

**Jon Tangaa Jensen**

**Studies towards  
the total synthesis of  
latrunculin A and latrunculin B**

## Acknowledgements

A thank to Prof. Dr. A. Fürstner for accepting me in his group and for his kind interest in my project.

I would also like to thank Dr. Liliana Parra-Rapado for her preliminary work on the project and for her suggestions for the work on latrunculin B.

Likewise, I would like to thank Dr. Dominic DeSouza for his important contribution to the latrunculin B project and for finishing the total synthesis of latrunculin B.

Also a thank to Karin Radkowski for constantly being helpful with anything practical in the lab.

Furthermore I would like to thank Dr. Martin Albert for fruitful discussions and interesting suggestions to my project.

Also I would like to thank Dr. Frank Glorius, Gereon Altenhoff, Kristian Burstein, Andrea Jantsch, Fabian Feyen, Dr. Jacques Ragot, Andreas Leitner and Dschun Song for a good working atmosphere on the 6<sup>th</sup> floor, and Doris Kremzow and Stefan Prühs for a friendly atmosphere in general.

The other members of the Fürstner group just like previous members of the Fürstner group are thanked for their help, support and interest in my work.

Furthermore, the technical staff and the administration at the MPI in Mülheim are thanked for their friendly help.

## Contents

<b>General theory</b>	<b>1</b>
<b>Latrunculines</b>	<b>5</b>
<b>Previous syntheses of latrunculin</b>	<b>9</b>
<b>Latrunculines by metathesis</b>	<b>12</b>
<b>Previous work in the group</b>	<b>16</b>
<b>Studies towards latrunculin B and A</b>	<b>21</b>
<b>Ketone fragment</b>	<b>21</b>
<b>The aldehyde fragment</b>	<b>26</b>
<b>The aldol reaction</b>	<b>32</b>
<b>Latrunculin A</b>	<b>36</b>
<b>Preparation of the molybdenum precatalyst</b>	<b>44</b>
<b>Ring closing enyne-yne metathesis</b>	<b>49</b>
<b>Aldol reaction for latrunculin A</b>	<b>51</b>
<b>Alkene cross metathesis</b>	<b>55</b>
<b>Vinyl ketone synthesis</b>	<b>60</b>
<b>Conclusion</b>	<b>64</b>
<b>Experimental</b>	<b>69</b>
<b>General information</b>	<b>69</b>
<b>Analytical methods</b>	<b>69</b>
<b>Chemicals prepared in the group</b>	<b>71</b>
<b>Experimental procedures</b>	
71	
<b>Literature</b>	<b>104</b>
<b>Appendix 1</b>	<b>111</b>

## Abbreviations

Ac	Acetyl
acac	Acetylacetonate
aq.	Aqueous
Bn	Benzyl
br	Broadened
CM	Cross Metathesis
conc.	Concentrated
Cy	Cyclohexyl
d	Doublet
$\delta$	Chemical Shift
dba	Dibenzylidene Acetone
DMAP	<i>N, N'</i> -Dimethylaminopyridin
DMF	Dimethylformamid
DMPU	<i>N, N'</i> -Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
EA	Ethyl Acetate
e.e.	Enantiomeric Excess
EI	Electron Ionisation
eq	Equivalent
Et	Ethyl
Fig.	Figure
GC-MS	Gas Chromatography-Mass Spectrometry
HPLC	High-Performance Liquid Chromatography
Hz	Hertz
IR	Infra Red
<i>J</i>	Coupling Constant
KHMDS	Potassium Hexamethyldisilazane
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropyl Amide
m	Multiplet
MCPBA	<i>m</i> -Peroxybenzoic acid
Me	Methyl
Mes	Mesitylene
MHz	MegaHertz
min	Minutes
<i>m/z</i>	Mass/Charge
MTBE	Methyl <i>tert</i> -Butyl Ether
<i>n</i>	Normal
<i>n</i> -BuLi	Lithium <i>n</i> -Butylide
NaHMDS	Sodium Hexamethyldisilazane
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
PMB	<i>p</i> -Methoxybenyl
Py	Pyridine
q	Quartet
RCAM	Ring Closing Alkyne Metathesis
Red-Al	Sodium <i>bis</i> (2-Methoxyethoxy)aluminium Hydride

r.t.	Room Temperature
s	Singlet
SEM	(Trimethylsilyl)ethoxymethyl
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl
<i>tert</i>	Tertiary
Teoc	2-(Trimethylsilyl)ethyl Carbamoyl
Tf	Triflate
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPAP	Tetra- <i>n</i> -propylammonium Perruthenate
UV	Ultra Violet

## General theory

In recent years metathesis reactions have become increasingly important because of the development of a number of catalysts that are efficient and tolerant to a variety of functional groups, allowing olefin and alkyne metathesis to be used as key step in total synthesis.<sup>1</sup> The metathesis itself is a formal exchange of alkylidene or alkylidyne moieties of a pair of alkenes or alkynes (Fig. 1).

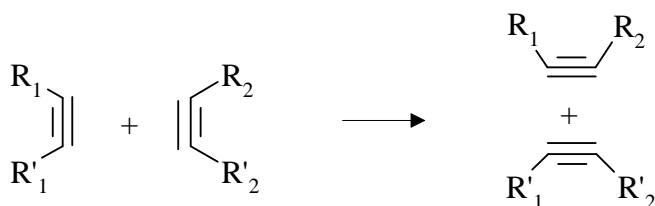


Fig.1: General reaction scheme for metathesis.

Olefin metathesis was first reported in a patent in 1955<sup>2</sup> and became industrially important in the following decades.<sup>3</sup> The first catalysts were typically chlorides or oxychlorides of tungsten, molybdenum or rhenium catalyzed by cocatalysts such as trialkyl aluminium or diethyl aluminium chloride. However, the oxophilicity of these compounds and the operational temperatures of more than 100 °C limited the scope of the reaction. The industrially important catalysts were mostly heterogeneous, but homogeneous catalysts were also employed.<sup>4</sup>

Alkene metathesis became synthetically relevant after Schrock *et al.* reported the homogeneous catalyst **1** which is able to perform alkene metathesis at ambient temperature.<sup>5</sup> In the following years Grubbs published two other homogeneous catalysts, **2**<sup>6</sup> and **3**,<sup>7</sup> that are in some cases also active at ambient temperature and tolerate even the presence of water (Fig. 2).

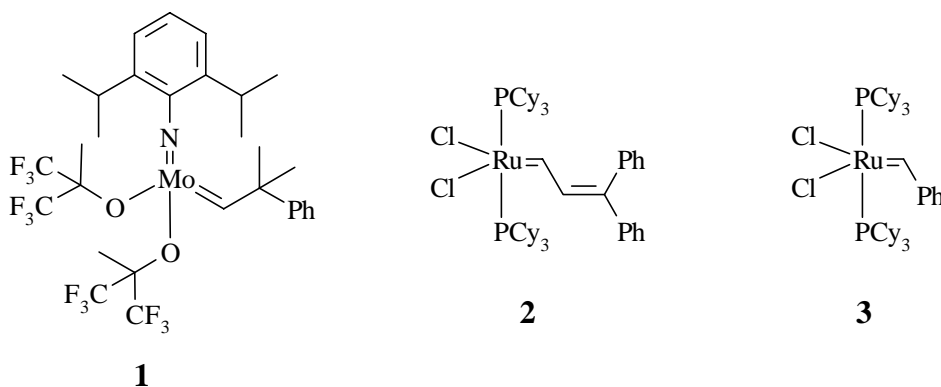


Fig. 2: Homogeneous catalysts for alkene metathesis.

The accepted mechanism of alkene metathesis was proposed by Chauvin. It involves two four membered metallacycles and two metal carbenes.<sup>8</sup> The metal carbene **A** adds to an alkene via a formal [2+2] cycloaddition to give the metallacycle **B**, which reacts via a [2+2] cycloreversion to give ethene and a new metal carbene, **C**. The latter then adds to another alkene to give metallacycle **D** which undergoes a [2+2] cycloreversion that results in a new product and regenerates the catalytically active metal carbene **A** (Fig. 3).

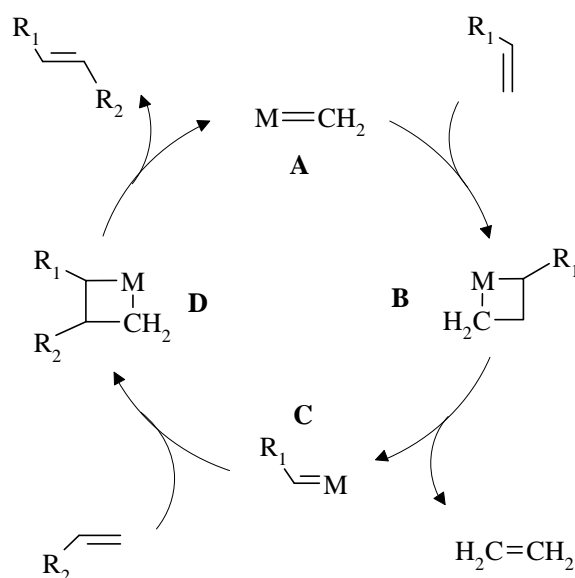


Fig. 3: The Chauvin mechanism for alkene metathesis.

In 1974 the first catalytic system for alkyne metathesis was published by Mortreux *et al.* who reported that a 1:6 mixture of hexacarbonyl molybdenum and resorcinol is catalytically active.<sup>9</sup> However, the reaction temperature of 160 °C constitutes a serious disadvantage. Although the catalytic system was further improved by changing to phenol and adjusting the ratio of hexacarbonyl molybdenum the phenol, a reaction temperature of 140 °C is still required, limiting the method to alkynes with no acid- or heat sensitive functionalities.<sup>10</sup>

In 1982 Villemin *et al.* reported that alkynes with ester-, acetate-, bromide- or carboxylic acid groups undergo alkyne metathesis when treated with hexacarbonyl molybdenum and *p*-chloro phenol in refluxing octane, whereas alkynes containing nitriles or alcohols only gave low conversions.<sup>11</sup> In 1995 Mori *et al.* used the Mortreux catalyst to perform alkyne cross metathesis, showing that unsymmetrical alkynes could be obtained in good yields by this route.<sup>12</sup> The catalytic system of Mortreux was further improved by Bunz *et al.* by

changing the solvent to *o*-dichlorobenzene, using *p*-(trifluoromethyl)phenol as additive and purging the reaction with nitrogen.<sup>13</sup>

In 1995 Mori proposed a reaction mechanism for alkyne metathesis without being able to prove the mechanism experimentally (Fig. 4).<sup>14</sup>

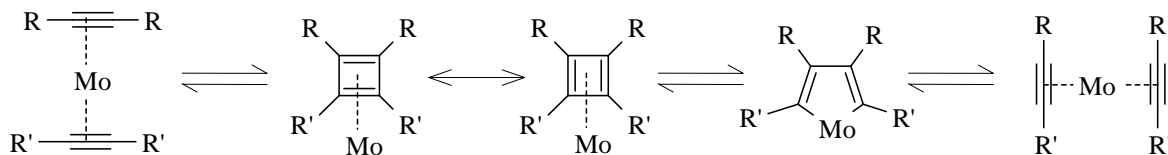


Fig. 4: The mechanism proposed by Mori for alkyne metathesis with the Mortreux catalyst.

In 1975 Katz suggested a possible reaction mechanism for alkyne metathesis, the alkylidyne mechanism, involving two metallacyclobutadienes as intermediates (Fig. 5).<sup>15</sup> This mechanism was verified experimentally by Schrock in the case of a tungsten-based catalyst.<sup>16</sup>

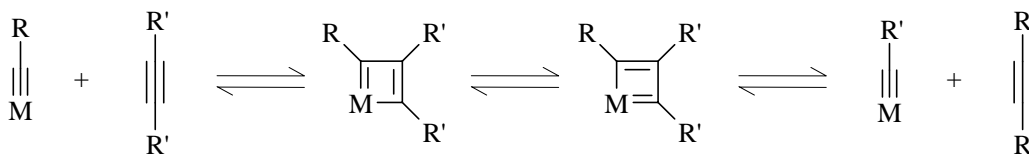


Fig. 5: The alkylidyne mechanism for alkyne metathesis.

A much more reactive and structurally well defined catalyst for alkyne metathesis was discovered by Schrock in 1981 (Fig. 6).<sup>17</sup> The tungsten (VI) complex **4** is catalytically active at ambient temperature, thus broadening the scope of alkyne metathesis significantly. For example, in 1998 Fürstner *et al.* reported the first ring closing alkyne metathesis with this catalyst and showed that it was possible to prepare 12 to 28 membered rings with ester or amide functionalities in good yields.<sup>18</sup> The importance of this result followed from the fact that alkynes can be selectively reduced to *Z*-configured alkenes, and thus macrocyclic alkenes with a defined configuration of the double bond became accessible by a metathesis route.

The tungsten-alkylidyne catalyst **4** developed by Schrock and co-workers<sup>17</sup> is sensitive towards donor groups such as thioethers, polyethers or amines. It does, however, tolerate the presence of free amide protons.



In 1999 Fürstner *et al.* published another catalyst for alkyne metathesis and ring closing alkyne metathesis based on the molybdenum complex **5** (Fig. 6).<sup>19</sup>

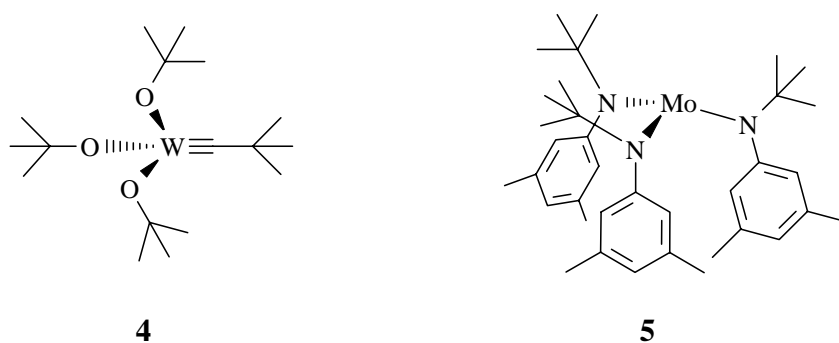


Fig. 6: The Schrock catalyst and the Cummins complex used by Fürstner *et al.* as precatalyst.

The molybdenum-based precatalyst **5** was originally reported by Cummins in 1995.<sup>20</sup> The complex *per se* is inactive, but when treated with chlorinated solvents such as dichloromethane at ambient temperature, two different well defined complexes arise, both of which are active catalysts for alkyne metathesis.

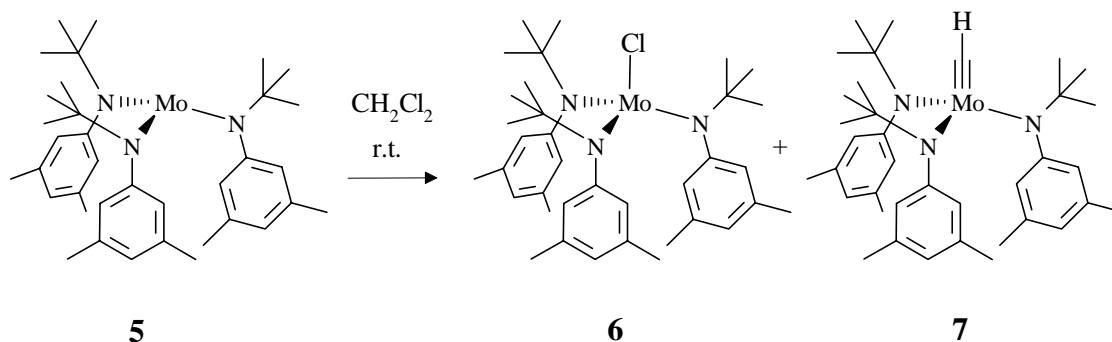


Fig. 7: Initial activation of **5** by  $\text{CH}_2\text{Cl}_2$  reported by Fürstner *et al.*

This catalytic system is in some aspects complementary to the Schrock catalyst **4** since it is less sensitive to donor ligands that deactivate the latter. Therefore it can be applied to substrates containing thioethers, basic tertiary nitrogen atoms or polyether chains.<sup>19</sup>

However, catalysts **6** and **7** do not tolerate unprotected alcohols or free amide protons.

In 2003 Moore *et al.* extended the method developed by Fürstner and published a similar catalyst **8**.<sup>21</sup> The modification made by Moore on this catalytic system gave a catalyst that performs well in presence of unprotected amides (Fig. 8).<sup>21</sup>

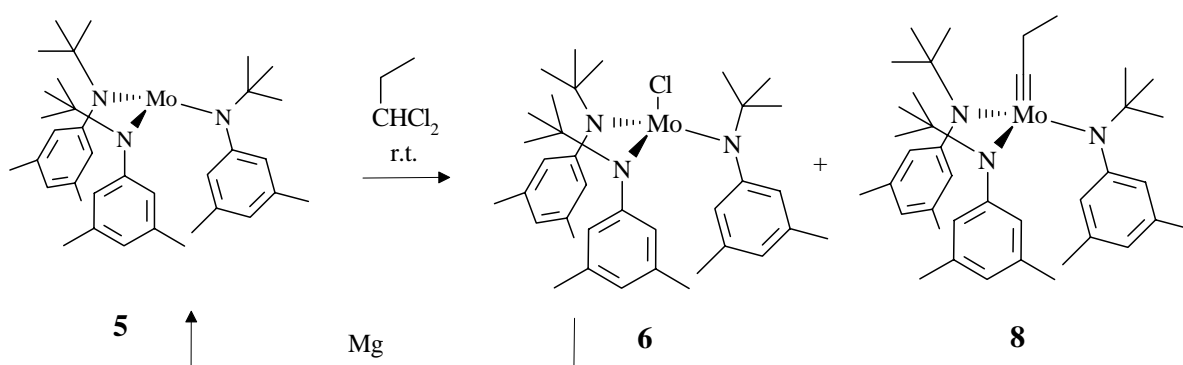


Fig. 8. The modification of the Fürstner catalyst developed by Moore *et al.*

## Latrunculines

The latrunculines were discovered in 1980 by Kashman and co-workers who isolated latrunculin A and latrunculin B from the Red Sea sponge *Latruncula magnifica*.<sup>22</sup> Unlike most sponges in the Red Sea, colonies of *Latruncula magnifica* appear never to be damaged or eaten by fish. The latrunculines were isolated from a reddish fluid that these organisms produce when squeezed manually.

The latrunculines were the first marine macrolides discovered to contain a 16- or 14-membered ring and they are unusual in that they contain the rare thiazolidinone moiety.<sup>23</sup>

Latrunculin A has later also been isolated from other sources such as the Fijian sponge *Spongia mycofijiensis*, an associated nudibranch *Chromodoris lochi*<sup>24</sup> and the sponge *Fasciospongia rimosa*.<sup>25</sup> In 1997 latrunculin B was isolated from the nudibranch *Chromodoris hamiltoni*<sup>26</sup> and in 2003 from the sponge *Negombata magnifica*.<sup>27</sup>

The structure of latrunculin A was determined by X-ray crystallography in 1980.<sup>28</sup>

In 1985 Kashmann also isolated latrunculin C and D, and fully characterised latrunculin B by assigning the <sup>1</sup>H and <sup>13</sup>C-NMR signals.<sup>29</sup> The structure of latrunculin C was assigned by chemical reduction of latrunculin B with sodium borohydride.

Recently an epimer of latrunculin B containing a thiazolidinone moiety with the opposite stereochemistry, 16-*epi*-latrunculin, has been isolated from the Red Sea sponge *Negombata magnifica*. This epimer was shown to possess cytotoxic and antiviral properties (Fig. 9).<sup>27</sup>

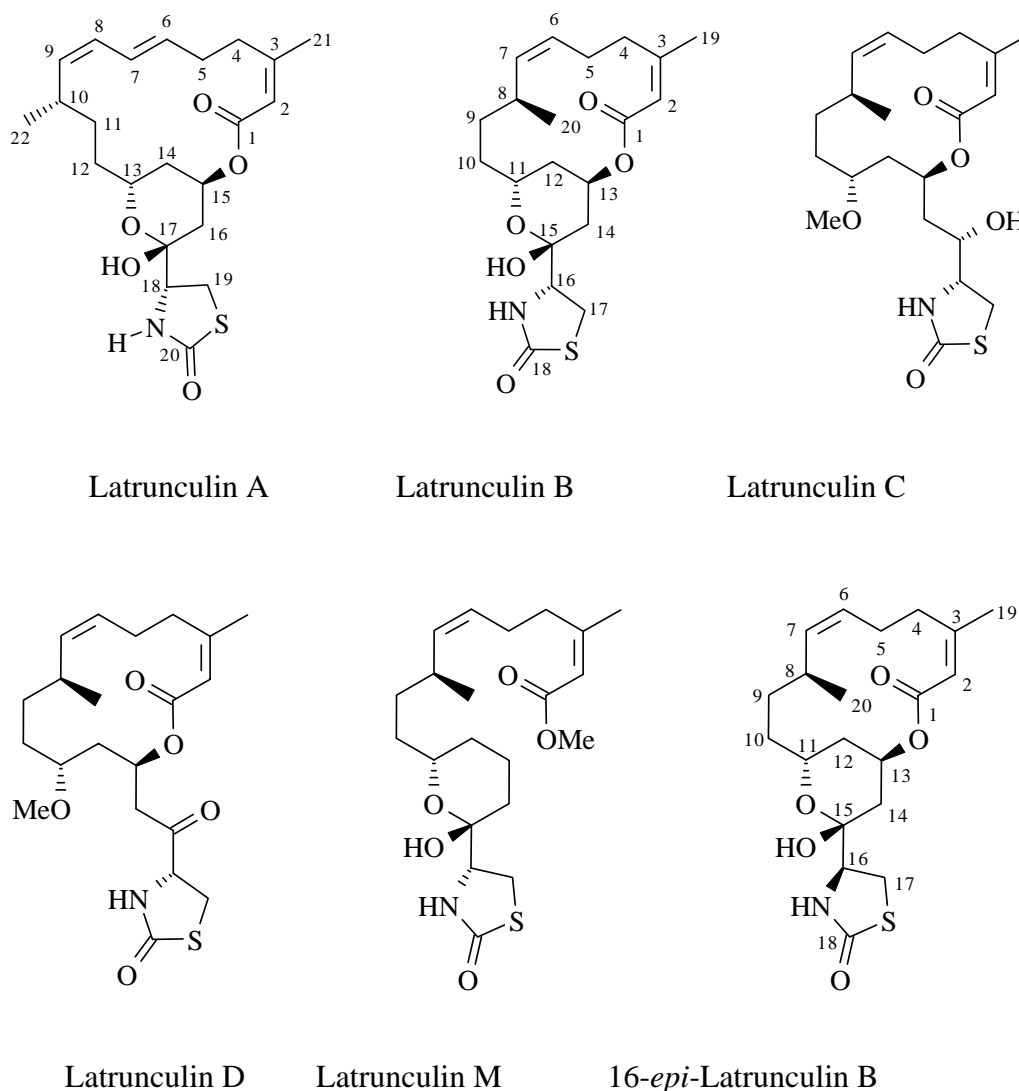


Fig. 9: Latrunculin natural products.

The biological activity of this family of compounds can be ascribed to a pronounced ability to inhibit actin polymerization<sup>23</sup> and in this way passivate great parts of the cytoskeleton. The main functions of the actin cytoskeleton is to provide structural support by organizing the organelles in the cell, maintain the cell shape and move cilia inside the cell. The cytoskeleton is not a passive framework, but undergoes constant rearrangement. Processes such as fertilisation, cell division and movements of microorganisms also depends on this cytoskeleton.

The cytoskeleton consists of three different types of filaments: Actin filaments, microtubuli and intermediate filaments. Actin, which is the most abundant protein in cells, forms the actin filaments. The dynamics of the actin filaments results from the reversible polymerization of the actin monomer (G-actin) to F-actin filaments. Polymerization and depolymerization of actin are therefore important parts of the cell function.<sup>30</sup>

Latrunculin A is an especially potent inhibitor of F-actin filament formation. It is commercially available and is extensively used in chemical biology as an agent to sequester monomeric actin in living cells.<sup>31</sup> Latrunculin A disrupts the actin cytoskeleton rapidly, specifically and reversibly by making a 1:1 stoichiometric complex with G-actin.<sup>32</sup> The structure of actin bound latrunculin A was solved by X-ray crystallography by Morton and co-workers in 2000.<sup>32</sup> This structure revealed that the thiazolidinone plays a central role in binding.

Several other toxins were reported to interfere with actin. Among them, the cytochalasins are commonly used compounds in chemical biology. The first of these natural products were discovered in 1966<sup>33</sup> and more than 20 cytochalasins are now known.<sup>34</sup> The cytochalasins A, B, C, D and E are commercially available (Fig. 10).

Cytochalasin D, that also prevents G-actin subunits from polymerizing to F-actin filaments, was previously a widely used actin-depolymerizing agent but has now been replaced by latrunculin A due to its higher activity and more specific mode of action.<sup>32</sup>

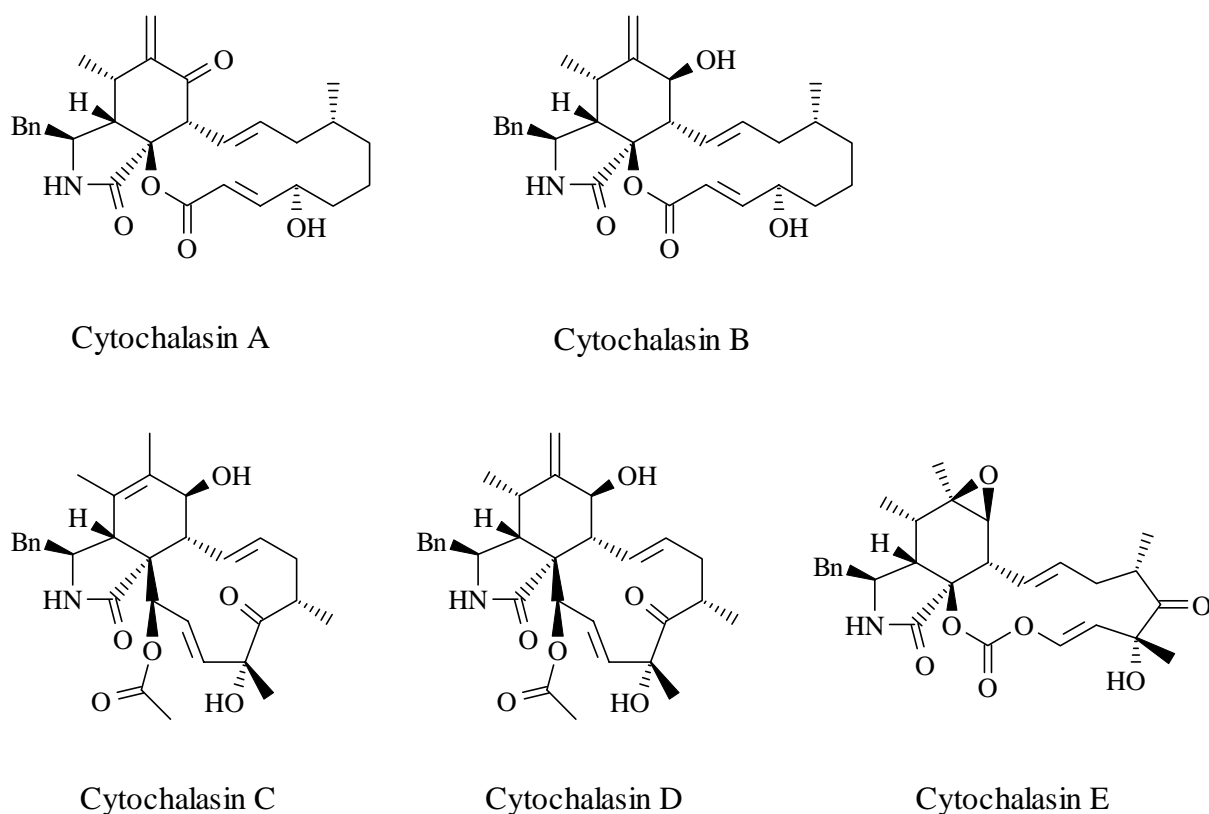
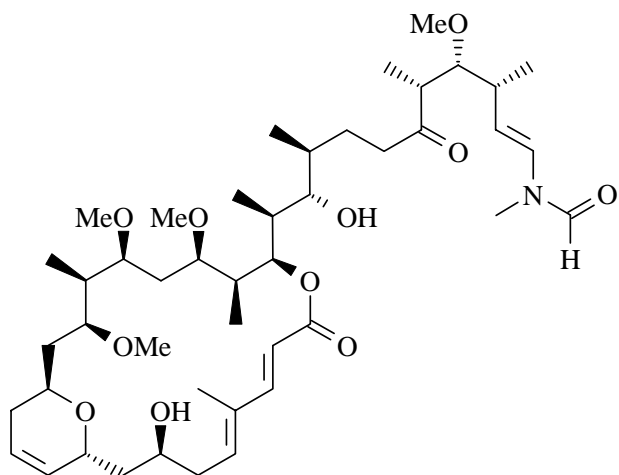
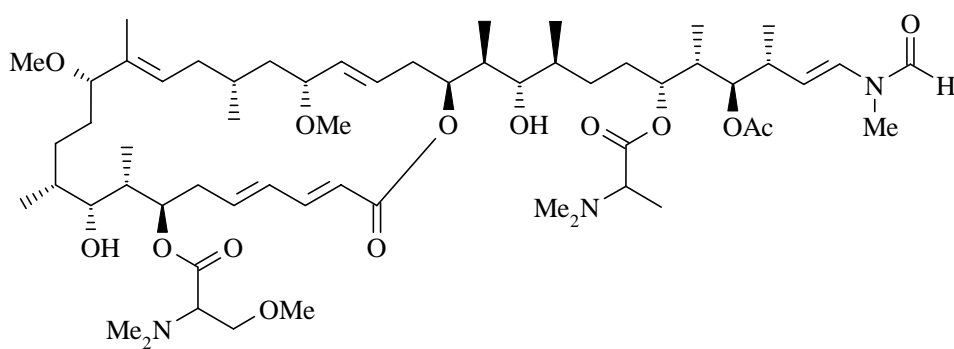


Fig. 10: Cytochalasins, actin binding drugs.

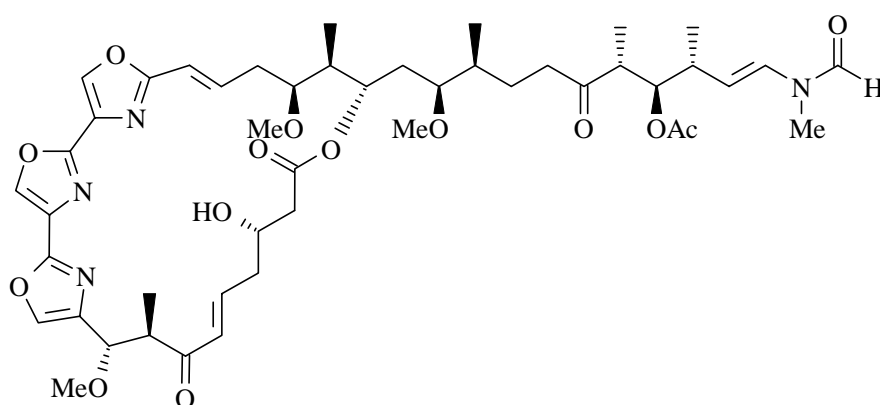
Further actin binding natural products have been isolated and prepared synthetically, such as scytophycin C<sup>35</sup> from *Scytonema pseudohofmanni*,<sup>36</sup> aplyronin A<sup>37</sup> from *Aplysia kurodia*<sup>38</sup> and mycalolide A<sup>39</sup> from *Tubastrea faulkneri*<sup>40</sup> (Fig. 11).



Scytophycin C



Aplyronin A



Mycalolide A

Fig. 11: Other actin binding macrolides.

For a recent review on actin binding macrolides, see reference 41.

## Previous syntheses of Latrunculin

The first synthetic approach to the latrunculines was published in 1985 by Kashmann *et al.*<sup>29</sup> who established a route to the thiazolidinone/tetrahydropyrane ring system found in latrunculin A and B. This route, however, was only a model study for the *de novo* synthesis of latrunculin B and a complete synthesis has not yet been published by these authors.

In 1986 Smith and co-workers reported the first total synthesis of latrunculin B,<sup>42</sup> followed by the synthesis of latrunculin A by Smith *et al.*<sup>43</sup> as well as White and Kawasaki.<sup>44</sup>

The approaches to both compounds developed by Smith involve the same strategy: Both natural products are available by appropriate Wittig reactions from the common intermediate **9**. The macrocycle was established via macrolactonization using a Mitsunobu reaction (Fig. 12).

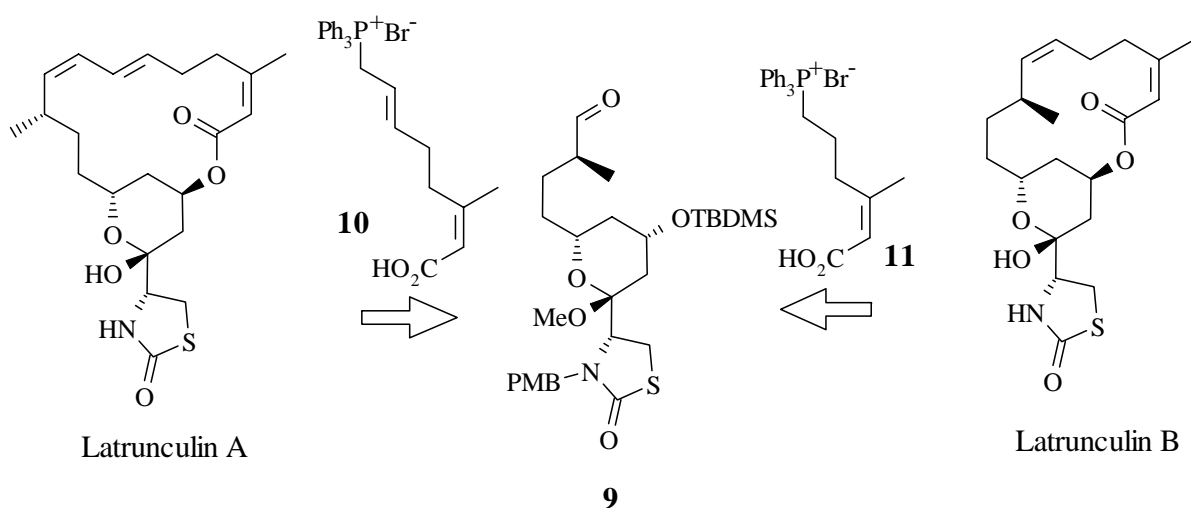


Fig. 12: The general strategy developed by Smith *et al.* for latrunculin A and B.

Aldehyde **9** was formed by an aldol reaction of ketone **13** with aldehyde **14**, affording the aldol product as a mixture of two epimers in a 4:1 ratio in favour of the  $\alpha$ -isomer (Fig. 13).

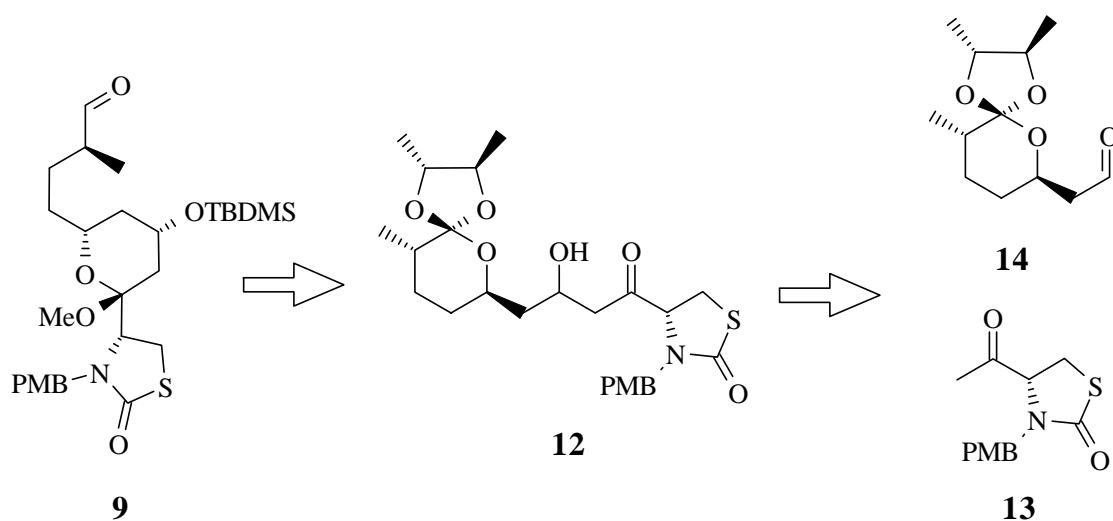


Fig. 13: Part of the strategy developed by Smith *et al.* for latrunculin A and B.

The synthesis developed by White also makes use of a Wittig reaction to establish the *Z*-configured olefin in the molecule followed by a macrolactonization. Furthermore, White used an aldol reaction between aldehyde **15** and ketone **16** as a key step (Fig. 14).

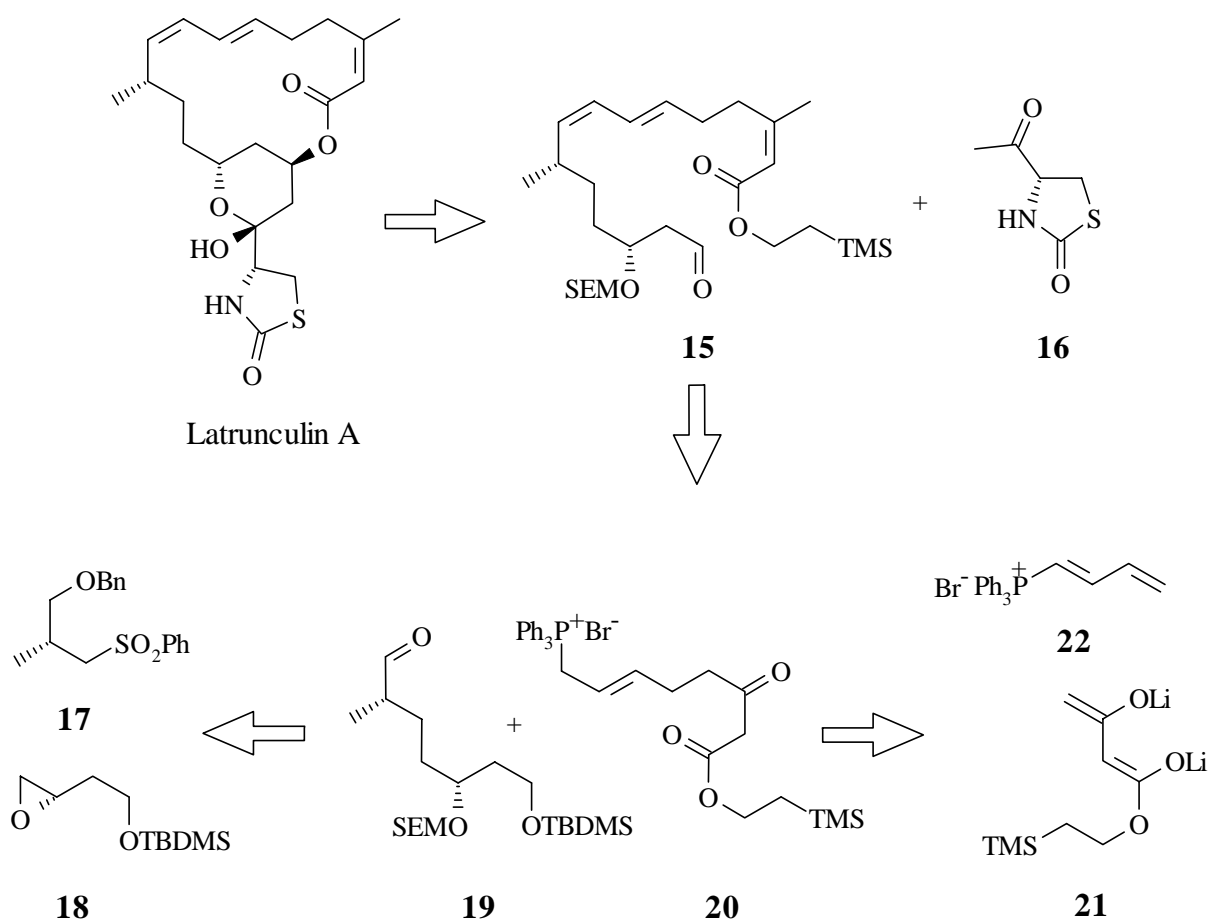


Fig. 14: The strategy developed by White and Kawasaki for latrunculin A.

The main difference between the approaches developed by Smith and White, respectively, lays in the order of events. White and Kawasaki made a Wittig reaction with the ylide derived from **20** with aldehyde **19** first and then employed an aldol reaction between fragment **15** and the unprotected ketone **16**, whereas Smith first performed an aldol reaction followed by a Wittig reaction.



## Latrunculines by metathesis

Our main interest in the latrunculin synthesis was the formation of the macrocycle by ring closing alkyne metathesis as an alternative to the macrolactonization strategies previously employed. Since latrunculin A, B, C and D all contains a *Z*-configured olefin, we wanted to investigate the possibility of reducing the resulting alkyne to a (*Z*)-alkene in the presence of one or two other double bonds. Figure 15 shows the key steps of our retrosynthesis for latrunculin B.

