# Syntheses and Biological Evaluation of Cruentaren A and Neopeltolide as well as their Analogues

# Synthesen und Biologische Evaluierung der Makrolide Cruentaren A und Neopeltolid sowie deren Analoga

DISSERTATION

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## Publications:

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# Table of Contents

# Abbreviations

| | |
|---|---|
| abs. | absolute |
| Ac | Acetyl |
| ADP | Adenosine diphosphate |
| aq. | aqueous |
| ar. (arom.) | aromatic |
| ATP | Adenosine 5'-triphosphate |
| BBN (9-) | 9-Borabicyclo[3.3.1]nonane |
| BAIB | Bis-acetoxyiodosobenzene |
| BINAP | 2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl |
| BINOL | 1,1'-Bi-2-naphthol |
| BOP | Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate |
| Bn | Benzyl |
| br | broad (NMR) |
| Boc | *tert*-Butoxycarbonyl |
| BOM | benzyloxymethyl |
| b.p. | Boiling point |
| Bu | Butyl |
| Bz | Benzoyl |
| *c* | Concentration |
| CAN | Cerium(IV) ammonium nitrate |
| CDI | 1,1'-Carbonyldiimidazole |
| COD | 1,5-Cyclooctadiene |
| COSY | Correlation Spectroscopy |
| Cp | Cyclopentadienyl |
| CSA | Camphor sulfonic acid |
| Cy | cyclohexyl |
| δ | Chemical shift in ppm (NMR) |
| d | Doublet (NMR) |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-8-ene |

| | |
|---|---|
| DCC | N,N'-Dicyclohexylcarbodiimide |
| DCE | Dichlorethane |
| DCM | Dichloromethane |
| *de* | Diastereomeric excess |
| DEAD | Diethyl azodicarboxylate |
| DEPT | Distortionless Enhancement by Polarization Transfer |
| DET | Diethyl tartrate |
| DIAD | Diisopropyl azodicarboxylate |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | Diisobutylaluminium hydride |
| DMA | Dimethylacetamide |
| DMAP | 4-Dimethylaminopyridine |
| DMB | 3,4-Dimethoxybenzyl |
| DME | Dimethoxyethane |
| DMF | N,N-Dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMSO | Dimethylsulfoxide |
| dr | Diastereomeric ratio |
| DTBMP | 2,6-di-*tert*-butyl-4-methylpyridine |
| *E* | trans |
| *ee* | Enantiomeric excess |
| EDCI | 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride |
| EI | Electron impact |
| ESI | Electronspray ionization |
| Et | Ethyl |
| $Et_2O$ | Diethyl ether |
| EtOAc | Ethyl acetate |
| g | gram(s) |
| GC | Gas chromatography |
| Grubbs 2$^{nd}$ | [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](tricyclohexylphosphine) benzylidene ruthenium dichloride |
| h | hour(s) |

| | |
|---|---|
| HBTU | 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HMPA | Hexamethylphosphoramide |
| HOBt | N-Hydroxybenzotriazole |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | Hertz |
| $IC_{50}$ | half maximal Inhibitory Concentration |
| Ipc | Isopinocampheyl |
| IR | Infrared |
| *i*Pr | isopropyl |
| *J* | coupling constant |
| L | liter(s) |
| LA | Lewis acid |
| LC | Liquid chromatography |
| LDA | Lithium diisopropylamide |
| HMDS | Hexamethyldisilazane |
| m | Multiplet (NMR) |
| *m*CPBA | *meta*-Chloroperoxybenzoic acid |
| Me | Methyl |
| mg | milligram |
| µg | microgram |
| MOM | Methoxymethyl |
| m.p. | Melting point |
| Ms | Methanesulfonyl |
| nM | nanomolar |
| NMO | N-Methylmorpholine-N-Oxide |
| NMR | Nuclear magnetic resonance |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| PCC | Pyridinium chlorochromate |
| Ph | Phenyl |
| Piv | Pivaloyl |
| PMB | *p*-Methoxybenzyl |

| | |
|---|---|
| PMP | *p*-Methoxyphenyl |
| PPTS | Pyridinium *para*-toluene sulfonate |
| *p*TSA | *para*-Toluene sulfonic acid |
| Py | Pyridine |
| q | Quartet (NMR) |
| RCAM | Ring-closing alkyne metathesis |
| RCM | Ring-closing metathesis |
| $R_f$ | Retention factor (TLC) |
| RT | Room temperature (ca. 23 °C) |
| s | Singlet (NMR) |
| t | Triplet (NMR) |
| TASF | Tris(dimethylamino)sulfonium difluorotrimetlylsilicate |
| TC | thiophene-2-carboxylate |
| TCBC | 2,4,6-trichloro-benzoyl chloride |
| TBAF | Tetrabutylammonium fluoride |
| TBDMS | *tert*-Butyldimethylsilyl |
| TBDPS | *tert*-Butyldiphenylsilyl |
| TBS | *tert*-Butyldimethylsilyl |
| TEMPO | 2,2,6,6-Tetramethylpiperidine-1-oxyl |
| TES | Triethylsilyl |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |
| TfO | Trifluoromethane sulfonate |
| TMEDA | Tetramethylethylendiamine |
| TMS | Trimethylsilyl |
| THP | Tetrahydropyranyl |
| Ts | *p*-Toluenesulfonyl |
| Triflate | Trifluoromethane sulfonate |
| UV | Ultraviolet |
| *Z* | cis |

# Chapter I

# Total Synthesis of Cruentaren A and Analogues

# 1 Introduction

The urgent need for the discovery and development of new pharmaceuticals for the treatment of cancer, AIDS, infectious diseases, as well as a host of other diseases demands that all approaches to drug discovery be exploited aggressively. Among the most important approaches, the one from natural products has made many unique and vital contributions to drug discovery. From the data presented by Newman et al.[1], the utility of natural products as sources of novel structures, but not necessarily the final drug entity, is still alive and well. Thus, in the area of cancer, over the time frame from around the 1940s to 2007, of the 155 small molecules, 47% are actually being either natural products or directly derived therefrom.

Although many complex natural products are very interesting from a biological point of view, they are usually present in organisms in low quantities. This sometimes significantly hampers extensive clinical research of such compounds. Thus, alternative sources and in the first place, chemical synthesis must provide access to required amounts as well as modified analogues that may have improved biological activity.[2] Another important role of total synthesis is to prove the assigned structure and determine absolute stereochemistry of complicated molecules.[3]

The total synthesis of complex natural products remains the most difficult, daunting, and challenging endeavor in organic chemistry. It is also the most humbling, exhilarating, and formative enterprise in our science. The sizes and complexities of the natural products synthesized today bear no resemblance to the substrates that were targeted in the beginning.[4] The assembly of complex natural products has stimulated the development of powerful synthetic methodologies that enable organic chemists to build, in a shorter time and more efficient manner, structures of previously undreamed complexity. The desire to imitate nature has led to the discovery and establishment of powerful biomimetic approaches, as exemplified by the Johnson synthesis of steroids.[5]

Benzolactones represent an important subclass of natural products among the polyketides.[6] They may be viewed as privileged structures in nature since there are so many of them and they do show a broad range of biological activity. From a biological point of view, benzolactones are secondary metabolites of bacteria, fungi, sponges, and small animals. They appear to be unnecessary for an organism's internal functioning but can be used for the

purpose of defense and intercellular communication. Polyketide fragments are derived from the oligomerization of propionyl and acetyl subunits in a similar process to fatty acid synthesis. Such fragments can include double bonds, saturated chains or even heterocycles.

Among the many benzolactones,[7] the recently described cruentaren A (**1-1**)[8] stands out due to its unique structural features and novel mode of action (**Figure 1**). It turned out that **1-1** is an inhibitor of mitochondrial F-ATPase from yeast.[9] Against the L929 cell line cruentaren A shows strong cytotoxicity with an $IC_{50}$ value of 1.2 ng $mL^{-1}$. With its 12-membered macrolactone and a side chain that is terminated with an acylated amino function, cruentaren A has some resemblance to the well known benzolactone enamides.[10] However, in contrast to cruentaren A, the benzolactone enamides target V-ATPase.[11]

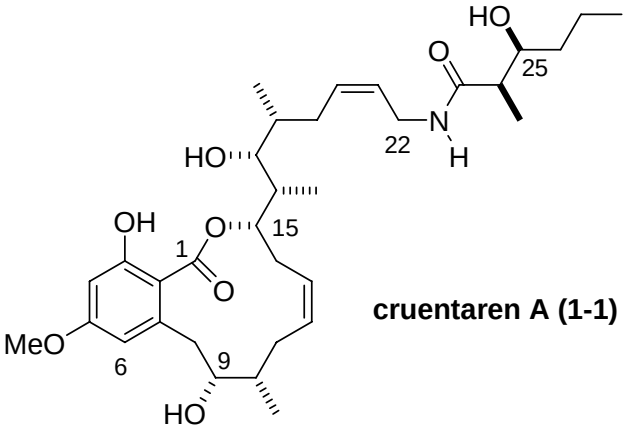



**Figure 1.** Structure of cruentaren A.

Since mitochondrial ATPases play a crucial role in the pathophysiology of several human disorders including cancer, selective inhibitors of such transport proteins constitute promising leads in the quest for novel chemotherapeutic agents.[12] It is therefore of considerable interest to evaluate the potential of cruentaren A in more detail.

The fascinating structure combined with the potent biological activity prompted us to embark on a total synthesis of cruentaren A. Clearly, it would be of interest to identify key structural elements that are essential for its unique biological activity. On the other hand, before we started this project there was no synthesis of this molecule reported in the literature. Therefore, the total synthesis of cruentaren A would prove the absolute configuration of all eight stereogenic centers.

The objective of our research was therefore aimed at the design of an efficient synthetic strategy, which would allow the total synthesis of cruentaren A itself, as well as other structural analogues of this novel natural product.

# 2 Literature Review

## 2.1 Biological Activity of Cruentaren A

The Gram-negative, fruiting body forming myxobacteria have emerged as a particularly rich source of secondary metabolites, which are characterized by a multitude of unrelated structures as well as by different biological activities with interesting mechanism of action.[13,14]

Recently, two novel metabolites, namely cruentaren A (**1-1**) and B (**2-1**), have been isolated from the myxobacterium *Byssovorax cruenta*. With an $IC_{50}$ value of 1.2 ng $mL^{-1}$ against the L929 cell line **1-1** is among the most cytotoxic compounds found in myxobacteria. Notably, the isomeric δ-lactone cruentaren B turned out to be essentially inactive. Initially, cruentaren A was patented as a pesticide[15] but in the meantime it turned out that it is an inhibitor of mitochondrial F-ATPase from yeast. Interestingly, it does not inhibit V-ATPase which is the molecular target of the benzolactone enamides.[11]

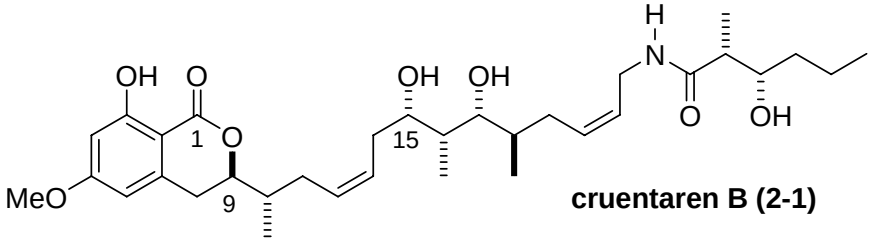



**Figure 2.** Structure of cruentaren B (**2-1**).

To explain the mode of action of cruentaren A, one should take a closer look at cell biology. As was mentioned previously, cruentaren A is a selective inhibitor of F-ATPase from the yeast. First we should consider the following questions: What is the role of F-ATPase? Why it is so important for living organisms?

F-ATPase is a transmembrane protein found in bacterial plasma membranes, mitochondrial inner membranes and in chloroplast thylakoid membranes. It uses a proton gradient to drive ATP synthesis by allowing the passive flux of protons across the membrane down their electrochemical gradient and using the energy released by the transport reaction to synthesize ATP from ADP and inorganic phosphate. In some bacteria, sodium ions may be used instead.

F-ATPase consists of two domains: $\mathbf{F_1}$, a peripheral enzyme complex which contains the catalytic activity of the synthase, and $\mathbf{F_O}$, an integral membrane protein complex (**Figure 3**). The $\mathbf{F_1}$ domain of the F-ATPase contains the binding sites for ATP and ADP and is involved in the catalytic reactions of the ATP synthesis. The $\mathbf{F_O}$ domain is embedded in the membrane

and provides a channel for the translocation of protons across the membrane. The **$F_1$** domain of F-ATPase functions as a rotary molecular motor: *in vitro* its γ-subunit rotates[16] against the surrounding $\alpha_3\beta_3$ subunits,[17] hydrolysing ATP in three separate catalytic sites on the β-subunits. It is widely believed that reverse rotation of the γ-subunit, driven by proton flow through the associated **$F_O$** domain of ATP synthase, leads to ATP synthesis in biological systems.[18]

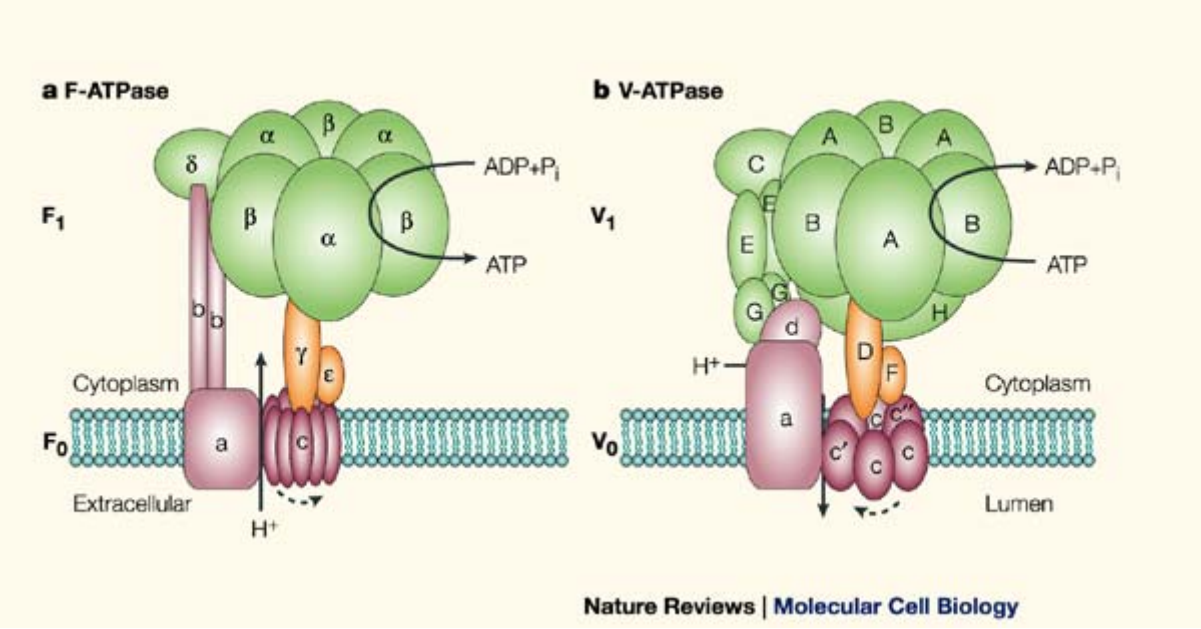



**Figure 3.** A schematic view of F- and V-ATP synthase (Nelson et al.[19])

Boyer proposed that the coupling between **$F_1$** and **$F_O$** domains is mechanical: **$F_O$** is a motor or turbine, driven by the proton flow, and **$F_1$** is another motor driven by ATP hydrolysis.[20] The two have a common shaft. Proton flow from bottom to top in **Figure 3** drives the shaft in the unique direction, say clockwise. ATP hydrolysis in **$F_1$** drives the shaft in the opposite direction, counterclockwise. When the free energy obtained from the downward flow of protons is greater than the free energy of ATP hydrolysis, the **$F_O$** motor rotates the common shaft in its genuine direction. The **$F_1$** motor is forced to rotate in its reverse direction, and thus ATP synthesized in its catalytic sites. If the energy obtained from ATP hydrolysis is higher, the **$F_1$** motor gains control and protons are pumped out. Boyer's idea came from the analysis of the chemical reaction in the **$F_1$** part. The **$F_1$** portion can be isolated in solution, and then it only hydrolyses ATP. Hence, the isolated enzyme is called **$F_1$-ATPase**. The **$F_1$-ATPase** consists of five types of subunits in the stoichiometry of $\alpha_3\beta_3\gamma\delta\varepsilon$. $\alpha_3\beta_3\gamma$-subunits suffice for ATPase activity and for rotation. Each β-subunit contributes one catalytic site for the synthesis – hydrolysis of ATP (the catalytic site resides at the interface between a β-subunit and a α-subunit, and is in part contributed from residue of α). It was found that the three

catalytic sites are completely equivalent in steady-state ATP hydrolysis by **$F_1$-ATPase** or in steady-state ATP synthesis – hydrolysis by the whole ATP synthase.

As the protons bind to the subunits of the **$F_O$** domains they cause parts of it to rotate. This rotation is propagated by a common shaft to the **$F_1$** domain. ADP and $P_i$ (inorganic phosphate) bind spontaneously to the three β subunits of the **$F_1$** domain, so that every time it goes through a 120° rotation ATP is released. This can be explained with *binding – change mechanism* for proton driven ATP synthesis, which was proposed by Boyer. This proposal states that changes in the properties of the three subunits allow sequential ADP and $P_i$ binding, ATP synthesis, and ATP release.

One of the well known inhibitors of F-ATPase is the natural antibiotic oligomycin. It blocks the synthesis of ATP by preventing the movement of protons through the **$F_O$** domain of ATP synthase.[21] It is primarily found to act as an inhibitor of mitochondrial respiration and swelling. This antibiotic is widely used as an inhibitor of oxidative phosphorylation.[22] Because of its activity, it can also be used to reduce the number of parameters (such as ER $Ca^{2+}$ release, exocytotoxicity and apoptosis) which are affected by mitochondrial depolarization.[23]

Recently Juan et al. performed a proteomic analysis on human breast carcinoma tissues to investigate the tumor-specific protein expression in breast carcinoma.[24] It was shown that ATP synthase was up-regulated in tumor tissues and was present on the plasma membrane of breast cancer cells. Furthermore, the breast cancer cells were treated with ATP synthase inhibitors and the inhibitory efficiency was examined. Aurovertin B, an ATP synthase inhibitor, was proved to have strong inhibition on the proliferation of several breast cancer cell lines, but little influence on the normal cell line MCF-10A. It was shown that aurovertin B inhibits proliferation of breast cancer cells by inducing apoptosis and arresting cell cycle at the $G_0/G_1$ phase and can be used as an antitumorigenic agent as well as may be exploited in cancer chemotherapy.

In a recent publication of Kunze et al.[25] it was shown that cruentaren A inhibits mitochondrial F-ATPases by targeting the catalytic **$F_1$**-domain and not via interaction with the membrane bound **$F_O$**-domain. As one can see from the **Table 1**, in contrast to cruentaren A, the **$F_O$**-targeting inhibitor oligomycin did not affect the **$F_1$**-ATPase activity.

**Table 1.** Inhibition of **$F_1$** ATPase solubilized from submitochondrial particles[25]

| Compound | Relative activity (%) | |
|---|---|---|
| | Beef heart | *S. cerevisiae* |
| Control without inhibitors | 100 | 100 |

| | | |
|---|---|---|
| Oligomycin 1 µM | 99.1±0.1 | 94.0±2.0 |
| Cruentaren A 1 µM | 3.3±0.8 | 3.0±0.7 |
| Cruentaren A 0.1 µM | 10.0±0.5 | 10.3±0.7 |

Inhibitory efficacy of cruentaren A was also tested on the V-ATPase and $Na^+/K^+$-ATPase. The latter belongs to the family of P-ATPase and is responsible for the preservation of $Na^+$ gradients across the plasma membrane. But even at a concentration of 1 µM in both cases no inhibition was observed.

This outcome seems surprising in view of the effect of the related benzolactone enamides which operate on V-ATPases via the $\mathbf{V_O}$-complex. However, in spite of their planar structural similarity, conformation and spatial arrangement of functional groups are quite different, as has been shown by X-ray crystal structure analyses of apicularen A and cruentaren A. From this point of view it is conceivable that these compounds interact with different binding sites in related proteins.

Furthermore, it turned out that cruentaren A inhibits the mitochondrial $\mathbf{F_1}$-ATPase from two evolutionarily rather distant eukaryotic organisms such as yeast and mammal but does not inhibit the $\mathbf{F_1}$-ATPase from *Escherichia coli*. Thus, one can speculate that it binds to the $\mathbf{F_1}$ subunit ε which has no bacterial counterpart.[26]

In addition, cruentaren A was checked for its impact on the growth of a variety of human cancer cell lines from different tissues (**Table 2**). The $IC_{50}$ values were comparable with those described for other benzolactones such as apicularen A[27] in the nanomolar range, even for the multi-drug-resistant cell line KB-V1.

**Table 2.** Growth inhibition of different human cancer lines by cruentaren A and apicularen[25]

| Cell line | Origin | $IC_{50}$ (ng/ml) | |
|---|---|---|---|
| | | **Cruentaren A** | **Apicularen A** |
| **KB-3-1** | Cervix carcinoma | 0.3 | 1.0 |
| **KB-V1** | Multi-drug resistant KB line | 0.6 | 10 |
| **K-562** | Chronic myelogenous leukemia | 0.6 | 1.0 |
| **U-937** | Histiocytic carcinoma | 0.1 | 1.5 |
| **A-549** | Lung carcinoma | 0.4 | 0.1 |
| **SK-V-3** | Ovarian carcinoma | 1.0 | 1.5 |
| **A-498** | Kidney carcinoma | 0.4 | 0.3 |

Despite the fact that the exact binding site of cruentaren A remains undefined, the described results substantiate, that this unique benzolactone is the most potential inhibitor of mitochondrial $\mathbf{F_1}$-ATPases. Thus, future understanding of the interaction of cruentaren A with

its binding side may provide irreplaceable knowledge for the rational development of therapeutic agents for cancer treatment.

## 2.2 Synthesis of Cruentaren A by Fürstner

One should mention that the first total synthesis of cruentaren A was developed in our group, featuring a ring-closing alkyne metathesis and double Lindlar reduction.[28] Recently, another RCAM based synthesis of cruentaren A was achieved by the Fürstner group.[29] Similar to our approach they decided to divide the molecule into two main subunits, functionalized benzoic acid **2-2** and an aliphatic fragment containing a stereotetrad (**2-3**) (**Figure 4**).

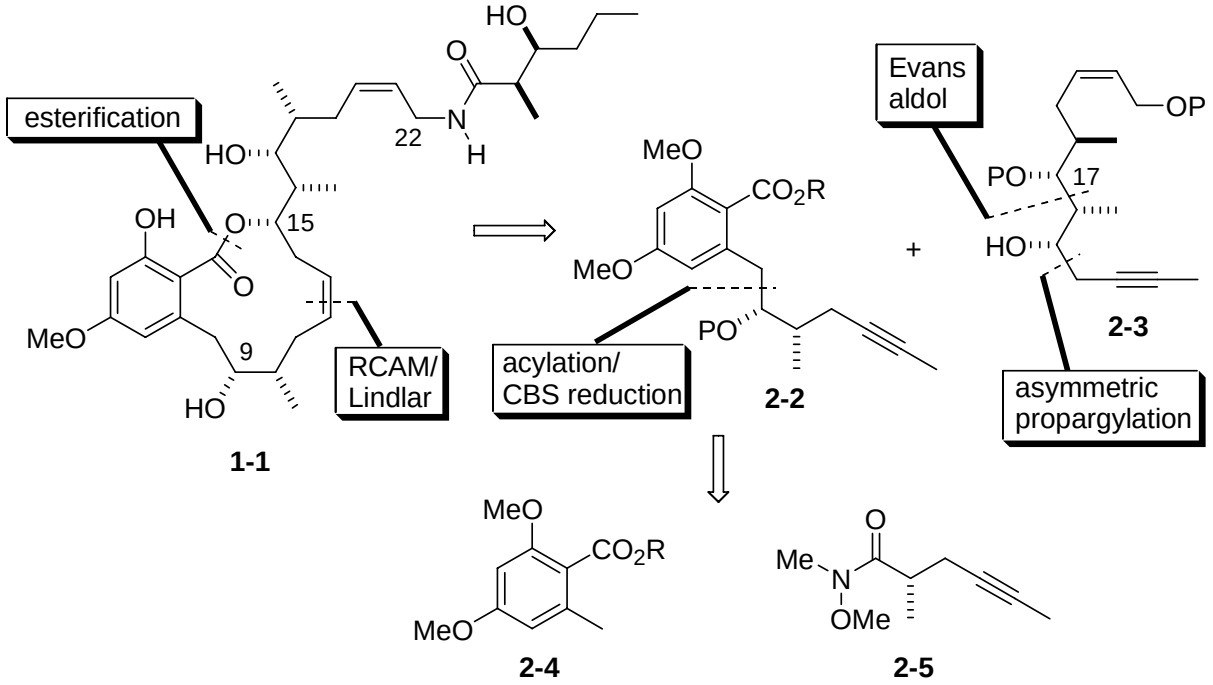
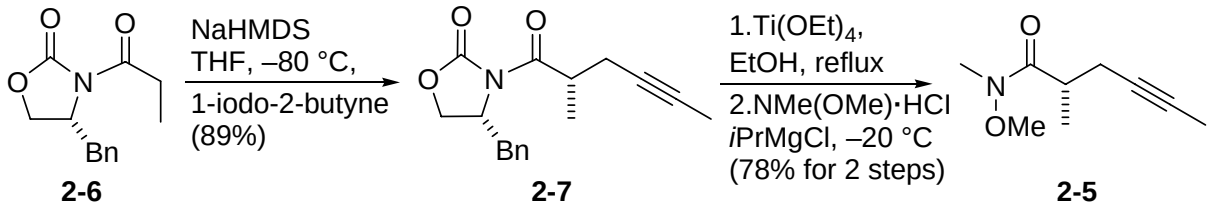
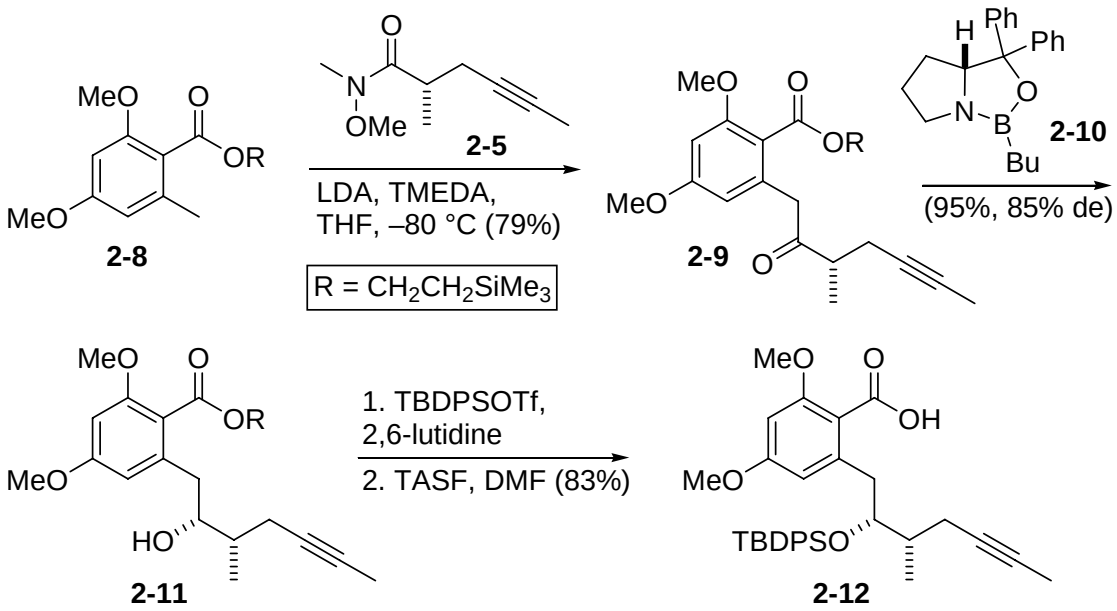



**Figure 4**. Key retrosynthetic cuts for cruentaren A by Fürstner and co-workers.[29]

Synthesis of fragment **2-2** started from silicon protected benzoic acid **2-8**, which was acylated with Weinreb amide **2-5** via the corresponding benzyllithium derivative (**Scheme 2**). A subsequent Corey-Bakshi-Shibata (CBS) reduction afforded alcohol **2-11** in 95% yield but with relatively low diastereomeric purity (*de* 85%). Next, protection of the secondary hydroxyl function, followed by selective cleavage of the trimethylsilylethyl ester furnished acid **2-12** in 83% overall yield. The synthesis of Weinreb amide **2-5** commenced with the alkylation of **2-6** with 1-iodo-2-butyne. Removal of the oxazolidinone auxiliary and coupling of the obtained acid with N,O-dimethylhydroxylamine completed the synthesis of amide **2-5**.

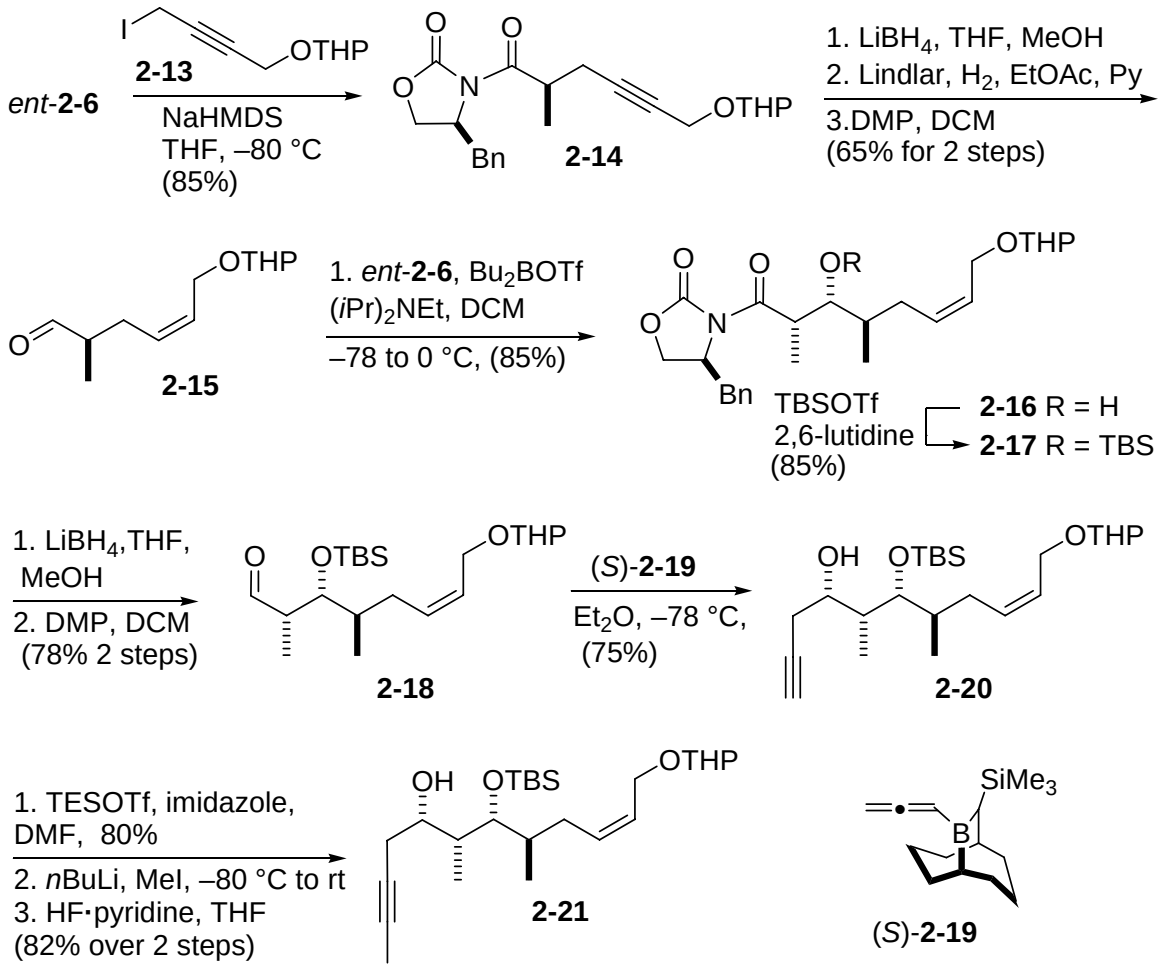



**Scheme 1.** Synthesis of Weinreb amide **2-5**.




**Scheme 2.** Synthesis of acid **2-12**.

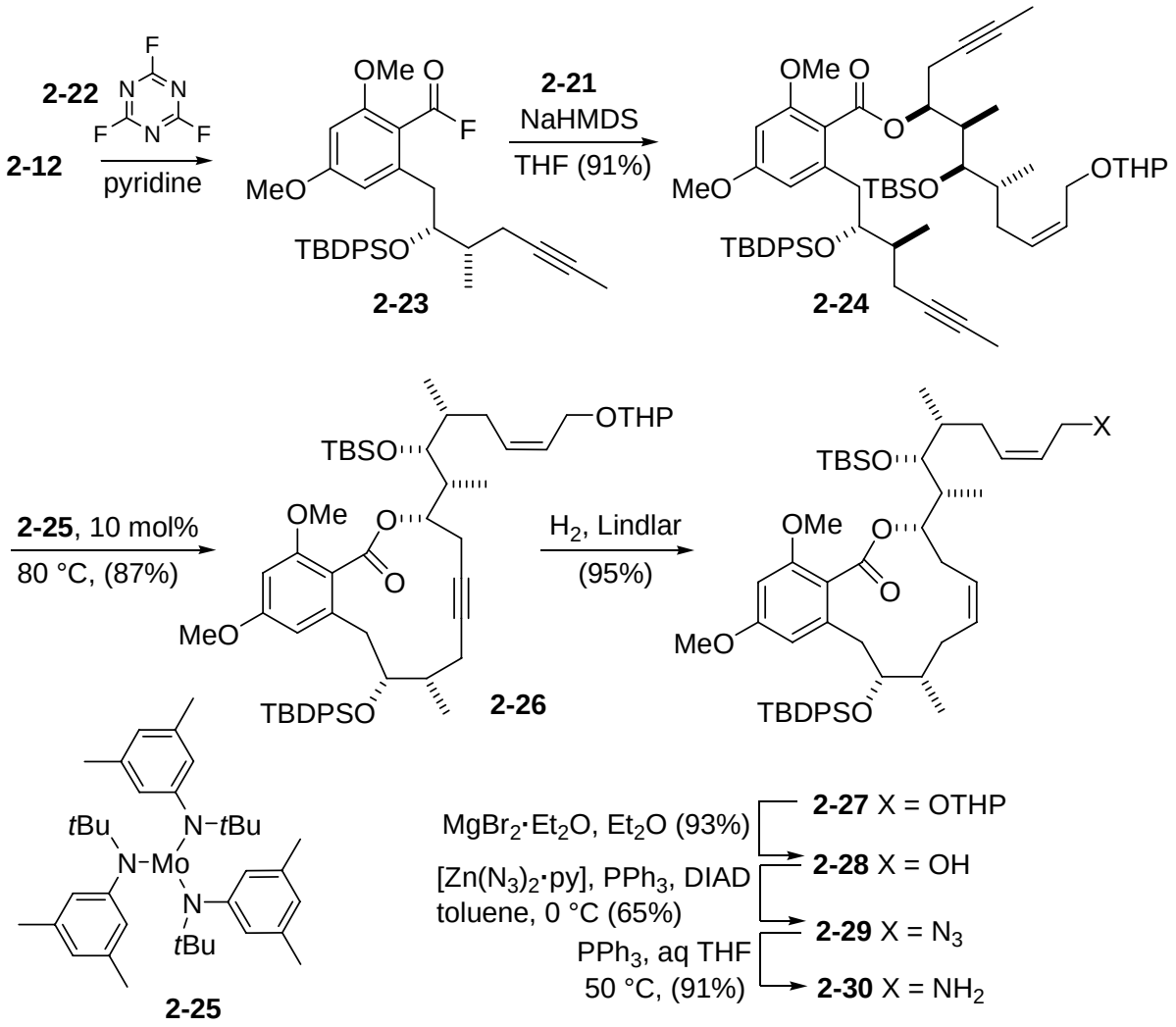
In a similar way for the introduction of the C18 methyl group they relied on the alkylation of *ent*-**2-6** with propargyl iodide **2-13** (**Scheme 3**). Reductive cleavage of auxiliary, followed by Lindlar reduction and Dess-Martin oxidation furnished aldehyde **2-15**. Subjection of the latter to an Evans aldol reaction gave adduct **2-16** in good overall yield and high selectivity (≥96% *de*). Simple transformations, namely TBS-protection, cleavage of oxazolidinone auxiliary and Dess-Martin oxidation secured aldehyde **2-18**. The last stereocenter was introduced using asymmetric propargylation methodology recently developed by Soderquist and co-workers.[30]




**Scheme 3.** Synthesis of alcohol **2-21**.

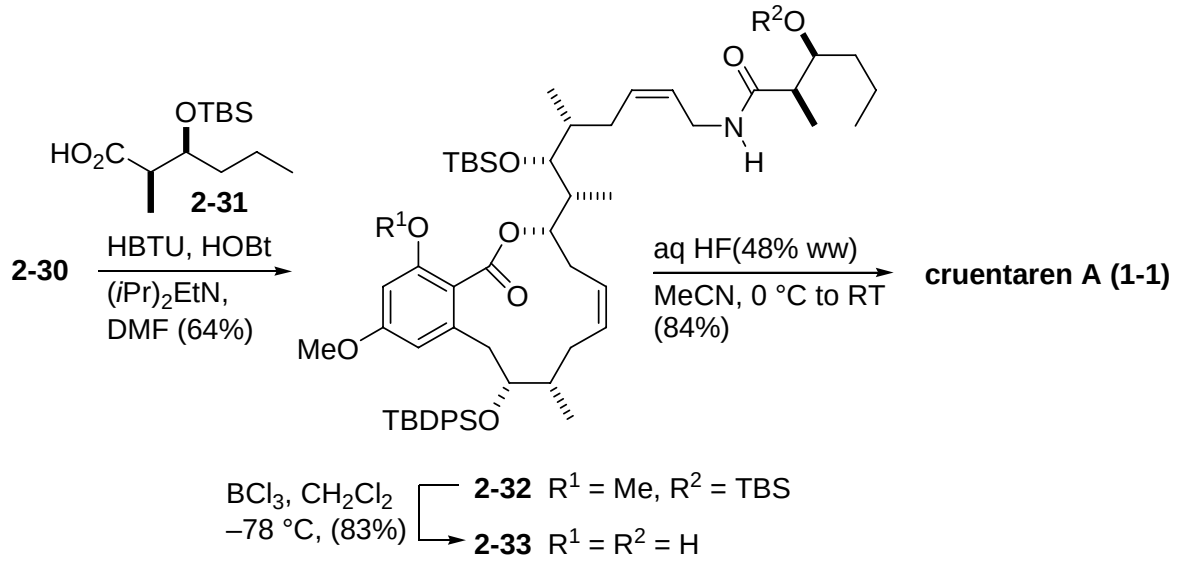
Exposure of aldehyde **2-18** to enantiopure allenylborane (*S*)-**2-19** afforded propargyl alcohol **2-20** in 75% yield and greater than 95% *de*. TES protection of the obtained hydroxyl function, followed by deprotonation of the terminal alkyne and subsequent treatment with methyl iodide established internal an alkyne fragment, required for RCAM reaction. Finally, selective TES deprotection mediated by HF·pyridine complex secured desired alcohol **2-21**.

After numerous attempts to couple acid **2-12** with alcohol **2-21**, it was finally found that the desired ester can be obtained by reacting the sodium alcoholate derived from **2-21** with acid fluoride **2-23** (**Scheme 4**). The latter was best prepared by treatment of **2-12** with 2,4,6-trifluoro-1,3,5-triazene (**2-22**) and pyridine. Ring closing of ester **2-24** was performed using the molybdenum complex **2-25**, activated in situ by $CH_2Cl_2$. This key transformation proceeded smoothly and provided cycloalkyne **2-26** in excellent yield. Lindlar reduction, followed by THP ether deprotection, azide group introduction under Mitsunobu conditions and subsequent Staudinger reduction furnished amine **2-30** in respectable overall yield.




**Scheme 4.** Synthesis of amine **2-30**.

After coupling of amine **2-30** with acid **2-31**, treatment of the obtained fully protected cruentaren A (**2-32**) with $BCl_3$ led to selective cleavage of the C3 methyl ether as well as removal of the TBS ether in the amide portion of the molecule (**Scheme 5**). Deprotection of the two remaining silicon groups turned out to be rather difficult. The use of standard fluorine sources met with failure (TBAF with or without HOAc or $NH_4Cl$; TASF/DMF, DMA or MeCN; HF·pyridine). This can be attributed to the tendency of the 9-OH group to engage in translactonization, which leads to cruentaren B. Finally, it was found that the crucial deprotection can be achived by using aqueous HF ($pK_a \approx 3.14$) in MeCN. This secured cruentaren A in 84% yield.




**Scheme 5.** Completion the synthesis of cruentaren A (**1-1**).

Although Fürstner and co-workers achieved a quite convergent synthesis of cruentaren A with 21 steps in the longest linear sequence, the final compound was obtained in only 3% overall yield. This can be attributed to the fact that in the final stage of the synthesis some steps turned out to be less efficient (transformation to azide 65%, amide coupling 64%).

In addition, a total synthesis of essentially inactive δ-lactone cruentaren B was recently reported by Chakraborty.[31] As key reactions for the establishment of chiral centers of the stereotetrad Mukaiyma and Evans aldol reaction were used. To fashion the *anti*-OH/Me pattern at C9/C10 a Brown's asymmetric crotylboration came to use. For the creation of the C7-C8 bond they relied on a Stille coupling reaction. Required *Z*-allylamide fragment was attached using a Wittig olefination.

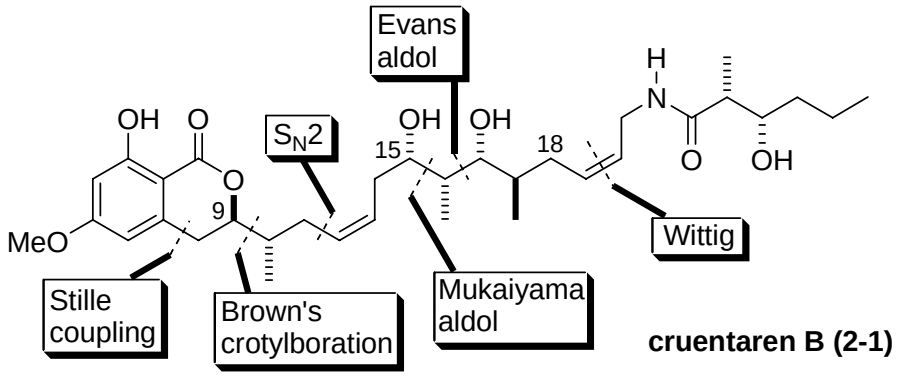



**Figure 5.** Retrosynthetic analysis of cruentaren B by Chakraborty.

Developed synthesis consists of 26 linear steps and provides cruentaren B in 7.1% overall yield.

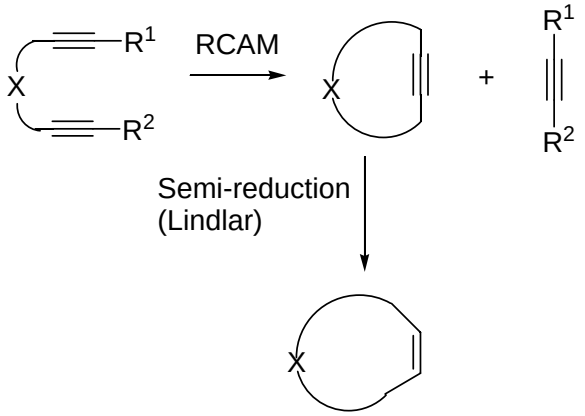
## 2.3 Key Reactions and its Mechanisms

For the synthesis of such complex molecules as cruentaren A one would need to apply a broad spectrum of well established and modern synthetic methodologies. Therefore, an overview of the most important reactions used for our cruentaren A synthesis is provided below. Since it is not possible to describe every method in detail in this thesis, for each reaction only the general information and the most representative examples of application are given.

### 2.3.1 Ring closing alkyne metathesis

Among the few limitations that infringe upon the superb overall application profile of ring-closing olefin metathesis (RCM), the lack of control over the configuration of the newly formed double bond constitutes a significant handicap when applied to macrocyclic systems.[32] The cycloalkenes formed are usually obtained as mixtures of *E* and *Z* isomers, with the *E* isomers dominating in most of the recorded examples. This constitutes a significant drawback in many natural product syntheses as can be clearly seen, for example in the epothilone case.[33]

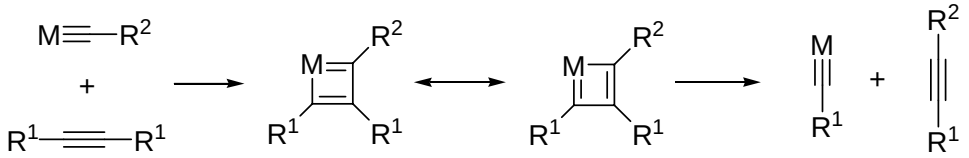
To avoid this inherent problem, recently a stereoselective approach to macrocyclic *Z* alkenes which comprises a ring-closing metathesis reaction of diyne substrates followed by semi-reduction of the resulting cycloalkyne products was proposed by Fürstner (**Scheme 6**).[34] The nature of the process allows for similar retrosynthetic logic as with RCM to be applied whilst having the additional benefit of introducing a predictable component for stereocontrol.




**Scheme 6.** Z-selective approach to macrocyclic systems using a RCAM/semi-reduction sequence.

Alkyne metathesis refers to the mutual exchange of the alkylidyne units between a pair of (non-terminal) acetylene derivatives. Whilst the nature of the catalytically active species formed *in situ* from suitable precursors remained elusive, Katz et al. proposed that metal carbynes likely account for the catalytic turnover in a sequence of formal [2+2] cycloaddition and

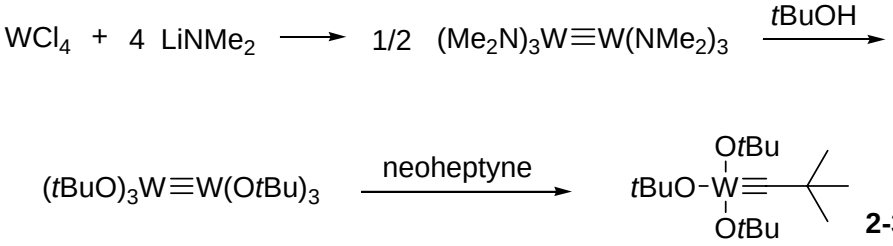
cycloreversion steps (**Scheme 7**).[35] The proposed mechanism was later experimentally proven by Schrock using high valent metal alkylidynes.[36] As additional proof of this theory was isolation and characterization of several intermediate metallacyclobutadiene complexes formed by [2+2] cycloaddition of alkylidynes and alkynes.[37]



**Scheme 7.** Mechanism of alkyne metathesis.

The first effective catalyst for alkyne metathesis was found by Mortreux et al.[38] It was shown that the desired transformation is effected by a homogenous mixture of $Mo(CO)_6$ (or related molybdenum sources) and simple phenol additives heated in high boiling solvents. The most widely used phenols for 'instant' activation of $Mo(CO)_6$ are 4-chlorophenol and 4-trifluormethylphenol. The simplicity and user-friendly nature of this catalyst system is offset somewhat by its rather limited tolerance of polar functional groups and the elevated temperatures (ca. 140–150 °C) required for initiating and maintaining catalytic activity. Recently, Grela et al. identified 2-fluorophenol and 2-fluoro-5-methylphenol as the optimal additives in various alkyne metatheses.[39]

A major breakthrough in rational catalyst design for alkyne metathesis came with the development of well-defined tungsten alkylidyne complexes by the Schrock group, of which catalyst $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$ (**2-34**) is the most widely used.[40] It operates under fairly mild conditions, sometimes ambient temperature, effecting up to several hundred catalytic turnovers per minute. Although complex **2-34** has recently been made commercially available, it can be efficiently prepared in large scale from $(t\text{BuO})_3\text{W}{\equiv}\text{W}(\text{O}t\text{Bu})_3$ and neoheptyne (**Scheme 8**).[41]

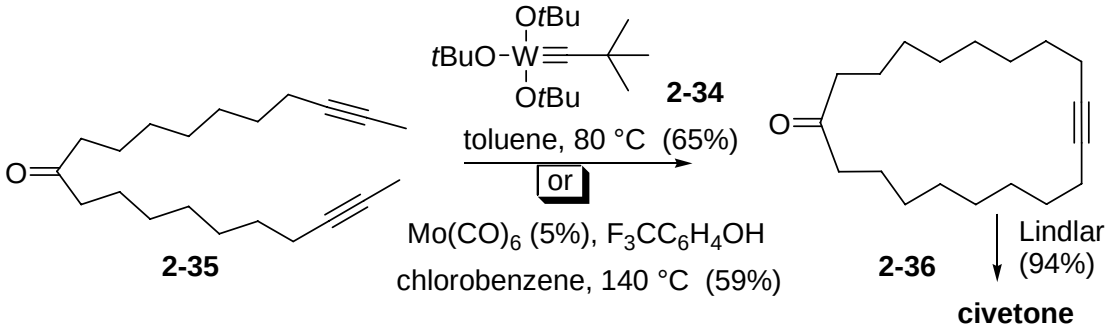


**Scheme 8.** Scaleable preparation of the tungsten alkylidyne complex **2-34**.

The first application of catalyst **2-34** in the synthesis of functionalized macrocycles was reported by Fürstner.[34b] It was shown that utilizing catalyst **2-34** cyclic products with ring sizes 12 or greater can be obtained in good to excellent yield. Moreover, ether, ester, enoate, amide, silyl ether, sulfonamide, carbamate and sulfone functionalities were accommodated in the

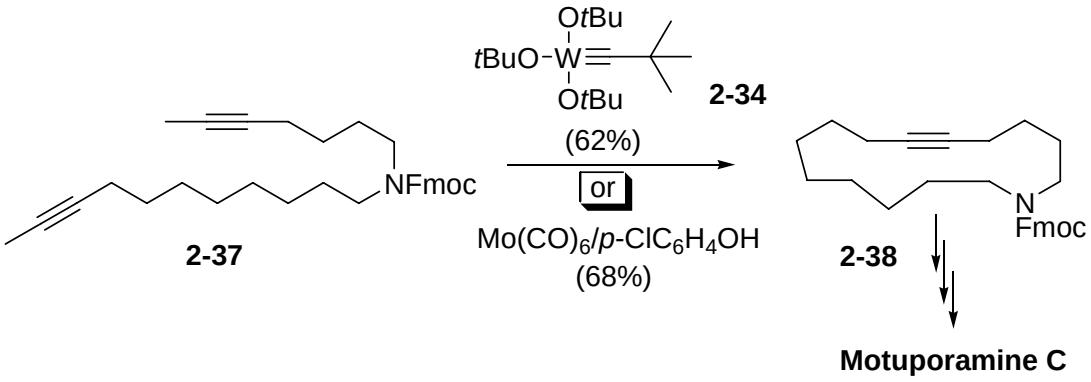
RCAM process catalysed by complex **2-34**.[34c] It should be noted, that due to incompatibility of terminal alkynes with catalyst **2-34** end-caped substrates with R = Me, Et are necessary for successful cyclization. At first RCAM was successfully employed in the synthesis of olfactory molecules: civetone, ambrettolide and yuzu lactone.

RCAM of the acyclic diyne **2-35** at 80 °C with catalyst **2-34** afforded the desired cycloalkyne **2-36** in good yield (**Scheme 9**). Subsequent Lindlar reduction furnished the valuable fragrance civetone.[42] Interestingly, the carbonyl functions of the starting material and product are kinetically inert toward the tungsten alkylidyne. Furthermore it was shown that *in situ* generated catalyst from a $Mo(CO)_6$/4-trifluormethylphenol mixture was also effective in metathesis reaction.



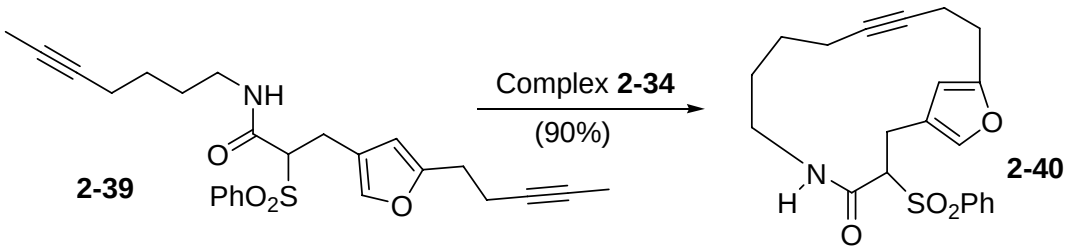

**Scheme 9.** Stereoselective synthesis of civetone by Fürstner et al.[42]

Other representative examples of utilization of RCAM are the syntheses of the insect repellent alkaloid epilachnene and the cytotoxic sponge extract motuporamine C[43] where the key ring closing could be achieved using either **2-34** or the '*in situ*' Mortreux system (**Scheme 10**).



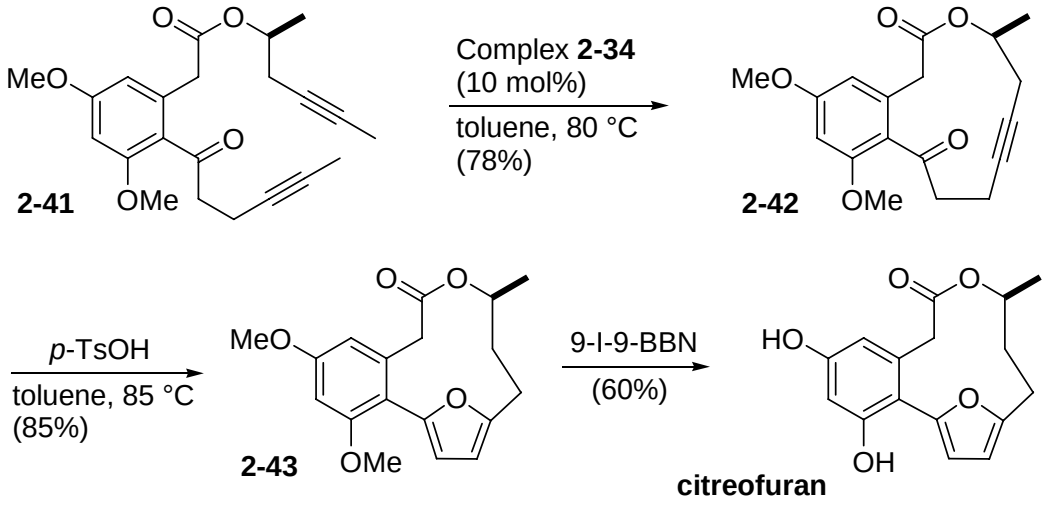

**Scheme 10.** Stereoselective synthesis of motuporamine C by Fürstner et al.[43]

During the Fürstner synthesis of nakadomarin A it was shown that the rather labile furan moiety could be tolerated along with the sulfone and amide group under the reaction conditions (**Scheme 11**).[34c]



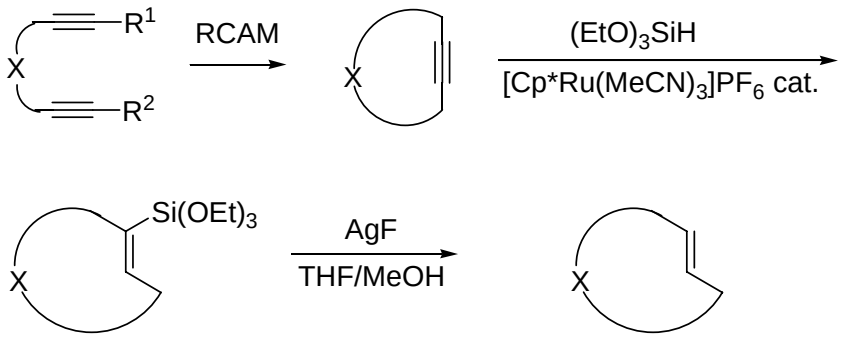

**Scheme 11.** Synthesis of the macrocyclic perimeter of nakadomarin A by Fürstner et al.[34c]

A very interesting application for RCAM was found during the elegant synthesis of citreofuran,[44] which belongs to the curvularin family of natural products. As is shown in **Scheme 12**, the readily prepared diyne **2-41** underwent smooth macrocyclization within 1 hour upon the addition of catalyst **2-34** (10 mol%) to a solution of substrate in toluene at 85 °C to afford 12-membered benzolactone **2-42** in 78% yield. The relative ease of this cyclization is likely to be due to the presence of the preexisting aromatic ring, which restricts the conformational degrees of freedom available to the starting material **2-41**. Treatment of **2-42** under acidic conditions initiated a transannular cycloaromatization that led to the formation of the furan **2-43**. Subsequent cleavage of both methyl ethers completed this concise synthesis of citreofuran.




**Scheme 12.** Total synthesis of citreofuran by Fürstner et al.[44]

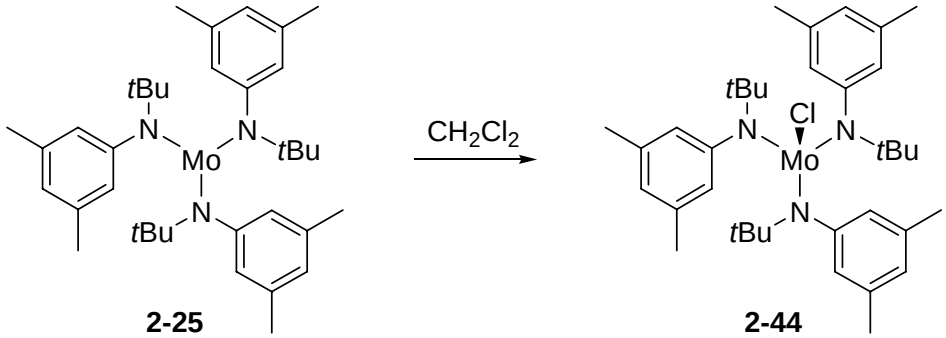
It is important also to recall the recent development of novel methodology for the conversion of alkynes into the corresponding *E*-alkene systems. A general and mild procedure based on a hydrosilylation/protodesilylation strategy was independently developed in both the Trost group, for acyclic substrates[45], and Fürstner group with cyclic systems.[46] The use of the cationic ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ and $(EtO)_3SiH$ for hydrosilylation of the alkynes affords a highly chemo- and streoselective *trans* addition in decent to excellent yields with good compatibility with a host of functional groups (**Scheme 13**).[47]




**Scheme 13.** Stereoselective synthesis of macrocyclic alkenes *via* RCAM followed by *trans*-selective hydrosilylation and protodesilylation.

It was shown that the use of AgF led to rapid, quantitative and selective desilylation under mild conditions without damaging the configurational integrity of the double bond. AgF can also be used in sub-stoichiometric amounts (2–20%) provided that TBAF is added to the medium as a stoichiometric fluoride source. The overall set of conditions holds promise for the application of this three step sequence to complex molecules.

Recently, the Fürstner group introduced the monochloro molybdenum complex **2-44** as a powerful precatalyst for alkyne metathesis. **2-44** is conveniently formed *in situ* by the activation of the corresponding trisamido complex **2-25** with $CH_2Cl_2$ as a chlorine source (**Scheme 14**).[48] Notably, another halogen sources ($CHCl_3$, $CCl_4$, $CH_2Br_2$, $CH_2I_2$, $C_6H_5CHCl_2$, $C_6H_5CH_2Cl$, $Me_3SiCl$) were successfully used for the activation of **2-25** in order to form metathesis active components.[48a]



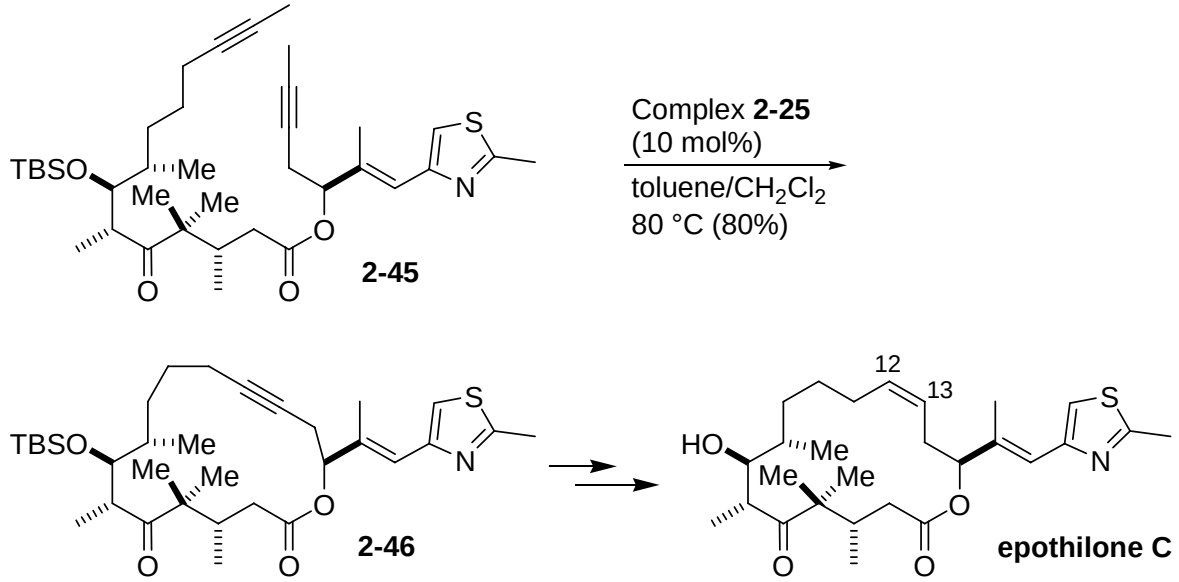

**Scheme 14.** Activation of the molybdenum trisamido complex **2-25** to form metathesis active component **2-44**.

Importantly, this system not only effects the formation of macrocyclic cycloalkynes of different ring sizes (12–26 membered) but also tolerates functional groups which completely shut down the catalytic activity of the tungsten alkylidyne catalyst **2-34**. Thus thioethers, basic nitrogen atoms and polyether chains survive conditions of the metathesis reaction. As a representative example one can mention the critical ring-closing step in the course of the total synthesis of cruentaren A,[29] where the utilization of catalyst **2-34** led only to the cleavage of

the terminal THP acetal without inducing the macrolactone formation. In contrast to this unsuccessful attempt, the use of the molybdenum complex **2-44** activated *in situ* by $CH_2Cl_2$ secured desired cycloalkyne in excellent yield.

Similarly to complex **2-34**, **2-25** is also compatible with a broad spectrum of functional groups (ester, isolated double bonds, silyl ethers, sulfones, aldehydes, nitro groups, ketones, alkyl chlorides, acetals and nitriles). However, 'acidic protons' such as those of secondary amides, which are tolerated by **2-34**, could not be endured by catalyst **2-25**, whereas tertiary amides are fully compatible. The enhanced functional group tolerance of **2-25** can be attributed to the big sterical demands of the molybdenum atom, preventing coordination of potential donor substrates onto the catalytically active template.

In addition, this newly developed catalytic system **2-25** along with Lindlar reduction was efficiently applied for the stereoselective construction of the C12–C13 double bond of epothilone C. Fürstner and co-workers found that the desired macrocyclization could be affected in a pleasing 80% yield by treatment of substrate **2-45** with the trisamido molybdenum catalyst precursor **2-25** (10 mol%) in a toluene/$CH_2Cl_2$ solvent mixture at 80 °C for 8 h (**Scheme 15**).[49] A subsequent Lindlar hydrogenation of the cycloalkyne established the required *Z* double bond.




**Scheme 15.** RCAM in the total synthesis of epothilone C.

Notably, the catalyst **2-25** rigorously distinguishes between the (reactive) alkyne moieties and the preexisting double bond of the precursor **2-45**. Thus, a useful feature of alkyne metathesis is that alkene systems are generally inert toward the catalyst. The particular choice of the catalyst system in this case was important, owing to its tolerance of both the sulfur and basic

nitrogen atoms of the thiazole ring, the presence of which would have been deleterious to the use of the Schrock catalyst **2-34**.

In conclusion, alkyne metathesis provides a widely applicable technology for the creation of alkyne system which thereafter can be used as branching set point for subsequent selective manipulations. In particular, the combination of alkyne ring-closing metathesis followed by stereoselective partial reduction of the triple bond offers an efficient, though indirect, method for the mild preparation of macrocyclic alkenes of well-defined *E* or *Z* stereochemistry. Application of classical tungsten alkylidyne complex **2-34** along with recently developed molybdenum trisamido precatalytic system **2-25** allows alkyne metathesis of highly functionalized substrates under mild conditions.

### 2.3.2 Evans aldol reaction

The aldol structural motif is one of the most frequently appearing in many natural products, especially in polyketides, from which many pharmaceuticals are derived, including the potent immunosuppressant FK506, the tetracycline antibiotics, and the antifungal agent amphotericin B. Extensive research on the aldol reaction has produced highly efficient methods which enable the otherwise challenging synthesis of molecules with complex architecture.

The directed aldol reaction is widely recognized as one of the most powerful carbon – carbon bond forming reaction available for the regio-, diastereo-, and enantioselective construction of complex intermediates.[50] The utility of the asymmetric aldol addition has been amply demonstrated through a multitude of synthetic application.[51] Despite recent advances in organocatalytic routes to asymmetric aldol reactions,[52] auxiliary based approaches remain steadfast as a principle means to achieve high yields of aldol adducts with reliably high stereocontrol. In addition, dibutylboron enolates of N-acyl oxazolidinones, pioneered by Evans, are the most commonly utilized enolates and are highly effective for the preparation of Evans *syn* products in asymmetric aldol additions.

In theory, up to four different stereoisomers can be generated in aldol reactions since two new stereocenters can be created by the process. A major breakthrough in understanding the stereochemical outcome of aldol reactions came with the proposal of Zimmerman and Traxler, according to which some aldol reactions proceed through six-membered chair-like transition states. This statement is now well known as Zimmerman-Traxler model.[53]

The configuration of the aldol product strongly depends on the geometry of the boron enolates used in these reactions: *E*-enolates give *anti* aldols whereas *Z*-enolates give *syn* aldols. These results can be easily explained by the transition states shown in **Figure 6**. The aldol addition proceeds via a chairlike, six-membered transition state, which is more rigid than those of alkali metal enolates. This tight transition state arises from the shorter boron–oxygen bond, which maximizes the 1,3-diaxial interactions ($R^3 \leftrightarrow L$) in the transition state. This strong dependence of the configuration of the aldol adducts on the geometry of the enolates enables *syn*- as well as *anti*-configured aldols to be made as desired.

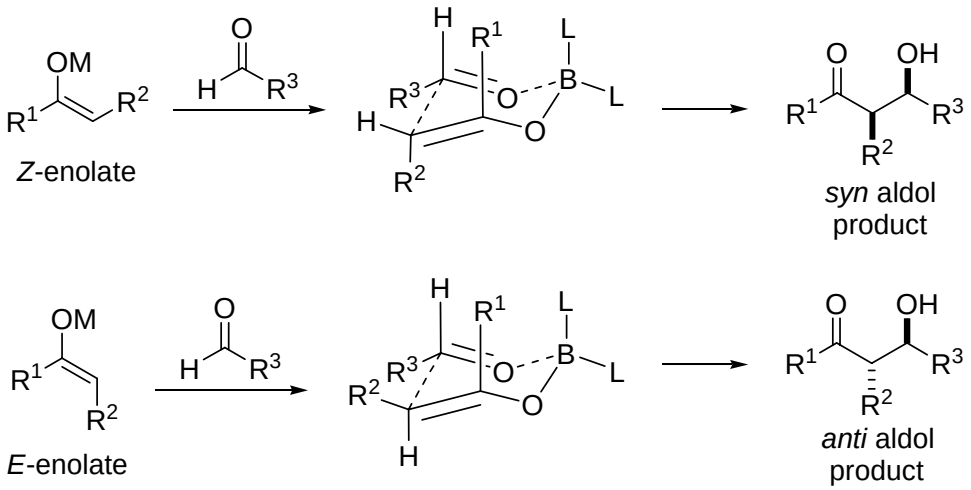



**Figure 6.** Aldol reactions of *Z*- and *E*-boron enolates with aldehydes.

The simplest and most common method for accomplishing asymmetric induction in any type of reaction is to utilize a chiral element within one of the reactants to direct its interaction with another. In 1981 Evans reported the application of *N*-acyl oxazolidinones as chiral auxiliaries for diastereoselective *syn* aldol reactions.[54] After pioneering, this strategy became a very important tool in the synthesis of a broad range of bioactive natural products. Since the acylated oxazolidinone is an imide, it can produce only *Z*-enolate upon treatment of dibutylboron triflate and a tertiary amine. As is known, boron forms a strong and short bond with oxygen and thus forms a tight six membered chair like transition state that leads to *syn* aldol adduct with high preference. Preferential formation of *syn* aldol arises from blockage of one side of the enolate by a bulky group in the oxazolidinone ring (**Figure 7**). In the reaction transition state, the carbonyl group of the oxazolidinone and the C–O bond of enolate arrange in an *anti* fashion to each other in order to minimize dipole-dipole repulsions. In this arrangement the aldehyde approaches the enolate from the less hindered side of the chiral auxiliary.

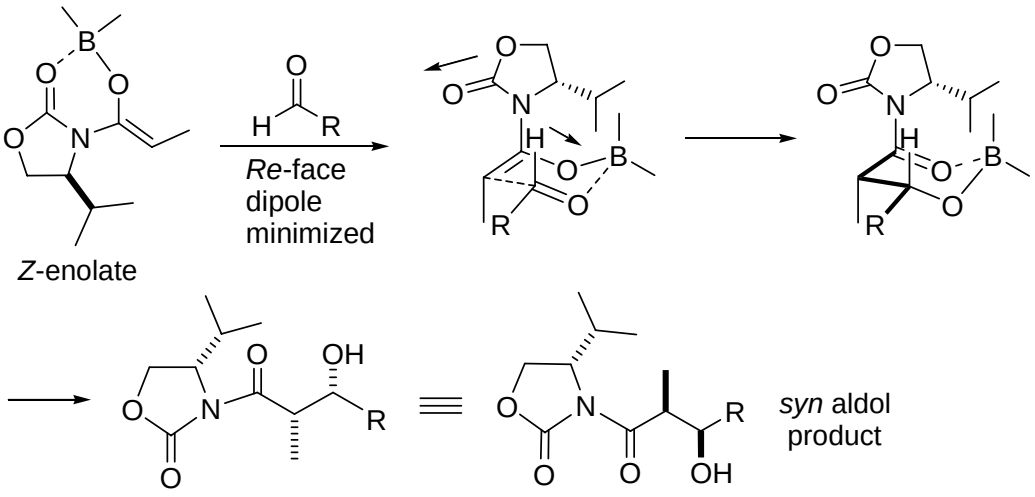



**Figure 7.** Favored transition state for Evans aldol reaction.

Extremely high diastereoselectivity (diastereomeric ratios up to 600:1 for matched cases and more then 20:1 for mismatched case with aldehydes bearing a stereogenic center at the α-position) and a broad spectrum of possible chemical transformation of obtained aldol adduct make this reaction an irreplaceable synthetic tool for modern organic synthesis. In order to increase the selectivity and simplify the procedure of purification of the obtained aldol adducts a huge number of oxazolidinones and thiazolidinethiones were prepared, most of which became commercially available in both enantiomeric forms (**Figure 8**).

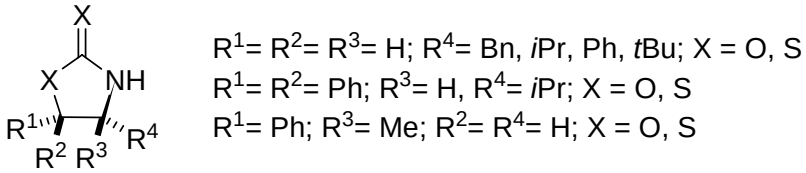
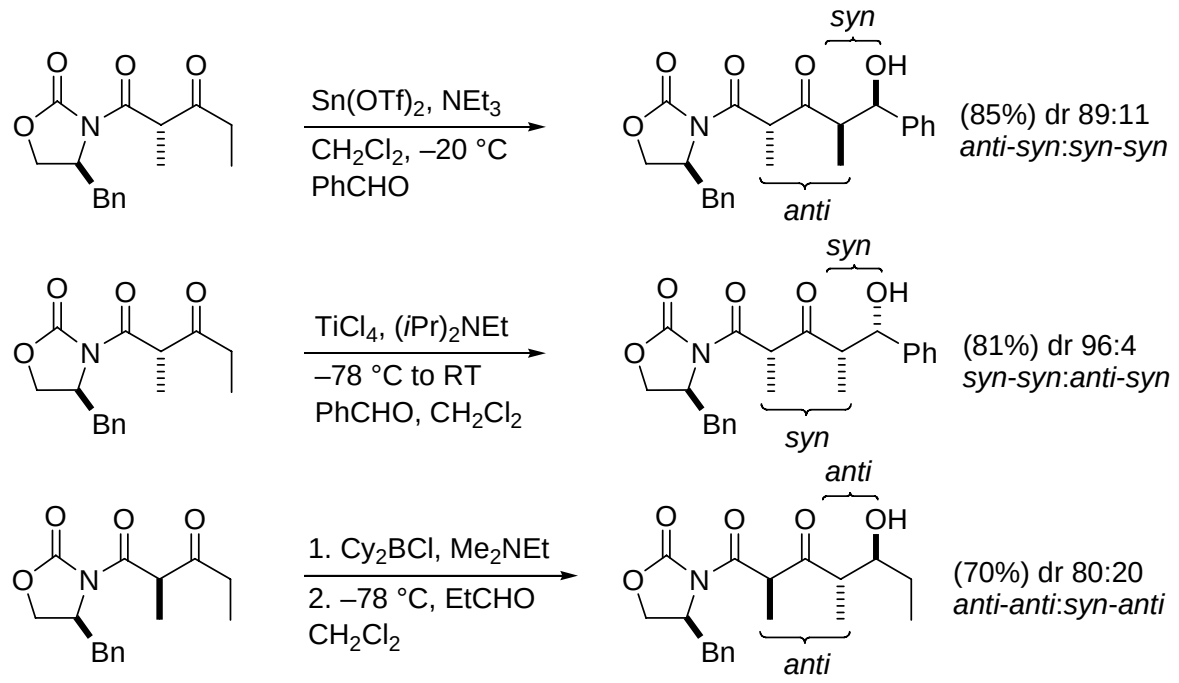



**Figure 8.** Structure of auxiliaries used for aldol reactions.

Due to its efficiency this methodology is widely used in the synthesis of polyketide natural products, and pharmaceuticals.[55] One of the first representative examples was a convergent synthesis of ionomycin[56] developed by Evans and co-workers. Other elegant applications of the boron enolate method can be found in the total synthesis of macrolide antibiotics rutamycin A,[57] cytovaricin,[51a] and macbecin.[58] The Novartis' large-scale synthesis of (+)-discodermolide showed that this reaction can be conducted in multigram amounts (up to 50 kg).

It is important to mention, that Evans efficiently extended his aldol methodology introducing a versatile approach to the assemblage of polypropionate systems. Depending on the Lewis acid used for β-keto imide enolisation one can assemble three of the four possible stereoarrays: *anti-syn*, *syn-syn*[59] and *anti-anti*[60] (**Scheme 16**).




**Scheme 16.** Application of Evans' extended aldol methodology.[59,60]

This approach was successfully applied by Smith and Brandt during the asymmetric synthesis of the potent cytotoxic agent (–)-callystatin A.[61]

One of the most important modifications of Evans' auxiliary was done by Crimmins and co-workers. It was shown that asymmetric aldol additions using chlortitanium enolates of *N*-acyloxazolidinone, oxazolidinethione, and thiazolidinethione propionates can proceed with high selectivity for the Evans or non-Evans *syn* product depending on the nature and amount of the base used to generate the enolates.[62] The change in facial selectivity in the aldol additions was proposed to be a result of switching of mechanistic pathways between chelated and nonchelated transition states. The reaction with boron enolates proceeds via the non-chelated transition state **2-49** and provides 'Evans' *syn* adducts **2-50**. However, the use of titanium tetrachloride for the enolisation allows the formation of the chelated transition state **2-51**, which leads to 'non Evans' *syn* adducts **2-52**.

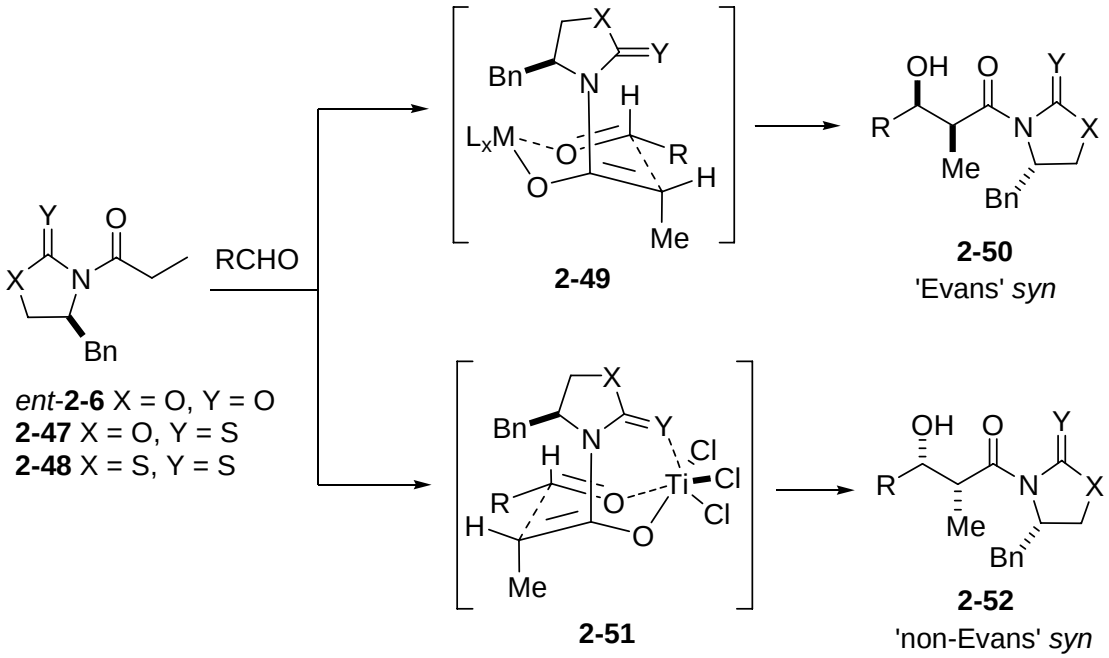


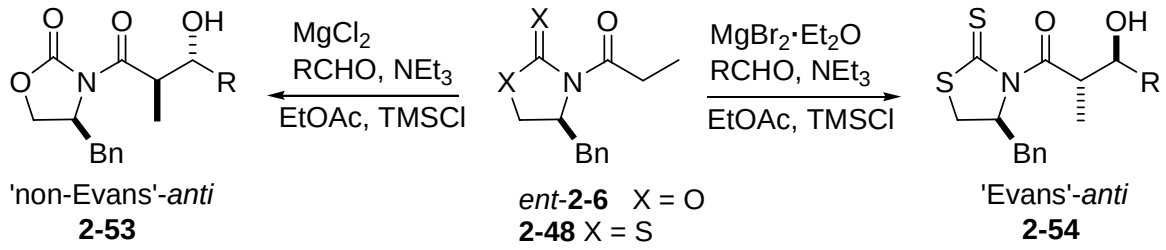

**Figure 9.** Non-chelated (**2-49**) and chelated (**2-51**) transition states in the asymmetric aldol addition using chlortitanium enolates of *N*-acyloxazolidinone, *N*-acyloxazolidinethiones and thiazolidinethiones.

The obtained experimental results were in full accordance with the proposed mechanism. The Evans *syn* products were obtained, via the non-chelated transition state **2-49**, when titanium enolates were formed in the presence of two equivalents of (–)-sparteine. It can be attributed to the coordination of second equivalent of amine to the metal center which prevents further coordination of the imide or thioimide carbonyl to the titanium. However, using only one equivalent of amine in the enolisation step resulted in preferential formation of non-Evans *syn* products. In this case the imide carbonyl or the thiocarbonyl coordinated to the metal center to produce the highly ordered chelated transition state **2-51**. Coordination of the imide carbonyl or thiocarbonyl to the metal center led to reversal of the $\pi$-facial orientation of the enolate in the transition state. In addition, *N*-acyloxazolidinethiones and thiazolidinethiones are significantly easily to remove.

Recently, Crimmins communicated a paper devoted to highly diastereoselective acetate aldol additions using chlorotitanium enolates of mesityl-substituted *N*-acetyloxazolidinethione and *N*-acetylthiazolidinethione auxiliaries.[63] These additions proceed in high yields and diastereoselectivities (93:7 to 98:2) for aliphatic, aromatic, and α,β-unsaturated aldehydes.

Most auxiliary-based aldol reactions require a stoichiometric addition of metal salt (B, Ti, Si etc.) to form the required enolate derivative. Lately, Evans and co-workers reported the first examples of metal-catalyzed aldol reactions by using both standard oxazolidinone *ent*-**2-6**[64]

and thiazolidinethione **2-48**[65] based auxiliaries. The addition of a magnesium halide (0.1–0.2 equiv.) to a EtOAc solution of the auxiliary and aldehyde in the presence of $NEt_3$ and TMSCl yielded 'non-Evans' **2-53** and 'Evans' *anti* aldol adduct **2-54** in high yield and with respectable selectivity (**Scheme 17**). However, this potentially valuable *anti*-aldol route was shown to be restricted to nonenolizable aldehydes under these conditions.



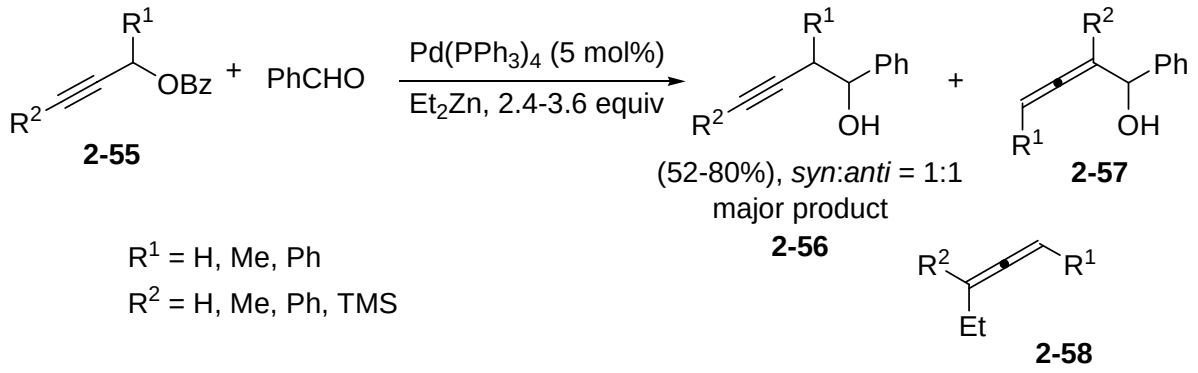

**Scheme 17.** Magnesium halide catalyzed *anti*-aldol reactions.

### 2.3.3 Addition of chiral allenylzincates to aldehydes (Marshall-Tamaru reaction)

Polyketide natural products have played a major role in the development of synthesis methodology for acyclic stereocontrol. The most common synthetic approach for constructing the various stereotriad[66] and higher subunits of these compounds involves diastereo- and enantioselective carbon–carbon bond forming reaction related to variants of the aldol reaction. Allylborane and boronate, allylsilane, and allyltitanate additions have also been applied with great success. Many of these approaches utilize a chiral auxiliary or substrate to effect stereochemical control. One of the most problematic tasks in stereotriad synthesis is introduction of the moiety with *anti* oriented methyl and hydroxyl groups. The most frequently used methods for this purpose are Brown asymmetric crotylboration and Abiko aldol reaction.

Addition of chiral nonracemic allenylmetal reagents to chiral aldehydes have also proven useful for the assembly of stereotriad and stereotetrad segments of polyketide natural products.[67] These reagents rely upon allene chirality to favor one of the two possible diastereomeric transition states in the addition and thus differ in fundamental way from the aforementioned methods in which a chiral auxiliary or catalyst provides the control element.

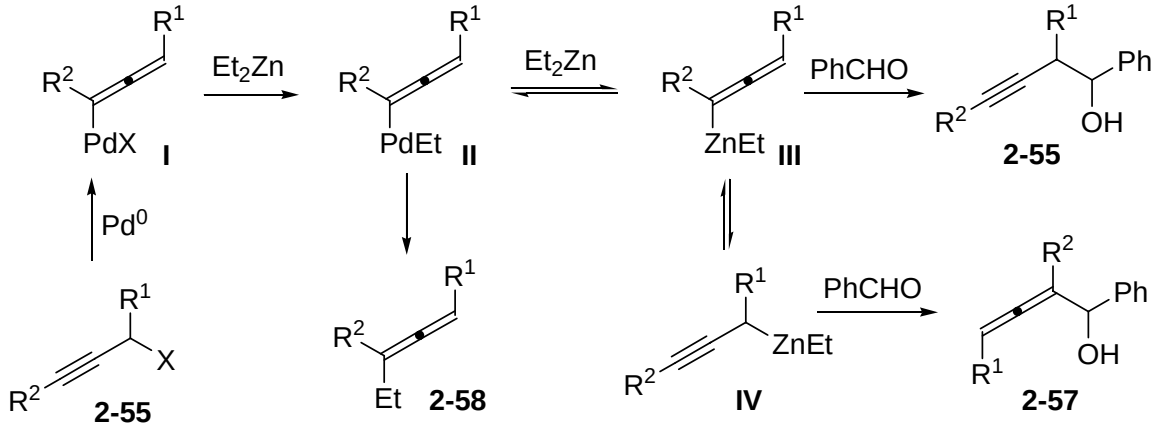
First insights in the application of allenylzinc compounds for the stereoselective synthesis were made by Tamaru and coworkers.[68] In 1996 they found that propargylpalladium complexes can undergo a nucleophilic addition to carbonyl compounds to provide homopropargyl alcohols **2-56** selectively (**Scheme 18**).




**Scheme 18.** Addition of propargylpalladium complexes to carbonyl compounds.

The propargylation of benzaldehyde proceeded smoothly at room temperature by stirring a solution of a propargyl benzoate **2-55** (1.2 equiv.), a carbonyl compound (1 equiv.), diethylzinc (2.4–3.6 equiv.), and tetrakis(triphenylphosphine)palladium (5 mol%) in THF under nitrogen.

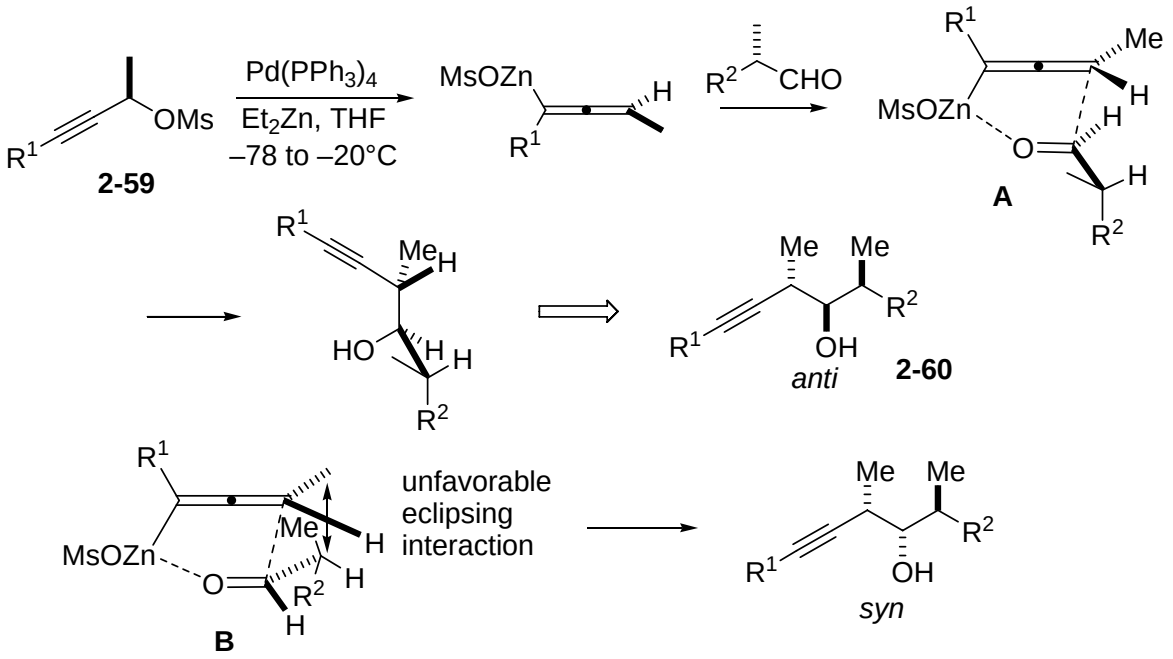
The outcome of this palladium-catalyzed propargylation of carbonyl compounds may be rationalized according to **Scheme 19**, under the assumption that both the transformation of **II** to a mixture of **III** and **IV** and the reactions of these two with benzaldehyde proceed much faster than the reductive elimination of **II** to provide **2-58**. The selective formation of the alcohols **2-56** may be attributed to the preponderance of **III** (with $C_{sp^2}$-M bonding) over **IV** (with $C_{sp^3}$-M bonding) in the equilibrium shown in **Scheme 19**.




**Scheme 19.** Mechanistic rationale for the propargylation and allenylation of benzaldehyde.

Significant improvement in the additions of in situ generated chiral allenylzinc reagents to aldehydes was achieved by the Marshall group.[69] They reported that enantioenriched propargylic mesylates can be efficiently converted to chiral allenylzinc reagents via transient allenylpalladium species by treatment with Pd(0)-phosphine catalyst in the presence of excess $Et_2Zn$. These zinc reagents undergo $S_E2'$ additions to various aldehydes to yield mainly the *anti* homopropargylic alcohol adducts of high ee. As a result of detailed investigation of this

reaction they found that the best leaving group is mesylate, the reaction is most efficient in THF with $Pd(OAc)_2 \cdot PPh_3$ as the catalyst system, and the best diastereoselectivity can be achieved when the reaction was carried out at –20 °C. The reaction proceeds via a distorted transition state (**Scheme 20**). The preference for *anti* over *syn* adducts can be attributed to an unfavourable eclipsing interaction between the allenyl Me and the aldehyde substituent in the transition state **B** leading to the *syn* adduct.




**Scheme 20.** Possible cyclic transition states for allenylzinc additions to aldehydes.

Interestingly, high diastereoselectivity was observed in additions to both enantiomers of α-methyl propanal derivatives to afford the *anti*,*anti* and *anti*,*syn* adducts. Thus, the preference for the *anti* transition state overrides Felkin–Anh considerations in these additions with a resulting absence of mismatching.[70] The suggested catalytic cycle for the metal exchange process was based on the previous investigations of the Tamaru[71] and Knochel[72] groups. A key feature of a possible catalytic cycle for the Pd–Zn exchange reaction involves reductive regeneration of the active Pd(0) catalyst from a Pd(II) intermediate through extrusion of ethylene (**Figure 10**). The $S_N2'$ reaction with Pd(0) catalyst results in formation of allenylpalladium intermediate **A** which subsequently reacts with diethylzinc to give the allenylzincate **C**. The latter undergoes $S_E2'$ additions to aldehyde which results in elimination of a Pd(II) intermediate. The palladation of propargylic mesylates was shown to take place with inversion,[73] and the predominant formation of *anti* adducts **2-60** strongly implicate a *syn* addition process which can be attributed to the cyclic transition state. Therefore, it can be assumed that the zincation reaction proceeds with retention of configuration.

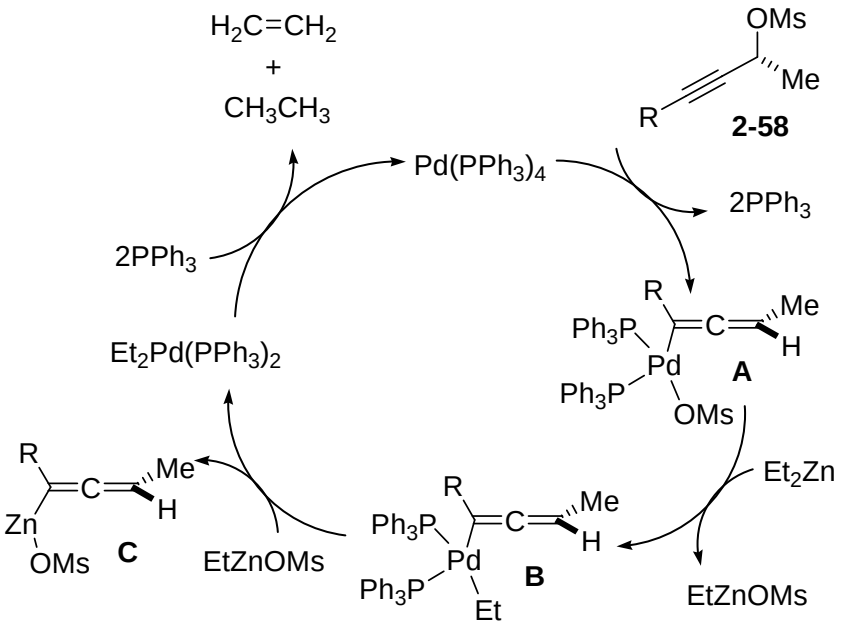
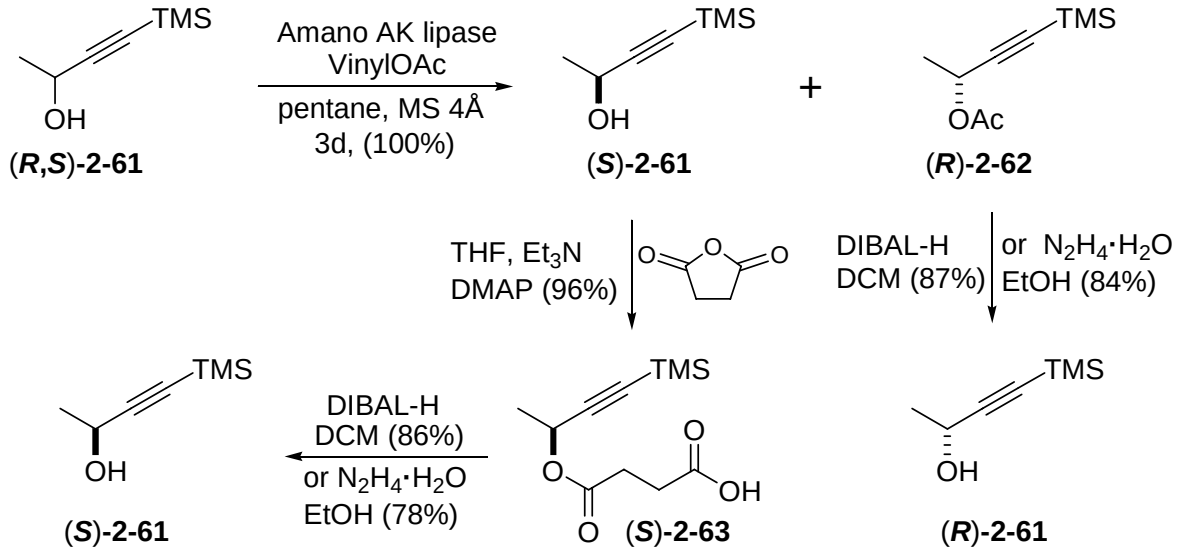



**Figure 10.** Possible catalytic cycle for Pd(0) catalyzed zincation of propargylic mesylates.

Although (*R*) and (*S*)-3-butyn-2-ol, precursors for corresponding mesylates are commercially available, their high cost limits widespread or large-scale application. Thus, an efficient synthetic route to the desired enantiomeric alcohols was developed. It is based on a kinetic resolution of 4-(TMS)-3-butyn-2-ol (*R*,*S*)-**2-61** mediated by Amano AK lipase in the presence of vinyl acetate. This enantioselective acetylation affords unchanged (*S*)-TMS-3-butyn-2-ol ((*S*)-**2-61**) and the corresponding (*R*)-acetate **2-62**, both with high ee (**Scheme 21**).[74] The two are readily separated through treatment of the mixture with succinic anhydride and extraction of the (*S*)-succinate **2-63** with aqueous $NaHCO_3$. Reduction of each ester with DIBAL-H affords the enantiomeric butynols (*S*)- and (*R*)-**61** of high ee.

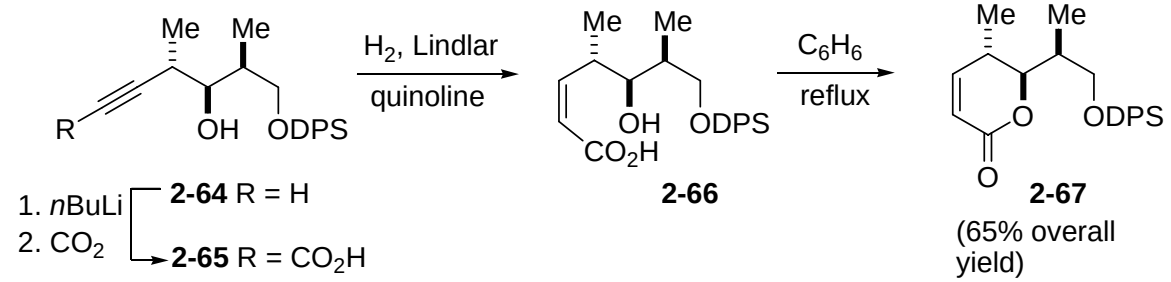
Alternatively, the acetate (*R*)-**2-62** or the succinate (*S*)-**2-63** can be cleaved with hydrazine hydrate in ethanol.[75] The acyl hydrazides formed in this reaction are water soluble and washed out by extraction.




**Scheme 21.** Kinetic resolution of racemic 4-(TMS)-3-butyn-2-ol with Amano AK lipase.

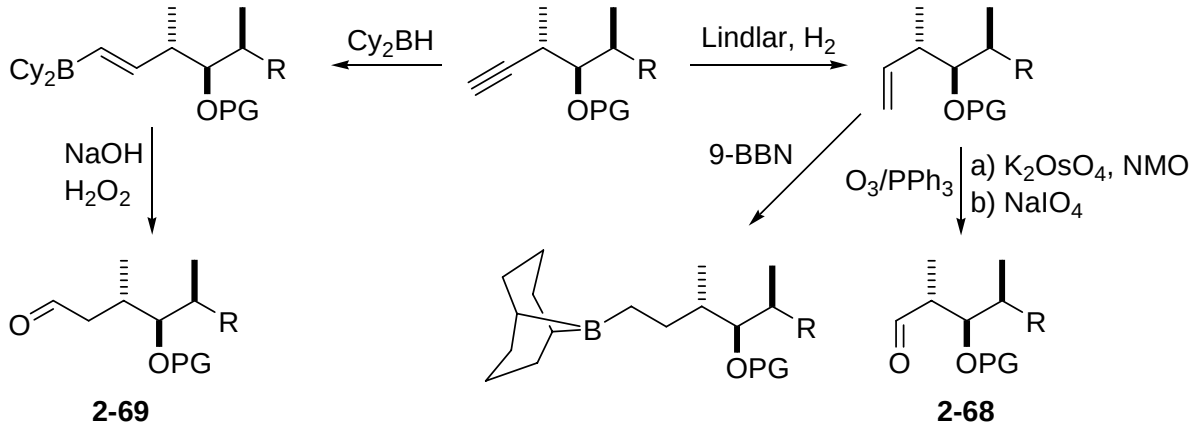
This chiral allenylzincate methodology provides access to all isomers of the homopropargylic alcohol stereodiad and stereotriad adducts with excellent diastereo- and enantioselectivity. The overall utility of the methodology is reflected in applications in the total synthesis of natural products such as zincosporin,[76] discodermolide,[77] (–)-callistatin A,[78] aplyronine A,[79] tautomycin,[80] leptofuranin D,[81] cytostatin.[82]

In addition, the acetylenic grouping of the adducts can be further elaborated, both functionally and for chain extension by a variety of protocols. It was shown that homopropargylic alcohol **2-64** can be converted to the unsaturated lactone (pentenolide) **2-67** through carboxylation of the lithiated alkynes with $CO_2$ followed by partial hydrogenation of triple bond and thermal lactonization (**Scheme 22**). The 4-alkylpentenolide moiety of **2-67** is found in a number of biologically active polypropionate natural products.[83]




**Scheme 22.** Conversion of homopropargylic alcohols to unsaturated ketones.

Catalytic hydrogenation of the obtained triple bond followed by oxidative degradation will lead to corresponding aldehyde **2-68**, whereas hydroboration with dicyclohexylborane followed by in situ oxidation of the obtained vinylborane intermediate provides homoaldehyde **2-69** (**Scheme 23**). In addition, intermediate vinyl- or alkylboranes can be efficiently used in cross-coupling reactions.[84]




**Scheme 23.** Possible transformation of homopropargylic alcohols.

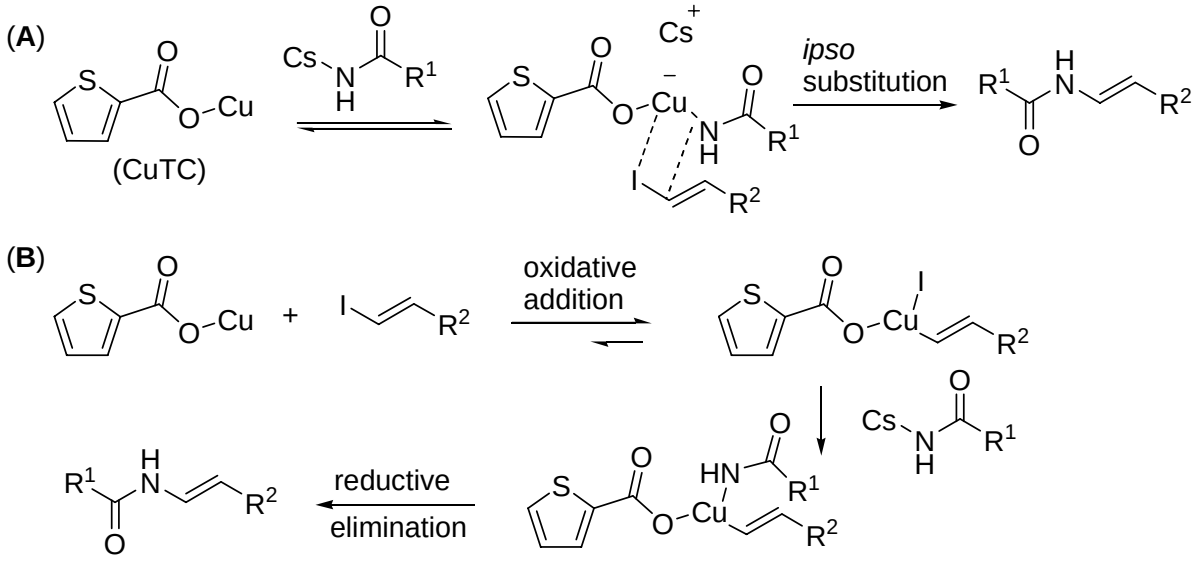
Other synthetic utilisation of the triple bond includes alkylation,[85] addition to aldehydes, epoxide opening, cross-coupling etc.

