S*C*H$_{3.,E}$), 30.42 (*C*$_{aliph.}$), 28.29

($C_{aliph.}$), 28.10 ($C_{aliph.,E}$), 28.05 ($C_{aliph.,Z}$), 28.01 ($C_{aliph.}$), 27.51 ($C_{aliph.}$), 25.93 ($C_{aliph.,Z}$), 25.62 ($C_{aliph.,E}$), 25.08 ($C_{aliph.,Z}$), 24.72 ($C_{aliph.,E}$).

IR: (ATR) ν (cm-1) = 2984 (w), 2916 (s), 2857 (w), 1724 (w), 1641 (w), 1605 (w), 1473 (w), 1457 (w), 1434 (m), 1354 (w), 1316 (w), 1227 (w), 1175 (w), 1138 (w), 1123 (w), 1075 (m), 1026 (w), 985 (w), 929 (s), 884 (m), 839 (m), 791 (w), 742 (w), 697 (m), 551 (w), 486 (w).

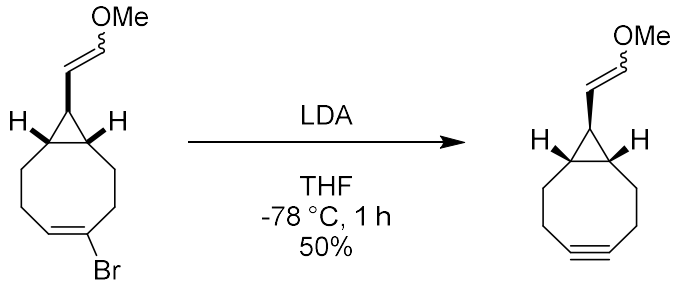
HRMS: (APCI+) m/z calcd. for [M+H$^+$]: 273.0307, found: 273.0315.

General procedure for the synthesis of products 36/37



A 1 M solution of LDA in THF (3.00 equiv.) was added dropwise to a solution of vinyl bromide (1.00 equiv.) in THF at -78 °C. The mixture was stirred for 1h at the same temperature then it was gradually warmed up to 0 °C and stirred for 90 min. A saturated, aqueous solution of NH_4Cl (10.0 mL) and Et_2O (10.0 mL) was added. Layers were separated and the aqueous one was extracted with Et_2O (2 x 10.0 mL). Combined organic layers were dried over Na_2SO_4, filtered and solvent was removed under reduced pressure. The crude was purified by column chromatography using *n*-pentane/MTBE (100:1) as eluent to afford the desired alkyne product.

(1*R*,8*S*,9*r*)-9-(2-methoxyvinyl)bicyclo[6.1.0]non-4-yne (36)



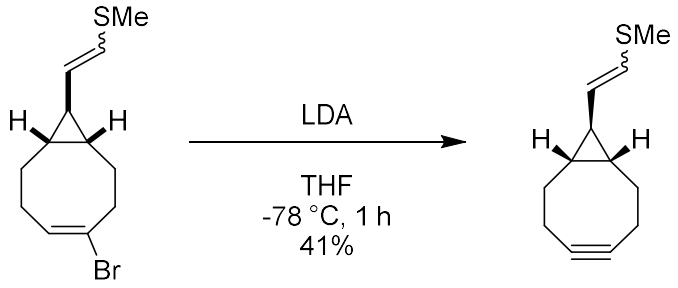
53 **36**

Following the general procedure from vinyl bromide (**53**, 0.30 g, 1.16 mmol) in THF (9.00 mL), alkyne (**36**, 0.10 g, 0.57 mmol, 50%) was obtained as pale oil.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 6.35 (d, 0.80H, CH_EOCH$_3$), 5.89 (D, 0.19H, CH_ZOCH$_3$), 4.56 (dd, 0.80H, CH_ECHOCH$_3$), 3.97 (dd, 0.20H, CH_ZCHOCH$_3$), 3.61 (s, 0.46H, OCH_{3Z}), 3.48 (s, 2.54H, OCH_{3Z}), 2.48 – 2.38 (m, 2H, C$H_{aliph.}$), 2.30 – 2.21 (m, 2H, C$H_{aliph.}$), 2.20 – 2.10 (m, 2H, C$H_{aliph.}$), 1.43 – 1.30 (m, 2H, C$H_{aliph.}$), 1.23 – 1.17 (m, 0.54H, C$H_{aliph.}$), 0.79 – 0.68 (m, 2.46H, C$H_{aliph.}$).