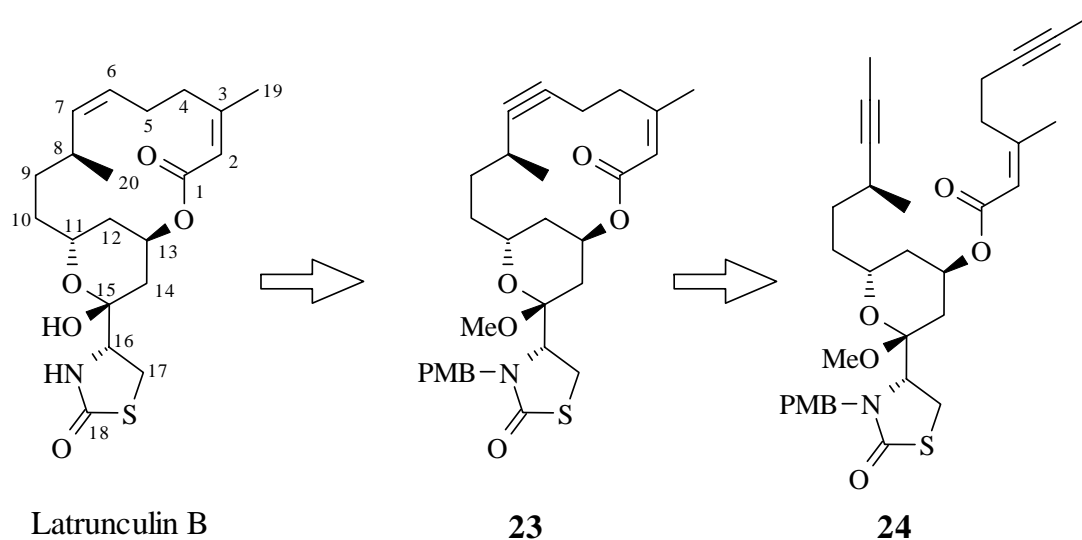


Fig. 15: The approach to latrunculin B used in this project.

The first disconnection is made between C-6 and C-7. The olefin comes from alkyne **23** derived from diyne **24** by ring closing alkyne metathesis.

Precursor **24** is divided into three fragments according to the following retroanalysis (Fig. 16).

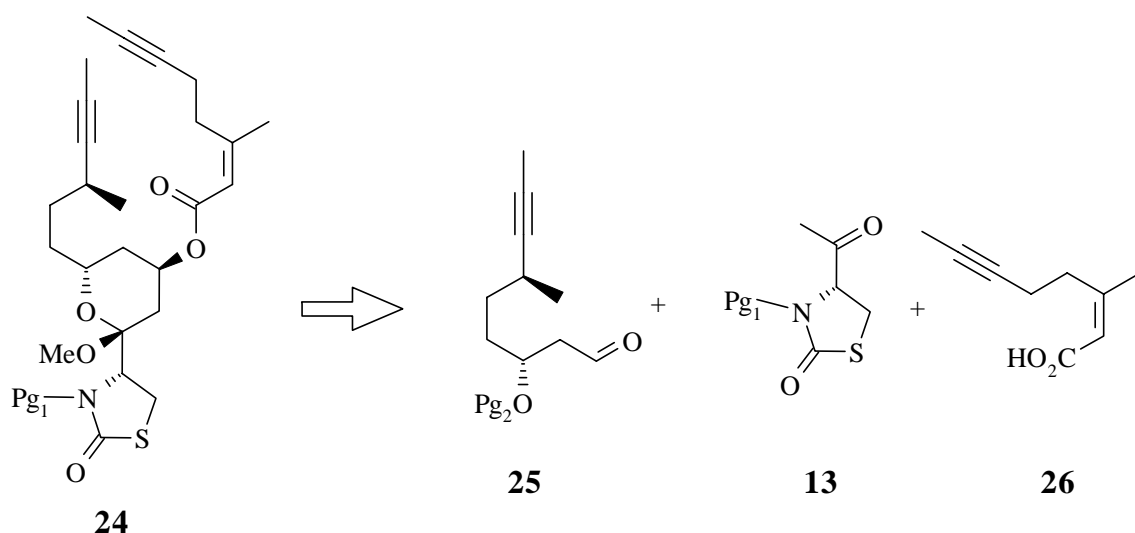


Fig. 16: Retrosynthetic plan for the latrunculin B precursor **24**.

Aldehyde **25** is to be coupled with ketone **13** in an aldol reaction. The aldol product should then be esterified with carboxylic acid **26**.

The retrosynthesis of fragment **13** is shown below (Fig. 17). The stereocenter comes from commercially available cysteine methyl ester hydrochloride. The methyl ketone is made from the carboxylic acid after selective protection of thiocarbamide **28**. The heterocycle is formed from cysteine ester **29** and carbonyldiimidazole.

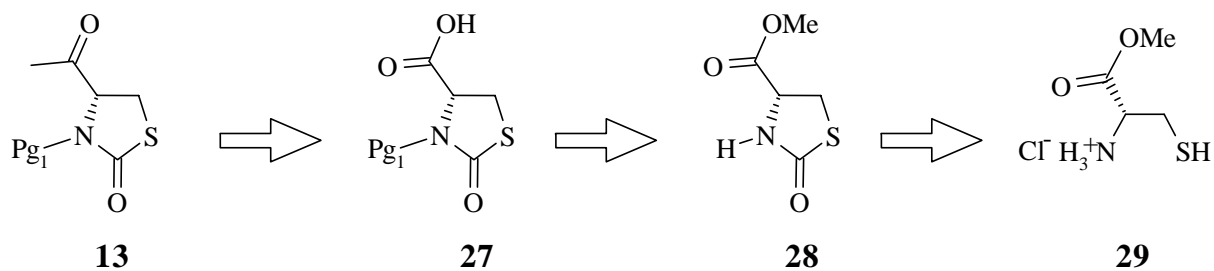


Fig. 17: Retrosynthesis of fragment **13**.

Compound **25** derives from the diprotected diol **31** which, in turn, can be obtained from alcohol **32** (Fig. 18).

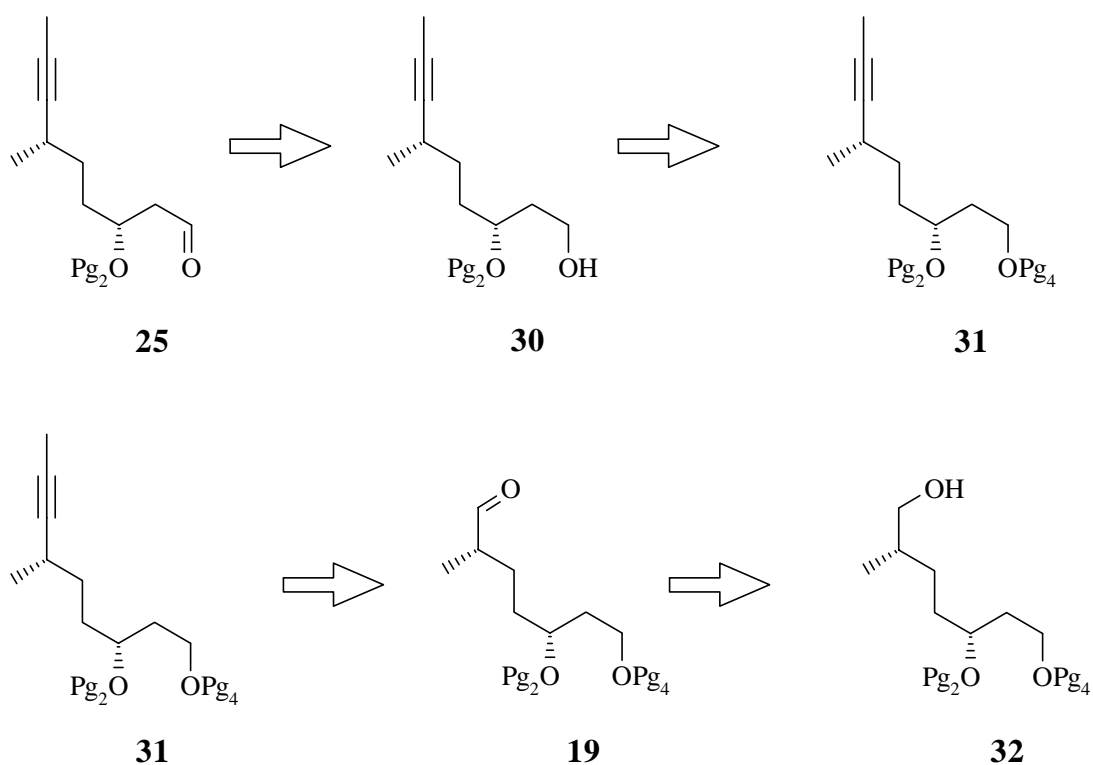


Fig. 18: Retrosynthesis of fragment **25**.

Fragment **32** is thought to derive from compound **35** that would result from coupling of sulfone **17** and epoxide **18** (Fig. 19).

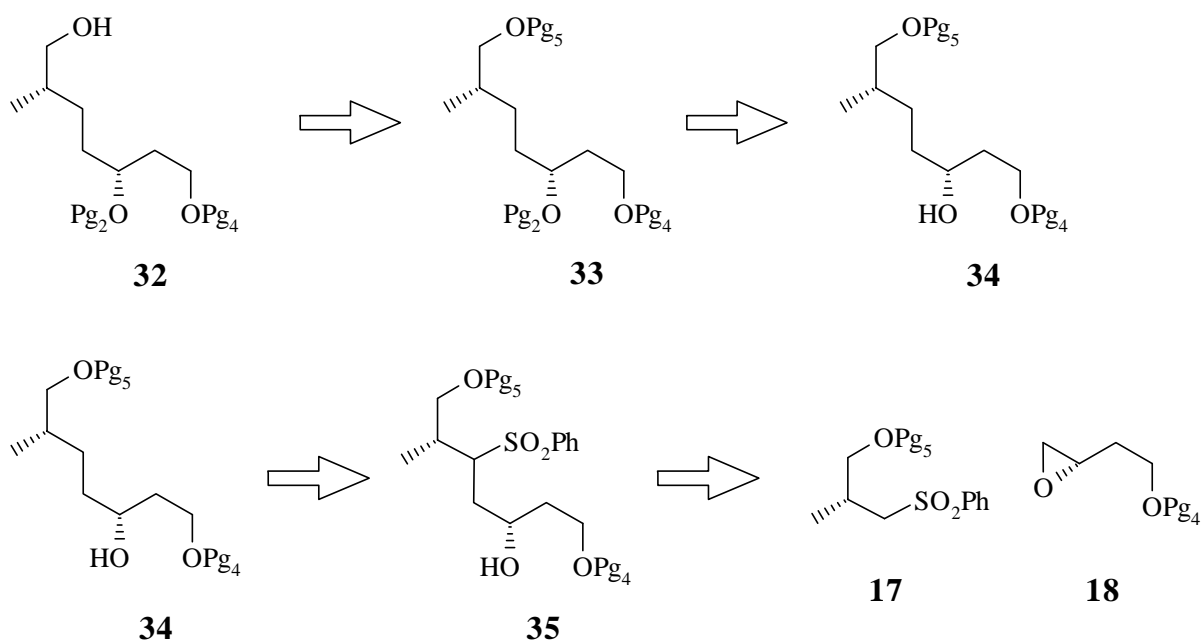


Fig. 19: Retrosynthesis of fragment **32**.



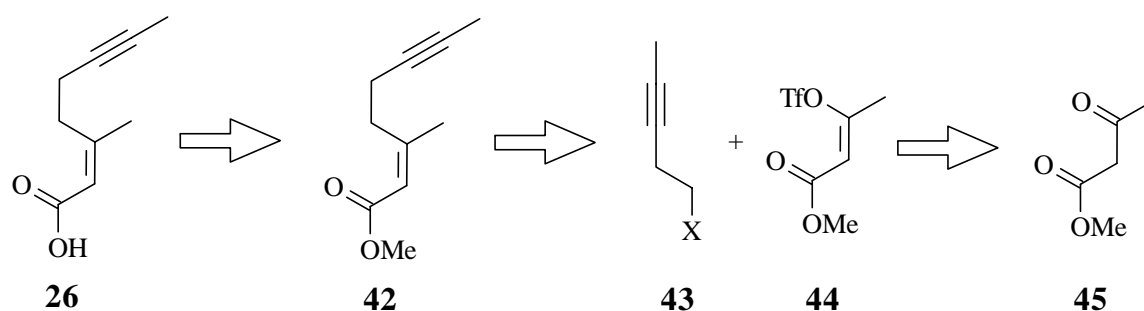


Fig. 22: Retrosynthetic analysis of carboxylic acid **26**.

Triflate **44** can be prepared from commercially available acetoacetic acid methyl ester, alkyl halide **43** would be generated from commercially available pent-3-yn-1-ol **46** by a functional group interconversion.

### Previous work in the group

Prior to this work, Dr. Parra-Rapado had been working in the group on latrunculin D, and some of her results were to be used in the approach to latrunculin A and B.

Following the retrosynthesis described above, Dr. Parra-Rapado prepared ketone fragment **13** with a PMB protecting group on nitrogen. Compound **28** was at that time commercially available. Unfortunately the final step of this sequence was plagued by low yields and partial racemization of the product. Dr. Parra-Rapado ascribed this partial racemization to an enantiomeric excess of only 80 - 90 % to the configurational lability of the intermediate acid chloride. A yield of 65 % was achieved once, but could not be reproduced (Fig. 23).

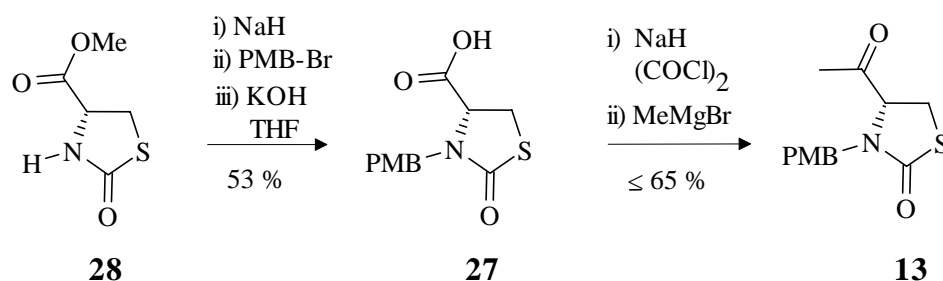


Fig. 23: Dr. Parra-Rapados approach to the ketone fragment **13**.

She prepared aldehyde **52** by a route similar to that of White and Kawasaki.<sup>42</sup> She did, however, develop a shorter route to the enantiopure epoxide **18** and employed this fragment in the synthesis of fragment **34** (Fig. 24).

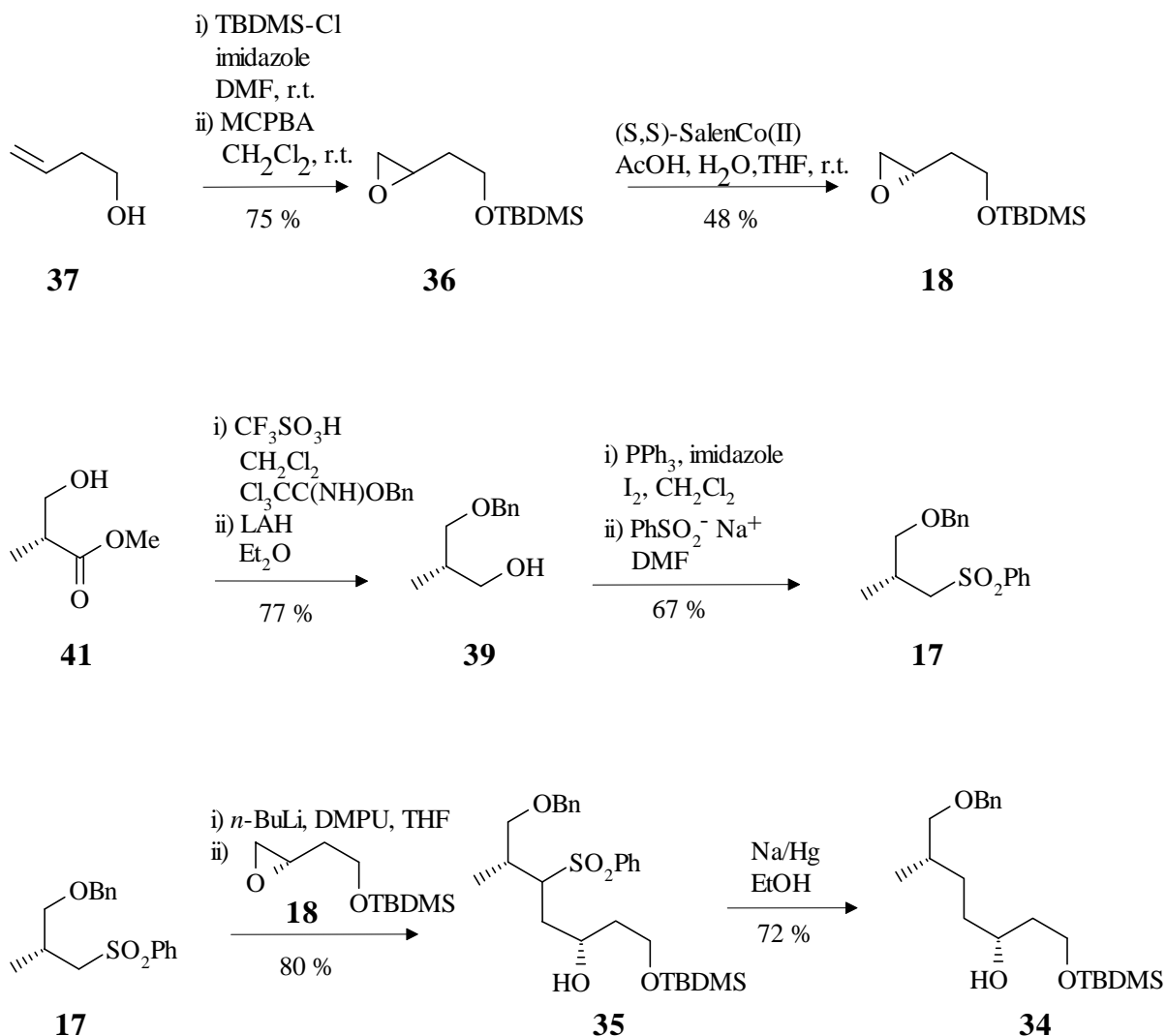


Fig. 24: Dr. Parra-Rapados synthesis of fragment **34**.

The last steps of her synthesis of aldehyde **52** are shown in Fig. 25.

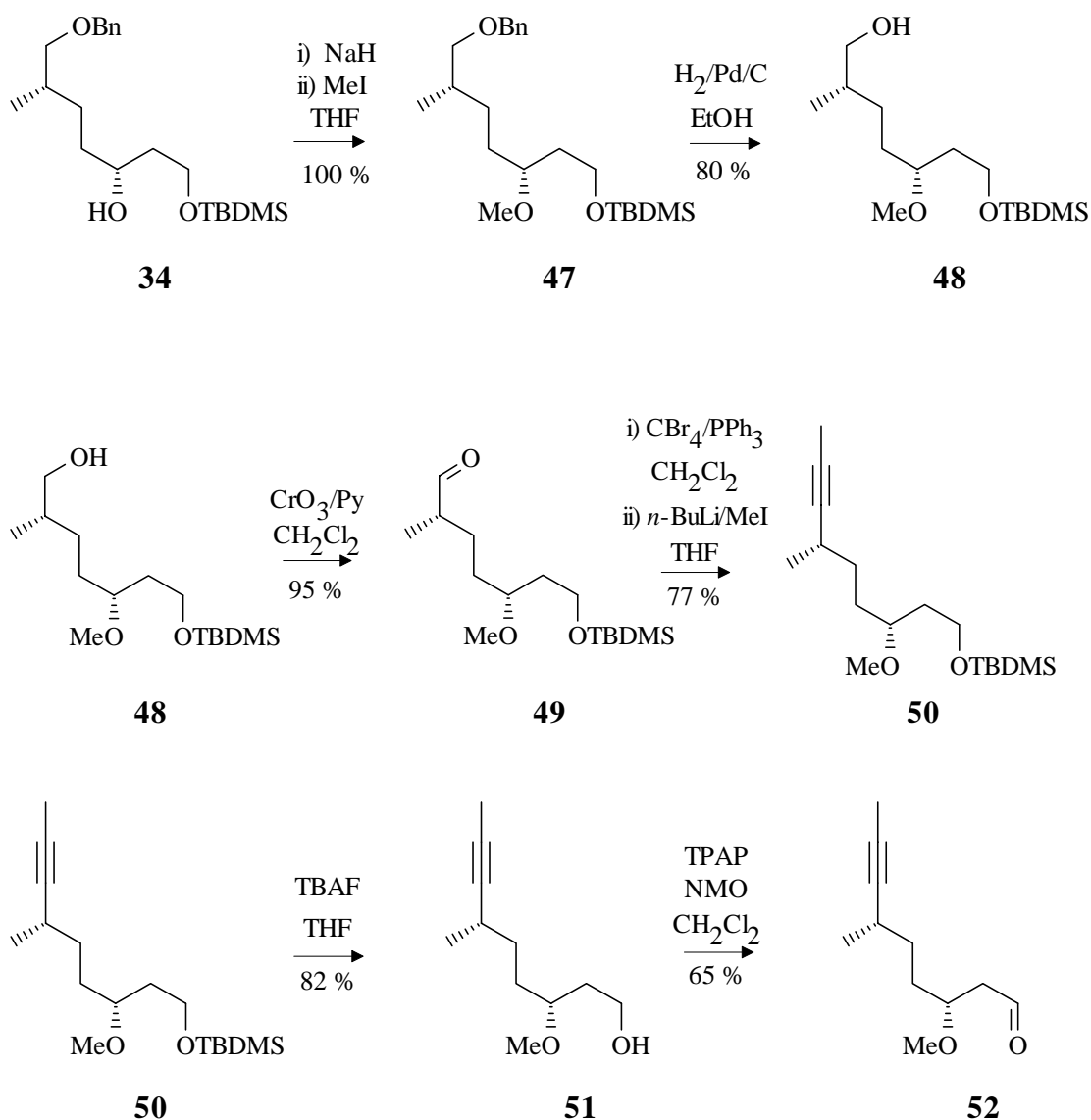


Fig. 25: Dr. Parra-Rapados synthesis of aldehyde **52** for the projected latrunculin D synthesis.

Dr. Parra-Rapado prepared carboxylic acid ester **42** via a zinc mediated, palladium-catalyzed cross coupling reaction (Fig. 26).

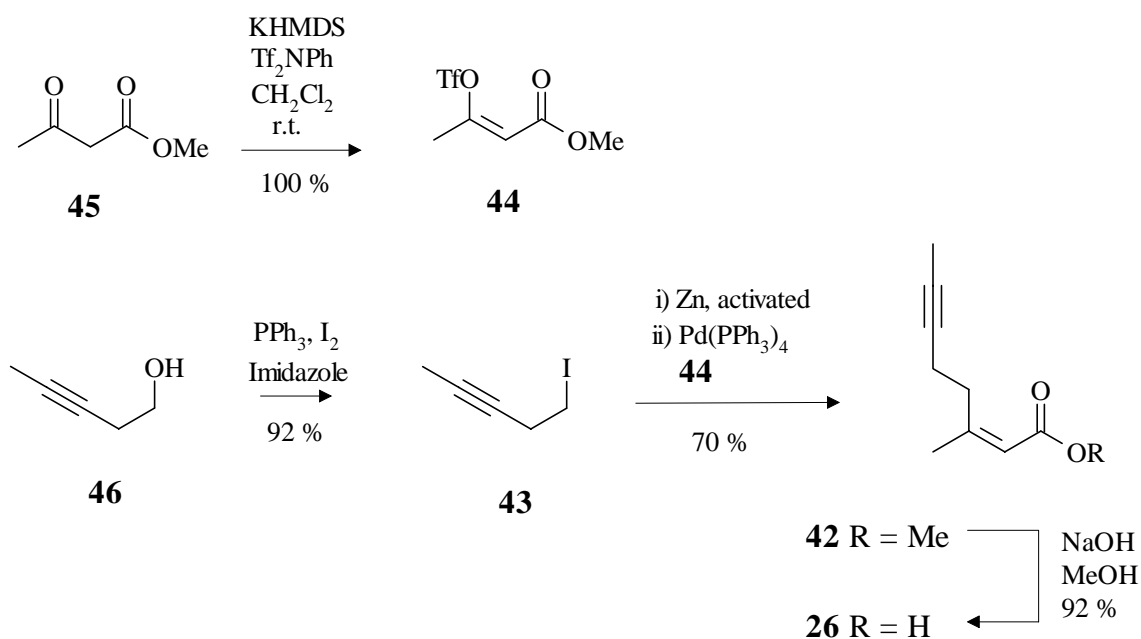


Fig. 26: Dr. Parra-Rapados synthesis of fragment **26**.

In the cross coupling step, iodide **43** was converted into the corresponding organozinc compound *in situ* on reaction with activated zinc. This organozinc compound was then coupled with triflate **44** in a palladium-catalyzed step.

Later it was shown by Dr. DeSouza that compound **42** can also be made by an iron-catalyzed reaction of the type developed in the Fürstner group (Fig. 27).<sup>46</sup>

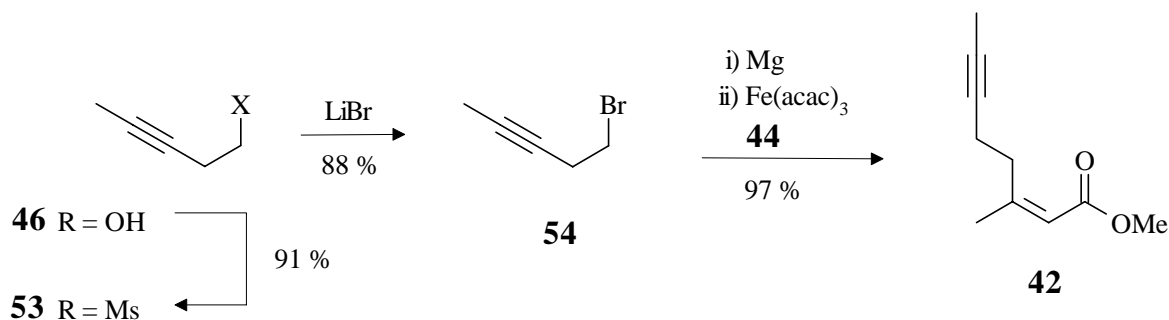


Fig. 27: An alternative to the zinc mediated cross coupling for making fragment **42**.

In a model study, Dr. Parra-Rapado esterified carboxylic acid **26** with alcohol **55** and showed that the resulting diyne **56** underwent RCAM when reacted with molybdenum complex **5** activated by  $\text{CH}_2\text{Cl}_2$ . It was at that time not clear if the methyl group next to the alkyne would exert steric hindrance, or if the conjugated ester would be left unchanged under these conditions (Fig. 28).



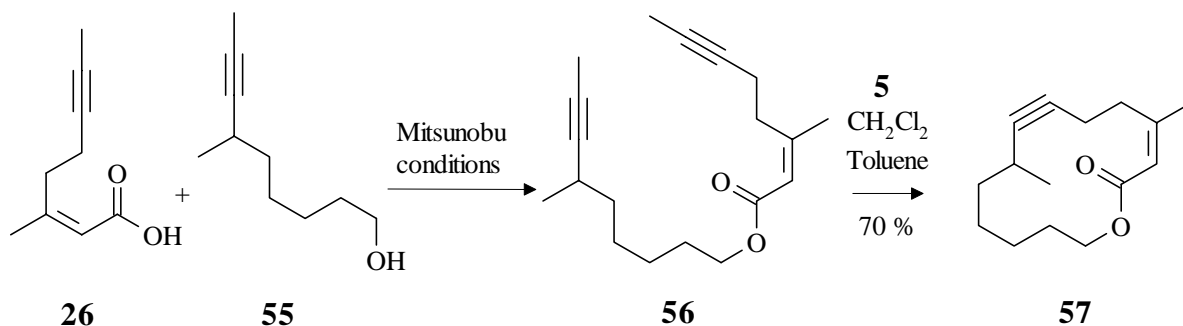


Fig. 28: Dr. Parra-Rapados model study.

Dr. Parra-Rapado investigated the aldol reaction between aldehyde **52** and ketone **13** but attempts to control the stereoselectivity in this step were not successful. She found that the lithium enolate of ketone **13** gave the aldol product **58** in 75 % yield in a 1:2 epimer ratio. It was not possible to determine the stereochemistry of the major isomer by NMR (Fig. 29).

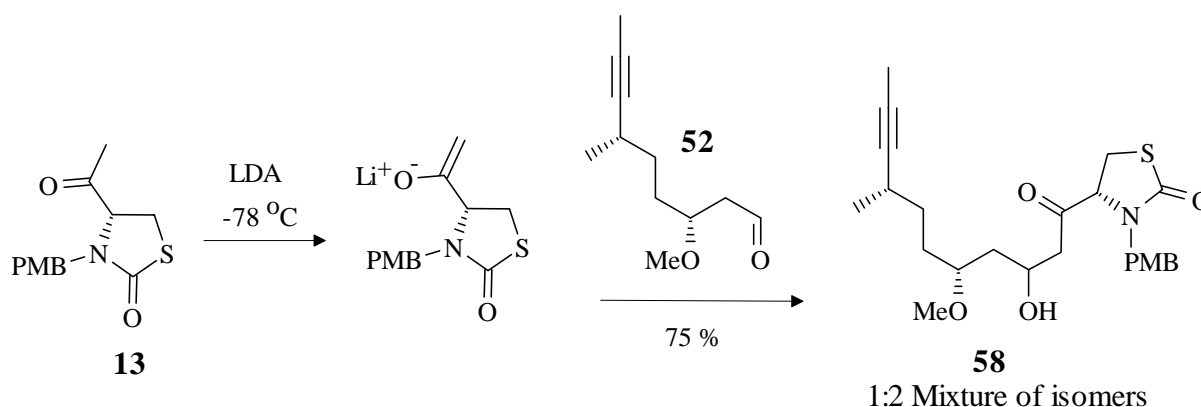


Fig. 29: The optimized conditions for the aldol reaction in Dr. Parra-Rapados work.

Attempts to esterify aldol product **58** with carboxylic acid **26** were unrewarding. The yields were not well reproducible and often low due to concomitant elimination. Esterification under Mitsunobu conditions gave only elimination, whereas conversion of the carboxylic acid into the corresponding acid chloride **59** using Ghosez' reagent<sup>47</sup> followed by addition of aldol product **58** provided the ester in very low yield (Fig. 30).

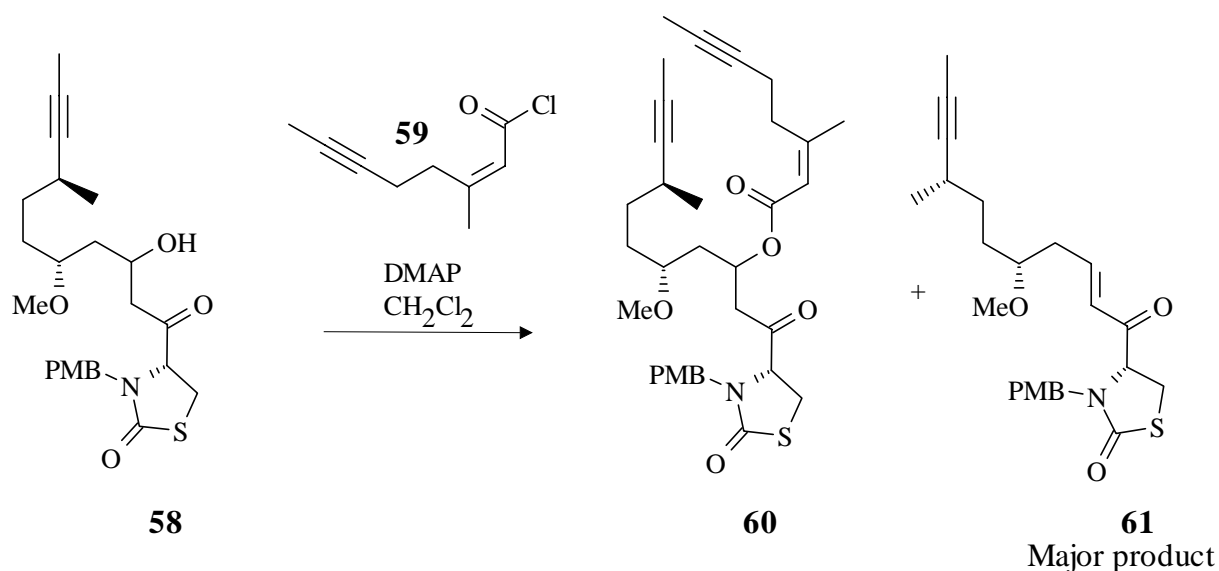


Fig. 30: Dr. Parra-Rapados attempt to form ester **60**.

As we wanted to use the above sequence for making latrunculin A and B, we faced at least two problems. The synthesis of ketone **13** was low yielding and the product was not enantiopure. Therefore it was necessary to establish a high yielding synthesis of the enantiopure ketone **13**. Furthermore, the aldol chemistry needed to be revisited and elimination had to be avoided when esterifying the aldol product with acid fragment **26**.

## Studies towards latrunculin B and A

### Ketone fragment

The first objective of my project was to develop a reproducible and high yielding synthesis of the *p*-methoxy benzyl protected ketone **13**.

A synthesis of this ketone is reported by Smith *et al.*<sup>42</sup> and the first steps in this approach were found to proceed smoothly (Fig. 31).

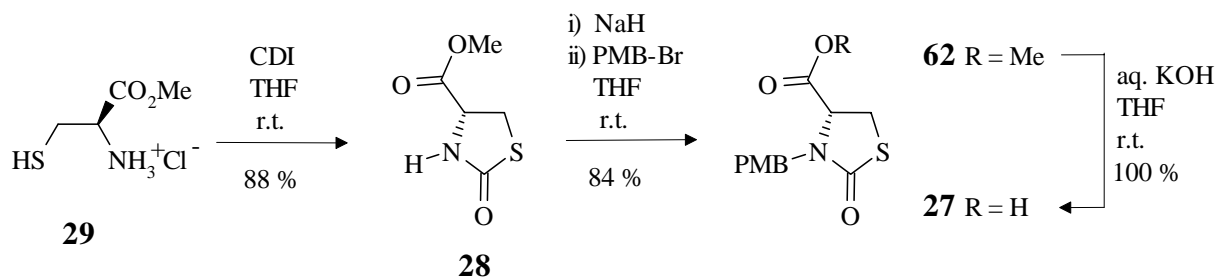


Fig. 31: The first three steps of the synthesis of ketone **13**.

Thiazolidinone **28** was formed from cysteine methyl ester hydrochloride on treatment with CDI in THF in 88 % yield.<sup>48</sup> This is an alternative to the method used by White and Kawasaki who used a mixture of carbon monoxide, oxygen and selenium for this transformation.<sup>44</sup> The nitrogen of the thiazolidinone ring was then protected with a PMB-group using freshly prepared PMB bromide to give **62** in 84 % yield (Fig. 31).

PMB bromide is unstable and decomposes partly overnight even when kept at -18 °C. It is therefore necessary to prepare it freshly before use by stirring the corresponding alcohol in 48 % HBr for two hours followed by extraction and distillation (Fig 32).

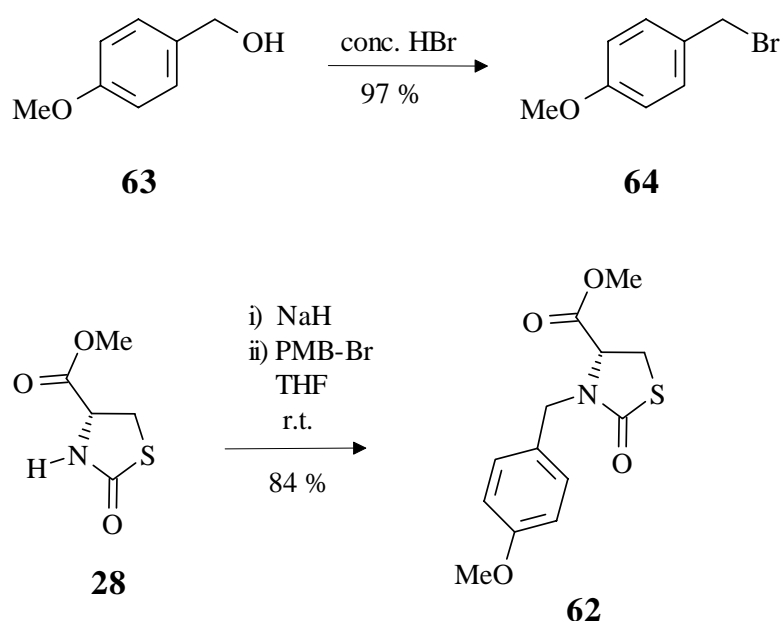


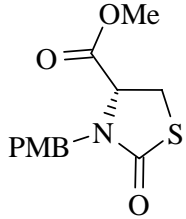
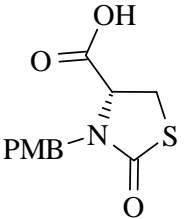
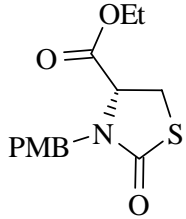
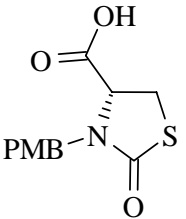
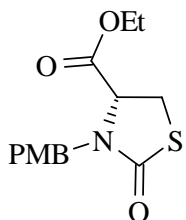
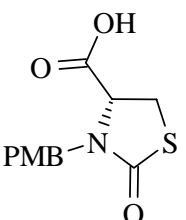
Fig. 32: Preparation of and protection with PMB bromide.

The initial reactions in this project were done using cysteine methyl ester **29** to give methyl esters **28** and **62**. However, the sale of **29** was stopped during these studies. The sequence was repeated with the commercially available cysteine ethyl ester hydrochloride. This minor change had only a small impact.

While methyl ester **62** was hydrolysed quantitatively with a mixture of aqueous potassium hydroxide and diethyl ether, this reaction gave only 81 % yield with ethyl ester **65**.

However, hydrolysis of ethyl ester **65** proceeded quantitatively with aqueous potassium hydroxide in 1,4-dioxane (Table 1).

Table 1: Hydrolysis of esters in different solvents.

Entry	Starting material	Product	Base	Solvent	Yield
1	 <b>62</b>	 <b>27</b>	aq. KOH	Et <sub>2</sub> O	100 %
2	 <b>65</b>	 <b>27</b>	aq. KOH	Et <sub>2</sub> O	81 %
3	 <b>65</b>	 <b>27</b>	aq. KOH	1,4-dioxane	100 %

By re-esterifying acid **27** with trimethylsilyldiazomethane<sup>49</sup> it was shown that little - if any - racemization occurred during the hydrolysis. The optical rotation of methyl ester **62** before hydrolysis was  $-73^\circ$  (Fig 33). After hydrolysis, reesterification and chromatography the optical rotation of the ester was  $-72^\circ$  ( $c = 1.96$  in  $\text{CHCl}_3$ ).

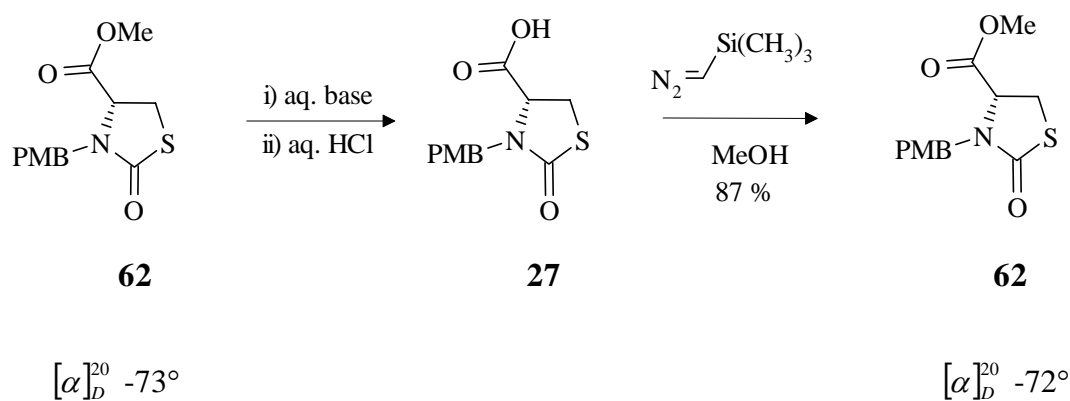


Fig. 33: Investigation of the impact of hydrolysis on optical rotation of ester **62**.

It was found that the conversion of **27** to **13** gave disappointing results even though literature reported 83 % yield for this transformation (Fig. 34).<sup>43</sup>

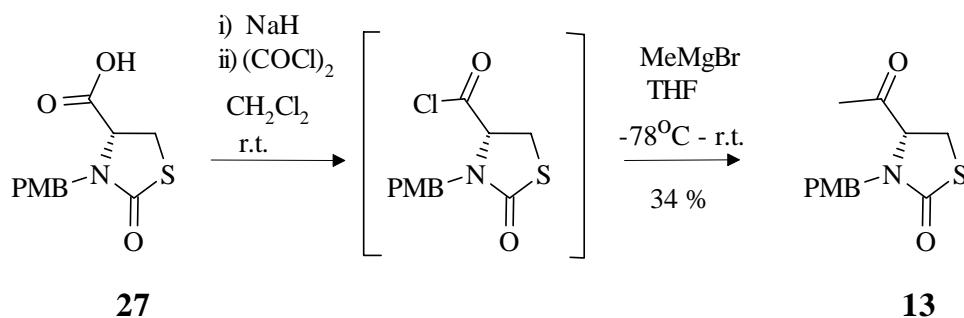


Fig. 34: Synthesis of ketone fragment **13**.

Acid **27** was converted into its acid chloride by use of sodium hydride and oxalyl chloride in dichloromethane and the reaction was monitored on TLC by quenching an aliquot with dry methanol. Once the acid chloride was formed, the solvent was removed *in vacuo*, the acid chloride was redissolved in dry THF and treated with methylmagnesium bromide. Numerous attempts to repeat the literature procedure gave only variable yields in the range 20 to 34 %. Moreover chiral HPLC showed that the ketone was partly racemized likely due to the known tendency of amino acid chlorides to suffer racemization.

In a control experiment the acid chloride was formed with oxalyl chloride and subsequently quenched with dry methanol to give ester **62** with an e.e. of only 90 %.

Therefore, an alternative procedure using free acid **27**, oxalyl chloride and a drop of DMF was used.<sup>50</sup> However, yields of **13** remained poor.

Also the use of Ghosez' reagent (N,N-dimethyl-2-methyl-1-chloro-1-propenamine)<sup>47</sup> led to the same disappointing result (Fig. 35).

