

Synthesis of (*E*)-Cycloalkenes and (*E,E*)-Cycloalkadienes  
by Ring Closing Diyne or Enyne-Yne Metathesis / Semi-  
Reduction and Studies towards Total Synthesis of  
Myxovirescin A<sub>1</sub>

**DISSERTATION**

Zur Erlangung des akademischen Grades eines

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A mes parents,

à ma famille,

et à mes amis...

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Ac	Acetyl	Me	Methyl
Anal	Elemental analysis	Ms	Mesyl
9-BBN	9-Borabicyclo[3.3.1]nonane	MHz	Megahertz
Bn	Benzyl	MOM	Methoxymethyl
Bu	Butyl	Mp	Melting point
CM	Cross-metathesis	Ms	methanesulfonyl
COSY	Correlation spectroscopy	MS	Mass spectrum
Cp	Cyclopentadienyl	MTBE	Methyl- <i>tert</i> -butylether
Cp*	Pentamethylcyclopentadienyl	NBS	N-Bromosuccinimide
$\delta$	Chemical shift	NCS	N-Chlorosuccinimide
DCC	Dicyclohexyl carbodiimide	NIS	N-Iodosuccinimide
DCM	Dichloromethane	NMO	N-Methylmorpholine-N-oxide
DEPT	Distortionless enhancement by polarisation transfer	NMR	Nuclear magnetic resonance
DiBAL-H	Diisobutylaluminium hydride	NOE(SY)	Nuclear Overhauser effect (spectroscopy) or nOe
DMAP	4-Dimethylaminopyridine	PCC	Pyridinium chlorochromate
DMF	Dimethylformamide	PDC	Pyridinium dichromate
DMSO	Dimethyl sulfoxide	Ph	Phenyl
Dppf	diphenylphosphinoferrocene	PMB	<i>p</i> -Methoxybenzyl
EDC	N <sup>'</sup> -(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride	PPh <sub>3</sub>	Triphenylphosphine
EI	Electron impact	PPTS	Pyridinium <i>p</i> -toluenesulfonate
Eq	Equivalent	RCAM	Ring closing alkyne metathesis
Et	Ethyl	RCM	Ring closing metathesis
FAB	Fast atom bombardment	ROM	Ring opening metathesis
FID	Flame ionisation detector	ROMP	Ring opening metathesis polymerisation
GC	Gas chromatography	RT	Room temperature
GC/MS	Gas chromatography coupled with a mass spectrum	Py	Pyridine
HMQC	Proton detected heteronuclear multiquantum coherence	TBAF	Tetrabutylammoniumfluoride
HRMS	High resolution mass spectrum	TBS	<i>tert</i> -Butyldimethylsilyl
Hz	Hertz	TES	Triethylsilyl
IR	Infrared spectroscopy	THF	Tetrahydrofuran
<i>J</i>	Coupling constant	THP	Tetrahydropyran
LAH	Lithiumaluminium hydride	TLC	Thin layer chromatography
		TMS	Trimethylsilyl
		UV	Ultraviolet spectroscopy

# INTRODUCTION

## I. Alkene and Alkyne Metathesis: Principle and Applications

Alkyne or alkene metathesis, as pictured in Figure 1, is a mutual alkylidyne or alkylidene exchange reaction of alkynes or alkenes. Formation of two carbon-carbon multiple-bond units in a single step is a remarkable and quite unique transformation in organic chemistry.<sup>[1]</sup>

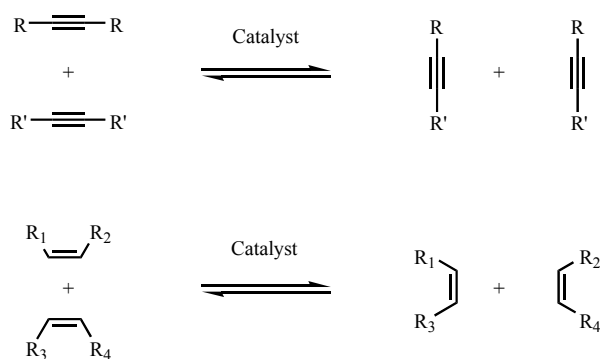


Figure 1. Metathesis of alkynes and alkenes

Since the discovery in the mid 1950's of the first example of alkene metathesis and later work on various alkylidene complexes, alkene metathesis has grown exponentially over the last decades. Nowadays, the most popular molybdenum and ruthenium-based catalysts are commercially available and more than 30 years of methodologic maturation has made of alkene metathesis a widely used tool in many fields of chemistry. Alkyne metathesis was discovered later (in the 1970's), is overall less developed and it was long only used for the synthesis of speciality polymers and simple acetylene derivatives. However, recent catalytic systems enable more efficient applications, notably in advanced organic synthesis. As shown in Figure 2 and Figure 3, alkene and alkyne metathesis can be applied in many different ways. Examples are illustrated below and include: cross-metathesis (CM), ring-closing metathesis (RCM for alkene and RCAM for alkynes), ring-opening metathesis (ROM), ring-opening metathesis polymerisation (ROMP), acyclic diene metathesis polymerisation (ADMET), and acyclic diyne metathesis polymerisation (ADIMET).

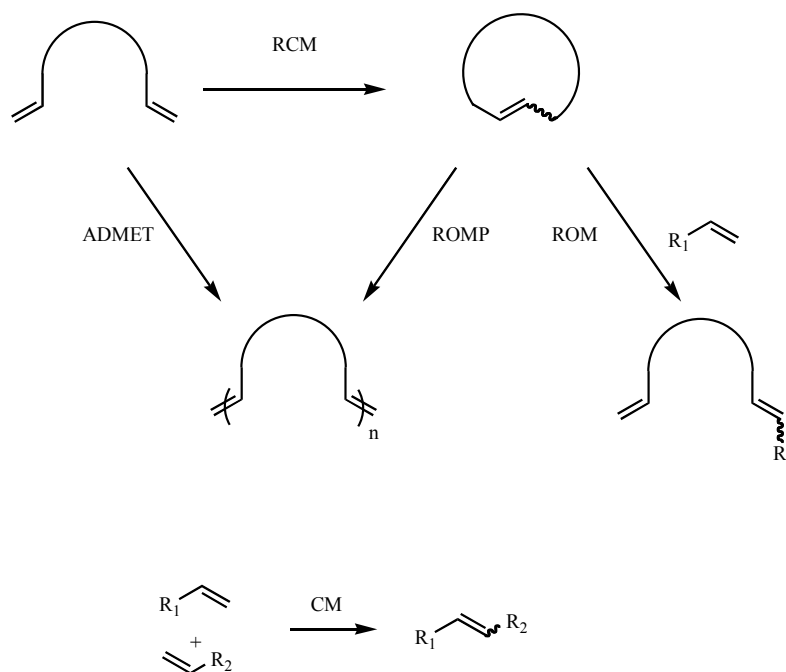


Figure 2. Applications of alkene metathesis

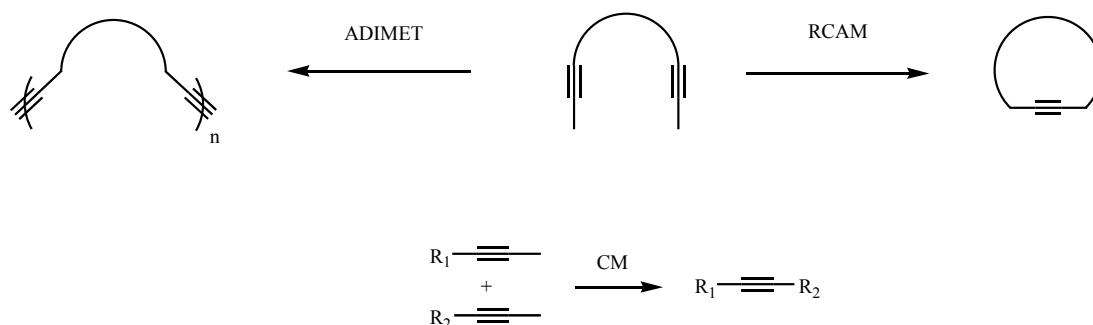


Figure 3. Applications of alkyne metathesis

## II. The Different Catalytic Systems for Alkyne Metathesis and their Properties

The first homogeneous alkyne metathesis was described by Mortreux and Blanchard.<sup>[2]</sup>  $Mo(CO)_6$  in the presence of phenol catalyses the metathesis of 1-phenyl-1-propyne derivatives at high temperature ( $>130^\circ C$ ). The exact nature of the catalytic species remains unknown and, because of the harsh conditions required as well as a low functional group tolerance (aldehydes, cyano groups, amines and thioethers are not tolerated), this method has only been used for the synthesis of



thermally-stable molecules (See Figure 4)<sup>[3-6]</sup> and the polymerisation of diynes.<sup>[4, 7, 8]</sup> Only internal alkynes undergo metathesis under these conditions, and methyl substituted acetylenes are most commonly utilised. A large number of phenols and other alcohols have been screened to improve the properties of the catalytic system but only little progress was achieved, the most effective co-catalysts being  $\alpha,\alpha,\alpha$ -*p*-trifluorocresol,<sup>[9]</sup> *p*-chlorophenol<sup>[10]</sup> and *o*-fluorophenol.<sup>[11]</sup> Following a different approach, Chauvin<sup>[12]</sup> and Bunz<sup>[13]</sup> developed independently two methods to enhance the activity of the Mortreux system. Both methodologies use a principle of pre-generation of the unknown catalyst at high temperature followed by the desired metathesis reaction at lower temperature. While Bunz<sup>[13]</sup> premixes hex-3-yne,  $\text{Mo}(\text{CO})_6$  and a phenol derivative (possibly creating a  $\text{Mo}^{\text{VI}}$  alkylidyne complex), Chauvin<sup>[12]</sup> uses dimethoxyethane to stabilise the active intermediate formed from  $\text{Mo}(\text{CO})_6$  and a phenol species. These methods allow to metathesise substrates that are problematic under Mortreux's original conditions, and more generally allow the reaction to be performed at lower temperatures. Unfortunately, they do not entirely solve the major problem of low tolerance towards many functional groups.

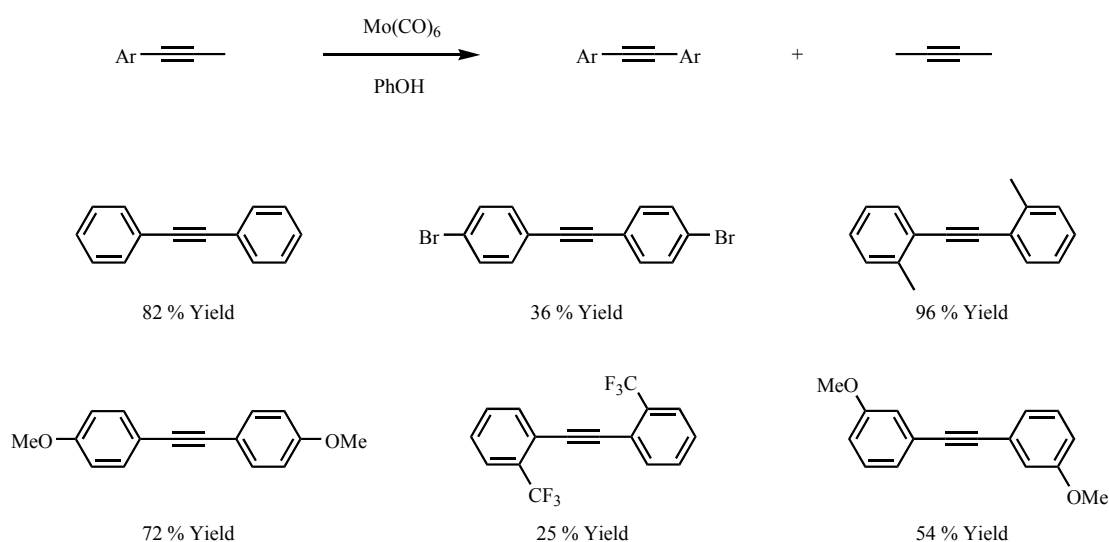
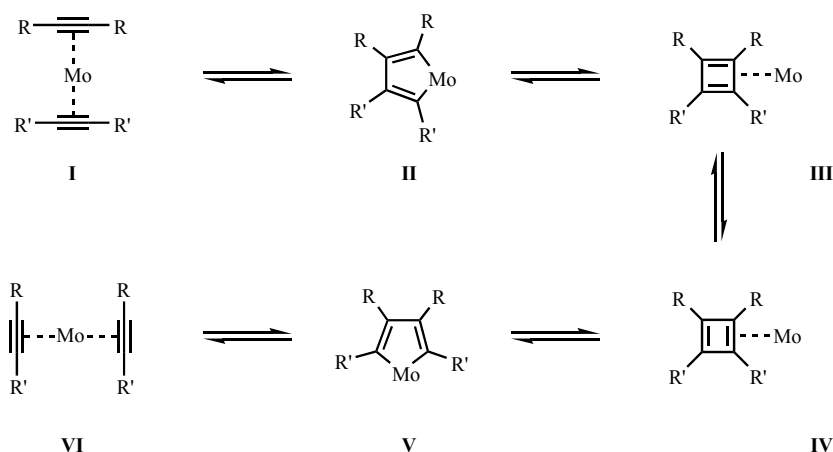


Figure 4. Examples of cross-metathesis products obtained with the standard Mortreux system<sup>[3]</sup>

Isolation of cyclotrimerisation products<sup>[6]</sup> in the presence of Mortreux's catalytic system led Mori and co-workers to consider a mechanistic pathway involving a 5-membered metallacycle as reactive intermediate (Scheme 1). Coordination of two alkyne units to the molybdenum catalyst leads to complex **I**. The latter gives metallacyclopentadiene **II** via an oxidative cyclisation which undergoes a reductive elimination to form a coordinated cyclobutadiene **III**. Isomerisation of this intermediate followed by formation of the corresponding metallacycle **V** and finally cycloreversion affords the desired metathesis products.



Scheme 1. Mechanistic pathway for Morteux catalytic systems proposed by Mori<sup>[6]</sup>

Since olefins were already known to be metathesised by alkylidene catalysts,<sup>[14-17]</sup> and since it was proposed that acetylenes could be metathesised analogously by carbyne complexes,<sup>[18]</sup> some attention was given to various alkylidyne complexes.<sup>[19, 20]</sup> Schrock was the first to make a significant breakthrough in alkyne metathesis by developing the highly active and well-defined tungsten<sup>VI</sup> alkylidyne complex (*t*-BuO)<sub>3</sub>WCC*t*-Bu **1** (Figure 5).<sup>[20]</sup> Tungsten catalysed metathesis requires manipulation under inert atmosphere and freshly dried solvents but shows a broader tolerance to functional groups and proceeds under milder conditions (between room temperature and 80°C). Substrates bearing potential donors such as thioethers, free amines, and crown ether segments, however, are incompatible with catalyst **1**. This system was successfully used for cross-metathesis and for the first examples of ring closing alkyne metathesis (RCAM).<sup>[21, 22]</sup>

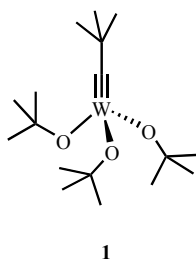
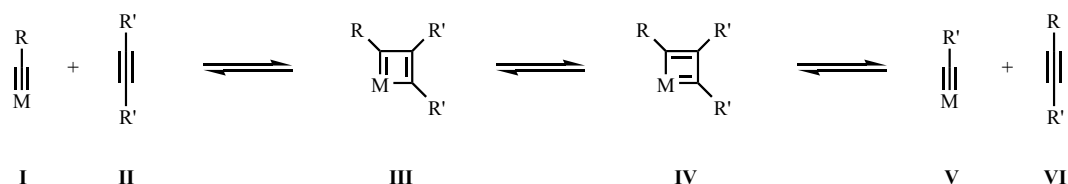


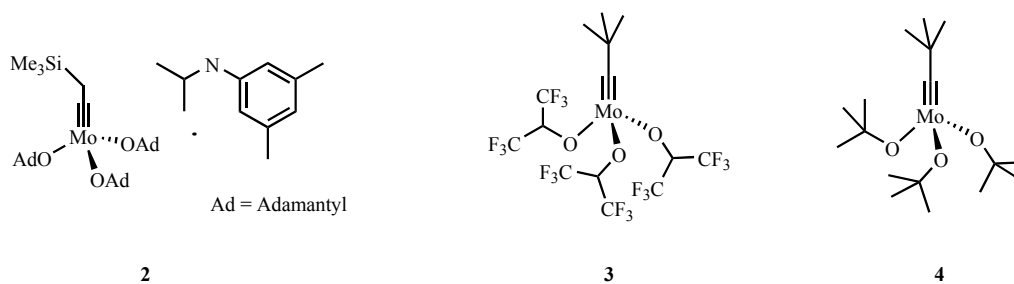
Figure 5. Schrock's tungsten alkylidyne metathesis catalyst **1**

Another mechanistic pathway must be considered for catalysis with alkylidyne species (Scheme 2),<sup>[18, 20]</sup> which is closely related to the Chauvin mechanism commonly used to explain alkene metathesis.<sup>[23]</sup> It involves metallacyclobutadiene **III** initially formed from the acetylenic compound **II** and the alkylidyne complex **I** via a [2+2] cycloaddition. Intermediate **III** undergoes isomerisation to **IV** followed by a ring opening and affords the expected product **VI** as well as new catalytically active alkylidyne complex **V**.



*Scheme 2. Adaptation of the Chauvin mechanism for alkylidyne catalysts*

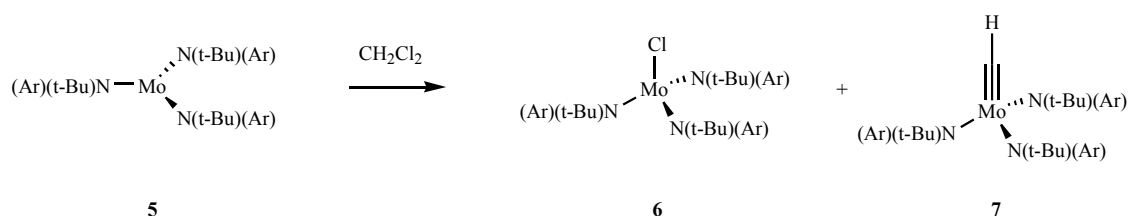
Since these first reports, further advances by Schrock<sup>[24]</sup> and more recently by Cummins<sup>[25]</sup> were made on molybdenum-based alkyne metathesis catalysts. They described similar trialkoxy alkylidyne molybdenum<sup>VI</sup> complexes **2** and **3** (Figure 6) which show high activity for alkyne metathesis even at room temperature. However, their scope has not been studied in detail. One should mention that the electronic nature of the alkoxy substituents is crucial for metathetic activity. Molybdenum catalyst **4** is very closely related to **2** and **3** but shows no metathetic activity<sup>[26]</sup>. Unfortunately, the difficult multistep synthesis and their high sensitivity toward moisture and air represent a major disadvantage, preventing the widespread use of these catalysts.



*Figure 6. Examples of catalytically active and inactive trialkoxy molybdenum alkylidyne complexes*

Schrock's tungsten complex **1** remained the most widely used catalyst until Fürstner developed a molybdenum catalyst<sup>[27]</sup> obtained *in situ* by activation of the previously described<sup>[28, 29]</sup> Mo[N(*t*-Bu)(Ar)]<sub>3</sub> **5** with methylene chloride. Under these conditions, a mixture of MoCl[N(*t*-Bu)(Ar)]<sub>3</sub> **6** and of the catalytically incompetent alkylidyne HCCMo[N(*t*-Bu)(Ar)]<sub>3</sub> **7** is formed (Scheme 3).<sup>[30]</sup> Fürstner proved that the active intermediate is derived from MoCl[N(*t*-Bu)(Ar)]<sub>3</sub> **6** and

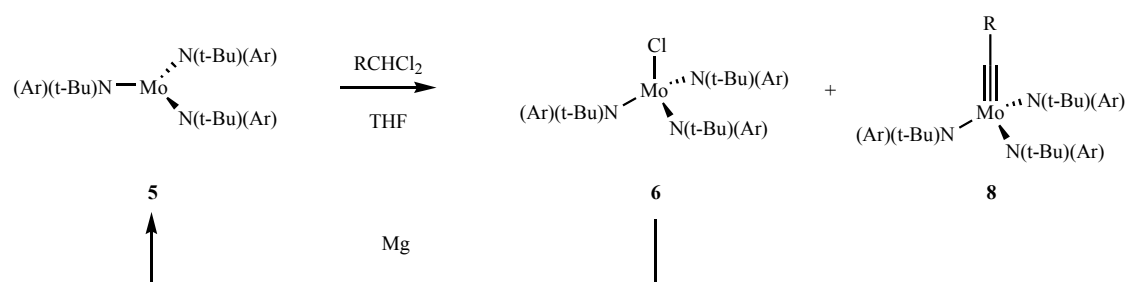
catalyses alkyne metathesis with a large functional group tolerance under mild conditions (80°C or lower). Contrary to **1**, complex **6** tolerates the presence of donors such as amines or thioethers. It was proposed<sup>[27, 30]</sup> that this property is due to the crowded pocket formed by the ligands around the molybdenum centre. This pocket is claimed to attenuate the Lewis acidic character of the molybdenum atom and to prevent coordination of donors to the metal.



Scheme 3. Activation of trisamido molybdenum complexes via addition of  $\text{CH}_2\text{Cl}_2$

Molybdenum complex **5** has been used as the precatalyst of choice for the dimerisation of simple molecules,<sup>[27, 30, 31]</sup> ring closure of larger macrocycles,<sup>[27, 30, 32-34]</sup> and cross-metathesis reactions of both simple substrates and more elaborated compounds in total synthesis.<sup>[32]</sup> Catalyst **6**, however, is sensitive toward “acidic” protons such as those of secondary amides or alcohols.<sup>[27, 30]</sup>

Following Fürstner’s work, Moore and co-workers<sup>[35]</sup> demonstrated that various molybdenum alkydine complexes **8** can be synthesised in high yields by treatment of trisamido molybdenum<sup>III</sup> **5** with geminal dihaloalkanes under reductive recycling conditions (Scheme 4).



Scheme 4. Preparation of trisamido alkydine molybdenum complexes

Trisamido alkydine molybdenum<sup>VI</sup> complexes usually do not undergo alkyne metathesis,<sup>[25, 35]</sup> but their *in situ* alcoholysis with phenols or alcohols produces highly active catalysts.<sup>[36]</sup> Among these alcohols, *p*-nitrophenol and  $\alpha,\alpha,\alpha$ -*p*-trifluorocresol gave the best results. Unfortunately, the presumably formed trialkoxy alkydine complexes have not been fully characterised. These alkydine complexes catalyse metathesis of compounds bearing a secondary amide functionality<sup>[36]</sup> or a polyether chain<sup>[35]</sup> and enable the synthesis of poly(2,5-thienylene ethynylene)s of high molecular

weight through alkyne metathesis.<sup>[37]</sup> As the catalysts are active at room temperature, the reaction vessel has to be set under dynamic vacuum to remove but-2-yne as the volatile by-product. This precaution is unnecessary at higher temperatures. The second product generated by metathetic alkyne exchange can also be removed via a gentle argon flow purging the system. This process is one of the driving forces of the reaction: one of the products formed is removed from the reaction mixture, thereby shifting the equilibrium to the right.

It was also found during the course of these studies that the size of the alkyl substituent on the acetylenic substrate plays a role in the present catalytic system (Table 1). In the presence of molybdenum alkylidyne **8** and *p*-nitrophenol, the alkyne metathesis by-product but-2-yne shows a greater tendency to polymerise than hex-3-yne, probably due to steric reasons (Figure 7).<sup>[20, 36]</sup>

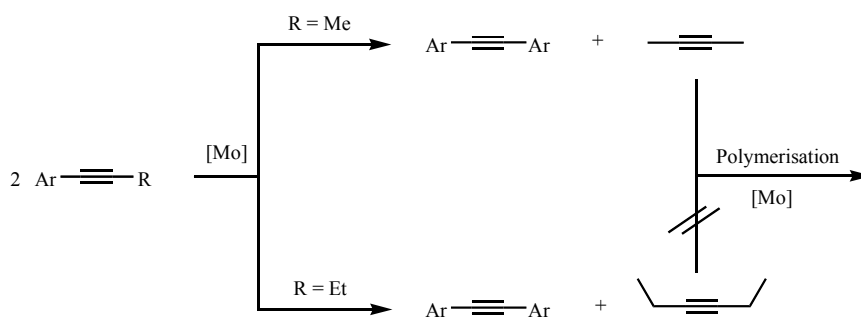


Figure 7. Advantage of ethyl substituted over methyl substituted alkynes

Polymerisation is thought to occur via a ring expansion mechanism and can be considered as a catalyst poisoning process. Replacing a methyl group by an ethyl on the substrate and removing hex-3-yne by a dynamic vacuum allowed homodimerisation of problematic substrates such as thiophene derivatives in high yields.

Table 1. Importance of the alkyl substituent on the alkyne moiety<sup>[36]</sup>

Substrate	Product	System 1 (R = Me)	System 2 (R = Et)
		58 %	93 %
		46 %	83 %
		<5 %	91 %

<sup>a</sup> The reactions were carried out at 30°C in 1,2,4-trichlorobenzene during 22h under 1 mm Hg.

### III. Ring Closing Metathesis

#### III.1. Alkene Ring Closing Metathesis (RCM)

Today, three catalysts are widely used which possess high activity as well as a very good tolerance towards a broad range of functional groups: molybdenum alkylidene **9**<sup>[38-40]</sup> and ruthenium carbene complexes **10** and **11** (Figure 8).<sup>[41-45]</sup> While these catalysts are now commercially available, the ruthenium-based ones are most popular and versatile because they are more stable and tolerate a larger range of functional groups than the molybdenum-based catalyst.<sup>[1]</sup>

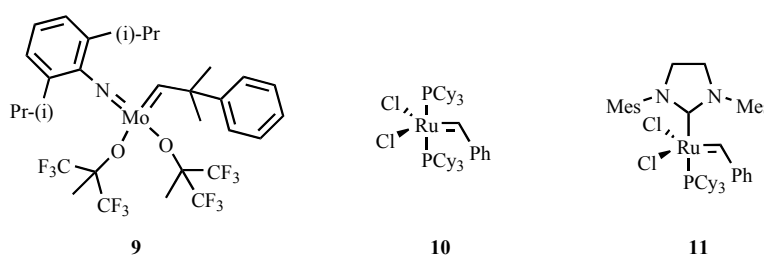


Figure 8. Various alkene metathesis catalysts

Ring closing metathesis is one of the most important application of alkene metathesis. Since two products are formed from one substrate, the cycloalkene and e.g. ethylene, the reaction is entropically driven. The equilibrium of this reversible reaction is shifted towards the formation of the products due to the release of ethylene. Competing oligomerisation or polymerisation of the substrate can be overcome by working under dilute conditions. While 5-7 membered rings are easily synthesised, larger cyclic substances (8-11 membered) are problematic due to ring-strain issues. When even longer dienes undergo RCM, no control over the stereochemistry of the double bond is possible. Until now the problem has not been efficiently solved and synthetic chemists have to face the formation of a mixture of (*E*) and (*Z*) isomers even if the (*E*)-isomer is usually favoured. Many examples illustrating this difficulty can be found in the literature, such as the epothilone derivative **12**,<sup>[46-48]</sup> the protected azamacrolide epilachene **13**,<sup>[49]</sup> and turriane **14** (Figure 9).<sup>[33]</sup>

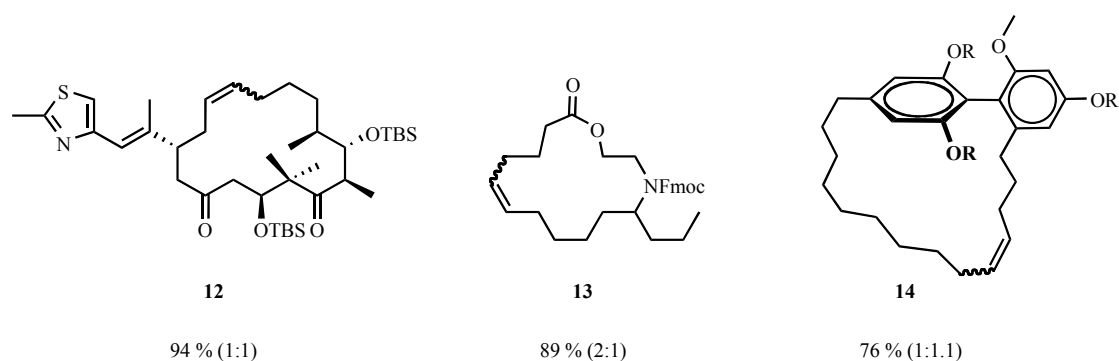


Figure 9. Reported examples of macrocycles formed by RCM

This difficulty is increased when the targeted molecule is a 1,3-diene. In this case, stereocontrol and a rigorous control over the site of attack by the metathesis catalyst must go hand in hand to avoid the formation of ring contracted products that are difficult to separate from the individual cycloalkadiene isomers (Figure 10).<sup>[50-57]</sup>

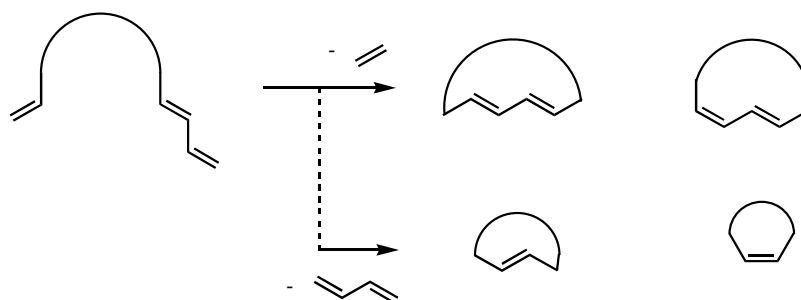


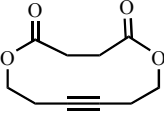
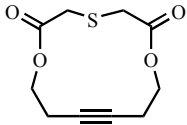
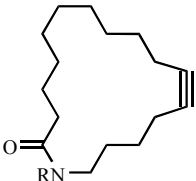
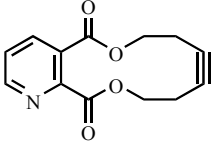
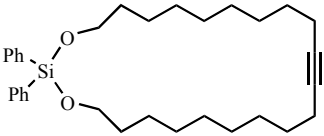
Figure 10. Chemoselectivity issues for RCM involving 1,3- dienes

Since no alkene metathesis catalysts have been developed that can ensure stereoselective double bond formation, other means had to be found to overcome this problem. Alkyne metathesis constitutes the alternative of choice for this purpose.

### III.2. Ring Closing Alkyne Metathesis (RCAM)

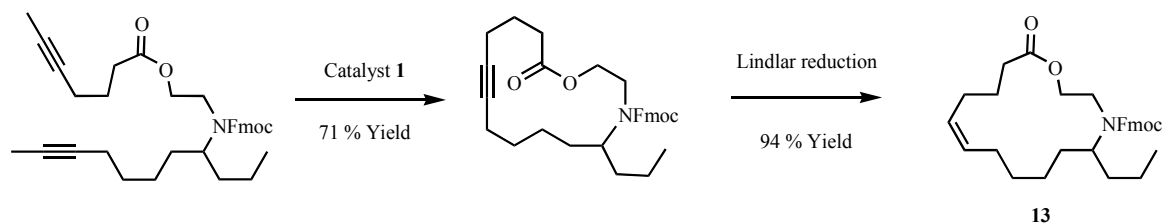
Mainly Schrock's tungsten<sup>VI</sup> catalyst **1** and the molybdenum<sup>VI</sup> catalyst **5** have been extensively used for ring closing purposes and are complementary with respect to their tolerance towards certain functional groups (Table 2).<sup>[21, 22, 30, 58, 59]</sup> Diynes also undergo cyclisation with the Mortreux system, but the very harsh conditions make it unattractive for the total synthesis of natural products.

Table 2. Examples of RCAM with different catalytic systems.

Product	Mo catalyst <b>5</b>	Mo(CO) <sub>6</sub> + ArOH	W catalyst <b>1</b>
	91 %	64 %	73 %
	84 %		0 %
	R = H 0 % R = Me 72 %	0 % 64 %	62 % 72 %
	88 %		0 %
	74 %		55 %



Alkyne metathesis followed by a Lindlar semi-reduction is a convenient method for the preparation of (*Z*)-alkenes in a stereocontrolled way. It has been successfully applied to the synthesis of natural products such as the azamacrolide **13**,<sup>[22]</sup> thus constituting an alternative to the alkene metathesis pathway (see Figure 9 and Scheme 5).



Scheme 5. Synthesis of **13** via alkyne metathesis

Stereoselective reduction of an alkyne moiety to the corresponding (*E*)-alkene would be the complement to Lindlar's methodology (Figure 11). Precedents for this transformation are available in the literature but none of the reported methods meets all criteria of selectivity and functional group tolerance required for applications to advanced organic synthesis. The methods are based on the use of chromium salts,<sup>[60-62]</sup> metal hydrides<sup>[63]</sup> and dissolving metal reduction (Birch type).<sup>[64]</sup> However, recent advances in metal-catalysed alkyne hydrosilylation hold the promise of solving this issue.

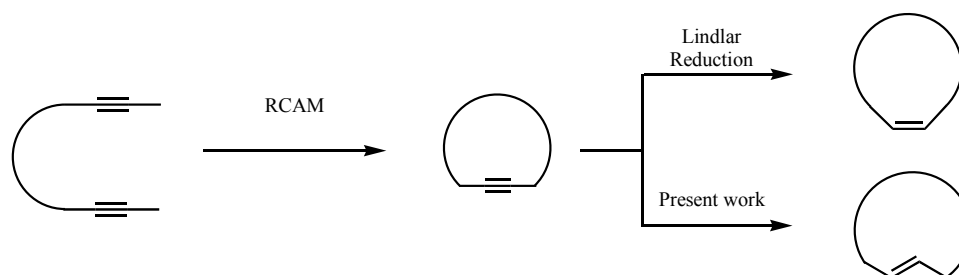


Figure 11. From cyclodiyne to stereodefined cycloalkenes

## IV. Hydrosilylation

### IV.1. Introduction

Hydrosilylation of alkynes is a very well documented preparative method for the synthesis of vinylsilanes.<sup>[65-69]</sup> It is known that transition metal catalysts, radical initiators and Lewis acids can induce addition of various silanes to acetylene derivatives. The most commonly used catalyst is hexachloroplatinic<sup>IV</sup> acid ( $\text{H}_2\text{PtCl}_6$ ) (Speier's catalyst), the activity of which was discovered in 1957.<sup>[70]</sup> Since the first report on hydrosilylation, many transition metal catalysts have been developed for this transformation, but the most active remain platinum-based: Speier's and Karstedt's catalyst (Figure 12).<sup>[71]</sup> They stereoselectively hydrosilylate internal and terminal alkynes via a *cis*-addition pathway. Generally, the reaction is highly chemoselective and many functional groups are tolerated (ketones, ester, nitrile, amine, ether, nitro group). Furthermore, alkynes are more reactive than alkenes and will be preferentially hydrosilylated.<sup>[67]</sup>

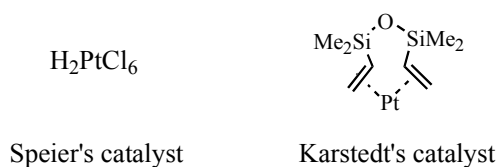


Figure 12. Common platinum-based hydrosilylation catalysts

Net *cis*-addition of a silane to an alkyne was long considered as the inevitable outcome of transition metal catalysed alkyne hydrosilylation until Ojima and co-workers found that net *anti*-addition can also occur.<sup>[72, 73]</sup> Various mechanisms were proposed which were unsatisfactory.<sup>[73, 74]</sup> Today, the commonly accepted catalytic cycle for hydrosilylation of alkynes has been presented independently by Ojima<sup>[73]</sup> and Crabtree<sup>[75]</sup> (Figure 13) and proposes a plausible explanation for the variable *cis*- and *trans*-addition patterns observed for different catalytic systems. However, it has been developed to explain results obtained with terminal alkynes. Any extension to the reaction of disubstituted acetylenes should therefore be done with particular care.

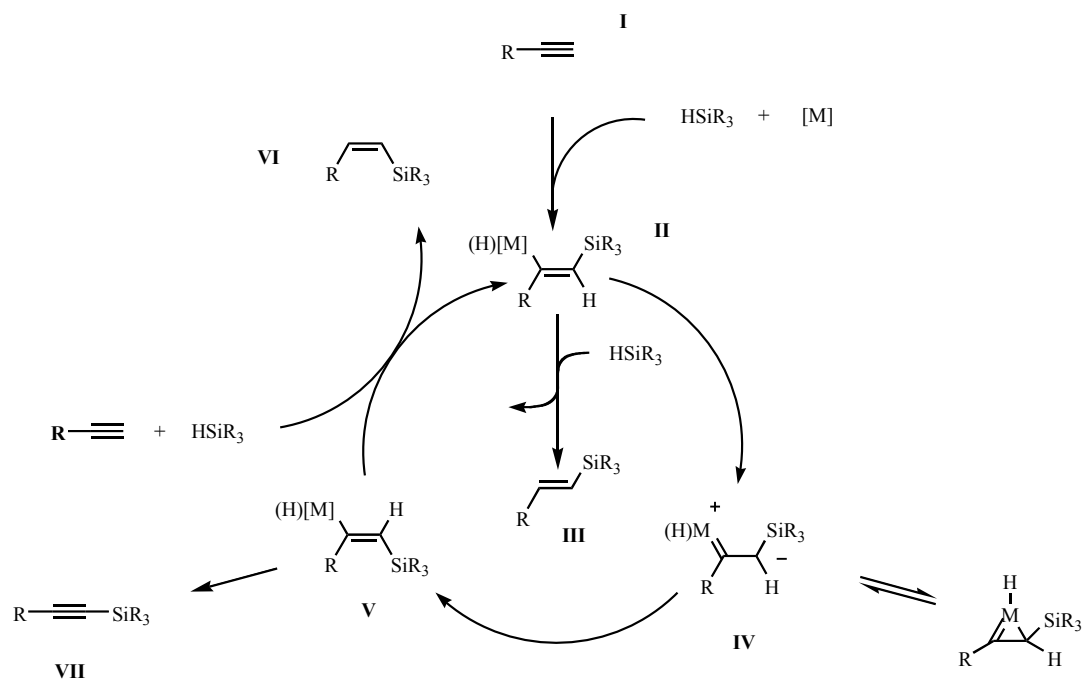


Figure 13. Ojima-Crabtree mechanism for hydrosilylation of 1-alkynes

Oxidative addition of a silane ( $\text{HSiR}_3$ ) to the metal followed by insertion of alkyne **I** into the metal silicon bond affords intermediate **II**. This species can either directly undergo reductive elimination to afford the (*E*)-configured alkene **III** or, because of steric repulsion between  $\text{SiR}_3$  and the metal, can isomerise to form the thermodynamically more stable intermediate **V** via a zwitterionic species **IV**. Reductive elimination of **V** affords the (*Z*)-configured vinylsilane **VI**. It is also reported<sup>[76]</sup> that **V** might undergo a  $\beta$ -hydride elimination to form an alkyne-silane **VII** (dehydrogenative product).

## IV.2. Hydrosilylation of Alkynes: Regio and Stereoselectivity

Stereo- and regioselectivity are the most difficult parameters to control in the hydrosilylation of acetylenes. The addition of a silane across a terminal alkyne can afford three different isomers **A-C** (Figure 14) and addition across an internal alkyne may lead to four different compounds **D-G**.

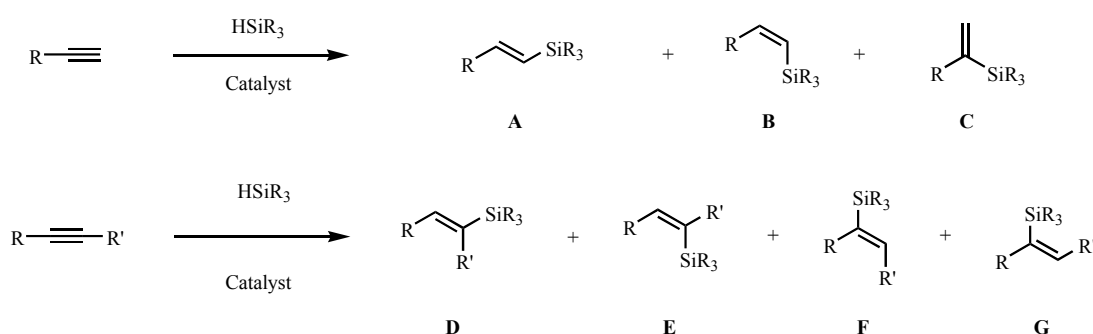
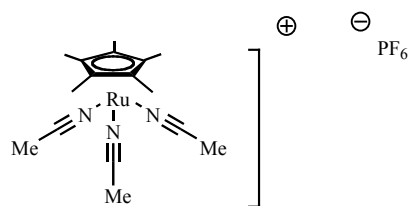


Figure 14. Stereo- and regiochemical possibilities in the hydrosilylation of acetylenic substrates

The hydrosilylation of monosubstituted alkynes is a well known process and can be directed towards the preferential formation of one of the three isomers.<sup>[65, 66]</sup> In the case of internal alkynes however, there is still room for improvement because very few catalysts satisfy both criteria of regio- and stereoselectivity.<sup>[66]</sup> Although the issue of regioselectivity is especially problematic for disubstituted acetylenes, the use of directing functional groups or intramolecular delivery of the reagent can afford the desired regioisomers.<sup>[66]</sup>

Compound **A** derives from a regioselective *cis*-addition and can be obtained with the classical platinum catalysts mentioned above. These complexes similarly promote the *cis*-hydrosilylation of internal alkynes but the regioselectivity is poor and affords a mixture of compounds **D** and **F**. Isomer **B** derives from *trans*-addition across the triple bond and can be obtained with  $[RuCl_2(p\text{-cymene})]_2$  as the catalyst.<sup>[77]</sup> This complex, however, only catalyses the *trans*-hydrosilylation of terminal alkynes. A method for the selective formation of **C** was recently reported by Trost and co-workers<sup>[78]</sup> using  $[Cp^*Ru(MeCN)_3]PF_6$  **15** (Figure 15).<sup>[79]</sup> Moreover, this cationic ruthenium complex also catalyses the hydrosilylation of disubstituted acetylenes in a *trans*-manner with very high chemoselectivity, although it provides a mixture of both regioisomers **E** and **G**.

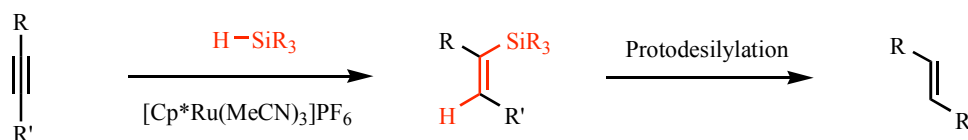


15

Figure 15. Ruthenium catalyst for *trans*-hydrosilylation of alkynes

Generally, catalytic systems for *trans*-selective hydrosilylation are rare<sup>[77, 80]</sup> and are either limited to terminal alkynes or suffer from a narrow scope. It has also been recently shown by Yamamoto and co-workers that some Lewis acids promote the reaction of terminal and internal alkynes in a *trans*-manner.<sup>[81-83]</sup> However, it seems that the reaction has only been tested on barely functionalised molecules.

The ability of **15** to produce (*Z*)-configured vinylsilanes has been independently applied by Trost<sup>[84]</sup> and Fürstner<sup>[85]</sup> to the synthesis of (*E*)-alkenes (Figure 16). Both authors report fluoride-mediated protodesilylations. Trost and co-workers describe a CuI-TBAF mediated desilylation in THF, while Fürstner and co-workers utilise AgF in aqueous THF/MeOH. Various functional groups are tolerated (alkene, ketone, ester, acetals, ethers) in both of these two-step synthetic approaches and examples are given for cyclic and acyclic systems.

Figure 16. Mild procedure for transformation of alkynes into the corresponding (*E*)-configured alkenes

According to the Ojima-Crabtree mechanism, it has initially been postulated that *trans*-hydrosilylation reactions proceed through initial *syn* silylmetalation, with subsequent isomerisation of the olefin prior to reductive elimination. However, examples of intramolecular hydrosilylation catalysed by ruthenium catalyst **15** reported by Trost and co-workers, show the formation of *endo*-products that cannot be explained by the Ojima-Crabtree mechanism (Figure 17).<sup>[86]</sup>

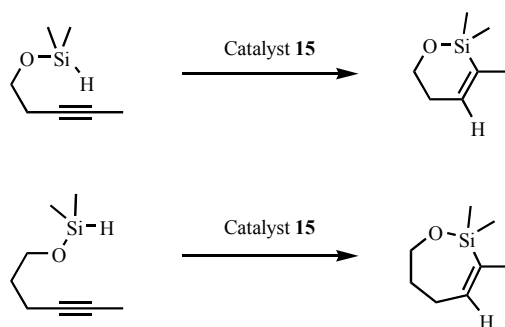


Figure 17. Intramolecular hydrosilylation catalysed by complex **15**<sup>[86]</sup>

Indeed, assuming that the reaction is intramolecular, an initial *cis*-addition of the ruthenium-silicon bond across the alkyne, postulated by the Ojima-Crabtree mechanism, would lead to an exceptionally strained 6-membered ring **16** (Figure 18), which is highly unlikely.

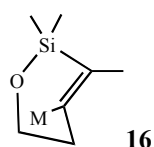


Figure 18. Exceptionally strained 6-membered ring<sup>[74]</sup>

Two different rationalisations for the formation of these *endo*-products were proposed. Trost suggested a route involving addition of the silicon-ruthenium bond across the alkyne using the orthogonal orbitals of the carbon-carbon triple bond to give directly the *trans*-hydrosilylation product (Figure 19).<sup>[86]</sup>

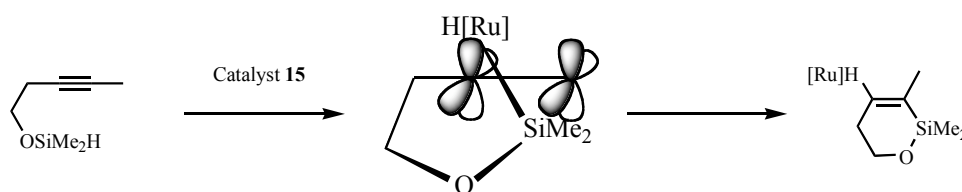
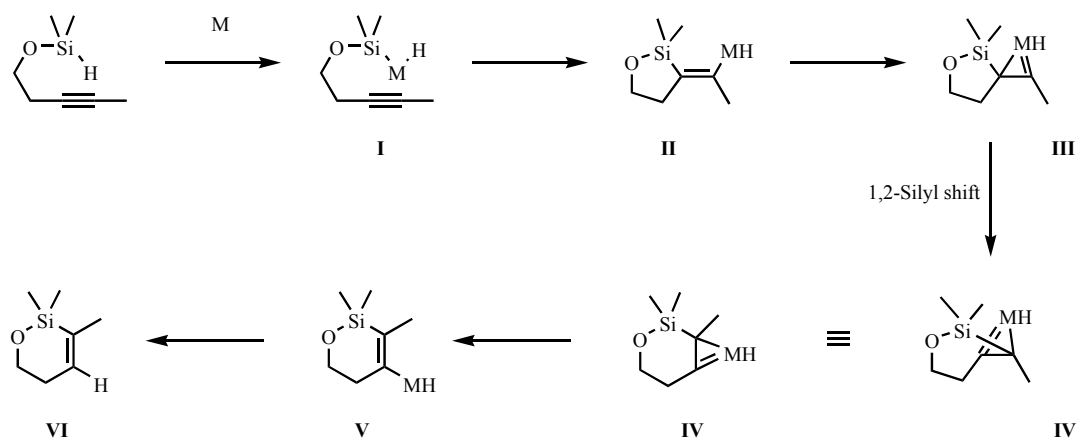


Figure 19. Trost's mechanistic proposal for *trans*-hydrosilylation of alkynes catalysed by **15**<sup>[86]</sup>

Crabtree proposes an adaptation of the Ojima-Crabtree mechanism (Scheme 6) involving an initial *syn*-addition of the silane across the acetylene unit leading to the formation of an exocyclic intermediate **II**, which, via formation of the  $\eta^2$ -vinyl intermediate **III** followed by a 1,2-silyl shift affords **IV**. Isomerisation of **IV** gives **V**, which undergoes reductive elimination to afford the endocyclic compound **VI**.



Scheme 6. Modification of the Ojima-Crabtree mechanism<sup>[74]</sup>

Subsequent to these proposals, the mechanism of hydrosilylation catalysed by complex **15** was investigated by Chung and co-workers.<sup>[87]</sup> They report investigations on the hydrosilylation of systems **17-19** (Figure 20) using density functional theory calculations (Figure 20).

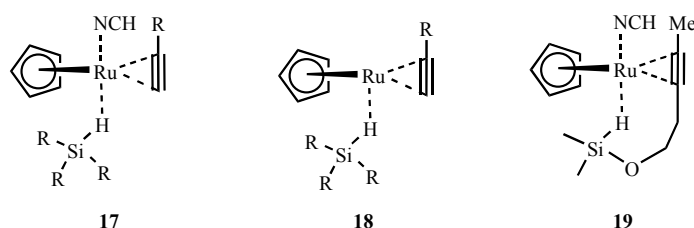


Figure 20. Models chosen for computational calculation<sup>[87]</sup>

The first important result arising from these calculations is that the insertion of the acetylene into the ruthenium-hydride bond is favoured over the insertion into the ruthenium-silyl bond. Furthermore, this insertion was found to be concerted with the oxidative addition of the silane to the metal (Figure 21).

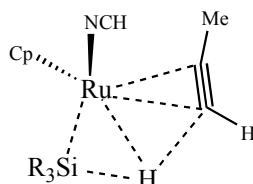


Figure 21. The oxidative addition of the silane to the ruthenium is concerted with the hydride insertion<sup>[87]</sup>

Their results also show that the particular regioselectivity and stereoselectivity observed for the inter- and intra-molecular hydrosilylations are consequences of this concerted process. The *trans*-addition stereochemistry (Figure 22) results from the formation of a metallacyclopropene intermediate (**21**) upon hydride-insertion followed by a stereospecific counterclockwise rotation of the C $\alpha$ -C $\beta$  bond (see structure **20**). The intermediate **21** undergoes a facile  $\alpha$ -silyl migration through a metallacyclopropene-like transition-state structure **22** to give the *trans*-addition product **23**.

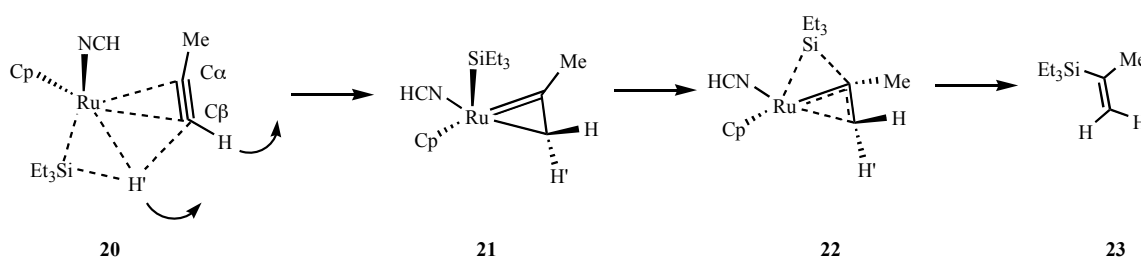


Figure 22. Origin of the stereochemistry in the ruthenium-catalysed hydrosilylation<sup>[87]</sup>

The origin of the regioselectivity of the ruthenium-catalysed hydrosilylation proposed by Chung and co-workers can be explained as follows (Figure 23). In Figure 23 are drawn simplified representations of the calculated hydride insertion structures for the reaction of triethylsilane with propyne. Transition structure **24** was calculated to be more stable than **25**. The energetic difference between both structures is proposed to be due to the steric interaction between the bulky silyl group and the propyne methyl group. The favoured transition structure **24** leads to product **23**, that is observed experimentally.

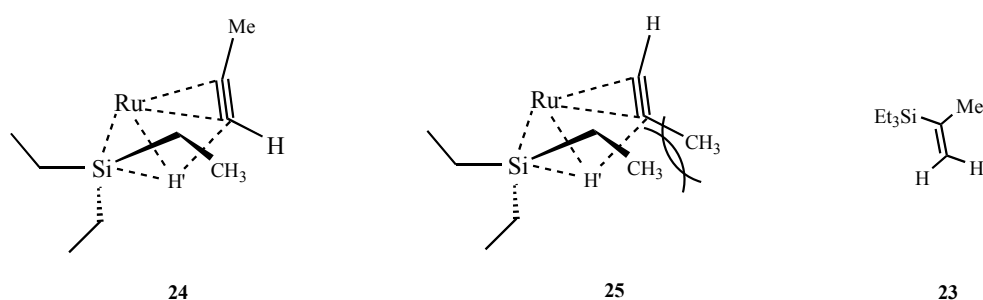


Figure 23. Origin of the regioselectivity in the ruthenium-catalysed hydrosilylation<sup>[87]</sup>

Thus, computational calculations propose a new mechanistic pathway for the hydrosilylation catalysed by ruthenium **15** that seems to rule out both original proposals made by Trost<sup>[86]</sup> and Crabtree.<sup>[74]</sup> Finally, it should be noted that these computational studies were carried out for intermolecular hydrosilylation of terminal alkynes and for intramolecular hydrosilylation of internal alkynes. Their extrapolation to an intermolecular hydrosilylation of internal alkynes must be done with some care.



## V. Palladium-Catalysed Cross-coupling Reactions

Mainly two different kinds of palladium-catalysed cross-coupling reactions have been used in the present thesis, which will be described more accurately in the following chapters. However some common considerations are presented below.

### V.1. Introduction

Carbon-carbon bond formation is one of the most important processes in organic chemistry and a great number of famous reactions have been developed over the last 100 years for this purpose. However, there was no general method allowing carbon-carbon bond formations between unsaturated species until the discovery of transition metal-catalysed cross-coupling reactions in the early 1970's. Kumada<sup>[88]</sup> and Corriu<sup>[89]</sup> developed independently reactions between Grignard reagents and vinyl or aryl halides in the presence of nickel-phosphine complexes. Following the discovery of catalytically active nickel complexes, many studies showed the high capacity of palladium to catalyse related transformations. At the same time several research groups reported studies on cross-coupling reaction involving various organometallic and organometalloids derivatives.<sup>[90]</sup> Since then, a wide range of different methodologies has been developed so that nickel and especially palladium cross-coupling reactions now belong to the most powerful synthetic tools for advanced organic synthesis, supramolecular chemistry and material science.

Nowadays, zinc, boron, tin, magnesium, silicon and copper derivatives are most commonly used in cross coupling reactions. The electrophilic substrates for carbon-carbon bond formation are usually organic halides and organic sulfonates.