### 2.3.4 Synthesis of enamides via copper-catalyzed coupling of amides with vinyl halides

Enamides are important synthetic intermediates,[86] as well as a structural component of many natural products. The most commonly used protocols for their preparation include direct addition of amides to alkynes,[87] acylation of imines,[88] the Curtius rearrangement of α,β-unsaturated acyl azides,[89] and the olefination of amides.[90] Although these protocols provide access to enamides, they suffer from either low yield or lack of stereocontrol on the double bond geometry. Transition metal-catalyzed C–N bond formation has been an area of intensive research during the past 15 years.

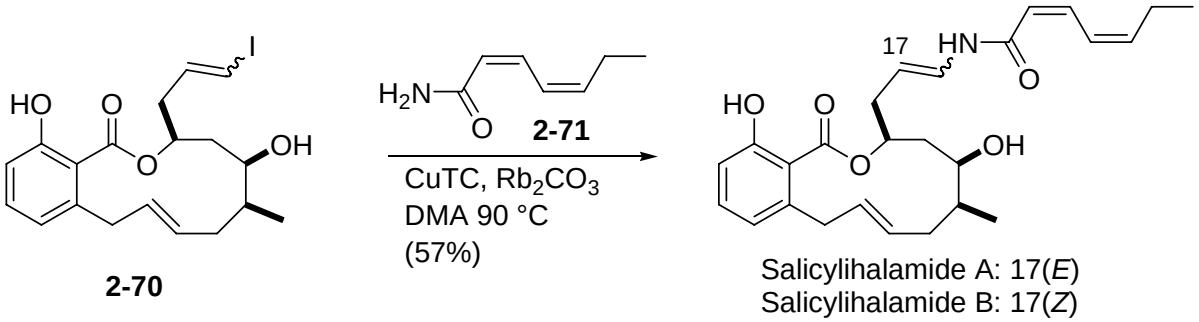
In 1991 Ogawa at al. reported the copper iodide-promoted substitution of vinyl bromides and potassium amides (1 equiv. of CuI, HMPA, 130 °C) to afford enamides in low to moderate (38–45%) yields.[91] More recently, using CuTC (TC = thiophene-2-carboxylate) as a catalyst, Porco described a copper catalyzed amidation of vinyl iodides to give enamides in moderate yields.[92] Developed methodology was applied to the synthesis of *O*-methyloxime enamide side chains related to the natural products lobotamides A-F, oximidine I and II, and CJ-12950. Also a possible mechanism of copper-catalyzed enamide formation was proposed.[92] According to scenario **A**, a cesium carboxamide may react with CuTC to afford a cuprate-like intermediate which forms the enamide after four-centered *ipso*-substitution of the vinyl iodide. In a second scenario (**B**), oxidative addition of the vinyl iodide to CuTC occurs which may be favored because of the carboxylate ligand (**Scheme 24**). Displacement of a copper

iodide intermediate by the cesium carboxamide would be followed by reductive elimination to afford the enamide product.



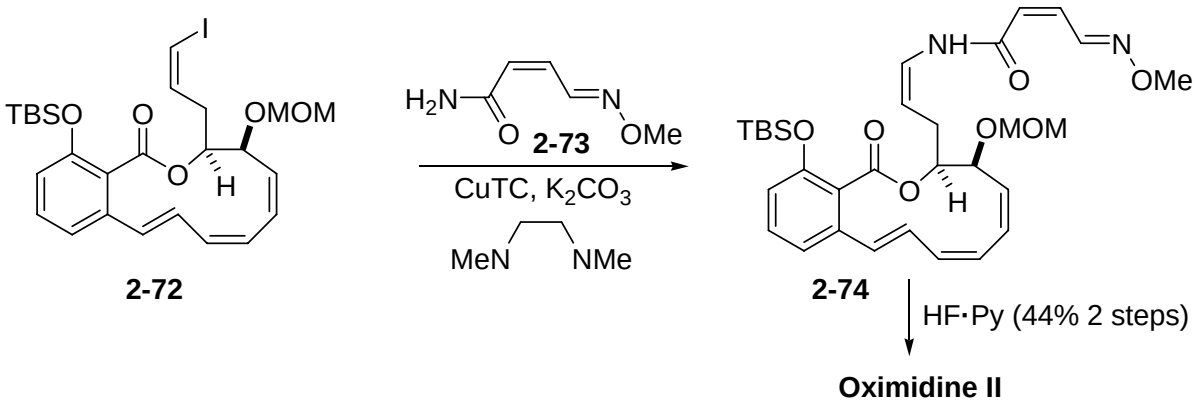

**Scheme 24.** Mechanistic scenarios for copper-catalyzed enamide formation.[92]

This methodology was successfully employed by Fürstner et al. in the total synthesis of salicylihalamide.[86b] Reaction of **2-70** with amide **2-71** (3 equiv) in the presence of CuTC (50 mol%) and $Rb_2CO_3$ (3 equiv) afforded a mixture of salicylhalamide A and B in 57% yield (**Scheme 25**). Notably the use of $Cs_2CO_3$ failed to afford any of the desired product under otherwise identical conditions.




**Scheme 25.** Synthesis of salicylihalamide A and B by Fürstner et al.[86b]

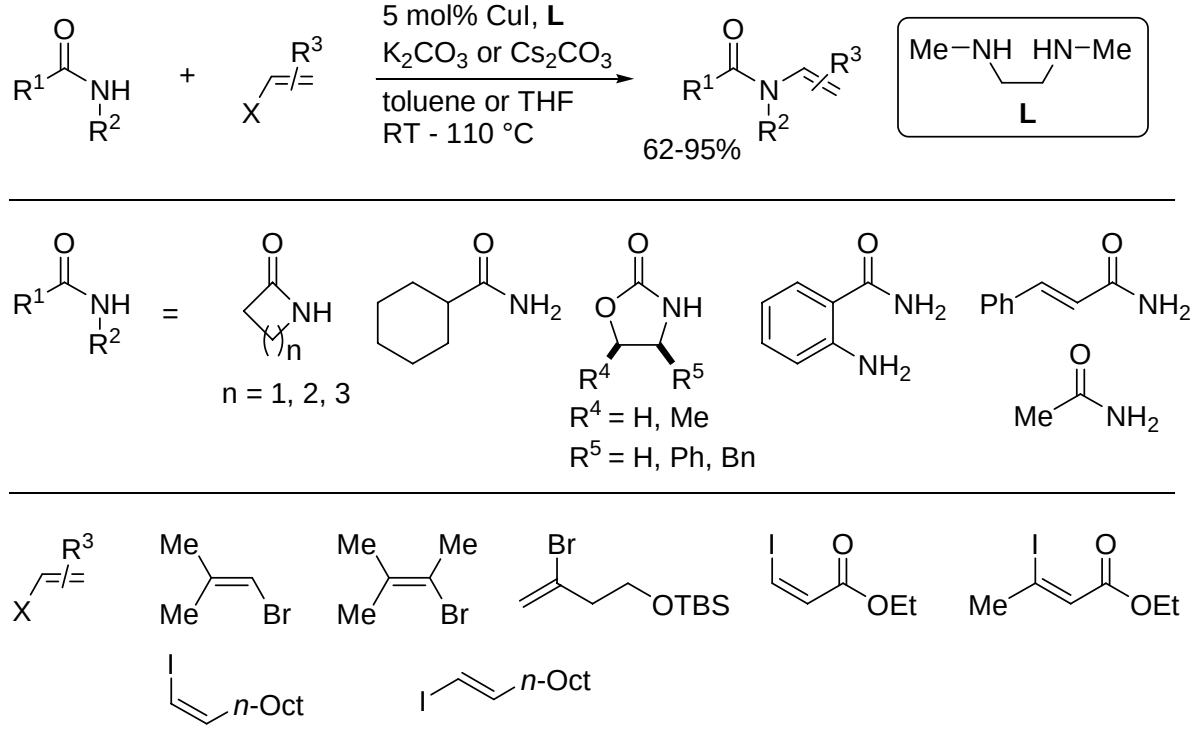
During the total synthesis of oximidine II by Porco et al. it turned out that amidation of **2-72** using conditions earlier reported for (*E*)-vinyl iodides[92] led to low yield due to competitive elimination under basic conditions. After a model study involving evaluation of various ligands and bases they found that **2-72** coupled smoothly with **2-73** employing stoichiometric amounts of CuTC–N,N'-dimethyl-ethylendiamine and $K_2CO_3$ as a base (**Scheme 26**).[93]




**Scheme 26.** Synthesis of oximidine II by Porco et al.[93]

Other examples of CuTC-catalyzed amidation of vinyl iodides include total synthesis of oximidine III[94] as well as synthesis of apicularen A[95] and its analogues.[96]

More recently Buchwald and co-workers developed a general and efficient copper-catalyzed method for the amination of vinyl bromides and iodides.[97] This protocol uses a combination of 5 mol% copper iodide and 20 mol% N.N'-dimethyl ethylendiamine in the presence of $K_2CO_3$ or $Cs_2CO_3$ as a base. Substrates bearing ester, silyl ether and amino groups were successfully coupled under the reaction conditions (**Scheme 27**). Both cyclic amides and acyclic amides could be combined with vinyl halides in excellent yields. It was shown that the coupling reaction of vinyl bromides required higher temperatures (110 °C) and longer stirring (15–30 h). In addition, di- and trisubstituted vinyl bromides were efficiently converted to the corresponding enamides in excellent yield.




**Scheme 27.** Scope of the copper-catalyzed amidation of vinyl halides.[97]

Importantly, the double bond geometry of the vinyl halides was retained under the reaction conditions.

The Buchwald copper-catalyzed protocol found its application in the total synthesis of the marine macrolide palmerolide A[98] and alkaloid ageladine A.[99] After all, due to the mild reaction conditions, broad scope, the operational simplicity and the functional group compatibility this methodology becomes a valuable synthetic tool for the installation of the structurally important enamide moiety.

# 3 Results and Discussion

## 3.1 Retrosynthetic Analysis

The target molecule, cruentaren A (**1-1**), features the following distinct fragments:

a) 12-memebered benzolactone;

b) *Z*-double bond in the ring;

c) Z-allylamide side chain.

As a key step for macrolactone formation, a ring closing alkyne metathesis (RCAM) followed by Lindlar reduction was deemed appropriate. As an option ring closing metathesis and classical macrolactonization strategies (Yamaguchi, Mitsunobu) might also be considered. Accordingly, we divided the target molecule into two main subunits: functionalized benzoic acid **3-1** and a stereotetrad containing fragment **3-2** (**Figure 11**).

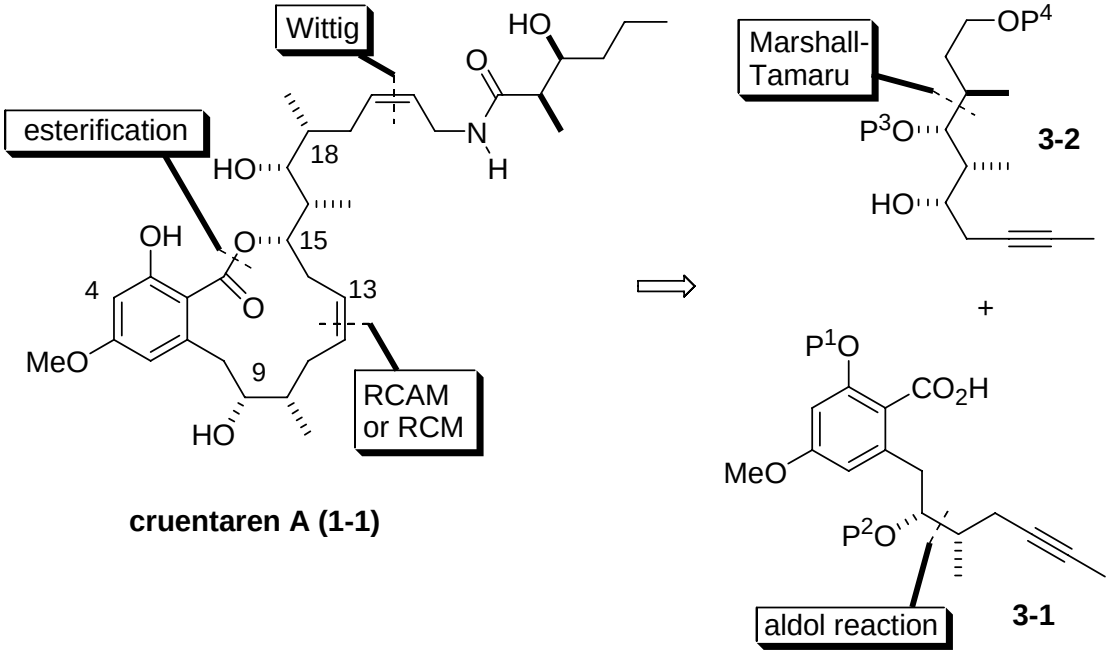



**Figure 11**. Retrosynthetic analysis for cruentaren A.

Alternatively, the C12–C13 bond could be secured by opening of epoxide **3-4** with the lithium salt of alkyne **3-3**. Lindlar reduction of the obtained triple bond could be done after or before the macrolactonization step (**Figure 12**).

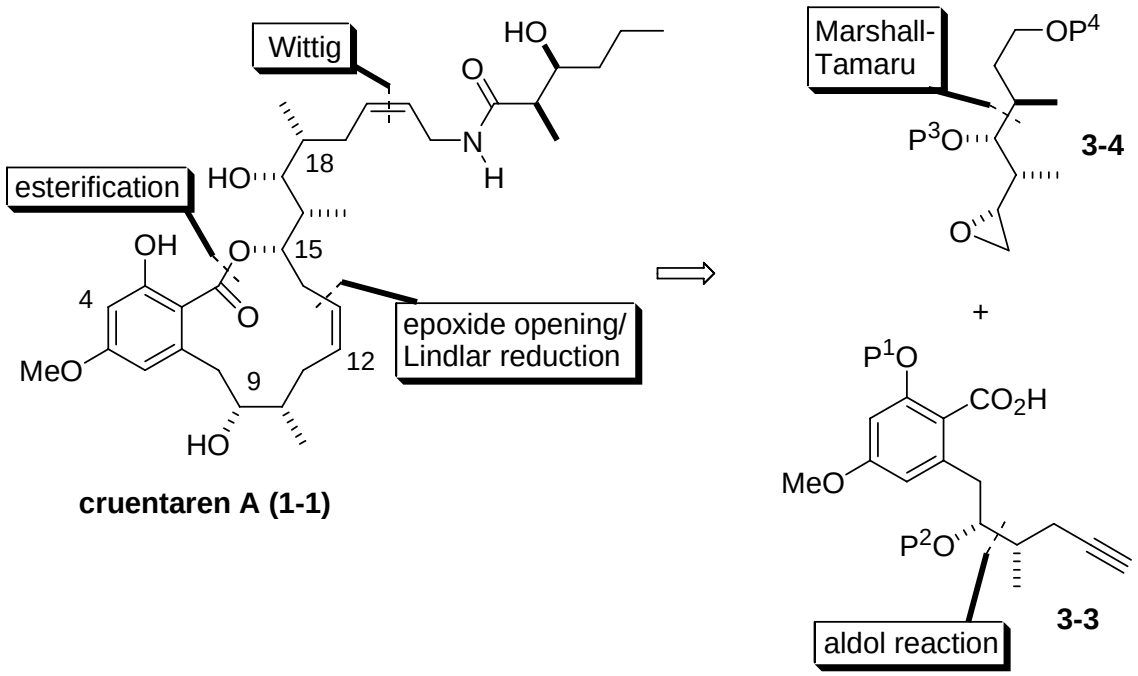



**Figure 12**. Alternative retrosynthetic analysis for cruentaren A.

The required functionalized benzoic acid **3-1** might be synthesized using an Evans aldol reaction of aldehyde **3-5** with pentynyloxazolidinone **3-6**. To provide the internal triple bond simple methylation of the corresponding acetylide was considered (**Figure 13**).

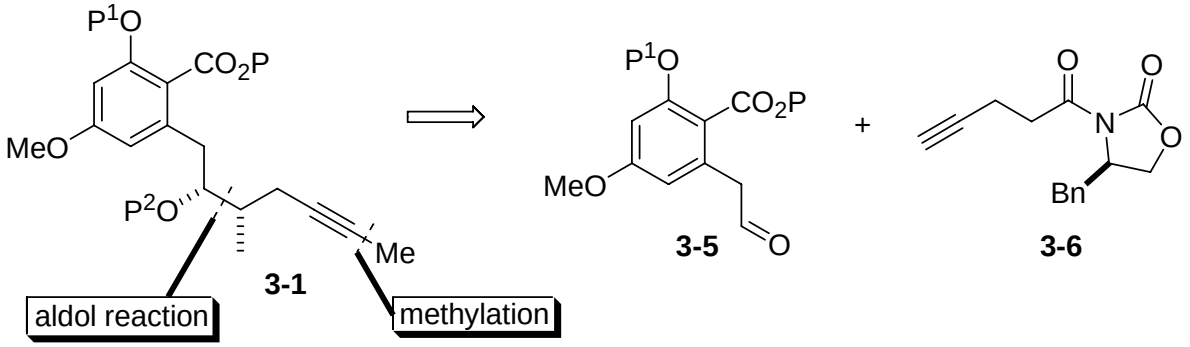



**Figure 13**. Retrosynthetic analysis for fragment **3-1**.

Fragment **3-2** logically originates from opening of epoxide **3-4** with the lithium salt of propyne or TMS-acetylene (**Figure 14**).

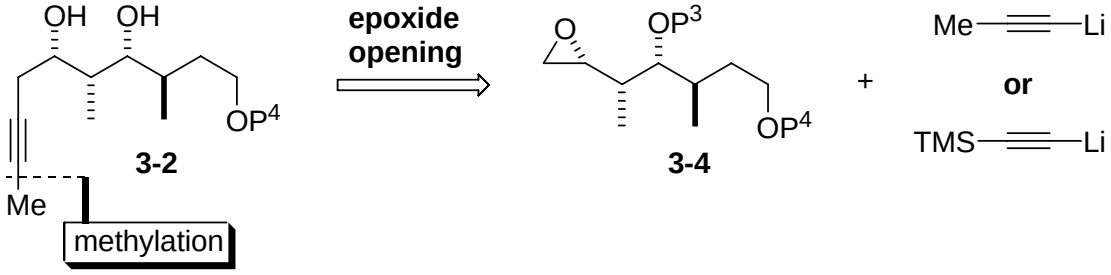



**Figure 14**. Retrosynthetic analysis for fragment **3-2**.

Obviously, epoxide **3-4** should result from diol **3-7,** which can be easily obtained from acetonide **3-8**. Compound **3-8** can be derived from alkyne **3-9** using a hydroboration – reduction sequence. As a key step in the synthesis of the alkyne **3-9** containing the stereotetrad, a Marshall-Tamaru reaction of known aldehyde **3-10**[100] was envisioned in order to fashion the *anti*-configuration at C17/C18 (**Figure 15**).

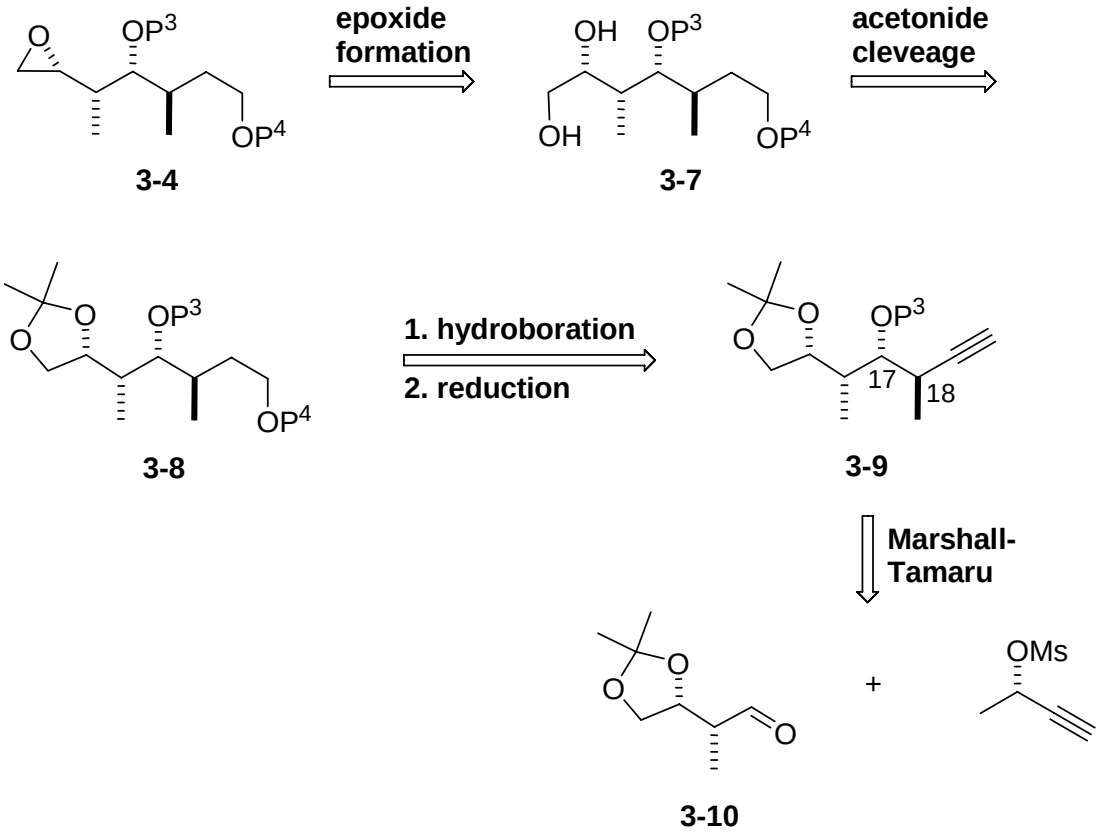



**Figure 15**. Retrosynthetic analysis for epoxide **3-4**.

## 3.2 Ring Closing Metathesis Model Study

### 3.2.1 Synthesis of diene 3-11

According to the retrosynthetic analysis, one of the options to create the macrolactone ring is a ring closing metathesis (RCM) reaction.[101] However, it is required that this reaction should provide the *Z*-alkene. Thus, our first goal en route to cruentaren A was to test the RCM strategy on a model substrate **3-11** to check for the *Z*/*E* ratio (**Figure 16**). The isopropyl group replaces the extended side chain. In order to prevent unwanted lactonization to the δ-lactone, a keto function can be used instead. Retrosynthetic analysis of terminal diene **3-11** shows that it might be obtained via an acylation of the benzylic anion derived from **3-12** with the Weinreb amide **3-13** using conditions, recently published by Winssinger et al.[102] Logically, ester **3-12** derives from the 2,4-dimethoxy-6-methylbenzoic acid **3-14** and commercially available alcohol **3-15**.

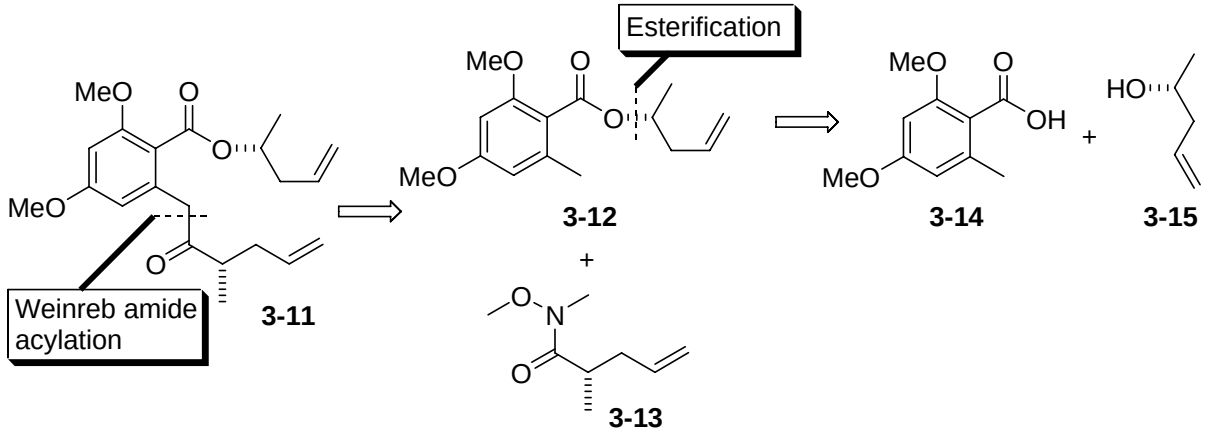
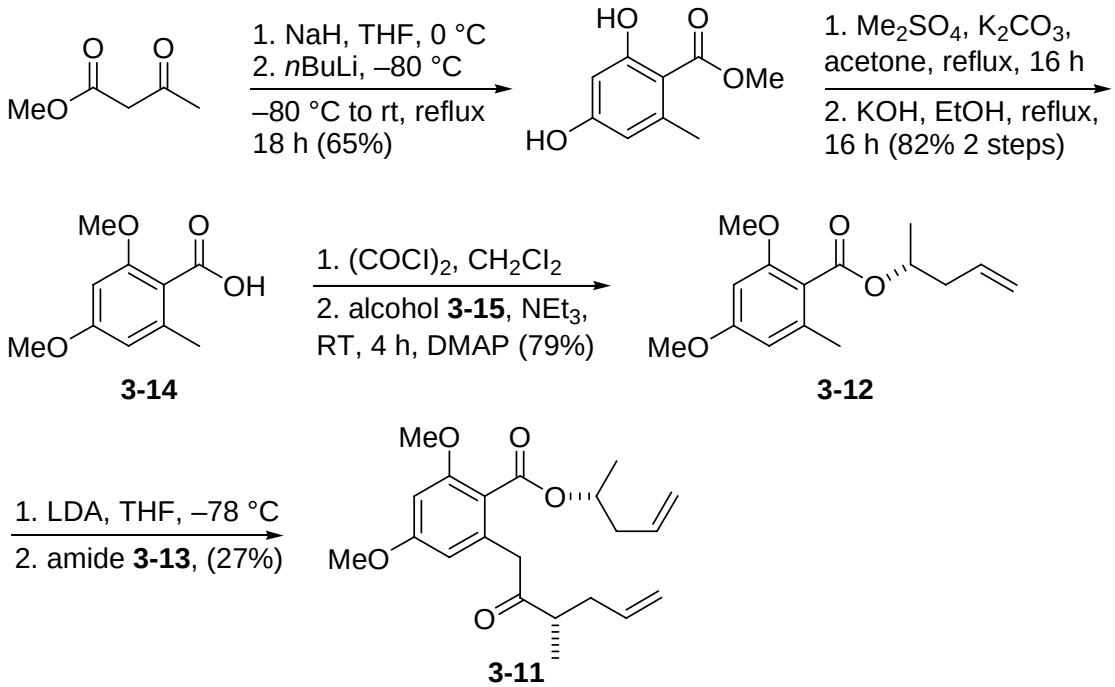


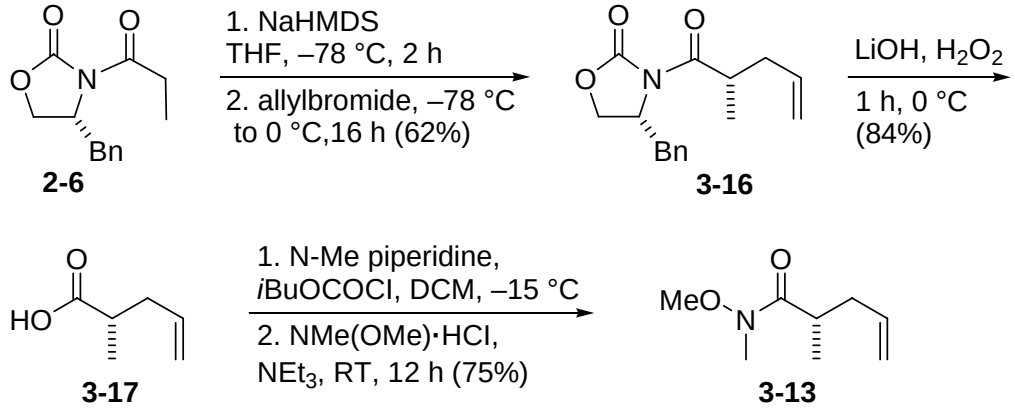

**Figure 16**. Retrosynthetic analysis for RCM precursor **3-11**.

Synthesis of acid **3-14** was done in accordance with published procedures. At first, methyl acetoacetate was subjected to a self-condensation reaction in the presence of NaH and *n*BuLi[103] (**Scheme 28**). The obtained 2,4-dihydroxy-6-methylbenzoate was methylated with $Me_2SO_4$ in the presence of $K_2CO_3$ as a base.[104] Subsequently, the methyl ester was saponified with KOH and the obtained acid was coupled with commercially available alcohol **3-15**.[102] This ester was deprotonated with freshly prepared LDA which was followed by addition of Weinreb amide **3-13**. Unfortunately, the desired ketone **3-11** was obtained only in 27% yield. All our attempts to optimize the conditions of this reaction previously described by Winnsinger et al.[102] were not successful.




**Scheme 28.** Synthesis of diene **3-11**.

Synthesis of Weinreb amide **3-13** started with enantioselective alkylation of Evans oxazolidinone **2-6** with allylbromide, following a previously described procedure[105] (**Scheme 29**). The obtained product was subjected to oxidative cleavage of the auxiliary using lithium peroxide in a THF/$H_2O$ mixture. This resulted in the formation of acid **3-17**, which was subsequently converted to Weinreb amide **3-13** via formation of the corresponding mixed anhydride[106].

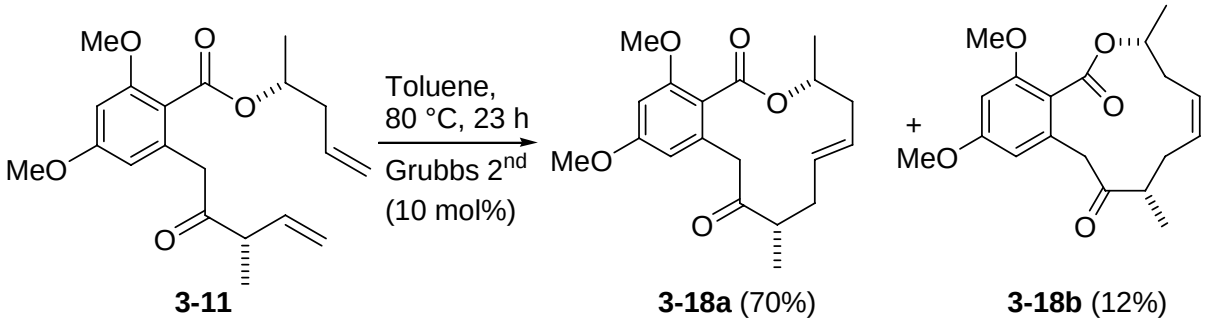



**Scheme 29.** Synthesis of Weinreb amide **3-13**.

### 3.2.2 Ring closing metathesis of diene 3-11

With sufficient amount of diene **3-11** in hand we started to investigate RCM conditions. Following a general procedure, substrate **3-11** was heated at 80 °C in degassed toluene in the

presence of 10 mol% of Grubbs 2nd catalyst. This resulted in the formation of a separable mixture of *E*- and *Z*-macrolactones in a ratio of 6:1 (**Scheme 30**).




**3-11** **3-18a** (70%) **3-18b** (12%)

**Scheme 30.** Ring closing metathesis of diene **3-11**.

Both of the macrolactones were crystalline solids. This allowed us to make an X-Ray analysis of the major product **3-18a**. As on can see from **Figure 17**, the alkene protons are oriented in different directions, which confirms that the major product has the undesired *E*-configuration of the double bond.

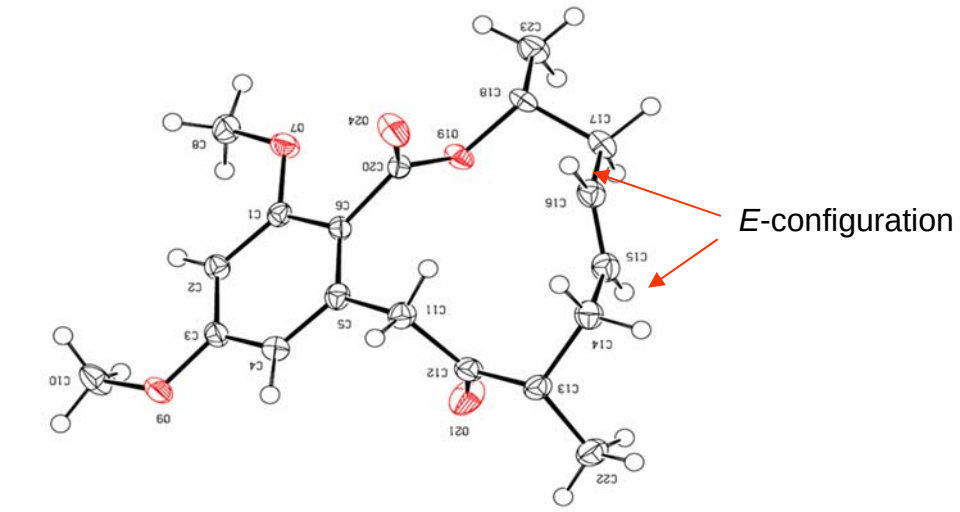


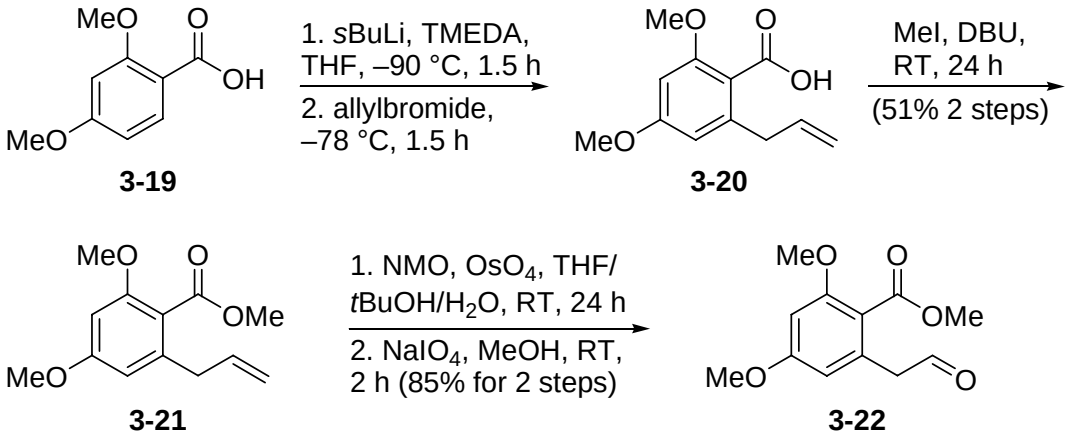

**Figure 17.** X-Ray analysis for the macrolactone **3-18a**.

One of the possible explanations of this outcome might be the fact, that the formation of the undesired *E*-isomer is thermodynamically more favorable. These disappointing results induced us to switch to the alternative strategy which is based on epoxide opening followed by classical macrolactonization. In this case the desired *Z*-alkene can be easily obtained from the corresponding alkyne via Lindlar reduction.

## 3.3 Epoxide Opening Strategy

### 3.3.1 Synthesis of alkyne 3-30

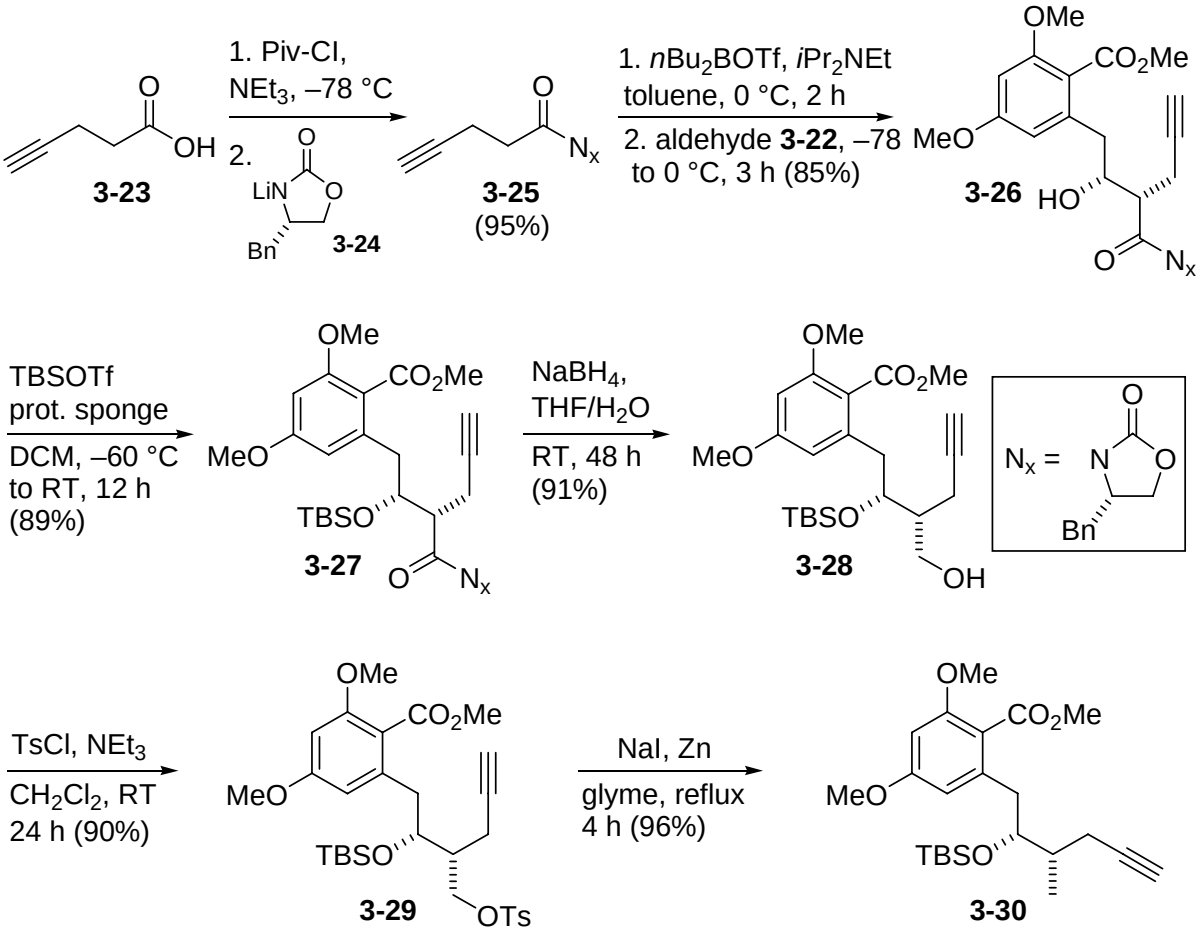
The synthesis of a benzoic acid building block **3-30** was started with commercially available 2,4-dimethoxybenzoic acid which was allylated via the dianion[107] followed by methylation.[108] Degradation of the terminal double bond to an aldehyde function was achieved by a dihydroxylation/periodate cleavage sequence[109] in good overall yield (**Scheme 31**). The $OsO_4$ required for this reaction was prepared from cheaper and relatively less toxic $K_2OsO_4 \cdot 2H_2O$ in accordance with a literature procedure.[110]




**Schema 31**. Synthesis of aldehyde **3-22**.

Obtained aldehyde **3-22** was combined with pentynyloxazolidinone **3-25** via an Evans aldol reaction using the standard boron enolate.[111] Trying different conditions, we have found that the highest yield (85%) of aldol adduct **3-26** could be obtained carrying the reaction in toluene. In comparison, the use of $CH_2Cl_2$ as solvent resulted in formation of **3-26** only in 55% yield. The required alkyne **3-25** was obtained through acylation of lithiated oxazolidinone **3-24** with commercially available pentynoic acid **3-23**, employing the mixed anhydride method[106] (**Scheme 32**). Protection of the secondary hydroxyl function of aldol adduct **3-26** as *tert*-butyldimethylsilyl ether using TBS triflate and proton sponge as base, furnished the corresponding TBS ether **3-27** in excellent yield. Interestingly, applying classical condition for TBS protection (TBS triflate, 2,6-lutidine) we were able to get the desired product only in 35–40% yield. This can be attributed to possible δ-lactone formation. $NaBH_4$ mediated reductive cleavage of the chiral auxiliary proceeds smoothly and produced the corresponding primary alcohol **3-28** in 91% yield.[112] Conversion of the primary alcohol to the corresponding methyl group was achieved by tosylation of the hydroxyl function followed

by treatment of the intermediate tosylate with zinc/sodium iodide.[113] This resulted in the formation of the required alkyne **3-30** in almost quantitative yield.

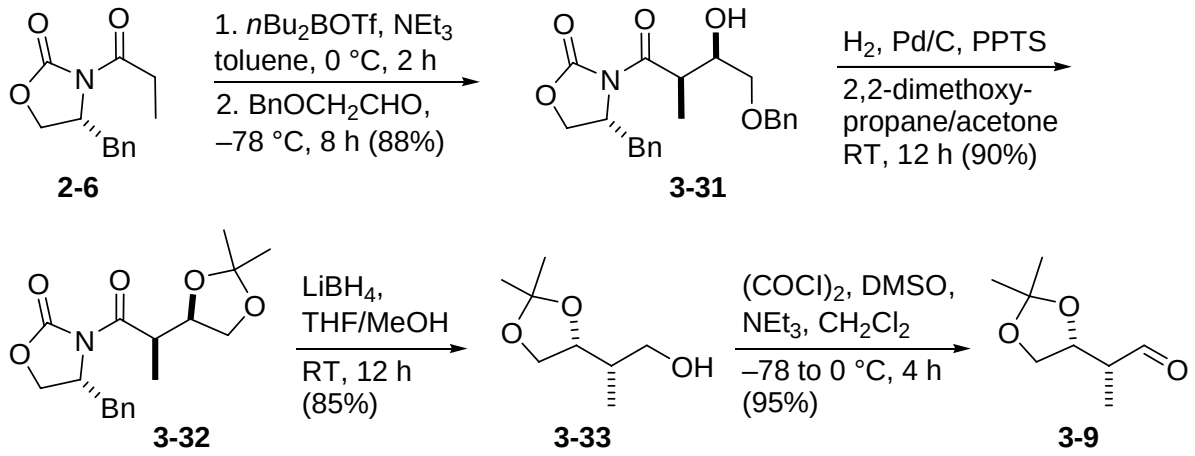



**Scheme 32.** Synthesis of alkyne **3-30**.

After having the desired alkyne **3-30** in hand we started the synthesis of the required epoxide fragment **3-4**.

### 3.3.2 Synthesis of epoxide 3-42

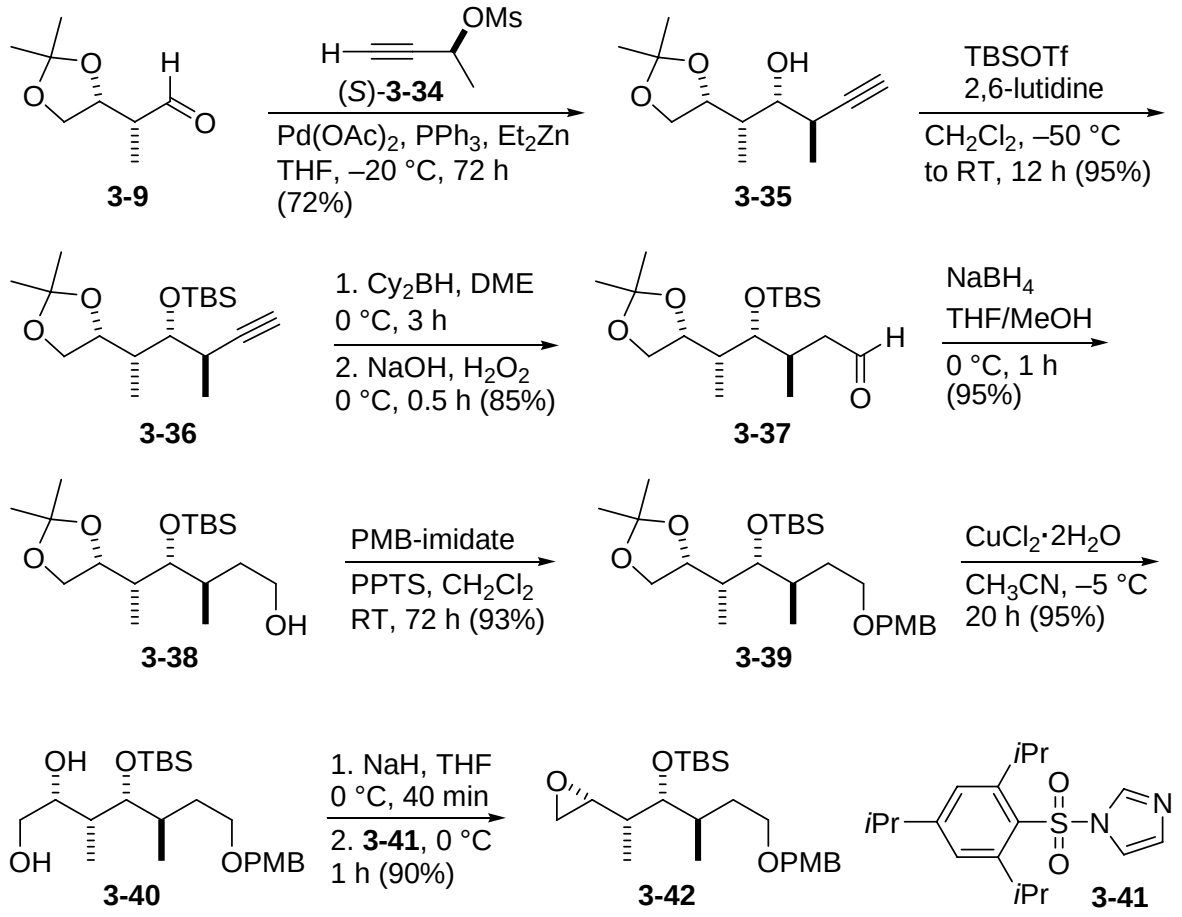
Aldehyde **3-9,** the substrate for the Marshall reaction was prepared in accordance with a published procedure. The aldol adduct obtained by Evans aldol reaction between oxazolidinone **2-6** and benzyloxyacetaldehyde was subjected to hydrogenolysis conditions in PPTS–2,2-dimethoxypropane–acetone, to afford an acetonide directly, which was transformed to alcohol **3-33** via reductive removal of the chiral auxiliary (**Scheme 33**). Swern oxidation of alcohol **3-33** proceeded smoothly and provided us with the corresponding aldehyde **3-9**.




**Scheme 33.** Synthesis aldehyde **3-9**.

Due to possible epimerization, aldehyde **3-9** is chemically unstable and was immediately introduced in the Marshall-Tamaru reaction.[81] Reaction of aldehyde **3-9** with propargylic mesylate (*S*)-**3-34**[74a] in the presence of $PPh_3$, palladium(II) acetate and diethylzinc resulted in formation of alkyne **3-35** with excellent diastereoselectivity (22:1) and good yield (**Scheme 34**). The only drawback of this reaction is the relatively long time required for complete consumption of aldehyde (72 h).

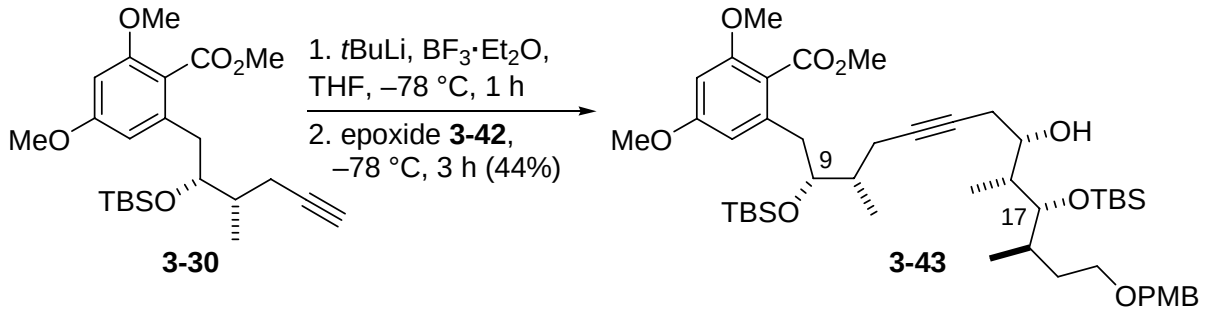
After silyl protection of the hydroxyl function, the triple bond of **3-36** was hydroborated with $Cy_2BH$. The vinylborane intermediate was in situ oxidized to aldehyde **3-37**.[81] Sodium borohydride reduction of the aldehyde gave primary alcohol **3-38**, which was protected using 4-methoxybenzyltrichloroacetimidate[114] leading to ether **3-39** in excellent yield. Cleavage of the acetonide moiety under mild conditions ($CuCl_2 \cdot 2H_2O$, acetonitrile, –5 °C)[115] afforded diol **3-40**. Other attempts to cleave the acetal of **3-39** (AcOH in THF at 50 °C, TFA in $CH_2Cl_2$, $FeCl_3/SiO_2$ in $CHCl_3$) were unsuccessful – deprotection of the acetonide moiety was always accompanied by unwanted TBS ether cleavage. Finally, diol **3-40** was converted to epoxide **3-42** via an efficient one-flask Fraser-Reid transformation.[116] At the beginning substrate **3-40** was deprotonated with sodium hydride which was followed by treatment of the obtained bis-alcoholate with trisimidazole **3-41**. This resulted in almost quantitative formation of the desired fragment **3-42**.




**Scheme 34.** Synthesis of epoxide **3-42**.

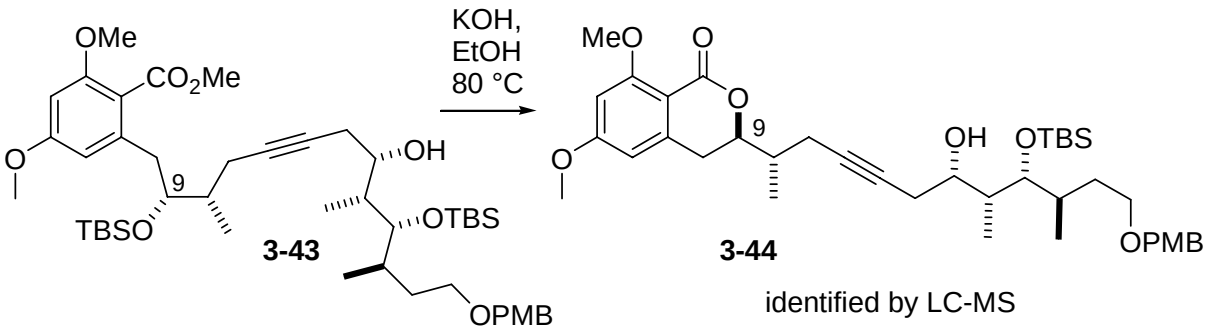
### 3.3.3 Coupling of alkyne 3-30 with epoxide 3-42

After the successful synthesis of alkyne **3-30** and epoxide **3-42** our next task was to combine these two big fragments. Deprotonation of alkyne **3-30** proved to be the most efficient with *tert*-butyllithium. All other attempts to perform this deprotonation, using *n*BuLi, LDA or mesityllithium were not successful because of decomposition (*n*BuLi was undergoing nucleophilic addition to the carboxyl function) or low reactivity (LDA, mesityllithium) of alkyne **3-30**. The obtained acetylide was treated with boron trifluoride-diethylether complex which was followed by addition of epoxide **3-42** (**Scheme 35**). Despite numerous attempts to optimize the conditions of this reaction, the desired product **3-43** was obtained only in moderate yield (44%). One of the explanations for the low yield could be the C17O–TBS group cleavage enhanced by neighbouring group participation of the 15-OH.




**Scheme 35.** Coupling of alkyne **3-30** with epoxide **3-42**.

Our next challenging task was to saponify ester **3-43** in order to get the seco-acid required for macrolactonization. This simple transformation in our case turned out to be rather difficult. The cleavage of the methyl ester of the substituted benzoic acid was attempted under various saponification conditions. Applying such mild reagents as LiOH in THF/MeOH/$H_2O$, TMSOK in THF,[117] $Me_3SnOH$ in 1,2-dichlorethane[118] no product was observed even after several days of stirring at ambient temperature or at 60 °C. Such a low reactivity of methyl benzoate **3-43** can be attributed to the presence of two electron-donating methoxy groups in the aromatic ring, which significantly deactivate the carboxylic function. This finding prompted us to use more hard conditions. But unfortunately, reaction of ester **3-43** with KOH in EtOH at 80 °C resulted in cleavage of TBS ether at C9 and formation of the corresponding isocoumarin **3-44** (**Scheme 36**). This was judged by LC-MS analysis of the crude reaction mixture, where the most intensive peak in the UV 254 nm corresponds to the mass $[M+Na]^+$ = 705.38, that is perfectly matching with the mass of δ-lactone **3-44**.



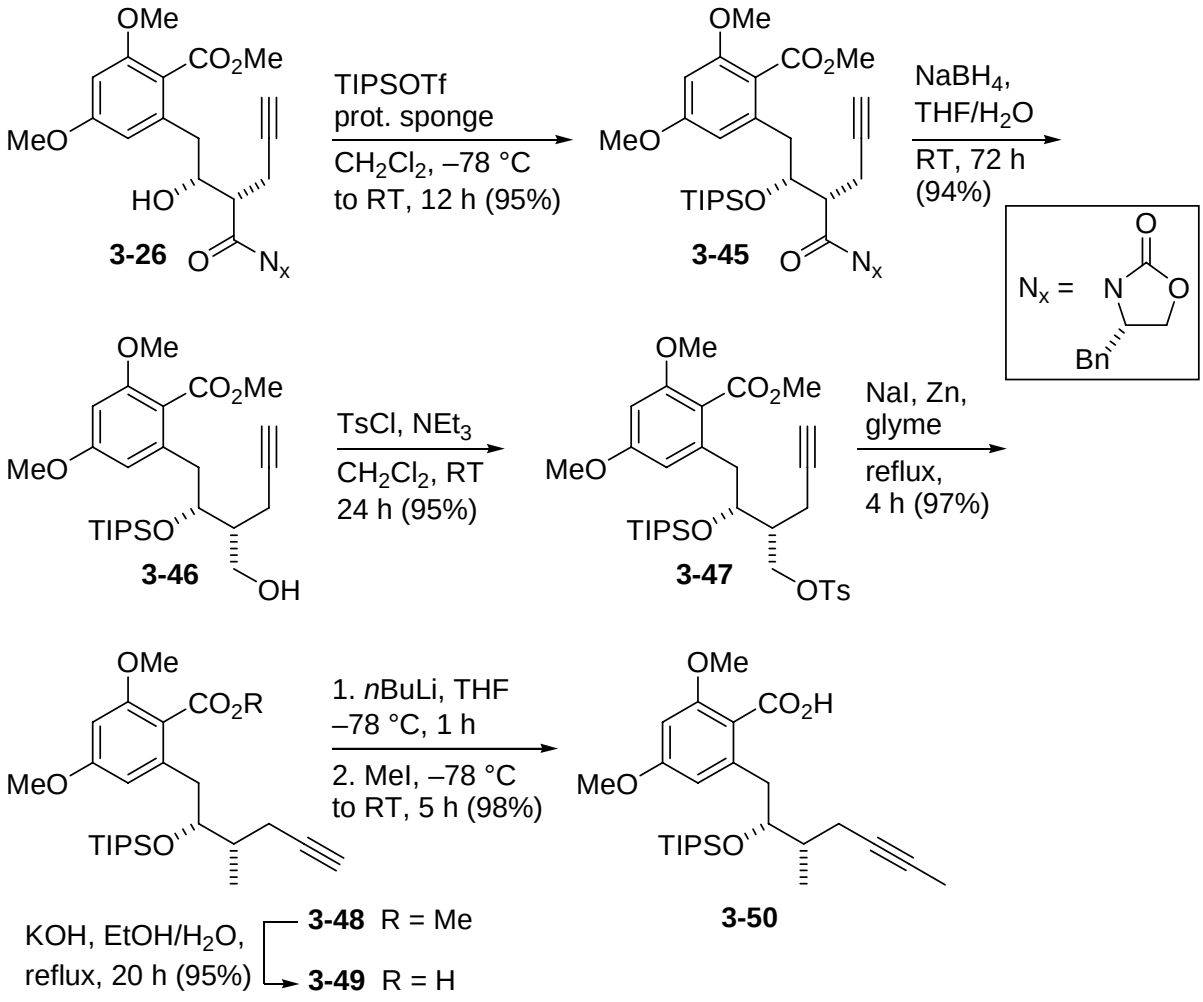

**Scheme 36.** Attempted cleavage of methyl ester.

These disappointing results persuade us to switch to another alternative strategy, namely ring-closing alkyne metathesis. This seemed promising since a model study revealed that the RCAM strategy might be feasible.[119] Having in hand useful building blocks **3-42** and **3-30** and concise routes for their preparation we started the synthesis of the required precursors.

## 3.4 Ring Closing Alkyne Metathesis Strategy

### 3.4.1 Synthesis of functionalized benzoic acid 3-50

This time the secondary hydroxyl function derived from the aldol reaction was intentionally protected as rather robust TIPS ether in order to survive the ester hydrolysis in the course of the synthesis of acid **3-50** and to prevent unwanted δ-lactone formation on the activated acid. All transformations described for TBS ether **3-27** were transferred to TIPS-protected aldol **3-45** (**Scheme 37**). After alcohol protection, the oxazolidinone auxiliary was cleaved with $NaBH_4$ and the obtained primary alcohol **3-46** subjected to tosylation. Intermediate tosylate **3-47** was treated with zinc/sodium iodide in refluxing 1,2-dimethoxyethane. This provided us with alkyne **3-48**. After saponification of the methyl ester **3-48**, the obtained alkynoic acid **3-49** was converted to the dianion which was alkylated at the acetylide using MeI. Gratifyingly, no unwanted δ-lactone formation was observed during the potassium hydroxyde mediated ester cleveage. This way, the acid **3-50** containing an internal alkyne required for the RCAM could be obtained in a concise manner.



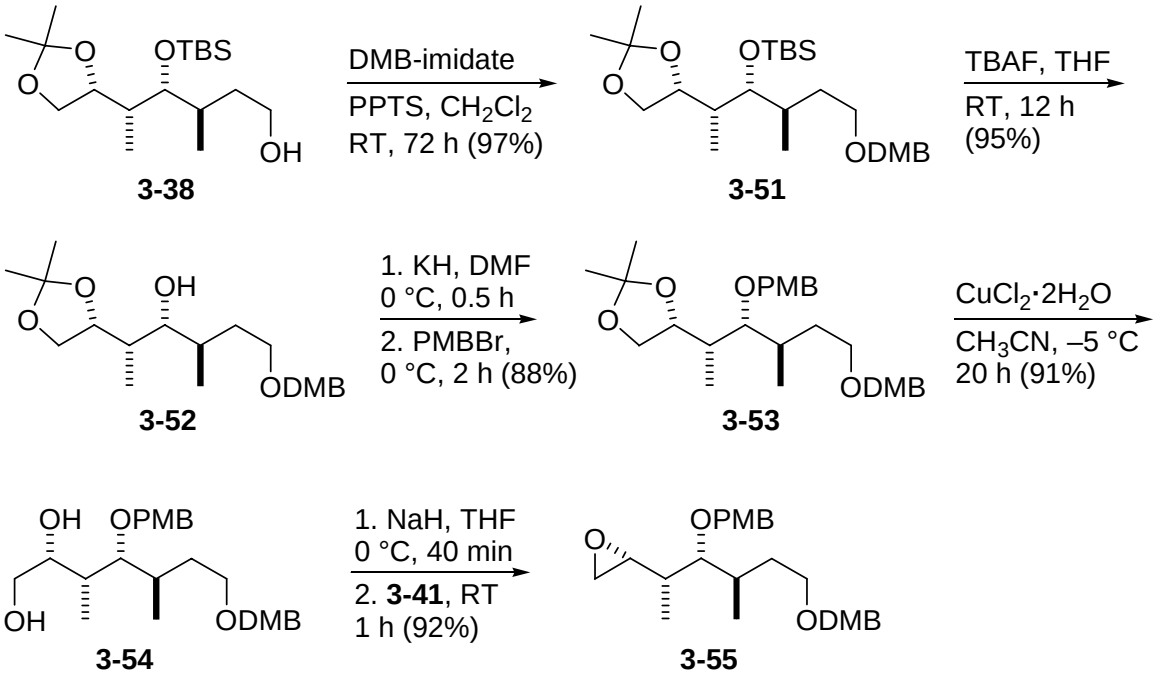

**Scheme 37**. Synthesis of acid **3-50**.

With synthesis of benzoic acid fragment **3-50** completed we started the synthesis of the second necessary fragment for the esterification, namely alcohol **3-60**.

### 3.4.2 Synthesis of alcohol 3-60

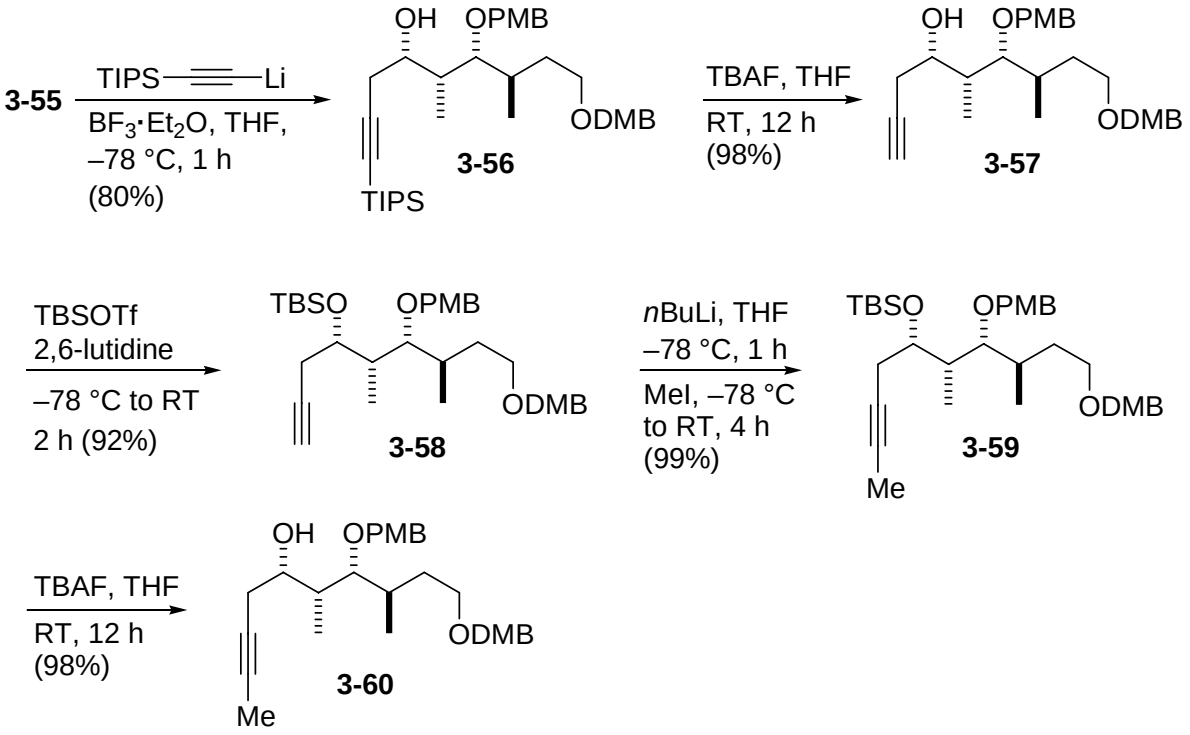
Although, the way to epoxide **3-42** was well established we decided to change some protective groups in order to avoid difficulties which might appear on the later stage of the synthesis. Thus, primary alcohol **3-38** was protected using 3,4-dimethoxybenzyltrichloroacetimidate leading to ether **3-51** in excellent yield.[120] It is known that DMB ethers, in comparison to PMB analogues, are less stable against oxidative agents such as DDQ and CAN.[121] This should allow us to perform a selective deprotection of the primary DMB group in presence of a secondary PMB ether. Thus, the TBS group was cleaved using TBAF in THF. This reaction proceeds smoothly and provided us with alcohol **3-52** in 95% yield (**Scheme 38**). Deprotonation of the secondary hydroxyl function with potassium hydride, followed by treatment of the alcoholate with freshly prepared 4-methoxybenzyl

bromide secured acetonide **3-53** in good yield. Subsequently, the acetonide moiety was cleaved under the same conditions as was described for compound **3-39** ($CuCl_2 \cdot 2H_2O$, acetonitrile, –5 °C). This afforded diol **3-54**, which was easily transformed to oxirane **3-55** using the one-pot procedure.




**Scheme 38.** Synthesis of epoxide **3-55**.

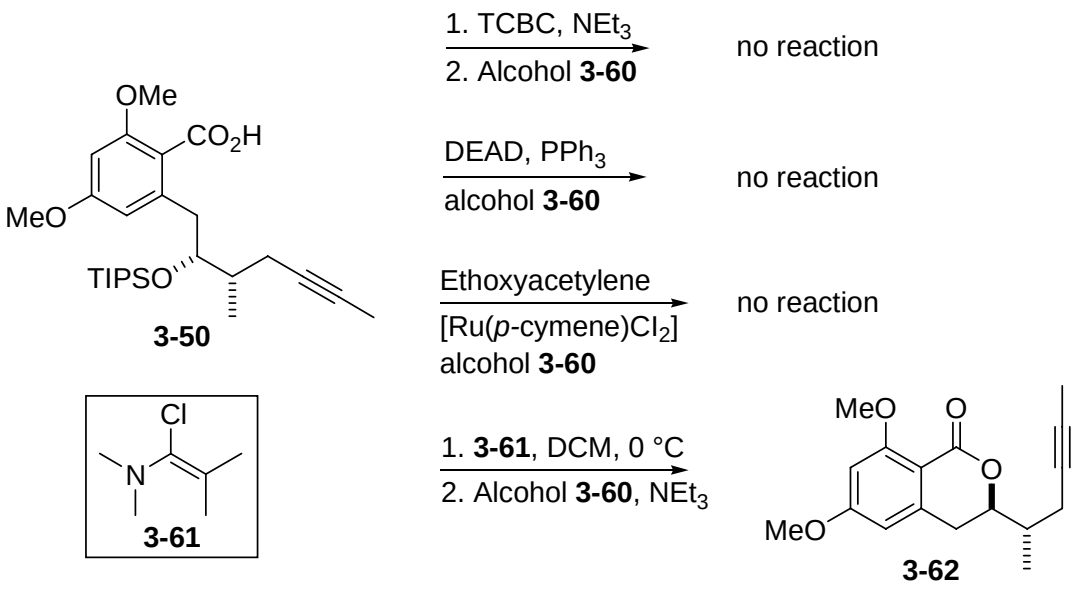
With epoxide **3-55** in hand we started to investigate the introduction of the internal alkyne necessary for the RCAM. As it was previously mentioned, the desired fragment can be established using an epoxide opening reaction with acetylide derived from propyne or silicon monoprotected acetylene. In the last case additional methylation of the terminal triple bond is required. A possible short-cut from epoxide **3-55** to the alkyne **3-60** was attempted by direct opening of the epoxide with propynyllithium. Unfortunately, the major product in this reaction using propynyllithium prepared *in-situ* from 1-bromopropene[122] turned out to be the corresponding bromohydrin. Opening of epoxide **3-55** with lithium triisopropylsilylacetylide resulted in formation of alcohol **3-56** (**Scheme 39**). Cleavage of the carbon-silicon bond proceeded smoothly and resulted in formation of alcohol **3-57** in almost quantitative yield. Subsequent protection of the hydroxyl function with TBSOTf afforded alkyne **3-58** which then could be deprotonated with *n*-butyllithium and treated with methyl iodide to give propyne deriviative **3-59**. A final treatment of the silyl ether **3-59** with TBAF furnished alcohol **3-60** in excellent yield. Although this sequence includes five chemical steps, all of them are highly efficient and require short reaction time, thus, all operations can be done in two days. Moreover, the desired alcohol **3-60** was obtained in 70% overall yield.




**Scheme 39.** Synthesis of alcohol **3-60**.

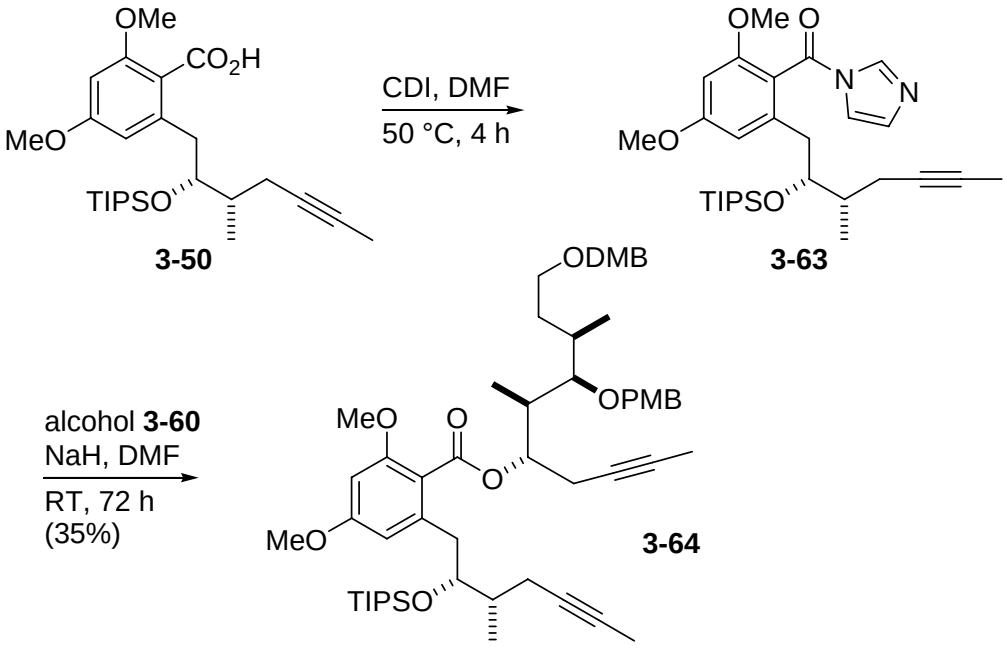
### 3.4.3 Esterification of acid 3-50 with alcohol 3-60

On this stage of our synthesis we faced one of the most challenging tasks of this project. Formation of an ester bond between acid **3-50** and alcohol **3-60** turned out to be rather difficult. Using standard Mitsunobu-,[123] Yamaguchi-,[124] or Trost[125] esterification no trace of product was observed. Also, attempts to make the desired ester using peptide coupling reagents like DCC/DMAP, or BOP were not successful. Another option for esterification of sterically hindered acids and alcohols relies on the reaction of an acid chloride with a sodium alcoholate. However, attempted conversion of acid **3-50** to the corresponding acid chloride was not possible. Instead, formation of the six-membered lactone **3-62** was observed (**Scheme 40**).




**Scheme 40.** Attempted esterification of acid **3-50**.

Eventually we found that the desired ester **3-64** could be obtained by reaction of the imidazolidine derivative[126,127] of acid **3-50** with the putative sodium alcoholate of alcohol **3-60**, prepared by stirring the alcohol with 1.2 equiv of NaH in DMF. Unfortunately this reaction proceeded very slowly (3 days) and ester **3-64** was obtained in only 35% yield. Very interesting is that the imidazolide derivative was found to be very stable and could be recovered from the reaction (**Scheme 41**).




**Scheme 41.** Synthesis of ester **3-64**.

As the main reason for such unfavorable esterification, big sterical demands of the secondary hydroxyl function as well as the functionalized benzoic acid can be considered. Keeping this

in mind, we decided to make the corresponding secondary hydroxyl function more accessible. An initial idea was to remove the PMB protecting group.

### 3.4.4 Synthesis of diol 3-71

As one can see, the desired diol can be obtained from epoxide **3-66**. The latter is easily accessible from one of the key intermediates used in the synthesis of epoxide **3-55** (**Figure 18**).

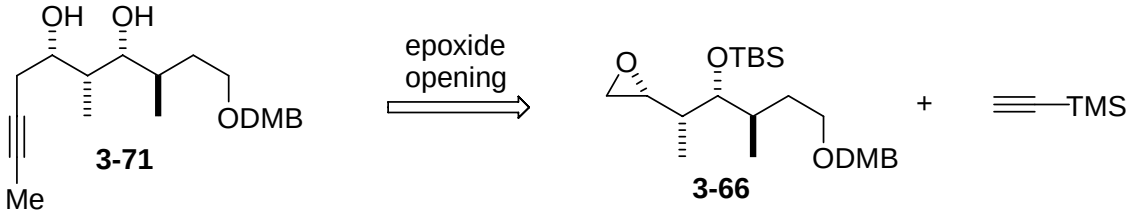
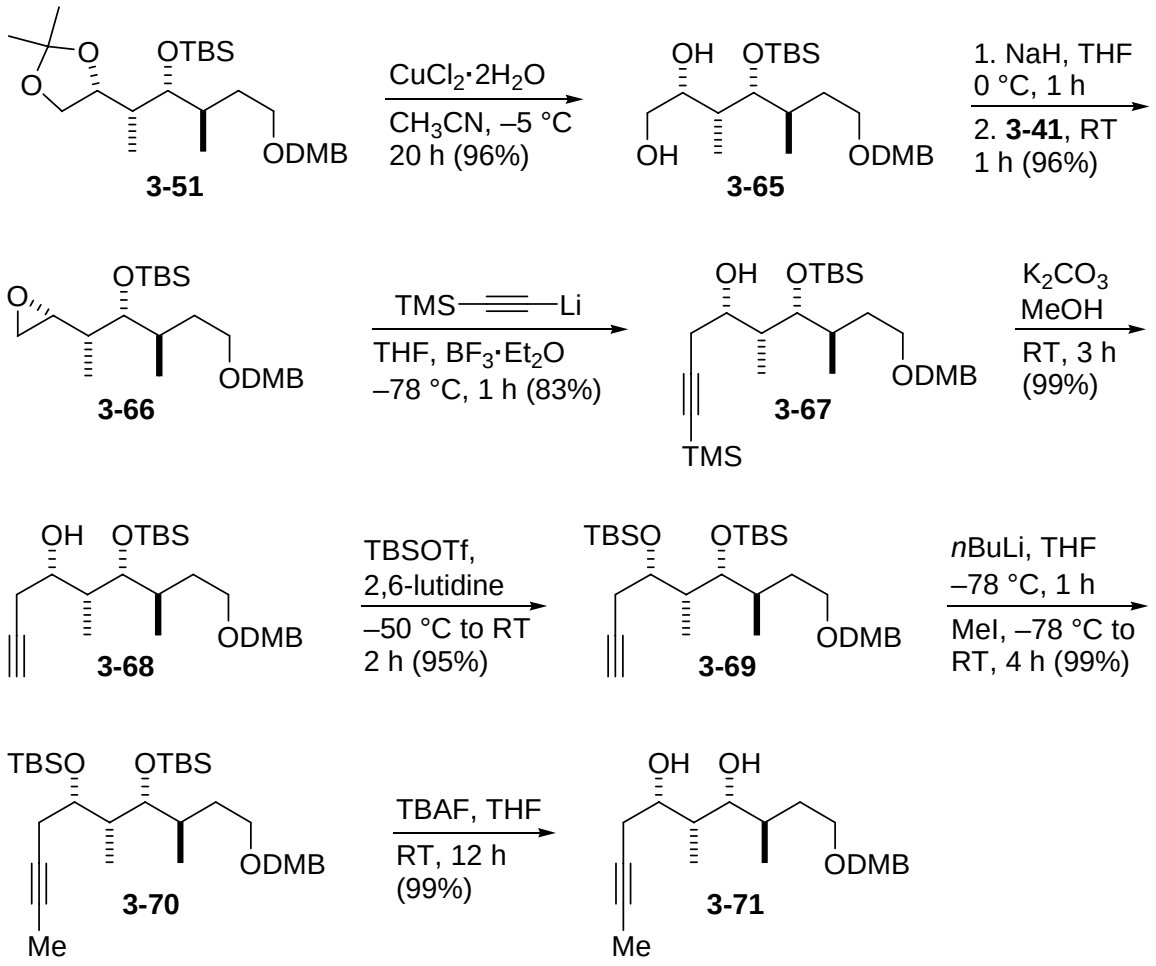



**Figure 18.** Retrosynthetic analysis for diol **3-71**.

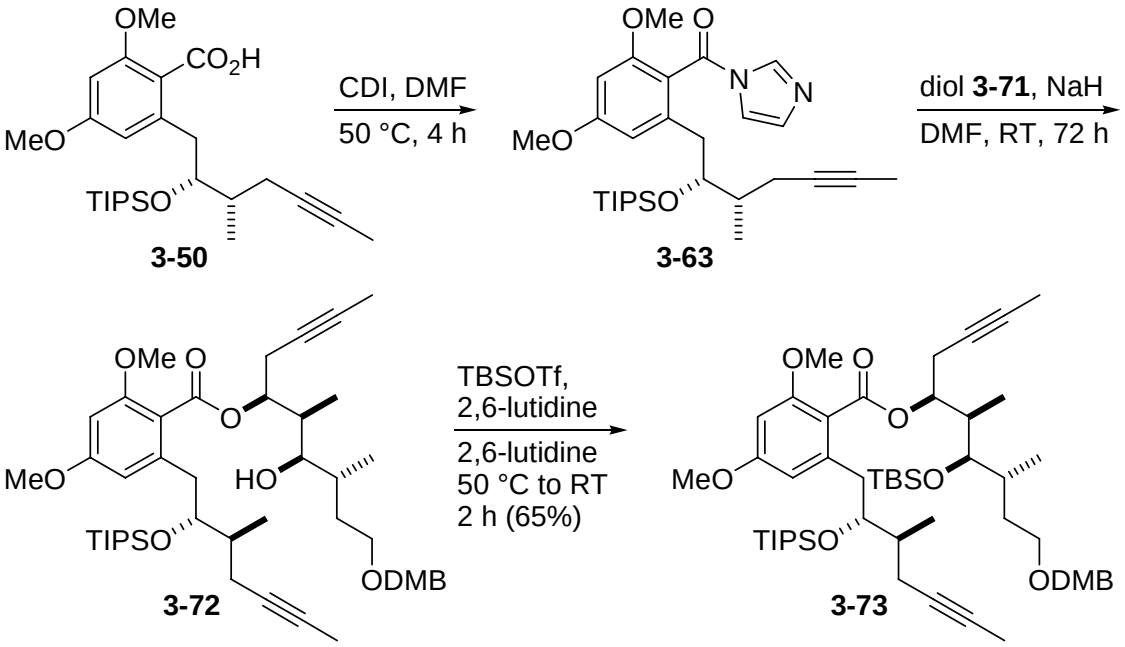
Hence, as the previously described DMB ether **3-51** was still available in gram amounts it was immediately subjected to react with $CuCl_2 \cdot 2H_2O$ in acetonitrile at –5 °C (**Scheme 42**). This furnished diol **3-65** in excellent yield. Thereafter, diol **3-65** was converted to epoxide **3-66**. Opening of epoxide **3-66** with lithium trimethylsilylacetylide resulted in formation of alcohol **3-67**. Cleavage of the carbon-silicon bond and protection of the hydroxyl function with TBSOTf afforded alkyne **3-69** which then was methylated to give propyne deriviative **3-70**. A final treatment of the bis-silyl ether **3-70** with TBAF furnished diol **3-71** in excellent yield.




**Scheme 42.** Synthesis of diol **3-71**.

### 3.4.5 Esterification of acid 3-50 with diol 3-71

Having in hand sufficient amounts of acid **3-50** and diol **3-71** our next task was to make their coupling using already developed methodology. Formation of activated intermediate **3-63** was achieved by stirring acid **3-50** with CDI at 50 °C for 4 h (monitoring by LC-MS). Obtained derivative was allowed to react with the putative disodium alcoholate of diol **3-71**, prepared by stirring the diol with 2.5 equiv of NaH in DMF (**Scheme 43**). This reaction resulted in formation of only one regioisomer. It is important to mention, that the rate and yield of esterification are highly dependent on the concentration of the substrates. Trying different conditions, we have found that the optimal concentrations of imidazolide intermediate **3-63** and diol **3-71** are 0.76 M and 0.54 M, respectively. If the concentration of the substrates is lower this reaction might proceed less efficient. The obtained hydroxyester **3-72** was protected as TBS ether to give ester **3-73** in 65% overall yield.




**Scheme 43.** Synthesis of ester **3-73**.

At this stage the regiochemistry of the ester formation could be inferred from the COSY spectrum of ester **3-73**. Most revealing in this context were cross peaks of the ester methine hydrogen $H_b$ to the vicinal methylene hydrogen atoms $H_{c,d}$ (**Figure 19**).

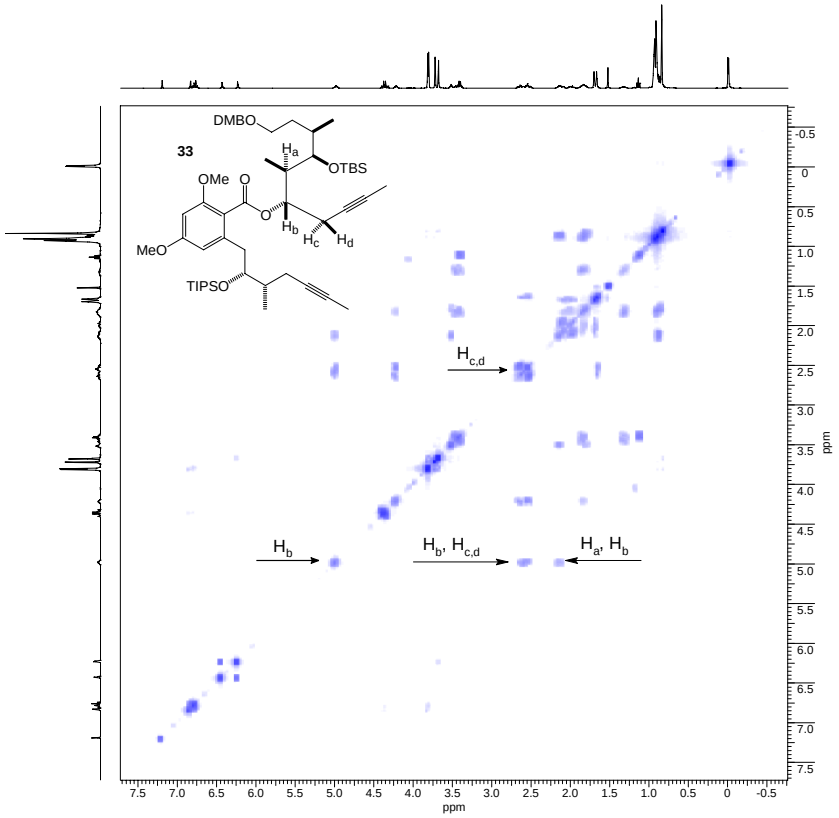


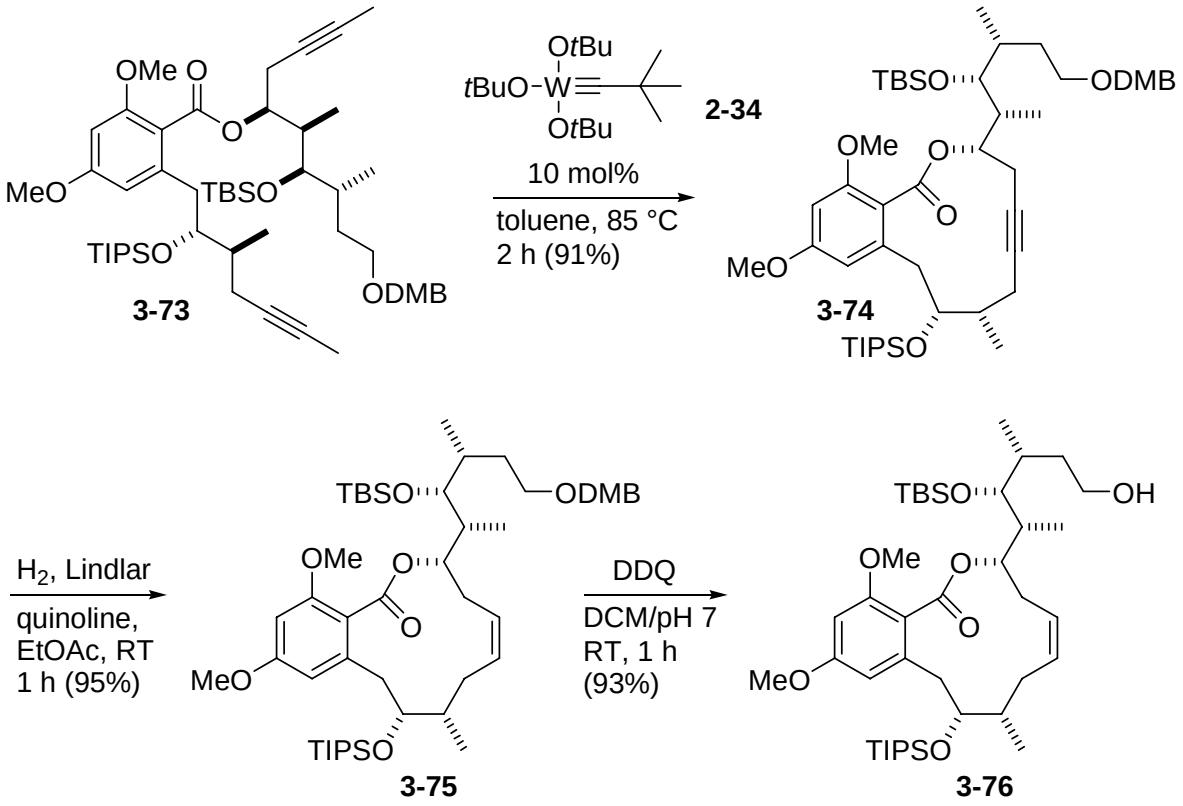

**Figure 19.** H-H Cosy spectrum (400 MHz, $CDCl_3$) of ester **3-73**.

As can be seen, we obtained the required precursor for RCAM in a very efficient manner. Our next task was to make the ring closure of compound **3-73** in order to reach the macrolactone core of cruentaren A.

### 3.4.6 Ring closing metathesis reaction and synthesis of the core structure of cruentaren A

The crucial RCAM reaction of ester **3-73** proceeded smoothly and resulted in the formation of macrolactone **3-74** in 91% yield (**Scheme 44**). Thus, addition 10 mol% of the tungsten carbine complex **2-34**[41] to a solution of the diyne **3-73** (0.009 M in degassed toluene!) and stirring the mixture for 2 h at 85 °C induced an efficient cyclization.[44] It was found that the tungsten carbine complex **2-34** is extremely moisture and oxygen sensitive. Thus, to obtain satisfactory results some precautions should be taken. We used the following technique: a freshly bought batch of the catalyst (100 mg from Strem Chemicals) was transferred into a glowbox and then weighted into 20–25 mg portions. Each portion was secured in a tightly closed brown glass vial with rubber septum cap and used when necessarily as a whole. The catalyst was introduced into the reaction as a solution in 0.5–1.0 ml of degassed toluene.

Creation of the *Z*-double bond was achieved using Lindlar reduction ($H_2$, Pd on $CaCO_3$, poisoned with lead, EtOAc/quinoline) on the alkyne **3-74** leading to lactone **3-75**. Under these conditions, no overreduction was observed. Finally, deprotection of the DMB group with DDQ led to macrolactone **3-76**, the core structure of cruentaren A.




**Scheme 44.** Synthesis of the core structure of cruentaren A.

After the synthesis of the macrolactone core was accomplished we made some test reactions in order to check the possibility of TIPS ether cleavage. Preliminary studies on a derivative of lactone **3-76** to cleave the silicon protecting groups with the HF·pyridine complex unfortunately led to the corresponding δ-lactone. As a way out of this dilemma, we relied on the triple bond in the macrolactone hoping that it would prevent this unwanted intramolecular translactonization due to steric reasons. The introduction of the two double bonds we decided to make at the final stage of the synthesis. Accordingly, the synthetic route was devised with this in mind.

### 3.4.7 Connection of the propargyl amide side chain

For the introduction of the *Z*-allylamine moiety Lindlar reduction of corresponding alkyne derivative was envisioned. Accordingly, to introduce the required propargylamine fragment we relied on the Bestmann one carbon elongation sequence. Later simple functional group manipulation followed by coupling of the obtained amide with hexanoic acid derivative **2-31** should lead to the carbon skeleton of cruentaren A (**Figure 20**).

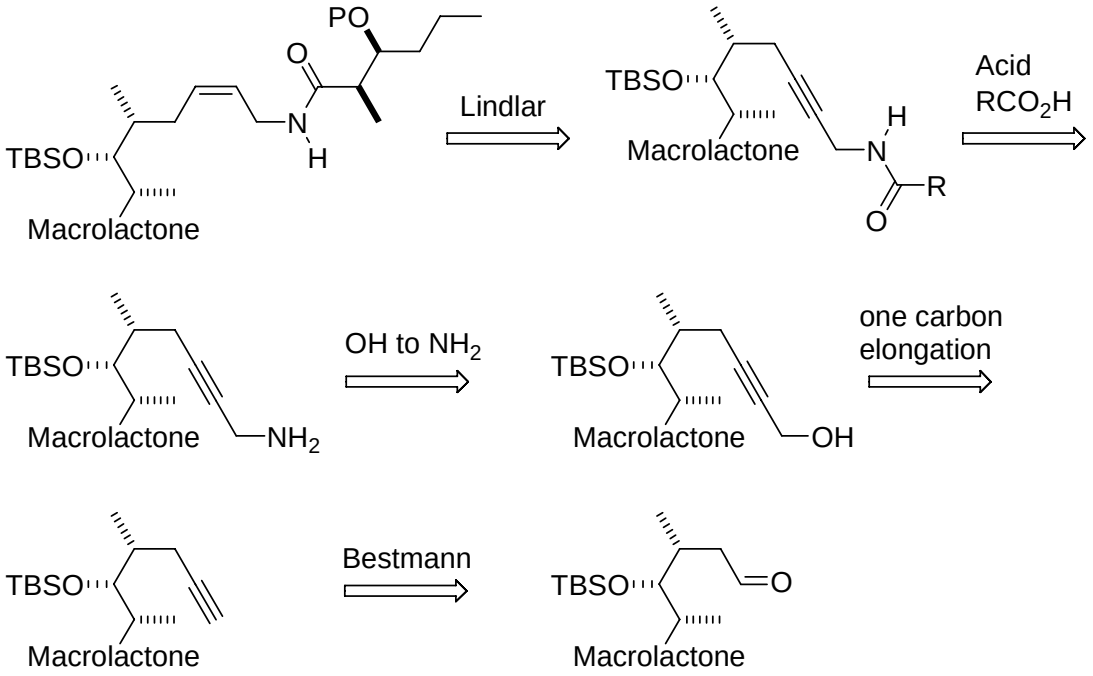
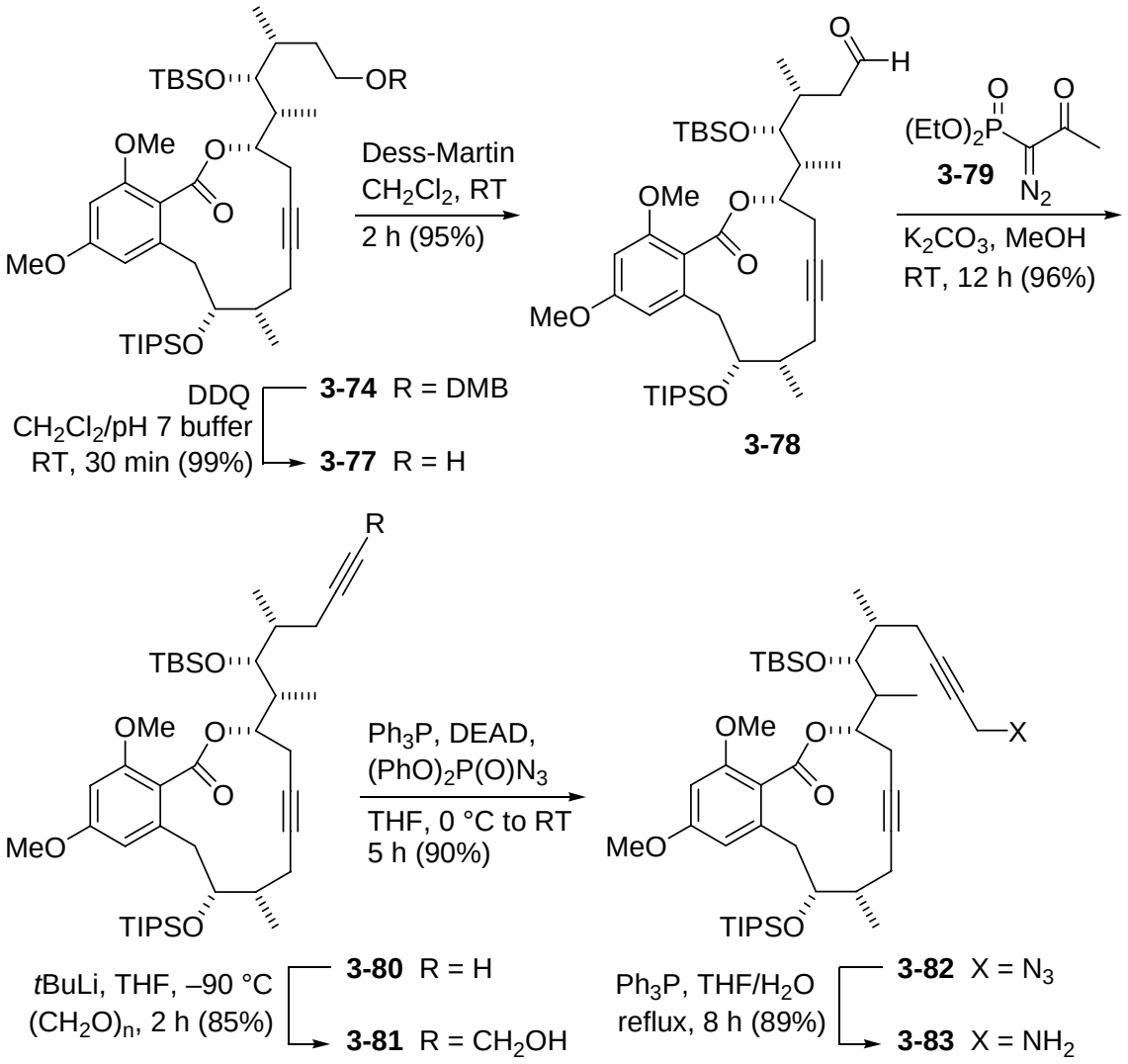


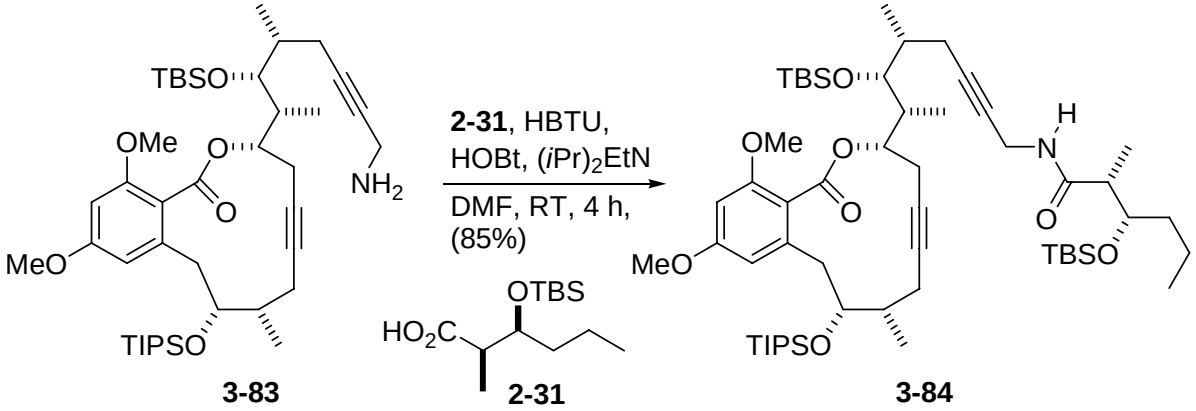

**Figure 20.** Retrosynthetic analysis for the installation of the Z-allylamide side chain.

First, the dimethoxybenzyl (DMB) group of **3-74** was removed under oxidative conditions[121] using DDQ in a pH 7 buffer/dichloromethane mixture[128] (**Scheme 45**). It is interesting to note, that already after 30 minutes stirring at ambient temperature TLC indicated complete consumption of starting material. A subsequent oxidation of the resulting primary alcohol **3-77** with the Dess-Martin periodinane[129] furnished aldehyde **3-78**. The aldehyde **3-78** was extended to the alkyne **3-80** by reacting it with the diazophosphonate **3-79**[130] in methanol in presence of potassium carbonate.[131] With alkyne **3-80** in hand a one carbon homologation was performed via deprotonation of the alkyne followed by addition of dried paraformaldehyde. In this step it is very important that prior to use paraformaldehyde it should be dried in vacuo (in a dessicator) over $P_2O_5$ for 2 days and then suspended in absolute THF and dried with molecular sieves (4 Å) for 1 day. This way the propargylalcohol **3-81** was obtained in good yield. For the introduction of the azide, Mitsunobu conditions were used.[132] Thus, reaction of alcohol **3-81** with $PPh_3$, diethyl azodicarboxylate (DEAD) and diphenylphosphoryl azide provided the azide **3-82** in excellent yield. Reduction of the azide function to the corresponding amine **3-83** was accomplished with triphenylphenylphosphine followed by hydrolysis of intermediate phosphinimine.[133] Due to high polarity of the corresponding propargyl amine, column chromatography was done using a DCM/MeOH/$NH_4OH$ = 9:1:0.01 mixture as eluant.




**Scheme 45.** Synthesis of propargylamine **3-83**.

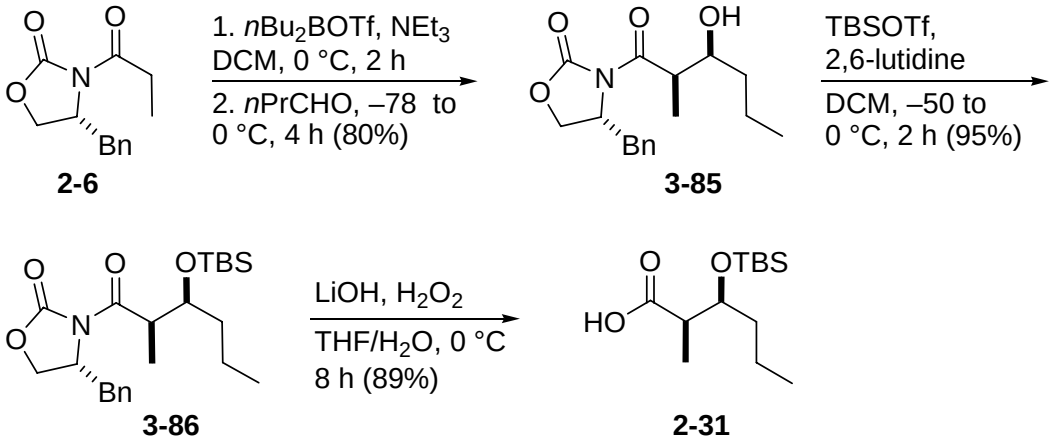
Condensation of the amine **3-83** with the hexanoic acid derivative **2-31** using HBTU in presence of HOBT in DMF as solvent proceeded smoothly and secured the amide **3-84** in 85% yield.




**3-83** **2-31** **3-84**

**Scheme 46.** Synthesis of cruentaren A skeleton **3-84**.

Synthesis of acid **2-31** started with an Evans aldol reaction of oxazolidinone **2-6** with butyraldehyde.[134] Subsequent protection of the secondary hydroxyl with TBS triflate in the presence of 2,6-lutidine as a base resulted in formation of TBS ether **3-86** (**Scheme 47**). Lithium peroxide mediated cleavage of the oxazolidinone auxiliary secured the required hexanoic acid derivative **2-31**.