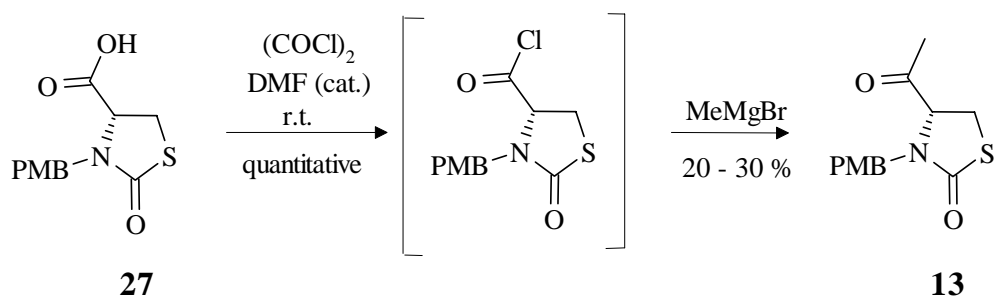


Fig. 35: Preparation of ketone **13**.

Grignard reagents do not always give good yields of ketones when reacted with acid chlorides, whereas different organocopper reagents often do.<sup>51</sup> However, addition of catalytic or stoichiometric amounts of copper (I) bromide to the reaction mixture only resulted in decomposition of the starting material. The same outcome was observed using stoichiometric amounts of lithium dimethylcuprate (Fig. 36).

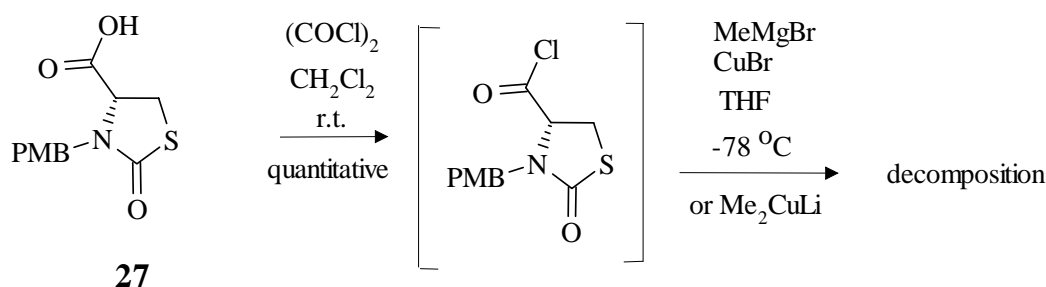


Fig. 36: Attempts to form ketone **13** via a copper mediated step.

This decomposition might be ascribed to the fact that organocopper reagents are able to add to thioesters,<sup>52</sup> hence attacking thiazolidinone at a competitive rate.

Iron compounds have in some cases been able to catalyze the addition of Grignard reagents to acid chlorides.<sup>53</sup> Therefore, an experiment was carried out in which three percent of iron (III) acetylacetonate were added to the acid chloride before addition of  $\text{CH}_3\text{MgBr}$ . This procedure raised the yield to 60 %. Further experiments revealed that the use of Ghosez' reagent for the formation of the acid chloride followed by the iron-catalyzed cross coupling with methylmagnesium bromide gave the best result, affording ketone **13** in 80 % yield (Fig 37).

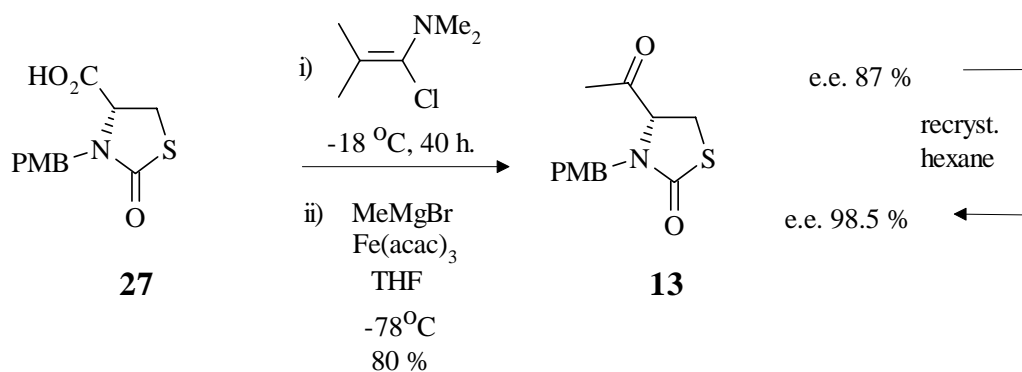


Fig. 37: The optimized formation of ketone **13**.

Considering that organocadmium,<sup>54</sup> organotin,<sup>55</sup> organolead,<sup>56</sup> and organomercury<sup>57</sup> compounds are alternatives for making ketones from acid chlorides, the use of iron obviously constitutes an advantage for safety and environmental reasons.

The enantiomeric purity of **13** was, however, only 87 % according to chiral HPLC.

Recrystallisation of the product from hexane raised the e.e. to 98.5 %. The structure of the thiazolidinone methyl ketone was proven by X-ray crystallography (Appendix) and its optical rotation was corrected to  $-60^\circ$  instead of the  $-38^\circ$  reported previously.<sup>43</sup>

The optical rotation of ketone **13** that was 87 % e.e. pure corresponded to the value reported by Smith and co-workers for what they believed to be the enantiopure ketone. This result strongly suggests that they also had partial racemization during their ketone formation. Moreover, they did report the formation of four products in the aldol reaction, two of which were minor products.<sup>43</sup> This result might be explained by assuming that the ketone that was used had not been enantiomerically pure.

## The aldehyde fragment

The preparation of aldehyde **25** followed the retrosynthetic scheme outlined in Fig. 18 to Fig. 21 in the chapter **Latrunculines by metathesis**.

Commercially available butenol **37** was protected as the corresponding TBDMS ether under classical conditions,<sup>58</sup> followed by MCPBA epoxidation of the resulting olefin **66** to give the desired epoxide **36** in an overall yield of 80 % (Fig. 38).

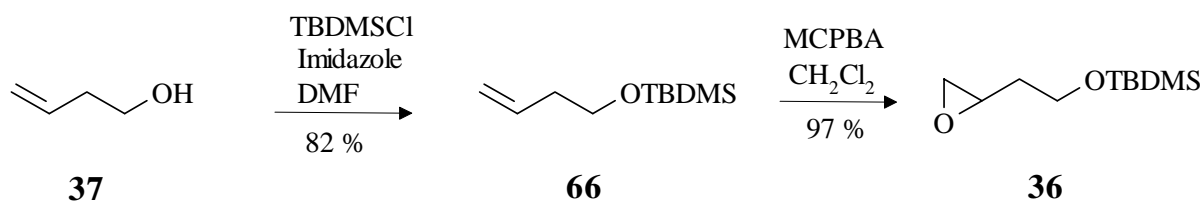


Fig. 38: Preparation of epoxide **36**.

One of the enantiomers of the racemic epoxide could be hydrolysed catalytically to the corresponding diol by use of a chiral Co(salen) complex.<sup>59</sup> This procedure was developed by Jacobsen *et al.* for ring opening with carboxylate ions,<sup>60</sup> or a thiol,<sup>61</sup> and for hydrolyzing an epoxide to a diol using cobalt as central ion in the salen complex.<sup>45</sup> This procedure has been used in a number of cases for terminal epoxides in molecules containing different

functional groups like benzyl ethers or acetate. The hydrolytic kinetic resolution can be easily controlled by limiting the amount of water (Fig. 39).

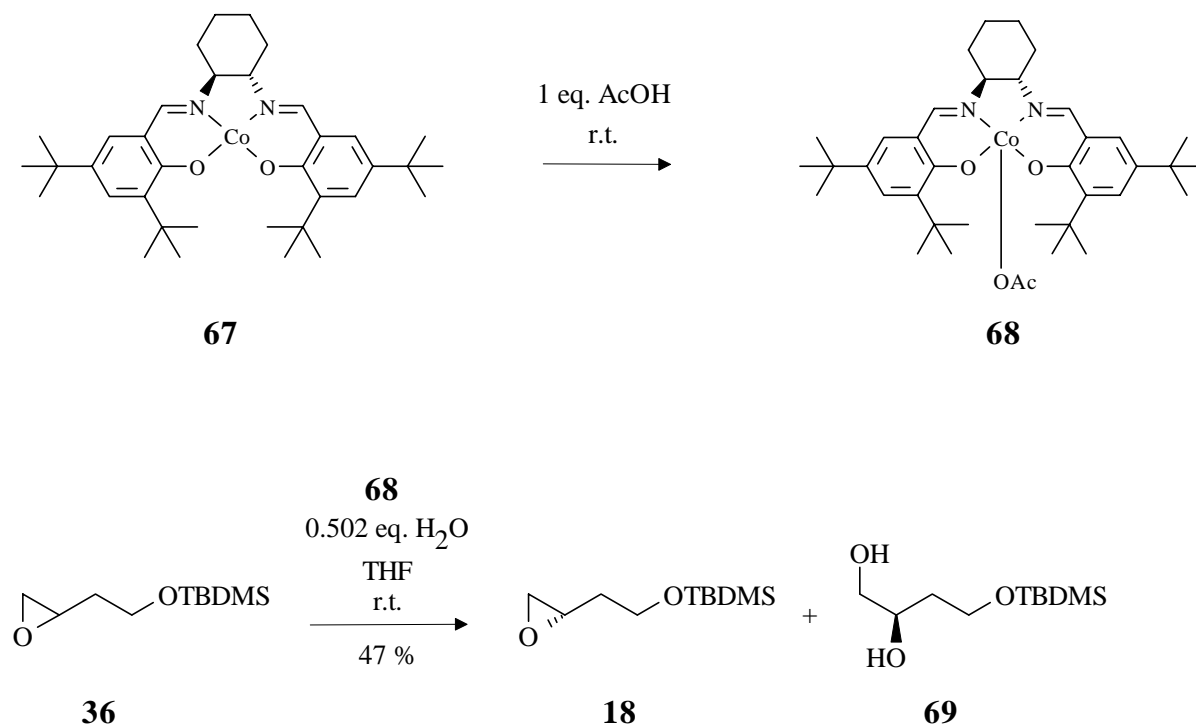


Fig. 39: Hydrolytic kinetic resolution of epoxide **36** with catalyst **68**.

The catalyst was prepared *in situ* by mixing Co(salen) precatalyst **67** with epoxide **36**, followed by the addition of acetic acid. The mixture was stirred at ambient temperature for one hour, before THF and water were added to start the hydrolysis. Acetic acid and the cobalt precatalyst were employed in the same molar ratio (2 mol%).

Since the two enantiomers do not interconvert during the reaction, only 50 % yield of the enantiopure epoxide is possible. Thus, the 47 % yield obtained in the hydrolysis of **36** corresponds to 94 % of the theoretical yield. Although half of epoxide **36** was wasted, this was acceptable since it was easily prepared.

The remaining epoxide **18** could be separated from diol **69** by Kugelrohr distillation, and was found to be enantiopure (ee  $\approx$  100 %) by chiral GC. The procedure was performed on a multigram scale.

Sulfone **17** was prepared from commercially available 3-hydroxy-2-methyl-propionic acid methyl ester **41**. This compound was first protected using benzyltrichloroacetimidate and a catalytic amount of trifluoromethanesulfonic acid to give benzyl ether **40** which was then reduced to alcohol **39** using lithium aluminium hydride (Fig. 40).



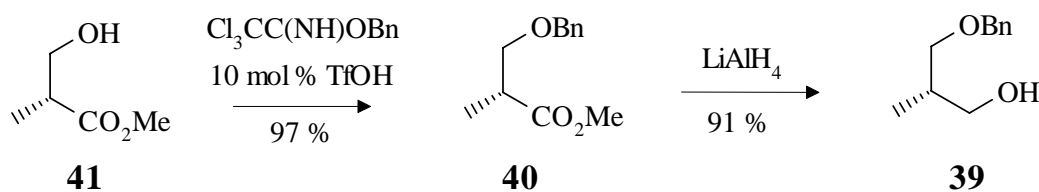


Fig. 40: Preparation of chiral monoprotected diol **39**.

No racemization occurred during these steps, as was confirmed by comparison of the optical rotations with those reported in the literature.<sup>44</sup>

Alcohol **39** was converted into iodide **38**. White prepared iodide **38** via a tosylate which was then substituted with sodium iodide in 59 % overall yield. The one step procedure using triphenylphosphine and iodine turned out to be superior.<sup>62</sup>

Iodide **38** was then reacted with sodium benzenesulfinate.<sup>63</sup> In this anion, the negative charge partially resides on the sulfur atom which functions as the nucleophile (Fig. 41).

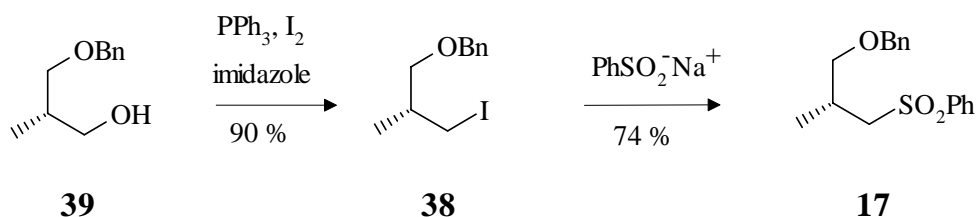


Fig. 41: Preparation of fragment **17**.

The reaction is a classical example of a  $\text{S}_{\text{N}}2$  reaction. DMF was used as an aprotic, dipolar solvent, and the reaction proceeded smoothly at 35 °C.

Sulfone **17** was then deprotonated at the  $\alpha$  position with *n*-butyllithium and reacted with epoxide **18**. This procedure gave two different epimers of hydroxy sulfone **35** which were not separated. The sulfone group in **35** was removed by treatment with sodium amalgam in ethanol to yield the enantiopure triol derivative **34** (Fig. 42).

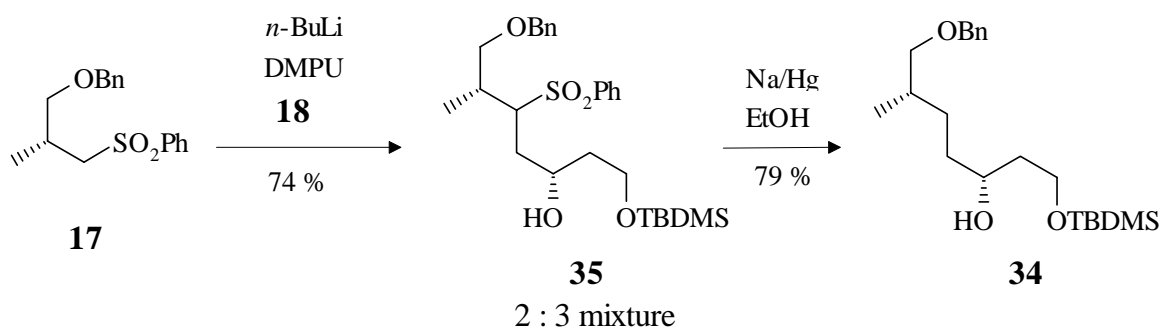


Fig. 42: Preparation of **34** by coupling of **17** and **18** and removal of the sulfone group.

Protection of alcohol **34** as the [2-(trimethylsilyl)ethoxy]methoxy ether (SEM group) was achieved in almost quantitative yield.

The subsequent deprotection of the benzyl group was made under standard conditions by hydrogenolysis with 10 % palladium on charcoal and a catalytic amount of hydrochloric acid (Fig. 43).

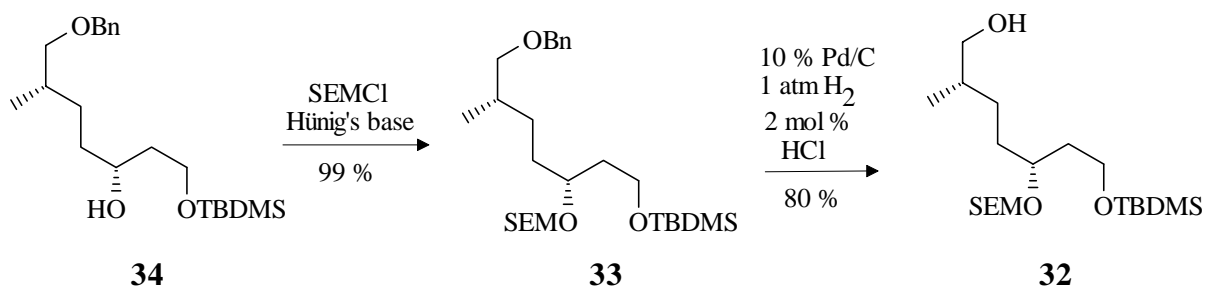


Fig. 43: Protection and deprotection to give alcohol **32**.

The conversion of alcohol **32** to aldehyde **19** was made by a Swern oxidation<sup>64</sup> with dry DMSO, oxalyl chloride and triethylamine at -78 °C (Fig. 44).

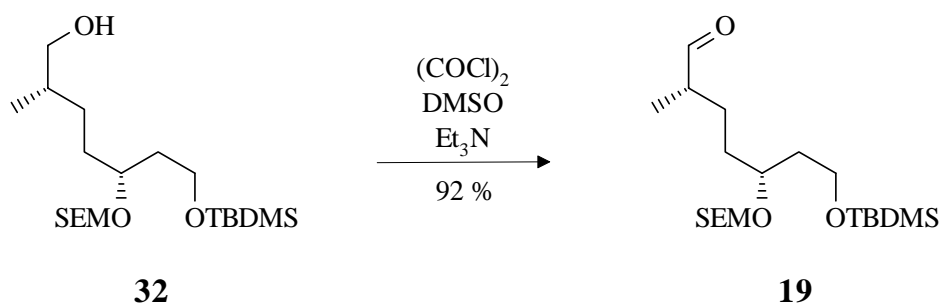


Fig. 44: Swern oxidation of alcohol **32**.

Aldehyde **19** was then converted into alkyne **31**. For this type of transformation, several different reactions have been developed, employing either Ohira's reagent ([1-diazo-2-oxopropyl]-dimethyl phosphonate),<sup>65</sup> or lithiated trimethylsilyldiazomethane.<sup>66</sup> However, we chose a Corey-Fuchs reaction using tetrabromomethane and triphenylphosphine for this transformation,<sup>67</sup> since it usually gives high yields and clean conversions.

The Corey-Fuchs reaction begins with the formation of ylide **70**, which is the reactive species that adds to the aldehyde to form dibromo olefin **71** (Fig. 45).

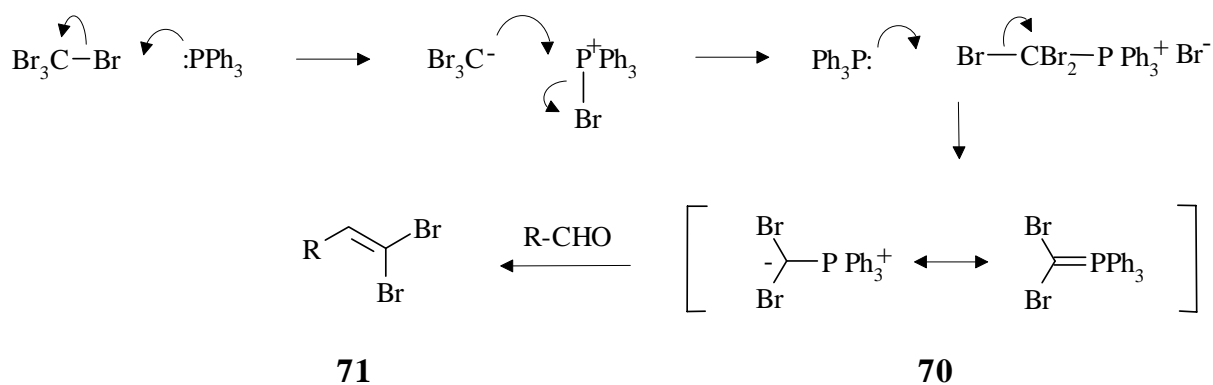


Fig. 45: Formation of the reactive species in the Corey-Fuchs reaction.

Dibromo olefin **71** was then mixed with 2 equivalents of *n*-butyllithium. In a first step, a lithiation to form a dibromo vinyl lithium compound takes place that easily eliminates lithium bromide to form a bromoalkyne. This bromoalkyne reacts with a second equivalent of *n*-butyllithium to generate an alkynyllithium species which can be alkylated with methyl iodide (Fig. 46).

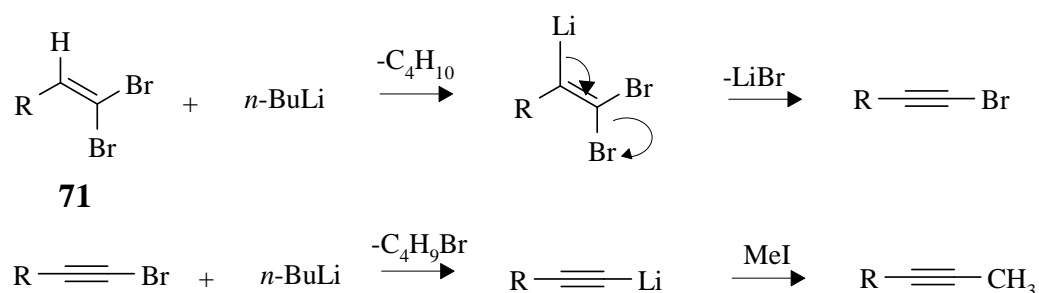


Fig. 46: The last step of the Corey-Fuchs reaction.

In the present case, the lithiation of dibromide **71** to form alkyne **31** gave an almost quantitative yield. As expected,<sup>68</sup> no racemization of the stereocenter next to the newly formed alkyne was observed and no diastereomers were detected by NMR (Fig. 47).

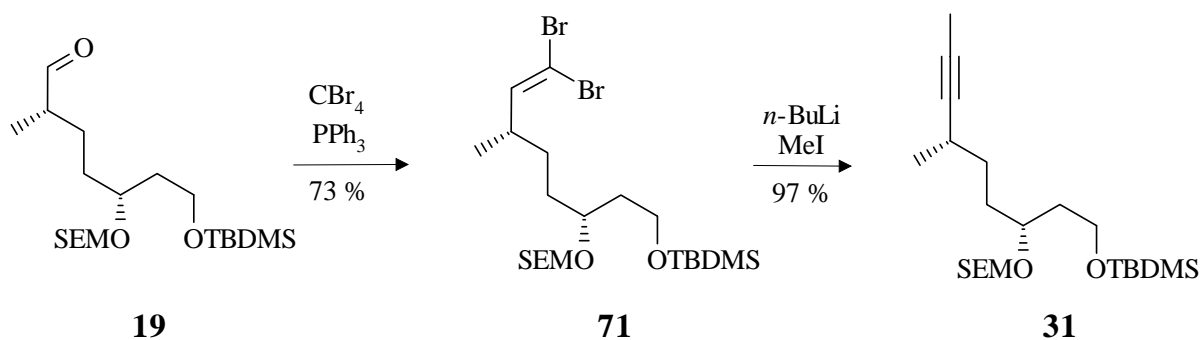


Fig. 47: Transformation of aldehyde **19** into alkyne **31** via a Corey-Fuchs reaction.

The selective deprotection of **31** using TBAF went smoothly without affecting the SEM group.<sup>69</sup> The transformation of alcohol **30** to aldehyde **25** was again made by a Swern oxidation, since the SEM protection previously had proven to be stable under these conditions (Fig. 48).

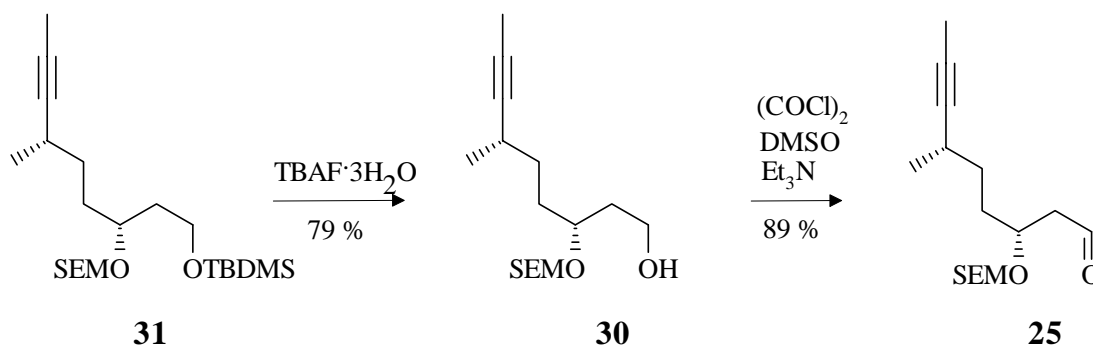


Fig. 48: Last steps of the synthesis of aldehyde **25**.

The crude aldehyde was only characterized by its <sup>1</sup>H-NMR spectrum and GC-MS, which showed a clean product. At this point, no signs of other diastereomers could be detected.

Aldehyde **25** was prepared in 12 steps and an overall yield of 12 % starting from 2-hydroxy-1-methyl propionic acid methyl ester **41**. In comparison, the intermediate aldehyde **19** used for the synthesis of fragment **31** was prepared by White and Kawasaki in 15 steps and 19 % overall yield whereas fragment **19** was prepared in 9 steps and in 25 % overall yield in this work.

## The aldol reaction

The aldol reaction is among the most investigated reactions in organic synthesis, and any advanced organic chemistry textbook deals with the many opportunities of controlling diastereoselectivity as well as enantioselectivity. Even though methods exist for obtaining excellent diastereo- and enantioselectivity in aldol reactions in many cases, no general method for stereocontrol has yet been published.

When dealing with diastereoselectivity, a number of models allows to predict the stereochemical outcome. Most widely used is the Zimmerman-Traxler transition state (Fig. 49).<sup>70</sup> Later models are the ones proposed by Evans<sup>71</sup> and Noyori.<sup>72</sup> These models have in common that the diastereoselectivity depends on the enolate configuration.

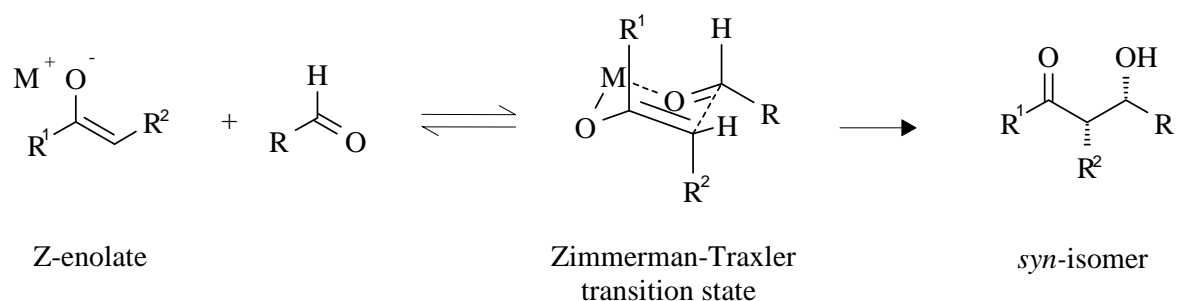


Fig. 49: The Zimmerman-Traxler transition state of an aldol reaction

Aldol reactions with methyl ketones often suffer from low selectivity.<sup>73</sup> In case of a chiral methyl ketone and a chiral aldehyde, double stereodifferentiation can occasionally occur so that mainly one epimer results.

However, in the work of Dr. Parra-Rapado on Latrunculin D, it was shown that an aldol reaction between the two key fragments **52** and **72** was rather unselective, affording a 1:2 mixture of the two epimeric alcohols. Moreover, Dr. Parra-Rapados work showed that the use of dialkylboron enolates did not significantly affect the ratio of the different epimers (Fig. 50).

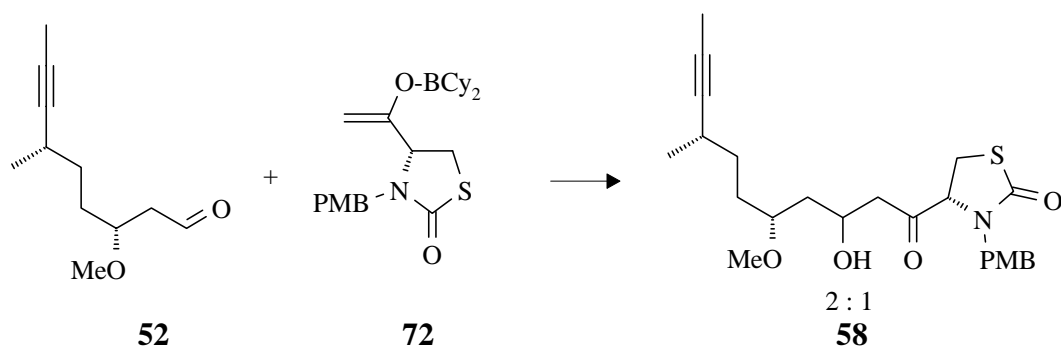


Fig. 50. Dr. Parra-Rapados aldol reaction between aldehyde **52** and enolate **72**.

Therefore Dr. Parra-Rapado concluded that the use of a lithium enolate anion of ketone **13** together with the aldehyde was the most efficient way to effect the aldol reaction, even though only very limited stereoselectivity was observed.

In order to carry out the aldol reaction between ketone **13** and aldehyde **25**, ketone **13** was deprotonated over 3 h at  $-78\text{ }^{\circ}\text{C}$  with LDA prepared *in situ* in THF, before aldehyde **25** was added to the enolate at this temperature (Fig. 51).

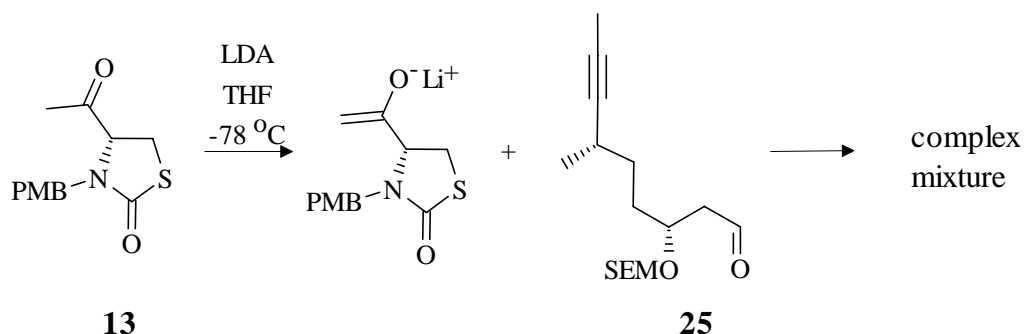


Fig. 51: Attempted aldol reaction between the enolate of ketone **13** and aldehyde **25**.

Although ketone **13** disappeared according to TLC when the reaction mixture was warmed to ambient temperature over 16 h, no defined product was obtained. In one experiment, the aldol reaction was carried out at  $-18\text{ }^{\circ}\text{C}$  overnight; in this case, GC-MS revealed that large amounts of ketone **13** and aldehyde **25** were left. Attempts to quench the reaction at  $-78\text{ }^{\circ}\text{C}$  did not improve the results.

It was suspected that the SEM group in **25** caused the problems since the analogously methoxy substituted aldehyde **52** had performed quite well in the work of Parra-Rapado. To clear this point a simple model substrate was prepared (Fig. 52).

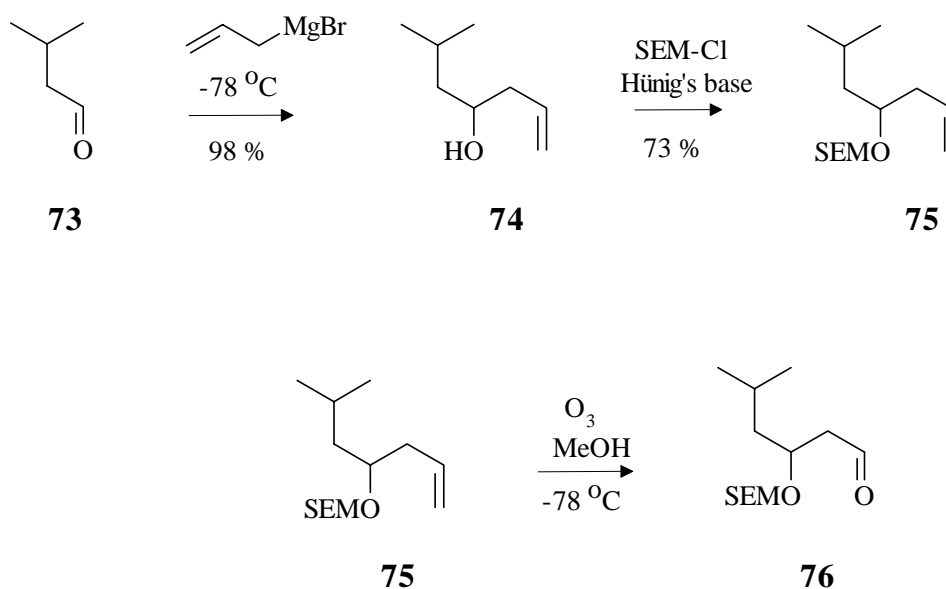


Fig. 52: Preparation of model substrate **76** similar to aldehyde **25**.

Addition of allylmagnesium bromide to aldehyde **73** and protection of the resulting alcohol **74** proceeded as expected, giving SEM-protected alkene **75** in 72 % yield.

The ozonolysis, however, gave an obscure product when performed in dichloromethane. According to TLC and GC-MS, a well defined product resulted which could be purified by chromatography. NMR revealed that this product was not an aldehyde. It was not possible to determine if the product was the ozonide by NMR investigation, but the spectra showed that the product was a mixture of two different isomers or an oligomer. The latter proposal was supported by mass spectrometry, since the mass of the product was higher than the expected mass of 260 units. The electrospray-ionisation mass spectra showed peaks at 1052 mass units and characteristic peaks at 609, 429 and 299 units. There are examples in the literature of successful ozonolysis of protected 4-hydroxy-1-alkenes using methanol or a mixture of methanol and dichloromethane as the solvent.<sup>74</sup>

When the ozonolysis of compound **75** was carried out in dry methanol a clean formation of aldehyde **76** resulted. The aldol reaction was performed with this simple model substrate and the enolate generated from ketone **13** with LiHMDS at low temperature and the resulting reaction mixture was investigated by HPLC. This mixture was found to contain a number of products, each of which had larger mass peaks than the expected  $m/z$  526 for the aldol product (Fig. 53).

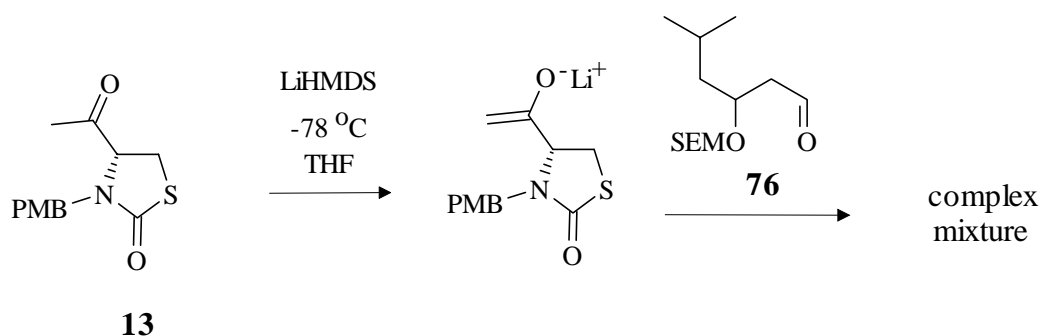


Fig. 53: Model study of the aldol reaction between **13** and **76**.

This result was similar to the aldol reaction between ketone **13** and aldehyde **25**. We therefore concluded that the -OSEM group was inappropriate for our purpose. We decided that a *tert*-butyldimethylsilyl group should be used for the aldehyde fragment which has previously been commonly used as a protecting group for alcohols in aldol reactions. However, the route outlined above was not suitable for introducing this group since another *tert*-butyldimethylsilyl protected alcohol is involved from the beginning of the aldehyde synthesis and selectivity problems might be foreseen. Therefore this route was not pursued any further.

In parallel work, Dr. De Souza, developed an alternative approach to the required aldehyde fragment. Dr. De Souza's strategy started from citronellene **77**, made use of a Brown allylation followed by protection to give the silylether **80**. Selective ozonolysis of the alkene gave the desired aldehyde **81** (Fig. 54).

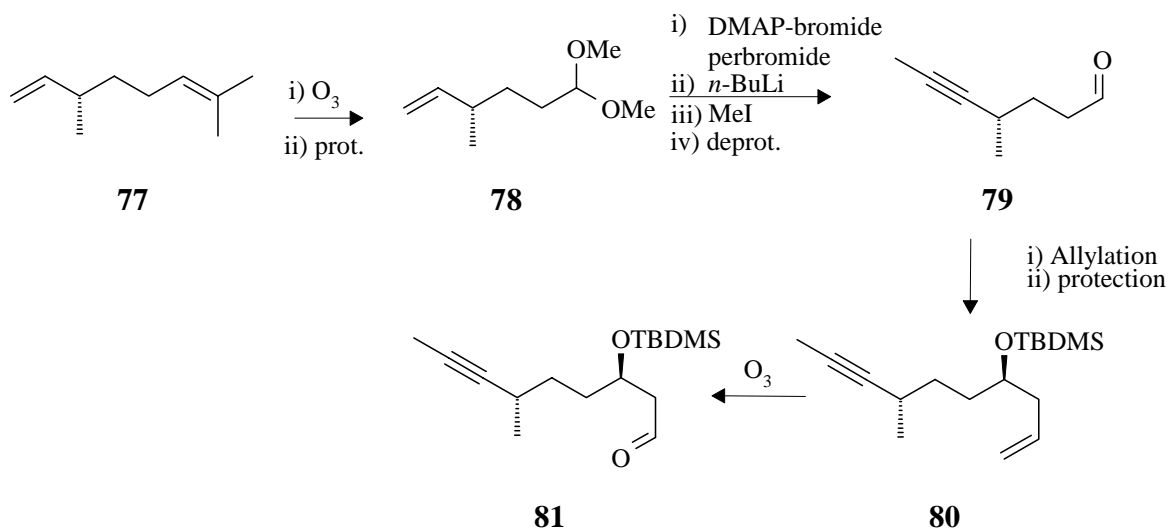


Fig. 54: Dr. DeSouza's synthesis of aldehyde **81**.



As expected, aldehyde **81** bearing the *tert*-butyldimethylsilyl protection group behaved well in the aldol chemistry. This result paved the way for our total synthesis of latrunculin B published recently.<sup>75</sup>

## Latrunculin A

Retrosynthetic cleavage of latrunculin A at the C-8/C-9 bond shows that this compound can be formed from alcohol **83** already used *en route* to latrunculin B and carboxylic acid **84** (Fig. 55).

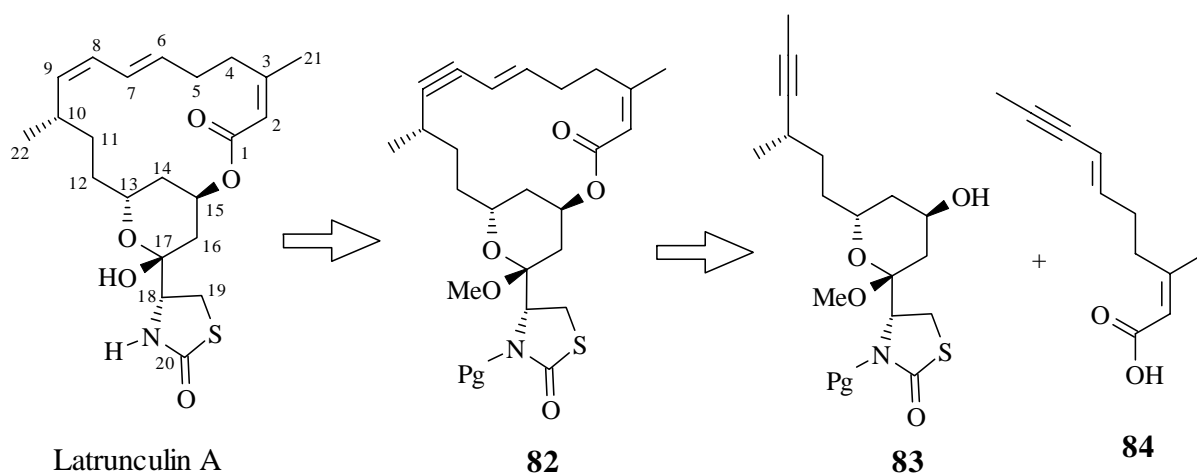


Fig. 55: Retrosynthesis of latrunculin A.

In 2004 Fürstner and co-workers reported what is believed to be the first examples of intramolecular enyne-yne RCAM to form 18- and 21-membered macrocycles with the Schrock catalyst **4**.<sup>76</sup> We therefore decided to investigate if enyne-yne RCAM would be a suitable strategy for the formation of the 16-membered macrocycle of latrunculin A. The first approach to **84** envisaged an iron-catalyzed cross coupling similar to the one successfully employed for the preparation of the more simple carboxylic acid **26** in the latrunculin B synthesis (Fig. 56).

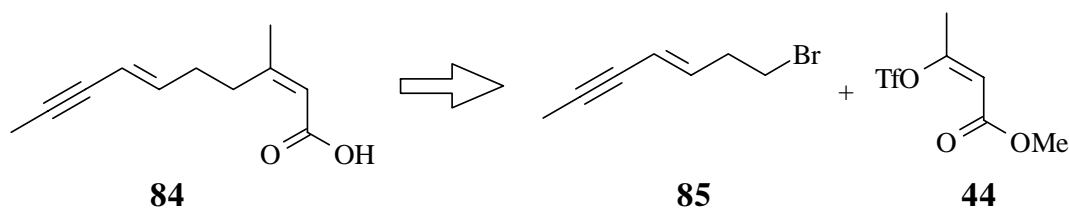


Fig. 56: Retrosynthesis of fragment **75**.

This type of cross coupling was originally described by Kochi in 1971<sup>77</sup> for vinyl bromides and Grignard compounds.<sup>78</sup> It was proposed that the catalytically active species in the reaction was either an iron +1 or iron (0) compound.<sup>79</sup>

In 2002 this type of transformation was further developed by Fürstner *et al.* who showed that the reaction was of far broader scope than previously reported. For instance, electron deficient aryl chlorides react easily with Grignard compounds at 0 °C to give almost quantitative yields of cross coupling products in many cases.<sup>46</sup>

The work by Fürstner and co-workers suggested that the nature of the iron compound added as precatalyst to the reaction mixture only plays a minor role.<sup>46</sup> Fe(acac)<sub>3</sub> was chosen as the precatalyst for practical reasons because it is cheap, anhydrous, nonhygroscopic and soluble in organic solvents such as THF and diethyl ether.