Many of the transition metal-catalysed reactions are named after the pioneers of their discovery and maturation. A "Suzuki cross-coupling" reaction refers to transformations involving organoboron reagents, and a carbon-carbon bond formation reaction is commonly named "Negishi cross-coupling" when organozinc reagents are involved. The "Heck reaction" refers to arylation, alkenylation or alkynylation of alkenes and the "Sonogashira reaction" refers to a palladium-copper-catalysed  $Csp^2$ - $Csp$  bond formation.

## V.2. General Mechanistic Considerations

Palladium (0) has been proven to be at the origin of most of the cross-coupling reactions. The species entering the catalytic cycle is presumably an electron deficient 14 electron complex **I**. This species can undergo an oxidative addition to a polarised organic halide **II** forming a *trans*-configured palladium<sup>II</sup> intermediate **III** which is transmetalated by compound **IV**, affording *trans*-configured **V**. Since reductive elimination occurs only when the groups R and Nu are *cis* to one another, an isomerisation of **V** to **VI** is required. *Cis*-configured **VI** undergoes reductive elimination affording the desired product **VII** and the palladium (0) intermediate **I** is regenerated that can enter into another cycle.

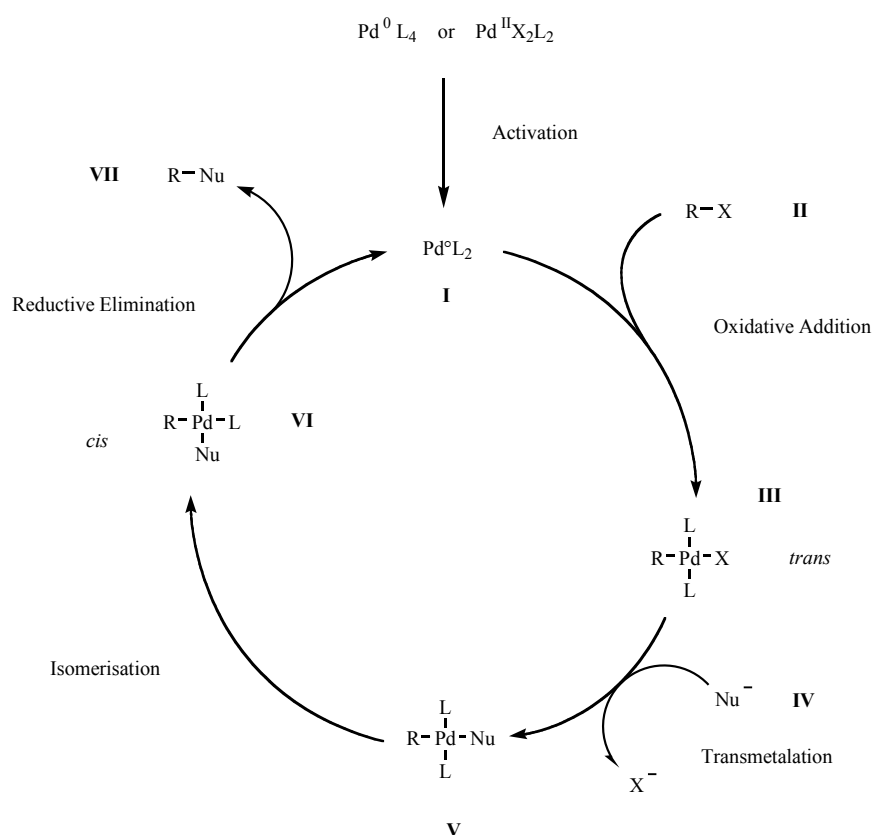


Figure 24. Generic catalytic cycle for cross-coupling reactions

Although evidences exist for each step of this mechanism, Figure 24 should be considered as a very simplified representation. Kinetic experiments have shown that depending on the nature of the substrates, each of the catalytic steps can be rate determining. Many parameters can interfere with the above mentioned reaction patterns enabling easier formation of one or another intermediate. The nature of the palladium catalyst, the electronic properties of the ligands and the presence of specific bases have a tremendous influence on the cross-coupling reaction and can be adjusted to optimise the formation of the desired cross-coupling products.

## Goals of the thesis

Alkene metathesis is a very powerful method for the formation of cyclic molecules. It has been successfully used for ring formation of many highly functionalised macrocycles. This transformation is one of the most difficult tasks in organic chemistry and therefore often the key step in many total syntheses. However, this method suffers from a major drawback, the lack of stereocontrol over the emerging double bond.

RCAM followed by a stereoselective semi-reduction represents a powerful alternative to this imperfection. Lindlar reduction efficiently provides (*Z*)-alkenes. A mild procedure for a stereo-complementary procedure, the reduction of cycloalkynes to (*E*)-cycloalkenes, has recently been reported from the Fürstner group.<sup>[85]</sup> This current work focussed on determining the scope and limitations of this approach. For this purpose, the preparation of molecules of various ring sizes, bearing different functional groups has been envisaged. Moreover, as (*E,E*)-configured 1,3-dienes are commonly found in macrocycles of biological interest it was decided to try to extend the procedure to the formation of conjugated 1,3-dienes of defined configuration (Figure 25).

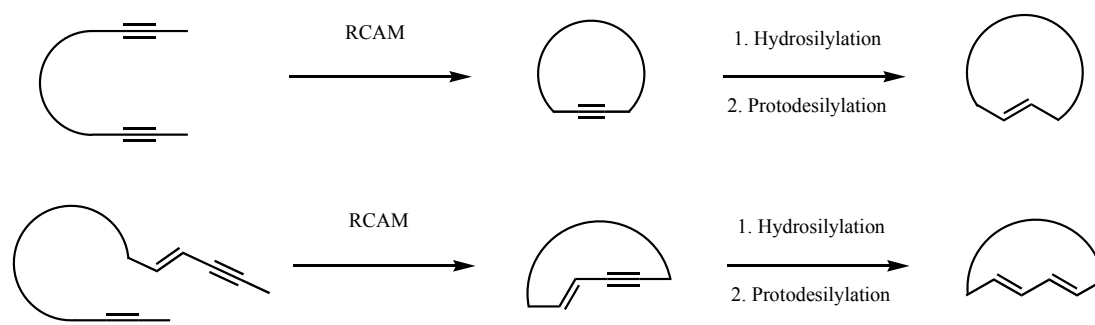


Figure 25. Synthesis of stereodefined (*E*)-cycloalkenes and (*E,E*)-1,3-cycloalkadienes

Furthermore, since an application in total synthesis is the most stringent test for a new methodology, the present thesis reports studies towards the implementation of our methodology for the formation of stereodefined cycloalkadienes into the synthesis of the macrocyclic antibiotic Myxovirescin A<sub>1</sub> (Figure 26).

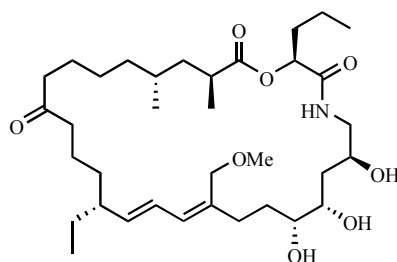


Figure 26. Myxovirescin A<sub>1</sub>

# RESULTS AND DISCUSSION

# I. Stereoselective formation of (*E*)-configured cycloalkenes

## I.1. Introduction

This chapter will focus on the stereoselective formation of (*E*)-cycloalkenes starting from linear diynes (Figure 27).

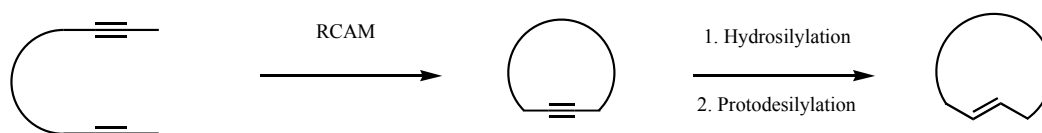


Figure 27. Formation of (*E*)-cycloalkenes via RCAM and semi-reduction

It was decided to apply the three-step procedure of RCAM/semi-reduction to a broad range of compounds, varying the size of the ring, the functionalities present in the molecules, and the direct chemical and electronic environment of the triple bonds (Figure 28). Esters are known to be compatible with the overall process<sup>[85]</sup> and are useful for the rapid assembly of diynes with various chain lengths (**26** to **29**). Moreover, the tolerance of the sequence towards amides (**30**) as well as the presence of phenyl groups at different positions relative to the alkyne moieties were investigated (**28** and **29**).

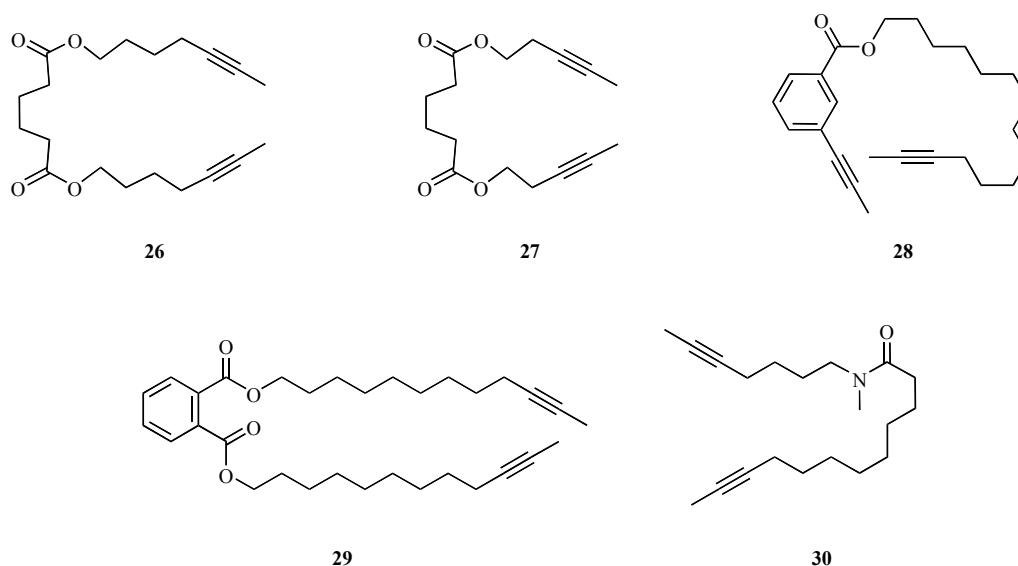


Figure 28. Various linear diynes

## I.2. Synthesis of the RCAM precursors

Among the different cyclic alkynes that were synthesised, only cyclododecyne **33** (Figure 29) was not prepared by RCAM from an acyclic precursor. It was obtained via a bromination and elimination sequence<sup>[91, 92]</sup> starting from commercially available cyclododecene **31**. Because several isomers were formed during both steps, careful distillation processes were necessary to obtain **33** in pure form.

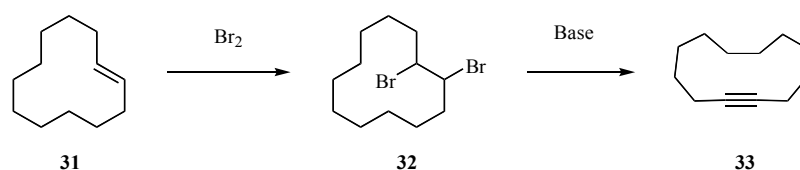
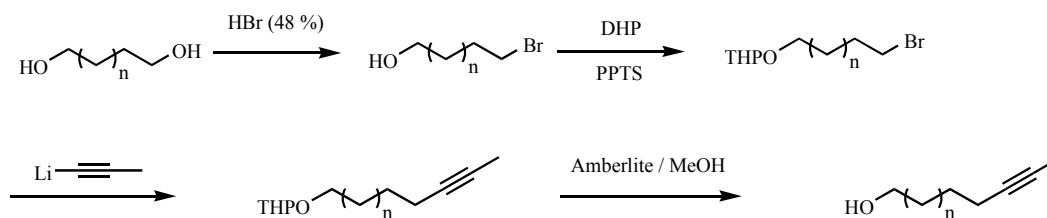


Figure 29. Generic scheme for the synthesis of cyclododecyne

The different alkyn-1-ols present in many of the following syntheses were previously prepared on large scale in the Fürstner laboratory via the following procedure.



Scheme 7. Generic scheme for the preparation of alkyn-1-ols

Diesters **26**, **27** and **29** were obtained by esterification under standard conditions from hexanedioyl dichloride **34** or phthaloyl dichloride **35** using alkyn-1-ols of different chain length (Figure 30).

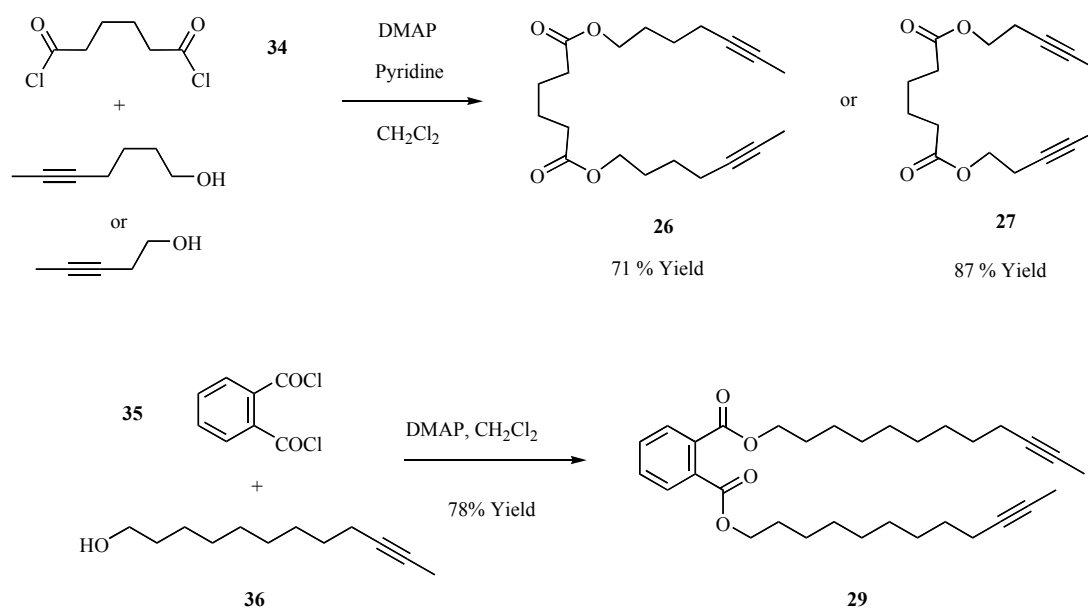
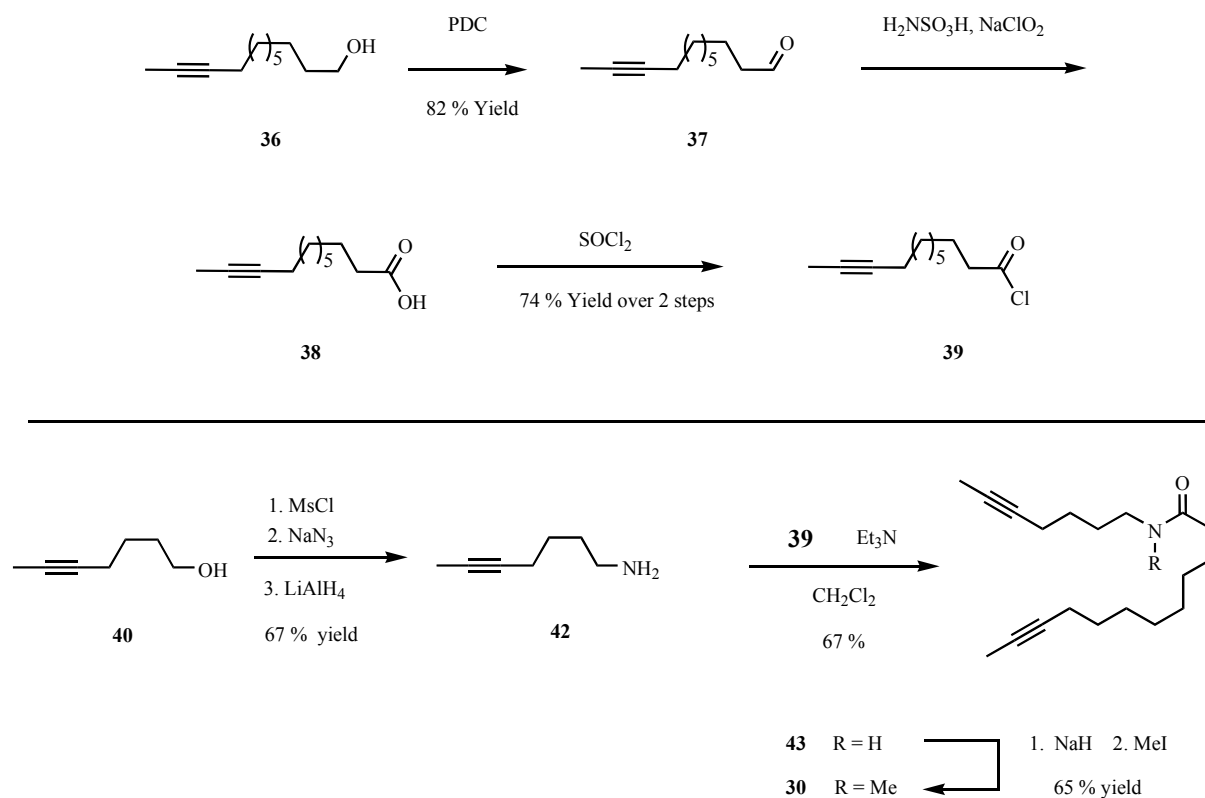


Figure 30. Synthesis of **26**, **27** and **29**, precursors for 14, 18 and 26-membered rings.

The transformation of dodec-10-yn-1-ol **36** into the corresponding carboxylic acid **38** was easily achieved via a two-step sequence. Aldehyde **37** was obtained from the corresponding alcohol **36** using either the Dess-Martin periodinane<sup>[93, 94]</sup> or PDC (pyridinium dichromate).<sup>[95, 96]</sup> Oxidation of **37** with sodium chlorite (NaClO<sub>2</sub>) and amidosulfonic acid (H<sub>2</sub>NSO<sub>3</sub>H) afforded the desired carboxylic acid **38** which was transformed into the corresponding acyl chloride **39** on treatment with thionyl chloride.

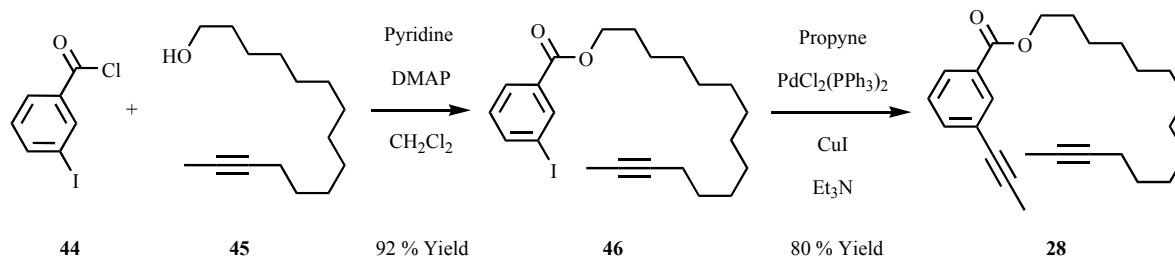


Scheme 8. Synthesis of **30**, precursor for 16-membered lactam.

Amine **42** was prepared by mesylation of alcohol **40** followed by nucleophilic substitution with  $\text{NaN}_3$  to give the corresponding azide **41** which was reduced with  $\text{LiAlH}_4$  to give amine **42**. Surprisingly, the use of  $\text{NaBH}_4$  for the reduction failed. This amine was then coupled with acid chloride **39** in the presence of triethylamine affording the expected amide **43**. Since some alkyne metathesis catalysts are sensitive to acidic protons, the amide function was methylated with methyl iodide in the presence of  $\text{NaH}$ , affording substrate **30** in good yield.



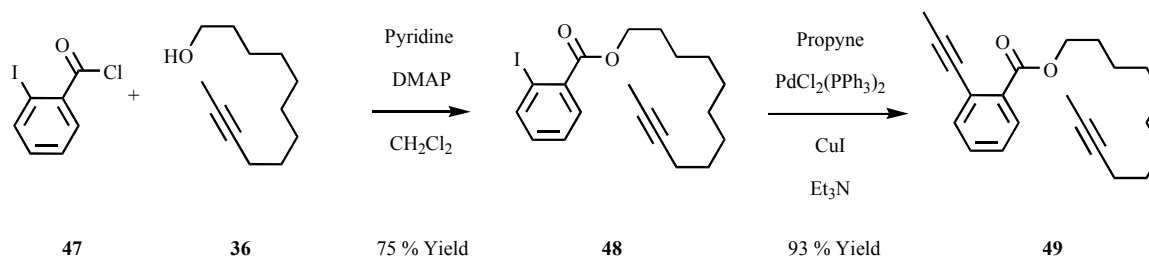
Since all RCAM precursors described above contain acetylene units substituted with  $sp^3$  hybridised carbons, it seemed appropriate to prepare compound **28** and **49** for comparison.



Scheme 9. Synthesis of **28**, precursor for a 19-membered aromatic ester

Commercially available *m*-iodobenzoyl chloride **44** was esterified with alcohol **45** under classical conditions affording the iodo-aromatic compound **46** in good yield (Scheme 9). Propynylation of this ester was reliably accomplished by a Sonogashira cross-coupling reaction<sup>[3]</sup> to give the desired diyne **28**.

Similarly, the *ortho*-substituted substrate **49** bearing a shorter side chain was synthesised by esterification of acid chloride **47** with alcohol **36** followed by propynylation of iodo-phenyl **48** (Scheme 10).

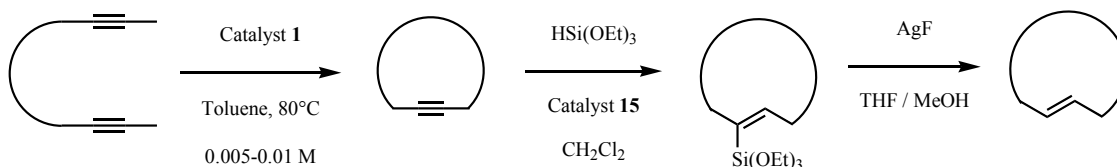


Scheme 10. Synthesis of *ortho*-substituted phenylpropyne **49**

## I.3. Synthesis of (*E*)-cycloalkenes

### I.3.1. Experimental conditions

The results of the reaction sequence represented in Scheme 11 are summarised in Table 3.



Scheme 11. From acyclic diynes to (*E*)-cycloalkenes

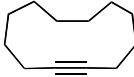
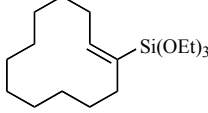
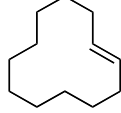
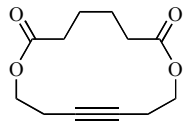
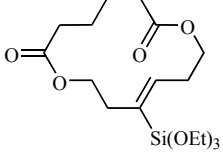
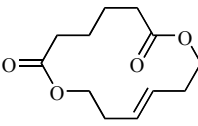
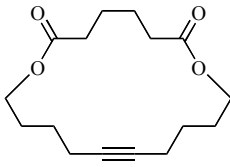
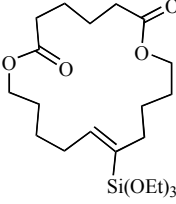
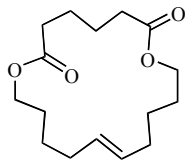
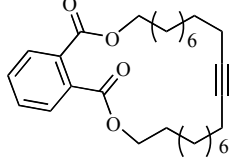
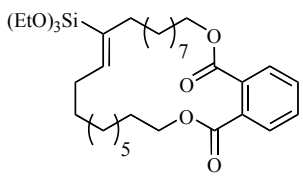
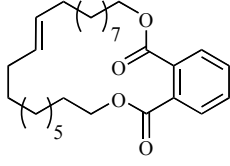
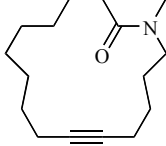
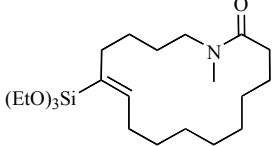
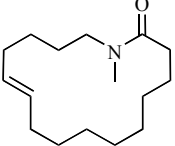
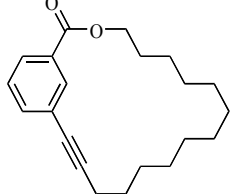
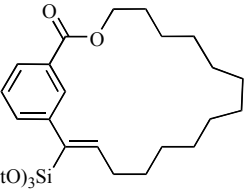
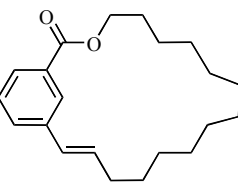
All RCAM experiments were carried out under inert atmosphere, with a gentle argon flow, in toluene at 80°C using 10 mol % of the Schrock tungsten alkylidyne catalyst **1**. In order to attenuate formation of oligomers, high dilution conditions were used (0.005-0.01 M).

All hydrosilylation reactions were carried out under argon in CH<sub>2</sub>Cl<sub>2</sub> between 0°C and room temperature using 1.2 eq of triethoxysilane **50** (HSi(OEt)<sub>3</sub>) and 1 mol % of [Cp\**Ru*(MeCN)<sub>3</sub>]PF<sub>6</sub> **15** (except for cycloalkyne **65**, for which 15 mol % of catalyst were necessary). Complex **15** was synthesised according to a procedure reported by Steinmetz and co-workers<sup>[79]</sup> in one step from [Cp\**Ru*Cl<sub>2</sub>]<sub>n</sub> by zinc reduction in acetonitrile in the presence of NaPF<sub>6</sub>. Hydrosilylation of unsymmetrical substrates led to the formation of regioisomers. The resulting vinylsiloxanes were purified by flash chromatography but tended to polymerise significantly over a few days, even at -18°C. In all cases, it is advisable to either proceed with the desilylation step directly after isolation or to store the products in solution.

Protodesilylations of the vinyl-siloxanes were carried out at room temperature in the dark using a slight excess of AgF suspended in an aqueous THF/MeOH (3/1) solution.

## I.3.2. Summary of the results

Table 3. Preparation of cycloalkynes by RCAM followed by conversion into (*E*)-cycloalkenes via vinylsilanes

Cycloalkyne	Yield	Vinylsiloxane <sup>a</sup>	Yield ( <i>Z</i> : <i>E</i> )	Cycloalkene <sup>a</sup>	Yield ( <i>E</i> : <i>Z</i> )
	<b>33</b>		<b>51</b> 90 % (91:9)		<b>52</b> 84 % (90:10)
	<b>53</b> 79 %		<b>54</b> 93 % (95:5)		<b>55</b> 92 % (95:5)
	<b>56</b> 80 %		<b>57</b> 88 % (98:2)		<b>58</b> 90 % (98:2)
	<b>59</b> 70 %		<b>60</b> 97 % (98:2)		<b>61</b> 90 % (98:2)
	<b>62</b> 68 %		<b>63</b> 95 % <sup>b</sup>		<b>64</b> 82 % (95:5)
	<b>65</b> 71 %		<b>66</b> 80 % <sup>b</sup>		<b>67</b> 74 % (93:7)

<sup>a</sup> All the *E*:*Z* ratios were estimated by gas chromatography except for **60** (HPLC estimation).

<sup>b</sup> Mixture of regioisomers

### I.3.3. Discussion

All the linear diynes presented in Figure 28 underwent cyclisation in the presence of catalyst **1** to afford cycloalkynes of ring size varying from 14 to 26 in good yields. Only the attempted RCAM of the *ortho*-substituted phenyl-propyne **49** (Scheme 10) was unsuccessful.

Cycloalkynes **33** and **53** were hydrosilylated under different conditions and the results are summarised in Table 4. Hydrosilylation of the 14-membered ring **53** (entry 3) at 0°C affords vinylsilane **54** in excellent yield and selectivity. Probably due to high strain released during the transformation of an alkyne into an alkene moiety, cyclododecyne is by far the most reactive substrate. With the most commonly used siloxane (HSi(OEt)<sub>3</sub>), the conversion is complete in less than 15 minutes at 0°C. Unfortunately, this high reactivity led to a relatively poor 91:9 isomeric ratio (Table 4, entry 1).

Table 4. Hydrosilylation of substrates **33** and **53** under different conditions

Entry	Substrate	Temperature	Silane	Yield	<i>Z:E</i> ratio
1	<b>33</b>	0°C	HSi(OEt) <sub>3</sub>	84 %	91:9
2	<b>33</b>	RT	HSi(OEt) <sub>3</sub>	/	78:22
3	<b>53</b>	0°C	HSi(OEt) <sub>3</sub>	92 %	95:5
4	<b>53</b>	RT	HSi(OEt) <sub>3</sub>	79 %	83:17
5	<b>33</b>	0°C	HSiEt <sub>3</sub>	/ <sup>a</sup>	62:38 <sup>b</sup>
6	<b>33</b>	0°C	HSi(Me)(OEt) <sub>2</sub>	98 %	96:4

<sup>a</sup> Reaction incomplete after one hour at room temperature.

<sup>b</sup> The ratio was determined from NMR data.

The hydrosilylation reaction is both reagent- and temperature dependant. While triethylsilane **68** (HSiEt<sub>3</sub>) reacted slowly with low stereoselectivity at 0°C (entry 5), the mixed methyldiethoxysilane **69** (HSi(Me)(OEt)<sub>2</sub>) afforded the corresponding vinylsilane **51a** in 98% yield (Figure 31) with the highest *Z:E* ratio (96:4) (entry 6). Unfortunately, protodesilylation of the corresponding “mixed” vinylsilane **51a** turned out to be problematic and afforded a lower yield. Higher temperatures increase the rate of the reaction but lead to lower stereoselectivities (entries 1-4).

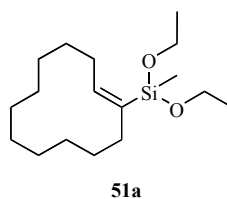


Figure 31. Vinylsilane **51a**

The (*E*)-configuration of all the double bonds of the final cycloalkenes was deduced from the spectroscopic data. Particularly diagnostic are the shifts of the allylic carbons in the  $^{13}\text{C}$  NMR spectra ( $\delta = 32\text{-}33$  ppm) whereas the corresponding position of the (*Z*)-isomers are known to be shielded and appear at higher field ( $\delta = 27\text{-}28$  ppm). Furthermore, for asymmetric molecules such as **64** and **67**, the coupling constant between two non-geminal ethylenic protons is characteristic ( $\delta = 13\text{-}19$  Hz for (*E*)-configured olefins and  $\delta = 4\text{-}12$  Hz for (*Z*)-configured olefins). Moreover, cycloalkene **55** was subjected to X-ray crystallography in order to avoid any ambiguity with regard to the olefin configuration. The structure in the solid state clearly shows an (*E*)-configured double bond (Figure 32).<sup>[97]</sup>

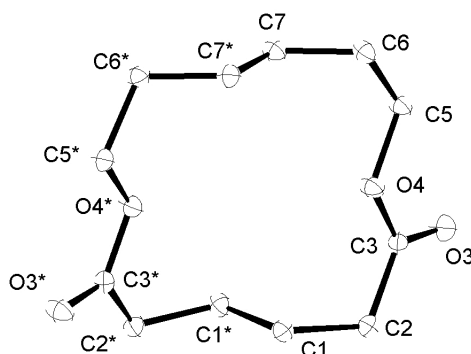


Figure 32. Molecular structure of (*E*)-cyclododecene **55** in the solid state

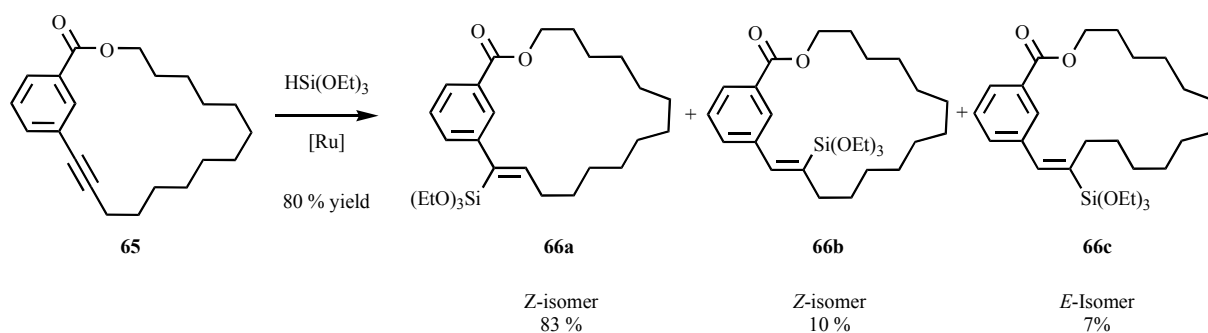
Protodesilylation of vinylsilanes **51** and **54** occurred nicely affording cyclododecene **52** and (*E*)-alkene **55** in good yield with retention of the *E*:*Z* ratio. When stored for a long time in the refrigerator, **52** tends to isomerise slowly and form the thermodynamically more stable (*E*)-isomer.

The yields and selectivities for the semi-reduced compounds **58** (18-membered ring) and **61** (26-membered ring) were excellent. In both cases, due to a large ring size, the alkyne moiety does not induce any particular ring strain which may explain the highly stereoselective course of the reaction. Likewise, the protodesilylation of the vinylsilanes **57** and **60** occurred smoothly in high yields.

The vinylsilane **63** was obtained as a 1:1 mixture of regioisomers. Due to the presence of two isomers and their respective rotameric structures, an accurate NMR analysis was impossible. Since protodesilylation of **63** occurred in good yield affording the desired (*E*)-alkene **64** with high stereoisomeric purity, no further NMR experiments on **63** (at high temperature) were undertaken.

Hydrosilylations of alkyne **65** using less than 15 mol% of catalyst **15** led to incomplete conversion. In order to bring the reaction to completion it was necessary to add successively small portions of catalyst (2 to 3 mol %). After every new introduction of the ruthenium complex **15**, the transformation proceeded further but stopped very rapidly. This suggests that the catalyst was progressively poisoned or deactivated. The protodesilylation of **66**, however, occurred under standard conditions affording cycloalkene **67** in high yield and isomeric purity.

Hydrosilylation of **65** afforded three products (Equation 1). The structures of these three isomers were determined by NMR. For each isomer, the position of the silyl group was deduced from the splitting pattern of the signal of the ethylenic proton and the stereochemistry of the double bond was deduced from nOe data (Figure 33).



Equation 1. Regio- and stereoselectivity of the hydrosilylation of the 19-membered lactone **65**

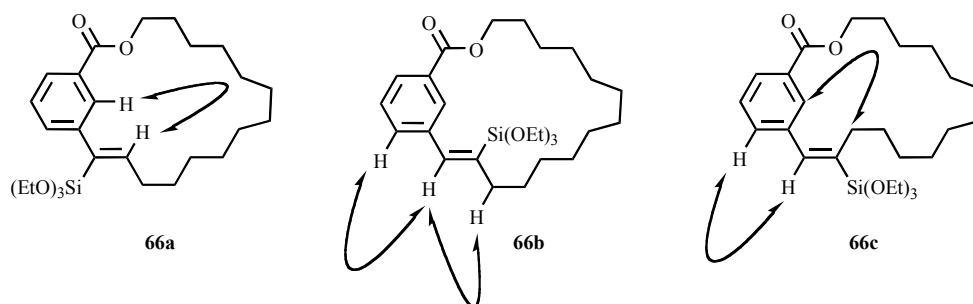


Figure 33. nOe interactions observed for compounds **66a**, **66b** and **66c**

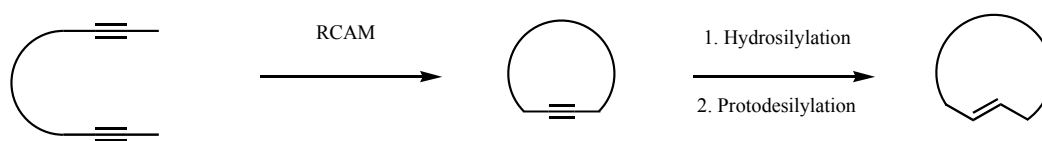
## I.4. Conclusion

A series of cycloalkynes of different ring size were prepared in good to excellent yields by ring closing alkyne metathesis of the corresponding acyclic diynes in the presence of the Schrock alkyldiyne complex **1**.

These compounds were subjected to hydrosilylation in the presence of triethoxysilane **50** and the ruthenium catalyst **15** in CH<sub>2</sub>Cl<sub>2</sub> between 0°C and room temperature. For most of the substrates the reaction proceeded smoothly even with catalyst loadings as low as 1 mol %. In all the cases the transformation occurred in a *trans*-manner with good to excellent selectivity. Although methyldiethoxysilane **69** afforded the best stereoselectivity with cyclododecyne **33**, triethoxysilane **50** turned out to be best suited for the subsequent protodesilylation and was therefore used in all further studies.

Protodesilylation of vinylsilanes with AgF (1.2 –1.5 eq.) at room temperature occurs rapidly and selectively for the vinylsiloxanes investigated without any noticeable isomerisation of the double bond.

Therefore, we have established a reliable method for the preparation of macrocyclic (*E*)-olefins (Scheme 12). However, questions remain for metathetic syntheses of cyclic conjugated alkynes and their transformation into the corresponding conjugated alkenes, which will be addressed in the following chapters.



*Scheme 12. Formation of (*E*)-cycloalkenes by RCAM and semi-reduction*

## II. Stereoselective formation of (*E,E*)-configured cycloalkenes

### II.1. Introduction

The formation of (*E,E*)-configured 1,3-cyclodienes via enyne-yne ring closing metathesis followed by hydrosilylation and desilylation of conjugated alkynes will be described in this chapter (Figure 34).



Figure 34. Formation of 1,3-dienes via RCAM and semi-reduction

Initially, a series of esters of type **70** possessing various chain lengths (Figure 35) were chosen as substrates for our model studies. However, as previous results had shown that conjugation was potentially a factor perturbing the ruthenium-catalysed hydrosilylation, it was decided to synthesise substrates with different conjugated systems. To study this aspect, unfunctionalised molecules such as enynes **71** -**74** were chosen. The synthesis of **75**, an important building block in the synthesis of esters of type **70** will also be described.

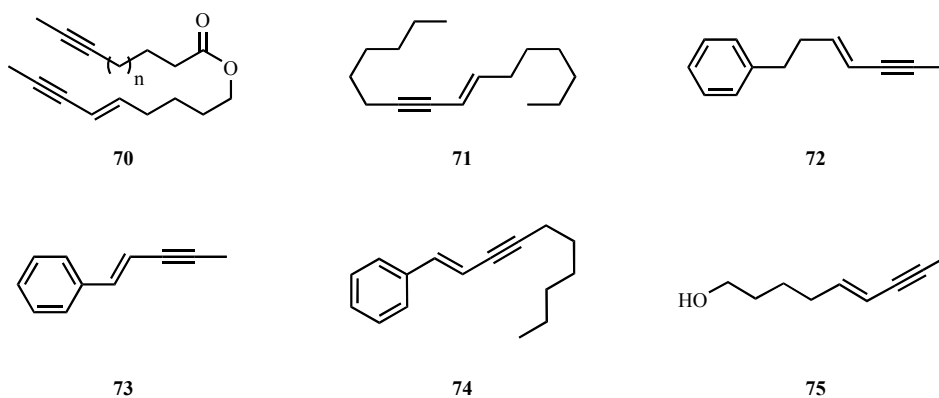


Figure 35. Various linear enynes



## II.2. Various Studies on Linear Substrates

### II.2.1. Introduction

Many methods for the formation of stereodefined 1,3-enynes systems exist but only those which were applied in this work will be described in this section. The most direct and flexible procedure for the formation of conjugated enynes is the palladium-catalysed alkylation of vinyl-halides (Figure 36).<sup>[98-102]</sup> Formation of (*E*)-configured vinyl-halides can be achieved via *cis*-hydrometalation<sup>[103-107]</sup> of a triple bond followed by treatment with an electrophilic halogen source such as bromine, NBS, NIS or iodine.<sup>[108]</sup>

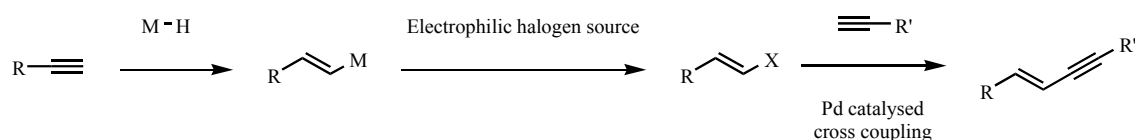


Figure 36. General formation of conjugated enynes

### II.2.2. Hydrometalation reactions

Many metal hydrides can add across unsaturated carbon-carbon bonds to form alkenylmetal intermediates which have found high interest in organic chemistry. The most commonly used hydrometalation reagents are:  $\text{BH}_3$ ,  $\text{AlH}_3$ , or their alkyl and aryl derivatives:  $\text{R}_2\text{Al-H}$  (DiBAL-H, RedAl-H),  $\text{R}_2\text{B-H}$  (9-BBN, catechol),  $\text{Cp}_2\text{Zr(Cl)H}$  (Schwartz's reagent<sup>[109]</sup>),  $\text{Bu}_3\text{Sn-H}$  and  $\text{R}_3\text{Si-H}$ . The generated alkenylmetals have very different reactivity patterns, ranging from the highly reactive organoaluminium derivatives to the very stable vinylsilanes which can be purified on silica gel.

Organoboron and organotin derivatives are widely used as nucleophilic reagents for palladium-catalysed cross-coupling reactions (Suzuki and Stille cross-coupling procedures).<sup>[110-112]</sup> Whilst organozirconium intermediates are rarely directly involved in palladium-catalysed carbon-carbon bond formation (for an exception see<sup>[113]</sup>), they can easily be transmetalated or react with an electrophilic halide source,<sup>[106]</sup> to form either vinyl-metal derivatives or vinyl-halides that are more suitable for cross-coupling.

Hydrometalations of acetylenes typically take place in a stereoselective *cis*-manner and are therefore widely used for the formation of (*E*)-configured olefins (Figure 37).

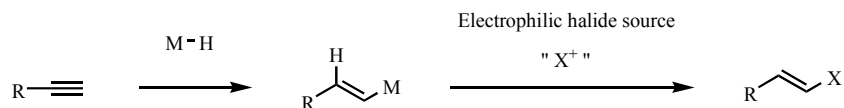


Figure 37. Formation of (*E*)-configured vinyl-halides

Thereby, the metal usually adds to the least hindered end of the alkyne moiety. Except for hydrosilylations,<sup>[65, 66]</sup> in which mixtures are formed, terminal acetylenes often undergo essentially regioselective hydrometalations. This regioselectivity is lower in the case of internal triple bonds. A review article comparing the regioselectivities of different hydrometalation reagents has been published.<sup>[103]</sup>

Different synthetic strategies can be used for the formation of (*Z*)-configured vinylstannanes or vinylsilanes *via* hydrometalation of the corresponding alkynylstannane and alkynylsilanes,<sup>[114, 115]</sup> followed by protonolysis (Figure 38).

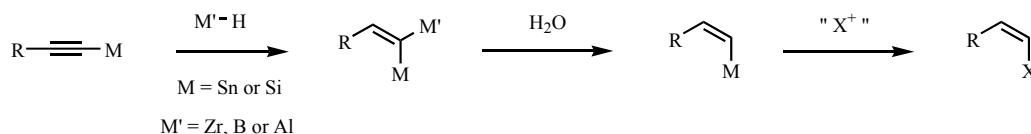


Figure 38. First alternative for formation of (*Z*)-configured vinyl metals

Direct transition metal catalysed hydrogenation of alkynylsilanes is also possible (Figure 39).<sup>[116]</sup> The stereospecific conversion of alkenylboronic acids into alkenyl bromides with inversion of configuration has also been reported by Brown and co-workers.<sup>[117]</sup>

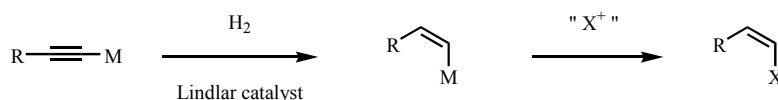


Figure 39. Second alternative for formation of (*Z*)-configured vinyl metals

Due to their high toxicity, tin derivatives are less commonly used. The reaction of vinylsilanes with electrophiles,<sup>[118, 119]</sup> depends on the nature of the substrate and leads sometimes to isomerisation of the double bond. However, utilisation of organosilicon reagents in carbon-carbon bond formation has been increasingly investigated in recent years.<sup>[119, 120]</sup>

Alkenyl-metal reagents such as alkenylalanes<sup>[105]</sup>, alkenylboranes<sup>[104]</sup> and alkenylzirconocenes<sup>[106, 107]</sup> undergo reaction with electrophiles with retention of configuration<sup>[121]</sup> at the double bond. They are therefore used for stereospecific constructions of olefins from acetylenic derivatives. Depending on the degree of functionalisation of the molecule bearing the alkyne moiety, either an aluminium hydride (low cost but low functional group tolerance), or boron hydride ( $R_2B-H$ ) or zirconium hydride ( $Cp_2Zr(Cl)H$ ) derivatives (higher cost and higher functional group tolerance) can be chosen.

### II.2.3. Alkynylation reactions

The most widely used method for  $Csp^2-Csp$  bond formation is the palladium-catalysed alkynylation reported in 1975 by Sonogashira.<sup>[101, 102, 122]</sup> This cross-coupling procedure is unique because no organometallic species has to be prepared prior to the addition of the catalyst and the electrophile. The reaction occurs in the presence of a base and catalytic amounts of palladium and copper. It can be seen as hybrid between the Castro-Stephen reaction<sup>[123]</sup> and the Heck alkynylation protocol<sup>[124]</sup> (Figure 40). In spite of a very high convenience, practicality and an immense scope (the original publication has been cited more than 1000 times) some limitations exist which are discussed below.

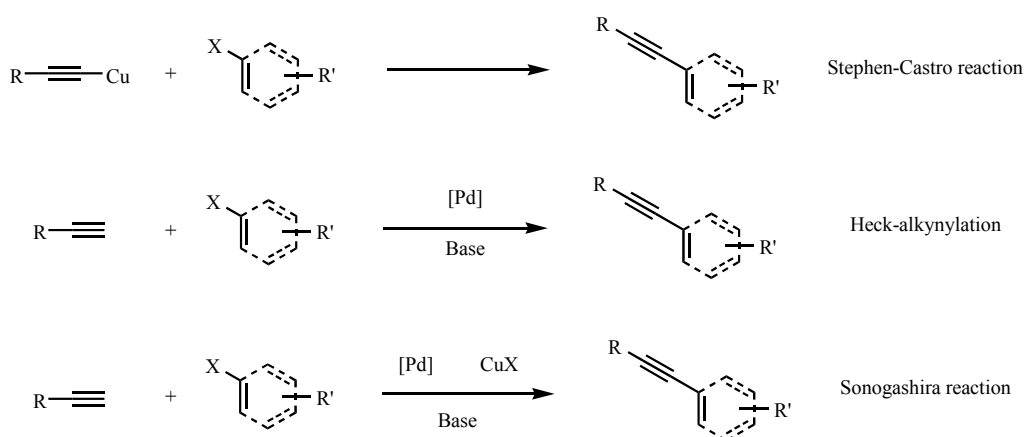


Figure 40. Various alkynylation reactions

Alternatively, various pre-formed alkynylmetals (mainly boron, zinc and tin derivatives) can be used for cross-coupling (Figure 41).<sup>[98]</sup> This method is reported to be even more efficient than the Sonogashira procedure in specific cases.<sup>[125]</sup> Notably, the palladium-copper catalysis does not allow to directly produce terminal alkynes using ethyne, due to competitive disubstitution.<sup>[125]</sup> In general, if the alkyne is a gas (such as ethyne and propyne) it is more convenient and practical to utilise the

corresponding commercially available alkynylmetal reagents. However, if the high reactivity of the corresponding organosodium, organolithium or Grignard reagent is not tolerated by any component of a reaction, they can easily be transmetalated into the corresponding alkynylzinc derivative (with  $\text{ZnCl}_2$  or  $\text{ZnBr}_2$ ) whose functional group tolerance is higher.<sup>[98, 100]</sup>

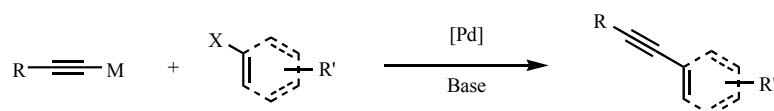


Figure 41. Palladium-catalysed reaction with alkynylmetals

Organoboron derivatives also proved to be highly useful. Fürstner<sup>[126]</sup> and Soderquist<sup>[127]</sup> independently published a palladium-catalysed procedure for  $\text{Csp}^2\text{-Csp}$  bond formation via a borate intermediate (Figure 42). Specifically, a very efficient and practical propynylation reagent **77** can be prepared at room temperature by reaction of 9-methoxy-9-borabicyclo[3.3.1]nonane **76** (9-OMe-9-BBN) with various propynyl alkali salts. Various alkynes can be cross-coupled in this way with different electrophiles.

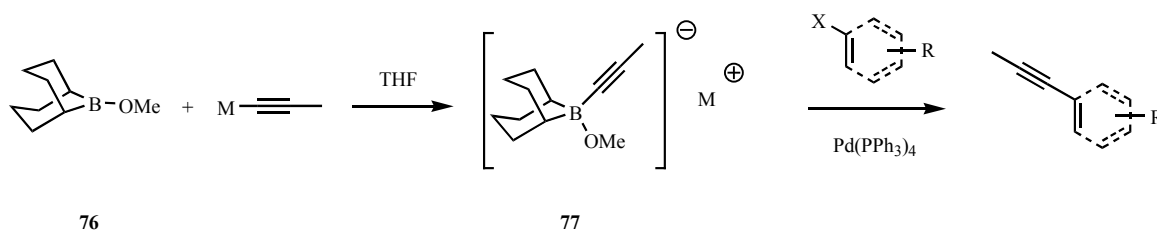
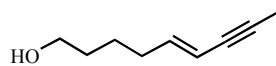


Figure 42. Boron-mediated palladium-catalysed propynylation

## II.2.4. Synthesis of linear conjugated enynes

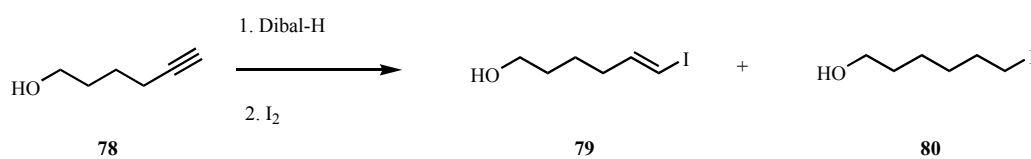
First, the formation of (*5E*)-non-5-en-7-yn-1-ol **75** (Figure 43) using inexpensive diisobutyl aluminium hydride (DiBAL-H) as the hydrometalation reagent was investigated.



**75**

Figure 43. (*5E*)-Non-5-en-7-yn-1-ol **75**

Hydroalumination of alkyn-1-ol **78** occurs at 50°C in hexane in the presence of 2 eq. of DiBAL-H. After disappearance of the starting material, the reaction was cooled to -78°C and carefully quenched with an electrophilic halogen source. The use of N-bromosuccinimide (NBS) afforded a complex mixture of (*E*)- and (*Z*)-configured olefins and many by-products. Similarly, when the reaction was quenched with I<sub>2</sub>, vinyl iodide **79** was formed but variable amounts of the inseparable side product **80** could not be avoided (Equation 2).



Equation 2. Observed side reaction during hydroalumination

According to the literature,<sup>[128]</sup> the alkyl iodide derives from a bis-hydroaluminated alkyne intermediate. Although no details were given concerning the possible mechanism, a conceivable pathway is shown in Figure 44.

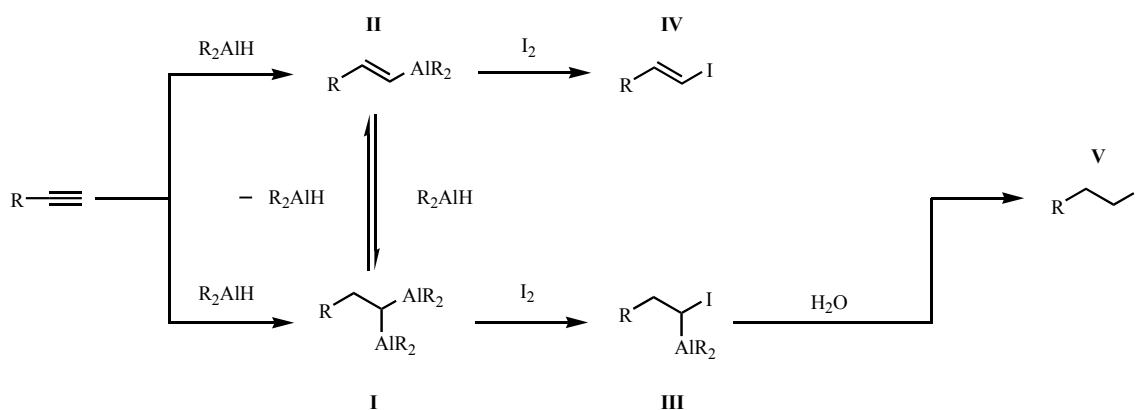
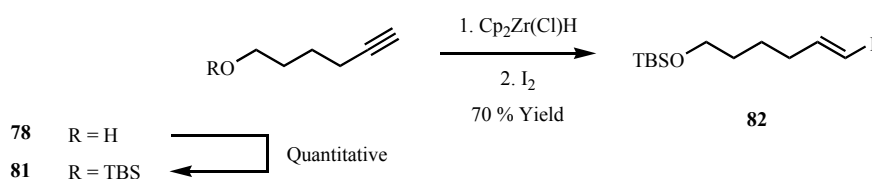


Figure 44. Plausible explanation for formation of the by-product **80**

It is known<sup>[105, 128]</sup> that two successive hydroaluminations of a triple bond preferentially afford the 1,1-dimetallic intermediate **I**. The latter has a limited stability and can easily undergo β-hydride elimination affording the desired intermediate **II**. However, if **I** reacts with I<sub>2</sub>, it might afford species **III** which can explain the formation of by-product **V** via protonolysis.

The subsequent propynylation was carried out with the mixture of iodo-derivatives **79** and **80**. Unfortunately, by-product **80** could not be separated from the desired enyne. Furthermore, as both steps were rather low yielding, it was decided to test other hydrometalation reagents.

The stereoselective formation of vinyl iodides using rather inexpensive chemicals was more difficult than anticipated. Further unsuccessful attempts were carried out with catechol borane as the hydrometalation reagent. The Schwartz's reagent (Cp<sub>2</sub>Zr(Cl)H) was finally tested on **81** affording the desired (*E*)-configured product **82** in good yield (Scheme 13). The primary alcohol function of the starting material **78** was protected before hydrometalation.

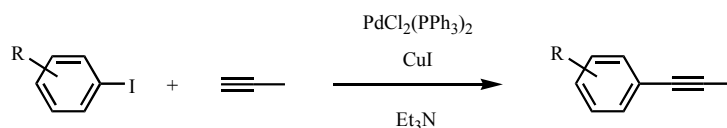


Scheme 13. Synthesis of (*E*)-non-5,7-enyn-1-ol **75** (hydrozirconation)

## II.2.4.1. Propynylations

The Sonogashira reaction has been especially studied with aromatic and heteroaromatic halides as electrophiles.<sup>[98, 101, 102]</sup> During the course of our research, several palladium-copper catalysed alkynylations with iodophenyl derivatives were carried out. The results are summarised in Table 5.