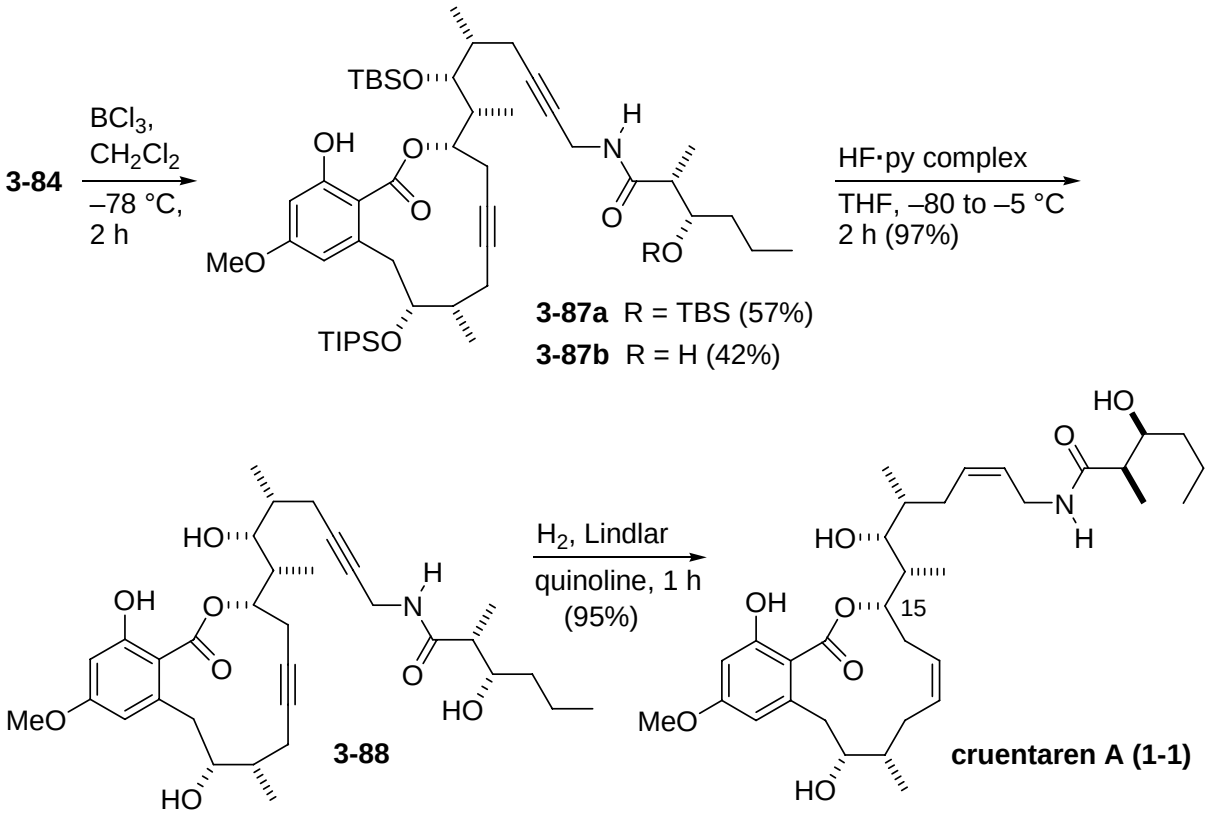

**2-6** **3-85** **3-86** **2-31**

**Scheme 47.** Synthesis of acid **2-31**.

### 3.4.8 Completion of the synthesis of cruentaren A

After the full skeleton of cruentaren A was established, our next tasks were: selective cleavage of the methyl ether next to the carboxyl function, global silyl removal and selective reduction of two triple bonds.

Accordingly, we set out to cleave the methyl ether at C3 in macrolactone **3-84**. This was achieved with boron trichloride in dichloromethane at –80 °C (**Scheme 48**).[135,136] Besides cleavage of the methyl ether, we also observed some cleavage of the silyl ether in the β-hydroxy amide part. One possible explanation for this can be coordination of boron trichloride to the carboxylic function of the propargylamide side chain. The mixture of the two compounds **3-87a** and **3-87b** was then subjected to the HF·pyridine complex[137] in THF, warming the mixture from – 80 °C to – 5 °C. Gratifyingly, we were able to isolate the tetraol **3-88** in almost quantitative yield. None of the unwanted δ-lactone was formed! The methine proton of lactone **3-88** resonates at δ = 5.34 ppm which is typical for the macrolactone. Thus, the triple bond in the lactone nicely served as a lock against translactonization. In the final step, a Lindlar reduction on the diyne **3-88** provided cruentaren A (**1-1**). Notably, no overreduction had occurred. The synthetic material was identical in all respects with natural cruentaren A.




**Scheme 48.** Completion of the synthesis of cruentaren A (**1-1**).

As one can see, an efficient synthesis of the novel macrolide cruentaren A was developed. We were able to produce 46 mg of the final compound in 7% overall yield with the longest linear sequence in 25 steps (starting from described alcohol **3-33**). Our approach features a ring closing alkyne metathesis reaction to form the macrolactone. After extension of the side chain to the propargyl amine **3-83**, condensation with the protected β-hydroxy acid **2-31** provided amide **3-84**. During the following two steps, that is cleavage of the C3 methyl ether and the silicon protecting groups, the triple bond in the ring served as a lock that prevented the unwanted translactonization to the δ-lactone. The final step of the synthesis was a Lindlar reduction of two triple bonds. The sequence is quite concise featuring many high yielding steps and should allow for the synthesis of various analogues.

## 3.5 Synthesis and Biological Evaluation of Cruentaren A Analogues

### 3.5.1 Synthesis of 3-OMe cruentaren (3-90)

As was mentioned previously, cruentaren A is a selective inhibitor of mitochondrial F-ATPase from yeast. Against the L929 cell line cruentaren A shows strong cytotoxicity with an

$IC_{50}$ value of 1.2 ng $mL^{-1}$. Since mitochondrial ATPases play a crucial role in the pathophysiology of several human disorders including cancer, cruentaren A or synthetic derivatives thereof could form the basis of future therapeutic strategies. As confirmation are results recently reported by Kunze and Sasse.[25] In this paper the influence of cruentaren A and apicularen A on the growth of a variety of human cancer cell lines from different tissues was studied. It was found that the $IC_{50}$ values for cruentaren A are comparable with those described for other benzolactones such as apicularen A, in the nanomolar range, even for the multi-drug-resistant cell line KB-V1.

With its 12-membered macrolactone and a side chain that is terminated with an acylated amino function, cruentaren A has some resemblance to the well known benzolactone enamides.[10] However, in contrast to cruentaren A, the benzolactone enamides target V-ATPase.[11] Clearly, it would be of interest to identify key structural elements that are essential for its biological activity.

With regard to the design of analogues we wanted to use the available stereotetrad building blocks and stick to the proven RCAM reaction. We intended to answer the following questions: How important is the carboxylic acid part of the amide? How important is the free OH at C3? Can we make enamides instead of *Z*-allylamides? While quite speculative, it could be that the allylamide isomerizes to an enamide that then might form a highly electrophilic acyliminium ion upon protonation (**Figure 21**).[138]

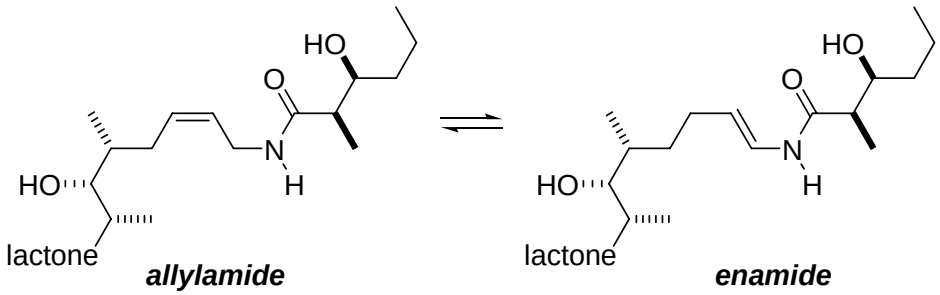
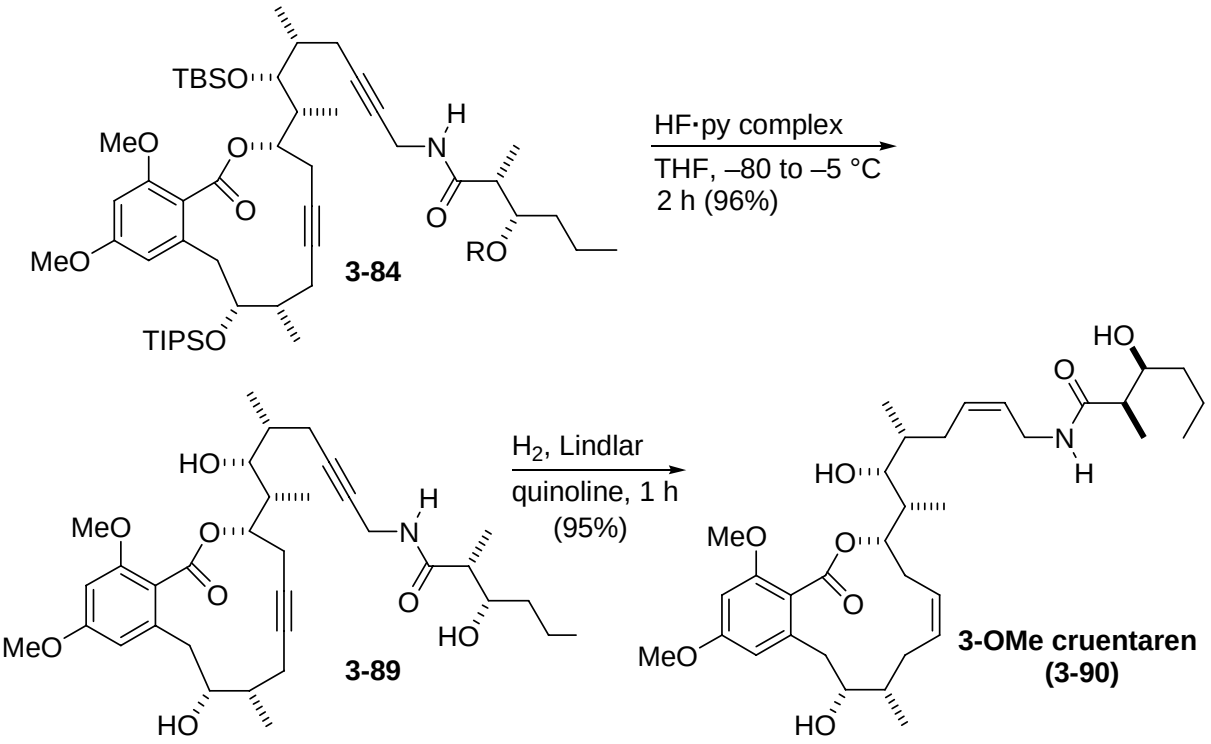



**Figure 21.** Possible isomerisation of allylamide to enamide.

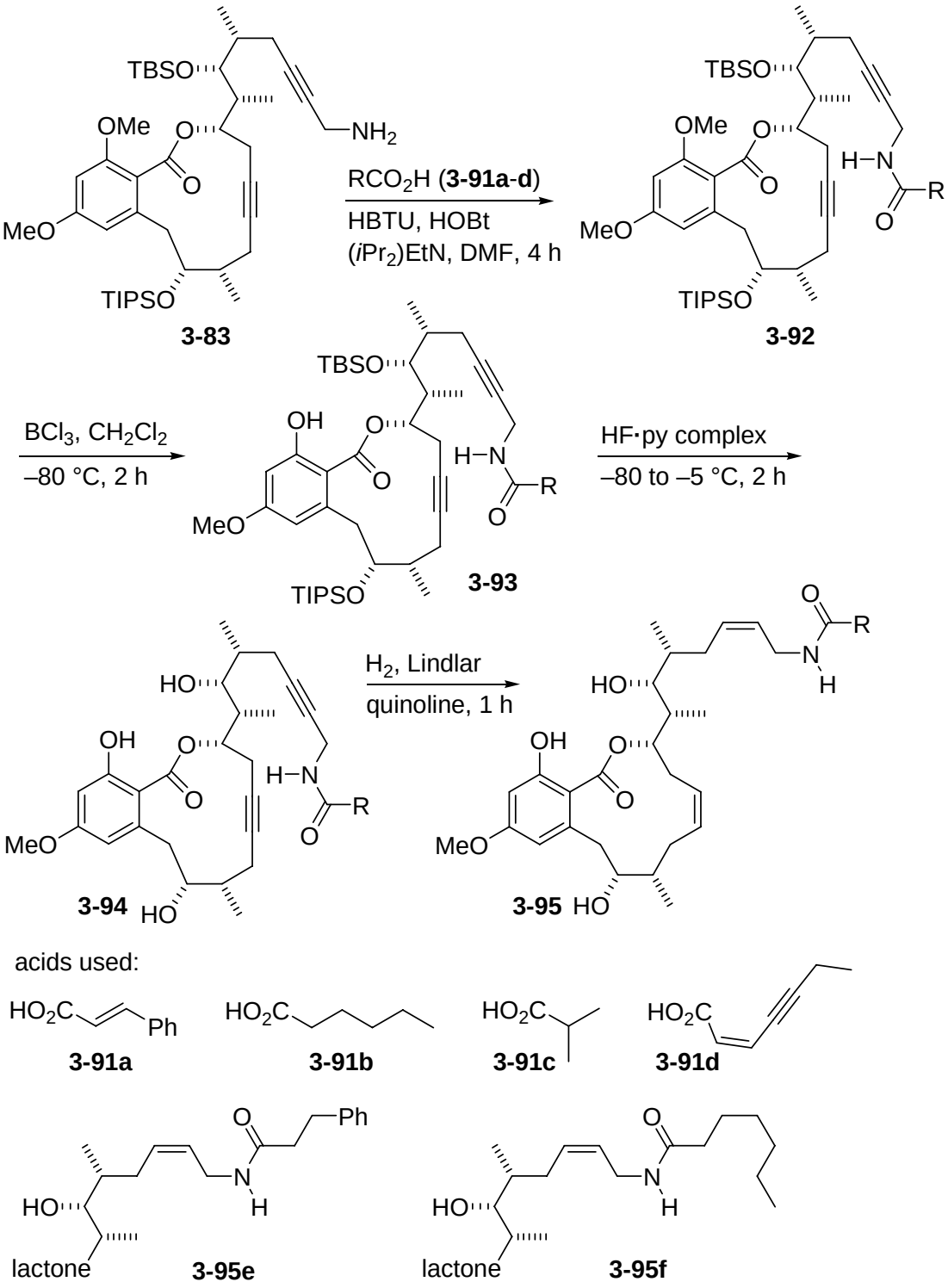
First, we decided to study the importance of free OH at C3. For the preparation of the desired analogue we turned back to the fully protected amide **3-84**. Omitting the cleavage of the C3 methyl ether and instead treating the lactone **3-84** with the HF·pyridine complex led to the triol **3-89** (**Scheme 49**). Similar to the synthesis of cruentaren A, a final Lindlar reduction delivered 3-OMe cruentaren **3-90** in excellent yield.




**Scheme 49.** Synthesis of 3-OMe cruentaren (**3-90**).

### 3.5.2 Modification of the carboxylic acid part of the amide

Another key intermediate of the total synthesis, the propargyl amine **3-83**, presented itself for derivatization reactions. Accordingly, the amine **3-83** was condensed with the acids **3-91a** – **3-91d** using HBTU in the presence of HOBt and Hünig's base in DMF (**Scheme 50**). These acylation reactions proceeded in quite good yields (**Table 3**). For these derivatives we chose to generate the original aromatic part with the 3-OH group. Selective ether cleavage on the lactones **3-92a** – **3-92d** using the well established boron trichloride mediated reaction furnished the corresponding 3-hydroxy compounds **3-93a** – **3-93d**, again in excellent yields. Treatment of the foregoing phenols with HF·pyridine complex provided corresponding triols **3-94a** – **3-94d** in almost quantitative chemical yields. The Lindlar reduction of the diynes **3-94b** and **3-94c** proceeded as expected to give the analogues **3-95b** and **3-95c**. Due to a possible overreduction the reaction was monitored by LC-MS. Unfortunately, in some cases product of overreduction was observed already after 30% conversion of starting diyne. As a result, from the reduction of diyne **3-94a** the analogue **3-95a** (74% yield) was obtained, but we also isolated the dihydro compound **3-95e** (24% yield), resulting from hydrogenation of the cinnamoyl double bond. In the case of the hept-2-en-4-ynamide **3-94d** we were able to isolate only the product **3-95f**, resulting from complete hydrogenation. The internal *Z*-double bond survived as in the other amide analogues.




**Scheme 50.** Synthesis of analogues with modified carboxylic acid part.

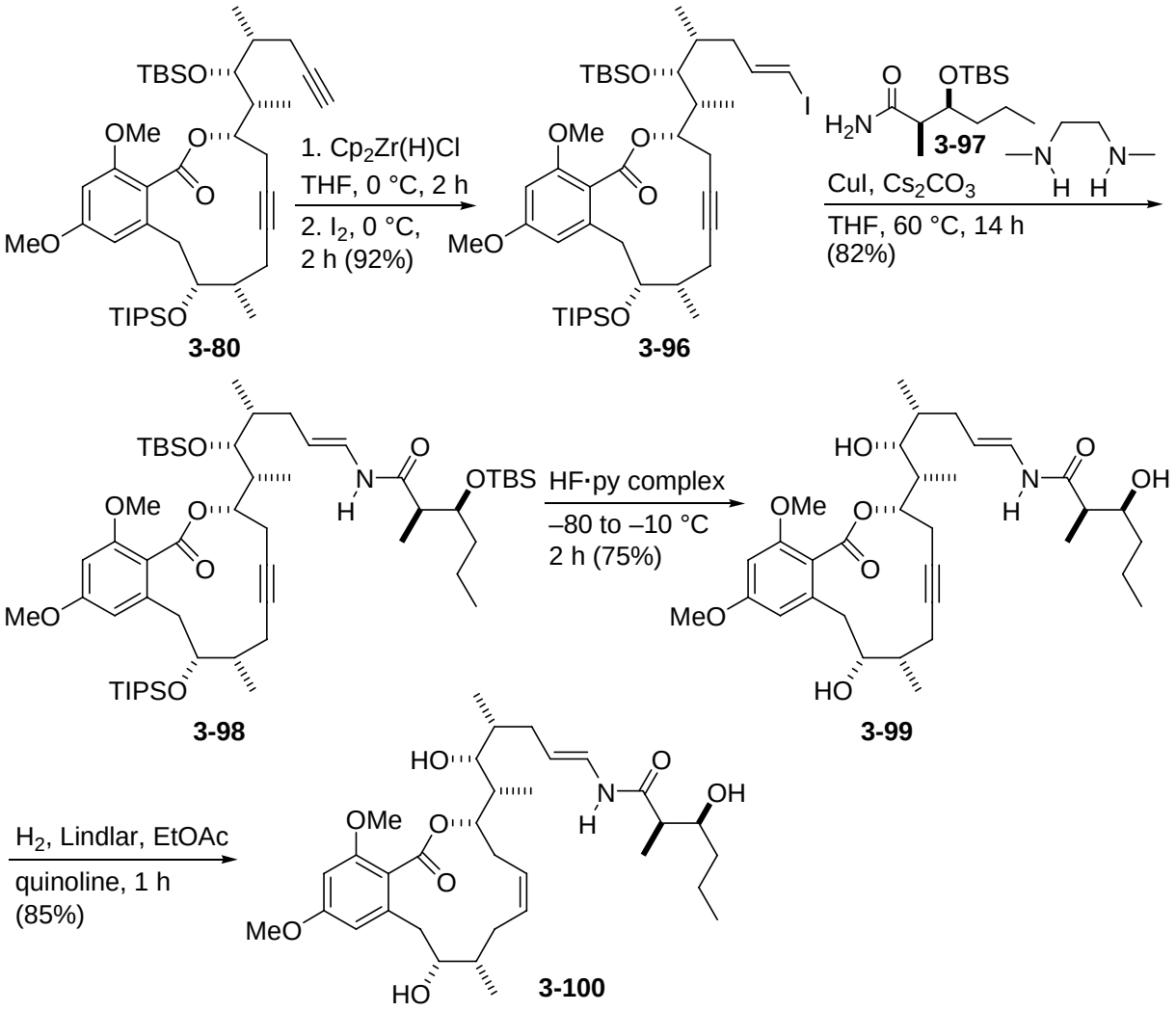
**Table 3.** Yields for the various steps for the synthesis of amide analogues **3-95** of cruentaren A

| | Transformation | | | |
|---|---|---|---|---|
| acid used | acylation | $BCl_3$ | HF·py | Lindlar |
| **3-91a** | 87 | 92 | 95 | 74[a] |
| **3-91b** | 88 | 86 | 93 | 93 |
| **3-91c** | 91 | 83 | 85 | 87 |
| **3-91d** | 85 | 89 | 92 | 73[b] |

[a] by-product dihydro derivative **3-95e**
[b] only the saturated heptanoyl derivative **3-95f** was formed under the Lindlar conditions

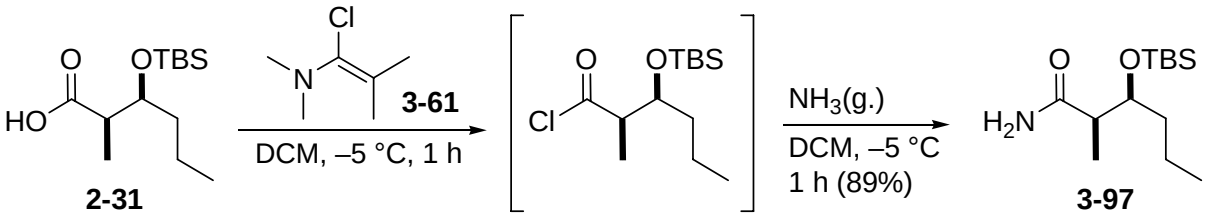
### 3.5.3 Synthesis of the enamide analogue 3-100

As a further branching point for the synthesis of analogues we indentified the lactone **3-80** with a propynyl terminus. We thought that the derived vinyl iodide might be useful for the synthesis of enamide derivatives. With this in mind, diyne **3-80** was subjected to hydrozirconation with the Schwartz reagent followed by addition of iodine to the intermediate vinylmetal species (**Scheme 51**). This secured required vinyl iodide **3-96** in excellent yield.[139] Notably, the introduction of the vinyl iodide moiety was also tried using Takai conditions on aldehyde **3-78**. But unfortunately this resulted in formation of an inseparable 4:1 mixture of *E*- and *Z*-vinyl iodides. Thereafter, a copper catalysed cross-coupling reaction of vinyl iodide **3-96** with the amide **3-97** under Buchwald conditions[97] was performed resulting in enamide **3-98** in high yield. Due to the expected sensitivity of the enamide to harsh acidic conditions the demethylation step was omitted. Nevertheless, the enamide survived the conditions (HF·pyridine complex) for global deprotection of the silyl ethers. A Lindlar reduction on diyne **3-99** completed the synthesis of enamide analogue **3-100**.




**Scheme 51.** Synthesis of the enamide analogue **3-100**.

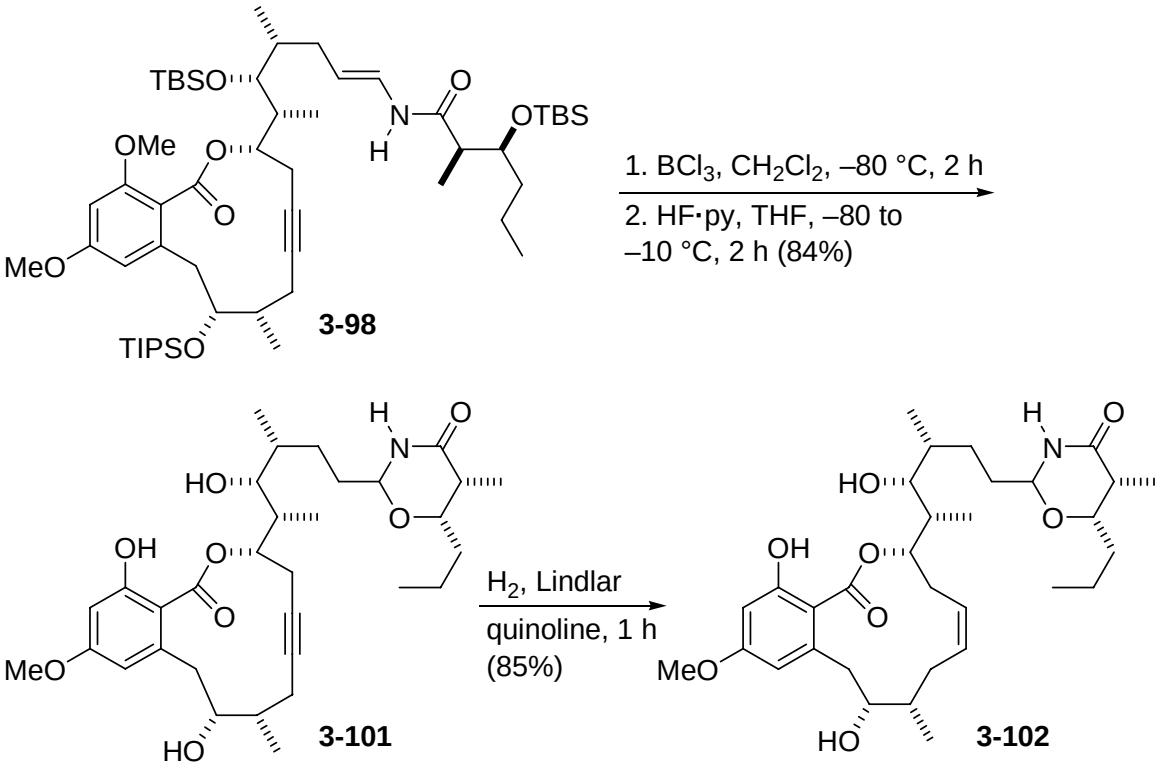
The required amide **3-97** was derived from the previously described carboxylic acid **2-31**. In order to avoid unwanted TBS ether cleavage formation of intermediate acid chloride was achieved using the Ghosez chloroenamine **3-61** (N-(1-chloro-2-methyl-1-propenyl)-N,N-dimethylamine) (**Scheme 52**).[140] This was followed by bubbling gaseous ammonia through the reaction mixture and secured amide **3-97** in high yield.




**Scheme 26.** Synthesis of amide **3-97**.

### 3.5.4 Synthesis of the oxazinan-4-one analogue 3-102

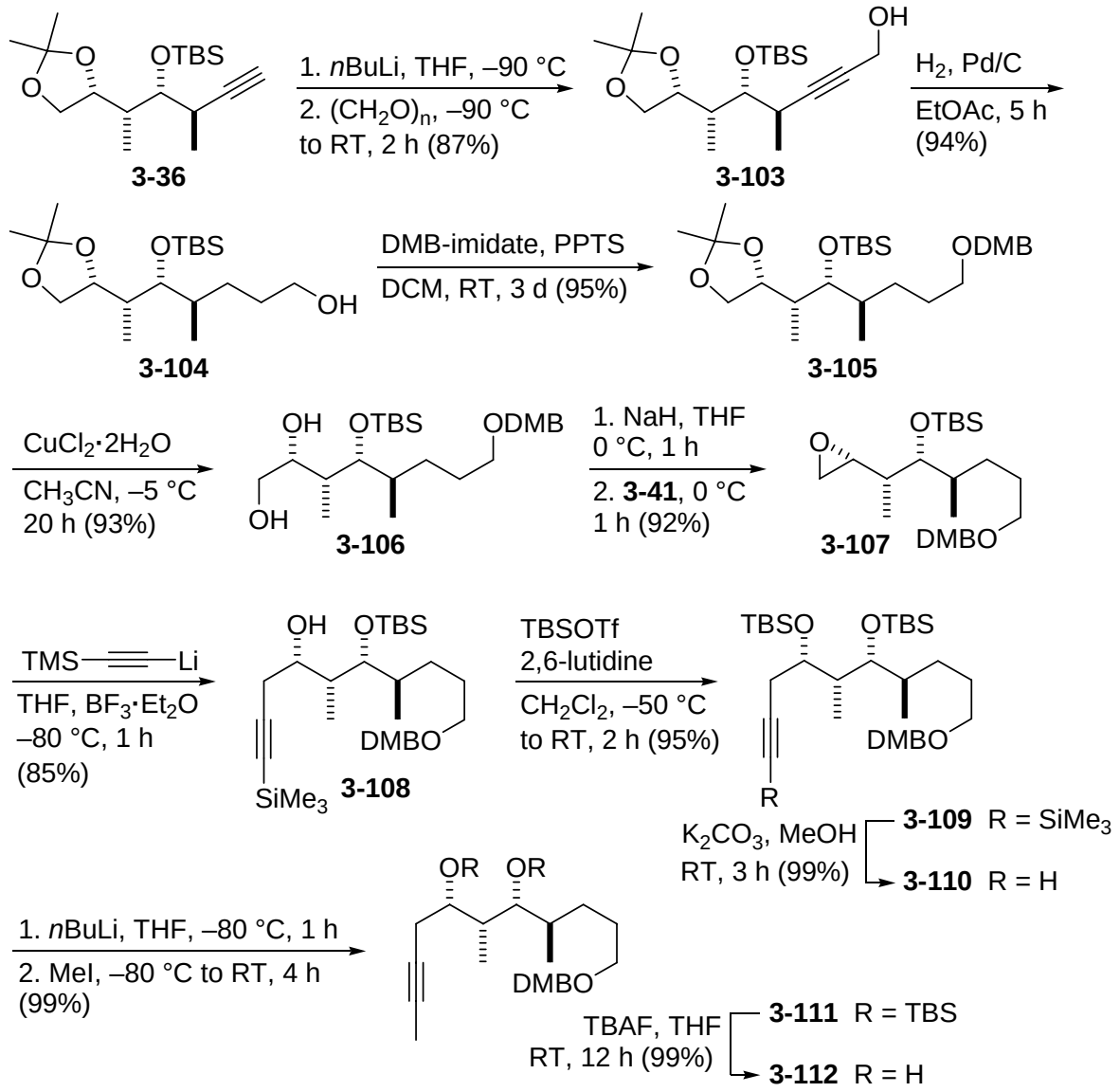
To get more information about structure-activity relationship of the obtained derivatives we attempted to generate the original aromatic part with the 3-OH group. If however, the enamide **3-98** was treated with boron trichloride to cleave the C3 O-methyl ether, followed by global silyl removal with HF·pyridine complex, a compound (**3-101**) lacking the enamide signals in the $^1$H NMR spectrum was isolated (**Scheme 53**). According to LC-MS analysis the mass was the same as expected for the enamide. The signal at $\delta$ = 5.02 ppm in the $^1$H NMR pointed to the presence of the 1,3-oxazinan-4-one. The formation of this heterocyclic ring system can easily be explained via the corresponding acyliminium ion. While we were not able to unambiguously assign the stereochemistry at the aminal carbon we assume a 2,6-*cis*-configuration (oxazinone-4-numbering). Chem3D calculations on 2,5,6-trimethyl-1,3-oxazinan-4-one showed the *cis*-2,6-diastereomer to be 5.65 kJ mol$^{-1}$ more stable than the corresponding 2,6-*trans* isomer. Lindlar reduction of the triple bond led to the oxazinan-4-one analogue **3-102**. It can be assumed that oxazinanone formation occurs upon treatment of the enamide **3-98** with $BCl_3$, since the HF·pyridine complex seems not to affect the enamide as could be shown with the deprotection of **3-98** to enamide **3-99**.




**Scheme 53.** Synthesis of the oxazinan-4-one analogue **3-102**.

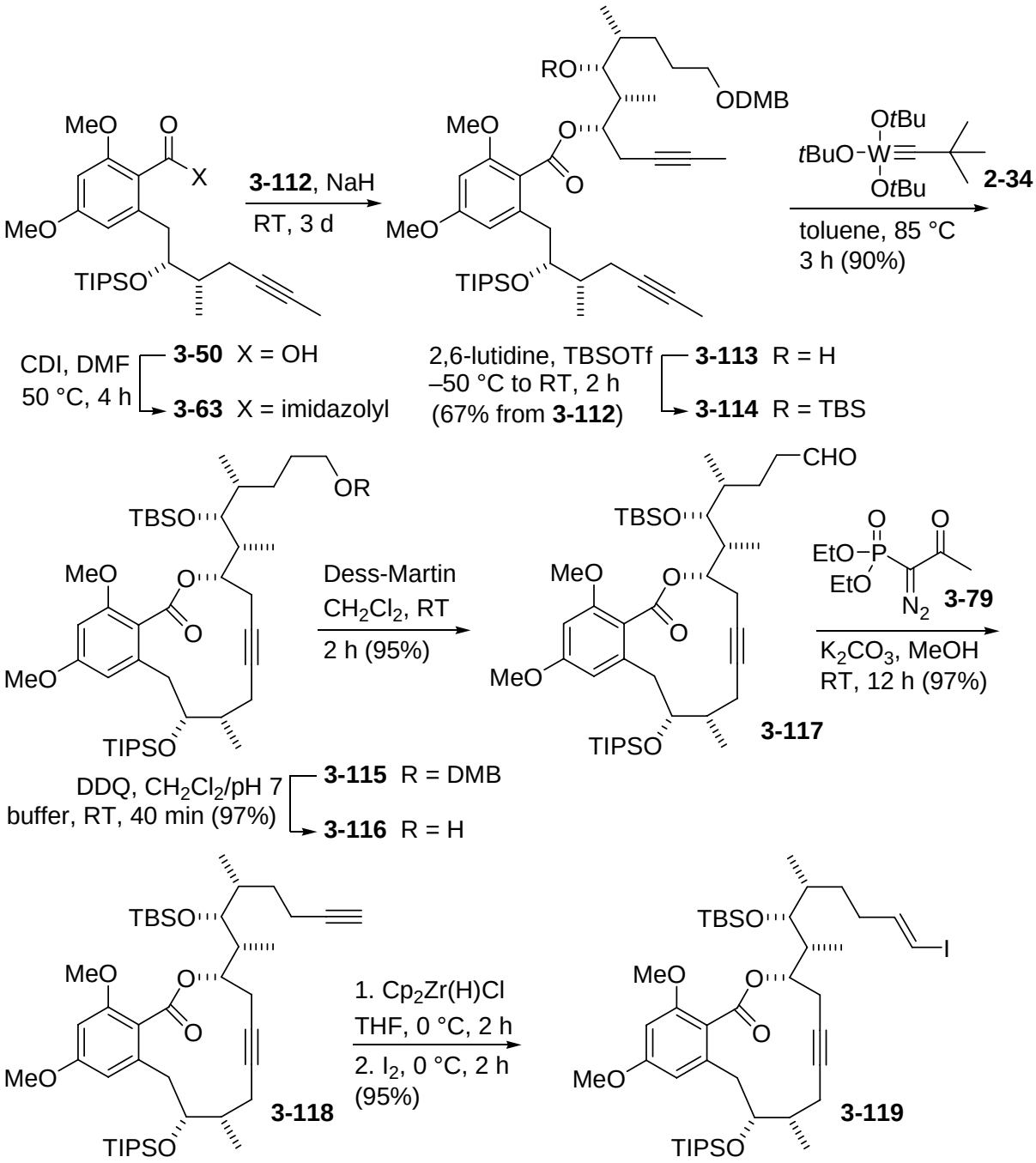
### 3.5.5 Synthesis of the vinyl iodide 3-119

To further probe the potential biological relevance of a cruentaren A enamide, the homologated enamide derivative of analogue **3-100** was targeted. In this case we could have used macrolactone **3-80**, with a propyne terminus, as starting material but instead we began with the stereotetrad containing building block **3-36** (**Scheme 54**). This compound which originated from a Marshall-Tamaru reaction was extended to the propargyl alcohol **3-103**. A hydrogenation reaction provided the propanol derivative **3-104**. Protection of the hydroxyl function with dimethoxybenzyl imidate to give **3-105** was followed by cleavage of the isopropylidene group using aqueous copper(II) chloride to provide diol **3-106**. The 1,2-diol was converted to the epoxide **3-107** using the arylsulfonyl derivative **3-41**. The stage was now set for epoxide opening with lithium trimethylsilylacetylide in presence of $BF_3{\cdot}OEt_2$. Silylation of **3-108** and removal of the acetylenic silyl group from **3-109** furnished alkyne **3-110**. In preparation for the RCAM reaction, the terminal alkyne **3-110** was converted to the inner alkyne **3-111** using *n*BuLi followed by MeI. Thereafter treatment of bis-silyl ether **3-111** with TBAF delivered diol **3-112**.




**Scheme 54.** Synthesis of diol **3-112**.

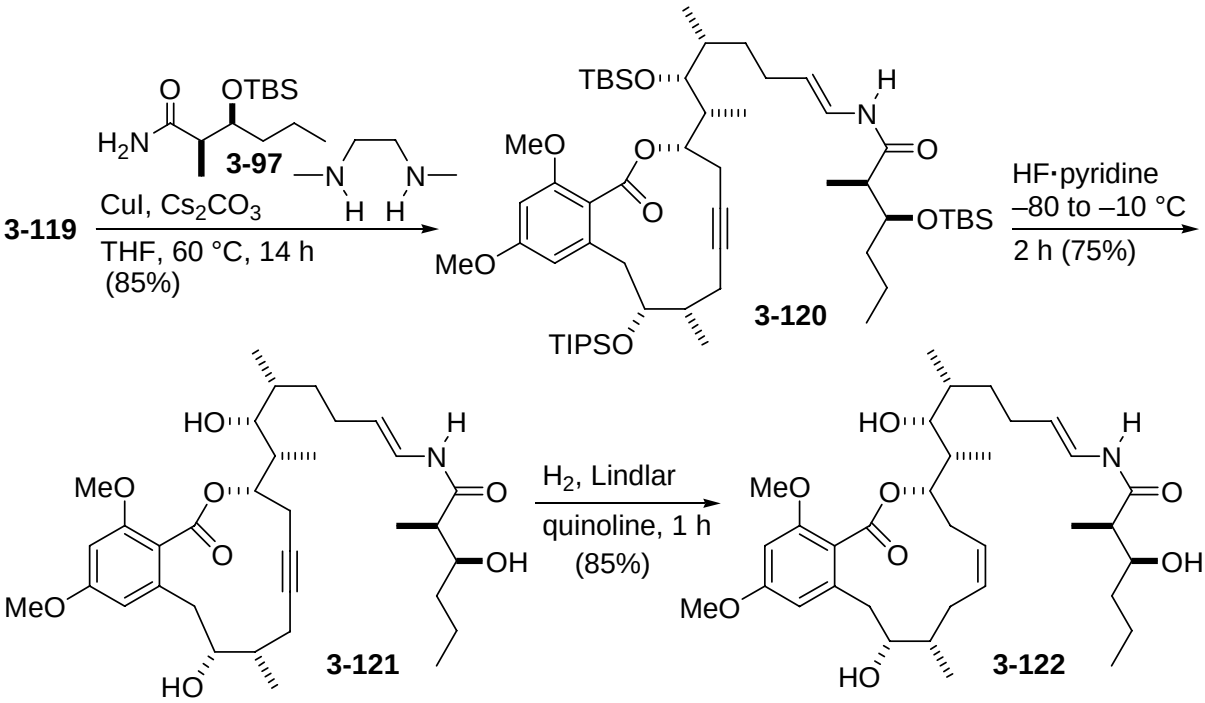
As we had found during the synthesis of the core structure **3-76**, esterification of benzoic acid **3-50** was best done with the diol **3-112** itself. After conversion of the acid to the corresponding carbonylimidazolide **3-63**, esterification with the sodium alcoholate of **3-112** proceeded smoothly and in a regioselective manner (**Scheme 55**). Silylation of the free hydroxyl function of **3-113** gave rise to the ester **3-114**, the substrate for the alkyne metathesis reaction. Based on the diol **3-112** the yield for the ester **3-114** amounted to 67%. The RCAM reaction of **3-114** with the Schrock catalyst **2-34** proceeded in excellent yield furnishing lactone **3-115**. In order to set up an (*E*)-vinyl iodide at the side chain terminus, the DMB protecting group was removed under oxidative conditions. The resulting primary alcohol **3-116** was oxidized to the aldehyde **3-117**. Extension of the aldehyde **3-117** to the alkyne was accomplished with the Bestmann-Ohira reagent **3-79** in presence of $K_2CO_3$. Finally, hydrozirconation and iodination provided the vinyl iodide **3-119**.




**Scheme 55.** Synthesis of vinyl iodide **3-119**.

### 3.5.6 Synthesis of the homologated enamide 3-122

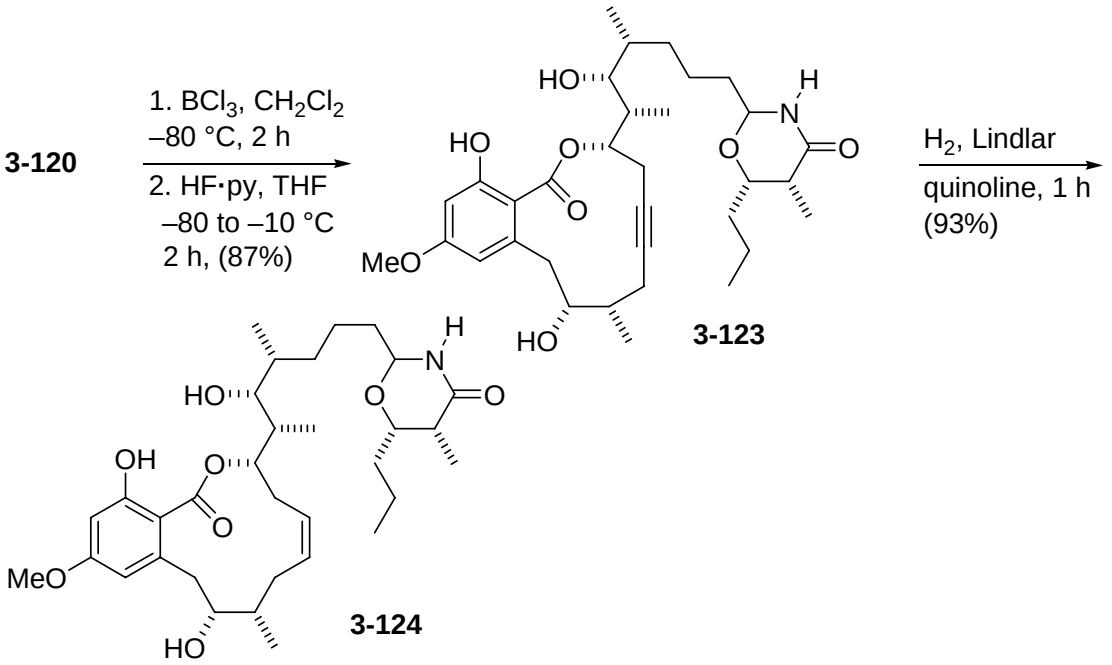
Synthesis of enamide **3-122** was accomplished applying conditions already developed for the analogue **3-100**. Accordingly, a cross-coupling reaction of vinyl iodide **3-119** with the amide **3-97** under the Buchwald conditions came to use in order to set up the enamide functionality (**Scheme 56**). HF·pyridine complex mediated global silicon ether cleavage on **3-120** secured alkyne **3-121**. Finally, Lindlar reduction of the triple bond furnished analogue **3-122**.




**Scheme 56.** Synthesis of enamide **3-122**.

### 3.5.7 Synthesis of the oxazinan-4-one analogue 3-124

If the enamide **3-120** was treated with $BCl_3$, cleavage of the C3 OMe ether was accompanied by the formation of the oxazinan-4-one **3-123** (**Scheme 57**). As was shown before, global deprotection of all silicon ethers proceeded cleanly by treatment with HF·pyridine complex in THF. Subsequently, Lindlar reduction of corresponding intermediate triol derived corresponding analogue **3-124**.




**Scheme 57.** Synthesis of the oxazinan-4-one analogue **3-124**.

Characteristic peaks for the oxazinanone part of **3-124** are as follows: 2-H (22-H) 4.71, N-H 6.40; $^{13}$C NMR C-2 (C-22) 83.8, C-4 (C-23) 174.6, C-5 (C-24) 38.8, C-6 (C-25) 72.9 ppm.

### 3.5.8 Biological testing

The described analogues as well as the diyne **3-88** were tested for cytotoxicity against the L929 cell line, and the inhibitory efficacy on F-ATPase in mitochondrial preparations of bovine heart. The obtained $IC_{50}$ values in the cell culture assay as well as the percentage of F-ATPase inhibition of the compounds at a concentration of 0.1 and 1.0 µM, respectively, are listed in **Table 4**. The analogues are ordered according to increasing $IC_{50}$ values against the L929 cell line.

**Table 4.** $IC_{50}$ values for cruentaren A and analogues against the L929 cell line

| entry | comp. | $IC_{50}$ [µg mL$^{-1}$] | $IC_{50}$ [µM] | Inhibition of F-ATPase activity [%][a] | | description |
|---|---|---|---|---|---|---|
| | | | | 1 µM | 0.1 µM | |
| 1 | **1-1** | $0.0004\pm5\times10^{-5}$ | $0.0007\pm8\times10^{-5}$ | 94 | 78 | cruentaren (synthetic)[b] |
| 2 | **1-1** | $0.0012\pm4\times10^{-5}$ | $0.002\pm1.9\times10^{-5}$ | 93 | 84 | cruentaren (natural) |
| 3 | **3-90** | 0.017±0.004 | 0.028±0.007 | 80 | 42 | 3-OMe-crue |
| 4 | **3-124** | 0.085±0.02 | 0.14±0.03 | 34 | 2 | 7C-oxazinanone-crue |
| 5 | **3-95c** | 0.3±0.01 | 0.56±0.02 | 44 | 30 | isobutanoyl-crue |
| 6 | **3-95e** | 2.4±0.1 | 4.0±0.2 | 47 | 32 | dihydro-cinnamoyl-crue |
| 7 | **3-95b** | 2.5±0.1 | 4.5±0.2 | 47 | 27 | hexanoyl-crue |
| 8 | **3-95f** | 2.9±0.3 | 5.0±0.5 | 67 | 48 | heptanoyl-crue |
| 9 | **3-122** | 3.0±0.4 | 5.0±0.7 | 47 | 8 | 7C-enamide-crue |
| 10 | **3-100** | 3.0±1.1 | 5.1±1.9 | 51 | 15 | 6C-enamide-crue |
| 11 | **3-95a** | 6.1±0.7 | 10.3±1.2 | 40 | 30 | cinnamoyl-crue |
| 12 | **3-88** | 6.5±0.4 | 11.1±0.7 | 21 | 10 | diyne-crue |
| 13 | **3-102** | 7.5±0.9 | 13.0±1.6 | 18 | 12 | 6C-oxazinanone-crue |

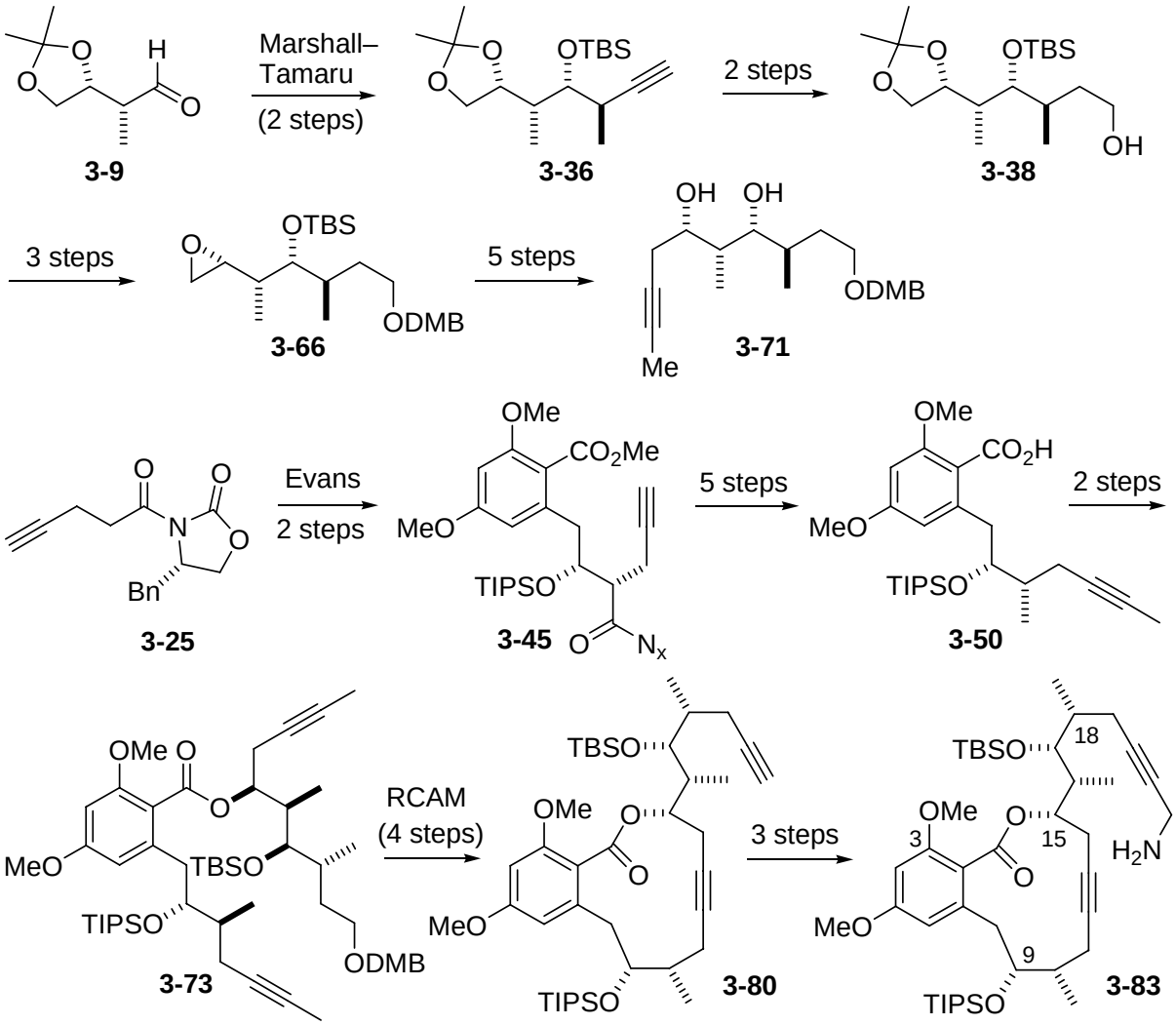
[a] The inhibition values are the mean values of at least two independent assays. The deviations did not exceed a range of ±10% inhibition. [b] The natural cruentaren A displayed a slightly lower activity ($IC_{50}$= (0.002±0.0019) µM, F-ATPase inhibition=93% at 1 µM). This might be attributed to different purity values. The value for the synthetic product does lie within the deviation of the natural material.

According to the table there are highly effective compounds. In most cases cytotoxicity and inhibitory activity against F-ATPase *in vitro* run parallel. However, there are some exceptions in this regard. For example, **3-95c** and analogues **3-95e**, **3-95b**, and **3-95f** differ in their cellular activity by a factor of almost 10 but display similar effects on the F-ATPase. This might be explained by differences in cellular uptake. The highest effective compound is cruentaren A itself (entry 1), followed by 3-OMe cruentaren (**3-90**) (entry 3). Furthermore, the

oxazinanone derivative with a 7 carbon side chain can be considered as highly cytotoxic, but it showed only low inhibitory efficacy in the F-ATPase assay (entry 4). Then there are compounds of intermediate cytotoxicity and F-ATPase activity, namely the cruentaren derivatives with modified carboxylic part in the side chain (**3-95c**, **3-95e**, **3-95b**; entries 5-7). In particular **3-95c** and **3-95b** make clear that the OH-group of the carboxylic acid part is extremely important as well as methyl group in α position to the carboxyl function. Finally, there are compounds that are essentially non toxic, starting with compound **3-95f**. Surprisingly, both enamides show neither a high cytotoxicity, nor significant inhibition of F-ATPase. One hypothesis in the design of the enamide analogues was that with a structural resemblance to typical V-ATPase inhibitors like apicularen A or salicylihalamide A these analogues would show corresponding activity. Because it could be supposed that an V-ATPase inhibitor would be highly cytotoxic, this shows that the enamide side is not sufficient to convert the F-ATPase inhibitor cruentaren A into an V-ATPase inhibitor. The most puzzling observation is the relatively high cytotoxicity of the oxazinanone **3-124** which shows only low inhibition of F-ATPase. We also checked for inhibitory effects on V-ATPase with $PtK_2$ potoroo cells. But when we investigated treated cells by fluorescent techniques, we did not observe the characteristic changes in the endoplasmatic reticulum that are typical for V-ATPase inhibitors. One explanation for the cytotoxicity of **3-124** could be that the heterocyclic ring is opened to an electrophilic acyliminium ion when taken up by the cells. The lack of activity for diyne cruentaren **3-88** can be attributed to conformational effects.

# 4 Conclusion I

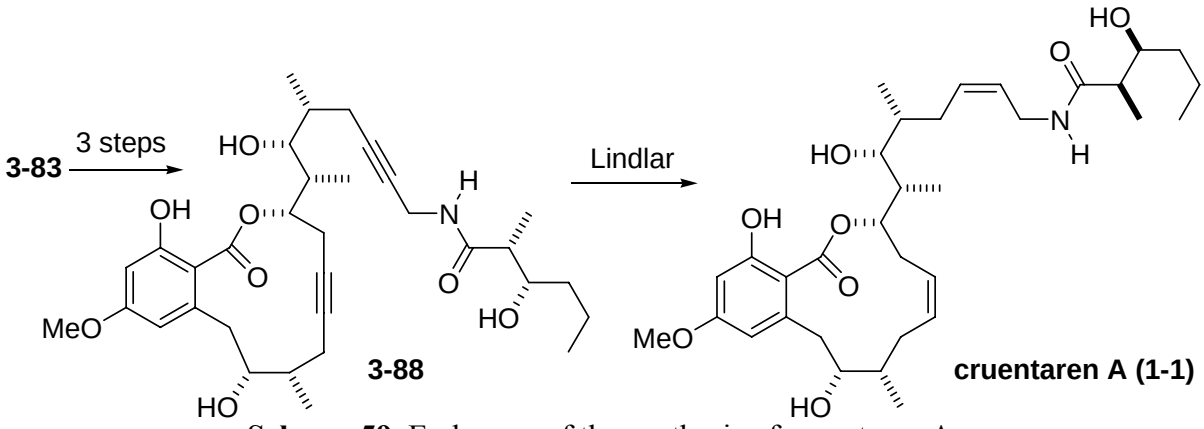
In summary, we developed an efficient synthesis of the novel macrolide cruentaren A. The key steps in this synthesis were a ring closing alkyne metathesis reaction to form the macrolactone, a Marshall–Tamaru *anti*-selective allenylzincate addition to establish the stereotetrad at C15-C18 and an Evans aldol reaction to fashion the *anti*-OH/Me pattern at C9/C10.




**Scheme 58.** Key intermediates in the synthesis of the propargylamine **3-83**.

Marshall reaction of the described aldehyde **3-9** allowed us to introduce two additional chiral centres as well as a four carbon building fragment in one chemical step. Simple functional group manipulations and introduction of an internal alkyne moiety secured fragment **3-71** in a highly efficient manner. Synthesis of acid **3-50** was based on an Evans aldol reaction between aldehyde **3-22** and pentynyloxazolidinone **3-25** using the standard boron enolate. Macrolactonization was performed by a very simple protocol using commercially available Schrock catalyst **2-34**. Application of a Bestmann one carbon elongation sequence furnished

propargyl amine **3-83** which was subsequently coupled with the protected β-hydroxy acid **2-31**. During the cleavage of the C3 methyl ether and the silicon protecting groups, the triple bond in the ring served as a lock that prevented the unwanted translactonization to the δ-lactone. The final step of the synthesis was a Lindlar reduction of two triple bonds. The sequence is quite concise and proceeded in 25 linear steps with overall yield of 7%. All chiral centers were essentially obtained *via* highly enantioselective methods.




**Scheme 59.** End game of the synthesis of cruentaren A.

Using the well established strategy a range of cruentaren A analogues were prepared. Structure activity relationship study proved that the OH and α-Me group of the carboxylic acid part are extremely important for the activity. Despite our expectations, two enamide analogues **3-100** and **3-122**, prepared via cross-coupling (amination) of the corresponding vinyl iodides were not active (**Figure 22**). The most puzzling observation was the relatively high cytotoxicity ($IC_{50}$ 140 nM) of the oxazinanone **3-124** which might be a metabolite of **1-1**.

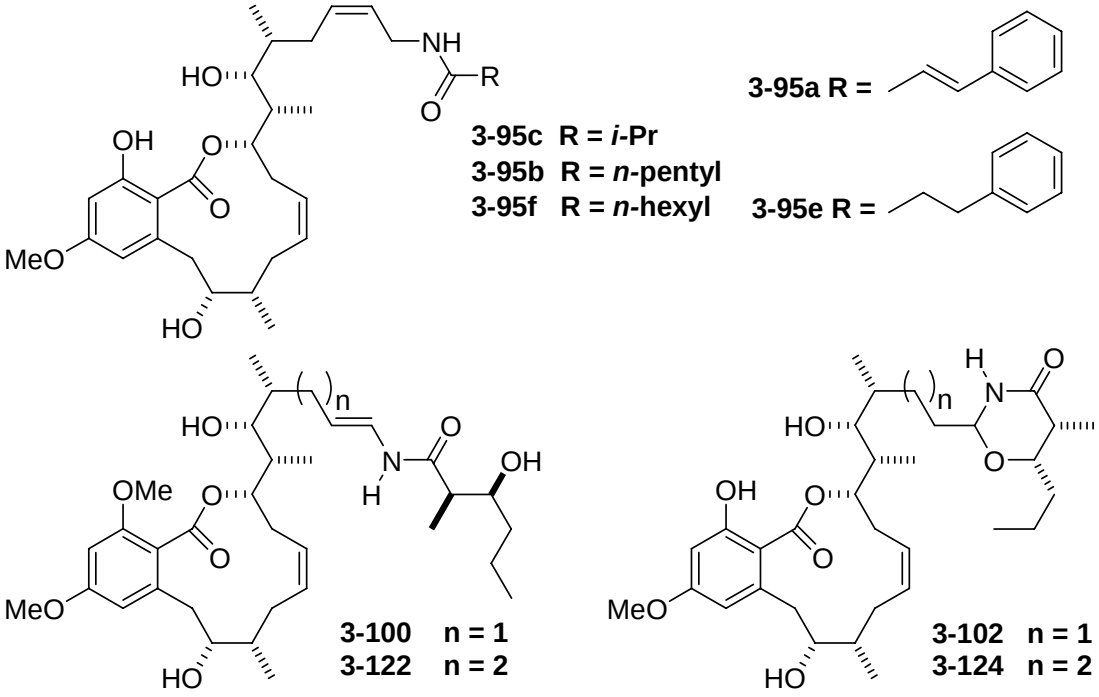



**Figure 22.** Structure of cruentaren A analogues.

# Chapter II

# Synthesis and Biological Evaluation of Neopeltolide and Analogues

# 5 Introduction

The marine environment, arguably the original source of all life, is a rich source of bioactive compounds. More than 70 percent of our planet's surface is covered by the oceans, and some experts feel that the potentially available biodiversity on the deep seafloor or coral reefs is greater than that existing in the rainforests.[141]

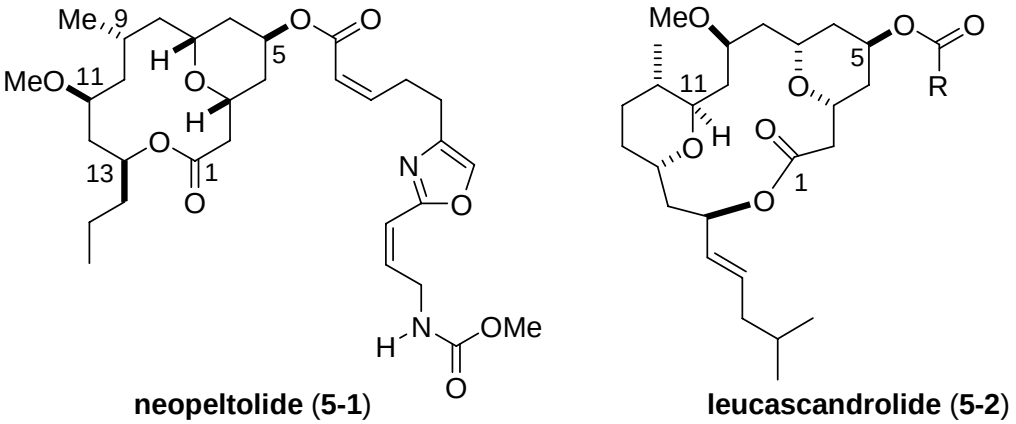
Considering the fact that many marine organisms have soft bodies and lead a sedentary lifestyle, a chemical system of defence becomes almost essential for survival. Marine organisms have evolved the ability to synthesize such toxic compounds or extracts or convert pertinent compounds from other marine microorganisms. Natural products from marine organisms might be released into the water and therefore rapidly diluted, accordingly they must be very potent materials to have the desired effect. The simplest sea animals like corals, sponges and plankton produce the most complex and toxic non-peptide substances ever known, such as palytoxin, brevetoxin and maitotoxin. Only 5 micrograms of these cytotoxic compounds can kill a human being within a few minutes. The richly available marine biodiversity that is available to us has to this point only been explored to an extremly limited extend. Furthermore, the primary chemical diversity available from marine organisms is most likely capable of delivering an even greater abundance of secondary metabolites for research use. For all of these reasons it is believed that the natural products that are available from the seas and oceans provide a tremendous opportunity for the discovery of novel therapeutic agents.

Marine organisms, particularly sponge invertebrates and associated bacteria, are an enormously rich source of structurally diverse secondary metabolites with unique molecular architectures.[142] These marine natural products often possess unusual and sometimes unexpected biological activities, making them valuable molecular probes for the investigation of biochemical pathways. Among these fascinating and eye-catching structures, a prominent class is the marine macrolides – highly oxygenated and stereochemically elaborate polyketides having a macrocyclic lactone as a conformational constrain.[143] Many marine macrolides demonstrate potent cell growth inhibition (antiproliferative properties) and offer considerable

promise as lead structures for the development of new anti-cancer chemotherapeutic agents, provided the supply issue can be resolved.

In general, the low natural abundance of marine macrolides coupled with the unsustainable and unacceptable ecological impact of large-scale isolation of the producting organisms preclude detailed biological evaluations, thus hampering their possible clinical development and exploitation in human medicine. These factors, combined with the impressive molecular architectures themselves, present compelling and formidable challenges to contemporary organic synthesis with regard to both strategy and methodology for their total synthesis in the laboratory. Furthermore, synthesis is also important for structure elucidation, including determination of the full absolute configuration, where spectroscopic methods may not have permitted a full assignment.

In 2007 the group of A. E. Wright described a novel macrolide named neopeltolide (**5-1**).[144] The producing deep-water sponge of the family *Neopeltidae* was collected off the north Jamaican coast. Neopeltolide turned out to be a very potent antitumor agent, inhibiting the proliferation of various cell lines in the low nanomolar range. The structural features of neopeltolide include a 14-membered macrolactone ring which contains an ether bridge forming a tetrahydropyran subunit. The hydroxyl group at C5 is acylated with an oxazole- and a carbamate-containing side chain which is identical to the one in the macrolide leucascandrolide (**5-2**).[145,146] Thus, one can assume the same biological targets for these two compounds.




**neopeltolide** (**5-1**) **leucascandrolide** (**5-2**)

**Figure 23.** Structures of neopeltolide and leucascandrolide.

Two recent total syntheses, one by Panek [147] and the other by Scheidt [148] corrected the stereochemical assignment at C11 and C13. Two additional reports on the total synthesis of neopeltolide have appeared to date.[149,150]

As a consequence of the natural supply of neopeltolide (**5-1**) being extremely limited ($4\times10^{-3}$% of frozen weight), a flexible and efficient synthesis is essential for further biological studies, while also opening access to *de novo* analogues. Moreover, the challenging and unusual polyketide structure combined with the potent biological activity prompted us to embark on a synthesis of **5-1**.

Our intention was to develop a strategy that would be flexible enough to access analogues and derivatives which might help to identify the biological target. Furthermore, analogues which could illuminate key structural features important for the activity were planned.

# 6 Literature Review

## 6.1 Isolation and Biological Activity of Neopeltolide

Lithistid sponges are renowned among marine organisms for their ability to produce a diverse array of biologically active metabolites.[151] Representative compounds include polyketides, cyclic peptides, alkaloids, pigments, and novel sterols. This extreme diversity of metabolites defied simple chemotaxonomic rationalization until it was shown that symbiotic microorganisms were responsible for the production of some representative compounds. In modern times lithistid sponges are predominantly found in deeper waters, which presents the collector with considerable logistical problems, and which has resulted in chemical investigations being concentrated on those genera that can be found at normal scuba depths.

Lithistid sponges of the family *Neopeltolidae* include the genera *Callipelta*, *Daedalopelta*, *Homophymia*, and *Neopelta*. Neopeltolide was isolated from the sponge of the genus *Daedalopelta*, which was collected at depths of 442 and 443 m off the north Jamaican cost. Extraction of frozen sponge, followed by vacuum-column chromatography and finally by preparative reversed-phase HPLC provided neopeltolide in $4\times10^{-3}$% yield of frozen weight.[144]

The macrolide portion of neopeltolide shows similarities to the macrolide ring seen in the callipeltoside, [152] lyngbyaloside, [153] and polycarvenoside. [154] Moreover, In addition neopeltolide also shows strong similarities to leucascandrolide A isolated from the calcareous sponge *Leucascandra caveolata*.[145] Leucascandrolide A has a 16-membered macrolide ring with a tetrahydrofuran ring, rather than the hemiketal, and the same oxazole-containing side chain found in neopeltolide. Tan et al. have hypothesized that the true biosynthetic origin of the callipeltosides and polycavernoside may be cyanobacteria that either live in association with the microorganisms or are derived from dietary sources.[155] D'Ambrosio et al. have proposed a microbial origin for the leucascandrolides, which are structurally unprecedented for calcareous sponges.[145] It is interesting to note the presence of neopeltolide, a structurally related compound in a lithistid sponge that occurs in deep-water habitats where limited if any light is present, and one might speculate that heterotrophic (organic compounds are used as carbon sources) cyanobacteria may be responsible for the biosynthesis of at least some of the metabolites found in deep-water lithistid sponges.

In preliminary biological studies, leucascandrolide A exhibited potent cytotoxic activity *in vitro* against KB oral epidermoid carcinoma and P388 leukemia cell lines ($IC_{50}$ = 0.05 and 0.25 μg/mL respectively), as well as significant inhibition of the pathogenic fungus *Candida*

*albicans.*[145] Additionally, following hydrolysis of the C5 ester linkage, biological testing of the 18-membered macrocyclic core and the separated side-chain demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity, while the oxazole-containing unsaturated side chain appears to be responsible for the antifungal activity.

As was shown by Wright and co-workers,[144] neopeltolide is a potent inhibitor of the growth of the fungal pathogen *Candida albicans*. It showed a growth inhibitory zone of 17 mm when tested at concentration of 25 μg/disk in the *C. albicans* disk diffusion assay and a minimum inhibitory concentration (MIC) in liquid culture of 0.625 μg/mL.

Neopeltolide is also potent inhibitor of tumor cell proliferation *in vitro*. In the MTT assay to determine effects of **5-1** on cell proliferation, $IC_{50}$ values of 1.2 nM against the A549 human lung adenocarcinoma, 5.1 nM against the NCI/ADR-RES ovarian sarcoma, and 0.56 nM against the P388 murine leukaemia were observed.[144] In the PAC-1 pancreatic cancer cell line and the DLD-1 colorectal adenocarcinoma cell line, both of which have p53 mutations, neopeltolide showed strong inhibition of cell proliferation at nanomolar concentration but did not give the typical sigmoidal curve, and instead showed 50% cell kill over an extended dose range. Accordingly it was assumed that **5-1** may be cytostatic (inhibition or suppression of a cellular growth and multiplication) to these cell lines rather than cytotoxic (cell-killing, cell-toxic). In addition, cell cycle analysis by flow cytometric methods indicated that neopeltolide caused a block of the cell cycle at the G1 phase at doses of 100 nM in the A549 lung adenocarcinoma cell line (**Table 5**).

**Table 5.** Effects of Neopeltolide on the Cell cycle of A549[144]

| treatment | Dose (nM) | cells in G1 phase (%) | cells in S phase (%) | cells in G2/M phase |
|---|---|---|---|---|
| nontreated control | | 47.13 | 39.05 | 13.82 |
| vehicle control | | 46.55 | 36.46 | 13.99 |
| paclitaxel | 100 | 1.56 | 0.00 | 98.44 |
| neopeltolide | 100 | 63.03 | 22.02 | 14.95 |
| | 10 | 59.66 | 30.27 | 10.07 |
| | 1 | 46.11 | 39.95 | 13.94 |
| | 0.1 | 46.4 | 40.01 | 13.59 |

Preliminary investigation into the mechanism of action of neopeltolide suggests that it does not act via interaction with tubulin or actin.[144]

Due to the promising biological activity of neopeltolide and its unknown mode of action further biological evaluation is very important.

## 6.2 Previous Neopeltolide Syntheses

Due to its promising biological profile and fascinating structure, neopeltolide attracted considerable synthetic attention from several group. The first two syntheses, one by Panek,[147] the other by Scheidt et al.[148] showed the original structural assignment to be partially wrong. As a result, the stereocenters at C11 and C13 had to be revised. Recently two more total syntheses of neopeltolide were achieved in the research groups of Lee[149] and Sasaki.[150]

### 6.2.1 Synthesis of Neopeltolide by Panek and co-workers[147]

Paneks' retrosynthetic strategy features a disconnection of the C19-C20 double bond to reveal the macrolide **6-1** and the oxazole side chain **6-2**. For the creation of the macrolactone ring they relied on Yamaguchi macrolactonization. Installation of the tetrahydropyran unit was based on an [4+2] annulation strategy between allylsilane **6-3** and aldehyde **6-4**. The latter was then traced back to dithiane **6-5** and epoxide **6-6**.

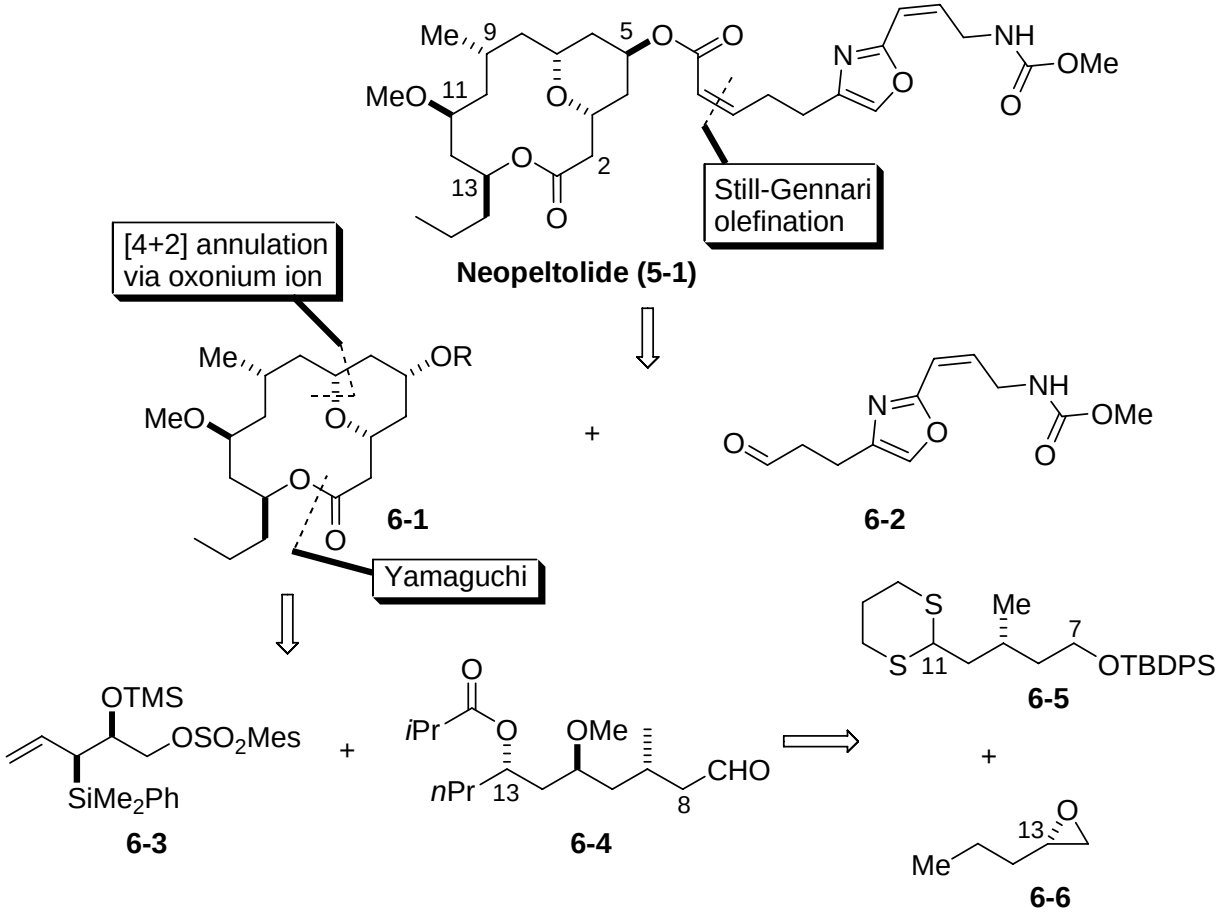
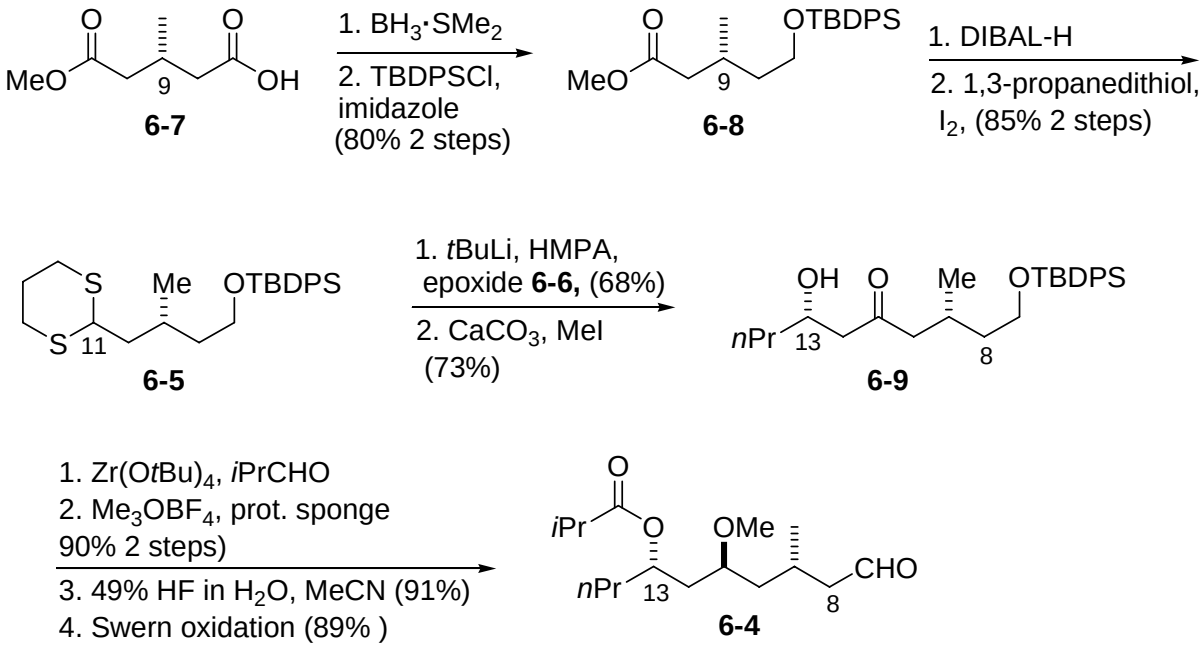



**Figure 24**. Retrosynthetic analysis of neopeltolide (**5-1**) by Panek and co-workers.[147]

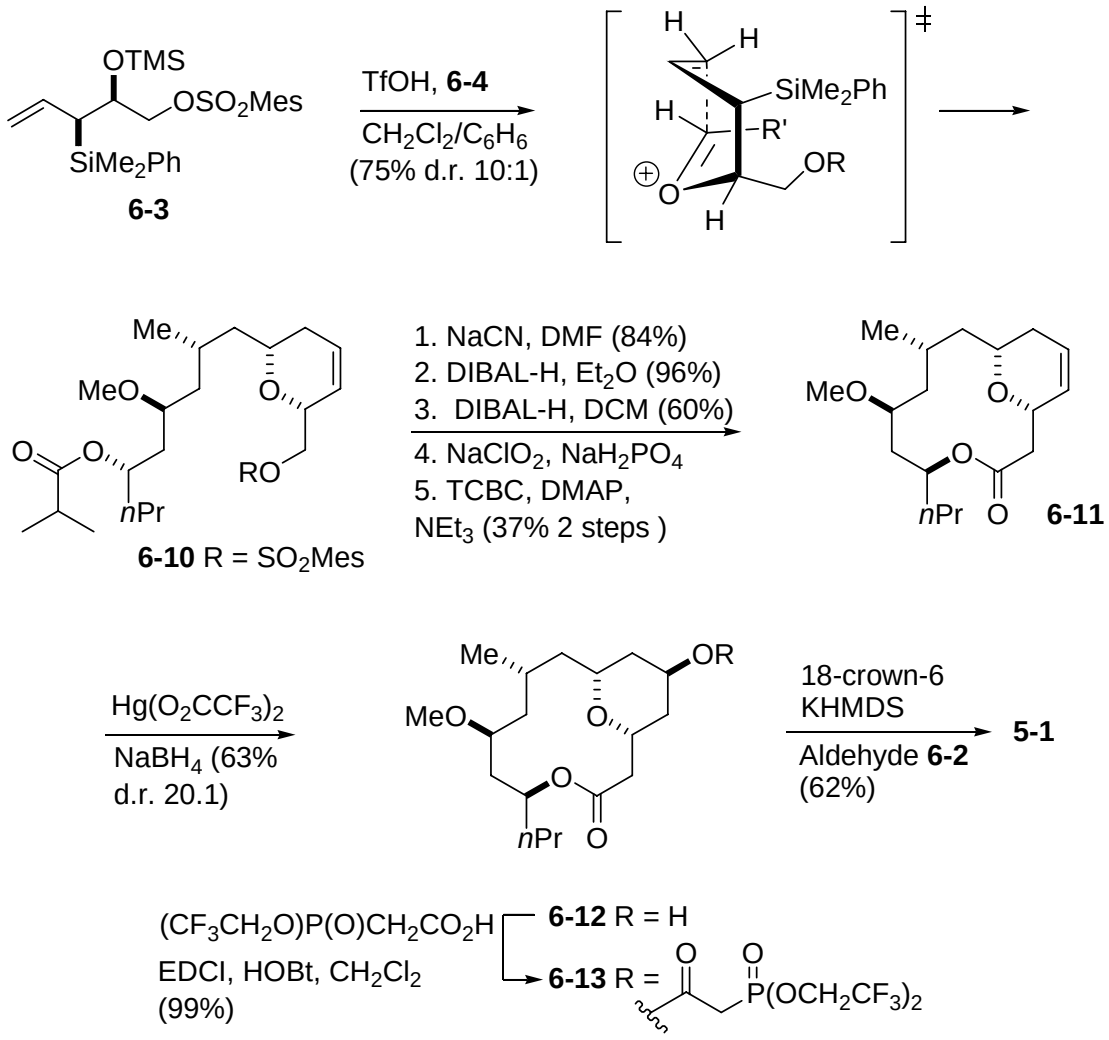
Synthesis of aldehyde **6-4** was started from commercially available, but relatively expensive (*R*)-(+)-3-methylglutarate **6-7** (**Scheme 60**). Chemoselective reduction of the carboxylic acid

followed by TBDPS protection provided ester **6-8**. Reduction of the ester function with subsequent dithioacetalization furnished dithiane **6-5**. Coupling of dithiane **6-5** with epoxide **6-6** followed by removal of the dithioketal group yielded ketone **6-9**. A modified Evans–Tishchenko reduction established the 1,3-*anti*-diol fragment. Protection of the secondary hydroxyl function, followed by silyl ether cleavage and Swern oxidation provided aldehyde **6-4**.




**Scheme 60.** Synthesis of the C7–C16 fragment **6-4**.

Aldehyde **6-4** was combined with allylsilane **6-3** to access dihydropyran **6-10** (**Scheme 61**). The sulfonate group was replaced with a nitrile moiety followed by DIBAL-H mediated cleavage of the acyl protecting group. Reduction of the nitrile to an aldehyde, followed by Pinnik oxidation provided the seco acid which afterwards was cyclized using the Yamaguchi protocol. Selective oxymercuration of the pyran double bond yielded the axial C5 alcohol **6-12**, which was subsequently transformed to phosphonoacetate **6-13**.




**Scheme 61.** Completion of neopeltolide (**5-1**) synthesis.

Deprotonation of **6-13** with KHMDS, followed by treatment with aldehyde **6-2** provided a 7:1 mixture of neopeltolide (**5-1**) and the corresponding *E* olefin in 62% overall yield.

The developed synthesis is based on the [4+2]-allylsilane annulation, and required a time-consuming preparation of building block **6-3**. Moreover, the longest linear sequence consist of 19 steps, starting from costly (*R*)-(+)-3-methylglutarate **6-7,** and provided neopeltolide in only 1.3% overall yield.

### 6.2.2 Synthesis of Neopeltolide by Scheidt and co-workers[148]

Scheidt and co-workers divided the molecule in two distinct fragments, namely macrolactone **6-14**, and oxazole-containing acid **6-15** (**Figure 25**). Their plan was to utilize a recently developed Lewis-acid catalyzed cyclization.[156] The linear precursor (**6-16**) to this macrolactonization was available from dioxinone acid **6-17** and alcohol **6-18**.

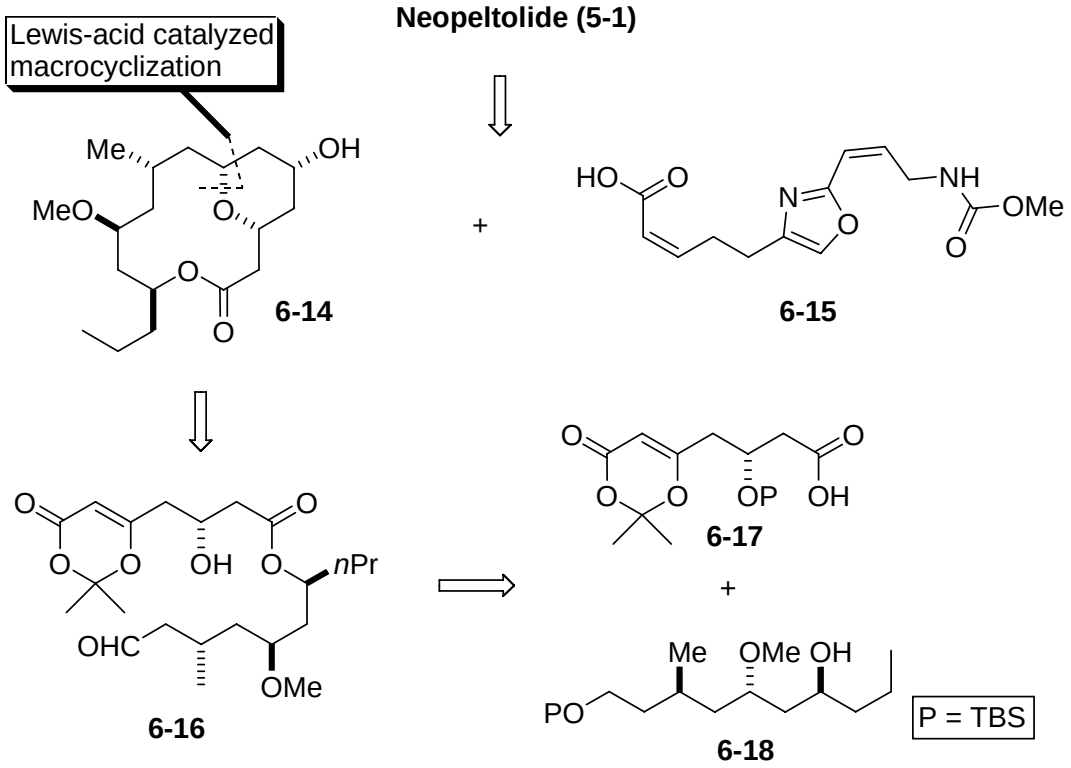
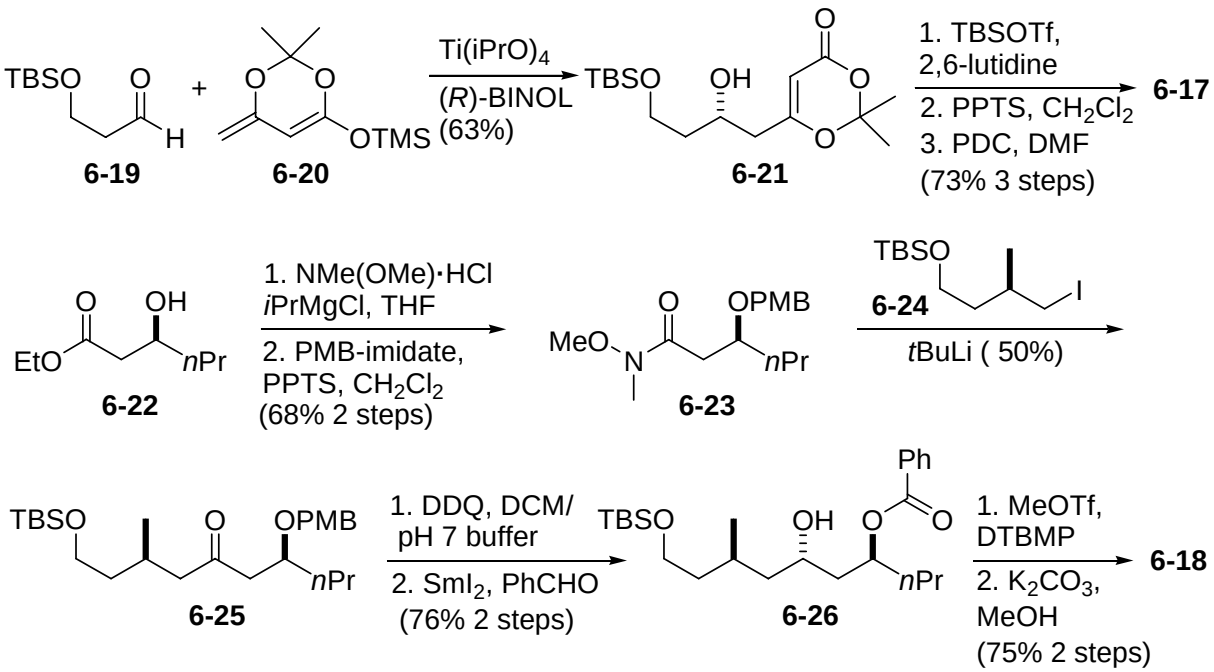



**Figure 25.** Retrosynthetic analysis of neopeltolide (**5-1**) according to Scheidt and co-workers.[148]

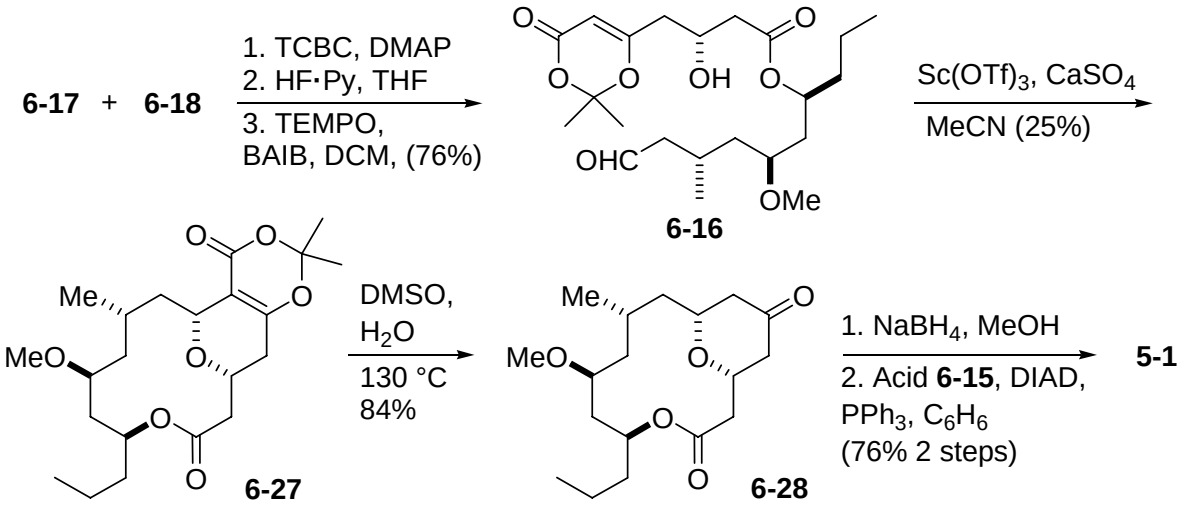
The synthesis of acid **6-17** began with the Ti(IV)-(*R*)-BINOL catalyzed aldol reaction between dienoxy silane **6-20** and protected saturated aldehyde **6-19** to afford secondary alcohol **6-21** (**Scheme 3**). Protection of the hydroxyl function was followed by deprotection and oxidation of the primary alcohol function furnishing dioxinone acid **19**.

The synthesis of the alcohol **6-18** commenced with the two-step conversion of β-hydoxy ester **6-22** to Weinreb amide **6-23**. Acylation of the alkyl lithium derived from **6-24** with amide **6-23** furnished ketone **6-25**. Removal of the PMB group followed by Evans-Tischenko reduction provided alcohol **6-26**. Methylation of free hydroxyl function with subsequent hydrolysis of benzoate secured alcohol **6-18**.




**Scheme 62.** Synthesis of acid **6-17** and alcohol **6-18**.

Acid **6-17** was coupled with alcohol **6-18** using the Yamaguchi protocol. Deprotection of both silyl ethers followed by selective oxidation of the primary alcohol afforded acyclic aldehyde **6-16**. The crucial $Sc(OTf)_3$ promoted macrocyclization provided macrolactone **6-27**, albeit only in moderate yield (25%). The tricyclic dioxinone was converted to alcohol **6-14** by heating in wet DMSO followed by a selective reduction of the ketone with $NaBH_4$. Mitsunobu reaction of the obtained alcohol **6-14** with acid **6-15** furnished neopeltolide (**5-1**).




**Scheme 63.** Completion of the neopeltolide (**5-1**) synthesis.

Although the aforementioned synthesis is quite convergent, due to the poor yield of the key macrolactonization step, the final product was obtained in only 0.5% overall yield. This is significantly limiting the application of the developed strategy to the synthesis of neopeltolide analogues.

### 6.2.3 Synthesis of Neopeltolide by Lee and co-workers[149]

According to this retrosynthetic analysis the pyran fragment as well as macrolactone ring could be prepared via intramolecular Prins cyclization of aldehydic homoallylic alcohol **6-29**. The latter can be derived from alcohol **6-30**.

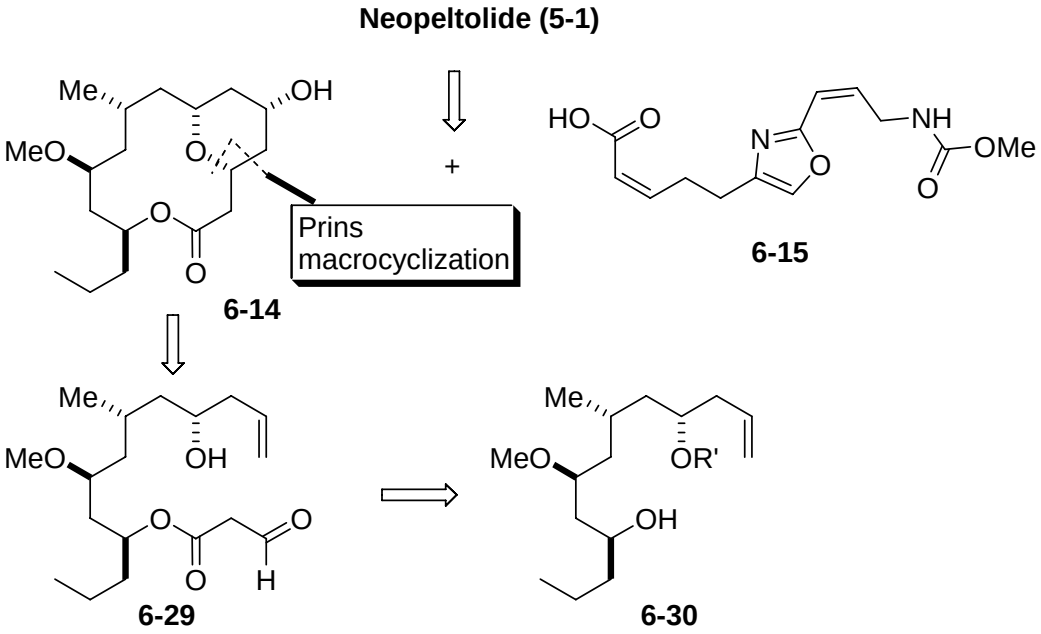
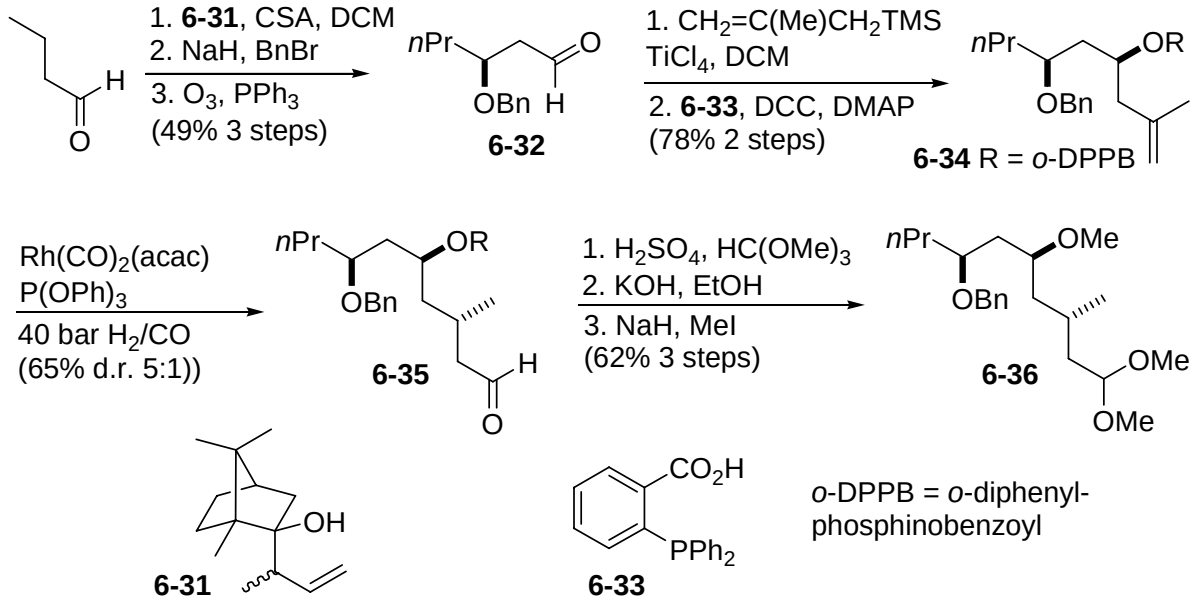


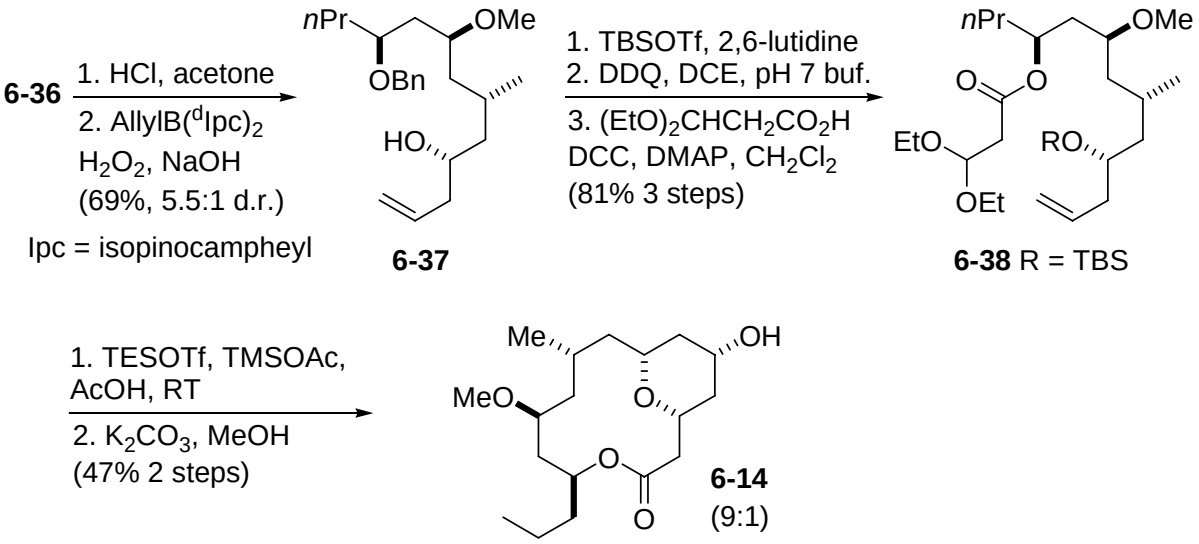

**Figure 26.** Retrosynthetic analysis of neopeltolide (**5-1**) by Lee et al.[149]

Asymmetric crotyl transfer reaction from **6-31** to butanal, followed by protection and ozonolysis afforded aldehyde **6-32** (**Scheme 64**). Subsequent $TiCl_4$ mediated methallylation of **6-32** and esterification of the obtained alcohol with acid **6-33** secured ester **6-34**. A substrate-directed hydroformylation of **6-34** provided aldehyde **6-35** in a 5:1 ratio. Dimethylacetal formation, hydrolysis and O-methylation furnished dimethyl acetal **6-36**.



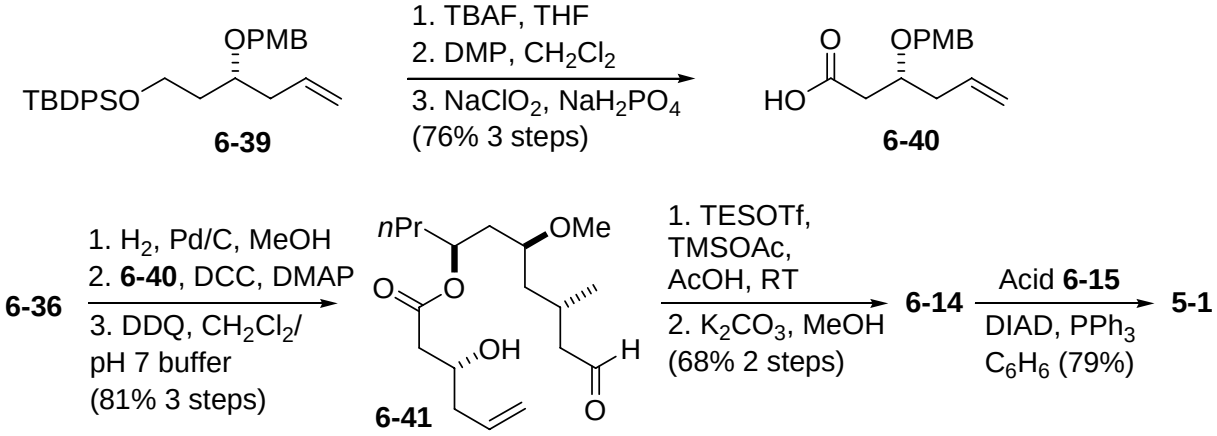

**Scheme 64.** Synthesis of dimethyl acetal **6-36**.

The aldehyde derived from **6-36** was introduced in a Brown allylation reaction, which furnished homoallylic alcohol **6-37** in a 5.5:1 diastereomeric ratio (**Scheme 65**). Subsequent TBS protection, followed by benzyl group cleavage and esterification with 3,3-diethoxypropanoic acid provided intermediate **6-38**. The crucial intramolecular Prins cyclization of **6-38** afforded macrolactone **6-14**, albeit only in 47% yield and with 9:1 selectivity.




**Scheme 65.** Synthesis of macrolactone **6-14**.

Due to the low yield of pyran **6-14** the Lee group developed an alternative Prins cyclization approach. The required substrate **6-41** was derived from aforementioned dimethyl acetal **6-36**. Deprotection of the benzyl ether, followed by esterification with acid **6-40** and prolonged exposure to DDQ produced intermediate **6-41** (**Scheme 66**). This time, the Prins cyclization proceeded more efficiently and provided macrolide **6-14** in reasonable yield. Mitsunobu esterification of alcohol **6-14** with acid **6-15** led to neopeltolide (**5-1**).




**Scheme 66.** Completion of the neopeltolide (**5-1**) synthesis.

After all, Lee and co-workers developed a quite convergent synthesis of neopeltolide, which consist of 15 linear steps and provides the final compound in 6.7% overall yield.

### 6.2.4 Synthesis of Neopeltolide by Sasaki and co-workers[150]

Following the general trend,[148,149] neopeltolide (**5-1**) was divided into macrolactone **6-14** and the oxazole-containing carboxylic acid **6-15**. Yamaguchi macrolactonization required the preparation of tetrahydropyran intermediate **6-42**. For the construction of the fragment **6-42**, in turn, they relied on a Suzuki–Miyaura coupling of enol phosphate **6-43** and alkylborate **6-44** (generated *in situ* from iodide **6-45**) and subsequent RCM.