The true nature of the catalytic species is still under investigation, though the mechanism for the coupling is believed to be partly understood. It probably involves a low valent iron-magnesium cluster as the active catalyst. In the beginning of the reaction, the precatalyst might be reduced to form an “inorganic Grignard compound,” [Fe(MgX)<sub>2</sub>], which inserts into a halide or pseudo halide. Iron (0) itself was found to be catalytically inactive.<sup>46</sup>

When applied to the latrunculin A synthesis, bromide **85** was to be converted into the corresponding Grignard reagent and then submitted to a cross coupling with triflate **44** in presence of a catalytic amount of Fe(acac)<sub>3</sub>.

Bromide **85** was first prepared according to the literature,<sup>80</sup> by ring opening of a cyclopropane derivative under acidic conditions (Fig. 57). The reaction has been reported to give a 47:53 ratio of the *Z*- and *E*- isomer when performed with **88** as the substrate and almost exclusively the *E*-isomer when performed with the cobalt complex **89** derived thereof.<sup>80</sup>

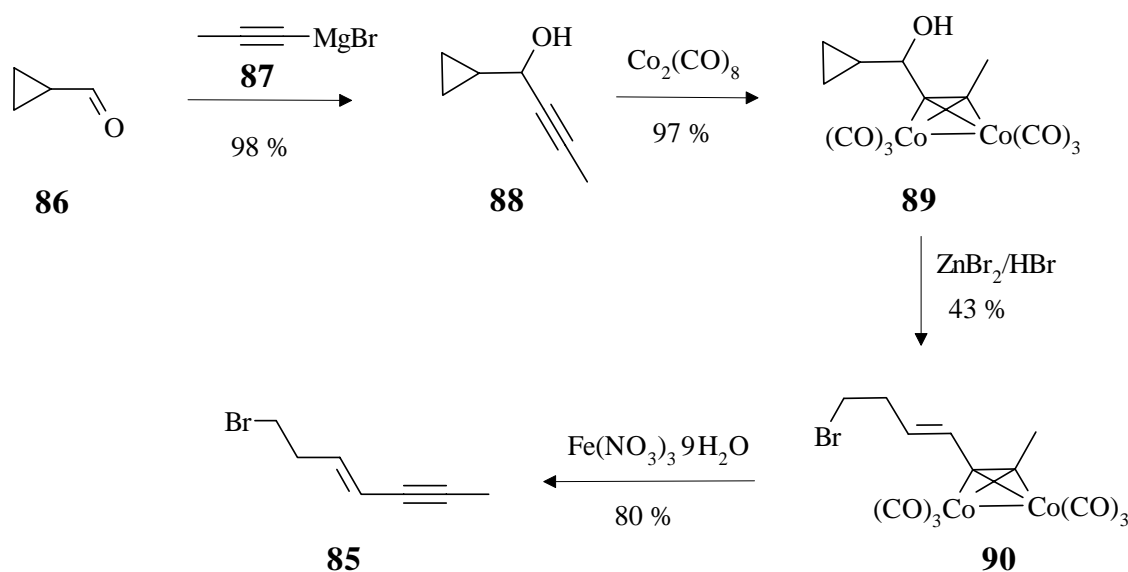


Fig. 57: Preparation of bromide **85**.

Cyclopropynyl alcohol **88** was easily prepared by reaction of propynylmagnesium bromide with commercially available cyclopropyl carbaldehyde **86**.

Treatment of **88** with a mixture of concentrated HBr and ZnBr<sub>2</sub> at -10 °C provided a ≈ 1:1 mixture of *Z* and *E* 1-bromo hept-3-en-5-yne according to GC-MS.

Next, alkyne **88** was protected with dicobalt octacarbonyl. Exposure of the cobalt complexed alcohol **89** with HBr and ZnBr<sub>2</sub>, gave varying results and rather low selectivity. In the original paper<sup>80</sup> a reaction mechanism involving a protonated hydroxy group is presented, but this type of ring opening likely involves a nonclassical carbocation (Fig. 58).

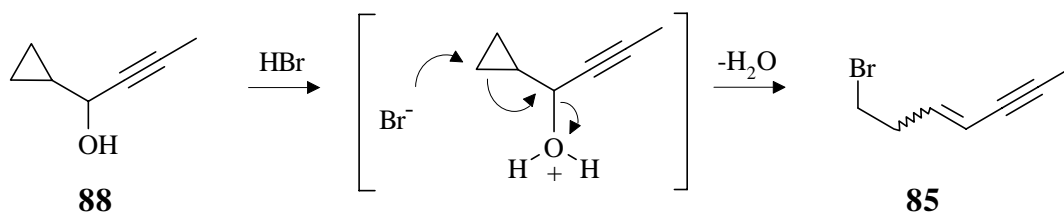


Fig. 58: Reaction mechanism proposed in the literature for formation of **85**.

Even though cobalt complex **89** was reported to undergo an almost exclusive conversion to the *E*-configured isomer, a mixture of the two isomers was formed in most cases when performed in our laboratory. Changing the solvent from diethyl ether to pentane, purification of cobalt complex **89** by flash chromatography, or changing the temperature to -20 °C or 0 °C did not solve the problem.

Therefore a more reliable sequence for the preparation of bromide **85** was developed (Fig. 59).

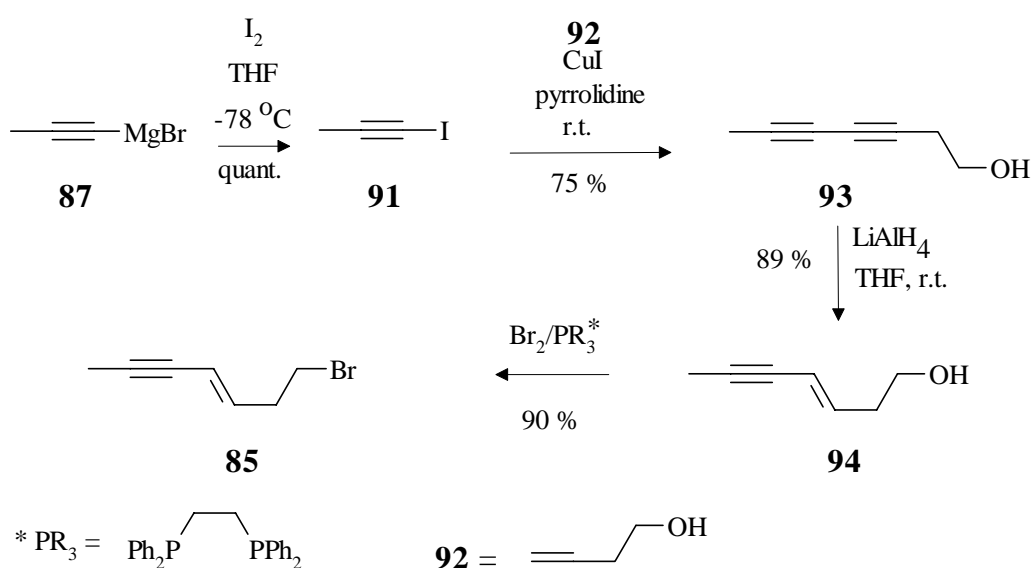


Fig. 59: Route to pure bromide **76**.

Propynylmagnesium bromide **87** was converted into iodide **91** by treatment with iodine at  $-78\text{ }^{\circ}\text{C}$  in THF. Under these conditions, addition of iodine to the triple bond is avoided, and only nucleophilic attack of the Grignard reagent on iodine is observed. Full consumption of iodine in the reaction mixture is easily observed by the color change from violet to light yellow.

After distilling off most of the solvent, the propynyl iodide was used directly in the subsequent Cadiot-Chodkiewicz coupling. This copper (I)-catalyzed reaction between an alkyne and an alkynyl halide<sup>81</sup> was developed in the 1950's,<sup>82</sup> and is a useful route to unsymmetrical 1,3-diynes.

Alami and Ferri reported that the use of copper (I) iodide as promotor and pyrrolidine as the solvent increases the yield in the reaction between aliphatic 1-alkynyl iodides and but-3-yn-1-ol.<sup>83</sup> When performing the Cadiot-Chodkiewicz coupling between iodide **91** and butynol **92** under these conditions the yields varied between 30 - 50 %. It was found that removal of the THF from the propynyl iodide before using it in the Cadiot-Chodkiewicz coupling raised the yield to 75 % (Fig. 60).

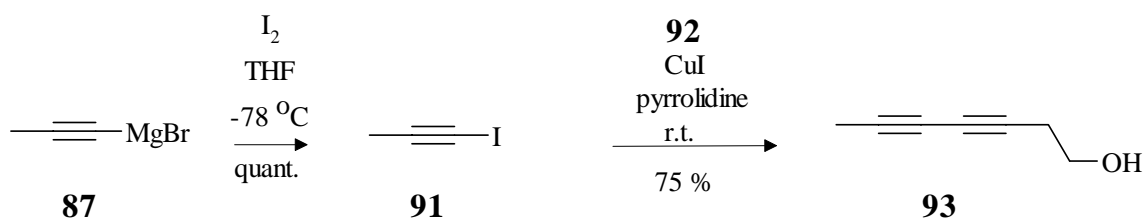


Fig. 60: The Cadiot-Chodkiewicz coupling between iodide **91** and butynol **92**.

The selective reduction of dialkynyl alcohols similar to **93** is known in the literature. Trost *et al.* reported the conversion of a dialkynyl alcohol to the *E*-enyne alcohol with Red-Al.<sup>84</sup> but also lithium aluminium hydride has been used successfully in selective reductions of substrates containing conjugated triple bonds.<sup>85</sup> Since lithium aluminium hydride is able to overreduce the product,<sup>86</sup> Red-Al was tested first (Fig. 61).

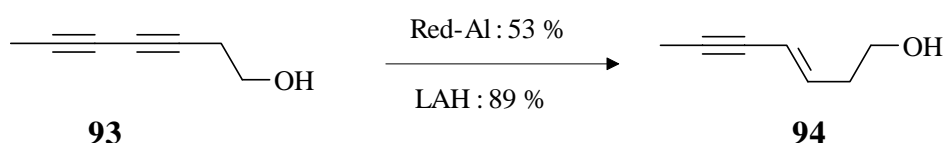


Fig. 61: Reduction of diyne **93**.

The Red-Al reduction was performed neat with no formation of side products, but the 2-methoxy ethanol derived from the Red-Al reagent was difficult to separate from product **94**.

Therefore lithium aluminium hydride was employed, which turned out to give the desired product **94** in good yield and purity after normal flash chromatography. Both reducing agents gave only *E*-**94** without any trace of the *Z*-isomer being detected by GC-MS.

In order to convert **94** to **85** without using strongly acidic conditions, a reagent based on bromine and a phosphine was used. For this purpose 1,2-bis(diphenylphosphino)ethane was employed instead of triphenylphosphine, because this phosphine was reported to increase the yields (Fig. 62).<sup>87</sup>

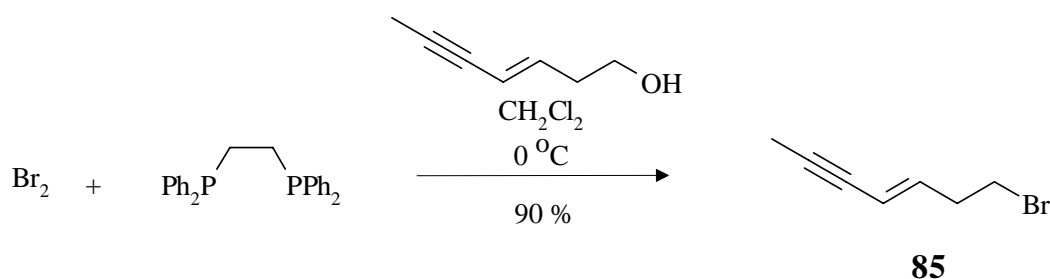


Fig. 62: Bromination of alcohol **94**.

Under these conditions, alcohol **94** underwent clean conversion to bromide **85**. Its volatility made the isolation difficult, but problems could be avoided by using only solvents with low boiling points such as dichloromethane, pentane and diethyl ether. Pure bromide **85** could be obtained in 90 % yield.

However, when bromide **85** was treated with either normal magnesium turnings at elevated temperatures (30 - 60 °C) in diethyl ether or THF, or with Rieke magnesium<sup>88</sup> at -30 °C, the Grignard reagent did not form. The consumption of the bromide over 30 - 120 min could be followed by GC-MS, although quenching of an aliquot of the reaction mixture with benzaldehyde in THF at ambient temperature showed that the desired Grignard compound had not formed (Fig. 63).

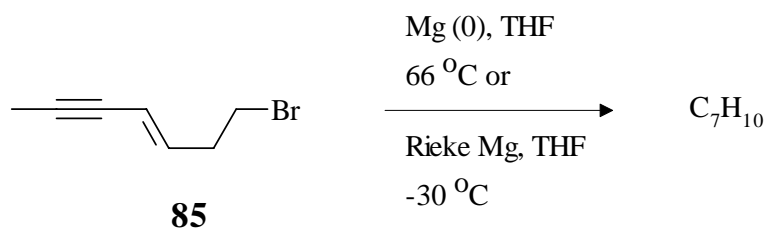


Fig. 63: Reaction of bromide **85** with magnesium.

Instead, according to GC-MS, a compound with a  $m/z$  94 arose, which was more volatile than the bromide. This product could not derive from elimination of hydrogen bromide, as a  $m/z$  of 92 would be expected in this case.

Rieke magnesium is known to react with bromides at low temperature,<sup>89</sup> and side reactions that appear with conventional magnesium turnings are often avoided or minimized. In the present case, however, the outcome was the same as with normal magnesium turnings, except that the reaction proceeded faster and at lower temperature.

Therefore we decided to explore a different route and use the commercially available Grignard reagent **95** in the iron-catalyzed cross coupling. The cross coupling should then be followed by formation of the enyne system by an olefination of the deprotected aldehyde (Fig. 64).

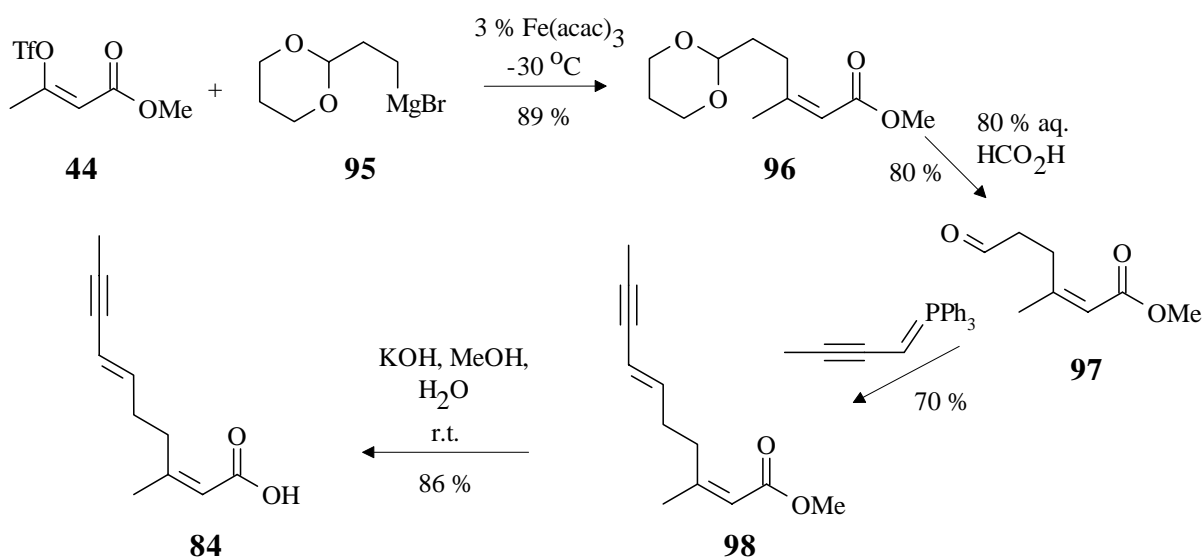


Fig. 64: Alternative route to carboxylic acid **84**.

Triflate **44** was prepared from acetoacetic acid methyl ester **45**.<sup>90</sup> Trifluoromethanesulfonic acid anhydride was added to keto ester **45** that had been deprotonated by sodium hydride. Triflate **44** formed in good yield and was easily isolated since it is stable to extraction and flash chromatography.

The reaction was stereoselective, giving only the desired (*Z*)-isomer (Fig. 65).

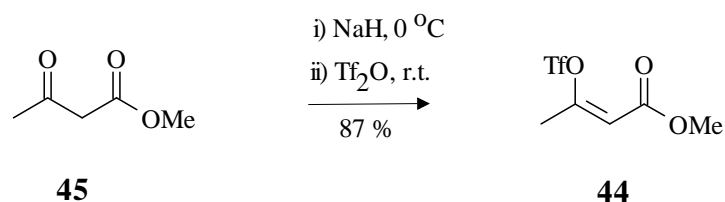


Fig. 65: Preparation of triflate **44**.

3 Mol % of  $\text{Fe}(\text{acac})_3$  was used as the precatalyst to effect the reaction of triflate **44** and Grignard compound **95** in THF at  $-20\text{ }^\circ\text{C}$  to  $-30\text{ }^\circ\text{C}$ . A black color appeared, which faded away after a few minutes, and the original orange color from  $\text{Fe}(\text{acac})_3$  reappeared. The coupling proceeded in good yield and only the desired product was observed from GC-MS. It is important to note that the Grignard reagent has to be added rapidly to the reaction mixture, as slow addition did not result in cross coupling. In this case no black color appeared and a mixture of products resulted.

A variety of methods for the deprotection of 1,3-dioxane acetals have been described in the literature. In our case, stirring of acetal **96** in 80 % aqueous formic acid gave aldehyde **97** in a reasonable yield (Fig. 66).<sup>91</sup>

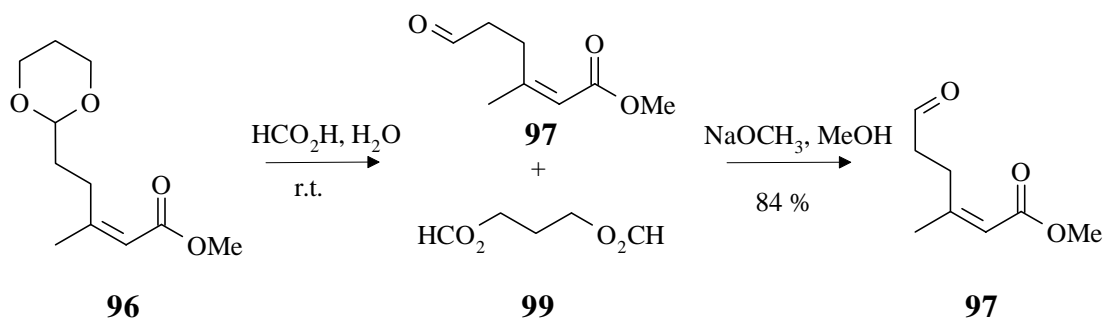


Fig. 66: Deprotection of acetal **96** to give aldehyde **97**.

During the deprotection 1,3-propanediol diformate **99** was formed, which was difficult to separate from the aldehyde. However, treatment of the crude product with a mixture of 5 mol % of sodium methoxide in dry methanol at ambient temperature for 30 min caused solvolysis of diformate **99** to give methyl formate and 1,3-propanediol, both of which could be easily removed. With this procedure, the yield of **97** was 84 %.

For the olefination of aldehyde **97** two different reagents were considered. First the Horner-Wadsworth-Emmons-type reagent **102**<sup>92</sup> was prepared. Although similar phosphonates have been used before,<sup>93</sup> this particular reagent has not yet been employed in olefination reactions (Fig. 67).

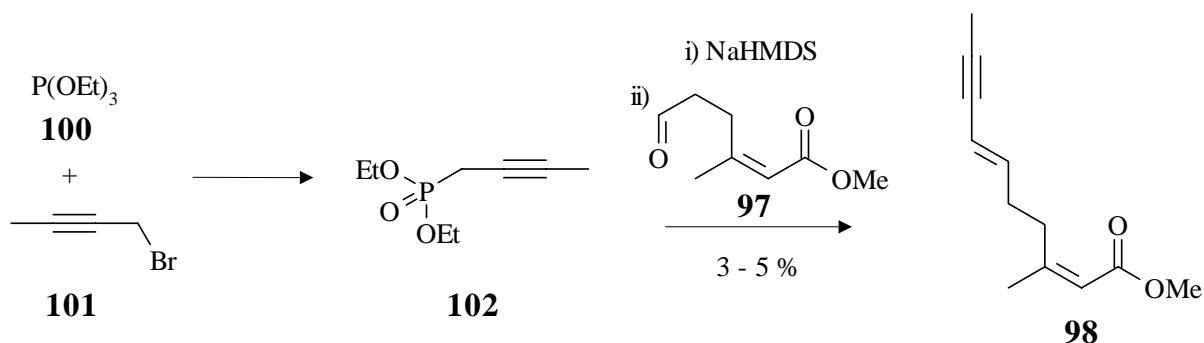


Fig. 67: Preparation of Horner-Wadsworth-Emmons reagent **102** and reaction with aldehyde **97**.

Phosphonate ester **102** was prepared via an Arbuzow rearrangement in 65 % yield by refluxing bromide **101** and triethyl phosphite **100** in *o*-xylene for 3 h. Attempted olefination of **97** with this salt gave only very low yields of **98**.

A related reagent that has previously been used in olefination reactions is the triphenylphosphonium salt **103** (Fig. 68).<sup>94</sup>

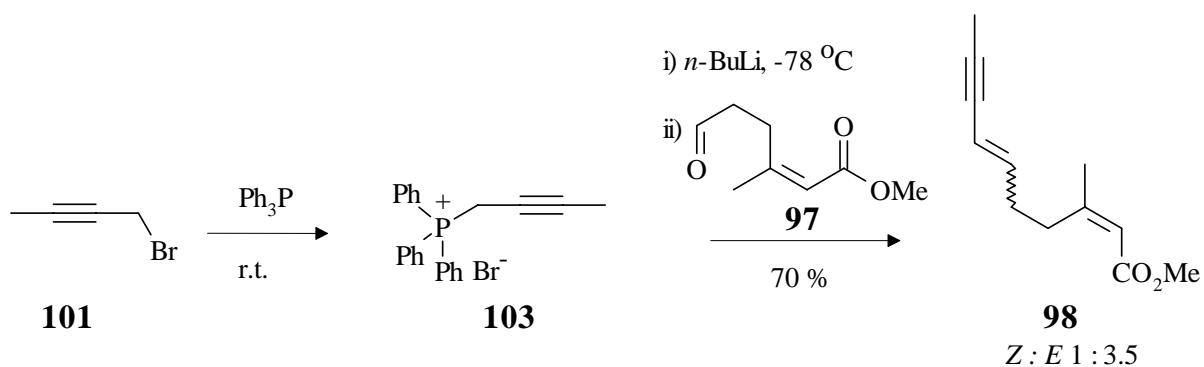


Fig. 68: Preparation of, and Wittig reaction with phosphonium reagent **103**.

Phosphonium salt **103** was formed in 69 % yield from but-2-ynyl bromide **101** and triphenylphosphine in toluene at ambient temperature. It was treated with *n*-BuLi at  $-78\text{ }^\circ\text{C}$  in THF, before aldehyde **97** was added at this temperature to the resulting red solution. The mixture was then allowed to reach ambient temperature over several hours.

A mixture of the *E* and *Z* olefins was formed in a ratio of 3.5 : 1 in favour of the *E* olefin. The ratio was determined by GC-MS followed by isolation and characterization by NMR.



The two isomers of enyne ester **98** were difficult to separate. Flash chromatography on silica gel led to partial separation, but a better separation was achieved using a Lobar column. This method gave the desired 3-methyl deca-(*Z,E*)-2,6-en-8-ynoic acid methyl ester **98** in 30 % yield as a pure product.

The hydrolysis of ester **98** was effected in aqueous base. Several reaction conditions previously reported turned out to result in isomerization or polymerization. DMF, 1,4-dioxane or DMSO together with aqueous potassium hydroxide all failed to give clean hydrolysis, which needed two days or more to proceed. Lithium hydroxide in different mixtures of organic solvents like THF<sup>95</sup>, DMF<sup>96</sup> or water<sup>97</sup> gave faster reactions, but no clean conversion. Only the use of potassium hydroxide in methanol<sup>98</sup> and water gave the hydrolysis product **84** in 86 % yield without side reactions, though the hydrolysis needed 48 h to finish (Fig. 69).

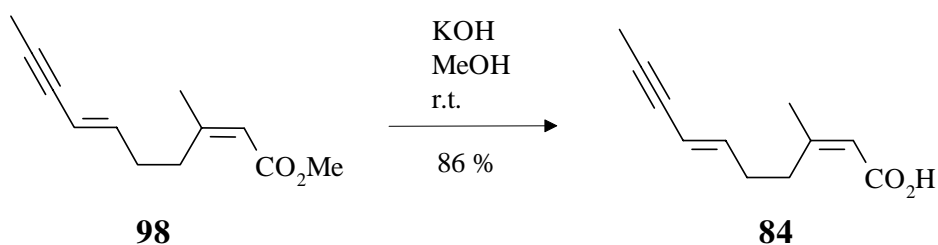


Fig. 69: Hydrolysis of ester **98** to give target **84**.

## Preparation of the molybdenum precatalyst

The Cummins-type complex **5** was made partly according to literature procedures,<sup>20</sup> but a few details were changed during the preparation (Fig. 70).

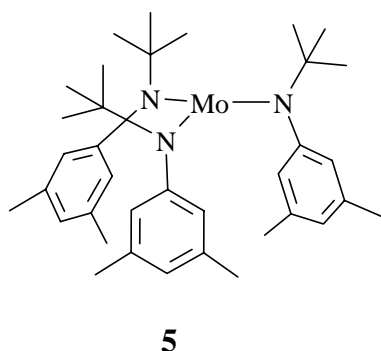


Fig. 70: Cummins complex **5**.

Preparation of 3,5-dimethyl-*N*-*tert*-butyl aniline **105** followed the procedure developed by Buchwald *et al.* which was optimized in our group by C. Mathes.<sup>19</sup>

Prior to the reaction, the palladium precatalyst, ligand **106** and sodium *tert*-butoxide were stirred in dry toluene at 40 °C for 15 min. Subsequent addition of *tert*-butyl amine followed by bromide **104** gave aniline **105** in excellent yield. The reaction of **104** with *tert*-butylamine catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub> was previously reported to take 8 h at 80 °C, but the reaction turned out to be complete within 45 min (Fig. 71).

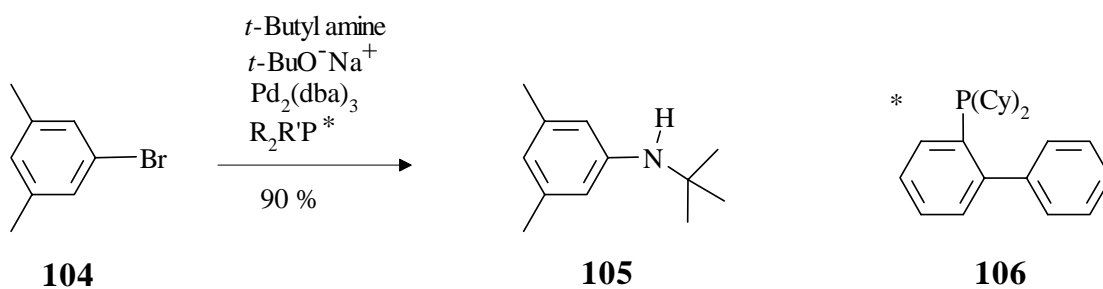
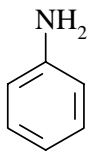
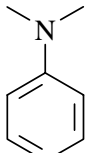
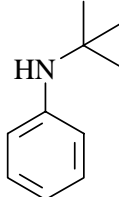
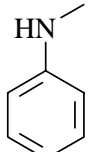
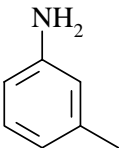
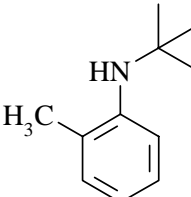


Fig. 71: Preparation of aniline ligand **105**.

Upon completion, the reaction was quenched with saturated aqueous ammonium chloride which, however, converted aniline **105** into its hydrochloride salt. Aniline **105** could be isolated by addition of potassium hydroxide to the solution and extraction with MTBE. Finally it was distilled to give the pure product as a colorless oil.

Comparison of the basicity of ammonia (  $pK_b = 4.75$  ) with aniline (  $pK_b = 9.4$  ) shows that aniline is an in the order of  $10^5$  weaker base than ammonia. The methyl groups on the aromatic ring and an alkyl substituent on the nitrogen should give rise to only a small change in the basicity (Table 2). Therefore it was puzzling how **105** could be basic enough to turn into its hydrochloride salt by reaction with ammonium chloride.

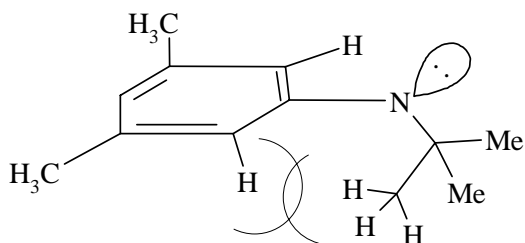
Table 2: Basicity of different anilines

Entry	Aniline	pK <sub>B</sub>	Entry	Aniline	pK <sub>B</sub>	Entry	Aniline	pK <sub>B</sub>
1		9.38 <sup>99</sup>	3		8.82 <sup>101</sup>	5		6.9 <sup>103</sup>
2		9.15 <sup>100</sup>	4		9.44 <sup>102</sup>	6		5.6 <sup>104</sup>

It is worth mentioning, however, that *N-tert*-butyl aniline (Entry 5), shows a pK<sub>B</sub> of less than 7.<sup>103</sup> Another example of such unexpected strong basicity is *N-tert*-butyl-2-methylaniline (Entry 6) that has a pK<sub>B</sub> of 5.6.<sup>104</sup>

In anilines the lone pair of nitrogen normally overlaps with the  $\pi$ -orbitals of the aromatic ring, thus lowering the basicity.

Considering 3,5-dimethyl-*N-tert*-butyl aniline **105** again, the sterically demanding *tert*-butyl group on nitrogen might force the lone pair out of conjugation with the aromatic ring thereby increasing the basicity of the nitrogen atom (Fig. 72).

Fig. 72: Possible sterical interactions in the aniline **105** molecule.

It was not possible to confirm this assumption by X-ray crystallography of aniline **105**, and the fact that the X-ray structure<sup>105</sup> of the Cummins-type complex **5** clearly shows that the

*tert*-butyl group twists the nitrogens lone pair out of conjugation with the aromatic ring does not necessary mean that this is also the case in the free aniline **105**.

Two different procedures for making MoCl<sub>3</sub>(THF)<sub>3</sub> have been published. The procedure used by Mathes in his preparation of the complex involves three steps (Fig. 73).<sup>19</sup>

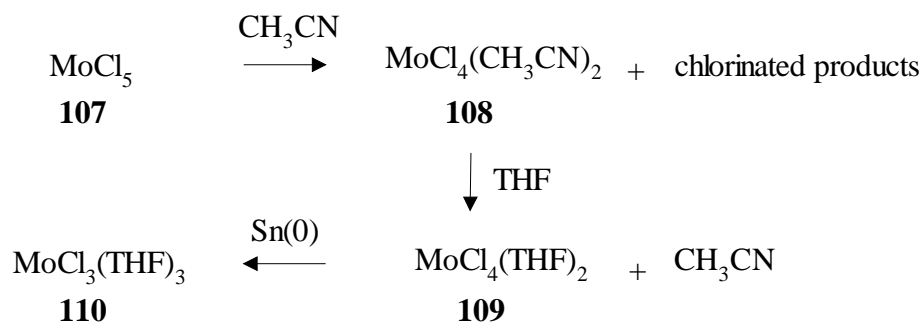


Fig. 73: The procedure originally used by Fürstner *et al.* for molybdenum complex **110**.

Later, a one pot procedure was published by Stoffelbach *et al.* which is also based on molybdenum (V) chloride as the starting material.<sup>106</sup> It uses diethyl ether instead of acetonitrile as the solvent, and tin (0) is present all the time.

In the Stoffelbach procedure, molybdenum (V) chloride is reduced to MoCl<sub>4</sub>(Et<sub>2</sub>O)<sub>2</sub> **111** by tin (0) in diethyl ether solution (Fig. 74).

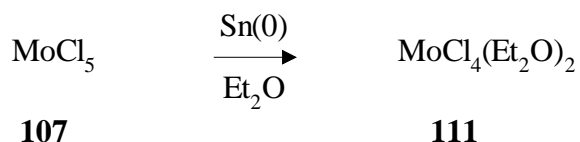


Fig. 74: Reduction of molybdenum (V) chloride to complex **111**.

Complex **111** reacts with added THF under substitution of the diethyl ether molecules to form the corresponding THF complex **109**. This reaction is an equilibrium and an excess of THF is necessary to ensure complete substitution.

The molybdenum (IV) center in **109** is easily reduced by tin (0) to molybdenum (III). This reduction is just as fast as the ligand substitution (Fig. 75). Metallic tin is, however, capable of over-reducing molybdenum (III) complex **110** to lower oxidation states, but Stoffelbach and co-workers reported that this over-reduction is slow in ether.<sup>106</sup>

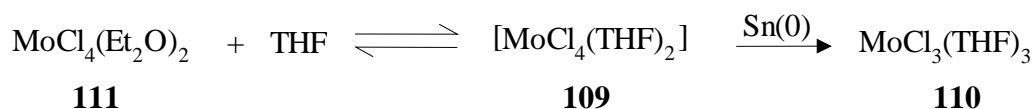


Fig. 75: Substitution of ether ligands in complex **111** and reduction to **110**.

In our laboratory, the Stoffelbach one pot procedure was carried out four times, but only succeeded once. The reason for this failure is likely the over-reduction of product **110**.

When failing, a brown, air-stable solid formed, whereas the desired product is an orange to pink air-sensitive compound.

Therefore the tin (0) was removed from the reaction during ligand exchange of diethyl ether for THF (Fig. 76).

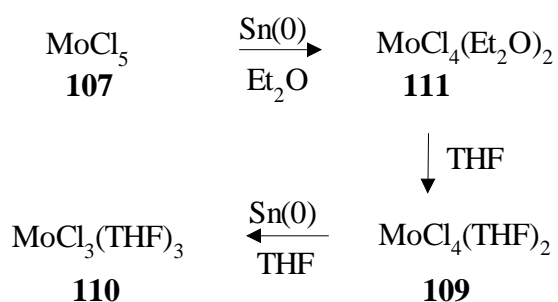


Fig. 76: A procedure similar to Stoffelbach's for making complex **110**.

Specifically, molybdenum (V) chloride was treated with coarse tin powder in diethyl ether, which afforded bis(diethyl ether) molybdenum (IV) chloride as an orange precipitate. The slurry was stirred vigorously and was then removed via cannula from the remaining tin powder. The precipitate was allowed to settle, the solvent was removed via cannula, THF was added and the mixture was stirred for 3 h to give  $\text{MoCl}_4(\text{THF})_2$  **109** as a yellow precipitate. Finally **109** was stirred in THF with coarse tin powder for 30 min to give **110** in 64 % yield as an orange to pink solid.

To form complex **5**, aniline **105** was deprotonated with *n*-butyllithium in hexane at -60 °C. Evaporation of most of the solvent followed by addition of diethyl ether gave a precipitate of lithium anilide diethyl ether complex **112** as very air-sensitive white crystals, which immediately turn dark green when exposed to air.

The white crystals were dissolved in diethyl ether and mixed with  $\text{Mo}(\text{THF})_3\text{Cl}_3$  at -120 °C and then stirred at ambient temperature for 16 h (Fig. 77).

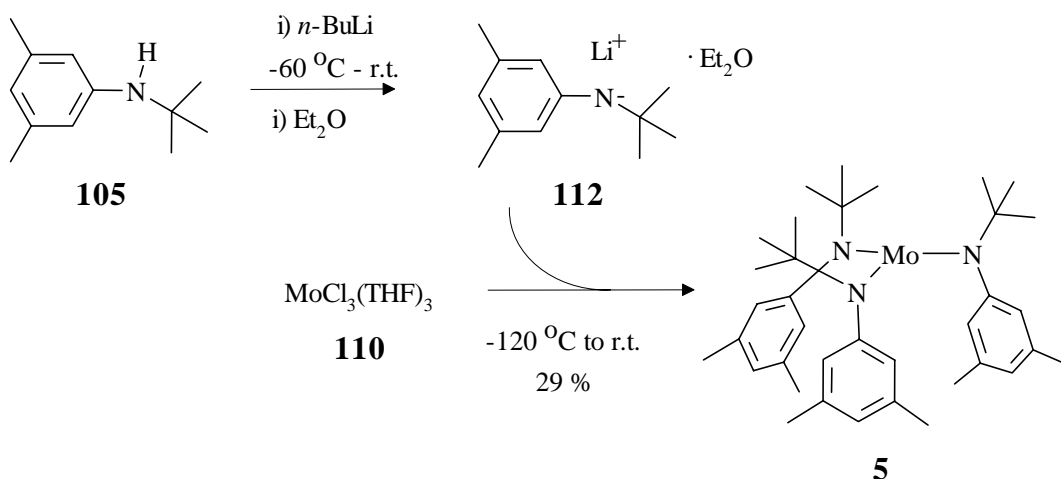


Fig. 77: Preparation of complex **5**.

Filtration of the now dark red to brownish slurry through Celite, concentration of the solution *in vacuo* and slow crystallization by cooling the solution of the complex from ambient temperature to  $-60\text{ }^\circ\text{C}$  over 12 h gave complex **5** as dark red crystals in 29 % yield. Complex **5** catalyzed the cyclisation of diyne **113** to give cycloalkyne **114** in 81 % yield. This RCAM has been performed previously<sup>107</sup> (Fig. 78).

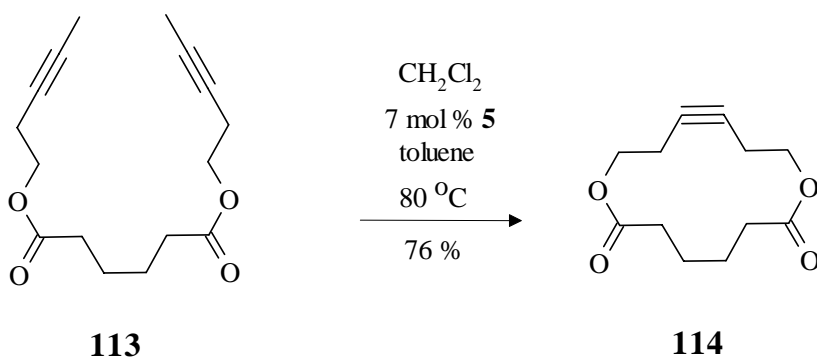


Fig. 78: Testing the RCAM precatalyst on substrate **113**.

### Ring closing enyne-yne metathesis

Next, it was tested if precatalyst **5** is able to catalyze the RCAM of a conjugated enyne to produce a 16-membered ring. The olefin in conjugation with the alkyne might interfere with the metathesis reaction and the presence of an alkyne and an *E*-configured olefin in the ring probably results in significant ring strain.

For this purpose, acid **84** was esterified with non-7-yn-1-ol **115** to give product **116** as model substrate for the RCAM reaction (Fig. 79).

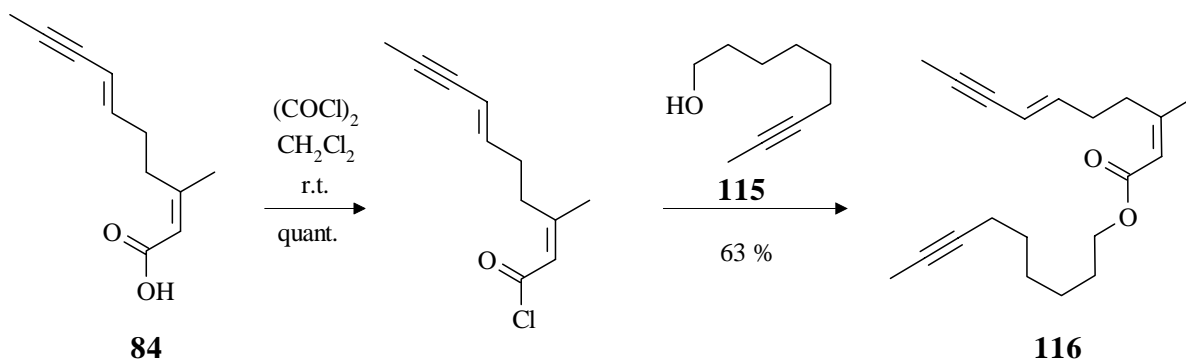


Fig. 79: Preparation of model substrate **116** for testing RCAM.

For the RCAM, two different catalytic systems were tested. We decided to limit the tests to the well defined molybdenum based catalyst developed by Füstner *et al.*<sup>18</sup> and the tungsten based catalyst **4** developed by Schrock *et al.*<sup>17</sup>

Molybdenum precatalyst **5** was dissolved in degassed toluene and activated by the addition of 25 equivalents of dichloromethane. The activation caused the red color of the solution to turn darker, and after five minutes the starting material for the RCAM was added and the solution was stirred at 80 °C for 16 h (Fig. 80).

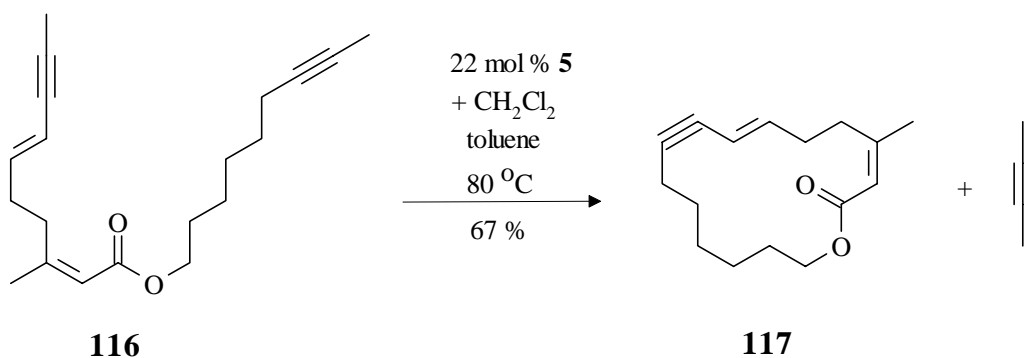


Fig. 80: RCAM of model substrate **116**.