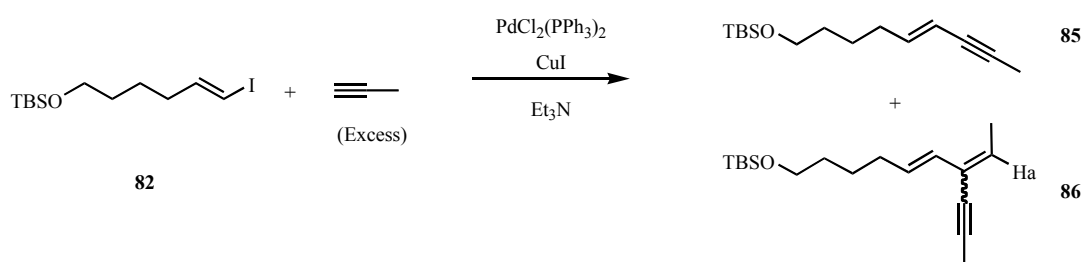
Table 5. Propynylation of aromatic halides by the Sonogashira procedure



Substrate	Product <sup>a</sup>	Yield
<b>83</b>	<b>84</b>	97 %
<b>46</b>	<b>28</b>	80 %
<b>48</b>	<b>49</b>	93 %

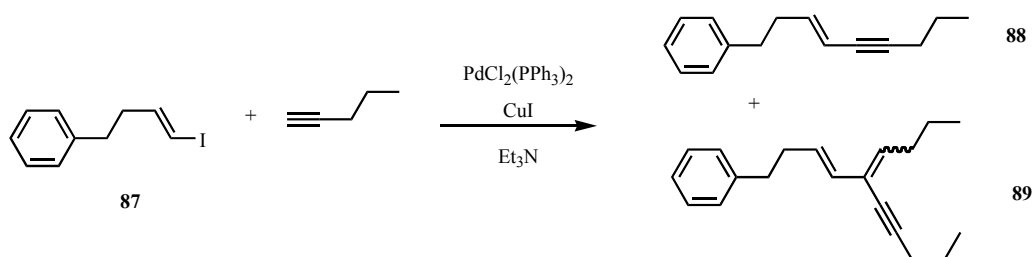
All the desired acetylenic derivatives were formed in good to excellent yield from the corresponding aromatic halides in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI and triethylamine.

Propynylation of vinyl-halide **82** under the same conditions led to the expected product **85** and various amounts (up to 15 %) of by-product **86**, obtained as single isomer (Equation 3). Although the exact stereochemistry of the second double bond has not been determined, the regiochemistry can be deduced from the splitting pattern of the signal of the ethylenic proton Ha. The reaction was always carried out overnight in the presence of an excess of propyne. In order to establish if this excess of the reagent was at the source of the problem, the same reaction was quenched rapidly before complete conversion. By-product **86** could still be observed indicating that the alkyne condensation reaction was competing with the cross-coupling process. Furthermore, it was not possible, in none of the following steps (silyl deprotection and esterification) to isolate by-products resulting from **86** from the desired compounds.



Equation 3. Side reaction occurring during the Sonogashira cross-coupling

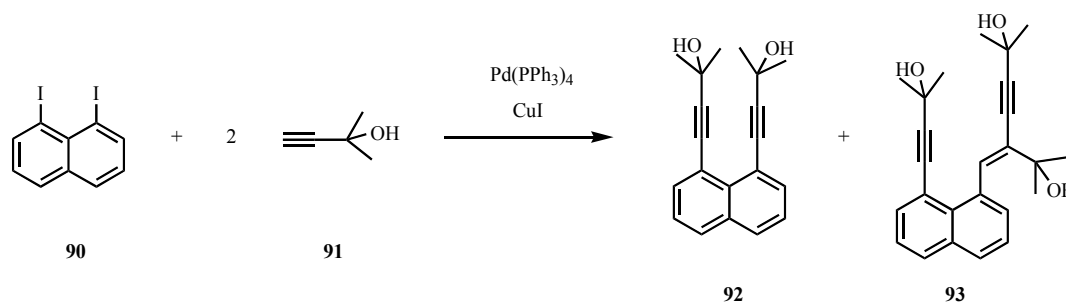
The cross-coupling between vinyl iodide **87** and hex-1-yne showed the same behaviour (Equation 4).



Equation 4. Alkyne condensation side reaction

A similar side reaction has recently been reported by Echavarren and co-workers.<sup>[129]</sup> 1,8-Diiodonaphthalene **90** reacts with a propargylic alcohol **91** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI as the catalytic system to form either the expected Sonogashira product **92** when *i*-Pr<sub>2</sub>NH is used as base, or enediyne **93** when pyrrolidine is used (Equation 5). The yield of the compound **93** is increased (up to 82 %) in the presence of Ag<sub>2</sub>O instead of CuI as co-catalyst.





Equation 5. Formation of a by-product under Sonogashira alkylation conditions<sup>[129]</sup>

Palladium-catalysed addition of terminal alkynes to internal alkynes has also been studied by Trost (Figure 45).<sup>[130]</sup> However, the reaction took place mainly in the presence of an electron withdrawing group on the acceptor acetylenic unit and is favoured by the use of electron rich phosphines.

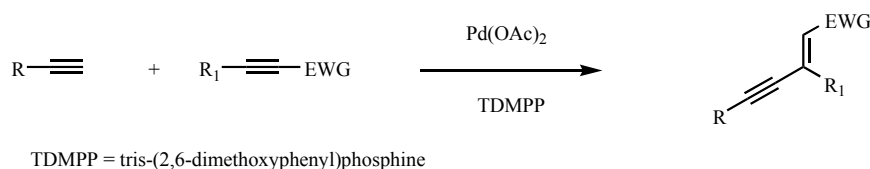
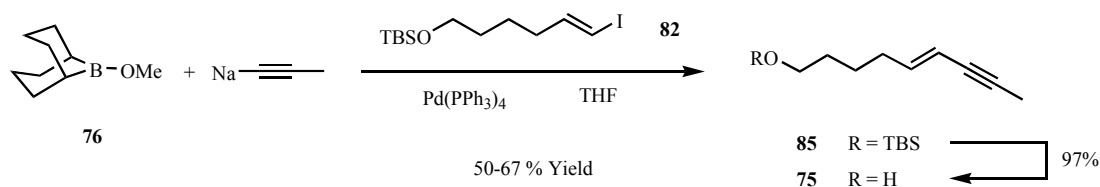


Figure 45. Type of palladium-catalysed condensation reaction reported by Trost and co-workers

To overcome this problem, we turned our attention to alkylation methods utilising preformed alkynylmetal reagents. Formation of the borate **77** (see chapter II.2.3.) from compound **76** in the presence of 1-propynylsodium occurred smoothly at room temperature. This reagent underwent a clean cross-coupling reaction with **82** giving reasonable yields of **85** without formation of any **86** (Scheme 14).

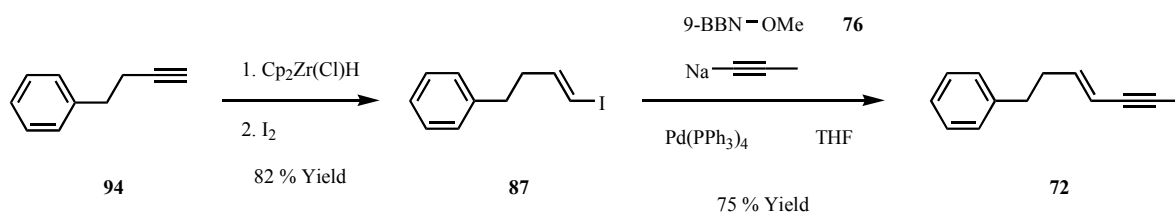


Scheme 14. Synthesis of (*5E*)-non-5-en-7-yn-1-ol **75** (alkynylation)

In conclusion, it was found that the Sonogashira-procedure is a very convenient and efficient method for Csp-Csp<sup>2</sup> bond formation and was always used as the method of first choice for the synthesis of conjugated enynes. However, in some cases, the product formed can easily undergo further condensation with the alkyne present in the medium. The boron mediated procedure for cross-coupling developed by Fürstner and Soderquist afforded a solution to this problem.

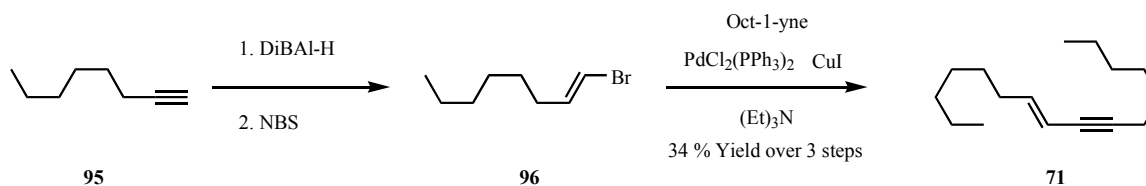
#### II.2.4.2. Synthesis of further enynes

Formation of vinyl iodide **87** was achieved via hydrozirconation of commercially available **94** followed by the addition of iodine. Subsequent propynylation afforded the desired enyne **72** in good yield (Scheme 15).



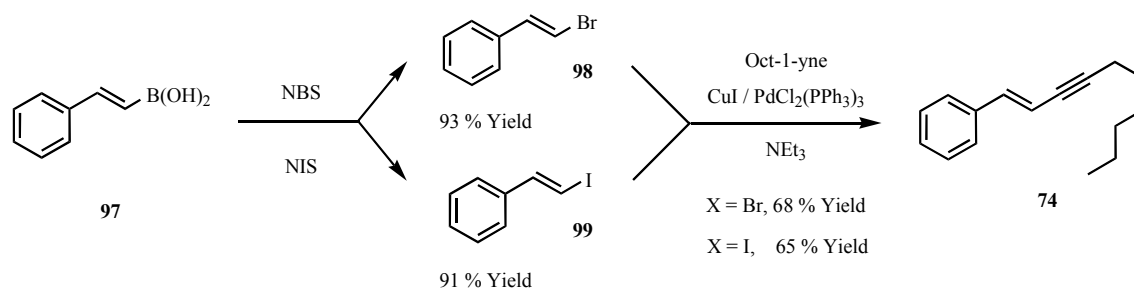
Scheme 15. Synthesis of (*3E*)-1-phenylhept-3-en-5-yne **72**

Unfunctionalised (*7E*)-hexadec-7-en-9-yne **71** was obtained in reasonable yield via hydroalumination of oct-1-yne **95**, treatment with NBS, and alkylation of the resulting alkenyl bromide **96** under Sonogashira conditions (Scheme 16); no noticeable by-product formation was observed in this case.



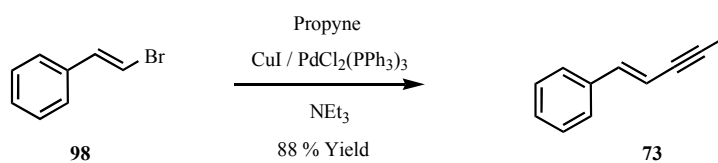
Scheme 16. Synthesis of (*7E*)-hexadec-7-en-9-yne **71**

The commercially available (*E*)-configured boronic acid **97** was easily transformed into the corresponding (*E*)-bromostyrene **98** or (*E*)-iodostyrene **99** by treatment with NBS or NIS.<sup>[108]</sup> Vinyl-halides **98** and **99** were then coupled with oct-1-yne according to the Sonogashira method affording the highly conjugated enyne system **74** in good yield (Scheme 17).



Scheme 17. Synthesis of (*E*)-1-phenyldec-1-en-3-yne **74**

(*E*)-1-phenylpent-1-en-3-yne **73** was similarly prepared in good yield via propynylation of vinyl bromide **98** under Sonogashira conditions (Equation 6).

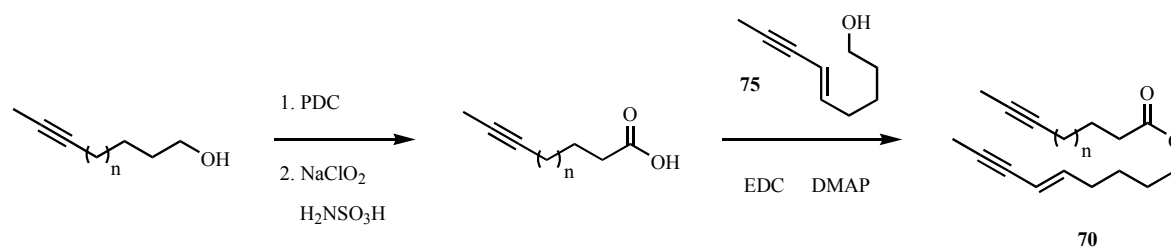


Equation 6. Synthesis of (*E*)-1-phenylpent-1-en-3-yne **73**

#### II.2.4.3. Synthesis of the precursors for RCAM

Building block (*5E*)-non-5-en-7-yn-1-ol **75** and various alkyne-1-ols were converted into a range of linear diynes of type **70**, which constitute precursors for enyne-yne (or enyne-enyne) ring closing metathesis. The results are summarised in Table 6.

Table 6. Preparation of the precursors for enyne-yne ring closing metathesis



Entry	Acid	Yield	Ester	Yield
1	<b>100</b>	72 %	<b>101</b>	80 %
2	<b>102</b>	63 %	<b>103</b>	75 %
3	<b>38</b>	82 %	<b>104</b>	84 %
4	<b>105</b>	76 %	<b>106</b>	88 %
5	<b>107</b>	/	<b>108</b>	81 %
6	<b>34</b>	/	<b>109</b>	77 %

All the monoesters and the phthalic acid derivative were obtained via standard esterification conditions<sup>[131]</sup> with EDC and DMAP in THF in good yields. Compound **107** derives from an esterification of phthalic anhydride with hex-4-yn-1-ol. The diester **109** bearing two enyne-moieties was obtained by esterification of hexanedioyl dichloride **34** with (*5E*)-non-5-en-7-yn-1-ol **75** in the presence of pyridine and DMAP.

## II.3. Metathesis Reactions of 1,3-Enynes

### II.3.1. Introduction

One of the most noticeable characteristics of the different alkyne metathesis catalysts is their high ability to differentiate between alkene and alkyne  $\pi$ -systems.<sup>[22, 30]</sup> To the best of our knowledge no example has been reported in which an alkene moiety was transformed in the presence of an alkyne metathesis catalyst. Alkylidene catalysts (especially ruthenium-based ones), however, catalyse enyne metathesis reactions.<sup>[132]</sup> It is plausible that the known alkyne metathesis catalysts are not electrophilic enough to undergo a reaction with less electron-rich double bonds. The lack of electrophilicity is indeed proposed by Schrock to explain the inaptitude of certain trialkoxide molybdenum alkylidyne complexes to catalyse metathesis (see Introduction).<sup>[24]</sup>

Alkyne metathesis of conjugated enynes has only been reported once<sup>[13]</sup> using an activated Mortreux catalytic system, but never with Schrock's tungsten alkylidyne complex **1**. Different mechanistic pathways have been proposed for these two catalytic systems and it was interesting to see if **1** would catalyse the desired reactions (alkyne cross-metathesis or ring closing alkyne metathesis) in the presence of a conjugated olefin. Encouraging precedence comes from the synthesis of compounds **110** and **111** via metathetic transformation reported by Schrock (Figure 46).<sup>[133]</sup> Moreover, complex **110** catalyses metathesis of hept-3-yne.<sup>[133]</sup> This suggests that no particular side reaction or loss of catalytic activity should be expected while reacting 1,3-enyne moieties with RCAM catalysts.

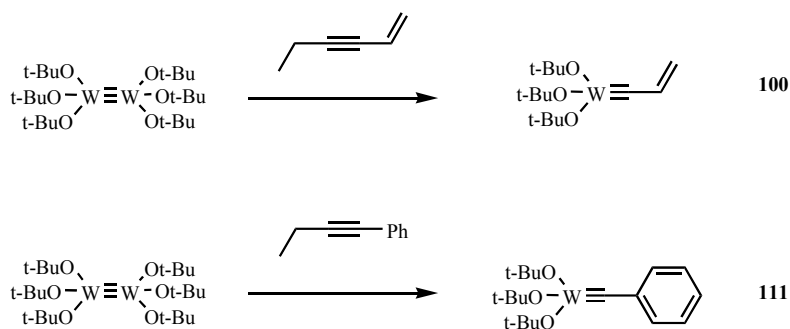


Figure 46. Synthesis of vinylidyne and benzyldiyne tungsten complexes

In spite of the potentially high synthetic interest drawn by the stereoselective synthesis of functionalised 1,3-enynes, no particular attention had previously been given to alkyne metathesis involving conjugated triple bonds. Potentially valuable applications of this transformation such as cross-metathesis and RCAM were therefore investigated.

### II.3.2. Metathesis reaction with 1,3-enynes

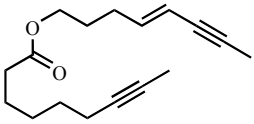
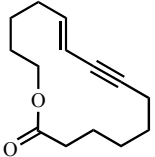
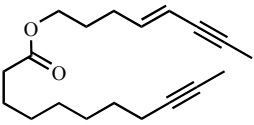
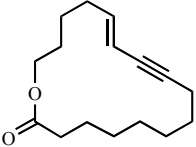
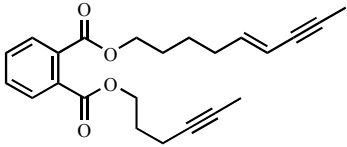
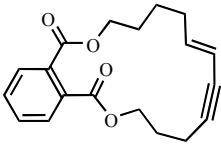
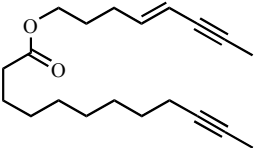
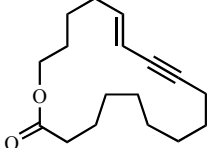
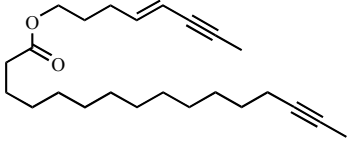
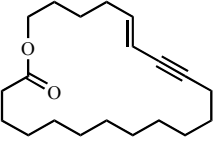
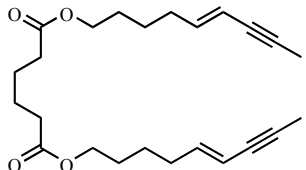
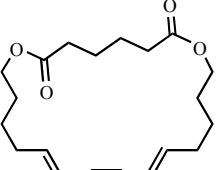
It was gratifying to find that the methyl-substituted enynes **72** and **85** underwent alkyne metathesis in the presence of  $(t\text{-BuO})_3\text{WCCMe}_3$  **1** (10 Mol %), in toluene, affording the desired products **112** and **113** in decent yields (Table 7). Even if the rate was slow, the alkylidyne complex **1** showed catalytic activity already at room temperature. The yields reported in Table 7 were calculated based on GC purity; NMR analysis of both homodimers revealed traces of an inseparable impurity. It should be noted that the homodimers are relatively unstable and tend to polymerise and decompose even at room temperature.

Table 7. Cross-metathesis reactions

Entry	Substrate	Product	Yield
1	<b>72</b>	<b>112</b>	68 %
2	<b>85</b>	<b>113</b>	67 %

### II.3.3. Ring closing enyne-yne metathesis

Table 8. Ring closing enyne-yne metathesis

Entry	Substrate	Product	Ring size	Yield
1			15	< 20 % <sup>a, b</sup>
2			17	60 %
3			17	< 20 % <sup>b</sup>
4			18	75 %
5			21	84 %
6			22	< 20 % <sup>b, c</sup>

<sup>a</sup> 20-40 % yield of cyclodimer

<sup>b</sup> The cyclic monomer was never isolated in pure form (presence of unreacted starting material)

<sup>c</sup> Up to 28 % yield of the cyclodimer was obtained at 0.02 M

All reactions were carried out between 70 and 80°C in dry toluene under high dilution conditions ( $\approx 0.001$  M) in the presence of 10 mol % of the Schrock alkylidyne catalyst **1**. A gentle argon flow through the toluene solution was utilised to remove but-2-yne from the system.

Good yields were obtained for the formation of 17, 18 and 21-membered cyclic esters **115**, **117** and **118** (Entries 2, 4 and 5), confirming the ability of the Schrock catalyst **1** to catalyse alkyne metathesis with 1,3-enyne systems. These results highlight the ability of this tungsten complex to distinguish between alkene and alkyne  $\pi$ -systems. Alkylidyne and alkylidene-based reactions are believed to be mechanically closely related, both following a Chauvin-type mechanism, but the tungsten complex **1** remains chemospecific in its mode of action.

Schrock's tungsten catalyst **1** had already shown its ability to close cyclic alkynes as small as 12-membered<sup>[21]</sup> (ring closure of 14-membered diester **53** via RCAM is reported in chapter I with 79 % yield). Furthermore, in all the reactions that were carried out for this study, a linear dimer has never been isolated. However, cyclic dimers were observed in quite large quantities in our attempts to close rings smaller than **115**. This result suggests that catalyst **1** shows high efficiency to undergo intramolecular cross-metathesis with any enyne derivative whose final ring size comprises more than 17 atoms. Since there is no other structural or electronic difference between **115** and **116** (both are 17-membered rings) besides the rigidity imposed by the *ortho*-disubstituted phenyl group, ring strain is the most plausible explanation for the difficulties encountered in our attempts to form cycles smaller than **115** (17-membered). A (*E*)-configured 1,3-enyne unit is a linear and fairly rigid six atom sequence obviously conferring high strain to any transition state passed through during the reaction as well as to the final product. The same argument is valid for dienyne **119** (Entry 6), possessing an even more extended rigid element, for which ring closure did not occur easily in spite of the reasonable final size of the cycle.

It is important to note that the catalyst's activity remains impressive under these very high dilution conditions. Even at 0.001 M, concentration of the substrate, the conversion was usually complete after one hour at 80°C. Since many organic substrates are thermally sensitive, short reaction times are beneficial. Preliminary experiments show that the temperature can be lowered further (50°C to 60°C) with no drastic loss of activity.

Attempts to form the 15-membered ring monoester **114** or the 17-membered phthalic derivative **116** in acceptable yields were unsuccessful (Entries 1 and 3). Problematic in these cases was also the separation of unreacted starting material from the cyclic monomer. Varying the dilution between 0.005 M and 0.0001 M did not affect the yield.



The cyclodimeric product derived from **101** was isolated in 20 % yield. NMR analysis showed the presence of the “head to tail” dimer **120** and the “head to head” dimer **121** (Figure 47).  $^{13}\text{C}$  shifts of the alkyne carbons are characteristic. When the C-sp is bound to a C-sp<sup>3</sup>,  $\delta = 79\text{-}81$  ppm and when the C-sp is bound to a C-sp<sup>2</sup>,  $\delta = 87\text{-}89$  ppm. The ratio **120:121** was  $\approx 2:1$ , potentially showing a difference of reactivity between conjugated alkynes and non-conjugated alkynes. Unfortunately, the ratio varied under seemingly identical conditions. Many attempts to favour formation of the cyclic dimer over the cyclic monomer were unsuccessful, with the major part of the substrate probably forming oligomers and polymers.

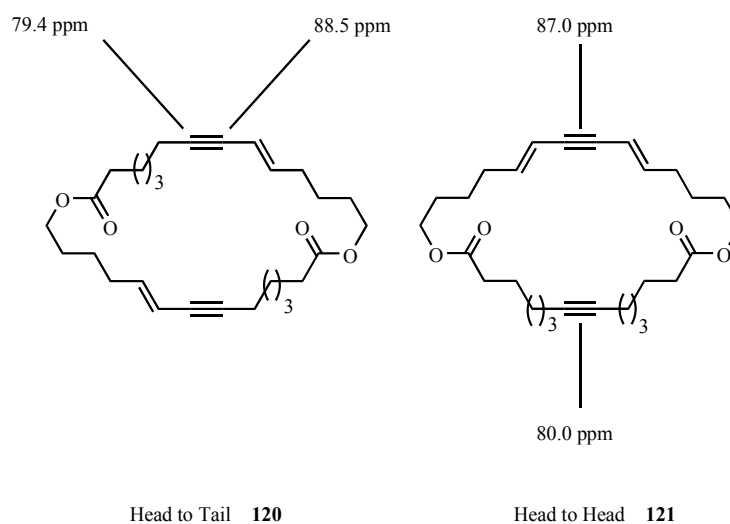


Figure 47. Cyclic dimeric structures

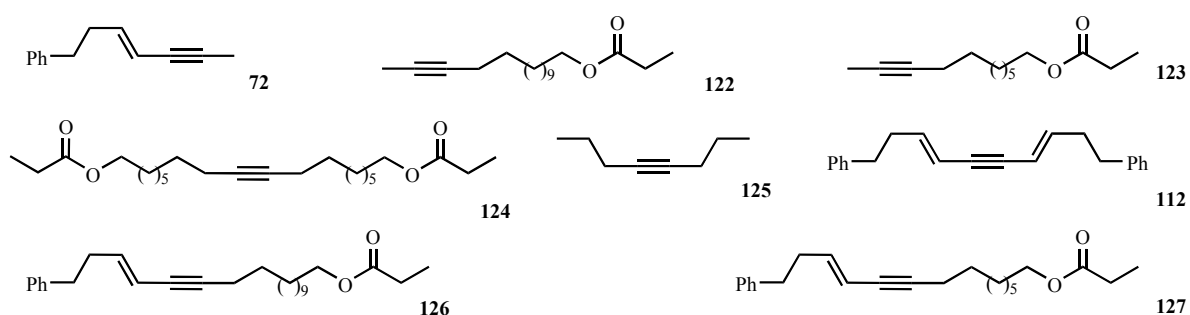
The slightly lower yield for cyclisation of the 17-membered monoester **115** (60 % instead of more than 75 % for the 18- and 21-membered) and the impossibility of closing a structurally different 17-membered diester may indicate a size limit of the RCAM method for enyne-yne cyclisation.

### II.3.4. Cross-metathesis Reactions

Mori<sup>[5, 6]</sup> and Bunz<sup>[3, 13]</sup> have investigated the cross-metathesis of alkynes for the formation of simple molecules, cyclic dimers, oligomers and polymers, while Fürstner<sup>[30-32]</sup> has reported some examples in total synthesis. Very recently, the development of a new catalytic system and methodological improvements on alkyne cross-metathesis promise a wider scope.<sup>[36]</sup>

We were willing to investigate the difference of reactivity between conjugated acetylenic substrates and non-conjugated ones in alkyne metathesis. The results are summarised in Table 9. All reactions were carried out in dry toluene (various concentrations 0.1-0.5 M) at 80°C in the presence of (*t*-BuO)<sub>3</sub>WCCMe<sub>3</sub> **1** under a slight argon flow. The esters **122** and **123** were obtained from treatment of the corresponding alcohols with propanoyl chloride, pyridine and DMAP.

Table 9. Cross-metathesis reactions



Entry	Substrate 1	Substrate 2	Products	Results
1	<b>72</b>	<b>72</b>	<b>112</b>	68 % Yield
2	<b>123</b>	<b>123</b>	<b>124</b>	67 % Yield
3	<b>72</b>	<b>125</b>	/	Deactivation or destruction of the catalyst. Very little amount of products is observed on gas chromatography (GC).
4	<b>122</b>	<b>112</b>	Dimer of <b>122</b>	Even if <b>126</b> is formed, the main product is the homodimer of <b>122</b> (GC)
5	<b>72</b>	<b>124</b>	<b>123 + 127</b>	43 % Yield <sup>a</sup>

<sup>a</sup> Calculated yield of the desired compound **127** (based on NMR ratio). The product could only be isolated as a mixture of H and C ( $\approx$  1:1).

Homodimerisation of alkyne **123** and enyne **72** occurred in decent yields (Entries 1 and 2). It can be noted that the reaction also took place at lower temperature (40°C) but the time to reach complete conversions was much higher (presence of starting material was observed after 15h).

Attempted cross-metathesis reactions, however, were quite disappointing. Surprisingly, almost no reaction occurred between **72** and **125**. Only traces of the desired product could be detected by GC analysis of the crude mixture. Reaction between **122** and **112** afforded mainly the homodimer **122**. Although the desired product **126** was also observed by gas chromatography, it had formed only in small amounts.

The best yield of cross-metathesis between homodimer **124** and enyne **72** was unfortunately lower than 50%. Furthermore the desired product **127** could not be separated from **123**.

From these results one can conclude that alkyl-substituted alkynes are more reactive than conjugated enynes towards alkyne metathesis reactions. It is supposed that a conjugated alkyne is not as electron-rich as a non-conjugated acetylenic compound and will therefore react less easily with the electrophilic tungsten catalyst **1**. It remains to be seen if this difference of reactivity might be useful in the future (for example some specific applications in successive ring closing alkyne metathesis steps).

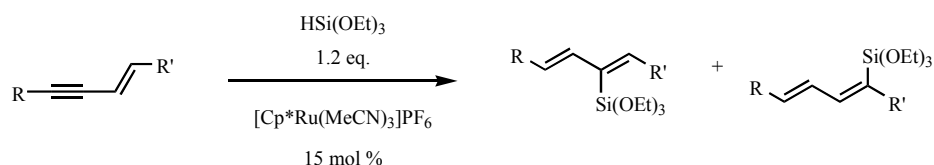
## II.4. Semi-Reduction of Conjugated Enyne Systems

The linear and macrocyclic molecules bearing a 1,3-enyne motif were submitted to the two-step procedure resulting in semi-reduction. Particular attention was given to their behaviour in the ruthenium-catalysed hydrosilylation reaction.

### II.4.1. Hydrosilylation of linear systems

As previously described, the hydrosilylation of the phenyl-substituted acetylenic substrate **65** with ruthenium catalyst **15** proved to be more demanding in catalyst loading than that of non-conjugated substrates and showed a certain degree of regioselectivity (See chapter I). The enynes **71-74** were prepared to see if this trend also applied to other conjugated systems. The results are summarised in Table 10.

Table 10. Hydrosilylation of various linear 1,3-dienes



Entry	Substrate	Product <sup>a</sup>	Yield
1	<b>71</b>	<b>128</b>	71 %
2	<b>74</b>	<b>129</b>	71 %
3	<b>72</b>	<b>130</b>	(≈ 49 %) <sup>b</sup>
4	<b>73</b>	<b>131</b>	<sup>c</sup>

<sup>a</sup> Mixture of regioisomers.

<sup>b</sup> Yield was calculated based on GC purity.

<sup>c</sup> The product was obtained as a complicated mixture.

Hydrosilylation of 1,3-enyne systems required 15 mol % of catalyst **15** to reach complete conversion. This is in striking contrast to the 1 mol % usually used for non-conjugated systems.

In all cases, the vinylsilanes were obtained as a mixture of isomers and some minor by-products. However, preparation of the alkenylsilanes **128** and **129** in decent yields was possible but necessitated a careful purification by flash chromatography (entries 1-2).

Synthesis of diene systems **130** and **131** (Entries 3 and 4) was more problematic. Three isomers of the desired product were observed by GC/MS in the crude mixture, indicating formation of an (*E*)-configured vinylsilane. Moreover, variable amounts of an unknown by-product were also detected by GC/MS (2-15%). This by-product was not separable from the desired vinylsilanes and could therefore not be characterised. The mass spectrum, however, showed that its molecular mass corresponded in each case to the molecular mass of the expected vinylsilane + 2 (Figure 48). Furthermore, the by-product seemed to be also protodesilylated in the presence of AgF because comparable amounts of another M+2 peak were found with the final diene.

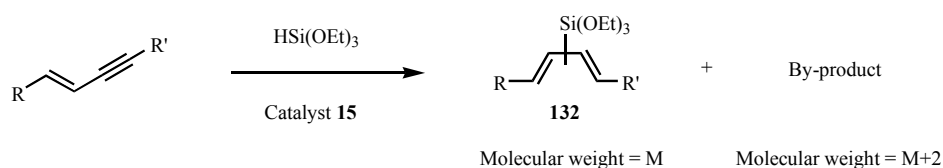


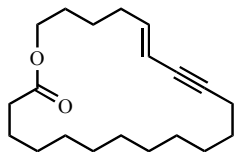
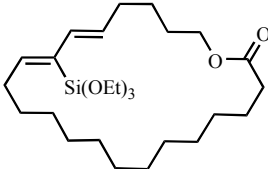
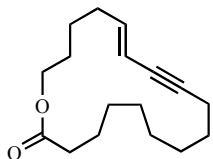
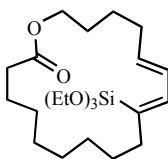
Figure 48. Hydrosilylation of 1,3-enynes

This by-product could possibly derive from the formal hydrogenation of compound **132**. It is indeed possible to imagine that a ruthenium hydride species could reduce one of the double bonds of **132**. To the best of our knowledge, such a side reaction leading to the formation of a reduced product has never been reported for transition metal-catalysed hydrosilylation and no reasonable explanation was found to clarify the formation of this by-product.

## II.4.2. Hydrosilylation of cyclic systems

The hydrosilylation of the 18- and 21-membered monoesters **117** and **118** under the same conditions was also carried out (Table 11).

Table 11. Hydrosilylation of 18- and 21-membered rings

Entry	Substrate	Product	Yield
1	 <b>118</b>	 <b>133</b>	(65) % <sup>a</sup>
2	 <b>117</b>	 <b>134</b>	20 %

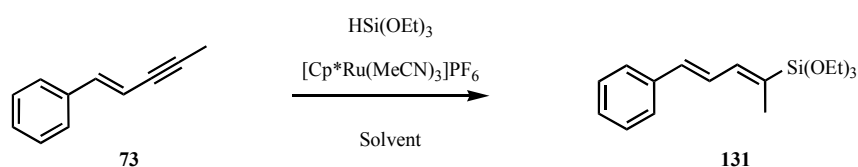
<sup>a</sup> Calculated for a mixture of isomers

The results were not entirely satisfying. The reaction was very demanding in catalyst loading and afforded a very complex mixture of isomers and by-products. Alkenylsilane **133** was obtained as a mixture of three unseparable components: the desired product, diverse isomers of the product and a by-product corresponding to the above-mentioned unknown side reaction. Similarly, hydrosilylation of **117** afforded a complex mixture but the major isomer **134** could be isolated in low yield, after meticulous purification.

In conclusion, hydrosilylation of conjugated triple bonds cannot be reliably carried out under the conditions developed by Trost. NMR studies showed, however, that the addition across the triple bond still occurs in a *trans*-manner affording the expected (*E,Z*)-configured dienylnsilane as major component, but the reaction suffers from an unexplained side reaction.

### II.4.3. Optimisation of the hydrosilylation reaction

A screening of various conditions aimed at improving both the yield and the selectivity of the hydrosilylation step was carried out. We were pleased to discover that the results for hydrosilylation varied significantly in the presence of different solvents. 1,3-Enyne **73** was chosen as test substrate because of its availability in large amounts and because it gave the worst results under the conditions originally developed by Trost (Equation 7).



Equation 7. Screening reaction

#### II.4.3.1. Summary of the results for the test substrate

The reactions were carried out at room temperature, with 1.2 eq. of silane and 6 mol % of initial catalyst loading. More catalyst was introduced in the reaction mixture if the conversion had stopped.

Table 12. Solvent screening

Entry	Solvent	Concentration	Observations
1	Acetone	0.5 M	No complete conversion in spite of very high catalyst loading (> 15 mol %).
2	THF	0.5 M	Complete conversion for a reasonable amount of catalyst (10 mol %) but formation of large amount of by-product (20%, GC).
3	Toluene	0.5 M	Very slow reaction, highly demanding in catalyst loading ( $\approx$ 15 mol %) but low amount of by-product is formed.
4	CH <sub>2</sub> Cl <sub>2</sub>	0.5 M	Complete conversion for a reasonable amount of catalyst (10-15 mol %) but formation of a large amount of by-product (4-15%, GC).
5	CH <sub>2</sub> Cl <sub>2</sub>	2 M	5h reaction, complete conversion, 78 % yield, for 10 mol % of catalyst and only 1.5 % of by-product (GC).
6	Neat	/	5h reaction, complete conversion, 82 % yield, for 10 mol % of catalyst and only < 1 % of by-product (GC).
7	Neat	/	Overnight reaction, complete conversion, 10 mol % of catalyst and > 10 % by-product (GC).

In spite of its common use with catalyst  $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ ,<sup>[78, 84, 86, 134]</sup> acetone turned out to be inappropriate for the hydrosilylation of enynes (entry 1). Toluene and THF generate extremely different results in terms of selectivity and reaction rate, but neither is acceptable in preparative terms (entries 2 and 3). However, the amount of by-product formed was clearly lowered in dichloromethane at higher concentration with acceptable catalyst loading (entry 5). Since dilution appeared to be a decisive parameter, and as the hydrosilylation reactions are commonly carried out without solvent,<sup>[66, 67]</sup> the reaction was attempted under neat conditions (entry 6). We were pleased to find that these conditions afforded similar results to those obtained in concentrated dichloromethane solutions, as well as having the advantage of being solvent-free. Formation of large amounts of by-product were, however, observed under neat conditions, when the reaction was left for longer reaction times (entry 7).

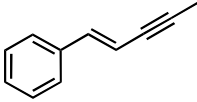
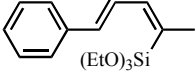
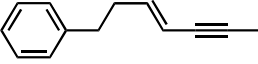
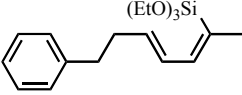
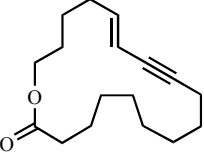
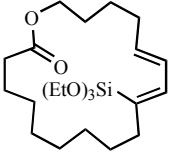
It is important to note that the catalyst is generally not soluble in the mixture formed by the substrate and the silane. Vigorous agitation is necessary to create a fine dispersion of the solid ruthenium complex in the oily phase. It has been observed that for small-scale experiments, the agitation cannot always produce the desired suspension, generating inactive catalyst agglomerates. This issue can be overcome by adding a minimal amount of dichloromethane (1.2-1.5 eq.) dissolving the agglomerates and enabling the reaction to go to completion.



## II.4.3.2. Comparison of results

Cyclic and acyclic 1,3 enynes were submitted to hydrosilylation under solvent-free conditions and the results were compared with the previous experiments.

Table 13. Comparison between hydrosilylation of alkynes under neat conditions and in dichloromethane

Entry	Substrate	Product	Conditions A	Conditions B
1	 <b>73</b>	 <b>131</b>	< 50 %	82 %
2	 <b>72</b>	 <b>130</b>	< 60 %	88 %
3	 <b>117</b>	 <b>134</b>	< 60 %	80 %

Conditions A : in dichloromethane ( $\approx 0.5$  M).

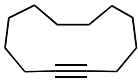
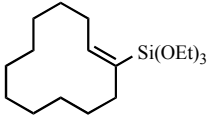
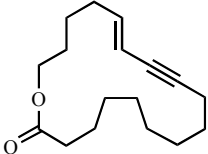
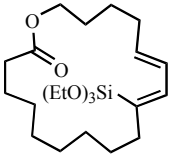
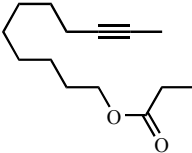
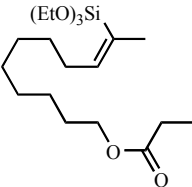
Conditions B : neat

Obviously, hydrosilylation under neat conditions leads to a much cleaner vinylsilane formation in higher yields. Lower loadings of catalyst are sufficient (5-10 mol % of the catalyst were commonly used) and reaction times are comparable (1-5h to reach complete conversion depending on the substrate).

## II.4.3.3. Further results for hydrosilylation of various alkynes under neat conditions

Further experiments were carried out with various substrates to study the scope of the procedure (Table 14). All the reactions were carried out neat, at room temperature, in the presence of 1.2-1.5 eq. of  $\text{HSi}(\text{OEt})_3$  and  $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$  (5-10 mol %).

Table 14. Hydrosilylation of various alkynes under neat conditions

Entry	Product	Product <sup>a</sup>	Yield ( <i>E</i> : <i>Z</i> )
1	 <b>33</b>	 <b>51</b>	85 % (91:9)
2	 <b>117</b>	 <b>134</b>	80 %
3	 <b>123</b>	 <b>135</b>	90 %

<sup>a</sup> Only one regioisomer is represented.

All hydrosilylations under solvent-free conditions were successful and afforded the desired vinylsilanes in high yields.

Hydrosilylation of cyclododecyne **33** under neat conditions afforded nearly identical results as those obtained under standard conditions but necessitated slightly more than 2 hours to reach complete conversion (instead of less than 15 min when the reaction was run in dichloromethane). Reaction times are in general longer for the solvent-free procedure; the reactions shown in entry 2 and 3 required more than 5 hours to reach complete conversion.

In spite of similar preparative results, all reactions carried out “neat” required higher catalyst loading than those performed in dichloromethane solutions. Loss of catalytic activity can be ascribed to the poor solubility of the ruthenium complex in the silane-substrate mixture. Reaction rates of

hydrosilylation under such “non-homogeneous” conditions depend on different parameters. As the ruthenium is meant to be active in homogeneous phase, only a small amount of it can be considered as taking part in the catalytic process. The apparent loss of activity is compensated by higher yields and purity of the product.

To summarise, cyclic and acyclic substrates as well as conjugated and non-conjugated systems were stereoselectively hydrosilylated in high yields. Serious troubles of purity and chemoselectivity appeared when conjugated enynes were submitted to standard hydrosilylation conditions. Carrying out the reaction neat or in highly concentrated dichloromethane solution, however, allowed us to prepare (*1E,3Z*)-1,3-dienylsilanes in high yields and high purity.

#### II.4.4. Regioselectivity of the ruthenium-catalysed hydrosilylation

Regioselectivity is not an important factor in the overall process of semi-reduction of alkynes because the silicon group is lost in the final step. The formation of (*E*)-configured alkenes only requires high stereoselectivity of the silane addition across the triple bond. For example, both compounds **136** and **137** lead to the same alkene **138** after protodesilylation (Figure 49).

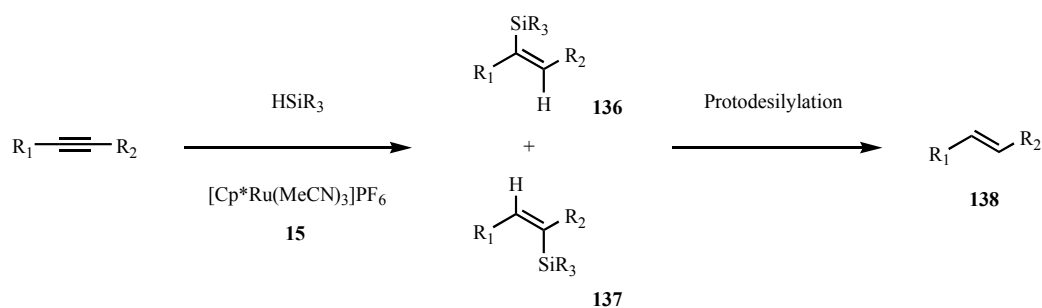


Figure 49. Low importance of hydrosilylation's regioselectivity in the overall process of semi-reduction

However, as vinylsilanes are valuable intermediates in organic synthesis,<sup>[120, 135]</sup> it was interesting to investigate the regioselectivity of the ruthenium-catalysed transformation.

Hydrosilylation of non-conjugated acetylenic derivatives leads to the formation of two regioisomers in a  $\approx 1:1$  mixture (see chapter I). However, it has been discovered that the presence of a phenyl substituent on the triple bond induces a certain degree of regioselectivity (Figure 50).

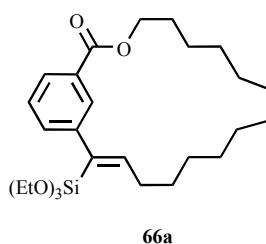


Figure 50. Major isomer obtained from hydrosilylation of cycloalkyne **65**

Similar trends were seen in the studies on conjugated enyne systems. NMR data (splitting patterns and coupling constants) allow to assign the regioisomers.

#### II.4.4.1. Regioselectivity of the hydrosilylation of unfunctionalised enyne **71**

The isomers **128** and **128a** were obtained via hydrosilylation of enyne **71** in dichloromethane, with a regioisomeric ratio of 85:15 (calculated from NMR data).

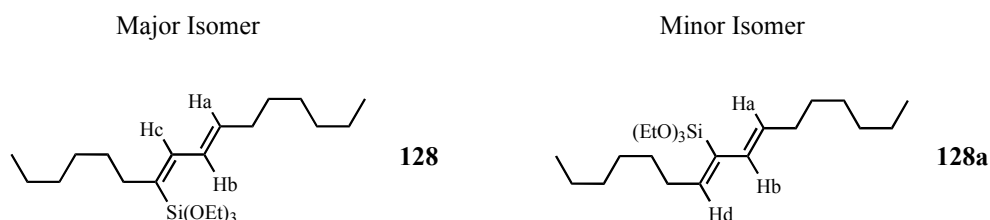


Figure 51. Regioisomers obtained from the hydrosilylation of enyne **71**

For both isomers, the protons Ha and Hb show similar NMR signals. The coupling constant of Ha and Hb is  $\approx 15$  Hz, which is characteristic for *trans*-configured ethylenic protons. The molecules can be differentiated by the signals of protons Hc and Hd. Hc couples only with Hb and its signal is a broad doublet with a characteristic coupling constant of  $\approx 11$  Hz. The NMR signal for Hd is a broad triplet with a coupling constant of  $\approx 7$  Hz. Hd does not couple with any ethylenic protons but with the neighbouring  $\text{CH}_2$ .

#### II.4.4.2. Regioselectivity of the hydrosilylation of cyclic enyne **117**

Hydrosilylation of enyne **117** in dichloromethane afforded a mixture of several isomeric compounds and by-products. One isomer, however, represented more than 80 % of the overall mixture (GC). This alkenylsilane was isolated and its structure elucidated by NMR experiments.

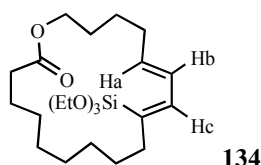


Figure 52. Major isomer for the hydrosilylation of cyclic enyne **117**

In this case it is not possible to calculate the exact coupling constants between the different protons and a spectrum simulation (carried out with gNMR) was required to certify the structure of the product (for the optimised parameters of the simulation see Table 15). After optimisation, the spectrum simulation gave signals whose splitting patterns were almost identical to those measured experimentally. From these data, it can be concluded that the silicon group resides on the terminal carbon of the diene unit.

Table 15. Parameters of the spectrum simulation

Proton	Shift (ppm)	Width (Hz)	J (Hz)			
			Ha	Hb	Hc	CH <sub>2</sub>
Ha	6.480	2.0		15.60		8.00
Hb	6.448	2.0	15.60		10.80	
Hc	5.520	2.0		10.80		
CH <sub>2</sub>	2.100	2.0	8.00			

A pronounced regioselectivity was only observed for hydrosilylation in CH<sub>2</sub>Cl<sub>2</sub>. GC/MS analysis of the same substrate hydrosilylated under neat conditions shows a mixture of two isomers of the same mass in a 58:42 ratio. Another isomeric ratio of 65:35 was found for an experiment carried out in the presence of a minimal amount of CH<sub>2</sub>Cl<sub>2</sub>.

II.4.4.3. Regioselectivity of the hydrosilylation of enynes **72** and **74**

Analogous to the two preceding examples, NMR data enabled us to determine the structures of the main regioisomers obtained by hydrosilylation of **72** and **74** (Figure 53).

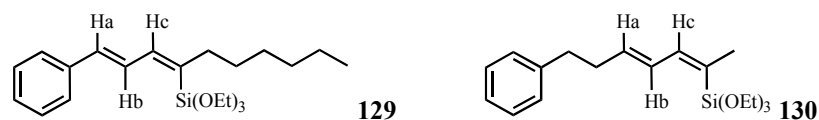


Figure 53. Major isomers obtained from the hydrosilylation of enynes **72** and **74**

Hydrosilylation of enyne **74** in dichloromethane afforded a regioisomeric mixture (ratio 80:20) in which compound **129** was the major isomer. Hydrosilylation of **72** in dichloromethane afforded a mixture of compounds (isomers and by-products). GC/MS gave evidence that isomer **130** was produced in large excess (more than 90% of the overall mixture). When the hydrosilylation of **72** was carried out neat, the regioisomeric ratio was lowered to  $\approx$  80:20 (GC).

#### II.4.4.5. Discussion

Chung and co-workers<sup>[87]</sup> proposed that the regioselectivity observed in the hydrosilylation of terminal alkynes may be explained by steric hindrance (see introduction). According to their proposal, the silyl group should end up at the most sterically crowded alkyne carbon. Since there is almost no difference of steric bulk in the vicinity of *sp*-hybridised carbon atoms in compound **71**, the argument proposed by Chung can therefore not be extrapolated to internal conjugated alkynes to explain the observed regioselectivity.

In each case the silicon group seems to be directed towards the terminal carbon atom of the enyne system. We suspected that the atomic charge repartition on the triple bond might be a preponderant parameter to explain this regioselectivity. It is reported in a review by Wipf<sup>[106]</sup> that regioselectivity of the hydrozirconation on a disubstituted styrene derivative can be explained by determination of atomic charges on both ethylenic carbon atoms. Direct extrapolation of this observation to our transition metal-catalysed hydrometalation is somewhat perilous, but we were tempted to believe that the presence of the phenyl group (or of an alkene) as substituent on the alkyne may induce differences in the electronic environment of both *sp*-hybridised carbon atoms. Charge repartition was therefore computationally calculated on two models (Figure 54). The structures were optimized using B3LYP (basis set 6-31+G\* for H, C and O atoms).

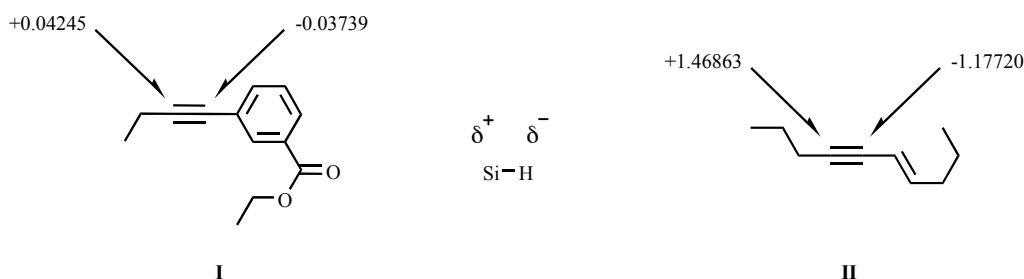


Figure 54. Charge repartition on the *sp*-hybridised carbon of two model molecules

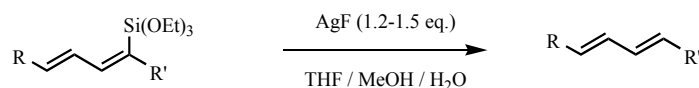
For model **I**, the carbon on the benzylic position is negatively charged while the other *sp*-hybridised carbon bears a positive charge. This electronic repartition fits with the experimental data, where the positively charged silicon group reacts with the negatively charged alkyne carbon. However the difference between the charges is not particularly significant. Importantly however, computational data for the model **II** do not fit with the experimental results although the difference between both values is much higher. The observed regioselectivity can unfortunately not be explained by this simple electronic argument.

## II.5. Protodesilylation of vinylsilanes

### II.5.1. Protodesilylation of conjugated vinylsilanes

We showed in a previous section that desilylation of non-conjugated vinylsilanes with AgF in aqueous THF/MeOH occurred smoothly and in good yields with no significant isomerisation of the double bond. The conjugated vinylsilanes that were successfully synthesised in the last section were submitted to protodesilylation under the same conditions and the results are summarised in Table 16.

Table 16. Protodesilylation of conjugated vinylsilanes



Entry	Substrate	Product	Yield ( <i>E,E</i> )
1	<b>128</b>	<b>139</b>	82 % (98 %)
2	<b>129</b>	<b>140</b>	79 % (97 %)
3	<b>130</b>	<b>141</b>	78 % (99 %)
4	<b>131</b>	<b>142</b>	73 % (97 %)
5	<b>134</b>	<b>143</b>	79 % (97 %)

As for non conjugated acetylenic compounds, protodesilylation occurred in good yields, under standard conditions and the final (*E,E*)-1,3-dienes were obtained with high isomeric purity.



We were pleased that the use of stoichiometric amounts of Ag<sup>I</sup> did not lead to any noticeable isomerisation of the double bonds and that no side reactions such as dimerisation or polymerisation were observed.

Desilylation only suffered from the presence of by-products in some of the starting materials. Vinylsilanes **128** and **129** (entries 1 and 2) were not hydrosilylated under neat conditions and contained traces of reduced material. Since the unknown reduced by-product seemed to be also desilylated under the reaction conditions affording another by-product, meticulous purification of the final dienes by chromatographic methods was necessary to obtain the desired products in high purity.

Semi-reduction of 1,3-enynes was hence successfully completed. Several cyclic and acyclic compounds were submitted to a two-step sequence of hydrosilylation-protodesilylation affording stereodefined (*E,E*)-1,3 dienes in high isomeric purity. We were pleased to observe that silver fluoride could be used without complications for the desilylation of more demanding and sensitive substrates such as dienylsilanes. The great ability of this silver salt to undergo carbon-silicon bond cleavage in our cases can possibly be extended to other silicon substituents and could become a standard procedure for silicon deprotection.

### II.5.2. Studies on catalytic protodesilylation

Silver fluoride was proven to be the most suitable reagent for the clean conversion of vinylsiloxanes to the corresponding alkenes with no noticeable isomerisation of the double bond.<sup>[85]</sup> Many other fluoride containing reagents were tested<sup>[85]</sup> but found inappropriate. Furthermore, other more classical methods commonly used to provide such transformation suffer from low functional group tolerance (strong mineral acid like HI) or only undergo complete conversion under forcing conditions (TBAF at 80°C), and thus offer the desired product in low yield. Even if the mode of action of AgF has not yet been elucidated in detail, the fact that it is far more effective than other fluoride sources suggests a synergetic action between the specific affinity of the fluoride anion for silicon and that of Ag<sup>I</sup> for  $\pi$ -systems. It is assumed that fluoride initially leads to a pentacoordinate silicate species,<sup>[136]</sup> thus facilitating a transmetalation to a transient vinylsilver intermediate that is immediately trapped to give the alkene product. Similar elementary steps have been proposed for the mechanism of cross-coupling reactions with fluoride activated vinylsiloxanes and palladium catalysts.<sup>[137, 138]</sup>

Trost developed a similar fluoride mediated transformation using TBAF in the presence of CuI.<sup>[84]</sup> In most of the cases the copper reagent is utilised in catalytic amount (10-20 mol %) even if, for some examples, over-stoichiometric amounts are necessary (the presence of a ketone seems to

disturb the catalytic conditions). Such a large amount of copper is claimed to buffer the activity of the fluoride source.