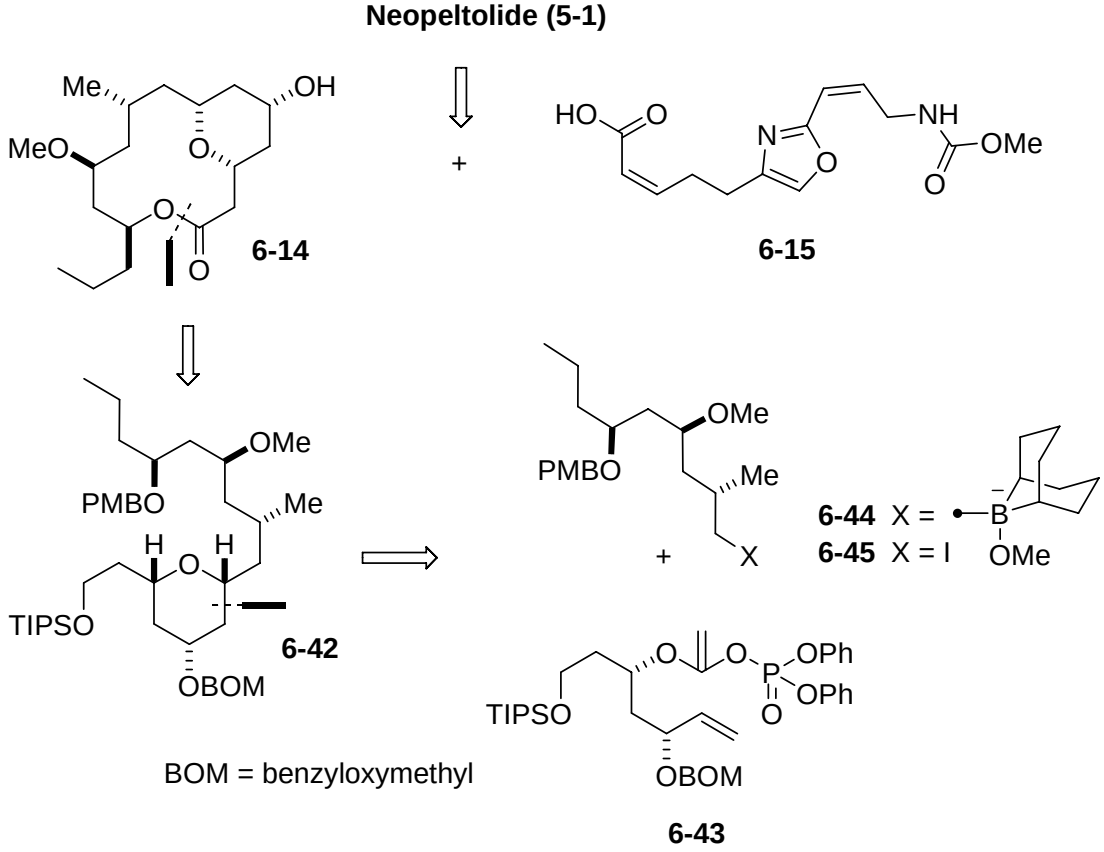
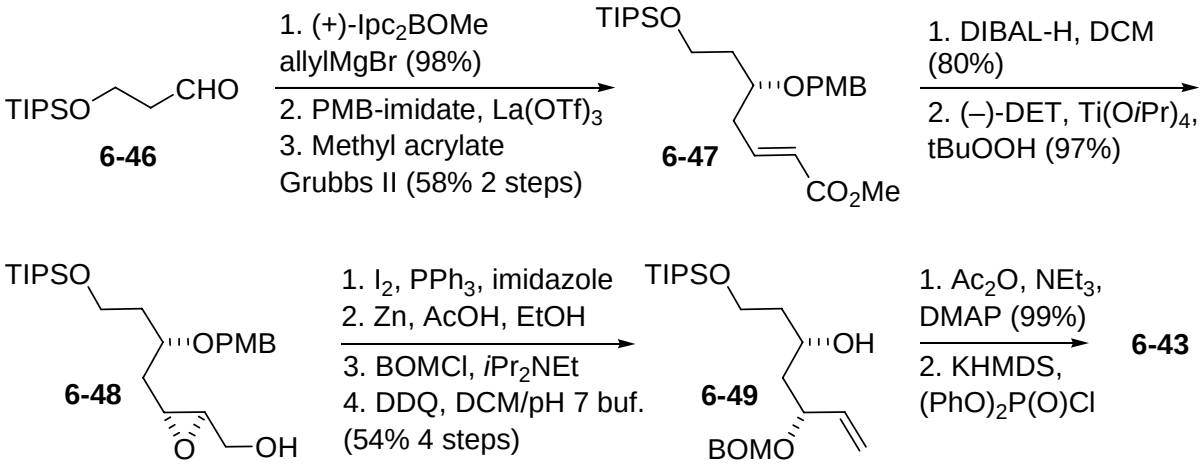


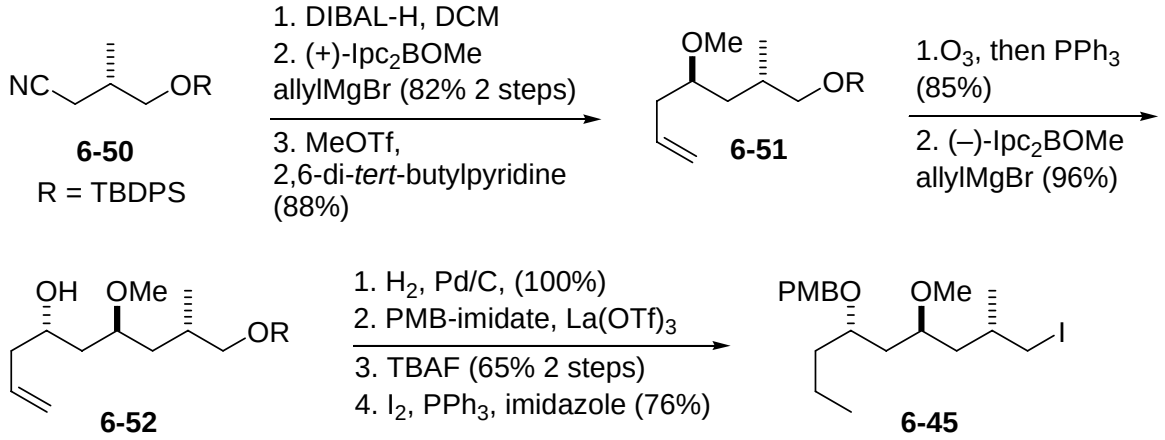

**Figure 27.** Retrosynthetic analysis of neopeltolide (**5-1**) by Sasaki and co-workers.[150]

The two stereocenters of **6-43** are based on an asymmetric allylation and a Sharpless asymmetric epoxidation. Asymmetric allylation of aldehyde **6-46** followed by PMB protection and olefin cross-metathesis provided enoate **6-47** in 57% yield (**Scheme 67**). After reduction of **6-47** to the corresponding allylic alcohol, Scharpless asymmetric epoxidation delivered epoxide **6-48**. An iodination/reductive ring-opening sequence on substrate **6-48**, followed by BOM protection and oxidative cleavage of the PMB ether led to alcohol **6-49** in good overall yield. The obtained alcohol was transformed to the corresponding acetate, which was subjected to enolization in the presence of $(PhO)_2P(O)Cl$. This resulted in formation of enol phosphate **6-43**.



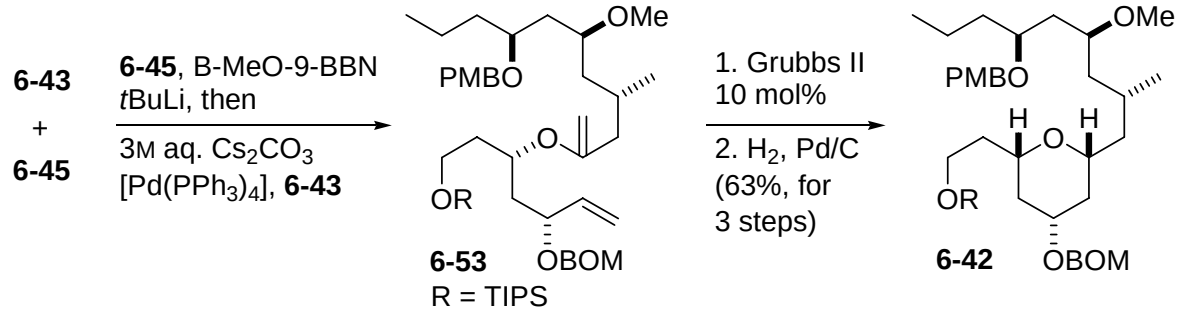

**Scheme 67.** Synthesis of enol phosphate **6-43**.

The synthesis of iodide **6-45** commenced with nitrile **6-50** (**Scheme 68**). DIBAL-H reduction of **6-50** followed by asymmetric allylation and methylation of the resulting secondary hydroxyl function secured alkene **6-51**. Ozonolysis of the double bond provided the corresponding aldehyde, which was allylated to alcohol **6-52**. The next sequence, which includes hydrogenation, PMB protection, desilylation and iodination, furnished required iodide **6-45**.



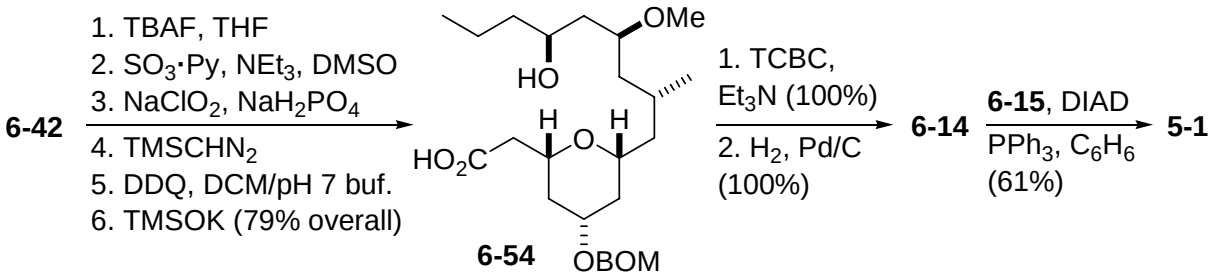

**Scheme 68.** Synthesis of iodide **6-45**.

Transformation of iodide **6-45** to alkylborate **6-44** was followed by treatment with $Cs_2CO_3$, $[Pd(PPh_3)_4]$ and enol phosphate **6-43**. This resulted in formation of diene **6-53**, which was subjected to RCM with subsequent stereoselective hydrogenation (**Scheme 69**).




**Scheme 69.** Synthesis of tetrahydropyran intermediate **6-42**.

Notably, transformation of obtained intermediate **6-42** to the neopeltolide core **6-14** required 8 steps, which make this synthesis quite long (**Scheme 70**). Finally, alcohol **6-14** was coupled with acid **6-15** under Mitsunobu conditions.




**Scheme 70.** Completion of the neopeltolide (**5-1**) synthesis.

In summary, the developed synthesis required 25 steps (longest linear sequence) and provided neopeltolide (**5-1**) in 8.3% overall yield, starting from relatively expensive (*R*)-(–)-3-hydroxy-2-methylpropionate. These facts are significantly hampering the application of the aforementioned strategy to the large-scale synthesis of neopeltolide or its analogues thereof.

## 6.3 Key Reactions and its Mechanisms

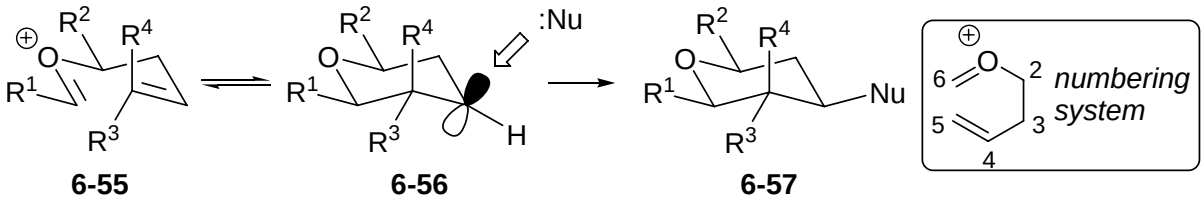
For the synthesis of such complex molecules as neopeltolide one would need to apply a broad spectrum of well established and modern synthetic methodologies. Therefore, an overview of the most important reactions used for our neopeltolide synthesis is provided below. Since it is not possible to describe every method in detail in this thesis, for each reaction only the general information and the most representative examples of application are given.

### 6.3.1 Prins cyclization

A large number of natural products and medicinally useful agents contain substituted tetrahydropyran rings; correspondingly a variety of methods have been developed for their stereocontrolled synthesis.[157] One of the most powerful transformations to generate highly substituted tetrahydropyrans with excellent stereoselectivity is the Prins cyclization.[158]

As with any reaction creating new stereogenic centers, the utility of the Prins cyclization is highly dependent on the degree of stereoselectivity associated with the transformation. Prins cyclizations are typically highly selective for the all-*cis* tetrahydropyran. Several factors are involved when rationalizing the stereochemical outcome for Prins cyclization reactions. The first rationale for the all-*cis* stereoselectivity has been set forth by computational work from

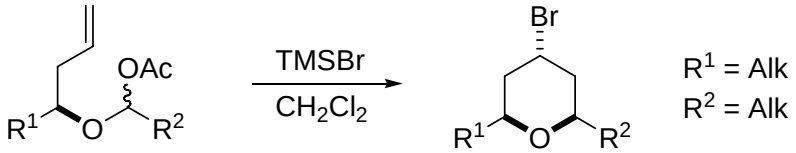
Alder.[159]Alder suggested that ring closure of an alkene into an oxocarbenium ion through a chair transition states leads to tetrahydropyranyl cation intermediate **6-56** (**Figure 28**). Tetrahydropyranyl cation **6-56** has increased stability due to delocalization. In the ring closure step, the C2 substituent lies in a favorable equatorial position and the (*E*)-oxocarbenium ion geometry is preferred[160] over the (*Z*)-oxocarbenium ion geometry. Therefore, chirality is transferred from C2 to the newly formed carbon–carbon bond. The stereocenter formed at C4 is controlled by the extensive delocalization of tetrahydropyranyl cation **6-56**. Favorable orbital overlap places the hydrogen at C4 in a pseudoaxial geometry, and, therefore nucleophilic attack occurs along an equatorial trajectory to deliver tetrahydropyran **6-57**. In this way, four stereogenic centers of the tetrahydropyran ring can be formed with high stereoselectivity from one initial stereocenter and defined alkene geometry.




**6-55** **6-56** **6-57**

**Figure 28.** Stereochemical outcome for Prins cyclizations.

Recently Rychnovsky and co-workers reported Prins cyclizations that are not consistent with this rationale.[161] Acetoxy ethers **6-58** upon treatment with bromotrimethylsilane (TMSBr), cyclize to produce 2,6-*cis*-4-*trans* tetrahydropyrans **6-59** (**Scheme 71**).



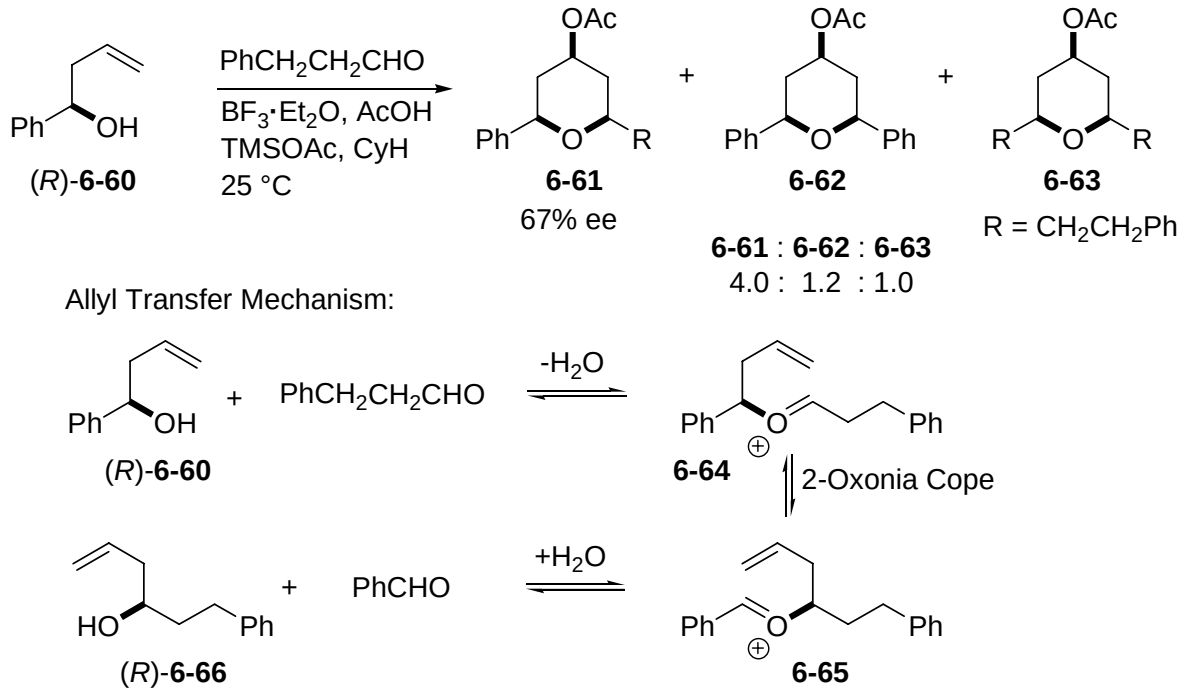

**6-58** **6-59**

**Scheme 71.** Axial-selective Prins cyclization.

Another important feature for a synthetically useful transformation is the ability to convert optically active starting materials into optically active products. Although typically proceeding with high stereochemical fidelity, the Prins reaction sometimes leads to partial or complete racemization.[162]

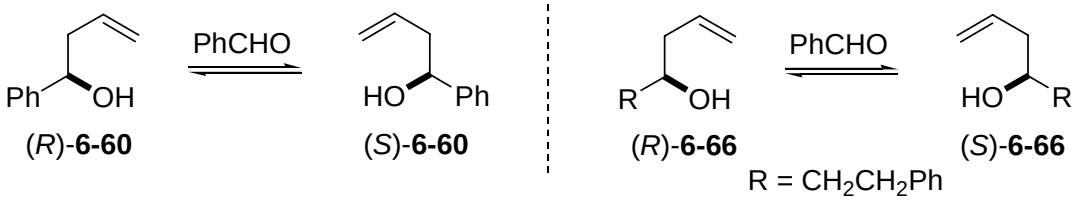
Oxonia Cope rearrangement is a competitive process in Prins cyclization and proceeds rapidly even at –78 °C. Rychnovsky et al. reported that treatment of optically enriched alcohol **6-60** (ee = 87%) with $BF_3{\cdot}Et_2O$ in the presence of hydrocinnamaldehyde and acetic acid led to tetrahydropyran **6-61** in 67% ee along with symmetric tetrahydropyrans **6-62** and **6-63** (**Scheme 72**).[163] The mechanism of racemization in this case can be attributed to an allyl transfer process. Alcohol (*R*)-**6-60** can condense with hydrocinnamaldehyde to generate

oxocarbenium ion **6-64** and liberate a molecule of water. 2-Oxonia Cope rearrangement of **6-64** will lead to oxocarbenium ion **6-65** which will undergo water mediated fragmentation to benzaldehyde and alcohol (*R*)-**6-66**.




**Scheme 72.** Racemization of Prins cyclization products by 2-oxonia Cope rearrangement.[163]

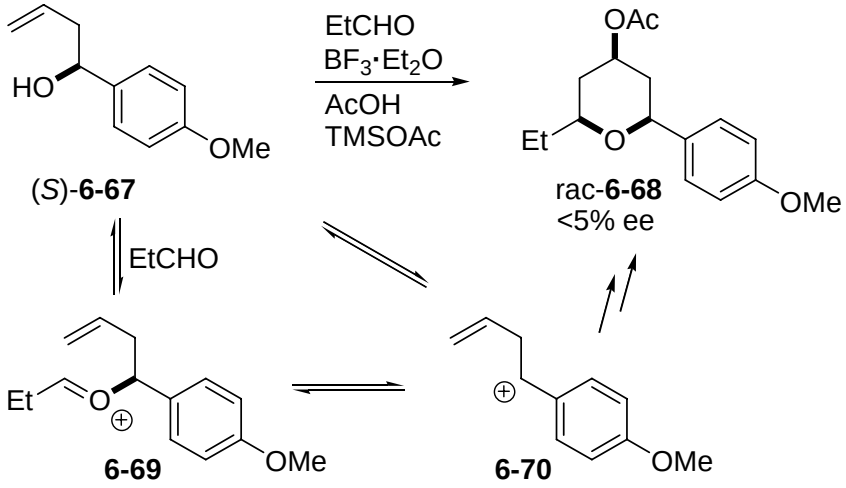
The formation of benzaldehyde and alcohol (*R*)-**6-66** allows for a symmetric 2-oxonia Cope rearrangement. Initial alcohol (*R*)-**6-60** can condense with benzaldehyde, undergo 2-oxonia Cope rearrangement, and then fragment with the addition of water to generate epimeric (*S*)-**6-60** (**Scheme 73**). Likewise, alcohol (*R*)-**6-66** can generate epimeric (*S*)-**6-66**. In this way, allyl transfer processes can lead to racemization in Prins cyclization reactions. It should be noted that this mechanism relies on the presence of water, which is generated upon direct Prins cyclizations between homoallylic alcohols and aldehydes.




**Scheme 73.** Racemization by symmetric 2-oxonia Cope rearrangement.

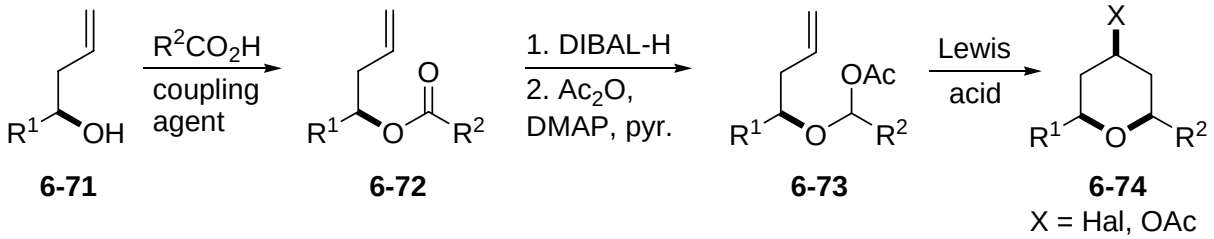
Another example of racemization during Prins cyclization was reported by Willis et al. It was shown that Prins cyclization of benzylic alcohols can lead to an extensive loss in enantiomeric excess due to a solvolysis mechanism.[164] Reacting of optically enriched alcohol (*R*)-**6-67** with propanal in the presence of $BF_3$·$Et_2O$ and acetic acid led to tetrahydropyran **6-68** in less then 5% ee (**Scheme 74**). This outcome can be attributed to the generation of stabilized benzylic

cation **6-70** by a solvolysis reaction of initial alcohol **6-67** or oxocarbenium ion **6-69**. This stabilized, achiral benzylic cation then recombines with propanal, providing racemic tetrahydropyran **6-68**. In general, Prins cyclization reactions utilizing electron-rich aromatic substrates often proceed with low stereochemical fidelity.




**Scheme 74.** Racemization in Prins cyclization by solvolysis mechanism.[164]

In order to minimize racemization during Prins cyclization and increase its compatibility to sensitive substrates many useful modifications of this reaction were developed. Rychnovsky reported that α-acetoxy ethers are ideal precursors to the oxocarbenium ion of the Prins cyclization due to regioselective solvolysis of the acetate upon treatment with Lewis acid.[165] The α-acetoxy ethers can be prepared by reductive acetylation of acyclic esters **6-72**, which allows the application of this methodology in the synthesis of complex structures (**Scheme 75**). Lewis acid or protic acid induced cyclizations of unsaturated α-acetoxy ethers substrates **6-73** lead to *cis*-2,6-dialkyltetrahydropyrans **6-74** with an equatorial halide or acetate at the 4-position.




**Scheme 75.** Utilization of α-acetoxy ethers in the Prins cyclization.[165]

The stereoselectivity of the Prins cyclization with α-acetoxy ether substrates is consistent with an *E*-oxocarbenium ion intermediate adopting a chair conformation (**Figure 29**). The oxocarbenium ions prefer an *E*-geometry with the hydrogen atom roughly eclipsing the hydrogen atom of the methine across the ether link, and this preference results in the formation of *cis*-2,6-dialkyl tetrahydropyran products.

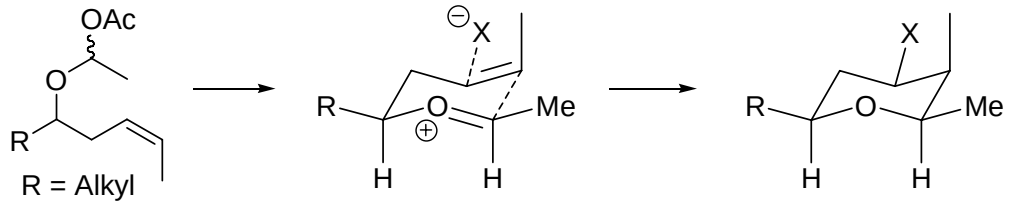
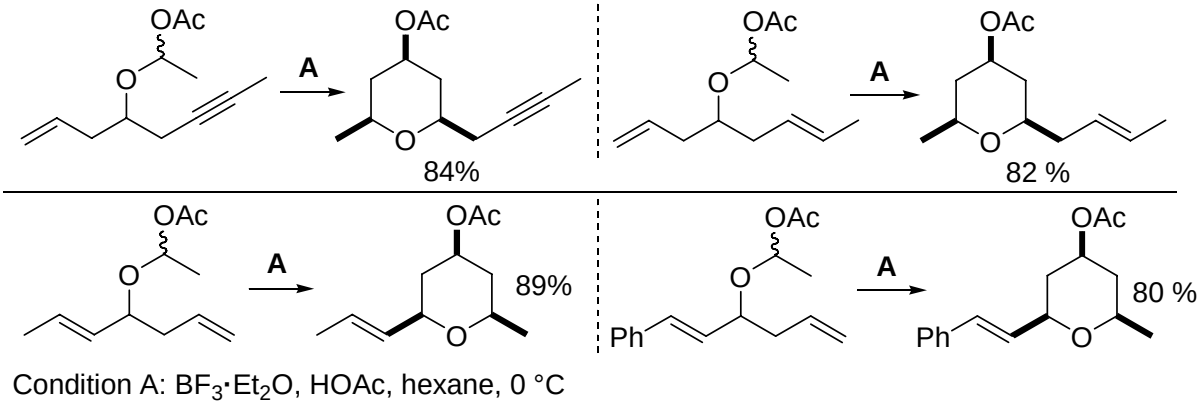



**Figure 29.** Stereochemical outcome for Prins cyclizations of α-acetoxy ethers.[165a]

In general, the Prins cyclization of substrates **6-73** are carried out using either $SnBr_4$ in $CH_2Cl_2$ at –78 °C or $BF_3{\cdot}Et_2O$ and HOAc in hexanes.[165]

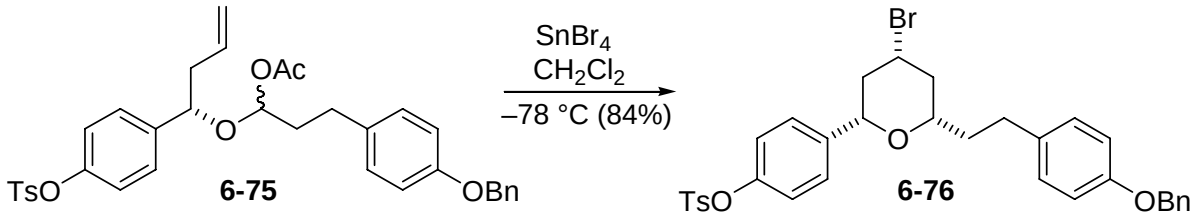
Notably, cyclizations of dienes and enynes often take place with useful levels of regioselectivity (**Scheme 76**).




**Scheme 76.** Prins cyclization of dienes and enynes.[165a]

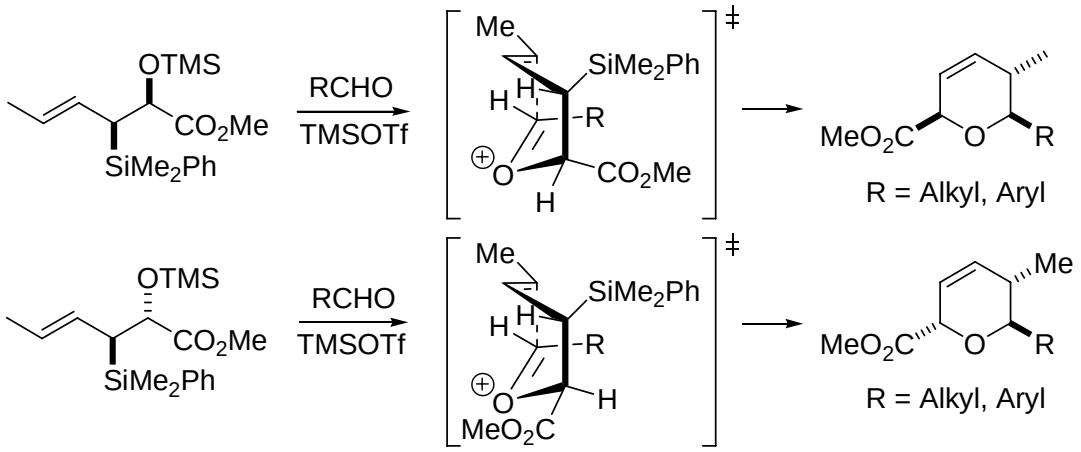
This methodology has been applied to a synthesis of the C22–C26 [166] and C3–C19 [167] segments of phorboxazole B, C18-C25 segment of Lasonolide A[168] and to the total synthesis of gambierol.[169]

During the total synthesis of (–)-centrolobine Rychnovsky and co-workers have found that the Prins cyclization of α-acetoxy ether **6-75**, promoted by $SnBr_4$ is much faster than promoted by $BF_3{\cdot}Et_2O$ and HOAc and thus suppresses the competing 2-oxonia Cope process (**Scheme 77**).



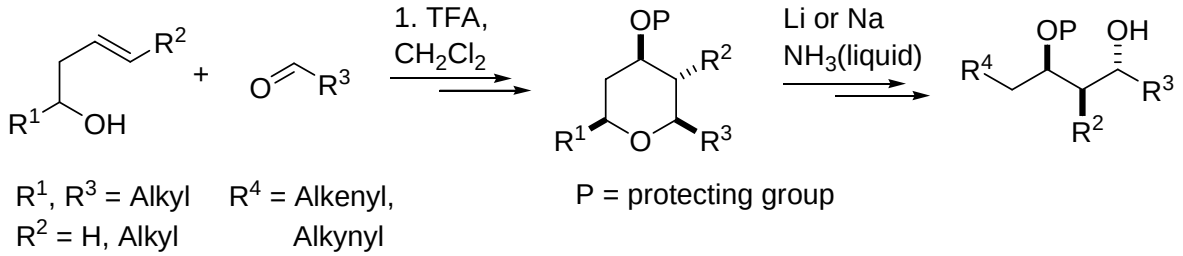

**Scheme 77.** Application of $SnBr_4$ mediated Prins cyclization.[163]

Another useful modification of Prins cyclization was developed in the Panek group. It was shown that *syn*-(*E*)- and *anti*-(*E*)-crotylsilanes react with aldehydes in the presence of Lewis acid to generate the 2,6-*cis*- and 2,6-*trans*-THP ring, respectively (**Scheme 78**).[170] This methodology was employed in the total synthesis of herboxidiene,[171] bistramide A,[172] leucascandrolide[146m] and kendomycine.[173]




**Scheme 78.** Chiral crotylsilanes for the synthesis of THP rings.[170]

Recently, Yadav et al. reported a new approach, based on the Prins cyclization, for the stereoselective synthesis of polyketid precursors containing *anti*-1,3-diols, flanked by a variety of alkyl branches and functional groups (**Scheme 79**).[174] After the Prins cyclization that generates three new stereocenters, the pyran ring is opened under reductive conditions to provide acyclic structures.




**Scheme 79.** Approach for the stereoselective synthesis of *anti*-1,3-diol fragments.[174]

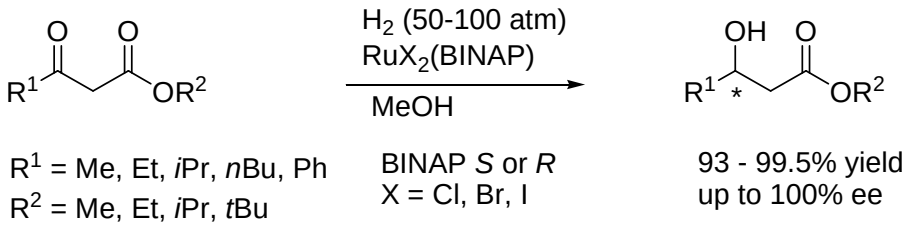
After all, nowadays the application of the Prins reaction to the synthesis of natural products has become commonplace, undoubtedly because of the convergent and efficient nature of the reaction for the formation of tetrahydropyran rings. The most recent examples of its utilization include total synthesis of calyxin,[175] clavosolide A,[176] dactylolide,[177] ratjadone A,[178] briarellins E and F,[179] and polycavernoside A.[180]

### 6.3.2 Asymmetric hydrogenation of *β*-keto esters (Noyori reduction)

Optically active *β*-hydroxy carboxylic esters are an extremely important class of intermediates for synthesis of different natural products and pharmaceuticals. Until the end of 1980 access to such compounds has relied mainly on biological or biochemical transformations.[181]

A major breakthrough in this field came with the fundamental work of Noyori.[182] In his pioneering paper he reported screening of different BINAP-Ru(II) complexes in the reduction of methyl 3-oxobutanoate to methyl 3-hydroxybutanoate.[183] As a result it was found that the

halogen-containing complexes having an empirical formula $RuX_2(BINAP)$ (X = Cl, Br or I), served as excellent catalyst precursors. The enantioselective hydrogenation using less than 0.1 mol% of catalyst proceeded smoothly in methanol under an initial hydrogen pressure of 50–100 atm.[184] A variety of prochiral *β*-keto esters were hydrogenated in nearly quantitative yields and with extremely high (up to 100%) enantioselectivities (**Scheme 80**). Esters of methyl, primary, secondary, and tertiary alcohols were equally employable.




**Scheme 80.** $RuX_2(BINAP)$ catalyzed asymmetric hydrogenation of *β*-keto esters.[183]

To explain the mechanism of $RuX_2(BINAP)$ catalyzed asymmetric hydrogenation of *β*-keto esters, one should take a closer look at its structure.

BINAP, 2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl, is a chiral ligand commonly used in formation of catalytic reagents. It is one of the most important commercially available catalyst ligand and has been widely used to achieve asymmetric catalysis under a variety of conditions.[185] This catalytic ligand is a fully aromatic and conformationally flexible atropo-isomeric $C_2$ diphosphine (**Figure 30**). The barrier to racemization is high due to steric hindrance that limits rotation about the bond linking the naphtyl groups. The dihedral angle is approximately 90°. Because the rotation about the binaphtyl *C1-C1'* pivot and *C2*- or *C2'*-P bonds is possible without seriously increasing the torsional strain, it can accommodate a range of transition metals, mainly of the second and third rows, such as Ru(II), Rh(I), palladium and iridium.[186] The axially dissymmetric $C_2$ chiral diphosphine exerts strong steric and electronic influences on transition metals complexes. Many of these species promote various asymmetric transformations such as hydrogenation, hydrosilylation, hydroboration, allylic alkylation and isomerization.

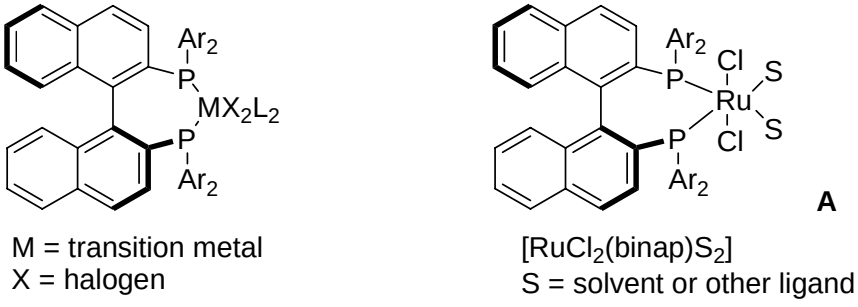
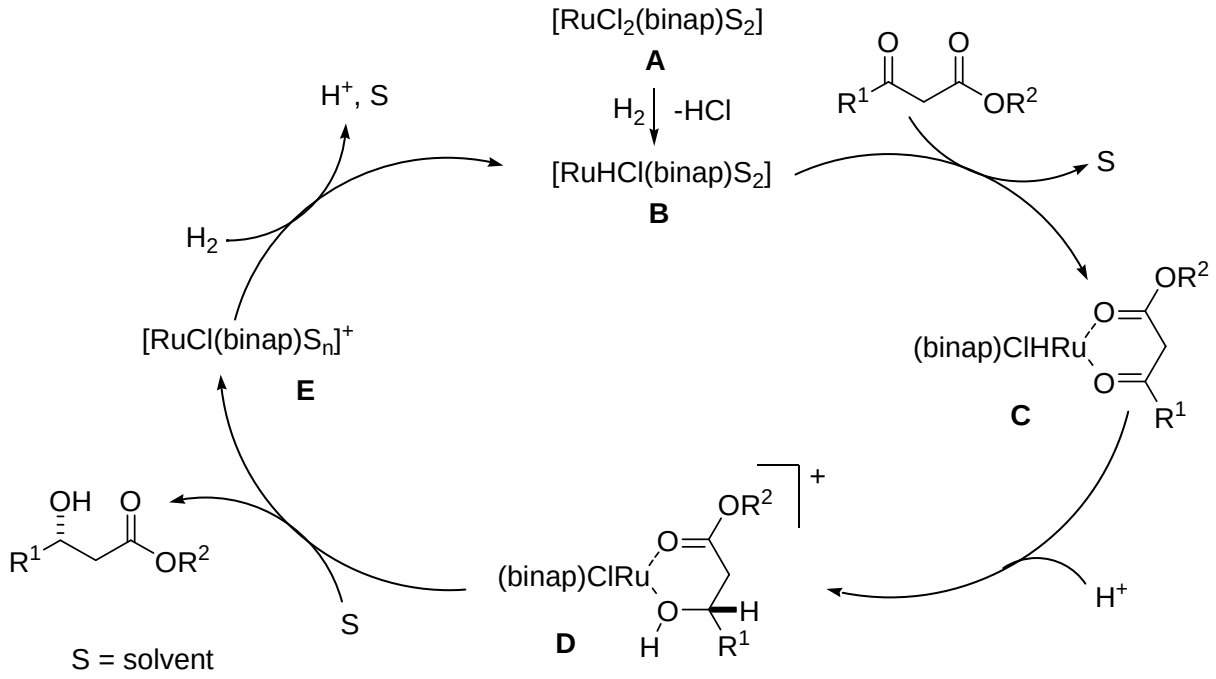



**Figure 30.** Structure of (*S*)-BINAP based metal complex.

BINAP-Ru dichloride catalysts have a very wide scope for the hydrogenation of *β*-keto esters. **Scheme 81** illustrates the mechanistic model for the (*S*)-(BINAP)-Ru-catalyzed hydrogenation of *β*-keto esters. The halide ligand in the Ru complex, which generates a strong hydrochloric acid and a RuHCl species by the action of $H_2$, is important to facilitate the hydride transfer from the Ru centre to the carbonyl carbon.[187] Intermediate **B** interacts reversibly with the *β*-keto ester to form the *σ*-type chelate complex **C**, in which metal-to-carbonyl hydride transfer is geometrically difficult. Then protonation occurs at the oxygen to increase the electrophilicity of the carbon and convert the geometry from *σ* to *π*, thereby facilitating the hydride migration. The hydroxy ester ligand compex in the resulting product **D** is liberated by solvent molecules. Reaction of the cationic Ru complex **E** with $H_2$ results in regeneration of catalytic intermediate **B**. Enantioselection with a ratio of >99:1 is generally achieved in the hydride transfer step from **C** to **D**. Here, the key is the carbonyl protonation in **C**, which is mediated by HCl[188] generated in the induction step **A** to **B**.




**Scheme 81.** Mechanism of (*S*)-BINAP-Ru catalyzed hydrogenation of *β*-keto esters.[185,186]

The chirality of BINAP is transmitted to other metal coordination sites through the chelate structure. The δ or λ geometry is highly skewed and determines the chiral disposition of the P-pnenyl rings that is crucial for generating outstanding chirality-discriminating ability at the reactive coordination sites. The transition states (TSs) in the hydride transfer step are stabilized by the ligation of the ester C–O to the Ru center.

In addition, the presence of the ester moiety interacting with the Ru center is crucial for both high reactivity and enantioselectivity. Due to the excellent chiral recognition ability of BINAP, the two stereo-determining transition states (TSs) are well differentiated with the

assistance of the oxygen-Ru interaction. According to **Figure 31**, the second and fourth quadrants are more crowded than the first and third quadrants because of shielding by the equatorial phenyl groups. The *S*-directing TS is highly favored over the *R*-generating diastereomer, which suffers from the substantial R/P-phenyl repulsive interaction.[186,189] The oxygen–Ru dative bond exerts a pivotal function in the acceleration of hydrogenation as well. *β*-Keto esters are hydrogenated smoothly even in acetone, containing a small amount of water. Although, BINAP-Ru dihalide catalyst have a very broad scope, they are not suitable for hydrogenation of simple, unfunctionalized ketones.

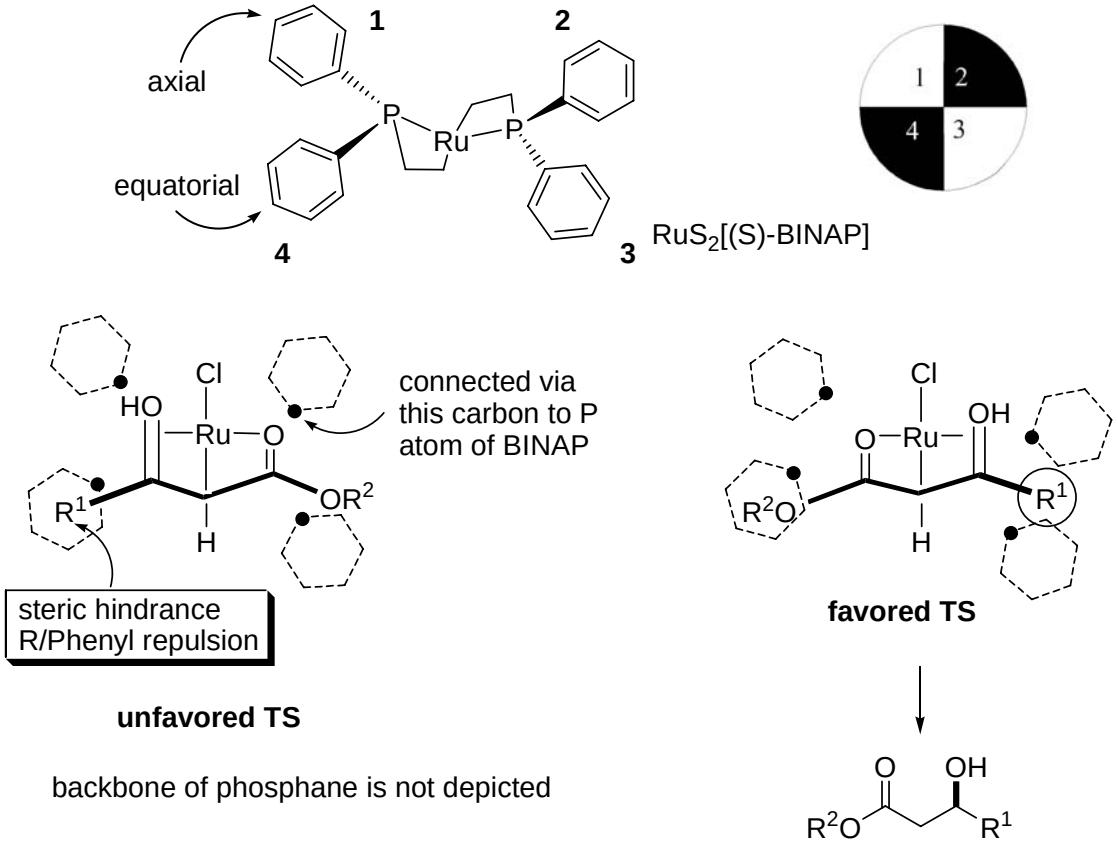



**Figure 31.** Stereochemical outcome for (*S*)-BINAP-Ru catalyzed hydrogenation of *β*-keto esters.

In addition, the halogen-containing BINAP-Ru complexes are efficient catalysts for the asymmetric hydrogenation of a range of functionalized ketones, wherein coordinative nitrogen, oxygen, and halogen atoms near C=O functions direct the reactivity and stereochemical outcome in an absolute sence.[190] A wide variety of achiral ketones were hydrogenated in an enantioselective manner to the corresponding chiral alcohols in 90–100% *ee* (**Figure 32**). In general, the reaction can be performed in alcohols, as a solvent, with up to 50% substrate concentration under 4–100 atm at room temperature with an substrate:catalyst ratio of up to 10 000:1 on any scale, even using >100 kg of the substrate.

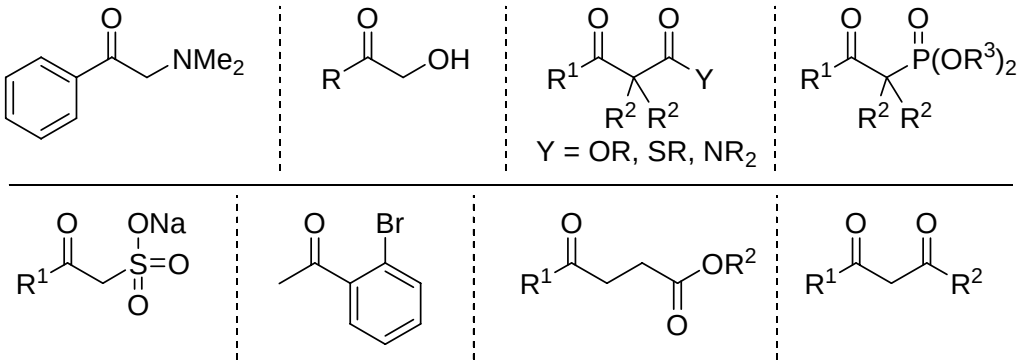



**Figure 32.** Scope of asymmetric hydrogenation of functionalized ketones.

Although the Ru(II)-BINAP system provides very high enantioselectivity over a wide range of substrates with remarkable turnover, in some cases temperatures greater than 80 °C or hydrogen pressures greater than 1000 psi (80 atm) are required to achieve high selectivities and yields.

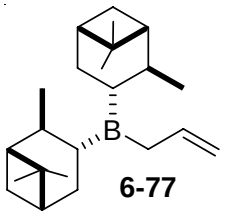
In 1992 King and co-workers reported that in the presence of 0.1 mol% of strong acid and using 0.02–0.05 mol% of $[RuCl_2(BINAP)]_2NEt_3$ complex, asymmetric hydrogenation can be conducted in a standard Parr shaker apparatus at low temperatures and readily attainable pressures (40 °C/30 psi $H_2$).[188a] In addition, they developed a simple and reproducible procedure for the preparation of purified catalyst.

Another valuable improvement of the original Noyori procedure was achieved by Genêt and co-workers.[191] It was shown that asymmetric hydrogenation of *β*-keto esters can be carried out at atmospheric pressure using chiral Ru(II) catalysts of general formula $[RuBr_2(L)]$, where L = BINAP, MeO-BIPHEP, Me-DUPHOS. These catalysts were easily prepared *in situ* by treatment of commercially available (COD)Ru(2-methylallyl)$_2$ in the presence of the appropriate chiral ligands.

Because of outstanding selectivity and efficiency, BINAP-Ru(II) catalyzed reductions have found wide application in the syntheses of complicated natural products, pharmaceuticals and fine chemicals. The most representative examples of its utilization include total syntheses of (–)-roxaticin,[192] (+)-mycoticin A,[193] taurospongin A,[194] roflamycoin,[195] and (+)-codaphniphylline.[196]

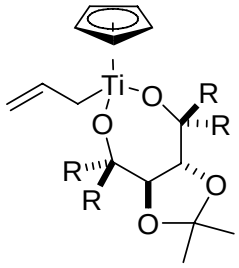
### 6.3.3 Enantioselective allylation of aldehydes using strained silacycles (Leighton allylation)

Due to the prevalence of secondary alcohols in bioactive natural products, many moderately to highly enantioselective chiral reagents and catalytic system for the allylation of aldehydes have been developed.[197] The most reliable reagents in this regard are based on chiral allylmetal derivatives. For example, as was shown by H. C. Brown and co-workers, chiral allyldiisopinocampheylborane (**6-77**), derived from the hydroboration of pinene turned out to give high *ee*-values in the addition to prochiral aldehydes (**Figure 33**).[198] However, the main drawback of this methodology is requirement of salt-free conditions and low temperatures (–100 °C), which is significantly limiting its application in a large scale synthesis. Other allylation reagents are derived from monocyclopentadienylchlorotitanium complexes containing two chiral alkoxy ligands, which in turn can be obtained from tartrate ester acetals by Grignard addition.[199] Although allyltitanation reactions generally proceed with respectable selectivity, the preparation of reagents **6-78** is rather complicated and time consuming process.




**6-77**

(+)-$Ipc_2BAll$




**6-78**

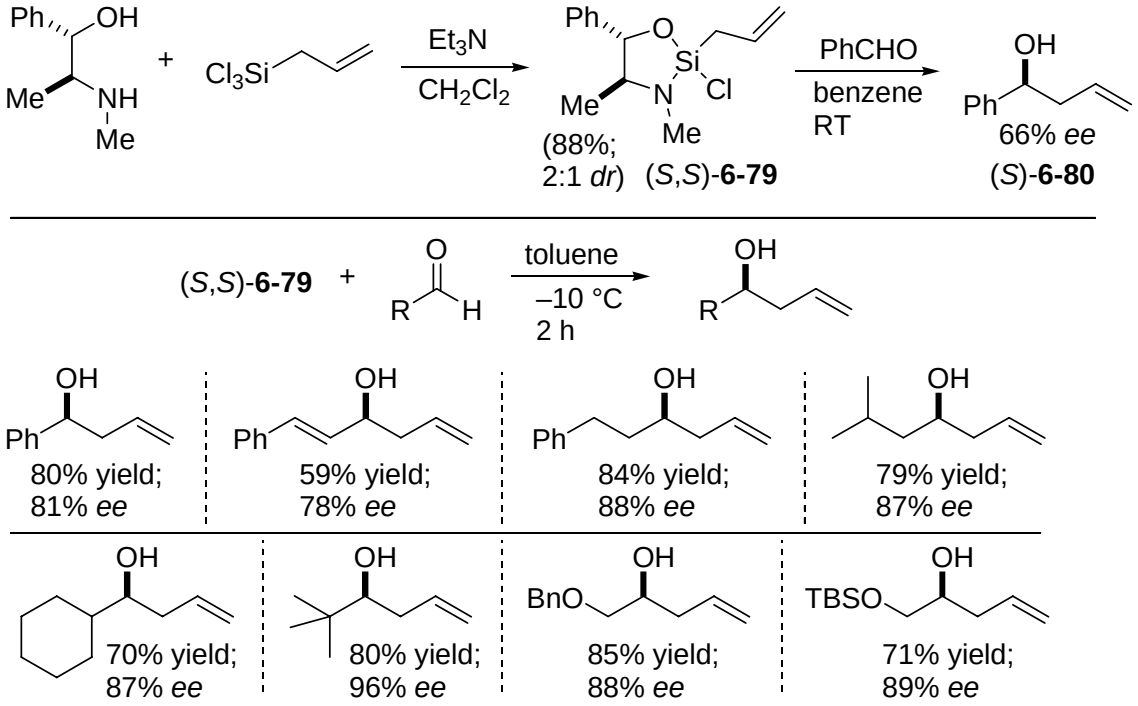
R = Alkyl, Aryl

**Figure 33.** Structure of (+)-$Ipc_2BAll$ (**6-77**) and cyclopentadienyldialkoxyallyltitanium complexes (**6-78**).

Thus, the development of new reagents for enantioselective allylation of aldehydes was undertaken by various groups. In terms of practically utility, an ideal reagent should be easily and inexpensively prepared in both enantiomeric forms; can be prepared in bulk and employed by using only trivial procedure; will allow easy separation and purification of the homoallylic alcohol products; and finally, be generally effective in terms of both efficiency and enantioselectivity.

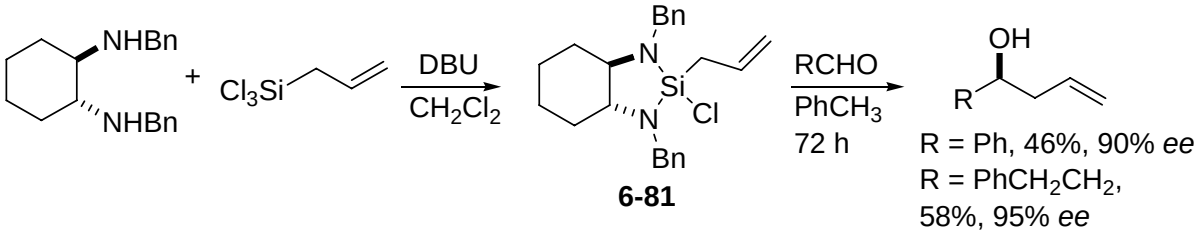
Significant progress in this field has been achieved by Leighton and co-workers. They reported that simply by constraining silicon in five-membered rings with 1,2-diols, 1,2-diamines, and 1,2-amino alcohols, sufficient Lewis acidity for uncatalyzed allylation reactions are obtained.[200] Because both enantiomers of pseudoephedrin are available and inexpensive it was chosen for initial study. Reaction of (*1S,2S*)-pseudoephedrine with allyltrichlorsilane and $NEt_3$ in $CH_2Cl_2$ allowed the isolation of allylsilane (*S,S*)-**6-79** in 88% yield (**Scheme 82**). Reaction of (*S,S*)-**6-79** with benzaldehyde in benzene at room temperature gave alcohol (*S*)-**6-**

**80** with 66% *ee*. After optimization of reaction conditions it was found that the best yields and *ee*-values can be achieved when reactions are carried out in toluene at –10 °C and with 0.2–0.4 M silane concentration. In order to investigate the scope of this reaction several different aldehydes were allylated under optimized conditions. As one can see, whereas enantioselectivities for aliphatic aldehydes are good (87–96%), they are unacceptably low for aromatic and conjugated aldehydes (78–81%).




**Scheme 82.** Enantioselective allylation of different aldehydes with allylsilane reagent (*S*,*S*)-**6-79**.[200]

In the same paper were also reported preliminary data regarding reagent **6-81**, which was found to provide improved enantioselectivity, but also low reactivity (**Scheme 83**). Allylsilane **6-81** was prepared by reacting (*1R*,*2R*)-*N*,*N'*-dibenzylcyclohexane-1,2-diamine with allyltrichlorsilane in the presence of DBU as a base.

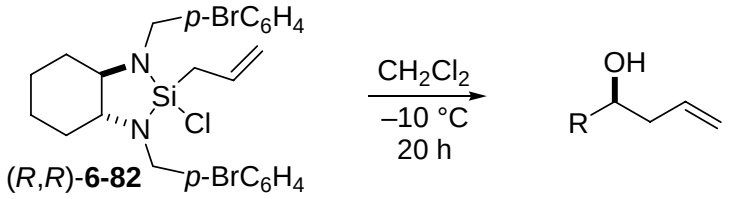



**Scheme 83.** Enantioselective allylation with allylsilane reagent **6-81**.[200]

Using obtained results as a starting point, they conducted a full investigation into the potential of the diamine-based system. During the optimization of the performance of reagent **6-81** it turned out that the use of $CH_2Cl_2$ as a solvent led to a significant increase in both the efficiency and enantioselectivity. In order to identify role of the benzyl substituent, the bis-(*p*-

methoxybenzyl) and bis-(*p*-bromobenzyl) analogues of **6-81** were prepared and screened for any effect on efficiency and selectivity.[201] As a result, the bis-(*p*-bromobenzyl)-diamine system was identified as most effective and convenient. Thus, it was used to optimize conditions and to examine the scope of the reaction. Allylation of aliphatic aldehydes with 1 equiv. of (*R*,*R*)-**6-82** at –10 °C in $CH_2Cl_2$ proceeded smoothly and provided the corresponding homoallylic alcohols in good to excellent yields and with excellent enantioselectivities (**Scheme 84**). Reactions at room temperatures were found to be slightly less selective, but the yields were significantly lower due to partial decomposition of the reagent.

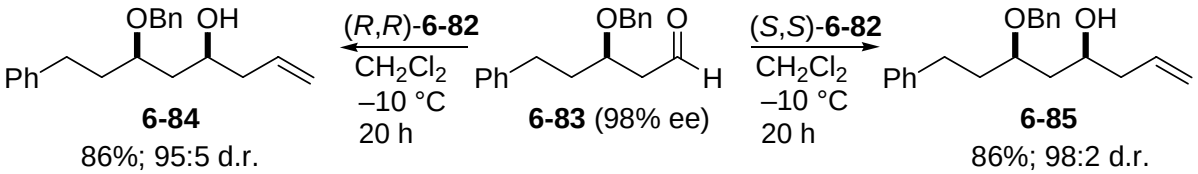
Reacting aromatic aldehydes with reagent (*R*,*R*)-**6-82** resulted in formation of chiral benzylic alcohols in respectable yields and with high *ee*-values. However, conjugated aldehydes proved still less efficient, but when the reaction was carried out at 8 °C for 72 h good yields and excellent enantioselectivities were obtained as well.




| R | Yield [%] | *ee* [%] | R | Yield [%] | *ee* [%] |
|---|---|---|---|---|---|
| $PhCH_2CH_2$ | 90 | 98 | Ph | 69 | 98 |
| $(CH_3)_2CHCH_2$ | 80 | 96 | *p*-$MeOC_6H_4$ | 62 | 96 |
| Cy | 93 | 96 | *p*-$CF_3C_6H_4$ | 66 | 96 |
| $PhCH_2OCH_2$ | 67 | 97 | (*E*)-PhCH=CH | 75 | 96 |
| $TBSOCH_2$ | 61 | 98 | (*E*)-*n*PrCH=CH | 71 | 95 |

**Scheme 84.** Scope of the enantioselective allylation with allylsilane reagent (*R*,*R*)-**6-82**.[201]

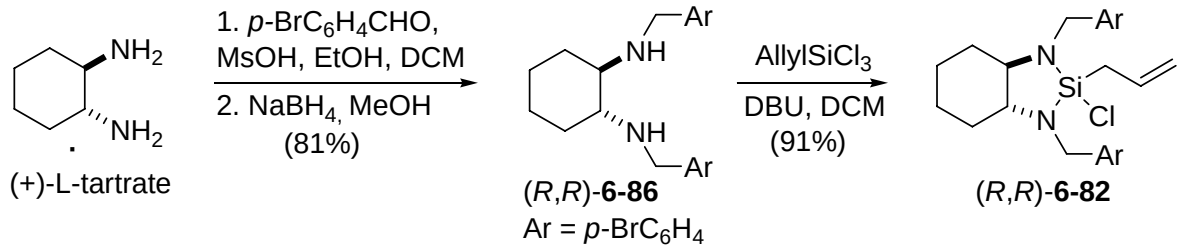
In addition, it was shown that the developed methodology can be successfully transferred to chiral aldehydes. Subjection of aldehyde **6-83** to the standard allylation conditions with (*R*,*R*)-**6-82** secured protected *syn*-alcohol **6-84** in 86% yield and 95:5 d.r. (**Scheme 85**). In a similar way, reaction of **6-83** with enantiomeric reagent (*S*,*S*)-**6-82** led to protected *anti*-alcohol **6-85** in 86% yield and 98:2 d.r.




**Scheme 85** Asymmetric allylation of chiral aldehydes.[201]

Notably, reagent **6-82** is a readily prepared stable solid that may be briefly handled in air with no apparent decomposition, and may be stored in a freezer under $N_2$ for long periods of time.

The cyclohexane diamine (*R*,*R*)-**6-86** was prepared via reductive amination from *p*-bromobenzaldehyde and (1*R*,2*R*)-(+)-1,2-diaminocyclohexane·L-tartrate (**Scheme 86**).




**Scheme 86.** Synthesis of allylsilane reagent (*R*,*R*)-**6-82**.[201]

As was mentioned before, allylsilanes **6-79**, **6-81**, **6-82** react without any additives with aldehydes because of ring-strain-release Lewis acidity, which still remains in such five-membered silacycles due to the long Si–N bonds and short C–N bonds. Originally, it was assumed that complexation of the aldehyde to the silane to give a trigonal bipyramidal intermediate is followed by allyl transfer. Recently Leighton and co-workers communicated a paper, devoted to detailed investigations of mechanism and stereoselectivity of asymmetric aldehyde allylations employing the strain-release activated silane reagents based on computational methods.[202] Some strain release is realized by reducing the Si–N-bond angle to roughly 90° in the trigonal bipyramidal arrangement. In this study the transition states for the stereoselective strain-release allylations have been located. Using the model based on these transition states the following components important for the stereoselectivity of diazasilane reagents were suggested: (a) attack of aldehyde oxygen on an apical position of the Si center (*anti* to an N); (b) an antiperiplanar arrangement of an O lone pair and the Si–Cl bond in the chair transition state; (c) location of the chlorine with the lone pair *anti* to the lone pair of apical N.

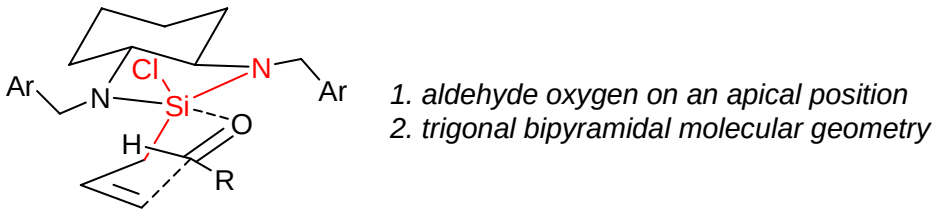



**Figure 34.** Possible transition state for Leighton allylation.

In addition, it was shown that strained silacycles can be successfully used for enantioselective allylation of acylhydrazones[203] and highly diastereo- and enantioselective crotylation of aldehydes.[204]

The developed methodology was efficiently employed in the total syntheses of dolabelide D,[205] apicularen A,[206] gigantecin,[207] anamarine,[208] and 10-*epi*-anamarine.[209]

More recently, it was demonstrated that even sterically hindered and functionalized aryl ketones can be allylated and crotylated with high enantioselectivities to provide access to unusual tertiary carbinol structures.[210]

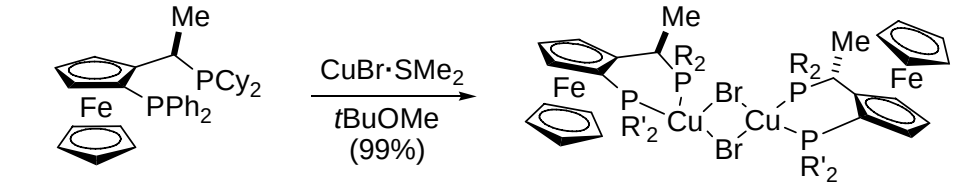
### 6.3.4 Asymmetric alkyl cuprate addition to α,*β*-unsaturated thioesters (Feringa–Minnaard reaction)

Due to the occurrence of polydeoxypropionate chains in numerous biologically relevant compounds many methods for their stereocontroled synthesis were developed. Many of these approaches utilize a chiral auxiliary (enolate alkylations,[211] conjugate additions,[212] allylic alkylations[213]) or substrate to effect stereochemical control. Recently, an attractive iterative catalytic asymmetric procedure was disclosed by Negishi and co-workers.[214] This methodology provides access to α,*ω*-diheterofunctional reduced polypropionates via 'one-pot' Zr-catalyzed asymmetric carboalumination–Pd-catalyzed cross-coupling tandem process.

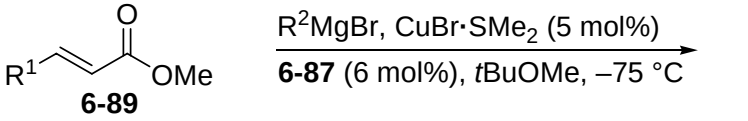
Other options for the introduction of the methyl bearing stereocenter are based on the use of commercially available and, usually, very costly chiral substrates, like Roche ester, 3-methylglutarate etc. Therefore, development of simple and efficient enantioselective methods for the construction of deoxypropionate subunits with absolute stereocontrol always was desirable goal for many chemists.

A major breakthrough in this area came with the pioneering work of Feringa and Minnaard.[215] Initially, it was reported that chiral Josiphos ligands[216,217] were very effective in promoting the Cu-catalyzed conjugate addition (CA) of alkyl Grignard reagents to α,*β*-unsaturated esters.[218] A broad range of *β*-substituted chiral esters was obtained in good yields and with excellent enantioselectivities (**Scheme 87**). Importantly, the use of sterically hindered esters, which usually help to avoid undesired 1,2-additions was not required. As was proved by X-ray analysis, reacting stoichiometric amounts of ligand Josiphos (**6-87**) with CuBr·$SMe_2$ resulted in formation of dinuclear copper catalyst complex **6-88**. Interestingly, complex **6-88** could also be recovered from the crude reaction mixture. While linear aliphatic Grignard reagents provided excellent results in the CA to α,*β*-unsaturated esters **6-89**, affording the products **6-90** with excellent region- and enantioselectivities, the addition of MeMgBr to methyl (2*E*)-hex-2-enoate showed the limitation of the methodology. Although the product was formed with high

enantioselectivity (93% *ee*), the reaction rate was prohibitively low because of decreased reactivity of MeMgBr.




(*R,S*)-Josiphos (**6-87**) **6-88** R = Cy; R' = Ph

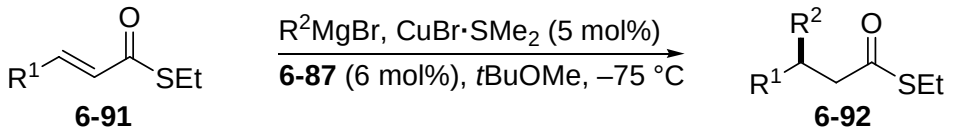



| $R^1$ | $R^2$ | Yield [%] | *ee* [%] |
|---|---|---|---|
| *n*Pr | Et | 99 | 93 |
| *n*Pent | Et | 89 | 88 |
| $PhCH_2CH_2$ | Et | 91 | 91 |
| $PhCH_2CH_2$ | *n*Bu | 94 | 92 |
| $PhCH_2$ | Et | 75 | 95 |
| $PhOCH_2$ | Et | 85 | 86 |

| $R^1$ | $R^2$ | Yield [%] | *ee* [%] |
|---|---|---|---|
| *i*Bu | *n*Bu | 87 | 88 |
| *i*Pr | Et | 93 | 87 |
| ***n*Pr** | **Me** | **19** | **93** |
| 2-furfuryl | Et | 62 | 86 |
| Ph | Et | 42 | 75 |

**Scheme 87.** Scope of the enantioselective CA of Grignard reagents to α,*β*-unsaturated esters.[218]

In order to make this methodology applicable to the synthesis of 1,3-dimethyl arrays, Feringa and co-workers switched to the more reactive but equally readily accessible α,*β*-unsaturated thioesters. The reduced electron delocalization in the thioester moiety, compared to oxoesters, results in a higher reactivity toward conjugated addition reactions, while the presence of thioester in the chiral product offers additional synthetic versatility. Gratifyingly, the addition of Grignard reagents to unsaturated thioesters **6-91** revealed the success of the approach.[219] The complex prepared in situ from $CuBr{\cdot}SMe_2$ (5 mol%) and (*R,S*)-Josiphos (6 mol%) catalyzed the CA of $R^2MgBr$, providing the *β*-alkyl-substituted thioesters **6-92** in high yields and with excellent regio- and enantioselectivities (**Scheme 88**). Bulky Grignard reagents, such as *i*PrMgBr and *i*BuMgBr, however, gave poor enantioselectivities under these conditions. It was assumed, that drastically higher yields obtained for the methyl adducts from α,*β*-unsaturated thioesters, compared to the oxoester analogues, were due to their inherent electronic properties which are close to those of enones.

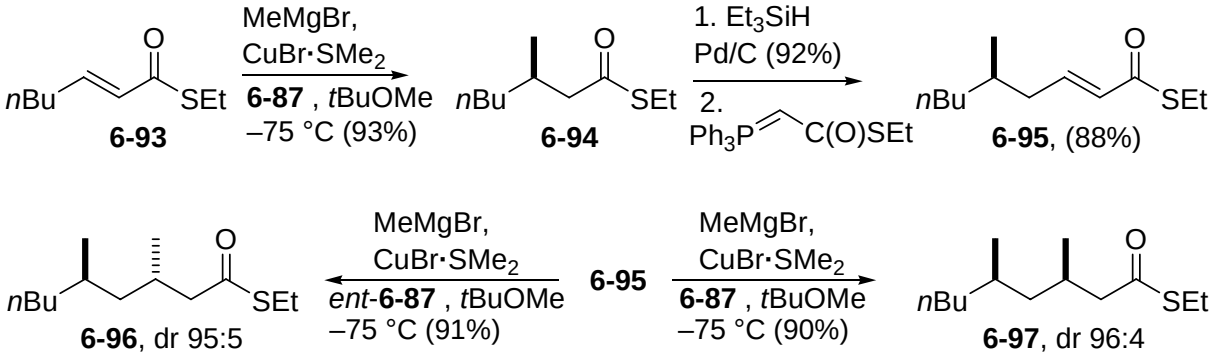



| $R^1$ | $R^2$ | Yield [%] | *ee* [%] |
|---|---|---|---|
| *n*Pent | Me | 90 | 96 |
| *n*Bu | Me | 93 | 95 |
| *n*Pr | Me | 92 | 96 |
| Et | Me | 92 | 92 |
| $BnO(CH_2)_3$ | Me | 94 | 95 |
| Ph | Me | 88 | 95 |

| $R^1$ | $R^2$ | Yield [%] | *ee* [%] |
|---|---|---|---|
| *n*Pent | Et | 89 | 86 |
| Et | *n*Pr | 87 | 85 |
| Me | *n*Bu | 90 | 90 |
| *n*Pent | *i*Pr | 93 | 25 |
| *n*Pent | *i*Bu | 80 | 15 |

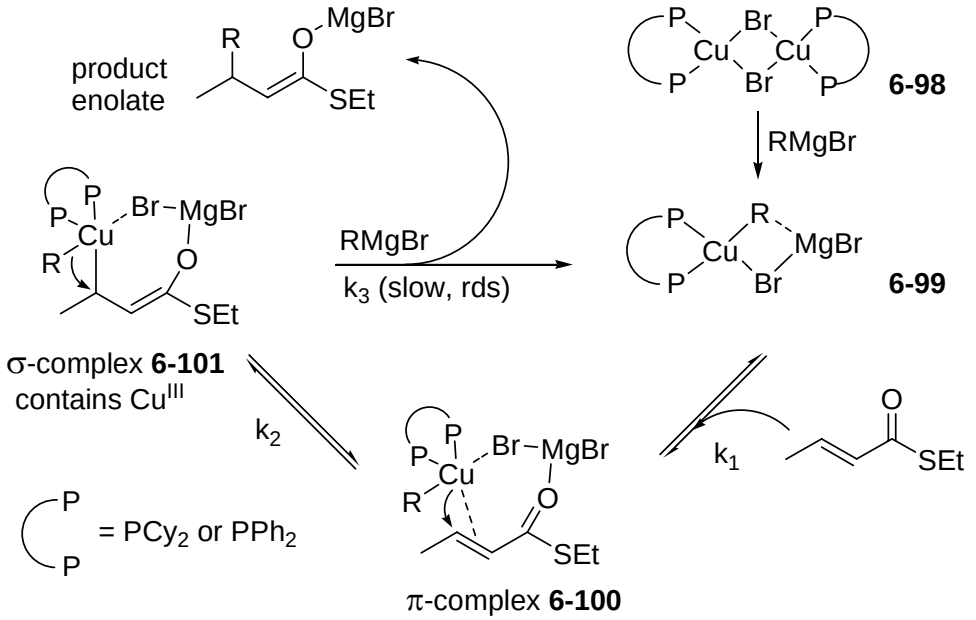
**Scheme 88.** Enantioselective CA of Grignard reagents ($R^2MgBr$) to α,β-unsaturated thioesters (**6-91**).[219]

Based on the optimized procedure, an iterative method to provide access to optically active *syn*- and *anti*-1,3-dimethyl arrays as well as deoxypropionate subunits was devised. The approach relies on sequential enantioselective CAs to unsaturated thioesters (**Scheme 89**).



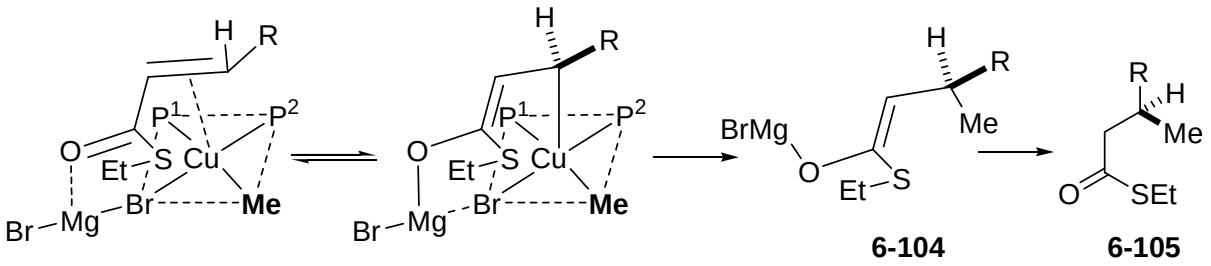

**Scheme 89.** Synthesis of *syn*- and *anti*-1,3-dimethyl arrays.[219]

In order to clarify the mechanism of these Cu-catalyzed reactions extensive kinetic and spectroscopic studies were conducted. According to these studies a possible reaction pathway was proposed (**Scheme 90**).[220] Reaction of the Grignard reagent converts the dimeric complex **6-98** to the reactive Cu-complex **6-99**. This will combine with the enoate to a π-complex **6-100**. In this entity Mg is bound to the oxygen, thereby activating it. In addition, one of the bromine atoms coordinates to the Cu center. The π-complex **6-100** rearranges to the σ-complex **6-101** which then collapses by reductive elimination to the enolate. A new Grignard reagent RMgBr regenerates the active catalytic intermediate **6-99**. The proposed catalytic cycle was proved to be in full accordance with the results of the kinetic study. The dependence of the reaction rate on the substrate and Grignard reagent indicated that both reactants are involved in the rate determining step. This step is preceded by fast equilibrium between substrate-bound σ-complex **6-101** and π-complex **6-100** and substrate unbound complex **6-99**.




**Scheme 90.** Proposed catalytic cycle for Cu-catalyzed conjugate additions.[220]

Optimized semiempirical calculations indicate that π-complex **6-102** adopts a square pyramidal geometry, which is stabilized via π-complexation of the alkene moiety to the Cu and, importantly, through the interactions between Mg and the carbonyl moiety of the thioester. Formation of the transition structure with the chairlike seven-membered ring conformation was proposed in the next step, where Cu forms a σ-bond approaching from the bottom side of the *β*-carbon leading to the $Cu^{III}$ intermediate **6-103** with the absolute stereochemistry shown (**Figure 35)**. To avoid steric interactions with the dicyclohexyl moieties at the nearby phosphorous, the final transfer of methyl group occurs as shown in **Figure 35**.




π-complex **6-102** σ-complex **6-103**

$P^1$ = $PPh_2$ group (attached to Cp)

$P^2$ = $PCy_2$ group (attached to benzylic position of Cp)

**Figure 35.** Working model for the enantioselective CA of Grignard reagents.[220]

The synthetic utility of the developed iterative catalytic protocol and the versatility of *β*-methyl-substituted thioesters were demonstrated in asymmetric total syntheses of multi-methyl-branched natural products. One can mention total syntheses of lardolure,[219] *β*-D-mannosyl phosphomycoketide (**6-106**),[221] phthioceranic (**6-107**)[222] and mycocerosic (**6-108**)[223] acids.

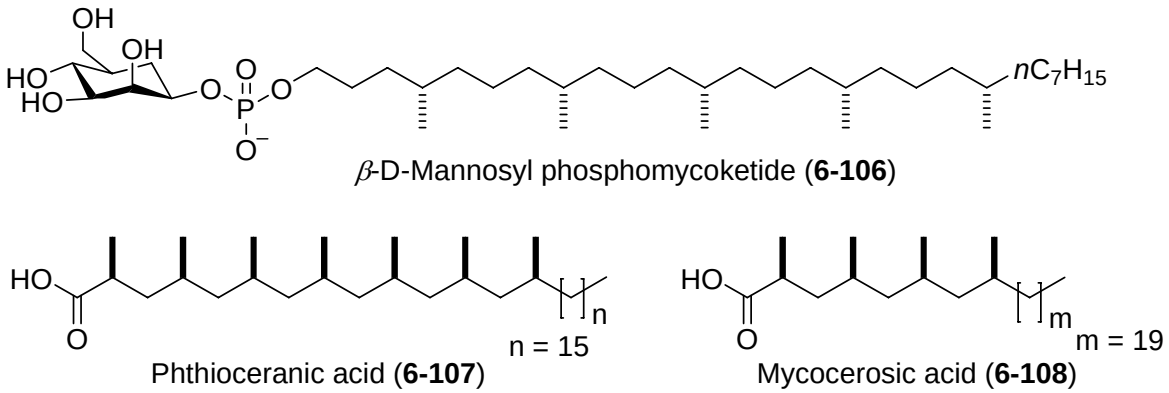
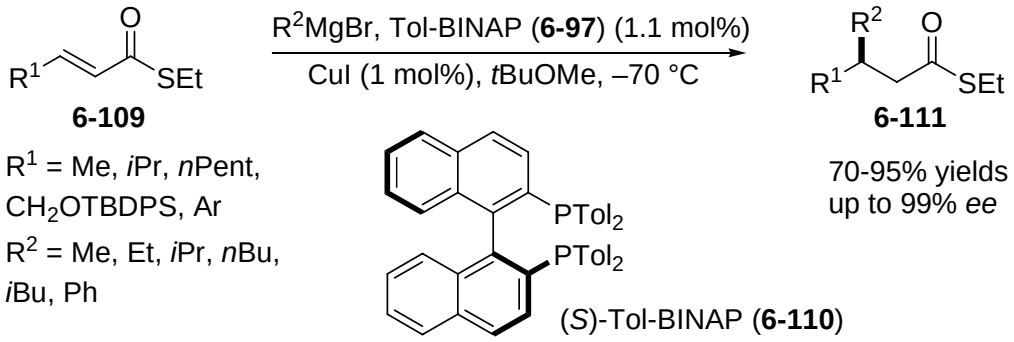



**Figure 36.** Structures of multi-methyl-branched natural products (**6-106**, **6-107**, **6-108**).

More recently, Feringa and co-workers reported, that the Tol-BINAP/CuI catalytic system allows for the enantioselective addition of a wide variety of Grignard reagents, including relatively unreactive MeMgBr and bulky Grignard reagents, to aliphatic α,β-unsaturated thioesters.[224] Moreover, it was shown that Tol-BINAP/CuI is a more active catalyst than Josiphos/CuBr in the conjugate addition of MeMgBr to cinnamic acid thioesters, giving excellent selectivities for these reactions (**Scheme 91**).



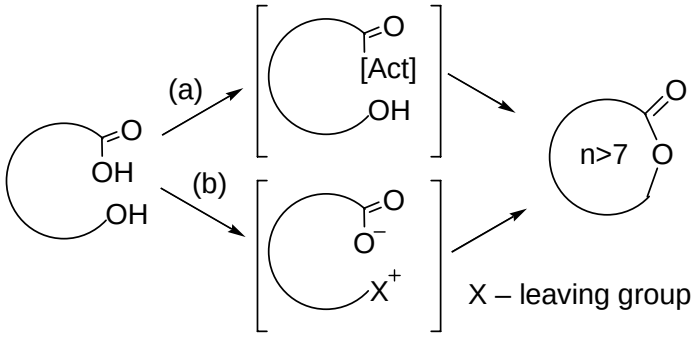

**Scheme 91.** Tol-BINAP/CuI-catalyzed CA of Grignard reagents to α,β-unsaturated thioesters.[224]

### 6.3.5 Yamaguchi macrolactonization

The macrocyclic framework is one of the most basic structures for natural and unnatural organic molecules. With the advent of modern isolation techniques, numerous large-ring lactones that possess interesting biological activity have been isolated. Natural macrocyclic lactones present a large spectrum of interesting properties from perfumery, to phytotoxicity, to pheromone or insecticide activity to medicinal (antibiotic, cytotoxic, antiangiogenesis) properties. The most representative examples of clinically useful macrolactones include the macrolide antibiotic erythromycin,[225] the cyclodepsipeptide FK228, which is currently in phase II clinical trials as anticancer drug, the antifungal agent roxaticine,[226] 20-membered apoptolidin, which selectively induces apoptosis in rat glia cells transformed with adenovirus E1A oncogenin the presence of normal cells, and promising the anti-cancer drugs

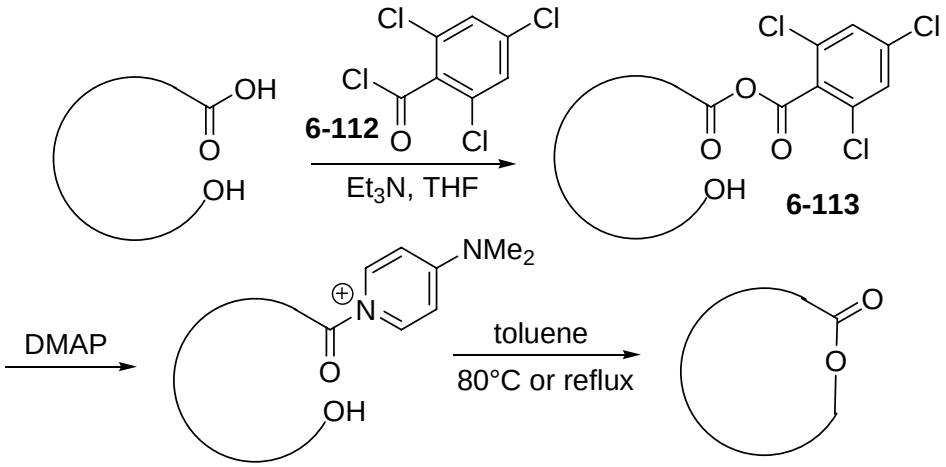
epothilones,[227] with a mode of action similar to Taxol® and the potential to overcome drug resistance.

Recently, several effective C–C bond forming methods such as olefin and alkyne metathesis, transition metal-promoted coupling (Nozaki-Hiyama-Kishi), Horner-Wadsworth-Emmons reactions have been widely studied for producing cyclic compounds.[228,229] However, macro-lactonization is still the most popular method for producing cyclic compounds including carboxylic ester moieties since there are some effective methods for constructing the ester linkage.[230] Due to entropic or enthalpic factors direct cyclization is generally not possible without activation of either the alcohol or the carboxylic acid terminal group (**Scheme 92**).




**Scheme 92**. Two different approaches to macrocyclic compounds.

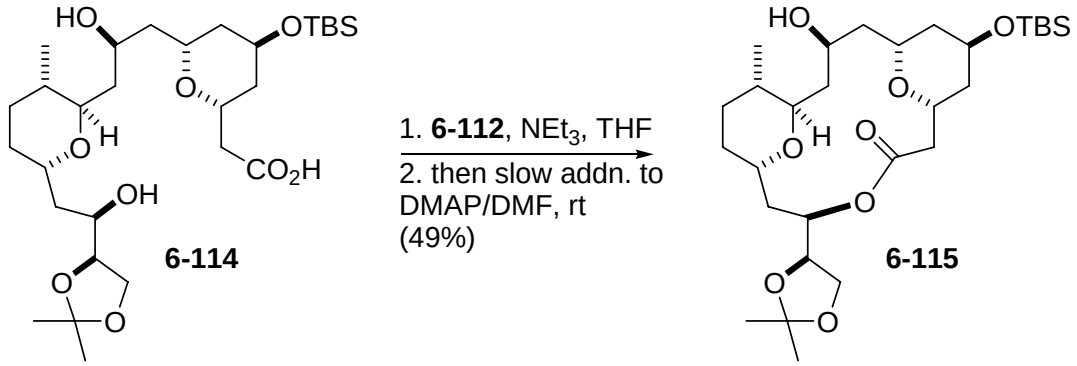
The need for relyable methods of forming large-ring lactones in the presence of sensitive functionality has led to the development of numerous methodologies. The most recognized of these is the Yamaguchi cyclization,[124] where the acid is activated as a mixed anhydride and esterification is facilitated by a high concentration of the acylation promoter 4-(dimethylamino)pyridine (DMAP). Due to the mild conditions and, generally, good yields, the Yamaguchi protocol and variations are widely used by synthetic chemists. The reaction sequence involves the formation of mixed anhydride **6-113** using the so-called Yamaguchi reagent i.e 2,4,6-trichlorobenzoyl chloride (TCBC) **6-112** in the presence of triethylamine or Hünig's base (**Scheme 93**). The use of THF as a solvent enables easy separation from obtained $NEt_3$-HCl, and subsequent concentration of the reaction mixture. Thereafter, the mixed anhydride is dissolved in toluene and slowly added by syringe pump to a highly diluted solution of DMAP (2–10 equiv) at high temperature (80 °C or reflux). Sometimes the desired macrolactonization proceeds smoothly even at ambient temperatures. Interestingly, the 2,6-dichloro derivative turned out to be also effective in this reaction. Regarding DMAP, the use of pyrolidinopyridine as a supernucleophilic catalyst has also been described.[231] In addition, a Yamaguchi macrolactonization, using polymer-supported DMAP was successfully employed in the total synthesis of epothilone C.[232]




**Scheme 93.** Mechanism of Yamaguchi macrolactonizations.

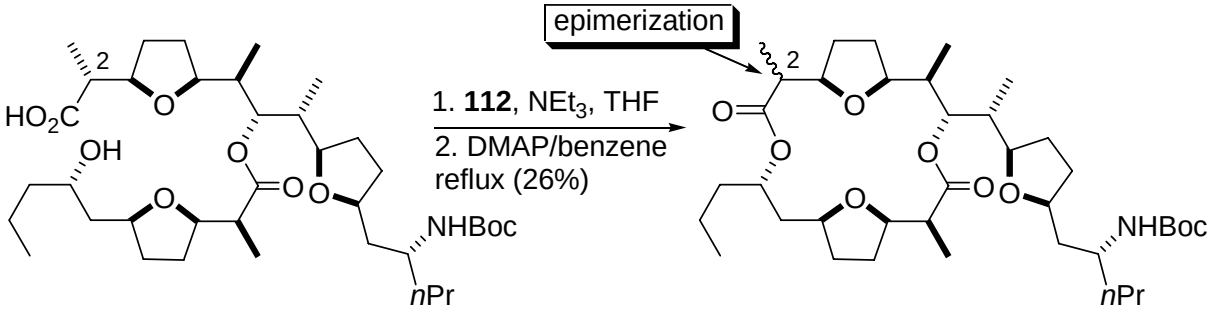
From the many variations and modifications of the original Yamaguchi procedure, two very relevant ones were developed in the Yonemitsu group during the total synthesis of erythonolide derivatives.[233] In the first of these two modifications ('modified Yamaguchi conditions'), the beneficial effect of direct additions of a large amount of DMAP to the preformed mixed anhydride, generally at room temperature and without the need for slow dilution was found. This protocol was successfully utilized in the total syntheses of oleandolide,[234] and bryostatin.[235] According to the second Yonemitsu modification ('Yonemitsu conditions'), the mixed anhydride is not preformed and DMAP is directly introduced at room temperature from the beginning. This protocol was successfully employed in the total synthesis of rutamycin B,[236] where utilization of Keck, Mukaiyama and Corey procedures completely failed. Although, there is still no rule about the best conditions to realize a Yamaguchi macrolactonization on a particular substrate, generally, the Yonemitsu conditions are proved to be more effective for rather large macrocycles, and classical Yamaguchi conditions on medium ring lactones.

During the total synthesis of leucascandrolide by Carreira[237] it was demonstrated that the lactonization of the seco-acid **6-114** under the usual conditions leads mainly to oligomerization, probably due to unfavorable hydrogen bonds (**Scheme 94**). To disrupt these interactions, the reaction was carried out in DMF, giving the 14-membered lactone in 49% yield. Notably, none of the 8-membered lactone was observed.




**Scheme 94.** Synthesis of leucascandrolide macrolactone by Carreira.[237]

The use of the highly basic DMAP and high temperature on base-sensitive substrates such as unsaturated acids, can often lead to $\alpha/\beta$ to $\beta/\gamma$ and $Z/E$ isomerisation[238] of conjugated double bonds, as well as epimerization of sensitive chiral centers. During the total synthesis of Pamamycin-607 by Jeong[239] et al., it was found that the high temperature Yamaguchi esterification leads to complete epimerization at C2, which is in α position to a carboxylic function (**Scheme 95**).




**Scheme 95.** Epimerization during Yamaguchi esterification.[239]

In order to avoid undesired isomerisation of conjugated double bonds, macrolactonization can be performed on ynoic seco-acids with subsequent reduction of obtained triple bond. This methodology was successfully applied in the total syntheses of phorboxazole B,[240] laulimalide,[241] and pateamine A analogues.[242]

Despite the aforementioned drawbacks, the Yamaguchi protocol still remains the most popular and reliable method for performing macrolactonization. This methodology and its variations have been successfully used in more than 250 synthetic applications.[243] Some representative examples of its utilization include total syntheses of tartrolon B,[244] callipeltoside,[128a] bafilomycin,[245] dictyostatin,[246] 44-membered swhinholide,[247] polycavernoside A[248] amphidinolides[249] etc.

# 7 Goal of Research

When we started this project there was no synthesis of neopeltolide reported in the literature. However, in the meantime, two total syntheses with the correct revised structure were almost simultaneously completed by the Panek[147] and Scheidt[148] groups. After we published a formal total synthesis of neopeltolide, two additional reports on the synthesis of this molecule were communicated by the Lee[149] and Sasaki[150] groups. After reviewing the total syntheses of neopeltolide from various groups, we could notice some significant drawbacks of their approaches.

Although the synthesis of Panek and co-workers being quite convergent, it needs too many steps, and provides the final compound in only 1.3% overall yield. The overall number of steps for constructing the natural product is 35, while the longest linear sequence consists of 19 steps, starting from expensive (*R*)-(+)-3-methylglutarate. Due to the poor overall yield and the presence of several low-yielding transformations, Panek's approach hardly can be used for the preparation of large amounts of neopeltolide and its analogues thereof.

In the Scheidt synthesis of neopeltolide, the tetrahydropyran ring and macrocycle were generated concurrently, albeit in only 25% yield. Although the longest linear sequence consists of only 18 steps, neopeltolide was obtained in very poor overall yield (0.5%). In addition, some key transformations proceed with acceptable yields (50–60%). Most likely, this synthesis was done just to demonstrate the application of the recently developed Scheidt methodology (Lewis acid-catalyzed Prins-type cyclization).[156]

According to the preliminary study, reported by Amy Wright, neopeltolide is two to three orders of magnitude more potent for some cancer cells than Taxol®, a common chemotherapy drug. In addition, the side chain of neopeltolide is identical to the one in the macrolide leucascandrolide, which is also highly cytotoxic. Thus, one can assume the same biological targets for these two compounds.

Neopeltolide is composed of the structural combination of the hydrophobic macrolactone core **A** and polar oxazole- and carbamate-containing side chain **B** (**6-15**). The interest for the construction of neopeltolide, as well as different analogues and derivatives, lies in the synthesis of the macrolide fragment. Although this fragment is quite compact, it contains six

stereogenic centers and a 2,4,6-trisubstituted tetrahydropyran ring, which makes the synthesis a challenging task.

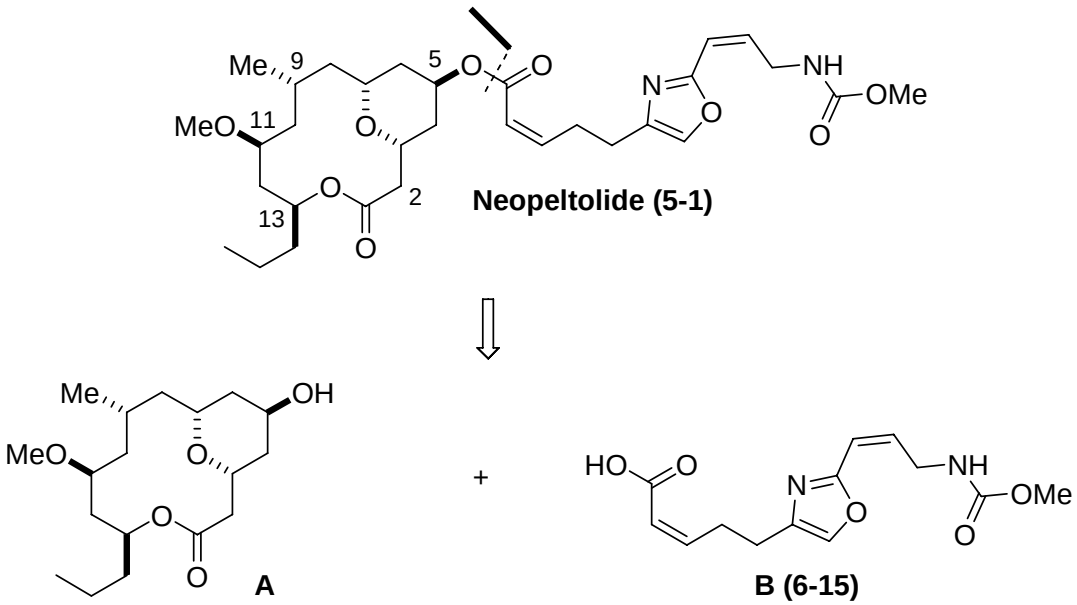



**Figure 37.** Retrosynthetic analysis of neopeltolide.

The promising biological activity combined with the fascinating structure prompted us to embark on a synthesis of neopeltolide. The objective of our study is the development of simple and reliable procedures for the synthesis of neopeltolide. The discovery of practical and useful new strategies requires that the key idea meet the important criteria: the devised approach should be flexible enough to access stereogenic and structural analogues that might help to identify the biological target. It means the strategy should involve efficient enantio- or diastereoselective reactions to generate each of the stereocenters independently, offering maximum flexibility. In this regard, we aimed to investigate the utility of recently developed reactions and methodologies. In addition, due to the modular built of neopeltolide, it was particularly interesting to prepare a range of analogues with different side chains at C5, which in turn should help to figure out whether the macrolactone or the oxazole-containing side chain are crucial for cytotoxicity as well as to identify *in vivo* biological targets and elucidate its mode of action.

# 8 Results and Discussion

## 8.1 Retrosynthetic Analysis

The target molecule, neopeltolide (**5-1**), features the following major fragments:

a) oxazole- and carbamate-containing side chain;

b) 14-memebered macrolactone ring that is bridged by an ether function;

c) 2,4,6-trisubstituted tetrahydropyran.

At first, we decided to make a disconnection of the oxazole-containing side chain **6-15** from the macrolactone core **6-14**. Opening of the lactone **6-14** would lead to the seco acid **8-1**, containing a substituted pyran. From a synthetic point of view one of the biggest challenges was a creation of desired pyran ring in a highly selective manner. For this reason we rely on a well developed Prins cyclization. Accordingly, the Prins strategy will require preparation of an aldehyde **8-2** and a homoallylic alcohol **8-3**. The TFA promoted Prins reaction would secure an equatorial 5-OH group. Thus, a Mitsunobu reaction would have to be used for the attachment of the side chain (**Figure 38**).

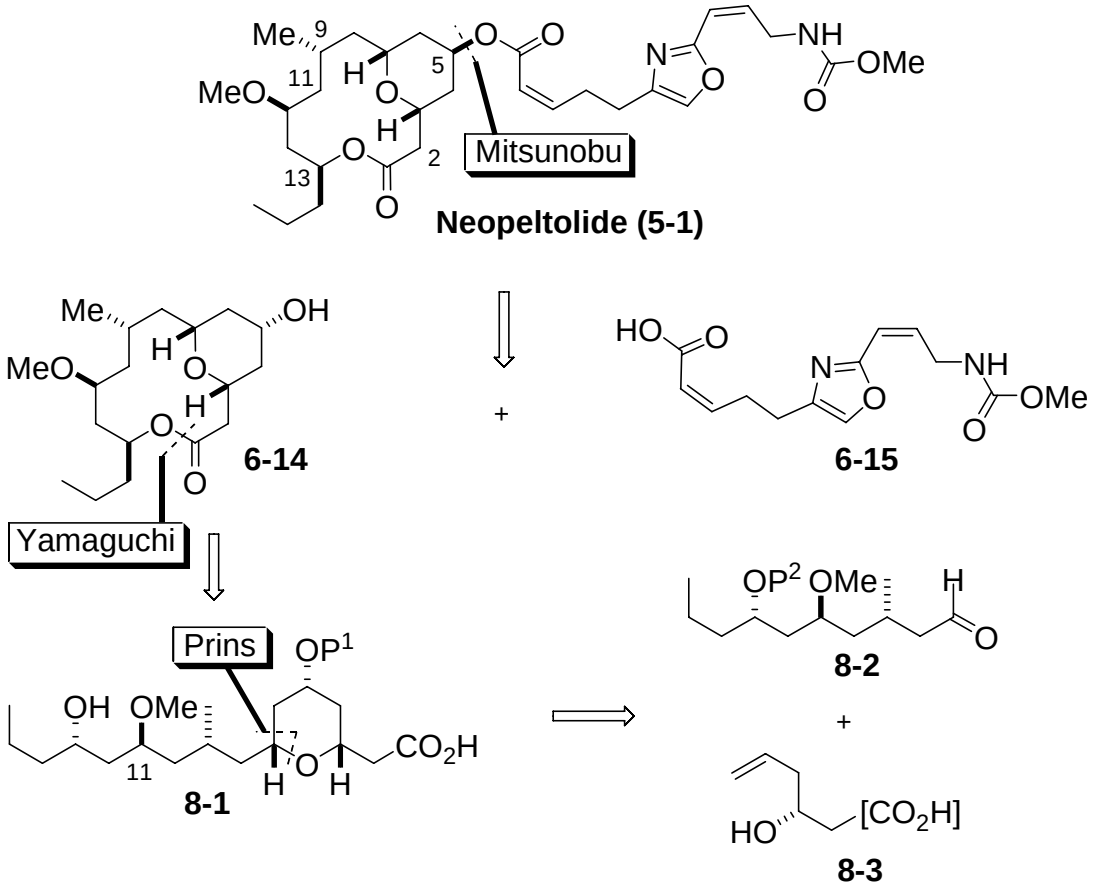



**Figure 38**. Key retrosynthetic cuts for neopeltolide (**5-1**).

A key question relates to the introduction of the subunit with the methyl group. In this regards, we chose a facial selective Michael addition using the Feringa-Minnaard reaction (**Figure 39**). Obviously the unsaturated thioester **8-4**, required for the previous reaction could be obtained from the corresponding aldehyde **8-5** via Wittig olefination. The necessary *anti*-1,3-diol fragment, in turn, should result from a Leighton allylation and a highly enantioselective Noyori reduction thereof. As one can see the homoallylic alcohol **8-3** necessary for the Prins reaction could be available by allylation of the known aldehyde **8-8**[250] applying aforementioned Leighton methodology.

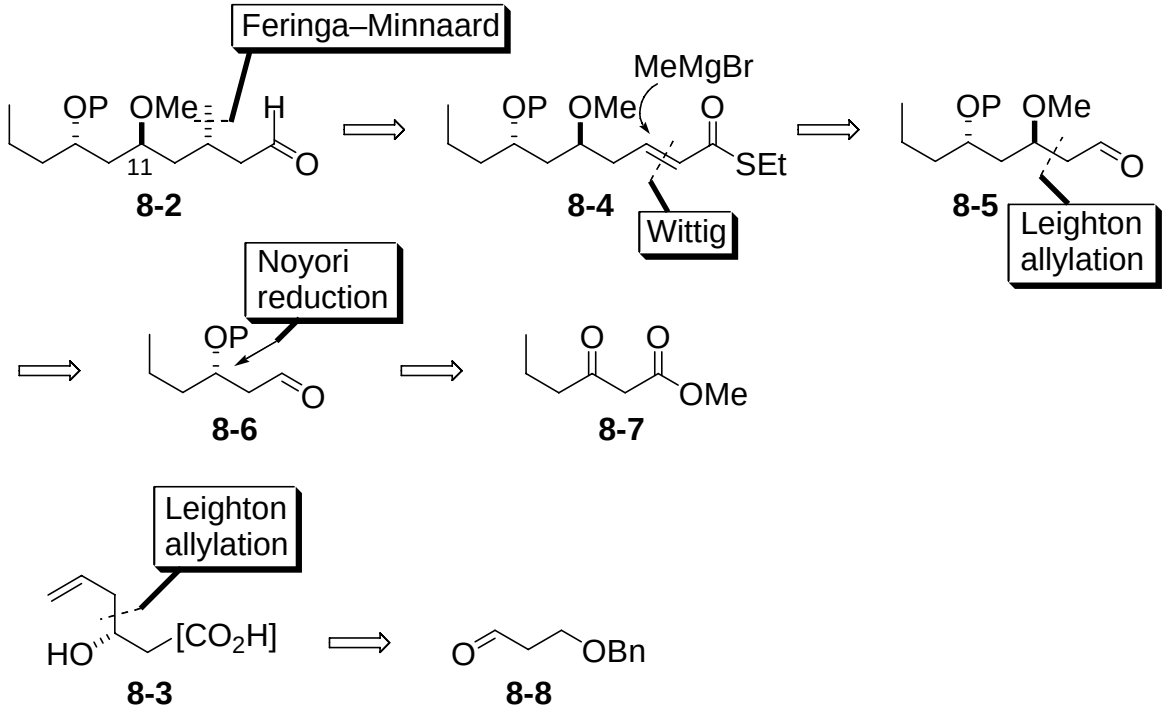



**Figure 39**. Retrosynthetic anylysis for the aldehyde **8-2**.

Although, more than six different synthesis of the oxazole bearing side chain, identical to that found in leucascandrolide were published,[146] we decided to develop our own approach. Following the general trend of previous described syntheses we rely on Still-Gennari olefination to establish the *cis*-enoate moiety of the side chain as a key step. Required aldehyde **8-9** could be derived from ester **8-10** (**Figure 40**). Introduction of *cis*-allylcarbamate subunit can be done using a classical Sonogashira coupling with subsequent Lindlar reduction. Triflate **8-12** logically originates from readily available oxazolone **8-14**.[251] The necessary alkyne **8-13**,[146a] in turn, should result from propargylamine and methyl chloroformate.