The analytical data are in accordance to literature.[10]

(2-((1*R*,8*S*,9*r*)-bicyclo[6.1.0]non-4-yn-9-yl)vinyl)(methyl)sulfane (37)



54 **37**

Following the general procedure from vinyl bromide (**54**, 0.17 g, 0.61 mmol) in THF (3.00 mL), alkyne (**37**, 0.05 g, 0.25 mmol, 41%) was obtained as yellow oil.

TLC: R_f = 0.55 (*n*-pentane/MTBE; 25:1).

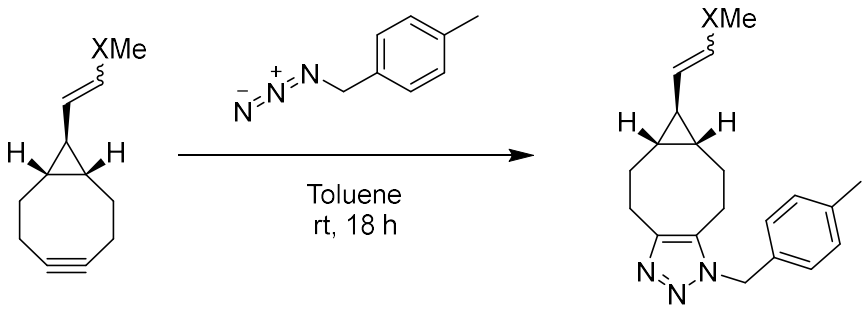
^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 5.96 (d, 0.67H, CH_ESCH_3), 5.80 (d, 0.33H, CH_ZSCH_3), 5.23 – 5.09 (m, 1H, CH_ECHSCH3, CH_ZCHSCH3), 2.52 – 2.38 (m, 2H, C$H_{aliph.}$), 2.38 – 2.30 (m, 1H, C$H_{aliph.}$), 2.28 (s, 0.90H, SC$H_{3,Z}$), 2.26 – 2.23 (m, 1H, C$H_{aliph.}$), 2.22 (S, 2.10H, SC$H_{3,E}$), 2.19 – 2.17 (m, 1H, C$H_{aliph.}$), 2.16 – 2.11 (m, 1H, C$H_{aliph.}$), 1.47 – 1.28 (m, 2H, C$H_{aliph.}$), 1.20 – 1.10 (m, 0.51H, C$H_{aliph.}$), 1.05 – 0.94 (m, 1.40H, C$H_{aliph.}$), 0.90 – 0.78 (m, 1H, C$H_{aliph.}$).

^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 132.57 (CH$_Z$SCH_3), 131.43 (CH$_E$SCH_3), 124.53 (CH$_Z$CHSCH_3), 121.07 (CH$_E$CHSCH_3), 98.87 (2x$C_{alkyne,Z}$), 98.83 (2x$C_{alkyne,E}$), 33.24 (SCH$_{3,Z}$), 33.17 (SCH$_{3,E}$), 28.33 ($C_{aliph.}$), 26.93 ($C_{aliph.}$), 26.58 ($C_{aliph.}$), 25.40 ($C_{aliph.}$), 21.50 ($C_{aliph.,Z}$), 21.45 ($C_{aliph.,E}$), 17.26 ($C_{aliph.}$), 15.50 ($C_{aliph.}$).

IR: (ATR) ν (cm-1) = 2983 (w), 2915 (m), 2847 (w), 1687 (w), 1605 (w), 1437 (m), 1356 (w), 1314 (w), 1293 (w), 1261 (w), 1232 (w), 1197 (w), 1165 (w), 1133 (w), 1071 (m), 974 (w), 928 (s), 907 (w), 806 (w), 761 (w), 729 (s), 648 (w), 571 (w), 516 (s), 464 (w).