In our case, silver fluoride showed great effectiveness even for desilylation of conjugated dienyilsilane moieties. However, the method suffers from the need for an over-stoichiometric (1.2-1.5 eq.) amount of silver. Although this is not a major issue in the last steps of a total synthesis, it might become a serious concern on larger scale applications. That is why it was decided to further investigate the reaction in order to reduce its cost and make it applicable to larger scale preparations.

### II.5.2.1. Strategy & results

The following mechanism for carbon-silicon bond cleavage might operate (Figure 55). The affinity of fluorine for silicon leads to the formation of ionic species **I** that rearranges to form a highly reactive vinylsilver intermediate **III** and a stable fluorosiloxane **II**, the formation of which would be the driving force. Intermediate **III** is trapped by a proton source (MeOH or H<sub>2</sub>O) providing the desired alkene **IV** and cationic silver. Even if the fluorosilane **II** might hydrolyse and release fluoride in solution, it is still probable that stoichiometric amounts of fluoride will be necessary for the formation of silicate complexes. Furthermore, it is possible that, in the presence of a stoichiometric amount of fluoride ions, AgF may be regenerated.

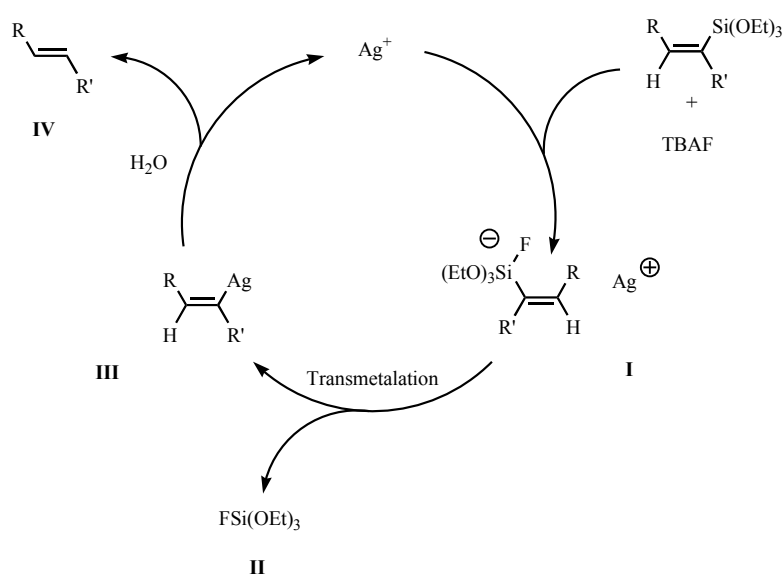
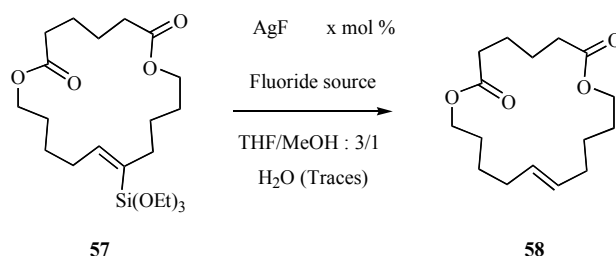


Figure 55. Plausible catalytic cycle for silver-catalysed desilylation of vinylsilanes

According to this hypothesis, many sources of fluoride were investigated as regenerating system to allow the use of only catalytic amounts of Ag<sup>I</sup>. Substrate **57** was chosen for the screening and the results are summarised in Table 17.

Table 17. Results for the screening on fluoride source

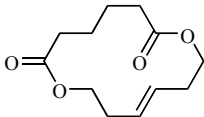
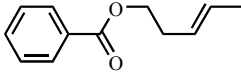
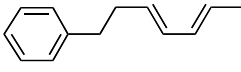


Entry	Fluorine source (1 eq.)	AgF	Yield
1	/	200 mol %	90 %
2	TBAF·3H <sub>2</sub> O	10 mol %	68 %
3	TBAF (1M in THF)	20 mol %	90 %
4	KF on aluminium oxide	10 mol %	Decomposition
5	KF	20 mol %	< 20 % yield

We were pleased to discover that silver fluoride could be used in catalytic quantities affording the desired product **58** in yields similar to those obtained under stoichiometric conditions. TBAF turned out to be the only suitable reagent that enabled turnover (entry 2 and 3). Best results were obtained with TBAF as solution in THF (entry 3). Other fluoride sources provided either complete decomposition of the starting material or very low yield (entry 4 and 5).

Further experiments were carried out, varying the substrates and the amount of silver fluoride. The results are summarised in Table 18.

Table 18. Comparison between stoichiometric and catalytic protodesilylations

Entry	Product	AgF (mol %) <sup>a</sup>	Yield
1	 <b>55</b>	200	90 %
2		20	86 %
3		10	84 %
4		2	86 %
5	 <b>146</b>	200	80 % <sup>b</sup>
6		10	94 %
7	 <b>141</b>	150	78 %
8		10	75 %

<sup>a</sup> All experiments were carried out at room temperature, shielded from light, in an aqueous THF/methanol (3/1) solution, in the presence of AgF as catalyst and TBAF (1M solution in THF).

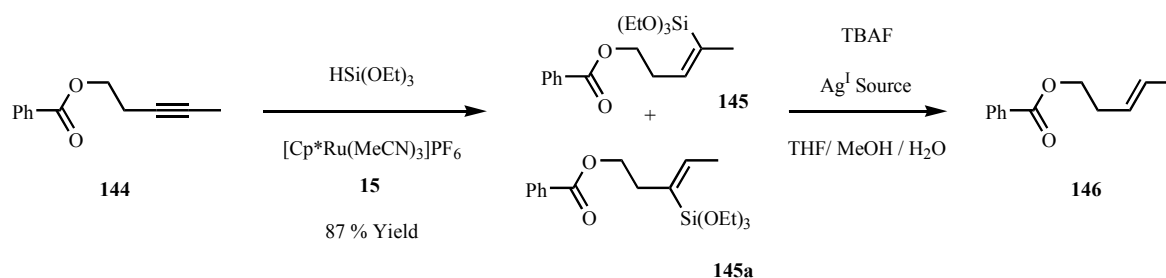
<sup>b</sup> This somewhat lower yield can be explained by partial polymerisation of the starting material during storage.

These results proved that the catalytic procedure proceeds with excellent effectiveness with loading as low as 2 mol % of silver fluoride (entries 1 to 4). For all the substrates tested, catalytic protodesilylation occurred in yields comparable to those obtained with stoichiometric amounts of silver fluoride.

## II.5.2.2. Discussion on the nature of the catalytic active species

In order to know if either AgF or any Ag<sup>+</sup> source was an active species for the catalysis, silver chloride (AgCl), silver oxide (Ag<sub>2</sub>O) and silver nitrate (AgNO<sub>3</sub>) were tested as catalysts and the results are summarised in Table 19.

Table 19. Catalytic activity of various silver sources



Entry	Ag <sup>I</sup> Source	Quantity	Yield
1	AgF	10 mol %	94 %
2	AgCl	10 mol %	<5 % <sup>a</sup>
3	AgNO <sub>3</sub>	10 mol %	76 %
4	Ag <sub>2</sub> O	14 mol %	43 %
5	Ag <sub>2</sub> O	100 mol % <sup>b</sup>	No conversion

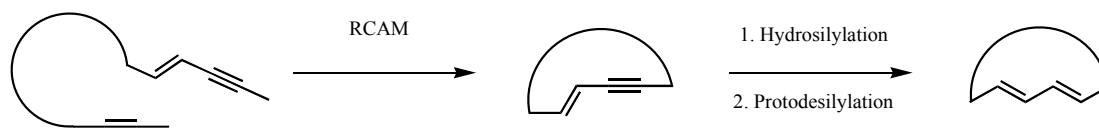
<sup>a</sup> Complete consumption of the starting material is observed

<sup>b</sup> No TBAF was used in this experiment

It was found that the presence of fluoride is crucial for the catalytic process (Entry 5), AgF is the most efficient silver source for protodesilylation (Entry 1), but silver oxide (Entry 4) and silver nitrate (Entry 3) also turned out to catalyse the reaction. Silver chloride, however, is unsuitable (Entry 2). Silver fluoride and silver nitrate are by far the most soluble of the four salts in water (solubility in cold water in gram per 100 cm<sup>3</sup>: AgCl: 8.9×10<sup>-5</sup>; Ag<sub>2</sub>O: 1.3×10<sup>-3</sup>; AgNO<sub>3</sub>: 122; AgF: 185)<sup>[139]</sup> suggesting that protodesilylation may only occur in the presence of a homogeneous catalyst.

## II.6. Conclusion

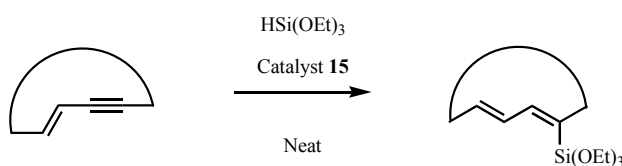
In summary, we have shown that the procedure for the formation of stereodefined (*E*)-cycloalkenes from acyclic diynes can be applied to 1,3-enyne systems (Scheme 18).



Scheme 18. Formation of (*E,E*)-cyclodienes by RCAM and semi-reduction

No particular chemical restriction has been observed for metathesis reactions involving conjugated alkynes and various homo-dimers. Also, macrocycles have been successfully synthesised in good yields by this route. Ring closing enyne-yne metathesis, however, is restricted to large rings probably due to unfavourable ring strain of smaller systems.

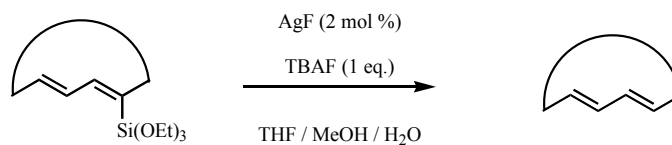
Conversion of linear and cyclic 1,3-enyne systems into the corresponding dienes proved to be more problematic. Variable amounts of by-products were produced under the standard conditions for ruthenium-catalysed hydrosilylation. Further experimentations proved that the solvent had significant effects on the reaction, and hydrosilylation of conjugated alkynes was best performed neat or in highly concentrated dichloromethane solution (Equation 8). Under these conditions, 1,3-enynes underwent hydrosilylation in high yields with low catalyst loading and without (or very little) formation of by-products. During the course of these studies several conjugated enynes were hydrosilylated in a *trans*-selective manner affording 1,3-diene silanes in high yields.



Equation 8. Hydrosilylation of 1,3-enynes under neat conditions

Stoichiometric amounts of silver fluoride in aqueous THF/MeOH proved effective for the desilylation of the diensilanes thus formed. The main drawbacks of this protodesilylation method is the cost of stoichiometric amounts of silver. Therefore a catalytic alternative was developed. Diverse (*E*)-configured alkenes and (*E,E*)-configured dienes were successfully prepared with a catalytic amount of AgF and in the presence of stoichiometric TBAF (Equation 9). In all the cases, the yield and the purity obtained were as high as under stoichiometric conditions and the reaction showed high

effectiveness even when loadings of AgF as low as 2 mol % were used. Various silver sources were screened for this protodesilylation and the most suitable salts turned out to be those with high solubility in water (silver fluoride and silver nitrate) suggesting that the overall process occurs in homogeneous phase.



Equation 9. Catalytic protodesilylation of vinylsilanes

## III. Studies Towards The Total Synthesis of Myxovirescin A<sub>1</sub>

### III.1. Introduction

The gliding bacteria *Myxococcus virescens* strain Mx v48 produce the myxovirescins A-T, macrocyclic lactam-lactones of different ring size and functional group patterns.<sup>[140]</sup> Myxovirescin A<sub>1</sub> (Figure 56) was first isolated in 1982<sup>[141]</sup> and its structure was elucidated in 1985.<sup>[142]</sup> It shows good *in vitro* activities against a range of bacteria<sup>[141, 143]</sup> and represents a new class of antibiotic with a unique mode of action.<sup>[144]</sup> It inhibits incorporation of diaminopimelic acid and uridine *N*-acetylglucosaminidiphosphate into bacterial cell walls. These latter two compounds are important components of peptidoglycane, a polymeric scaffold in bacteria cell walls. This scaffold is crucial for the structural integrity of the cell and can be seen as a protective device against external attack. If construction of the above-mentioned polymer is inhibited, the cell will not be able to grow, its overall stability will be endangered and an important part of its defence will be knocked out.

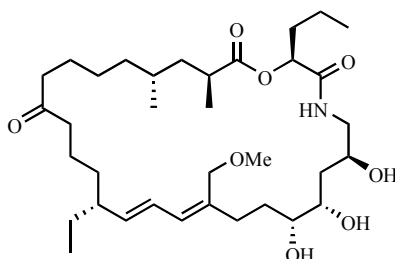
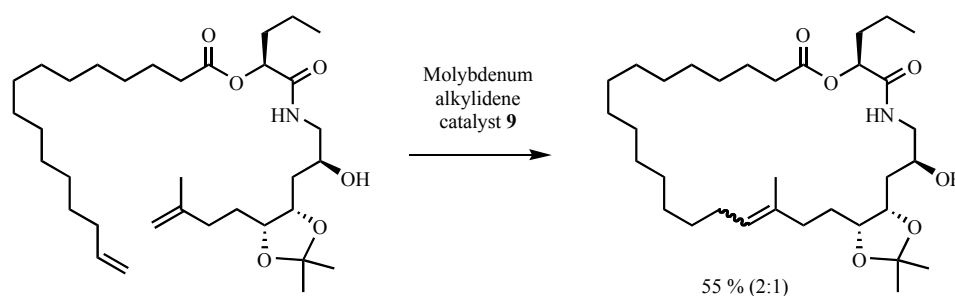


Figure 56. Myxovirescin A<sub>1</sub>

Further tests of Myxovirescin A<sub>1</sub> would require large amounts of Myxovirescin that cannot be provided by fermentation means.<sup>[145]</sup> Moreover, its complex structure, the presence of several stereocentres of various nature as well as its large ring size make Myxovirescin A<sub>1</sub> an interesting candidate for total synthesis.

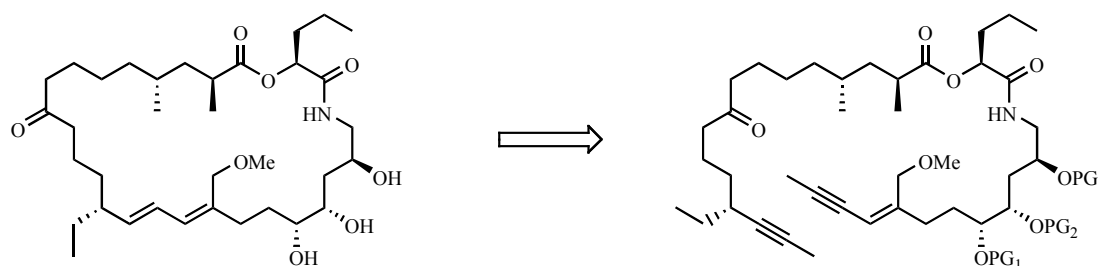
To date, two total syntheses have been published by Williams<sup>[146]</sup> and Seebach.<sup>[140, 147, 148]</sup> However, in both cases, more than 40 steps were required. Very recently, Dutton and co-workers published the synthesis of simplified analogues that turned out to be at least equipotent to Myxovirescin A<sub>1</sub> in terms of bioactivity.<sup>[145]</sup> The synthesis of the most potent analogue was carried out in less than 20 steps and was based on ring closing alkene metathesis. Unfortunately, the metathetic ring closure involving a trisubstituted alkene was problematic and afforded the macrocyclic olefin as a 2:1 mixture of (*E*:*Z*) isomers (Equation 10) with a very high catalyst loading (50 mol %).





Equation 10. RCM step in the preparation of an analogue of Myxovirescin A<sub>1</sub><sup>[145]</sup>

Since ring closing alkene metathesis seems not to be an effective procedure for a stereoselective formation of Myxovirescin analogues, the diene subunit appears to be an interesting target that might allow the application of the methodology described in the preceding chapters (Scheme 19).



Scheme 19. Retrosynthetic analysis for the diene unit of Myxovirescin A<sub>1</sub>

However, although the chain size is appropriate for ring closure (greater than 17 members), the alkene of the enyne moiety in this case is trisubstituted and is not (*E*)-configured as in all the cases reported so far in this work. Successful formation of this diene unit in spite of the steric bulk and the electronic nature of the CH<sub>2</sub>-OMe group is a challenging goal and would represent an interesting test of our synthetic approach for the stereoselective preparation of 1,3-cycloalkadienes.

In conclusion, no total synthesis Myxoverescine A<sub>1</sub> has been proposed that is practical. Furthermore, the Myxovirescin family, which features a large number of structurally related molecules, possesses a unique antibiotic mode of action. Finally its diene substructure might qualify for an application of our stereoselective formation of conjugated double bonds. Consequently, it was decided to work on new synthetic pathways towards the synthesis of this natural product.

### III.2. Elaboration and Retrosynthetic Analysis of a Model

As alkyne metathesis catalyst **1** is known to be inactive in the presence of donor substrates such as amines, thioether or polyether chains,<sup>[27, 30]</sup> the potential influence of a methoxy group in the direct proximity of the alkyne moiety (Figure 57) had to be evaluated before starting the total synthesis program.

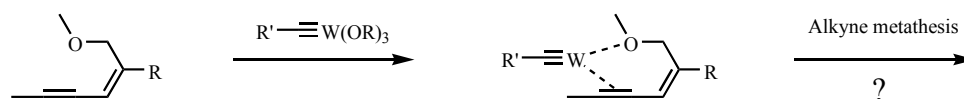


Figure 57. Possible influence of the methoxy group in the direct environment of the alkyne moiety

Since electronic and steric effects of the methoxy substituent may interfere with the RCAM step, initial studies focussed on a model substrate. Compound **147** was designed for this purpose (Figure 58).

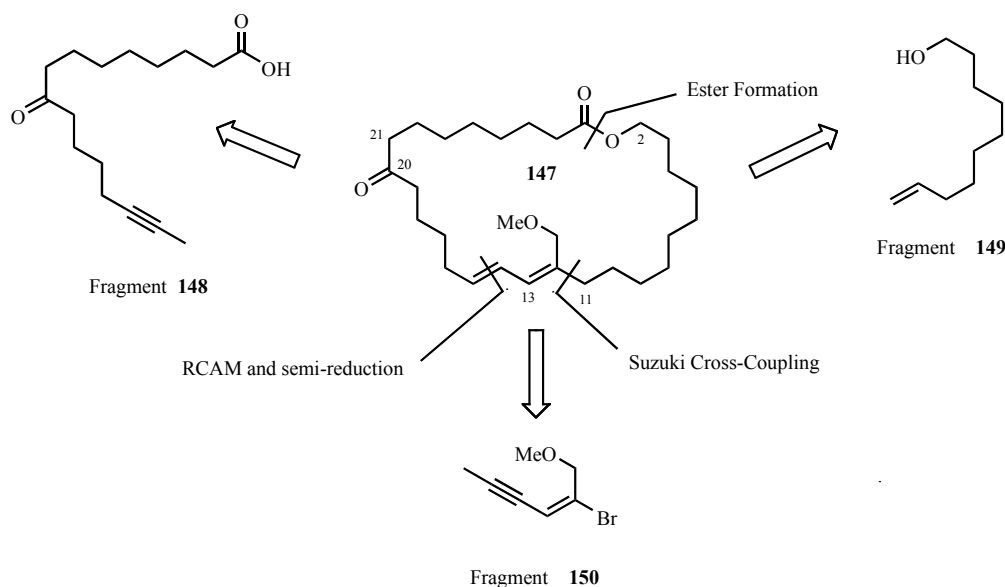


Figure 58. Model of Myxovirescin A<sub>1</sub> and retrosynthetic disconnections

The model and its retrosynthetic analysis match several disconnections envisaged for a later total synthesis of Myxovirescin A<sub>1</sub>. The ring size, the diene subunit, the ketone and the ester functions were preserved in this simplified structure, while all stereocentres were removed to ensure a rapid assembly. It was expected that every functional group present in Myxovirescin A<sub>1</sub> would be compatible with the key steps of our synthetic approach.

This simplified target molecule **147** can be disconnected into the fragments **148**, **149** and **150**. The macrolactone would be closed via RCAM, followed by semi-reduction with the two-step sequence involving hydrosilylation-protodesilylation. Fragment **150** and fragment **149** should be assembled via a Suzuki cross-coupling reaction while the carboxylic acid of fragment **148** should be connected to the alcohol function of **149** by esterification. Formation of the C<sub>20</sub>-C<sub>21</sub> bond should be obtained via the nucleophilic attack of a Grignard reagent on an aldehyde followed by oxidation.

The trisubstituted alkene **150** is the only part of the model that would appear unchanged in the projected total synthesis. The disconnection between carbons C<sub>11</sub> and C<sub>12</sub> is not the most convenient on a retrosynthetic point of view, but it would enable easy access to other members of the Myxovirescin family, since many analogues have different substituents at C<sub>12</sub> (Figure 59).

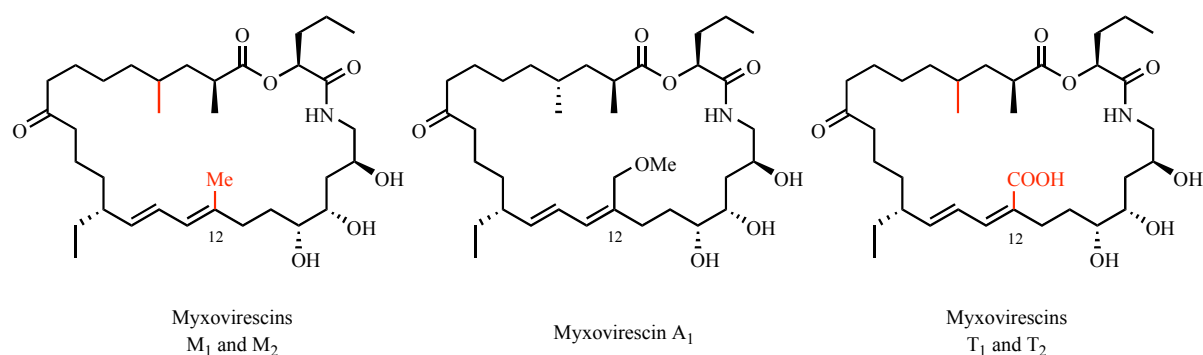
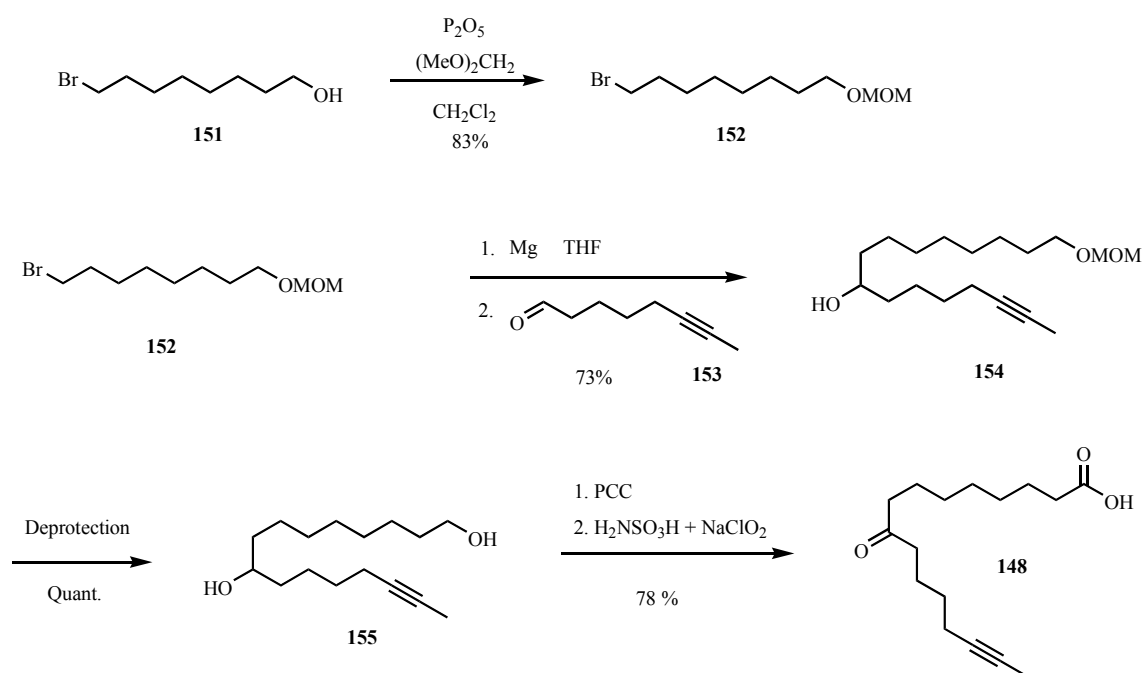


Figure 59. Structurally related members of the Myxovirescin family

### III.3. Synthesis of the Model

#### III.3.1. Synthesis of fragment **148**

Commercially available alcohol **151** was reacted with a large excess of dimethoxymethane in the presence of phosphorus pentoxide at room temperature to afford the methoxymethyl-protected alcohol **152** in good yield.<sup>[149]</sup> Aldehyde **153** was obtained from the corresponding primary alcohol by oxidation with pyridinium chlorochromate in dichloromethane (Scheme 20).<sup>[95]</sup>



Scheme 20. Synthesis of the fragment **148**

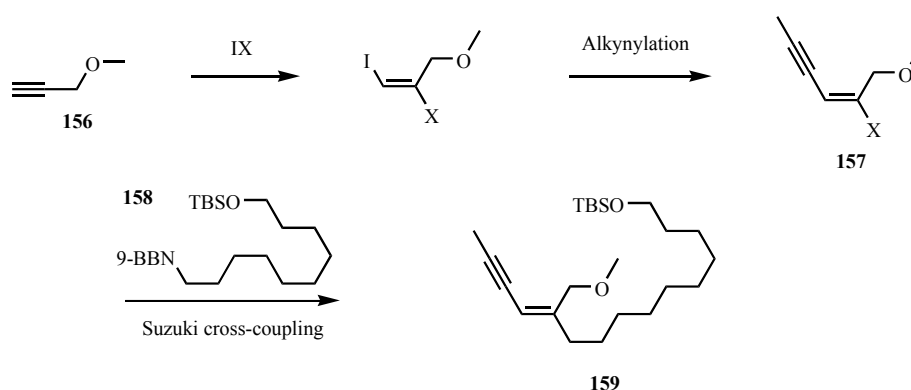
Treatment of **152** with a slight excess of magnesium in THF afforded the corresponding Grignard reagent that was treated with aldehyde **153** to afford, after hydrolysis, alkynol **154** in 73 % yield. Quantitative deprotection of the MOM group under acidic conditions (1 eq. of aqueous HCl 1M) gave diol **155**, which was oxidised in two steps to afford the corresponding carboxylic acid **148** in good yield.

The overall yield for the formation of fragment **148** is 47 % over five steps.

### III.3.2. Synthesis of fragments **149** and **150**, first approach

#### III.3.2.1. Introduction

The first synthetic pathway envisaged for the preparation of enyne **159** is depicted in Scheme 21. The formation of fragment **157** was planned in two steps from commercially available **156**, via *trans*-iodohalogenation followed by alkynylation. The latter transformation should be achieved either via the Sonogashira palladium-copper procedure or via the boron-mediated Fürstner-Soderquist variant of the Suzuki coupling (see chapter II). Vinyl halide **157** would then be cross-coupled with borane **158** to deliver building block **159**.



Scheme 21. First synthetic pathway

Iodohalogenation of triple bonds generally occurs in a *trans*-selective manner.<sup>[150, 151]</sup> Nucleophilic attack of a carbon-carbon multiple bond on a I<sup>+</sup> species has been proposed to lead to the formation of a bridged iodonium intermediate **161** (Figure 60).<sup>[150, 152-154]</sup> This highly electrophilic intermediate will then react with chloride, in an *anti*-manner, to form a *trans*-1,2-dihalogeno olefin. However, the regioselectivity of this nucleophilic attack can be difficult to predict possibly leading to an isomeric mixture of **162** and **163**.

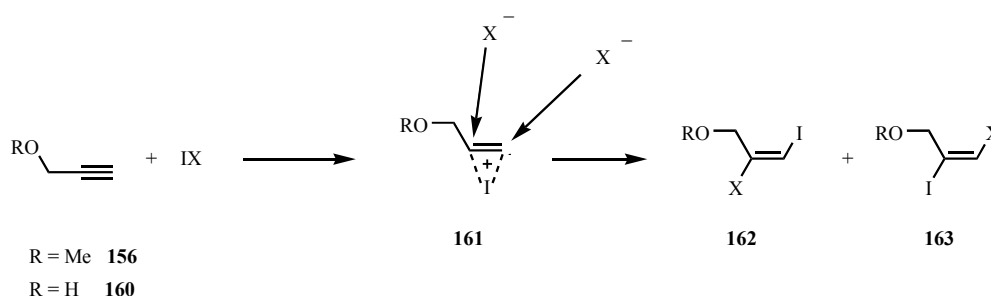
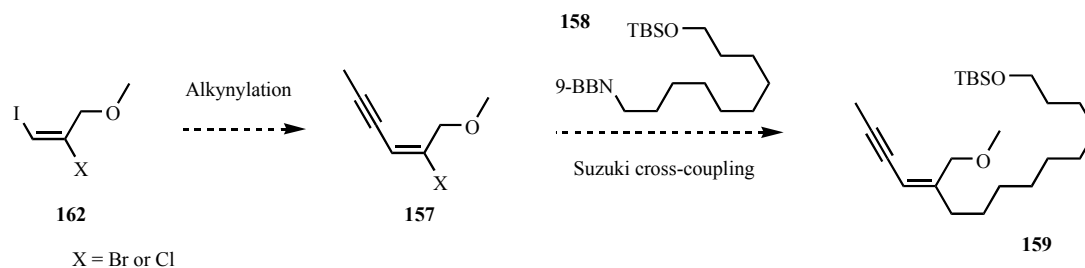


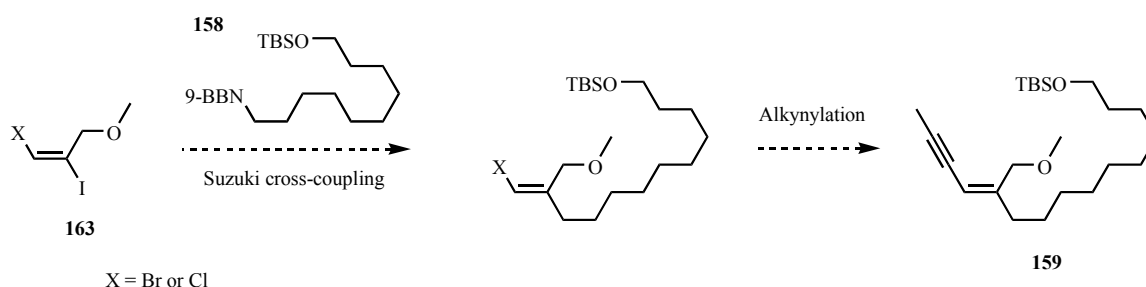
Figure 60. Iodohalogenation, reported mechanism

The synthesis of building block **157** is based on the different reactivity of iodo- and bromo-olefins in palladium-catalysed cross-coupling reactions. Vinyl iodides are usually more reactive than the corresponding bromo-derivatives and a chemoselective propynylation of **162** should afford the desired compound **157** (Equation 11).<sup>[155, 156]</sup>



Equation 11. Envisaged formation of fragment **159** via alkylation of a trisubstituted vinyl iodide

Should the regioisomeric dihalogeno alkene **163** be predominantly obtained, the palladium-catalysed steps would simply be reversed to obtain the desired fragment (Scheme 22).



Scheme 22. Preparation of **159** through a different strategy

### III.3.2.2. Studies on the heterodihalogenation of an acetylene moiety

The iodo-chlorination of the triple bond turned out to be more problematic than expected. Many attempts were carried out in different organic solvents at various temperatures with both propargylic alcohol **160** and its methyl ether derivative **156** in the presence of iodomonochloride. Unfortunately none of these conditions resulted in a clean reaction (see Figure 61 for details). Whilst the two expected regioisomers were obtained, the reaction also afforded various amounts of by-product **164**.

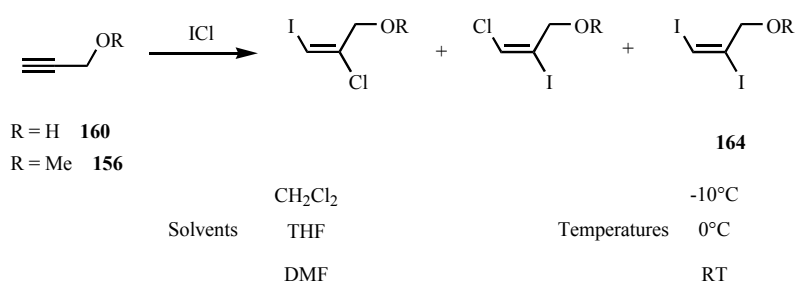


Figure 61. Dihalogenation in organic solvents

Since by-product **164** derives from competitive nucleophilic attack of iodide on the bridged ionic complex **161**, it was decided to increase drastically the amount of chloride in solution and to apply a procedure described by Negishi for the dihalogenation of acetylene in aqueous HCl.<sup>[156, 157]</sup>

Treatment of methyl-propargyl ether **156** in HCl (1N) with ICl afforded a 1:1 mixture of isomers of the desired dihalogenated olefin in 78 % yield with no trace of side reactions (Figure 62). A similar result was obtained for the corresponding iodobromination.<sup>[156]</sup>

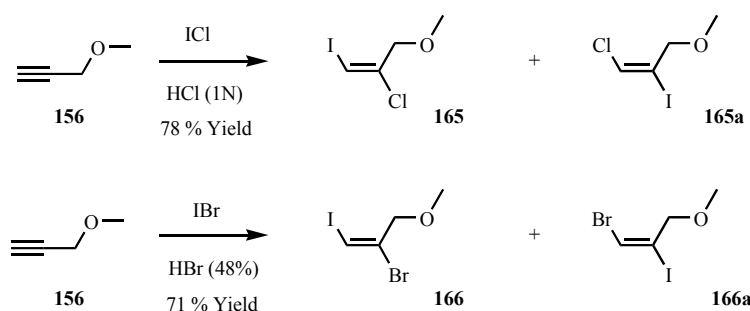
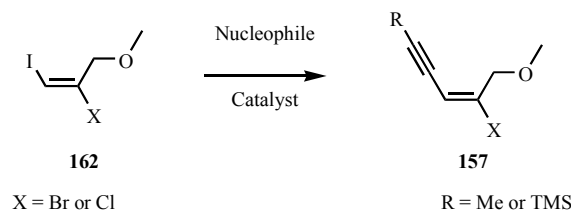


Figure 62. Dihalogenation in aqueous HX solutions

According to the very high *trans*-stereoselectivity in Negishi's acetylene dihalogenation<sup>[156, 157]</sup> and the ability of  $\text{I}^+$  to form iodonium intermediates,<sup>[150, 152-154]</sup> it was presumed that the product was a mixture of the two possible (*E*)-configured regioisomers. Disappointingly, separation of the two compounds was impossible by classical chromatographic methods. Hoping for a possible separation at a later step, the mixture was submitted to the propynylation reaction.

### III.3.2.3. Studies on the propynylation of dihalogenated olefinic substrates

Alkynylation of substrates of type **162** (Equation 12) under the Sonogashira conditions<sup>[98]</sup> or in the presence of alkynyl zinc derivatives<sup>[98, 155, 156, 158, 159]</sup> under various conditions was unsuccessful.



Equation 12. Alkynylation of 1,2-dihaloolefins

This result was quite surprising since many examples of the chemoselective alkynylation of vinyl iodides in the presence of vinyl chlorides<sup>[157]</sup> or vinyl bromides<sup>[155, 156]</sup> were reported for similar substrates. However, we were able to synthesise compounds **168** and **170** from **167** and **169** respectively in the presence of **77** and Pd(PPh<sub>3</sub>)<sub>4</sub> in decent to good yields (Figure 63).

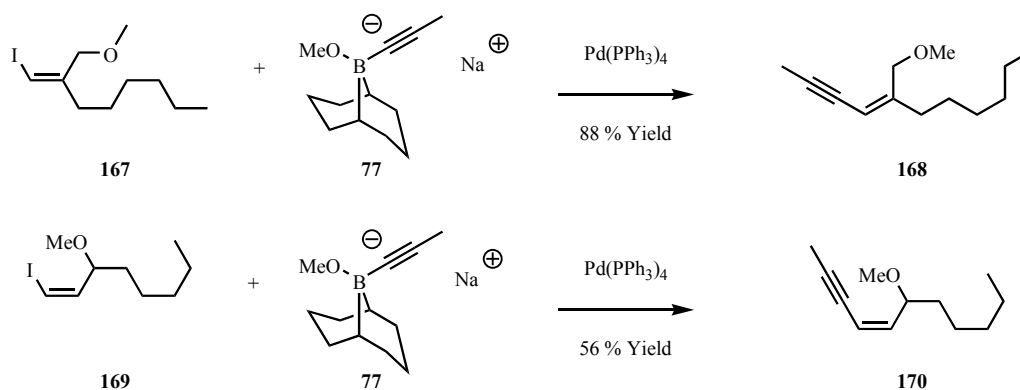
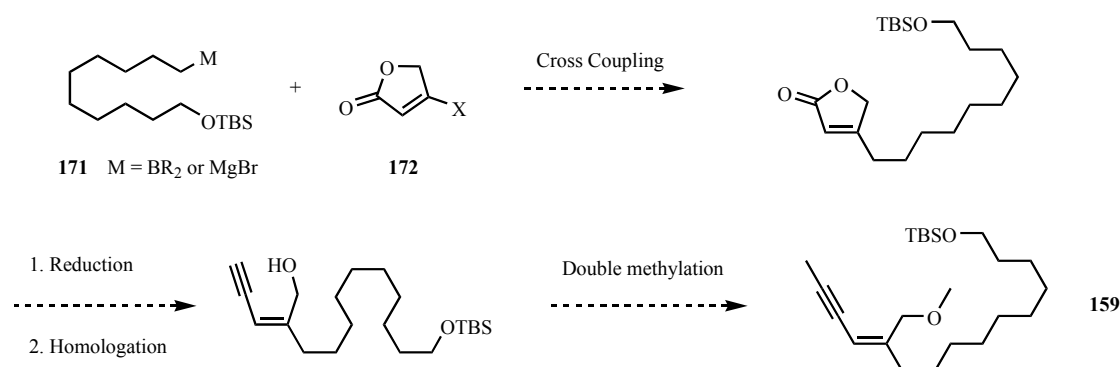


Figure 63. Synthesis of **168** and **170** via propynylation of vinyl iodides **167** and **169**

Because the alkynylation of *trans*-1,2-dihaloolefins was unsuccessful, the first strategy was abandoned.



### III.3.3. Synthesis of fragments **159**, second approach



Scheme 23. Second approach for the synthesis of fragment **159**

The revised strategy represented in Scheme 23 is less convergent than the previous one because the cross-coupling step occurs earlier in the synthesis. Nevertheless, the overall number of steps remains low, the envisaged hemi-acetal homologation is well precedented<sup>[160]</sup> and the methylation of the alcohol and the alkyne could be performed in a single operation.

Two methods for cross-coupling between compounds **171** and **172** were investigated: a boron-mediated palladium-catalysed Suzuki procedure and an iron-catalysed carbon-carbon formation. The required substrates were readily prepared. Triflate **173** and bromo lactone **174** can both be synthesised in one step according to described procedures (Figure 64),<sup>[161, 162]</sup> and the two cross-coupling nucleophilic reagents **171** are obtained by either classical hydroboration of the corresponding alkene or Grignard formation from the corresponding alkyl bromide.

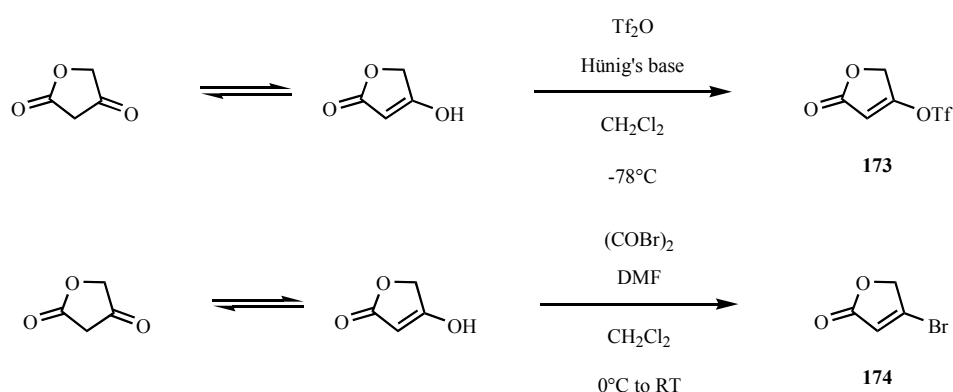
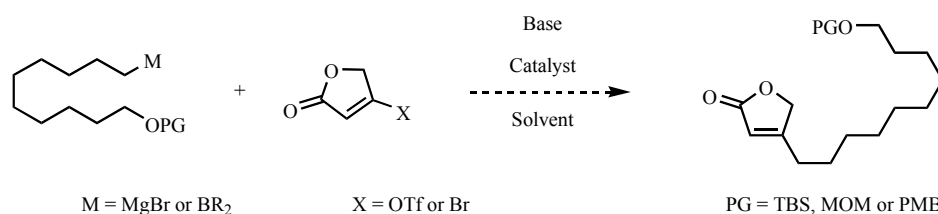


Figure 64. Formation of the compounds **173** and **174**<sup>[161, 162]</sup>

The following cross-coupling reaction (Equation 13) was carried out under many different conditions but the formation of the desired product was not observed. It is suspected that under palladium-catalysed conditions, large quantities of the  $\beta$ -hydride elimination product are formed. Although this elimination product was not isolated, a peak consistent with its formation was observed by GC/MS.

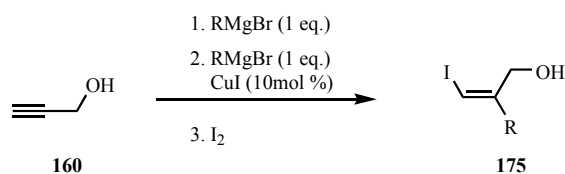


Equation 13. Connection of two fragments by cross-coupling reactions

As electrophiles **173** and **174** did not undergo the projected cross-coupling reaction under various conditions, this route was not pursued any further. Attention was then turned to the synthesis of fragment **150**, in the hope that this electrophile would be more suitable for Suzuki cross-coupling reactions.

### III.3.4. Synthesis of fragments **149** and **150**, copper-catalysed approach

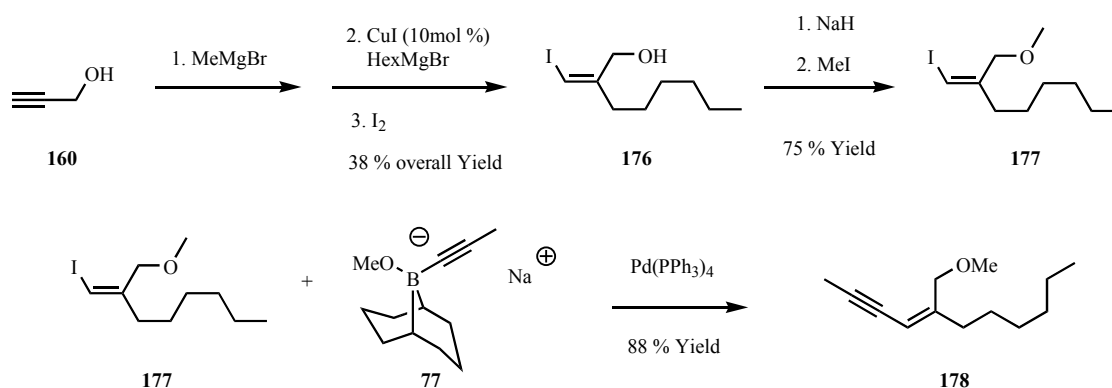
During the course of our investigations, a one-step procedure for the synthesis of compounds of type **175** involving a copper-catalysed nucleophilic attack<sup>[163-165]</sup> on propargylic alcohol was published (Equation 14).<sup>[166]</sup> The yields reported in these publications vary largely according to the nature of the nucleophile, but since the method appeared to show good stereoselectivity due to a magnesium assisted mechanism,<sup>[163]</sup> it was considered to adopt this procedure to the preparation of our target molecule.



Equation 14. Stereoselective formation of trisubstituted iodoolefinic derivatives

As illustrated below, preparation of **176** was carried out according to the reported procedure. A sacrificial base (methylmagnesium bromide) was used to deprotonate the free alcohol, after which

the copper-catalysed nucleophilic attack of the hexylmagnesium bromide could take place. Indeed, whilst the functionalised Grignard reagent could have been used in excess to act both as a base and the nucleophile, such a protocol would not be attractive in the context of a total synthesis (Scheme 24).



Scheme 24. Synthesis of **178** via copper-catalysed carbon-carbon formation and alkyne metathesis

Product **176** was isolated from the undesired isomers in 38 % yield. Alcohol **176** was then methylated and the resulting vinyl iodide **177** was submitted to alkynylation to afford enyne **178** in good yield. Thorough analysis of the NMR data (<sup>1</sup>H, <sup>13</sup>C, NOESY and nOe) enabled us to establish the (*Z*)-configuration of compound **178**. Figure 65 represents the important nOe interactions observed; the dashed arrows represent weaker interactions.

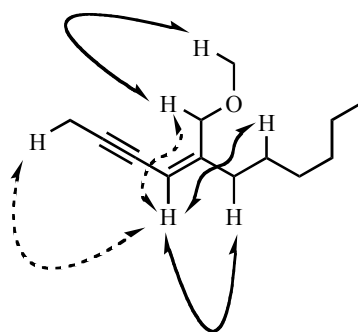
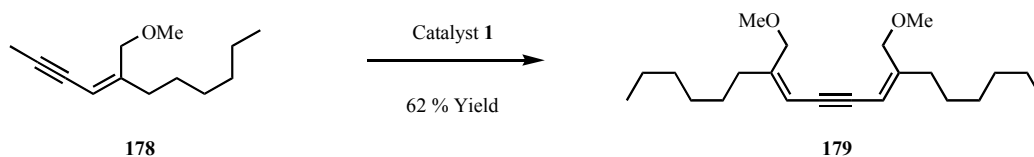


Figure 65. Results from NOESY and nOe for enyne **178**

Unfortunately, the application of this method to the envisaged total synthesis is seriously limited by the low yield of the carbocupration/iodination, so that further investigations were not undertaken.

However, the crowded (*Z*)-configured enyne **178** was used to prepare compound **179** in decent yield using catalyst **1** (Equation 15).



Equation 15. Synthesis of compound **179** via enyne-enyne metathesis

This is the first example for alkyne cross-metathesis with a crowded (*Z*)-configured enyne bearing a donor site (methoxy group) in proximity of the acetylene (Figure 66).

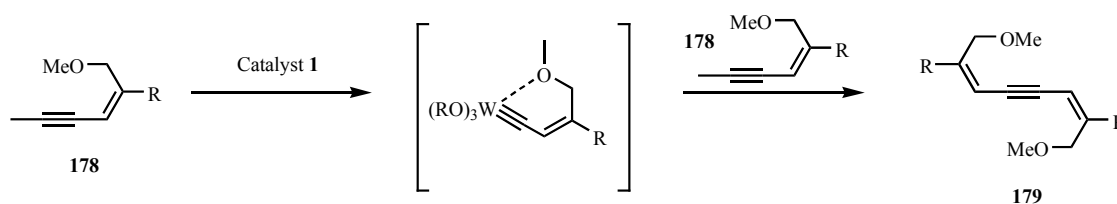
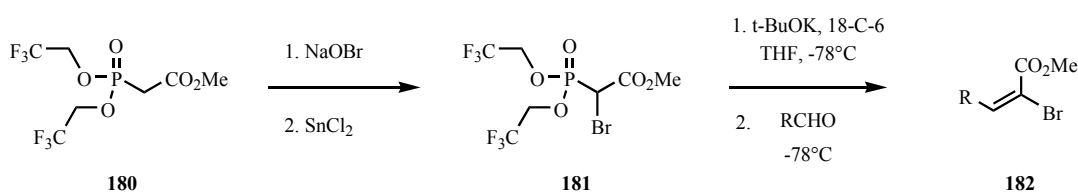


Figure 66. First example of enyne-enyne metathesis in the presence of a donor site in proximity of the acetylene

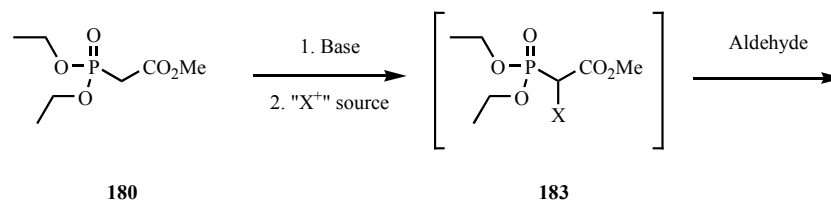
### III.3.4.2. Synthesis of fragment **150** by a Horner-Wadsworth-Emmons (HWE) reaction

The final approach was inspired by a recent article of Kogen and co-workers who stereoselectively synthesised (*E*)-configured  $\alpha$ -bromoacrylates **182** from aldehydes and the bromo-phosphonoacetate **181** (Scheme 25).<sup>[167]</sup>



Scheme 25. Reported synthesis of (*E*)-configured  $\alpha$ -bromoacrylates **182**<sup>[167]</sup>

The two-step synthesis of reagent **181** (via formation of the dibromo-phosphonate followed by a reduction with SnCl<sub>2</sub>) is only applicable on large scale. We were therefore willing to simplify this sequence and tried to form the bromo-phosphonoacetate **181** *in situ*, starting from commercially available phosphonoacetate **180**. Another recent publication describes a procedure for an *in situ* generation of similar halogeno-phosphonates **183** under basic conditions (Scheme 26).<sup>[168]</sup>

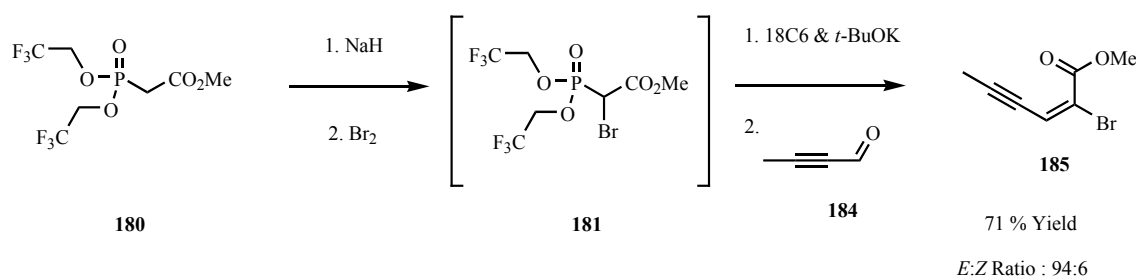


Scheme 26. *In situ* generation of  $\alpha$ -halogenophosphonates **183**<sup>[168]</sup>

It was planned to combine both procedures to gain easy access to an alkynyl substituted (*E*)- $\alpha$ -bromoacrylate.

The presence of the electron withdrawing trifluoroethyl groups on the phosphonate is essential for the stereoselectivity of the reaction.<sup>[167, 169]</sup> However these functional groups might enhance the acidity of the protons at the adjacent carbon atom and therefore favour an undesired deprotonation in the presence of a strong base. It is also reported that the nature of the base in the HWE reaction is crucial for obtaining high yields and selectivity.<sup>[167]</sup> It was therefore suspected that an accurate optimisation of the temperature as well as of the amount of bases and electrophiles would be required.

To our delight, we found conditions that gave product **185** in 71 % yield and an *E*:*Z* ratio of 94:6. The isomers were easily separated by chromatography and the desired isomer was obtained stereochemically pure in 67 % yield (Scheme 27). The stereochemistry of **185** could not be determined at this stage and was deduced from structural analyses of subsequent compounds. The deprotonation steps as well as the HWE reaction were carried out at -78°C in dry THF. Higher temperatures are necessary for the formation of the bromoderivative **181** in the presence of bromine (room temperature). *In situ* preparation of intermediate **181** was best performed in the presence of 1.05 eq. of sodium hydride and 1.15 eq. of Br<sub>2</sub>. The HWE reaction occurred in high yield and selectivity when 1.4 eq. of 18-Crown-6 and 1.1 eq. of potassium *tert*-butoxide were used.

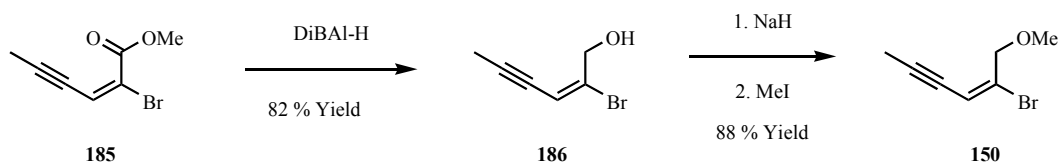


Scheme 27. Formation of (*E*)-configured bromoacrylate **185**

The only drawback of the procedure is the preparation of aldehyde **184**. Oxidation of the corresponding alcohol occurs quantitatively under several conditions but the volatility of the product

makes its isolation highly difficult. It was impossible to isolate it from either low or high-boiling organic solvents. Therefore, it was used as a dilute solution in dichloromethane ( $\approx 0.15$  M).

The rest of the synthesis of fragment **150** (Scheme 28) was carried out with no particular difficulties (Scheme 28). Reduction of the ester moiety required more than 5 eq. of DiBAL-H to go to completion, but gave alcohol **186** in 82 % yield. Methylation of **186** afforded fragment **150** in 88 % yield.



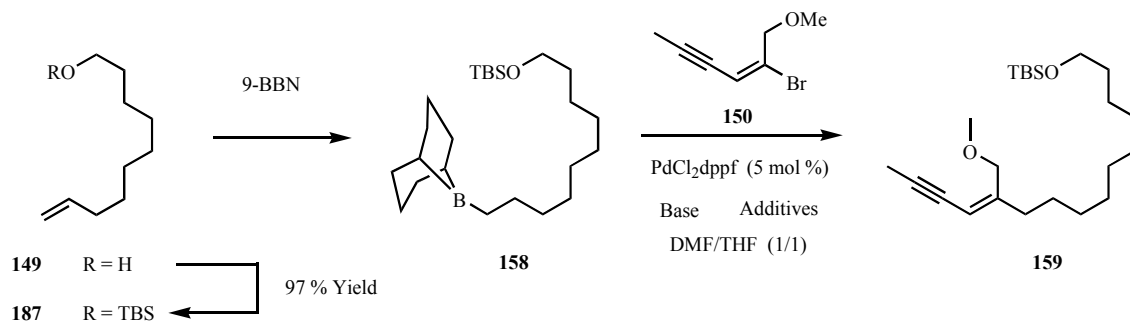
Scheme 28. Final steps for the synthesis of **150**

The building block **150** was synthesised via a three-step sequence in stereochemically pure form in 48 % overall yield. Stereochemical assignments were based on 1D and 2D NMRs as well as NOESY and nOe analyses carried out on an *E:Z* mixture of **186**. The observed nOe interactions, which enabled us to ascribe the (*E*)-configuration to the major isomer, are represented in Figure 67.