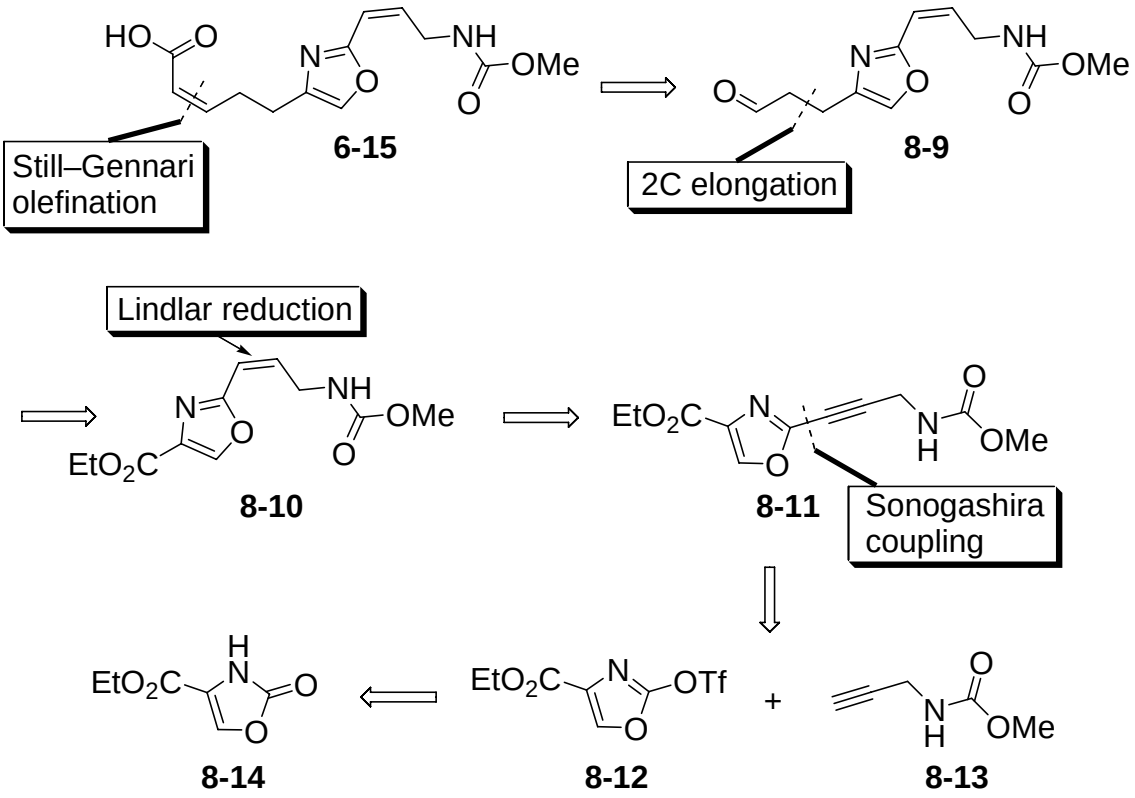


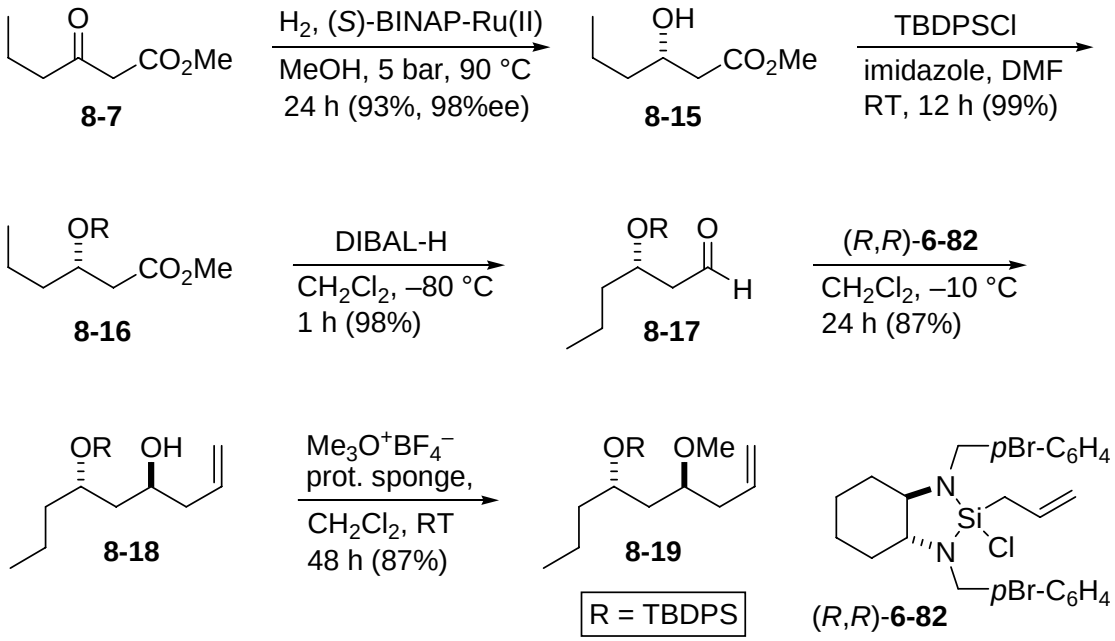

**Figure 40**. Retrosynthetic anylysis for the side chain **6-15**.

As one can see, we conceived a strategy that would be flexible enough to access structural analogues which might help to identify the biological target. Furthermore, analogues which could illuminate key structural features important for the activity were planned.

## 8.2 Synthesis of the Neopeltolide Macrolactone

### 8.2.1 Synthesis of aldehyde 8-24

The synthesis began with 3-ketoester **8-7** which was subjected to an enantioselelctive Noyori hydrogenation[182] using (*S*)-BINAP-Ru(II) as chiral catalyst (**Scheme 96**). Required chiral complex was in situ prepared from commercially available (*S*)-BINAP and $[RuCl_2(benzene)]_2$ in full accordance with an *Organic Synthesis* procedure.[184] Reduction was carried out in a Parr hydrogenation vessel under pressure of hydrogen (5 bar) at 90 °C during 24 hours. This secured desired hydroxy ester **8-15** in 93% yield and with excellent selectivity (98% ee). The enantiomeric excess of the isolated hydroxyester was determined by chiral GC (**Figure 41**). Silylation of the alcohol **8-15** produced ether **8-16** in almost quantitative yield. This was followed by ester reduction using DIBAL-H[252] at –80 °C in dichloromethane leading to aldehyde **8-17**. Chain extension was performed with the Leighton reagent (*R*,*R*)-**6-82**,[201] containing (*R*,*R*)-1,2-diaminocyclohexane moiety. Remarkably, we were able to recover the chiral diamine in 90% yield that makes this method very attractive for large-scale allylations. Furthermore, in the $^{13}C$ NMR spectrum of **8-18** there was no other diastereomer visible, indicating the excellent selectivity in the allylation reaction. The alcohol function in the 1,3-*anti*-diol **8-18** was protected using Meerwein's salt in presence of proton sponge.[253] Under other conditions (NaH, MeI, THF, 0 °C) partial migration of the silyl group was observed.




**Scheme 96.** Synthesis of alkene **8-19**.

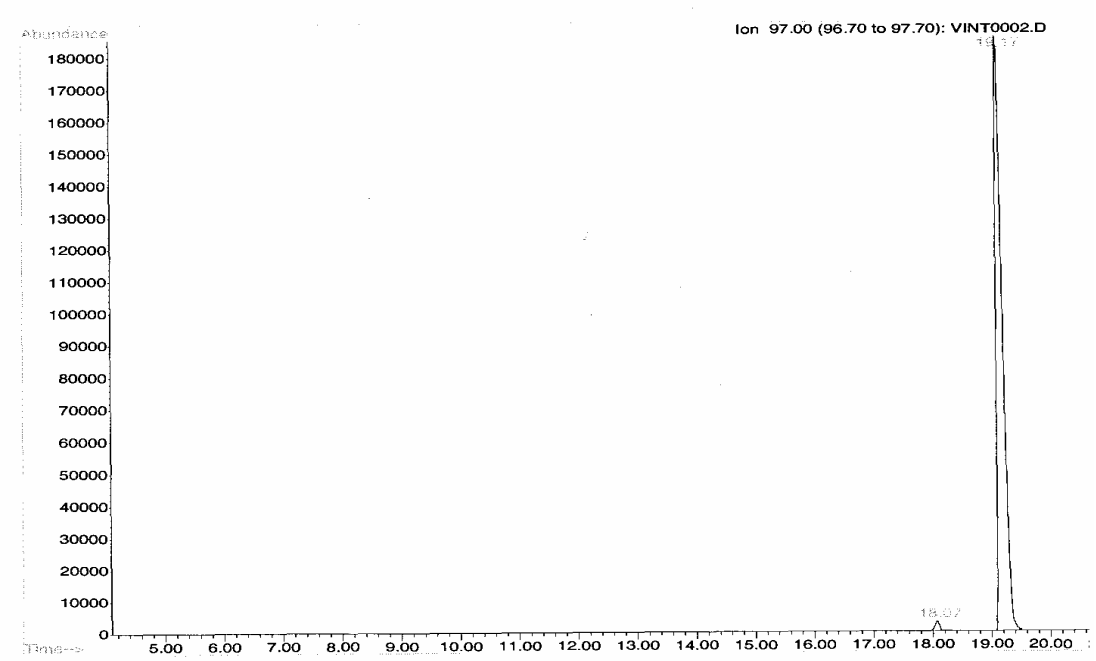
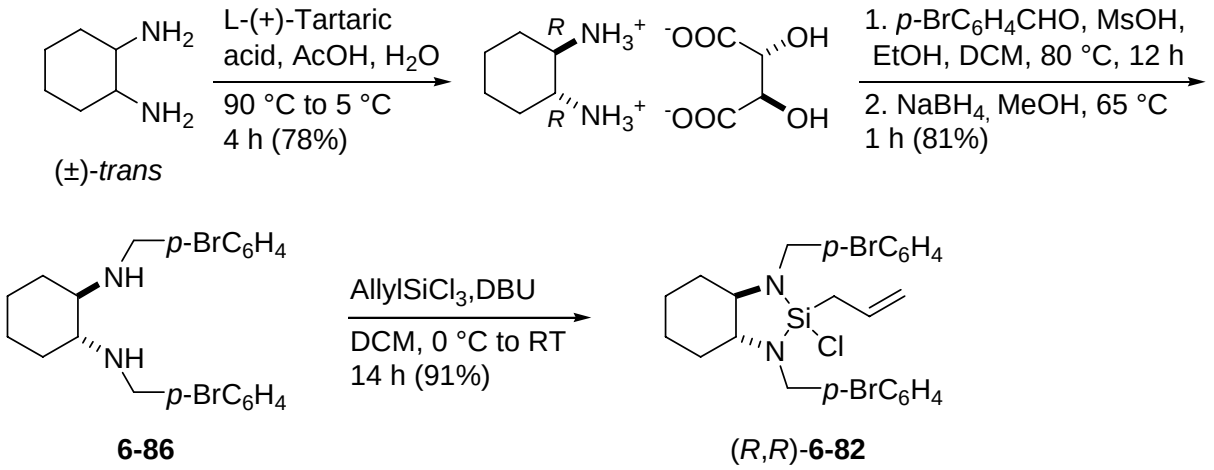



**Figure 41.** Chiral GC of methyl (3*S*)-3-hydroxyhexanoate (**8-15**), minor isomer $t_R$ = 18.07, major isomer $t_R$ = 19.17. Resolution was done using chiral column: 30% Lipodex E (octakis-(2,6-di-*n*-pentyl-3-butyryl)-γ-cyclodextrin) in dimethyl polysiloxane PS 255 (70%).

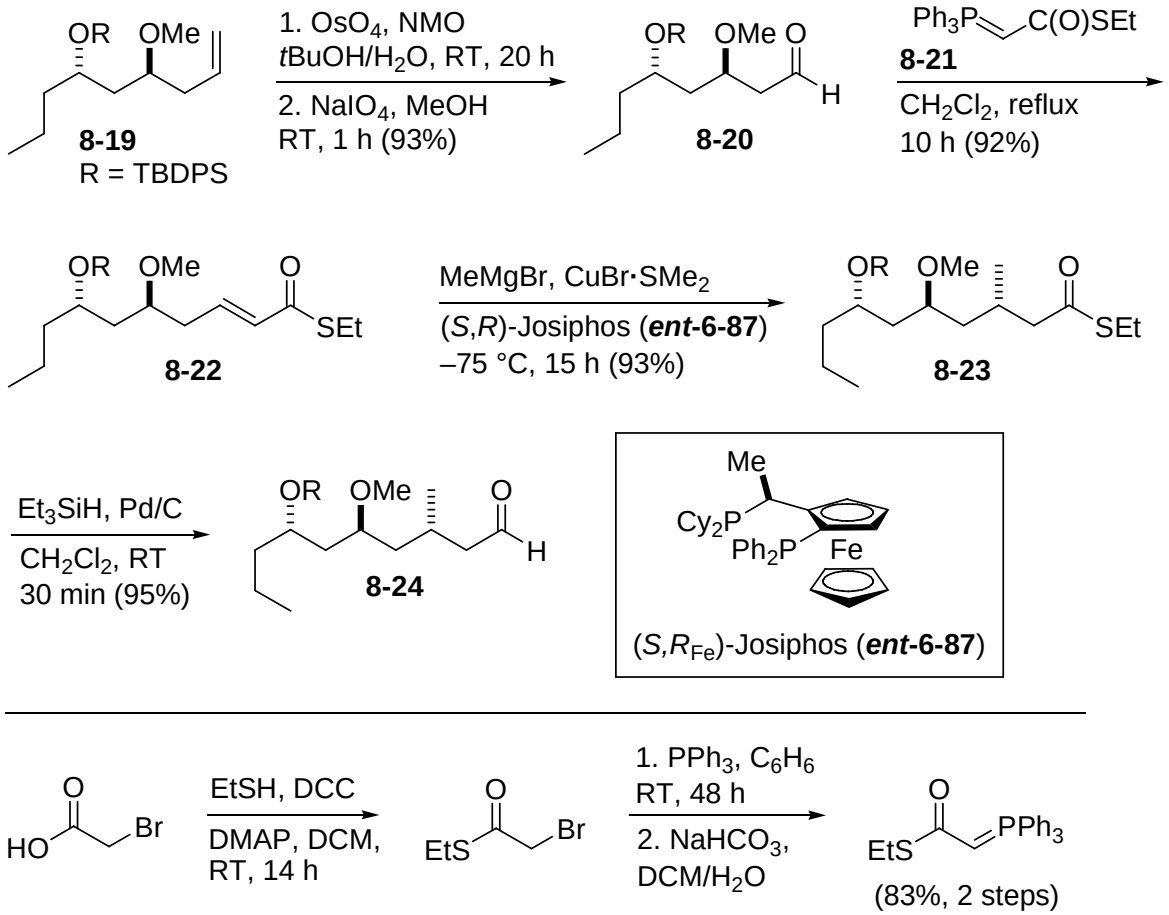
Synthesis of the required (*R*,*R*)-Leighton reagent **6-82** started from the resolution of racemic *trans*-1,2-diaminocyclohexane (**Scheme 97**). This was performed via crystallization of diamine with L-(+)-tartaric acid in full accordance to a published procedure.[254] Obtained tartrate was subjected to reductive amination reaction with *p*-bromobenzaldehyde, which proceeds via formation of corresponding intermediate diimine.[201] Subsequent treatment of foregoing *bis*-(*p*-bromobenzyl)-diamine **6-86** with allyl trichlorosilane in the presence of DBU as a base furnished the desired reagent (*R*,*R*)-**6-82**. It should be noted that all steps of this sequence are experimentally simple, the final product does not require additional purification and can be directly introduced in the allylation reaction. All this together allowed us to produce the required reagent (*R*,*R*)-**6-82** in up to 25 g scale.




**Scheme 97.** Synthesis of the Leighton reagent (*R*,*R*)-**6-82**.

With the desired *anti*-1,3-diol in hand we started the introduction of the subunit bearing the methyl group. Degradation of the terminal double bond to an aldehyde function was achieved using a well established a dihydroxylation/periodate cleavage sequence in excellent overall yield (93%) (**Scheme 98**). Obtained aldehyde **8-20** was efficiently extended to the unsaturated thioester **8-22** using the stabilized Wittig reagent **8-21**.[255] The latter can be prepared in two steps, starting from bromoacetic acid and ethanethiol. The resulting *S*-ethyl bromoethanethioate was allowed to react with $PPh_3$ which was followed by treatment of obtained triphenylphosphonium salt with an aqueous solution of $NaHCO_3$. This provided sufficient amounts of required ylide **8-21**.

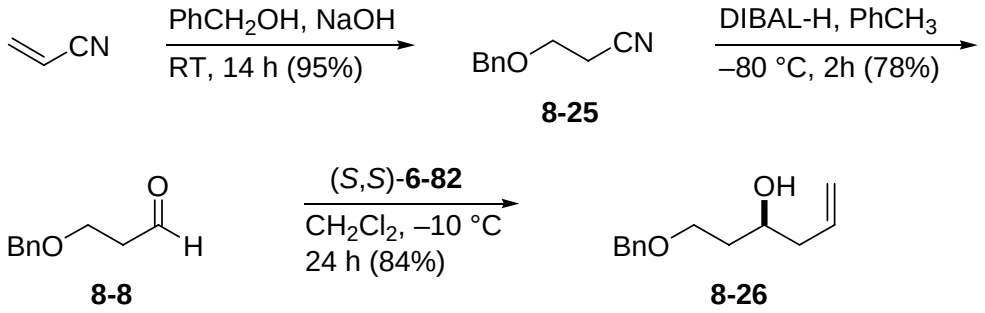
A conjugate addition reaction of methylmagnesium bromide (1.2 equiv) to **8-22** in presence of $CuBr{\cdot}SMe_2$ (3.4 mol%) and the chiral diphosphine (*S,R*)-Josiphos (***ent*-6-87**)[216,217] (4 mol%) produced the decanoate **8-23** in high yield. Only one set of signals was observed for **8-23** in the $^{13}C$ NMR spectrum. Reduction of the thioester with $Et_3SiH$ in presence of Pd/C gave an almost quantitative yield of aldehyde **8-24**.




**Scheme 98.** Synthesis of aldehyde **8-24**.

### 8.2.2 Synthesis of homoallylic alcohol 8-26

The homoallylic alcohol **8-26** required for the Prins reaction was available by allylation of the aldehyde **8-8** with the Leighton reagent (*S*,*S*)-**6-82** (**Scheme 99**). Foregoing aldehyde was prepared by DIBAL-H reduction of the nitrile **8-25**,[256] resulting from Michael addition of benzylalcohol to acrylonitrile. Synthesis of (*S*,*S*)-**6-82** was accomplished in the same way as was described for (*R*,*R*)-**6-82**.



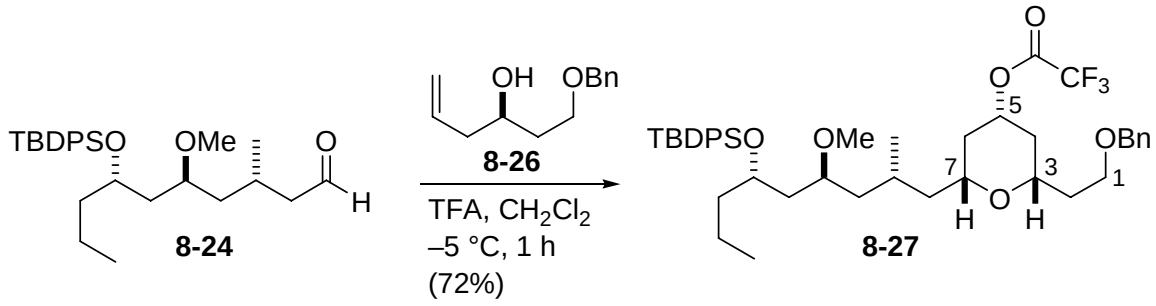

**Scheme 99.** Synthesis of homoallylic alcohol **8-26**.

Remarkably, both substrates for the key Prins reaction were prepared in high yield and with excellent selectivity using the recently developed Leighton allylation methodology as key step.

### 8.2.3 Synthesis of pyran 8-27 via Prins cyclization

For the crucial Prins reaction the homoallylic alcohol **8-26** and aldehyde **8-24** were reacted in dichloromethane in presence of trifluoroacetic acid (**Scheme 100**). Trying different conditions, we have found that the highest yield (72%) of pyran **8-27** could be obtained carrying the reaction at –5 °C with 10 equiv. of trifluoroacetic acid. This can be explained by significant TBDPS ether cleavage at higher temperatures. Besides the major product **8-27** the formation of a small amount of another isomer (major/minor = 8:1) was observed. Unfortunately, the isomers could not be separated by column chromatography. The formation of the desired tetrahydropyran can be envisioned to proceed via oxonium ion **A** with an all equatorial orientation of the substituents in the chair-like transition state (**Figure 42**). In the ring closure step, the C2 substituent lies in a favorable equatorial position and the (*E*)-oxocarbenium ion geometry is preferred over the (*Z*)-oxocarbenium ion geometry. Therefore, chirality is transferred from C2 to the newly formed carbon–carbon bond. The stereocenter formed at C4 is controlled by the extensive delocalization of tetrahydropyranyl cation **B**. Favorable orbital overlap places the hydrogen at C4 in a pseudoaxial geometry, and, therefore nucleophilic attack occurs along an equatorial trajectory to deliver tetrahydropyran **8-27**. The

minor product turned out to be the C5 epimer of the trifluoroacetat **8-27**. There was no erosion of stereochemistry at C3 and C7, respectively.




**Scheme 100.** Prins reaction between aldehyde **8-24** and alcohol **8-26**.

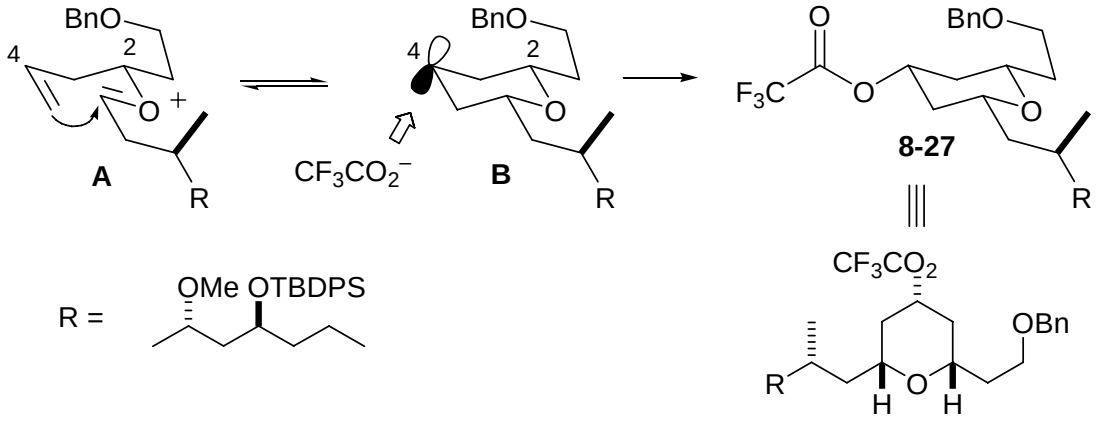
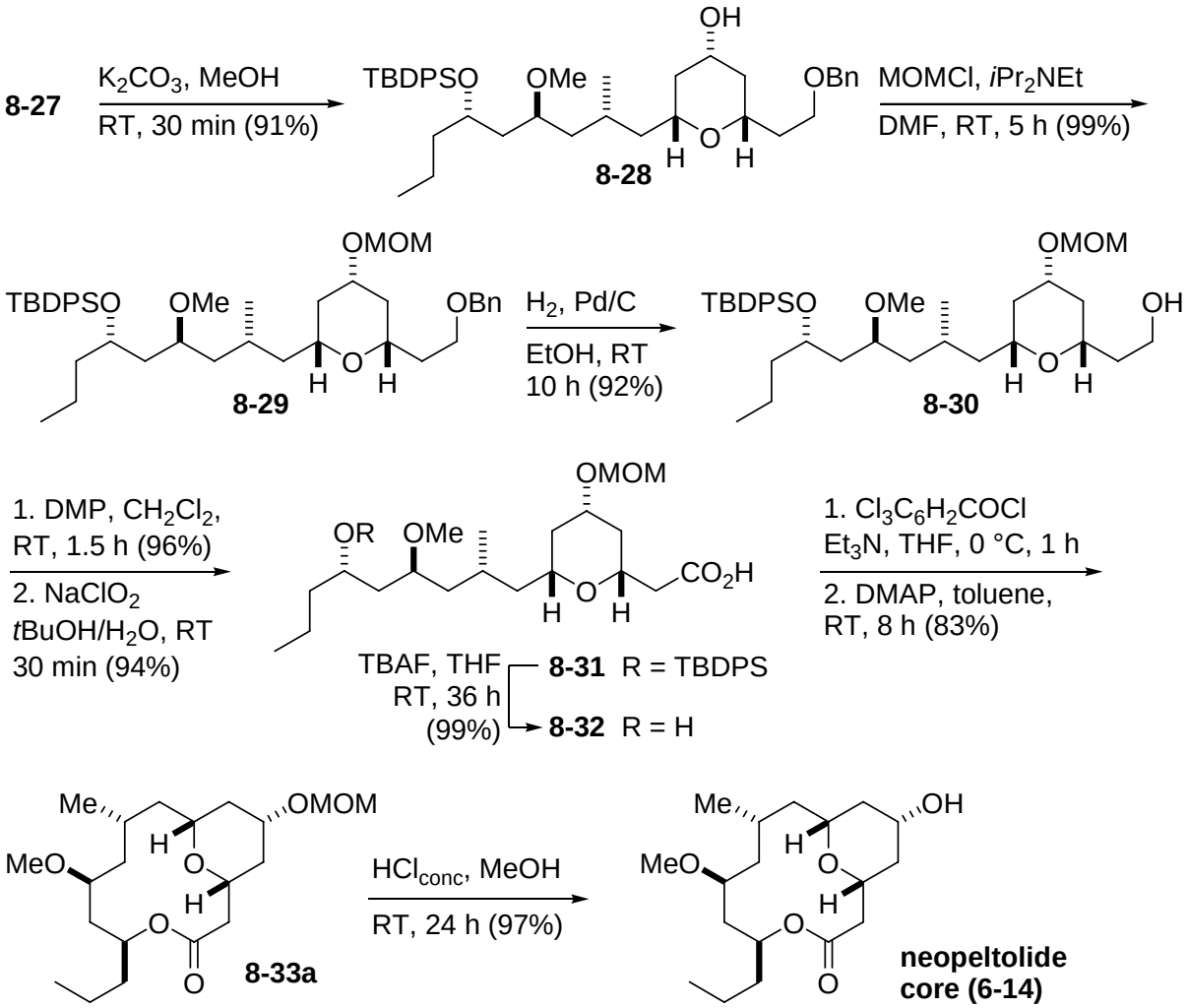



**Figure 42.** Proposed chair-like transition state **A**.

### 8.2.4 Completion the synthesis of the neopeltolide core structure 6-14

At first, the labile trifluoroacetate was cleaved under basic conditions and the resulting alcohol **8-28** was protected as MOM ether using MOMCl and Hünig's base in DMF at ambient temperature (**Scheme 101**). The MOM group was chosen in order to make possible a selective cleavage of benzyl and TBDPS ether respectively. Subsequent debenzylation under reductive conditions ($H_2$, Pd/C) led to primary alcohol **8-30**. Oxidation of **8-30** using a well established sequence consisting of Dess-Martin and sodium chlorite oxidation[257] furnished acid **8-31** in high overall yield. Fluoride-induced cleavage of the silylether led to seco-acid **8-32**. Employing classical Yamaguchi conditions,[124,243] the acid cyclized in high yield to macrolactone **8-33a**. At this stage the minor isomer (**8-33b**) resulting from the Prins reaction could be separated. A final cleavage of the MOM-protecting group completed the synthesis of the neopeltolide core structure **6-14** {$[\alpha]^{20}_D$ = +18.4 (*c* 0.1, $CHCl_3$)}. The NMR spectra of **6-14** perfectly matched the one reported by Scheidt et al.[148]



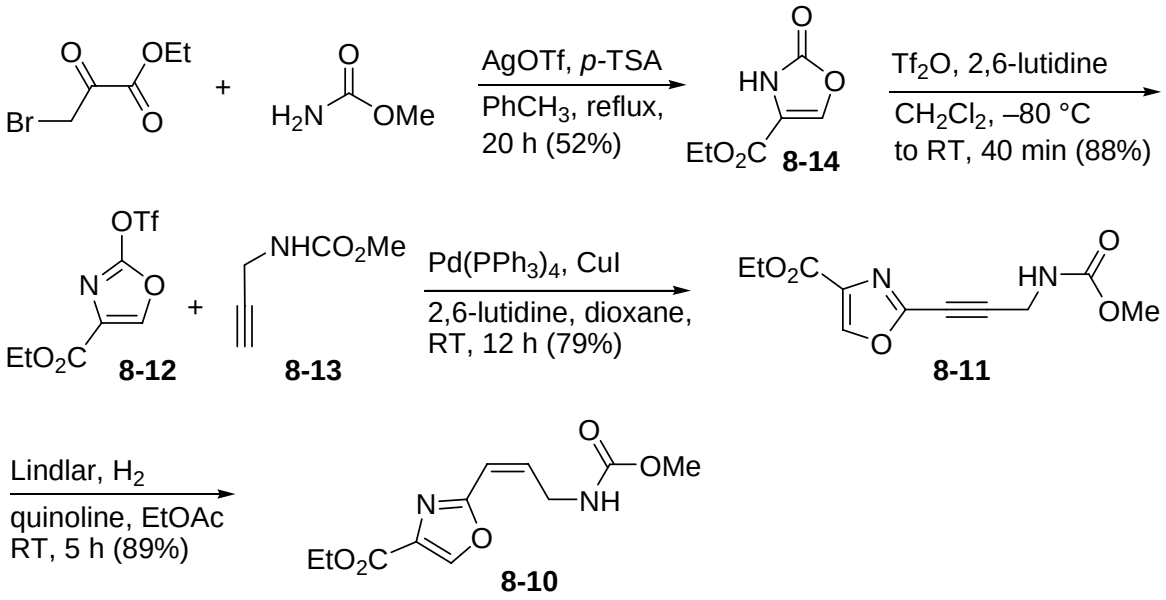

**Scheme 101.** Synthesis of neopeltolide core **6-14**.

After all, starting from keto ester **8-7**, the synthesis of neopeltolide core **6-14** required 17 steps in the longest linear sequence and produced lactone **6-14** in 23% overall yield. In this regard it compares favorably with the other known routes.[147,148,149,150]

## 8.3 Synthesis of Oxazole-Containing Acid 6-15

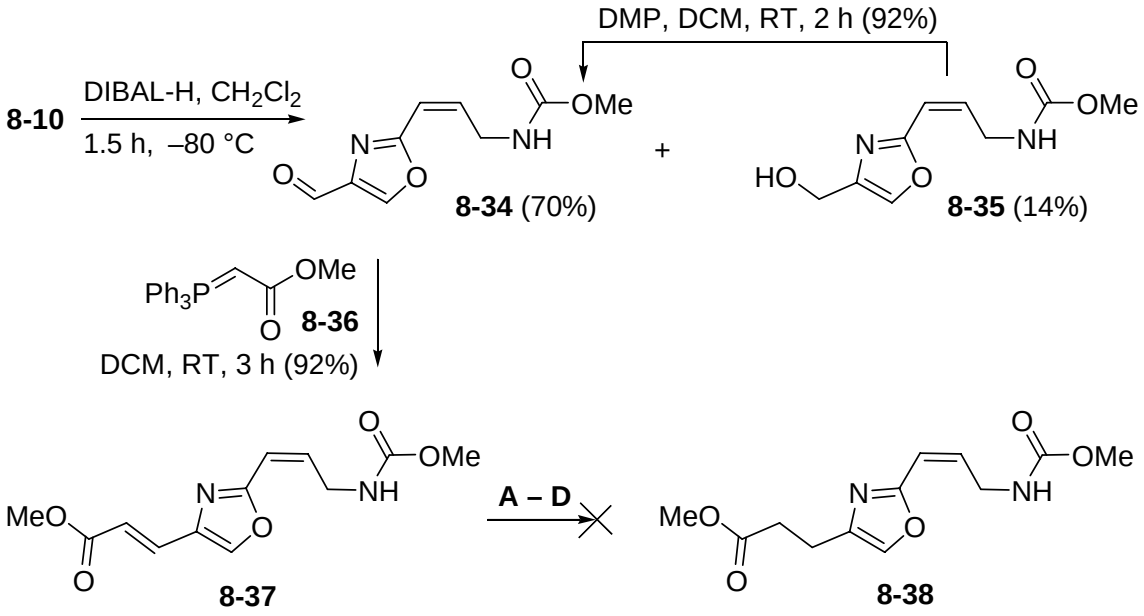
With the core structure of neopeltolide in hand, attention was now focused on the preparation of the oxazole-containing side chain **6-15** in order to explore the viability of our planned endgame to deliver neopeltolide and its analogues thereof. As shown in **Scheme 102**, the key step in the preparation of the side chain **6-15** was a Sonogashira coupling, where the required oxazole triflate **8-12** was derived from known oxazolone **8-14** – the condensation product of ethyl 3-bromopyruvate with methyl carbamate in the presence of *p*-TSA and AgOTf.[251] Reaction of oxazolone **8-14** with $Tf_2O$ in the presence of 2,6-lutidine provided the corresponding triflate **8-12**, which was immediately subjected to react with alkyne **8-13** under

Sonogashira coupling conditions ($Pd(PPh_3)_4$, CuI, 2,6-lutidine, 1,4-dioxane) developed by Panek and co-workers,[258] to provide the important side-chain precursor **8-11**. Triflate **8-12** may be for several days stored in a freezer (–20 °C) and used as needed. $Pd(PPh_3)_4$ was prepared accordingly to the literature procedure,[259] and immediately introduced in the coupling reaction. Thereafter, the *Z*-double bond was created using Lindlar reduction ($H_2$, Pd on $CaCO_3$, poisoned with lead EtOAc/quinoline) on the foregoing alkyne **8-11** leading to ester **8-10**.




**Scheme 102.** Synthesis of ester **8-10**.

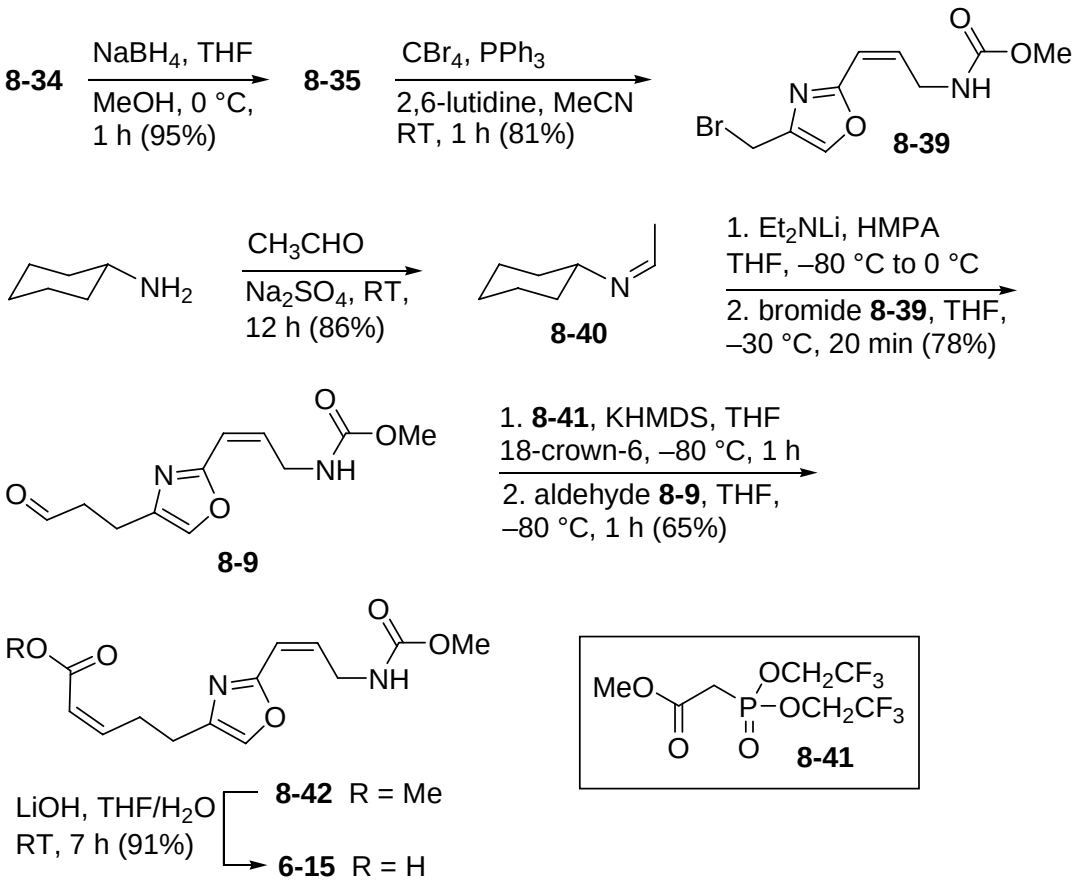
The next task was to realize a two carbon extension to aldehyde **8-9**, required for Still-Gennari olefination. Reduction of ester **8-10** with DIBAL-H in DCM furnished aldehyde **8-34** along with some amounts of corresponding alcohol **8-35**, which was easily converted back to **8-34** via Dess-Martin oxidation (**Scheme 103**). In order to introduce a two carbon building block, aldehyde **8-34** was subjected to Wittig olefination with (methoxycarbonylmethylene)-triphenylphosphorane **8-36**. This resulted in formation of unsaturated ester **8-37**. The next challenging task was conjugate reduction of the obtained unsaturated ester. Our initial attempt was to use the Mg – methanol system as the most efficient and reliable method in this regard.[260] Unfortunately, despite numerous efforts to optimize condition for this reaction, we were not able to conduct the desired reduction selectively. Using other described methods ($NiCl_2$, $NaBH_4$ in MeOH;[261] $CuCl_2$, $NaBH_4$ in MeOH;[262] $ZnCl_2$, Mg in $H_2O$[263]) was not successful as well. According to LC-MS analysis, besides the desired product always significant amounts of overreduction products derived from the Z-alkene were obtained.




| | Conditions | Results |
|---|---|---|
| **A** | Mg, MeOH, RT | No selecivity |
| **B** | $NiCl_2$, Mg, $NaBH_4$, MeOH, RT | No selecivity |
| **C** | $CuCl_2$, Mg, $NaBH_4$, MeOH, RT | No selecivity |
| **D** | $ZnCl_2$, Mg, $H_2O$, RT | No selecivity |

**Scheme 103.** Attempted synthesis of ester **8-38**.

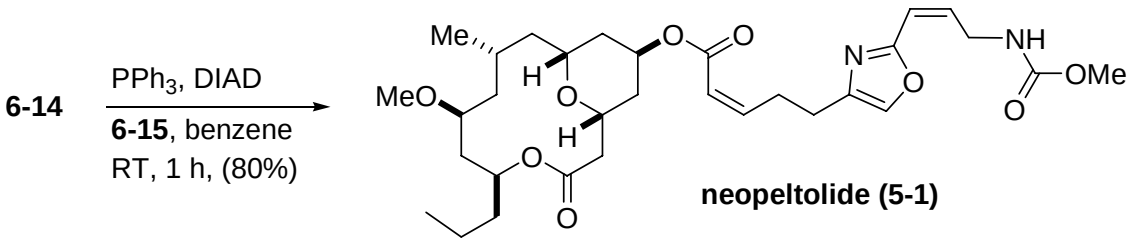
After unsuccessful attempts to perform a selective reduction of the conjugated double bond we revised our strategy and decided to make the two carbon homologation using methodology recently developed by Kozmin.[264,146d] Thus, aldehyde **8-34** was reduced to alcohol **8-35**[146a] using sodium borohydride in THF/MeOH mixture (**Scheme 104**). Transformation of the hydroxyl function to the corresponding bromide **8-39** was achieved using well established Appel methodology ($CBr_4$, $PPh_3$ and 2,6-lutidine in $CH_3CN$ at ambient temperature).[265] It should be noted that $CBr_4$ must be very pure (Fluka), and without any trace of water. Afterwards, conversion of acetaldehyde to the corresponding cyclohexyl imine **8-40**, followed by lithiation[266] with lithium diethylamide and alkylation with freshly prepared bromide **8-39**, afforded aldehyde **8-9** in 74% yield. *Z*-Selective olefination using Still-Gennari reagent **8-41** [267] proceeded with excellent selectivity (*Z*:*E* = 11:1) and in good yield. Finally, saponification of obtained ester **8-42** completed the assembly of the side chain subunit **6-15**.




**Scheme 104.** Completion of the synthesis of the side chain **6-15**.

## 8.4 Completion of the Neopeltolide Synthesis

Designed to invert the relative stereochemistry at the C5, the end game entailed a Mitsunobu esterification of alcohol **6-14** with oxazole-containing acid **6-15** (**Scheme 105**). Gratifyingly, treatment of the two coupling fragments with $PPh_3$ and DIAD afforded neopeltolide (**5-1**) in 80% yield. $\{[\alpha]^{20}_D = +23.8$ (*c* 0.24, MeOH)$\}$. The NMR spectra of **5-1** were in excellent agreement with those reported in the literature.[144,147,148]




**Scheme 105.** Completion of the neopeltolide (**5-1**) synthesis.

We have hence completed a convergent total synthesis of this potent antitumor agent, which favourably compares with the previous approaches in terms of all usual empirical indices (ca.

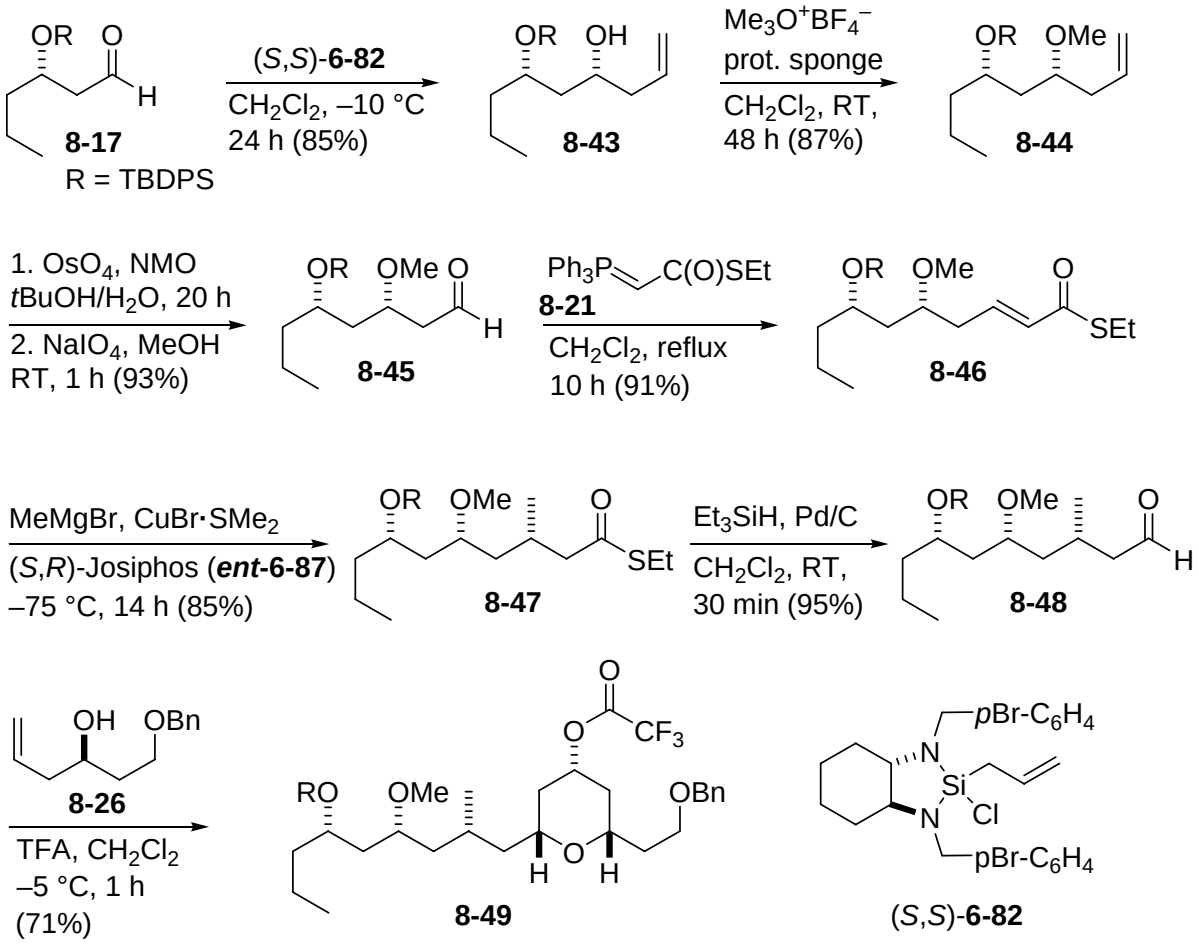
18% overall yield, 18 steps in the longest linear sequence). The developed strategy is very efficient and should allow for the preparation of further neopeltolide analogues.

## 8.5 Synthesis of Neopeltolide Analogues

### 8.5.1 Synthesis of 11-*epi* neopeltolide (8-57)

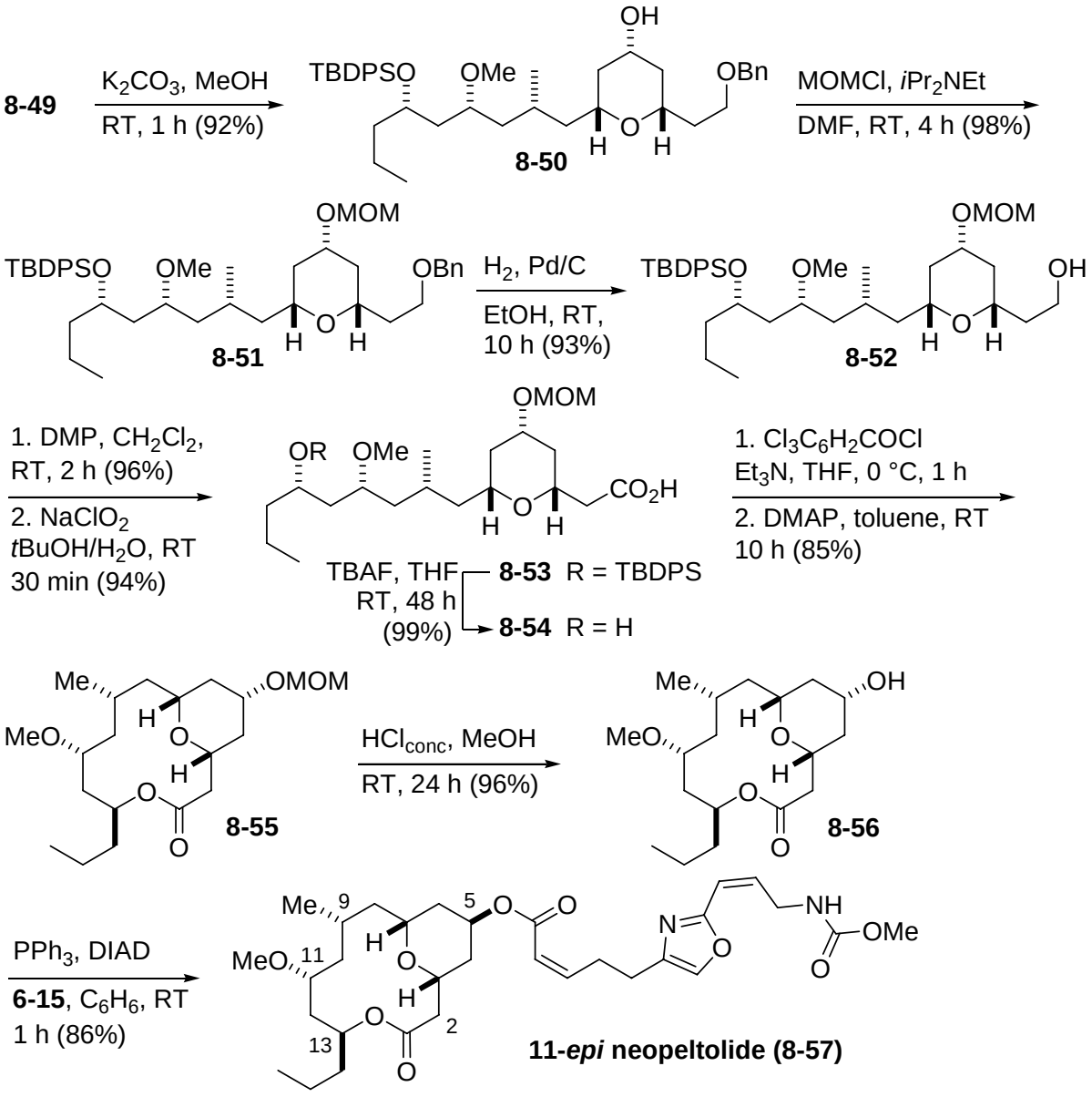
Due to the potent biological activity of neopeltolide and its structure similarity to another cytotoxic natural product leucascandrolide, which in addition might have the same mode of action it would be of interest to identify key structural elements that are essential for its cytotoxicity. Furthermore, because of its modular built, a range of analogues with different side chains at C5 are conceivable, which in turn should help to figure out which parts of the macrolactone or oxazole-containing side chain are crucial for cytotoxicity as well as to identify *in vivo* biological targets and elucidate its mode of action.

In order to delineate the role of the C11 methyl ether for the interaction with an active site, we decided to find out how important is the stereochemistry at C11. Keeping this in mind, for the Leighton allylation of aldehyde **8-17** reagent (*S*,*S*)-**6-82** came to use (**Scheme 106**). This resulted in exclusive formation of 1,3-*syn*-diol **8-43** in 85% yield. Further transformations to the aldehyde **8-48** were done in full accordance with procedures described for **8-24**. Thus, protection of the free hydroxyl function in the 1,3-*syn*-diol **8-43** using Meerwein's salt in presence of proton sponge followed by oxidative degradation of the terminal double bond led to aldehyde **8-45** in excellent overall yield. Extension of obtained aldehyde **8-45** to the substrate for the Feringa–Minnard reaction **8-46** was achieved using the stabilized Wittig reagent **8-21**. A conjugate addition of *in situ* preformed methyl cuprate in the presence of chiral diphosphine (*S,R*)-Josiphos ***ent*-6-87** (4 mol%) secured the decanoate **8-47** in 85% yield. According to $^{13}C$ NMR spectrum of thioester **8-47**, exclusively one diastereomer was obtained. Reduction of the thioester with $Et_3SiH$ in presence of Pd/C gave an almost quantitative yield of aldehyde **8-48**. For the crucial Prins reaction the previously described homoallylic alcohol **8-26** and aldehyde **8-48** were reacted in dichloromethane at –5 °C in presence of trifluoroacetic acid (10 equiv). This furnished desired pyran **8-49** in 71% yield. As in the case of compound **8-27**, besides the major product **8-49** the formation of a small amount of another isomer (major/minor = 8:1) was observed.




**Scheme 106.** Synthesis of pyran **8-49**.

A few simple functional group manipulations: basic cleavage of the trifluoroacetate, MOM protection of the resulting alcohol **8-50**, and debenzylation led to primary alcohol **8-52** (**Scheme 107**). Oxidation of **8-52** using the well established sequence consisting of Dess-Martin and sodium chlorite oxidation furnished acid **8-53**. TBAF mediated cleavage of the silylether led to seco-acid **8-54** which was subsequently subjected to the Yamaguchi macrolactonization protocol. This way macrolactone **8-55** was obtained in 85% yield. At this stage the minor isomer resulting from the Prins reaction could be separated (9%). A final cleavage of the MOM-protecting group provided us with secondary alcohol **8-56**, which was introduced in the Mitsunobu estrefication with oxazole-containing acid **6-15**. This resulted in formation of 11-epi neopeltolide (**8-57**) in 86% yield.

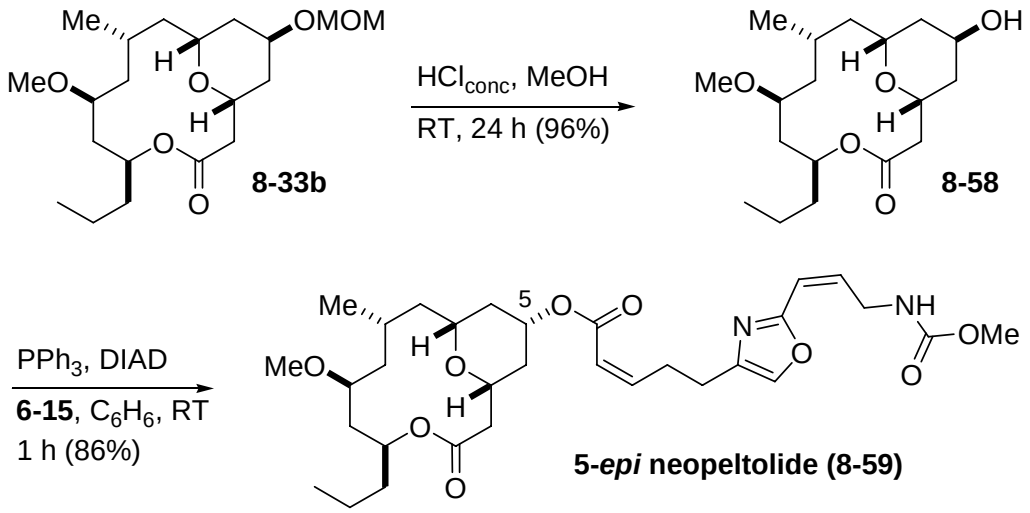



**Scheme 107.** Completion of the synthesis of 11-*epi* neopeltolide (**8-57**).

As one can see, this concise synthesis of 11-*epi* neopeltolide (**8-57**) once more proves the high efficiency of our approach.

### 8.5.2 Synthesis of 5-*epi* neopeltolide (8-59)

As a further branching point for the synthesis of analogues we identified the lactone **8-33b,** the minor isomer resulting from the Prins reaction and separated at the macrolactonization stage. Analysis of the NOESY spectrum of lactone **8-33b** indicated that hydrogens at C3 and C5 of the pyran ring are in *cis*-orientation to each other. Acid promoted cleavage of the MOM ether secured macrolactone **8-58** (**Scheme 108**). Finally, Mitsunobu esterification with oxazole-containing acid **6-15** furnished 5-*epi* neopeltolide **8-59**.




**Scheme 108.** Completion of the synthesis of 5-*epi* neopeltolide (**8-59**).

### 8.5.3 Synthesis of analogues with modified side chains

In order to shed light on the importance of the oxazole-containing side chain for the biological activity of neopeltolide we aimed at the synthesis of some analogues with different oxazole-containing acids (**Figure 43**). With regard to the design of modified acids we wanted to use some of the key intermediates from the synthesis of fragment **6-15**.

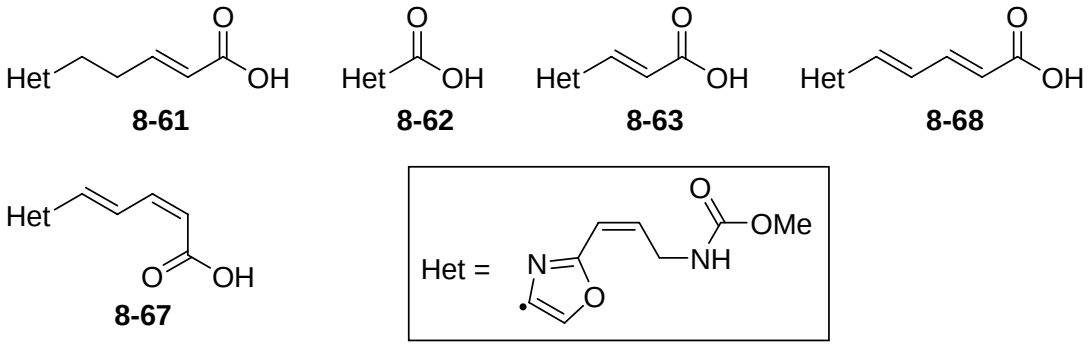
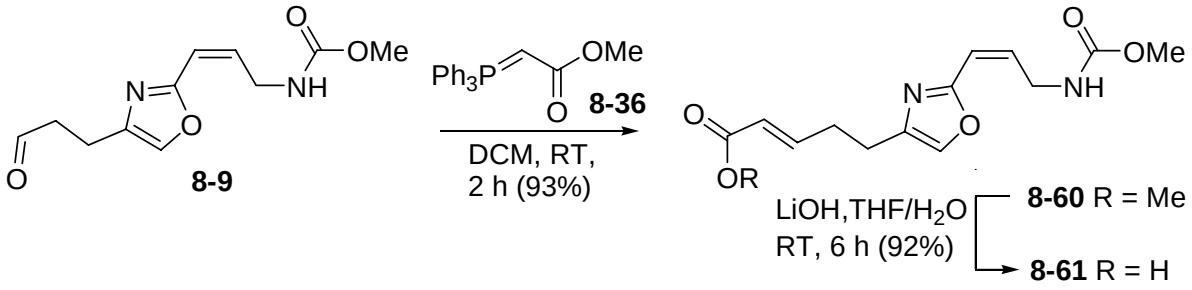


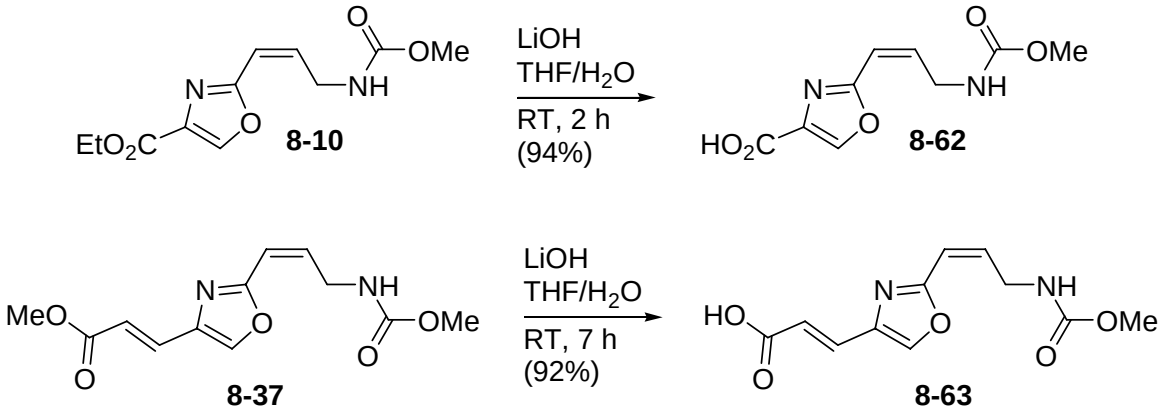

**Figure 43.** Structures of designed oxazole-containing acids.

At first, subjection of aldehyde **8-9** to the classical Wittig olefination with phosphorane **8-36** resulted in formation of *trans*-enoate **8-60** (**Scheme 109**). Subsequent treatment of ester **8-60** with lithium hydroxide secured the first configurational analogue **8-61**.



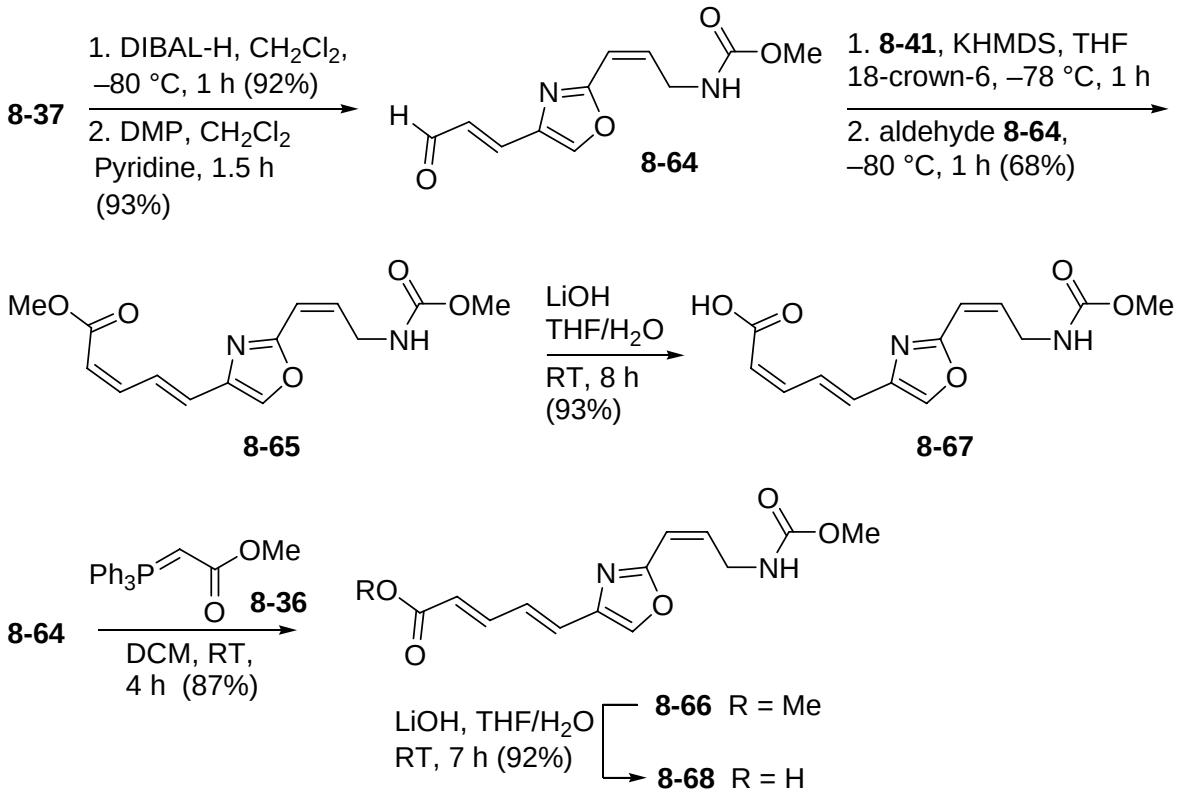

**Scheme 109.** Synthesis of acid **8-61**.

Continuing with the synthesis of analogues, saponification of ester **8-10** with potassium hydroxide provided acid **8-62**, in which the four carbon bridge between the oxazole ring and carboxylic function was lacking (**Scheme 110**). In a similar way, lithium hydroxide mediated methyl ester cleavage of **8-37** produced corresponding acid **8-63**. The latter is two carbons shorter than the previously synthesized acid **8-61**.




**Scheme 110.** Synthesis of acids **8-62** and **8-63**.

To access further configurational analogues of the original acid **6-15** we continued to use the synthetic potential of unsaturated ester **8-37**. Thus, we attempted to reduce the methyl ester to the aldehyde function in order to accomplish further derivatization. Unfortunately, it was rather difficult to conduct this reaction selectively. Even using 1 equivalent of DIBAL-H, along with desired aldehyde significant amounts of the corresponding alcohol were observed. Therefore, ester **8-37** was completely reduced to the alcohol by treatment with 2.5 equivalents of DIBAL-H, which was followed by Dess-Martin oxidation (**Scheme 111**). This sequence provided required unsaturated aldehyde **8-64** in 85% overall yield. Direct subjection of this aldehyde to the Still-Gennari olefination protocol secured (*E*,*Z*)-dienoate **8-65**. On the other hand, reaction of aldehyde **8-64** with phosphorane **8-36** established the (*E*,*E*)-dienoate moiety. Both esters were subsequently saponified with lithium hydroxide in a THF/$H_2O$ mixture. This provided us with two other valuable oxazole-containing acids **8-67** and **8-68**. In comparison to the original side chain **6-15**, introduction of additional double bond between C4 and C5 will make the structure more rigid which, in turn, might be crucial for the ligand–receptor interaction.

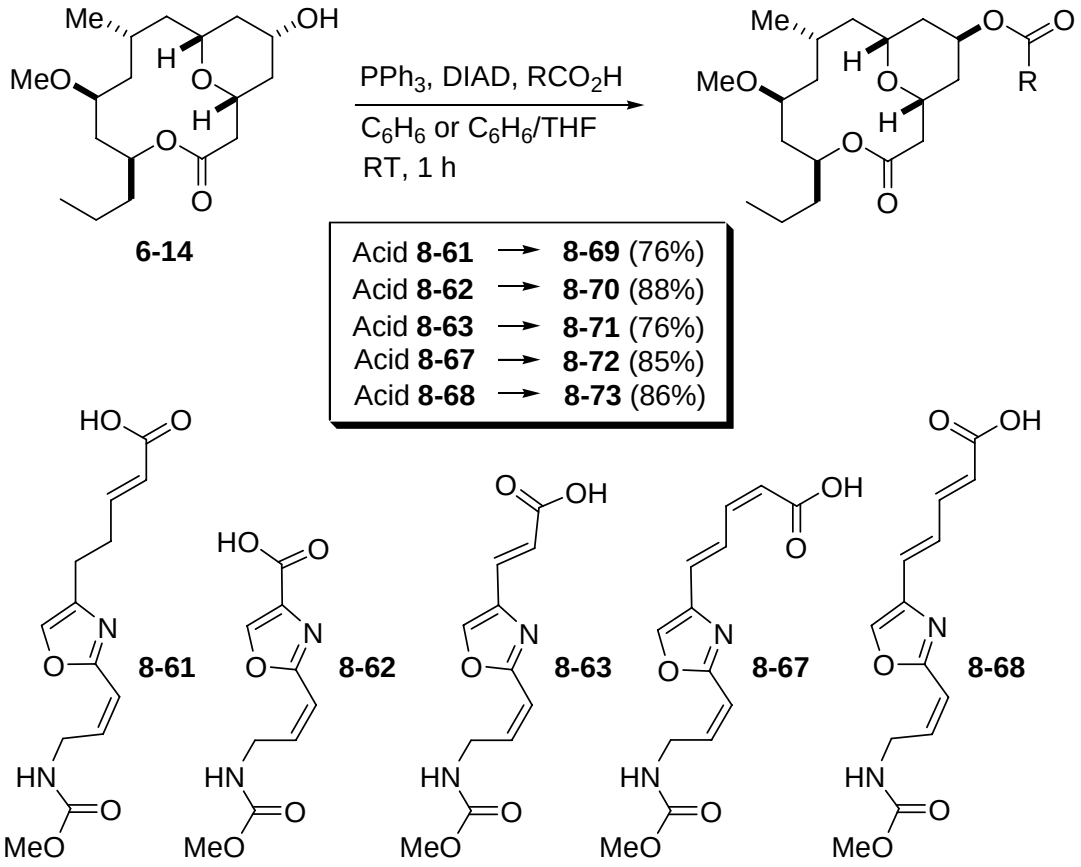



**Scheme 111.** Synthesis of acids **8-67** and **8-68**.

After all, a number of different oxazole-containing acid were synthesized using methodology applied for the synthesis of acid **6-15**. Next, coupling of these acids with the neopeltolide core should provide a set of configurational analogues.

### 8.5.4 Coupling of oxazole-containing acids with the neopeltolide core

Neopeltolide alcohol **6-14** was coupled with the oxazole-containing acids **8-61** – **8-63**, **8-67** and **8-68** applying classical Mitsunobu conditions ($PPh_3$, DIAD in benzene or benzene/THF mixture) (**Scheme 112**). In order to increase the solubility of the carboxylic acid sometimes coupling reactions were conducted in benzene/THF mixture. Notably, all these reactions required only one hour to go to completion and furnished the desired analogues **8-69** – **8-73** in good yields.




**Scheme 112.** Synthesis of neopeltolide analogues **8-69** – **8-73**.

### 8.5.5 Biological testing

The described analogues as well as macrolactones **6-14** and **8-56** were tested for cytotoxicity against the L929 cell line. The obtained $IC_{50}$ values in the cell culture assay are listed in **Table 6**. The analogues are ordered according to increasing $IC_{50}$ values against the L929 cell line.

**Table 6.** $IC_{50}$ values for neopeltolide and analogues against the L929 cell line

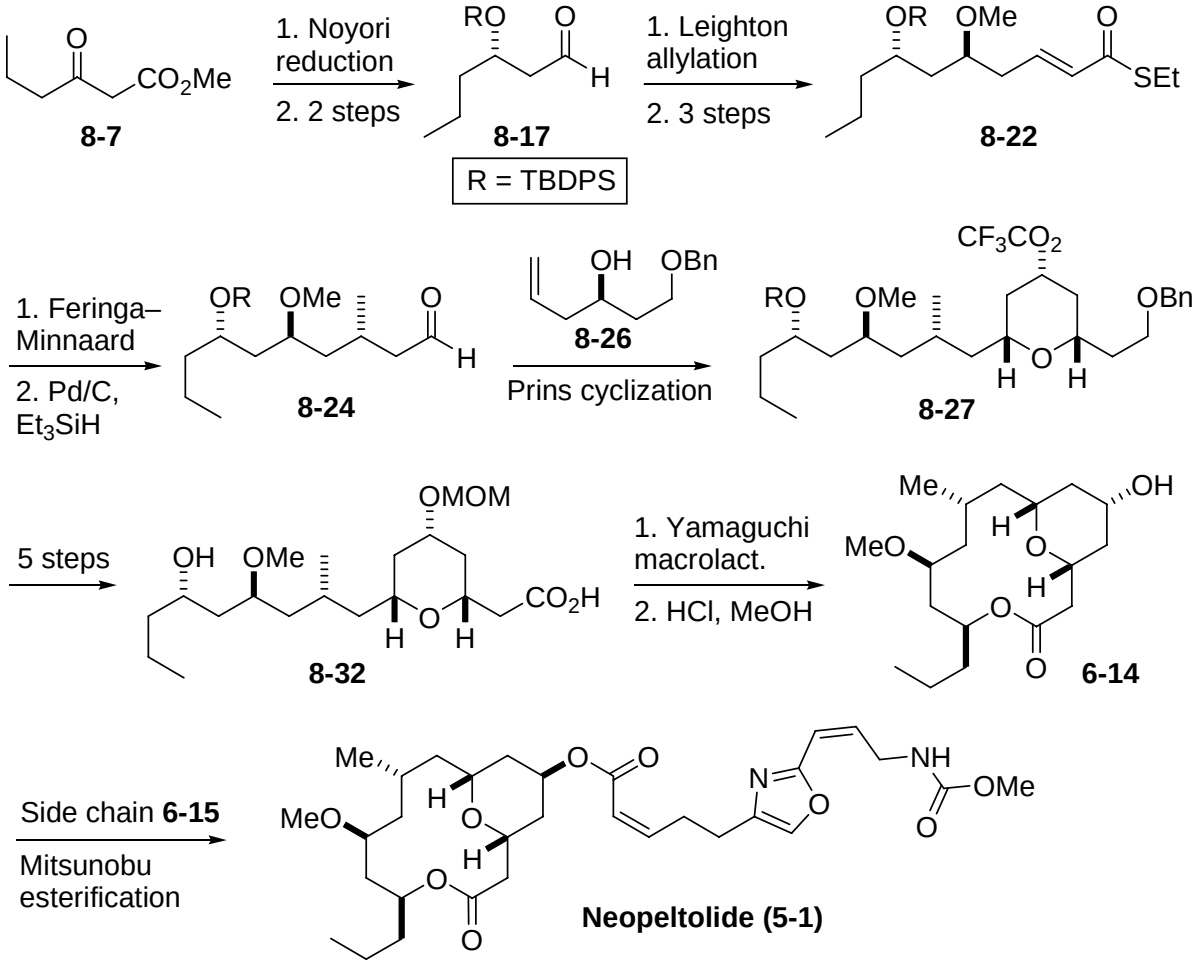
| entry | comp. | $IC_{50}$ [ng·mL$^{-1}$] | $IC_{50}$ [nM] | description |
|---|---|---|---|---|
| 1 | **8-72** | 0.094 | 0.16 | neo-diene-*ZE* |
| 2 | **5-1** | 0.15 | 0.25 | neopeltolide |
| 3 | **8-73** | 1.2 | 2.0 | neo-diene-*EE* |
| 4 | **8-57** | 1.3 | 2.2 | 11-*epi*-neo |
| 5 | **8-69** | 2.6 | 4.4 | neo-*trans* |
| 6 | **8-59** | 5.0 | 8.5 | 5-*epi*-neo |
| 7 | **8-71** | 630 | 1120 | neo-short |
| 8 | **8-70** | 2400 | 4473 | neo-oxazole |
| 9 | **6-14** | 4000 | 12195 | neo-macrolactone |
| 10 | **8-56** | 4000 | 12195 | 11-*epi*-neo-macrolactone |

According to the Table there are highly effective compounds. Surprisingly, the most cytotoxic compound is neo-diene-*ZE* (**8-72**) (entry 1), which is almost two times more active than neopeltolide (**5-1**) itself. This increase of activity might be the result of constraining an original flexible bridge between the oxazole ring and *Z*-enoate moiety, leading to the fixation of one of the most favorable conformations. The next active compound after neopeltolide is neo-diene-*EE* (**8-73**) (entry 3). But in this case we can observe some drop of activity, in comparison to neopeltolide. Obviously, this fact can be explained by the crucial role of the configuration of the unsaturated ester. Inversion of the stereochemistry at C11 also resulted in decrease of cytotoxicity (entry 4). Hence, one can assume that the corresponding methoxy group is important for lipophilic interaction with protein receptor. Analogue neo-*trans* (**8-69**) (entry 5) serves as an additional proof for the significant influence of the double bond configuration on the efficiency of ligand–receptor interaction. Expressly, conversion of neopeltolide to the corresponding 5-*epi* analogue **8-59** (entry 6) resulted in more than 33 times decrease of activity. Finally, there are compounds that are essentially non toxic, starting with compound **8-71**. According to this data we can conclude that the four carbon bridge between the oxazole ring and carboxylate moiety is necessary for high activity. Moreover, removal of the oxazole-containing side chain leads to complete lack of activity (entry 9, 10).
In conclusion, the obtained results proved that the oxazole-containing side chain, conformation, configuration and length of carbon linkage between carboxylate and oxazole ring as well as absolute configuration of stereocenters at C5 and C11 are crucial for the biological activity of neopeltolide. The further away from the side chain are the changes in the core, the less dramatic are the changes in activity (entry 4 vs. entry 6).

First hints about the target came from observation of the phenotype of L929 mouse fibroblast cells treated with neopeltolide. Under the microscope a so-called fried-egg phenotype was observed. Other natural products with a similar phenotype turned out to be inhibitors of mitochondrial function. These compounds include antimycin A, myxothiazole, stigmatellin and crocacin. This hypothesis was confirmed in experiments with submitochondrial particles (SMP) from bovine heart. It was observed that neopeltolide inhibits NADH oxidation with SMP from bovine heart at very low concentrations ($IC_{50}$ = 7 ng·mL$^{-1}$). Accordingly, one can conclude that neopeltolide is a specific inhibitor of eukaryotic respiratory chain. More detailed investigation revealed that neopeltolide is targeting complex III in mitochondria, while the preceeding complex I is still being reduced in presence of neopeltolide.

# 9 Conclusion II

In summary, we developed an efficient synthesis of the complex macrolide neopeltolide (**5-1**). The key steps in this synthesis are a Prins cyclization to fashion the pyran ring, a Leighton allylation to establish the stereocenters at C11 and C3 and a Feringa–Minnaard asymmetric methyl cuprate addition to introduce the methyl group at C9.

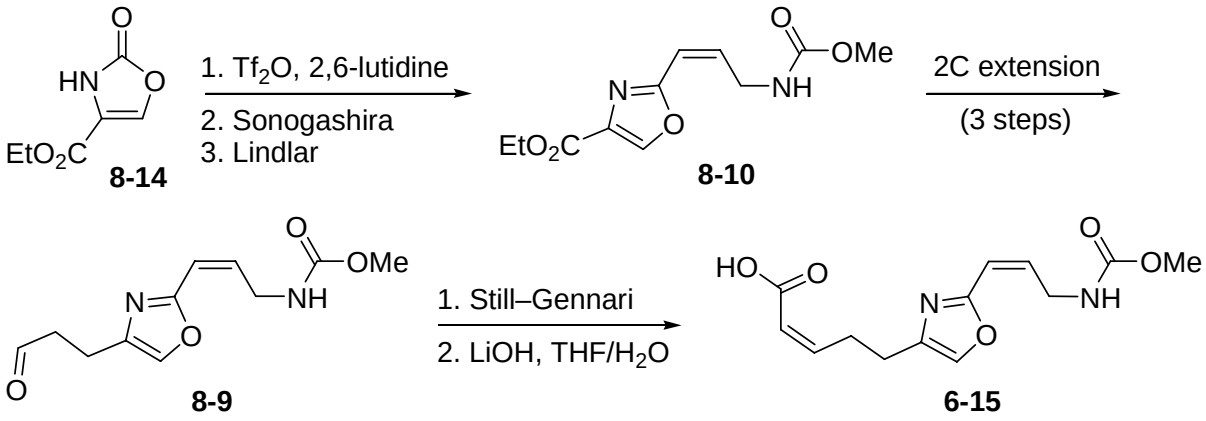



**Scheme 113.** Key intermediates in the synthesis of neopeltolide (**5-1**).

Noyori reduction of keto ester **8-7** efficiently adjusted the first stereocenter. Subsequent Leighton allylation, followed by simple functional group manipulations and Wittig olefination extended aldehyde **8-17** to unsaturated thioester **8-22**. A facial selective Feringa–Minnaard conjugate addition, followed by reduction of the resulting thioester secured aldehyde **8-24**, which was conveniently combined with homoallylic alcohol **8-26** using a Prins cyclization. After the pyran core was established, a few simple transformations led to the seco-acid **8-32**. Cyclization of acid **8-32**, employing classical Yamaguchi conditions with subsequent deprotection accomplished the synthesis of the neopeltolide core **6-14**. Finally, Mitsunobu esterification of alcohol **6-14** with oxazole-containing acid **6-15** produced neopeltolide (**5-1**).

It should be noted, that our synthesis favourably compares with the previous approaches in terms of all usual empirical indices (ca. 18% overall yield, 18 steps in the longest linear sequence). In addition, all chiral centers were essentially obtained via catalytic and highly enantio-selective methods.

The synthesis of acid **6-15** involved 8 steps and proceeded in 18% overall yield from known oxazolone **8-14**. Our strategy was based on a Sonogashira coupling reaction, Lindlar reduction and Still–Gennari olefination. Moreover, application of key intermediates of this route allowed us to prepare a range of different oxazole-containing acids (**8-61** – **8-63**, **8-67**, **8-68**), which afterwards were successfully employed for the preparation of neopeltolide analogues.




**Scheme 114.** Key intermediates in the synthesis of acid **6-15**.

According to cellular assays analogue **8-72** was almost two times more active that neopeltolide (**5-1**) itself, that was explained by fixation of the active conformation via introduction of additional double bond. Drop of activity in cases of compound **8-69**, **8-70** and **8-71** was attributed to the crucial role of the conformation and length of the four carbon linkage between carboxylate and oxazole ring. In addition, complete lack of activity of macrolactones **6-14** and **8-56** one more time confirms that oxazole-containing fragment is important for cytotoxicity.

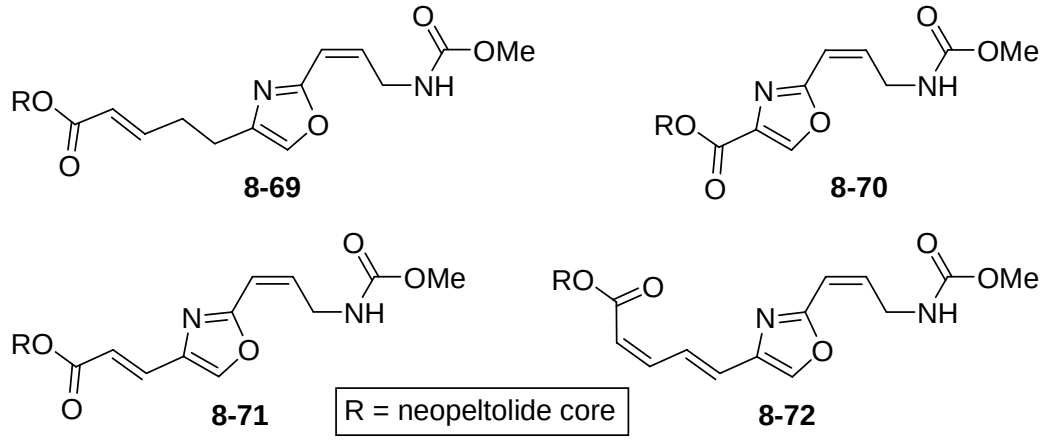



**Figure 44.** Structures of neopeltolide analogues **8-69** – **8-72**.

# 10 Experimental Section

## 10.1 General Remarks

### 10.1.1 Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

### 10.1.2 NMR-spectroscopy

All the spectra were measured on a Bruker Avance 400 spectrometer, which operates at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$ nuclei, respectively. The spectra of some final compounds were measured at 600 MHz (Bruker AMX 600 MHz). $^{1}H$ (400 MHz, 600 MHz) and $^{13}C$ NMR (100 MHz, 150 MHz) spectra were recorded at 295 K either in $CDCl_3$ or $CD_3OD$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ ($\delta H$ = 7.25 ppm, $\delta C$ = 77.0 ppm), $CD_3OD$ ($\delta H$ = 3.30 ppm, $\delta C$ = 49.0 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, *J* = coupling constant (Hz), integration, peak assignment in italic form).

### 10.1.3 Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray ionization method (ESI). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage

of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL $min^{-1}$. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

### 10.1.4 Polarimetry

Optical rotations were measured on a Perkin-Elmer Polarimeter Model 341. They are reported as follows: $[\alpha]^{temperature}_{D}$ (concentration, solvent). The unit of *c* is g/100 mL. Anhydrous $CH_2Cl_2$, $CHCl_3$ or MeOH was used as a solvent. For the measurement the sodium D line = 589 nm was used.

### 10.1.5 Melting Points

Melting points were determined with a Büchi Melting point B-540 apparatus and were not corrected.

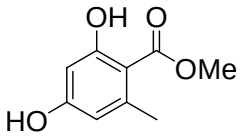
### 10.1.6 Chromatographic Methods

Flash column chromatography was performed using flash silica gel (40-63 μm, 230-400 mesh ASTM) from Macherey-Nagel.
Gas chromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas $H_2$. Chiral gas chromatographic analyses were carried out on 13.5 m × 0.25 mm column filled with deactivated fused silica with 30% 6-TBDMS-2,3-diacetyl-β-cyclodextrin in PS 086 ($d_f$ = 0.13 μm) and carrier gas $H_2$ at 50 kPa and 30 °C.
For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system.
Analytical thin layer chromatography (TLC) was performed on precoated with silica gel 60 $F_{254}$ plates (Merck) or Polygram Sil G/$UV_{254}$ (Macherey Nagel). The compounds were visualized by $UV_{254}$ light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$] and 0.4 g $Ce(SO_4)_2{\cdot}4H_2O$ were dissolved in 400 mL of 10% $H_2SO_4$. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g $Na_2CO_3$ in 250 mL $H_2O$.

## 10.2 Experimental Procedures

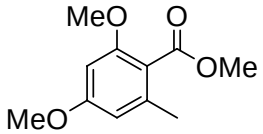
All the experimental procedures are arranged to reflect the synthetic sequences shown in the schemes.

**Methyl 2,4-dihydroxy-6-methylbenzoate**[103]



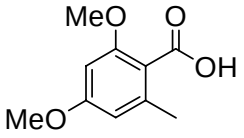

Methyl acetoacetate (20.0 g, 172.2 mmol, 1 equiv) was added dropwise to a stirred suspension of NaH (6.2 g, 258.4 mmol, 1.5 equiv; previously washed with hexane) in 100 ml of absolute THF at 0 °C. The solution was cooled to –80 °C and a 2.5M solution of *n*BuLi (65.5 ml, 163.6 mmol, 0.95 equiv) was added dropwise. The reaction mixture was warmed to ambient temperature, stirred overnight and refluxed for 24 h. After the reaction was cooled to 0 °C, it was acidified to pH = 1–2 with 6N HCl, strirred for additional 1 h, and extracted with EtOAc (4 × 200 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 3:1) to give 10.2 g (65% yield) of methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate) as a colorless solid. $\mathbf{R_f}$ = 0.70 (petroleum ether/EtOAc, 1:1); **m.p.** 137–139 °C, Lit.[103] 136–138 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.47 (s, 3H, Ar-C$H_3$), 3.91 (s, 3H, $OCH_3$), 6.22 (d, *J* = 2.3 Hz, 1H, aryl H), 6.27 (d, *J* = 2.3 Hz, 1H, aryl H), 11.77 (s, 2H, OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 24.3 (Ar-*C*$H_3$), 51.9 ($OCH_3$), 101.2 (C-3), 105.6 (C-5), 111.4 (C-1), 144.0 (C-6), 160.3 (C-2), 165.2 (C-4), 172.1 (*C*$O_2$Me).

**Methyl 2,4-dimethoxy-6-methylbenzoate**[104]



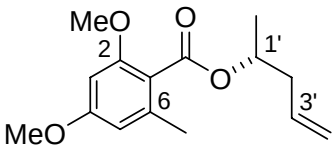

To the mixture of methyl 2,4-dihydroxy-6-methylbenzoate (5.0 g, 27.4 mmol, 1 equiv), anhydrous $K_2CO_3$ (9.5 g, 68.5 mmol, 2.5 equiv) in absolute acetone (100 ml) was added $Me_2SO_4$ and the reaction was refluxed for 16 h. Then the reaction mixture was cooled to ambient temperature, $K_2CO_3$ was filtered off, and the filtrate was concentrated in vacuo. The residue was redissolved in $Et_2O$ (300 ml) and washed with 4M aqeous NaOH (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and the obtained residue was purified by flash chromatography (hexane/EtOAc, 4:1) to give 5.1 g (88% yield) of methyl 2,4-dimethoxy-6-methylbenzoate as a colorless solid. $\mathbf{R_f}$ = 0.37 (hexane/EtOAc, 4:1); **m.p.** 43–44 °C, Lit.[104] 44–45 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.27 (s, 3H, Ar-C$H_3$), 3.78 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 6.30 (s, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.9 (Ar-*C*$H_3$), 52.0 ($CO_2CH_3$), 55.3 ($OCH_3$), 55.9 ($OCH_3$), 96.1 (C-3), 106.6 (C-5), 116.3 (C-1), 138.3 (C-6), 158.2 (C-2), 161.3 (C-4), 168.7 (*C*$O_2$Me).

**2,4-Dimethoxy-6-methylbenzoic acid (3-14)**[268]



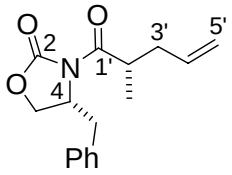

A solution of methyl 2,4-dimethoxy-6-methylbenzoate (3.55 g, 16.9 mmol) in a 10% solution of KOH in a mixture of ethanol/water (130 mL, 95:5) was refluxed for 16 h. After cooling, most of the ethanol was removed in vacuo. The residue was diluted with water (60 mL), acidified (pH ~ 1) by slow addition of aqueous hydrochloric acid (6N) and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford acid **3-14** (3.1 g, 93% yield) as colorless crystals. $\mathbf{R_f}$ = 0.31 (petroleum ether/EtOAc, 1:1); **m.p.** 141–143 °C, Lit.[268] 140–142 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H, Ar-C$H_3$), 3.82 (s, 3H, $OCH_3$), 3.92 (s, 3H, $OCH_3$), 6.37 (s, 1H, aryl H), 6.41 (s, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 22.5 (Ar-*C*$H_3$), 55.4 ($OCH_3$), 56.5 ($OCH_3$), 96.5 (C-3), 109.0 (C-5), 112.3 (C-1), 143.9 (C-6), 159.5 (C-2), 162.2 (C-4), 168.6 (*C*$O_2$Me).

### (1*R*)-1-Methylbut-3-enyl 2,4-dimethoxy-6-methylbenzoate (3-12)[102]



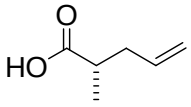

Oxalyl chloride (1.0 mL, 11.5 mmol, 1.3 equiv) was added at 0 °C to a solution of acid **3-14** (2.24 g, 11.5 mmol, 1.3 equiv) in anhydrous $CH_2Cl_2$ (45 mL) and catalytic DMF (50 µL). The solution was then stirred at 25 °C. After 1 h, the reaction was recooled at 0 °C, and treated sequentially with $Et_3N$ (3.6 mL, 26.1 mmol, 2.9 equiv), (2*R*)-pent-4-en-2-ol **3-15** (0.90 ml, 8.8 mmol, 1 equiv) and a solution of DMAP (70 mg, 0.57 mmol) in anhydrous $CH_2Cl_2$ (5 mL). The reaction was followed by TLC until consumption of the starting material (ca 4 h). It was then diluted with $CH_2Cl_2$ (150 mL), washed with saturated $NH_4Cl$ aqeous (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc, 10:1) provided ester **3-12** (1.84 g, 79% yield) as a colorless oil. $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –1.8 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.3 Hz, 3H, 1'-$CH_3$), 2.28 (s, 3H, Ar-C$H_3$), 2.30–2.40 (m, 1H, 2'-H), 2.41–2.50 (m, 1H, 2'-H), 3.77 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 5.06–5.15 (m, 2H, 4'-H), 5.16–5.26 (m, 1H, 1'-H), 5.77–5.89 (m, 1H, 3'-H), 6.29 (s, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.5 (1'-$CH_3$), 19.8 (Ar-*C*$H_3$), 40.2 (C-2'), 55.3 ($OCH_3$), 55.8 ($OCH_3$), 70.8 (C-1'), 96.2 (C-3), 106.5 (C-5), 117.1 (C-1), 117.6 (C-4'), 133.9 (C-3'), 137.8 (C-6), 158.0 (C-2), 161.2 (C-4), 167.8 (*C*$O_2$R);
**HRMS** (ESI): calcd for $C_{15}H_{20}NaO_4$ $[M+Na]^+$: 287.12538, found 287.12541.

### (4*R*)-4-Benzyl-3-[(2*S*)-2-methylpent-4-enoyl]-1,3-oxazolidin-2-one (3-16)[105]



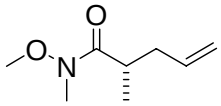

A solution of NaHMDS (2.0M in THF, 13.6 mL, 27.1 mmol) was added via syringe pump over 25 min to a solution of compound **2-6** (5.6 g, 24.0 mmol) in THF (70 mL) at −78 °C and the resulting mixture was stirred at that temperature for 2 h. Allylbromide (9.0 mL, 103.4 mmol) was then introduced and stirring was continued at –78 °C for 1 h and at 0 °C for 16 h. The reaction was quenched with saturated aqeous $NH_4Cl$ (100 mL) and diluted with EtOAc (200 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL), the combined organic layers were washed with brine (100 mL), dried ($Na_2SO_4$), filtered and evaporated, and the crude product was purified by flash chromatography (petroleum ether/EtOAc, 8:1) to yield the corresponding allylation product **3-16** (4.1 g, 62% yield) as a colorless oil which crystallized upon standing. $\mathbf{R_f}$ = 0.25 (petroleum ether/EtOAc, 8:1); **m.p.** 29–30 °C, Lit.[105] 28 °C; $\mathbf{[\alpha]^{20}_D}$ = –42.6 (*c* 1.2, $CHCl_3$), Lit.[105] $\mathbf{[\alpha]^{20}_D}$ = –41.7 (*c* 1.0, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.8 Hz, 2'-$CH_3$), 2.19–2.28 (m, 1H, 3'-H), 2.48–2.57 (m, 1H, 3'-H), 2.69 (dd, *J* = 13.4, 9.9 Hz, 1H, PhC$H_2$), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H, PhC$H_2$), 3.86 (q, *J* = 6.8 Hz, 1H, 2'-H), 4.12–4.21 (m, 2H, 5-H), 4.64–4.72 (m, 1H, 4-H), 5.03–5.13 (m, 2H, 5'-H), 5.76–5.88 (m, 1H, 4'-H), 7.18–7.35 (m, 5H, Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 16.4 (2'-$CH_3$), 37.1 (C-2'), 37.9 (Ph*C*$H_2$), 38.0 (C-3'), 55.4 (C-4), 66.0 (C-5), 117.2 (C-5'), 127.3 (*p*CH ar Ph), 128.9 (*m*CH ar Ph), 129.4 (*o*CH ar Ph), 135.2 (C-4'), 135.3 (*i*CH ar Ph), 153.1 (C-2), 176.5 (C-1');
**HRMS** (ESI): calcd for $C_{16}H_{19}NNaO_3$ $[M+Na]^+$: 296.12626, found 296.12639.

### (2*S*)-2-Methylpent-4-enoic acid (3-17)



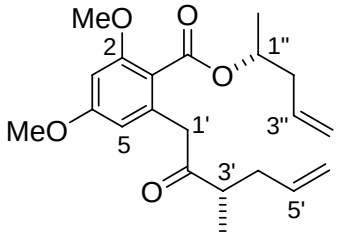

To a solution of allylation product **3-16** (3.4 g, 12.3 mmol) in THF/$H_2O$ (36 mL/9 mL) at 0 °C was slowly added $H_2O_2$ (30 % aq., 5.60 mL, 50.0 mmol) followed by a solution of $LiOH{\cdot}H_2O$ (1.03 g, 24.6 mmol) in water (8 mL). The reaction was stirred at 0 °C for 1 h before it was quenched with saturated aqeous $Na_2SO_3$ to destroy excess $H_2O_2$. Most of the THF was evaporated and the pH of the aqueous phase was adjusted to 12–13 upon addition of NaOH (1M). Extraction with $CH_2Cl_2$ (3 × 50 mL) removed the chiral auxillary. The aqueous phase was then acidified with HCl (2M) until pH = 1–2 was reached and extracted with EtOAc (3 × 75 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated to yield acid **3-17** (1.17 g, 84% yield) as a pale yellow oil. $\mathbf{R_f}$ = 0.32 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +9.0 (*c* 2.0, $CHCl_3$), Lit.[269] $\mathbf{[\alpha]^{20}_D}$ = +9.2 (*c* 1.9, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.8 Hz, 2-$CH_3$), 2.14–2.24 (m, 1H, 3-H), 2.38–2.47 (m, 1H, 3-H), 2.49–2.60 (m, 1H, 2-H), 5.02–5.11 (m, 2H, 5-H), 5.69–5.81 (m, 1H, 4-H), 9.72 (br s, 1H, COOH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 16.3 (2-$CH_3$), 37.4 (C-2), 39.1 (C-3), 117.2 (C-5), 135.1 (C-4), 182.5 (C-1');
**HRMS** (ESI): calcd for $C_6H_{11}NaO_2$ $[M–H]^–$: 113.06080, found 113.06073.

**(2*S*)-*N*-Methoxy-*N*,2-dimethylpent-4-enamide (3-13)**[106]



To a solution of acid **3-17** (0.96 g, 8.4 mmol) in $CH_2Cl_2$ (30 mL) was added N-methylpiperidine (4.4 mL, 36.1 mmol) followed by isobutylchloroformate (2.3 mL, 18.1 mmol) at –15 °C. The mixture was stirred at –15 °C for 1 h followed by addition of N,O-dimethylhydroxylamine hydrochloride (2.13 g, 21.8 mmol). After being stirred at –15 °C for 15 min, the mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution, and the aqueous layer was extracted twice with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column (petroleum ether/EtOAc, 4:1) to give Weinreb amide **3-13** (0.99 g, 75% yield) as a colorless oil. $\mathbf{R_f}$ = 0.40 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +17.3 (*c* 3.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.8 Hz, 2-$CH_3$), 2.06–2.15 (m, 1H, 3-H), 2.36–2.45 (m, 1H, 3-H), 2.86–2.98 (m, 1H, 2-H), 3.17 (s, 3H, $NCH_3$), 3.67 (s, 3H, $OCH_3$), 4.97–5.08 (m, 2H, 5-H), 5.68–5.81 (m, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 17.0 (2-$CH_3$), 35.1 (C-2), 37.8 (C-3), 61.5 ($OCH_3$), 116.4 (C-5), 136.2 (C-4);
**HRMS** (ESI): calcd for $C_8H_{15}NNaO_2$ $[M+Na]^+$: 180.09950, found 180.09958.

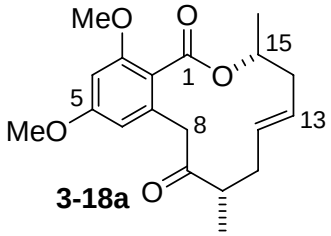
**(1*R*)-1-Methylbut-3-enyl 2,4-dimethoxy-6-[(3*S*)-3-methyl-2-oxohex-5-enyl]benzoate (3-11)**[102]



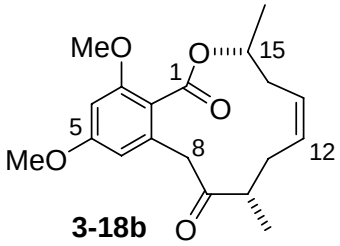

A solution of ester **3-12** (244 mg, 0.92 mmol) in anhydrous THF (2 mL) was treated at –78 °C with freshly made LDA (1.84 mL 1M in THF, 1.84 mmol). After 5 min of stirring, a solution of Weinreb amide **3-13** (144 mg, 0.92 mmol) in THF (1.0 mL) was added dropwise. The resulting mixture was then stirred for 15 min at –78 °C and quenched by addition of saturated aqueous $NH_4Cl$. Upon warming to room temperature, the reaction mixture was diluted with EtOAc, washed several times with saturated aqeous $NH_4Cl$, brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography afforded ketone **3-11** (90 mg, 27% yield) as a colorless oil. $\mathbf{R_f}$ = 0.55 (petroleum ether/$Et_2O$, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +32.1 (*c* 2.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.06 (*J* = 6.8 Hz, 3H, 3'-$CH_3$), 1.32 (d, *J* = 6.3 Hz, 3H, 1''-$CH_3$), 2.02–2.11 (m, 1H, 4'-H), 2.29–2.45 (m, 3H, 2''-H, 4'-H), 2.65–2.74 (m, 1H, 3'-H), 3.68–3.84 (m, 8H, $OCH_3$, 1'-H), 4.96–5.19 (m, 5H, 4''-H, 6'-H, 1''-H ), 5.62–5.74 (m, 1H, 5'-H), 5.77–5.89 (m, 1H, 3''-H), 6.26 (d, *J* = 2.0 Hz, 1H, aryl H), 6.36 (d, *J* = 2.0 Hz, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 16.0 (3'-$CH_3$), 19.4 (1''-$CH_3$), 19.8 (Ar-*C*$H_3$), 37.0 (C-4'), 40.2 (C-2''), 44.8 (C-3'), 46.4 (C-1'), 55.3 ($OCH_3$), 55.7 ($OCH_3$), 71.0 (C-1''),

97.6 (C-3), 107.0 (C-5), 116.8 (C-6'), 117.0 (C-1), 117.5 (C-4''), 133.9 (C-3''), 134.9 (C-6), 135.6 (C-5'), 158.7 (C-2), 161.4 (C-4), 167.4 ($CO_2R$), 209.8 (C-2');
**HRMS** (ESI): calcd for $C_{21}H_{28}NaO_5$ $[M+Na]^+$: 383.18344, found 383.18339.

**(*E*)-Macrolactone 3-18a and (*Z*)-macrolactone 3-18b**




**3-18a**



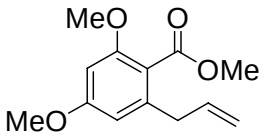

**3-18b**

To a solution of ester **3-11** (80 mg, 0.22 mmol) in degassed toluene (22 mL) was added a solution of Grubbs 2nd catalyst (17.0 mg, 0.02 mmol) in toluene (0.5 mL) and the mixture was stirred at 80 °C for 23 h. For workup, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/$Et_2O$, 1:1) to give (*E*)-macrolactone **3-18a** (51 mg, 70% yield) as a colorless solid. For the X-Ray analysis compound **3-18a** was recrystallized from diisopropyl ether. Besides **3-18a** some of (*Z*)-isomer **3-18b** (9 mg, 12% yield) was isolated.

Compound **3-18a**
**$R_f$** = 0.35 (petroleum ether/$Et_2O$, 1:1); **m. p.** 147–148 °C; **$[\alpha]^{20}_D$** = +82.4 (*c* 0.5, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.10 (*J* = 6.8 Hz, 3H, 10-$CH_3$), 1.31 (d, *J* = 6.6 Hz, 3H, 15-$CH_3$), 2.05–2.20 (m, 2H, 11-H, 14-H), 2.25–2.33 (m, 1H, 11-H), 2.45–2.52 (m, 1H, 14-H), 2.81–2.90 (m, 1H, 10-H), 3.50 (d, *J* = 18.2 Hz, 1H, 8-H), 3.74 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.95 (d, *J* = 18.2 Hz, 1H, 8-H), 5.15–5.23 (m, 1H, 15-H), 5.38–5.51 (m, 2H, 12-H, 13-H ), 6.21 (d, *J* = 2.0 Hz, 1H, aryl H), 6.35 (d, *J* = 2.0 Hz, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 16.8 (10-$CH_3$), 20.2 (15-$CH_3$), 36.6 (C-11), 38.8 (C-14), 45.9 (C-10), 47.7 (C-8), 55.3 ($OCH_3$), 55.7 ($OCH_3$), 70.4 (C-15), 97.5 (C-4), 107.8 (C-6), 117.9 (C-2), 128.2 (C-13), 129.6 (C-12), 133.3 (C-7), 157.5 (C-3), 160.8 (C-5), 168.1 (C-1), 210.0 (C-9);
**HRMS** (ESI): calcd for $C_{19}H_{24}NaO_5$ $[M+Na]^+$: 355.15159, found 355.15156.