The procedure was successfully carried out twice. In the first run 22 mol % of catalyst were used giving product **117** in 67% yield. The second run used only 6 mol % of catalyst and gave **117** in 66% yield.

However, some starting material remained unchanged and could be re-isolated from the reaction mixture.

An important result of the model study was that no isomerization of the double bond in conjugation to the alkyne was observed, that the conjugated ester group was unchanged after the reaction, and that no dimerization of the starting alkyne **116** was observed.

RCAM of model substrate **116** with tungsten complex **4** was carried out in degassed toluene using 20 mol % of the catalyst (Fig. 81).

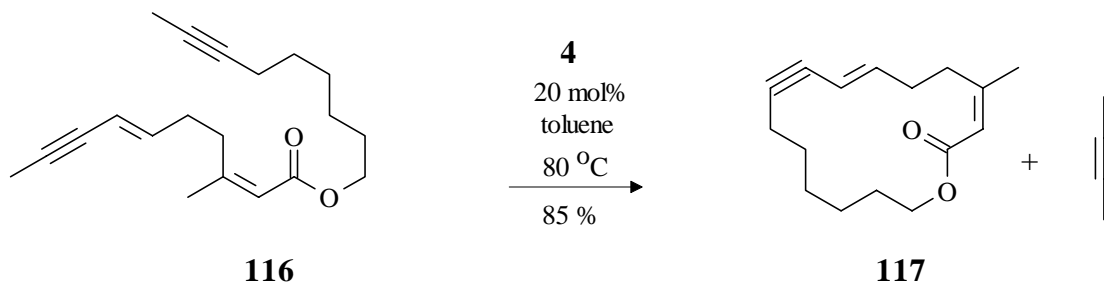


Fig. 81: RCAM of model substrate **116** with tungsten catalyst **4**.

In this experiment, argon was bubbled through the solution during the reaction. Diyne **116** was dissolved in the solvent at 80 °C before the catalyst was added. The yellow solution turned orange to red, indicating that the catalyst was active and that the reaction proceeded. After 90 min no starting diyne **116** could be detected by GC-MS. Product **117** was isolated in 85 % yield.

These results showed that RCAM of enynes could be performed with both catalysts in good yields without isomerization or dimerization of the substrate. An application to the total synthesis of latrunculin A therefore seemed promising.

## Aldol reaction for latrunculin A

Smith *et al.* reported in their synthesis of latrunculin A, that attempted deprotection of the PMB group of the thiazolidinone in the last step destroyed the conjugated diene of the macrolactone. Therefore they used a 2-(trimethylsilyl)ethyl carbamoyl group (Teoc group) for the protection of the nitrogen atom, which could be deprotected in presence of the diene without problems (Fig. 82).<sup>43</sup>



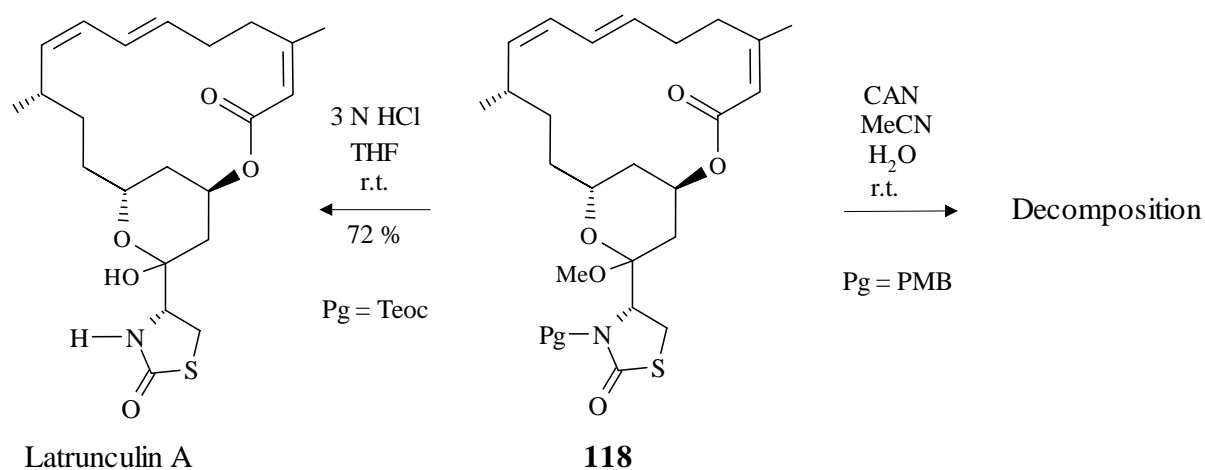


Fig. 82: The deprotection by Smith *et al.* to give latrunculin A.

We thus considered to test if the Teoc-protected thiazolidinone could be used in the aldol reaction. PMB protected ketone **13** was deprotected to give **16** which was then converted into **121** according to the literature (Fig. 83).<sup>108</sup>

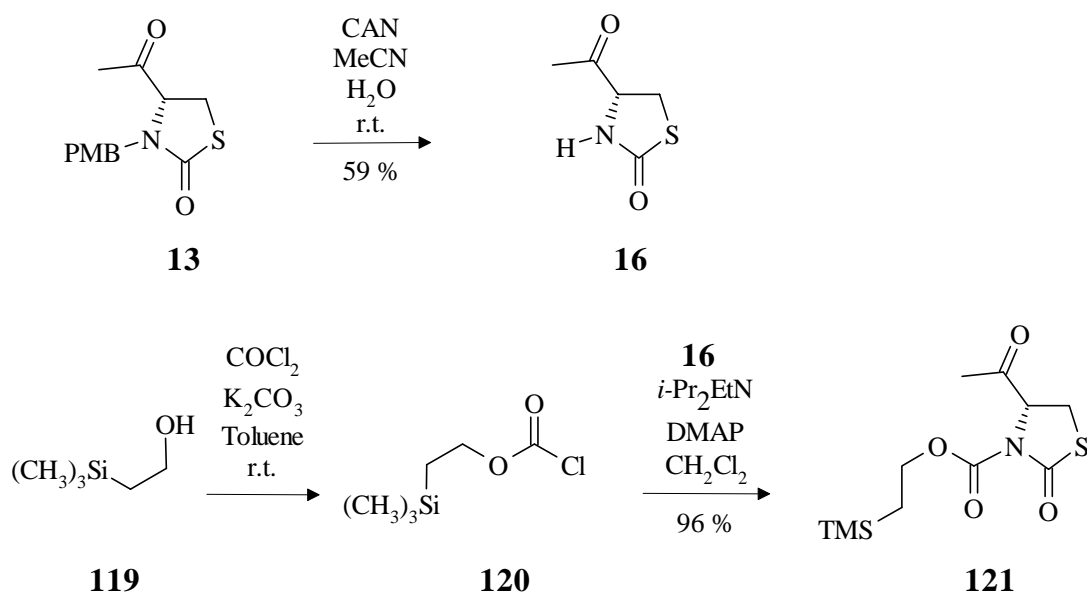


Fig. 83: Deprotection of **13** and reprotection with a Teoc-group to give **121**.

However, when **121** was treated with LDA at -78 °C for 2 h and then quenched, the Teoc protected ketone had almost completely decomposed (Fig. 84).

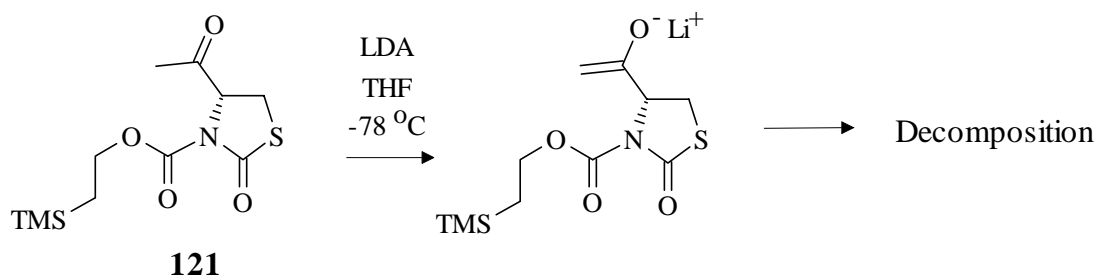


Fig. 84: Deprotonation of **121** with LDA at low temperature.

Therefore it was considered to perform the aldol reaction with ketone **16**, since a similar reaction had been described by White and Kawasaki. These authors treated unprotected thiazolidinone methyl ketone **16** with LDA at low temperature to give a dianion which was first complexed with cerium (III) chloride and then reacted with aldehyde **15** to give the aldol product in 60 % yield.<sup>44</sup>

However, the aldol reaction between **16** and the simple aldehyde **73** gave a 1 : 1 mixture of the two isomers in only 20 % yield. Even more disappointing, *tert*-butyldimethylsilyl protected  $\beta$ -hydroxy aldehyde **123** did not afford the desired product at all (Fig. 85).

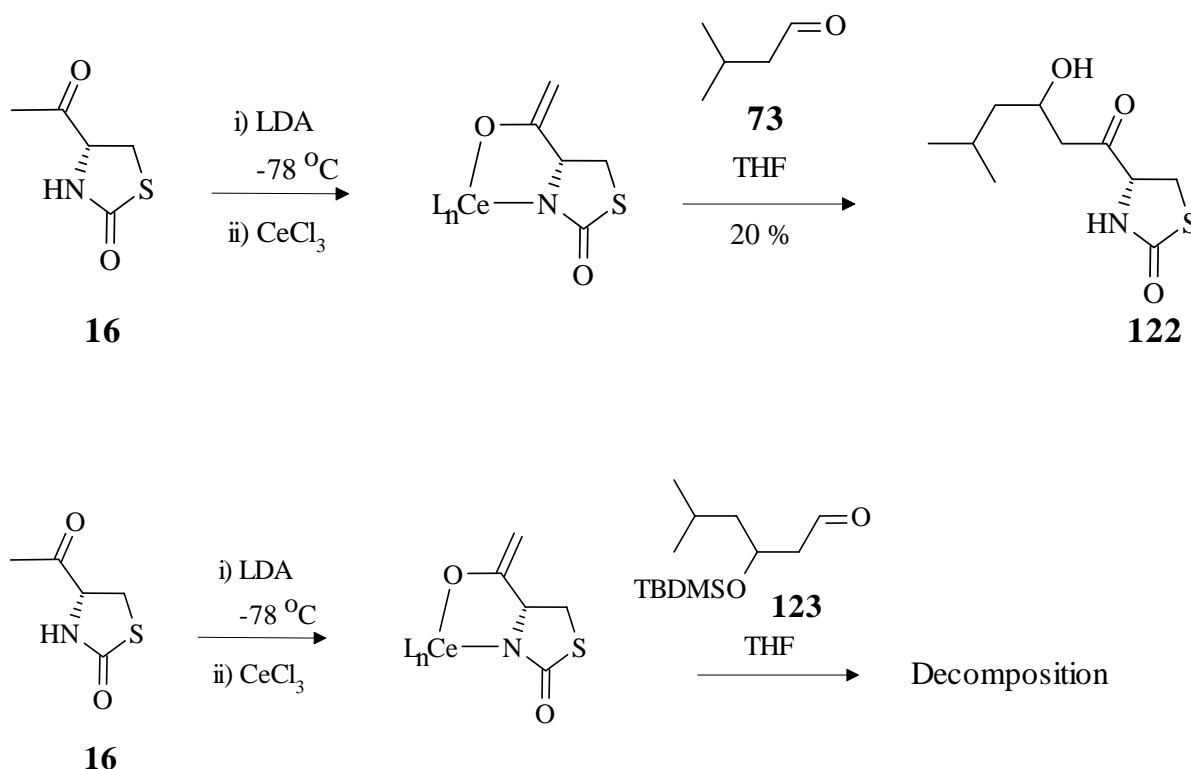


Fig. 85: Aldol reaction between aldehydes **73** and **123** and ketone **16**.

These results suggested that an alternative to the aldol reaction had to be found.

In this context it is worth mentioning that Dr. DeSouza had observed that an enone system had formed during deprotection and equilibration of his aldol product **124**. This enone system **126** was able to ring close to give a hemiketal as a mixture of the two possible epimers **127** and **128** in a 2.8:1 ratio (Fig. 86).

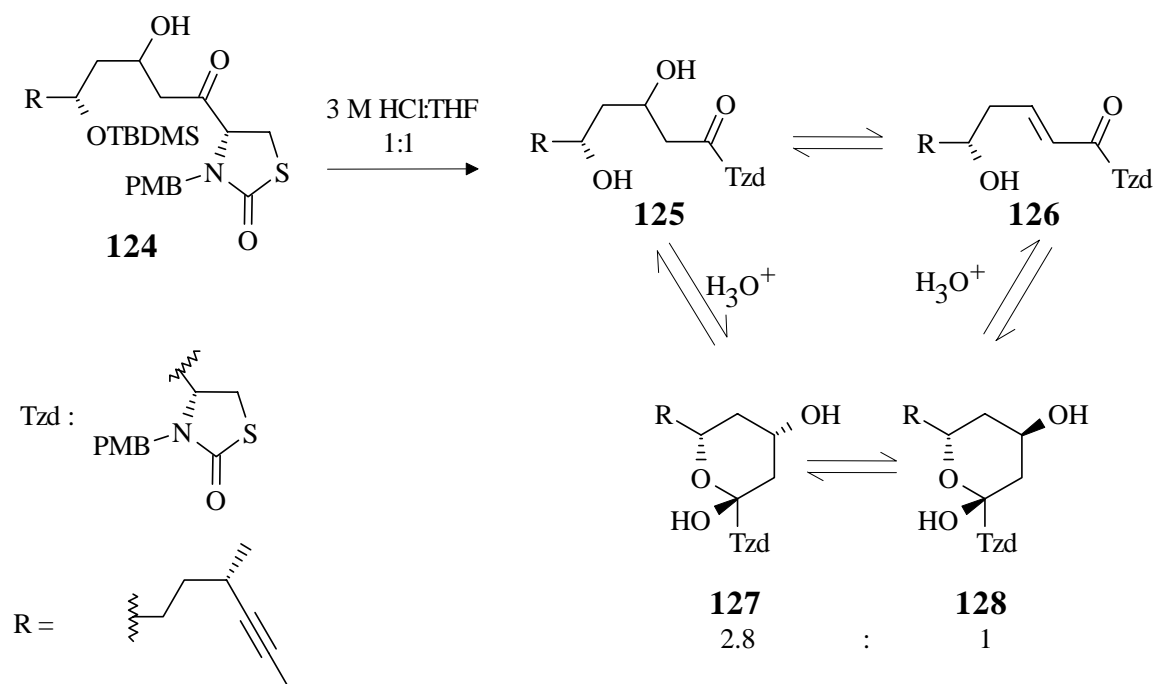


Fig. 86: Dr. DeSouza's deprotection and subsequent equilibration of aldol product **124**.

Since alkene **80** had already been prepared by Dr. DeSouza, a route using alkene cross metathesis of this compound to give enone **129** was investigated (Fig. 87).

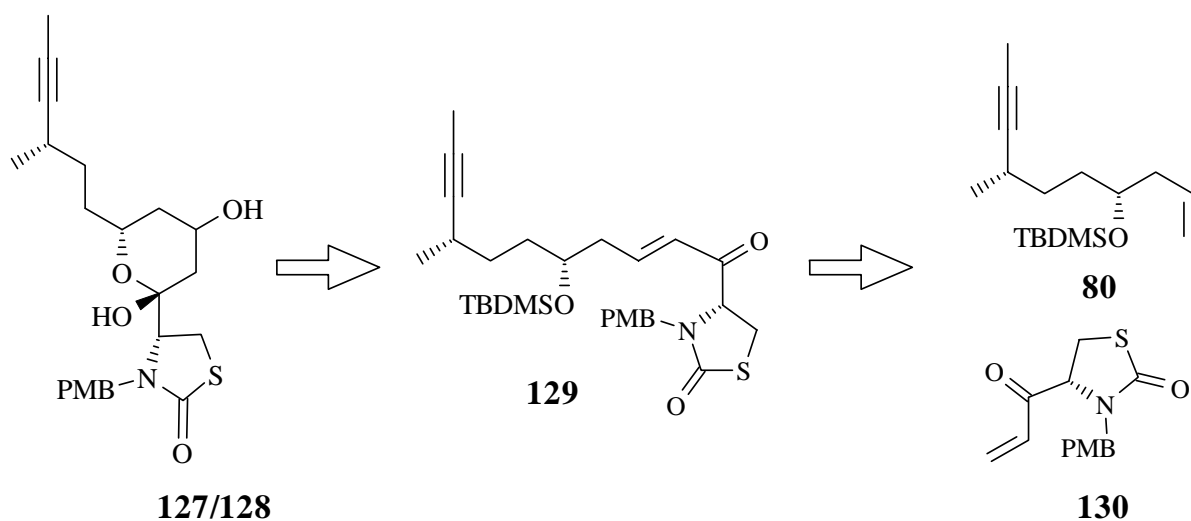


Fig. 87: Envisaged alternative to the aldol reaction for making fragment **127/128** by cross metathesis.

## Alkene cross metathesis

Recently Grubbs developed a guideline for controlling cross metathesis (CM) reactions of two different alkenes by comparing the reactivities of catalysts towards olefin functionalization and substitution. This, together with the tolerance towards a number of functional groups and the excellent control over the *cis/trans* ratio makes CM a valuable method for C-C bond formation.<sup>109, 1</sup>

Normally in a CM, an equilibrium mixture of homo- and cross metathesis products is formed. However, certain substitution patterns, such as 1,2-disubstituted alkenes in conjugation with an electron withdrawing group, deactivate the olefin towards metathesis, causing this product to accumulate (Fig. 88).

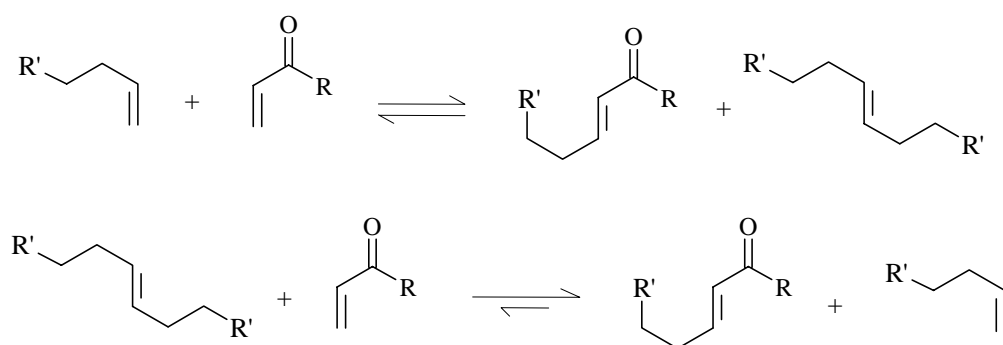


Fig. 88: Controlled CM.

The Grubbs second generation catalyst **131** and catalyst **132** developed by Hoveyda *et al.* have been reported to tolerate a large number of functionalities and to perform alkene cross metathesis in high yields (Fig. 89).<sup>110</sup>

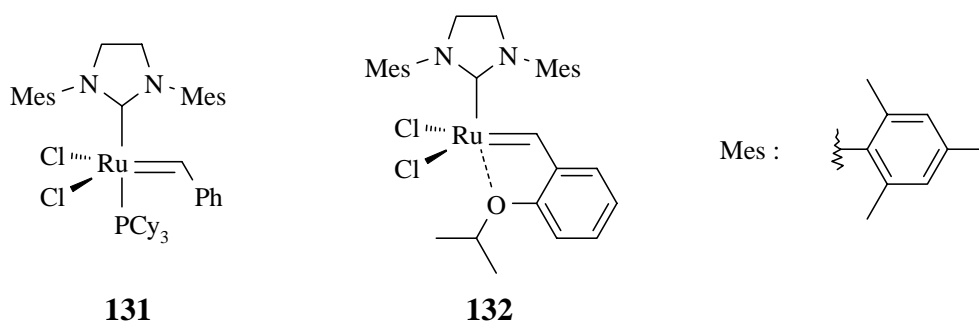
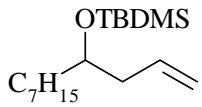
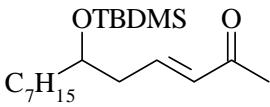
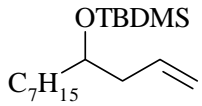
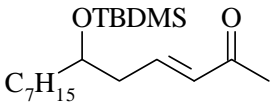
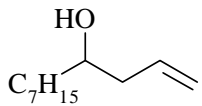
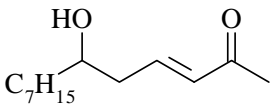
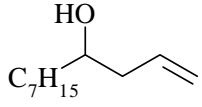
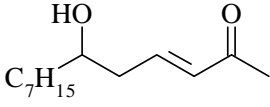


Fig. 89: Two catalysts for CM, Grubbs second generation catalyst **131** and Hoveyda's catalyst **132**.

The first model investigated was the CM reaction of a protected and an unprotected homoallylic alcohol with butenone (Table 3).

Table 3: CM of two different model alkenes with butenone.

Entry	Starting material	Product	Catalyst	Yield
1	 $C_7H_{15}$	 $C_7H_{15}$	<b>131</b>	79 <sup>a</sup>
2	 $C_7H_{15}$	 $C_7H_{15}$	<b>132</b>	95 <sup>b</sup>
3	 $C_7H_{15}$	 $C_7H_{15}$	<b>131</b>	85 <sup>a</sup>
4	 $C_7H_{15}$	 $C_7H_{15}$	<b>132</b>	55 <sup>b</sup>

[a] 1.9 mol% catalyst, 40<sup>o</sup> C/16 h. [b] 3.4 mol% catalyst, r.t./3 h.

In all cases, only the *E*-configured isomers **135** or **136** were obtained after work up. Next, model substrate **137** containing a non-terminal alkyne was employed (Fig.90).

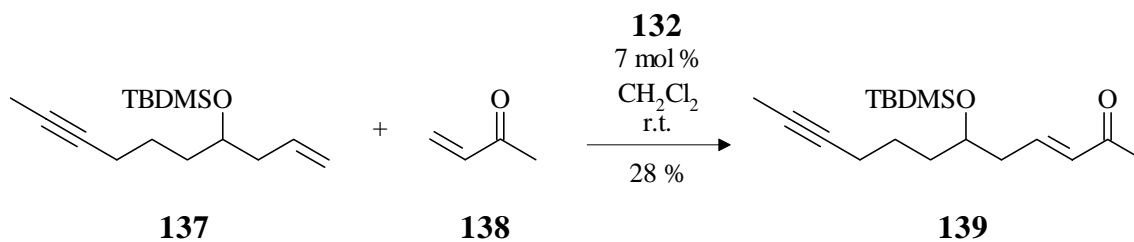


Fig. 90: Model study of CM with butenone and an alkyne containing homoallylic ether.

This substrate gave only low yield of **139** and several sideproducts were detected. It was concluded that the alkyne interfered with the desired CM reaction. We therefore tested if it was possible to protect the alkyne moiety as a dicobalthexacarbonyl complex during CM (Fig. 91).

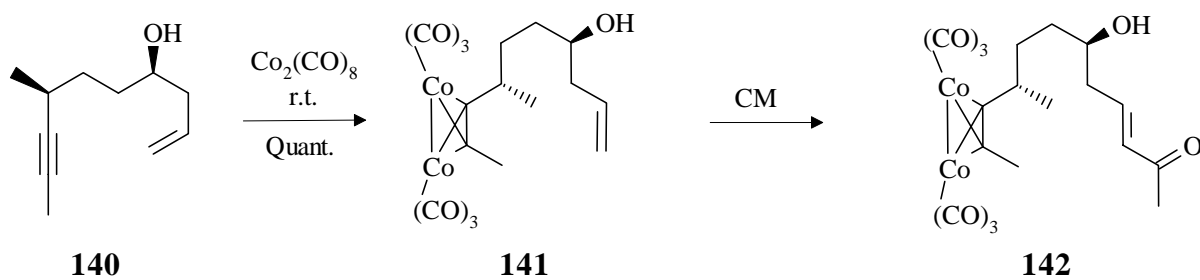
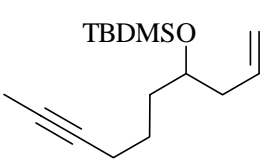
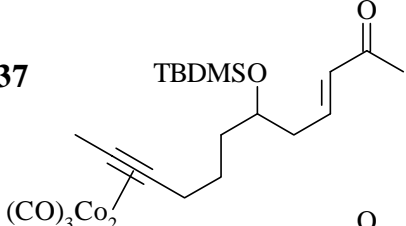
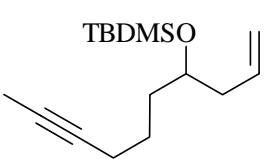
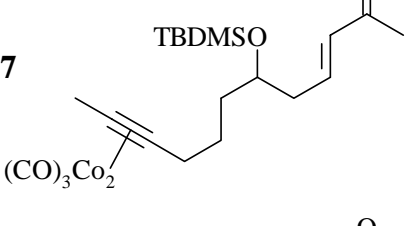
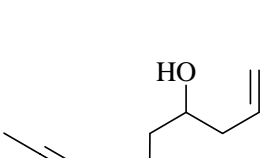
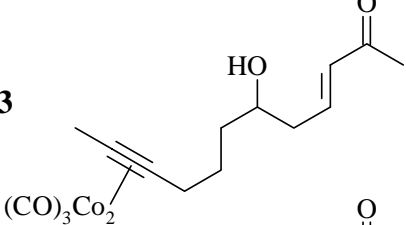
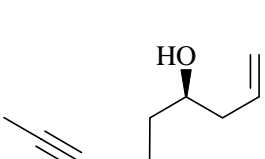
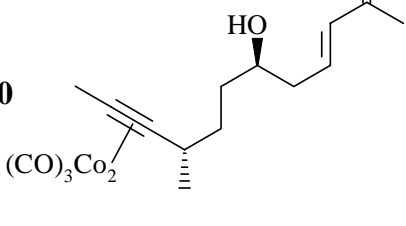


Fig. 91: Protection of alkyne **140** prior to CM.

The protection of the alkyne with  $\text{Co}_2(\text{CO})_8$  was carried out in pentane at ambient temperature and was quantitative. CM only proceeded when the complex was purified by flash chromatography prior to use.

Three different substrates were protected as their dicobalthexacarbonyl complexes and tested as substrates for CM (Table 4).

Table 4: CM of dicobalthexacarbonyl protected enynes.

Entry	Starting material	Product	Catalyst	Yield
1	 <b>137</b>	 <b>144</b>	<b>131</b>	17 <sup>a</sup>
2	 <b>137</b>	 <b>144</b>	<b>131</b>	40-73 <sup>b</sup>
3	 <b>143</b>	 <b>145</b>	<b>132</b>	84 <sup>c</sup>
4	 <b>140</b>	 <b>142</b>	<b>132</b>	82 <sup>d</sup>

[a] 7 mol% catalyst, 6 eq. butenone, 40<sup>o</sup> C/24 h. [b] 10 mol% catalyst, 8 eq. butenone 40<sup>o</sup> C/2 h.

[c] 13 mol% catalyst, 5 eq. butenone, r.t./3 h. [d] 6 mol% catalyst, 5 eq. butenone, r.t./3 h.

The yields turned out to be strongly dependent on the reaction conditions.

Using catalyst **131** and stirring for 24 h, the yield of **144** was low (Entry 1), whereas increased catalyst loading and an increased amount of butenone improved the results. The yields, however, varied between 40 and 73 % (Entry 2).

Using catalyst **132** and substrate **143**, the CM proceeded in 84 % yield (Entry 3).

Importantly, the yields were well reproducible.

CM's were carried out in dichloromethane. Again only the *E* isomers of the products were observed.

In an attempt to demask compound **144**, the complex was treated with tetrabutyl ammonium fluoride in THF at ambient temperature.<sup>111</sup> However, GC-MS showed formation of several products including addition products containing fluoride (Fig. 92).

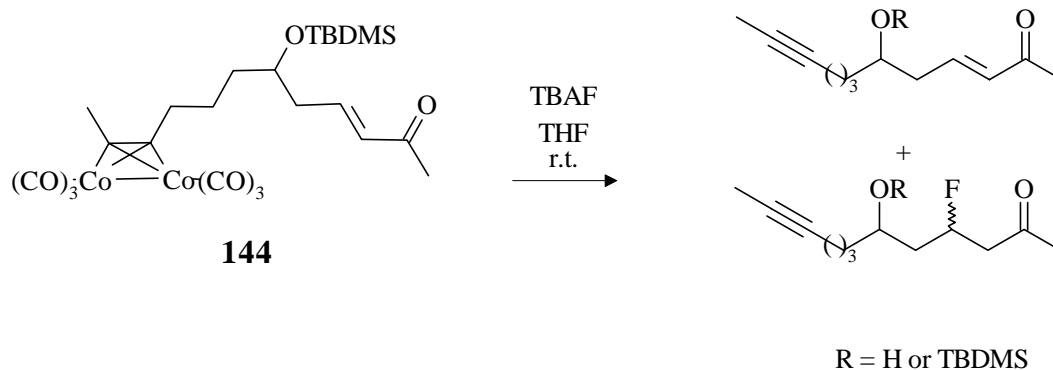


Fig. 92: Attempted demasking of protected alkyne **144** with TBAF.

Gratifyingly, when treated with  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  in ethanol at ambient temperature for fifteen minutes the dicobalthexacarbonyl protection group was removed and complex **142** could be deprotected cleanly in 88 % yield (Fig. 93).

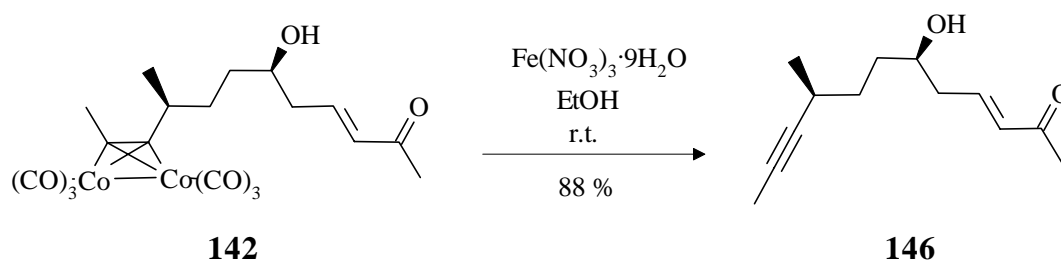


Fig. 93: Deprotection of dicobalthexacarbonyl group.

According to GC-MS and TLC, only one product was formed, and NMR analysis showed this to be the *E*-isomer. The overall yield of **146** after protection, CM and deprotection was 72 %.



## Vinyl ketone synthesis

For the envisaged CM, the corresponding thiazolidinone vinyl ketone **149** is required (Fig. 94).

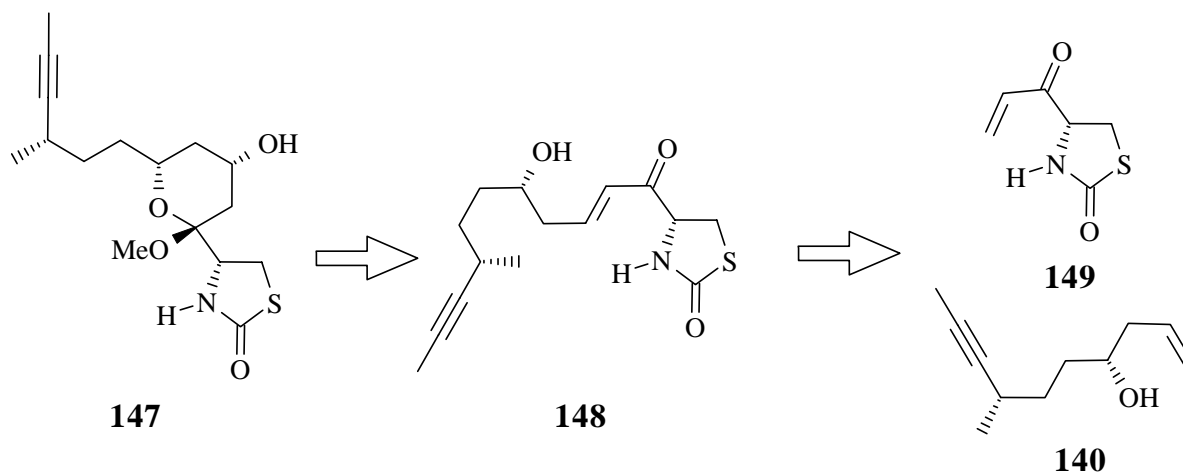


Fig. 94: The CM that would lead to dehydrated aldol product **149**.

We decided to start from oxothiazolidine carboxylic acid or a derivative thereof, since these are easily available in optical pure form.

The iron-catalyzed cross coupling successfully used for the synthesis of methyl ketone **13** cannot be applied because vinylmagnesium halides are known to undergo side reactions in presence of  $\text{Fe}(\text{acac})_3$ .<sup>112</sup>

Vinyl ketones have been made by elimination reactions of sulfoxides even in rather complex molecules.<sup>113</sup> Therefore a short route starting from thiazolidinone carboxylic acid ethyl ester **151** was tested, based on a Claisen-type condensation between sulfoxide **152** and ester **151** followed by an elimination of benzenesulfinic acid to give vinyl ketone **149** (Fig. 95).

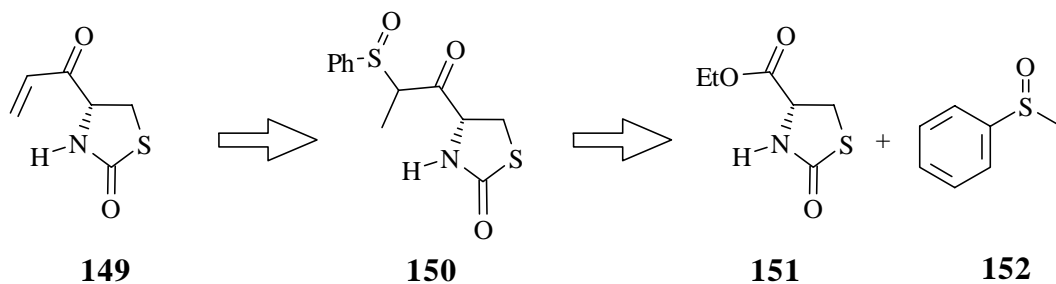


Fig. 95: Retrosynthesis of vinyl ketone **149**.

Ethyl phenyl sulfoxide **152** was prepared according to a literature procedure as a viscous oil (Fig. 96).<sup>114</sup>

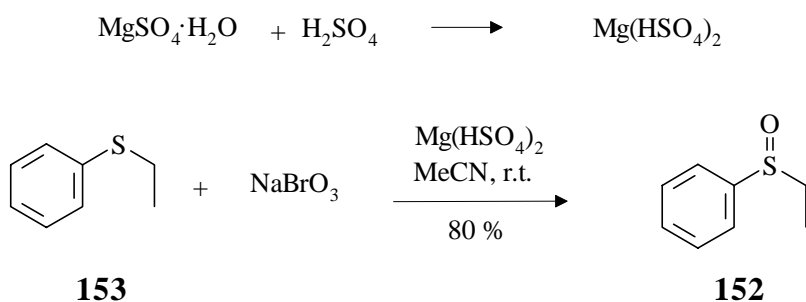


Fig. 96: Preparation of ethyl phenyl sulfoxide **152**.

Magnesium hydrogensulfate was made by treatment of magnesium sulfate with concentrated sulfuric acid.<sup>115</sup> The bromate oxidation of **153** was made with some safety precautions since bromates and organic compounds can react violently upon mixing. Although **152** can be crystallized from pentane, flash chromatography gave the pure compound as an oil in good yield.

Converting compound **151** into **154** and treating this with the deprotonated sulfoxide in presence of LDA resulted in full consumption of the starting material and formation of two new products (Fig. 97).

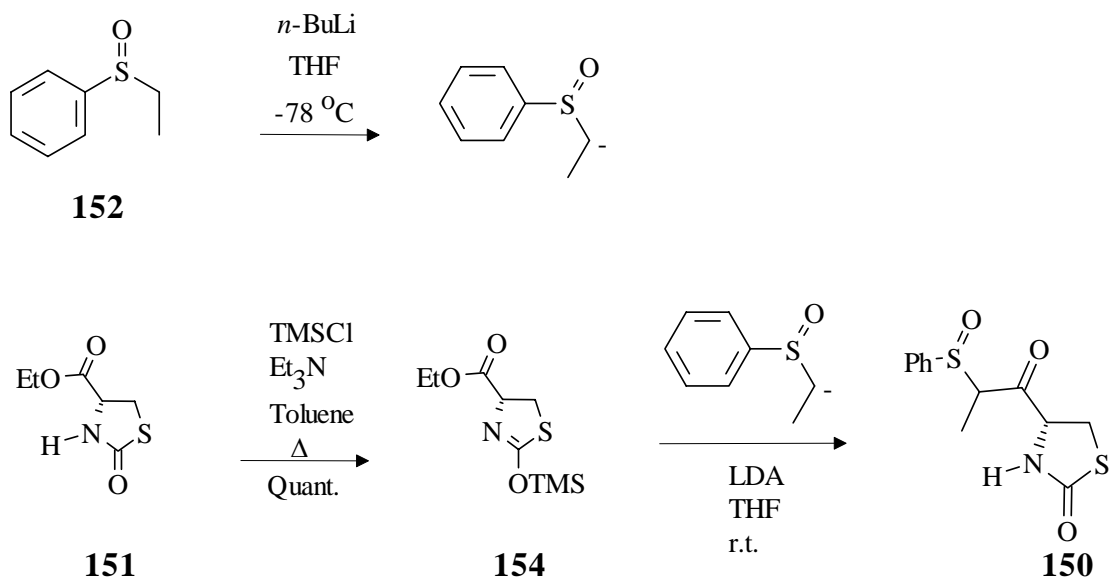


Fig. 97: Claisen-type condensation of sulfoxide anion with **154**.

Unfortunately, the two products degraded upon attempted purification by flash chromatography. Therefore the crude product was refluxed in *p*-xylene in order to see if

the elimination could be achieved. No desired vinyl ketone **149** was obtained although benzenesulphonic acid was isolated from the reaction mixture.

Two other approaches to vinyl ketones have been described, both of which are based on the conversion of an acid chloride. One is a Stille-type palladium-catalyzed reaction of an acid chloride and trimethylvinylstannane<sup>116</sup> and this method has been utilized with acid chlorides bearing a stereocenter in the  $\alpha$  position to the acid chloride.<sup>117</sup>

The other method, a Friedel-Craft-type acylation with one equivalent of aluminium chloride<sup>118</sup> or titanium tetrachloride<sup>119</sup> and vinyl silanes<sup>120</sup> has been used only in cases where no stereocenters were present  $\alpha$  to the acid group.

The Stille-type reaction was tested with the acid chloride derived from the unprotected thiazolidinone acid **155** by heating the acid chloride to 80 °C for 4 h or 16 h together with trimethylvinylstannane and 0.36 mol % or 0.95 mol % catalyst **156** in toluene. Likewise, the Friedel-Craft-type reaction was tested on the acid chloride of acid **155** with 1.5 equivalents of  $\text{AlCl}_3$  (Fig. 98).

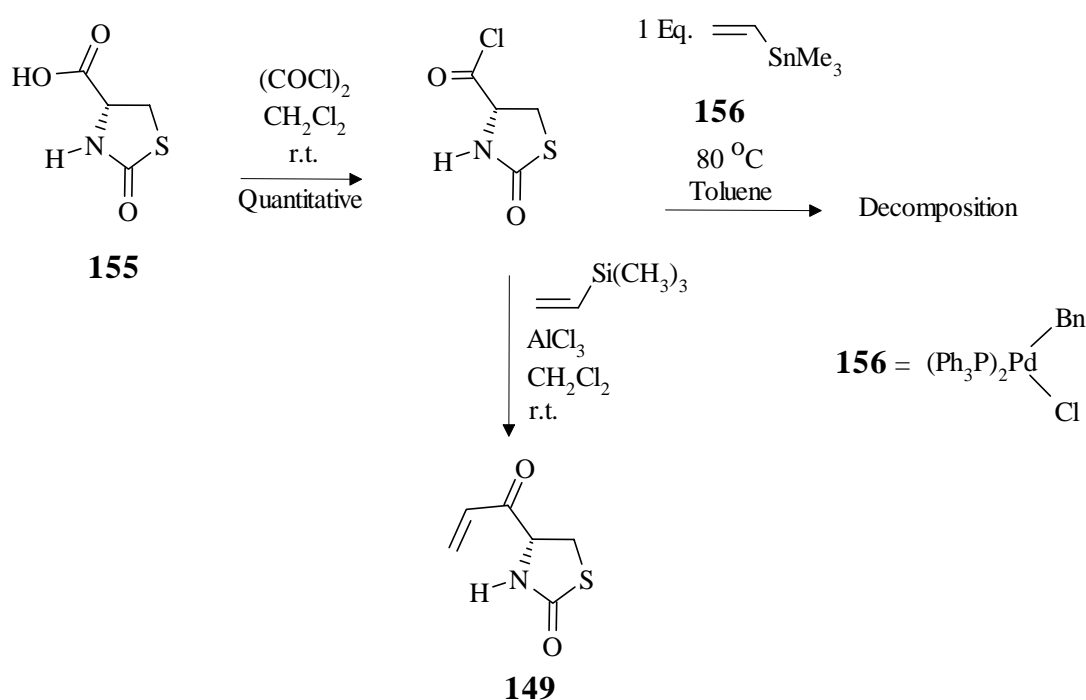


Fig. 98: Attempted Stille-type coupling and Friedel-Craft acylation of the acid chloride of **155**.

In the Stille-type reaction, the acid chloride was consumed. However, a complicated reaction mixture resulted.

In the Friedel-Craft-type reaction the acid chloride was consumed within 15 min and a single product was formed according to TLC and GC-MS. When purified by flash chromatography or when heated to 40 °C during work up, however, decomposition of the product was observed.

Although a NMR and a GC-MS of the crude product suggested that vinyl ketone **149** had formed, this compound could not be isolated.

## Conclusion

The goal of the work presented here was to establish a route to latrunculin B and A and we wanted to explore the possibility of utilizing ring closing alkyne metathesis as an alternative to macrolactonization to establish the two different macrocycles.

Retrosynthesis of latrunculin A and B showed that these two targets could derive from the same fragment **83** and two different carboxylic acids **84** and **26** (Fig. 99).