Figure 67. Determinant nOe effects for (*E*)-**186** and (*Z*)-**186**

Finally, various experiments were carried out to cross-couple compounds **150** and **158**. The results are summarised in Table 20. Initial TBS protection of alcohol **149** occurred in quantitative yield, after which hydroboration of the resulting alkene **187** was carried out overnight in THF with a slight excess of 9-BBN. This excess of 9-BBN was destroyed with one drop of water prior to the addition of the mixture to the DMF solution containing the vinyl bromide **150** and the catalyst mixture.

Table 20. Results for Suzuki cross-coupling reaction between **150** and **158**

Entry	Base	Additives	Yield of <b>159</b>
1	NaOH	H <sub>2</sub> O	(≈ 21 %) <sup>a</sup>
2	<i>t</i> -BuOK <sup>b</sup>	H <sub>2</sub> O	7 %
3	Cs <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O + AsPh <sub>3</sub>	90 %
4	Cs <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	70 %

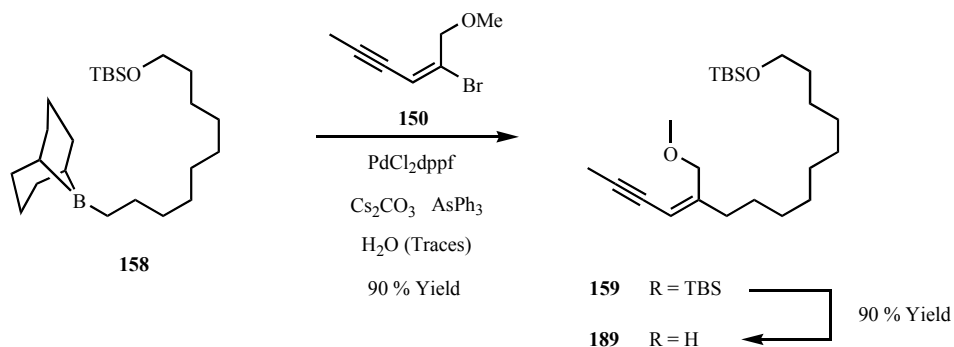
<sup>a</sup> Calculated yield. The product could not be separated from the starting material.

<sup>b</sup> The borate intermediate was formed prior to addition on the vinyl bromide.

Use of a pre-formed borate in “wet” DMF (entry 2) afforded only a low yield of the desired product, but its isolation and characterisation were possible. GC/MS analysis suggested that β-hydride elimination occurred under these conditions. Similarly, in the presence of aqueous sodium hydroxide, the reaction occurred but did not go to completion even at higher temperatures (entry 1). In both cases (entries 1 and 2), GC/MS control of the reaction showed many unidentified by-products. Luckily, the combined use of triphenylarsine (AsPh<sub>3</sub>), cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>), PdCl<sub>2</sub>(dppf) and traces of water afforded the cross-coupling product **159** in 90 % yield (entry 3). In order to determine which of the different components (AsPh<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, water) was decisive, an experiment was carried out without AsPh<sub>3</sub> (entry 4). The reaction occurred with similar speed and cleanness, but the yield was somewhat lower.

It can be concluded that the presence of cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>) as base is crucial for the success of the Suzuki cross-coupling reaction and that AsPh<sub>3</sub> is beneficial. Under these optimised

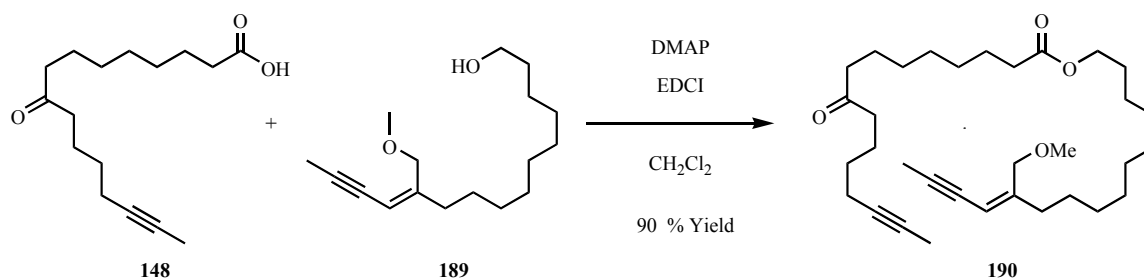
conditions (AsPh<sub>3</sub>, PdCl<sub>2</sub>(dppf) and Cs<sub>2</sub>CO<sub>3</sub>), the conversion was complete after half an hour. Finally, deprotection of the TBS group with TBAF afforded the desired fragment **189** in good yield.



Scheme 29. Last steps of the synthesis of fragment **189**

### III.3.5. Final Steps

Esterification of **148** with **189** occurred smoothly affording the acyclic enediyne compound **190** in good yield (Equation 16).



Equation 16. Formation of the acyclic enediyne **190**

The ring closing alkyne-enyne metathesis step was more problematic. Schrock's tungsten alkylidyne catalyst **1** showed poor reactivity under the previously optimised conditions. Utilisation of 10 mol % of the catalyst afforded low conversion and a mixture of products after 15 h at 80°C. The best result was 40 % yield, using 0.5 equivalent of catalyst **1**. Under these conditions, one by-product was isolated, which was shown to be compound **192** (Figure 68).





Since alkyldiyne complex **1** showed the ability to form a ring as large as 26 (see chapter I), to catalyse metathesis with conjugated alkynes (chapter II), and to be active in the presence of a methoxy group in its proximity (chapter III), it is unclear why it failed to close the macrocycle **191** more efficiently.

Comparative cross-metathesis experiments showed that conjugated alkynes are less reactive than non-conjugated ones. This result is re-confirmed by the isolation of by-product **192** showing that the non-conjugated triple bond is more prone to react with catalyst **1** than the conjugated triple bond. This difference of reactivity between both alkynes in **180** is probably enhanced by the steric hindrance engendered by the methoxy group near the enyne.

Considering that enyne-yne metathesis macrocyclisation is a difficult transformation, that the reaction is carried out under high dilution conditions, and that the enyne moiety of **190** is intrinsically poorly reactive and sterically crowded, it is reasonable to consider that the process of ring closure would be slow. Since the tungsten alkyldiyne **1** is sensitive to the presence donor sites, it can be imagined that the methoxy group in the vicinity of the acetylene may gradually degrade or deactivate this catalyst (Figure 69). This would explain why catalyst **1** failed to promote RCAM efficiently. Furthermore, since molybdenum complex **5** is known to be less sensitive to donor substituents, the presence of the methoxy group on the substrate obviously does not diminish its activity, allowing the reaction to go to completion.

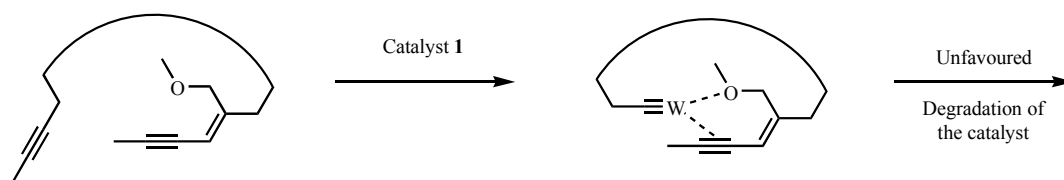
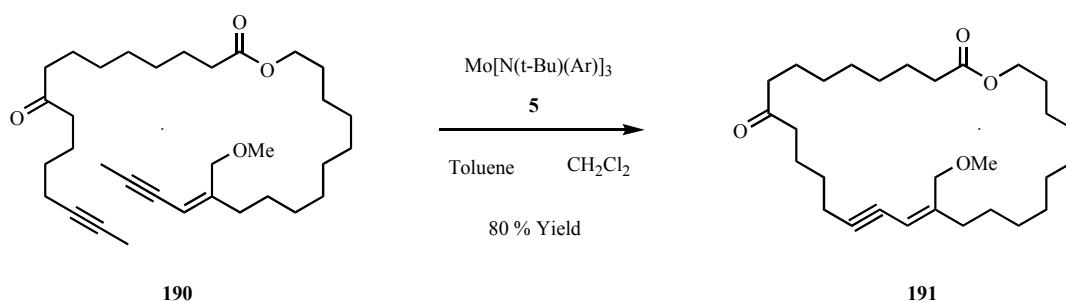


Figure 69. Plausible explanation for the low efficiency of catalyst **1** to promote RCAM

### III.4. Conclusion

The synthesis of an analogue of Myxovirescin A<sub>1</sub> was successfully completed. For this purpose, a ring closing alkyne metathesis involving a sterically crowded (1*Z*)-1,3-enyne system was conducted in excellent yield (Equation 17) using molybdenum complex **5** as the catalyst.



Equation 17. RCAM of a functionalised substrate

Furthermore, stereoselective semi-reduction of the first (1*Z*)-1,3-enyne system via hydrosilylation-protodesilylation occurred in decent yield affording a macrocyclic (1*Z*,2*E*)-diene. The methodology for the formation of conjugated and non-conjugated stereodefined alkenes developed along this work was thereby proven to be effective on a functionalised substrate. This result demonstrates the great potential of our methodology and promises further applications in other synthetic settings. In this context, Myxovirescin A<sub>1</sub> represents indeed an excellent target for further studies.

During the course of our work, particular attention was given to the synthesis of the building block **150** (Figure 70).

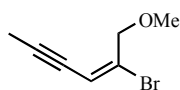
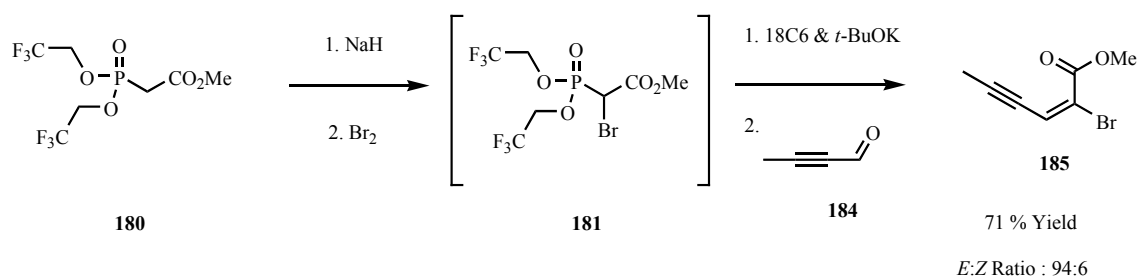


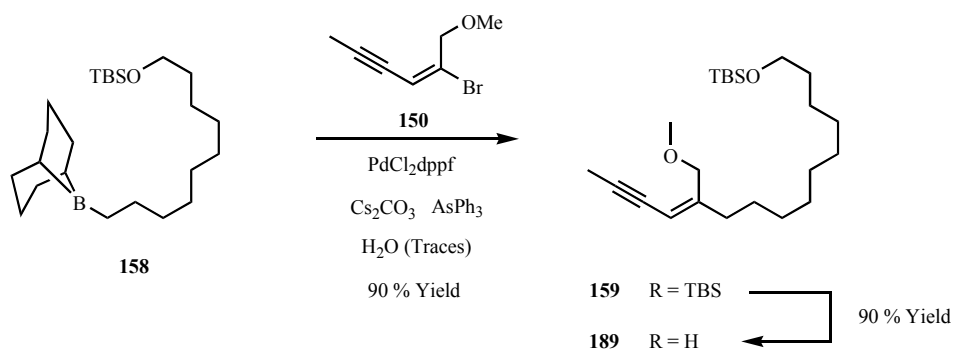
Figure 70. Fragment **150**

Several pathways for the preparation of fragment **150** were investigated. Although the most economic and convergent synthesis failed to produce this building block, we managed to prepare the enyne precursor **185** in high yield and stereoselectivity via the *in situ* formation of  $\alpha$ -bromophosphonate **181** (Scheme 31).



Scheme 31. Stereoselective synthesis of enyne **185**

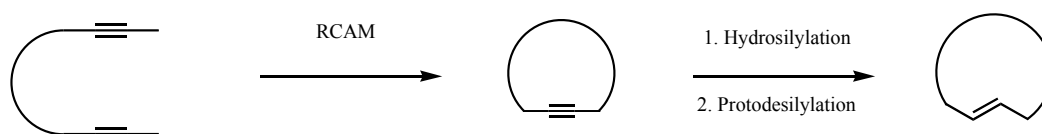
Whereas most of the connections between the building blocks were readily implemented in high yields, the Suzuki cross-coupling reaction used for the formation of building block **159** turned out to be problematic. Fortunately, scrupulous screening of various reaction parameters led to optimised conditions that allowed the desired carbon-carbon bond to be formed in excellent yield (Equation 18).



Equation 18. Suzuki cross-coupling between fragments **158** and **150**

# CONCLUSION

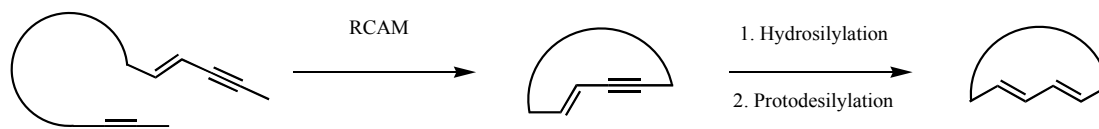
Olefin metathesis is a highly effective method for the formation of cyclic alkenes. However, in the case of macrocycles, it often suffers from low stereoselectivity. Consequently, synthetic tools need to be developed for the stereoselective formation of large cycloalkenes. Alkyne metathesis arose as a powerful method to overcome this selectivity issue. Indeed, Ring Closing Alkyne Metathesis (RCAM) followed by *cis*-selective Lindlar hydrogenation generate (*Z*)-cycloalkenes in good yields and excellent stereoselectivity. However, the formation of the corresponding (*E*)-cycloalkene from the cycloalkyne under practical and mild conditions remained difficult until Trost and Fürstner reported independently a two-step procedure of ruthenium-catalysed *trans*-hydrosilylation / desilylation offering an excellent entry into this series.



Scheme 32. Formation of (*E*)-cycloalkenes via RCAM and semi-reduction

Following this lead, a large series of (*E*)-cycloalkenes of different ring size and bearing various functionalities were prepared in good yield and excellent selectivity.

Stereoselective formation of large cycloalkadienes via olefin metathesis is even more challenging because problems of chemoselectivity may also arise. It was therefore interesting to extend the method to the formation of (*E,E*)-cycloalkadienes.

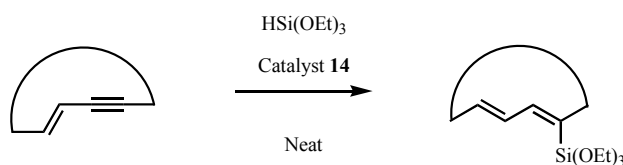


Scheme 33. Formation of (*E,E*)-cycloalkadienes via ring closing enyne-yne metathesis and semi-reduction

In this context, the formation of cyclic 1,3-enynes via the first examples of ring closing enyne-yne metathesis have been successfully implemented in high yields. The tungsten alkylidyne catalyst (*t*-BuO)<sub>3</sub>WC≡C*t*-Bu turned out to be well suited for this purpose. Due to the strain imposed by the formed enyne, however, the method is limited to rings greater than 16-membered.

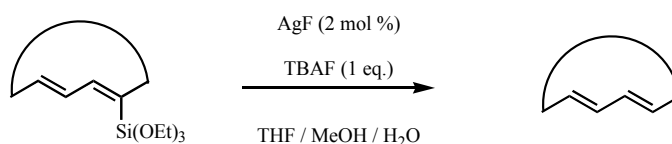
The ruthenium-catalysed hydrosilylation of alkynes could not be directly extended to conjugated enynes due to the formation of numerous by-products and the insufficient reactivity of the catalyst. A scrupulous screening of the reaction conditions showed that the nature of the solvent has a significant impact on the reaction. We found that the ruthenium-catalysed hydrosilylation of conjugated alkynes occurs in excellent yields and selectivity when carried out under neat conditions.

Thus, numerous cyclic and acyclic dienylsilanes were prepared through a highly stereoselective process.



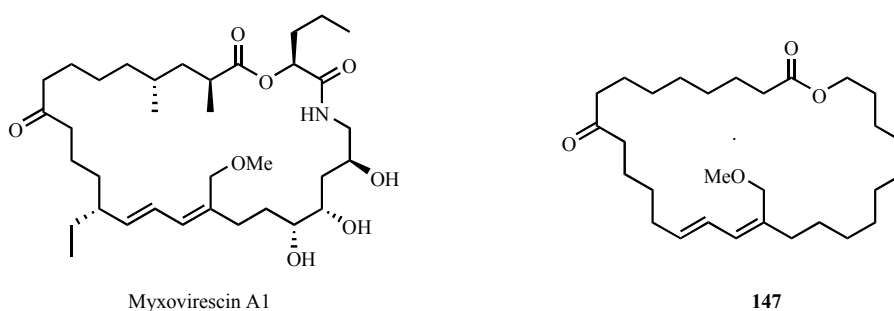
Equation 19. Hydro-silylation of conjugated enynes under solvent-free conditions

Silver fluoride turned out to be very effective for the desilylation of conjugated dienylsilanes and enabled the formation of cyclic and linear (1*E*,3*E*)-dienes in good yields and excellent selectivity. Importantly, this transformation can be performed with catalytic amounts of silver in the presence of a fluoride source (TBAF). This catalytic desilylation proceeds with the same yields and selectivity as the stoichiometric method. Furthermore, the procedure was compatible with both conjugated and non-conjugated vinylsilanes.



Equation 20. Catalytic protodesilylation of vinylsilanes

In order to demonstrate the potential of the developed methodologies, their application to a more complex synthetic setting was envisaged. To this end, the potent antibiotic Myxovirescin A<sub>1</sub> was chosen as biologically active target. Since the formation of the 1,3-diene unit in this compound represents a challenging extension of our methodology, it was decided to initially focus on the synthesis of the simplified but closely related structure **147**.



The synthesis of this model was successfully completed via ring closing enyne-yne metathesis and the stereoselective semi-reduction of the resulting conjugated enyne as the key steps. Furthermore, many issues that occurred during preparation of the fragments and their interconnections were solved, offering an excellent basis for the envisaged total synthesis of Myxovirescin A<sub>1</sub>.

# EXPERIMENTAL PART



## I. General.

### I.1. Solvents

All reactions were carried out under argon in pre-dried glassware using Schlenk techniques. The solvents were dried by distillation over the indicated drying agents and were stored and transferred under argon: acetone (pre-treatment over molecular sieves 4Å, then CaH<sub>2</sub>); CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, DMF, acetonitrile (CaH<sub>2</sub>); toluene, THF, diethyl ether, hexane, pentane (Na); MeOH, EtOH (Mg).

### I.2. Thin layer chromatography

Thin layer chromatography was performed on Polygram SIL G/UV plates (Macherey-Nagel, Darmstadt) using either hexanes/ethyl acetate or pentanes/diethyl ether in various proportions as the eluent and were visualised with UV light ( $\lambda = 254$  or  $366$  nm) and either a cerium ammoniumnitrate/NH<sub>4</sub>Mo<sub>2</sub>O<sub>7</sub> (5 %) solution or a KMnO<sub>4</sub> (1 %) solution.

### I.3. Flash chromatography

Merck silica gel (230-400 mesh) using either hexanes/ethyl acetate or pentanes/diethyl ether in various proportions as the eluent.

## II. Analytic methods

### II.1. NMR spectroscopy

NMR spectra were recorded on Bruker DPX 300, AMX 400, DMX 600 spectrometers in CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub>. Chemical shifts ( $\delta$ ) are given in ppm relative to the residual peak of CHCl<sub>3</sub> (7.26 ppm) or CHDCl<sub>2</sub> (5.30 ppm), coupling constants ( $J$ ) in Hz. The multiplicity in the <sup>13</sup>C NMR refers to the geminal protons (DEPT).

### II.2. Infrared spectroscopy

Infrared spectra were recorded on Nicolet FT-7199 spectrometer, wavenumbers ( $\nu$ ) are indicated in cm<sup>-1</sup>.

### II.3. Mass spectroscopy

MS spectra were recorded on Varian CH-5 (70eV) and Finnigan MAT 8200 and 8400 (70 eV) spectrometers. High Resolution Mass Spectra (HRMS) were recorded on a Finnigan MAT SSQ 7000 (70eV) spectrometer.

## II.4. Gas chromatography and high precision liquid chromatography

Reaction control was also done by gas chromatography coupled with a mass spectrometer (GC/MS) on Hewlett Packard HP 6890 (or HP 6890 or Agilent 6890) instruments with a HP 5973 mass detector (Column: HP-5MS, crosslinked 5 % phenylmethylsiloxane, 30 m length, 0.25 mm diameter).

Analytical measurement with liquid chromatography (HPLC) were done on a Hewlett Packard HP 1090 instrument.

## II.5. Elemental analysis

The elemental analyses were recorded by H. Kolbe, Mülheim an der Ruhr.

## II.6. Melting points

Melting points were measured in open tubes on a Büchi Melting Point B-540 apparatus.

## III. Chemicals

Pentadec-13-yn-1-ol **45**, dodec-10-yn-1-ol **36**, undec-9-yn-1-ol, non-7-yn-1-ol, cyclododecyne **33**, oct-6-yn-1-ol, hex-4-yn-1-ol, pent-3-yn-1-ol, hex-5-yn-1-ol **78**, 9-methoxy-9-borabicyclo[3.3.1]nonane **76**, 1-propynylsodium, 1-propynyllithium, were previously synthesised in the laboratories and were used as received.

Hept-5-yn-1-ol,<sup>[170]</sup> [Cp\**Ru*(MeCN)<sub>3</sub>]PF<sub>6</sub> **14**,<sup>[79]</sup> (tBuO)<sub>3</sub>W≡CCMe<sub>3</sub> **1**,<sup>[133]</sup> were prepared according to literature procedure.

Commercially available reagents (Aldrich, Fluka, Strem, Lancaster) were used as received.

## IV. General procedures

### General procedure 1: ring closing metathesis.

The tungsten catalyst **1**,  $(t\text{BuO})_3\text{W}\equiv\text{CCMe}_3$  (0.05-0.1 mmol, 5-10 mol%) was added to a solution of the diyne (1 mmol) in 1000 ml of freshly distilled toluene (0.001M) under argon. The solution was stirred at 80°C for 1-8h under a gentle argon flow. The reaction was monitored by TLC or gas chromatography and quenched with MeOH. Evaporation of the solvent and purification of the residue by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) afforded the desired cycloalkyne in analytically pure form.

### General procedures 2A and 2B: hydrosilylation.

#### Procedure 2A

The ruthenium catalyst **15**,  $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$  (0.01-0.05 mmol, 1-5 mol%) was added to a solution of the alkyne (1 mmol, 1eq) and triethoxysilane (1.2 mmol, 1.2eq) in 2 ml  $\text{CH}_2\text{Cl}_2$  at 0°C. The resulting mixture was immediately allowed to warm to room temperature and stirred for 15 min to 12h depending on the substrate. The mixture was filtered through a short pad of silica which was carefully rinsed with  $\text{Et}_2\text{O}$ . The combined filtrates were evaporated and the residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to afford the desired vinylsilane. Most of the vinylsilanes polymerise very easily and were therefore stored in solution at -18°C or used immediately in the next step.

#### Procedure 2B (for conjugated enyne systems)

The ruthenium catalyst **15**,  $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$  (0.05-0.1 mmol, 5-10 mol %) was added to a solution of the alkyne (1 mmol, 1 eq) in  $\text{HSi}(\text{OEt})_3$  (1.2-1.5 mmol, 1.2-1.5eq) at room temperature, the resulting mixture was very vigorously stirred for 2 to 5h. If the suspension of the catalyst turned out to be unstable and to form aggregates, a minimal amount of dichloromethane was added (1-1.5 eq) to dissolve the complex. The mixture was filtered through a short pad of silica which was carefully rinsed with  $\text{Et}_2\text{O}$ . The combined filtrates were evaporated and the residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to afford the desired vinylsilane. Most of the vinylsilanes polymerise very easily and were therefore stored in solution at -18°C.

### General procedure 3A: protodesilylation.

A solution of the vinylsilane (0.5 mmol, 1 eq) in 1 ml THF was added to a suspension of AgF (0.75 mmol, 1.5 eq) in THF / MeOH / H<sub>2</sub>O (1.0 ml / 0.5 ml / 25  $\mu$ l) at room temperature and the resulting mixture was stirred in the dark for 5h. The insoluble residues were filtered off and carefully washed with Et<sub>2</sub>O. The combined filtrates were evaporated and the residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to give the alkene in analytically pure form.

### General procedure 3B: catalytic protodesilylation.

A solution of the vinylsilane (0.5 mmol, 1 eq) in 0.5 ml THF was added to a suspension of AgF (0.02-0.1 mmol, 2-10 mol %) in THF / MeOH / H<sub>2</sub>O (1.0 ml / 0.5 ml / 25  $\mu$ l) at room temperature. TBAF (1M in THF, 0.5 mmol, 1 eq) was added and the resulting mixture was stirred at room temperature for 5h under argon and in the dark. The insoluble residues were filtered off and carefully washed with Et<sub>2</sub>O. The combined filtrates were evaporated and the residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to give the alkene in analytically pure form.

### General procedure 4: formation of vinyl iodides.

Cp<sub>2</sub>Zr(Cl)H] (1.05 mmol, 1.05eq) was added to a solution of the terminal alkyne (1 mmol, 1eq) in 5 ml THF. The reaction was quenched at room temperature with a solution of iodine (1.2 mmol, 1.2eq) in 5 ml THF until the red colour persisted. The resulting mixture was first washed with a half saturated solution of NH<sub>4</sub>Cl and then with an aq. solution of Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>. The different aqueous layers were extracted separately with MTBE. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. Purification by flash chromatography (using pentanes/Et<sub>2</sub>O in different proportions as the eluent) afforded the desired vinyl iodide.

## General procedure 5: propynylation using a Suzuki-like cross coupling.

9-Methoxy-9-borabicyclo[3.3.1]nonane (1.5 mmol, 1.5eq) was added to a suspension of 1-propynylsodium (Me-C≡C-Na) (1.5 mmol, 1.5eq) in 5 ml THF and the resulting mixture was stirred until a clear solution was obtained. [Pd(PPh<sub>3</sub>)<sub>4</sub>] (0.05 mmol, 5 mol%) and the vinyl iodide (1 mmol, 1eq) were added and the solution was stirred at room temperature for 2-3h. The reaction was quenched with a half saturated solution of NH<sub>4</sub>Cl, the aqueous layer was extracted with MTBE, the combined organic phases were washed with a saturated NH<sub>4</sub>Cl solution and brine, before being dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by flash chromatography (using pentanes/Et<sub>2</sub>O in different proportions as the eluent) to give the desired product.

## General procedure 6: alkynylation according to the Sonogashira method.

CuI (0.05 mmol, 5mol%), [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (0.05 mmol, 5 mol %) and the alkyne (1 mmol, 1eq) were added to a solution of the vinyl halide (1 mmol, 1eq) in 5 ml Et<sub>3</sub>N. The reaction mixture turned from yellow to dark brown and the conversion was monitored by TLC. The reaction was quenched by a saturated NH<sub>4</sub>Cl solution. The aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to give the desired product.

## General procedure 7: propynylation according to the Sonogashira method.

CuI (5mol%) and [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (0.05 mmol, 5 mol %) were added to a solution of the vinyl halide (1 mmol, 1eq) in 5 ml Et<sub>3</sub>N. The reaction vessel was then purged with propyne and the reaction was carried out under 1 atm of propyne at room temperature. The mixture turned from yellow to dark brown and the conversion was monitored by TLC. The reaction was quenched with a saturated NH<sub>4</sub>Cl solution. The aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to give the desired product.

## General procedure 8: esterification.

4-Dimethylamino pyridine (DMAP, 1.5 mmol, 1.5eq), N-ethyl-N'-(dimethylaminopropyl)-carbodiimidehydrochloride (EDC, 1.5 mmol, 1.5eq) and the carboxylic acid (1 mmol, 1eq) were added to a solution of the alcohol (1 mmol, 1eq) in 5 ml dichloromethane. The mixture was stirred overnight at room temperature and quenched with water. The organic layers were washed with HCl (1N), the aqueous phase was extracted with dichloromethane, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to give the desired ester.

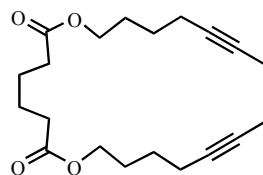
## General procedure 9: oxidation of an alkyn-1-ol into the corresponding carboxylic acid.

Pyridinium dichromate (1.5 mmol, 1.5eq) was added to a solution of the alcohol (1 mmol, 1 eq) in 10 ml dichloromethane. The mixture was stirred overnight and filtered through a short pad of silica using dichloromethane as the eluent. The filtrate was evaporated to afford the expected aldehyde.

To a solution of this aldehyde (1 mmol, 1eq) and amidosulfonic acid (H<sub>2</sub>NSO<sub>3</sub>H, 1.2 mmol, 1.2eq) in 5 ml THF was added a solution of sodium chlorite (NaClO<sub>2</sub>, 1.2 mmol, 1.2eq) in 5 ml H<sub>2</sub>O. The mixture immediately turned yellow. The mixture was stirred for 30 min before being diluted with MTBE (10 ml) and H<sub>2</sub>O (10 ml). The aqueous layer was extracted with MTBE, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was purified by flash chromatography (using hexanes/ethyl acetate in different proportions as the eluent) to give the desired carboxylic acid.

## V. Analytical data

### Dihept-5-ynyl hexanedioate (**26**).



Pyridine (713 mg, 9 mmol, 2.2eq), DMAP (catalytic amount) and hept-5-yn-1-ol (919 mg, 8.2 mmol, 2eq) were added to a solution of hexandioyl dichloride (750 mg, 4.1 mmol, 1eq) in 20 ml  $\text{CH}_2\text{Cl}_2$ . The resulting solution was stirred overnight and quenched with an aq. HCl solution (1N). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to afford product **26** (974 mg, 2.9 mmol, 71% yield) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 4.07 (t,  $J = 6.57$  Hz, 4H), 2.31 (m, 4H), 2.16 (m, 4H), 1.76 (t,  $J = 2.55$  Hz, 6H), 1.61-1.74 (m, 8H), 1.52 (m, 4H).

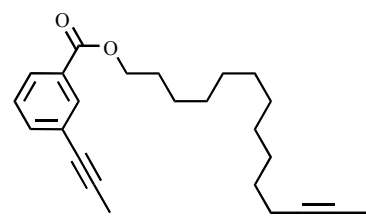
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.3, 78.5, 64.0, 33.9, 27.8, 25.4, 24.4, 18.4, 3.4.

IR (KBr)  $\nu = 2949, 2921, 2865, 1735, 1173$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 334 [ $\text{M}^+$ ] (4), 223 (12), 173 (8), 139 (11), 129 (45), 111 (66), 95 (100), 79 (59), 67 (24), 55 (43), 41 (20).

HRMS ( $\text{C}_{20}\text{H}_{30}\text{O}_4 + \text{Na}$ ): calculated: 357.204179u, found: 357.20417u.

### Tetradec-12-ynyl-(3-Prop-1-ynyl benzoate) (**28**).



Tetradec-12-ynyl-(3-Prop-1-ynyl benzoate) **28** (2.32 g, 6.34 mmol, 80% yield) was obtained as a white solid from pentadec-13-ynyl-(3-iodo-benzoate) **46** (3.6 g, 7.93 mmol) in the presence of

propyne (excess), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (280 mg, 0.4 mmol, 5 mol %) and CuI (78 mg, 0.4 mmol, 5 mol %) in 15 ml Et<sub>3</sub>N, following the general procedure 7.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.04 (t, *J* = 1.65 Hz, 1H), 7.90 (dt, *J* = 1.4 Hz, *J* = 7.8 Hz, 1H), 7.54 (dt, *J* = 1.4 Hz, *J* = 7.7 Hz), 7.34 (t, *J* = 7.7 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 2.09 (m, 2H), 2.05 (s, 3H), 1.73 (m, 5H), 1.21-1.46 (m, 18H).

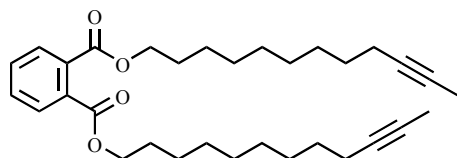
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 166.1, 135.6, 132.6, 130.7, 128.5, 128.3, 124.4, 86.8, 79.4, 78.9, 75.3, 29.6, 29.5, 29.5, 29.3, 29.2, 29.1, 28.9, 28.7, 26.0, 18.7, 4.3, 3.4.

IR (KBr)  $\nu$  = 2920, 2848, 2251, 1715, 1607, 1467, 1278, 855, 768, 723, 696 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 368 (22), 366 (81) [M<sup>+</sup>], 351 (6), 255 (3), 227 (20), 226 (12), 215 (13), 214 (27), 213 (25), 210 (9), 195 (16), 183 (17), 182 (19), 181 (16), 169 (23), 161 (48), 160 (70), 143 (100), 116 (12), 115 (73), 114 (5), 95 (18), 94 (5), 93 (12), 89 (8), 79 (13), 68 (15), 67 (23), 55 (39), 43 (11), 41 (25).

HRMS (C<sub>25</sub>H<sub>33</sub>O<sub>2</sub>): calculated: 366.2588u, found: 366.255538u.

#### Phthalic acid didodec-10-ynyl ester (**29**).



Pyridine (682 mg, 8.63 mmol, 2.2eq), DMAP (80 mg, 0.72 mmol, 0.2eq) and dodec-10-yn-1-ol **36** (1.31 g, 7.2 mmol, 2eq) were added to a solution of phthaloyl dichloride (730 mg, 3.60 mmol, 1eq) in 20 ml CH<sub>2</sub>Cl<sub>2</sub>. The resulting solution was stirred overnight and quenched with HCl (1N). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated to afford product **29** (1.391 g, 2.82 mmol, 78% yield) as a white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ (ppm): 7.71 (m, 2H), 7.50 (m, 2H), 4.29 (t, *J* = 6.8 Hz, 4H), 2.11 (m, 4H), 1.77 (t, *J* = 2.6 Hz, 6H), 1.72 (m, 4H), 1.21-1.51 (m, 24H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ (ppm): 167.7, 132.3, 130.9, 128.8, 79.3, 75.3, 65.8, 29.4, 29.2, 29.1, 29.1, 28.8, 28.5, 25.9, 18.7, 3.5.

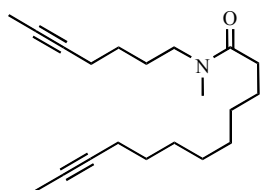


IR (KBr)  $\nu$  = 2929, 2855, 1728, 1600, 1580, 1466, 1448, 1286, 1127, 1027, 744  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity): 494 [ $M^+$ ] (10), 313 (8), 312 (3), 285 (1), 245 (1), 203 (1), 165 (4), 164 (3), 161 (2), 149 (100), 134 (2), 122 (6), 120 (2), 108 (9), 104 (2), 97 (7), 96 (6), 95 (48), 94 (9), 93 (12), 79 (12), 77 (3), 76 (1), 68 (11), 67 (21), 66 (4), 55 (26), 43 (7).

HRMS ( $\text{C}_{32}\text{H}_{46}\text{O}_4$ ): calculated: 494.339610u, found: 494.339984u.

**[*N*-(hept-5-ynyl)-*N*-methyl]carbamoyldodec-10-ynoic acid (**30**).**



*N*-(Hept-5-ynyl) carbamoyldodec-10-ynoic acid **43** (500 mg, 1.72 mmol, 1 eq) was slowly added to a suspension of NaH (83 mg, 3.44 mmol, 2eq) in 20 ml DMF at 0°C. The resulting solution was stirred for 30 min at 0°C and the cooling bath was removed before methyl iodide (1.23 g, 8.66 mmol, 5 eq) was added. The reaction was stirred at room temperature for 24h and then quenched by addition of water and MTBE at 0°C. The organic layer was washed with brine and the aqueous phase was extracted with MTBE. The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Flash chromatography of the residue afforded the desired product **30** (340mg, 1.08 mmol, 65% yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 rotamers, 3.23 and 3.31 (m, 2H together), 2.84 and 2.90 (s, 3H together), 2.24 (m, 2H), 2.11 (m, 4H), 1.73 (m, 6H), 1.16-1.66 (m, 16H).

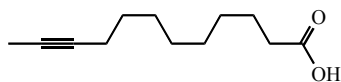
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 rotamers, 79.6, 79.1, 78.6, 76.3, 75.8, 75.4, 49.8, 47.2, 35.4, 33.9, 33.3, 32.3, 29.88, 29.83, 29.78, 29.6, 29.5, 29.3, 28.0, 26.9, 26.7, 26.5, 25.9, 25.5, 19.0, 18.8, 18.8, 3.5.

IR (KBr)  $\nu$  = 2929, 2856, 1648, 1458, 1403, 725  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 303 [ $M^+$ ] (16), 288 (18), 250 (28), 222 (16), 210 (3), 208 (12), 194 (12), 192 (3), 180 (34), 167 (51), 152 (64), 135 (3), 126 (22), 125 (61), 124 (47), 114 (14), 110 (47), 99 (5), 98 (10), 97 (19), 95 (45), 94 (19), 93 (14), 91 (8), 86 (15), 79 (18), 73 (10), 70 (53), 67 (31), 57 (16), 55 (36), 44 (100), 41 (25), 29 (5).

HRMS (C<sub>20</sub>H<sub>33</sub>N<sub>1</sub>O<sub>1</sub>): calculated: 303.256214u, found: 303.256159u.

### Dodec-10-ynoic acid (**38**).



Dodec-10-ynoic acid **38** (2.25 g, 11.5 mmol, 82% overall yield) was obtained as a white solid from dodec-10-yn-1-ol **36** (2.549 g, 14 mmol) following the general procedure 9. The first oxidation was carried out with PDC (7.99 g, 21.2 mmol, 1.5 eq) in 50 ml dichloromethane and the second oxidation with H<sub>2</sub>NSO<sub>3</sub>H (1.63 g, 16.8 mmol, 1.2 eq) and NaClO<sub>2</sub> (1.90 g, 18.8 mmol, 1.2 eq) in 15 ml THF and 15 ml water.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 2.34 (t, *J* = 7.50 Hz, 2H), 2.13 (m, 2H), 1.77 (t, *J* = 2.55 Hz, 3H), 1.62 (m, 2H), 1.45 (m, 2H), 1.26-1.40 (m, 9H).

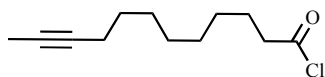
<sup>13</sup>C NMR (100 MHz) δ (ppm): 180.2, 79.3, 75.3, 34.0, 29.1, 28.99, 28.97, 28.9, 28.8, 24.6, 18.7, 3.4.

IR (KBr) ν = 3030, 2931, 2852, 2659, 1692, 1410, 1287, 926 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 196 [M<sup>+</sup>] (0.5), 167 (2), 149 (3), 140 (2), 136 (4), 109 (10), 95 (38), 81 (34), 68 (100), 55 (28), 42 (18), 27 (6).

HRMS (C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>): calculated: 196.146330u, found: 196.146533u.

### Dodec-10-ynoyl chloride (**39**).

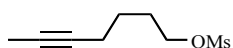


Thionyl chloride (SO<sub>2</sub>Cl<sub>2</sub>, 1.2 g, 10 mmol, 2.13 eq) was added to a solution of dodec-10-ynoic acid **38** (936 mg, 4.78 mmol, 1 eq) in 5 ml CH<sub>2</sub>Cl<sub>2</sub> at 0°C. The reaction was monitored by GC/MS. Solvent and reagent were evaporated to afford the desired acid chloride which was used directly for the amide formation.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 2.88 (t,  $J = 7.3$  Hz, 2H), 2.07 (m, 2H), 1.73 (t,  $J = 2.56$  Hz, 3H), 1.66 (m, 2H), 1.41 (m, 2H), 1.31 (m, 8H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 174.2, 79.5, 75.5, 47.5, 29.5, 29.3, 29.2, 29.1, 28.8, 25.5, 19.0, 3.5.

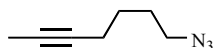
#### Trifluoromethane sulfonic acid-hept-5-ynyl ester (41a).



Triethylamine (2.17 g, 21.5 mmol, 1.2eq) and methanesulfonyl chloride (2.25 g, 19.6 mmol, 1.1eq) were added to a solution of hept-5-yn-1-ol **40** (2 g, mmol, 17.9 mmol, 1eq) in 20 ml  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ . The reaction was stirred for 1h and then quenched with water. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , the organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to afford the desired mesylate that was directly used for the next step without further purification.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm) : 4.19, (t,  $J = 6.45$  Hz, 2H), 2.94 (s, 3H), 2.13 (m, 2H), 1.80 (m, 2H), 1.70 (t,  $J = 2.55$  Hz, 3H), 1.53 (m, 2H).

#### 7-Azidohept-2-yne (41).



Sodium azide (1.57 g, 24 mmol, 1.35 eq) was added to a solution of the mesylate in 15 ml DMSO at room temperature. The reaction was stirred overnight and quenched with water. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was carefully (water bath at room temperature) evaporated. Purification by flash chromatography afforded the expected product **41** (1.65 g, 12.05 mmol, 67% yield over two steps) as a colourless oil.

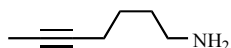
$^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 3.21 (t,  $J = 6.8$  Hz, 2H), 2.08 (m, 2H), 1.67 (t,  $J = 2.50$  Hz, 3H), 1.4-1.67 (m, 6H).

$^{13}\text{C}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 79.0, 76.6, 66.4, 51.9, 28.7, 26.9, 19.0, 15.8.

IR (KBr)  $\nu = 2944, 2921, 2864, 2097, 1455, 1437, 1271$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 137 [ $M^+$ ] (1), 108 (34), 106 (4), 81 (46), 80 (68), 79 (27), 78 (4), 77 (22), 68 (36), 62 (2), 54 (3), 53 (100), 52 (21), 51 (27), 50 (14), 43 (28), 42 (63), 41 (86), 39 (63), 27 (55).

### Hept-5-ynyl amine (42).



$\text{LiAlH}_4$  (150 mg, 3.92 mmol, 1.06 eq) was added to a solution of azide **41** (510 mg, 3.70 mmol, 1 eq) in 5 ml diethyl ether at  $0^\circ\text{C}$ . The reaction was stirred for 30 min and carefully quenched with cold water. The resulting mixture was filtered, the two layers were separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated, affording the desired amine **42** (314 mg, 2.83 mmol, 76% yield) as a colourless oil.

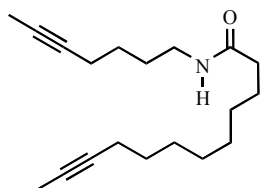
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 2.57 (m, 2H), 2.03 (m, 2H), 1.67 (t,  $J = 2.53$  Hz, 3H), 1.40 (m, 4H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 79.7, 76.0, 42.5, 33.9, 27.2, 19.3, 3.1.

IR (KBr)  $\nu = 3330, 2934, 2920, 2860, 1577, 1474, 1320, 817$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 111 [ $M^+$ ] (0.8), 110 (7), 96 (24), 83 (35), 56 (40), 30 (100), 27 (8).

### *N*-(hept-5-ynyl)carbamoyl dodec-10-ynoic acid (43).



A solution of dodec-10-ynoyl chloride **39** in 10 ml  $\text{CH}_2\text{Cl}_2$  (610 mg, 2.83 mmol, 1eq) was added to a solution of hept-5-ynylamine **42** (314 mg, 2.83 mmol, 1eq) and triethylamine (680 mg, 6.73 mmol, 2.4 eq) in 10 ml  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ . The reaction was refluxed for 1h and quenched with water. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Flash chromatography of the residue (using pentanes/ $\text{Et}_2\text{O}$ : 50/50 as the eluent) afforded the expected amide **43** (550 mg, 1.90 mmol, 67% yield) as a colourless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 5.40 (broad s, 1H), 3.13 (m, 2H), 2.03 (m, 6H), 1.67 (m, 6H), 1.1-1.7 (m, 16H).

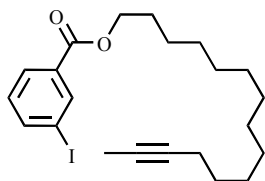
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 2 rotamers, 173.0, 79.5, 79.0, 76.00, 75.5, 39.2, 37.1, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.8, 26.1, 19.0, 18.7, 3.5.

IR (KBr)  $\nu$  = 3286, 2927, 2851, 1635, 1542  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 289 [ $\text{M}^+$ ] (23), 274 (6), 261 (3), 236 (29), 234 (5), 208 (6), 166 (21), 161 (8), 153 (37), 148 (4), 138 (34), 137 (5), 136 (6), 135 (6), 119 (6), 112 (34), 111 (100), 110 (46), 100 (7), 95 (75), 94 (6), 91 (11), 87 (8), 84 (10), 83 (23), 79 (34), 77 (11), 72 (13), 67 (36), 60 (4), 59 (7), 58 (16), 56 (48), 55 (53), 54 (6), 53 (30), 43 (16), 41 (44), 30 (36), 29 (9).

HRMS ( $\text{C}_{19}\text{H}_{31}\text{N}_1\text{O}_1$ ): calculated: 289.240564u, found: 289.240788u.

#### Pentadec-13-ynyl (3-iodo-benzoate) (**46**).



Pyridine (929 mg, 11.7 mmol, 1.2 eq), DMAP (10 mol%), and pentadec-13-yn-1-ol **45** (2 g, 8.92 mmol, 1 eq) were added to a solution of 3-iodobenzoyl chloride (2.61 g, 9.79 mmol, 1.1 eq) in 12 ml  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred overnight and quenched with HCl (1N). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Flash chromatography of the residue (using hexanes/ethyl acetate: 20/1 as the eluent) afforded pentadec-13-ynyl (3-iodo-benzoate) **46** (4.09g, 9.01 mmol, 92% yield) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.75 (m, 4H), 4.29 (t,  $J$  = 6,6 Hz, 2H), 2.10 (m, 2H), 1.74 (m, 5H), 1.31 (m, 18H).

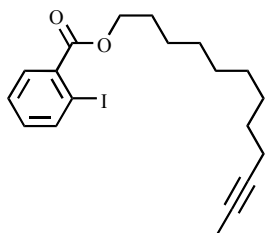
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.2, 137.7, 131.0, 130.0, 100.5, 79.4, 75.3, 65.4, 29.56, 29.52, 29.50, 29.48, 29.24, 29.2, 29.10, 28.89, 28.64, 25.98, 18.17, 3.46.

IR (KBr)  $\nu$  = 2923, 2848, 1714, 1567, 1467, 1294, 741, 713  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 454 (7) [ $M^+$ ], 387 (6), 231 (42), 203 (12), 164 (3), 139 (10), 121 (10), 104 (4), 96 (17), 95 (29), 93 (13), 83 (17), 81 (25), 79 (13), 76 (14), 68 (100), 67 (27), 55 (29), 41 (20).

HRMS ( $C_{22}H_{31}I_1O_2$ ): calculated: 454.136877 u, found: 454.13634 u.

**(Dodec-13-ynyl)-2-iodo-benzoate (48).**



Dodec-10-yn-1-ol **36** (526 mg, 2.86 mmol, 1 eq) was added to a solution of commercially available 2-iodo-benzoylchloride **47** (764 mg, 3.08 mmol, 1.1 eq), pyridine (272 mg, 3.44 mmol, 1.2 eq), and DMAP (catalytic amount) in 30 ml dichloromethane. The reaction was stirred overnight and quenched with an aq. HCl solution (1N). The aqueous layer was extracted with dichloromethane, the combined organic phases were dried over  $Na_2SO_4$ , and the solvent was evaporated. Purification by flash chromatography (using hexane/ethyl acetate: 4/1 as the eluent) afforded the desired product **48** (885 mg, 2.15 mmol, 75 % yield) as a white solid.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.98 (d,  $J = 1.1$  Hz, 1H), 7.77 (d,  $J = 1.1$  Hz, 1H), 7.39 (dt,  $J = 7.6$  Hz,  $J = 1.1$  Hz, 1H), 7.13 (m, 1H), 4.33 (t, 6.7 Hz, 2H), 2.11 (m, 2H), 1.77 (m, 5H), 1.25-1.50 (m, 12H).

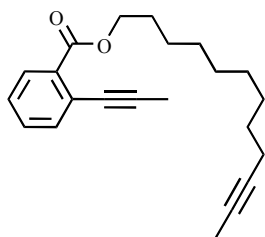
$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm) : 166.7, 141.2, 135.7, 132.4, 130.8, 127.8, 93.9, 79.4, 75.3, 65.8, 29.4, 29.2, 29.1 (2 Carbons), 28.8, 28.6, 26.0, 18.7, 3.4.

IR (KBr)  $\nu = 3063, 2929, 2854, 1729, 1584, 1464, 1430, 1384, 1288, 1250, 1133, 1100, 741$   $cm^{-1}$ .

MS:  $m/z$  (relative intensity) 412 [ $M^+$ ] (4), 345 (13), 285 (6), 249 (55), 248 (66), 231 (100), 203 (21), 164 (16), 135 (18), 121 (21), 96 (39), 68 (48), 55 (27), 41 (26).

HRMS ( $C_{19}H_{25}I_1O_2$ ): calculated: 412.089927u, found: 412.089868u.

**(Pentadec-13-ynyl)-2-prop-1-ynyl-benzoate (49).**



(Pentadec-13-ynyl)-2-prop-1-ynyl-benzoate **49** (306 mg, 0.95 mmol, 93 % yield) was obtained as a white solid from (dodec-13-ynyl)-3-iodo-benzoate **48** (419 mg, 1.02 mmol, 1 eq) in the presence of propyne (excess), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (36 mg, 0.05 mmol, 5 mol %) and CuI (10 mg, 0.05 mmol, 5 mol %), in 10 ml Et<sub>3</sub>N, following the general procedure 7.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.78 (dd, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.40 (dt, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H), 7.30 (dt, *J* = 7.6 Hz, *J* = 1.3 Hz, 1H), 4.31 (t, *J* = 6.7 Hz, 2H), 2.11 (m, 5H), 1.77 (m, 5H), 1.25-1.50 (m, 12H).

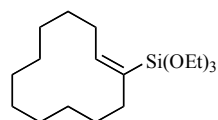
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) : 166.6, 134.2, 132.2, 131.3, 130.1, 127.1, 124.4, 91.2, 79.3, 78.5, 75.3, 65.2, 29.4, 29.3, 29.1, 29.0, 28.8, 28.7, 26.0, 18.7, 4.7, 3.4.

IR (KBr)  $\nu$  = 3064, 2929, 2855, 2245, 2216, 1729, 1711, 1598, 1567, 1484, 1445, 1289, 1247, 1131, 1081, 758 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 324 [M<sup>+</sup>] (4), 309 (6), 239 (11), 209 (23), 195 (31), 187 (21), 169 (22), 161 (58), 143 (100), 132 (33), 115 (71), 105 (18), 95 (15), 67 (23), 55 (33), 41 (33).

HRMS (C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>): calculated: 324.208930u, found: 324.209139u.

### 1(*Z*)-1-(Triethoxysilyl)-cyclododecene (**51**).

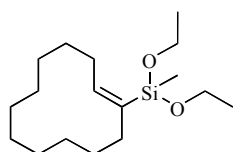


1(*Z*)-1-(Triethoxysilyl)-cyclododecene **51** (176 mg, 0.54 mmol, 90 % yield) was obtained as a colourless oil from cycloalkyne **33** (100 mg, 0.61 mmol, 1 eq) in the presence of triethoxysilane (120 mg, 0.73 mmol, 1.2 eq) and catalyst **15** (3 mg, 0.0061 mmol, 1 mol %) in 2 ml dichloromethane, following the general procedure 2A. *E/Z* ratio: 9:91 (GC)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.25 (tt,  $J = 7.8$ ,  $J = 1.1$  Hz, 1H), 3.82 (q,  $J = 7.0$  Hz, 6H), 2.30 (m, 2H), 2.18 (m, 2H), 1.49-1.52 (m, 4H), 1.41 (m, 2H), 1.34 (m, 2H), 1.26-1.29 (m, 8H), 1.21 (t,  $J = 7.0$  Hz, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 149.7, 131.4, 58.2, 36.6, 32.1, 27.0, 26.7, 26.2, 26.0, 25.8, 24.4, 24.1, 24.0, 18.2.

### 1-(Z)-1-(Methyldiethoxysilyl)-cyclododecene (**51a**).



1-(Z)-1-(Methyldiethoxysilyl)-cyclododecene **51a** (178 mg, 0.6 mmol, 98 % yield) was obtained as a colourless oil from cycloalkyne **33** (100 mg, 0.61 mmol, 1 eq) in the presence of diethoxymethylsilane (102 mg, 0.73 mmol, 1.2 eq) and catalyst **15** (3.1 mg, 0.0061 mmol, 1 mol %) in 1 ml dichloromethane, following the general procedure 2A. *E/Z* ratio: 4:96 (GC).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.25 (broad t,  $J = 7.8$  Hz, 1H), 3.76 (qm,  $J = 7.0$  Hz, 4H), 2.31 (m, 2H), 2.21 (m, 2H), 1.25-1.58 (m, 16H), 1.22 (t,  $J = 7.0$  Hz, 6H), 0.25 (s, 3H).

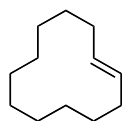
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) : 148.5, 134.3, 58.0, 36.4, 31.9, 27.23, 26.9, 26.3, 26.0, 25.9, 25.3, 25.0, 24.3, 24.12, 24.07, 18.3, -2.5.

IR (KBr)  $\nu = 2972, 2925, 2859, 1606, 1461, 1389, 1105, 1082, 952, 758\text{ cm}^{-1}$ .

MS: *m/z* (relative intensity) 298 [ $\text{M}^+$ ] (1), 283 (3), 164 (10), 133 (100), 119 (4), 105 (6), 89 (11), 77 (11), 61 (6), 41 (3).

HRMS ( $\text{C}_{17}\text{H}_{34}\text{O}_2\text{Si}_1$ ): calculated: 298.232809u, found: 298.232704u.

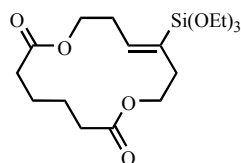


**(E)-Cyclododecene (52).**

(E)-Cyclododecene **52** (75 mg, 45 mmol, 84 % yield) was obtained as a colourless oil from vinylsilane **51** (176 mg, 0.54 mmol, 1 eq) in the presence of AgF (103 mg, 0.81 mmol, 1.5 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 2A. *E/Z* ratio: 90:10 (GC).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 5.37 (tt,  $J = 4.1, 1.0$  Hz, 2H), 2.06 (q,  $J = 6$  Hz, 4H), 1.39-1.47 (m, 4H), 1.25-1.37 (m, 9H), 1.29 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 131.4, 32.1, 26.3, 25.6, 25.0, 24.6.