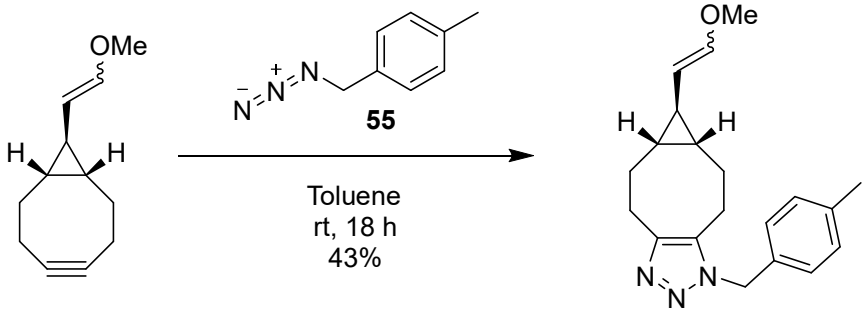
HRMS: (APCI+) m/z calcd. for [M+H$^+$]: 193.1056, found: 193.1051.

General procedure for the synthesis of products 56/57



To a solution of alkyne (1 equiv.) in toluene was added dropwise a 2 M solution of 1-(azidomethyl)-4-methylbenzene (1.2 equiv.) in toluene. The solution was stirred overnight at room temperature then the solvent was removed under reduced pressure. The crude was purified by column chromatography was performed using *n*-pentane/MTBE (50:1 then 20:1 then 1:10) as eluent to afford the desired triazole.

(5a*S*,6*S*,6a*R*)-6-(2-methoxyvinyl)-1-(4-methylbenzyl)-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-d][1,2,3]triazole (56)



36 **56**

Following the general procedure from alkyne (**36**, 0.10 g, 0.57 mmol) in toluene (3.00 mL), triazole (**56**, 0.08 g, 0.24 mmol, 43%) was obtained as white solid.

TLC: R_f = 0.33 (MTBE/*n*-pentane; 5:1).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 7.2 (d, 2H, C$H_{2,aromatic}$), 7.00 (d, 2H, C$H_{2,aromatic}$), 6.28 (d, 0.65H, CH_EOCH$_3$), 5.84 (d, 0.32H, CH_ZOCH$_3$), 5.42 (s, 2H, CH_2Bn), 4.45 (m, 0.68H, CH_ECHOCH$_3$), 3.85 (m, 0.39H, CH_ZCHOCH$_3$), 3.58 (s, 1.03H, OC$H_{3,Z}$), 3.45 (s, 1.90H, OC$H_{3,E}$), 3.15 – 3.10 (m, 0.43H, C$H_{aliph.,Z}$), 3.09 – 3.05 (m, 0.54H, C$H_{aliph.,E}$), 2.90 – 2.80 (m, 1H, C$H_{aliph.}$),

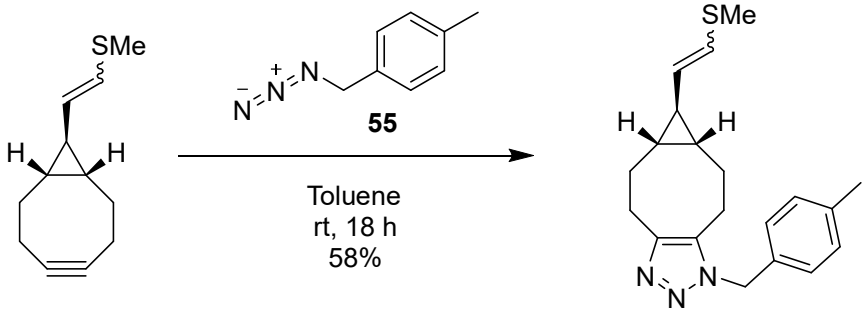
2.78 – 2.69 (m, 1H, C$H_{aliph.}$), 2.54 – 2.44 (m, 1H, C$H_{aliph.}$), 2.43 – 2.34 (m, 1H, C$H_{aliph.}$), 2.32 (s, 3H, PhCH_3), 2.25 – 2.15 (m, 1H, C$H_{aliph.}$), 1.29 – 1.20 (m, 2H, C$H_{aliph.}$), 0.86 – 0.78 (m, 2H, C$H_{aliph.}$), 0.73 – 0.60 (m, 1H, C$H_{aliph.}$).