Compound **3-18b**
**$R_f$** = 0.27 (petroleum ether/$Et_2O$, 1:1); **m. p.** 132–133 °C; **$[\alpha]^{20}_D$** = +64.1 (*c* 2.2, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.14 (*J* = 6.8 Hz, 3H, 10-$CH_3$), 1.29 (d, *J* = 6.3 Hz, 3H, 15-$CH_3$), 1.98–2.12 (m, 2H, 11-H), 2.39–2.50 (m, 2H, 14-H), 2.65–2.75 (m, 1H, 10-H), 3.56 (d, *J* = 18.4 Hz, 1H, 8-H), 3.77 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.95 (d, *J* = 18.4 Hz, 1H, 8-H), 5.28–5.38 (m, 1H, 15-H), 5.55–5.65 (m, 2H, 12-H, 13-H ), 6.14 (d, *J* = 2.3 Hz, 1H, aryl H), 6.37 (d, *J* = 2.3 Hz, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 17.2 (10-$CH_3$), 20.9 (15-$CH_3$), 33.5 (C-11), 34.5 (C-14), 45.1 (C-10), 50.0 (C-8), 55.3 ($OCH_3$), 55.8 ($OCH_3$), 71.0 (C-15), 97.6 (C-4), 107.4 (C-6), 117.7 (C-2), 128.4 (C-13), 129.3 (C-12), 133.8 (C-7), 158.2 (C-3), 161.1 (C-5), 167.1 (C-1), 209.7 (C-9);
**HRMS** (ESI): calcd for $C_{19}H_{24}NaO_5$ $[M+Na]^+$: 355.15159, found 355.15164.

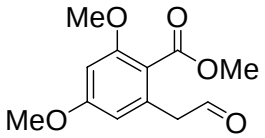
**Methyl 2-allyl-4,6-dimethoxybenzoate (3-21)**




**2-Allyl-4,6-dimethoxybenzoic acid (3-20):**[107] A 1-L three-necked round bottom flask, equipped with a digital thermometer, a mechanical stirrer, and a dropping funnel, was charged with TMEDA (40 mL, 260 mmol, 2.2 equiv) and dry THF (100 mL), flushed with argon, and cooled to –90 °C with 2-propanol/liquid $N_2$. To this solution was added *s*BuLi (200 mL, 260 mmol, 1.3 M in cyclohexane, 2.2 equiv) slowly, maintaining the temperature below –90 °C. The resulting pale yellow solution was stirred for an additional 30 min followed by the dropwise addition of a solution of 2,4-dimethoxybenzoic acid 1 (21.8 g, 120 mmol, 1.0 equiv) in dry THF (120 mL) over 30 min, maintaining the internal temperature at –90 °C. The reaction mixture was stirred further, while warming to –78 °C until an orange colored and nearly clear solution was obtained (approximately 1 h). After addition of allyl bromide (40 mL, 470 mmol, 4.1 equiv) over 1 h at –78 °C, the resulting mixture was stirred for another 30 min and then treated slowly with water (100 mL) and warmed to room temperature. After separation of the layers, the aqueous layer was washed twice with $Et_2O$ (100 mL), and then the organic layers were discarded. The aqueous layer was acidified with 6 N HCl (150 mL) and extracted with $CH_2Cl_2$ (3 × 500 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 21.0 g of crude acid (**3-20**), which was used in next step without additional purification.

**Methyl 2-allyl-4,6-dimethoxybenzoate (3-21):**[108] To a cooled (0 °C) solution of 2-allyl-4,6-dimethoxybenzoic acid (**3-20**) (21.0 g, 94.6 mmol) in THF (500 mL) were added 1,8-diazabicyclo-[5.4.0]undec-7-en (DBU) (14.1 mL, 14.3 g, 94.6 mmol) and iodomethane (17.7 mL, 40.2 g, 93.6 mmol), successively. After the mixture was stirred for 24 h at room temperature, the precipitate was removed by filtration over celite. The filter cake was rinsed with $Et_2O$ (300 mL). The filtrate was washed with $H_2O$ (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to yield 14.45 g (51% for 2 steps) of methyl ester **3-21** as a colorless oil. $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc, 8:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.28 (d, *J* = 6.6 Hz, 2H, ArC*H*$_2$CH=CH$_2$), 3.73 (s, 6H, $OCH_3$, $CO_2CH_3$), 3.79 (s, 3H, $OCH_3$), 4.96–4.98 (m, 1H, ArCH$_2$CH=C*H*$_2$), 4.99–5.02 (m, 1H, ArCH$_2$CH=C*H*$_2$), 5.77–5.87 (m, 1H, ArCH$_2$C*H*=CH$_2$), 7.19 (s, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 37.8 (Ar*C*H$_2$CH=CH$_2$), 51.7 ($CO_2$*C*H$_3$), 55.0, 55.6 ($OCH_3$), 96.3 (C-5), 105.6 (C-3), 115.9 (C-1), 116.0 (ArCH$_2$CH=*C*H$_2$), 135.9 (ArCH$_2$*C*H=CH$_2$), 139.9 (C-2), 157.9 (C-6), 161.2 (C-4), 168.2 (*C*O$_2$CH$_3$);
**HRMS** (ESI): calcd for $C_{13}H_{16}NaO_4$ $[M+Na]^+$: 259.2535, found 259.2534.

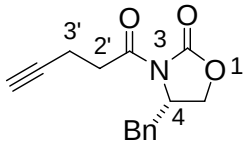
**Methyl 2,4-dimethoxy-6-(2-oxoethyl)benzoate (3-22)**[109]



To a solution of alkenoic ester **3-21** (7.38 g, 31.3 mmol) in a mixture of THF/*t*BuOH (200/30 mL) was added 4-methyl-morpholine-N-oxide (8.76 g, 62.6 mmol) and an aqueous solution of $OsO_4$ (20 mL of a 0.032 M solution, 0.64 mmol, 2 mol%, prepared from $K_2OsO_4 \cdot 2H_2O$ (236 mg, 0.64 mmol))[110] at 0 ºC. After being stirred at room temperature for 24 h, 10% $Na_2S_2O_3$ solution was added to the mixture. After 30 min, the diol was extracted with EtOAc and the combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel followed by rinsing the pad with EtOAc. Removal of the solvent from the combined filtrate gave the crude diol.

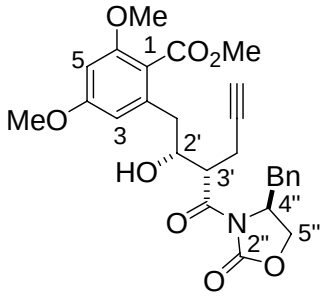
$NaIO_4$ (10.1 g, 47.0 mmol, 1.5 equiv) was added to a solution of crude diol in 90% MeOH (300 mL). After stirring at room temperature for 2 h, most of the methanol was removed in vacuo and the residue extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, and filtered. After concentration, the residue was purified by flash chromatography ($CH_2Cl_2$/EtOAc, 9:1) to give aldehyde **3-22** as a colorless oil (6.3 g, 85%). $\mathbf{R_f}$ = 0.45 ($CH_2Cl_2$/EtOAc, 9:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.63 (s, 2H, ArC$H_2$CHO), 3.81 (s, 3H, $CO_2CH_3$), 3.82, 3.84 (2 s, 3H each, $OCH_3$), 6.31 (s, 1H, aryl H), 6.42 (s, 1H, aryl H), 9.67 (s, 1H, CHO); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 48.9 (Ar$C$H$_2$CHO), 52.1 ($CO_2CH_3$), 55.4, 56.0 ($OCH_3$), 97.9 (C-3), 107.5 (C-5), 116.1 (C-1), 133.6 (C-6), 159.3 (C-2), 162.1 (C-4), 167.7 ($CO_2CH_3$), 198.7 (CHO).

**(4*S*)-4-Benzyl-3-pent-4-ynoyl-1,3-oxazolidin-2-one (3-25)**




To a solution of 4-pentynoic acid (**3-23**) (4.48 g, 45.7 mmol) in THF (180 mL) were added $NEt_3$ (8.1 mL, 55 mmol) and PivCl (6.15 mL, 48 mmol) at –78 °C. The resulting mixture was stirred for 15 min at –78 °C, allowed to warm up to room temperature, stirred for 30 min and recooled to –78 °C. Now, a precooled (–90 °C) solution of lithiated (*S*)-(-)-4-benzyl-2-oxazolidinone (**3-24**) (8.90 g, 50.3 mmol), generated by treatment of the oxazolidinone solution in THF (100 mL) at –78 °C with *n*BuLi (2.5 M solution in hexane, 20.0 mL, 50.0 mmol) was cannulated to the mixed anhydride solution. After 15 min at –78 °C, the resulting suspension was warmed to room temperature within 2 h. The reaction mixture was treated with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:4) afforded oxazolidinone **3-25** (11.20 g, 95%) as colorless crystals. $\mathbf{R_f}$ = 0.35 (petroleum ether/EtOAc, 4:1); **m.p.** = 88–89 °C; $\mathbf{[\alpha]^{20}_D}$ = +98.6 (*c* 1.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.00 (dd, *J* = 2.5, 2.5 Hz, 1H, C≡CH), 2.57–2.61 (m, 2H, 3'-H), 2.78–2.81 (m, 1H, $PhCH_2$), 3.11–3.24 (m, 2H, 2'-H), 3.28–3.32 (m, 1H, $PhCH_2$), 4.17–4.24 (m, 2H, 2-H), 4.66–4.72 (m, 1H, 4-H), 7.19–7.21 (m, 2H, aryl H), 7.27–7.35 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 (C-3'), 35.1 (C-2'), 38.1 ($PhCH_2$), 55.5 (C-4), 66.7 (C-5), 69.3 ($CH_2C{\equiv}CH$), 82.9 ($CH_2C{\equiv}CH$), 127.7 (*p*CH ar), 129.3 (*m*CH ar), 129.7 (*o*CH ar), 129.7 (*i*C ar), 153.2 (C-2), 171.6 (C-2).

**Methyl 2-((2*R*,3*S*)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-2-hydroxyhex-5-ynyl)-4,6-dimethoxybenzoate (3-26)**[111]

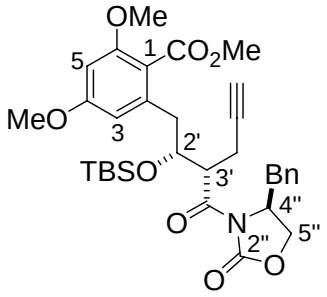



To a stirred solution of pentynoyloxazolidinone **3-25** (9.3 g, 36.2 mmol) in absolute toluene (250 mL) was added *n*$Bu_2$BOTf (40 mL, 1M in $CH_2Cl_2$) dropwise to maintain the internal temperature at –10 °C. After stirring for 5 min at –10 °C, *i*$Pr_2$NEt (7.2 ml, 43.4 mmol) was added dropwise, while maintaining the internal temperature at –10 °C. The solution turned from dark orange to light yellow after this addition. The reaction mixture was stirred for 2 h at 0 °C and then cooled to –78 °C before a solution of aldehyde **3-22** (9.50 g, 40.0 mmol) in toluene (50 mL) was added at –78 °C. The reaction mixture was stirred at this temperature for 1 h and then allowed to warm to 0 °C. After stirring at 0 °C for 3 h, the reaction was quenched by addition of phosphate buffer pH = 7, (120 mL), and methanol (100 ml). The mixture was cooled to an internal temperature at –5 °C followed by the addition of 30% $H_2O_2$ (80 mL). The reaction mixture was stirred at 0 °C for 1 h. All volatiles were removed in vacuo and the residue was extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with $H_2O$ (100 mL), saturated NaCl solution (100 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the crude aldol product, which was purified by flash chromatography ($CH_2Cl_2$/EtOAc, 85:15) to give aldol product **3-26** (15.21 g, 85%) as a colorless solid. $\mathbf{R_f}$ = 0.45 ($CH_2Cl_2$/EtOAc, 85:15); **m.p.** = 47–48 °C; $\mathbf{[\alpha]^{20}_D}$ = +67.3 (*c* 2.1, $CH_2Cl_2$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.02 (dd, *J* = 2.5, 2.5 Hz, 1H, C≡CH), 2.68–2.96 (m, 5H, 4'-H, 1'-H, $PhCH_2$), 3.62–3.65 (m, 1H, $PhCH_2$), 3.78 (s, 3H, $CO_2CH_3$), 3.80, 3.90 (2 s, 3H each, $OCH_3$), 4.12–4.24 (m, 4H, 5''-H, 4''-H, 3'-H), 4.70–4.76 (m, 1H, 2'-H), 6.35 (d, *J* = 2.0 Hz, 1H, aryl H), 6.42 (d, *J* = 2.0 Hz, 1H, aryl H), 7.23–7.35 (m, 5H, Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 16.8 (*C*$H_2$C≡CH), 37.8 ($PhCH_2$), 38.9 (C-1'), 48.3 (C-3'), 52.7 ($CO_2CH_3$), 55.4 ($OCH_3$), 55.9 (2 C, $OCH_3$, C-4''), 66.1 (C-5''), 70.1 (C≡*C*H), 81.5 (*C*≡CH), 97.5 (C-5), 106.4 (C-3), 116.2 (C-1),127.3 (*p*CH ar Ph), 128.9 (2 C, *m*CH ar Ph), 129.5 (2 C, *o*CH ar Ph), 135.2 (*i*C ar Ph), 139.5 (C-2), 153.2 (C-2''), 158.6 (C-4), 162.0 (C-6), 169.7 ($CO_2CH_3$), 172.9 (C=O);

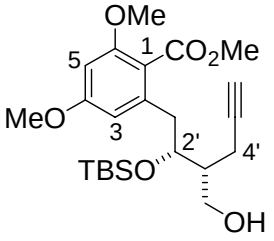
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{27}H_{29}NNaO_8$: 518.1785, found 518.1784.

**Methyl 2-((2*R*,3*S*)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-2-{[*tert*-butyl(dimethyl)silyl]oxy}hex-5-ynyl)-4,6-dimethoxybenzoate (3-27)**




A solution of aldol adduct **3-26** (3.0 g, 6.0 mmol) in $CH_2Cl_2$ (50 mL) was cooled to –60 °C and protone sponge (3.34 g, 15.6 mmol) was added, followed by TBSOTf (1.8 ml, 7.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After complete reaction (monitoring by TLC) water was added and the mixture extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 4:1) afforded silyl ether **3-27** (3.30 g, 89% yield) as a colorless oil. $\mathbf{R_f}$ = 0.25 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +55.2 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.35 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), 0.86 (s, 9H, $Si(C(CH_3)_3)$), 2.00 (s, 1H, C≡CH), 2.57–2.66 (m, 1H, 4'-H), 2.71–2.94 (m, 4H, 1'-H, 4'-H, Ph$CH_2$), 3.21–3.27 (m, 1H, $PhCH_2$), 3.74 (s, 3H, $CO_2CH_3$), 3.78 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.08–4.20 (m, 3H, 4''-H, 5''-H), 4.29–4.34 (m, 1H, 2'-H), 4.59–4.64 (m, 1H, 3'-H), 6.32 (d, *J* = 2.0 Hz, 1H, aryl H), 6.51 (d, *J* = 2.0 Hz, 1H, aryl H), 7.20–7.34 (m, 5H, Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –5.2 ($Si(CH_3)_2$), 17.6 ($CH_2$C≡CH), 17.9, 25.9 ($Si(C(CH_3)_3)$), 37.6 (C-1'), 39.5 ($PhCH_2$), 47.6 (C-3'), 52.3 ($CO_2CH_3$), 55.4 ($OCH_3$), 55.6 ($OCH_3$), 55.9 (C-4''), 66.0 (C-5''), 70.2 (C≡CH), 81.5 (C≡CH), 97.4 (C-5), 107.6 (C-3), 117.2 (C-1),127.2 (*p*CH ar Ph), 128.8 (2 C, *m*CH ar Ph), 129.5 (2 C, *o*CH ar Ph), 135.4 (*i*C ar Ph), 138.0 (C-2), 152.8 (C-2''), 158.0 (C-4), 161.1 (C-6), 168.4 ($CO_2CH_3$), 172.2 (C=O);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{43}NNaO_8Si$: 632.26501, found 632.26578.

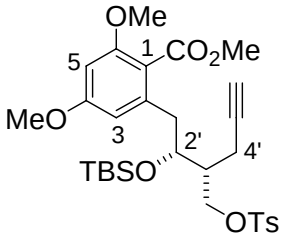
**Methyl 2-[(2*R*,3*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-(hydroxymethyl)hex-5-ynyl]-4,6-dimethoxybenzoate (3-28)**[112]




To a stirred solution of compound **3-27** (3.03 g, 5.0 mmol) in THF (185 mL) was added a solution of $NaBH_4$ (1.0 g, 25.0 mmol) in $H_2O$ (35 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 2 d at room temperature until TLC analysis showed complete consumption of starting material **3-27**. The mixture was treated with saturated $NH_4CI$ solution and stirred for 1 h. After separation of the layers, the $H_2O$ phase was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography

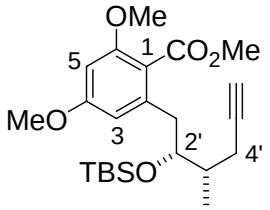
($CH_2Cl_2$/EtOAc, 9:1) of the residue afforded primary alcohol **3-28** (1.99 g, 91% yield) as colorless crystals. $\mathbf{R_f}$ = 0.74 ($CH_2Cl_2$/EtOAc, 85:15); **m.p.** = 61–63 °C; $\mathbf{[\alpha]^{20}_D}$ = +17.6 (*c* 3.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.35 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), 0.86 (s, 9H, $Si(C(CH_3)_3)$), 2.03 (s, 1H, C≡CH), 2.11–2.29 (m, 3H, 3'-H, 4'-H), 2.68 (dd, *J* = 13.6, 9.1, 1H, 1'-H), 2.89 (dd, *J* = 13.6, 4.5, 1H, 1'-H), 3.74–3.80 (m, 8H, C*H*$_2$OH, $CO_2CH_3$, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.13–4.19 (m, 1H, 2'-H), 6.34 (d, *J* = 2.0 Hz, 1H, aryl H), 6.37 (d, *J* = 2.0 Hz, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$), 16.8 (*C*$H_2$C≡CH), 17.8, 25.8 ($Si(C(CH_3)_3)$), 37.1 (C-1'), 44.7 (C-3'), 52.2 ($CO_2CH_3$), 55.3 ($OCH_3$), 56.0 ($OCH_3$), 63.3 ($CH_2OH$), 69.7 (C≡*C*H), 74.0 (C-2'), 82.7 (*C*≡CH), 97.1 (C-5), 108.0 (C-3), 116.7 (C-1), 139.0 (C-2), 158.4 (C-4), 161.1 (C-6), 168.7 (*C*$O_2CH_3$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{23}H_{36}NaO_6Si$: 459.21734, found 459.21719.

**Methyl 2-[(2*R*,3*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-({[(4-methylphenyl)sulfonyl]oxy}methyl)hex-5-ynyl]-4,6-dimethoxybenzoate (3-29)**



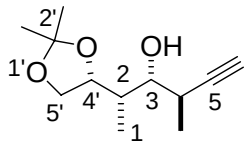

To a cooled to 0 °C solution of alcohol **3-28** (1.8 g, 4.12 mmol) in $CH_2Cl_2$ (65 mL) were added DMAP (50 mg, 0.41 mmol), $Et_3N$ (2.9 mL, 20.6 mmol) and *p*toluenesulfonyl chloride (1.57 g, 8.24 mmol). The mixture was stirred for 24 h at room temperature. Then $H_2O$ was added, and the aqueous layer extracted with $CH_2Cl_2$. The organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$) of the residue afforded tosylate **3-29** (2.19 g, 90% yield) as a colorless oil. $\mathbf{R_f}$ = 0.27 ($CH_2Cl_2$); $\mathbf{[\alpha]^{20}_D}$ = +3.8 (*c* 1.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.33 (s, 3H, $Si(CH_3)_2$), –0.10 (s, 3H, $Si(CH_3)_2$), 0.76 (s, 9H, $Si(C(CH_3)_3)$), 1.92–1.99 (m, 1H, 3'-H), 2.03 (s, 1H, C≡CH), 2.17–2.32 (m, 2H, 4'-H), 2.43 (s, 3H, $CH_3$ of Ts), 2.53 (dd, *J* = 13.6, 8.3 Hz, 1H, 1'-H), 2.79 (dd, *J* = 13.6, 5.3 Hz, 1H, 1'-H), 3.78 (s, 3H, $CO_2CH_3$), 3.78 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.04–4.15 (m, 3H, $CH_2OTs$, 2'-H), 6.28 (d, *J* = 2.0 Hz, 1H, aryl H), 6.33 (d, *J* = 2.0 Hz, 1H, aryl H), 7.31 (d, *J* = 8.1 Hz, 2H, ar of Ts), 7.76 (d, *J* = 8.1 Hz, 2H, ar of Ts); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –5.2 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$), 15.8 (*C*$H_2$C≡CH), 17.8, 21.6 ($CH_3$ of Ts), 25.8 ($Si(C(CH_3)_3)$), 37.7 (C-1'), 42.7 (C-3'), 52.3 ($CO_2CH_3$), 55.4 ($OCH_3$), 56.0 ($OCH_3$), 69.2 ($CH_2OTs$), 70.1 (C≡*C*H), 71.2 (C-2'), 81.7 (*C*≡CH), 97.1 (C-5), 107.5 (C-3), 116.7 (C-1), 128.0 (2 C, C-2, C-6 of Ts), 129.8 (2 C, C-3, C-5 of Ts), 132.8 (C-1 of Ts), 138.4 (C-2), 144.7 (C-1 of Ts), 158.4 (C-4), 161.1 (C-6 ar), 168.5 (*C*$O_2CH_3$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{30}H_{42}NaO_8SSi$: 613.22619, found 613.22662.

**Methyl 2-((2*R*,3*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylhex-5-ynyl)-4,6-dimethoxybenzoate (3-30)**[113]




A mixture of tosylate **3-29** (2.14 g, 3.6 mmol), NaI (2.70 g, 18.2 mmol), activated zinc dust (2.84 g, 36.3 mol) and glyme (180 ml) was refluxed for 4 h under stirring. Then the reaction mixture was cooled to ambient temperature and filtered through a pad of celite. The filtrate was washed with $H_2O$ (50 mL) and the $H_2O$ fraction extracted with $Et_2O$ (2 × 200 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1) of the residue afforded ester **3-30** (1.47 g, 96% yield) as colorless oil. $\mathbf{R_f}$ = 0.26 ($CH_2Cl_2$); $\mathbf{[\alpha]^{20}_D}$ = +19.5 (*c* 1.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.34 (s, 3H, $Si(CH_3)_2$), –0.05 (s, 3H, $Si(CH_3)_2$), 0.82 (s, 9H, $Si(C(CH_3)_3)$), 1.00 (d, *J* = 6.8 Hz, 3H, 3'-$CH_3$), 1.78–1.87 (m, 1H, 3'-H), 1.95 (t, *J* = 6.8 Hz, 1H, C≡CH), 2.04–2.12 (m, 1H, 4'-H), 2.21–2.31 (m, 1H, 4'-H), 2.54 (dd, *J* = 13.6, 8.3 Hz, 1H, 1'-H), 2.77 (dd, *J* = 13.6, 4.6 Hz, 1H, 1'-H), 3.78 (s, 3H, $CO_2CH_3$), 3.79 (s, 3H, $OCH_3$), 3.84-3.90 (m, 4H, $OCH_3$, 2'-H), 6.32 (d, *J* = 2.0 Hz, 1H, aryl H), 6.37 (d, *J* = 2.0 Hz, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –5.0 ($Si(CH_3)_2$), –5.0 ($Si(CH_3)_2$), 15.0 (3'-$CH_3$), 18.0, 21.2 (C-4'), 25.9 ($Si(C(CH_3)_3)$), 37.2 (C-1'), 38.2 (C-3'), 52.2 ($CO_2CH_3$), 55.3 ($OCH_3$), 56.0 ($OCH_3$), 69.1 (C≡*C*H), 75.3 (C-2'), 83.7 (*C*≡CH), 96.8 (C-5), 107.9 (C-3), 116.8 (C-1), 139.5 (C-2), 158.2 (C-4), 161.0 (C-6), 168.7 ($CO_2CH_3$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{23}H_{36}NaO_5Si$: 443.22242, found 443.22255.

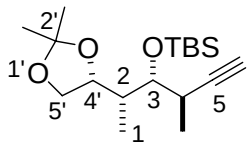
**(2*S*,3*R*,4*R*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-methylhex-5-yn-3-ol (3-35)**




a) **Preparation of (2*R*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]propanal (3-9):** To a cooled (–78 °C) solution of oxalyl chloride (5.0 mL, 56.5 mmol) in dry $CH_2Cl_2$ (150 mL) was added a solution of dimethylsulfoxide (9.0 mL, 92.0 mmol) in $CH_2Cl_2$ (50 mL) and the mixture was stirred at –78 °C for 30 min. Then, a solution of (2*S*)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]propan-1-ol[100] (**3-33**) (6.05 g, 37.5 mmol) in $CH_2Cl_2$ (50 mL) was added and after additional stirring at –78 °C for 30 min, triethylamine (26.5 mL, 180 mmol) was added and the reaction mixture allowed to warm to room temperature over 4 h. The mixture was diluted with $CHCl_3$ and then mixed with water. The organic layer was washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Concentration must be carried out with special care because of the high volatility of the aldehyde. The crude aldehyde **3-9** (5.72 g, 97% yield) was used in the next reaction without further purification.
b) **(2*S*,3*R*,4*R*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-methylhex-5-yn-3-ol (3-35):**[81] To a stirred solution of $Pd(OAc)_2$ (163.0 mg, 0.73 mmol, 0.050 equiv) in THF (240 mL) at –78 °C were added $PPh_3$ (191 mg, 0.73 mmol, 0.050 equiv), aldehyde **3-9** (5.72 g, 36.3

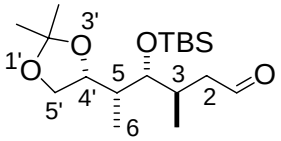
mmol), and mesylate (*S*)-**3-34**[74a] (7.95 g, 54.0 mmol, 1.50 equiv). Thereafter, diethylzinc (109 mL, 1 M in hexane, 3.00 equiv) was added over 20 min, and after stirring for 5 min, the mixture was warmed to –20 °C and stirred for 3 d at this temperature. The reaction mixture was treated with $NH_4Cl/Et_2O$ (1:1) and the layers were separated. The $Et_2O$ layer was washed with saturated NaCl solution and stirred with $MgSO_4$ and norite decolorizing charcoal. The mixture was filtered and concentrated in vacuo, followed by purification of the residue by flash chromatography (EtOAc/hexanes, 10:1) to give 5.54 g (72%) of alkyne **3-35** as a separable 96:4 mixture of diastereomers as a light yellow oil. $\mathbf{R_f}$ = 0.65 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +2.9 (*c* 2.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.8 Hz, 3H, 1-H), 1.16 (d, *J* = 6.8 Hz, 3H, 4-$CH_3$), 1.32 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.72–1.81 (m, 1H, 2-H), 2.13 (s, 1H, C≡CH), 2.20–2.38 (br s, 1H, OH), 2.60–2.71 (m, 1H, 4-H), 3.37–3.46 (m, 1H, 3-H), 3.70 (dd, *J* = 7.6, 7.6 Hz, 1H, 5'-H), 4.03 (dd, *J* = 7.8, 7.8 Hz, 1H, 5'-H), 4.19 (dd, *J* = 12.6, 6.3 Hz, 1H, 4'-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.2 (C-1), 17.3 (4-$CH_3$), 25.2 ($C(CH_3)_2$), 26.4 ($C(CH_3)_2$), 30.7 (C-4), 38.0 (C-2), 67.3 (C-5'), 70.8 (HC≡C), 75.7 (C-3), 78.2 (C-4'), 85.8 (HC≡*C*), 108.8 ($C(CH_3)_2$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}NaO_3$: 235.1305, found 235.1303.

### (4*S*)-4-[(1*S*,2*R*,3*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,3-dimethylpent-4-ynyl]-2,2-dimethyl-1,3-dioxolane (3-36)



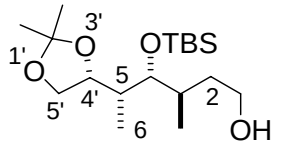

A solution of alcohol **3-35** (3.18 g, 15.0 mmol) in $CH_2Cl_2$ (50 mL) was cooled to –50 °C and 2,6-lutidine (5.20 ml, 45.0 mmol) was added, followed by TBSOTf (4.50 mL, 19.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. Then it was diluted with water and extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 20:1) afforded silyl ether **3-36** (4.65 g, 95% yield) as a colorless oil. $\mathbf{R_f}$ = 0.27 (petroleum ether/EtOAc, 20:1); $\mathbf{[\alpha]^{20}_D}$ = +1.2 (*c* 2.25, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.06 (s, 3H, $Si(CH_3)_2$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.90 (s, 9H, $Si(C(CH_3)_3)$), 1.01 (d, *J* = 6.8 Hz, 3H, 1'-$CH_3$), 1.18 (d, *J* = 7.0 Hz, 3H, 3'-$CH_3$), 1.33 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.88–1.95 (m, 1H, 1'-H), 2.07 (s, 1H, C≡CH), 2.62–2.68 (m, 1H, 3'-H), 3.49–3.53 (m, 1H, 2'-H), 3.66–3.72 (m, 1H, 5-H), 4.04–4.17 (m, 2H, 5-H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.2 ($Si(CH_3)_2$), 11.9 (1'-$CH_3$), 17.4 (3'-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 25.6 ($C(CH_3)_2$), 26.0 ($Si(C(CH_3)_3)$), 26.8 ($C(CH_3)_2$), 31.3 (C-3'), 40.4 (C-1'), 68.4 (C-5), 70.6 (HC≡C), 75.6 (C-2'), 78.0 (C-4), 86.6 (HC≡*C*), 108.3 ($C(CH_3)_2$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{34}NaO_3Si$: 349.2169, found 349.2166.

### (3*R*,4*R*,5*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methylhexanal (3-37)[81]




To a cooled (0 °C) solution of $BH_3{\cdot}SMe_2$ (94%, 1.44 mL, 13.82 mmol, 1.3 equiv) in dry 1,2-dimethoxyethane (90 mL) was added freshly distilled cyclohexene (2.91 mL, 28.7 mmol, 2.7 equiv). After 15 min, the mixture was warmed to room temperature. The resultant cloudy suspension was stirred for 1 h then cooled to 0 °C, before and alkyne **3-36** (3.47 g, 10.63 mmol, 1.0 equiv) in 1,2-dimethoxyethane (25 mL) was added. After 5 min the reaction mixture was warmed to room temperature when it eventually became clear in color. After stirring for 3 h, the solution was cooled to 0 °C and treated with 1N NaOH (250 mL) followed by dropwise addition of $H_2O_2$ (80 mL, 30% solution in $H_2O$). The mixture was stirred for 5 min at 0 °C and 20 min at room temperature, then recooled to 0 °C and the residual peroxide was quenched by careful dropwise addition of saturated aqueous $Na_2S_2O_3$ solution. The mixture was allowed to warm to room temperature and diluted with ether (200 mL). The ether layer was washed with saturated NaCl solution and water, and the combined aqueous layers were extracted with ether (3 × 100 mL). The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give 3.11 g (85%) of aldehyde **3-37** as slightly yellow oil. $\mathbf{R_f}$ = 0.55 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –9.3 (*c* 1.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 0.94–1.00 (m, 6H, 6-H, 3-$CH_3$), 1.31 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.70–1.75 (m, 1H, 3-H), 2.13–2.21 (m, 1H, 2-H), 2.27–2.37 (m, 1H, 5-H), 2.60–2.67 (m, 1H, 2-H), 3.42–3.46 (m, 1H, 4-H), 3.58 (dd, *J* = 7.6, 7.6 Hz, 1H, 5'-H), 3.97 (dd, *J* = 7.6, 7.6 Hz, 1H, 5'-H), 4.13 (dd, *J* = 6.6, 6.0 Hz, 1H, 4'-H), 9.74 (s, 1H, CHO); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.2 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), 11.1 (C-6), 18.2 (3-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 25.4 ($C(CH_3)_2$), 26.0 ($Si(C(CH_3)_3)$), 26.6 ($C(CH_3)_2$), 31.7 (C-3), 40.0 (C-5), 47.0 (C-2), 67.9 (C-5'), 76.4 (C-4), 76.7 (C-4'), 108.7 ($C(CH_3)_2$), 202.8 (CHO).

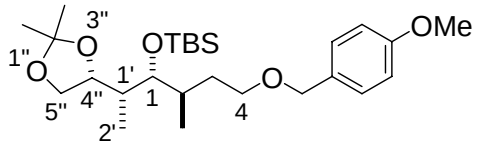
**(3*R*,4*R*,5*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methylhexan-1-ol (3-38)**




To a cooled (0 °C) solution of aldehyde **3-37** (3.11 g, 9.0 mmol) in a mixture of THF/MeOH (3:1, 50 mL) was added sodium borohydride (0.5 g, 13.5 mmol) and the reaction mixture was stirred at this temperature for 1 h. Then it was treated with saturated $NH_4Cl$ solution and all volatiles were removed in vacuo. The aqueous residue was extracted with $CH_2Cl_2$, and the combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 2:1) afforded alcohol **3-38** (2.96 g, 95% yield) as a colorless oil. $\mathbf{R_f}$ = 0.48 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = +4.2 (*c* 2.75, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 0.94 (d, *J* = 7.1 Hz, 3H, 6-H), 0.96 (d, *J* =

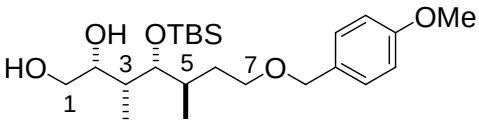
7.1 Hz, 3H, 3-$CH_3$), 1.33 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.70–1.78 (m, 3H, 3-H, 2-H), 1.83–1.91 (m, 1H, 5-H), 1.95 (br s, 1H, OH), 3.43–3.47 (m, 1H, 4-H), 3.54–3.63 (m, 2H, 5'-H, 1-H), 3.68–3.75 (m, 1H, 1-H), 3.98 (dd, $J$ = 7.6, 7.6 Hz, 1H, 5'-H), 4.18 (dd, $J$ = 6.8, 6.8 Hz, 1H, 4'-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.3 ($Si(CH_3)_2$), –4.0 ($Si(CH_3)_2$), 11.2 (C-6), 17.6 (3-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 25.4 ($C(CH_3)_2$), 26.0 ($Si(C(CH_3)_3)$), 26.6 ($C(CH_3)_2$), 33.5 (C-3), 35.2 (C-2), 39.8 (C-5), 60.9 (C-1), 68.0 (C-5'), 76.7 (C-4), 77.1 (C-4'), 108.8 ($C(CH_3)_2$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{38}NaO_4Si$: 369.2432, found 369.2428.

### *tert*-Butyl({(1*R*,2*R*)-1-{(1*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-4-[(4-methoxybenzyl)oxy]-2-methylbutyl}oxy)dimethylsilane (3-39)[120c]




To a solution of alcohol **3-38** (1.86 g, 5.4 mmol) in $CH_2Cl_2$ (50 mL) were added 4-methoxybenzyltrichloroacetimidate (4.56 g, 16.2 mmol) and PPTS (1.36 g, 5.4 mmol) at 0 °C. The resultant mixture was stirred for 3 d at room temperature before saturated aqueous $NaHCO_3$ solution was added. After separation of the layers, the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded ether **3-39** (2.34 g, 93% yield) as a colorless oil. $\mathbf{R_f}$ = 0.57 (petroleum ether/EtOAc, 20:1); $\mathbf{[\alpha]^{20}_D}$ = –2.0 (*c* 1.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.87–0.93 (m, 12H, $Si(C(CH_3)_3)$, 2'-H), 0.98 (d, $J$ = 6.8 Hz, 3H, 2-$CH_3$), 1.32 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.65–1.83 (m, 4H, 1'-H, 3-H, 2-H), 3.40–3.51 (m, 3H, 1-H), 4-H), 3.57 (dd, $J$ = 7.3, 7.3 Hz, 1H, 5''-H), 3.79 (s, 3H, $OCH_3$), 3.94–4.06 (m, 2H, 5''-H, 4''-H), 4.36–4.46 (m, 2H, $CH_2$ of PMB), 6.86 (d, $J$ = 8.4 Hz, 2H, aryl H), 7.24 (d, $J$ = 8.4 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.4 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 11.6 (C-2'), 16.3 (2-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 25.5 ($C(CH_3)_2$), 26.0 ($Si(C(CH_3)_3)$), 26.7 ($C(CH_3)_2$), 32.7 (C-2), 35.4 (C-3), 39.3 (C-1'), 55.2 ($OCH_3$), 68.1 (C-5''), 68.5 (C-4), 72.5 ($CH_2$ of PMB), 76.2 (C-1), 78.3 (C-4''), 108.4 ($C(CH_3)_2$), 113.7, 113.9, 129.2, 129.7, 130.6, 159.1 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{46}NaO_5Si$: 489.30067, found 489.30042.

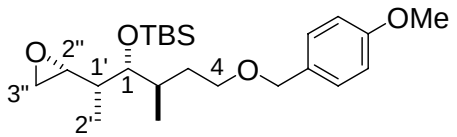
### (2*R*,3*R*,4*R*,5*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]-3,5-dimethylheptane-1,2-diol (3-40)[115]




$CuCl_2 \cdot 2H_2O$ (6.14 g, 36.0 mmol, 10 equiv) was added to a solution of acetal **3-39** (1.68 g, 3.6 mmol) in $CH_3CN$ (100 mL) at –10 °C. The reaction mixture was stirred for 20 h at –5 °C,

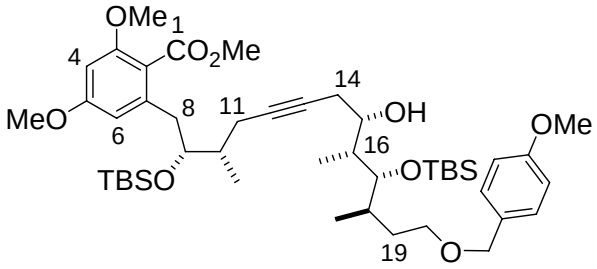
treated with saturated $NH_4Cl$ solution (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, saturated $NH_4Cl$ solution and saturated NaCl solution, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1→1:1) to give diol **3-40** (1.46 g, 95%) as a colorless oil. $\mathbf{R_f}$ = 0.56 (petroleum ether/EtOAc, 1:2); $\mathbf{[\alpha]^{20}_D}$ = +1.3 (*c* 1.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H, $Si(CH_3)_2$), 0.87–0.95 (m, 15H, $Si(C(CH_3)_3)$, 3-$CH_3$, 5-$CH_3$), 1.28–1.38 (m, 1H, 6-H), 1.65–1.73 (m, 1H, 5-H), 1.74–1.86 (m, 1H, 6-H), 1.87–1.95 (m, 1H, 3-H), 2.52 (br s, 2H, OH), 3.38–3.56 (m, 5H, 7-H, 4-H, 1-H, 2-H), 3.62–3.67 (m, 1H, 1-H), 3.81 (s, 3H, $OCH_3$), 4.45 (dd, *J* = 18.4, 11.6 Hz, 2H, $CH_2$ of PMB), 6.89 (d, *J* = 8.4 Hz, 2H, aryl H), 7.26 (d, *J* = 8.4 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.3 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), 10.4 (3-$CH_3$), 17.5 (5-$CH_3$), 18.2 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 32.6 (C-5), 34.1 (C-6), 38.7 (C-3), 55.2 ($OCH_3$), 65.4 (C-1), 68.4 (C-7), 73.1 ($CH_2$ of PMB), 77.8 (C-2), 113.7, 129.4.1, 130.2, 159.72 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{23}H_{42}NaO_5Si$: 449.26937, found 449.26882.

### *tert*-Butyl[((1*R*,2*R*)-4-[(4-methoxybenzyl)oxy]-2-methyl-1-{(1*R*)-1-[(2*R*)-oxiran-2-yl]ethyl}butyl)oxy]dimethylsilane (3-42)[116]



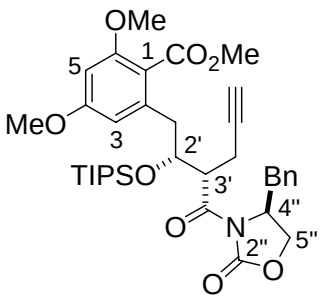

To a solution of diol **3-40** (152 mg, 0.356 mmol) in THF (12 mL) at 0 °C was added NaH (60% wt. in mineral oil, 44 mg, 1.07 mol, 3.0 equiv). The resulting mixture was warmed to room temperature and stirred for 40 min. The mixture was cooled to 0 °C before N-(2,4,6-triisopropylbenzenesulfonyl)imidazole (**3-41**) (125 mg, 0.377 mmol, 1.1 equiv) was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with water (10 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate/petroleum ether, 1:10) provided epoxide **3-42** (131 mg, 90% yield) as a colorless oil. $\mathbf{R_f}$ = 0.70 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +3.6 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.06 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.89–0.94 (m, 12H, $Si(C(CH_3)_3)$, 2'-H), 1.07 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 1.27–1.40 (m, 2H, 3-H, 1'-H), 1.76–1.85 (m, 2H, 3-H, 2-H), 2.52–2.56 (m, 1H, 3''-H), 2.71–2.75 (m, 1H, 3''-H), 2.80–2.85 (m, 1H, 2''-H), 3.40–3.58 (m, 3H, $CH_2$OPMB, CH(OTBS)), 3.82 (s, 3H, $OCH_3$), 4.43 (dd, *J* = 18.6, 11.6 Hz, 2H, $CH_2$ of PMB), 6.89 (d, *J* = 8.6 Hz, 2H, aryl H), 7.26 (d, *J* = 8.6 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.1 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 13.1 (C-2'), 16.8 (2-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 32.1 (C-3), 34.6 (C-2), 40.3 (C-1'), 47.7 (C-3''), 55.3 (C-2''), 56.0 (2C, $OCH_3$), 68.5 ($CH_2$OPMB), 72.6 ($CH_2$ of PMB), 77.9 (CH(OTBS)), 113.7, 129.2, 130.7, 159.1 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{23}H_{40}NaO_4Si$: 431.25881, found 431.25852.

### Alcohol 3-43



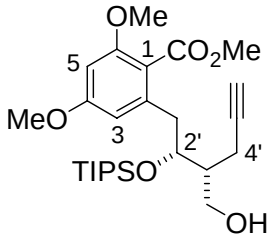

*t*BuLi (140 µL, 1.5 M in pentane, 0.21 mmol) was added to a solution of alkyne **3-30** (90 mg, 0.21 mmol) in THF (3.5 mL) at –78 °C in a dropwise fashion. The acetylide solution was stirred at –78 °C for 1 h before a solution of $BF_3{\cdot}OEt_2$ (30 µL, 0.21 mmol) was added. Stirring was continued for 15 min at –78 °C. Then, a solution of epoxide **3-42** (58 mg, 0.14 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at –78 °C for 3 h and then quenched with saturated $NH_4Cl$ solution. The layers were separated and the aqueous layer was extracted twice with $Et_2O$. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil, which was purified by flash chromatography (petroleum ether/EtOAc, 10:1→5:1) to furnish alcohol **3-43** (52 mg) in 44% yield. $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +8.0 (*c* 1.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.37 (s, 3H, $Si(CH_3)_2$), –0.07 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 6H, $Si(CH_3)_2$), 0.81 (s, 9H, $Si(C(CH_3)_3)$), 0.85–0.94 (m, 15H, 18-$CH_3$, 16-$CH_3$, $Si(C(CH_3)_3)$), 0.97 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.12–1.27 (m, 2H, 19-H), 1.30–1.40 (m, 1H, 18-H), 1.72–1.92 (m, 4H, 10-H, 11-H, 16-H, 14-H), 2.00–2.08 (m, 1H, 11-H), 2.17–2.24 (m, 1H, 8-H), 2.32–2.36 (m, 2H), 2.46–2.54 (m, 1H, 14-H), 2.58–2.61 (m, 1H, 8-H), 2.72–2.78 (m, 1H, 15-H), 3.38–3.51 (m, 2H, 20-H), 3.63–3.67 (m, 1H, 17-H), 3.75–3.81 (m, 9H, $OCH_3$), 3.84–3.90 (m, 4H, 9-H, $OCH_3$), 4.36–4.46 (m, 2H, $CH_2$ of PMB), 6.32 (s, 1H, H-6), 6.37 (s, 1H, H-4), 6.86 (d, *J* = 8.6 Hz, 2H, aryl H), 7.24 (d, *J* = 8.6 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), –5.0 ($Si(CH_3)_2$), –4.3 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 9.2 (16-$CH_3$), 14.8 (10-$CH_3$), 16.4, 17.9, 18.3 (18-$CH_3$), 21.8 (C≡C$CH_2$), 25.5 (C≡C$CH_2$), 25.9 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 32.6 (C-19), 35.1 (C-18), 37.0 (C-16), 38.8 (C-8), 39.4 (C-10), 55.1 ($OCH_3$), 55.2 ($OCH_3$), 55.3 ($OCH_3$), 55.9 ($OCH_3$), 68.4 (C-20), 72.5 ($CH_2$ of PMB), 72.7 (C-15), 75.3, 77.7 (C-17), 77.9 (C-9), 81.4 ($CH_2C$≡C), 96.8 (C-3), 108.1 (C-6), 113.7 (ar of PMB), 116.8 (C-2), 129.2 (ar of PMB), 130.6 (ar of PMB), 139.7 (C-7), 158.1 (C-5), 159.1 (ar of PMB), 160.9 (C-3), 168.7 ($CO_2R$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{46}H_{76}NaO_9Si_2$: 851.49201, found 851.49172.

**(Methyl 2-{(2*R*,3*S*)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-2-[(triisopropylsilyl)oxy]hex-5-ynyl}-4,6-dimethoxybenzoate (3-45)**



A solution of aldol adduct **3-26** (9.42 g, 19.0 mmol) in $CH_2Cl_2$ (100 mL) was cooled to –60 °C and protone sponge (14.58 g, 67.8 mmol) was added, followed by TIPSOTf (6.64 ml, 24.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After complete reaction (monitoring by TLC) water was added and the mixture extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 4:1) afforded silyl ether **3-45** (11.77 g, 95% yield) as a colorless oil. $\mathbf{R_f}$ = 0.43 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +59.6 (*c* 2.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.05–1.09 (m, 21H, Si(C*H*($CH_3$)$_2$), 2.03 (s, 1H, C≡CH), 2.57–2.69 (m, 2H, 4'-H), 2.76–2.92 (m, 2H, 1'-H), 2.99–3.04 (m, 1H, $PhCH_2$), 3.19-3.23 (m, 1H, $PhCH_2$), 3.73 (s, 3H, $CO_2CH_3$), 3.80 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.02–4.04 (m, 1H, 4''-H), 4.08–4.19 (m, 2H, 5''-H), 4.46–4.49 (m, 1H, 2'-H), 4.61–4.66 (m, 1H, 3'-H), 6.32 (s, 1H, aryl H), 6.65 (s, 1H, aryl H), 7.18–7.32 (m, 5H, Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.0 (*C*H($CH_3$)$_2$), 18.0 (*C*$H_2$C≡CH), 18.2 (CH(*C*$H_3$)$_2$), 37.6 (C-1'), 39.4 ($PhCH_2$), 46.8 (C-3'), 52.4 ($CO_2$*C*$H_3$), 55.4 ($OCH_3$), 55.6 ($OCH_3$), 55.9 (C-4''), 65.9 (C-5''), 70.2 (C≡*C*H), 81.5 (*C*≡CH), 97.5 (C-5), 106.7 (C-3), 117.1 (C-1),127.1 (*p*CH ar Ph), 128.8 (2 C, *m*CH ar Ph), 129.5 (2 C, *o*CH ar Ph), 135.6 (*i*C ar Ph), 137.3 (C-2), 152.6 (C-2''), 157.9 (C-4), 161.2 (C-6), 168.4 ($CO_2CH_3$), 172.0 (C=O);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{49}NNaO_8Si$: 674.3120, found 674.3123.

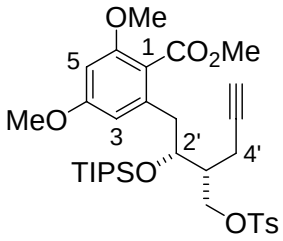
**Methyl 2-{(2*R*,3*R*)-3-(hydroxymethyl)-2-[(triisopropylsilyl)oxy]hex-5-ynyl}-4,6-dimethoxybenzoate (3-46)**




To a stirred solution of compound **3-45** (9.5 g, 14.6 mmol) in THF (400 mL) was added a solution of $NaBH_4$ (3.24 g, 87.6 mmol) in $H_2O$ (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 3 d at room temperature until TLC analysis showed complete consumption of starting material **3-45**. The mixture was treated with saturated $NH_4CI$ solution and stirred for 1 h. After separation of the layers, the $H_2O$ phase was extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/EtOAc, 9:1) of the residue afforded primary alcohol **3-46** (6.56 g, 94% yield) as colorless crystals. $\mathbf{R_f}$ = 0.41 ($CH_2Cl_2$/EtOAc, 9:1); **m.p.** = 110–111 °C; $\mathbf{[\alpha]^{20}_D}$ = +6.9 (*c* 2.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.98–1.02 (m, 21H, Si(C*H*($CH_3$)$_2$), 1.97 (s, 1H, C≡CH), 2.00–2.02 (m, 1H, 3'-H), 2.20–2.23 (m, 2H, 4'-H), 2.81–2.85 (m, 2H, 1'-H), 3.76–3.81 (m, 8H, C*H*$_2$OH, $CO_2CH_3$, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.39–4.41 (m, 1H, 2'-H), 6.33 (s, 1H, aryl H), 6.40 (s, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.8 (*C*H($CH_3$)$_2$), 16.2 (*C*$H_2$C≡CH), 18.0 (CH(*C*$H_3$)$_2$), 18.1 (CH(*C*$H_3$)$_2$), 37.7 (C-1'), 44.3 (C-3'), 52.2 ($CO_2CH_3$), 55.3 ($OCH_3$), 56.0 ($OCH_3$), 63.4 ($CH_2OH$), 69.6 (C≡*C*H), 73.9 (C-2'), 83.1 (*C*≡CH), 97.1 (C-5), 107.2 (C-3), 116.9 (C-1), 138.5 (C-2), 158.4 (C-4), 161.2 (C-6), 168.7 ($CO_2CH_3$);

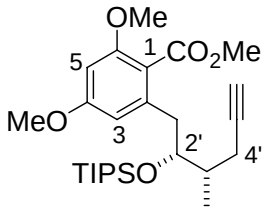
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{42}NaO_6Si$: 501.2643, found 501.2645.

**Methyl 2,4-dimethoxy-6-{(2*R*,3*R*)-3-({[(4-methylphenyl)sulfonyl]oxy}methyl)-2-[(triisopropylsilyl)oxy]hex-5-ynyl}benzoate (3-47)**




To a cooled to 0 °C solution of alcohol **3-46** (4.32 g, 9.00 mmol) in $CH_2Cl_2$ (150 mL) were added DMAP (245 mg, 2.0 mmol), $Et_3N$ (6.30 mL, 45 mmol) and *p*toluenesulfonyl chloride (3.43 g, 18 mmol). The mixture was stirred for 24 h at room temperature. Then $H_2O$ was added, and the aqueous layer extracted with $CH_2Cl_2$. The organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$) of the residue afforded tosylate **3-47** (5.42 g, 95% yield) as a colorless oil. $\mathbf{R_f}$ = 0.31 ($CH_2Cl_2$); $\mathbf{[\alpha]^{20}_D}$ = +2.3 (*c* 3.55, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.91–0.96 (m, 21H, Si(C*H*(C*H*$_3$)$_2$), 1.84–1.87 (m, 1H, 3'-H), 1.98 (s, 1H, C≡CH), 2.18–2.28 (m, 2H, 4'-H), 2.42 (s, 3H, $CH_3$ of Ts), 2.63–2.68 (m, 1H, 1'-H), 2.74–2.80 (m, 1H, 1'-H), 3.77 (s, 6H, $CO_2CH_3$, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.08–4.17 (m, 2H, $CH_2OTs$), 4.32–4.36 (m, 1H, 2'-H), 6.32–6.33 (m, 2H, aryl H), 7.29 (d, *J* = 8.0 Hz, 2H, ar of Ts), 7.73 (d, *J* = 8.0 Hz, 2H, ar of Ts); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.7 (*C*H(CH$_3$)$_2$), 15.5 (*C*H$_2$C≡CH), 18.0 (CH(*C*H$_3$)$_2$), 18.1 (CH(*C*H$_3$)$_2$), 21.6 ($CH_3$ of Ts), 37.7 (C-1'), 42.1 (C-3'), 52.2 ($CO_2CH_3$), 55.3 ($OCH_3$), 56.0 ($OCH_3$), 69.2 ($CH_2OTs$), 70.0 (C≡*C*H), 71.5 (C-2'), 81.8 (*C*≡CH), 97.3 (C-5), 106.5 (C-3), 116.9 (C-1), 128.0 (2 C, C-2, C-6 of Ts), 129.7 (2 C, C-3, C-5 of Ts), 132.7 (C-1 of Ts), 137.9 (C-2), 144.6 (C-1 of Ts), 158.3 (C-4), 161.3 (C-6 ar), 168.5 (*C*O$_2$CH$_3$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{48}NaO_8SSi$: 655.2731, found 655.2737.

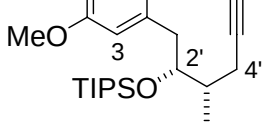
**Methyl 2,4-dimethoxy-6-{(2*R*,3*S*)-3-methyl-2-[(triisopropylsilyl)oxy]hex-5-ynyl}benzoate (3-48)**




A mixture of tosylate **3-47** (5.40 g, 8.5 mmol), NaI (12.75 g, 85 mmol), activated zinc dust (11.1 g, 170 mmol) and glyme (500 mL) was refluxed for 4 h under stirring. Then the reaction mixture was cooled to ambient temperature and filtered through a pad of celite. The filtrate was washed with $H_2O$ (100 mL) and the $H_2O$ fraction extracted with $Et_2O$ (2 × 300 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1) of

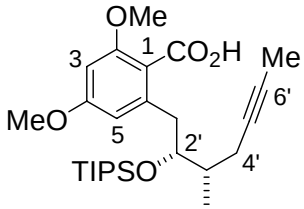
the residue afforded ester **3-48** (4.31 g, 97% yield) as colorless crystals. $\mathbf{R_f}$ = 0.38 (petroleum ether/EtOAc, 10:1); **m.p.** = 56–57 °C; $\mathbf{[\alpha]^{20}_D}$ = +22.1 (*c* 5.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.97–1.05 (m, 24H, Si(C*H*(C*H*$_3$)$_2$), 3'-$CH_3$), 1.87–1.90 (m, 1H, 3'-H), 1.93 (s, 1H, C≡CH), 2.04–2.10 (m, 1H, 4'-H), 2.19–2.24 (m, 1H, 4'-H), 2.61-2.66 (m, 1H, 1'-H), 2.72–2.77 (m, 1H, 1'-H), 3.76 (s, 3H, $CO_2CH_3$), 3.78 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.10–4.13 (m, 1H, 2'-H), 6.31 (s, 1H, aryl H), 6.40 (s, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.8 (*C*H(CH$_3$)$_2$), 15.0 (3'-$CH_3$), 18.0 (CH(*C*H$_3$)$_2$), 18.1 (CH(CH$_3$)$_2$), 21.1 (C-4'), 37.1 (C-1'), 37.9 (C-3'), 52.1 ($CO_2$*C*H$_3$), 55.3 ($OCH_3$), 55.9 ($OCH_3$), 69.0 (C≡*C*H), 75.8 (C-2'), 83.8 (*C*≡CH), 96.9 (C-5), 107.3 (C-3), 117.0 (C-1), 139.3 (C-2), 158.2 (C-4), 161.0 (C-6), 168.7 ($CO_2CH_3$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{42}NaO_5Si$: 485.2694, found 485.2692.

**2,4-Dimethoxy-6-{(2*R*,3*S*)-3-methyl-2-[(triisopropylsilyl)oxy]hex-5-ynyl}benzoic acid (3-49)**



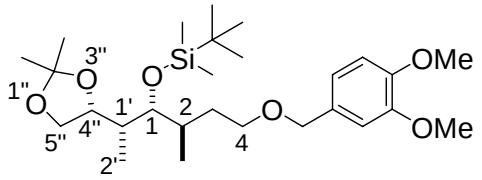

A solution of methyl ester **3-48** (3.1 g, 6.7 mmol) in a 10% solution of KOH in a mixture of ethanol/water (100 mL, 95:5) was refluxed for 20 h. After cooling, most of the ethanol was removed in vacuo. The residue was diluted with water (60 mL), acidified (pH ~ 3) by slow addition of aqueous hydrochloric acid (1N) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc/HOAc, 4:1:0.01) afforded acid **3-49** (2.85 g, 95% yield) as colorless crystals. $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 4:1); **m.p.** = 106–107 °C; $\mathbf{[\alpha]^{20}_D}$ = +74.3 (*c* 1.75, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.88–0.94 (m, 21H, Si(C*H*(C*H*$_3$)$_2$), 1.07 (d, *J* = 6.8 Hz, 3H, 3'-$CH_3$), 2.04 (dd, *J* = 2.5, 2.5 Hz, 1H, C≡CH), 2.08–2.14 (m, 1H, 3'-H), 2.18–2.29 (m, 2H, 4'-H), 2.80–2.88 (m, 2H, 1'-H), 3.81 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.37–4.41 (m, 1H, 2'-H), 6.37 (d, *J* = 2.0 Hz, 1H, aryl H), 6.40 (d, *J* = 2.0 Hz, 1H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.6 (*C*H(CH$_3$)$_2$), 13.5 (3'-$CH_3$), 17.7 (CH(*C*H$_3$)$_2$), 17.9 (CH(*C*H$_3$)$_2$), 22.7 (C-4'), 35.2 (C-1'), 38.2 (C-3'), 55.4 ($OCH_3$), 56.3 ($OCH_3$), 69.8 (C≡*C*H), 77.2 (C-2'), 82.6 (*C*≡CH), 97.5 (C-5), 107.7 (C-3), 116.2 (C-1), 141.2 (C-2), 159.5 (C-4), 162.1 (C-6), 166.5 ($CO_2H$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{25}H_{40}NaO_5Si$: 471.2537, found 471.2538.

**2,4-Dimethoxy-6-{(2*R*,3*S*)-3-methyl-2-[(triisopropylsilyl)oxy]hept-5-ynyl}benzoic acid (3-50)**



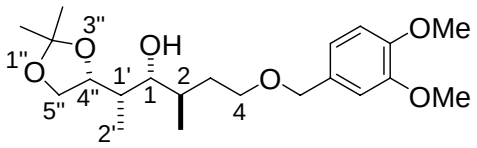
A solution of acid **3-49** (1.02 g, 2.2 mmol) in THF (45 mL) was treated with *n*BuLi (2.64 mL, 2.5 M in hexanes, 6.6 mmol, 3 equiv) in a dropwise fashion at –78 °C. After being stirred for 1 h at –78 °C, methyl iodide (0.685 mL, 11 mmol) was added at –78 °C and the reaction mixture allowed to warm to room temperature over 5 h. After addition of $H_2O$ (10 mL), all volatiles were removed in vacuo. The residue was redissolved in $H_2O$ (30 mL), acidified (pH ~ 3) by slow addition of aqueous hydrochloric acid (1N) and extracted with EtOAc (3 × 40 mL). Flash chromatography (petroleum ether/EtOAc/HOAc, 4:1:0.01) afforded acid **3-50** (1.04 g, 98% yield) as a colorless solid. $\mathbf{R_f}$ = 0.38 (petroleum ether/EtOAc, 4:1); **m.p.** = 102–103 °C; $\mathbf{[\alpha]^{20}_D}$ = +113.9 (*c* 2.1, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.87–0.93 (m, 21H, Si(C*H*(C*H*$_3$)$_2$), 1.02 (d, *J* = 6.8 Hz, 3H, 3'-$CH_3$), 1.77 (s, 7'-$CH_3$), 2.06–2.10 (m, 1H, 3'-H), 2.11–2.21 (m, 2H, 4'-H), 2.75–2.81 (m, 2H, 1'-H), 3.79 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 4.37–4.41 (m, 1H, 2'-H), 6.35 (d, *J* = 2.0 Hz, 1H, aryl H), 6.37 (d, *J* = 2.0 Hz, 1H, aryl H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 3.4 (7'-$CH_3$), 12.6 (*C*H($CH_3$)$_2$), 13.5 (3'-$CH_3$), 17.6 (CH(*C*H$_3$)$_2$), 17.9 (CH(*C*H$_3$)$_2$), 23.0 (C-4'), 34.7 (C-1'), 38.5 (C-3'), 55.3 ($OCH_3$), 56.1 ($OCH_3$), 77.0 (C≡C), 77.1 (C-2'), 77.1 (C≡C), 97.3 (C-5), 107.0 (C-3), 116.8 (C-1), 140.5 (C-2), 159.3 (C-4), 161.9 (C-6), 167.4 ($CO_2H$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{42}NaO_5Si$: 485.2694, found 485.2693.

### *tert*-Butyl[((1*R*,2*R*)-4-[(3,4-dimethoxybenzyl)oxy]-1-{(1*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-2-methylbutyl)oxy]dimethylsilane (3-51)



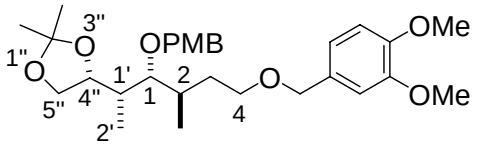

To a solution of alcohol **3-38** (2.92 g, 8.4 mmol) in $CH_2Cl_2$ (50 mL) were added 3,4-dimethoxybenzyltrichloroacetimidate[120b] (7.86 g, 25.2 mmol) and PPTS (2.1 g, 8.4 mmol) at 0 °C. The resultant mixture was stirred for 3 d before saturated aqueous $NaHCO_3$ solution was added. After separation of the layers, the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded ether **3-51** (4.05 g, 97% yield) as a colorless oil. $\mathbf{R_f}$ = 0.46 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –1.9 (*c* 2.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, Si($CH_3$)$_2$), 0.04 (s, 3H, Si($CH_3$)$_2$), 0.86–0.92 (m, 12H, Si(C($CH_3$)$_3$), 2'-H), 0.98 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 1.31 (s, 3H, C($CH_3$)$_2$), 1.37 (s, 3H, C($CH_3$)$_2$), 1.64–1.82 (m, 4H, 1'-H, 3-H, 2-H), 3.40–3.51 (m, 3H, 1-H), 4-H), 3.58 (dd, *J* = 7.3, 7.3 Hz, 1H, 5''-H), 3.86 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.03–4.17 (m, 2H, 5''-H, 4''-H), 4.41 (dd, *J* = 21.7, 11.6 Hz, 2H, $CH_2$ of DMB), 6.79–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.4 (Si($CH_3$)$_2$), –3.8 (Si($CH_3$)$_2$), 11.6 (C-2'), 16.3 (2-$CH_3$), 18.3 (Si(*C*($CH_3$)$_3$)), 25.5 (C(*C*H$_3$)$_2$), 26.0 (Si(C(*C*H$_3$)$_3$)), 26.7 (C(*C*H$_3$)$_2$), 32.6 (C-2), 35.4 (C-3), 39.3 (C-1'), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.1 (C-5''), 68.6 (C-4), 72.8 ($CH_2$ of DMB), 76.3 (C-1), 78.3 (C-4''), 108.4 (*C*($CH_3$)$_2$), 110.8, 110.9, 120.1, 131.1, 148.5, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{27}H_{48}NaO_6Si$: 519.3112, found 519.3111.

**(2*S*,3*R*,4*R*)-6-[(3,4-Dimethoxybenzyl)oxy]-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylhexan-3-ol (3-52)**




To a solution of silyl ether **3-51** (1.45 g, 2.9 mmol) in THF (5 mL) was added TBAF (8.7 mL, 1M in THF, 8.7 mmol) at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 2:1→1:1) afforded alcohol **3-52** (1.05 g, 95% yield) as a colorless oil. $\mathbf{R_f}$ = 0.51 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +1.0 (*c* 2.0, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.8 Hz, 3H, 2'-H), 0.94 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 1.33 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.48–1.58 (m, 1H, 3-H), 1.65–1.83 (m, 2H, 3-H, 2-H), 1.87–1.98 (m, 1H, 1'-H), 3.23–3.30 (m, 2H, 1H, OH), 3.45–3.60 (m, 2H, 4-H), 3.67 (dd, *J* = 7.6, 7.6 Hz, 1H, 5''-H), 3.86 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.00–4.05 (m, 1H, 5''-H), 4.15–4.22 (m, 1H, 4''-H), 4.43 (s, 2H, $CH_2$ of DMB), 6.79–6.89 (m, 3H, aryl H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 7.2 (C-2'), 16.7 (2-$CH_3$), 25.3 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 33.6 (C-2), 34.4 (C-3), 37.5 (C-1'), 55.7 ($OCH_3$), 55.9 ($OCH_3$), 67.6 (C-5''), 68.3 (C-4), 72.8 ($CH_2$ of DMB), 77.6 (C-1), 79.7 (C-4''), 108.8 ($C(CH_3)_2$), 110.8, 111.0, 120.2, 130.7, 148.5, 149.0 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{21}H_{34}NaO_6$: 405.22531, found 405.22518.

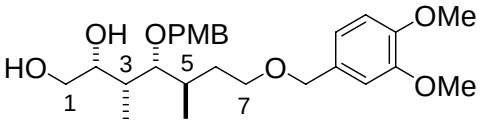
**(4*R*)-4-{(1*S*,2*R*,3*R*)-5-[(3,4-Dimethoxybenzyl)oxy]-2-[(4-methoxybenzyl)oxy]-1,3-dimethylpentyl}-2,2-dimethyl-1,3-dioxolane (3-53)**




To a solution of alcohol **3-52** (0.96 g, 2.5 mmol) in DMF (5 mL) was added potassium hydride (0.86 g of (~35%) dispersion in mineral oil, 7.5 mmol) at 0 °C (ice bath). The reaction mixture was stirred at this temperature for 30 min and then treated with 4-methoxybenzylbromide (1.87 g, 10 mmol). After stirring for 2 h at 0 °C saturated $NH_4Cl$ solution was added and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1→4:1) afforded compound **3-53** (1.10 g, 88% yield) as a colorless oil. $\mathbf{R_f}$ = 0.92 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = –5.6 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 3H, 2'-H), 1.03 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 1.31 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.80–2.01 (m, 3H, 1'-H, 3-H, 2-H), 3.05–3.09 (m, 1H, 1-H), 3.43–3.55 (m, 2H, 4-H), 3.61 (dd, *J* = 7.7, 7.7 Hz, 1H, 5''-H), 3.78 (s, 3H, $OCH_3$), 3.86 (s, 6H, $OCH_3$), 3.89–3.94 (m, 1H, 5''-H), 4.02–4.09 (m, 1H, 4''-H), 4.37–4.43 (m, 4H, $CH_2$ of DMB and PMB), 6.79–6.91 (m, 5H, aryl H), 7.24 (d, *J* = 8.3 Hz, 2H, aryl

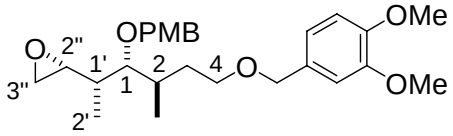
H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 10.8 (C-2'), 16.6 (2-$CH_3$), 25.3 (C($CH_3$)$_2$), 26.7 (C($CH_3$)$_2$), 32.4 (C-2), 32.9 (C-3), 38.5 (C-1'), 55.3 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 67.9 (C-5''), 68.5 (C-4), 72.8 ($CH_2$ of DMB), 73.3 ($CH_2$ of PMB), 78.3 (C-1), 83.7 (C-4''), 108.5 ($C$($CH_3$)$_2$), 110.8, 110.9, 113.7, 113.9, 128.6, 129.0, 130.9, 131.1, 148.5, 149.0, 159.0 (aryl C); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{29}H_{42}NaO_7$: 525.28227, found 525.28224.

### (2*R*,3*R*,4*R*,5*R*)-7-[(3,4-Dimethoxybenzyl)oxy]-4-[(4-methoxybenzyl)oxy]-3,5-dimethylheptane-1,2-diol (3-54)




$CuCl_2$·$2H_2O$ (3.07 g, 18.0 mmol, 10 equiv) was added to a solution of acetal **3-53** (0.92 g, 1.8 mmol) in $CH_3CN$ (50 mL) at –10 °C. The reaction mixture was stirred for 20 h at –5 °C, treated with saturated $NH_4Cl$ solution (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water, saturated $NH_4Cl$ solution and saturated NaCl solution, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1→1:1→0:1) to give diol **3-54** (0.76 g, 91%) as a colorless oil. $\mathbf{R_f}$ = 0.38 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = –4.1 (*c* 1.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.92–0.96 (m, 6H, 3-$CH_3$, 5-$CH_3$), 1.40–1.51 (m, 1H, 6-H), 1.76–1.87 (m, 2H, 5-H, 6-H), 1.88–1.97 (m, 1H, 3-H), 2.19 (br s, 1H, OH), 3.02 (br s, 1H, OH), 3.37–3.40 (m, 1H, 4-H), 3.43–3.55 (m, 4H, 7-H, 1-H, 2-H), 3.75–3.83 (m, 4H, 1-H, $OCH_3$), 3.83–3.87 (m, 6H, $OCH_3$), 4.38–4.46 (m, 3H, $CH_2$ of DMB, $CH_2$ of PMB), 4.57 (d, *J* = 10.9 Hz, 1H, $CH_2$ of PMB), 6.79–6.88 (m, 5H, aryl H), 7.24 (d, *J* = 8.6 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.7 (3-$CH_3$), 16.4 (5-$CH_3$), 32.4 (C-5), 32.4 (C-6), 36.7 (C-3), 55.2 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 65.1 (C-1), 68.3 (C-7), 72.8 ($CH_2$ of DMB), 73.0 ($CH_2$ of PMB), 86.2 (C-2), 110.8, 111.1, 113.8, 120.2, 129.2, 130.3, 130.9, 148.5, 148.9, 159.2 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{38}NaO_7$: 485.25097, found 485.25080.

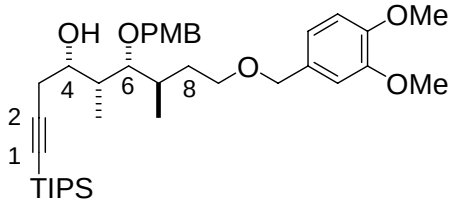
### (2*R*)-2-{(1*S*,2*R*,3*R*)-5-[(3,4-Dimethoxybenzyl)oxy]-2-[(4-methoxybenzyl)oxy]-1,3-dimethylpentyl}oxirane (3-55)




To a solution of diol **3-54** (694 mg, 1.5 mmol) in THF (20 mL) at 0 °C was added NaH (60% wt. in mineral oil, 180 mg, 4.5 mmol, 3.0 equiv). The resulting mixture was warmed to room temperature and stirred for 40 min. The mixture was cooled to 0 °C before N-(2,4,6-triisopropylbenzenesulfonyl)imidazole (**3-41**) (552 mg, 1.65 mmol, 1.1 equiv) was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with water (10 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over

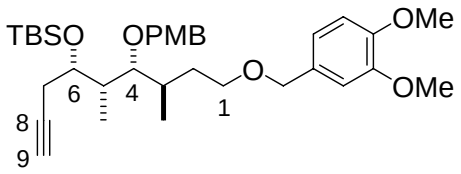
$MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate/petroleum ether, 1:10) provided epoxide **3-55** (612 mg, 2.58 mmol, 92% yield) as a colorless oil. $\mathbf{R_f}$ = 0.21 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +2.0 (*c* 1.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 3H, 2'-H), 1.09 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 1.38–1.53 (m, 2H, 3-H, 1'-H), 1.88–2.01 (m, 2H, 3-H, 2-H), 2.53–2.57 (m, 1H, 3''-H), 2.68–2.72 (m, 1H, 3''-H), 2.82–2.87 (m, 1H, 2''-H), 3.17–3.21 (m, 1H, CH(OPMB)), 3.42–3.56 (m, 2H, $CH_2$ODMB), 3.78 (s, 3H, $OCH_3$), 3.85–3.88 (m, 6H, $OCH_3$), 4.41 (dd, *J* = 17.9, 11.6 Hz, 2H, $CH_2$ of DMB), 4.50 (dd, *J* = 17.7, 10.9 Hz, 2H, $CH_2$ of DMB), 6.79–6.89 (m, 5H, aryl H), 7.25 (d, *J* = 8.6 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.1 (C-2'), 16.7 (2-$CH_3$), 32.0 (C-3), 32.9 (C-2), 39.2 (C-1'), 47.3 (C-3''), 55.2 (C-2''), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.4 ($CH_2$ODMB), 72.8 ($CH_2$ of DMB), 74.1 ($CH_2$ of PMB), 85.6 (CH(OPMB)), 110.8, 110.9, 113.7, 120.1, 129.1, 130.8, 131.1, 148.5, 148.9, 159.1 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{36}NaO_6$: 467.24041, found 467.24024.

**(4*S*,5*R*,6*R*,7*R*)-9-[(3,4-Dimethoxybenzyl)oxy]-6-[(4-methoxybenzyl)oxy]-5,7-dimethyl-1-(triisopropylsilyl)non-1-yn-4-ol (3-56)**




*n*BuLi (0.73 mL, 2.5 M in hexane, 1.83 mmol) was added to a solution of (triisopropylsilyl)acetylene (0.43 mL, 1.91 mmol) in THF (2 mL) at –78 °C in a dropwise fashion. The acetylide solution was stirred at –78 °C for 1 h before a solution of $BF_3{\cdot}OEt_2$ (0.46 mL, 3.8 mmol) was added. Stirring was continued for 50 min at –78 °C. Then, a solution of epoxide **3-55** (0.28 g, 0.63 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at –78 °C for 25 min and then quenched with saturated $NH_4Cl$ solution. The layers were separated and the aqueous layer was extracted twice with $Et_2O$. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil, which was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to furnish alcohol **3-56** (0.315 g) in 80% yield. $\mathbf{R_f}$ = 0.63 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –20.9 (*c* 1.6, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.90–0.96 (m, 6H, 7-$CH_3$, 5-$CH_3$), 0.99–1.09 (m, 21H, Si(C*H*(C*H*$_3$)$_2$), 1.40–1.51 (m, 1H, 8-H), 1.91–2.01 (m, 1H, 8-H), 2.04–2.16 (m, 2H, 5-H, 7-H), 2.33–2.52 (m, 2H, 3-H), 3.05 (br s, 1H, OH), 3.36–3.41 (m, 1H, 6-H), 3.45–3.58 (m, 2H, 9-H), 3.77 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 3.88–3.94 (m, 1H, 4-H), 4.38–4.47 (m, 3H, $CH_2$ of DMB, $CH_2$ of PMB), 4.59 (d, *J* = 10.4 Hz, 1H, $CH_2$ of PMB), 6.79–6.89 (m, 5H, aryl H), 7.24 (d, *J* = 8.3 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 6.8 (5-$CH_3$), 11.1 (*C*H($CH_3$)$_2$), 16.0 (7-$CH_3$), 18.6 (CH(*C*$H_3$)$_2$), 25.9 (C-3), 32.5 (C-8), 32.6 (C-7), 37.1 (C-5), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 68.2 (C-9), 72.7 (C-4), 73.1 ($CH_2$ of DMB), 82.6 (C-6), 87.4 (C-1), 105.2 (C-2), 110.8, 110.9, 113.8, 120.1, 129.3, 130.2, 131.0, 148.5, 148.9, 159.2 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{37}H_{58}NaO_6Si$: 649.38949, found 649.38966.

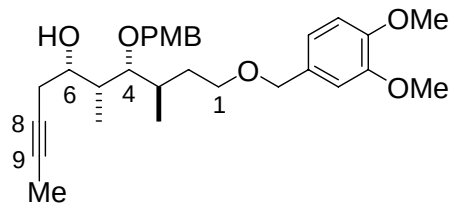
**_tert_-Butyl[((1*S*)-1-{(1*S*,2*R*,3*R*)-5-[(3,4-dimethoxybenzyl)oxy]-2-[(4-methoxybenzyl)oxy]-1,3-dimethylpentyl}but-3-ynyl)oxy]dimethylsilane (3-58)**




**a)** **TIPS deprotection:** To a solution of alcohol **3-56** (0.30 g, 0.48 mmol) in THF (1 mL) was added TBAF (1 mL, 1 M in THF, 1.0 mmol) at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1→2:1) afforded terminal alkyne **3-57** (221 mg, 98% yield) which was used directly in the next step. TLC (petroleum ether/EtOAc, 2:1), $R_f = 0.46$.

**b)** **TBS protection:** A solution of alkyne **3-57** (0.217 g, 0.46 mmol) in $CH_2Cl_2$ (4 mL) was cooled to –50 °C. Then 2,6-lutidine (0.214 mL, 1.84 mmol) followed by TBSOTf (0.211 mL, 0.92 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was treated with water and extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1) afforded silyl ether **3-58** (0.247 g, 92% yield) as a colorless oil.
**$R_f$** = 0.57 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = –1.8 (*c* 1.2, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (m, 3H, $Si(CH_3)_2$), 0.07 (m, 3H, $Si(CH_3)_2$), 0.91 (s, 9H, $Si(C(CH_3)_3)$), 0.98–1.03 (m, 6H, 3-$CH_3$, 5-$CH_3$), 1.44–1.51 (m, 1H, 2-H), 1.89–2.13 (m, 4H, 2-H, 3-H, 9-H, 5-H), 2.28–2.43 (m, 2H, 7-H), 3.25–3.31 (m, 1H, 4-H), 3.48–3.57 (m, 2H, 1-H), 3.77–3.89 (m, 10H, 6-H, $OCH_3$), 4.38–4.56 (m, 4H, $CH_2$ of DMB and PMB), 6.80–6.91 (m, 5H, aryl H), 7.26 (d, *J* = 8.6 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.7 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), 9.8 (5-$CH_3$), 17.2 (3-$CH_3$), 18.0 ($Si(C(CH_3)_3)$), 24.5 (C-7), 25.8 ($Si(C(CH_3)_3)$), 30.8 (C-2), 32.3 (C-3), 39.7 (C-5), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 68.4 (C-1), 70.2 (C-9), 71.8 (C-6), 72.5 ($CH_2$ of DMB), 74.1 ($CH_2$ of DMB), 81.8 (C-8), 84.3 (C-4), 110.8, 110.9, 113.6, 120.0, 128.9, 131.2, 131.3, 148.3, 148.9, 158.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{34}H_{52}NaO_6Si$: 607.34254, found 607.34227.

**(5*S*,6*R*,7*R*,8*R*)-10-[(3,4-Dimethoxybenzyl)oxy]-7-[(4-methoxybenzyl)oxy]-6,8-dimethyldec-2-yn-5-ol (3-60)**

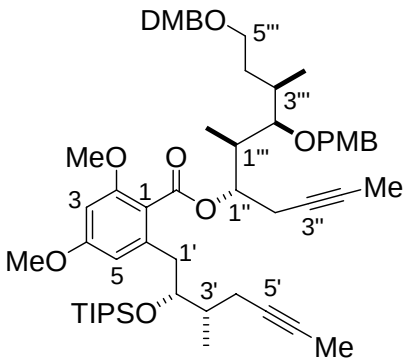



**a)** **Methylation:** To a solution of alkyne **3-58** (210 mg, 0.36 mmol) in THF (5 mL) was added *n*BuLi (26 µL, 2.5 M solution in hexane, 0.65 mmol, 1.8 equiv) dropwise at –78 °C.

Stirring was continued for 1 h at –78 °C before methyl iodide (140 µL, 2.2 mmol) was added at –78 °C. The reaction mixture was allowed to warm to room temperature over 4 h. After quenching with water (3 mL), all volatiles were removed in vacuo and the residue was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to furnish the propyne derivative **3-59** (213 mg, 99% yield), which was used directly in the next step. TLC (petroleum ether/EtOAc, 4:1), $R_f = 0.62$.

**b) TBS deprotection:** To a solution of silyl ether **3-59** (209 mg, 0.35 mmol) in THF (1 mL) was added TBAF (1.5 mL, 1 M in THF) at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 2:1→1:1) afforded alcohol **3-60** (166 mg, 98% yield) as a colorless oil. $\mathbf{R_f} = 0.54$ (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D} = –20.0$ (*c* 1.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.90–0.98 (m, 6H, 3-$CH_3$, 6-$CH_3$), 1.42–1.53 (m, 1H, 2-H), 1.75–1.78 (m, 3H, 10-H), 1.90–2.08 (m, 3H, 2-H, 3-H, 5-H), 2.21–2.39 (m, 2H, 7-H), 3.36–3.41 (m, 1H, 4-H), 3.49–3.59 (m, 2H, 1-H), 3.78 (s, 3H, $OCH_3$), 3.82–3.87 (m, 7H, 6-H, $OCH_3$), 4.39–4.48 (m, 3H, $CH_2$ of DMB and PMB), 4.57 (d, *J* = 10.6 Hz, 1H, $CH_2$ of PMB), 6.80–6.90 (m, 5H, aryl H), 7.24 (d, *J* = 7.1 Hz, 2H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 3.5 (C≡C*C*$H_3$), 7.4 (5-$CH_3$), 16.3 (3-$CH_3$), 25.0 (C-7), 32.3 (C-2), 32.6 (C-3), 37.8 (C-5), 55.2 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.4 (C-1), 72.8 ($CH_2$ of DMB), 73.1 ($CH_2$ of DMB), 73.9 (C-6), 75.8 (C-8), 77.7 (C-9), 86.8 (C-4), 110.8, 111.0, 113.8,120.2, 129.3, 130.4, 131.0, 148.5, 149.0, 159.2 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{29}H_{40}NaO_6$: 507.27171, found 507.27139.

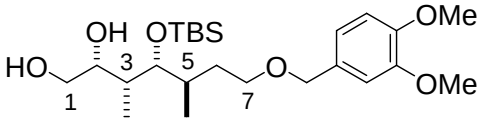
**Ester 3-64**




A solution of alcohol **3-60** (26 mg, 0.053 mmol) in anhydrous DMF (0.5 mL) was stirred in the presence of sodium hydride (60% wt. in mineral oil, 2.5 mg, 0.064 mmol, 1.2 equiv) at 0 °C for 10 min and for a further 1 h at room temperature. In a separate flask, to a solution of acid **3-50** (42 mg, 0.09 mmol) in anhydrous DMF (0.7 mL) was added CDI (18 mg, 0.11 mmol), and the reaction mixture allowed to stir for 4 h at 50 °C. Then, the solution of the imidazolide derivative of acid **3-63** (analyzed by LC-MS) was cooled to 0 °C and added to the above solution of the sodium salt of alcohol **3-60** at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 days. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed

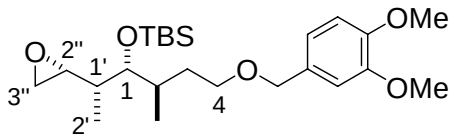
with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo to provide ester **3-64** (17 mg, 35% yield) as a colorless oil. $\mathbf{R_f}$ = 0.35 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +6.8 (*c* 1.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.95–1.03 (m, 27H, 3'''-$CH_3$, 1'''-$CH_3$, Si(CH($CH_3$)$_2$)$_3$), 1.06 (d, *J* = 6.6 Hz, 3H, 3'-$CH_3$), 1.46–1.55 (m, 1H, 4'''-H), 1.72 (s, 3H, C≡C$CH_3$), 1.75 (s, 3H, C≡C$CH_3$), 1.87–2.09 (m, 4H, 4'''-H, 3'''-H, 3'-H, 4'-H), 2.12–2.22 (m, 1H, 4'-H), 2.30–2.39 (m, 1H, 1'''-H), 2.57–2.74 (m, 4H, 2''-H, 1'-H), 3.28–3.33 (m, 1H, CH(OPMB)), 3.46–3.59 (m, 2H, $CH_2$ODMB), 3.74 (s, 3H, $OCH_3$), 3.77–3.79 (m, 6H, $OCH_3$), 3.85–3.88 (m, 6H, $OCH_3$), 4.24–4.31 (m, 1H, CH(OTIPS)), 4.38–4.54 (m, 4H, $CH_2$ of DMB and PMB), 5.10–5.16 (m, 1H, 1''-H), 6.30 (s, 1H, 5-H), 6.50 (s, 1H, 3-H), 6.79–6.90 (m, 5H, aryl H), 7.25 (d, J = 8.6 Hz, 2H, aryl H of PMB); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 3.5 (C≡C$CH_3$), 3.6 (C≡C$CH_3$), 10.0 (1'''-$CH_3$), 12.9 (*C*H($CH_3$)$_2$), 14.6 (3'-$CH_3$), 17.2 (3'''-$CH_3$), 18.1 (CH(*C*$H_3$)$_2$), 18.2 (CH(*C*$H_3$)$_2$), 22.1 (C≡C*C*$H_2$), 22.2 (C≡C*C*$H_2$), 31.2 (C-4'''), 32.9 (C-3'''), 36.2 (C-1'), 37.5 (C-1'''), 38.8 (C-3'), 55.3 ($OCH_3$), 55.6 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.8 (C-5'''), 72.6 ($CH_2$ of DMB), 74.1 ($CH_3$*C*≡C), 74.6 ($CH_3$*C*≡C), 75.3 (C-2'), 76.6 ($CH_2$*C*≡C), 78.0 ($CH_2$*C*≡C), 78.1 (C-1''), 83.9 (C-2'''), 96.7 (C-3), 106.9 (C-5), 110.8 (ar of DMB), 110.9 (ar of DMB), 113.7, 117.7 (C-1), 120.1 (ar of DMB), 128.9, 131.1, 131.3 (ar of DMB), 139.1 (C-6), 148.4 (ar of DMB), 148.9 (ar of DMB), 157.8 (C-4), 159.0, 160.8 (C-2), 167.8 ($CO_2$R);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{55}H_{80}NaO_{10}Si$: 951.54130, found 951.54063.

**(2*R*,3*R*,4*R*,5*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(3,4-dimethoxybenzyl)oxy]-3,5-dimethylheptane-1,2-diol (3-65)**



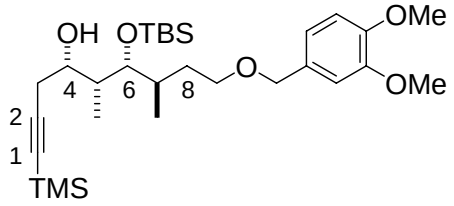

$CuCl_2$·$2H_2O$ (7.31 g, 43.0 mmol, 10 equiv) was added to a solution of acetal **3-51** (2.14 g, 4.3 mmol) in $CH_3CN$ (100 mL) at –10 °C. The reaction mixture was stirred for 20 h at –5 °C, treated with saturated $NH_4Cl$ solution (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water, saturated $NH_4Cl$ solution and saturated NaCl solution, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1→1:1) to give diol **3-65** (1.89 g, 96%) as a colorless oil. $\mathbf{R_f}$ = 0.61 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +1.5 (*c* 2.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, Si($CH_3$)$_2$), 0.84–0.93 (m, 15H, Si(C($CH_3$)$_3$), 3-$CH_3$, 5-$CH_3$), 1.26–1.38 (m, 1H, 6-H), 1.63–1.71 (m, 1H, 5-H), 1.76–1.97 (m, 2H, 6-H, 3-H), 2.71 (br s, 2H, OH), 3.38–3.55 (m, 5H, 7-H, 4-H, 1-H, 2-H), 3.61 (dd, *J* = 3.5, 3.5 Hz, 1H, 1-H), 3.86 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.41 (dd, *J* = 20.7, 11.6 Hz, 2H, $CH_2$ of DMB), 6.79–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.3 (Si($CH_3$)$_2$), –3.9 (Si($CH_3$)$_2$), 10.4 (3-$CH_3$), 17.7 (5-$CH_3$), 18.2 (Si(*C*($CH_3$)$_3$)), 26.0 (Si(C(*C*$H_3$)$_3$)), 32.6 (C-5), 34.1 (C-6), 38.8 (C-3), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 65.4 (C-1), 68.4 (C-7), 73.0 ($CH_2$ of DMB), 78.0 (C-2), 110.8, 111.1, 120.3, 130.7, 148.6, 149.0 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{24}H_{44}NaO_6Si$: 479.2799, found 479.2801.

**_tert_-Butyl[((1_R_,2_R_)-4-[(3,4-dimethoxybenzyl)oxy]-2-methyl-1-{(1_R_)-1-[(2_R_)-oxiran-2-yl]ethyl}butyl)oxy]-dimethylsilane (3-66)**




To a solution of diol **3-65** (1.23 g, 2.7 mmol) in THF (50 mL) at 0 °C was added NaH (60% wt. in mineral oil, 0.324 g, 8.1 mol, 3.0 equiv). The resulting mixture was warmed to room temperature and stirred for 40 min. The mixture was cooled to 0 °C before N-(2,4,6-triisopropylbenzenesulfonyl)imidazole (**3-41**) (1.0 g, 3.0 mmol, 1.1 equiv) was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with water (20 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate/petroleum ether, 1:10) provided epoxide **3-66** (1.132 g, 2.58 mmol, 96% yield) as a colorless oil. $\mathbf{R_f}$ = 0.49 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +4.4 (*c* 1.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.85–0.93 (m, 12H, $Si(C(CH_3)_3)$, 2'-H), 1.04 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 1.28–1.38 (m, 2H, 3-H, 1'-H), 1.76–1.85 (m, 2H, 3-H, 2-H), 2.50–2.54 (m, 1H, 3''-H), 2.69–2.73 (m, 1H, 3''-H), 2.78–2.83 (m, 1H, 2''-H), 3.38-3.54 (m, 3H, $CH_2$ODMB, CH(OTBS)), 3.85 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.41 (dd, *J* = 20.0, 11.6 Hz, 2H, $CH_2$ of DMB), 6.78–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.2 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 13.0 (C-2'), 16.8 (2-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 32.1 (C-3), 34.5 (C-2), 40.3 (C-1'), 47.6 (C-3''), 55.7 (C-2''), 55.9 (2C, $OCH_3$), 68.5 ($CH_2$ODMB), 72.8 ($CH_2$ of DMB), 77.9 (CH(OTBS)), 110.8, 110.9, 120.1, 131.1, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{24}H_{42}NaO_5Si$: 461.2694, found 461.2696

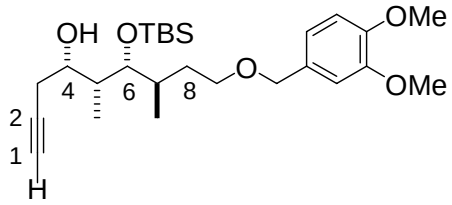
**(4_S_,5_R_,6_R_,7_R_)-6-{[_tert_-Butyl(dimethyl)silyl]oxy}-9-[(3,4-dimethoxybenzyl)oxy]-5,7-dimethyl-1-(trimethylsilyl)non-1-yn-4-ol (3-67)**




*n*BuLi (0.96 mL, 2.5 M in hexane, 2.4 mmol) was added to a solution of (trimethylsilyl)acetylene (0.34 mL, 2.4 mmol) in THF (10 mL) at –78 °C in a dropwise fashion. The acetylide solution was stirred at –78 °C for 1 h before a solution of $BF_3{\cdot}OEt_2$ (0.304 mL, 2.4 mmol) was added. Stirring was continued for 50 min at –78 °C. Then, a solution of epoxide **3-66** (0.526 g, 1.2 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at –78 °C for 10 min and then quenched with saturated $NH_4Cl$ solution. The layers were separated and the aqueous layer was extracted twice with $Et_2O$. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil, which was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to furnish alcohol

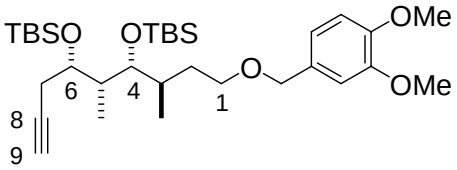
**3-67** (0.532 g) in 83% yield. $\mathbf{R_f}$ = 0.64 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –8.1 (*c* 2.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.12 (s, 9H, $Si(CH_3)_3$), 0.85–0.93 (m, 15H, $Si(C(CH_3)_3)$, 7-$CH_3$, 5-$CH_3$), 1.30–1.41 (m, 1H, 8-H), 1.72–1.81 (m, 1H, 8-H), 1.85–1.93 (m, 2H, 5-H, 7-H), 2.38–2.42 (m, 2H, 3-H), 3.40–3.53 (m, 2H, 9-H), 3.63–3.67 (m, 1H, 6-H), 3.78–3.84 (m, 1H, 4-H), 3.85 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.41 (dd, *J* = 21.2, 11.6 Hz, 2H, $CH_2$ of DMB), 6.78–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.4 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 0.0 ($Si(CH_3)_3$), 8.9 (5-$CH_3$), 16.4 (7-$CH_3$), 18.2 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 26.4 (C-3), 32.7 (C-8), 35.0 (C-7), 39.0 (C-5), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 68.4 (C-9), 72.4 (C-4), 72.8 ($CH_2$ of DMB), 78.1 (C-6), 87.0 (C-1), 103.7 (C-2), 110.8, 110.9, 120.1, 131.0, 148.5, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{29}H_{52}NaO_5Si_2$: 559.3246, found 559.3247.

### ((4*S*,5*R*,6*R*,7*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-[(3,4-dimethoxybenzyl)oxy]-5,7-dimethylnon-1-yn-4-ol (3-68)



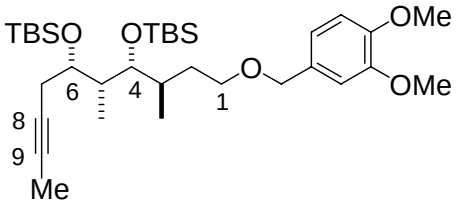

To a solution of alcohol **3-67** (0.53 g, 0.99 mmol) in methanol (20 mL) was added anhydrous $K_2CO_3$ (0.69 g, 5 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with water (10 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (ethyl acetate/petroleum ether, 1:4) provided alcohol **3-68** (0.458 g, 99% yield) as a colorless oil. $\mathbf{R_f}$ = 0.58 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –5.9 (*c* 2.9, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.86–0.94 (m, 15H, $Si(C(CH_3)_3)$, 7-$CH_3$, 5-$CH_3$), 1.32–1.41 (m, 1H, 8-H), 1.73–1.82 (m, 1H, 8-H), 1.83–1.94 (m, 2H, 5-H, 7-H), 1.98 (dd, *J* = 2.5, 2.5 Hz, 1H, 1-H), 2.28–2.41 (m, 2H, 3-H), 2.55 (d, *J* = 3.0 Hz, 1H, OH), 3.39–3.54 (m, 2H, 9-H), 3.64–3.69 (m, 1H, 6-H), 3.83–3.89 (m, 7H, 4-H, $OCH_3$), 4.42 (dd, *J* = 22.2, 11.6 Hz, 2H, $CH_2$ of DMB), 6.79–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.4 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 8.9 (5-$CH_3$), 16.7 (7-$CH_3$), 18.2 ($Si(C(CH_3)_3)$), 25.0 (C-3), 26.0 ($Si(C(CH_3)_3)$), 32.7 (C-8), 34.8 (C-7), 39.3 (C-5), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.4 (C-9), 70.3 (C-1), 72.2 (C-4), 72.9 ($CH_2$ of DMB), 78.3 (C-6), 81.4 (C-2), 110.8, 111.0, 120.2, 130.9, 148.5, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{26}H_{44}NaO_5Si$: 487.2850, found 487.2849.

### 4-[({(3*R*,4*R*,5*R*,6*S*)-4,6-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3,5-dimethyl-8-nonynyl}oxy)methyl]-1,2-bis(methyloxy)benzene (3-69)




A solution of alcohol **3-68** (0.456 g, 0.98 mmol) in $CH_2Cl_2$ (5 mL) was cooled to –50 °C. Then 2,6-lutidine (0.341 ml, 2.94 mmol) followed by TBSOTf (0.296 ml, 1.27 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was treated with water and extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 20:1) afforded bis-silyl ether **3-69** (0.538 g, 95% yield) as a colorless oil. $\mathbf{R_f}$ = 0.70 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +8.4 (*c* 2.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01–0.09 (m, 12H, $Si(CH_3)_2$), 0.86–0.95 (m, 24H, $Si(C(CH_3)_3)$, 3-$CH_3$, 5-$CH_3$), 1.31–1.41 (m, 1H, 2-H), 1.75–1.89 (m, 2H, 2-H, 3-H), 1.91 (dd, *J* = 2.5, 2.5 Hz, 9-H), 1.93–2.01 (m, 1H, 5-H), 2.27–2.43 (m, 2H, 7-H), 3.40–3.55 (m, 3H, 1-H, 4-H), 3.74–3.81 (m, 1H, 6-H), 3.86 (s, 1H, $OCH_3$), 3.87 (s, 1H, $OCH_3$), 4.43 (dd, *J* = 27.3, 11.6 Hz, 2H, $CH_2$ of DMB), 6.79–6.90 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), –3.4 ($Si(CH_3)_2$), 10.4 (5-$CH_3$), 17.5 (3-$CH_3$), 18.1 (Si(*C*$(CH_3)_3$)), 18.5 (Si(*C*$(CH_3)_3$)), 25.4 (C-7), 25.9 (Si(C(*C*$H_3)_3$)), 26.2 (Si(C(*C*$H_3)_3$)), 31.0 (C-2), 34.1 (C-3), 40.2 (C-5), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.8 (C-1), 70.3 (C-9), 71.8 (C-6), 72.6 ($CH_2$ of DMB), 76.7 (C-4), 81.5 (C-8), 110.8, 110.9, 120.1, 131.3, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{32}H_{58}NaO_5Si_2$: 601.3715, found 601.3718.

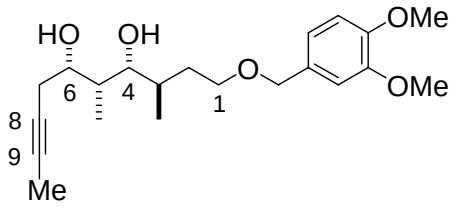
**4-[({(3*R*,4*R*,5*R*)-4,6-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3,5-dimethyl-8-decynyl}oxy)methyl]-1,2-bis(methyloxy)benzene (3-70)**




To a solution of alkyne **3-69** (0.508 g, 0.88 mmol) in THF (5 mL) was added *n*BuLi (0.63 mL, 2.5 M solution in hexane, 1.58 mmol, 1.8 equiv) dropwise at –78 °C. Stirring was continued for 1 h at –78 °C before methyl iodide (0.274 mL, 4.4 mmol) was added at –78 °C. The reaction mixture was allowed to warm to room temperature over 4 h. After quenching with water (3 mL), all volatiles were removed in vacuo and the residue was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to furnish the propyne derivative **3-70** (0.532 g, 99% yield). $\mathbf{R_f}$ = 0.75 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +3.4 (*c* 2.6, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01–0.08 (m, 12H, $Si(CH_3)_2$), 0.85–0.95 (m, 24H, $Si(C(CH_3)_3)$, 3-$CH_3$, 5-$CH_3$), 1.32–1.45 (m, 1H, 2-H), 1.73 (dd, *J* = 2.3, 2.3 Hz, 3H, C≡C$CH_3$), 1.77–1.89 (m, 2H, 2-H, 3-H), 1.90–1.97 (m, 1H, 5-H), 2.21–2.35 (m, 2H, 7-H), 3.41–3.55 (m, 3H, 1-H, 4-H), 3.68–3.76 (m, 1H, 6-H), 3.86 (s, 1H, $OCH_3$), 3.87 (s, 1H, $OCH_3$), 4.42 (dd, *J* =

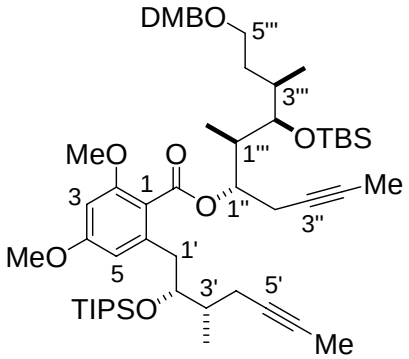
24.5, 11.6 Hz, 2H, $CH_2$ of DMB), 6.79–6.90 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), –3.4 ($Si(CH_3)_2$), 3.5 (C≡C*C*$H_3$), 10.5 (5-$CH_3$), 17.6 (3-$CH_3$), 18.1 (Si(*C*$(CH_3)_3$)), 18.5 (Si(*C*$(CH_3)_3$)), 25.7 (C-7), 25.9 (Si(C(*C*$H_3)_3$)), 26.2 (Si(C(*C*$H_3)_3$)), 30.8 (C-2), 34.1 (C-3), 40.2 (C-5), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 69.0 (C-1), 72.4 (C-6), 72.6 ($CH_2$ of DMB), 76.4 (C-8), 76.8 (C-4), 77.4 (C-9), 110.8, 110.9, 120.0, 131.3, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{60}NaO_5Si_2$: 615.3872, found 615.3870.

**(3*R*,4*R*,5*R*,6*S*)-1-[(3,4-Dimethoxybenzyl)oxy]-3,5-dimethyldec-8-yne-4,6-diol (3-71)**




To a solution of silyl ether **3-70** (0.517 mg, 0.87 mmol) in THF (3 mL) was added TBAF (4.35 mL, 1 M in THF) at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 2:1→1:1) afforded diol **3-71** (0.314 g, 99% yield) as a colorless oil. $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –10.0 (*c* 2.2, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.80–0.90 (m, 6H, 3-$CH_3$, 6-$CH_3$), 1.65–1.80 (m, 6H, 2-H, 10-H, 3-H), 1.82–1.90 (m, 1H, 5-H), 2.20–2.43 (m, 2H, 7-H), 3.42–3.51 (m, 3H, 1-H, 4-H), 3.84–3.93 (m, 7H, 6-H, $OCH_3$), 4.44 (s, 2H, $CH_2$ of DMB), 6.79–6.87 (m, 3H, aryl H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 3.5 (C≡C*C*$H_3$), 15.2 (5-$CH_3$), 17.4 (3-$CH_3$), 24.8 (C-7), 34.4 (C-2), 35.5 (C-3), 36.5 (C-5), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.2 (C-1), 73.2 ($CH_2$ of DMB), 75.7 (C-6), 75.9 (C-8), 77.3 (C-9), 80.9 (C-4), 110.9, 111.0, 120.4, 129.9, 148.7, 149.0 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{21}H_{32}NaO_5$: 387.2142, found 387.2145.