**11-(Triethoxysilyl)-1,8-dioxacyclotetradec-11-ene-2,7-dione (54).**

11-(Triethoxysilyl)-1,8-dioxacyclotetradec-11-ene-2,7-dione **54** (241 mg, 0.62 mmol, 93% yield) was obtained as a colourless oil from cycloalkyne **53** (150 mg, 0.67 mmol, 1 eq) in the presence of triethoxysilane (131 mg, 0.80 mmol, 1.4 eq) and catalyst **15** (3.4 mg, 0.007 mmol, 1 mol %) in 1 ml  $\text{CH}_2\text{Cl}_2$ , following the general procedure 2A. *Z/E* ratio: 95/5 (GC).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.13 (m, 1H), 4.16 (m, 4H), 3.80 (q,  $J = 6.90$  Hz, 6H), 2.63 (m, 2H), 2.44 (m, 2H), 2.30 (m, 4H), 1.61 (m, 4H), 1.20 (t,  $J = 6.90$  Hz, 9H).

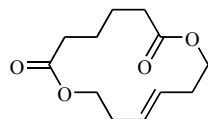
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.2, 173.0, 146.4, 131.3, 64.1, 63.5, 58.1, 36.9, 35.0, 34.9, 30.7, 24.7, 24.3, 18.1.

IR (KBr)  $\nu = 2975, 1727, 1626, 1282, 1082, 787$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 388 [ $\text{M}^+$ ] (0.15), 343 (8), 269 (2), 242 (55), 198 (87), 163 (78), 135 (100), 119 (42), 79 (41), 55 (19), 29 (5).

HRMS (C<sub>18</sub>H<sub>35</sub>O<sub>7</sub>Si<sub>1</sub>+H): calculated: 389.199559u, found: 389.199279u.

**1,8-Dioxacyclotetradec-(11*E*)-ene-2,7-dione (**55**).**



1,8-Dioxacyclotetradec-(11*E*)-ene-2,7-dione **55** (53 mg, 0.23 mmol, 92 % yield) was obtained as colourless needles from vinylsilane **54** (98 mg, 0.25 mmol, 1 eq) in the presence of AgF (48 mg, 0.38 mmol, 1.5 eq) in THF (2ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A. *E/Z* ratio: 95:5 (GC).

Mp = 95-96°C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 5.46 (tt, *J*=3.8, 1.5 Hz, 1H), 4.14 (dd, *J*=6.4, 4.5 Hz, 2H), 2.29-2.45 (m, 4H), 1.64 (m, 2H).

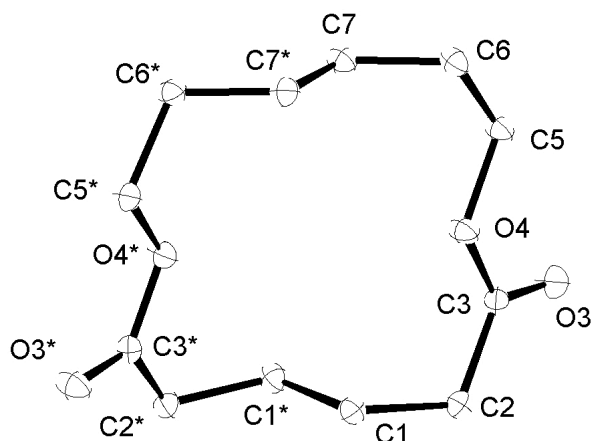
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 173.1, 129.2, 63.1, 35.0, 31.9, 24.7.

IR (KBr)  $\nu$  = 1719, 1284, 961 cm<sup>-1</sup>.

MS: *m/z* (relative intensity): 196 (1), 129 (3), 101 (3), 80 (100), 79 (14), 68 (31), 67 (16), 55 (12).

Anal. (C<sub>12</sub>H<sub>18</sub>O<sub>4</sub>) calculated. C 63.70, H 8.02, found C 63.81, H 8.09.

HRMS (C<sub>12</sub>H<sub>19</sub>O<sub>4</sub>+H): calculated: 227.128335u, found: 227.128483u.

**Crystal structure of 55.****Crystal data and structure refinement.**

Empirical formula	C <sub>12</sub> H <sub>18</sub> O <sub>4</sub>	
Color	colourless	
Formula weight	226.26 g · mol <sup>-1</sup>	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	<b>C2/c, (no. 15)</b>	
Unit cell dimensions	a = 7.7012(3) Å	a = 90°.
	b = 16.4386(6) Å	b = 93.009(2)°.
	c = 9.1563(4) Å	g = 90°.
Volume	1157.56(8) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.298 Mg · m <sup>-3</sup>	
Crystal size	0.20 x 0.11 x 0.06 mm <sup>3</sup>	
Reflections collected	8942	
Independent reflections	2195 [R <sub>int</sub> = 0.0534]	
Reflections with I > 2σ(I)	1726	
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0448	wR <sup>2</sup> = 0.1357
R indices (all data)	R <sub>1</sub> = 0.0617	wR <sup>2</sup> = 0.1490

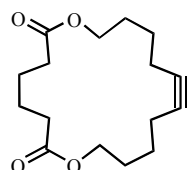
**Table 2. Bond lengths [Å] and angles [°]**

C(1)-C(2)	1.5277(13)	C(1)-C(1)*	
1.5228(19)	C(1)-H(1A)	0.985(14)	C(1)-

H(1B)	1.000(15)	C(2)-C(3)	
1.5021(13)	C(2)-H(2A)	0.986(16)	C(2)-
H(2B)	0.990(14)	O(3)-C(3)	
1.2084(11)	C(3)-O(4)	1.3401(11)	O(4)-
C(5)	1.4548(11)	C(5)-C(6)	
1.5114(13)	C(5)-H(5A)	0.980(16)	C(5)-
H(5B)	0.970(17)	C(6)-C(7)	
1.4980(13)	C(6)-H(6A)	1.013(14)	C(6)-
H(6B)	0.923(14)	C(7)-C(7)*	
1.3196(19)	C(7)-H(7)	0.963(16)	
C(2)-C(1)-C(1)*	112.86(10)	C(2)-C(1)-H(1A)	106.8(8)
C(1)*-C(1)-H(1A)	111.0(8)	C(2)-C(1)-H(1B)	111.0(9)
C(1)*-C(1)-H(1B)	108.7(10)	H(1A)-C(1)-H(1B)	106.3(12)
C(3)-C(2)-C(1)	115.73(8)	C(3)-C(2)-H(2A)	106.0(9)
C(1)-C(2)-H(2A)	109.1(10)	C(3)-C(2)-H(2B)	106.9(8)
C(1)-C(2)-H(2B)	110.7(8)	H(2A)-C(2)-H(2B)	108.1(12)
O(3)-C(3)-O(4)	122.84(9)	O(3)-C(3)-C(2)	124.32(9)
O(4)-C(3)-C(2)	112.81(8)	C(3)-O(4)-C(5)	115.63(7)
O(4)-C(5)-C(6)	107.56(7)	O(4)-C(5)-H(5A)	110.6(9)
C(6)-C(5)-H(5A)	111.6(9)	O(4)-C(5)-H(5B)	108.6(9)
C(6)-C(5)-H(5B)	112.9(9)	H(5A)-C(5)-H(5B)	105.5(14)
C(7)-C(6)-C(5)	113.28(8)	C(7)-C(6)-H(6A)	110.9(9)
C(5)-C(6)-H(6A)	105.7(8)	C(7)-C(6)-H(6B)	109.4(9)
C(5)-C(6)-H(6B)	109.7(8)	H(6A)-C(6)-H(6B)	107.8(12)
C(7)*-C(7)-C(6)	124.77(12)	C(7)*-C(7)-H(7)	118.9(9)
C(6)-C(7)-H(7)	116.2(9)		

Symmetry transformations used to generate equivalent atoms: \* -x,y,-z+3/2

### 1,8-Dioxacyclooctadec-13-yne-2,7-dione (56).



1,8-Dioxacyclooctadec-13-yne-2,7-dione **56** (134 mg, 0.48 mmol, 80% yield) was obtained as a colourless oil from diyne **26** (200 mg, 0.6 mmol, 1 eq) in the presence of catalyst **1** (28 mg, 0.006 mmol, 10 mol %) in 60 ml toluene, following the general procedure 1.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 4.11 (t,  $J = 6.67$  Hz, 4H), 2.33 (m, 4H), 2.18 (m, 4H), 1.77 (m, 4H), 1.68 (m, 4H), 1.53 (m, 4H).

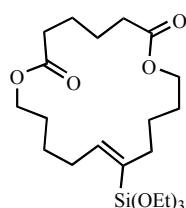
$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 173.2, 80.3, 64.0, 34.4, 27.8, 25.4, 24.8, 18.4.

IR (KBr)  $\nu = 2948, 2866, 2235, 1733, 1245$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 280 [ $\text{M}^+$ ] (2), 252 (2), 207 (1), 179 (5), 151 (19), 134 (82), 119 (36), 106 (46), 91 (77), 79 (65), 67 (45), 55 (100), 41 (58), 29 (27).

HRMS ( $\text{C}_{16}\text{H}_{24}\text{O}_4+\text{H}$ ): calculated: 281.175285u, found: 281.175010u.

**(13Z)-13-(Triethoxysilyl)-1,8-dioxacyclooctadec-13-ene-2,7-dione (57).**

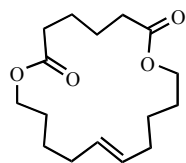


(13Z)-13-(Triethoxysilyl)-1,8-dioxacyclooctadec-13-ene-2,7-dione **57** (125 mg, 0.28 mmol, 98% yield) was obtained as a colourless oil from cycloalkyne **56** (80 mg, 0.29 mmol, 1 eq) in the presence of triethoxysilane (56 mg, 0.34 mmol, 1.2 eq) and catalyst **15** (1.4 mg, 0.0028 mmol, 1 mol %) in 1 ml  $\text{CH}_2\text{Cl}_2$ , following the general procedure 2A.  $Z/E$  ratio: 98/2 (GC).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.05 (t,  $J = 7.54$  Hz, 1H) 4.09 (m, 4H), 3.80 (q,  $J = 7.00$  Hz, 6H), 2.31 (m, 6H), 2.13 (m, 2H), 1.38-1.71 (m, 12H), 1.22 (t,  $J = 7.00$  Hz, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.3, 147.9, 132.2, 64.3, 64.2, 58.1, 36.2, 34.7, 34.6, 31.0, 28.1, 27.5, 26.1, 25.7, 25.01, 24.99, 18.2.

MS:  $m/z$  (relative intensity) 444 [ $\text{M}^+$ ] (0.5), 398 (100), 296 (3), 255 (4), 217 (33), 163 (38), 108 (27), 79 (29), 55 (11), 29 (2).

**(13E)-1,8-Dioxacyclooctadec-13-ene-2,7-dione (58).**

(13E)-1,8-Dioxacyclooctadec-13-ene-2,7-dione **58** (41 mg, 0.145 mmol, 90% yield) was obtained as a white solid from vinylsilane **57** (70 mg, 0.16 mmol, 1 eq) in the presence of AgF (41 mg, 0.32 mmol, 2 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A. *E/Z* ratio: 98/2 (GC).

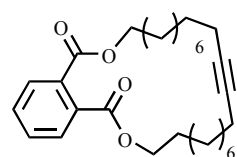
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.35 (m, 2H), 4.07 (t,  $J = 6.65$  Hz, 4H), 2.31 (m, 4H), 2.01 (m, 4H), 1.55-1.66 (m, 8H), 1.40 (m, 4H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.2, 130.6, 64.2, 34.5, 31.6, 27.6, 25.4, 24.9.

IR (KBr)  $\nu = 3024, 2932, 2858, 1734, 1241, 971$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 282 [ $\text{M}^+$ ] (12), 264 (1), 153 (1), 136 (100), 121 (39), 108 (62), 79 (62), 55 (67), 29 (15).

HRMS ( $\text{C}_{16}\text{H}_{26}\text{O}_4+\text{Na}$ ): calculated: 305.172879u, found: 305.17255u.

**Benzo-[c]-1,6-dioxa-2,5-dioxocyclooctacos-16-yne (59).**

Benzo-[c]-1,6-dioxa-2,5-dioxocyclooctacos-16-yne **59** (186 mg, 0.43 mmol, 70% yield) was obtained as a white solid from diyne **29** (300 mg, 0.61 mmol) in the presence of catalyst **1** (29 mg, 0.061 mmol, 10 mol %) in 60 ml toluene, following the general procedure 1.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  (ppm): 7.66 (m, 2H), 7.51 (m, 2H), 4.29 (t,  $J = 6.6$  Hz, 4H), 2.16 (m, 4H), 1.72 (m, 4H), 1.21-1.51 (m, 24H).

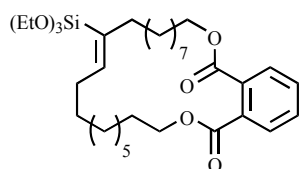
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  (ppm): 167.8, 132.3, 130.9, 128.9, 80.5, 66.0, 29.7, 29.3, 29.2, 28.6, 28.5, 28.3, 26.3, 18.5.

IR (KBr)  $\nu$  = 2926, 2852, 1745, 1735, 1578, 1464, 1450, 1297, 1281, 1133, 1078, 746  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity): 440 [ $\text{M}^+$ ] (9), 312 (4), 292 (3), 291 (2), 259 (4), 245 (4), 178 (11), 167 (3), 164 (17), 151 (2), 149 (100), 136 (5), 134 (1), 121 (15), 111 (9), 110 (7), 104 (3), 97 (12), 95 (15), 92 (2), 80 (16), 79 (17), 78 (2), 77 (5), 76 (2), 67 (21), 55 (23), 54 (5), 43 (6), 41 (16), 29 (3).

HRMS ( $\text{C}_{28}\text{H}_{40}\text{O}_4$ ): calculated: 440.292660u, found: 440.293118u.

**(17Z)-17-(Triethoxysilyl)-6,29-dioxa benzocyclooctacos-17-ene-5,30-dione (60).**



(17Z)-17-(Triethoxysilyl)-6,29-dioxa benzocyclooctacos-17-ene-5,30-dione **60** (147 mg, 0.24 mmol, 97% yield) was obtained as a colourless oil from cycloalkyne **59** (111 mg, 0.23 mmol), in the presence of triethoxysilane (50 mg, 0.3 mmol, 1.2 eq) and catalyst **15** (1.27 mg, 0.0023 mmol, 1 mol %) in 2 ml dichloromethane, following the general procedure 2A. *Z/E* ratio (HPLC): 98/2.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  (ppm): 7.70 (m, 2H), 7.50 (m, 2H), 6.05 (m, 1H), 4.27 (t,  $J$  = 6.6 Hz, 4H), 3.78 (q,  $J$  = 7.0 Hz, 6H), 2.26 (m, 2H), 2.11 (m, 2H), 1.70 (m, 4H), 1.16-1.46 (m, 33H).

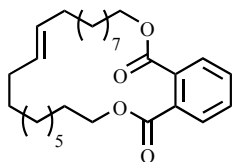
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  (ppm): 167.8, 148.6, 132.3, 132.2, 131.8, 130.9, 130.9, 129.0, 128.8, 66.0, 58.0, 36.9, 31.5, 29.7, 29.5, 29.5, 29.3, 29.2, 29.0, 28.6, 27.7, 26.2, 18.2.

IR (KBr)  $\nu$  = 2971, 2926, 2854, 1729, 1601, 1580, 1448, 1388, 1289, 1104, 780, 743  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity): 604 [ $\text{M}^+$ ] (9), 560 (13), 558 (100), 512 (13), 311 (9), 283 (39), 255 (6), 239 (4), 238 (2), 227 (7), 181 (2), 165 (2), 163 (45), 159 (1), 153 (1), 137 (8), 135 (19), 125 (2), 124 (4), 122 (2), 119 (28), 107 (13), 95 (8), 91 (7), 82 (7), 81 (10), 80 (6), 79 (12), 69 (7), 67 (9), 63 (3), 57 (2), 55 (8), 54 (2), 43 (3).

HRMS (C<sub>34</sub>H<sub>56</sub>O<sub>7</sub>Si<sub>1</sub>): calculated: 604.379534u, found: 604.379109.

**(17E)-6,29-Dioxabenzocyclooctacos-17-ene-5,30-dione (61).**



(17E)-6,29-Dioxabenzocyclooctacos-17-ene-5,30-dione **61** (55 mg, 0.124 mmol, 90% yield) was obtained as a white solid from vinylsilane **60** (80 mg, 0.13 mmol) in the presence of AgF (33 mg, 0.26 mmol, 2 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A. *E/Z* ratio (HPLC): 98/2.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  (ppm): 7.71 (m, 2H), 7.52 (m, 2H), 5.32 (m, 2H), 4.28 (t, *J* = 6.6 Hz, 4H), 2.00 (m, 4H), 1.72 (m, 4H), 1.16-1.46 (m, 24H).

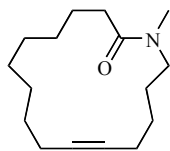
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  (ppm): 167.7, 132.3, 130.9, 130.7, 128.9, 66.0, 32.0, 29.5, 29.3, 29.2, 28.8, 28.6, 28.0, 26.2.

IR (KBr)  $\nu$  = 3067, 3025, 2925, 2853, 1730, 1600, 1465, 1448, 1288, 1126, 968, 742 cm<sup>-1</sup>.

MS: *m/z* (relative intensity): 442 [M<sup>+</sup>] (57), 424 (4), 294 (7), 276 (2), 167 (5), 151 (5), 149 (100), 136 (3), 124 (13), 122 (4), 121 (10), 105 (4), 104 (3), 98 (3), 96 (31), 95 (21), 82 (30), 80 (9), 79 (6), 77 (3), 76 (2), 67 (26), 56 (4), 55 (33), 54 (12), 43 (8), 41 (21), 39 (1).

HRMS (C<sub>28</sub>H<sub>42</sub>O<sub>4</sub>+Na): calculated: 465.298079u, found: 465.29800u.

**1-(N-Methyl)-azacyclohexadec-11-yn-2one (62).**



1-(N-Methyl)-azacyclohexadec-11-yn-2one **62** (173 mg, 0.7 mmol, 68% yield) was obtained as a colourless oil from amide **30** (310 mg, 1.02 mmol, 1 eq) in the presence of catalyst **1** (52 mg, 0.11 mmol, 11 mol %) in 90 ml toluene, following the general procedure 1.



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 rotamers, 3.39 and 3.28 (m, 2H together), 2.97 and 2.86 (s, 3H together), 2.51 (m, 2H), 2.16 (m, 4H), 1.51-1.76 (m, 4H), 1.21-1.51 (m, 12H).

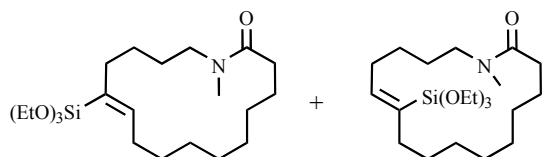
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 rotamers, 173.2, 173.1, 81.0, 80.9, 80.2, 50.8, 47.0, 35.9, 33.7, 32.8, 32.6, 28.6, 28.4, 28.4, 28.2, 28.0, 27.8, 27.4, 27.3, 27.00, 26.96, 26.9, 25.9, 25.3, 19.1, 19.0, 18.2.

IR (KBr)  $\nu$  = 2928, 2855, 1641, 1483, 1458, 1437, 1400, 577  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 249 [ $\text{M}^+$ ] (25), 248 (21), 221 (4), 208 (7), 206 (12), 193 (4), 178 (8), 167 (5), 165 (9), 164 (9), 152 (18), 136 (6), 135 (4), 126 (6), 124 (28), 123 (3), 12 (6), 114 (6), 113 (7), 11 (35), 98 (8), 94 (8), 91 (11), 86 (18), 80 (7), 79 (21), 77 (10), 74 (5), 73 (15), 70 (100), 68 (4), 67 (15), 57 (17), 55 (24), 54 (3), 44 (76), 41 (22), 29 (5).

HRMS ( $\text{C}_{16}\text{H}_{27}\text{N}_1\text{O}_1$ ): calculated: 249.209264u, found: 249.209070u.

**(11Z)-N-Methyl-12-(triethoxysilyl)-azacyclohexadec-11-en-2-one (63)** and **(11Z)-N-methyl-11-(triethoxysilyl)-azacyclohexadec-11-en-2-one (63a)**.



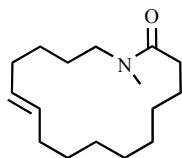
(11Z)-N-Methyl-12-(triethoxysilyl)-azacyclohexadec-11-en-2-one **63** and (11Z)-N-methyl-11-(triethoxysilyl)-azacyclohexadec-11-en-2-one **63a** (62 mg, 0.15 mmol, 95% yield) were obtained as a colourless oil from cycloalkyne **62** (38 mg, 0.15 mmol, 1 eq) in the presence of triethoxysilane (32 mg, 0.19 mmol, 1.2 eq) and catalyst **15** (1.0 mg, 0.002 mmol, 1.3 mol %) in 1 ml dichloromethane, following the general procedure 2A.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 rotamers, 6.01 (m, 1H), 3.76 (m, 6H), 3.29 (m, 2H), 2.94 and 2.85 (m, 3H), 2.26 (m, 4H), 2.12 (m, 2H), 1.11-1.66 (m, 26H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 rotamers, 173.3, 173.24, 173.17, 172.92, 149.58, 149.23, 149.08, 148.10, 133.02, 132.82, 132.67, 131.82, 58.51, 58.39, 58.32, 54.52, 54.16, 53.80, 53.44, 53.08, 51.24, 51.21, 47.40, 47.29, 38.01, 37.56, 37.31, 36.48, 35.75, 35.61, 33.85, 33.65, 32.91, 32.86, 32.63, 32.34, 32.31, 31.90, 31.76, 31.02, 29.71, 29.22, 28.98, 28.88, 28.83, 28.60, 28.50, 28.32, 28.20,

28.11, 28.07, 27.88, 27.85, 27.80, 27.73, 27.26, 27.23, 27.11, 27.07, 26.92, 26.70, 26.39, 26.06, 26.01, 25.80, 25.49.

**(11*E*)-*N*-Methylazacyclohexadec-11-en-2-one (64).**



(11*E*)-*N*-Methylazacyclohexadec-11-en-2-one **64** (42 mg, 0.17 mmol, 82% yield) was obtained as a colourless oil from vinylsilanes **63** and **63a** (85 mg, 0.21 mmol, 1 eq) in the presence of AgF (53 mg, 0.42 mmol, 2 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A. *E/Z* ratio: 97/3 (GC).

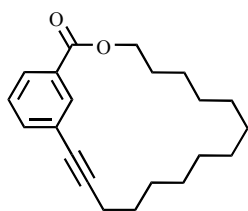
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 2 rotamers, 5.23 (m, 2H), 3.20 and 3.30 (m and t,  $J = 7.7$  Hz, 2H together), 2.80 and 2.90 (s, 3 H together), 2.20 (m, 2H), 1.92 (m, 4H), 1-.16 (m, 16H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 2 rotamers, 173.3, 173.1, 131.6, 131.5, 131.3, 131.1, 51.3, 47.6, 36.0, 34.0, 33.0, 32.6, 32.52, 32.49, 31.3, 28.9, 28.7, 28.5, 28.3, 27.9, 27.51, 27.45, 27.41, 27.06, 26.98, 26.90, 26.2, 25.6

IR (KBr)  $\nu = 3022, 300, 2926, 2853, 1642, 968 \text{ cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 251 [ $\text{M}^+$ ] (32), 236 (2), 210 (3), 208 (4), 156 (2), 152 (3), 126 (7), 114 (8), 113 (5), 111 (1), 110 (2), 99 (3), 98 (6), 97 (2), 87 (12), 86 (13), 80 (2), 79 (5), 77 (1), 74 (9), 73 (15), 70 (39), 67 (14), 57 (11), 55 (25), 54 (9), 45 (5), 44 (100), 41 (32), 39 (5), 31 (1), 29 (6).

HRMS ( $\text{C}_{16}\text{H}_{29}\text{N}_1\text{O}_1$ ): calculated: 251.224914u, found: 251.225135u.

**3-Oxabicyclo[16.3.1]docosa-1(22),18,20-trien-16-yn-2-one (65).**

3-Oxabicyclo[16.3.1]docosa-1(22),18,20-trien-16-yn-2-one **65** (182 mg, 0.58 mmol, 71% yield) was obtained as a white solid from diyne **28** (300 mg, 0.82 mmol) in the presence of catalyst **1** (47 mg, 0.082 mmol, 10 mol %) in 80 ml toluene, following the general procedure 1.

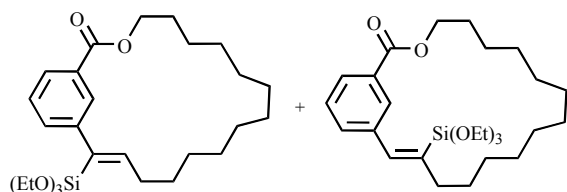
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.98 (m, 2H), 7.53 (dt  $J = 0.5$  Hz,  $J = 7.7$  Hz, 1H), 7.38 (dt  $J = 1.45$  Hz,  $J = 7.7$  Hz, 1H), 4.32 (m, 2H), 2.46 (m, 2H), 1.75 (m, 2H), 1.26-1.66 (m, 18H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.1, 135.2, 132.5, 130.7, 128.9, 128.4, 124.4, 91.3, 80.4, 65.7, 29.3, 29.2, 28.4, 28.2, 28.1, 27.9, 27.8, 27.6, 26.9, 19.0.

IR (KBr)  $\nu = 2927, 2855, 2228, 1722, 1600, 1580, 1460, 909, 816, 754, 725, 684$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 313 (23), 312 [ $\text{M}^+$ ] (100), 214 (9), 213 (5), 188 (4), 187 (38), 186 (18), 184 (17), 171 (13), 162 (14), 161 (7), 159 (11), 154 (6), 153 (8), 150 (7), 144 (25), 142 (41), 141 (36), 135 (21), 129 (66), 119 (6), 117 (28), 116 (21), 115 (53), 114 (46), 113 (10), 95 (41), 93 (14), 91 (21), 88 (10), 80 (22), 79 (17), 78 (5), 67 (42), 55 (80), 43 (27), 41 (72).

HRMS ( $\text{C}_{21}\text{H}_{28}\text{O}_2$ ): calculated: 312.208930u, found: 312.208644u.

**17-(Triethoxysilyl)-3-oxa-bicyclo[16.3.1]docosa-1(22),16,18,20-tetraen-2-one (66) and 16-(triethoxysilyl)-3-oxa-bicyclo[16.3.1]docosa-1(22),16,18,20-tetraen-2-one (66b).**

17-(Triethoxysilyl)-3-oxa-bicyclo[16.3.1]docosa-1(22),16,18,20-tetraen-2-one **66** and 16-(triethoxy silyl)-3-oxa-bicyclo[16.3.1]docosa-1(22),16,18,20-tetraen-2-one **66b** (112 mg, 0.24 mmol, 80% yield) were obtained as a colourless oil from cyclalkyne **65** (92 mg, 0.3 mmol) in the presence of

triethoxysilane (63 mg, 0.38 mmol, 1.2 eq) and catalyst **15** (23 mg, 0.047 mmol, 15 mol %) in 1.5 ml dichloromethane, following the procedure 2A.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): main product (**66**): 7.96 (dt,  $J = 7.7$  Hz,  $J = 1.5$  Hz, 1H), 7.85 (t,  $J = 1.5$  Hz, 1H), 7.50 (dt,  $J = 7.7$  Hz,  $J = 1.5$  Hz, 1H), 7.38 (t,  $J = 7.7$  Hz, 1H), 6.44 (t,  $J = 7.5$  Hz, 1H), 4.37 (m, 2H), 3.83 (q,  $J = 7$  Hz, 6H), 2.58 (m, 2H), 1.81 (m, 2H), 1.57 (m, 4H), 1.34-1.49 (m, 14H), 1.21 (t,  $J = 7$  Hz, 9H).

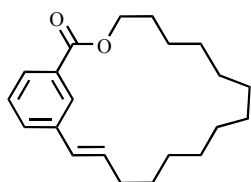
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): main Product (**66**): 166.9, 153.2, 145.3, 134.5, 132.6, 130.5, 128.1, 127.5, 127.4, 65.2, 58.5, 31.2, 28.9, 28.4, 28.3, 28.4, 28.4, 27.9, 27.9, 27.7, 27.6, 26.7, 18.1.

IR (KBr)  $\nu = 2973, 2926, 2856, 1721, 1597, 1582, 1481, 1460, 1442, 1104, 1081, 781, 755, 726, 697, 681$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 476 [ $\text{M}^+$ ] (72), 432 (1), 431 (38), 430 (100), 412 (3), 401 (5), 385 (11), 384 (29), 359 (3), 291 (23), 265 (31), 255 (23), 163 (38), 135 (18), 119 (33), 107 (14), 79 (20), 55 (12).

HRMS ( $\text{C}_{27}\text{H}_{44}\text{O}_5\text{Si}_1$ ): calculated: 476.295804 u, found: 476.296057 u.

### 3-Oxabicyclo[16.3.1]docosa-1(22),16,18,20-tetraen-2-one (**67**).



3-Oxabicyclo[16.3.1]docosa-1(22),16,18,20-tetraen-2-one **67** (63 mg, 0.2 mmol, 74% yield) was obtained as a colourless oil from vinylsilanes **66** and **66b** (130 mg, 0.27 mmol) in the presence of AgF (50 mg, 0.39 mmol, 1.5 eq) in THF (2 ml), MeOH (0.5 ml) and water (0.25  $\mu\text{l}$ ), following the general procedure 3A. *E/Z* Ratio: 94/6 (GC).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.04 (m, 1H), 7.90 (dt,  $J = 7.35$  Hz,  $J = 1.6$  Hz, 1H), 7.37 (m, 2H), 6.41 (d,  $J = 15.8$  Hz, 1H), 6.26 (dt,  $J = 15.8$  Hz,  $J = 7.0$  Hz), 4.31 (t,  $J = 5.3$  Hz, 2H), 2.28 (m, 2H), 1.75 (m, 2H), 1.16-1.66 (m, 18H).

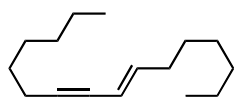
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.6, 138.3, 132.2, 131.0, 130.8, 129.6, 128.6, 128.1, 125.8, 65.6, 31.6, 29.5, 28.9, 28.8, 28.5, 28.3, 28.2, 28.1, 27.6, 27.1, 26.9.

IR (KBr)  $\nu$  = 3063, 2926, 2854, 1721, 1653, 1600, 1584, 1483, 1460, 965, 816, 748, 686  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 314 [ $\text{M}^+$ ] (52), 296 (1), 233 (2), 201 (6), 188 (13), 174 (10), 162 (13), 148 (100), 129 (42), 115 (84), 109 (18), 95 (30), 82 (41), 67 (34), 55 (75), 41 (64).

HRMS ( $\text{C}_{21}\text{H}_{30}\text{O}_2$ ): calculated: 314.224580 u, found: 314.224826 u.

**(7E)-hexadec-7-en-9-yne (71).**



9.07 ml of a 1M solution of DiBAI-H in hexane were added to a solution of commercially available oct-1-yne **95** (1 g, 9.07 mmol, 1eq) in 10 ml hexane at  $-78^\circ\text{C}$ . The resulting mixture was allowed to warm to room temperature and was then heated to  $50^\circ\text{C}$ . After 5h at that temperature, the solution was cooled to  $-78^\circ\text{C}$  before NBS (1.78 g, 9.98 mmol, 1.1 eq) was added. After 30 min at room temperature, the reaction was washed with an aq.  $\text{Na}_2\text{S}_2\text{O}_5$  solution, the aqueous phase was extracted with pentane, the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to afford crude vinyl bromide **96** (colourless oil) that was directly used for the next step.

$\text{PdCl}_2(\text{PPh}_3)_2$  (318 mg, 0.45 mmol, 5 mol %), CuI (87 mg, 0.45 mmol, 5 mol %) and oct-1-yne (1 g, 9.07 mmol, 1 eq) were added to a solution of vinyl bromide **96** in 10 ml triethylamine. The reaction was stirred for 3h, then the solvent was evaporated and the residue was purified by flash chromatography (using pentane as the eluent) to afford the desired enyne **71** (281 mg, 1.27 mmol, 34% overall yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 5.93 (dt,  $J = 15.8$  Hz,  $J = 7.0$  Hz, 1H), 5.35 (dm,  $J = 15.8$  Hz, 1H), 2.17 (dt,  $J = 7.0$  Hz,  $J = 2.0$  Hz, 2H), 1.98 (m, 2H), 1.42 (m, 2H), 1.10-1.41 (m, 14H), 0.81 (m, 6H).

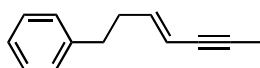
$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 143.7, 110.2, 89.0, 79.5, 33.3, 32.1, 31.8, 29.33, 29.29, 29.2, 29.0, 23.02, 22.98, 19.6, 14.2.

IR (KBr)  $\nu$  = 3020, 2957, 2928, 2857, 2871, 2218, 1466, 1378, 953  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 220 [ $M^+$ ] (35), 191 (7), 178 (5), 163 (3), 149 (14), 135 (31), 121 (33), 107 (64), 93 (92), 79 (100), 67 (88), 55 (46), 41 (66), 29 (43).

HRMS ( $C_{16}H_{28}$ ): calculated: 220.219100u, found: 220.219314u.

**(4E)-7-Phenyl-hept-4-en-2-yne (72).**



(4E)-7-Phenyl-hept-4-en-2-yne **72** (387 mg, 2.27 mmol, 75% yield) was obtained as a colourless oil from vinyl iodide **87** (780 mg, 3.02 mmol, 1 eq) in the presence of 9-methoxy-9-BBN (613  $\mu$ l, 3.63 mmol, 1.2 eq), 1-propynylsodium (225 mg, 3.63 mmol, 1.2 eq) and  $Pd(PPh_3)_4$  (175 mg, 0.15 mmol, 5 mol %) in 10 ml THF, following the general procedure 5.

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.11-7.30 (m, 5H), 6.06 (dt,  $J = 15.8$  Hz,  $J = 7.2$  Hz, 1H), 5.45 (dm,  $J = 15.8$  Hz, 1H), 2.68 (m, 2H), 2.39 (m, 2H), 1.90 (m, 3H).

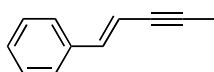
$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  (ppm): 142.0, 141.3, 128.4, 128.3, 125.9, 110.5, 84.5, 78.2, 35.2, 34.7, 4.2.

IR (KBr)  $\nu = 3085, 3062, 3026, 2915, 2852, 2223, 1603, 1496, 1453, 955, 747, 699$   $cm^{-1}$ .

MS:  $m/z$  (relative intensity) 170 [ $M^+$ ] (1), 155 (27), 142 (6), 129 (6), 117 (27), 91 (100), 77 (20), 65 (13), 51 (6), 39 (7).

HRMS ( $C_{13}H_{14}$ ): calculated: 170.109550u, found: 170.109334u.

**(1E)-1-Phenyl-pent-1-en-3-yne (73).**



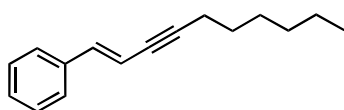
(1E)-1-Phenyl-pent-1-en-3-yne **73** (679 mg, 4.78 mmol, 88% yield) was obtained as a colourless oil from vinyl bromide **98** (1 g, 5.5 mmol, 1 eq), in the presence of  $PdCl_2(PPh_3)_2$  (191 mg, 0.27 mmol, 5 mol %), CuI (52 mg, 0.27 mmol, 5 mol %) and propyne (excess) in 10 ml triethylamine,

following the general procedure 7. The analytical and spectroscopic data matched those reported in the literature.<sup>[171]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.18-7.38 (m, 5H), 6.85 (d, *J* = 16.2 Hz, 1H), 6.11 (dq, *J* = 16.2 Hz, *J* = 2.40 Hz, 1H), 2.00 (d, *J* = 2.40 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 140.0, 136.5, 128.6, 128.2, 126.0, 108.8, 88.3, 78.9, 4.5.

#### (1*E*)-1-Phenyldec-1-en-3-yne (74).



(1*E*)-1-Phenyldec-1-en-3-yne **74** (558 mg, 2.63 mmol) was obtained as a colourless oil from (2*E*)-2-bromo-1-phenylethene **98** (670 mg, 3.66 mmol, 1 eq) and hex-1-yne (604 mg, 5.49 mmol, 1.5 eq) in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (129 mg, 0.19 mmol, 5 mol %), and CuI (35 mg, 0.19 mmol, 5 mol %) in 5 ml triethylamine, following the general procedure 6 (68% yield). The analytical and spectroscopic data matched those reported in the literature.<sup>[172]</sup>

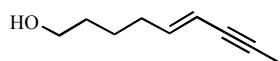
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.30 (m, 5H), 6.85 (d, *J* = 16.2 Hz, 1H), 6.14 (dt, *J* = 16.2 Hz, *J* = 2.27 Hz, 1H), 2.35 (dt, *J* = 7.05 Hz, *J* = 2.3 Hz, 2H), 1.56 (m, 2H), 1.36 (m, 6H), 0.89 (m, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 139.9, 136.6, 128.6, 128.2, 108.9, 93.1, 79.7, 31.4, 28.8, 28.6, 22.5, 19.7, 14.0.

IR (KBr)  $\nu$  = 3081, 3060, 3028, 2955, 2930, 2857, 2211, 1615, 1596, 1576, 1466, 952, 747, 691 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 212 [M<sup>+</sup>] (47), 183 (13), 165 (2), 154 (9), 153 (10), 152 (6), 143 (50), 142 (42), 141 (100), 139 (11), 130 (7), 128 (39), 126 (1), 121 (2), 117 (5), 115 (46), 102 (3), 95 (2), 91 (29), 89 (3), 80 (2), 79 (10), 78 (2), 76 (2), 67 (3), 63 (4), 55 (8), 51 (3), 43 (5), 41 (8), 39 (4), 29 (5).

#### Non-5-en-7-yn-1-ol (75).



TBAF (3.93 ml, 3.93 mmol, 1.5 eq) was slowly added to a solution of *tert*-butyldimethyl(non-5-en-7-ynyloxy)silane **85** (660 mg, 2.62 mmol) in 10ml THF. The reaction was stirred at room temperature for 2h and was then quenched with a saturated aq. NaHCO<sub>3</sub> solution. The aqueous layer was extracted several times with MTBE. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. Flash chromatography of the residue (using pentanes/diethylether 4/1 as the eluent) afforded the expected product **75** (351 mg, 2.62 mmol, colourless oil) in quantitative yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 6.00 (dt, *J* = 15.80 Hz, *J* = 7.05 Hz, 1H), 5.41 (dm, *J* = 15.80 Hz, 1H), 3.60 (t, *J* = 6.20 Hz, 2H), 2.08 (m, 2H), 1.89 (d, *J* = 2.15 Hz, 3H), 1.56 (m, 4H), 1.45 (m, 2H).

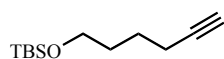
<sup>13</sup>C NMR (100 MHz) δ (ppm): 142.8, 110.2, 84.2, 78.3, 62.7, 32.6, 32.1, 25.0, 4.1.

IR (KBr)  $\nu$  = 3333, 3019, 2934, 2917, 2860, 2224, 1632, 1455, 1437, 1060, 957 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 138 [M<sup>+</sup>] (26), 123 (17), 120 (2), 115 (1), 110 (10), 109 (20), 107 (14), 104 (2), 103 (8), 97 (3), 94 (15), 92 (42), 91 (100), 84 (11), 83 (5), 79 (78), 77 (79), 75 (1), 74 (1), 68 (23), 67 (25), 66 (33), 62 (2), 57 (10), 55 (11), 51 (20), 50 (6), 41 (17), 40 (7), 39 (26), 31 (21), 29 (9), 27 (16).

HRMS (C<sub>9</sub>H<sub>14</sub>O<sub>1</sub>): calculated: 138.104465u, found: 138.104319u.

#### Hex-5-ynyl-1-oxy-*tert*-butyldimethylsilane (**81**).



Commercially available hex-5-yn-1-ol **78** (5g, 5 mmol, 1 eq) was added to a solution of imidazole (8.7 g, 11.8 mmol, 2.5 eq) and *tert*-butyldimethylsilylchloride (9.24 g, 5.9 mmol, 1.2 eq) in 50 ml DMF. Conversion was complete after 1h and the reaction was quenched with addition of 50 ml of a saturated solution of NH<sub>4</sub>Cl. The aqueous layer was extracted with MTBE, the combined organic phases were washed with water (7×10 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. Purification by flash chromatography (using pentanes/ether: 98/2 as the eluent) afforded the desired product **81** as a colourless oil (quantitative yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 3.62 (t, *J* = 6.0 Hz, 2H), 2.20 (dt, *J* = 6.8 Hz, *J* = 2.6 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.60 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H).



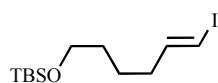
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 84.6, 68.2, 62.6, 31.8, 25.9, 25.0, 18.3, 18.2, -5.3.

IR (KBr)  $\nu$  = 3314, 2954, 2930, 2896, 2858, 2119, 1472, 1463, 1388, 1255, 1108, 836, 776, 631  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 211 [ $\text{M}^+$ ] (0.01), 155, (3), 79 (4), 75 (100), 59 (4), 41 (2).

HRMS ( $\text{C}_{12}\text{H}_{24}\text{O}_1\text{Si}_1+\text{H}$ ): calculated: 213.167569u, found: 213.167392u.

#### ***tert*-Butyl(6-iodo-hex-5-enyloxy)dimethylsilane (82).**



*tert*-Butyl(6-iodo-hex-5-enyloxy)dimethylsilane **82** (938 mg, 2.76 mmol, 70% yield) was obtained as a colourless oil from alkyne **81** (835 mg, 3.93 mmol) in the presence of  $\text{Cp}_2\text{Zr}(\text{Cl})\text{H}$  (1.2 g, 3.93 mmol) in 15 ml THF, following the general procedure 4.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.50 (dt,  $J$  = 14.4 Hz,  $J$  = 7.2 Hz, 1H), 5.98 (dt,  $J$  = 14.4 Hz,  $J$  = 1.45 Hz), 3.60 (t,  $J$  = 3.5 Hz, 2H), 2.07 (m, 2H), 1.48 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H).

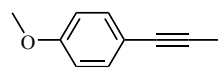
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 146.5, 74.5, 62.8, 35.8, 33.5, 32.0, 25.9, 24.7, 18.3, -5.3.

IR (KBr)  $\nu$  = 3049, 2952, 2929, 2894, 2857, 1606, 1471, 1462, 1360, 1255, 1106, 1006, 941, 836, 775  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 340 [ $\text{M}^+$ ] (0.43), 285 (3), 283 (64), 241 (1), 215 (5), 187 (2), 185 (80), 167 (4), 155 (15), 127 (2), 125 (1), 115 (2), 101 (3), 99 (2), 85 (2), 81 (100), 80 (2), 79 (10), 78 (4), 77 (3), 75 (62), 73 (17), 64 (2), 58 (4), 57 (3), 55 (5), 54 (1), 53 (5), 47 (4), 45 (7), 41 (8), 39 (6), 29 (4).

HRMS ( $\text{C}_{12}\text{H}_{25}\text{I}_1\text{O}_1\text{Si}_1$ ): calculated: 341.079766u, found: 341.079982u.

#### **1-Methoxy-4-prop-1-ynyl-benzene (84).**

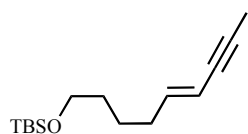


1-Methoxy-4-prop-1-ynyl-benzene **84** was obtained as a colourless oil from commercially available 1-methoxy-3-iodo-benzene **83** (5 g, 21.4 mmol, 1 eq) in the presence of propyne (excess), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (750 mg, 1.07 mmol, 5 mol %) and CuI (400 mg, 2.15 mmol, 10 mol %) in 30 ml Et<sub>3</sub>N, following the general procedure 7 (97 % yield). The analytical and spectroscopic data matched those reported in the literature.<sup>[3]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.32 (m, 2H), 6.81 (m, 2H), 3.80 (s, 3H), 2.04 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) : 159.0, 132.8, 116.2, 113.8, 84.1, 79.4, 55.2, 4.2.

***tert*-Butyldimethyl-(non-5-en-7-ynyloxy)silane (85).**



*tert*-Butyldimethyl-(non-5-en-7-ynyloxy)silane **85** (667 mg, 2.65 mmol, 67% yield) was obtained as a colourless oil from *tert*-butyl (6-iodo-hex-5-enyloxy)dimethylsilane **82** (1.348 g, 3.96 mmol) in the presence of 9-methoxy-9-BBN (1.205 g, 1.34 ml, 7.92 mmol), 1-propynylsodium (412 mg, 7.92 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (415 mg, 0.36 mmol, 9 mol %), following the general procedure 5.

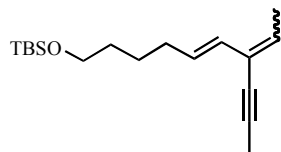
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 6.04 (dt, *J* = 15.8 Hz, *J* = 7.0 Hz, 1H), 5.44 (dm, *J* = 15.8 Hz), 3.59 (t, *J* = 6.3 Hz, 2H), 2.09 (m, 2H), 1.92 (d, *J* = 2.1 Hz), 1.47 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 143.2, 84.1, 78.4, 62.9, 32.7, 32.2, 25.9, 25.1, 18.3, 4.1, -5.3.

IR (KBr)  $\nu$  = 3020, 2953, 2929, 2896, 2857, 2224, 1472, 1463, 1255, 1101, 1006, 956, 836, 776 cm<sup>-1</sup>.

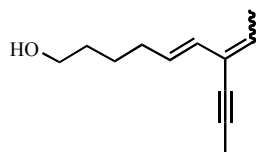
MS: *m/z* (relative intensity) 252 [M<sup>+</sup>] (0.08), 195 (33), 155 (3), 153 (4), 151 (4), 149 (5), 141 (4), 123 (2), 121 (1), 119 (18), 117 (2), 101 (7), 99 (5), 97 (14), 93 (7), 92 (4), 91 (24), 81 (3), 79 (9), 77 (14), 76 (8), 75 (100), 74 (2), 73 (15), 58 (3), 57 (2), 53 (3), 51 (1), 47(4), 45 (5), 41 (7), 39 (3), 29 (4).

HRMS (C<sub>15</sub>H<sub>28</sub>O<sub>1</sub>Si<sub>1</sub>): calculated: 253.198769u, found: 253.198953u.

***tert*-Butyl-(7-ethylidene-dec-5-en-8-ynyloxy)-dimethyl-silane (86).**

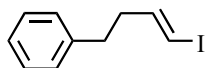
*tert*-Butyl-(7-ethylidene-dec-5-en-8-ynyloxy)-dimethyl-silane **86** was obtained as a by-product during propynylation of vinyl iodide **82**, following the general procedure 6. Characteristic data:

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.73 (d,  $J = 15.7$  Hz, 1H), 5.82 (dt,  $J = 15.8$  Hz,  $J = 7.0$  Hz, 1H), 5.26 (broad s, 1H), 3.62 (t,  $J = 6.3$  Hz, 2H), 2.20 (m, 2H), 2.02 (d,  $J = 2.3$  Hz, 3H), 1.84 (broad s, 3H), 1.37-1.60 (m), 0.9 (s, 9H), 0.05 (s, 6H).

**7-Ethylidene-dec-5-en-8-yn-1-ol (86a).**

7-Ethylidene-dec-5-en-8-yn-1-ol **86a** was obtained as a by-product during the silyl-deprotection of compound **86**. Characteristic data:

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.70 (d,  $J = 15.7$  Hz, 1H), 5.80 (dt,  $J = 15.8$  Hz,  $J = 7.0$  Hz, 1H), 5.26 (broad s, 1H), 3.64 (m), 2.21 (m, 2H), 2.01 (s, 3H), 1.83 (m, 3H), 1.35-1.6 (m).

**(1*E*)-4-Phenyl-1-iodobut-3-ene (87).**

(1*E*)-4-Phenyl-1-iodobut-3-ene **87** (780 mg, 3.02 mmol, 82% yield) was obtained as a colourless oil from commercially available alkyne **94** (477 mg, 3.67 mmol, 1 eq) in the presence of the  $\text{Cp}_2\text{Zr}(\text{Cl})\text{H}$  (980 mg, 3.80 mmol, 1.03 eq) in 10 ml THF, following the general procedure 4.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.14-7.33 (m, 5H), 6.56 (dt,  $J = 14.4$  Hz,  $J = 7.1$  Hz, 1H), 6.04 (dt,  $J = 14.4$  Hz,  $J = 1.4$  Hz, 1H), 2.72 (m, 2H), 2.38 (m, 2H).

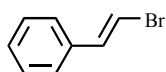
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 145.5, 140.8, 128.42, 128.36, 126.1, 75.3, 37.7, 34.7.

IR (KBr)  $\nu = 3061, 3025, 2924, 2854, 1604, 1496, 1453, 1205, 940, 753, 698$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 258 [ $\text{M}^+$ ] (4), 167 (1), 131 (48), 115 (1), 91 (100), 77 (2), 65 (7), 51 (4), 39 (6).

HRMS ( $\text{C}_{10}\text{H}_{11}\text{I}_1$ ): calculated: 257.990547u, found: 257.990715u.

### (1E)-1-Bromostyrene (98).

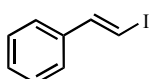


*N*-Bromosuccinimide (910 mg, 5.1 mmol, 1.3 eq) was added to a solution of commercially available boronic acid **97** (580 mg, 3.92 mmol, 1 eq) in 10 ml acetonitrile. After 2h at room temperature the reaction was quenched by addition of a  $\text{Na}_2\text{SO}_3$  solution. The aqueous phase was extracted with pentane, the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Purification of the residue by flash chromatography afforded the desired vinyl bromide **98** (671 mg, 3.67 mmol, 93 % yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 7.31 (m, 5H), 7.11 (d,  $J = 14.9$  Hz, 1H), 6.77 (d,  $J = 14.9$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 137.5, 136.3, 129.1, 128.7, 126.5, 106.8.

### (1E)-1-Iodostyrene (99).



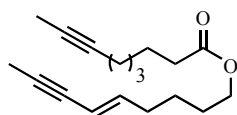
*N*-Iodosuccinimide (NIS, 540 mg, 2.59 mmol, 1.2 eq) was added to a solution of commercially available boronic acid **97** (320 mg, 2.16 mmol, 1 eq) in 10 ml acetonitrile. The colour of the mixture turned rapidly to orange then dark brown. After 2h at room temperature the reaction was quenched by

addition of an aq. Na<sub>2</sub>SO<sub>3</sub> solution. The aqueous phase was extracted with pentane, the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. Purification of the residue by flash chromatography afforded the desired vinyl iodide **99** as a colourless oil (457 mg, 1.98 mmol, 92 % yield).

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 7.44 (d, *J* = 14.9 Hz, 1H), 7.30 (m, 5H), 6.86 (d, *J* = 14.9 Hz, 1H).

<sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 145.4, 138.1, 129.1, 128.8, 127.4, 76.9.

#### Non-5-en-7-ynyl non-7-ynoate (**101**).



Non-5-en-7-ynyl non-7-ynoate **101** (264 mg, 0.97 mmol, 80 % yield) was obtained as a colourless oil from non-7-ynoic acid **100** (210 mg, 1.36 mmol, 1.1 eq) and non-5-en-7-yn-1-ol **75** (167 mg, 1.21 mmol, 1 eq) in the presence of EDC (697 mg, 3.63 mmol, 3 eq) and DMAP (458 mg, 3.75 mmol, 3 eq) in 25 ml dichloromethane, following the general procedure 8.

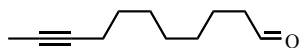
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 6.01 (dt, *J* = 15.9 Hz, *J* = 7.0 Hz, 1H), 5.47 (dm, *J* = 15.9 Hz, 1H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 6.6 Hz, 2H), 2.14 (m, 4H), 1.94 (dd, *J* = 2.25 Hz, 0.3 Hz, 3H), 1.79 (t, *J* = 2.55 Hz, 3H), 1.64 (m, 4H), 1.46 (m, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) : 173.7, 142.4, 110.4, 84.4, 79.0, 78.2, 75.5, 64.0, 34.2, 32.4, 28.7, 28.4, 28.0, 25.2, 24.5, 18.6.

IR (KBr)  $\nu$  = 3018, 2937, 2860, 2222, 1734, 1457, 1263, 1173, 959 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 274 [M<sup>+</sup>] (6), 259 (5), 245 (3), 231 (4), 215 (4), 203 (4), 187 (12), 173 (18), 159 (28), 145 (21), 120 (29), 105 (84), 95 (66), 91 (100), 85 (15), 79 (65), 67 (51), 55 (46), 41 (41).

HRMS (C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>): calculated: 274.193280u, found: 274.193191u.

**Undec-9-yn-1-al (102a).**

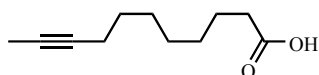
Undec-9-yn-1-al **102a** and undec-9-ynoic acid **102** (136 mg, 0.75 mmol) were obtained as white solids from undec-9-yn-1-ol (200 mg, 1.19 mmol) following the general procedure 9 (63% overall yield). The first oxidation was carried out with PDC (672 mg, 1.79 mmol, 1.5 eq) in 5ml dichloromethane and the second oxidation with H<sub>2</sub>NSO<sub>3</sub>H (138 mg, 1.4 mmol, 1.2 eq) and NaO<sub>2</sub>Cl (161 mg, 1.4 mmol, 1.2 eq) in 5 ml THF and 5 ml water.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 9.69 (t, *J* = 4.5 Hz, 1H), 2.35 (dt, *J* = 1.8 Hz, *J* = 7.4 Hz, 2H), 2.04 (m, 2H), 1.70 (t, *J* = 2.5 Hz, 3H), 1.51-1.61 (m, 2H), 1.34-1.44 (m, 2H), 1.19-1.34 (m, 6H).

<sup>13</sup>C NMR (100 MHz) δ (ppm): 202.8, 79.2, 75.4, 43.8, 29.0, 28.9, 28.8, 28.6, 22.0, 18.6, 3.4.

IR (KBr) ν = 2932, 2857, 1725, 726 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 166 [M<sup>+</sup>] (0.02), 133 (2.), 123 (3), 107 (7), 95 (21), 79 (27), 68 (100), 55 (39), 41 (56), 27 (24).

**Undec-9-ynoic acid (102).**

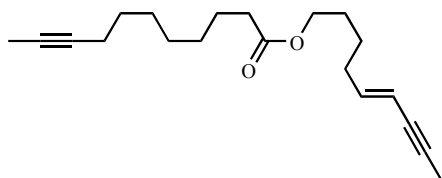
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 2.29 (t, *J* = 7.4 Hz, 2H), 2.05 (m, 2H), 1.71 (t, *J* = 2.4 Hz, 3H), 1.58 (m, 2H), 1.18-1.47 (m, 9H).

<sup>13</sup>C NMR (75 MHz) δ (ppm): 179.9, 79.2, 75.4, 34.0, 28.9, 28.9, 28.7, 28.6, 24.6, 18.7, 3.4.

IR (KBr) ν = 3036, 2930, 2855, 1690, 918 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 182 [M<sup>+</sup>] (0.3), 164 (1), 135 (3), 122 (7), 95 (24), 81 (28), 68 (100), 55 (32), 41 (30).