^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 146.54 (N$C_{aromatic}$), 145.69 (CH_EOCH_3), 145.55 (CH_ZOCH_3), 138.02 (N$C_{aromatic}$), 133.39 ($C_{aromatic}$), 132.56 ($C_{aromatic}$), 129.68 (2x$C_{aromatic}$), 127.03 (2x$C_{aromatic}$), 109.93 (CH_ZCHOCH_3), 105.95 (CH_ECHOCH_3), 59.77 ($OCH_{3,Z}$), 56.22 ($OCH_{3,E}$), 51.96 ($NCH_{2,E}$Bn), 49.58 ($NCH_{2,Z}$Bn), 27.38 ($CH_{aliph.,E}$), 27.31 ($CH_{aliph.,Z}$), 27.12 ($CH_{aliph.}$), 26.53 ($CH_{aliph.,E}$), 26.47 ($CH_{aliph.,Z}$), 26.24 ($CH_{aliph.,Z}$), 26.16 ($CH_{aliph.,E}$), 25.99 ($CH_{aliph.}$), 25,51 ($CH_{aliph.,Z}$), 25.41 ($CH_{aliph.,E}$), 23.68 ($CH_{aliph.Z}$), 23.13 ($CH_{aliph.,E}$), 21.38 ($CH_{aliph.,Z}$), 21.23 ($CH_{aliph.,E}$).

IR: (ATR) ν (cm^{-1}) = 2990 (w), 2924 (w), 2854 (w), 2826 (w), 1651 (m), 1558 (w), 1513 (w), 1451 (w), 1428 (w), 1383 (w), 1361 (w), 1312 (w), 1254 (m), 1208 (s), 1182 (w), 1155 (w), 1136 (s), 1106 (s), 1024 (w), 984 (w), 952 (m), 917 (s), 837 (w), 817 (w), 793 (s), 747 (w), 731 (w), 680 (w), 648 (w), 624 (w), 524 (w), 473 (s).

HRMS: (APCI+) m/z calcd. for [M^+]: 324.2070, found: 324.2078.

(5a*S*,6*S*,6a*R*)-1-(4-methylbenzyl)-6-(2-(methylthio)vinyl)-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-d][1,2,3]triazole (57)



37 **57**

Following the general procedure from alkyne (**37**, 0.05 g, 0.23 mmol) in toluene (1.40 mL), triazole (**57**, 0.05 g, 0.14 mmol, 58%) was obtained as pale yellow solid.

TLC: R_f = 0.33 (MTBE/*n*-pentane; 5:1).

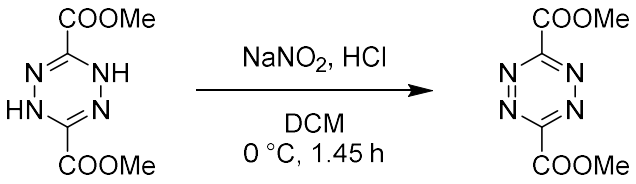
^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 7.12 (d, 2H, C$H_{2,aromatic}$), 7.00 (d, 2H, C$H_{2,aromatic}$), 5.90 (d, 0.77H, CH_ESCH_3), 5.76 (d, 0.28H, CH_ZSCH_3), 5.42 (s, 2H, CH_2Bn), 5.11 – 5.00 (m, 1H, CH_ECHSCH_3, CH_ZCHSCH_3), 3.15 – 3.10 (m, 0.47H, C$H_{aliph.,Z}$), 3.09 – 3.05 (m, 0.62H, C$H_{aliph,E}$), 2.90 – 2.81 (m, 1H, C$H_{aliph.}$), 2.80 – 2.70 (m, 1H, C$H_{aliph.}$), 2.54 – 2.46 (m, 1H, C$H_{aliph.}$), 2.45 – 2.35 (m, 1H, C$H_{aliph.}$), 2.27 (s, 0.61H, S$CH_{3,Z}$), 2.19 (s, 2.17H, S$CH_{3,E}$), 1.35 – 1.30 (m, 1H, C$H_{aliph.}$), 1.30 – 1.27 (m, 1H, C$H_{aliph.}$), 1.26 – 1.24 (m, 2H, C$H_{aliph.}$), 1.03 – 0.94 (m, 2H, C$H_{aliph.}$), 0.86 – 0.82 (m, 2H, C$H_{aliph.}$), 0.81 – 0.75 (m, 1H, C$H_{aliph.}$).