**Ester 3-73**




A solution of diol **3-71** (296 mg, 0.81 mmol) in anhydrous DMF (1.5 mL) was stirred in the presence of sodium hydride (60% wt. in mineral oil, 81 mg, 2.03 mmol, 2.5 equiv) at 0 °C for

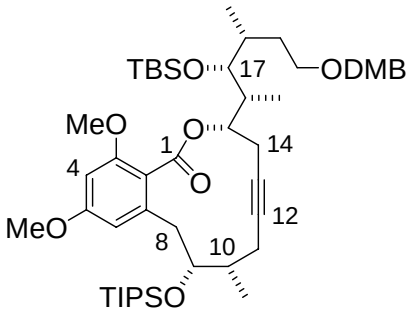
10 min and for a further 1 h at room temperature. In a separate flask, to a solution of acid **3-50** (595 mg, 1.29 mmol) in anhydrous DMF (1.7 mL) was added CDI (260 mg, 1.55 mmol), and the reaction mixture allowed to stir for 4 h at 50 °C. Then, the solution of the imidazolide derivative of acid **3-63** (analyzed by LC-MS) was cooled to 0 °C and added to the above solution of the disodium salt of diol **3-71** at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 days. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo to provide 0.87 g of crude hydroxyester **3-72**, which was used in the next step without further purification.

A solution of crude hydroxyester **3-72** (0.87 g, 0.81 mmol) in $CH_2Cl_2$ (10 mL) was cooled to –50 °C, then 2,6-lutidine (0.58 mL, 5.0 mmol) followed by TBSOTf (0.46 mL, 2.0 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h before it was treated with water. After separation of the layers, the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1→4:1) afforded ester **3-73** (0.485 g, 65% yield for 2 steps) as a colorless oil. Besides ester **3-73** some unreacted imidazolide derivative of acid **3-63** (307 mg, 30%) was isolated. $\mathbf{R_f}$ = 0.43 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +29.3 (*c* 1.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.02–0.09 (m, 6H, $Si(CH_3)_2$), 0.86–1.04 (m, 39H, 3’’’-$CH_3$, 1’’’-$CH_3$, 3’-$CH_3$, $Si(CH(CH_3)_2)_3$), 1.31–1.44 (m, 1H, 4’’’-H), 1.73 (s, 3H, C≡C$CH_3$), 1.76 (s, 3H, C≡C$CH_3$), 1.81–1.97 (m, 3H, 4’’’-H, 3’’’-H, 3’-H), 2.00-2.09 (m, 1H, 4’-H), 2.12–2.24 (m, 2H, 1’’’-H, 4’-H), 2.54–2.74 (m, 4H, 2’’-H, 1’-H), 3.42–3.60 (m, 3H, $CH_2$ODMB, CH(OTBS)), 3.74 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.84–3.89 (m, 6H, $OCH_3$ of DMB), 4.23–4.31 (m, 1H, CH(OTIPS)), 4.42 (dd, *J* = 20.5, 11.6, 2H, $CH_2$ of DMB), 4.99–5.07 (m, 1H, 1’’-H), 6.29 (s, 1H, 5-H), 6.49 (s, 1H, 3-H), 6.78–6.90 (m, 3H, aryl H of DMB);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.8 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 3.5 (C≡C$CH_3$), 3.6 (C≡C$CH_3$),10.5 (1’’’-$CH_3$), 12.9 (*C*H$(CH_3)_2$), 14.6 (3’-$CH_3$), 16.9 (Si*C*$(CH_3)_3$), 18.0 (CH(*C*$H_3)_2$), 18.1 (CH(*C*$H_3)_2$), 18.5 (3’’’-$CH_3$), 22.1 (C≡C*C*$H_2$), 22.2 (C≡C*C*$H_2$), 26.2 (Si(C(*C*$H_3)_3$)), 31.8 (C-4’’’), 34.8 (C-3’’’), 36.1 (C-1’), 37.8 (C-1’’’), 38.8 (C-3’), 55.2 ($OCH_3$), 55.6 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 68.9 (C-5’’’), 72.7 ($CH_2$ of DMB), 74.6 ($CH_3$*C*≡C), 74.8 ($CH_3$*C*≡C), 75.2 (C-2’), 76.1 ($CH_2$*C*≡C), 76.6 ($CH_2$*C*≡C), 77.9 (C-2’’’), 78.1 (C-1’’), 96.6 (C-3), 106.9 (C-5), 110.8 (ar of DMB), 110.9 (ar of DMB), 117.8 (C-1), 120.1 (ar of DMB), 131.3 (ar of DMB), 139.0 (C-6), 148.4 (ar of DMB), 148.9 (ar of DMB), 157.8 (C-4), 160.7 (C-2), 167.4 ($CO_2$R);

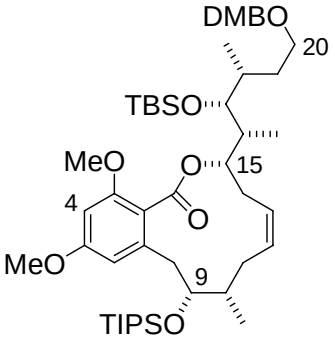
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{53}H_{86}NaO_9Si_2$: 945.5703, found 945.5707.

## Macrolactone 3-74[44]




To a solution of ester **3-73** (269 mg, 0.29 mmol) in toluene (33 mL) was added a solution of ($t$BuO)$_3$W≡CCMe$_3$ (**2-34**)[41] (13.8 mg, 0.029 mmol) in toluene (1.0 mL) and the mixture was stirred at 85 °C for 2 h. For workup, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give macrolactone **3-74** as an amorphous solid (229 mg, 91%). $\mathbf{R_f}$ = 0.56 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –29.3 ($c$ 2.9, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.02–0.09 (m, 6H, Si($CH_3$)$_2$), 0.82–1.00 (m, 39H, 18-$CH_3$, 16-$CH_3$, 10-$CH_3$, Si(C$H$(C$H_3$)$_2$)$_3$), 1.28–1.39 (m, 1H, 19-H), 1.63–1.98 (m, 5H, 19-H, 18-H, 10-H, 11-H, 16-H), 2.09–2.19 (m, 1H, 11-H), 2.35–2.45 (m, 4H, 14-H, 8-H), 3.34–3.54 (m, 3H, 20-H, 17-H), 3.73 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.84–3.89 (m, 6H, $OCH_3$ of DMB), 3.96–4.02 (m, 1H, 9-H), 4.37 (dd, $J$ = 19.7, 11.6 Hz, 2H, $CH_2$ of DMB), 5.38–5.52 (m, 1H, 15-H), 6.30 (s, 1H, 6-H), 6.40 (s, 1H, 4-H), 6.78–6.90 (m, 3H, ar of DMB); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 (Si($CH_3$)$_2$), –3.6 (Si($CH_3$)$_2$), 11.3 (16-$CH_3$), 13.0 ($C$H($CH_3$)$_2$), 17.2 (10-$CH_3$), 17.8 (CH($C$H$_3$)$_2$), 18.1 (CH($C$H$_3$)$_2$), 18.4 (18-$CH_3$), 23.3 (C≡C$C$H$_2$), 23.5 (C≡C$C$H$_2$), 26.1 (Si(C($C$H$_3$)$_3$)), 31.7 (C-19), 34.5 (C-18), 37.5 (C-16), 38.6 (C-8), 40.3 (C-10), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 55.8 ($OCH_3$), 68.6 (C-20), 72.7 ($CH_2$ of DMB), 76.0 (C-15), 77.2 (C-17), 79.7 (C-9), 81.2 ($CH_2C$≡C), 96.6 (C-3), 108.2 (C-6), 110.8 (ar of DMB), 110.9 (ar of DMB), 118.1 (C-2), 120.1 (ar of DMB), 131.2 (ar of DMB), 139.4 (C-7), 148.4 (ar of DMB), 148.9 (ar of DMB), 157.2 (C-5), 160.2 (C-3), 167.4 ($CO_2$R); **HRMS** (ESI): [M+Na]$^+$ calcd for $C_{49}H_{80}NaO_9Si_2$: 891.5233, found 891.5231.

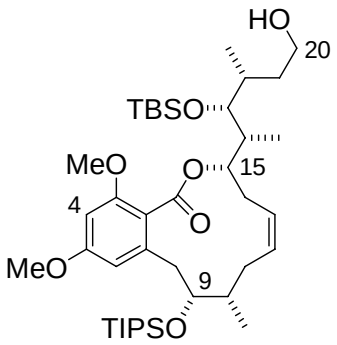
**Cycloalkene 3-75**




A 50 mL round-bottom flask was charged with macrolactone **3-74** (229 mg, 0.265 mmol) and a stir bar. EtOAc (25.0 mL) and quinoline (86 mg, 0.672 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, posioned with lead 230 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 4 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The

residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give lactone **3-75** as an amorphous solid (218 mg, 95%). $\mathbf{R_f}$ = 0.58 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +14.4 (*c* 2.9, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.07 (s, 3H, $Si(CH_3)_2$), –0.02 (s, 3H, $Si(CH_3)_2$), 0.81–0.99 (m, 39H, 18-$CH_3$, 16-$CH_3$, 10-$CH_3$, $Si(CH(CH_3)_2)_3$), 1.32–1.44 (m, 1H, 19-H), 1.57–2.05 (m, 7H, 19-H, 18-H, 10-H, 11-H, 16-H, 14-H), 2.09–2.26 (m, 2H,11-H, 8-H), 2.58–2.73 (m, 1H, 14-H), 3.07–3.16 (m, 1H, 8-H), 3.35–3.54 (m, 3H, 20-H, 17-H), 3.72 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.84–3.90 (m, 6H, $OCH_3$ of DMB), 3.92–3.99 (m, 1H, 9-H), 4.38 (dd, *J* = 16.9, 11.4 Hz, 2H, $CH_2$ of DMB), 5.19–5.27 (m, 1H, 15-H), 5.34 (dd, *J* = 11.1, 11.1 Hz, 1H, 12-H), 5.51 (dd, *J* = 11.1, 11.1 Hz, 1H, 13-H), 6.29 (s, 1H, H-6), 6.32 (s, 1H, H-4), 6.78–6.91 (m, 3H, ar of DMB); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.2 (16-$CH_3$), 12.8 ($CH(CH_3)_2$), 13.9, 17.6 (10-$CH_3$), 17.8 ($CH(CH_3)_2$), 18.0 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 26.1 ($Si(C(CH_3)_3)$), 31.1 (C-19), 32.15 ($CH_2C$=C), 32.2 ($CH_2C$=C), 34.3 (C-8), 34.4 (C-18), 39.8 (C-10), 41.0 (C-16), 55.1 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 56.1 ($OCH_3$), 68.9 (C-20), 72.8 ($CH_2$ of DMB), 73.3 (C-9), 76.5 (C-15), 77.2 (C-17), 97.2 (C-4), 109.2 (C-6), 110.8 (ar of DMB), 111.0 (ar of DMB), 116.7 (C-2), 120.2 (ar of DMB), 127.5 (C=C), 129.2 (C=C), 131.2 (ar of DMB), 140.5 (C-7), 148.4 (ar of DMB), 148.9 (ar of DMB), 158.6 (C-5), 160.4 (C-3), 166.1 ($CO_2R$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{49}H_{82}NaO_9Si_2$: 893.5390, found 893.5389.

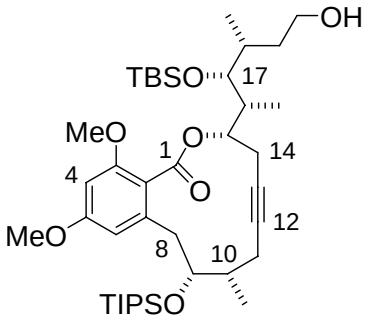
**Alcohol 3-76**




To a cooled (0 °C) solution of DMB ether **3-75** (218 mg, 0.25 mmol) in a mixture of $CH_2Cl_2/H_2O$ (20:1, 21 mL) was added DDQ (74 mg, 0.325 mmol, 1.3 equiv). The mixture was allowed to warm to room temperature and stirred for 30 min. Then it was treated with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded lactone **3-76** (167 mg, 93% yield) as a colorless oil. $\mathbf{R_f}$ = 0.50 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +9.5 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.05 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), 0.81–1.00 (m, 39H, 18-$CH_3$, 16-$CH_3$, 10-$CH_3$, $Si(CH(CH_3)_2)_3$), 1.45–1.68 (m, 2H, 19-H), 1.86–2.05 (m, 4H, 18-H, 10-H, 16-H, 14-H), 2.08–2.26 (m, 3H, 11-H, 8-H), 2.62–2.78 (m, 1H, 14-H), 3.10 (d, *J* = 13.1 Hz, 1H, 8-H), 3.41–3.47 (m, 1H, 17-H), 3.52–3.59 (m, 1 H, 20-H), 3.64–3.72 (m, 1 H, 20-H), 3.73 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.95 (d, *J* = 10.8 Hz, 1H, 9-H), 5.24–5.39 (m, 2H, 15-H, 12-H), 5.55 (dd, *J* = 11.1, 11.1 Hz, 1H, 13-H), 6.30 (s, 1H, H-6), 6.33 (s, 1H, H-4); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 11.3 (16-$CH_3$), 12.8 ($CH(CH_3)_2$), 13.9, 17.7 (10-$CH_3$), 17.8 ($CH(CH_3)_2$), 18.0 ($CH(CH_3)_2$), 18.5

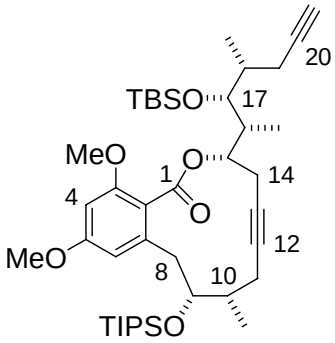
(18-$CH_3$), 26.1 (Si(C($CH_3$)$_3$)), 32.2 ($CH_2$C=C), 32.4 ($CH_2$C=C), 33.7 (C-18), 34.0 (C-19), 34.3 (C-8), 39.8 (C-10), 41.3 (C-16), 55.2 ($OCH_3$), 56.2 ($OCH_3$), 60.3 (C-20), 73.3 (C-9), 74.2 (C-15), 77.1 (C-17), 97.2 (C-4), 109.2 (C-6), 116.6 (C-2), 127.4 (C=C), 129.3 (C=C), 140.5 (C-7), 158.5 (C-5), 160.4 (C-3), 166.3 ($CO_2$R);
**HRMS** (ESI): [M+Na]+ calcd for $C_{40}H_{72}NaO_7Si_2$: 721.4889, found 721.4888.

**Alcohol 3-77**




To a cooled (0 °C) solution of DMB ether **3-74** (491 mg, 0.56 mmol) in a mixture of $CH_2Cl_2$/pH = 7 phosphate buffer (20:1, 42 mL) was added DDQ (166 mg, 0.73 mmol, 1.3 equiv). The mixture was allowed to warm to room temperature and stirred for 30 min. Then it was treated with saturated $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded alcohol **3-77** (400 mg, 99% yield) as an amorphous solid. $\mathbf{R_f}$ = 0.44 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –30.5 (*c* 1.5, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, Si($CH_3$)$_2$), 0.07 (s, 3H, Si($CH_3$)$_2$), 0.86–0.99 (m, 36H, 18-$CH_3$, 16-$CH_3$, Si(C($CH_3$)$_3$), Si($CH$($CH_3$)$_2$)$_3$), 1.04 (d, *J* = 7.1 Hz, 3H, 10-$CH_3$), 1.43–1.52 (m, 1H, 19-H), 1.59–1.70 (m, 1H, 19-H), 1.86–2.06 (m, 4H, 11-H, 10-H, 16-H), 2.10–2.19 (m, 1H, 18-H), 2.34–2.53 (m, 4H, 8-H, 14-H), 3.51-3.58 (m, 2H, 20-H, 17-H), 3.63–3.71 (m, 1H, 20-H), 3.76 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.98 (br d, *J* = 8.6 Hz, 1H, 9-H), 5.43–5.56 (m, 1H, 15-H), 6.31 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (s, *J* = 2.0 Hz, 1H, 4-H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 (Si($CH_3$)$_2$), –3.4 (Si($CH_3$)$_2$), 11.5 (16-$CH_3$), 13.0 ($CH$($CH_3$)$_2$), 15.3 (10-$CH_3$), 17.5 (Si($C$($CH_3$)$_3$)), 17.9 (CH($CH_3$)$_2$), 18.1 (CH($CH_3$)$_2$), 18.4 (18-$CH_3$), 23.3 (C-14), 23.6 (C-11), 26.1 (Si(C($CH_3$)$_3$)), 33.8 (C-18), 34.4 (C-19),37.6 (C-16), 38.6 (C-8), 40.4 (C-10), 55.2 ($OCH_3$), 55.9 ($OCH_3$), 60.4 (C-20), 74.2 (C-15), 76.5 (C-17), 79.6 (C-9), 81.3 (C-12), 96.7 (C-4), 108.3 (C-2), 118.0 (C-6), 139.5 (C-7), 157.2 (C-5), 160.3 (C-3), 167.5 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{40}H_{70}O_7Si_2Na$ 741.45523, found 741.45582.

**Alkyne 3-80**

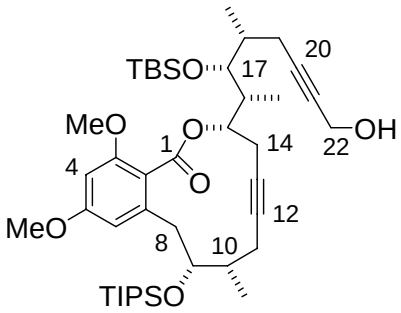



**a) Preparation of 3-methylhexanal derivative 3-78**: To a cooled (0 °C) solution of alcohol **3-77** (272 mg, 0.38 mmol) in $CH_2Cl_2$ (7 mL) was added a solution of Dess-Martin periodinane (15% wt, 1.25 mL, 0.61 mmol). After stirring for 0.5 h at 0 °C and for 2 h at room temperature, the reaction mixture was concentrated, loaded on a flash silica gel column, and eluted with petroleum ether/EtOAc, 4:1 to give 259 mg (95%) of aldehyde **3-78**, which was used directly in the next reaction. TLC (petroleum ether/EtOAc, 4:1): $R_f$ = 0.75.

**b) Alkyne 3-80:** Diethyl-1-diazo-2-oxopropylphosphonate (**3-79**)[130] (176 mg, 0.72 mmol, 2 equiv) was added to a solution of aldehyde **3-78** obtained in the previous step (259 mg, 0.36 mmol) and $K_2CO_3$ (170 mg, 1.22 mmol, 3.4 equiv) in MeOH (7 mL) followed by stirring of the mixture for 12 h at room temperature. The reaction mixture was diluted with $Et_2O$ (60 mL), washed with an aqueous solution (5%) of $NaHCO_3$ (20 mL). The layers were separated and the organic layer dried over $Na_2SO_4$. After filtration and evaporation of the solvent the residue was purified by flash chromatography (EtOAc/petroleum ether, 10:1) to give 247 mg (96%) of alkyne **3-80** as an amorphous solid. $\mathbf{R_f}$ = 0.78 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –24.1 (*c* 1.9, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.07–0.10 (m, 6H, $Si(CH_3)_2$), 0.86–0.98 (m, 33H, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 0.99–1.08 (m, 6H, 18-$CH_3$, 10-$CH_3$), 1.76–1.87 (m, 1H, 16-H), 1.90–2.20 (m, 7H, 21-H, 19-H, 10-H, 11-H, 18-H), 2.33–2.48 (m, 3H, 8-H, 14-H), 2.50–2.58 (m, 1H, 8-H), 3.54–3.59 (m, 1H, 17-H), 3.75 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.01 (br d, *J* = 8.8 Hz, 1H, 9-H), 5.42–5.54 (m, 1H, 15-H), 6.32 (d, *J* = 1.8 Hz, 1H, 6-H), 6.41 (s, *J* = 1.8 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.1 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 17.0 (10-$CH_3$), 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 21.7 (C-19), 23.3 (C-14), 23.8 (C-11), 26.2 ($Si(C(CH_3)_3)$), 36.7 (C-18), 37.6 (C-16), 38.6 (C-8), 40.8 (C-10), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 69.5 (C-21), 74.7 (C≡C), 75.3 (C-15), 77.2 (C-17), 79.6 (C≡C), 81.3 (C≡C), 83.5 (C-9), 96.7 (C-4), 108.3 (C-2), 118.1 (C-6), 139.4 (C-7), 157.2 (C-5), 160.3 (C-3), 167.4 (C-1);

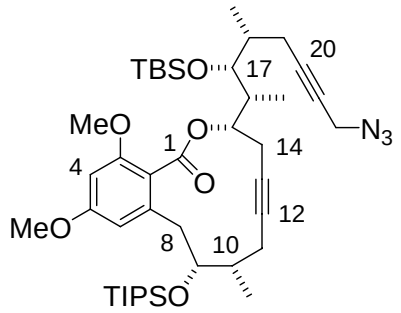
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{41}H_{68}O_6Si_2Na$ 735.44466, found 735.44503.

**Propargyl alcohol 3-81**




To a solution of alkyne **3-80** (230 mg, 0.32 mmol) in THF (9 mL) was added *t*BuLi (0.32 mL, 1.5 M solution in pentane, 0.48 mmol, 1.5 equiv) dropwise at –90 °C. Stirring was continued for 1 h at –90 °C before paraformaldehyde (96 mg, 3.2 mmol, 10 equiv) was added at –90 °C. The reaction mixture was allowed to warm to room temperature over 1 h and stirred for an additional 1 h. After quenching of the reaction with $H_2O$ (3 mL), the mixture was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1 → 4:1) of the residue afforded alcohol **3-81** (202 mg, 85% yield) as an amorphous solid. Besides product **3-81** some unreacted alkyne **3-80** (32 mg, 14%) was isolated. $\mathbf{R_f}$ = 0.59 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –21.3 (*c* 1.5, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H, $Si(CH_3)_2$), 0.86–1.07 (m, 39H, 18-$CH_3$, 10-$CH_3$, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.55–1.62 (m, 1H, 19-H), 1.76–1.85 (m, 1H, 16-H), 1.90–2.19 (m, 4H, 19-H, 10-H, 11-H, 18-H), 2.25–2.56 (m, 5H, 8-H, 11-H, 14-H), 3.53–3.60 (m, 1H, 17-H), 3.75 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.96–4.03 (m, 1H, 9-H), 4.17–4.23 (m, 2H, 22-H), 5.42–5.58 (m, 1H, 15-H), 6.32 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (s, *J* = 2.0 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.8 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 11.3 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 17.3 (10-$CH_3$), 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 21.8 (C-19), 23.3 (C-14), 23.7 (C-11), 26.1 ($Si(C(CH_3)_3)$), 36.9 (C-18), 37.5 (C-16), 38.6 (C-8), 40.7 (C-10), 51.4 (C-22), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 69.5 (C-21), 75.4 (C-15), 77.2 (C-17), 79.6 (C≡C), 79.6 (C-9), 81.4 (C≡C), 85.4 (C≡C), 96.7 (C-4), 108.2 (C-2), 118.1 (C-6), 139.4 (C-7), 157.3 (C-5), 160.3 (C-3), 167.5 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{42}H_{70}O_7Si_2Na$ 765.45523, found 765.45592.

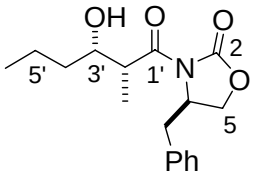
## Propargyl azide 3-82




To a stirred 0 °C solution of alcohol **3-81** (192 mg, 0.26 mmol) in THF (5 mL) was added triphenylphosphine (341 mg, 1.3 mmol, 5 equiv), DEAD (0.6 mL, 40% wt solution in toluene,

1.3 mmol, 5 equiv), and diphenylphosphoryl azide (0.29 mL, 1.3 mmol, 5 equiv). After being stirred for 5 h at room temperature the solvent was removed under reduced pressure, and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give 180 mg (90%) of azide **3-82** as an amorphous colorless solid. $\mathbf{R_f}$ = 0.77 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –21.7 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.07–0.10 (m, 6H, $Si(CH_3)_2$), 0.87–1.07 (m, 39H, 18-$CH_3$, 10-$CH_3$, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.76–1.85 (m, 1H, 16-H), 1.91–2.04 (m, 2H, 18-H, 19-H), 2.10–2.22 (m, 2H, 19-H, 10-H), 2.27–2.57 (m, 6H, 8-H, 11-H, 14-H), 3.56–3.62 (m, 1H, 17-H), 3.75 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.81–3.87 (m, 2H, 22-H), 3.96–4.04 (m, 1H, 9-H), 5.40–5.57 (m, 1H, 15-H), 6.32 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (s, *J* = 2.0 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.1 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 17.0 (10-$CH_3$), 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 22.0 (C-19), 23.3 (C-14), 23.7 (C-11), 26.1 ($Si(C(CH_3)_3)$), 36.8 (C-18), 37.6 (C-16), 38.6 (C-8), 40.3 (C-22), 40.7 (C-10), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 73.3 (C-15), 75.1 (C-17), 77.2 (C≡C), 77.2 (C≡C), 79.6 (C-9), 81.3 (C≡C), 87.1 (C≡C), 96.6 (C-4), 108.3 (C-2), 118.1 (C-6), 139.4 (C-7), 157.2 (C-5), 160.3 (C-3), 167.4 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{42}H_{69}N_3O_6Si_2Na$ 790.46171, found 790.46251.

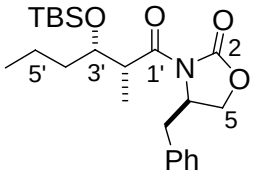
**(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-hydroxy-2-methylhexanoyl]-1,3-oxazolidin-2-one (3-85)**




To a stirred solution of (4*R*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one (**2-6**) (0.49 g, 2.1 mmol) in absolute $CH_2CI_2$ (10 mL) was added *n*$Bu_2BOTf$ (2.3 mL, 1M in $CH_2Cl_2$) dropwise to maintain the internal temperature at –5 °C. After stirring for 5 min at –5 °C, $NEt_3$ (0.37 ml, 2.63 mmol) was added dropwise, while maintaining the internal temperature at –5 °C. The solution turned from dark orange to light yellow after this addition. The reaction mixture was stirred for 2 h at 0 °C and then cooled to –78 °C before a solution of freshly distilled butyraldehyde (0.21 ml, 2.4 mmol) in $CH_2CI_2$ (1 mL) was added at –78 °C. The reaction mixture was stirred at this temperature for 1 h and then allowed to warm to 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched by addition of phosphate buffer pH = 7, (6 mL), and methanol (5 mL). The mixture was cooled to an internal temperature of –5 °C followed by the addition of 30% $H_2O_2$ (1 mL). The reaction mixture was stirred at 0 °C for 1 h. All volatiles were removed in vacuo and the residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with $H_2O$ (10 mL), saturated NaCl solution (10 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the crude aldol product, which was purified by flash chromatography (petroleum ether/EtOAc, 3:2) affording the aldol product **3-85** (512 mg, 80% yield) as a colorless oil. $\mathbf{R_f}$ = 0.4 (petroleum ether/EtOAc, 3:2); $\mathbf{[\alpha]^{20}_D}$ = –52.6 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.0 Hz, 3H, 6'-H), 1.24 (d, *J* = 7.2 Hz, 3H, 2'-$CH_3$), 1.30–1.42 (m, 2H, 4'-H, 5'-H), 1.45–1.56 (m, 2H, 4'-H, 5'-H), 2.55 (br s, 1H, 3'-OH), 2.72–2.80 (m, 1H, 5-H), 3.23 (dd, *J* = 13.4, 2.8 Hz, 1H, 5-H), 3.71–3.77 (m, 1H, 2'-H), 3.92–3.97 (m, 1H, 3'-H), 4.15–4.23 (m, 2H, $CH_2Ph$), 4.63-4.72 (m, 1H, 4-H), 7.17–7.35 (m, 5H, Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 10.3 (2'-$CH_3$), 14.0 (C-6'), 19.2 (C-

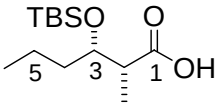
5'), 35.9 (C-4'), 37.8 (*C*$H_2$Ph), 42.1 (C-2'), 55.1 (C-4), 66.2 (C-5), 71.2 (C-3'), 127.4 (*p*CH ar Ph), 129.0 (*m*CH ar Ph), 129.4 (*o*CH ar Ph), 135.0 (*i*CH ar Ph), 153.0 (C-2), 177.6 (C-1');
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{23}NO_4Na$: 328.1519, found 328.1516.

### (4*R*)-4-Benzyl-3-((2*R*,3*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylhexanoyl)-1,3-oxazolidin-2-one (3-86)




A solution of the foregoing aldol adduct[134] **3-85** (0.48 g, 1.57 mmol) in $CH_2Cl_2$ (10 mL) was cooled to –50 °C. Then, 2,6-lutidine (0.73 mL, 6.3 mmol) followed by TBSOTf (0.51 mL, 2.2 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was treated with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1) afforded the OH-protected compound **3-86** (0.63 g, 95% yield) as a colorless solid. $\mathbf{R_f}$ = 0.78 (petroleum ether/EtOAc, 4:1); **m.p.** = 112–113 °C; $\mathbf{[\alpha]^{20}_D}$ = –57.1 (*c* 1.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.02 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), 0.84–0.94 (m, 12H, 6'-H, $Si(C(CH_3)_3)$), 1.19 (d, *J* = 6.8 Hz, 3H, 2'-$CH_3$), 1.24–1.42 (m, 2H, 4'-H, 5'-H), 1.44–1.55 (m, 2H, 4'-H, 5'-H), 2.70–2.80 (m, 1H, 5-H), 3.29 (dd, *J* = 13.4, 2.8 Hz, 1H, 5-H), 3.80–3.89 (m, 1H, 2'-H), 3.96–4.03 (m, 1H, 3'-H), 4.12–4.19 (m, 2H, $CH_2Ph$), 4.55–4.64 (m, 1H, 3-H), 7.18–7.37 (m, 5H, Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.9 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), 11.4 (2'-$CH_3$), 14.4 (C-6'), 18.0 ($Si(C(CH_3)_3)$), 18.4 (C-5'), 25.8 ($Si(C(CH_3)_3)$), 37.6 (C-4'), 37.8 ($CH_2Ph$), 42.8 (C-2'), 55.8 (C-4), 66.0 (C-5), 72.7 (C-3'), 127.3 (*p*CH ar Ph), 128.9 (*m*CH ar Ph), 129.5 (*o*CH ar Ph), 135.2 (*i*CH ar Ph), 153.1 (C-2), 175.3 (C-1');
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{23}H_{37}NNaO_4Si$: 442.2384, found 442.2384.

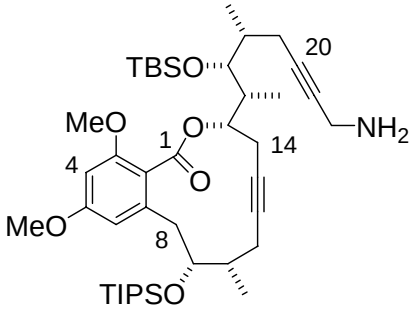
### (2*R*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylhexanoic acid (2-31)




To a stirred solution of oxazolidinone **3-86** (570 mg, 1.36 mmol) in a THF/$H_2O$ mixture (6:1, 14 mL) were added 30% aqueous $H_2O_2$ (0.8 mL, 6.0 mmol) and a solution of $LiOH{\cdot}H_2O$ (126 mg, 3.0 mmol) in $H_2O$ (2 mL) sequentially at 0 °C. After 8 h, saturated aqueous $Na_2SO_3$ solution (2 mL) was added, and stirring continued at 0 °C for a further 30 min. The solution was poured into a mixture of diethyl ether and 1N aqueous HCl. The organic phase was separated and washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc/HOAc, 4:1:0.01) of the residue afforded acid **2-31** (313 mg, 89% yield) as a colorless oil. $\mathbf{R_f}$ = 0.71 (petroleum

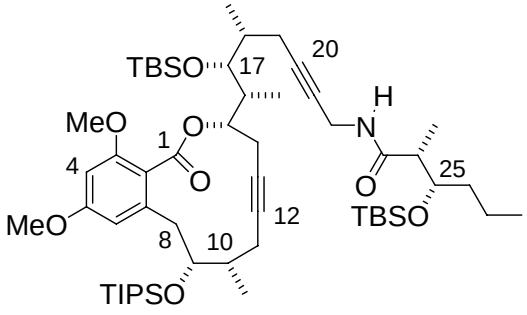
ether/EtOAc, 4:1); $[\alpha]^{20}_{D}$ = –20.5 (*c* 2.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.06 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.83–0.94 (m, 12H, 6-H, $Si(C(CH_3)_3)$), 1.11 (d, *J* = 7.1 Hz, 3H, 2-$CH_3$), 1.22–1.51 (m, 4H, 4-H, 5-H), 2.52–2.63 (m, 1H, 2-H), 3.92–4.02 (m, 1H, 3-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.8 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), 11.1 (2-$CH_3$), 14.1 (C-6), 18.0 ($Si(C(CH_3)_3)$), 18.6 (C-5), 25.7 ($Si(C(CH_3)_3)$), 36.2 (C-4), 44.4 (C-2), 73.5 (C-3), 179.0 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{13}H_{28}O_3SiNa$: 283.1699, found 283.1697.

**Propargylamine 3-83**




To a solution of the azide **3-82** (173 mg, 0.23 mmol) in THF (12 mL) were added triphenylphosphine (0.60 g, 2.30 mmol) and $H_2O$ (83 mg, 4.6 mmol). Then the mixture was refluxed for 8 h. Analysis of the reaction mixture by TLC ($CH_2Cl_2$/MeOH/$NEt_3$, 9:1:0.01; detection, molibdate solution) showed complete conversion of starting material to a product at $R_f$ 0.48. The solvent was removed in vacuo, and the resulting yellow oil (0.85 g) was purified by flash chromatography ($CH_2Cl_2$/MeOH/$NH_4OH$, 9:1:0.01; detection molibdate solution) to afford amine **3-83** (154 mg, 89%) as a colorless amorphous solid, which was used directly in the next reaction.

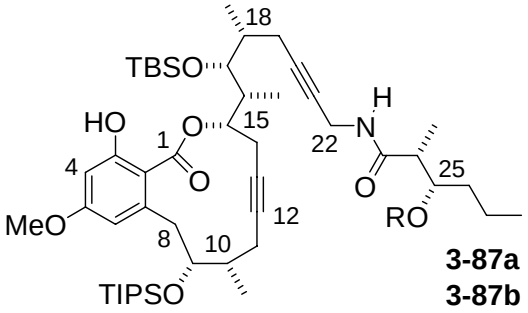
**Hexanamide 3-84**




To a solution of amine **3-83** (154 mg, 0.21 mmol, 1 equiv) in dry DMF (5 mL) were added the carboxylic acid **2-31** (87 mg, 0.34 mmol, 1.6 equiv), HBTU (159 mg, 0.42 mmol, 2 equiv), HOBt (57 mg, 0.42 mmol, 2 equiv), and N,N-diisopropylethylamine (0.36 mL, 2.1 mmol, 10 equiv). After the mixture was stirred at room temperature for 4 h, $H_2O$ (10 mL) was added and the obtained emulsion was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, filtered, and

concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1 → 4:1) to give 176 mg (85%) of amide **3-84** as a slightly yellow amorphous solid. $\mathbf{R_f}$ = 0.65 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –15.6 (*c* 4.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.07–0.10 (m, 12H, $Si(CH_3)_2$), 0.85–1.01 (m, 48H, 24-$CH_3$, 28-H, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.02–1.10 (m, 6H, 18-$CH_3$, 10-$CH_3$),1.15–1.46 (m, 4H, 26-H, 27-H, 18-H), 1.72–1.83 (m, 1H, 16-H), 1.87–2.05 (m, 3H, 10-H, 11-H), 2.09–2.19 (m, 1H, 19-H), 2.23–2.32 (m, 1H, 19-H), 2.33–2.56 (m, 5H, 8-H, 14-H, 24-H), 3.46–3.53 (m, 1H, 17-H), 3.68–3.80 (m, 8H, $OCH_3$, 25-H, 26-H), 3.94–4.04 (m, 3H, 9-H, 22-H), 5.39–5.57 (m, 1H, 15-H), 6.31 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (s, *J* = 2.0 Hz, 1H, 4-H), 6.59 (br s, 1H, NH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.1 (16-$CH_3$), 12.6 (24-$CH_3$), 13.0 ($CH(CH_3)_2$), 14.2 (C-28), 17.2 (10-$CH_3$), 17.8 ($CH(CH_3)_2$), 17.9 ($Si(C(CH_3)_3)$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 19.2 (C-27), 21.9 (C-19), 23.3 (C-14), 23.9 (C-11), 25.8 ($Si(C(CH_3)_3)$), 26.1 ($Si(C(CH_3)_3)$), 29.4 (C-22), 34.8 (C-26), 36.8 (C-18), 37.6 (C-16), 38.6 (C-8), 41.0 (C-10), 45.5 (C-24), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 74.7 (C-17), 75.6 (C-9), 76.8 (C-15), 77.1 (C-25), 77.2 (C≡C), 79.5 (C≡C), 81.3 (C≡C), 82.7 (C≡C), 96.7 (C-4), 108.3 (C-6), 118.1 (C-2), 139.4 (C-7), 157.2 (C-5), 160.2 (C-3), 167.3 (C-1), 173.5 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{55}H_{97}NO_8Si_3Na$ 1006.64142, found 1006.64065.

**2-Hydroxy-4-methoxybenzoate (3-87a) and 2-hydroxy-4-methoxybenzoate (3-87b)**




**3-87a** R = TBS (57%)
**3-87b** R = H (42%)

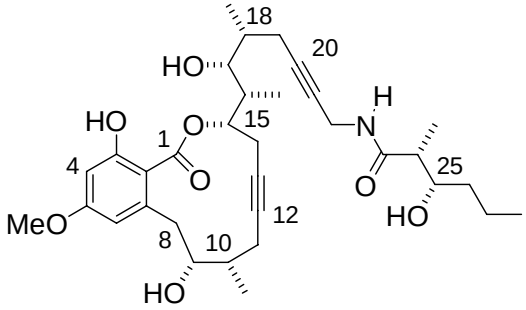
A solution of amide **3-84** (112 mg, 0.114 mmol) in $CH_2Cl_2$ (5 mL) was treated with $BCl_3$ (0.46 mL, 1.0 M in $CH_2Cl_2$, 0.46 mmol, 4 equiv) at –78 °C. The reaction was stirred for 2 h at –78 °C before a saturated solution of NaOAc (5 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/EtOAc, 9:1 → 4:1) afforded phenol **3-87a** (62.1 mg, 57% yield) and the phenol with additional TBS-deprotection **3-87b** (40 mg, 41% yield).

Compound **3-87a**:
$\mathbf{R_f}$ = 0.85 ($CH_2Cl_2$/EtOAc, 85:15); $\mathbf{[\alpha]^{20}_D}$ = +14.0 (*c* 3.1, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.04–0.10 (m, 12H, $Si(CH_3)_2$), 0.85–1.10 (m, 54H, 24-$CH_3$, 28-H, 16-$CH_3$, 18-$CH_3$, 10-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.27–1.65 (m, 4H, 26-H, 27-H), 1.74–1.87 (m, 1H, 16-H), 1.92–2.68 (m, 8H, 10-H, 11-H, 19-H, 8-H, 14-H, 24-H), 2.80–3.00 (m, 1H, 14-H), 3.45–3.53 (m, 1H, 17-H), 3.68–3.81 (m, 5H, $OCH_3$, 25-H, 26-H), 3.95–4.05 (m, 2H, 22-H), 4.16–4.28 (m, 1H, 9-H), 5.10–5.30 (m, 1H, 15-H), 6.35 (s, 2H, 6-H, 4-H), 6.62 (br s, 1H, NH), 11.26 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), 10.9 (16-$CH_3$), 12.6 (24-$CH_3$), 13.0 ($CH(CH_3)_2$), 14.2 (C-28), 16.5 (10-$CH_3$),

17.9 (Si(*C*(CH$_3$)$_3$)), 18.2 (CH(*C*H$_3$)$_2$), 18.4 (18-CH$_3$), 19.3 (C-27), 22.0 (C-19), 22.8 (C-14), 23.9 (C-11), 25.9 (Si(C(*C*H$_3$)$_3$)), 26.1 (Si(C(*C*H$_3$)$_3$)), 29.4 (C-22), 29.7, 34.8 (C-26), 37.4 (C-16), 38.6 (C-8), 45.5 (C-24), 55.2 (OCH$_3$), 74.8 (C-25), 75.0 (C-15), 75.5 (C-9), 77.2 (*C*≡C), 82.2 (C-9), 98.9 (C-4), 143.7 (C-7), 163.4 (C-5), 164.7 (C-3), 171.0 (C-1), 173.5 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{54}H_{95}NO_8SiNa$ 992.62577, found 992.62514.

Compound **3-87b**:
**R$_f$** = 0.36 ($CH_2Cl_2$/EtOAc, 85:15); **[α]$^{20}_D$** = +19.8 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.07 (3, 6H, Si(CH$_3$)$_2$), 0.85–1.10 (m, 51H, , 28-H, 16-CH$_3$, 18-CH$_3$, 10-CH$_3$, Si(C(C*H*$_3$)$_3$), Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.16 (d, *J* = 7.1 Hz, 3H, 24-CH$_3$), 1.27–1.52 (m, 4H, 26-H, 27-H), 1.75–1.90 (m, 1H, 18-H), 1.95–2.37 (m, 6H, 11-H, 19-H, 8-H, 24-H), 2.39–2.50 (m, 1H, 14-H), 2.53–2.69 (m, 1H, 10-H), 2.85–2.98 (m, 1H, 14-H), 3.15 (d, 1H, 25-OH), 3.53–3.60 (m, 1H, 17-H), 3.79 (s, 3H, OCH$_3$), 3.83–3.90 (m, 1H, 25-H), 3.96–4.04 (m, 2H, 22-H), 4.15–4.30 (m, 1H, 9-H), 5.14–5.29 (m, 1H, 15-H), 6.02 (br s, 1H, NH), 6.35 (s, 2H, 6-H, 4-H), 11.23 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 (Si(CH$_3$)$_2$), 11.0 (16-CH$_3$), 11.0 (24-CH$_3$), 13.0 (*C*H(CH$_3$)$_2$), 14.0 (C-28), 16.5 (10-CH$_3$), 17.9 (Si(*C*(CH$_3$)$_3$)), 18.2 (CH(*C*H$_3$)$_2$), 18.4 (18-CH$_3$), 19.2 (C-27), 22.0 (C-19), 22.7 (C-14), 25.9 (C-11), 26.0 (Si(C(*C*H$_3$)$_3$)), 29.5 (C-22), 35.7 (C-26), 37.4 (C-16), 44.6 (C-24), 55.2 (OCH$_3$), 71.7 (C-25), 74.6, 75.5 (C-9), 76.9 (C-15), 77.2 (*C*≡C), 82.6 (*C*≡C), 98.9 (C-4), 143.7 (C-7), 163.4 (C-5), 164.6 (C-3), 171.1 (C-1), 175.9 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{48}H_{81}NO_8Si_2Na$ 878.53929, found 878.53906.

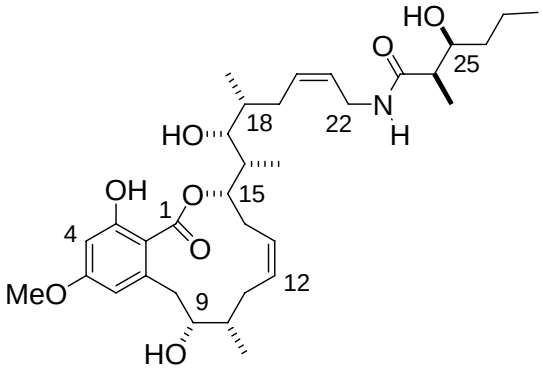
**Deprotected macrolactone 3-88**




To a stirred solution of the mixture of **3-87a** (62 mg, 0.064 mmol) and **3-87b** (40 mg, 0.046 mmol) in THF (0.8 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.6 mL). The reaction mixture was allowed to warm to –5 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 63 mg (97%) of tetraol **3-88**. **R$_f$** = 0.52 ($CH_2Cl_2$/MeOH, 9:1); **[α]$^{20}_D$** = +29.2 (*c* 0.65, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.86–0.95 (m, 9H, 16-CH$_3$, 18-CH$_3$, 28-H), 1.01 (d, *J* = 6.8 Hz, 3H, 10-CH$_3$), 1.12 (d, *J* = 7.1 Hz, 3H, 24-CH$_3$), 1.20–1.52 (m, 4H, 26-H, 27-H), 1.70–1.82 (m, 1H, 19-H), 1.84–1.94 (m, 1H, 18-H), 2.00–2.10 (m, 1H, 19-H), 2.11–2.40 (m, 6H, 8-H, 11-H, 16-H, 24-H), 2.48–2.64 (m, 2H, 14-H, 17-OH), 2.74–2.83 (m, 1H, 14-H), 2.84–2.95 (m, 1H, 10-H), 3.28 (br s, 1H, 25-OH), 3.55–3.63 (m, 1H,

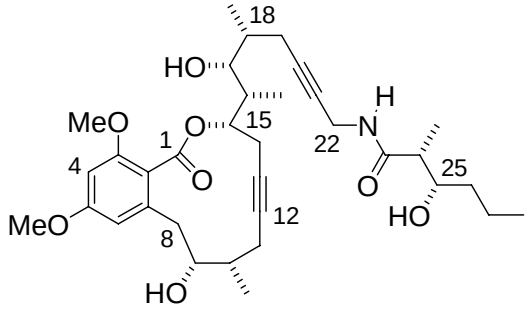
17-H), 3.69–3.76 (m, 1H, 25-H), 3.79 (s, 3H, $OCH_3$), 3.89–4.00 (m, 3H, 9-H, 22-H), 5.30–5.38 (m, 1H, 15-H), 6.35–6.46 (m, 3H, 4-H, 6-H, NH), 10.97 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.44 (16-$CH_3$), 11.1 (24-$CH_3$), 14.0 (C-28), 16.1 (18-$CH_3$), 16.4 (10-$CH_3$), 19.2 (C-27), 21.1 (C-19), 22.5 (C-14), 23.0 (C-11), 29.4 (C-22), 35.7 (C-26), 36.6 (C-18), 37.3 (C-16), 38.3 (C-8), 44.7 (C-24), 55.3 ($OCH_3$), 71.7 (C-25), 73.9 (C-17), 75.2 (C-9), 76.9 (C-15), 77.5 (*C*≡C), 79.2 (*C*≡C), 81.7 (*C*≡C), 83.1 (*C*≡C), 99.5 (C-4), 106.7 (C-2), 111.3 (C-6), 143.1 (C-7), 163.5 (C-5), 164.2 (C-3), 170.6 (C-1), 176.0 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{47}NO_8Na$ 608.31939, found 608.31943.

**Cruentaren A (1-1)**



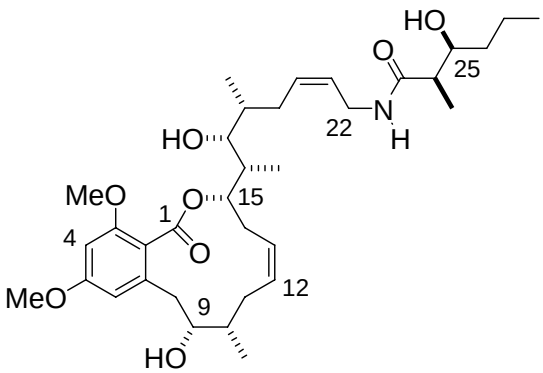

A 50 mL round-bottom flask was charged with diyne **3-88** (45 mg, 0.077 mmol) and a stir bar. EtOAc (18 mL) and quinoline (16 mg, 0.123 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, posioned with lead, 45 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give cruentaren A (**1-1**) as a colorless oil (43 mg, 95%). $\mathbf{R_f}$ = 0.44 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –3.3 (*c* 0.6, $CH_2Cl_2$); **$^1$H NMR** (600 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 7.0 Hz, 3H, 18-$CH_3$), 0.89 (d, *J* = 7.0 Hz, 3H, 16-$CH_3$), 0.92 (t, *J* = 7.1 Hz, 3H, 28-H), 1.02 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.14 (d, *J* = 7.2 Hz, 3H, 24-$CH_3$), 1.28–1.34 (m, 2H, 26-H, 27-H), 1.41–1.51 (m, 2H, 26-H, 27-H), 1.58 (br s, 1H, 25-OH), 1.70 (qddd, *J* = 6.8, 6.8, 2.3, 2.0 Hz, 1H, 18-H), 1.92–2.06 (m, 3H, 10-H, 11-H, 16-H), 2.19–2.30 (m, 4H, 8-H, 14-H, 19-H), 2.28 (dq, *J* = 7.2, 2.8 Hz, 1H, 24-H), 2.32 (dt, *J* = 14.3, 11.7 Hz, 1H, 11-H), 2.73 (br s, 1H, 17-OH), 2.82 (dt, *J* = 14.3, 11.5 Hz, 1H, 14-H), 3.12 (br s, 1H, 9-OH), 3.45 (dd, *J* = 9.2, 2.3 Hz, 1H, 17-H), 3.64 (d, *J* = 10.6 Hz, 1H, 9-H), 3.75 (dd, *J* = 12.8, 1.8 Hz, 1H, 8-H), 3.80 (s, 3H, $OCH_3$), 3.80–3.86 (m, 2H, 22-H, 25-H), 3.91 (dddd, *J* = 14.8, 7.4, 5.8, 1.5 Hz, 1H, 22-H), 5.29 (ddd, *J* = 11.7, 5.6, 2.0 Hz, 1H, 15-H), 5.38–5.42 (m , 1H, 21-H), 5.44 (ddd, *J* = 11.0, 4.5, 2.0 Hz, 1H, 13-H), 5.49 (ddd, *J* = 11.0, 2.9, 1.0 Hz, 1H, 12-H), 5.53–5.59 (m, 1H, 20-H), 6.11 (br t, *J* = 5.2 Hz, 1H, NH), 6.30 (d, *J* = 2.6 Hz, 1H, 6-H), 6.36 (d, *J* = 2.6 Hz, 1H, 4-H), 11.48 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.6 (16-$CH_3$), 11.2 (24-$CH_3$), 14.0 (C-28), 14.1 (10-$CH_3$), 16.1 (18-$CH_3$), 19.2 (C-27), 29.8 (C-14), 30.6 (C-19), 31.6 (C-11), 35.8 (C-26), 36.5 (C-22), 36.5 (C-8), 36.8 (C-18), 38.3 (C-10), 39.3 (C-16), 44.8 (C-24), 55.4 ($OCH_3$), 71.8 (C-25), 73.1 (C-9), 74.7 (C-17), 78.0 (C-15), 99.6 (C-4), 104.9 (C-2), 112.3 (C-6), 125.8 (C-13), 126.7 (C-21), 130.9 (C-20), 132.1 (C-12), 143.7 (C-7), 163.5 (C-5), 165.7 (C-3), 171.5 (C-1), 176.5 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{51}NO_8Na$ 612.35069, found 612.35108.

**Deprotected macrolactone 3-89**



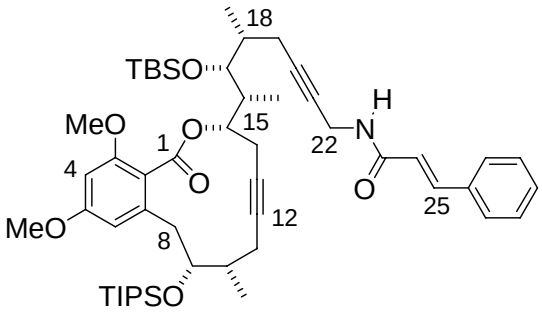

To a stirred solution of the amide **3-84** (20 mg, 0.02 mmol) in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –5 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 11.5 mg (96%) of triol **3-89**. $\mathbf{R_f}$ = 0.50 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –2.0 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3H, 28-H), 0.92–0.96 (m, 6H, 16-$CH_3$, 18-$CH_3$), 1.04 (d, *J* = 7.1 Hz, 3H, 10-$CH_3$), 1.10 (d, *J* = 7.1 Hz, 3H, 24-$CH_3$), 1.20–1.31 (m, 2H, 26-H, 27-H), 1.35–1.48 (m, 2H, 26-H, 27-H), 1.74–1.83 (m, 1H, 19-H), 1.93–2.00 (m, 2H, 18-H, 19-H), 2.05–2.13 (m, 1H, 11-H), 2.16–2.22 (m, 1H, 16-H), 2.23–2.32 (m, 2H, 11-H, 24-H), 2.38–2.54 (m, 4H, 14-H, 8-H, OH), 2.59–2.81 (m, 2H, 14-H, 10-H), 3.31 (dd, *J* = 13.6, 2.3 Hz, 1H, 17-H), 3.40 (br s, 1H, OH), 3.69 (dd, *J* = 8.2, 4.9 Hz, 1H, 25-H), 3.77–3.87 (m, 8H, 8-H, 9-H, $OCH_3$), 3.89–4.06 (m, 2H, 22-H), 5.51–5.57 (m, 1H, 15-H), 6.36 (d, *J* = 1.8 Hz, 1H, 6-H), 6.39–6.46 (m, 2H, 4-H, NH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 7.4 (16-$CH_3$), 11.0 (24-$CH_3$), 14.0 (C-28), 15.6 (18-$CH_3$), 16.2 (10-$CH_3$), 19.1 (C-27), 22.5 (C-19), 22.7 (C-14), 22.7 (C-11), 29.6 (C-22), 35.5 (C-26), 35.8, 36.0 (C-18), 38.1 (C-16), 38.1 (C-8), 44.5 (C-24), 55.5 ($OCH_3$), 55.7 ($OCH_3$), 71.6 (C-25), 75.0 (C-17), 75.4 (C-9), 77.2 (C-15), 77.6 (*C*≡C), 79.8 (*C*≡C), 81.6 (*C*≡C), 82.0 (*C*≡C), 96.7 (C-4), 106.6 (C-2), 117.8 (C-6), 138.8 (C-7), 157.0 (C-5), 161.3 (C-3), 168.6 (C-1), 176.2 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{34}H_{49}NaNO_8$ 622.33559, found 622.33581.

**3-OMe-cruentaren (3-90)**



A 10 mL round-bottom flask was charged with diyne **3-89** (11.0 mg, 0.018 mmol) and a stir bar. EtOAc (4 mL) and quinoline (3.7 mg, 0.029 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned with lead, 11 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 3-OMe-cruentaren (**3-90**) as a colorless oil (10.5 mg, 95%). $\mathbf{R_f}$ = 0.46 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +31.1 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.83–0.93 (m, 6H, 28-H, 18-$CH_3$), 0.97 (m, *J* = 6.8 Hz, 3H, 16-$CH_3$), 1.05 (d, *J* = 6.6 Hz, 3H, 10-$CH_3$), 1.12 (d, *J* = 7.3 Hz, 3H, 24-$CH_3$), 1.17–1.34 (m, 2H, 26-H, 27-H), 1.37–1.50 (m, 2H, 26-H, 27-H), 1.70–1.99 (m, 5H, 19-H, 18-H, 11-H, OH), 2.18–2.31 (m, 4H, 16-H, 8-H, 24-H), 2.35–2.52 (m, 2H, 14-H, 11-H), 2.65–2.83 (m, 2H, 14-H, OH) 2.89–2.98 (m, 1H, 10-H), 3.36 (br s, 1H, OH), 3.42–3.49 (m, 1H, 17-H), 3.71–3.78 (m, 4H, 25-H, $OCH_3$), 3.79–3.99 (m, 6H, 9-H, 22-H, $OCH_3$), 5.40 (dd, *J* = 9.7, 5.2 Hz, 1H, 15-H), 5.44–5.53 (m, 3H, 12-H, 13-H, 21-H), 5.57–5.67 (m, 1H, 20-H), 6.23 (t, *J* = 5.2 Hz, 1H, NH), 6.31–6.37 (m, 2H, 6-H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.0 (16-$CH_3$), 11.2 (24-$CH_3$), 14.0 (C-28), 16.1 (18-$CH_3$), 19.2 (C-27), 29.7 (C-14), 30.0 (C-19), 31.6 (C-11), 35.7 (C-26), 36.3 (C-22), 36.4 (C-8), 37.5 (C-18), 38.0 (C-10), 39.5 (C-16), 44.6 (C-24), 55.4 ($OCH_3$), 55.9 ($OCH_3$), 71.8 (C-25), 76.0 (C-17), 77.2 (C-9), 78.3 (C-15), 97.1 (C-4), 106.7 (C-2), 116.8 (C-6), 126.7 (C-21), 131.1 (C-20), 131.4 (C-12), 139.3 (C-7), 158.4 (C-5), 161.5 (C-3), 166.9 (C-1), 176.5 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{34}H_{53}NaNO_8$ 626.36689, found 626.36668.

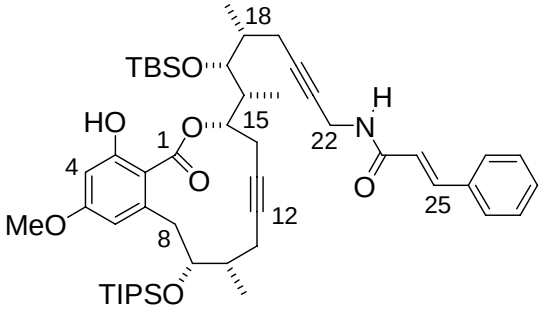
**Cinnamic acid amide 3-92a**




To a solution of amine **3-83** (20 mg, 0.027 mmol, 1 equiv) in dry DMF (2 mL) were added the *E*-cinnamic acid (**3-91a**) (6.4 mg, 0.043 mmol, 1.6 equiv), HBTU (20.5 mg, 0.054 mmol, 2 equiv), HOBt (7.3 mg, 0.054 mmol, 2 equiv), and N,N-diisopropylethylamine (48 μL, 0.27 mmol, 10 equiv). After the mixture was stirred at room temperature for 4 h, $H_2O$ (5 mL) was added and the obtained emulsion was extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1 → 4:1) to give 20.5 mg (87%) of amide **3-92a** as a colorless amorphous solid. $\mathbf{R_f}$ = 0.39 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –13.1 (*c* 1.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.87–1.02 (m, 39H, 16-$CH_3$, 18-$CH_3$, 10-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.72–1.83 (m, 1H, 16-H), 1.91–2.11 (m, 3H, 19-H, 18-H), 2.12–2.20 (m, 1H, 11-H), 2.22–2.30 (m, 1H, 10-H), 2.33–2.55 (m, 4H, 8-H, 14-H, 11-H), 3.60–3.65 (m, 1H, 17-H), 3.73 (s, 3H, $OCH_3$), 3.75-3.83 (m, 4H, $OCH_3$, 8-H), 4.00–

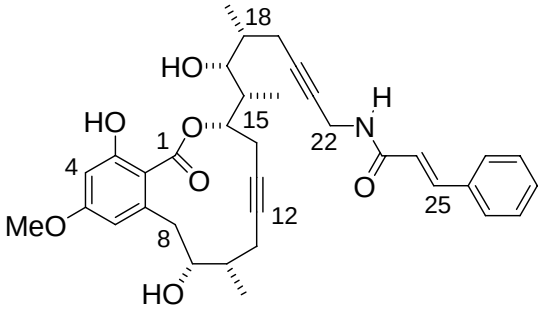
4.18 (m, 3H, 9-H, 22-H), 5.47–5.59 (m, 1H, 15-H), 6.02 (br s, 1H, NH), 6.31 (d, $J$ = 2.0 Hz, 1H, 6-H), 6.40–6.46 (m, 2H, 4-H, 25-H), 7.29–7.34 (m, 3H, *o*-, *p*-CH of Ph), 7.41–7.47 (m, 2H, *m*-CH of Ph), 7.62 (d, $J$ = 15.7 Hz, 1H, 24-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 ($Si(CH_3)_2$), 11.4 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 17.2 (10-$CH_3$), 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 21.7 (C-19), 23.1 (C-14), 23.7 (C-11), 26.1 ($Si(C(CH_3)_3)$), 30.0 (C-22), 37.2 (C-18), 37.3 (C-16), 38.6 (C-8), 40.3 (C-10), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 75.0 (C-17), 76.6 (C-9), 77.2 (C-15), 79.6 (C≡C), 81.7 (C≡C), 83.2 (C≡C), 96.6 (C-4), 108.2 (C-6), 118.0 (C-2), 120.2 (C-24), 127.8 (C-4'), 128.7 (C-3'), 129.6 (C-2'), 134.8 (C-1'), 139.4 (C-7), 141.2 (C-25), 157.4 (C-5), 160.4 (C-3), 165.4 (C-1), 167.6 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{51}H_{77}NNaO_7Si_2$ 894.51308, found 894.51309.

**2-Hydroxy-4-methoxybenzoate 3-93a**



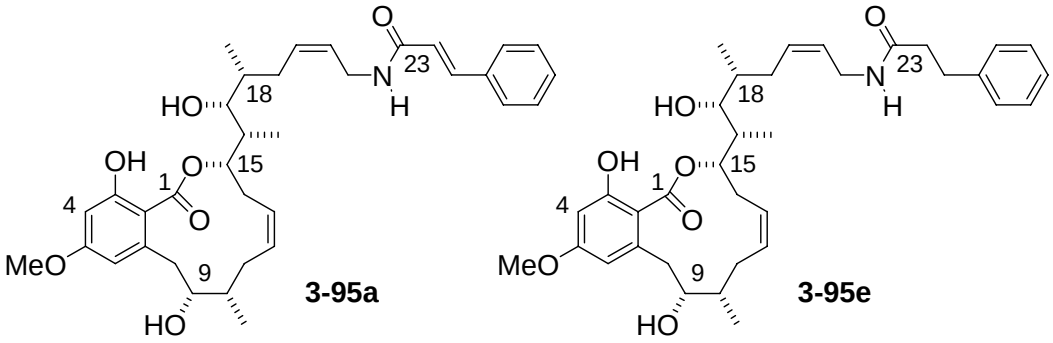

A solution of amide **3-92a** (18 mg, 0.02 mmol) in $CH_2Cl_2$ (3 mL) was treated with $BCl_3$ (80 μL, 1.0 M in $CH_2Cl_2$, 0.08 mmol, 4 equiv) at –80 °C. The reaction was stirred for 2 h at –80 °C before a saturated solution of NaOAc (3 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded phenol **3-93a** (15.8 mg, 92%) as a slightly yellow oil. **$R_f$** = 0.4 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = +17.0 (*c* 0.7, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.05-0.08 (m, 6H, $Si(CH_3)_2$), 0.85–1.05 (m, 39H, 16-$CH_3$, 18-$CH_3$, 10-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.67–1.91 (m, 2H, 16-H, 19-H), 1.94-2.20 (m, 4H, 19-H, 18-H, 11-H), 2.23–2.35 (m, 2H, 10-H, 14-H), 2.44–2.52 (m, 1H, 8-H), 2.55-2.67 (m, 1H, 14-H), 2.85–2.97 (m, 1H, 8-H), 3.56–3.62 (m, 1H, 17-H), 3.77 (s, 3H, $OCH_3$), 4.10–4.15 (m, 2H, 22-H), 4.17–4.25 (m, 1H, 9-H), 5.19–5.28 (m, 1H, 15-H), 5.81 (br s, 1H, NH), 6.33–6.42 (m, 3H, 6-H, 4-H, 25-H), 7.32–7.39 (m, 3H, *o*-, *p*-CH of Ph), 7.47–7.53 (m, 2H, *m*-CH of Ph), 7.64 (d, $J$ = 15.7 Hz, 1H, 24-H), 11.22 (br s, 1H, 3-OH);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 ($Si(CH_3)_2$), 11.1 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 16.6 (10-$CH_3$), 18.2 ($CH(CH_3)_2$), 18.2 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 22.1 (C-19), 22.7 (C-14), 26.0 ($Si(C(CH_3)_3)$), 30.0 (C-22), 36.7 (C-18), 37.4 (C-16), 55.2 ($OCH_3$), 74.6 (C-17), 75.6 (C-9), 76.9 (C≡C), 77.2 (C-15), 82.7 (C≡C), 83.2 (C≡C), 98.9 (C-4), 104.2 (C-6), 119.7 (C-2), 120.0 (C-24), 127.8 (C-4'), 128.8 (C-3'), 129.8 (C-2'), 134.7 (C-1'), 141.6 (C-7), 143.3 (C-25), 163.4 (C-3), 164.6 (C-5), 165.3 (C-1), 171.1 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{50}H_{75}NO_7Si_2Na$ 880.49743, found 880.49810.

**Deprotected macrolactone 3-94a**




To a stirred solution of the phenol **3-93a** (14 mg, 0.016 mmol) in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –5 °C. After 2 h, the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 9.0 mg (95%) of triol **3-94a**. $\mathbf{R_f}$ = 0.56 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +11.7 (*c* 0.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.91–0.96 (m, 6H, 16-$CH_3$, 18-$CH_3$), 1.02 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.74–1.85 (m, 2H, 16-H, 18-H), 2.00–2.10 (m, 2H, 19-H, 18-H), 2.15–2.27 (m, 4H, 19-H, 11-H, OH), 2.28–2.37 (m, 2H, 11-H, 8-H), 2.38–2.46 (m, 1H), 2.57–2.65 (m, 1H, 14-H), 2.77–2.85 (m, 1H, 14-H), 2.88–2.98 (m, 1H, 10-H), 3.63–3.69 (m, 1H, 17-H), 3.72-3.76 (m, 1H, 8-H), 3.91-3.99 (m, 1H, 9-H), 4.11–4.16 (m, 2H, 22-H), 5.32–5.39 (m, 1H, 15-H), 5.97 (br s, 1H, NH), 6.34–6.43 (m, 3H, 6-H, 4-H, 25-H), 7.33–7.40 (m, 3H, *o*-, *p*-CH of Ph), 7.46–7.52 (m, 2H, *m*-CH of Ph), 7.63 (d, *J* = 15.7 Hz, 1H, 24-H), 11.00 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.5 (16-$CH_3$), 14.1 (24-$CH_3$), 16.2 (18-$CH_3$), 16.5 (10-$CH_3$), 21.1 (C-19), 22.5 (C-14), 23.0 (C-11), 29.9 (C-22), 35.7 (C-26), 36.7 (C-18), 37.3 (C-16), 38.4 (C-8), 55.4 ($OCH_3$), 73.8 (C-17), 75.3 (C-9), 77.2 (C-15), 77.6 (*C*≡C), 79.3 (*C*≡C), 81.8 (*C*≡C), 83.3 (*C*≡C), 99.5 (C-4), 106.5 (C-2), 111.5 (C-6), 120.0 (C-24), 127.8 (C-4'), 128.8 (C-3'), 129.8 (C-2'), 134.7 (C-1'), 141.7 (C-7), 143.2 (C-25), 163.7 (C-5), 164.5 (C-3), 165.5 (C-1), 170.7 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{35}H_{41}NaNO_7$ 610.27752, found 610.27802.

**Cinnamoyl cruentaren 3-95a and diyhdrocinnamoyl cruentaren 3-95e**



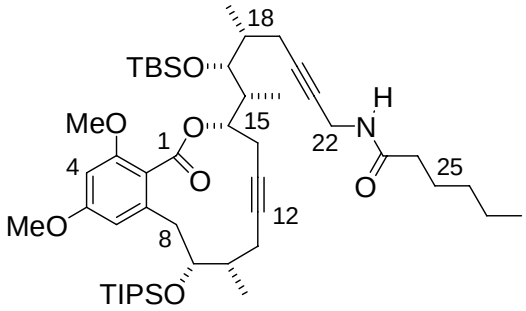

To a stirred solution of diyne **3-94a** (4.2 mg, 0.007 mmol) in EtOAc (2 mL) containing quinoline (1.5 mg, 0.01 mmol) was added Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned

with lead, 4.2 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. Flash chromatography of the residue ($CH_2Cl_2$/MeOH, 95:5 → 9:1) afforded cinnamide **3-95a** (3.1 mg, 74%) and phenylpropionamide **3-95e** (1.0 mg, 24%).

Compound **3-95a**:
**$R_f$** = 0.64 ($CH_2Cl_2$/MeOH, 9:1); **$[\alpha]^{20}_D$** = +8.3 (*c* 0.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.92 (d, *J* = 7.1 Hz, 3H, 16-$CH_3$), 0.97 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.70–1.79 (m, 2H, 18-H, OH), 1.93–2.06 (m, 3H, 10-H, 11-H, 16-H), 2.16–2.26 (m, 2H, 14-H, 19-H), 2.28–2.40 (m, 3H, 11-H, 8-H, 19-H), 2.79–2.96 (m, 1H, 14-H), 3.51 (dd, *J* = 9.4, 1.8 Hz, 1H, 17-H), 3.61–3.67 (m, 1H, 9-H), 3.72–3.74 (m, 1H, 8-H), 3.75–3.80 (m, 4H, $OCH_3$, OH), 3.87–3.95 (m, 1H, 22-H), 4.05-4.14 (m, 1H, 22-H), 5.27–5.35 (m, 1H, 15-H), 5.42–5.52 (m, 3H, 21-H, 12-H, 13-H), 5.53–5.63 (m, 1H, 20-H), 6.02 (br s, 1H, NH), 6.30 (d, *J* = 2.6 Hz, 1H, 6-H), 6.35–6.41 (m, 2H, 4-H, 25-H), 7.32–7.39 (m, 3H, *o*-, *p*-CH of Ph), 7.46–7.51 (m, 2H, *m*-CH of Ph), 7.62 (d, *J* = 15.7 Hz, 1H, 24-H), 11.50 (br s, 1H, 3-OH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{35}H_{45}NaNO_7$ 614.30882, found 614.30923.

Compound **3-95e**:
**$R_f$** = 0.58 ($CH_2Cl_2$/MeOH, 9:1); **$[\alpha]^{20}_D$** = +6.4 (*c* 0.1, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.90 (d, *J* = 7.1 Hz, 3H, 16-$CH_3$), 1.00 (d, *J* = 6.6 Hz, 3H, 10-$CH_3$), 1.63–1.77 (m, 1H, 18-H), 1.90–2.50 (m, 12H, 10-H, 11-H, 16-H, 14-H, 19-H, 8-H, 25-H, OH), 2.78–2.90 (m, 1H, 14-H), 2.91–2.99 (m, 2H, 24-H), 3.43–3.50 (m, 1H, 17-H), 3.61–3.67 (m, 1H, 9-H), 3.72–3.82 (m, 5H, 8-H, 22-H, $OCH_3$), 3.85–3.97 (m, 1H, 22-H), 5.25–5.36 (m, 2H, 15-H, 21-H), 5.40–5.59 (m, 3H, 12-H, 13-H, 20-H), 5.7 (br s, 1H, NH), 6.28–6.32 (m, 1H, 6-H), 6.34–6.39 (m, 1H, 4-H), 7.15–7.22 (m, 3H, *m*-, *p*-CH of Ph), 7.24–7.31 (m, 2H, *o*-CH of Ph), 11.50 (br s, 1H, 3-OH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{47}NO_8Na$ 616.32447, found 616.32467.

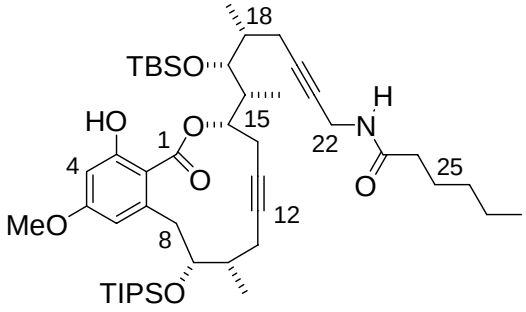
**Capronamide 3-92b**




To a solution of amine **3-83** (20 mg, 0.027 mmol, 1 equiv) in dry DMF (2 mL) were added capronic acid (**3-91b**) (5.4 µl, 0.043 mmol, 1.6 equiv), HBTU (20.5 mg, 0.054 mmol, 2 equiv), HOBt (7.3 mg, 0.054 mmol, 2 equiv), and N,N-diisopropylethylamine (48 µL, 0.27 mmol, 10 equiv). After the mixture was stirred at room temperature for 4 h, $H_2O$ (5 mL) was added and the obtained emulsion was extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum

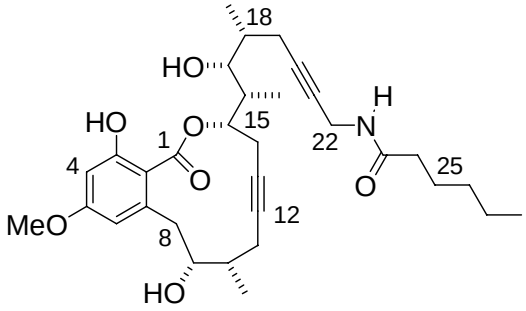
ether/EtOAc, 10:1 → 4:1) to give 20.0 mg (88%) of amide **3-92b** as a colorless amorphous solid. $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –17.9 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.06 ppm (s, 6H, $Si(CH_3)_2$), 0.84–1.01 (m, 39H, 16-$CH_3$, 18-$CH_3$, 28-H, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.04 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.25–1.44 (m, 4H, 26-H, 27-H), 1.54–1.68 (m, 2H, 25-H), 1.72–1.86 (m, 2H, 16-H, 18-H), 1.89–2.04 (m, 3H, 10-H, 11-H), 2.04–2.56 (m, 8H, 8-H, 14-H, 24-H, 19-H), 3.54–3.58 (m, 1H, 17-H), 3.75 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.95–4.04 (m, 3H, 9-H, 22-H), 5.42–5.54 (m, 1H, 15-H), 5.62 (br s, 1H, NH), 6.32 (s, 1H, 6-H), 6.41 (s, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.8 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 11.4 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 13.9 (C-28), 17.3 (10-$CH_3$), 17.9 ($Si(CH(CH_3)_2)_3$), 18.1 (($Si(CH(CH_3)_2)_3$), 18.4 (18-$CH_3$), 21.7 (C-19), 22.4 (C-27), 23.3 (C-14), 23.8 (C-11), 25.3 (C-25), 26.1 ($Si(C(CH_3)_3)$, 29.7 (C-22), 31.5 (C-26), 36.5 (C-18), 36.9 (C-16), 37.5 (C-10), 38.6 (C-8), 40.7 (C-24), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 75.4 (C-9), 77.2 (C≡C), 79.6 (C≡C), 81.4 (C≡C), 83.0 (C≡C), 96.7 (C-4), 108.3 (C-6), 118.1 (C-2), 139.4 (C-7), 157.3 (C-5), 160.3 (C-3), 167.5 (C-1), 172.7 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{48}H_{81}NNaO_7Si_2$: 862.54438, found 862.54445.

**2-Hydroxy-4-methoxybenzoate 3-93b**



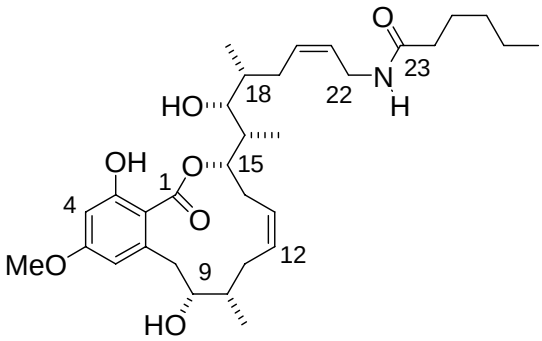

A solution of amide **3-92b** (19 mg, 0.023 mmol) in $CH_2Cl_2$ (3 mL) was treated with $BCl_3$ (92 µL, 1.0 M in $CH_2Cl_2$, 0.092 mmol, 4 equiv) at –80 °C. The reaction was stirred for 2 h at –80 °C before a saturated solution of NaOAc (3 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded phenol **3-93b** (16.3 mg, 86%). $\mathbf{R_f}$ = 0.40 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +15.0 (*c* 0.9, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01–0.08 (m, 6H, $Si(CH_3)_2$), 0.85–1.06 (m, 42H, 10-$CH_3$, 16-$CH_3$, 18-$CH_3$, 28-H, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.28–1.34 (m, 4H, 26-H, 27-H), 1.55–2.13 (m, 7H, 11-H, 16-H, 18-H, 19-H, 25-H), 2.14–2.20 (m, 3H, 19-H, 24-H), 2.20–2.65 (m, 4H, 8-H, 10-H, 14-H), 2.85–2.96 (m, 1H, 14-H), 3.58 (dd, *J* = 6.3, 2.0 Hz, 1H, 17-H), 3.78 (s, 3H, $OCH_3$), 3.96–4.02 (m, 2H, 22-H), 4.16–4.25 (m, 1H, 9-H), 5.17–5.24 (m, 1H, 15-H), 5.53–5.60 (m, 1H, NH), 6.32–6.37 (m, 2H, 6-H, 4-H), 11.22 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 ($Si(CH_3)_2$), 11.1 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 13.9 (C-28), 16.5 (10-$CH_3$), 18.2 ($Si(CH(CH_3)_2)_3$), 18.2 ($Si(CH(CH_3)_2)_3$), 18.4 (18-$CH_3$), 22.0 (C-19), 22.4 (C-14), 22.8 (C-11), 25.3 (C-25), 26.1 ($Si(C(CH_3)_3)$), 29.7 (C-22), 31.5 (C-26), 36.5 (C-18), 37.5 (C-8), 55.2 ($OCH_3$), 74.6 (C-17), 75.6 (C-9), 77.2 (C≡C), 82.4 (C≡C), 98.9 (C-4), 143.7 (C-7), 163.4 (C-5), 164.6 (C-3), 171.1 (C-1), 172.6 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{47}H_{79}NNaO_7Si_2$: 848.52873, found 848.52881.

**Deprotected macrolactone 3-94b**



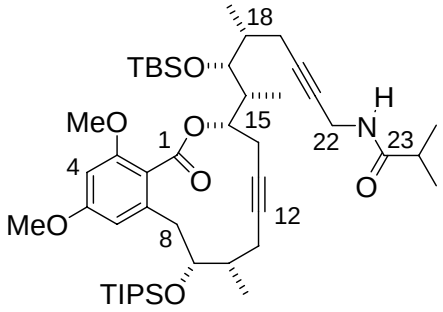

To a stirred solution of the phenol **3-93b** (16 mg, 0.019 mmol) in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –5 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 9.8 mg (93%) of triol **3-94b**. $\mathbf{R_f}$ = 0.46 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +27.5 (*c* 0.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 9H, 16-$CH_3$, 18-$CH_3$, 28-H), 1.02 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.22–1.34 (m, 4H, 26-H, 27-H), 1.54–1.64 (m, 2H, 25-H), 1.65–1.71 (m, 1H, OH), 1.73–1.85 (m, 2H, 18-H, 19H), 1.98–2.08 (m, 1H, 19-H), 2.09–2.41 (m, 7H, 8-H, 11-H, 16-H, 24-H, OH), 2.55–2.64 (m, 1H, 14-H), 2.76–2.85 (m, 1H, 14-H), 2.85–2.96 (m, 1H, 10-H), 3.57–3.63 (m, 1H, 17-H), 3.73–3.82 (m, 4H, 8-H, $OCH_3$), 3.91–4.01 (m, 3H, 9-H, 22-H), 5.31–5.38 (m, 1H, 15-H), 5.77 (br s, 1H, NH), 6.38 (d, *J* = 2.5 Hz, 1H, 6-H), 6.41 (d, *J* = 2.5 Hz, 1H, 4-H), 11.03 (s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.5 (16-$CH_3$), 13.9 (C-28), 16.1 (18-$CH_3$), 16.5 (10-$CH_3$), 21.1 (C-19), 22.4 (C-27), 22.5 (C-14), 23.0 (C-11), 25.3 (C-25), 29.6 (C-22), 31.4 (C-26), 35.7 (C-18), 36.5 (C-16), 36.6 (C-24), 37.4 (C-10), 38.4 (C-8), 55.4 ($OCH_3$), 73.9 (C-17), 75.3 (C-9), 76.9 (C-15), 77.2 (*C*≡C), 77.4, 79.2 (*C*≡C), 81.6 (*C*≡C), 83.2 (*C*≡C), 99.5 (C-4), 106.5 (C-2), 111.5 (C-6), 143.3 (C-7), 163.6 (C-5), 164.6 (C-3), 170.6 (C-1), 172.8 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{32}H_{45}NNaO_7$ 578.30882, found 578.30901.

**Hexanoyl cruentaren 3-95b**



A 5 mL round-bottom flask was charged with diyne **3-94b** (9.1 mg, 0.016 mmol) and a stir bar. EtOAc (2 mL) and quinoline (3.3 mg, 0.026 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned with lead, 9.1 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) afforded hexanoyl cruentaren **3-95b** (8.6 mg, 96%). $\mathbf{R_f}$ = 0.55 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +13.5 (*c* 0.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.84–0.91 (m, 6H, 16-$CH_3$, 28-H), 1.01 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.23–1.32 (m, 4H, 26-H, 27-H), 1.54–1.65 (m, 2H, 25-H), 1.65–1.75 (m, 1H, 18-H), 1.90–2.09 (m, 3H, 10-H, 11-H, 16-H), 2.13 (t, *J* = 7.7 Hz, 2H, 24-H), 2.16–2.41 (m, 6H, 8-H, 11-H, 14-H, 19-H, OH), 2.77–2.89 (m, 1H, 14-H), 3.01 (br s, 1H, OH), 3.42–3.47 (m, 1H, 17-H), 3.61–3.67 (m, 1H, 9-H), 3.72–3.82 (m, 5H, 8-H, 22-H, $OCH_3$), 3.89–3.97 (m, 1H, 22-H), 5.25–5.32 (m, 1H, 15-H), 5.33–5.58 (m, 4H, 21-H, 12-H, 13-H, 20-H), 5.68–5.76 (m, 1H, NH), 6.30 (d, *J* = 2.6 Hz, 1H, 6-H), 6.36 (d, *J* = 2.6 Hz, 1H, 4-H), 11.51 (s, 1H, 3-OH);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.7 (16-$CH_3$), 13.9 (C-28), 14.2 (10-$CH_3$), 16.0 (18-$CH_3$), 22.4 (C-27), 25.4 (C-25), 29.6 (C-14), 29.7 (C-19), 30.7 (C-26), 31.4 (C-11), 31.6 (C-14), 36.6 (C-8), 36.8 (C-10), 38.2 (C-22), 39.1 (C-16), 55.4 ($OCH_3$), 73.1 (C-17), 74.3 (C-9), 77.2 (*C*≡C), 78.2 (*C*≡C), 99.6 (C-4), 105.0 (C-2), 112.3 (C-6), 126.0 (C-13), 127.0 (C-21), 130.6 (C-20), 132.0 (C-12), 143.7 (C-7), 163.5 (C-5), 165.7 (C-3), 171.5 (C-1), 173.3 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{32}H_{49}NNaO_7$ 582.34012, found 582.34061.

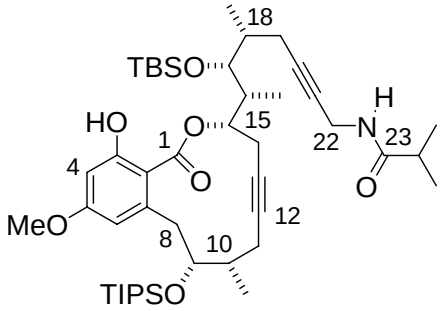
**Isobutyramide 3-92c**




To a solution of amine **3-83** (20 mg, 0.027 mmol, 1 equiv) in dry DMF (2 mL) were added the isobutyric acid (**3-91c**) (4.0 µl, 0.043 mmol, 1.6 equiv), HBTU (20.5 mg, 0.054 mmol, 2 equiv), HOBt (7.3 mg, 0.054 mmol, 2 equiv), and N,N-diisopropylethylamine (48 µL, 0.27 mmol, 10 equiv). After the mixture was stirred at room temperature for 4 h, $H_2O$ (5 mL) was added and the obtained emulsion was extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1 → 4:1) to give 20 mg (91%) of amide **3-92c** as a colorless amorphous solid. $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –20.0 (*c* 1.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.06 ppm (s, 6H, $Si(CH_3)_2$), 0.85–1.02 (m, 36H, 16-$CH_3$, 18-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.04 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.15 (d, *J* = 6.8 Hz, 6H, 24-$CH_3$), 1.60–1.73 (m, 1H, 18-H), 1.77–1.87 (m, 1H, 16-H), 1.91–2.09 (m, 3H, 10-H, 11-H), 2.10–2.20 (m, 1H, 19-H), 2.21–2.30 (m, 1H, 19-H), 2.31–2.55 (m, 5H, 8-H, 14-H, 24-H), 3,56 (t, *J* = 4.3 Hz, 1H, 17-H), 3.75 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.95–4.04 (m, 3H, 9-H, 22-H), 5.42–5.55 (m, 1H, 15-H),

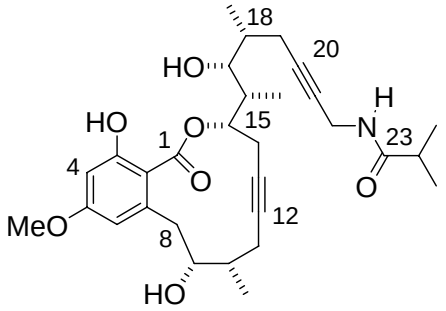
5.60 (br s, 1H, NH), 6.32 (d, $J$ = 2.0 Hz, 1H, 6-H), 6.41 (d, $J$ = 2.0 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.8 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 11.4 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 17.3 (10-$CH_3$), 17.9 ($Si(CH(CH_3)_2)_3$), 18.1 ($Si(CH(CH_3)_2)_3$), 18.4 (18-$CH_3$), 19.5 (24-$CH_3$), 21.7 (C-19), 22.3 (C-14), 23.8 (C-11), 26.1 ($Si(C(CH_3)_3)$), 29.7 (C-22), 35.4 (C-18), 36.9 (C-16), 37.6 (C-10), 38.6 (C-8), 40.7 (C-24), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 75.4 (C-9), 76.8 (C-15), 77.2 (C≡C), 79.6 (C≡C), 81.4 (C≡C), 83.0 (C≡C), 96.7 (C-4), 108.3 (C-6), 118.1 (C-2), 139.4 (C-7), 157.3 (C-5), 160.3 (C-3), 167.5 (C-1), 176.4 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{46}H_{77}NNaO_7Si_2$ 834.51308 , found 834.51395.

**2-Hydroxy-4-methoxybenzoate 3-93c**



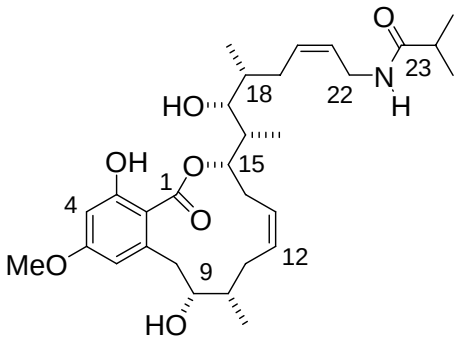

A solution of amide **3-92c** (18 mg, 0.022 mmol) in $CH_2Cl_2$ (3 mL) was treated with $BCl_3$ (88 µL, 1.0 M in $CH_2Cl_2$, 0.088 mmol, 4 equiv) at –80 °C. The reaction was stirred for 2 h at –80 °C before a saturated solution of NaOAc (3 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded phenol **3-93c** (14.6 mg, 83%). **$R_f$** = 0.41 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = +21.0 (*c* 0.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H, $Si(CH_3)_2$), 0.86–1.05 (m, 39H, 10-$CH_3$, 16-$CH_3$, 18-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.15 (d, $J$ = 6.8 Hz, 6H, 24-$CH_3$), 1.71–1.90 (m, 2H, 16-H, 18-H), 1.94–2.20 (m, 3H, 10-H, 11-H, 19-H), 2.21–2.39 (m, 4H, 11-H, 19-H, 24-H, 8-H), 2.42–2.50 (m, 1H, 8-H), 2.52–2.68 (m, 1H, 14-H), 2.85–2.97 (m, 1H, 14-H), 3.55–3.60 (m, 1H, 17-H), 3.79 (s, 3H, $OCH_3$), 3.97–4.01 (m, 2H, 22-H), 4.15–4.26 (m, 1H, 9-H), 5.17–5.26 (m, 1H, 15-H), 5.57 (br s, 1H, NH), 6.33–6.37 (m, 2H, 4-H, 6-H), 11.22 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 ($Si(CH_3)_2$), 11.1 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 16.5 (10-$CH_3$), 18.2 ($Si(CH(CH_3)_2)_3$), 18.2 ($Si(CH(CH_3)_2)_3$), 18.4 (18-$CH_3$), 19.5 (24-$CH_3$), 22.1 (C-19), 22.9 (C-14), 26.1 ($Si(C(CH_3)_3)$), 29.7 (C-22), 35.5 (C-18), 37.5 (C-8), 55.2 ($OCH_3$), 74.6 (C-17), 75.6 (C-9), 77.2 (C≡C), 82.5 (C≡C), 98.9 (C-4), 143.7 (C-7), 163.4 (C-5), 164.7 (C-3), 171.1 (C-1), 176.3 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{45}H_{75}NNaO_7Si_2$: 820.49743, found 820.49791.

**Deprotected macrolactone 3-94c**




To a stirred solution of the phenol **3-93c** (13.8 mg, 0.017 mmol) in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –5 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 7.6 mg (85%) of triol **3-94c**. $\mathbf{R_f}$ = 0.57 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +24.0 (*c* 0.75, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.89–0.95 (m, 6H, 16-$CH_3$, 18-$CH_3$), 1.03 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.10–1.15 (m, 6H, 24-$CH_3$), 1.73–1.87 (m, 2H, 18-H, 19-H), 2.04–2.10 (m, 1H, 19-H), 2.13–2.39 (m, 5H, 8-H, 11-H, 16-H, 24-H), 2.55–2.64 (m, 1H, 14-H), 2.76–2.85 (m, 1H, 14-H), 2.92 (dd, *J* = 13.4 Hz, 10.9 Hz, 1H, 10-H), 3.57–3.67 (m, 2H, 17-H, OH), 3.76 (dd, *J* = 13.4 Hz, 3.5 Hz, 1H, 8-H), 3.80 (s, 3H, $OCH_3$), 3.90–4.02 (m, 3H, 9-H, 22-H), 5.31–5.38 (m, 1H, 15-H), 5.74 (br s, 1H, NH), 6.39 (d, *J* = 2.6 Hz, 1H, 6-H), 6.41 (d, *J* = 2.6, 1H, 4-H), 11.04 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.5 (16-$CH_3$), 16.1 (18-$CH_3$), 16.5 (10-$CH_3$), 19.5 (24-$CH_3$), 21.1 (C-19), 22.5 (C-14), 23.0 (C-11), 29.7 (C-22), 35.4 (C-18), 35.8 (C-16), 36.7 (C-24), 37.4 (C-10), 38.4 (C-8), 55.4 ($OCH_3$), 73.9 (C-17), 75.3 (C-9), 76.9 (C-15), 77.2 (*C*≡C), 77.8, 79.2 (*C*≡C), 81.6 (*C*≡C), 83.2 (*C*≡C), 99.5 (C-4), 106.4 (C-2), 111.5 (C-6), 143.3 (C-7), 163.7 (C-5), 164.7 (C-3), 170.7 (C-1), 176.5 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{30}H_{41}NaNO_7$ 550.27752, found 550.27757.

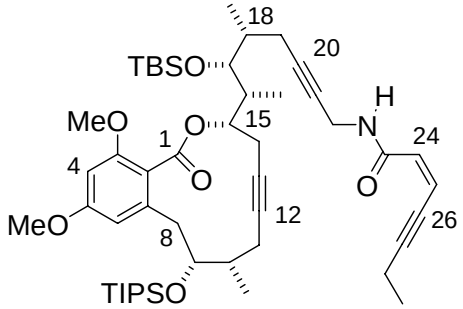
**Methylpropanoyl cruentaren 3-95c**




A 5 mL round-bottom flask was charged with diyne **3-94c** (5.5 mg, 0.01 mmol) and a stir bar. EtOAc (2 mL) and quinoline (2.3 mg, 0.018 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned with lead, 6.0 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The mixture

was filtered through a pad of celite and the filtrate concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) afforded methylpropanoyl cruentaren **3-95c** (4.6 mg, 87%). $\mathbf{R_f}$ = 0.6 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +10.4 (*c* 0.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3H, 16-$CH_3$), 0.89 (d, *J* = 7.1 Hz, 3H, 18-$CH_3$), 1.01 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.13 (d, *J* = 6.8 Hz, 6H, 24-$CH_3$), 1.57 (br s, 1H, OH), 1.64–1.74 (m, 1H, 18-H), 1.92–2.04 (m, 3H, 10-H, 11-H, 16-H), 2.17–2.40 (m, 6H, 8-H, 11-H, 14-H, 19-H, 24-H), 2.76–2.87 (m, 1H, 14-H), 3.02 (br s, 1H, OH), 3.42–3.49 (m, 1H, 17-H), 3.61–3.67 (m, 1H, 9-H), 3.73–3.82 (m, 5H, 8-H, 22-H, $OCH_3$), 3.88–3.94 (m, 1H, 22-H), 5.26–5.33 (m, 1H, 15-H), 5.34–5.59 (m, 4H, 12-H, 13-H, 21-H, 20-H), 5.66–5.75 (m, 1H, NH), 6.30 (d, *J* = 2.6 Hz, 1H, 6-H), 6.36 (d, *J* = 2.6 Hz, 1H, 4-H), 11.51 (s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.7 (16-$CH_3$), 14.1 (10-$CH_3$), 16.1 (18-$CH_3$), 19.6 (24-$CH_3$), 29.6 (C-14), 30.7 (C-19), 31.6 (C-11), 35.6 (C-22), 36.7 (C-8), 36.8 (C-18), 38.2 (C-16), 39.21 (C-24), 55.4 ($OCH_3$), 73.0 (C-17), 74.3 (C-9), 77.2 (*C*≡C), 78.2 (*C*≡C), 99.6 (C-4), 105.0 (C-2), 112.3 (C-6), 126.0 (C-13), 127.0 (C-21), 130.6 (C-20), 132.0 (C-12), 143.7 (C-7), 163.5 (C-5), 165.7 (C-3), 171.5 (C-1), 177.0 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{30}H_{45}NaNO_7$ 554.30937, found 554.30964.

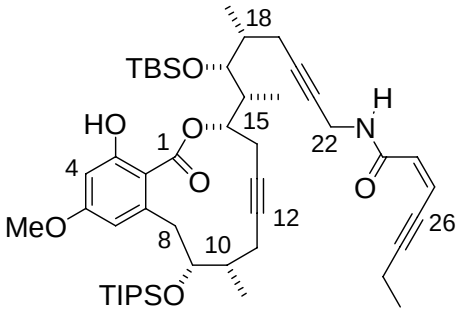
**(2Z)-Hept-2-en-4-ynamide 3-92d**




To a solution of amine **3-83** (22 mg, 0.03 mmol, 1 equiv) in dry DMF (2 mL) were added the (2*Z*)-hept-2-en-4-ynoic acid (**3-91d**)[90b] (6.0 mg, 0.048 mmol, 1.6 equiv), HBTU (22.8 mg, 0.06 mmol, 2 equiv), HOBt (8.1 mg, 0.06 mmol, 2 equiv), and N,N-diisopropylethylamine (108 μL, 0.6 mmol, 10 equiv). After the mixture was stirred at room temperature for 4 h, $H_2O$ (5 mL) was added and the obtained emulsion was extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1 → 4:1) to give 21.6 mg (85%) of amide **3-92d** as a colorless amorphous solid. $\mathbf{R_f}$ = 0.23 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –21.6 (*c* 2.1, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.04–0.08 (m, 6H, $Si(CH_3)_2$), 0.87–0.97 (m, 33H, 18-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 0.98–1.07 (m, 6H, 16-$CH_3$, 10-$CH_3$), 1.24 (t, *J* = 7.3 Hz, 3H, 29-H), 1.75–1.85 (m, 1H, 16-H), 1.90–2.07 (m, 3H, 10-H, 18-H, 11-H), 2.10–2.19 (m, 1H, 19-H), 2.26–2.34 (m, 1H, 19-H), 2.35–2.54 (m, 7H, 8-H, 14-H, 28-H, 11-H), 3.49–3.54 (m, 1H, 17-H), 3.74 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.96–4.03 (m, 1H, 9-H), 4.06–4.13 (m, 2H, 22-H), 5.41–5.54 (m, 1H, 15-H), 5.95–6.07 (m, 2H, 24-H, 25-H), 6.31 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (d, *J* = 2.0 Hz, 1H, 4-H), 7.31 (br s, 1H, NH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.9 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.3 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 13.3 (C-29), 13.5 (C-28), 17.4 (10-$CH_3$), 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 21.8 (C-19), 23.3 (C-14), 23.9

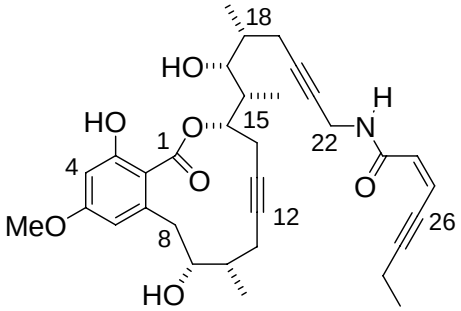
(C-11), 26.1 (Si(C(*C*H$_3$)$_3$)), 29.7 (C-22), 36.7 (C-18), 37.6 (C-16), 38.6 (C-8), 41.0 (C-10), 55.2 (OCH$_3$), 55.7 (OCH$_3$), 74.5 (C-17), 75.7 (C-9), 76.5 (C-15), 76.5 (*C*≡C), 77.2 (C-25), 77.2 (*C*≡C), 79.5 (*C*≡C), 81.4 (*C*≡C), 83.1 (*C*≡C), 96.7 (C-4), 108.3 (C-6), 116.6 (C-25), 118.1 (C-2), 132.5 (C-24), 139.4 (C-7), 157.2 (C-5), 160.3 (C-3), 164.4 (C-1), 167.4 (C-23);
**HRMS** (ESI): [M+Na]$^+$ calcd for $C_{49}H_{77}NNaO_7Si_2$ 870.51308, found 870.51317.

**2-Hydroxy-4-methoxybenzoate 3-93d**



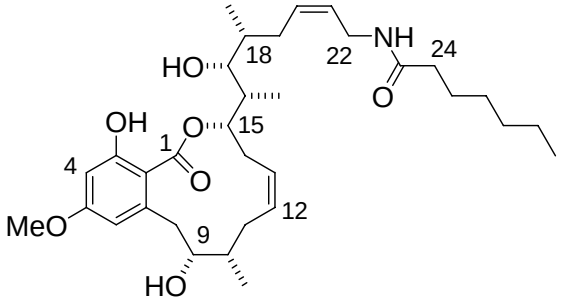

A solution of amide **3-92d** (19 mg, 0.022 mmol) in $CH_2Cl_2$ (2 mL) was treated with $BCl_3$ (89 µL, 1.0 M in $CH_2Cl_2$, 0.089 mmol, 4 equiv) at –80 °C. The reaction was stirred for 2 h at –80 °C before a saturated solution of NaOAc (3 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded phenol **3-93d** (16.3 mg, 89%). **R$_f$** = 0.38 (petroleum ether/EtOAc, 4:1); **[α]$^{20}_D$** = +18.4 (*c* 1.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.04–0.08 (m, 6H, Si(CH$_3$)$_2$), 0.87–1.05 (m, 39H, 18-CH$_3$, 16-CH$_3$, 10-CH$_3$, Si(C(C*H*$_3$)$_3$), Si(C*H*(C*H*$_3$)$_2$)$_3$)), 1.24 (t, *J* = 7.3 Hz, 3H, 29-H), 1.75–1.89 (m, 2H, 16-H, 18-H), 1.95–2.18 (m, 3H, 10-H, 11-H, 19-H), 2.24–2.35 (m, 2H, 19-H, 14-H), 2.40–2.49 (m, 4H, 8-H, 28-H), 2.50–2.62 (m, 1H, 11-H), 2.85–2.96 (m, 1H, 14-H), 3.49–3.54 (m, 1H, 17-H), 3.78 (s, 3H, OCH$_3$), 4.07–4.12 (m, 2H, 22-H), 4.17–4.26 (m, 1H, 9-H), 5.14–5.26 (m, 1H, 15-H), 6.00–6.08 (m, 2H, 24-H, 25-H), 6.33–6.36 (m, 2H, 6-H, 4-H), 7.32 (br s, 1H, NH), 11.23 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 (Si(CH$_3$)$_2$), –3.9 (Si(CH$_3$)$_2$), 11.0 (16-CH$_3$), 13.0 (*C*H(CH$_3$)$_2$), 13.3 (C-29), 13.5 (C-28), 16.6 (10-CH$_3$), 18.2 (CH(*C*H$_3$)$_2$), 18.2 (CH(*C*H$_3$)$_2$), 18.4 (18-CH$_3$), 22.0 (C-19), 22.8 (C-14), 26.1 (Si(C(*C*H$_3$)$_3$)), 29.6 (C-22), 34.3 (C-18), 37.4 (C-16), 55.2 (OCH$_3$), 75.0 (C-17), 75.4 (C-9), 76.5 (C-15), 76.9 (*C*≡C), 77.2 (C-25), 82.6 (*C*≡C), 98.9 (C-4), 104.6 (C-6), 116.6 (C-25), 132.5 (C-24), 143.7 (C-7), 163.4 (C-5), 164.4 (C-3), 164.7 (C-1), 171.1 (C-23);
**HRMS** (ESI): [M+Na]$^+$ calcd for $C_{48}H_{75}NNaO_7Si_2$ 856.49743, found 856.49761.