**Non-5-en-7-ynyl undec-9-ynoate (103).**



Non-5-en-7-ynyl undec-9-ynoate **103** (328 mg, 1.09 mmol, 75% yield) was obtained as a colourless oil from carboxylic acid **102** (264 mg, 1.45 mmol, 1 eq) and non-5-en-7-yn-1-ol **75** (200 mg, 1.45 mmol, 1 eq) in the presence of EDC (417 mg, 2.17 mmol, 1.5 eq), and DMAP (265 mg, 2.17 mmol, 1.5 eq) in 10 ml dichloromethane, following the general procedure 8.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.95 (dt,  $J = 15.90$  Hz, 1H), 5.37 (dm,  $J = 15.90$  Hz, 1H), 3.98 (t,  $J = 6.60$  Hz, 2H), 2.22 (t,  $J = 7.50$  Hz, 2H), 2.04 (m, 4H), 1.85 (dd,  $J = 2.25$  Hz,  $J = 0.4$  Hz, 3H), 1.71 (t,  $J = 2.55$  Hz, 3H), 1.55 (m, 4H), 1.39 (m, 4H), 1.20-1.35 (m, 6H).

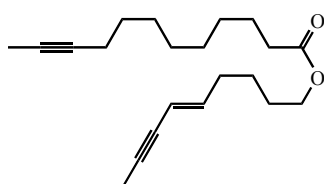
$^{13}\text{C}$  NMR (100 MHz)  $\delta$  (ppm): 173.9, 142.4, 110.4, 84.3, 79.3, 78.2, 76.7, 64.0, 34.3, 32.4, 29.01, 28.96, 28.8, 28.6, 28.0, 25.2, 24.9, 18.7, 4.1, 3.4.

IR (KBr)  $\nu = 3020, 2932, 2857, 2224, 1735, 1633, 1172, 958$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 302 [ $\text{M}^+$ ] (3), 287 (5), 245 (2), 201, (4), 173 (21), 159 (36), 120 (32), 105 (93), 91 (100), 79 (52), 67 (36), 55 (33), 29 (7).

HRMS ( $\text{C}_{20}\text{H}_{30}\text{O}_2$ ): calculated: 302.224580u, found: 302.224911u.

#### Non-5-en-7-ynyl dodec-10-ynoate (**104**).



Non-5-en-7-ynyl dodec-10-ynoate **104** (231 mg, 0.73 mmol, 84% yield) was obtained as a colourless oil from dodec-10-ynoic acid **38** (170 mg, 0.87 mmol, 1 eq) and non-5-en-7-yn-1-ol **75** (120 mg, 0.87 mmol, 1 eq) in the presence of EDC (250 mg, 1.3 mmol, 1.5 eq) and DMAP (159 mg, 1.3 mmol, 1.5 eq) in 5 ml dichloromethane, following the general procedure 8.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.01 (dt,  $J = 15.8$  Hz,  $J = 7.0$  Hz, H), 5.43 (dm,  $J = 15.8$  Hz, 1H), 4.04 (t,  $J = 6.5$  Hz, 2H), 2.27 (t,  $J = 7.5$  Hz, 2H), 2.10 (m, 4H), 1.91 (d, 3H), 1.77 (t,  $J = 2.55$  Hz, 3H), 1.56 (m, 6H), 1.16-1.51 (m, 10H).

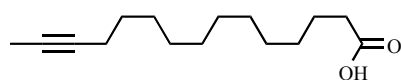
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  (ppm): 173.9, 142.4, 110.4, 84.3, 79.3, 78.2, 75.3, 64.0, 34.3, 32.4, 29.12, 29.08, 29.01, 28.96, 28.8, 28.0, 25.2, 24.9, 18.7, 4.1, 3.4.

IR (KBr)  $\nu = 2930, 2856, 2221, 1734, 1634, 1240, 1176, 959$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 316 [ $\text{M}^+$ ] (5), 301 (6), 247 (1), 229 (2), 203 (3), 191 (3), 185 (4), 174 (8), 165 (8), 161 (11), 159 (43), 158 (3), 157 (6), 146 (10), 144 (2), 143 (4), 137 (5), 120 (38), 108 (7), 105 (65); 104 (2), 101 (2), 95 (33), 92 (13), 91 (100), 85 (23), 84 (2), 79 (55), 68 (11), 67 (41), 66 (7), 55 (42), 43 (14), 41 (29).

HRMS ( $\text{C}_{21}\text{H}_{32}\text{O}_2$ ): theory: 316.240230u, found: 316.239851u.

#### Pentadec-13-ynoic acid (**105**).



Pentadec-13-ynoic acid **105** (968 mg, 4.07 mmol, 76% yield) was obtained as a white solid from pentadec-13-yn-1-ol **45** (1.273, 5.68 mmol), following the general procedure 9. The first oxidation was carried out with PDC (3.2 g, 8.51 mmol, 1.5 eq) in 25 ml dichloromethane and the second oxidation with  $\text{H}_2\text{NSO}_3\text{H}$  (580 mg, 5.98 mmol, 1.2 eq) and  $\text{NaO}_2\text{Cl}$  (672 mg, 5.98 mmol, 1.2 eq) in 20 ml THF and 20 ml water.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2.34 (t,  $J = 7.50$  Hz, 2H), 2.10 (m, 2H), 1.77 (t,  $J = 2.5$  Hz, 3H), 1.62 (m, 2H), 1.45 (m, 2H), 1.21-1.39 (m, 15H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 178.4, 79.4, 75.3, 33.7, 29.5, 29.5, 29.39, 3.2, 29.1, 29.1, 29.0, 28.9, 24.7, 28.7, 3.5.

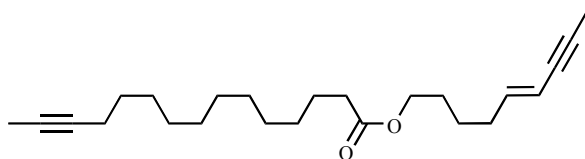
IR (KBr)  $\nu = 3042, 2918, 2846, 2886, 1690, 919, 724$   $\text{cm}^{-1}$ .



MS:  $m/z$  (relative intensity) 238 [ $M^+$ ] (0.9), 209 (1), 196 (2), 149 (2), 147 (1), 140 (3), 126 (3), 98 (8), 96 (18), 95 (65), 94 (5), 91 (3), 85 (2), 79 (13), 77 (4), 73 (5), 68 (100), 67 (49), 66 (4), 60 (6), 55 (42), 45 (5), 43 (13), 41 (33), 39 (8), 29 (7).

HRMS ( $C_{15}H_{26}O_2$ ): calculated: 238.193280u, found: 238.193374u.

#### Non-5-en-7-ynyl hexadec-14-ynoate (**106**).



Non-5-en-7-ynyl hexadec-14-ynoate (243 mg, 0.68 mmol, 88% yield) **106** was obtained as a white solid from pentadec-13-ynoic acid **105** (202 mg, 0.85 mmol) and non-5-en-7-yn-1-ol **75** (106 mg, 0.77 mmol) in the presence of EDC (442 mg, 2.30 mmol) and DMAP (291 mg, 2.38 mmol) in 5 ml dichloromethane, following the general procedure 8.

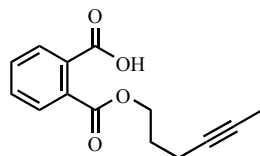
$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm): 6.01 (dt,  $J = 15.8$  Hz,  $J = 7.05$  Hz, 1H), 5.43 (dm,  $J = 15.8$  Hz, 1H), 4.04 (t,  $J = 6.6$  Hz, 2H), 2.27 (t,  $J = 7.55$  Hz, 2H), 2.10 (m, 4H), 1.92 (d,  $J = 2.1$  Hz, 3H), 1.78 (t,  $J = 2.55$  Hz, 3H), 1.61 (m, 4H), 1.45 (m, 4H), 1.21-1.39 (m, 14H).

$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm): 173.9, 142.4, 110.4, 84.3, 79.4, 78.2, 75.3, 63.9, 34.3, 32.4, 29.5, 29.5, 29.4, 29.2, 29.1, 29.1, 28.9, 28.0, 25.2, 25.0, 18.7, 4.1, 3.4.

IR (KBr)  $\nu = 3020, 2925, 2854, 2224, 1737, 1457, 1438, 1172, 957, 723$   $cm^{-1}$ .

MS:  $m/z$  (relative intensity) 358 [ $M^+$ ] (9), 343 (10), 330 (2), 289 (2), 171 (1), 221 (5), 203 (2), 199 (2), 191 (4), 174 (12), 165 (8), 159 (59), 158 (3), 157 (6), 148 (7), 147 (19), 146 (12), 144 (2), 143 (2), 121 (19), 120 (47), 115 (1), 108 (12), 105 (99), 104 (2), 98 (2), 95 (35), 92 (100), 91 (97), 79 (56), 71 (5), 68 (11), 67 (44), 66 (7), 55 (44), 43 (17), 40 (9).

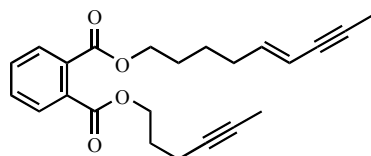
HRMS ( $C_{24}H_{38}O_2$ ): calculated: 358.287180u, found: 358.287357u.

**Phthalic acid mono-hex-4-ynyl ester (107).**

Pyridine (462 mg, 5.84 mmol, 1.2 eq), DMAP (catalytic quantity) and hex-4-yn-1-ol (477 mg, 4.87 mmol, 1 eq) were added to a solution of phthalic anhydride (874 mg, 5.84 mmol, 1.2 eq) in 10 ml dichloromethane. The solution was stirred overnight and quenched with an aq. HCl solution (1N). The aqueous layer was extracted with dichloromethane, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Flash chromatography of the residue (eluent: hexanes/ethyl acetate: 4/1) afforded the desired product **107** as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.91 (m, 1H), 7.71 (m, 1H), 7.57 (m, 2H), 4.42 (t,  $J = 6.34$  Hz, 2H), 2.28 (m, 2H), 1.91 (m, 2H), 1.73 (t,  $J = 7.54$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 171.9, 168.1, 133.1, 132.1, 130.9, 130.1, 129.8, 128.9, 77.7, 76.4, 64.8, 27.8, 15.5, 3.3.

**(Hex-4-ynyl)(non-5-en-7-ynyl) phthalate (108).**

Carboxylic acid **107** (235 mg, 0.96 mmol, 1.1 eq) was added to a solution of alcohol **75** (120 mg, 0.87 mmol, 1 eq), EDC (250 mg, 1.3 mmol, 1.5 eq) and DMAP (250 mg, 2.05 mmol, 2.35 eq) in 10 ml dichloromethane. The solution was stirred overnight and quenched with an aq. HCl solution (1N). The aqueous layer was extracted with dichloromethane, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Flash chromatography of the residue (eluent: hexanes/ethyl acetate: 9/1) afforded the desired product **108** (259 mg, 0.71 mmol, 81 % yield) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.70 (m, 2H), 7.50 (m, 2H), 6.01 (dt,  $J = 15.80$  Hz,  $J = 7.10$  Hz, 1H), 5.44 (dm,  $J = 15.80$  Hz, 1H), 4.38 (t,  $J = 6.37$  Hz, 2H), 4.29 (t,  $J = 6.62$  Hz, 2H), 2.27 (m, 2H), 2.13 (m, 2H), 1.90 (m, 5H), 1.73 (m, 5H), 1.50 (m, 2H).

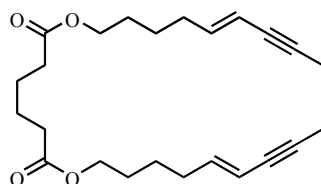
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 167.6, 167.5, 142.3, 132.3, 132.0, 131.0, 130.9, 128.9, 128.8, 110.5, 84.4, 78.2, 77.6, 76.3, 65.4, 64.5, 32.4, 28.0, 27.9, 25.2, 15.5, 4.1, 3.4.

IR (KBr)  $\nu$  = 3070, 3019, 2954, 2919, 2856, 2223, 1726, 1600, 1580, 1447, 1286, 1128, 959, 744  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 366 [ $\text{M}^+$ ] (2), 268 (2), 247 (3), 229 (28), 183 (13), 159 (10), 149 (100), 120 (52), 105 (53), 92 (72), 79 (71), 53 (27), 41 (19), 29 (3).

HRMS ( $\text{C}_{23}\text{H}_{26}\text{O}_4+\text{Na}$ ): calculated: 389.172879u, found: 389.17298u.

### Dinon-5-en-7-ynyl hexanedioate (**109**).



Pyridine (242 mg, 3.06 mmol, 2.4eq), DMAP (catalytic amount) and non-5-en-7-yn-1-ol **75** (351 mg, 2.54 mmol, 2eq) were added to a solution of hexandioyl dichloride (232mg, 1.27 mmol, 1eq) in 15 ml  $\text{CH}_2\text{Cl}_2$ . The resulting solution was stirred overnight and quenched with an aq. HCl solution (1N). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to afford the expected product **109** (377 mg, 0.97 mmol, 77 % yield) as a white solid.

Mp = 37-38°C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.01 (dt,  $J$  = 7.05 Hz,  $J$  = 15.7 Hz, 2H), 5.43 (dm,  $J$  = 15.8 Hz, 2H), 4.05 (t,  $J$  = 6.6 Hz, 4H), 2.31 (m, 4H), 2.10 (m, 4H), 1.91 (dd,  $J$  = 2.25 Hz,  $J$  = 0.37 Hz, 6H), 1.63 (m, 8H), 1.43 (m, 4H).

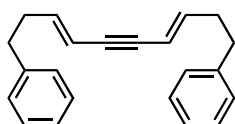
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.3, 142.4, 110.4, 84.4, 78.2, 64.1, 33.9, 32.4, 28.0, 25.2, 24.4, 4.1.

IR (KBr)  $\nu$  = 3025, 3000, 2958, 2929, 2866, 2222, 1734, 1631, 1174, 963  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 386 [ $M^+$ ] (10), 299 (2), 249 (6), 186 (11), 185 (33), 184 (9), 183 (18), 171 (27), 157 (26), 129 (23), 120 (25), 105 (70), 92 (63), 91 (95), 79 (100), 77 (64), 67 (27), 55 (43), 41 (22).

HRMS ( $C_{24}H_{34}O_4$ ): calculated: 386.245710u, found: 386.245439u.

**(3E,7E)-1,10-Diphenyldeca-3,7-dien-5-yne (112).**



(3E,7E)-1,10-Diphenyldeca-3,7-dien-5-yne **112** (55 mg, 0.19 mmol, 68% yield) was obtained as a colourless oil from enyne **72** (98 mg, 0.58 mmol, 1 eq) in the presence of catalyst **1** (18 mg, 0.038 mmol, 7 mol %) in 5 ml toluene (0.1M), following the general procedure 1.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.11-7.46 (m, 5H), 6.12 (dt,  $J = 15.38$  Hz,  $J = 7.07$  Hz, 2H), 5.59 (d,  $J = 15.38$  Hz, 2H), 2.70 (m, 4H), 2.40 (m, 4H).

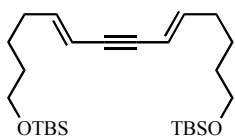
$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm): 143.0, 141.2, 128.4 (integration for 2C), 126.0, 110.4, 87.0, 35.2, 34.9.

IR (KBr)  $\nu = 3086, 3062, 2926, 2858, 1601, 1496, 1453, 957, 749, 698$   $cm^{-1}$ .

MS:  $m/z$  (relative intensity) 286 [ $M^+$ ] (14), 195 (14), 181 (5), 167 (13), 129 (6), 117 (38), 91 (100), 79 (4), 65 (11), 51 (2), 39 (3).

HRMS ( $C_{22}H_{22}$ ): calculated: 286.172150u, found: 286.172392u.

**(5E,9E)-1,14-Bis(tert-butyltrimethylsilyloxy)-tetradeca-5,9-dien-7-yne (114).**



(5*E*,9*E*)-1,14-Bis(*tert*-butyldimethylsilyloxy)-tetradeca-5,9-dien-7-yne **113** (58 mg, 0.13 mmol, 67% yield), was obtained as a colourless oil from enyne **85** (97 mg, 0.38 mmol) in the presence of catalyst **1** (16 mg, 0.033 mmol, 8.8 mol %) in 1.5 ml toluene, following the general procedure 1.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.66 (dt, *J* = 7.15 Hz, *J* = 15.31 Hz, 2H), 5.59 (dm, *J* = 15.31 Hz, 2H), 3.62 (m, 4H), 2.15 (m, 4H), 1.50 (m, 8H), 0.91 (s, 18H), 0.08 (s, 12H).

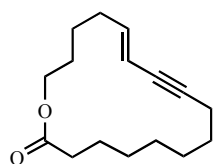
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 144.1, 109.8, 86.9, 62.9, 32.9, 32.2, 26.0, 25.1, 18.3, -5.3.

IR (KBr)  $\nu$  = 3020, 2952, 2929, 2895, 2857, 2188, 1636, 1618, 1101, 953, 836, 775 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 450 [M<sup>+</sup>] (5), 393 (27), 303 (8), 261 (74), 235 (17), 187 (63), 147 (100), 91 (26), 75 (84), 67 (14), 59 (12).

HRMS (C<sub>26</sub>H<sub>50</sub>O<sub>2</sub>Si<sub>2</sub>): calculated: 450.334937u, found: 450.334850u.

#### Oxacycloheptadec-12-en-10-yn-2-one (**115**).



Oxacycloheptadec-12-en-10-yn-2-one **115** (50 mg, 0.20 mmol, 60% yield) was obtained as a colourless oil from diyne **103** (102 mg, 0.34 mmol) in the presence of catalyst **1** (12.5 mg, 0.026 mmol, 8 mol %) in 350 ml toluene, following the general procedure 1.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 5.96 (dt, *J* = 15.80 Hz, *J* = 7.3 Hz, 1H), 5.36 (dm, *J* = 15.80 Hz, 1H), 4.02 (m, 2H), 2.23 (m, 4H), 2.04 (m, 2H), 1.2-1.68 (m, 14H).

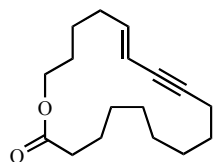
<sup>13</sup>C NMR (100 MHz) δ (ppm): 173.9, 143.6, 110.7, 88.6, 80.8, 63.8, 34.8, 31.5, 28.1, 27.3, 27.2, 26.9, 26.1, 24.9, 24.6, 18.7.

IR (KBr)  $\nu$  = 2932, 2858, 1733, 1457, 1241, 1182, 958 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 248 [M<sup>+</sup>] (9), 189 (4), 177 (2), 161 (3), 147 (8), 133 (15), 120 (100), 105 (70), 91 (74), 79 (42), 67 (19), 55 (19), 41 (22), 29 (6).

HRMS (C<sub>16</sub>H<sub>24</sub>O<sub>2</sub>): calculated: 248.17763u, found: 248.177453u.

**Oxacyclooctadec-13-en-11-yn-2-one (117).**



Oxacyclooctadec-13-en-11-yn-2-one **117** (33 mg, 0.13 mmol, 75% yield) was obtained as a colourless oil from diyne **104** (53 mg, 0.17 mmol) in the presence of catalyst **1** (8 mg, 0.017 mmol, 10 mol %) in 170 ml toluene, following the general procedure 1.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 5.91 (dd, *J* = 15.8 Hz, *J* = 7.3 Hz, 1H), 5.43 (dm, *J* = 15.8 Hz, 1H), 4.11 (t, *J* = 5.8 Hz, 2H), 2.30 (m, 4H), 2.12 (m, 2H), 1.16-1.76 (m, 16H).

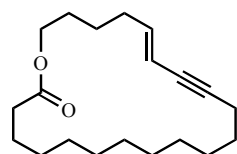
<sup>13</sup>C NMR (100 MHz) δ (ppm) (only 16 Carbon visible): 173.7, 142.6, 111.0, 88.8, 80.3, 63.7, 34.7, 31.5, 29.1, 28.3, 28.2, 27.7, 27.4, 25.3, 24.7, 18.9.

IR (KBr) ν = 3018, 2930, 2856, 2216, 1735, 1459, 1178, 957 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 262 [M<sup>+</sup>] (13), 234 (1), 203 (2), 178 (2), 161 (5), 147 (8), 133 (16), 120 (100), 105 (55), 91 (60), 79 (39), 67 (24), 55 (33), 43 (12), 29 (14).

HRMS (C<sub>17</sub>H<sub>28</sub>O<sub>2</sub>+Na): calculated: 285.183049u, found: 285.18286u. E/Z Ratio: 97/3 (GC).

**Oxacyclodocos-17-en-15-yn-2-one (118).**



Oxacyclodocos-17-en-15-yn-2-one **118** (75 mg, 0.25 mmol, 84% yield) was obtained as a colourless oil from diyne **106** (105 mg, 0.29 mmol) in the presence of catalyst **1** (10.5 mg, 0.022 mmol, 7.8 mol %) in 300 ml toluene, following the general procedure 1.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.99 (dt,  $J = 15.8$  Hz,  $J = 7.1$  Hz, 1H), 5.44 (dm,  $J = 15.8$  Hz, 1H), 4.10 (t,  $J = 6.0$  Hz, 2H), 2.30 (m, 4H), 2.12 (m, 2H), 1.62 (m, 4H), 1.21-1.54 (m, 18H).

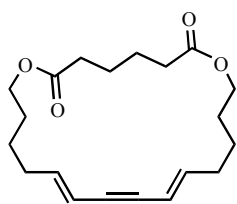
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  (ppm): 173.8, 142.4, 110.5, 89.0, 79.7, 63.7, 34.4, 32.1, 29.7, 29.4, 29.1, 28.8, 28.6, 27.9, 27.8, 27.8, 27.5, 25.4, 25.3, 19.1.

IR (KBr)  $\nu = 3016, 2927, 2855, 2202, 1734, 1672, 1460, 1243, 1170, 957, 724$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 304 [ $\text{M}^+$ ] (12), 276 (2), 261 (0.8), 245 (0.95), 175 (2), 161 (5), 148 (4), 146 (1), 121 (16), 120 (100), 117 (6), 115 (1), 105 (53), 104 (2), 94 (18), 92 (37), 91 (58), 82 (7), 80 (21), 79 (36), 71 (2), 67 (19), 55 (18), 54 (2), 43 (6), 41 (19), 39 (3), 29 (4).

HRMS ( $\text{C}_{20}\text{H}_{32}\text{O}_2$ ): calculated: 304.240230u, found: 304.240154u.

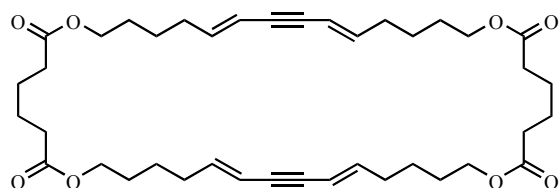
### 1,8-Dioxa-cyclodocosa-13,17-dien-15-yne-2,7-dione (119).



1,8-Dioxa-cyclodocosa-13,17-dien-15-yne-2,7-dione **119** was obtained as a colourless oil from diyne **109**, following the general procedure 1 (<20 % yield). It was not possible to remove traces of unreacted starting material. Characteristic data:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.06 (dt,  $J = 15.2$  Hz,  $J = 7.4$  Hz, 2H), 5.56 (d,  $J = 15.2$  Hz, 2H), 4.07 (t,  $J = 6.0$  Hz, 4H), 2.34 (m, 4H), 2.16 (m, 4H), 1.3-1.7 (m, 16H).

### 1,8,23,30-Tetraoxa-cyclotetratetraconta-13,17,35,39-tetraene-15,37-diyne-2,7,24,29-tetraone (119a).

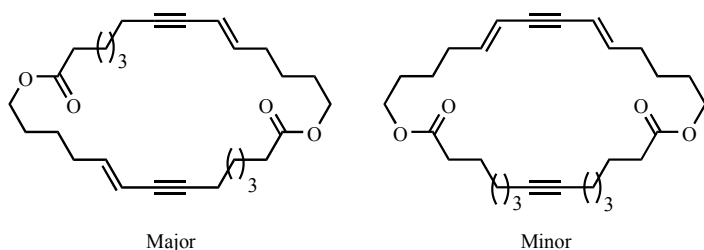


1,8,23,30-Tetraoxa-cyclotetratetraconta-13,17,35,39-tetraene-15,37-diyne-2,7,24,29-tetraone **119a** was obtained as by-product during cyclisation of diyne **109**, following the general procedure 1. Characteristic data:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.08 (dt,  $J = 15.2$  Hz,  $J = 7.2$  Hz, 4H), 5.58 (d,  $J = 15.2$  Hz, 4H), 4.07 (t,  $J = 6.2$  Hz, 8H), 2.32 (m, 8H), 2.15 (m, 8H), 1.57-1.72 (m, 16H), 1.40-1.53 (m, 8H).

MS:  $m/z$  (relative intensity) 664 [ $\text{M}^+$ ] (90), 463 (10), 435 (7), 263 (11), 261 (21), 247 (20), 233 (21), 221 (23), 145 (26), 129 (87), 117 (69), 91 (100), 79 (50), 67 (53), 55 (100), 43 (29).

**1,16-Dioxa-cyclotriconta-10,25-diene-8,23-diyne-2,17-dione (120)** and **1,16-dioxa-cyclotriconta-21,25-diene-8,23-diyne-2,15-dione (121)**.



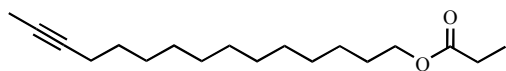
1,16-Dioxa-cyclotriconta-10,25-diene-8,23-diyne-2,17-dione **120** and 1,16-dioxa-cyclotriconta-21,25-diene-8,23-diyne-2,15-dione **121** were obtained as by-products during cyclisation of diyne **101**, following the general procedure 1.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): mixture of two isomers, 6.09 (minor isomer, dt,  $J = 15.2$  Hz,  $J = 7.3$  Hz, 0.67 H), 6.06 (major isomer, dt,  $J = 15.8$  Hz,  $J = 7.1$  Hz, 1.33 H), 5.59 (minor isomer, broad d,  $J = 15.2$  Hz, 0.67 H), 5.46 (major isomer, dm,  $J = 15.8$  Hz, 1.33 H), 4.06 (m, 4H), 2.31 (m, 8H), 2.13 (m, 8H), 1.30-1.70 (m, 16H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) : 173.7, 143.6 (minor isomer), 142.4 (major isomer), 110.4 (both isomers), 88.5 (major isomer), 87.0 (minor isomer), 80.0 (minor isomer), 79.4 (major isomer), 64.03 (major isomer), 64.00 (minor isomer), 34.4 (minor isomer), 34.3 (major isomer), 32.5 (both), 28.9, 28.4, 28.2, 28.1, 27.8, 25.4 (major isomer), 25.2 (minor isomer), 24.7 (minor isomer), 24.6 (major isomer), 19.1, 18.6.

MS:  $m/z$  (relative intensity) 440 [ $\text{M}^+$ ] (39), 325 (13), 257 (7), 223 (12), 197 (15.2), 183 (20), 129 (32), 117 (45), 105 (51), 91 (100), 79 (62), 67 (52), 55 (68), 41 (39).



**Pentadec-13-ynyl propanoate (122).**

Pyridine (50 mg, 0.63 mmol, 1.27 eq), DMAP (catalytic amount) and propionyl chloride (57 mg, 0.6 mmol, 1.2 eq) were added to a solution of alcohol **45** (112 mg, 0.5 mmol, 1 eq) in 5 ml dichloromethane. The mixture was stirred overnight and quenched with 10 ml of an aq. HCl solution (1N). The aqueous layer was extracted with dichloromethane, the organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated to afford the desired product **122** (135 mg, 0.48 mmol, 96 % yield) as a colourless oil.

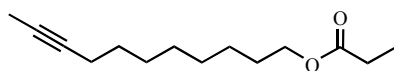
<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 4.05 (t, *J* = 6.8 Hz, 2H), 2.31 (q, *J* = 7.6 Hz, 2H), 2.10 (m, 2H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.61 (m, 2H), 1.45 (m, 2H), 1.21-1.40 (m, 16H), 1.13 (t, *J* = 7.6 Hz, 3H)

<sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 174.6, 79.4, 75.3, 64.5, 29.6, 29.52, 29.50 (2 C), 29.23, 29.16, 29.1, 28.9, 28.6, 27.6, 25.9, 18.7, 9.1, 3.4.

IR (KBr)  $\nu$  = 2978, 2926, 2855, 1740, 1464, 1186, 1084, 722 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 281 [M<sup>+</sup>] (1), 280 (4), 223 (2), 213 (2), 206 (5), 177 (3), 163 (3), 149 (6), 135 (11), 121 (16), 109 (20), 95 (52), 81 (41), 68 (100), 57 (59), 55 (40), 41 (27), 29 (20).

HRMS (C<sub>18</sub>H<sub>32</sub>O<sub>2</sub>): calculated: 281.248055u, found: 281.24750u

**Undec-9-ynyl propanoate (123).**

Pyridine (850 mg, 10.76 mmol, 1.27 eq), DMAP (catalytic amount) and propionyl chloride (905 mg, 9.6 mmol, 1.2 eq) were added to a solution of undec-9-yn-1-ol (1.439 g, 7.99 mmol, 1 eq) in 15 ml dichloromethane. The mixture was stirred overnight and quenched with 10 ml of an aq. HCl solution (1N). The aqueous layer was extracted with dichloromethane, the organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated to afford the desired product **123** (1.767 mg, 7.89 mmol, 98 % yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 4.05 (t,  $J = 6.8$  Hz, 2H), 2.31 (q,  $J = 7.6$  Hz, 2H), 2.10 (m, 2H), 1.77 (t,  $J = 2.6$  Hz, 3H), 1.61 (m, 2H), 1.45 (m, 2H), 1.21-1.40 (m, 8H), 1.13 (t,  $J = 7.6$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 174.6, 79.3, 75.3, 64.4, 29.09, 28.99, 28.7, 28.6, 27.6, 18.7, 9.1, 8.4, 3.4.

IR (KBr)  $\nu = 2930, 2857, 1736, 1463, 1181, 1083$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 224 [ $\text{M}^+$ ] (2), 195 (1), 167 (1), 157 (7), 150 (9), 135 (10), 121 (29), 107 (23), 93 (44), 79 (50), 68 (100), 57 (86), 55 (50), 41 (34), 29 (44).

HRMS ( $\text{C}_{14}\text{H}_{24}\text{O}_2+\text{H}$ ): calculated: 225.185455u, found: 225.185144u

#### Propionic acid 18-propionyloxy-octadec-9-ynyl ester (**124**).



Propionic acid 18-propionyloxy-octadec-9-ynyl ester **124** (198 mg, 0.50 mmol, 67 % yield) was obtained as a white solid from alkyne **123** (336 mg, 1.5 mmol, 1 eq) in the presence of catalyst **1** (40 mg, 0.085 mmol, 5.6 mol %) in 2 ml toluene, following the general procedure 1.

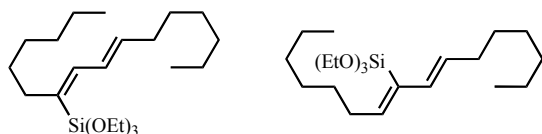
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 4.05 (t,  $J = 6.8$  Hz, 4H), 2.31 (q,  $J = 7.6$  Hz, 4H), 2.13 (m, 4H), 1.61 (m, 4H), 1.46 (m, 4H), 1.24-1.41 (m, 16H), 1.13 (t,  $J = 7.6$  Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 174.6, 80.2, 64.4, 29.12, 29.08, 29.0, 28.7, 28.6, 27.6, 25.8, 18.7, 9.1.

IR (KBr)  $\nu = 2979, 2932, 2856, 1739, 1463, 1187, 1084, 725$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 394 [ $\text{M}^+$ ] (1), 320 (7), 263 (4), 238 (5), 224 (5), 164 (48), 150 (76), 135 (50), 121 (81), 107 (30), 94 (42), 81 (52), 67 (49), 57 (100), 5(42), 41 (20), 29 (26).

HRMS ( $\text{C}_{24}\text{H}_{42}\text{O}_4+\text{H}$ ): calculated: 395.316135u, found: 395.315590u

**(7Z,9E)-(7-Triethoxysilyl)-hexadec-7,9-diene (128) and (7Z,9E)-(8-triethoxysilyl)-hexadec-7,9-diene (128a).**

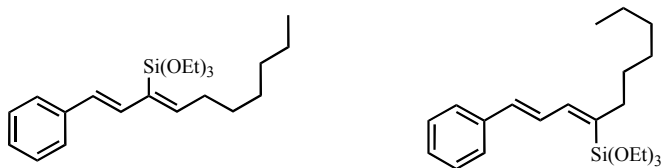
Major isomer

Minor isomer

(7Z,9E)-(7-Triethoxysilyl)-hexadec-7,9-diene **128** and (7Z,9E)-(8-triethoxysilyl)-hexadec-7,9-diene **128a** (137 mg, 0.36 mmol, 71% yield) were obtained as colourless oil from enyne **71** (110 mg, 0.5 mmol, 1 eq) in the presence of triethoxysilane (103 mg, 0.63 mmol, 1.7 eq) and catalyst **15** (25 mg, 0.05 mmol, 14 mol %) in 1 ml CH<sub>2</sub>Cl<sub>2</sub>, following the general procedure 2A. Regioisomeric ratio: 85/15.

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 5.55- 6.55 (m, 3H), 3.71 (m, 6H), 2.26 (m, 0.6H), 2.02 (m, 3.4H), 1.15-1.40 (m, H), 1.12 (m, 9H), 0.79 (m, 6H).

<sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 150.4, 145.7, 137.2, 135.4, 134.1, 130.9, 130.6, 58.7, 58.5, 38.1, 33.8, 33.0, 32.18, 32.15, 31.9, 30.9, 30.4, 30.09, 29.96, 29.6, 29.5, 29.3, 23.0, 18.4, 14.26, 14.24.

**(1E,3Z)-1-Phenyl-3-(triethoxysilyl)-deca-1,3-diene (129) and (1E,3Z)-1-phenyl-4-(triethoxysilyl)-deca-1,3-diene (129a).**

(1E,3Z)-1-Phenyl-3-(triethoxysilyl)-deca-1,3-diene **129** and (1E,3Z)-1-phenyl-4-(triethoxysilyl)-deca-1,3-diene **129a** (111 mg, 0.30 mmol, 71% yield) were obtained as a mixture (colourless oil) from enyne **74** (85 mg, 0.4 mmol, 1 eq) in the presence of triethoxysilane (83 mg, 0.51 mmol, 1.2 eq) and catalyst **15** (32 mg, 0.065 mmol, 16 mol %) in 1 ml CH<sub>2</sub>Cl<sub>2</sub>, following the general procedure 2A. Regioisomeric ratio 75/25 (GC).

<sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ (ppm): 7.05-7.40 (m, 6H), 6.74 (m, 1H), 6.44 (m, 0.88H), 6.11 (m, 0.12H), 3.69-3.76 (m, 6H), 2.35 and 2.14 (m, 2H), 1.05-1.45 (m, 17H), 0.81 (m, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 153.5, 145.1, 139.0, 138.6, 138.1, 135.4, 133.9, 130.9, 129.5, 129.0, 128.9, 128.8, 127.8, 127.2, 126.8, 126.4, 58.7, 38.3, 32.3, 32.24, 32.19, 30.8, 30.3, 30.2, 29.64, 29.58, 23.1, 18.5, 18.4, 14.3.

**(2Z,4E)-2-(Triethoxysilyl)-7-phenylhept-2,4-diene (130) and (2Z,4E)-3-(triethoxysilyl)-7-phenylhept-2,4-diene (130a).**



(2Z,4E)-2-(Triethoxysilyl)-7-phenylhept-2,4-diene **130** and (2Z,4E)-3-(triethoxysilyl)-7-phenylhept-2,4-diene **130a** (92 mg, 0.28 mmol, 88% yield) were obtained as a colourless oil from enyne **72** (53 mg, 0.31 mmol, 1 eq) in the presence of triethoxysilane (82  $\mu\text{l}$ , 0.62 mmol, 2 eq) and catalyst **15** (14.4 mg, 0.029, 9 mol %) in 50  $\mu\text{l}$  dichloromethane, following the general procedure 2B.

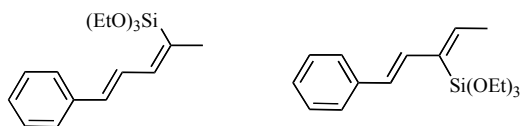
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.11-7.28 (m, 5H), 5.62 (m, 1.6H), 6.38 (m, 0.2H), 6.07 (m, 0.2H), 5.91 (m, 0.2H), 5.69 (m, 0.8H), 3.78 and 3.79 (2q,  $J = 7.0$  Hz, 6H), 2.69 (m, 2H), 2.39 (m, 2H), 1.95 (d,  $J = 7.3$  Hz, 0.6H), 1.85 (s, 2.4H), 1.21 (t,  $J = 7.0$  Hz, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 145.5, 144.4, 142.1, 141.8, 135.5, 135.2, 131.6, 130.5, 129.3, 128.7, 128.41, 128.38, 128.2, 128.2, 125.8, 125.6.

IR (KBr)  $\nu = 3063, 3086, 3027, 2974, 2926, 2884, 1642, 1604, 1583, 1102, 1079, 961, 780, 733, 699$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 334 [ $\text{M}^+$ ] (10), 243 (9), 199 (6), 163 (100), 135 (9), 119 (21), 107 (6), 91 (8), 79 (14), 45 (3).

HRMS ( $\text{C}_{19}\text{H}_{30}\text{O}_3\text{Si}_1$ ): calculated: 334.196424u, found: 334.196538u.

**(1E,3Z)-1-Phenyl-4-(triethoxysilyl)-pent-1,3-diene (131) and (1E,3Z)-1-phenyl-3-(triethoxysilyl)-pent-1,3-diene (131a).**

(1E,3Z)-1-Phenyl-4-(triethoxysilyl)-pent-1,3-diene **131** and (1E,3Z)-1-phenyl-3-(triethoxysilyl)-pent-1,3-diene **131a** (90 mg, 0.29 mmol, 82% yield) were obtained as a colourless oil from enyne **73** (51 mg, 0.36 mmol, 1 eq) in the presence of triethoxysilane (112 mg, 0.71 mmol, 2 eq) and catalyst **15** (16 mg, 0.032 mmol, 8.8 mol %), following the general procedure 2B.

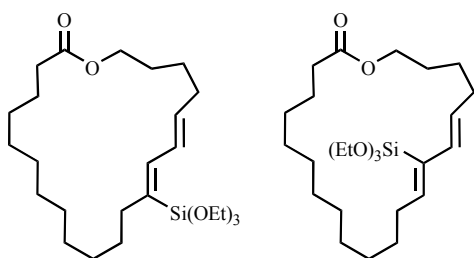
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.08-7.48 (m, 6H), 6.83 (m, 1H), 6.64 (m, 0.1H), 6.49 (m, 0.8H), 6.24 (m, 0.1H), 3.80 and 3.79 (2q,  $J = 7.00$  Hz, 6H), 2.05 (d,  $J = 7.30$  Hz, 0.3H), 1.95 (d,  $J = 1.22$  Hz, 2.7H), 1.23 (t,  $J = 7.00$  Hz, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 147.0, 145.4, 137.6, 134.7, 133.5, 132.2, 128.8, 128.6, 128.4, 127.7, 127.4, 126.8, 126.4, 126.1, 125.8, 58.4, 58.3, 23.9, 18.2, 18.2.

IR (KBr)  $\nu = 3060, 3025, 2974, 2926, 2885, 1623, 1599, 1583, 1492, 1449, 1166, 1102, 1080, 964, 780, 748, 692$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 306 [ $\text{M}^+$ ] (47), 262 (12), 216 (27), 163 (100), 142 (36), 119 (45), 107 (16), 79 (30), 63 (14), 45 (8).

HRMS ( $\text{C}_{17}\text{H}_{26}\text{O}_3\text{Si}_1$ ): calculated: 306.165124u, found: 306.165012u.

**16-(Triethoxysilyl)-oxacyclodocosa-15,17-dien-2-one (133) and 15-(triethoxysilyl)-oxacyclodocosa-15,17-dien-2-one (133a).**

16-(Triethoxysilyl)-oxacyclodocosa-15,17-dien-2-one **133** and 15-(triethoxysilyl)-oxacyclodocosa-15,17-dien-2-one **133a** (30 mg, 0.064 mmol, 65% yield) were obtained as a colourless oil from enyne **118** (36 mg, 0.118 mmol) in the presence of triethoxysilane (23 mg, 0.142 mmol, 1.2 eq) and catalyst **15** (9 mg, 0.18 mmol, 15 mol %) in 1 ml dichloromethane, following the general procedure 2A.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.56-6.66 (m, 3H), 4.07 (m, 2H), 3.80 (m, 6H), 2.29 (m, 2H), 2.17 (m, 4H), 1.61 (m, 4H), 1.16-1.51 (m, 27H).

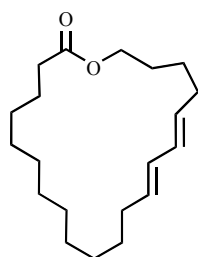
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.8, 146.2, 136.0, 132.7, 130.9, 64.0, 58.1, 36.4, 34.3, 29.3, 2.3, 29.0, 28.6, 28.5, 28.3, 27.9, 26.8, 25.7, 25.3, 18.2.

IR (KBr)  $\nu$  = 2973, 2926, 2855, 1737, 1640, 1576, 1243, 1166, 1103, 1079, 959  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 468 [ $\text{M}^+$ ] (3), 424 (15), 422 (79), 378 (9), 376 (16), 375 (2), 332 (4), 331 (6), 330 (14), 304 (9), 302 (2), 297 (2), 288 (2), 269 (2), 245 (4), 191 (2), 189 (14), 176 (2), 165 (5), 163 (100), 161 (3), 135 (24), 134 (3), 131 (2), 119 (40), 108 (7), 107 (24), 106 (3), 97 (2), 91 (15), 82 (2), 80 (12), 79 (33), 78 (2), 73 (2), 67 (11), 63 (7), 55 (10), 43 (5), 41 (6).

HRMS ( $\text{C}_{26}\text{H}_{48}\text{O}_5\text{Si}_1+\text{Na}$ ): calculated: 491.316873u, found: 491.31725u.

#### Oxacyclodocosa-15,17-dien-2-one (**133b**).



Oxacyclodocosa-15,17-dien-2-one **133b** (15 mg, 0.049 mmol, 79% calculated yield) was obtained as a colourless oil from vinylsilanes **133** and **133a** (29 mg, 0.062 mmol) in the presence of AgF (16 mg, 0.14 mmol, 2 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu\text{l}$ ), following the general procedure 3A.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.99 (m, 2H), 5.50 (m, 2H), 4.08 (t,  $J$  = 6.6 Hz, 2H), 2.30 (t,  $J$  = 6.7 Hz, 2H), 2.08 (m, 4H), 1.61 (m, 4H) 1.16 (m, 18H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 173.9, 132.5, 131.2, 130.9 (Integration for 2 Carbons), 64.0, 34.4, 31.8, 31.6, 29.5, 29.2, 28.9, 28.7, 28.3, 28.1, 28.0, 27.8, 27.1, 25.4, 25.3.

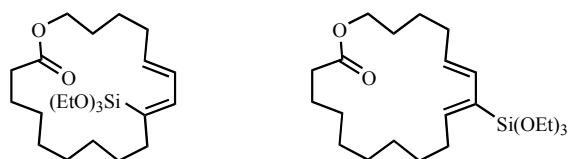
IR (KBr)  $\nu$  = 3014, 2926, 2854, 1736, 1659, 1623, 1460, 1247, 1169, 987, 725  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 308 [ $\text{M}^+$ ] (4), 278 (11), 263 (1), 238 (2), 224 (4), 196 (1), 163 (5), 149 (12), 135 (31), 121 (48), 107 (32), 94 (68), 80 (100), 67 (58), 55 (46), 41 (40), 29 (9).

HRMS ( $\text{C}_{20}\text{H}_{34}\text{O}_2$ ): calculated: 306.255880u, found: 306.255638u.

GC: 86.3% of the main isomer, 9.4% of another isomer and 4.3% of a side product whose mass is 308  $\text{g}\cdot\text{mol}^{-1}$ .

**12-(Triethoxysilyl)-oxacyclooctadeca-11,13-dien-2-one (134) and 11-(triethoxysilyl)-oxacyclooctadeca-11,13-dien-2-one (134a).**



12-(Triethoxysilyl)-oxacyclooctadeca-11,13-dien-2-one **134** and 11-(triethoxysilyl)-oxacyclooctadeca-11,13-dien-2-one **134a** (34 mg, 0.08 mmol, 80% yield) were obtained as a colourless oil from enyne **117** (25.5 mg, 0.097 mmol) in the presence of triethoxysilane (50  $\mu\text{l}$ , 0.133 mmol, 1.4 eq) and catalyst **15** (6 mg, 0.012 mmol, 12 mol %), following the general procedure 2B.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.53 (m, 2H), 5.59 (m, 1H), 4.07 (t,  $J$  = 6.4 Hz, 2H), 3.79 (q,  $J$  = 7.0 Hz, 6H), 2.21 (m, 6H), 1.36-1.61 (m, 6H), 1.06-1.36 (m, 19H).

$^{13}\text{C}$  NMR (100 MHz)  $\delta$  (ppm): 173.6, 146.6, 136.0, 132.5, 131.4, 64.0, 58.1, 36.8, 34.5, 31.9, 29.7, 29.6, 28.8, 28.4, 28.2, 27.9, 26.0, 25.6, 24.6.

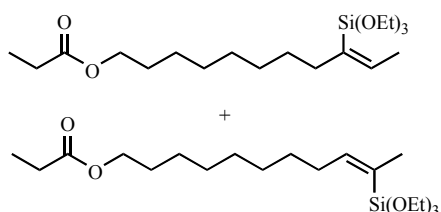
IR (KBr)  $\nu$  = 2973, 2927, 2857, 1737, 1640, 1577, 1256, 1168, 1103, 1080, 959, 782  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity): 426 (7), 382 (12), 38 (86), 336 (7), 334 (14), 301 (2), 290 (4), 289 (5), 288 (12), 273 (2), 262 (9), 255 (2), 245 (2), 227 (2), 189 (16), 176 (3), 165 (5), 163 (100), 161 (3), 159

(2), 135 (23), 134 (4), 131 (3), 119 (37), 108 (6), 107 (24), 106 (4), 97 (2), 91 (19), 81 (8), 80 (11), 79 (35), 73 (2), 67 (8), 63 (7), 55 (8), 45 (2), 43 (3), 41 (5), 29 (2).

HRMS (C<sub>23</sub>H<sub>42</sub>O<sub>8</sub>): calculated: 449.269923u, found: 449.26947u.

**2(Z)-3-(Triethoxysilyl)-undec-2-enyl propanoate (135) and 2(Z)-2-(triethoxysilyl)-undec-2-enyl propanoate (135a).**

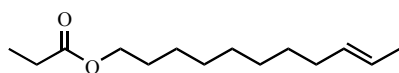


2(Z)-3-(Triethoxysilyl)-undec-2-enyl propanoate **135** and 2(Z)-2-(triethoxysilyl)-undec-2-enyl propanoate **135a** (62 mg, 0.16 mmol, 90% yield) were obtained as a colourless oil from the corresponding alkyne **123** (40 mg, 0.179 mmol, 1 eq) in the presence of triethoxysilane (42  $\mu$ l, 0.219 mmol, 1.2 eq) and catalyst **15** (9 mg, 0.018 mmol, 10 mol %), following the general procedure 2B.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 6.08-6.15 (m, 1H), 3.99 (t,  $J$  = 6.7 Hz, 2H), 3.75 (2q,  $J$  = 7.0 Hz, 6H), 2.25 (q,  $J$  = 7.6 Hz, 2H), 2.16 (m, 1.33H), 2.00 (m, 0.66H), 1.79 (d,  $J$  = 7.0 Hz, 0.99H), 1.73 (d,  $J$  = 1.3 Hz, 1.98H), 1.55 (m, 3H), 1.18-1.34 (m, 10H), 1.16 (2t,  $J$  = 7.0 Hz, 9H), 1.07 (t,  $J$  = 7.6 Hz, 3H).

MS:  $m/z$  (relative intensity) 388 [M<sup>+</sup>] (0.1), 342 (55), 250 (10), 214 (5), 191 (100), 163 (73), 147 (11), 13 (33), 119 (35), 79 (15), 57 (16).

**2-(E)-Undec-2-enyl propanoate (135b).**



2-(E)-Undec-2-enyl propanoate **135b** (23 mg, 0.10 mmol, 95 % yield) was obtained as a colourless oil from vinylsilanes **135** and **135a** (41.5 mg, 0.11 mmol, 1 eq) in the presence of AgF (20 mg, 0.16 mmol, 1.5 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A. *E:Z* ratio: 97:3 (GC).



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.34 (m, 2H), 3.99 (t,  $J = 6.8$  Hz, 2H), 2.25 (q,  $J = 7.6$  Hz, 2H), 1.89 (m, 2H), 1.55 (m, 5H), 1.24 (m, 10H), 1.07 (t,  $J = 7.6$  Hz, 3H).

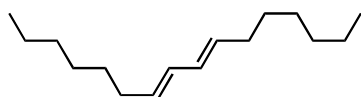
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 174.6, 131.6, 124.6, 64.5, 32.6, 29.5, 29.3, 29.2, 29.0, 28.6, 27.6, 25.9, 17.9, 9.1.

IR (KBr)  $\nu = 3021, 2927, 2855, 1740, 1187, 966$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 226 [ $\text{M}^+$ ] (0.6), 152 (39), 123 (12), 110 (28), 96 (37), 68 (100), 55 (70), 29 (33).

HRMS ( $\text{C}_{14}\text{H}_{26}\text{O}_2 + \text{Na}$ ): calculated: 249.183049u, found: 249.18298u.

**(7E,9E)-Hexadec-7-9-diene (139).**



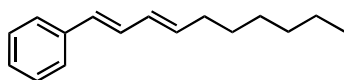
(7E,9E)-Hexadec-7-9-diene **139** (37 mg, 0.17 mmol, 82 % yield) was obtained as a colourless oil from vinylsilanes **128** and **128a** (70 mg, 0.18 mmol) in the presence of AgF (43 mg, 0.34 mmol, 1.85 eq) in THF (2ml), MeOH (0.5 ml) and water (25  $\mu\text{l}$ ), following the general procedure 3A. 97% of the (E,E)-isomer (GC). The analytical and spectroscopic data matched those reported in the literature.<sup>[173]</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.98 (m, 2H), 5.55 (m, 2H), 2.03 (m, 4H), 1.16-1.46 (m, 16H), 0.87 (m, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 132.0, 130.0, 32.2, 31.4, 29.0, 28.5, 22.2, 13.7.

IR (KBr)  $\nu = 3014, 2957, 2925, 2855, 1622, 1378, 985, 724$   $\text{cm}^{-1}$ .

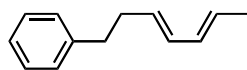
MS:  $m/z$  (relative intensity) 222 [ $\text{M}^+$ ] (35), 151, (7), 138 (15), 110 (52), 95 (44), 81 (56), 67 (100), 55 (26), 41 (34), 29 (17).

**(1*E*,3*E*)-1-Phenyldeca-1,3-diene (140).**

(1*E*,3*E*)-1-Phenyldeca-1,3-diene **140** (27 mg, 0.13 mmol, 79 % yield) was obtained as a colourless oil from vinylsilanes **129** and **129a** (60 mg, 0.16 mmol, 1 eq) in the presence of AgF (40 mg, 0.31 mmol, 2 eq) in THF (2 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A. 97% of the (*E,E*)-isomer (GC). The analytical and spectroscopic data matched those reported in the literature.<sup>[174]</sup>

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  (ppm): 7.20 (m, 5H), 6.68 (dd,  $J = 15.6$  Hz,  $J = 10.4$  Hz, 1H), 6.34 (d,  $J = 15.6$  Hz, 1H), 6.12 (dd,  $J = 10.4$  Hz,  $J = 0.67$  Hz, 1H), 5.76 (dt,  $J = 15.2$  Hz,  $J = 7.0$  Hz, 1H), 2.06 (m, 2H), 1.28 (m, 8H), 0.81 (m, 3H).

<sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  (ppm): 138.2, 136.6, 130.9, 130.1, 130.0, 129.0, 127.5, 126.5, 32.3, 32.2, 29.7, 29.3, 23.1, 14.3.

**(2*E*,4*E*)-7-Phenylhepta-2,4-diene (141).**

(2*E*,4*E*)-7-Phenylhepta-2,4-diene **141** 32 mg, 0.19 mmol) was obtained as a colourless oil from vinylsilanes **130** and **130a** (80 mg, 0.24 mmol, 1 eq), in the presence of AgF (45 mg, 0.36 mmol, 1.5 eq) in THF (1.5 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3A (78% yield). *E/Z* ratio: > 99% of the (*E,E*)-isomer (GC).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 7.13-7.30 (m, 5H), 6.01 (m, 2H), 5.57 (m, 2H), 2.68 (m, 2H), 2.36 (m, 2H), 1.71 (m, 3H).

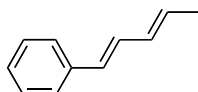
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 141.9, 131.6, 130.8, 128.4, 128.3, 127.2, 125.8, 35.9, 34.4, 18.0.

IR (KBr)  $\nu = 3085, 3063, 3017, 2928, 2853, 1604, 1496, 1453, 1377, 988, 745, 698$  cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 172 [ $M^+$ ] (17), 143 (4), 104 (2), 91 (31), 81 (100), 79 (13), 53 (8), 27 (2).

HRMS (C<sub>13</sub>H<sub>16</sub>): calculated: 172.125200u, found: 172.125499u.

**(1*E*,3*E*)-1-Phenyl-pent-1,4-diene (142).**

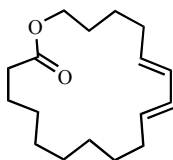


(1*E*,3*E*)-1-Phenyl-pent-1,4-diene **142** (30 mg, 0.21 mmol, 70% yield) was obtained as a colourless oil from vinylsilanes **131** and **131a** (87 mg, 0.29 mmol, 1 eq), in the presence of AgF (78 mg, 0.61 mmol, 2 eq) in THF (1.5 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure for 3A. 97% of the (*E,E*)-isomer (GC). The analytical and spectroscopic data matched those reported in the literature.<sup>[175]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 7.39 (m, 2H), 7.31 (m, 2H), 7.20 (m, 1H), 6.77 (dd,  $J = 15.7$  Hz,  $J = 10.4$  Hz, 1H), 6.44 (d,  $J = 15.7$  Hz, 1H), 6.24 (m, 1H), 5.85 (dq,  $J = 15.0$  Hz,  $J = 6.8$  Hz, 1H), 1.84 (dd,  $J = 6.8$  Hz,  $J = 1.5$  Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 137.7, 131.8, 130.3, 129.7, 129.3, 128.5, 127.0, 126.1, 18.3.