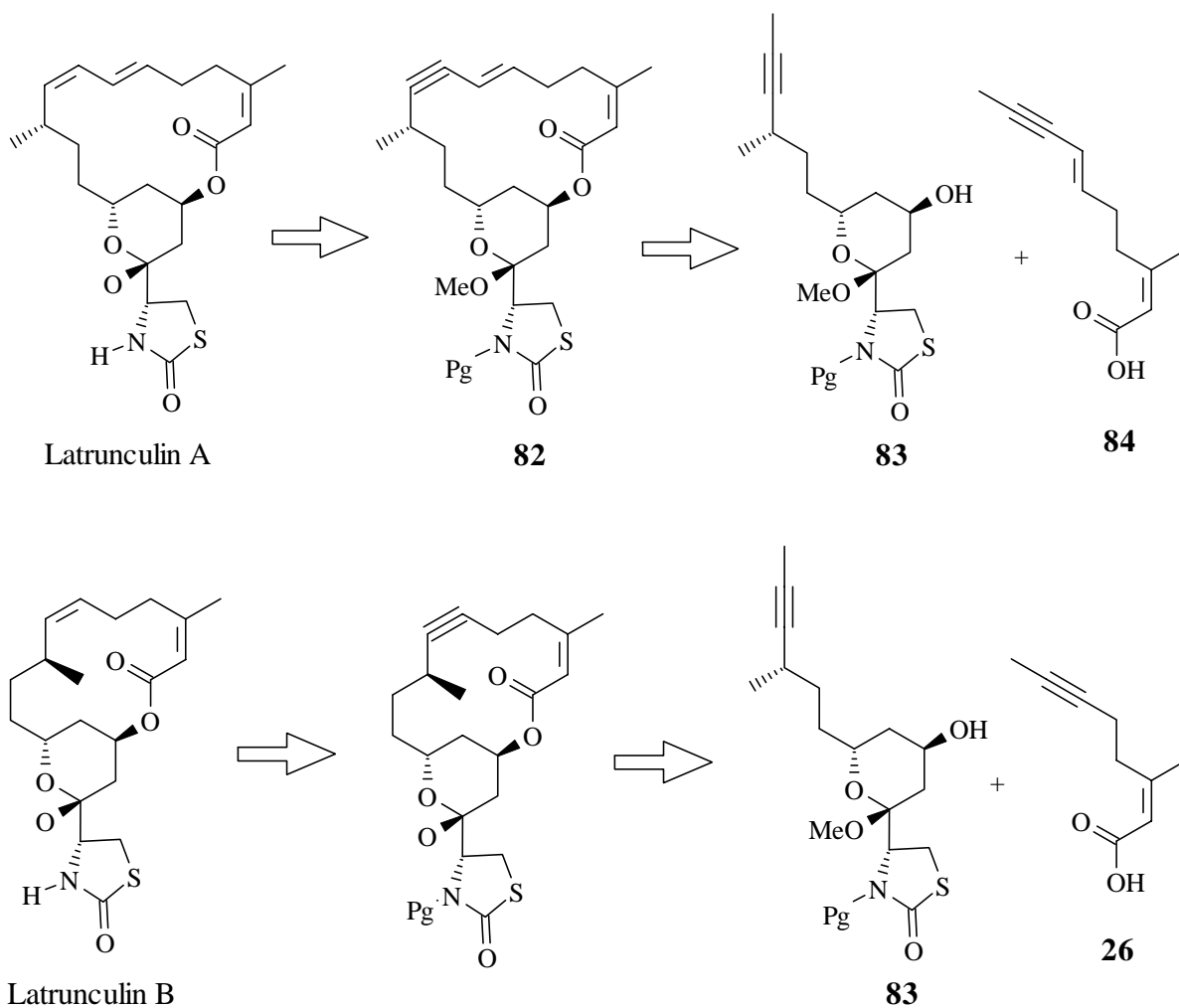


Fig. 99: Retrosynthesis of latrunculin A and B leading to the same key intermediate **83**.

The key intermediate **83** was planned to be obtained via an aldol reaction between the two fragments **25** and **13** (Fig. 100).

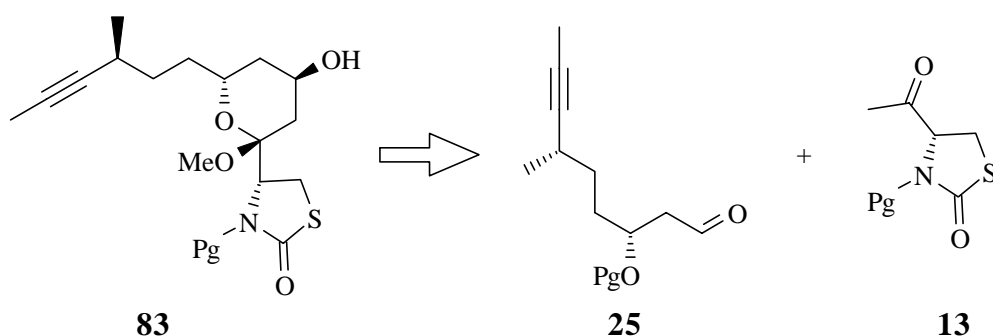


Fig. 100: Retrosynthesis of key intermediate **83**.

The two enantiopure key fragments, **13** and **25**, were prepared in good yields, which allowed for the investigation of an aldol reaction as a way to form the intermediate **83**. Ketone **13** was made in 44 % overall yield in 4 steps (Fig. 101).

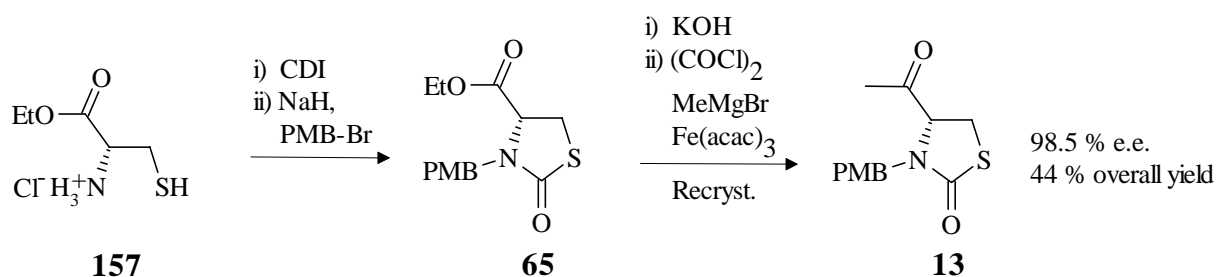


Fig. 101: Synthesis of ketone **13**.

Using  $\text{Fe}(\text{acac})_3$  as catalyst in the last step for preparing ketone **13** followed by recrystallization of the product from hexane provided the enantiopure ketone (e.e. = 98.5 %) in good yield on a multigram scale. This procedure is significantly more productive and much better reproducible than a literature method<sup>43</sup> that only gave yields in the range of 20 to 34 % and furthermore resulted in partial racemization of the stereocenter when performed in our laboratory.

Aldehyde **25** was prepared in 13 steps in 12 % overall yield from hydroxy-2-(*R*)-methylpropanoic acid methyl ester **41** as the starting material. The key steps were the hydrolytic kinetic resolution to give enantiopure epoxide **18**, the coupling of sulfone **17** with epoxide **18**, and the Corey-Fuchs reaction that established the propynyl group (Fig. 102).

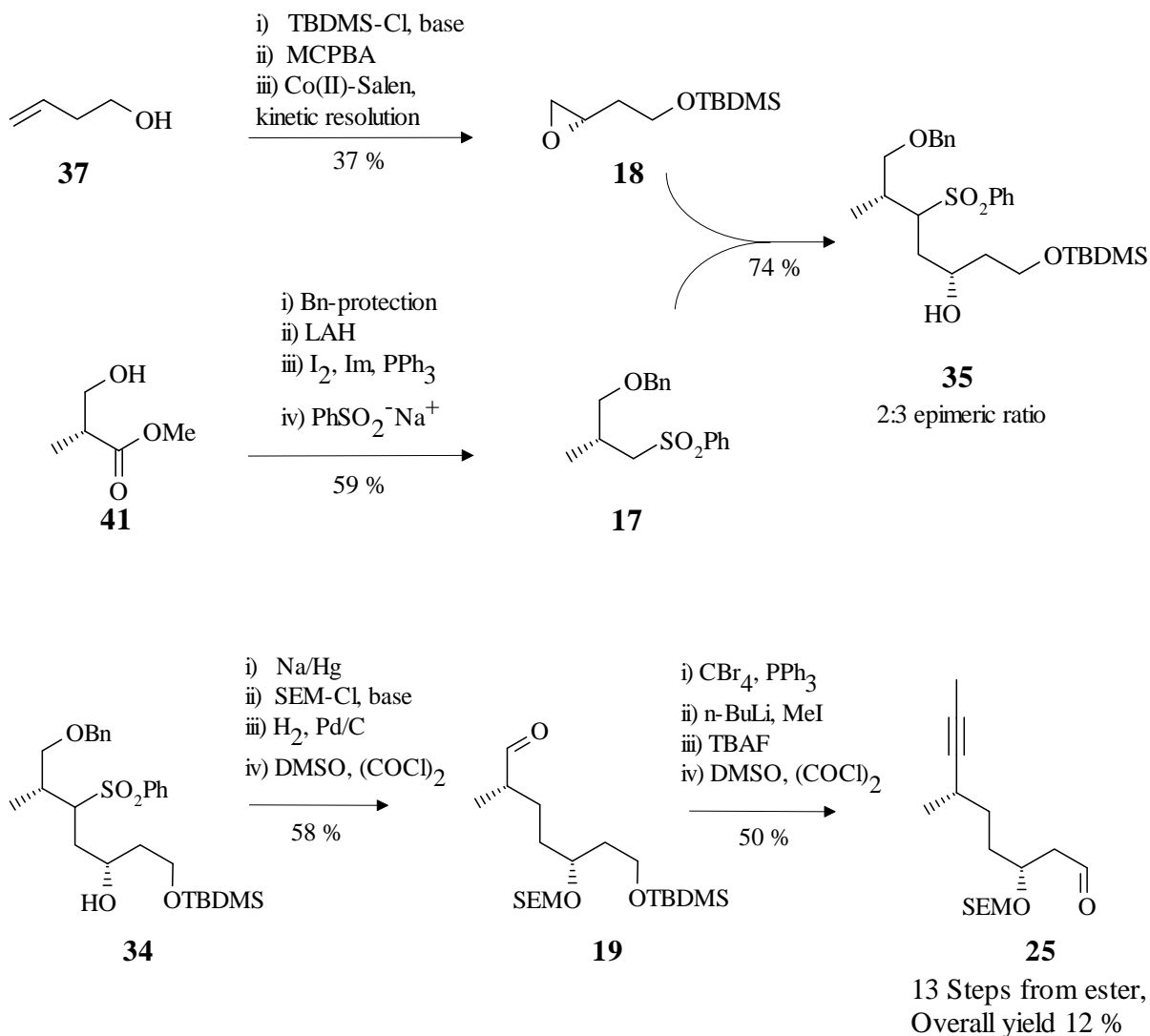


Fig. 102: First steps of the synthesis of aldehyde **25**.

An aldol reaction between the two fragments **13** and **25** was investigated, but the starting materials were only fully consumed when the reaction was allowed to reach ambient temperature. The SEM protection group was found too labile for these reaction conditions. Therefore an alternative procedure for fragment coupling was considered. We investigated the possibility of using olefin cross metathesis instead of an aldol reaction to get to key fragment **129** and optimized the reaction conditions in a model study (Fig. 103).

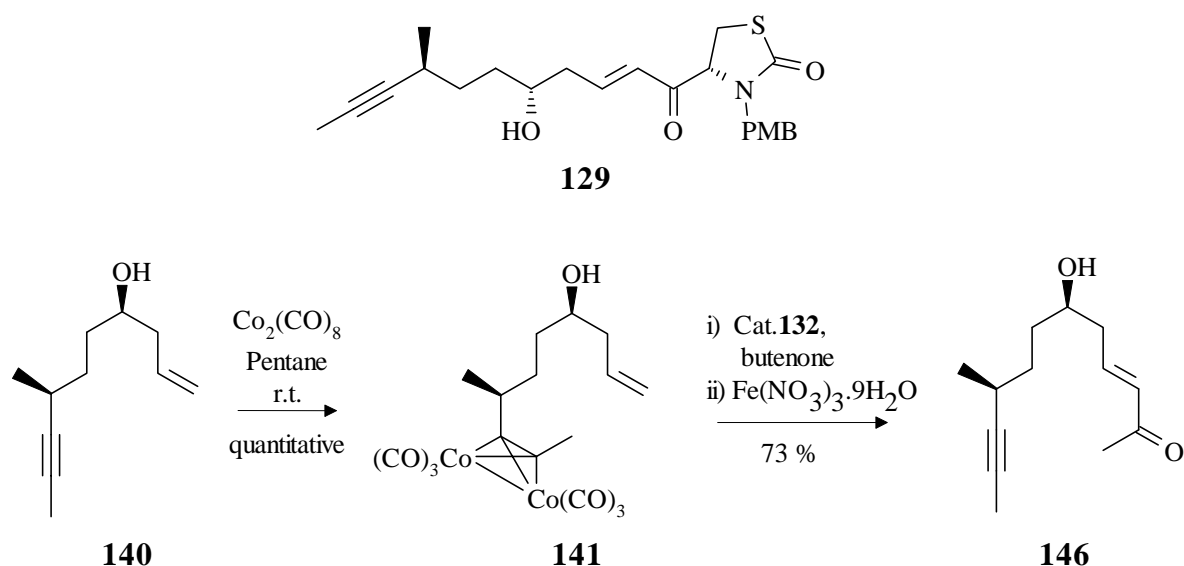


Fig. 103: Masking of alkyne containing homoallylic alcohol **140** followed by CM and demasking.

The olefin cross metathesis could be performed in good yield on a model substrate containing an alkyne protected as a dicobalthexacarbonyl complex. After CM, this protecting group could be removed cleanly to give product **146** in good yield.

Carboxylic acid **84** required for the synthesis of latrunculin A by enyne-yne metathesis was prepared in five steps and an overall yield of 17 %. The key step was the  $\text{Fe}(\text{acac})_3$ -catalyzed cross coupling between triflate **44** and the commercially available Grignard reagent **95** (Fig. 104).

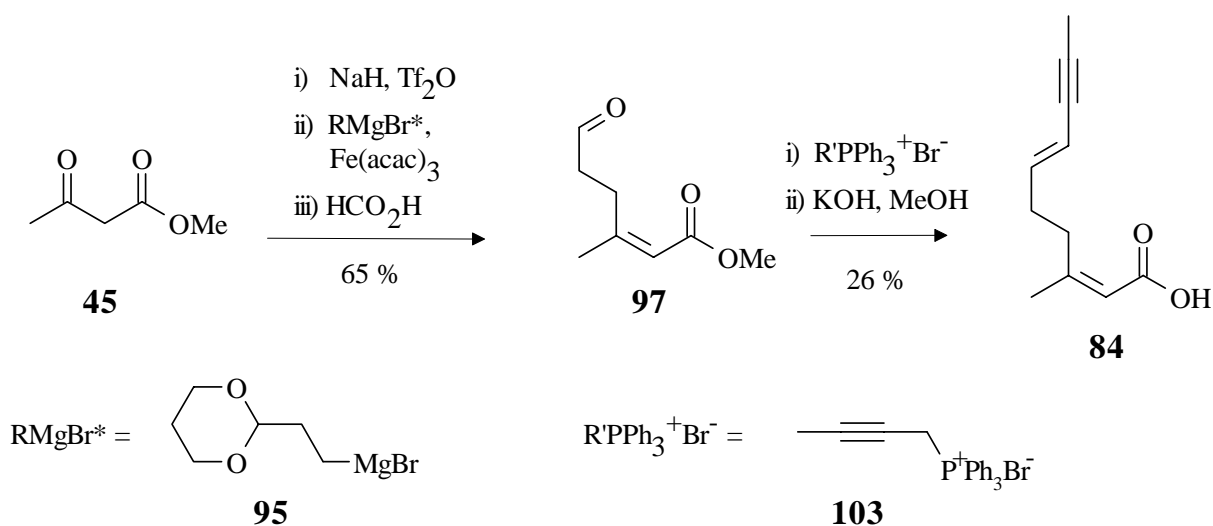


Fig. 104: Preparation of carboxylic acid **84** for latrunculin A.



In order to investigate if enyne-yne metathesis might qualify for the formation of the 16-membered macrocycle of latrunculin A, two different RCAM catalysts, molybdenum precatalyst **5** and tungsten catalyst **4**, were tested on a model substrate (Fig. 105).

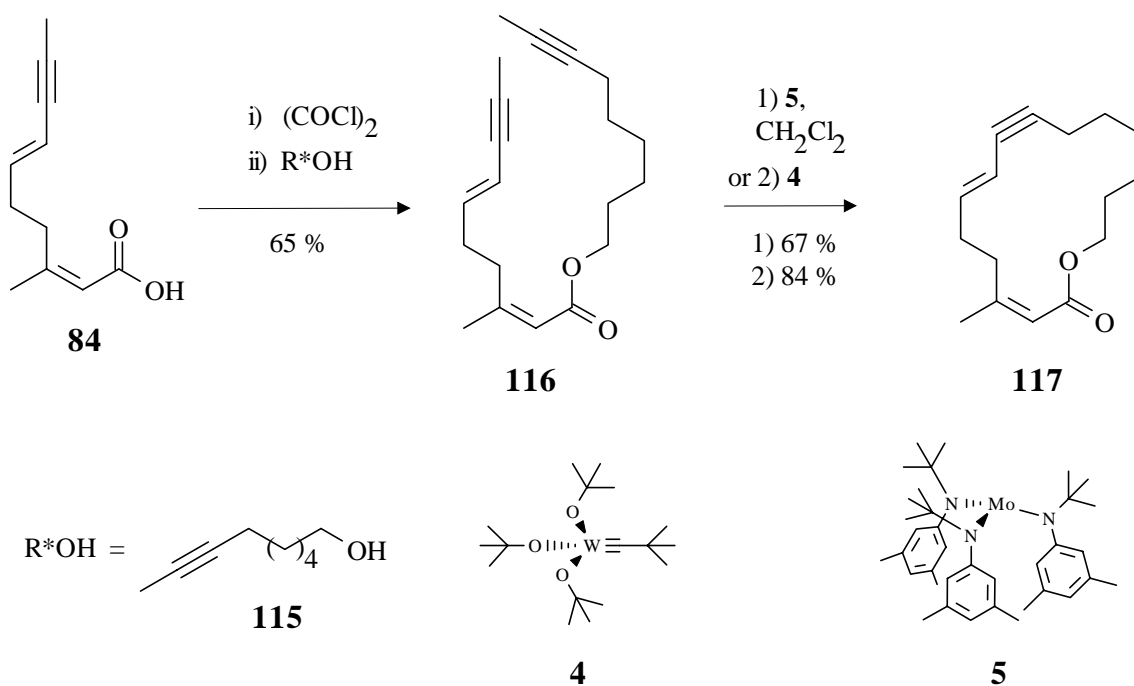


Fig. 105: Preparation of model substrate **116** and RCAM of **116** with two different catalysts.

Macrocycle **117** was obtained in good yield with both of the catalysts, and neither isomerization of the olefins or dimerization of the starting material were observed. Therefore it seems promising to establish the macrocycle in latrunculin A by RCAM of an open chain diyne similar to **116**.

## **Experimental**

### **General information**

Dry ethers were obtained by distillation from Na/K alloy, DMF and dichloromethane by distillation from  $\text{CaH}_2$ , dry toluene for metathesis was degassed under vacuum three times and then distilled from Na. Dry pentane, hexane and toluene was made by distillation from Na. Dry dimethyl sulphoxide, ethyl acetate, acetonitrile and acetone were dried over  $4\text{\AA}$  molecular sieves. Methanol was dried over  $3\text{\AA}$  molecular sieves. All reactions except the hydrolysis of esters were carried out under Ar and in flame dried glassware.

Analytical thin-layer chromatography was performed using precoated plates (Polygram SIL G/UV) with a fluorescent indicator and detection was made with UV light of wavelength 254 nm and visualization with an aqueous solution of cerium ammonium nitrate and ammonium molybdate in sulfuric acid, or in a basic aqueous potassium permanganate solution followed by heating with an hot air gun.

Chromatography was performed on silica gel from Merck (type 9385, 230 - 400 mesh and  $60\text{\AA}$  poresize).

### **Analytical methods**

#### **Analytical gas chromatography**

GC-MS was made on a Hewlett Packard HP 6890 GC-MS with a HP 5973 mass detector and a HP-5MS capillar column with crosslinked 5 % phenylmethylsiloxane of 30 m length and inner diameter of 0.25 mm.

Chiral gas chromatography was made on the same GC with a SE543053 column of the same size.

#### **Chiral liquid chromatography**

Chiral HPLC was made on a Shimadzu LC-8A apparatus with an UV detector using 220 nm UV light and a Merck NW50, 01/27 column of 204 mm length and inner diameter of 4.8 mm.

### **NMR spectroscopy**

NMR spectra were recorded with a Bruker AMX 300 ( $^1\text{H}$ : 300.1 MHz,  $^{13}\text{C}$ : 75.5 MHz) or a Bruker AV 400 ( $^1\text{H}$ : 400.1 MHz,  $^{13}\text{C}$ : 100.5 MHz) spectrometer. The chemical shifts ( $\delta$ ) were measured in ppm and calibrated relative to  $\text{CDCl}_3$  ( $^1\text{H}$  and  $^{13}\text{C}$  spectra) as internal standard; the coupling constants ( $J$ ) are reported in Hertz.

### **Mass spectroscopy**

EI Mass spectra were recorded with a Finnigan MAT 8200 or a Finnigan 8400 spectrometer. High resolution mass spectra were recorded with a Finnigan Mat 95 spectrometer.

### **Infrared spectroscopy**

Infrared spectra were recorded with a Nicolet FT-7199 spectrometer. Wavenumbers of characteristic or strong peaks are reported in  $\text{cm}^{-1}$ .

### **Optical rotations**

Optical rotations were measured with a Digital Polarimeter 343 Plus from Perkin Elmer using a wavelength of 589 nm (sodium-line) in a 10 cm cuvette at 20.0 °C.

### **Elemental analysis**

Elemental analysis was carried out at the microanalytical laboratory of H. Kolbe in Mülheim an der Ruhr.

### **X-ray crystallography**

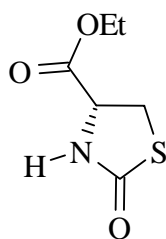
X-ray crystallography was made by the group of Dr. Lehmann at the Max-Planck-Institute für Kohlenforschung in Mülheim an der Ruhr.

## Chemicals prepared in the group

I thank Mr. Günther Seidel for 7-nonyl-1-ol **115** and 1,6-hexadioic acid bis(3-pentyn-1-ol) diester **113**, Dr. Dominic DeSouza for (*R*)-4-hydroxy-(*R*)-7-methyl-1-decen-8-yne **143** and 4-hydroxy-1-undecene **134** and Dr. Douglas Kirk for 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-dodecen-8-yne **133**.

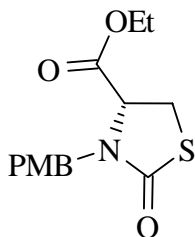
## Experimental procedures

### (*4R*)-2-Oxo-4-thiazolidinecarboxylic acid ethyl ester (**151**)<sup>43</sup>



To a slurry of cysteine ethyl ester hydrochloride (65.87 g, 0.3548 mol) in dry THF (1 L), was added carbonyldiimidazole (57.63 g, 0.3554 mol) at r.t. in small portions. The mixture was stirred for 20 h, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 3:2 → 1:1) to yield **148** as an oil (54.80 g, 88% yield):  $[\alpha]_D^{20}$   $-51.8^\circ$  (c 3.14,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t, 3 H,  $J = 7.1$  Hz), 3.54 (dd, 1 H,  $J = 5.0, 11.4$  Hz), 3.65 (dd, 2 H,  $J = 8.3, 11.4$  Hz), 4.21 (q, 2 H,  $J = 7.1$  Hz), 4.39 (ddd, 1 H,  $J = 0.9, 5.0, 8.28$  Hz), 6.82 (br s, 1 H);  $^{13}\text{C-NMR}$   $\delta$  13.9, 14.0, 31.7, 56.0, 62.2, 170.0, 174.7; IR 3248, 2983, 1735, 1670, 1445, 1395, 1371, 1348, 1307, 1193, 1145, 1092, 1020, 978, 952, 859, 709,  $666\text{ cm}^{-1}$ ; MS (EI)  $m/z$  (rel. intensity) 175 (22) 102 (107) 74 (60).

**(4*R*)-3-[(4-Methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid ethyl ester**  
**(65)**<sup>43</sup>

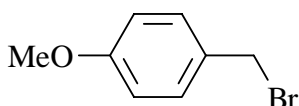


To a slurry of sodium hydride (7.00 g, 0.29 mol) in dry THF (500 mL) was added a solution of (4*R*)-3-[(4-methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid ethyl ester (50.20 g, 0.2865 mol) in dry THF (350 mL) at  $-15\text{ }^{\circ}\text{C}$  over a period of 45 min. The mixture was stirred at this temp. for 3 h until a clear solution was formed.

4-Methoxybenzyl bromide (115.43 g, 0.574 mol) in THF (200 mL) was added and the mixture was stirred at r.t. for 20 h, before it was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (500 mL). The phases were separated, the aqueous phase was extracted with MTBE (2 x 500 mL), and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and evaporated. Flash chromatography of the residue (hexane/EA 3:1) gave **65** as an oil (70.67 g, 84 % yield):

$[\alpha]_D^{20} -96.7^{\circ}$  (c 1.30, EtOH);  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.28 (t, 3 H,  $J = 7.1$  Hz), 3.31 (dd, 1 H,  $J = 3.1, 11.4$  Hz), 3.45 (dd, 1 H  $J = 8.6, 11.4$  Hz), 3.77 (s, 3 H), 3.97 (d, 1 H,  $J = 14.8$  Hz), 4.10 (dd, 1 H,  $J = 3.1, 8.5$  Hz), 4.22 (q, 3 H,  $J = 7.2$  Hz), 5.05 (d, 1 H,  $J = 14.8$  Hz), 6.84 (d, 2 H,  $J = 8.7$  Hz), 7.14 (d, 2 H,  $J = 8.6$  Hz);  $^{13}\text{C-NMR}$   $\delta$  14.1, 29.0, 47.3, 55.3, 59.3, 62.1, 114.2, 127.5, 129.8, 159.4, 169.9, 171.5; MS (EI)  $m/z$ (rel. intensity) 295 (2) 167 (2) 134 (2) 121 (33).

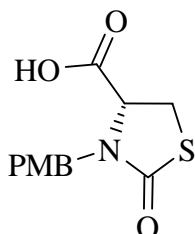
**4-(Methoxyphenyl)methyl bromide (64)**<sup>42</sup>



4-(Methoxyphenyl) methyl alcohol (74 mL, 0.59 mol) was stirred at r.t. with hydrobromic acid (48 %, 150 mL, 1.32 mol) for 3 ½ h. The mixture was then poured into a solution of  $\text{Na}_2\text{CO}_3$  (70 g, 0.66 mol) in water (600 mL). The mixture was extracted with MTBE (300 mL), the organic phase was dried ( $\text{MgSO}_4$ ), filtered and evaporated to give **64** as an oil (115.43 g, 97 % yield);  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.79 (s, 3 H), 4.49 (s, 2 H), 6.85 (d,

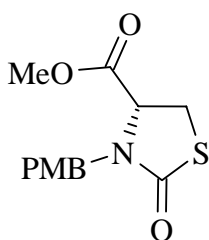
2 H,  $J = 8.7$  Hz), 7.31 (d, 2 H,  $J = 8.7$  Hz);  $^{13}\text{C}$ -NMR  $\delta$  33.9, 55.3, 114.2, 129.9, 130.4, 159.6; MS (EI)  $m/z$  (rel. intensity) 202 (1), 200 (1), 122 (2), 121 (21), 91 (1), 78 (2).

**(4*R*)-3-[(4-Methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid (27)**<sup>43</sup>



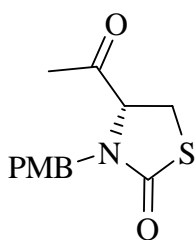
A solution of (4*R*)-3-[(4-methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid ethyl ester (1.09 g, 3.69 mmol) and KOH (0.64 g, 11.4 mmol) in water (10 mL) and 1,4-dioxane (14 mL) was stirred at r.t. for 1 h. The reaction was quenched with 3 M HCl (10 mL) and MTBE (60 mL) was added, the phases were separated and the aqueous phase was extracted with MTBE (2 x 25 mL). The combined organic phases were washed with brine (2 x 10 mL), dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was redissolved in dichloromethane (20 mL) and evaporated to yield **27** as an oil (0.96 g, 97 % yield).  $[\alpha]_D^{20} - 67.5^\circ$  (c 1.23, EtOH);  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.36 (dd, 1 H,  $J = 2.4, 11.4$  Hz), 3.47 (dd, 1 H,  $J = 9.0, 11.4$  Hz), 3.74 (s, 3 H), 3.97 (d, 1 H,  $J = 14.8$  Hz), 4.15 (dd, 1 H,  $J = 2.4, 8.6$  Hz), 5.07 (d, 1 H,  $J = 14.8$  Hz), 6.82 (d, 2 H,  $J = 8.5$  Hz), 7.19 (d, 2 H,  $J = 8.4$  Hz), 8.51 (br. s, 1 H);  $^{13}\text{C}$ -NMR  $\delta$  29.0, 47.3, 55.3, 58.9, 114.3, 127.2, 129.8, 159.4, 172.3, 173.4.

**(4*R*)-3-[(4-Methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid methyl ester (62)**



To a solution of (4*R*)-3-[(4-methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid (43.0 mg, 0.161 mmol) in dry MeOH (2 mL) was added trimethylsilyldiazomethane (2 M in hexane, 0.80 mL, 1.6 mmol) at r.t. and gas evolution was observed. After stirring for 15 min, the reaction was quenched with AcOH (2 mL) and stirred for 2 h. The solution was partitioned between brine (25 mL) and MTBE (25 mL), the phases were separated, the aqueous phase was extracted with MTBE (3 x 25 mL), the combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 4:1) to yield **62** as an oil (39.2 mg, 87 % yield).  $[\alpha]_D^{20}$  -72.0° (c 1.96 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 3.31 (dd, 1 H, *J* = 3.1, 11.4 Hz), 3.45 (dd, 1 H, *J* = 8.6, 11.4 Hz), 3.75 (s, 3 H), 3.77 (s, 3 H), 3.97 (d, 1 H, *J* = 14.8 Hz), 4.10 (dd, 1 H, *J* = 3.1, 8.5 Hz), 5.05 (d, 1 H *J* = 14.8 Hz), 6.84 (d, 2 H, *J* = 8.6 Hz), 7.14 (d, 2 H, *J* = 8.6 Hz); <sup>13</sup>C-NMR δ 27.0, 47.4, 53.0, 55.3, 58.7, 114.0, 127.6, 129.8, 159.5, 170.4, 171.5; MS (EI) *m/z* (rel. intensity) 281 (5), 222 (1), 195 (2), 135 (4), 121 (40).

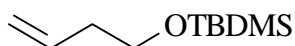
**(4*R*)-4-Acetyl-3-[(4-methoxyphenyl)methyl]-2-thiazolidinone(13)**<sup>43</sup>



To a solution of (4*R*)-3-[(4-methoxyphenyl)methyl]-2-oxo-4-thiazolidinecarboxylic acid (0.200 g, 0.748 mmol) in dry THF (5 mL) was added 1-chloro-2,*N,N*-trimethylprop-1-en-1-ylamine (0.50 mL, 3.78 mmol) at -78 °C. The mixture was kept at -18 °C for 40 h. The solution was then cooled to -78 °C and a mixture of iron (III) acetylacetonate (3.9 mg, 0.011 mmol) and MeMgBr (3.0 M in THF, 0.55 mL, 1.65 mmol) was added. The temperature was raised to 0 °C and the reaction mixture was stirred at this temperature for 30 min. For work up, the reaction was quenched with sat. aq. NH<sub>4</sub>Cl (10 mL). The phases were separated and the aqueous phase extracted with MTBE (2 x 75 mL), the combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 3:1) to yield **13** as an oil (0.16 g, 80 % yield, 87.4 % e.e., chiral HPLC). Recrystallization from hexane furnished the product as white, thin needles (98.5 % e.e., chiral HPLC),  $[\alpha]_D^{20}$  -62.2° (c 0.97, EtOH); <sup>1</sup>H-NMR (400MHz,

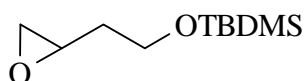
CDCl<sub>3</sub>)  $\delta$  2.10 (s, 3 H), 3.08 (dd, 1 H,  $J = 3.9, 11.5$  Hz), 3.47 (dd, 1 H,  $J = 9.3, 11.5$  Hz), 3.75 (s, 3 H), 3.86 (d, 1 H,  $J = 14.7$  Hz), 4.07 (dd, 1 H,  $J = 3.9, 9.3$  Hz), 4.96 (d, 1 H,  $J = 14.7$  Hz), 6.82 (d, 2 H,  $J = 8.7$  Hz), 7.08 (d, 2 H,  $J = 8.6$  Hz); <sup>13</sup>C-NMR  $\delta$  26.1, 27.6, 47.3, 55.2, 65.4, 114.2, 127.1, 129.8, 159.4, 171.5, 204.4; IR 3015, 2912, 2843, 1719, 1658, 1612, 1585, 1512, 1463, 1439, 1393, 1356, 1308, 1286, 1239, 1201, 1185, 1175, 1162, 1151, 1110, 1027, 998, 942, 902, 824, 812, 799, 762, 747, 706, 670; MS (EI)  $m/z$  (rel. intensity) 265, 222 (8), 121 (60) (215).

**(3-Butenyloxy)(1,1-dimethylethyl)dimethyl silane (66)**<sup>121</sup>



To a stirred solution of but-3-en-1-ol (16.33 g, 0.2265 mol) in dry DMF (350 mL) was added imidazole (23.19 g, 0.3406 mol) and *tert*-butyldimethylsilylchloride (52.40 g, 0.3477 mol) at r.t. and the resulting solution was stirred for 16 h. The reaction mixture was partitioned between water (350 mL) and MTBE (350 mL), the phases were separated and the aqueous phase was extracted with MTBE (350 mL). The organic phases were collected, washed with brine (2 x 400 mL), dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (pentane) to give **66** as a colorless oil (34.84 g, 82 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  0.04 (s, 6 H), 0.088 (s, 9 H), 2.26 (dt, 2 H,  $J = 1.2, 6.8, 6.9$  Hz), 3.64 (t, 2 H,  $J = 6.8$  Hz), 4.99 (d, 1 H,  $J = 1.3$  Hz) 5.01 (d, 1 H,  $J = 15.0$  Hz), 5.75 (m, 1 H); <sup>13</sup>C-NMR  $\delta$  -5.3, -2.9, 26.0, 37.5, 62.8, 116.3, 135.4

**(1,1-Dimethylethyl)dimethyl(2-oxiranyloxy) silane (36)**<sup>122</sup>

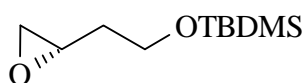


To a stirred solution of (3-butenyloxy)(1,1-dimethylethyl)dimethyl silane (34.81 g, 0.1868 mol) in dichloromethane (800 mL) at r.t. was added MCPBA (70 - 75 % w.w., 83.84 g, 0.36 mol). The solution was stirred for 16 h whereupon a heavy, white precipitate was formed. The reaction was quenched with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 % aq. sol., 1.0 L), the phases were separated, the aqueous phase was extracted with dichloromethane (500 mL), the organic



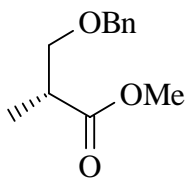
phases were collected, washed with sat. aq. NaHCO<sub>3</sub> (2 x 500 mL) and brine (500 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to give **36** as a colorless oil (36.69 g, 97 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.73 (m, 2 H), 2.52 (dd, 1 H, *J* = 2.7, 5.1 Hz), 2.78 (dd, 1 H, *J* = 4.1, 5.0 Hz), 2.99 (m, 1 H), 3.78 (m, 2 H); <sup>13</sup>C-NMR δ -5.5, -5.4, 18.3, 25.9, 35.9, 47.2, 50.0, 60.0; Mass MS (EI) *m/z* (rel. intensity) 145 (2), 127 (1), 115 (6), 101 (1), 99 (1), 89 (5), 85 (3), 75 (6), 73 (3), 59 (4).

**(*S*)-(1,1-Dimethylethyl)dimethyl(2-oxiranylethoxy) silane (**18**)**<sup>44</sup>



Racemic (1,1-dimethylethyl)dimethyl(2-oxiranylethoxy) silane (24.59 g, 0.1215 mol) was mixed with (*S,S*)-**67** (1.50 g, 2.5 mmol) and acetic acid (0.146 g, 2.4 mmol) and the mixture was stirred at r.t. for 1 h. The mixture was cooled to 0 °C and dry THF (22.5 mL) and water (1.10 g, 61.0 mmol) was added. The solution was stirred for 16 h while allowing to reach r.t. The solvents were removed *in vacuo*, and the residue was purified by Kugelrohr distillation (75 °C, 3·10<sup>-1</sup> atm.) to give **18** as a colorless oil (11.57 g, 94 % yield). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -13.2° (c 2.1 in CHCl<sub>3</sub>). Chiral GC: ≈100 % e.e. *Spectroscopic data see above.*

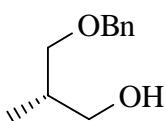
**(*R*)-2-Methyl-3-(phenylmethoxy)propanoic acid methyl ester (**40**)**<sup>44</sup>



To a solution of (*R*)-2-methyl-3-hydroxypropanoic acid methyl ester (1.10 g, 9.31 mmol) in dry pentane (14 mL) and dry dichloromethane (14 mL) was added 1,1,1-trichloroacetimidate benzyl ester (3.06 g, 12.1 mmol) followed by trifluoromethanesulfonic acid (0.17 g, 1.13 mmol). The mixture was stirred for 48 h whereupon a precipitate was formed. The precipitate was filtered off and the filtrate was washed with water (2 x 50 mL)

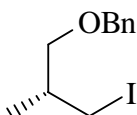
and sat. aq. NaHCO<sub>3</sub> (2 x 50 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (pentane/MTBE, 7:1) to give **40** as a colorless oil (1.88 g, 97 % yield).  $[\alpha]_D^{20}$  -11.7° (c 3.95 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.18 (d, 3 H, *J* = 7.1 Hz), 2.79 (m, 1 H, *J* = 7.1 Hz), 3.49 (dd, 1 H, *J* = 4.9, 9.3 Hz), 3.65 (dd, 1 H, *J* = 1.7, 9.3 Hz), 3.69 (s, 3 H), 4.52 (s, 2 H), 7.3 (m, 5 H); <sup>13</sup>C-NMR δ 40.2, 51.7, 72.0, 73.1, 127.58, 127.60, 128.4, 138.2, 175.3.

**(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propanol (39)**<sup>44</sup>



To a slurry of LiAlH<sub>4</sub> (7.66 g, 202 mmol) in dry diethyl ether (60 mL) was dropwise added a solution of (*R*)-2-methyl-3-(phenylmethoxy)propanoic acid methyl ester (9.32 g, 44.75 mmol) in dry diethyl ether (30 mL) at 0 °C and the mixture was stirred at this temperature for 10 min. The solution was then stirred at r.t. for 1 h, cooled again to 0 °C and carefully quenched with water (20 mL). The mixture was stirred for 16 h at r.t. before MgSO<sub>4</sub> was added. The MgSO<sub>4</sub> was filtered off and the filtrate was evaporated to yield **39** as a colorless oil (7.36 g, 97 % yield).  $[\alpha]_D^{20}$  -17.6° (c 4.20 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.88 (d, 3 H, *J* = 7.0 Hz), 2.03 (m, 1 H), 2.62 (dd, 1 H, *J* = 4.7, 6.7), 3.42 (dd, 1 H, *J* = 8.2, 9.1 Hz), 3.58 (m, 3 H), 4.52 (s, 2 H), 7.30 (m, 5 H); <sup>13</sup>C-NMR δ 13.4, 35.5, 67.8, 73.3, 75.4, 127.6, 127.7, 128.4, 137.9.

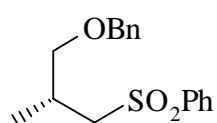
**[[*R*]-3-Iodo-2-methylpropoxy]methyl]-benzene (38)**<sup>44</sup>



To a solution of triphenylphosphine (15.19 g, 57.91 mmol) and imidazole (3.94 g, 57.9 mmol) in dry dichloromethane (90 mL) was added iodine (14.71 g, 57.96 mmol) at r.t. whereupon a yellow precipitate was formed. (*R*)-2-Methyl-3-(phenylmethoxy)-1-

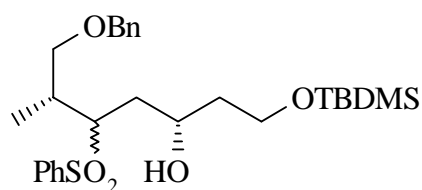
propanol (6.96 g, 38.6 mmol) in dry dichloromethane (10 mL) was added and the slurry was stirred at r.t. for 16 h. The mixture was filtered, the filtrate was evaporated and the residue was purified by flash chromatography (pentane/EA 1:1) to yield **38** as a pale yellow oil (9.68 g, 86 % yield).  $[\alpha]_D^{20}$  -10.8° (c 2.65 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.98 (d, 3 H, *J* = 7.0 Hz), 1.78 (m, 1 H), 3.34 (m, 4 H), 4.51 (s, 2 H), 7.30 (m, 5 H); <sup>13</sup>C-NMR δ 13.7, 17.7, 35.2, 73.2, 74.1, 127.6, 128.4, 138.3.