^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 145.44 (N$C_{aromatic}$), 137.94 (N$C_{aromatic}$), 133.95 (CH_ZSCH_3), 133.13 ($C_{aromatic}$), 132.38 ($C_{aromatic}$), 131.64 (CH_ESCH_3), 130.55 (CH_ESCH3), 129.57 (2x$C_{aromatic}$), 126.90 (2x$C_{aromatic}$), 123.53 ($CH_ZCHSCH3$), 121.18 (CH_ECHSCH_3), 51.85 (NCH_2), 40.40 ($SCH_{3,Z}$), 40.02 ($SCH_{3,E}$), 29.76 ($CH_{aliph.,Z}$), 28.78 ($CH_{aliph.,E}$), 27.11 ($CH_{aliph.,E}$), 27.08 ($CH_{aliph.,Z}$), 26.51 ($CH_{aliph.,Z}$), 26.44 ($CH_{aliph.,Z}$), 26.24 ($CH_{aliph.,E}$), 26.16 ($CH_{aliph.,E}$), 26.05 ($CH_{aliph.,E}$), 25.77 ($CH_{aliph.,Z}$), 22.95 ($CH_{aliph.,Z}$), 22.92 ($CH_{aliph.,E}$), 21.10 ($CH_{aliph.}$), 15.47 ($CH_{aliph.}$).

IR: (ATR) ν (cm^{-1}) = 2966 (w), 2917 (m), 2853 (w), 1556 (w), 1513 (m), 1452 (m), 1427 (w), 1358 (m), 1318 (w), 1262 (w), 1239 (w), 1224 (w), 1181 (w), 1136 (w), 1111 (w), 1084 (m), 1023 (m), 984 (m), 950 (w), 921 (s), 835 (w), 792 (s), 744 (m), 697 (w), 680 (w), 649 (w), 628 (w), 521 (w), 472 (s).

HRMS: (APCI+) m/z calcd. for [M+H$^+$]: 340.1842, found: 340.1850.

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (59)



58 **59**

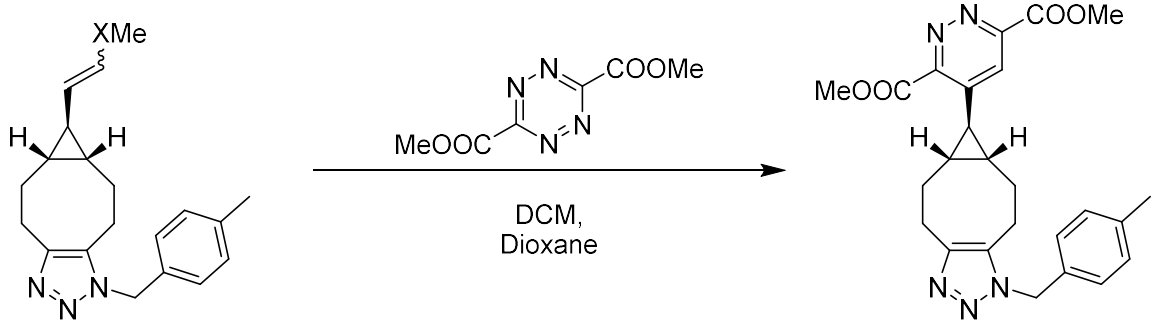
To a solution of tetrazine (**51**, 0.10 g, 0.50 mmol) at 0 °C were bubbled the nitrous gases generated by adding dropwise a solution of $NaNO_2$ 6M (0.42 g, 6.09 mmol) to concentrated HCl (1.00 mL). The solution was stirred for 15 min at the same temperature then it was gradually warmed up to rt and stirred for 90 min. The solvent was removed under reduced pressure to get tetrazine (**52**, 0.10 g, 0.50 mmol, quant.) as red solid.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 4.23 (s, 2H, COOC*H*$_3$).