**Oxacyclooctadeca-11,13-dien-2-one (143).**



Oxacyclooctadeca-11,13-dien-2-one **143** (22 mg, 0.083 mmol, 79% yield) was obtained as a colourless oil from vinylsilanes **134** and **134a** (45 mg, 0.106 mmol) in the presence of AgF (20 mg, 0.16 mmol, 1.5 eq) in THF (2 ml), MeOH (0.5 ml) and H<sub>2</sub>O (25  $\mu$ l), following the general procedure 3A. GC: 94-97% of the (*E,E*) conjugated diene.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 5.98 (m, 2H), 5.44 (m, 2H), 4.06 (t,  $J = 7.1$  Hz, 2H), 2.26 (t,  $J = 6.5$  Hz, 2H), 2.09 (m, 4H), 1.51-1.61 (m, 4H), 1.28-1.42 (m, 4H), 1.13-1.33 (m, 8H).

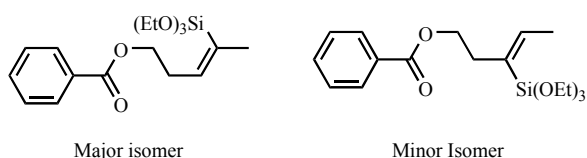
<sup>13</sup>C NMR (100 MHz)  $\delta$  (ppm): 137.7, 132.5, 132.1, 131.2, 130.6, 63.9, 34.6, 31.9, 31.5, 29.2, 28.3, 28.1, 27.7, 27.5, 26.6, 25.4, 24.5.

IR (KBr)  $\nu = 2929, 2857, 1733, 1460, 1175, 975 \text{ cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 264 [ $M^+$ ] (55), 236 (9), 182 (5), 163 (5), 149 (15), 135 (31), 121 (52), 107 (39), 94 (88), 80 (99), 79 (100), 67 (81), 55 (58), 41 (73).

HRMS ( $C_{17}H_{30}O_2$ ): calculated: 264.208930u, found: 264.209119u.

**2(Z)-3-(Triethoxysilyl)-pent-2-enyl benzoate (145) and 2(Z)-3-(triethoxysilyl)-pent-2-enyl benzoate (145a).**



2(Z)-3-(Triethoxysilyl)-pent-2-enyl benzoate **145** and 2(Z)-3-(triethoxysilyl)-pent-2-enyl benzoate **145a** (291 mg, 0.83 mmol, 87 % yield, regioisomeric ratio: 67:33) were obtained as a colourless oil from alkyne **144** (176 mg, 0.97 mmol, 1 eq) in the presence of triethoxysilane (202  $\mu\text{l}$ , 1.12 mmol, 1.2 eq) and catalyst **15** (4.7 mg, 0.097 mmol, 1 mol %) in 1.5 ml dichloromethane, following the general procedure 2A.

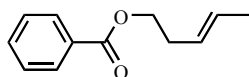
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): major isomer: 8.40 (m, 2H), 7.55 (m, 1H), 7.53 (m, 2H), 6.23 (tq,  $J = 7.5 \text{ Hz}$ ,  $J = 1.0 \text{ Hz}$ , 1H), 4.35 (t,  $J = 6.7 \text{ Hz}$ , 2H), 3.83 (q,  $J = 7.0 \text{ Hz}$ , 6H), 2.75 (td,  $J = 6.75 \text{ Hz}$ ,  $J = 1.1 \text{ Hz}$ , 2H), 1.83 (m, 3H), 1.24 (t,  $J = 7.0 \text{ Hz}$ , 9H). Minor isomer: 8.40 (m, 2H), 7.55 (m, 1H), 7.53 (m, 2H), 6.39 (qt,  $J = 7.0 \text{ Hz}$ ,  $J = 1.0 \text{ Hz}$ , 1H), 4.36 (t,  $J = 7.1 \text{ Hz}$ , 2H), 3.82 (q,  $J = 7.0 \text{ Hz}$ , 6H), 2.56 (broad t,  $J = 7.1 \text{ Hz}$ ), 1.89 (broad d,  $J = 7.0 \text{ Hz}$ , 3H), 1.23 (t,  $J = 7.0 \text{ Hz}$ , 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.6, 145.1, 141.8, 132.8, 132.7, 130.9, 130.7, 130, 5, 129.6, 129.5, 128.9, 128.2, 128.1, 65.1, 64.8, 58.3, 58.2, 36.8, 31.2, 23.7, 18.2, 18.1, 18.

IR (KBr)  $\nu = 2974, 2926, 2886, 1722, 1622, 1603, 1585, 1452, 1274, 1108, 1080, 1027, 959, 780, 712 \text{ cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 352 [ $M^+$ ] (0.5), 307 (7), 261 (3), 230 (73), 215 (21), 201 (15), 186 (81), 163 (37), 135 (68), 119 (22), 105 (100), 91 (9), 77 (37), 63 (8), 51 (5).

HRMS ( $C_{18}H_{28}O_5Si_1+\text{Na}$ ): calculated: 375.160373u, found: 375.159902u.

**2(*E*)-Pent-2-enyl benzoate (146).**

2(*E*)-Pent-2-enyl benzoate **146** (44 mg, 0.23 mmol, 94% yield) was obtained as a colourless oil from vinylsilanes **145** and **145a** (87 mg, 0.24 mmol, 1 eq) in the presence of AgF (3.1 mg, 0.024 mmol, 10 mol %) and TBAF (1M in THF, 250  $\mu$ l, 0.25 mmol, 1 eq) in THF (3 ml), MeOH (0.5 ml) and water (25  $\mu$ l), following the general procedure 3B (80% yield). *E:Z* ratio: >99:1 (GC).

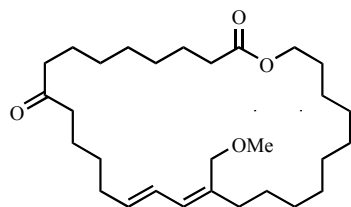
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.05 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.49 (m, 1H), 5.60 (m, 1H), 4.32 (t,  $J = 6.8$  Hz, 2H), 2.45 (m, 2H), 1.68 (m, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.6, 132.8, 130.5, 129.5, 128.3, 128.0, 126.3, 64.6, 32.1, 17.7.

IR (KBr)  $\nu = 3063, 3030, 3001, 2960, 2918, 2856, 1720, 1603, 1584, 1492, 1452, 1315, 1276, 1112, 967, 711$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 190 [ $\text{M}^+$ ] (0.4), 123 (6), 105 (80), 77 (37), 68 (100), 51 (11), 41 (6).

HRMS ( $\text{C}_{12}\text{H}_{14}\text{O}_2$ ): calculated: 190.099380u, found: 190.099221u.

**(15*E*,17*Z*)-18-Methoxymethyl-oxa-cyclooctacos-15,17-diene-2,10-dione (147).**

Enyne **191** (27 mg, 0.059 mmol, 1 eq) was hydrosilylated in the presence of triethoxysilane (50  $\mu$ l, 0.36 mmol, 6 eq) and catalyst **15** (9 mg, 0.018 mmol) following to the general procedure 2B. The resulting vinyl silane was immediately submitted to protodesilylation in the presence of AgF (10.3 mg, 0.081 mmol, 1.8 eq) in THF (3 ml), MeOH (0.5 ml) and water (25 $\mu$ l), following the general

procedure 3A affording 18-methoxymethyl-oxa-cyclooctacos-15,17-diene-2,10-dione **147** (13 mg, 0.028 mmol, 50 % overall yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.34 (dd,  $J = 11.0, 14.9$  Hz, 1H), 5.97 (d,  $J = 11.0$  Hz, 1H), 5.62 (dt,  $J = 7.1, 14.9$  Hz, 1H), 4.07 (t,  $J = 6.4$  Hz, 2H), 4.01 (s, 2H), 3.29 (s, 3H), 2.38 (m, 4H), 2.29 (t,  $J = 7.3$  Hz, 2H), 2.12 (m, 4H), 1.20-1.66 (m, 30H).

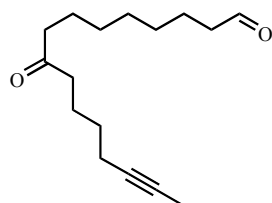
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 211.5, 173.9, 136.0, 134.2, 129.0, 126.2, 69.8, 64.4, 57.8, 42.7, 42.5, 35.0, 34.4, 32.4, 29.2, 29.29.1, 29.0, 28.9 (2C), 28.83 (2C), 28.75, 28.6, 28.5, 27.4, 25.8, 24.8, 23.7, 23.3.

IR (KBr)  $\nu = 3027, 2928, 2855, 1734, 1713, 1655, 1617, 1187, 969$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 463 (3), 462 [ $\text{M}^+$ ] (8), 431 (32), 430 (100), 412 (7), 262 (3), 171 (7), 120 (30), 105 (21), 81 (18), 55 (31), 41 (14).

HRMS ( $\text{C}_{29}\text{H}_{50}\text{O}_4+\text{Na}$ ): calculated: 485.360679u, found: 485.36098u.

### 9-Oxo-hexadec-14-ynal (**148a**).



Dess-Martin periodinane (3 eq., 0.25 M in dichloromethane) was added to a solution of diol **155** in dichloromethane (300 mg, 1.18 mmol, 1 eq) at room temperature. The solution was stirred for 5h and quenched with an aq. solution of NaOH (1N). The mixture was washed with an aq. solution of  $\text{Na}_2\text{S}_2\text{O}_5$ , the aqueous layer was extracted with dichloromethane, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated to afford the desired aldehyde **148a** (298 mg, 1.18 mmol, quantitative yield) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 9.68 (t,  $J = 1.88$  Hz, 1H), 2.32 (m, 6H), 2.05 (m, 2H), 1.69 (t,  $J = 2.50$  Hz, 3H), 1.31-1.64 (m, 8H), 1.15-1.30 (m, 6H).

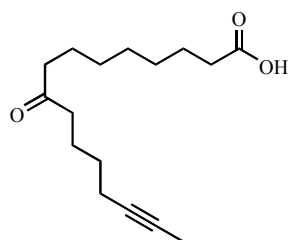
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  (ppm): 211.01, 202.73, 78.66, 75.72, 43.800, 42.63, 42.21, 29.09, 28.95, 28.90, 28.48, 23.65, 22.98, 21.93, 18.49, 3.39.

IR (KBr)  $\nu$  = 29.24, 2863, 2849, 1711, 1701, 1419, 1092, 718  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 250 [ $\text{M}^+$ ] (0.36), 235 (2), 175 (2), 155 (20), 138 (14), 123 (48), 109 (53), 95 (76), 81 (45), 67 (100), 55 (93), 41 (67).

HRMS ( $\text{C}_{16}\text{H}_{26}\text{O}_2+\text{Na}$ ): calculated: 273.183049u, found: 273.18346u.

### 9-Oxo-hexadec-14-ynoic acid (**148**).



$\text{H}_2\text{NSO}_3\text{H}$  (140 mg, 1.44 mmol, 1.2 eq.) and a solution of  $\text{NaClO}_2$  (163 mg, 1.44 mmol, 1.2 eq.) in 6 ml water were added to a solution of aldehyde **148a** (300 mg, 1.2 mmol, 1 eq) in 6 ml THF. The solution immediately turned yellow and was diluted with water and MTBE after 1h. The aqueous layers were extracted with MTBE, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Purification by flash chromatography (using hexan/ethylacetate: 2/1 as the eluent) afforded the desired carboxylic acid **148** (249 mg, 0.94 mmol, 78 % yield) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2.32 (m, 4H), 2.27 (t,  $J$  = 7.50 Hz, 2H), 2.05 (m, 2H), 1.69 (t,  $J$  = 2.53 Hz, 3H), 1.15-1.64 (m, 14H).

$^{13}\text{C}$  NMR (100 MHz)  $\delta$  (ppm): 211.17, 179.74, 78.67, 75.72, 42.66, 42.21, 33.93, 28.96, 28.80, 28.50, 24.54, 23.69, 23.00, 18.49, 3.37.

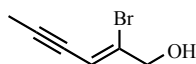
IR (KBr)  $\nu$  = 2934, 2924, 2908, 2862, 2849, 1701, 1419, 1305, 738  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 266 [ $\text{M}^+$ ] (1), 248 (6), 186 (12), 171 (50), 138 (55), 123 (70), 110 (20), 95 (81), 81 (41), 67 (58), 55 (100), 41 (48).

HRMS (C<sub>16</sub>H<sub>26</sub>O<sub>3</sub>+Na): calculated: 289.177964u, found: 289.178040u.

Anal. (C<sub>16</sub>H<sub>26</sub>O<sub>3</sub>) calculated. C 72.14, H 9.84, found C 72.12, H 9.84.

**(2E)-2-Bromo-hex-2-en-4-yn-1-ol (150a).**

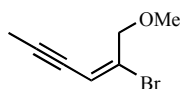


(2E)-2-Bromo-hex-2-en-4-yn-1-ol **150a** was obtained under the same reaction conditions as the corresponding (Z)-isomer **150** starting from an *E:Z* mixture of methyl-2-bromo-hex-2-en-4-ynoate **185**.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 6.23 (qt, *J* = 2.4 Hz, *J* = 1.4 Hz, 1H), 4.30 (dq, *J* = 1.3 Hz, *J* = 0.65 Hz, 2H), 2.18 (broad s, 1H), 2.01 (dt, *J* = 2.3 Hz, *J* = 0.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 134.6, 111.4, 93.2, 76.0, 67.6, 4.6.

**(2E)-2-Bromo-1-methoxy-hex-2-en-4-yne (150).**



Methyl iodide (50 μl, 0.8 mmol, 3.1 eq) and alcohol **186** (45 mg, 0.26 mmol, 1 eq) were added successively to a suspension of NaH (15 mg, 0.62 mmol, 2.4 eq) in 2 ml THF at 0°C. The reaction was stirred for 1h and quenched with an aqueous solution of NH<sub>4</sub>Cl. The aqueous layer was extracted with Et<sub>2</sub>O, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated. Purification by flash chromatography (using pentane/Et<sub>2</sub>O: 95/5 as the eluent) afforded the expected product **150** (43 mg, 0.23 mmol, 88 % yield) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 6.12 (q, *J* = 2.5 Hz, 1H), 4.33 (s, 2H), 3.35 (s, 3H), 1.95 (d, *J* = 2.5 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 134.3, 116.8, 92.8, 75.1, 72.8, 57.5, 4.5.

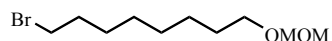
IR (KBr) ν = 3032, 2927, 2823, 2223, 1604, 1109 cm<sup>-1</sup>.



MS:  $m/z$  (relative intensity) 190 [ $M^+$ ] (15), 188 [ $M^+$ ] (15), 159 (2), 157 (2), 109 (100), 78 (17), 77 (17), 53 (30), 39 (14), 29 (5).

HRMS ( $C_7H_9Br_1O_1$ ): calculated: 187.983690u, found: 187.983809u.

### 1-Bromo-8-methoxymethoxy-octane (**152**).



Dimethoxymethane (30 ml, excess) and bromoalcohol **151** (840 mg, 4.02 mmol, 1 eq) were added successfully to a suspension of  $P_2O_5$  (3g, 21.1 mmol, 5 eq) in 40 ml dichloromethane. The mixture was stirred for 30 min before complete conversion was reached. Prior to work-up, the brown precipitate was filtered and the filtrate was rinsed with dichloromethane. Work-up with an aq.  $NaHCO_3$  solution was followed by extraction with dichloromethane. The combined organic layers were dried over  $Na_2SO_4$  and evaporated. Purification of the residue by flash chromatography (using 95/5 pentane/ether 4/1 as the eluent) afforded the desired protected alcohol **152** (840 mg, 3.32 mmol, 83 % yield) as a colourless oil.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm): 4.55 (s, 2H), 3.45 (t,  $J = 6.57Hz$ , 2H), 3.34 (t,  $J = 6.82Hz$ , 2H), 3.29 (s, 3H), 1.79 (m, 2H), 1.52 (m, 2H), 1.22-1.41 (m, 8H).

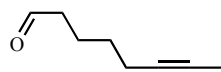
$^{13}C$  NMR (75 MHz)  $\delta$  (ppm): 96.39, 67.78, 55.06, 33.87, 32.77, 29.67, 29.19, 28.68, 28.08, 26.09.

IR (KBr)  $\nu = 2988, 2931, 2856, 1465, 1215, 1145, 1112, 1048, 919, 645, 563\text{ cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 253 [ $M^+$ ] (0.65), 239 (0.18), 221 (0.70), 204 (2.63), 190 (3.04), 148 (2.57), 109 (5.61), 75 (15.00), 69 (14.28), 55 (11.77), 45 (100), 41 (11.55), 29 (5.81).

HRMS ( $C_{10}H_{21}Br_1O_2$ ): calculated: 253.080330u, found: 253.080019u.

### Oct-6-ynal (**153**).



Oct-8-yn-1-ol (1.215 g, 9.6 mmol, 1 eq) was added dropwise to a suspension of PDC (5.44 g, 14.5 mmol, 1.5 eq) in 25 ml dichloromethane at room temperature. The solution was stirred overnight,

then filtered through silica gel (using dichloromethane as the eluent). The solvent was evaporated and the resulting mixture was purified by distillation (100-115°C for 1 mbar) to afford the desired aldehyde **153** (707 mg, 5.7 mmol, 59 % yield) as a colourless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 9.76 (t,  $J = 1.7$  Hz, 1H), 2.43(dt,  $J = 7.3$  Hz, 1.7 Hz, 2H), 2.14 (m, 2H), 1.76 (t,  $J = 2.6$  Hz, 3H), 1.72 (m, 2H), 1.50 (m, 2H).

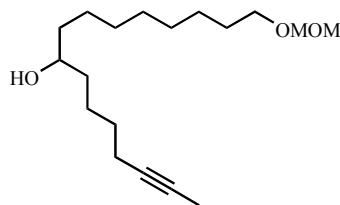
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  (ppm): 202.4, 78.5, 76.0, 33.3, 28.4, 23.8, 21.23, 10.46, 3.36.

IR (KBr)  $\nu = 2940, 2921, 2722, 1724, 1437, 1334, 1077$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 124 [ $\text{M}^+$ ] (2), 123 (8), 109 (32), 95(57), 91 (38), 79 (89), 67 (99), 53 (91), 41 (100), 27 (64).

HRMS ( $\text{C}_8\text{H}_{13}\text{O}_1+\text{H}$ ): calculated: 125.096640u, found: 125.096579u.

#### 16-Methoxymethoxy-hexadec-2-yn-8-ol (**154**).



Magnesium turnings (150 mg, 6.2 mmol) were heated under reduced pressure prior to the addition of freshly distilled THF (15 ml). 1 ml of a solution of bromoderivative **152** (647 mg, 2.56 mmol) in 9 ml THF was added to the mixture at room temperature. Once the reaction had started, the rest of the **152** solution was added dropwise. The mixture was refluxed for 2h before being cooled to room temperature. The solution of aldehyde **153** (220 mg, 1.77 mmol, 1 eq) in 7 ml THF was carefully added. The mixture was stirred overnight before being quenched with water and filtered. The aqueous layer was extracted with dichloromethane, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Purification by flash chromatography afforded the desired alcohol **154** (389 mg, 1.31 mmol, 73 % yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 4.54 (s, 2H), 3.52 (m, 1H), 3.44 (t,  $J = 6.64\text{Hz}$ , 2H), 3.29 (s, 3H), 2.06 (m, 2H), 1.70 (t,  $J = 2.54\text{Hz}$ , 3H), 1.15-1.55 (m, 21H).

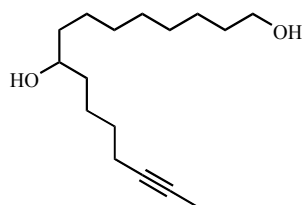
$^{13}\text{C}$  NMR (100 MHz)  $\delta$  (ppm): 96.37, 79.08, 75.50, 71.81, 67.85, 55.04, 37.46, 36.96, 29.71, 29.60, 29.52, 29.34, 29.05, 26.16, 25.59, 24.89, 18.68, 3.41.

IR (KBr)  $\nu$  = 3435, 2929, 2856, 1463, 1214, 1146, 1112, 1044, 919  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 304 [ $\text{M}^+$ ] (0.40), 235 (1.94), 203 (1.76), 171 (20.16), 135 (7.61), 123 (16.19), 109 (12.40), 95 (24.01), 81 (40.67), 67 (35.79), 55 (38.98), 45 (100), 29 (9.32).

HRMS ( $\text{C}_{18}\text{H}_{34}\text{O}_3+\text{Na}$ ): calculated: 321.240564u, found: 321.24062u.

### Hexadec-14-yne-1,9-diol (**155**).



100  $\mu\text{l}$  of HCl (12N, 1.16 eq.) were added to a solution of compound **154** (386 mg, 1.21 mmol, 1 eq) in methanol (10 ml). The solution was refluxed for 3h and stirred overnight at room temperature. The reaction was quenched with an aq. solution of  $\text{NaHCO}_3$  and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated to afford the desired diol **155** (307 mg, 1.21 mmol, quantitative yield) as a colourless oil.

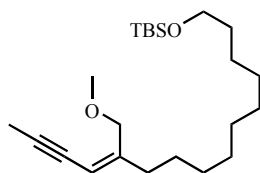
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 3.54 (t,  $J$  = 6.63Hz, 2H), 3.52 (m, 1H), 2.05 (m, 2H), 1.69 (t,  $J$  = 2.52Hz, 3H), 1.62 (broad s, 2H), 1.16-1.53 (m, 20H).

$^{13}\text{C}$  NMR (100 MHz)  $\delta$  (ppm): 79.09, 75.49, 71.76, 62.89, 37.40, 36.92, 32.72, 29.56, 28.50, 29.30, 29.03, 25.68, 25.55, 24.87, 18.66, 3.38.

IR (KBr)  $\nu$  = 3326, 2924, 2851, 1464, 1118, 1072, 858, 663  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 254 [ $\text{M}^+$ ] (0.1), 207 (2.05), 159 (22.73), 135 (16.46), 125 (31.92), 123 (30.11), 107 (32.30), 95 (29.67), 81 (97.64), 67 (86.93), 55 (100), 43 (81.55), 29 (21.26).

HRMS ( $\text{C}_{16}\text{H}_{30}\text{O}_2+\text{Na}$ ): calculated: 277.214349u, found: 277.21450u.

**(11Z)-11-Methoxymethylpentadec-11-en-13-ynyl-1-oxy(*tert*-butyl-dimethyl)-silane (159).**

9-BBN (45 mg, 0.37 mmol, 1.85 eq.) was added to a solution of the alkene **187** (38 mg, 0.20 mmol, 1.45 eq.) in dry THF at 0°C. The solution was allowed to warm to room temperature and was stirred overnight. In another Schlenk, were mixed vinyl bromide **150** (38 mg, 0.2 mmol), cesium carbonate (123 mg, 0.38 mmol, 1.85 eq.), triphenylarsine (9 mg, 0.03 mmol, 15 mol%) and PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (12 mg, 0.015 mmol, 7 mol %) in DMF (3 ml). Before the solution of the alkylboronate was transferred to the second Schlenk, 2 drops of water were added in order to quench the excess of 9-BBN. The resulting solution was stirred for 30 min (the reaction was monitored by GC/MS) and quenched with a saturated NH<sub>4</sub>Cl solution. The mixture was washed with water, the aqueous layer was extracted with ether, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. Purification by flash chromatography afforded the desired product **159** (69 mg, 0.18 mmol, 90 % yield) as a colourless oil.

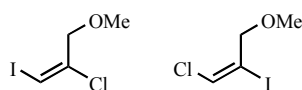
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 5.41 (m, 1H), 4.14 (s, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.30 (s, 3H), 2.12 (m, 2H), 1.93 (d, *J* = 2.3 Hz, 3H), 1.22-1.52 (m, 16H), 0.89 (s, 9H), 0.04 (s, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 149.9, 108.1, 89.4, 76.3, 71.3, 63.3, 57.8, 33.5, 32.9, 29.6, 29.5, 29.43, 29.40, 29.3, 27.6, 26.0, 25.8, 18.3, 4.3, -5.3.

IR (KBr)  $\nu$  = 2928, 2855, 2221, 1630, 1471, 1463, 1255, 1098, 836, 755, 662 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 380 [M<sup>+</sup>] (3), 365 (3), 350 (1), 323 (38), 308 (53), 217 (21), 161 (20), 147 (22), 109 (52), 93 (100), 75 (82), 55 (35), 41 (23).

HRMS (C<sub>23</sub>H<sub>44</sub>O<sub>2</sub>Si<sub>1</sub>): calculated: 380.311059u, found: 380.310661u.

**(1E)-2-Chloro-1-iodo-3-methoxy-propene (165) and (1E)-1-chloro-2-iodo-3-methoxy-propene (165a).**

3-Methoxy propyne **156** (2.572 g, 36.7 mmol, 1 eq) was added dropwise to a solution of aq. HCl (50 ml, 3N) and iodomonochloride (ICl, 5.970 g, 36.7 mmol, 1 eq) at  $-10^{\circ}\text{C}$ . After 30 min the solution had turned yellow and was extracted 3 times with diethyl ether. The organic layers were washed with an aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_5$ , dried over  $\text{Na}_2\text{SO}_4$  and evaporated to afford the products **165** and **165a** (6.712 g, 28.9 mmol, 78 % yield) as a colourless oil.

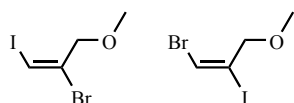
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.71 (t,  $J = 1.1$  Hz, 1H), 6.63 (broad s, 1H), 4.30 (d,  $J = 0.3$  Hz, 2H), 4.21 (d,  $J = 1.1$  Hz, 2H), 3.39 (s, 3H), 3.33 (s, 3H).

IR (KBr)  $\nu = 3070, 2989, 2928, 2822, 1600, 1106, 779, 675$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 232 [ $\text{M}^+$ ] (58), 201 (17), 127 (14), 107 (35), 105 (100), 75 (20), 55 (31), 49 (40), 45 (55), 39 (86), 29 (30).

HRMS ( $\text{C}_4\text{H}_6\text{Cl}_1\text{I}_1\text{O}_1$ ): calculated: 231.915190u, found: 231.915079u.

**(1E)-2-Bromo-1-iodo-3-methoxy-propene (166) and (1E)-1-bromo-2-iodo-3-methoxy-propene (166a).**

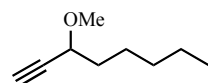


Iodomobromide (1.7 g, 8.22 mmol, 1.05 eq) was added to a solution of 1-methoxyprop-2-yne **156** (555 mg, 7.83 mmol, 1 eq), in HBr (40 ml, 48% in  $\text{H}_2\text{O}$ ) at  $0^{\circ}\text{C}$ . The mixture was stirred for 30 min at room temperature and was then extracted several times with diethylether. The combined organic layers were washed with an aqueous  $\text{Na}_2\text{S}_2\text{O}_5$  solution, dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to afford the products **166** and **166a** (1.537 g, 5.54 mmol, 71 % yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.89 (t,  $J = 1.0$  Hz, 0.58 H), 6.88 (broad s, 0.42 H), 4.31 (s, 0.84 H), 4.18 (d,  $J = 1.0$  Hz, 1.16 H), 3.38 (s, 1.26 H), 3.34 (s, 1.74 H).

$^{13}\text{C}$  NMR (100 MHz)  $\delta$  (ppm): 123.6, 108.9, 95.6, 77.6, 75.9, 74.4, 57.7, 57.6.

**3-Methoxy-oct-1-yne (169a).**



Methyl iodide (4.3 g, 30.52 mmol, 1.4 eq.) and oct-1-yn-3-ol (2.68 g, 21.2 mmol, 1 eq) were added to a suspension of NaH (524 mg, 21.8 mmol, 1.03 eq) in 20 ml THF. The solution was stirred for 21h at 50°C and carefully quenched with an aqueous NH<sub>4</sub>Cl solution. The aqueous layer was extracted with diethyl ether and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. Purification by flash chromatography (eluent: pentan/ether: 98/2) afforded the desired compound **169a** (1.653 g, 11.8 mmol, 56 % yield) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 3.93 (dt, *J* = 6.6 Hz, 2.0 Hz, 1H), 3.41 (s, 3H), 2.42 (d, *J* = 2.0, 1H), 1.65-1.80, m, 2H), 1.45 (m, 2H), 1.23-1.40 (m, 4H), 0.89 (m, 3H).

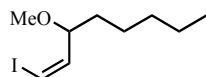
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 82.8, 73.6, 71.1, 56.4, 35.5, 31.5, 24.8, 22.5, 14.0.

IR (KBr)  $\nu$  = 3310, 2930, 2861, 1465, 1096 cm<sup>-1</sup>.

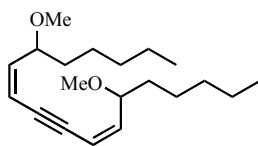
MS: *m/z* (relative intensity) 139 (0.3), 93 (7), 84 (11), 69 (100), 55 (4), 39 (13).

HRMS (C<sub>9</sub>H<sub>16</sub>O<sub>1</sub>+H): calculated: 141.127940u, found: 141.127819u.

**(1Z)-1-Iodo-3-methoxy-oct-1-ene (169).**



DiBAL-H (1.73 ml, 1.73 mmol, 1.2 eq) was added to a suspension of InCl<sub>3</sub> (380 mg, 1.72 mmol, 1.2 eq) in 4 ml THF at -78°C. The mixture was stirred 30 min before Et<sub>3</sub>B (0.3 ml, 0.3 mmol, 1M solution, 17 mol %) and alkyne **169a** (200 mg, 1.43 mmol, 1 eq) were added. The solution was stirred at -78°C for 2.5h. The reaction was treated with iodine (225 mg, 1.77 mol). The mixture was allowed to warm to room temperature and was quenched with saturated solutions of NaHCO<sub>3</sub> and Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated to afford the expected product **169** that was used directly for the next step.

**(7Z,11Z)-6,13-Dimethoxy-octadeca-7,11-dien-9-yne (170a).**

(7Z,11Z)-6,13-Dimethoxy-octadeca-7,11-dien-9-yne **170a** (17 mg, 0.06 mmol, 55 % yield) was obtained as a colourless oil from 6-methoxy-undec-4-en-2-yne **170** (36.5 mg, 0.2 mmol, 1 eq) in the presence of catalyst **1** (10 mg, 0.021 mmol, 10 mol %) in 1.5 ml toluene, following the general procedure 1.

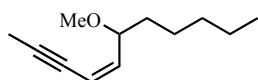
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 diastereoisomers 5.72-5.85 (m, 4H), 4.16 (m, 2H), 3.30 (m, 6H), 1.64 (m, 2H), 1.23-1.52 (m, 14H), 0.88 (m, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2 diastereoisomers 143.8, 111.9, 90.6, 79.0, 56.5, 35.0 (2C), 31.9 (2C), 24.9, 22.6, 14.0.

IR (KBr)  $\nu$  = 2970, 2928, 1738, 1366, 1092, 734  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 306 [ $\text{M}^+$ ] (8), 235 (100), 217 (19), 147 (29), 121 (16), 91 (19), 43 (35).

HRMS ( $\text{C}_{20}\text{H}_{34}\text{O}_2$ ): calculated: 306.255880u, found: 306.256123u.

**(4Z)-6-Methoxy-undec-4-en-2-yne (170).**

6-Methoxy-undec-4-en-2-yne **170** (96 mg, 0.53 mmol, 56 % yield) was obtained as a colourless oil from vinyl iodide **169** (255 mg, 0.95 mmol, 1 eq) in the presence of 9-methoxy-9-BBN (230  $\mu\text{l}$ , 1.35 mmol, 1.4 eq), 1-propynylsodium (84 mg, 1.35 mmol, 1.4 eq) and  $\text{Pd}(\text{PPh}_3)_4$  (70 mg, 0.06 mmol, 6.4 mol %) in 5 ml of THF, following the general procedure 5.

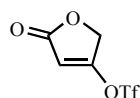
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.59-5.68 (m, 2H), 4.15 (m, 1H), 3.29 (s, 3H), 1.97 (m, 3H), 1.61 (m, 1H), 1.23-1.50 (m, 7H), 0.88 (m, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 142.5, 112.4, 90.9, 78.6, 75.9, 56.3, 35.0, 31.8, 24.8, 22.6, 14.0, 4.3.

MS:  $m/z$  (relative intensity) 180 [ $\text{M}^+$ ] (3), 123 (4), 109 (100), 91 (8), 77 (8), 53 (14), 41 (8).

HRMS ( $\text{C}_{12}\text{H}_{20}\text{O}_1$ ): calculated: 180.151415u, found: 180.151846u.

### Trifluoromethanesulfonic acid 5-oxo-2,5-dihydrofuran-3-yl ester (**173**).<sup>[162]</sup>



Ethyl-diisopropylamine (4.36 ml, 2.45 mmol, 1 eq.) and triflic anhydride (4.16 ml, 2.45 mmol, 1 eq.) were added to a solution of tetronic acid (2.448 g, 2.45 mmol, 1 eq.) in 20 ml of dichloromethane at  $-78^\circ\text{C}$ . The reaction was allowed to warm up to room temperature and quenched with water. The aqueous layer was extracted with dichloromethane, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Purification by flash chromatography (using hexanes/ethyl acetate: 1/1 as the eluent) afforded the desired product **173** (5.11 g, 2.20 mmol, 90% yield) as a colourless oil.

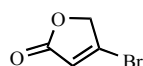
$^1\text{H}$ -NMR (400 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  (ppm): 6.06 (t,  $J = 1.8$  Hz, 1H), 4.89 (d,  $J = 1.8$  Hz, 2H).

$^{13}\text{C}$ -NMR (100 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  (ppm): 169.2, 167.3, 118.8 (q,  $J_{\text{CF}} = 321.9$  Hz), 105.0, 68.0.

IR (film)  $\nu = 3143, 2953, 1789, 1760, 1652, 1439, 1248, 1221, 815, 606$   $\text{cm}^{-1}$ .

MS (EI):  $m/z$  (relative intensity) 232 [ $\text{M}^+$ ] (1), 167 (2), 139 (49), 69 (100), 41 (31).

### 4-Bromo-5H-furan-2-one (**174**).<sup>[161]</sup>



Oxalyl bromide (10.0 mL, 108 mmol, 1.2 eq) was added dropwise over 1 h to a stirred suspension of tetronic acid (9.00 g, 89.9 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (200 ml) and anhydrous DMF (9 mL) under argon, while carefully maintaining the internal temperature at  $0^\circ\text{C}$ . The yellow



solution turned green and was stirred successively at 0 °C for 1 h and room temperature for 2 h. H<sub>2</sub>O (250 ml) was added, the layers separated and the aqueous phase further extracted with Et<sub>2</sub>O (4 × 100 ml). The combined organic extracts were washed successively with H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), filtered and evaporated. Recrystallisation of the residual solid from Et<sub>2</sub>O afforded bromofuranone **174** as white needles (11.9 g, 81%).

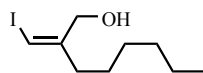
Mp 76-77 °C

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 4.84 (d, *J* = 1.5 Hz, 1H), 6.32 (s, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 170.8, 146.3, 121.7, 74.9.

IR (KBr)  $\nu$  = 1776, 1748, 1600, 1264, 1154, 1014, 867 cm<sup>-1</sup>.

#### (2Z)-2-iodomethylene-octan-1-ol (**176**).



Methylmagnesium bromide (3M in ether, 3.75 ml, 11.3 mmol, 1 eq.) was added dropwise to a solution of propargyl alcohol **160** (632 mg, 11.3 mmol) in diethyl ether (50 ml). The solution was stirred vigorously during 30 min and cooled to -15°C before addition of copper iodide (10 mol%) and hexylmagnesium bromide (13.5 mmol, 1.2 eq) in 30ml THF. The solution was allowed to reach room temperature and was stirred for 2h. The solution was cooled to -78°C and was treated with an excess of iodine. After the exothermic reaction ceased, the solution was allowed to warm to room temperature and was stirred for 2h. The reaction was quenched with a saturated NH<sub>4</sub>Cl solution. The aqueous phase was extracted with diethyl ether, the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. Careful purification by flash chromatography afforded the desired isomer **176** (1.153 g, 4.47 mmol 38 % yield) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 6.01 (s, 1H), 4.25 (s, 2H), 2.31 (dt, *J* = 1.2 Hz, 7.7 Hz, 2H), 1.58 (broad s, 1H), 1.47 (m, 2H), 1.22-1.37 (m, 6H), 0.88 (m, 3H).

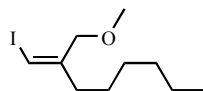
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 150.3, 75.9, 67.0, 35.9, 31.6, 28.9, 27.7, 22.5, 14.0.

IR (KBr)  $\nu$  = 3316, 3054, 2954, 2927, 2856, 1610, 1377, 1021, 770 cm<sup>-1</sup>.

MS:  $m/z$  (relative intensity) 268 [ $M^+$ ] (23), 198 (2), 183 (14), 123 (15), 81 (55), 67 (28), 57 (100), 43 (47), 29 (26).

HRMS ( $C_9H_{17}I_1O_1$ ): calculated: 268.032412u, found: 268.032502u.

**(1Z)-1-Iodo-2-methoxymethyl-oct-1-ene (177).**



Methyl iodide (150  $\mu$ l, 2.41 mmol, 3.2 eq.) and alcohol **176** (200 mg, 0.75 mmol, 1 eq) were added to a suspension of NaH (50 mg, 2.08 mmol, 2.8 eq) in 5 ml THF. The solution was stirred for 3h at room temperature and carefully quenched with a saturated  $NH_4Cl$  solution. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried over  $Na_2SO_4$  and evaporated. Purification by flash chromatography (using pentanes/ether: 95/5 as the eluent) afforded the desired product **177** (157 mg, 0.56 mmol, 75 % yield) as a colourless oil.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm): 6.08 (broad s, 1H), 4.06 (s, 2H), 3.33 (broad s, 3H), 2.25 (dt,  $J = 1.15$  Hz, 7.7 Hz, 2H), 1.45 (m, 2H), 1.23-1.36 (m, 6H), 0.88 (m, 3H).

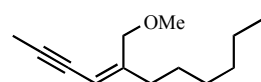
$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm): 148.2, 76.6, 75.8, 58.0, 35.6, 31.6, 28.9, 27.7, 22.6, 14.0.

IR (KBr)  $\nu = 3055, 2955, 2926, 2857, 1611, 1377, 1109$   $cm^{-1}$ .

MS:  $m/z$  (relative intensity) 282 [ $M^+$ ] (9), 197 (7), 155 (28), 123 (5), 81 (27), 71 (100), 55 (17), 45 (38), 41 (25), 29 (11).

HRMS ( $C_{10}H_{19}I_1O_1$ ): calculated: 282.048062u, found: 282.048389u.

**(4Z)-5-Methoxymethyl-undec-4-en-2-yne (178).**



5-Methoxymethyl-undec-4-en-2-yne **178** (88 mg, 0.45 mmol, 88 % yield) was obtained as a colourless oil from vinyl iodide **177** (145 mg, 0.51 mmol, 1 eq) in the presence of 9-methoxy-9-BBN

(159  $\mu$ l, 0.89 mmol, 1.7 eq), 1-propynylsodium (50 mg, 0.80 mmol, 1.6 eq) and Pd(PPh<sub>3</sub>)<sub>4</sub> (27 mg, 0.026 mmol, 5 mol %) in 5 ml THF, following the general procedure 5.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 5.41 (m, 1H), 4.14 (s, 2H), 3.30 (s, 3H), 2.13 (m, 2H), 1.97 (d,  $J$  = 2.35 Hz, 3H), 1.44 (m, 2H), 1.27 (m, 6H), 0.88 (m, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 150.0, 108.1, 89.4, 76.4, 71.4, 57.8, 33.5, 31.7, 29.0, 27.6, 22.6, 14.0, 4.3.

IR (KBr)  $\nu$  = 2956, 2927, 2819, 2221, 1457, 1377, 1108, 1088, 725 cm<sup>-1</sup>.

MS:  $m/z$  (relative intensity) 194 [M<sup>+</sup>] (19), 123 (13), 109 (100), 91 (10), 77 (9), 53 (8), 45 (10), 29 (5).

HRMS (C<sub>13</sub>H<sub>22</sub>O<sub>1</sub>): calculated: 194.167065u, found: 194.066859u.

**(7Z,11Z)-7,12-Bis-methoxymethyl-octadeca-7,11-dien-9-yne (179).**



7,12-Bis-methoxymethyl-octadeca-7,11-dien-9-yne **179** (22 mg, 0.066 mmol, 62 % yield) was obtained as a colourless oil from 5-methoxymethyl-undec-4-en-2-yne **178** (41.5 mg, 0.21 mmol, 1 eq) in the presence of catalyst **1** (7.4 mg, 0.016 mmol, 7.5 mol %) in 2 ml toluene, following the general procedure 1.

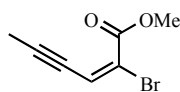
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 5.61 (s, 2H), 4.18 (s, 4H), 3.32 (s, 6H), 2.18 (t,  $J$  = 7.6 Hz, 4H), 1.45 (m, 4H), 1.29 (m, 12H), 0.88 (m, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 150.6, 107.6, 89.8, 71.2, 57.5, 33.4, 31.3, 28.7, 27.2, 22.2, 13.7.

IR (KBr)  $\nu$  = 2956, 2927, 2184, 1632, 1109, 1089, 725 cm<sup>-1</sup>.

MS:  $m/z$  (relative intensity) 334 [M<sup>+</sup>] (50), 319 (39), 303 (31), 263 (26), 249 (100), 231 (37), 217 (15), 147 (24), 121 (22), 91 (28), 43 (55), 29 (13).

HRMS (C<sub>22</sub>H<sub>38</sub>O<sub>2</sub>): calculated: 334.287180u, found: 334.287202u.

**(2E)-Methyl-2-Bromo-hex-2-en-4-ynoate (185).**

Phosphonate **180** (278 mg, 0.87 mmol, 1 eq) was added dropwise to a suspension of NaH (22 mg, 0.92 mmol, 1.05 eq) in THF at  $-78^{\circ}\text{C}$ . The mixture was stirred for 5 min at  $-78^{\circ}\text{C}$ , warmed to  $0^{\circ}\text{C}$  and stirred for 30 min before addition of  $\text{Br}_2$  (161 mg, 1 mmol, 1.15 eq) at  $0^{\circ}\text{C}$ . The resulting mixture was allowed to warm to room temperature and was stirred for 2h. The solution was cooled to  $-78^{\circ}\text{C}$  and following reagents were added in this order: crown ether (18 Crown 6, 323 mg, 1.22 mmol, 1.3 eq), *t*-BuOK (1.71 ml, 0.96 mmol, 1.1 eq of a 0.5 M THF solution) and but-2-ynal **184** (excess). The reaction was stirred at  $-78^{\circ}\text{C}$  for 2.5h before it was quenched with  $\text{NH}_4\text{Cl}$  and  $\text{Na}_2\text{S}_2\text{O}_5$  solutions. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Careful purification by flash chromatography (eluent: pentan/ $\text{Et}_2\text{O}$ : 95/5) afforded the expected (*E*)-configured product **185** (118 mg, 0.58 mmol, 67 % yield of the (*E*)-Isomer) as a colourless oil.

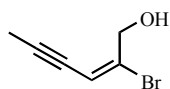
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.62 (q,  $J = 2.7$  Hz, 1H), 3.84 (s, 3H), 2.04 (d,  $J = 2.7$  Hz, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 162.2, 124.9, 121.4, 99.6, 76.7, 53.1, 5.1.

IR (KBr)  $\nu = 3020, 2953, 2220, 1725, 1579, 1225$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 204 [ $\text{M}^+$ ] (28), 202 [ $\text{M}^+$ ] (28), 173 (14), 171 (14), 145 (12), 143 (12), 123 (100), 91 (13), 63 (27), 39 (6).

HRMS ( $\text{C}_7\text{H}_7\text{Br}_1\text{O}_2$ ): calculated: 201.962955u, found: 201.963202u.

**(2E)-2-Bromo-hex-2-en-4-yn-1-ol (186).**

A solution of DiBAL-H (6.1 ml, 6.1 mmol, 6.1 eq) in  $\text{CH}_2\text{Cl}_2$  was added dropwise to a solution of methyl-2-bromo-hex-2-en-4-ynoate **185** (205 mg, 1 mmol, 1 eq) in diethyl ether at  $-78^{\circ}\text{C}$ . The

solution was stirred at  $-78^{\circ}\text{C}$  for 2h before the dry ice / acetone bath was removed and the reaction was quenched with an aqueous solution of Rochelle's salt when the internal temperature had reached  $-30^{\circ}\text{C}$ . The mixture was vigorously stirred until a clear phase separation was obtained. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Purification by flash chromatography (using pentanes/ $\text{Et}_2\text{O}$ : 70/30 as the eluent) afforded the expected product **186** (135 mg, 0.76 mmol, 76 % Yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.00 (qt,  $J = 2.4$  Hz,  $J = 0.5$  Hz, 1H), 4.48 (s, 2H), 2.18 (broad s, 1H), 1.95 (d,  $J = 2.5$  Hz, 3H).

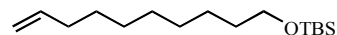
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 137.0, 114.6, 93.0, 74.8, 64.5, 4.5.

IR (KBr)  $\nu = 3348, 3033, 2916, 2219, 1604, 1061, 1030$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 176 [ $\text{M}^+$ ] (46), 174 [ $\text{M}^+$ ] (46), 161 (7), 159 (7), 119 (4), 117 (4), 95 (90), 77 (20), 67 (84), 51 (43), 41 (100), 27 (14).

HRMS ( $\text{C}_6\text{H}_7\text{Br}_1\text{O}_1$ ): calculated: 173.968040u, found: 173.967948u.

#### Dec-9-enyloxy-(*tert*-butyldimethyl)-silane (**187**).



Commercially available alcohol **149** (500 mg, 3.2 mmol, 1eq.) was added to a solution of imidazole (545 mg, 8 mmol, 2.5eq.) and *tert*-butyldimethylchlorosilane (565 mg, 3.68 mmol, 1.15 eq.) in 10 ml DMF. The solution was stirred under argon for 1h, before it was diluted with 20 ml MTBE and the reaction was quenched with 20 ml  $\text{H}_2\text{O}$ . The organic layers were washed 7 times with small amounts of water. The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. The residue was purified by flash chromatography (using pentanes/ether: 95/5 as the eluent) to afford the desired product **187** (871 mg, 3.2 mmol, quantitative yield) as a colourless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.75 (m, 1H), 4.89 (m, 2H), 3.54 (t,  $J = 6.6$  Hz, 2H), 1.98 (m, 2H), 1.45 (m, 2H), 1.18-1.38 (m, 10H).

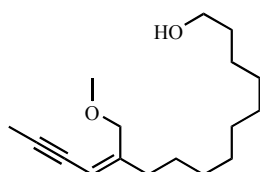
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  (ppm): 139.2, 114.1, 63.3, 33.8, 32.9, 29.5, 29.4, 29.1, 28.9, 26.0, 25.8, 18.4, -5.3.

IR (KBr)  $\nu$  = 3078, 2928, 1641, 1472, 1463, 1361, 1255, 1101, 992, 939, 909, 836, 775, 661  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 270 [ $M^+$ ] (0.09), 213 (40), 185 (2), 167 (0.68), 129 (1), 115 (2), 89 (10), 75 (100), 55 (5), 41 (5).

HRMS ( $\text{C}_{16}\text{H}_{34}\text{O}_1\text{Si}_1$ ): calculated: 271.245179u, found: 271.245324u.

**(11Z)-11-Methoxymethyl-pentadec-11-en-13-yn-1-ol (189).**



TBAF (1M, 160  $\mu\text{l}$ , 0.16 mmol, 1 eq) in THF was added dropwise to a solution of enyne **159** (60 mg, 0.16 mmol, 1 eq) at room temperature. After 1h, the reaction was quenched with an aq.  $\text{NaHCO}_3$  solution, the aqueous layer was extracted with MTBE, the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Purification of the residue by flash chromatography (using hexane/ethyl acetate: 2/1 as the eluent) afforded the desired alcohol **189** (38 mg, 0.14 mmol, 90 % yield) as a colourless oil.

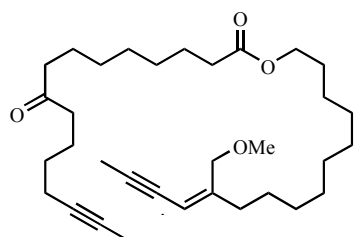
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.41 (m, 1H), 4.15 (s, 2H), 3.63 (t,  $J$  = 6.6 Hz, 2H), 3.30 (s, 3H), 2.12 (m, 2H), 1.97 (d,  $J$  = 2.3 Hz, 3H), 1.56 (m, 2H), 1.22-1.48 (m, 15H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 149.9, 108.1, 89.5, 76.3, 71.3, 63.1, 57.8, 33.5, 32.8, 29.53, 29.45, 29.40, 29.37, 29.31, 27.6, 25.7, 4.4.

IR (KBr)  $\nu$  = 3372, 2926, 2854, 2220, 1628, 1465, 1375, 1087, 722  $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 266 [ $M^+$ ] (8), 251 (5), 165 (2), 151 (5), 123 (18), 109 (100), 91 (10), 77 (7), 55 (6), 45 (7).

HRMS ( $\text{C}_{17}\text{H}_{28}\text{O}_2$ ): calculated: 266.224580u, found: 266.224228u.

**(11Z)-11-Methoxymethyl-pentadec-11-en-13-ynyl-9-oxo-hexadec-14-ynoate (190).**

Carboxylic acid **148** (72 mg, 0.27 mmol, 1.1 eq) was added to a solution of alcohol **189** (65 mg, 0.24 mmol, 1 eq), EDC (94 mg, 0.49 mmol, 2 eq) and DMAP (59 mg, 0.49 mmol, 2 eq) in 15 ml dichloromethane. The mixture was stirred for 6h before work up with HCl (1N). The aqueous layers were extracted with dichloromethane, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. Purification by flash chromatography (using hexane/ethylacetate: 4/1 as the eluent) afforded the desired product **190** (117 mg, 0.23 mmol, 90 % yield) as a colourless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 5.40 (m, 1H), 4.13 (s, 2H), 4.03 (t, *J* = 6.7 Hz, 2H), 3.28 (s, 3H), 2.37 (m, 4H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.11 (m, 4H), 1.95 (d, *J* = 2.3 Hz, 3H), 1.75 (t, *J* = 2.6 Hz, 3H), 1.17-1.72 (m, 30H).

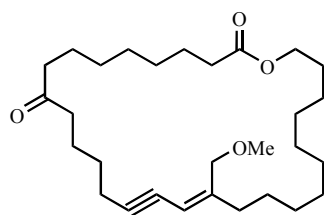
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 211.0, 173.8, 149.9, 108.1, 89.4, 78.7, 76.3, 75.7, 71.3, 64.4, 57.8, 42.7, 42.2, 34.3, 33.5, 29.42 (2 C), 29.37, 29.28, 29.18, 29.0 (2 C), 28.9, 28.6, 28.5, 27.6, 25.9, 24.9, 23.7, 23.0, 18.5, 4.3, 3.4.

IR (KBr) ν = 2920, 2850, 2215, 1726, 1726, 1703, 1377, 1176, 1107, 719 cm<sup>-1</sup>.

MS: *m/z* (relative intensity) 514 [M<sup>+</sup>] (30), 499 (20), 482 (10), 402 (4), 249 (5), 133 (17), 123 (4), 109 (100), 105 (17), 81 (30), 55 (34), 43 (15).

HRMS (C<sub>33</sub>H<sub>54</sub>O<sub>4</sub>): calculated: 514.402.210u, found: 514.402448u.

Anal (C<sub>33</sub>H<sub>54</sub>O<sub>4</sub>) calculated. C 76.99, H 10.57, found C 76.81, H 10.65.

**(17Z)-18-Methoxymethyl-oxa-cyclooctacos-17-en-15-yne-2,10-dione (191).**

Molybdenum catalyst **5** (7.5 mg, 0.016 mmol, 10 mol %) and freshly distilled  $\text{CH}_2\text{Cl}_2$  (120  $\mu\text{l}$ , 1.87 mmol, 15 eq.) were added at room temperature to a solution of diyne **190** (60 mg, 0.12 mmol, 1 eq) in freshly distilled toluene (85 ml). The mixture was stirred at 80°C for 15h under a gentle argon flow. After complete conversion, the reaction was quenched with 5 ml of methanol. The solvent was evaporated and the residue was purified by flash chromatography (using hexanes/ethyl acetate: 90/10 as the eluent) to afford the desired macrocycle **191** (43 mg, 0.093 mmol, 80 % yield) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.44 (m, 1H), 4.14 (s, 2H), 4.07 (t,  $J = 6.2$  Hz, 2H), 3.30 (s, 3H), 2.32-2.47 (m, 6H), 2.28 (t,  $J = 7.3$  Hz, 2H), 2.15 (t,  $J = 6.9$  Hz, 2H), 1.19-1.81 (m, 30H).

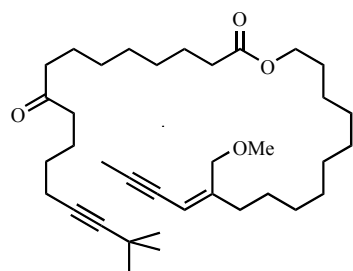
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 211.3, 173.9, 149.7, 108.3, 93.5, 77.8, 71.3, 64.3, 57.8, 42.4, 42.3, 34.4, 33.2, 29.08, 29.07, 28.90, 28.88, 28.79, 28.70, 28.52, 28.49, 28.0, 27.0, 25.7, 24.9, 23.7, 23.2, 19.2.

IR (KBr)  $\nu = 2927, 2855, 2213, 1734, 1714, 1175, 1107, 1089$   $\text{cm}^{-1}$ .

MS:  $m/z$  (relative intensity) 460 [ $\text{M}^+$ ] (98), 445 (14), 428 (100), 410 (25), 259 (10), 131 (62), 91 (68), 55 (98), 41 (43).

HRMS ( $\text{C}_{29}\text{H}_{48}\text{O}_4$ ): calculated: 483.345029u, found: 483.34560u.



**(11Z)-11-Methoxymethyl-pentadec-11-en-13-ynyl-16-tert-butyl-9-oxo-heptadec-14-ynoate (192).**

11(Z)-(11-Methoxymethyl-pentadec-11-en-13-ynyl)-16-tert-butyl-9-oxo-heptadec-14-ynoate **192** was obtained as a by-product during the cyclisation of compound **191** in the presence of catalyst **1** following the general procedure 1.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 5.41 (m, 1H), 4.15 (s, 2H), 4.05 (t,  $J = 6.7$  Hz, 2H), 3.30 (s, 3H), 2.39 (m, 4H), 2.28 (t,  $J = 7.5$  Hz, 2H), 2.13 (m, 4H), 1.97 (d,  $J = 2.3$  Hz, 3H), 1.22-1.72 (m, 30H), 1.19 (s, 9H).

MS:  $m/z$  (relative intensity) 556 [ $\text{M}^+$ ] (54), 541 (16), 509 (17), 499 (30), 467 (19), 291 (11), 233 (7), 151 (24), 137 (29), 123 (32), 109 (100), 55 (46), 43 (25), 41 (20), 29 (6).

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