**(R)-[[2-Methyl-3-phenylmethoxy)propyl]sulfonyl]-benzene (17)**<sup>44</sup>



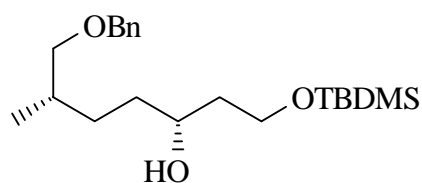
To a solution of [[(2*R*)-3-iodo-2-methylpropoxy]methyl]-benzene (21.8 g, 75.1 mmol) in dry DMF (330 mL) was added sodium benzenesulfinate (18.53 g, 0.1129 mol) and the resulting solution was stirred for 16 h. The reaction mixture was partitioned between water (500 mL) and MTBE (800 mL), the phases were separated, the organic phase was washed with water (500 mL) and brine (600 mL), dried (MgSO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography (hexane:EA 4 :1 → 2:1) to give **17** as a colorless oil (16.95 g, 75 % yield).  $[\alpha]_D^{20}$  -4.3° (c 0.60 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.12 (d, 3 H, *J* = 6.9 Hz), 2.40 (m, 1 H), 2.93, (dd, 1 H, *J* = 7.8, 14.3 Hz), 3.30 (dd, 1 H, *J* = 6.6, 9.5 Hz), 3.41 (dd, 1 H, *J* = 4.5, 9.4 Hz), 4.41 (d, 2 H, *J* = 1.7 Hz), 7.30 (m, 5 H), 7.55 (m, 2 H), 7.7.65 (m, 1 H), 7.90 (m, 2 H); <sup>13</sup>C-NMR δ 17.0, 29.3, 59.1, 72.7, 73.4, 127.3, 127.5, 127.6, 128.2, 129.1, 133.4, 138.0.

**(3*S*, 5*R*)-1-[[1,1-Dimethyl)dimethylsilyl]oxy]-6-methyl-7-(phenylmethoxy)-5-(phenylsulfonyl)-3-heptanol (35)**<sup>44</sup>



To a solution of sulfone **17** (6.00 g, 19.71 mmol) in dry THF (45 mL) was added *n*-BuLi (1.60 M in hexane, 15.0 mL, 24.0 mmol) at -78 °C and the solution was stirred at this temperature for 1 h. Dry DMPU (3.60 mL, 3.82 g, 29.8 mmol) was introduced and after 30 min a solution of epoxide **18** (3.821 g, 18.90 mmol) in dry THF (15 mL) was added over a period of 10 min. The resulting solution was stirred for 16 h while slowly reaching r.t. The reaction was quenched with sat. aq. NH<sub>4</sub>Cl (30 mL), partitioned between sat. aq. NH<sub>4</sub>Cl (150 mL) and MTBE (200 mL), the phases were separated, the aqueous phase was extracted with MTBE (200 mL), the organic layers were collected, washed with sat. aq. NH<sub>4</sub>Cl (2 x 200 mL), dried (MgSO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography (pentane:MTBE 4 :1) to give **35** as a colorless oil (7.09 g, 74 % yield). The product was a mixture of two epimers in the ratio 2:3.  $[\alpha]_D^{20}$  9.2° (c 3.2 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.04 (s, 6 H), 0.05 (s, 6 H), 0.87 (s, 9 H), 1.01 (d, 3 H, *J* = 7.0 Hz), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.58 (m, 2 H), 1.82 (m, 1 H), 2.03 (m, 1 H), 2.35 (m, 1 H), 2.55 (m, 1 H), 3.32 (s, 1 H), 3.35 (s, 1 H), 3.55 (m, 1 H), 3.6 - 3.9 (m, 4 H), 4.37 (s, 1 H), 4.48 (s, 1 H), 7.18 - 7.38 (m, 5 H), 7.48 - 7.78 (m, 3 H), 7.85 - 7.95 (m, 2 H); <sup>13</sup>C-NMR δ -5.6, -5.5, -5.5, -5.4, 11.7, 15.1, 18.1, 25.9, 30.9, 31.9, 33.0, 34.5, 38.2, 38.8, 61.0, 61.8, 62.4, 63.1, 68.8, 69.9, 71.6, 72.7, 72.8, 73.0, 127.5, 127.6, 127.7, 128.4, 128.4, 127.7, 129.1, 133.5, 137.9, 138.5, 139.6.

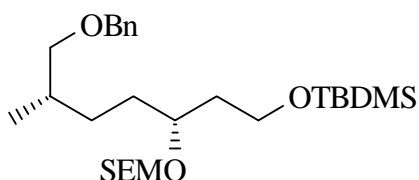
**(3*R*, 5*S*)-1-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-methyl-7-(phenylmethoxy)-3-heptanol (34)**<sup>44</sup>



Small pieces of sodium (5.07 g, 0.221 mmol) were added slowly to mercury (41 mL) while keeping the temperature at 20 - 25 °C. After 30 min the sulfone mixture **35** (5.74 g, 11.3 mmol) in ethanol (90 mL) was added and the two-phase system was stirred at r.t. for 16 h. The ethanolic solution was decanted, the mercury was washed with ethanol (2 x 50 mL), the combined ethanolic phases were evaporated to an oil which was partitioned between brine (250 mL) and MTBE (250 mL). The phases were separated, the aqueous phase was extracted with MTBE (2 x 100 mL), the organic phases were collected, dried (MgSO<sub>4</sub>) and

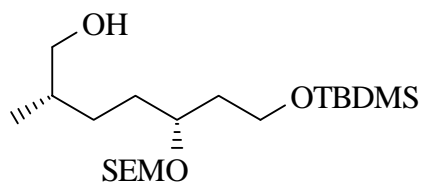
evaporated and the residue was purified by flash chromatography (pentane:MTBE 4 :1) to give **34** as a colorless oil (3.29 g, 79 % yield).  $[\alpha]_D^{20}$  9.4° (c 3.5 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.01 (s, 6 H), 0.83 (s, 9 H), 0.88 (d, 3 H, *J* = 7.0 Hz), 1.05 - 1.26 (m, 1 H), 1.35 - 1.45 (m, 2 H), 1.45 - 1.65 (m, 1 H), 1.65 - 1.80 (m, 1 H), 3.18 (dd, 1 H, *J* = 7.0, 9.0 Hz), 3.28 (dd, 1 H, *J* = 6.0, 9.0 Hz), 3.68 - 3.80 (m, 1 H), 3.80 - 3.90 (m, 1 H), 4.44 (s, 2 H), 7.26 - 7.33 (m, 5 H); <sup>13</sup>C-NMR δ -5.6, -5.5, 17.2, 18.1, 25.9, 29.5, 33.6, 34.8, 38.1, 62.9, 72.6, 73.0, 75.9, 127.4, 127.5, 128.3, 128.4, 138.8.

**(3'R, 8S)-2,2,12,12,13,13-Hexamethyl-8-[3-methyl-4-(phenylmethoxy)butyl]-5,7,11-trioxa-2,12disilatetradecane (33)**<sup>44</sup>



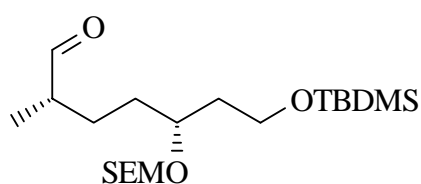
To a solution of (3*R*, 5*S*)-1-[[1,1-dimethylethyl]dimethylsilyl]oxy]-6-methyl-7-(phenylmethoxy)-3-heptanol (0.930 g, 2.54 mmol) in dry dichloromethane (10 mL) were added Hünig's base (1.40 mL, 1.03 g, 8.0 mmol) and [2-(trimethylsilyl)ethoxy]-methoxy chloride (0.725 g, 4.35 mmol) and the resulting solution was stirred at 40 °C for 4 h. The reaction mixture was cooled to r.t. and partitioned between sat. aq. NaHCO<sub>3</sub> (50 mL) and MTBE (50 mL). The phases were separated, the aqueous phase was extracted with MTBE (2 x 50 mL), the combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated to yield an oil which was purified by flash chromatography (hexane/EA 9:1) to yield **33** as a colorless oil (1.30 g, 96 % yield).  $[\alpha]_D^{20}$  -3.8° (c 3.7 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.01 (s, 9 H), 0.04 (s, 6 H), 0.89 (s, 9 H), 0.94 (d, 3 H, *J* = 6.7 Hz), 1.07 - 1.22 (m, 1 H), 1.43 - 1.64 (m, 3 H), 1.64 - 1.83 (m, 3 H), 3.23 (dd, 1 H, *J* = 6.7, 9.0 Hz), 3.33 (dd, 1 H, *J* = 6.7, 9.0 Hz), 3.53 - 3.74 (m, 5 H), 4.49 (s, 2 H), 4.69 (s, 2 H), 7.26 - 7.40 (m, 5 H); <sup>13</sup>C-NMR δ -5.3, -1.4, 17.2, 18.1, 18.3, 25.9, 29.1, 32.1, 33.7, 37.6, 59.8, 65.1, 73.0, 75.0, 75.8, 93.9, 127.4, 127.5, 128.3, 138.8.

**(2*S*, 5*R*)-7-[[1,1-Dimethyl)dimethylsilyl]oxy]-2-methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-heptanol (32)**<sup>44</sup>



A solution of benzyl ether **33** (1.28 g, 2.576 mmol), aq. HCl (10 %, 20  $\mu$ L, 55  $\mu$ mol) and palladium (10 % on charcoal, 212 mg) in EA (21 mL) was stirred at r.t. under a hydrogen atmosphere (1 atm.) for 45 min. For work up, triethylamine (110  $\mu$ L, 0.080 g, 0.62 mmol) was added, the mixture was filtered through silica gel, the filtrate was evaporated and the residue was purified by flash chromatography (hexane/EA 4:1) to yield **32** as a colorless oil (0.84 g, 80 % yield).  $[\alpha]_D^{20}$   $-5.1^\circ$  (c 2.80 in  $\text{CHCl}_3$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.01 (s, 9H), 0.03 (s, 6 H), 0.88 (s, 9 H), 0.89 - 0.97 (m, 5 H), 1.05 - 1.20 (m, 1 H), 1.40 - 1.75 (m, 6 H), 1.88 (br. s, 1 H), 3.35 - 3.75 (m, 7 H), 4.68 (s, 2 H);  $^{13}\text{C-NMR}$   $\delta$  -5.4, -1.5, 16.7, 18.0, 18.2, 25.7, 28.5, 32.0, 35.9, 37.6, 59.8, 65.2, 67.9, 75.1, 93.9.

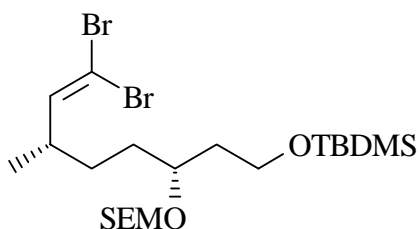
**(2*S*, 5*R*)-7-[[1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-heptanal (19)**<sup>44</sup>



To a solution of oxalyl chloride (0.70 mL, 1.02 g, 8.02 mmol) in dry dichloromethane (20 mL) was dropwise added dry DMSO (1.20 mL, 1.32 g, 16.9 mmol) at  $-78^\circ\text{C}$ . After 20 min a solution of (2*S*, 5*R*)-7-[[1,1-dimethyl)dimethylsilyl]oxy]-2-methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-heptanol (0.92 g, 2.226 mmol) in dry dichloromethane (15 mL) was added and the mixture was stirred at  $-78^\circ\text{C}$  for 45 min.  $\text{Et}_3\text{N}$  (4.3 mL, 31 mmol) was added and the solution was stirred for 1 h before it was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (20 mL) and partitioned between sat. aq.  $\text{NH}_4\text{Cl}$  (100 mL) and MTBE (100 mL). The phases were separated, the aqueous phase was extracted with MTBE (2 x 75 mL), the

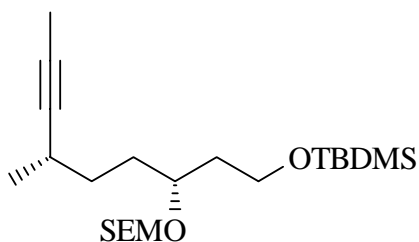
combined organic phases were washed with brine (50 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to yield **19** as a colorless oil (0.80 g, 92 % yield).  $[\alpha]_D^{20}$  22.4° (c 1.09 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ -0.02 (s, 9 H), 0.01 (t, 2 H, *J* = 3.3 Hz), 0.07 (s, 6 H), 0.87 (s, 9 H), 1.09 (d, 3 H, *J* = 6.7 Hz), 1.40 (m, 2 H), 1.55 (m, 2 H), 1.68 (m, 2 H), 2.30 (m, 1 H), 3.55 (m, 1 H), 3.60 (m, 2 H), 3.65 (m, 2 H), 4.67 (d, 2 H, *J* = 0.6 Hz), 9.60 (d, 1 H, *J* = 0.61.9 Hz); <sup>13</sup>C-NMR δ -5.4, -5.1, -1.5, 13.4, 18.1, 25.9, 26.1, 32.0, 37.5, 46.3, 59.6, 65.2, 74.7, 94.0, 204.8

**1.1-Dibromo-3-(*S*)-methyl-8-[[1,1-dimethylethyl]dimethylsilyl]oxy]-6-(*R*)-[[2-(trimethylsilyl)ethoxy]methoxy]-1-octene (71)**



To a solution of (2*S*, 5*R*)-7-[[1,1-dimethylethyl]dimethylsilyl]oxy]-2-methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-heptanal (0.80 g, 1.98 mmol) and triphenylphosphine (1.79 g, 6.83 mmol) in dry dichloromethane (50 mL) was slowly added tetrabromomethane (1.16 g, 3.50 mmol) in dry dichloromethane (20 mL) at -15 °C. The resulting yellow solution was stirred for 90 min before a mixture of EA and pentane (1 : 9, 50 mL) was added. The mixture was then filtered through silica gel and the filtrate was evaporated to yield **71** as a pale yellow oil (0.81 g, 73 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ -0.02 (s, 9 H), 0.01 (t, 2 H, *J* = 3.3 Hz), 0.07 (s, 6 H), 0.88 (s, 9 H), 1.00 (d, 3 H, *J* = 6.7 Hz), 1.24 (m, 2 H), 1.44 (m, 2 H), 1.68 (m, 2 H), 2.43 (m, 1 H), 3.56 (m, 1 H), 3.60 (m, 2 H), 3.66 (m, 2 H), 4.69 (d, 2 H, *J* = 1.4 Hz), 6.15 (d, 1 H, *J* = 9.5 Hz); <sup>13</sup>C-NMR δ -5.3, -1.4, 0.0, 18.2, 19.4, 26.0, 31.7, 32.5, 37.7, 38.5, 59.7, 65.2, 74.8, 87.6, 94.1, 144.0; MS (EI) *m/z* (rel. intensity) 261 (1), 226 (1), 213 (4), 201 (2) 199 (2), 177 (2), 157 (1), 147 (12), 131 (4), 119 (5), 103 (16), 101 (14), 89 (8), 75 (12), 73 (60).

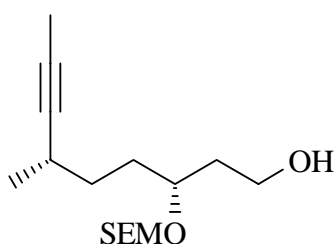
**1-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-(S)-methyl-3-(R)-[[2-(trimethylsilyl)ethoxy]methoxy]-7-nonyne (31)**



To a solution of 1.1-dibromo-3-(S)-methyl-8-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-(R)-[[2-(trimethylsilyl)ethoxy]methoxy]-1-octene (0.81 g, 1.45 mmol) in dry THF (8 mL) was added a solution of *n*-BuLi (1.60 M in hexane, 3.4 mL, 5.44 mmol) at -78 °C and the resulting solution was stirred at this temperature for 90 min. Methyl iodide (0.50 mL, 1.14 g, 5.5 mmol) was added and stirring continued for 16 h while allowing the mixture to reach ambient temperature. The reaction was quenched with sat. aq. NH<sub>4</sub>Cl (5 mL), the mixture was partitioned between sat. aq. NH<sub>4</sub>Cl (30 mL) and MTBE (30 mL), the phases were separated and the aqueous phase was extracted with MTBE (2 x 30 mL). The combined organic phases were washed with brine (100 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to an oil which was purified by flash chromatography (hexane/EA 9:1) to yield **31** as a colorless oil (0.58 g, 97 % yield).  $[\alpha]_D^{20}$  22.4° (c 1.09 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.03 (s, 9 H), 0.04 (s, 6 H), 0.86 (s, 9H), 0.87 - 0.96 (m, 2 H), 1.11 (d, 3 H, *J* = 6.9 Hz), 1.35 - 1.45 (m, 2 H), 1.55 - 1.75 (m, 5 H), 1.76 (d, 3 H, *J* = 2.4 Hz), 2.35 (m, 1 H), 3.50 - 3.74 (m, 5 H), 4.67 (s, 2 H); <sup>13</sup>C-NMR δ -5.3, -1.4, 3.5, 18.1, 18.3, 21.5, 25.9, 32.4, 32.7, 37.7, 59.8, 65.1, 65.7, 74.5, 75.7, 83.6, 93.8; IR 2954, 2930, 2859, 2802, 2739, 1472, 1463, 1409, 1378, 1361, 1334, 1250, 1192, 1151, 1097, 1055, 1031, 971, 938, 922, 860, 835, 775, 693, 664 cm<sup>-1</sup>; MS (EI) *m/z* (rel. intensity) 299 (2), 283 (2), 271 (2), 261 (3), 239 (3), 197 (3), 165 (3), 147 (10), 135 (6), 133, (4), 131 (5), 107 (8), 103 (13), 101 (15), 93 (8), 89 (7), 75 (11), 73 (55); HR MS *m/z* 437.25 [(M + Na)<sup>+</sup>, calcd for C<sub>22</sub>H<sub>46</sub>Si<sub>2</sub>O<sub>3</sub>, 437.25]. Anal. calcd. for C<sub>22</sub>H<sub>46</sub>Si<sub>2</sub>O<sub>3</sub>: C, 63.70; H, 11.18. Found: C, 61.55; H, 10.91.

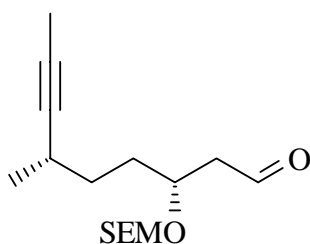


**1-Hydroxy-6-(S)-methyl-3-(R)-[[2-(trimethylsilyl)ethoxy]methoxy]-7-nonyne (30)**



To a stirred solution of 1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-(S)-methyl-3-(R)-[[2-(trimethylsilyl)ethoxy]methoxy]-7-nonyne (0.27 g, 0.651 mmol) in dry THF (4 mL) was added a solution of TBAF trihydrate (0.60 g, 1.90 mmol) in dry THF (1.5 mL) at r.t. and the resulting solution was stirred for 16 h. The solvent was removed *in vacuo* and the resulting oil was purified by flash chromatography (pentane/MTBE, 3:1) to yield **30** as a colorless oil (0.154 g, 79 % yield).  $[\alpha]_D^{20}$  -30.8° (c 1.85 in CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.03 (s, 9 H), 0.93 (dd, 3 H, *J* = 8.2, 9.0 Hz), 1.11 (d, 3 H, *J* = 6.9 Hz), 1.35 - 1.48 (m, 2 H), 1.50 - 1.82 (m, 6 H), 2.10 (br s, 1 H), 2.25 - 2.43 (m, 1 H), 3.50 - 3.83 (m, 5 H), 4.69 (s, 2 H); <sup>13</sup>C-NMR δ -1.8, 3.5, 18.1, 21.5, 26.0, 32.5, 32.7, 36.7, 59.8, 65.6, 75.9, 76.2, 83.4, 94.2; IR 3425, 2950, 2923, 2879, 1632, 1453, 1418, 1376, 1336, 1289, 1249, 1190, 1152, 1098, 1057, 1027, 973, 937, 921, 860, 836, 766, 693, 667, 607 cm<sup>-1</sup>; MS (EI) *m/z* (rel. intensity) 269 (1), 197 (12), 182 (4), 173 (3), 147 (11), 135 (4), 109 (10), 107 (12), 103 (25), 101 (8), 93 (10), 75 (18), 73 (60), 67 (11); ); HR MS *m/z* 323.10 [(M + Na)<sup>+</sup>, calcd for C<sub>16</sub>H<sub>32</sub>SiO<sub>3</sub>, 323.10]. Anal. calcd. for C<sub>16</sub>H<sub>32</sub>SiO<sub>3</sub>: C, 63.95; H, 10.73. Found: C, 64.08; H, 10.70.

**6-(S)-methyl-1-oxo-3-(R)-[[2-(trimethylsilyl)ethoxy]methoxy]-7-nonyne (25)**

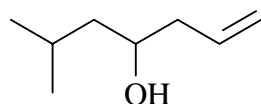


To a solution of oxalyl chloride (0.0500 mL, 72.8 mg, 0.573 mmol) in dry dichloromethane (3 mL) was added dry DMSO (0.100 mL, 0.110 g, 1.41 mmol) at - 78 °C.

After stirring at this temperature for 30 min, a solution of 1-hydroxy-6-(*S*)-methyl-3-(*R*)-[[2-(trimethylsilyl)ethoxy]methoxy]-7-nonyne (44 mg, 0.146 mmol) in dry dichloromethane (2.8 mL) was added and the mixture was stirred at -78 °C for 150 min. Dry triethylamine (0.70 mL, 5.03 mmol) was added and stirring continued for 45 min before the reaction was quenched with sat. aq. NH<sub>4</sub>Cl (10 mL). The mixture was partitioned between sat. aq. NH<sub>4</sub>Cl (25 mL) and MTBE (25 mL), the phases were separated, the aqueous phase was extracted with MTBE (2 x 25 mL), the organic phases were collected, dried (MgSO<sub>4</sub>), filtered and evaporated to yield **25** as a colorless oil (39 mg, 88 % yield). MS (EI) *m/z* (rel. intensity) 197 (1), 181 (1), 171 (1), 149 (4), 135 (12), 121 (12), 107 (10), 101 (11), 91 (12), 79 (15), 75 (60), 73 (25), 67 (17).

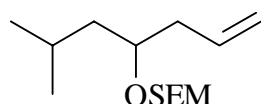
*The crude product was used in the next step without further characterization.*

### 6-Methyl-1-hepten-4-ol (**74**)<sup>123</sup>



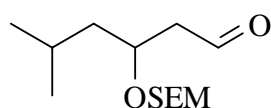
To a solution of allylmagnesium bromide (1.0 M in THF, 20.5 mL, 20.5 mmol) in diethyl ether (50 mL) was added 3-methylbutanal (2.1 mL, 1.69 g, 19.6 mmol) at -70 °C and the solution was stirred for 16 h while allowing to reach r.t. The reaction was quenched with sat. aq. NH<sub>4</sub>Cl (10 mL), partitioned between water (100 mL), sat. aq. NH<sub>4</sub>Cl (25 mL) and MTBE (150 mL). The phases were separated, the aqueous phase was extracted with MTBE (100 mL + 50 mL), the combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated to yield **74** as a colorless oil (2.45 g, 98 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.89 (d, 3 H, *J* = 6.6 Hz), 0.90 (d, 3 H, *J* = 6.6 Hz), 1.23 (m, 1 H), 1.39 (m, 1 H), 1.66 (s, 1 H), 1.80 (m, 1 H), 2.12 (m, 1 H), 2.29 (m, 1 H), 3.70 (m, 1 H), 5.10 (dm, 2 H, *J* = 12.5 Hz), 5.80 (m, 1 H); <sup>13</sup>C-NMR δ 22.1, 23.4, 24.7, 42.5, 46.1, 68.8, 118.0, 134.9; MS (EI) *m/z* (rel. intensity) 110 (1), 95 (2), 87 (25), 71 (8), 69 (50).

### 6-Methyl-4-[2-(trimethylsilyl)ethoxy]-1-heptene (75)



To a solution of 6-methyl-1-hepten-4-ol (0.194 g, 1.51 mmol) in dry dichloromethane (5 mL) and diethyl-*n*-propyl amine (0.80 mL, 0.59 g, 4.58 mmol) was added SEMCl (0.40 mL, 0.38 g, 2.26 mmol) at r.t. The resulting solution was stirred at 40 °C for 210 min and then at r.t. for 16 h, before it was partitioned between sat. aq. NaHCO<sub>3</sub> (30 mL) and MTBE (40 mL). The phases were separated and the aqueous phase was extracted with MTBE (3 x 50 mL). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 20:1) to yield **75** as a colorless oil (0.364 g, 93 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.02 (s, 9 H), 0.85 (m, 2 H), 0.88 (d, 3 H, *J* = 2.4 Hz), 0.89 (d, 3 H, *J* = 2.8 Hz), 1.24 (m, 1 H), 1.44 (m, 1 H), 1.73 (m, 1 H), 2.26 (m, 2 H), 3.62 (m, 2 H), 3.69 (m, 1 H), 4.64 (d, 1 H, *J* = 7.2 Hz), 4.72 (d, 1 H, *J* = 6.8 Hz), 5.02 (m, 1 H), 5.06 (m, 1 H), 5.82 (m, 1 H); <sup>13</sup>C-NMR δ -1.5, 18.1, 22.3, 23.3, 24.4, 39.3, 43.8, 64.9, 65.1, 74.7, 93.5, 117.0, 134.9; MS (EI) *m/z* (rel. intensity) 185 (1), 159 (30), 143 (6), 129 (3), 117 (1), 103 (27), 73 (45).

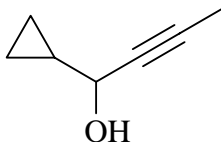
### 5-Methyl-3-[2-(trimethylsilyl)ethoxy]-hexanal (76)



A solution of 6-methyl-4-[2-(trimethylsilyl)ethoxy]-1-heptene (0.172 g, 0.665 mmol) in dry methanol (20 mL) was cooled to -78 °C before ozone from an ozone generator was bubbled through until a blue color persisted. The ozone supply was stopped and Ar was bubbled through the solution for 30 min until the blue color had disappeared. Dimethylsulfide (0.50 mL, 0.42 g, 6.80 mmol) was added and the reaction mixture was stirred for 1 h at -78 °C before it was allowed to reach ambient temperature. The solvent was removed *in vacuo* to leave **76** as a colorless oil (0.162 g, 94 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.02 (s, 9 H), 0.88 (d, 3 H, *J* = 2.4 Hz), 0.89 (d, 3 H, *J* = 2.8 Hz), 0.95 (m, 2 H), 1.20 (m, 1 H), 1.42 (m, 1 H), 1.73 (m, 1 H), 1.88 (m, 2 H), 3.49 (m, 2 H), 4.10 (m, 1 H),

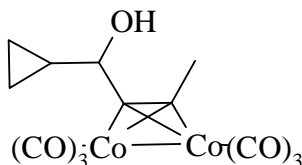
5.03 (d, 1 H,  $J = 6.2$  Hz), 5.12 (d, 1 H,  $J = 6.2$  Hz), 9.78 (s, 1 H);  $^{13}\text{C}$ -NMR  $\delta$  -0.1, 19.8, 24.0, 24.2, 24.5, 42.8, 50.9, 66.6, 73.1, 95.8, 203.0

### $\alpha$ -1-Propynyl-cyclopropanemethanol (**88**)<sup>83</sup>



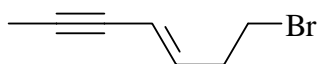
To a solution of propynyl magnesium bromide (0.5 M in THF, 11.0 mL, 5.5 mmol) was added a solution of cyclopropyl carbaldehyde (0.295 g, 4.21 mmol) in dry diethyl ether (6 mL) at 0 °C. The reaction was stirred at r.t. for 5 h before sat. aq.  $\text{NH}_4\text{Cl}$  (15 mL) and MTBE (15 mL) were added. The phases were separated and the aqueous phase was extracted with MTBE (3 x 10 mL). The combined organic phases were dried ( $\text{K}_2\text{CO}_3$ ), filtered and evaporated to yield **88** as a colorless oil (0.403 g, 98 % yield).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  0.37 (m, 2 H), 0.48 (m, 2 H), 1.17 (m, 1 H), 1.80 (d, 3 H,  $J = 2.1$  Hz), 2.03 (s, 1 H), 4.09 (m, 1 H);  $^{13}\text{C}$ -NMR  $\delta$  1.4, 3.1, 3.4, 17.3, 65.9, 78.1, 81.0; ; MS (EI)  $m/z$  (rel. intensity) 109 (2), 95 (5), 91 (4), 82 (50), 69 (8), 53 (9).

### Dicobalt hexacarbonyl- $\alpha$ -1-propynyl-cyclopropanemethanol (**89**)<sup>83</sup>



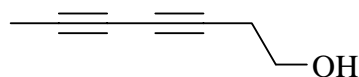
To a solution of  $\text{Co}_2(\text{CO})_8$  (0.679 g, 1.89 mmol) in dry pentane (10 mL) was added  $\alpha$ -1-propynyl-cyclopropanemethanol (0.160 g, 1.45 mmol) and the dark solution was stirred at r.t. for 16 h while evolution of gas was observed. The solvent was removed *in vacuo* and the resulting dark red oil was purified by flash chromatography (hexane/EA 9:1) to yield **89** as a dark red oil (0.559 g, 97 % yield).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  0.6 (m, 4 H), 1.16 (d, 1 H,  $J = 59$  Hz), 1.96 (d, 1 H,  $J = 50$  Hz), 2.67 (s, 3 H), 4.05 (s, 1 H) All signals were broadened.

**(3E)-1-Bromo-3-hepten-5-yne (85)**<sup>83</sup>



To a solution of dicobalt hexacarbonyl- $\alpha$ -1-propynyl-cyclopropanemethanol (0.214 g, 0.54 mmol) in diethyl ether (10 mL) was dropwise added a mixture of HBr (48 % ww., 0.40 mL) and ZnBr<sub>2</sub> (0.50 g, 22 mmol) at -16 °C. The resulting two-phase system was stirred vigorously at -16 °C for 15 min. The reaction mixture was partitioned between water (30 mL) and pentane (30 mL), the phases were separated and the organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to yield a brown oil which was purified by flash chromatography (pentane) to yield a dark red oil (0.106 g, 43 %). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  2.68 (s, 3 H), 2.72 (s, 2 H), 3.41 (d, 1 H,  $J = 6.8$  Hz) 3.43 (d, 1 H,  $J = 6.6$  Hz), 6.00 (m, 1 H,  $J = 6.8, 7.4$ ), 6.57 (d, 1 H,  $J = 15.0$ ); This product was slurried in a mixture of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (0.542 g, 1.34 mmol) and ethanol (1.0 mL) at 75 °C for 2 min and then at r.t. for 25 min. The reaction was partitioned between water (40 mL) and pentane (40 mL), the phases were separated and the organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to yield **85** as a colorless oil (32 mg, 34 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  1.91 (d, 3 H,  $J = 2.1$  Hz), 2.62 (dq, 2 H,  $J = 0.9, 7.0$  Hz), 3.37 (t, 2 H,  $J = 7.1$  Hz) 5.55 (m, 1 H), 5.98 (dt, 1H,  $J = 7.03, 15.8$  Hz); <sup>13</sup>C-NMR  $\delta$  4.2, 31.3, 36.0, 77.7, 85.8, 113.0, 138.6; MS (EI)  $m/z$  (rel. intensity) 174 (4), 172 (4), 93 (8), 91 (14), 79 (4), 77 (18), 65 (4), 51 (3).

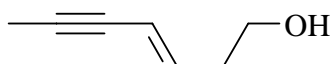
**3,5-Heptadiyn-1-ol (93)**<sup>124</sup>



To a solution of I<sub>2</sub> (2.469 g, 9.728 mmol) in dry THF (11.0 mL) was dropwise added a solution of propynyl magnesium bromide (0.5 M in THF, 20.0 mL, 10.0 mmol) at -78 °C and the resulting yellowish slurry was stirred at r.t. for 1 h. The flask was equipped with a Vigreux column and the solvent was distilled off until 1/5 of the volume was left. The residue was mixed with but-3-yn-1-ol (1.417 g, 20.22 mmol) and pyrrolidine (14 mL) and cooled to -10 °C before CuI (0.321 g, 1.69 mmol) was added. After stirring for 1 h at r.t., the reaction was partitioned between sat. aq. NH<sub>4</sub>Cl (80 mL) and MTBE (50 mL), the

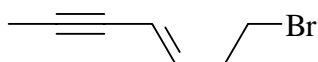
phases were separated and the aqueous phase was extracted with MTBE (3 x 50 mL), the combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 4:1) to yield **93** as a pale yellow oil (0.79 g, 75 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.78 (s, 1 H), 1.88 (t, 3 H, *J* = 1.2 Hz), 2.50 (tq, 2 H, *J* = 1.2, 6.3 Hz), 3.71 (t, 2 H, *J* = 6.2 Hz); <sup>13</sup>C-NMR δ 4.1, 23.6, 60.9, 67.2, 70.2, 73.1, 73.8; IR 3296, 2915, 1711, 1419, 1375, 1330, 1246, 1184, 1041, 846 cm<sup>-1</sup> MS (EI) *m/z* (rel. intensity) 108 (10), 89 (1), 78 (10), 74 (2), 63 (2), 51 (6).

**(3E)-3-Hepten-5-yn-1-ol (94)**<sup>124</sup>



To a solution of LiAlH<sub>4</sub> (1.0 M in THF, 4.5 mL, 4.5 mmol) was added a solution of 3,5-heptadiyn-1-ol (0.400 g, 3.70 mmol) in dry THF (5 mL) at 0 °C and the resulting solution was stirred at r.t. for 3 h. The reaction mixture was cooled with an ice bath, carefully quenched with sat. aq. NaHCO<sub>3</sub> (5 mL) and partitioned between HCl (1.0 M, 25 mL) and MTBE (40 mL). The phases were separated and the aqueous phase was extracted with MTBE (2 x 20 mL). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 10:1) to yield **94** as an oil (0.362 g, 89 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.60 (s, 1 H), 1.90 (dd, 3 H, *J* = 0.4, 2.3 Hz), 2.32 (ddq, 2 H, *J* = 0.4, 1.4, 6.3 Hz) 3.64 (t, 2 H, *J* = 6.3 Hz), 5.52 (dm, 1 H, *J* = 16 Hz), 5.99 (ddt, 1 H, *J* = 0.4, 7.2, 16.0 Hz); <sup>13</sup>C-NMR 4.1, 27.0, 36.3, 61.6, 85.0, 112.9, 138.6; IR 3338, 2917, 2225, 1427, 1376, 1171, 1042, 953 cm<sup>-1</sup>; MS (EI) *m/z* (rel. intensity) 110 (5), 95 (2), 91 (2), 79 (12), 77 (11), 65 (2), 53 (3).

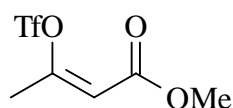
**(3E)-1-Bromo-3-hepten-5-yne (85)**<sup>83</sup>



To a solution of 1,2-bis(diphenylphosphino)ethane (1.482 g, 3.720 mmol) in dry dichloromethane (10 mL) was added Br<sub>2</sub> (0.38 mL, 1.18 g, 7.4 mmol) at 0 °C. A solution of (3E)-3-hepten-5-yn-1-ol (0.310 g, 2.81 mmol) in dry dichloromethane (5 mL) was

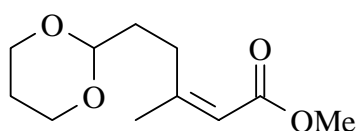
added to the pale yellow solution. The reaction mixture was stirred at r.t. for 30 min before a mixture of diethyl ether (15 mL) and pentane (15 mL) was added and the resulting slurry was stirred at r.t. for 16 h before it was filtered through silica gel (1 cm). The filtrate was evaporated carefully (40 °C, 700 mmHg) to yield **85** as a colorless oil (0.439 g, 90 % yield).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.91 (d, 3 H,  $J = 2.1$  Hz), 2.62 (dq, 2 H,  $J = 0.9, 7.0$  Hz), 3.37 (t, 2 H,  $J = 7.1$  Hz) 5.55 (m, 1 H), 5.98 (dt, 1H,  $J = 7.03, 15.8$  Hz);  $^{13}\text{C-NMR}$   $\delta$  4.2, 31.3, 36.0, 77.7, 85.8, 113.0, 138.6 MS (EI)  $m/z$  (rel. intensity) 174 (4), 172 (4), 93 (8), 91 (14), 79 (4), 77 (18), 65 (4), 51 (3).

**(2Z)-3-[[Trifluoromethyl)sulfonyl]oxy]-2-butenic acid methyl ester (**44**)<sup>94</sup>**



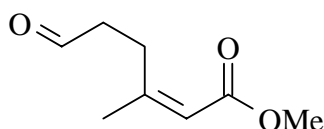
To a slurry of sodium hydride (0.498 g, 20.8 mmol) in dry dichloromethane (60 mL) was dropwise added methyl acetoacetate (2.408 g, 20.74 mmol) at 0 °C. After the gas evolution had ceased, trifluoromethanesulfonic acid anhydride (4.00 mL, 6.68 g, 23.7 mmol) was added and the resulting solution was stirred at r.t. for 1 h. The reaction mixture was partitioned between dichloromethane (50 mL) and HCl (1 M, 25 mL), the phases were separated, the organic phase was washed with sat. aq.  $\text{NaHCO}_3$  (100 mL), dried ( $\text{MgSO}_4$ ), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA, 10:1) to yield **44** as an oil (4.46 g, 87 % yield).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.18 (s, 3 H,  $J = 0.3$  Hz), 3.75 (d, 3 H), 5.74 (s, 1H,  $J = 1.0$  Hz);  $^{13}\text{C-NMR}$   $\delta$  20.9, 51.9, 112.3, 118.3 (q,  $J = 1273$  Hz), 155.3, 162.6 MS (EI)  $m/z$  (rel. intensity) 248 (2), 217 (4), 179 (1), 169 (2), 153 (2), 98 (1), 87 (4), 69 (7), 59 (4).

**(2Z)-6-(1,3-Dioxane-2-yl)-3-methyl-2-hexenoic acid methyl ester (**96**)**



To a solution of iron (III) acetylacetonate (25.0 mg, 0.0708 mmol) and (2Z)-3-[[trifluoromethyl)sulfonyl]oxy]-2-butenic acid methyl ester (1.308 g, 5.270 mmol) in dry THF (35 mL) was added a solution of 2-(1,3 dioxane-2-yl)-ethyl magnesium bromide (0.5 M, 11.0 mL, 5.50 mmol) in one portion at -30 °C, causing a color change from orange to black. The reaction mixture was stirred at -30 °C for 10 min during which time the black color disappeared and the solution turned orange again. The solution was stirred at 10 °C for 1 h and then at r.t. for 16 h before it was quenched with sat. aq. NH<sub>4</sub>Cl, and partitioned between MTBE (25 mL) and water (15 mL). The phases were separated and the aqueous phase was extracted with MTBE (2 x 30 mL). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA, 10:1) to yield **96** as an oil (1.01 g, 89% yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.30 (dsep, 1 H, *J* = 1.3, 13.5 Hz), 1.73 (m, 2 H), 1.86 (d, 3 H, *J* = 1.4 Hz), 2.05 (m, 1 H), 2.67 (m, 2 H), 3.64 (s, 3 H), 3.73 (m, 2 H), 4.07 (m, 2 H), 4.54 (t, 2 H, *J* = 5.1 Hz), 5.64 (t, 1 H, *J* = 0.6 Hz); <sup>13</sup>C-NMR δ 25.1, 25.8, 28.0, 33.5, 50.8, 66.9, 102.0, 116.0, 160.1, 166.6; IR 2953, 2850, 1715, 1647, 1433, 1402, 1377, 1333, 1283, 1233, 1194, 1141, 1088, 1074, 1044, 1019, 1004, 946, 927, 889, 851, 735 cm<sup>-1</sup>; MS (EI) *m/z* (rel. intensity) 213 (1), 183 (1), 138 (5), 125 (1), 113 (3), 100 (7), 87 (25), 67 (2), 59 (4).

**(2Z)-3-Methyl-6-oxo-2-hexenoic acid methyl ester (97)**

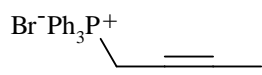


A solution of (2Z)-6-(1,3-dioxane-2-yl)-3-methyl-2-hexenoic acid methyl ester (1.41 g, 6.58 mmol) in aqueous formic acid (80 %, 32 mL, 850 mmol) was stirred at r.t. for 16 h. The reaction mixture was partitioned between MTBE (300 mL) and brine (100 mL), the phases were separated, the organic phase was washed with brine (100 mL), sat. aq. Na<sub>2</sub>CO<sub>3</sub> (2 x 100 mL), dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was dissolved in dry methanol (20 mL). Sodium methoxide (13 mg, 0.24 mmol) was added and the solution was stirred at r.t. for 30 min before it was partitioned between MTBE (300 mL) and brine (100 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated to yield **97** as an oil (0.87 g 84 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.89 (d, 3 H, *J* = 1.4 Hz), 2.60 (dt, 2 H, *J* = 1.6,



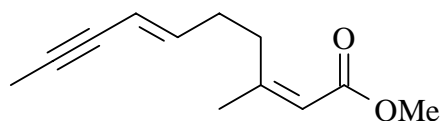
7.5 Hz), 2.90 (t, 2 H,  $J = 7.7$  Hz), 3.66 (s, 3 H), 5.70 (d, 1 H,  $J = 1.1$  Hz), 9.78 (s, 1 H);  $^{13}\text{C}$ -NMR  $\delta$  25.2, 26.1, 42.1, 50.9, 116.9, 158.3, 166.5, 201.4; IR 2951, 2726, 1710, 1647, 1435, 1379, 1232, 1173, 1143, 1080, 1019, 921, 854, 735, 667  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  (rel. intensity) 138 (2), 125 (3), 111 (1), 97 (8), 95 (7), 82 (2), 69 (4), 67 (6), 59 (2), 55 (2).

### 1-(Triphenylphosphonium)-but-2-yne bromide (**103**)<sup>98</sup>



A solution of triphenylphosphine (3.066 g, 11.69 mmol) and 1-bromo but-2-yne (1.201 g, 9.031 mmol) in dry toluene (12 mL) was stirred at r.t. for 20 h whereupon a precipitate formed. The precipitate was filtered off and washed with hexane (3 x 2 mL) to yield phosphonium salt **103** (2.448 g, 69 % yield) as a pale brown solid.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  1.60 (dt, 3 H,  $J = 2.5, 6.3$  Hz), 4.88 (dd, 2 H,  $J = 2.5, 14.8$  Hz), 7.65 - 7.90 (m, 15 H);  $^{13}\text{C}$ -NMR  $\delta$  3.6 (d,  $J = 12.8$  Hz), 18.1 (d,  $J = 223$  Hz), 66.1 (d,  $J = 55.2$  Hz), 84.7 (d,  $J = 37.2$  Hz), 117.5 (d,  $J = 348.8$  Hz), 130.2 (d,  $J = 51.6$  Hz), 133.7 (d,  $J = 29.2$  Hz), 135.2; IR 2997, 2824, 1586, 1485, 1434, 1178, 1111, 995, 851, 752, 719, 690.