^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 160.39 (2 x N*C*$_{aromatic}$), 159.16 (2 x *C*OOMe), 54.60 (2 x COO*C*H$_3$).

The analytical data were in accordance to literature.[54]

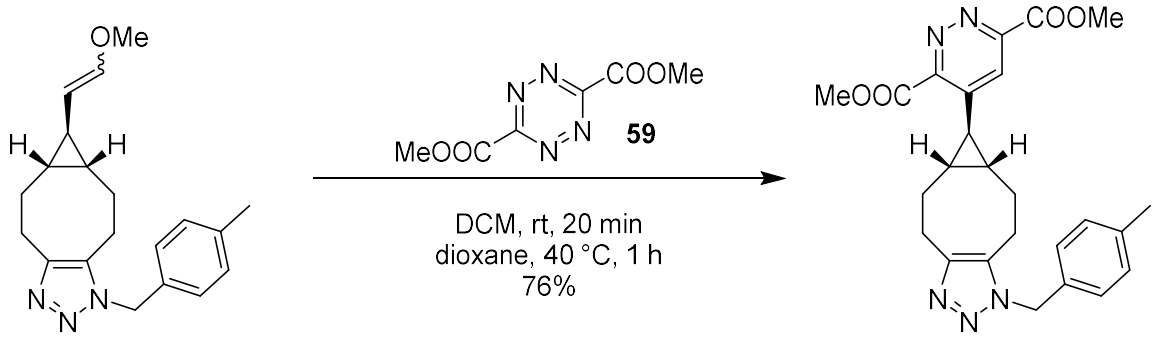
General procedure for the synthesis of dimethyl 4-(1-(4-methylbenzyl)-1,4,5,5a,6,6a,7,8-octahydrocyclopropa[5,6]cycloocta[1,2-d][1,2,3]triazol-6-yl)pyridazine-3,6-dicarboxylate (60)



To a solution of alkene (0.12 mmol, 1.60 equiv.) in DCM (0.62 mL) a solution of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (0.08 mmol, 1.00 equiv.) in DCM (0.39 mL) was added dropwise at rt. After stirring at the same temperature until the colour

changed from red to yellow, solvent was removed under reduced pressure. The oil was dissolved in dioxane (2.00 mL) and the solution was stirred on a heating plate, following the reaction with TLC until completition. Solvent was removed under reduced pressure. Column chromatography using DCM/MeOH (30:1) gave pyridazine as solid.