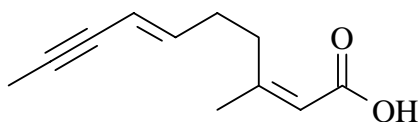
### 3-Methyl-(Z,E)-2,6-decadien-8-ynoic acid methyl ester (**98**)



To a slurry of 1-(triphenylphosphonium)-but-2-yne bromide (1.560 g, 3.947 mmol) in dry THF (25 mL) was added a solution of *n*-BuLi (1.6 M, 2.40 mL, 3.84 mmol) at  $-78$  °C and the mixture was stirred for 45 min whereupon the slurry turned into a deep red solution. A solution of (Z $Z$ )-3-methyl-6-oxo-2-hexenoic acid methyl ester (0.450 g, 2.88 mmol) in dry THF (4 mL) was added, the reaction mixture was stirred for 16 h while allowing it to slowly reach r.t. The reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (20 mL) and partitioned between MTBE (150 mL) and brine (30 mL). The phases were separated, the organic

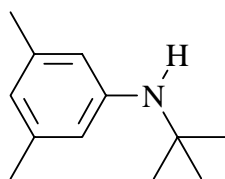
phase was washed with water (4 x 50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 50:1) to yield a 1:3.5 mixture of the (*Z*)-6 and (*E*)-6 isomers (0.382 g 70 %). Purification with a Lobar-column (hexane/EA 50:1) gave **98** as a colorless oil (166 mg, 30 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.85 (d, 3 H *J* = 1.4 Hz), 1.89 (d, 3 H, *J* = 2.2 Hz), 2.22 (dt, 1 H, *J* = 1.0, 8.0 Hz), 2.24 (dt, 1 H, *J* = 1.0, 7.3 Hz), 2.66 (d, 1 H, *J* = 8.0 Hz), 2.69 (d, 1 H, *J* = 7.5 Hz), 5.44 (dm, 1 H, *J* = 15.8 Hz), 5.65 (t, 1 H, *J* = 0.6 Hz), 6.02 (dt, 1 H, *J* = 7.1, 15.8 Hz); <sup>13</sup>C-NMR δ 4.2, 18.7, 30.7, 40.0, 50.8, 78.0, 84.8, 110.9, 115.7, 140.3, 141.1, 158.8, 167.1; MS (EI) *m/z* (rel. intensity) 192 (1), 177 (5), 160 (15), 145 (12), 133 (20), 117 (14), 105 (10), 91 (11), 79 (27), 77 (30).

### 3-Methyl-(*Z,E*)-2,6-decadien-8-ynoic acid (**84**)



To a solution of 3-methyl-(*Z,E*)-2,6-decadien-8-ynoic acid methyl ester (77.0 mg, 0.400 mmol) in methanol (4 mL) and water (0.5 mL) was dropwise added an aqueous solution of KOH (0.5 M, 4.0 mL, 2.0 mmol) at 0 °C. The mixture was stirred at r.t. for 48 h before hydrochloric acid (1 M, 2 mL, 2 mmol), brine (10 mL) and MTBE (15 mL) were added. The phases were separated and the aqueous phase was extracted with MTBE (3 x 10 mL). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated to yield **84** as a white solid (61.6 mg, 86 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.89 (s, 3 H), 1.90 (s, 3H), 2.25 (ddd, 2 H, *J* = 7.1, 7.3, 7.4 Hz), 2.70 (dd, 2 H, *J* = 7.5, 8.0 Hz), 5.45 (ddd, 1 H, *J* = 1.6, 3.8, 15.8 Hz), 5.70 (s, 1 H), 6.03 (dt, 1 H, *J* = 7.0, 15.7 Hz) 9.5 -10.5 (br s, 1H); <sup>13</sup>C-NMR δ 4.2, 25.6, 31.4, 32.7, 110.7, 115.8, 141.7, 162.2; IR 2914, 2579, 2222, 1683, 1633, 1441, 1416, 1374, 1288, 1259, 1194, 1074, 952, 865, 803, 714 cm<sup>-1</sup>.

### ***N*-(1,1-Dimethylethyl)-3,5-benzenamine (105)**<sup>19</sup>



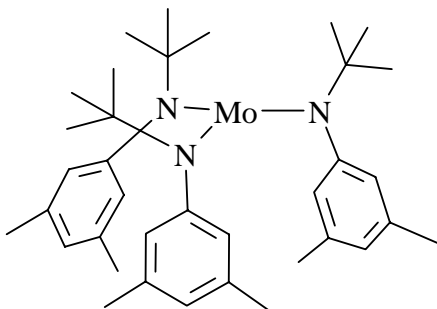
To a solution of Pd<sub>2</sub>dba<sub>3</sub> (0.233 g, 0.254 mmol), sodium *tert*-butoxide (6.85 g, 71.3 mmol) and dicyclohexyl(1-biphenyl)phosphine (0.177 g, 0.505 mmol) in dry toluene (65 mL) was added *tert*-butyl amine (6.5 mL, 62 mmol) followed by dropwise addition of 1-bromo-3,5-dimethyl benzene (5.5 mL, 40 mmol) at 40 °C. The resulting mixture was stirred at 80 °C for 1 h. A heavy crystalline precipitate formed during the reaction. The reaction mixture was cooled to r.t. and quenched with sat. aq. NH<sub>4</sub>Cl (10 mL). The solvents were removed *in vacuo* and the residue was partitioned between toluene (30 mL) and aq. KOH (3 M, 30 mL), the phases were separated and the aqueous phase was extracted with toluene (2 x 30 mL). The combined organic phases were dried (KOH), filtered and evaporated. The residue was purified by distillation (90 °C, 0.3 mmHg) to yield **105** as an oil (6.41 g, 90 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.35 (s, 9 H), 2.26 (d, 6 H, *J* = 0.8 Hz), 3.3 (br. s, 1 H), 6.41 (q, 2 H, *J* = 0.6 Hz), 6.44 (sep, 1 H, *J* = 0.6 Hz); <sup>13</sup>C-NMR δ 21.5, 30.1, 51.3, 115.4, 120.2, 138.3, 146.8; IR 2967, 1599, 1519, 1473, 1408, 1390, 1363, 1340, 1221, 1183, 1030, 992, 995, 820, 693 cm<sup>-1</sup>; MS (EI) *m/z* (rel. intensity) 177 (5), 162 (15), 146 (1), 121 (7), 106 (2), 91 (1), 77 (2).

### **Tris-(tetrahydrofurano)-molybdenum (III) chloride, Mo(THF)<sub>3</sub>Cl<sub>3</sub> (110)**<sup>106</sup>

Molybdenum (V) chloride (7.36 g, 26.9 mmol) was slurried in dry diethyl ether (70 mL) at r.t. together with coarse tin powder (3.87 g, 32.6 mmol) for 2 h, causing an orange precipitate to form. The slurry was stirred while removing the precipitate via a big cannula without transferring any tin. The tin free slurry was transferred to another flask, the precipitate was allowed to settle and the solvent removed via cannula. Dry THF (45 mL) was added and the slurry was stirred at r.t. for 3 ½ h. Coarse tin powder (3.625 g, 30.5 mmol) was added and the slurry was stirred vigorously for 30 min. The orange precipitate was removed as a slurry as described above, the slurry was filtered under Ar with a Schlenk filter, the pink to orange residue was washed with dry THF (2 x 6 mL) and dried

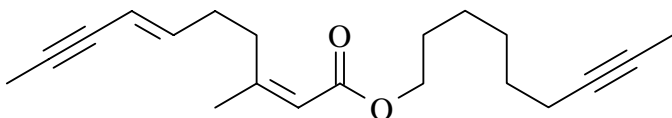
in a stream of argon to yield **110** as an orange to pink colored powder (7.26 g, 64 %). IR 2980, 2903, 1448, 1341, 1295, 1244, 1177, 1038, 1009, 918, 847.

***N*-(1,1-Dimethylethyl)-3,5-benzenamine molybdenum(III) salt (**5**)<sup>19</sup>**



To a solution of *N*-(1,1-dimethylethyl)-3,5-benzenamine (1.184 g, 6.679 mmol) in dry hexane (30 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 4.20 mL, 6.7 mmol) at -60 °C and the solution was stirred for 16 h while allowing it to slowly reach r.t. The solvent was removed *in vacuo* and dry diethyl ether (1.0 mL, 9.6 mmol) was added at -30 °C leading to the formation of a white crystalline precipitate. After stirring for 1 h, the slurry was allowed to reach r.t. The solvent was removed via cannula. The remaining white crystals were dissolved in dry diethyl ether (35 mL) and added to a slurry of tris-(tetrahydrofurano) molybdenum (III) chloride (1.407 g, 3.361 mmol) in dry diethyl ether (15 mL) at -120 °C. The reaction mixture was stirred at r.t. for 3 h, filtered through Celite under Ar to yield a deep red brown solution. The solution was concentrated *in vacuo* to 1/4 of its volume, cooled to -60 °C over 10 h in a cryomate and kept at this temperature for additional 20 h to yield **5** as dark red crystals (0.40 g, 29 % yield).

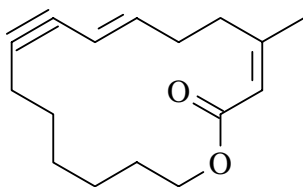
**3-Methyl-(*Z,E*)-2,6-decadien-8-ynoic acid 1-(7-nonynyl) ester (**116**)**



To a solution of 3-methyl-(*Z,E*)-2,6-decadien-8-ynoic acid (31.0 mg, 0.174 mmol) in dry dichloromethane (3 mL) was added oxalyl chloride (15.0  $\mu$ L, 22.2 mg, 0.175 mmol)

followed by 1 drop of dry DMF, and the resulting solution was stirred for 4 h while gas evolution was observed. 7-Nonyn-1-ol (27.7 mg, 0.198 mmol) was added and the resulting solution was stirred for 24 h. The reaction mixture was then partitioned between brine (15 mL) and MTBE (25 mL), the phases were separated, the aqueous phase was extracted with MTBE (3 x 10 mL), the combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated to yield **116** as an oil (32.9 mg, 63 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.32 (m, 4 H), 1.40 (m, 4 H), 1.58 (dq, 2 H, *J* = 0.5, 6.9 Hz), 1.71 (t, 3 H, *J* = 2.5 Hz), 1.80 (d, 3 H, *J* = 1.4 Hz), 1.85 (d, 3 H, *J* = 2.0 Hz), 2.05 (m, 2 H), 2.19 (q, 2 H, *J* = 7.4 Hz), 2.62 (t, 2 H, *J* = 7.4 Hz), 4.01 (t, 2 H, *J* = 6.7 Hz), 5.40 (dm, 1 H, *J* = 15.8), 5.60 (s, 1 H), 5.98 (dt, 1 H, *J* = 7.1, 15.7 Hz); <sup>13</sup>C-NMR δ 3.4, 4.2, 18.6, 25.2, 25.6, 28.5, 28.9, 31.4, 32.6, 63.7, 75.5, 78.2, 79.2, 84.4, 110.5, 116.9, 141.9, 158.7, 166.3; IR 2933, 2857, 1711, 1647, 1441, 1376, 1226, 1170, 1139, 1087, 1051, 954, 855, 731 cm<sup>-1</sup>; MS (EI) *m/z* (rel. intensity) 285 (1), 257 (1), 241 (1), 227 (1), 213 (2), 199 (3), 185 (10), 178 (10), 171 (15), 160 (25), 145 (30), 133 (50), 117 (28), 105 (25), 91 (27), 79 (65), 67 (25), 55 (26).

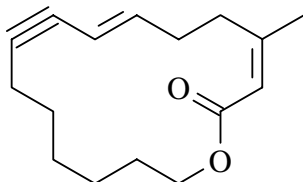
#### 1-Oxa-4-methyl pentadec-(*Z,E*)-3,7-dien-9-yn-2-one (**117**)



To a solution of molybdenum precatalyst **5** (3.52 mg, 5.63 μmol) in dry, degassed toluene (1.5 mL) was added dry dichloromethane (45 μL, 0.4 mmol) at r.t. The solution was stirred for 15 min before 3-methyl-(*Z,E*)-2,6-decadien-8-ynoic acid 1-(7-nonynyl) ester (26.8 mg, 0.0890 mmol) in toluene (2 mL) was added. The solution was stirred at 80 °C for 16 h, quenched with dry methanol (1 mL) and stirred at r.t. for 1 h. The brown mixture was evaporated and the residue was purified by flash chromatography (hexane/EA 15:1) to give **117** as an oil (14.5 mg, 67 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.50 (m, 6 H), 1.65 (m, 2 H), 1.83 (d, 3 H, *J* = 1.6 Hz), 2.25 (m, 4 H), 2.86 (dd, 2 H, *J* = 6.19, 6.35 Hz), 4.16 (dd, 2 H, *J* = 5.45, 5.58 Hz), 5.23 (dm, 1 H, *J* = 14.39 Hz), 5.74 (d, 1 H, *J* = 1.25 Hz), 5.86 (dtr, 1 H, *J* = 7.65, 15.74 Hz); <sup>13</sup>C-NMR δ 19.0, 24.1, 25.4, 27.4, 27.7, 28.7, 30.7, 31.1, 62.6, 80.4, 88.6, 110.7, 118.2, 141.6, 156.1, 166.9; IR 2924, 2856, 1714, 1649, 1442, 1376, 1320, 1260, 1237, 1160, 1140, 1083, 1048, 1015, 980, 957, 851, 799, 718 cm<sup>-1</sup>; MS (EI) *m/z* (rel.

intensity) 246 (2) 231 (1) 218 (1) 207 (2) 201 (1) 187 (1) 171 (2) 159 (4) 145 (5) 131 (10) 117 (6) 105 (8) 91 (13) 79 (7) 67 (4) 55 (4).

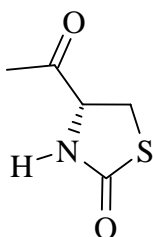
### 1-Oxa-4-methyl pentadec-(*Z,E*)-3,7-dien-9-yn-2-one (117)



To a solution of 3-methyl-(*Z,E*)-2,6-decadien-8-ynoic acid 1-(7-nonyl) ester (13.4 mg, 0.0445 mmol) in dry, degassed toluene (21 mL) was added a solution of tungsten catalyst **4** (4.3 mg, 0.0091 mmol) in dry toluene (1.5 mL) at 80 °C in a flask with a reflux condenser while Ar was bubbled through the reaction mixture. The solution turned reddish orange after 15 min, and was stirred at 80 °C for 90 min before it was filtered through silica gel (hexane/EA 10:1). The filtrate was evaporated and the residue was purified by flash chromatography (hexane/EA 10:1) to yield **117** as an oil (9.4 mg, 85 % yield).

*Spectroscopic data see above.*

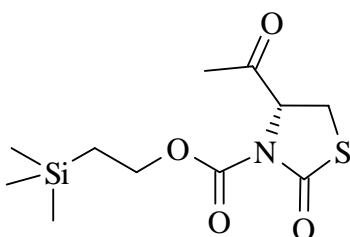
### (4*R*)-4-Acetyl-2-thiazolidinone (16)<sup>44</sup>



To a solution of (4*R*)-4-acetyl-3-[(4-methoxyphenyl)methyl]-2-thiazolidinone (0.2467 g, 0.9298 mmol) in a mixture of water (0.9 mL) and acetonitrile (3.6 mL) was added a solution of cerium ammonium nitrate (1.023 g, 1.866 mmol) in a mixture of water (1.5 mL) and acetonitrile (6.0 mL) at r.t. The solution was stirred at r.t. for 200 min before it was partitioned between brine (30 mL) and dichloromethane (50 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (4 x 40 mL). The

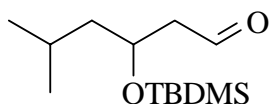
combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 2:1 → 1:1) to give **16** as a yellowish oil (80 mg, 59 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.59 (s, 1 H), 2.27 (s, 3 H), 3.48 (dd, 1 H, *J* = 6.5, 11.1 Hz), 3.68 (dd, 1 H, *J* = 8.4, 11.2 Hz), 4.35 (ddd, 1 H, *J* = 1.1, 6.5, 8.4 Hz); <sup>13</sup>C-NMR δ 26.0, 31.3, 62.5, 204.80, 204.82; IR 3252, 2924, 1721, 1659, 1496, 1417, 1352, 1298, 1175, 1143, 1091, 1018, 988, 951, 913, 705 cm<sup>-1</sup>.

**(-)-4-Acetyl-3-[[2-(trimethylsilyl)ethyl]carbamoyl]-2-thiazolidinone (121)**



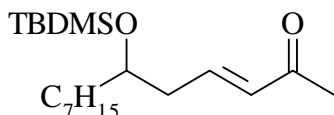
To a slurry of 2-(trimethylsilyl)ethanol (0.2003 g, 1.694 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.210 g, 1.52 mmol) in dry toluene (1 mL) was added a solution of phosgene (20 % ww. in toluene, 1.4 mL, 3 mmol) at -15 °C and the resulting mixture was stirred at this temperature for 1 h and then at r.t. for 12 h. The resulting slurry was filtered through MgSO<sub>4</sub> under argon and the filtrate was evaporated. The residue and DMAP (12.3 mg, 0.101 mmol) was dissolved in dry dichloromethane (2.5 mL). Hünig base (0.34 mL, 0.25 g, 1.95 mmol) and (4*R*)-4-acetyl-2-thiazolidinone (80.0 mg, 0.55 mmol) were added at 0 °C, and the reaction was stirred at 0 °C for 2 h before it was quenched with ethanol (2 mL) and partitioned between sat. aq. NH<sub>4</sub>Cl (30 mL), water (5 mL) and EA (30 mL). The phases were separated and the aqueous phase was extracted with EA (3 x 20 mL). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by flash chromatography (hexane/EA 2:1) to yield **121** as a pale yellow oil which turned solid upon standing (0.153 g, 96 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.01 (s, 9 H), 1.07 (m, 2 H), 2.28 (s, 3 H), 3.22 (dd, 1 H, *J* = 2.5, 11.6 Hz), 3.59 (dd, 1 H, *J* = 8.9, 11.6 Hz), 4.32 (m, 2 H), 4.92 (dd, 1 H, *J* = 2.5, 8.8 Hz); <sup>13</sup>C-NMR δ -1.5, 17.6, 26.3, 26.7, 64.9, 66.6, 150.9, 168.8, 203.0; MS (EI) *m/z* (rel. intensity) 246 (4), 219 (1), 202 (1), 174 (25), 158 (20), 101 (18), 73 (55).

### 3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-methyl-hexanal (**123**)



Ozone from an ozone generator was bubbled through a solution of 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-methyl-1-heptene (0.380 g, 1.57 mmol) in dry methanol (15 mL) at -78 °C until a blue color persisted. Argon was bubbled through the solution until it became colorless, and the reaction was quenched with triphenylphosphine (0.668 g, 2.5 mmol). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (hexane/EA 50:1) to yield **123** as a colorless oil (77 mg, 20 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.86 (s, 9H), 0.88 (d, 3 H, *J* = 6.6 Hz), 0.89 (d, 3 H, *J* = 6.6 Hz), 1.34 (m, 1 H), 1.46 (m, 1 H), 1.63 (sep, 1 H, *J* = 6.7 Hz), 2.50 (tm, 2 H), 4.21 (m, 1 H), 9.80 (dd, 1 H, *J* = 2.2, 2.9 Hz).

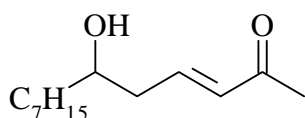
### 6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-oxo-3-tridecene (**135**)



To a solution of butenone (200.0 μL, 168.4 mg, 2.403 mmol) and 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-undecene (137.4 mg, 0.4829 mmol) in dry dichloromethane (3.0 mL) was added catalyst **132** (10.1 mg, 0.0162 mmol) and the solution was stirred at r.t. for 3 h. EA (1 mL) was added and the solvents were removed *in vacuo* and the residue was purified by flash chromatography (hexane/EA 10:1) furnishing **135** as a colorless oil (150.2 mg, 95 % yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.02 (s, 3 H), 0.3 (s, 3 H), 0.86 (t, 3 H, *J* = 1.6 Hz), 0.87 (s, 9 H), 1.25 (m, 8 H), 1.41 (m, 2 H), 2.2 (s, 3 H), 2.34 (m, 2 H), 3.77 (q, 1 H, *J* = 5.5 Hz), 6.06 (dt, 1 H, *J* = 1.0, 16.0 Hz), 6.80 (dt, 1 H, *J* = 6.4, 16.0 Hz); <sup>13</sup>C-NMR δ -4.51, -4.47, 14.1, 18.1, 22.6, 25.3, 25.8, 29.2, 29.6, 31.8, 37.4, 40.3, 71.4, 133.2, 145.3, 198.4; IR 2928, 2856, 1701, 1678, 1630, 1463, 1360, 1251, 1174, 1072, 1005, 981, 939, 833, 807, 773, 723, 666.

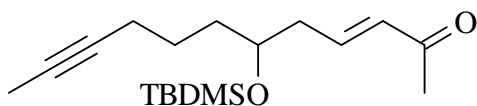


### 6-Hydroxy-2-oxo-3-tridecene (136)



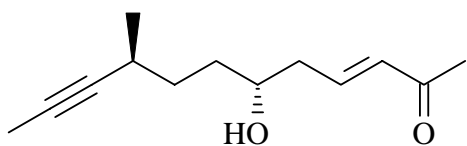
To a solution of butenone (145.0  $\mu\text{L}$ , 206.3 mg, 2.943 mmol) and 4-hydroxy-1-undecene (100.3 mg, 0.5890 mmol) in dry dichloromethane (1.0 mL) was added a solution of catalyst **131** (9.3 mg, 0.011 mmol) in dry dichloromethane (1 mL) and the resulting red solution was stirred at 45  $^{\circ}\text{C}$  for 16 h. EA (2 mL) was added, the solvents were removed *in vacuo* and the residue was purified by flash chromatography (hexane/EA 2:1) to give **136** as a colorless oil (106.8 mg, 85 % yield).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.86 (t, 3 H,  $J = 6.8$  Hz), 1.27 (m, 8 H), 1.47 (m, 2 H), 1.53 (s, 1 H), 1.83 (m, 2 H), 2.24 (s, 3 H), 2.33 (m, 1 H), 2.41 (m, 1 H), 3.73 (m, 1 H), 6.13 (dt, 1 H,  $J = 1.6, 16.0$  Hz), 6.83 (dt, 1 H,  $J = 7.3, 16.0$  Hz);  $^{13}\text{C-NMR}$   $\delta$  14.1, 22.6, 25.6, 27.0, 29.2, 29.5, 31.8, 37.4, 40.4, 70.7, 133.5, 144.3, 198.3; IR 3441, 2926, 2855, 1669, 1626, 1465, 1424, 1361, 1254, 1176, 1126, 978, 872, 834, 771, 723  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  (rel. intensity) 194 (1), 179 (2), 129 (1), 121 (1), 109 (1), 100 (1), 95 (15), 84 (40), 69 (25), 55 (10).

### 6-[[1,1-Dimethylethyl]dimethylsilyloxy]-2-oxo-3-dodecen-10-yne (139)



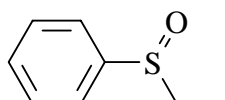
To a solution of 4-[[1,1-dimethylethyl]dimethylsilyloxy]-1-dodecen-8-yne (11.7 mg, 0.0439 mmol) and butenone (20  $\mu\text{L}$ , 17 mg, 0.24 mmol) in dry dichloromethane (0.3 mL) was added catalyst **132** (7.2 mg, 0.012 mmol) and the mixture was stirred at r.t. for 150 min. The reaction mixture was filtered through silica gel, the filtrate was evaporated and the residue was purified by flash chromatography (hexane/EA 20:1) to give **139** as a colorless oil (3.8 mg, 28 % yield).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.04 (s, 3 H), 0.07 (s, 3 H), 0.89 (s, 9 H), 1.50 - 1.60 (m, 4 H), 1.77 (t, 3 H,  $J = 2.5$  Hz), 2.13 (m, 2 H,  $J = 2.5$  Hz), 2.25 (s, 3 H), 2.37 (m, 2 H), 3.83 (m, 1 H), 6.05 (dd, 1 H,  $J = 1.2, 14.8$  Hz), 6.82 (m, 1 H);  $^{13}\text{C-NMR}$   $\delta$  -4.5, 3.5, 18.1, 18.8, 24.6, 25.8, 26.7, 36.4, 40.3, 70.9, 72.5, 79.5, 133.3, 145.1, 204.0; MS (EI)  $m/z$  (rel. intensity) 143 (4), 141 (9), 133 (1), 93 (4), 91 (1), 75 (11), 73 (6), 59 (1).

**(R)-9-Methyl-(R)-6-hydroxy-2-oxo-3-dodecen-10-yne (146)**



To a solution of (*R*)-4-hydroxy-(*R*)-7-methyl-1-decen-8-yne 23.1 mg, 0.139 mmol) in dry pentane (6 mL) was added  $\text{Co}_2(\text{CO})_8$  (48.3 mg, 0.1412 mmol) and the dark solution was stirred at r.t. for 90 min. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (hexane/EA 8:1) to give 62.6 mg of a dark red oil. This oil and butenone (57.5  $\mu\text{L}$ , 48.4 mg, 0.691 mmol) were dissolved in dry dichloromethane (0.25 mL) and catalyst **132** (5.0 mg, 8.1  $\mu\text{mol}$ ) was added. The reaction mixture was stirred at r.t. for 3 h with evolution of gas. EA (1 mL) was added, the solvents were removed *in vacuo* and the residue was purified by flash chromatography (hexane/EA 3:2) to give 56.2 mg of a dark red oil. This oil was mixed with a solution of iron (III) nitrate nonahydrate (466 mg, 1.15 mmol) in ethanol (0.90 mL) and pentane (0.5 mL) at r.t. and was stirred for 15 min. The resulting mixture was partitioned between water (10 mL), brine (10 mL) and MTBE (20 mL), the phases were separated and the aqueous phase was extracted with MTBE (3 x 10 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 1:1) to give **146** as a colorless oil (20.9 mg, 72 % yield).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.11 (d, 3 H,  $J = 6.9$  Hz), 1.45 (m, 2 H), 1.62 (m, 2 H), 1.75 (d, 3H,  $J = 2.4$  Hz), 2.22 (d, 3 H,  $J = 2.8$  Hz), 2.38 (m, 2 H), 3.78 (m, 1 H), 6.12 (dt, 1 H,  $J = 1.4, 16.0$  Hz), 6.82 (dt, 1H,  $J = 7.3, 16.0$  Hz);  $^{13}\text{C-NMR}$   $\delta$  3.4, 21.5, 25.7, 26.9, 32.9, 35.0, 40.4, 70.4, 70.7, 76.2, 83.2, 133.4, 144.3, 198.4; MS (EI)  $m/z$  (rel. intensity) 207 (1), 175 (1), 147 (1), 125 (2), 105 (3), 95 (3), 84 (15), 79 (5), 69 (8), 55 (5).

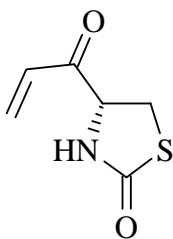
**Ethylsulfinyl-benzene (152)**<sup>120</sup>



Magnesium sulfate monohydrate (2.120 g, 15.32 mmol) was dissolved in conc. sulfuric acid (5.0 mL) and the solution was stirred at 70 °C for 3 h. After cooling to 0 °C, diethyl ether (20 mL) was added slowly, precipitating white crystals, which were filtered off and air-dried to yield magnesiumhydrogensulfate (2.41 g, 72 % yield). IR 3531, 3482, 2934, 1621, 1176, 1081, 1041, 868, 775, 671  $\text{cm}^{-1}$ .

To a slurry of magnesium hydrogensulfate (0.372 g, 1.70 mmol) and sodium bromate (0.639 g, 4.23 mmol) in dry acetonitrile (45 mL) was added ethyl phenyl sulfide (0.572 g, 4.13 mmol) and the resulting reaction mixture was stirred for 16 h, filtered, the precipitate was washed with dichloromethane (40 mL). The combined organic phases were washed with sat. aq.  $\text{NaHCO}_3$  (10 mL), dried ( $\text{MgSO}_4$ ), filtered and evaporated, and the residue was purified by flash chromatography (hexane/EA 1:1) to yield **152** as a colorless oil (0.51 g, 80 % yield).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.02 (t, 3 H,  $J = 7.3$  Hz), 2.75 (dq, 1 H,  $J = 7.3, 13.5$  Hz), 3.01 (dq, 1 H,  $J = 7.3, 13.5$  Hz), 7.50 - 7.68 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  5.2, 48.6, 124.0, 129.0, 130.5, 143.6; MS (EI)  $m/z$  (rel. intensity) 154 (4), 138 (4), 126 (10), 110 (3), 97 (2), 91 (1), 78 (12).

#### (*R*)-4-(1-Oxo-propenyl)-2-thiazolidinone (149)



To a slurry of (*R*)-2-thiazolidinone-4-carboxylic acid (84.2 mg, 0.572 mmol) in dry dichloromethane (2.5 mL) was added oxalyl chloride (50  $\mu\text{L}$ , 73.9 mg, 0.582 mmol) followed by 1 drop of dry DMF at r.t. and evolution of gas was observed. The reaction mixture was stirred for 45 min whereupon the precipitate dissolved. The reaction was cooled to 10 °C and anhydrous aluminium chloride (114 mg, 0.855 mmol) and vinyltrimethylsilane (125  $\mu\text{L}$ , 86.4 mg, 0.862 mmol) were added. The resulting solution was stirred at r.t. for 15 min, quenched with sat. aq.  $\text{NaHCO}_3$  (20 mL), the phases were separated and the aqueous phase was extracted with dichloromethane (5 x 20 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and evaporated to yield 29 mg of an oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.29 (dd, 1 H,  $J = 8.4, 11.0$  Hz), 3.61 (dd, 1 H,  $J = 7.3, 11.0$  Hz),

4.93 (t, 1 H,  $J = 7.8$  Hz), 6.12 (d, 1 H,  $J = 5.2$  Hz), 6.59 (d, 1 H,  $J = 5.2$  Hz), 7.17 (d, 1 H,  $J = 7.8$  Hz), 7.25 (d, 1 H,  $J = 8.1$  Hz);  $^{13}\text{C}$ -NMR  $\delta$  37.9, 59.1, 125.9, 129.7, 175.5, 175.9; MS (EI)  $m/z$  (rel. intensity) 155 (6), 132 (1), 100 (4), 85 (5), 73 (10).

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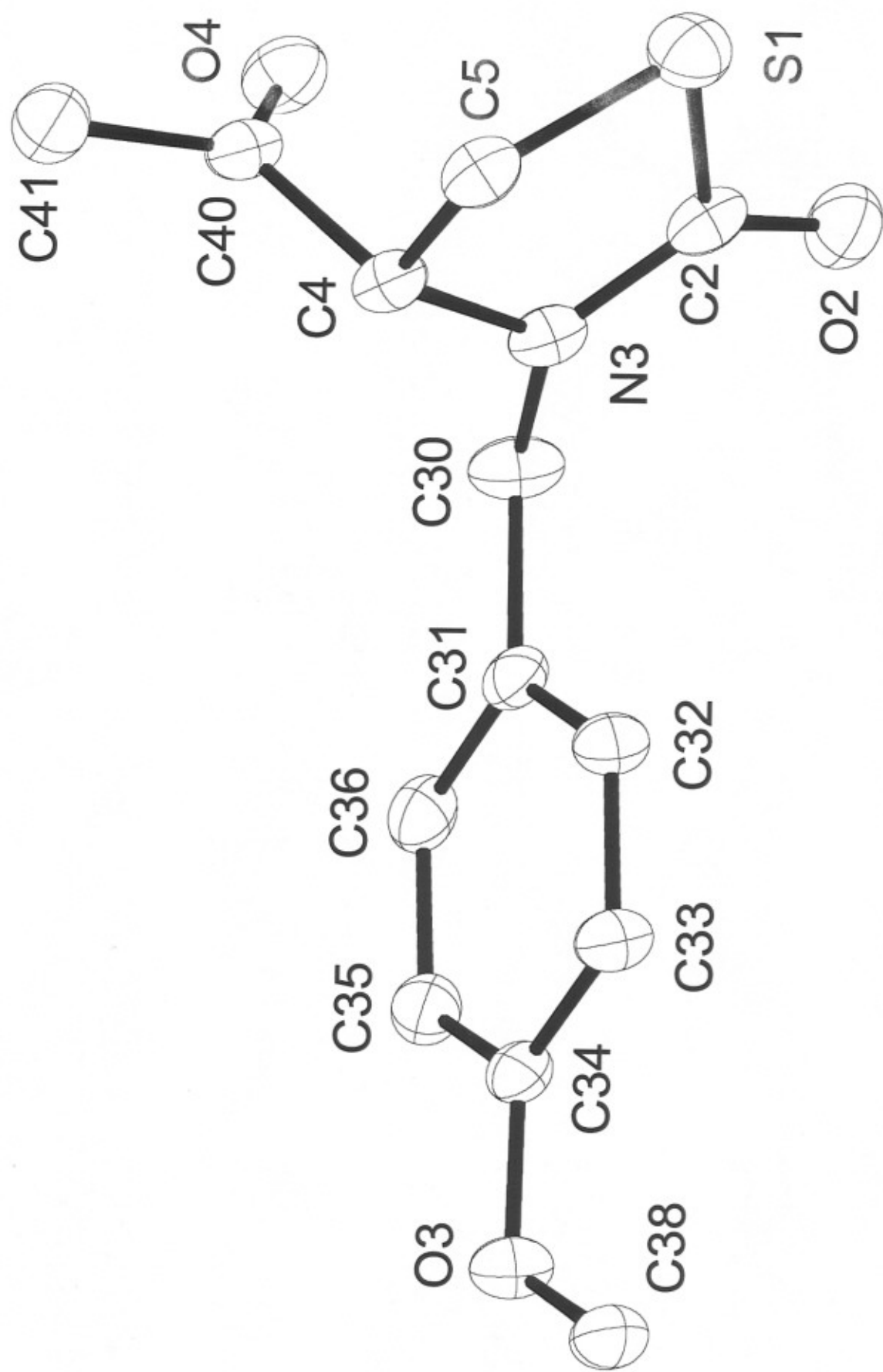
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**Table 1. Crystal data and structure refinement.**

Identification code	4606	
Empirical formula	C <sub>13</sub> H <sub>13</sub> N O <sub>3</sub> S	
Color	colorless	
Formula weight	263.30 g · mol <sup>-1</sup>	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	<b>P 2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, (no. 19)</b>	
Unit cell dimensions	a = 5.3552(2) Å	α = 90°.
	b = 10.6947(3) Å	β = 90°.
	c = 23.0315(8) Å	γ = 90°.
Volume	1319.07(8) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.326 Mg · m <sup>-3</sup>	
Absorption coefficient	0.245 mm <sup>-1</sup>	
F(000)	552 e	
Crystal size	0.24 x 0.10 x 0.04 mm <sup>3</sup>	
θ range for data collection	4.20 to 31.00°.	
Index ranges	-7 ≤ h ≤ 7, -15 ≤ k ≤ 15, -33 ≤ l ≤ 30	
Reflections collected	18482	
Independent reflections	4193 [R <sub>int</sub> = 0.0812]	
Reflections with I > 2σ(I)	3286	
Completeness to θ = 27.75°	99.5 %	
Absorption correction	Psi-scan	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	4193 / 0 / 165	
Goodness-of-fit on F <sup>2</sup>	1.082	
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0662	wR <sup>2</sup> = 0.1405
R indices (all data)	R <sub>1</sub> = 0.0931	wR <sup>2</sup> = 0.1522
Absolute structure parameter	-0.07(12)	
Largest diff. peak and hole	0.486 and -0.281 e · Å <sup>-3</sup>	



**Table 3. Bond lengths [Å] and angles [°].**

S(1)-C(2)	1.782(3)	S(1)-C(5)	1.802(3)
C(2)-O(2)	1.216(3)	C(2)-N(3)	1.353(4)
O(3)-C(34)	1.372(3)	O(3)-C(38)	1.427(3)
N(3)-C(4)	1.444(3)	N(3)-C(30)	1.470(3)
O(4)-C(40)	1.200(3)	C(4)-C(5)	1.539(4)
C(4)-C(40)	1.540(4)	C(30)-C(31)	1.512(4)
C(31)-C(32)	1.377(4)	C(31)-C(36)	1.395(4)
C(32)-C(33)	1.396(4)	C(33)-C(34)	1.378(4)
C(34)-C(35)	1.388(4)	C(35)-C(36)	1.383(4)
C(40)-C(41)	1.505(4)		
C(2)-S(1)-C(5)	92.10(13)	O(2)-C(2)-N(3)	126.8(3)
O(2)-C(2)-S(1)	123.1(2)	N(3)-C(2)-S(1)	110.1(2)
C(34)-O(3)-C(38)	117.3(2)	C(2)-N(3)-C(4)	116.6(2)
C(2)-N(3)-C(30)	119.6(2)	C(4)-N(3)-C(30)	121.0(2)
N(3)-C(4)-C(5)	106.4(2)	N(3)-C(4)-C(40)	111.6(2)
C(5)-C(4)-C(40)	110.1(2)	C(4)-C(5)-S(1)	104.78(18)
N(3)-C(30)-C(31)	112.6(2)	C(32)-C(31)-C(36)	117.9(2)
C(32)-C(31)-C(30)	122.6(2)	C(36)-C(31)-C(30)	119.4(2)
C(31)-C(32)-C(33)	121.5(2)	C(34)-C(33)-C(32)	119.7(3)
O(3)-C(34)-C(33)	124.2(2)	O(3)-C(34)-C(35)	115.9(2)
C(33)-C(34)-C(35)	119.9(2)	C(36)-C(35)-C(34)	119.7(3)
C(35)-C(36)-C(31)	121.4(3)	O(4)-C(40)-C(41)	123.3(3)
O(4)-C(40)-C(4)	120.9(3)	C(41)-C(40)-C(4)	115.8(2)

**Table 2. Atomic coordinates and equivalent isotropic displacement parameters ( $\text{\AA}^2$ ).**  
 $U_{\text{eq}}$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	$U_{\text{eq}}$
S(1)	-0.4497(1)	-0.8941(1)	-0.2246(1)	0.032(1)
C(2)	-0.5634(6)	-0.7925(2)	-0.2800(1)	0.027(1)
O(2)	-0.7384(4)	-0.7217(2)	-0.2728(1)	0.035(1)
O(3)	0.1510(4)	-0.3910(2)	-0.4786(1)	0.029(1)
N(3)	-0.4310(4)	-0.8089(2)	-0.3294(1)	0.025(1)
O(4)	-0.6095(4)	-1.0370(2)	-0.3613(1)	0.032(1)
C(4)	-0.2612(5)	-0.9137(2)	-0.3307(1)	0.024(1)
C(5)	-0.1814(5)	-0.9371(2)	-0.2674(1)	0.028(1)
C(30)	-0.5158(6)	-0.7491(3)	-0.3834(1)	0.030(1)
C(31)	-0.3295(5)	-0.6555(2)	-0.4067(1)	0.023(1)
C(32)	-0.1603(5)	-0.5945(3)	-0.3717(1)	0.025(1)
C(33)	0.0035(5)	-0.5050(2)	-0.3940(1)	0.026(1)
C(34)	-0.0035(5)	-0.4762(2)	-0.4523(1)	0.024(1)
C(35)	-0.1767(5)	-0.5341(2)	-0.4882(1)	0.027(1)
C(36)	-0.3352(6)	-0.6238(2)	-0.4655(1)	0.027(1)
C(38)	0.3280(6)	-0.3280(3)	-0.4427(1)	0.029(1)
C(40)	-0.3869(5)	-1.0315(2)	-0.3558(1)	0.025(1)
C(41)	-0.2135(6)	-1.1362(3)	-0.3726(1)	0.032(1)

**Table 4. Anisotropic displacement parameters ( $\text{\AA}^2$ ).**

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [ h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12} ].$$

	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
S(1)	0.038(1)	0.032(1)	0.027(1)	0.005(1)	-0.001(1)	-0.001(1)
C(2)	0.030(1)	0.019(1)	0.033(1)	0.001(1)	-0.006(1)	-0.005(1)
O(2)	0.034(1)	0.028(1)	0.043(1)	-0.003(1)	0.002(1)	0.003(1)
O(3)	0.033(1)	0.026(1)	0.029(1)	0.008(1)	0.001(1)	-0.004(1)
N(3)	0.028(1)	0.020(1)	0.028(1)	0.005(1)	-0.003(1)	-0.003(1)
O(4)	0.026(1)	0.028(1)	0.041(1)	0.000(1)	-0.003(1)	-0.004(1)
C(4)	0.022(1)	0.019(1)	0.031(1)	0.003(1)	-0.001(1)	-0.002(1)
C(5)	0.028(1)	0.023(1)	0.033(1)	0.001(1)	-0.005(1)	-0.003(1)
C(30)	0.029(2)	0.030(1)	0.032(1)	0.012(1)	-0.007(1)	-0.007(1)
C(31)	0.025(1)	0.015(1)	0.028(1)	0.001(1)	0.001(1)	0.002(1)
C(32)	0.028(1)	0.023(1)	0.024(1)	0.005(1)	-0.001(1)	-0.001(1)
C(33)	0.028(1)	0.023(1)	0.026(1)	0.004(1)	-0.002(1)	-0.004(1)
C(34)	0.026(1)	0.017(1)	0.028(1)	0.004(1)	0.004(1)	0.004(1)
C(35)	0.033(2)	0.024(1)	0.023(1)	0.001(1)	0.000(1)	0.001(1)
C(36)	0.032(1)	0.024(1)	0.026(1)	-0.005(1)	-0.003(1)	-0.002(1)
C(38)	0.029(2)	0.024(1)	0.035(2)	0.002(1)	0.005(1)	-0.004(1)
C(40)	0.029(2)	0.021(1)	0.025(1)	0.004(1)	-0.002(1)	-0.005(1)
C(41)	0.032(2)	0.029(1)	0.036(2)	-0.002(1)	0.000(1)	0.000(1)