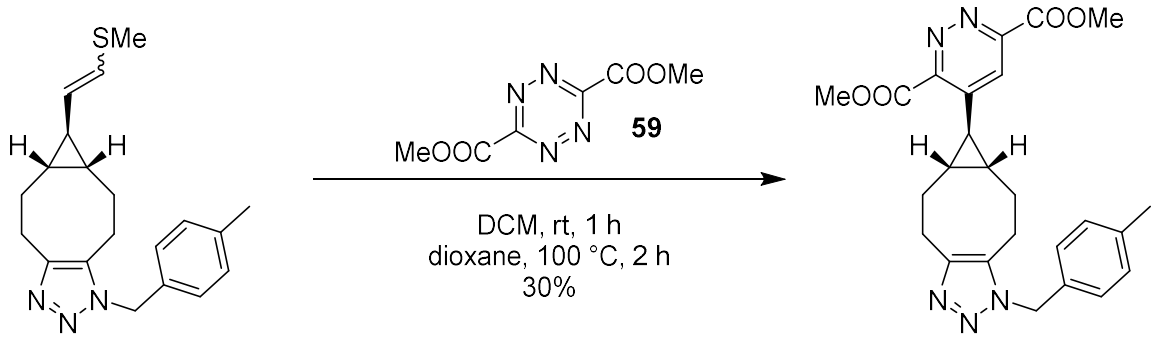
a) Synthesis of 60 from 56



56 **60**

Following the general procedure, starting from alkene **56**, the solution was stirred in DCM for 30 min at room temperature. Then the solvent was removed, and the crude was taken with dioxane and stirred at 40 °C for 1 h to afford the desired pyridazine (**60**, 0.03 g, 0.06 mmol, 76%) after column chromatography.

b) Synthesis of 60 from 57



57 **60**

Following the general procedure, starting from alkene **57**, the solution was stirred in DCM for 1h at room temperature. Then the solvent was removed, and the crude was

taken with dioxane and stirred at 100 °C for 2 h to afford the desired pyridazine (**60**, 0.01 g, 0.02 mmol, 30%) after column chromatography.

TLC: R_f = 0.56 (DCM:MeOH; 10:1).

^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 7.57 (s, 1H, C*H*CCOOMe), 7.15 (d, 2H, C$H_{2,aromatic}$), 7.03 (d, 2H, C$H_{2,aromatic}$), 5.46 (d, 2H, CH_2Bn), 4.06 (d, 6H, 2x COOCH_3), 3.20 – 3.15 (m, 1H, C$H_{aliph.}$), 2.97 – 2.93 (m, 1H, C$H_{aliph.}$), 2.86 – 2.83 (m, 1H, C$H_{aliph.}$), 2.82 – 2.80 (m, 1H, C$H_{aliph.}$), 2.60 – 2.55 (m, 1H, C$H_{aliph.}$), 2.54 – 2.50 (m, 1H, C$H_{aliph.}$), 2,32 (s, 3H, PhCH_3), 1.65 – 1.61 (m, 1H, C$H_{aliph.}$), 1.50 – 1.44 (m, 2H, C$H_{aliph.}$), 1.31 – 1.26 (m, 2H, C$H_{aliph.}$).

^{13}C-NMR: (75 MHz, $CDCl_3$): δ = 165.63 (*C*OOMe), 164.65 (*C*OOMe), 154.22 (N*C*$_{aromatic}$), 151.77 (N*C*$_{aromatic}$), 145.34 (N*C*$_{aromatic}$), 145.28 (N*C*$_{aromatic}$), 138.50 (*C*$_{aromatic}$), 132.99 (*C*$_{aromatic}$), 132.48 (*C*$_{aromatic}$), 130.01 (*C*$_{aromatic}$), 129.95 (*C*$_{aromatic}$), 127.27 (*C*$_{aromatic}$), 127.12 (*C*$_{aromatic}$), 123.36 (*C*$_{aromatic}$), 53.92 (COO*C*H$_3$), 53.72 (COO*C*H$_3$), 52.34 (N*C*H$_2$Bn), 31.03 (*C*H$_{aliph.}$), 30.91 (*C*H$_{aliph.}$), 27.39 (*C*H$_{aliph.}$), 26.45 (*C*H$_{aliph.}$), 25.93 (*C*H$_{aliph.}$), 25.52 (*C*H$_{aliph.}$), 22.85 (*C*H$_{aliph.}$), 21.45 (*C*H$_{aliph.}$).

IR: (ATR) ν (cm^{-1}) = 2922 (s), 2853 (m), 1730 (s), 1579 (w), 1516 (w), 1439 (m), 1396 (w), 1377 (w), 1262 (s), 1192 (w), 1136 (s), 1119 (m), 1029 (w), 1003 (w), 980 (w), 956 (w), 795 (w), 733 (w), 476 (w).

HRMS (APCI+) m/z calcd. for [M+H$^+$] = 462.2136, found: 462.2146.

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