**Deprotected macrolactone 3-94d**




To a stirred solution of the phenol **3-93d** (15 mg, 0.018 mmol in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –5 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 9.3 mg (92%) of triol **3-94d**. $\mathbf{R_f}$ = 0.55 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +31.8 (*c* 0.9, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.88–0.96 (m, 6H, 18-$CH_3$, 16-$CH_3$), 1.01 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.24 (t, *J* = 7.3 Hz, 3H, 29-H), 1.65 (br s, 1H, OH), 1.68–1.72 (m, 1H, 16-H), 1.74–1.82 (m, 1H, 18-H), 2.01–2.10 (m, 1H, 10-H), 2.12–2.39 (m, 5H, 11-H, 19-H, 14-H, OH), 2.41–2.49 (m, 2H, 28-H), 2.53–2.61 (m, 1H, 11-H), 2.76–2.87 (m, 2H, 14-H, 8-H), 3.52–3.59 (m, 1H, 17-H), 3.77–3.86 (m, 4H, $OCH_3$, 8-H), 3.91–3.99 (m, 1H, 9-H), 4.07–4.13 (m, 2H, 22-H), 5.31–5.38 (m, 1H, 15-H), 6.00–6.07 (m, 2H, 24-H, 25-H), 6.38 (d, *J* = 2.5 Hz, 1H, 6-H), 6.41 (d, *J* = 2.5 Hz, 1H, 4-H), 7.37 (br s, 1H, NH), 11.05 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 8.5 (16-$CH_3$), 13.3 (C-29), 13.5 (C-28), 16.1 (10-$CH_3$), 21.2 (18-$CH_3$), 22.6 (C-19), 23.0 (C-14), 29.6 (C-22), 35.9, 36.6 (C-18), 37.5 (C-16), 38.2 (C-8), 55.4 ($OCH_3$), 74.1 (C-17), 74.9 (C-9), 76.5 (C-15), 76.8 (*C*≡C), 77.2 (C-25), 79.1 (*C*≡C), 81.9 (*C*≡C), 83.2 (*C*≡C), 99.5 (C-4), 104.8 (C-2), 106.2 (C-6), 111.7, 116.7 (C-25), 132.4 (C-24), 143.3 (C-7), 163.7 (C-5), 164.5 (C-3), 164.7 (C-1), 170.7 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{41}NNaO_7$ 586.27752, found 586.27737.

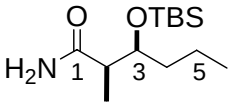
**Heptanoyl cruentaren 3-95f**




A 5 mL round-bottom flask was charged with triol **3-94d** (7.0 mg, 0.012 mmol) and a stir bar. EtOAc (2 mL) and quinoline (2.4 mg, 0.02 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned with lead, 7.0 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 2 h. The reaction mixture

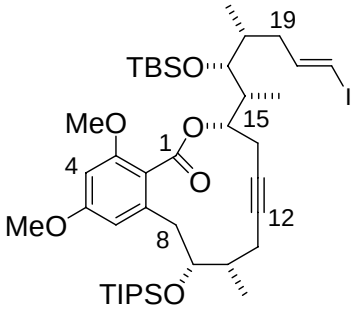
was filtered through a pad of celite and the filtrate concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) afforded heptanamide **3-95f** (5.1 mg, 73%). $\mathbf{R_f}$ = 0.51 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +16.4 (*c* 0.5, $CH_2Cl_2$); **$^1$H NMR** (600 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.83–0.92 (m, 6H, 16-$CH_3$, 29-H), 1.01 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.22–1.37 (m, 8H, 25-H, 26-H, 27-H, 28-H), 1.65–1.75 (m, 1H, 18-H), 1.90–2.07 (m, 4H, 10-H, 11-H, 16-H, OH), 2.11–2.41 (m, 7H, 8-H, 14-H, 19-H, 24-H, 11-H), 2.77–2.88 (m, 1H, 14-H), 2.97–3.04 (m, 1H), 3.41–3.49 (m, 1H, 17-H), 3.61–3.68 (m, 1H, 9-H), 3.71–3.82 (m, 5H, 8-H, 22-H, $OCH_3$), 3.90–3.99 (m, 1H, 22-H), 5.25–5.32 (m, 1H, 15-H), 5.34–5.59 (m, 4H, 21-H, 13-H, 12-H, 20-H), 5.69 (br t, *J* = 5.3 Hz, 1H, NH), 6.30 (d, *J* = 2.5 Hz, 1H, 6-H), 6.36 (d, *J* = 2.5 Hz, 1H, 4-H), 11.51 (br s, 1H, 3-OH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{51}NNaO_7$ 596.35577, found 596.35590.

### (2*R*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylhexanamide (3-97)



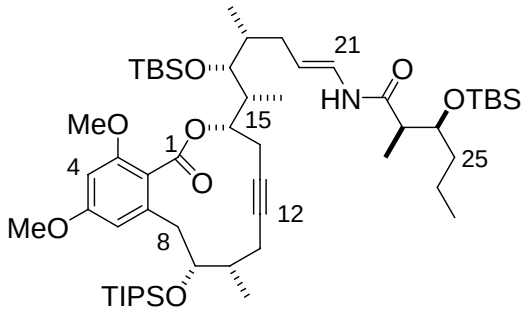

The Ghosez chloroenamine (N-(1-chloro-2-methyl-1-propenyl)-N,N-dimethylamine) (**3-61**)[140] (123 μL, 0.92 mmol) was slowly added via syringe to a solution of acid **2-31** (120 mg, 0.46 mmol) in $CH_2Cl_2$ (1 mL) at –5 °C followed by stirring of the mixture for 1 h at that temperature. After the solvent was evaporated in vacuo affording the acid chloride as slightly yellow oil. The crude acid chloride was redissolved in $CH_2Cl_2$ (5 mL) and gaseous ammonia was bubbled through this solution during 1 h. The reaction mixture was diluted with $H_2O$ and extracted trice with $CH_2Cl_2$. The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc/$NEt_3$, 4:1:0.01→2:1:0.01) afforded amide **3-97** (105 mg, 89%) as a colorless oil. $\mathbf{R_f}$ = 0.49 (petroleum ether/EtOAc/$NEt_3$, 2:1:0.01); $\mathbf{[\alpha]^{20}_D}$ = –44.0 (*c* 2.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.02, 0.02 (2s, 6H, $Si(CH_3)_2$), 0.77–0.83 (m, 12H, 6-H, $Si(C(CH_3)_3)$), 0.99 (d, *J* = 7.1 Hz, 3H, 2-$CH_3$), 1.11–1.22 (m, 1H, 5-H), 1.31–1.40 (m, 3H, 4-H, 5-H), 2.36–2.45 (m, 1H, 2-H), 3.65–3.71 (m, 1H, 3-H), 6.37 (br s, 1H, NH), 6.53 (br s, 1H, NH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.8 ($Si(CH_3)_2$), –4.8 ($Si(CH_3)_2$), 12.6 (2-$CH_3$), 14.0 (C-6), 17.8 ($Si(C(CH_3)_3)$), 19.0 (C-5), 25.7 ($Si(C(CH_3)_3)$), 34.8 (C-4), 45.4 (C-2), 74.4 (C-3), 177.0 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{13}H_{29}NNaO_2Si$: 282.18598, found 282.18592.

### *E*-Vinyl iodide 3-96




[$Cp_2Zr(H)Cl$] (31 mg, 0.12 mmol) was added to a solution of alkyne **3-80** (44 mg, 0.06 mmol) in THF (1.5 mL) at 0 °C and the resulting mixture was stirred for 2 h at that temperature. A solution of $I_2$ (0.24 ml, 0.5M in THF, 0.12 mmol) was then added dropwise and stirring was continued for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (5 mL). The mixture was repeatedly extracted with $Et_2O$. The combined organic layers were dried ($MgSO_4$), filtered and evaporated, and the residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give *E*-vinyl iodide **3-96** as an amorphous solid (52 mg, 92%) which was used directly in the next step. TLC (petroleum ether/EtOAc, 4:1): $R_f = 0.74$.

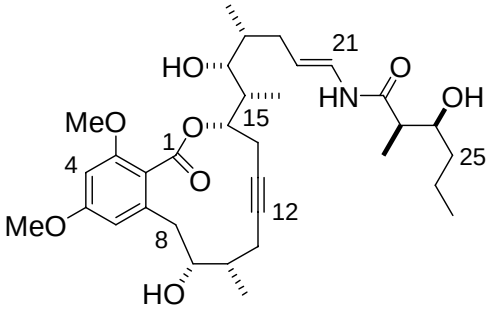
**Enamide 3-98**




A Schlenk tube was charged with CuI (10.5 mg, 0.055 mmol, 1 equiv), amide **3-97** (28.5 mg, 0.11 mmol, 2 equiv), and $Cs_2CO_3$ (46 mg, 0.14 mmol, 2.5 equiv). The tube was evacuated and backfilled with argon. N,N'-Dimethylethylenediamine (12.0 µL, 0.11 mmol, 2 equiv), vinyl iodide **3-96** (52 mg, 0.055 mmol) and THF (1.0 mL) were added under argon. The Schlenk tube was closed and immersed in an oil bath, preheated to 60 °C. The mixture was stirred for 14 h. After the resulting pale blue suspension was allowed to reach room temperature, ethyl acetate (5 mL) was added. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1→4:1) to give enamide **3-98** as an amorphous solid (44 mg, 82%). $\mathbf{R_f} = 0.66$ (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D} = -23.5$ (*c* 1.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.03–0.07 (m, 6H, $Si(CH_3)_2$), 0.08–0.11 (m, 6H, $Si(CH_3)_2$), 0.84–0.98 (m, 48H, 24-$CH_3$, 27-H, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.02–1.10 (m, 6H, 18-$CH_3$, 10-$CH_3$), 1.16–1.26 (m, 1H, 26-H), 1.31–1.50 (m, 3H, 25-H, 26-H), 1.65–1.75 (m, 2H, 18-H, 16-H), 1.76–1.84 (m, 1H, 11-H), 1.90–1.99 (m, 1H, 10-H), 2.10–2.27 (m, 2H, 19-H), 2.35–2.54 (m, 5H, 8-H, 14-H, 23-H, 11-H), 3.45–3.49 (m, 1H, 17-H), 3.72–3.78 (m, 8H, $OCH_3$, 24-H, 8-H), 3.97–4.03 (m, 1H, 9-H), 4.92–5.01 (m, 1H, 20-H), 5.38–5.51 (m, 1H, 15-H), 6.31 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (d, *J* = 2.0 Hz, 1H, 4-H), 6.73 (dd, *J* = 14.0, 10.6 Hz, 1H, 21-H), 8.08 (br d, *J* = 10.6 Hz, 1H,

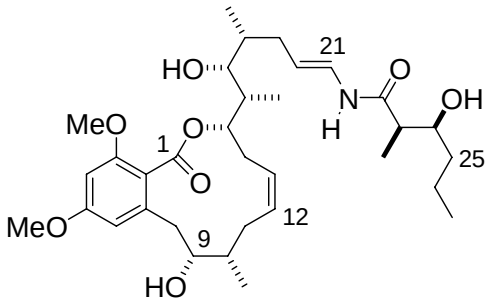
NH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.3 (16-$CH_3$), 12.4 (23-$CH_3$), 13.0 ($CH(CH_3)_2$), 14.1 (C-27), 16.7 (10-$CH_3$), 17.9 ($CH(CH_3)_2$), 17.9 ($Si(C(CH_3)_3)$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 19.4 (C-26), 23.3 (C-14), 23.7 (C-11), 25.9 ($Si(C(CH_3)_3)$), 26.1 ($Si(C(CH_3)_3)$), 32.6 (C-19), 34.7 (C-25), 37.6 (C-18), 38.1 (C-16), 38.6 (C-8), 40.7 (C-10), 45.6 (C-23), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 74.9 (C-17), 76.2 (C-9), 77.2 (C-24), 79.7 (C≡C), 81.2 (C≡C), 96.6 (C-4), 108.3 (C-6), 110.9 (C-20), 118.2 (C-2), 123.4 (C-21), 139.4 (C-7), 157.2 (C-5), 160.2 (C-3), 167.4 (C-1), 170.9 (C-22);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{54}H_{97}NaNO_8Si_3$ 994.64142, found 994.64053.

**Triol 3-99**



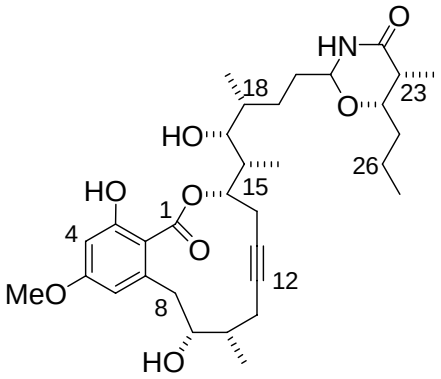

To a stirred solution of the enamide **3-98** (10 mg, 0.01 mmol) in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –10 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 4.4 mg (75%) of triol **3-99**. $\mathbf{R_f}$ = 0.47 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –3.3 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.90–0.98 (m, 6H, 27-H, 10-$CH_3$), 1.10 (d, *J* = 7.1 Hz, 3H, 16-$CH_3$), 1.16 (d, *J* = 7.3 Hz, 3H, 23-$CH_3$), 1.28–1.39 (m, 2H, 25-H, 26-H), 1.41–1.51 (m, 2H, 25-H, 26-H), 1.58–1.67 (m, 2H, 19-H, OH), 1.90–2.02 (m, 4H, 18-H, 19-H, 11-H, OH), 2.05–2.14 (m, 1H, 16-H), 2.29–2.40 (m, 2H, 8-H, 10-H), 2.46–2.63 (m, 3H, 14-H, 11-H), 2.71–2.79 (m, 1H, 23-H), 2.85 (br s, 1H, OH), 3.29–3.26 (m, 1H, 8-H), 3.45–3.49 (m, 1H, 17-H), 3.78 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.83–3.90 (m, 2H, 9-H, 24-H), 5.10–5.19 (m, 1H, 20-H), 5.46–5.52 (m, 1H, 15-H), 6.35 (d, *J* = 2.0 Hz,1H, 6-H), 6.41 (d, *J* = 2.0 Hz,1H, 4-H), 6.75 (dd, *J* = 14.2, 10.4 Hz, 1H, 21-H), 7.52 (d, *J* = 10.4 Hz, 1H, NH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{49}NaNO_8$ 610.33504, found 610.33433.

**Enamide analogue 3-100**




To a stirred solution of diyne **3-99** (4.0 mg, 0.007 mmol) in EtOAc (2 mL) containing quinoline (1.4 mg, 0.011 mmol) was added Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned with lead, 4.0 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give enamide **3-100** as a colorless oil (3.4 mg, 85%). $\mathbf{R_f}$ = 0.52 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –4.3 (*c* 0.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.93 (t, *J* = 6.8 Hz, 3H, 27-H), 0.98 (d, *J* = 6.8 Hz, 3H, 16-$CH_3$), 1.05 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.16 (d, *J* = 7.3 Hz, 3H, 23-$CH_3$), 1.28–1.40 (m, 2H, 25-H, 26-H), 1.42–1.71 (m, 4H, 25-H, 26-H, 19-H, OH), 1.88–1.99 (m, 4H, 18-H, 19-H, 11-H, 14-H), 2.07–2.21 (m, 1H, 16-H), 2.27–2.37 (m, 2H, 8-H, 10-H), 2.37–2.50 (m, 1H, 11-H), 2.70–3.00 (m, 4H, 23-H, 14-H, 8-H, OH), 3.45–3.52 (m, 1H, 17-H), 3.71–3.81 (m, 7H, $OCH_3$, 24-H), 3.85–3.91 (m, 1H, 9-H), 5.09–5.19 (m, 1H, 20-H), 5.40 (dd, *J* = 9.9, 4.0 Hz, 1H, 15-H), 5.48–5.54 (m, 2H, 12-H, 13-H), 6.33–6.36 (m, 2H, 6-H, 4-H), 6.74 (dd, *J* = 14.2, 10.4 Hz, 1H, 21-H), 7.52 (d, *J* = 10.4 Hz, 1H, NH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{51}NaNO_8$ 612.35069, found 612.35104.

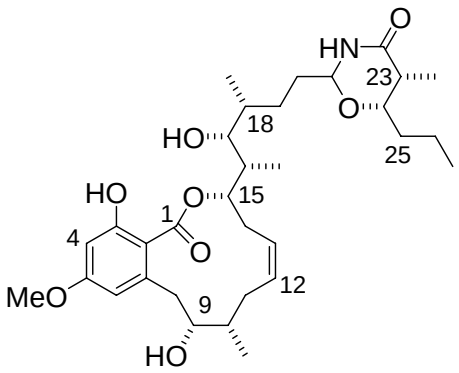
**Oxazinane-4-one 3-101**




**a) *ortho*-demethylation:** A solution of enamide **3-98** (16 mg, 0.016 mmol) in $CH_2Cl_2$ (2 mL) was treated with $BCl_3$ (64 µL, 1.0 M in $CH_2Cl_2$, 0.064 mmol, 4 equiv) at –80 °C. The reaction was stirred for 2 h at –80 °C before a saturated solution of NaOAc (5 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo to give 14 mg of crude 2-hydroxy-4-methoxybenzoate which was used in the next step without futher purification.

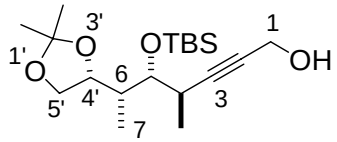
**b) global deprotection:** To a stirred solution of the crude 2-hydroxy-4-methoxybenzoate (14 mg) in THF (0.8 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.6 mL). The reaction mixture was allowed to warm to –10 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 7.6 mg (84% for 2 steps) of triol **3-101**. $\mathbf{R_f}$ = 0.40 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +11.5 (*c* 0.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.6 Hz, 3H, 18-$CH_3$), 0.88–0.96 (m, 6H, 27-H, 16-$CH_3$), 1.01 (d, *J* = 6.8 Hz, 3H, 10-$CH_3$), 1.15 (d, *J* = 7.1 Hz, 3H, 23-$CH_3$), 1.29–1.56 (m, 6H, 25-H, 26-H, 19-H, 20-H), 1.71–1.87 (m, 3H, 18H, 19H, 11-H), 2.00–2.35 (m, 6H, 16-H, 8-H, 11-H, 23-H, OH), 2.58–2.85 (m, 3H, 14-H, 10-H), 2.90 (br s, 1H, OH), 3.24 (dd, *J* = 9.6, 2.3 Hz, 1H, 24-H), 3.74–3.78 (m, 1H, 17-H), 3.80 (s, 3H, $OCH_3$), 3.83–3.90 (m, 1H, 8-H), 3.94–4.00 (m, 1H, 9-H), 5.02 (t, *J* = 8.6 Hz, 1H, 21-H), 5.26–5.30 (m, 1H, 15-H), 6.20 (br d, *J* = 8.8 Hz, 1H, NH), 6.36–6.40 (m, 2H, 4-H, 6-H), 11.2 (br s, 1H, 3-OH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{32}H_{47}NaNO_8$ 596.31994, found 596.31968.

**Oxazinan-4-one analogue 3-102**



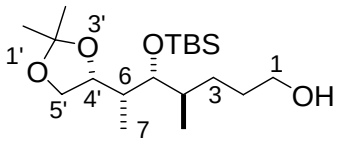

To a stirred solution of alkyne **3-101** (6.0 mg, 0.01 mmol) in EtOAc (2.5 mL) containing quinoline (2.1 mg, 0.016 mmol) was added Lindlar's catalyst (5 wt% Pd on $CaCO_3$, poisoned with lead, 6.0 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give analogue **3-102** as a colorless oil (5.4 mg, 90%). $\mathbf{R_f}$ = 0.39 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –7.1 (*c* 0.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.66 (d, *J* = 6.6 Hz, 3H, 18-$CH_3$), 0.89–0.95 (m, 6H, 27-H, 16-$CH_3$), 1.05 (d, *J* = 6.6 Hz, 3H, 10-$CH_3$), 1.15 (d, *J* = 7.1 Hz, 3H, 23-$CH_3$), 1.27–1.54 (m, 8H, 25-H, 26-H, 19-H, 20-H), 1.71–1.99 (m, 5H, 18-H, 19-H, 16-H, OH), 2.11–2.21 (m, 2H, 10-H, 11-H), 2.25–2.34 (m, 2H, 8-H, 14-H), 2.43–2.54 (m, 1H, 14-H), 2.84–2.96 (m, 1H, 11-H), 3.01 (d, *J* = 2.5 Hz, 1-H, OH), 3.24 (dd, *J* = 9.9, 1.5 Hz, 1H, 24-H), 3.62–3.68 (m, 1H, 17-H), 3.80 (s, 3H, $OCH_3$), 3.82–3.91 (m, 2H, 8-H, 9-H), 5.02–5.09 (m, 1H, 21-H), 5.15 (dd, *J* = 10.7, 6.2 Hz, 1H, 15-H), 5.32–5.40 (m, 1H, 13-H), 5.44–5.54 (m, 1H, 12-H), 6.19 (br d, *J* = 9.1 Hz, 1H, NH), 6.33 (d, *J* = 2.5 Hz, 1H, 6-H), 6.36 (d, *J* = 2.5 Hz, 1H, 4-H), 11.7 (br s, 1H, 3-OH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{32}H_{49}NaNO_8$ 598.33504, found 598.33534.

**(4*R*,5*R*,6*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylhept-2-yn-1-ol (3-103)**




To a solution of alkyne **3-36** (2.03 g, 6.2 mmol) in THF (30 mL) was added *n*BuLi (3.72 mL, 2.5 M solution in hexane, 9.3 mmol, 1.5 equiv) dropwise at –90 °C. Stirring was continued for 1 h at –90 °C before paraformaldehyde (1.86 g, 62 mmol, 10 equiv) was added at –90 °C. The reaction mixture was allowed to warm to room temperature over 1 h and stirred for an additional 1 h. After quenching of the reaction with $H_2O$ (20 mL), the mixture was extracted with $Et_2O$ (3 × 80 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1 → 2:1) of the residue afforded alcohol **3-103** (1.92 g, 87%) as an amorphous solid. $\mathbf{R_f}$ = 0.47 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +3.7 (*c* 2.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 0.99 (d, *J* = 6.8 Hz, 3H, 7-H), 1.14 (d, *J* = 7.1 Hz, 3H, 4-$CH_3$), 1.32 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.89–1.98 (m, 1H, 6-H), 2.19 (t, *J* = 6.0 Hz, 1H, OH), 2.62–2.70 (m, 1H, 4-H), 3.51–3.56 (m, 1H, 5-H), 3.71–3.77 (m, 1H, 5'-H), 4.00–4.13 (m, 2H, 5'-H, 4'-H), 4.13–4.23 (m, 2H, 1-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.4 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), 12.0 (C-7), 16.7 (4-$CH_3$), 18.2 ($Si(C(CH_3)_3)$), 25.5 ($C(CH_3)_2$), 25.7 ($Si(C(CH_3)_3)$), 26.8 ($C(CH_3)_2$), 31.9 (C-4), 39.7 (C-6), 51.2 (C-1), 68.0 (C-5'), 75.0 (C-5), 78.3 (C-4'), 80.9 (C-2), 88.5 (C-3), 108.5 ($C(CH_3)_2$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{19}H_{36}NaO_4Si$ 379.22751, found 349.22761.

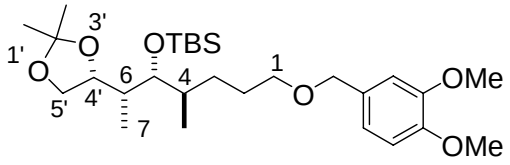
**(4*R*,5*R*,6*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylheptan-1-ol (3-104)**




A 250 mL round-bottom flask was charged with alcohol **3-103** (1.4 g, 3.9 mmol) and a stir bar. EtOAc (120 mL) and 10% Pd/C (0.7 g, 50 wt%) were added with stirring. The reaction was placed under $H_2$ atmosphere and stirred for 5 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 → 2:1) to give primary alcohol **3-104** as a colorless oil (1.32 g, 94%). $\mathbf{R_f}$ = 0.66 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –1.5 (*c* 2.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01, 0.05 (2s, 6H, $Si(CH_3)_2$), 0.86–0.92 (m, 12H, 7-H, $Si(C(CH_3)_3)$), 0.97 (d, *J* = 6.8 Hz, 3H, 4-$CH_3$), 1.03–1.14 (m, 1H, 2-H), 1.33 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.43–1.53 (m, 2H, 3-H, 2-H), 1.55–1.69 (m, 3H, 3-H, 4-H, OH), 1.72–1.78 (m, 1H, 6-H), 3.39–3.43 (m, 1H, 5-H), 3.55–3.65 (m, 3H, 5'-H, 1-H), 3.95–4.02 (m, 1H, 5'-H), 4.09 (dd, *J* = 6.8, 6.8 Hz, 1H, 4'-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.3 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), 11.4 (C-7), 16.3 (4-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 25.5 ($C(CH_3)_2$),

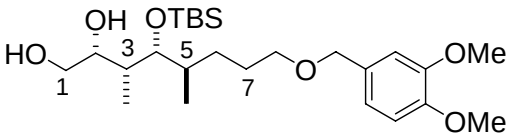
26.0 (Si(C($CH_3$)$_3$)), 26.7 (C($CH_3$)$_2$), 28.6 (C-2), 30.6 (C-3), 37.8 (C-4), 39.3 (C-6), 62.9 (C-1), 68.2 (C-5'), 76.3 (C-5), 77.9 (C-4'), 108.6 ($C$($CH_3$)$_2$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{19}H_{40}NaO_4Si$ 383.25881, found 383.25916.

### *tert*-Butyl[((1*R*,2*R*)-5-[(3,4-dimethoxybenzyl)oxy]-1-{(1*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-2-methylpentyl)oxy]dimethylsilane (3-105)




To a solution of alcohol **3-104** (1.05 g, 2.9 mmol) in $CH_2Cl_2$ (15 mL) were added 3,4-dimethoxybenzyltrichloroacetimidate (2.7 g, 8.7 mmol) and PPTS (1.1 g, 4.4 mmol) at 0 °C. The resultant mixture was stirred at room temperature for 3 d before saturated aqueous $NaHCO_3$ solution was added. After separation of the layers, the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded DMB ether **3-105** (1.4 g, 95%) as a colorless oil. $\mathbf{R_f}$ = 0.49 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –1.0 (*c* 4.1, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.00, 0.03 (2s, 6H, Si($CH_3$)$_2$), 0.85–0.90 (m, 12H, Si(C($CH_3$)$_3$), 2'-H), 0.97 (d, $J$ = 6.8 Hz, 3H, 2-$CH_3$), 1.03–1.12 (m, 1H, 4-H), 1.31 (s, 3H, C($CH_3$)$_2$), 1.37 (s, 3H, C($CH_3$)$_2$), 1.64–1.82 (m, 5H, 1'-H, 3-H, 2-H, 4-H), 3.35–3.44 (m, 3H, 1-H, 5-H), 3.54–3.61 (m, 1H, 5''-H), 3.85 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 3.95–4.02 (m, 2H, 5''-H, 4''-H), 4.41 (s, 2H, $CH_2$ of DMB), 6.78–6.87 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.4 (Si($CH_3$)$_2$), –3.9 (Si($CH_3$)$_2$), 11.5 (C-2'), 15.9 (2-$CH_3$), 18.3 (Si($C$($CH_3$)$_3$)), 25.5 (C($C$$H_3$)$_2$), 26.0 (Si(C($C$$H_3$)$_3$)), 26.7 (C($C$$H_3$)$_2$), 27.9 (C-4), 29.5 (C-3), 38.6 (C-2), 39.2 (C-1'), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 68.1 (C-5''), 70.4 (C-5), 72.8 ($CH_2$ of DMB), 76.0 (C-1), 78.4 (C-4''), 108.3 ($C$($CH_3$)$_2$), 110.8, 110.9, 120.2, 131.1, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{28}H_{50}NaO_6Si$ 533.32689, found 533.32678.

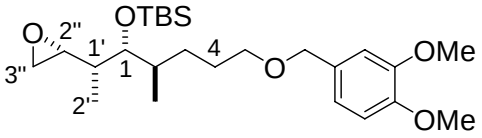
### (2*R*,3*R*,4*R*,5*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-8-[(3,4-dimethoxybenzyl)oxy]-3,5-dimethyloctane-1,2-diol (3-106)




$CuCl_2$·$2H_2O$ (4.3 g, 24.5 mmol, 10 equiv) was added to a solution of acetal **3-105** (1.25 g, 2.45 mmol) in $CH_3CN$ (100 mL) at –10 °C. The reaction mixture was stirred for 20 h at –5 °C, treated with saturated $NH_4Cl$ solution (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water, saturated $NH_4Cl$ solution and saturated NaCl solution, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1→1:2) to give diol **3-106** (1.07 g, 93%) as a colorless oil. $\mathbf{R_f}$ = 0.5 (petroleum ether/EtOAc, 1:2);

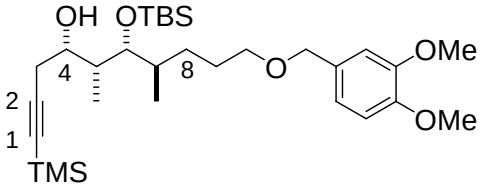
**$[\alpha]^{20}_D$** = –2.5 (*c* 2.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.02, 0.05 (2s, 6H, $Si(CH_3)_2$), 0.85–0.93 (m, 15H, $Si(C(CH_3)_3)$, 3-$CH_3$, 5-$CH_3$), 1.05–1.15 (m, 1H, 7-H), 1.42–1.57 (m, 2H, 6-H, 7-H), 1.63–1.75 (m, 3H, 5-H, 3-H, 6-H), 2.05 (br s, 1H, OH), 3.39–3.58 (m, 4H, 8-H, 4-H, 1-H), 3.60–3.64 (m, 1H, 1-H), 3.67–3.73 (m, 1H, 2-H), 3.85 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.41 (s, 2H, $CH_2$ of DMB), 6.79–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.4 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 9.9 (3-$CH_3$), 16.0 (5-$CH_3$), 18.2 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 27.8 (C-7), 29.3 (C-6), 37.5 (C-5), 38.1 (C-3), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 65.2 (C-1), 70.2 (C-8), 72.8 ($CH_2$ of DMB), 74.9 (C-4), 77.8 (C-2), 110.8, 111.1, 120.3, 130.9, 148.5, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{25}H_{46}NaO_6Si$ 493.29559, found 493.29593.

### *tert*-Butyl[((1*R*,2*R*)-5-[(3,4-dimethoxybenzyl)oxy]-2-methyl-1-{(1*R*)-1-[(2*R*)-oxiran-2-yl]ethyl}pentyl)oxy]dimethylsilane (3-107)



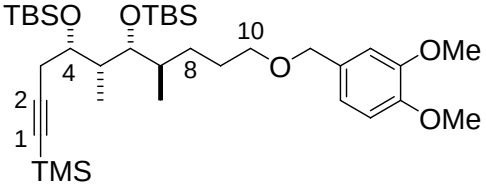

To a solution of diol **3-106** (0.94 g, 2.0 mmol) in THF (25 mL) at 0 °C was added NaH (60% wt. in mineral oil, 0. 24 g, 6.0 mol, 3.0 equiv). The resulting mixture was warmed to room temperature and stirred for 40 min. The mixture was cooled to 0 °C before N-(2,4,6-triisopropylbenzenesulfonyl)imidazole (**3-41**) (0.74 g, 2.2 mmol, 1.1 equiv) was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with water (20 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (EtOAc/petroleum ether, 1:10) provided epoxide **3-107** (0.83 g, 1.82 mmol, 92%) as a colorless oil. **$R_f$** = 0.51 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = +3.0 (*c* 1.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01, 0.05 (2s, 6H, $Si(CH_3)_2$), 0.86–0.91 (m, 12H, $Si(C(CH_3)_3)$, 2'-H), 1.05 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 1.30–1.37 (m, 1H, 3-H), 1.44–1.76 (m, 5H, 3-H, 2-H, 4-H, 1'-H), 2.70–2.76 (m, 1H, 3''-H), 2.80–2.85 (m, 1H, 3''-H), 2.78–2.83 (m, 1H, 2''-H), 3.39–3.45 (m, 2H, $CH_2$ODMB), 3.50–3.54 (m, 1H, CH(OTBS)), 3.86 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.42 (s, 2H, $CH_2$ of DMB), 6.79–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.2 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 12.7 (C-2'), 16.2 (2-$CH_3$), 18.3 ($Si(C(CH_3)_3)$), 26.0 ($Si(C(CH_3)_3)$), 27.9 (C-4), 29.0 (C-3), 37.9 (C-2), 40.1 (C-1'), 47.6 (C-3''), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 56.3 (C-2''), 70.5 ($CH_2$ODMB), 72.9 ($CH_2$ of DMB), 77.5 (CH(OTBS)), 110.8, 111.0, 120.2, 131.1, 148.5, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{25}H_{44}NaO_5Si$ 475.28502, found 475.28542.

### (4*S*,5*R*,6*R*,7*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-10-[(3,4-dimethoxybenzyl)oxy]-5,7-dimethyl-1-(trimethylsilyl)dec-1-yn-4-ol (3-108)




A solution of *n*BuLi (2.1 mL, 2.5 M in hexane, 5.22 mmol) was added to a solution of (trimethylsilyl)acetylene (0.73 mL, 5.22 mmol) in THF (12 mL) at –80 °C in a dropwise fashion. The acetylide solution was stirred at –80 °C for 1 h before a solution of $BF_3{\cdot}OEt_2$ (0.66 mL, 5.22 mmol) was added. Stirring was continued for 50 min at –80 °C. Then, a solution of epoxide **3-107** (0.787 g, 1.74 mmol) in THF (3 mL) was added dropwise. The reaction was stirred at –80 °C for 20 min and then quenched with saturated $NH_4Cl$ solution. The layers were separated and the aqueous layer was extracted twice with $Et_2O$. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil, which was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to furnish alcohol **3-108** (0.814 g, 85%) as colorless oil. $\mathbf{R_f}$ = 0.48 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –4.6 (*c* 3.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.03, 0.06 (2s, 6H, $Si(CH_3)_2$), 0.11 (s, 9H, $Si(CH_3)_3$), 0.85–0.93 (m, 15H, $Si(C(CH_3)_3)$, 7-$CH_3$, 5-$CH_3$), 1.05–1.25 (m, 1H, 9-H), 1.39–1.59 (m, 2H, 8-H, 9-H), 1.62–1.75 (m, 2H, 7-H, 8-H), 1.85–1.93 (m, 1H, 5-H), 2.32 (d, *J* = 3.5 Hz, 1H, OH), 2.38 (d, *J* = 6.6 Hz, 2H, 3-H), 3.41 (t, *J* = 6.6 Hz, 2H, 10-H), 3.63–3.67 (m, 1H, 6-H), 3.70–3.76 (m, 1H, 4-H), 3.84 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.40 (dd, *J* = 21.2, 11.6 Hz, 2H, $CH_2$ of DMB), 6.78–6.89 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.4 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 0.0 ($Si(CH_3)_3$), 8.6 (5-$CH_3$), 15.6 (7-$CH_3$), 18.2 ($Si(C(CH_3)_3)$), 25.9 ($Si(C(CH_3)_3)$), 26.2 (C-3), 27.9 (C-9), 29.5 (C-8), 38.2 (C-7), 38.6 (C-5), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 70.3 (C-10), 72.8 ($CH_2$ of DMB), 73.4 (C-4), 78.2 (C-6), 87.0 (C-1), 103.6 (C-2), 110.8, 110.9, 120.2, 131.0, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{30}H_{54}NaO_5Si_2$ 573.34020, found 573.34077.

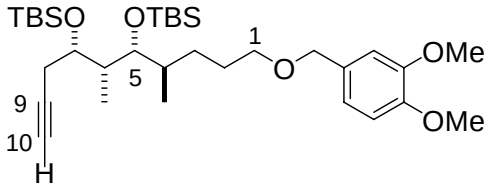
**(5*R*,6*R*,7*S*)-5-{(1*R*)-4-[(3,4-Dimethoxybenzyl)oxy]-1-methylbutyl}-2,2,3,3,6,9,9,10,10-nonamethyl-7-[3-(trimethylsilyl)prop-2-ynyl]-4,8-dioxa-3,9-disilaundecane (3-109)**




A solution of alcohol **3-108** (0.80 g, 1.45 mmol) in $CH_2Cl_2$ (10 mL) was cooled to –50 °C. Then 2,6-lutidine (0.69 ml, 5.8 mmol) followed by TBSOTf (0.54 ml, 2.32 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was treated with water and extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 20:1) afforded bis-silyl ether **3-109** (0.915 g, 95%) as a colorless oil. $\mathbf{R_f}$ = 0.74 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +4.6 (*c* 2.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01-0.04 (m, 9H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.11 (s, 9H, $Si(CH_3)_3$), 0.85–0.94 (m, 24H, $Si(C(CH_3)_3)$, 7-$CH_3$, 5-$CH_3$), 1.07–1.17 (m, 1H, 9-H), 1.43–1.56 (m, 2H, 8-H, 9-H), 1.59–1.66

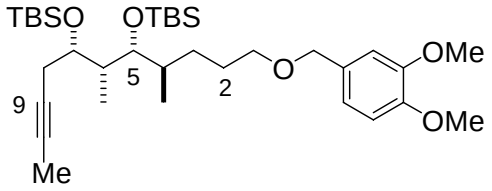
(m, 1H, 8-H), 1.68–1.77 (m, 1H, 7-H), 1.86–1.94 (m, 1H, 5-H), 2.38 (ddd, *J* = 30.8, 17.1, 5.7 Hz, 2H, 3-H), 3.36–3.48 (m, 2H, 10-H), 3.50–3.54 (m, 1H, 6-H), 3.67–3.74 (m, 1H, 4-H), 3.86 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 4.42 (s, 2H, $CH_2$ of DMB), 6.79–6.89 (m, 3H, aryl H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.5 ($Si(CH_3)_2$), –4.1 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), –3.5 ($Si(CH_3)_2$), 0.02 ($Si(CH_3)_3$), 10.6 (5-$CH_3$), 16.7 (7-$CH_3$), 18.1 ($Si(C(CH_3)_3)$), 18.5 ($Si(C(CH_3)_3)$), 25.9 ($Si(C(CH_3)_3)$), 26.2 ($Si(C(CH_3)_3)$), 26.7 (C-3), 28.1 (C-9), 28.2 (C-8), 37.8 (C-7), 40.2 (C-5), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 70.7 (C-10), 72.5 (C-4), 72.8 ($CH_2$ of DMB), 76.2 (C-6), 86.3 (C-1), 104.6 (C-2), 110.8, 111.0, 120.2, 131.2, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{68}NaO_5Si_3$: 687.42668, found 687.42711.

**(5*R*,6*R*,7*S*)-5-{(1*R*)-4-[(3,4-Dimethoxybenzyl)oxy]-1-methylbutyl}-2,2,3,3,6,9,9,10,10-nonamethyl-7-prop-2-ynyl-4,8-dioxa-3,9-disilaundecane (3-110)**



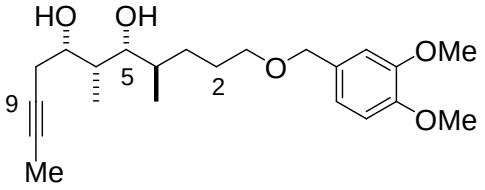

To a solution of bis-silyl ether **3-109** (0.91 g, 1.37 mmol) in methanol (25 mL) was added anhydrous $K_2CO_3$ (1.89 g, 13.7 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with water (10 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (ethyl acetate/petroleum ether, 1:4) provided compound **3-110** (0.803 g, 99%) as a colorless oil. **$R_f$** = 0.69 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = +7.6 (*c* 2.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.01–0.03 (m, 9H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.85–0.94 (m, 24H, $Si(C(CH_3)_3)$, 4-$CH_3$, 6-$CH_3$), 1.05–1.16 (m, 1H, 2-H), 1.45–1.76 (m, 4H, 2-H, 3-H, 4-H), 1.89 (t, *J* = 2.3 Hz, 1H, 10-H), 1.91–2.01 (m, 1H, 6-H), 2.25–2.42 (m, 2H, 8-H), 3.35–3.46 (m, 2H, 1-H), 3.49–3.55 (m, 1H, 5-H), 3.72 (dd, *J* = 10.9, 5.1 Hz, 1H, 7-H), 3.83 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.40 (s, 2H, $CH_2$ of DMB), 6.76–6.87 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.7 ($Si(CH_3)_2$), –4.3 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 10.4 (6-$CH_3$), 16.8 (4-$CH_3$), 17.9 ($Si(C(CH_3)_3)$), 18.4 ($Si(C(CH_3)_3)$), 25.2 (C-8), 25.7 ($Si(C(CH_3)_3)$), 26.1 ($Si(C(CH_3)_3)$), 27.9 (C-2), 28.0 (C-3), 37.5 (C-4), 39.9 (C-6), 55.6 ($OCH_3$), 55.7 ($OCH_3$), 70.2 (C-10), 70.5 (C-1), 72.0 (C-7), 72.6 ($CH_2$ of DMB), 76.2 (C-5), 81.3 (C-9), 110.7, 110.8, 120.0, 131.1, 148.3, 148.8 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{60}NaO_5Si_2$: 615.38715, found 615.38703.

**(5*S*,6*R*,7*R*)-5-But-2-ynyl-7-{(1*R*)-4-[(3,4-dimethoxybenzyl)oxy]-1-methylbutyl}-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (3-111)**



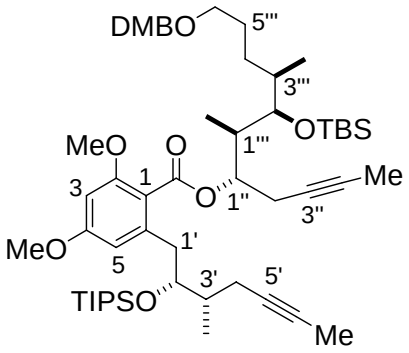
To a solution of alkyne **3-110** (0.79 g, 1.33 mmol) in THF (10 mL) was added *n*BuLi (0.96 mL, 2.5 M solution in hexane, 2.40 mmol, 1.8 equiv) dropwise at –80 °C. Stirring was continued for 1 h at –80 °C before methyl iodide (0.38 mL, 6.65 mmol) was added at –80 °C. The reaction mixture was allowed to warm to room temperature over 4 h. After quenching with water (3 mL), all volatiles were removed in vacuo and the residue was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to furnish the propyne derivative **3-111** (0.80 g, 99%). $\mathbf{R_f}$ = 0.72 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +4.2 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.00–0.04 (m, 9H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.84–0.89 (m, 21H, $Si(C(CH_3)_3$), 4-$CH_3$), 0.92 (d, *J* = 6.8 Hz, 3H, 6-$CH_3$), 1.05–1.17 (m, 1H, 2-H), 1.45–1.57 (m, 3H, 2-H, 3-H) 1.59–1.66 (m, 1H, 4-H), 1.72 (t, *J* = 2.0 Hz, 3H, 10-$CH_3$), 1.89–1.97 (m, 1H, 6-H), 2.20–2.36 (m, 2H, 8-H), 3.37–3.47 (m, 2H, 1-H), 3.50–3.54 (m, 1H, 5-H), 3.69 (dd, *J* = 10.9, 5.1 Hz, 1H, 7-H), 3.86 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.42 (s, 2H, $CH_2$ of DMB), 6.79–6.89 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.5 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), –3.5 ($Si(CH_3)_2$), 3.5 (10-$CH_3$), 10.5 (6-$CH_3$), 17.0 (4-$CH_3$), 18.1 (Si(*C*$(CH_3)_3$)), 18.5 (Si(*C*$(CH_3)_3$)), 25.6 (C-8), 25.9 (Si(C(*C*$H_3)_3$)), 26.2 (Si(C(*C*$H_3)_3$)), 27.9 (C-2), 28.2 (C-3), 37.6 (C-4), 40.1 (C-6), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 70.8 (C-1), 72.7 (C-7), 72.8 ($CH_2$ of DMB), 76.4 (C-9), 76.5 (C-5), 77.2 (C-10), 110.8, 110.9, 120.1, 131.2, 148.4, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{34}H_{62}NaO_5Si_2$: 629.40280, found 629.40278.

**(5*S*,6*R*,7*R*,8*R*)-11-[(3,4-Dimethoxybenzyl)oxy]-6,8-dimethylundec-2-yne-5,7-diol (3-112)**




To a solution of silyl ether **3-111** (0.79 g, 1.30 mmol) in THF (2 mL) was added TBAF (6.5 mL, 1 M in THF) at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 2:1→1:2) afforded diol **3-112** (0.486 g, 99%) as a colorless oil. $\mathbf{R_f}$ = 0.56 (petroleum ether/EtOAc, 1:2); $\mathbf{[\alpha]^{20}_D}$ = +5.2 (*c* 1.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.8 Hz, 3H, 6-$CH_3$), 0.84 (d, *J* = 7.1 Hz, 3H, 4-$CH_3$), 1.16–1.29 (m, 1H, 2-H), 1.48–1.65 (m, 2H, 2-H, 3-H), 1.66–1.75 (m, 2H, 4-H, 3-H), 1.76 (t, *J* = 2.3 Hz, 3H, 10-$CH_3$), 1.81–1.88 (m, 1H, 6-H), 2.20–2.43 (m, 2H, 8-H), 3.20 (br s, 2H, OH), 3.40–3.50 (m, 3H, 1-H, 5-H), 3.84–3.93 (m, 7H, 7-H, $OCH_3$), 4.42 (s, 2H, $CH_2$ of DMB), 6.79–6.88 (m, 3H, aryl H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 3.5 (10-$CH_3$), 4.1 (6-$CH_3$), 15.6 (4-$CH_3$), 25.3 (C-8), 26.4 (C-2), 29.2 (C-3), 36.0 (C-4), 36.7 (C-6), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 70.5 (C-1), 72.9 ($CH_2$ of DMB), 75.5 (C-9), 75.7 (C-7), 77.9 (C-10), 80.7 (C-5), 110.8, 111.0, 120.3, 130.9, 148.5, 148.9 (aryl C);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{22}H_{34}NaO_5$: 401.22985, found 401.22968.

**Ester 3-114**

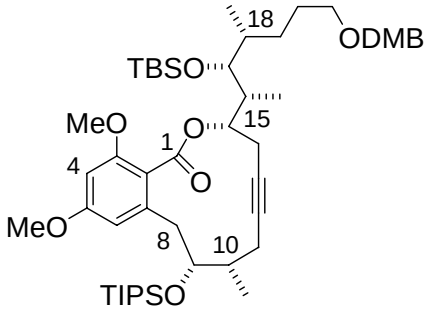



A solution of diol **3-112** (470 mg, 1.24 mmol) in anhydrous DMF (2.5 mL) was stirred in the presence of sodium hydride (60% wt. in mineral oil, 124 mg, 3.1mmol, 2.5 equiv) at 0 °C for 10 min and for a further 1 h at room temperature. In a separate flask, to a solution of acid **3-50** (917 mg, 2.0 mmol) in anhydrous DMF (3.5 mL) was added CDI (390 mg, 2.4 mmol), and the reaction mixture allowed to stir for 4 h at 50 °C. Then, the solution of the imidazolide derivative **3-63** (analyzed by LC-MS) was cooled to 0 °C and added to the above solution of the disodium salt of diol **3-112** at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 days. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo to provide 1.01 g of crude hydroxyester **3-113**, which was used in the next step without further purification.

A solution of crude hydroxyester **3-113** (1.01 g, 1.23 mmol) in $CH_2Cl_2$ (10 mL) was cooled to –50 °C, then 2,6-lutidine (0.58 mL, 4.9 mmol) followed by TBSOTf (0.46 mL, 2.0 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h before it was treated with water. After separation of the layers, the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 10:1→4:1) afforded ester **3-114** (0.778 g, 67% for 2 steps, based on diol **3-112**) as a colorless oil. Besides ester **3-114** some unreacted imidazolide derivative **3-63** (295 mg, 30%) was isolated. $\mathbf{R_f}$ = 0.46 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = +24.8 (*c* 2.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = –0.01, 0.02 (2s, 6H, $Si(CH_3)_2$), 0.83–0.89 (m, 12H, $Si(C(CH_3)_3)$, 3'''-$CH_3$), 0.89 –0.97 (m, 27H, 1'''-$CH_3$, 3'-$CH_3$, $Si(CH(CH_3)_2)_3$), 1.04–1.11 (m, 1H, 5'''-H), 1.45–1.58 (m, 3H, 4'''-H, 5'''-H), 1.66 (t, *J* = 2.3 Hz, 3H, C≡C$CH_3$), 1.71 (t, *J* = 2.3 Hz, 3H, C≡C$CH_3$), 1.80–1.91 (m, 1H, 3'-H), 1.96–2.05 (m, 2H, 3'''-H, 4'-H), 2.07–2.20 (m, 2H, 1'''-H, 4'-H), 2.49–2.71 (m, 4H, 2''-H, 1'-H), 3.34–3.40 (m, 2H, $CH_2$ODMB), 3.50–3.54 (m, 1H, CH(OTBS)), 3.69 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.80–3.84 (m, 6H, $OCH_3$ of DMB), 4.21–4.36 (m, 1H, CH(OTIPS)), 4.37 (s, 2H, $CH_2$ of DMB), 4.93–5.00 (m, 1H, 1''-H), 6.24 (d, *J* = 2.3 Hz, 1H, 5-H), 6.43 (d, *J* = 2.3 Hz, 3-H), 6.74–6.85 (m, 3H, aryl H of DMB); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –3.7 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 3.5 (C≡C$CH_3$), 3.5 (C≡C$CH_3$), 10.3 (1'''-$CH_3$), 12.9 (*C*H($CH_3$)$_2$), 14.6 (3'-$CH_3$), 16.5 (Si*C*($CH_3$)$_3$), 18.0 (CH(*C*$H_3$)$_2$), 18.2 (CH(*C*$H_3$)$_2$), 18.5 (3'''-$CH_3$), 22.1 (C≡*C*$CH_2$), 22.1 (C≡C*C*$H_2$), 26.1 (Si(C(*C*$H_3$)$_3$)), 28.0 (C-5'''), 28.7 (C-4'''), 36.2 (C-1'), 37.5 (C-3'''), 37.8 (C-1'''), 38.8 (C-3'), 55.2 ($OCH_3$), 55.6 ($OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 70.7 (C-6'''), 72.8 ($CH_2$ of DMB), 74.6 ($CH_3$*C*≡C), 74.9 ($CH_3$*C*≡C), 75.2 (C-2'), 76.0 ($CH_2$*C*≡C), 76.6

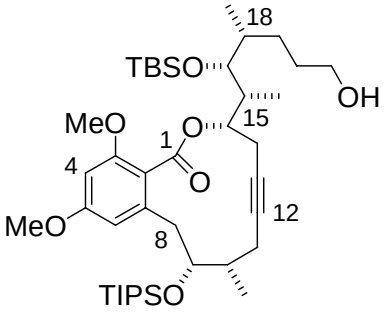
($CH_2C{\equiv}C$), 77.9 (C-2'''), 78.1 (C-1''), 96.7 (C-3), 107.0 (C-5), 110.8 (ar of DMB), 111.0 (ar of DMB), 117.9 (C-1), 120.2 (ar of DMB), 131.2 (ar of DMB), 139.0 (C-6), 148.4 (ar of DMB), 148.9 (ar of DMB), 157.8 (C-4), 160.7 (C-2), 167.7 ($CO_2R$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{54}H_{88}NaO_9Si_2$ 959.58591, found 959.58513.

**Macrolactone 3-115**



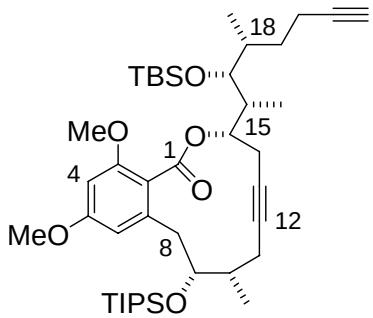

To a solution of ester **3-114** (650 mg, 0.69 mmol) in toluene (81 mL) was added a solution of ($t$BuO)$_3$W≡CCMe$_3$ (**2-34**) (32.8 mg, 0.069 mmol) in toluene (1.0 mL) and the mixture was stirred at 85 °C for 3 h. For workup, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give macrolactone **3-115** as an amorphous solid (553 mg, 90%). $\mathbf{R_f}$ = 0.63 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –19.0 ($c$ 2.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.01–0.06 (m, 6H, Si($CH_3$)$_2$), 0.87–0.97 (m, 36H, 18-$CH_3$, 10-$CH_3$, Si(C($CH_3$)$_3$), Si(C$H$(C$H_3$)$_2$)$_3$), 1.03 (d, $J$ = 6.8 Hz, 3H, 16-$CH_3$), 1.40–1.52 (m, 2H, 20-H), 1.60–1.85 (m, 4H, 19-H, 11-H, 16-H), 1.89–1.98 (m, 1H, 18-H), 2.09–2.19 (m, 1H, 11-H), 2.35–2.51 (m, 4H, 14-H, 8-H, 10-H), 3.37 (dd, $J$ = 6.4, 6.4 Hz, 2H, 21-H), 3.48 (dd, $J$ = 4.3, 4.3 Hz, 1H, 17-H), 3.71–3.79 (m, 7H, 8-H, $OCH_3$), 3.84–3.87 (m, 6H, $OCH_3$ of DMB), 3.98–4.02 (m, 1H, 9-H), 4.40 (s, 2H, $CH_2$ of DMB), 5.35–5.50 (m, 1H, 15-H), 6.30 (d, $J$ = 2.0, 1H, 6-H), 6.40 (d, $J$ = 2.0, 1H, 4-H), 6.78–6.88 (m, 3H, ar of DMB); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 (Si($CH_3$)$_2$), –3.7 (Si($CH_3$)$_2$), 11.2 (16-$CH_3$), 12.9 ($C$H(C$H_3$)$_2$), 16.7 (10-$CH_3$), 17.8 (CH($C$H$_3$)$_2$), 18.0 (CH($C$H$_3$)$_2$), 18.3 (18-$CH_3$), 23.3 (C≡C$C$H$_2$), 23.5 (C≡C$C$H$_2$), 26.1 (Si(C($C$H$_3$)$_3$)), 27.7 (C-20), 28.4 (C-19), 37.4 (2C, C-16, C-18), 38.5 (C-8), 40.3 (C-10), 55.1 ($OCH_3$), 55.7 ($OCH_3$), 55.7 ($OCH_3$), 55.8 ($OCH_3$), 70.3 (C-21), 72.7 ($CH_2$ of DMB), 76.0 (C-15), 77.2 (C-17), 79.6 (C-9), 81.2 ($CH_2C{\equiv}C$), 96.6 (C-3), 108.2 (C-6), 110.8 (ar of DMB), 110.9 (ar of DMB), 118.1 (C-2), 120.1 (ar of DMB), 131.1 (ar of DMB), 139.3 (C-7), 148.4 (ar of DMB), 148.9 (ar of DMB), 157.2 (C-5), 160.2 (C-3), 167.3 ($CO_2R$);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{50}H_{82}NaO_9Si_2$ 905.53896, found 905.53829.

**Alcohol 3-116**




To a cooled (0 °C) solution of DMB ether **3-115** (540 mg, 0.61 mmol) in a mixture of $CH_2Cl_2$/pH = 7 phosphate buffer (20:1, 32 mL) was added DDQ (194 mg, 0.85 mmol, 1.4 equiv). The mixture was allowed to warm to room temperature and stirred for 40 min. Then it was treated with saturated $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded alcohol **3-116** (435 mg, 97%) as an amorphous solid. $\mathbf{R_f}$ = 0.42 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –28.0 (*c* 4.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.02, 0.06 (2s, 6H, $Si(CH_3)_2$), 0.86–0.96 (m, 36H, 18-$CH_3$, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.02 (d, *J* = 7.1 Hz, 3H, 10-$CH_3$), 1.05–1.10 (m, 1H, 20-H), 1.38–1.51 (m, 2H, 20-H, 19-H), 1.55–1.73 (m, 3H, 19-H, 11-H, OH), 1.76–1.82 (m, 1H, 11-H), 1.86–1.97 (m, 1H, 16-H), 2.10–2.18 (m, 1H, 18-H), 2.34–2.51 (m, 4H, 8-H, 14-H, 10-H), 3.50 (dd, *J* = 4.3, 4.3 Hz, 1H, 17-H), 3.55 (dd, *J* = 6.3, 6.3 Hz, 2H, 21-H), 3.70–3.78 (m, 7H, 8-H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.96–4.02 (m, 1H, 9-H), 5.37–5.50 (m, 1H, 15-H), 6.31 (d, *J* = 2.3 Hz, 1H, 6-H), 6.40 (s, *J* = 2.3 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.4 (16-$CH_3$), 12.9 ($CH(CH_3)_2$), 16.7 (10-$CH_3$), 17.8 ($Si(C(CH_3)_3)$), 18.0 ($CH(CH_3)_2$), 18.3 (18-$CH_3$), 23.2 (C-14), 23.4 (C-11), 26.1 ($Si(C(CH_3)_3)$), 28.0 (C-20), 30.7 (C-19), 37.4 (C-16), 37.4 (C-18), 38.6 (C-8), 40.3 (C-10), 55.1 ($OCH_3$), 55.8 ($OCH_3$), 62.9 (C-21), 76.0 (C-15), 76.7 (C-17), 77.3 (C≡C), 79.6 (C-9), 81.2 (C-12), 96.7 (C-4), 108.3 (C-2), 118.1 (C-6), 139.4 (C-7), 157.2 (C-5), 160.2 (C-3), 167.4 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{41}H_{72}NaO_7Si_2$ 755.47088, found 755.47080.

**Alkyne 3-118**

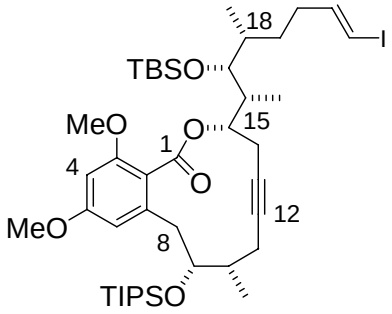



**a) Aldehyde 3-117:** To a cooled (0 °C) solution of alcohol **3-116** (198 mg, 0.27 mmol) in $CH_2Cl_2$ (6 mL) was added a solution of Dess-Martin periodinane (15% wt, 1.02 mL, 0.49 mmol). After stirring for 0.5 h at 0 °C and for 2 h at room temperature, the reaction mixture was concentrated, loaded on a flash column, and eluted with petroleum ether/EtOAc, 4:1 to

give 188 mg (95%) of aldehyde **3-117**, which was used directly in the next reaction. TLC (petroleum ether/EtOAc, 4:1): $R_f = 0.69$.

**b) Alkyne 3-118:** Diethyl-1-diazo-2-oxopropylphosphonate (**3-79**) (124 mg, 0.52 mmol, 2 equiv) was added to a solution of aldehyde **3-117** obtained in the previous step (188 mg, 0.26 mmol) and $K_2CO_3$ (122 mg, 0.88 mmol, 3.4 equiv) in MeOH (5 mL) followed by stirring of the mixture for 12 h at room temperature. The reaction mixture was diluted with $Et_2O$ (50 mL), washed with an aqueous solution (5%) of $NaHCO_3$ (20 mL). The layers were separated and the organic layer dried over $Na_2SO_4$. After filtration and evaporation of the solvent the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:10) to give 179 mg (97%) of alkyne **3-118** as an amorphous solid. $\mathbf{R_f} = 0.78$ (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D} = -32.2$ (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta = 0.03–0.07$ (m, 6H, $Si(CH_3)_2$), 0.86–0.99 (m, 36H, 16-$CH_3$, 18-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.04 (d, $J = 7.1$ Hz, 3H, 10-$CH_3$), 1.20–1.32 (m, 1H, 20-H), 1.61–1.71 (m, 1H, 20-H), 1.75–1.84 (m, 1H, 16-H), 1.87–1.98 (m, 3H, 19-H, C≡CH), 2.02–2.28 (m, 3H, 10-H, 11-H, 18-H), 2.36–2.47 (m, 4H, 8-H, 14-H, 11-H), 3.52 (dd, $J = 4.3$, 4.3 Hz, 1H, 17-H), 3.71–3.79 (m, 7H, 8-H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.97–4.02 (m, 1H, 9-H), 5.40–5.52 (m, 1H, 15-H), 6.31 (d, $J = 2.0$ Hz, 1H, 6-H), 6.41 (s, $J = 2.0$ Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta = -4.0$ ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 11.3 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 16.4 (10-$CH_3$), 16.5 (C-20), 17.8 ($CH(CH_3)_2$), 18.0 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 23.2 (C-14), 23.3 (C-11), 26.1 ($Si(C(CH_3)_3)$), 30.8 (C-19), 36.5 (C-18), 37.5 (C-16), 38.6 (C-8), 40.4 (C-10), 55.1 ($OCH_3$), 55.7 ($OCH_3$), 68.4 (C-22), 74.8 (C≡C), 75.6 (C-15), 77.2 (C-17), 79.6 (C≡C), 81.2 (C≡C), 84.5 (C-9), 96.6 (C-4), 108.2 (C-2), 118.1 (C-6), 139.4 (C-7), 157.2 (C-5), 160.2 (C-3), 167.3 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{42}H_{70}NaO_6Si_2$ 749.46031, found 749.46039.

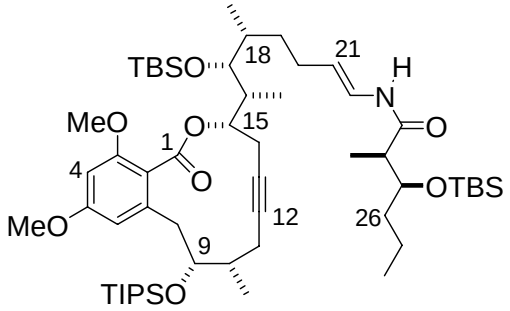
### *E*-Vinyl iodide 3-119




$[Cp_2Zr(H)Cl]$ (38 mg, 0.14 mmol) was added to a solution of alkyne **3-118** (51 mg, 0.07 mmol) in THF (1.5 mL) at 0 °C and the resulting mixture was stirred for 2 h at that temperature. A solution of $I_2$ (0.28 ml, 0.5M in THF, 0.14 mmol) was then added dropwise and stirring was continued for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (5 mL), and the mixture was repeatedly extracted with $Et_2O$. The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give *E*-vinyl iodide **3-119** as an amorphous solid (66 mg, 95%). $\mathbf{R_f} = 0.77$ (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D} = -21.0$ (*c* 3.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta = 0.03–0.07$ (m, 6H, $Si(CH_3)_2$), 0.84–0.97 (m, 36H, 16-$CH_3$, 18-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3$), 1.04 (d, $J = 6.8$ Hz, 3H, 10-$CH_3$), 1.20–1.26 (m, 1H, 20-H), 1.43–1.54 (m, 1H, 19-H), 1.64–1.72 (m, 1H, 20-H), 1.74–1.82 (m, 1H, 16-H), 1.87–

1.98 (m, 2H, 19-H, 18-H), 2.02–2.20 (m, 2H, 10-H, 11-H), 2.37–2.48 (m, 4H, 8-H, 14-H, 11-H), 3.52 (dd, *J* = 4.3, 4.3 Hz, 1H, 17-H), 3.72–3.81 (m, 7H, 8-H, $OCH_3$), 3.97–4.02 (m, 1H, 9-H), 5.39–5.44 (m, 1H, 15-H), 5.90 (d, *J* = 14.4 Hz, 1H, 22-H), 6.33 (d, *J* = 2.0 Hz, 1H, 6-H), 6.36–6.45 (m, 2H, 4-H, 21-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.0 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 11.5 (16-$CH_3$), 13.0 ($CH(CH_3)_2$), 16.4 (10-$CH_3$), 16.5 (C-20), 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 23.2 (C-14), 23.2 (C-11), 26.1 ($Si(C(CH_3)_3)$), 30.8 (C-19), 34.1 (C-20), 37.4 (C-18), 37.5 (C-16), 38.6 (C-8), 40.0 (C-10), 55.2 ($OCH_3$), 55.8 ($OCH_3$), 74.5 (C-22), 75.4 (C-15), 77.2 (C-17), 79.6 (C≡C), 81.4 (C-9), 96.6 (C-4), 108.4 (C-2), 118.0 (C-6), 139.4 (C-7), 146.6 (C-21), 157.3 (C-5), 160.3 (C-3), 167.3 (C-1);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{42}H_{71}INaO_6Si_2$ 877.37261, found 877.37329.

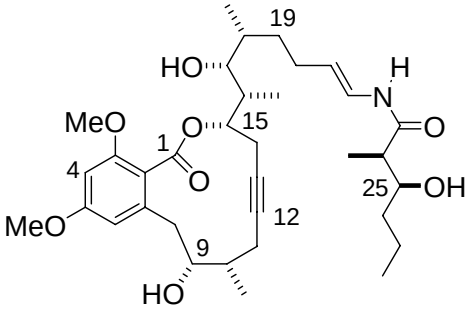
**Enamide 3-120**




A Schlenk tube was charged with CuI (14.0 mg, 0.075 mmol, 1 equiv), amide **3-97** (39 mg, 0.15 mmol, 2 equiv), and $Cs_2CO_3$ (62 mg, 0.19 mmol, 2.5 equiv). The tube was evacuated and backfilled with argon. N,N'- Dimethylethylenediamine (16.0 µL, 0.15 mmol, 2eq), vinyl iodide **3-119** (64 mg, 0.075 mmol) and THF (1.0 mL) were added under argon. The Schlenk tube was closed with a glass stopper, immersed in a preheated to 60 °C oil bath and the reaction mixture was stirred for 14 h. After the resulting pale blue suspension was allowed to reach room temperature, ethyl acetate (5 mL) was added and the reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 10:1→4:1) to give enamide **3-120** as an amorphous solid (63 mg, 85%). $\mathbf{R_f}$ = 0.72 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –23.9 (*c* 1.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.02–0.07 (m, 6H, $Si(CH_3)_2$), 0.08–0.10 (m, 6H, $Si(CH_3)_2$), 0.85–1.01 (m, 48H, 24-$CH_3$, 28-H, 16-$CH_3$, $Si(C(CH_3)_3)$, $Si(CH(CH_3)_2)_3)$, 1.02–1.10 (m, 6H, 18-$CH_3$, 10-$CH_3$), 1.16–1.27 (m, 3H, 20-H, 27-H), 1.30–1.52 (m, 5H, 26-H, 27-H, 18-H, 19-H), 1.74–1.83 (m, 1H, 16-H), 1.86–1.99 (m, 2H, 10-H, 11-H), 2.04–2.19 (m, 2H, 19-H, 11-H), 2.36–2.55 (m, 5H, 8-H, 14-H, 24-H), 3.43–3.48 (m, 1H, 17-H), 3.71–3.79 (m, 7H, $OCH_3$, 25-H), 3.97–4.03 (m, 1H, 9-H), 4.94–5.03 (m, 1H, 21-H), 5.35–5.49 (m, 1H, 15-H), 6.31 (d, *J* = 2.0 Hz, 1H, 6-H), 6.41 (d, *J* = 2.0 Hz, 1H, 4-H), 6.73 (dd, *J* = 14.2, 10.6 Hz, 1H, 22-H), 8.08 (br d, *J* = 10.6 Hz, 1H, NH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 11.2 (16-$CH_3$), 12.6 (24-$CH_3$), 13.0 ($CH(CH_3)_2$), 14.1 (C-28), 16.5 (10-$CH_3$), 17.9 ($Si(C(CH_3)_3)$), 17.9($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 18.4 (18-$CH_3$), 19.3 (C-27), 23.3 (C-14), 23.6 (C-11), 25.9 ($Si(C(CH_3)_3)$), 26.2 ($Si(C(CH_3)_3)$), 27.7 (C-20), 32.5 (C-19), 34.7 (C-26), 37.0 (C-18), 37.6 (C-16), 38.6 (C-8), 40.6 (C-10), 45.6 (C-24), 55.2 ($OCH_3$), 55.7 ($OCH_3$), 75.0 (C-17), 76.1 (C-9), 76.8 (C-15),

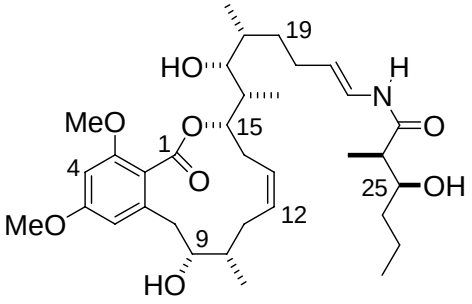
77.2 (C-25), 79.6 (*C*≡C), 81.2 (*C*≡C), 96.7 (C-4), 108.3 (C-6), 112.2 (C-21), 118.2 (C-2), 122.6 (C-22), 139.4 (C-7), 157.2 (C-5), 160.2 (C-3), 167.4 (C-1), 171.0 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{55}H_{99}NNaO_8Si_3$ 1008.65707, found 1008.65733.

**Deprotected macrolactone 3-121**



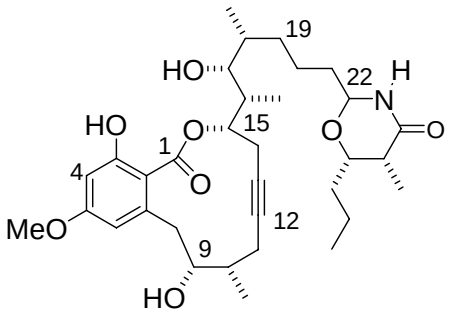

To a stirred solution of the enamide **3-120** (12 mg, 0.012 mmol) in THF (0.4 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.3 mL). The reaction mixture was allowed to warm to –10 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 6.1 mg (85%) of triol **3-121**. $\mathbf{R_f}$ = 0.38 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –4.2 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3H, 18-$CH_3$), 0.91 (t, *J* = 7.1 Hz, 3H, 28-H), 0.99 (d, *J* = 7.1 Hz, 3H,10-$CH_3$), 1.10 (d, *J* = 7.1 Hz, 3H, 16-$CH_3$), 1.14 (d, *J* = 7.1 Hz, 3H, 24-$CH_3$), 1.24–1.50 (m, 5H, 26-H, 27-H, 20-H), 1.55–1.77 (m, 4H, 19-H, 20-H, OH), 1.89–2.02 (m, 3H, 18-H, 19-H, 11-H), 2.05–2.20 (m, 3H, 16-H, 24-H, 11-H), 2.24–2.33 (m, 1H, 8-H), 2.46–2.62 (m, 3H, 14-H, 10-H, OH), 2.73–2.82 (m, 1H, 14-H), 3.09 (br s, 1H, OH), 3.27 (dd, *J* = 13.8, 2.7 Hz, 1H, 8-H), 3.38–3.44 (m, 1H, 17-H), 3.75–3.89 (m, 8H, $OCH_3$, 9-H, 25-H), 5.01–5.10 (m, 1H, 21-H), 5.42–5.50 (m, 1H, 15-H), 6.34 (d, *J* = 2.0 Hz,1H, 6-H), 6.40 (d, *J* = 2.0 Hz,1H, 4-H), 6.70 (dd, *J* = 14.2, 10.4 Hz, 1H, 22-H), 7.68 (d, *J* = 10.4 Hz, 1H, NH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{34}H_{51}NNaO_8$ 624.35069, found 624.35092.

**Enamide analogue 3-122**



A 5 mL round-bottom flask was charged with diyne **3-121** (3.0 mg, 0.005 mmol) and a stir bar. EtOAc (2 mL) and quinoline (1.0 mg, 0.08 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, posioned with lead, 3 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give enamide **3-122** as a colorless oil (2.7 mg, 90%). $\mathbf{R_f}$ = 0.41 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –5.6 (*c* 0.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.84–0.89 (m, 6H, 28-H, 18-$CH_3$), 1.01–1.06 (m, 6H, 10-$CH_3$, 16-$CH_3$), 1.14 (d, *J* = 7.1 Hz, 3H, 24-$CH_3$), 1.21–1.31 (m, 4H, 26-H, 27-H, 20-H), 1.34–1.49 (m, 2H, 26-H, 27-H), 1.57 (br s, 1H, OH), 1.63–1.75 (m, 2H, 18-H, 19-H), 1.81–2.07 (m, 5H, 10-H, 11-H, 16-H, 19-H, 8-H), 2.15–2.24 (m, 1H, 14-H), 2.25–2.40 (m, 1H, 24-H), 2.58 (br s, 1H, OH), 2.74–2.86 (m, 1H, 11-H), 2.92–3.00 (m, 1H, 8-H), 2.82 (dt, *J* = 14.3, 11.5 Hz, 1H, 14-H), 3.29–3.39 (m, 2H, 17-H, OH), 3.69–3.76 (m, 4H, 25-H, $OCH_3$), 3.77–3.83 (m, 4H, 9-H, $OCH_3$), 5.10–5.19 (m, 1H, 21-H), 5.36 (dd, *J* = 10.2, 3.2 Hz, 1H, 15-H), 5.41–5.56 (m, 2H, 12-H, 13-H), 6.32–6.36 (m, 2H, 6-H, 4-H), 6.76 (dd, *J* = 14.2, 10.6 Hz, 1H, 22-H), 7.69 (d, *J* = 10.4 Hz, 1H, NH);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{34}H_{53}NO_8Na$ 626.36689, found 626.36672.

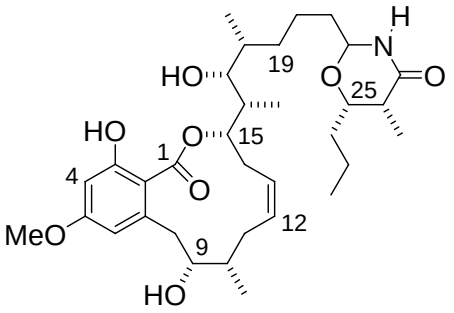
**Oxazinane-4-one 3-123**




**a)** ***ortho*-demethylation:** A solution of enamide **3-120** (18 mg, 0.018 mmol) in $CH_2Cl_2$ (2 mL) was treated with $BCl_3$ (72 μL, 1.0 M in $CH_2Cl_2$, 0.072 mmol, 4 equiv) at –80 °C. The reaction was stirred for 2 h at –80 °C before a saturated solution of NaOAc (5 mL) was added. After separation of the layers, the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo to give 17 mg of crude 2-hydroxy-4-methoxybenzoate which was used in the next step without futher purification.
**b)** **global deprotection:** To a stirred solution of the crude 2-hydroxy-4-methoxybenzoate (17 mg) in THF (0.8 mL, in a plastic test tube) was added at –80 °C dropwise HF·pyridine complex (70% HF, 0.6 mL). The reaction mixture was allowed to warm to –10 °C. After 2 h the mixture was partioned between an ice-cooled mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the $H_2O$ layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give 9.2 mg (87% for 2 steps) of triol **3-123**. $\mathbf{R_f}$ = 0.38 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +14.0 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.6 Hz, 3H, 18-$CH_3$), 0.91–0.97 (m, 6H, 28-H, 16-$CH_3$), 1.04 (d, *J* = 7.1 Hz, 3H, 10-

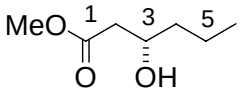
$CH_3$), 1.19 (d, $J$ = 7.3 Hz, 3H, 24-$CH_3$), 1.27–1.75 (m, 10H, 19-H, 26-H, 27-H, 20-H, 21-H), 1.95–2.21 (m, 4H, 18-H, 16-H, 11-H, OH), 2.28–2.36 (m, 3H, 8-H, 24-H, OH), 2.54–2.73 (m, 3H, 14-H, 10-H, 11-H), 2.78–2.86 (m, 1H, 14-H), 3.53 (d, $J$ = 8.8 Hz, 1H, 17-H), 3.69–3.78 (m, 2H, 25-H, 8-H), 3.80 (s, 3H, $OCH_3$), 3.91–3.99 (m, 1H, 9-H), 4.79 (t, $J$ = 5.6 Hz, 1H, 22-H), 5.37–5.43 (m, 1H, 15-H), 6.38–6.40 (m, 2H, 4-H, 6-H), 6.76 (br s, 1H, NH), 11.1 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 7.9 (16-$CH_3$), 12.0 (24-$CH_3$), 14.0 (C-28), 16.4 (18-$CH_3$), 16.7 (10-$CH_3$), 18.8 (C-27), 20.9, 21.7 (C-14), 22.3 (C-11), 29.7 (C-20), 32.5 (C-19), 33.3 (C-21), 35.6 (C-26), 36.0, 36.3 (C-18), 37.8 (C-16), 38.2 (C-8), 40.0 (C-24), 55.4 ($OCH_3$), 71.0 (C-25), 75.1 (C-9), 76.2 (C-15), 77.2 (*C*≡C), 79.0 (*C*≡C), 83.0 (C-22), 84.0, 99.4 (C-4), 110.2 (C-6), 142.0 (C-7), 162.0 (C-5), 163.0 (C-3), 170.2 (C-1), 175.0 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{49}NaNO_8$ 610.33504, found 610.33543.

**Oxazinan-4-one analogue 3-124**



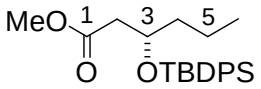

A 10 mL round-bottom flask was charged with alkyne **3-123** (9.0 mg, 0.015 mmol) and a stir bar. EtOAc (5 mL) and quinoline (3.0 mg, 0.024 mmol) were added with stirring. This was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, posioned with lead, 9 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred for 1 h. The reaction mixture was filtered through a pad of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5 → 9:1) to give analogue **3-124** as a colorless oil (8.4 mg, 93%). $\mathbf{R_f}$ = 0.38 ($CH_2Cl_2$/MeOH, 9:1); $\mathbf{[\alpha]^{20}_D}$ = –9.4 (*c* 0.8, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.78 (d, $J$ = 6.6 Hz, 3H, 18-$CH_3$), 0.89–0.96 (m, 6H, 28-H, 16-$CH_3$), 1.01 (d, $J$ = 6.8 Hz, 3H, 10-$CH_3$), 1.17 (d, $J$ = 7.3 Hz, 3H, 24-$CH_3$), 1.27–1.60 (m, 10H, 19-H, 26-H, 27-H, 20-H, 21-H), 1.82 (br s, 1H, OH), 1.93–2.10 (m, 3H, 18-H, 11-H, 16-H), 2.17–2.42 (m, 5H, 10-H, 14-H, 11-H, 8-H), 2.78–2.89 (m, 1H, 24-H), 3.38–3.47 (m, 1H, 17-H), 3.62–3.75 (m, 3H, 9-H, 8-H, 25-H), 3.79 (s, 3H, $OCH_3$), 4.71 (t, $J$ = 4.6 Hz, 1H, 22-H), 5.23 (dd, $J$ = 11.0, 4.2 Hz, 1H, 15-H), 5.38–5.54 (m, 2H, 12-H, 13-H), 6.30 (d, $J$ = 2.5 Hz, 1H, 6-H), 6.36 (d, $J$ = 2.5 Hz, 1H, 4-H), 6.40 (br s, 1H, NH), 11.6 (br s, 1H, 3-OH); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 9.0 (16-$CH_3$), 12.0 (24-$CH_3$), 14.0 (C-28), 14.2 (18-$CH_3$), 15.8 (10-$CH_3$), 18.9 (C-27), 20.8 (C-20), 29.4 (C-14), 29.7 (C-11), 31.6 (C-19), 32.0 (C-21), 33.3 (C-26), 36.3, 36.7, 37.1 (C-18), 37.8 (C-16), 38.3 (C-8), 38.8 (C-24), 40.1 (C-10), 55.4 ($OCH_3$), 72.9 (C-25), 75.5 (C-9), 78.0 (C-15), 83.8 (C-22), 99.7 (C-4), 104.8 (C-2), 112.4 (C-6), 125.6 (C-13), 132.3 (C-12), 143.6 (C-7), 163.6 (C-5), 165.9 (C-3), 171.5 (C-1), 174.6 (C-23);
**HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{51}NaNO_8$ 612.35069, found 612.35076.

**Methyl (3*S*)-3-hydroxyhexanoate (8-15)**[184]



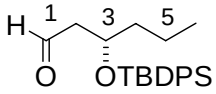

A 100-mL, dry Schlenk tube was charged with methyl 3-oxobutanoate (**8-7**) (21.6 g, 0.15 mol) and degassed methanol (50 mL). The resulting solution was further degassed and then transferred by cannula to a dry, argon-filled, 500 mL Parr hydrogenation vessel. To this mixture was added the in situ prepared [(*S*)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex (120 mg, 0.14 mmol, 0.09 mol%) in degassed methanol (5 mL) under a stream of argon. The hydrogenation vessel was attached to a hydrogen source and hydrogen was introduced into the reaction vessel until the pressure gauge indicates 2 atm. The pressure was carefully released to 1 atm by opening the stop valve. This procedure was repeated three times, and finally hydrogen was pressurized to 5 atm. The yellowish orange solution was vigorously shaked at 90 °C for 24 h during which time the hydrogen cylinder was kept connected. After the reaction mixture was allowed to cool to room temperature, the stop valve was opened, excess hydrogen was carefully bled off, and the apparatus was disassembled. The resulting orange solution was poured into a 250 mL, round-bottomed flask, and the hydrogenation vessel was rinsed with dichloromethane (3 × 25 mL). The solvent was removed by a rotary evaporator, and the residue was distilled to give 20.45 g (0.14 mol, 93% yield) of methyl (3*S*)-3-hydroxyhexanoate (**8-15**) (98% *ee*, bp 65 °C, 1 mm Hg). $\mathbf{R_f}$ = 0.56 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = +24.3 (*c* 3.5, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.1 Hz, 3H, 5-$CH_3$), 1.30–1.55 (m, 4H, 4-H, 5-H), 2.35–2.54 (m, 2H, 2-H), 2.88 (d, *J* = 3.3 Hz, 1H, OH), 3.69 (s, 3H, $OCH_3$), 3.94–4.06 (m, 1H, 3-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (5-$CH_3$), 18.6 (C-5), 38.6 (C-4), 41.1 (C-2), 51.7 ($OCH_3$), 67.7 (C-3), 173.5 (C-1);
**HRMS** (ESI): calcd for $C_7H_{14}NaO_3$ $[M+Na]^+$: 169.08352, found 169.08335.

### Methyl (3*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}hexanoate (8-16)



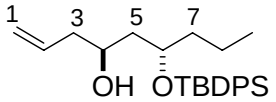

To a solution of methyl (3*S*)-3-hydroxyhexanoate (**8-15**) (7.30 g, 50.0 mmol) in anhydrous DMF (70 mL) were added imidazole (6.80 g, 100 mmol), DMAP (122 mg, 1 mmol), and TBDPS-chloride (16.44 g, 15.6 mL, 60 mmol) at 0 °C. The mixture was stirred for 12 h while it warmed to room temperature, and then diluted with water (100 mL). The product was extracted with $CH_2CI_2$ (3 × 75 mL). The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 20:1) afforded silyl ether **8-16** (19.26 g, 99% yield) as a colorless oil. $\mathbf{R_f}$ = 0.49 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +16.3 (*c* 1.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.3 Hz, 3H, 5-$CH_3$), 1.03 (s, 9H, Si(C($CH_3$)$_3$)), 1.16–1.30 (m, 2H, 5-H), 1.39–1.46 (m, 2H, 4-H), 2.38–2.53 (m, 2H, 2-H), 3.54 (s, 3H, $OCH_3$), 4.15–4.23 (m, 1H, 3-H), 7.33–7.45 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.71 (m, 4H, *o*CH ar Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (5-$CH_3$), 17.9 (C-5), 19.3 (Si(*C*($CH_3$)$_3$)), 26.9 (Si(C(*C*$H_3$)$_3$)), 39.3 (C-4), 41.9 (C-2), 51.3 ($OCH_3$), 70.2 (C-3), 127.5, 129.5, 134.0, 134.2, 135.9, 135.9 (C of $SiPh_2$), 172.0 (C-1);
**HRMS** (ESI): calcd for $C_{23}H_{32}NaO_3Si$ $[M+Na]^+$: 407.20129, found 407.20119.

### (3*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}hexanal (8-17)[252]




To a solution of ester **8-16** (14.3 g, 37.2 mmol) in dry dichloromethane (200 mL), at –80 °C, was added dropwise diisobutylaluminium hydride (1M in hexanes, 39.0 mL, 39.0 mmol, 1.05 equiv). The solution was stirred at –80 °C for 30 min, quenched with saturated aqueous $NH_4Cl$ solution and warmed up to room temperature. It was then treated with saturated potassium sodium tartrate solution (Rochelle salt)/$Et_2O$ (400:400 ml) and the mixture was vigorously stirred for 10 min. After the layers were separated, the water layer was extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 10:1) afforded aldehyde **8-17** (12.91 g, 98% yield) as a colorless oil. $\mathbf{R_f}$ = 0.53 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +5.8 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.3 Hz, 3H, 5-$CH_3$), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.16–1.30 (m, 2H, 5-H), 1.46–1.54 (m, 2H, 4-H), 2.47 (dd, *J* = 5.6, 2.5 Hz, 2H, 2-H), 4.17–4.24 (m, 1H, 3-H), 7.35–7.46 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.70 (m, 4H, *o*CH ar Ph), 9.70 (t, *J* = 2.5 Hz, 1H, C*H*O); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 (5-$CH_3$), 18.1 (C-5), 19.3 (Si(*C*($CH_3$)$_3$)), 26.9 (Si(C(*C*$H_3$)$_3$)), 39.5 (C-4), 50.2 (C-2), 69.1 (C-3), 127.6, 127.7, 129.7, 129.8, 133.7, 133.9, 135.8, 135.9 (C of $SiPh_2$), 202.2 (C-1);
**HRMS** (ESI): calcd for $C_{22}H_{30}NaO_2Si$ $[M+Na]^+$: 377.19073, found 377.19095.

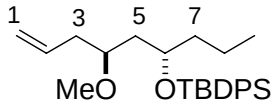
### (4*S*,6*S*)-6-{[*tert*-Butyl(diphenyl)silyl]oxy}non-1-en-4-ol (8-18)




To a cooled (–20 °C) solution of (*R*,*R*)-**6-82** (17.7 g, 32.0 mmol, 1.1 equiv) in $CH_2Cl_2$ (160 mL) was added a solution of aldehyde **8-17** (10.3 g, 29.1 mmol, 1.0 equiv) in $CH_2Cl_2$ (20 mL). The mixture was then placed in a freezer (–10 °C) and maintained at that temperature for 24 h (without stirring). The reaction was quenched, while still cold, with 1N HCl (100 mL) and EtOAc (100 mL) and the mixture was vigorously stirred at room temperature for 15 min. The resulting white precipitate of (*R*,*R*)-*N*,*N*'-bis-(4-bromo-benzyl)-cyclohexane-1,2-diamine dihydrochloride was filtered off, washed with $Et_2O$ (3 × 50 mL) and dried in vacuo (recovered 15.2 g, 91% of (*R*,*R*)-diamine dihydrochloride). The combined filtrates were poured into a separatin funnel, and the layers were separated. The aqueous layer was extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were washed with $H_2O$ (100 mL), saturated NaCl solution (100 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash chromatography (petroleum ether/EtOAc, 20:1 to 10:1) to give homoallylic alcohol **8-18** (10.03 g, 87%) as a colorless oil. $\mathbf{R_f}$ = 0.47 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +11.1 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.67 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.98–1.19 (m, 11H, Si(C($CH_3$)$_3$), 8-H), 1.38–1.48 (m, 1H, 7-H), 1.55–1.73 (m, 3H, 7-H, 5-H), 2.11–2.28 (m, 2H, 3-H), 3.16 (d, *J* = 1.5 Hz, 1H, OH), 3.96–4.05 (m, 2H, 4-H, 6-H), 5.04–5.07 (m. 1H, 1-H), 5.08–5.12 (m, 1H, 1-H), 5.74–5.87 (m, 1H, 2-H), 7.36–7.47 (m, 6H, *m*CH, *p*CH ar Ph), 7.69–7.76 (m, 4H, *o*CH ar Ph); **$^{13}$C NMR** (100

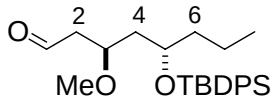
MHz, $CDCl_3$): δ = 13.8 (8-$CH_3$), 18.4 (C-8), 19.2 (Si(*C*($CH_3$)$_3$)), 27.0 (Si(C(*C*$H_3$)$_3$)), 38.0 (C-7), 40.5 (C-5), 42.2 (C-3), 67.6 (C-4), 72.2 (C-6), 117.2 (C-1), 127.5, 127.6, 129.7, 129.7, 133.5, 133.8 (C of $SiPh_2$), 134.9 (C-2), 135.9 (C of $SiPh_2$);
**HRMS** (ESI): calcd for $C_{25}H_{36}NaO_2Si$ $[M+Na]^+$: 419.23768, found 419.23775.

### *tert*-Butyl{[(1*S*,3*S*)-3-methoxy-1-propylhex-5-enyl]oxy}diphenylsilane (8-19)




To a solution of alcohol **8-18** (6.25 g, 15.8 mmol) in $CH_2Cl_2$ (200 mL), protected from light, were added $Me_3OBF_4$ (8.2 g, 55.3 mmol) and proton sponge (16.9 g, 79.0 mmol) at room temperature, followed by stirring of the mixture for 48 h. After complete reaction (monitoring by TLC), water was added (50 ml) and the mixture extracted with $CH_2Cl_2$. The combined organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 40:1 to 20:1) afforded methyl ether **8-19** (5.66 g, 87% yield) as a colorless oil. $\mathbf{R_f}$ = 0.63 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +14.9 (*c* 3.0, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 1.09 (s, 9H, Si(C($CH_3$)$_3$)), 1.19–1.38 (m, 2H, 8-H), 1.40–1.47 (m, 2H, 7-H), 1.59–1.65 (m, 2H, 5-H), 2.15–2.22 (m, 2H, 3-H), 3.13 (s, 3H, $OCH_3$), 3.33–3.41 (m, 1H, 4-H), 3.97–4.05 (m, 1H, 6-H), 5.01–5.05 (m. 1H, 1-H), 5.06–5.08 (m. 1H, 1-H), 5.67–5.79 (m, 1H, 2-H), 7.36–7.47 (m, 6H, *m*CH, *p*CH ar Ph), 7.71–7.76 (m, 4H, *o*CH ar Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.7 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 27.1 (Si(C(*C*$H_3$)$_3$)), 37.6 (C-3), 39.8 (C-7), 41.6 (C-5), 56.0 ($OCH_3$), 70.5 (C-6), 76.9 (C-4), 117.0 (C-1), 127.4, 127.4, 129.4, 134.4, 134.5 (C of $SiPh_2$), 134.8 (C-2), 135.9, 136.0 (C of $SiPh_2$);
**HRMS** (ESI): calcd for $C_{26}H_{38}NaO_2Si$ $[M+Na]^+$: 433.25333, found 433.25319.

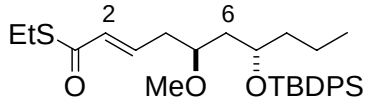
### (3*R*,5*S*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-methoxyoctanal (8-20)




To a solution of methyl ether **8-19** (5.56 g, 13.6 mmol) in a mixture of THF/*t*BuOH (180/40 mL) was added 4-methyl-morpholine-N-oxide (3.70 g, 27.0 mmol) and an aqueous solution of $OsO_4$ (10 mL of a 0.027 M solution, 0.27 mmol, 2 mol%, prepared from $K_2OsO_4 \cdot 2H_2O$ (100 mg, 0.27 mmol)) at 0 °C. After being stirred at room temperature for 20 h, 100 ml of 10% $Na_2S_2O_3$ solution was added to the mixture. After 30 min, the diol was extracted with EtOAc and the combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel followed by rinsing the pad with EtOAc. Removal of the solvent from the combined filtrate gave the crude diol.
$NaIO_4$ (4.4 g, 21.0 mmol, 1.5 equiv) was added to a solution of crude diol in 90% MeOH (200 mL). After stirring at room temperature for 1 h, most of the methanol was removed in vacuo

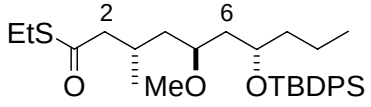
and the residue extracted with $Et_2O$ (3 × 150 mL). The combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, and filtered. After concentration, the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1→5:1) to give aldehyde **8-20** as a colorless oil (5.10 g, 93% over 2 steps). $\mathbf{R_f}$ = 0.35 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +5.1 (*c* 1.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.1 Hz, 3H, 7-$CH_3$), 1.05 (s, 9H, Si(C($CH_3$)$_3$)), 1.16–1.36 (m, 2H, 7-H), 1.37–1.45 (m, 2H, 6-H), 1.52–1.61 (m, 1H, 4-H), 1.71–1.80 (m, 1H, 4-H), 2.30–2.44 (m, 2H, 2-H), 3.09 (s, 3H, $OCH_3$), 3.69–3.77 (m, 1H, 3-H), 3.87–3.94 (m, 1H, 5-H), 7.34–7.45 (m, 6H, *m*CH, *p*CH ar Ph), 7.66–7.72 (m, 4H, *o*CH ar Ph), 9.65 (t, *J* = 2.5 Hz, 1H, C*H*O); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (7-$CH_3$), 17.7 (C-7), 19.4 (Si(*C*($CH_3$)$_3$)), 27.0 (Si(C(*C*$H_3$)$_3$)), 39.6 (C-6), 42.2 (C-4), 48.0 (C-2), 56.3 ($OCH_3$), 70.2 (C-5), 73.3 (C-3), 127.5, 127.5, 129.6, 129.6, 134.3, 134.5, 135.9, (C of $SiPh_2$), 201.3 (C-1);
**HRMS** (ESI): calcd for $C_{26}H_{40}NaO_4Si$ [M+$CH_3OH$+Na]$^+$: 467.25881, found 467.25872.

### *S*-Ethyl (2*E*,5*S*,7*S*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-5-methoxydec-2-enethioate (8-22)




A solution of the aldehyde **8-20** (3.46 g, 8.40 mmol) and ylide **8-21** (16.8 mmol, 6.11 g) in $CH_2Cl_2$ (160 mL) was heated at reflux for 10 h. The solution was concentrated under reduced pressure and purified by column flash chromatography (petroleum ether/EtOAc, 40:1→20:1) to afford the desired *α,β*-unsaturated thioester **8-22** as a colorless oil (3.84 g, 92% ). $\mathbf{R_f}$ = 0.47 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +2.0 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.3 Hz, 3H, 9-$CH_3$), 1.05 (s, 9H, Si(C($CH_3$)$_3$)), 1.14–1.33 (m, 5H, 9-H, $SCH_2CH_3$), 1.36–1.43 (m, 2H, 8-H), 1.49–1.65 (m, 2H, 6-H), 2.20–2.26 (m, 2H, 4-H), 2.95 (q, *J* = 14.9 Hz, 2H, S*CH*$_2$$CH_3$), 3.06 (s, 3H, $OCH_3$), 3.33–3.41 (m, 1H, 5-H), 3.89–3.97 (m, 1H, 7-H), 6.08 (d, *J* = 15.7 Hz, 1H, 2-H), 6.75–6.84 (m, 1H, 3-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.66–7.70 (m, 4H, *o*CH ar Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (9-$CH_3$), 14.8 ($SCH_2CH_3$), 17.7 (C-9), 19.4 (Si(*C*($CH_3$)$_3$)), 23.0 (S*C*$H_2$$CH_3$), 27.1 (Si(C(*C*$H_3$)$_3$)), 36.3 (C-4), 39.8 (C-8), 42.0 (C-6), 56.3 ($OCH_3$), 70.4 (C-7), 76.4 (C-5), 127.4, 127.5, 129.5, 129.5 (C of $SiPh_2$), 130.7 (C-2), 134.3, 134.5, 135.9 (C of $SiPh_2$), 141.0 (C-3), 189.8 (C-1);
**HRMS** (ESI): calcd for $C_{29}H_{42}NaO_3SSi$ [M+Na]$^+$: 521.25161, found 521.25138.

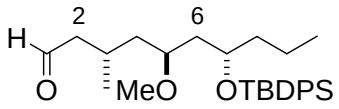
### *S*-Ethyl (3*S*,5*S*,7*S*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-5-methoxy-3-methyldecanethioate (8-23)




CuBr·$Me_2S$ (27.0 mg, 0.130 mmol, 3.4 mol%) and (*S,R*)-Josiphos ***ent*-6-87** (100.0 mg, 0.156 mmol, 4.1 mol%) were dissolved in *t*BuOMe (34 mL) and stirred at room temperature for 30 min under nitrogen. The mixture was cooled to –75 °C and MeMgBr (3M solution in $Et_2O$, 1.67 ml, 5.0 mmol, 1.3 equiv) was added dropwise. After stirring for 10 min, a solution of thioester **8-22** (1.90 g, 3.81 mmol, 1 equiv) in *t*BuOMe (4.20 mL) was added via a syringe pump over 3 h.

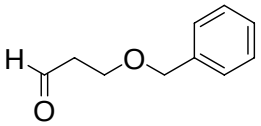
The reaction mixture was stirred at –75 °C for 12 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous $NH_4Cl$ solution was then added, the phases were separated and the aqueous layer extracted with $Et_2O$ (3 × 60 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by column flash chromatography (petroleum ether/EtOAc, 30:1→20:1) to afford the desired 1,4-addition adduct **8-23** as a colorless oil (1.82 g, 93% ). $\mathbf{R_f}$ = 0.52 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –4.5 (*c* 2.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.3 Hz, 3H, 9-$CH_3$), 0.88 (d, *J* = 6.6 Hz, 3H, 3-$CH_3$), 0.93–1.02 (m, 1H, 9-H), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.17–1.42 (m, 8H, 4-H, 9-H, $SCH_2CH_3$, 8-H), 1.42–1.50 (m, 1H, 6-H), 1.63–1.72 (m, 1H, 6-H), 2.04–2.16 (m, 1H, 3-H), 2.25–2.32 (m, 1H, 2-H), 2.47 (dd, *J* = 14.4, 5.7 Hz, 1H, 2-H), 2.86 (q, *J* = 14.9 Hz, 2H, $SCH_2CH_3$), 3.09 (s, 3H, $OCH_3$), 3.25–3.34 (m, 1H, 5-H), 3.82–3.89 (m, 1H, 7-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.65–7.71 (m, 4H, *o*CH ar Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (9-$CH_3$), 14.8 ($SCH_2CH_3$), 17.8 (C-9), 19.4 (Si(*C*($CH_3$)$_3$)), 19.6 (3-$CH_3$), 23.2 ($SCH_2CH_3$), 27.1 (Si(C(*C*$H_3$)$_3$)), 27.9 (C-3), 39.5 (C-8), 41.0 (C-4), 41.9 (C-6), 51.5 (C-2), 55.6 ($OCH_3$), 70.5 (C-7), 75.4 (C-5), 127.4, 127.5, 129.4, 129.4, 134.4, 134.6, 135.9 (C of $SiPh_2$), 198.8 (C-1);
**HRMS** (ESI): calcd for $C_{30}H_{46}NaO_3SSi$ $[M+Na]^+$: 537.28291, found 537.28303.

### (3*S*,5*S*,7*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-5-methoxy-3-methyldecanal (8-24)



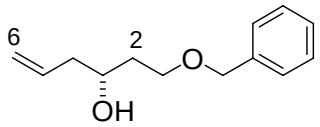

To a stirred mixture of the thioester **8-23** (904 mg, 1.76 mmol) and Pd/C (90.0 mg, 10% wt) in $CH_2Cl_2$ (15 mL) was added $Et_3SiH$ (840 μL, 5.30 mmol, 3 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 30 min. The catalyst was filtered off through a pad of Celite and washed with $CH_2Cl_2$. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 10:1 to 5:1) to give the pure aldehyde **8-24** (759 mg, 95%) as a slightly yellow oil. $\mathbf{R_f}$ = 0.29 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –11.7 (*c* 2.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.3 Hz, 3H, 9-$CH_3$), 0.88 (d, *J* = 6.3 Hz, 3H, 3-$CH_3$), 0.97–1.01 (m, 1H, 9-H), 1.03 (s, 9H, Si(C($CH_3$)$_3$)), 1.17–1.35 (m, 3H, 4-H, 9-H), 1.36–1.49 (m, 3H, 6-H, 8-H), 1.66–1.74 (m, 1H, 6-H), 2.06–2.19 (m, 2H, 2-H, 3-H), 2.24–2.33 (m, 1H, 2-H), 3.09 (s, 3H, $OCH_3$), 3.21–3.29 (m, 1H, 5-H), 3.79–3.87 (m, 1H, 7-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.70 (m, 4H, *o*CH ar Ph), 9.66 (s, 1H, C*H*O); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (9-$CH_3$), 17.8 (C-9), 19.4 (Si(*C*($CH_3$)$_3$)), 20.0 (3-$CH_3$), 24.9 (C-3), 27.0 (Si(C(*C*$H_3$)$_3$)), 39.5 (C-8), 41.4 (C-6), 41.9 (C-4), 51.3 (C-2), 55.7 ($OCH_3$), 70.5 (C-7), 75.6 (C-5), 127.4, 127.5, 129.5, 134.3, 134.6, 135.9 (C of $SiPh_2$), 202.6 (C-1);
**HRMS** (ESI): calcd for $C_{29}H_{46}NaO_4Si$ $[M+MeOH+Na]^+$: 509.30576, found 509.30549.

### 3-(Benzyloxy)propanal (8-8)



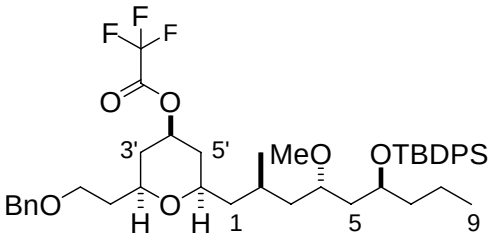
Dibal-H (1M in hexane, 21 mL, 21 mmol) was added to a solution of 3-(benzyloxy)propanenitrile (**8-25**)[256] (2.41 g, 15.0 mmol) in toluene (40 mL) at –80 °C, under nitrogen atmosphere. The solution was allowed to warm to 0 °C and stirred at this temperature for 2 h. After the mixture was partioned between an ice-cooled mixture of $Et_2O$ (100 mL) and saturated potassium sodium tartrate (Rochelle salt) (100 mL) it was stirred until the layers became clear. The organic layer was separated and the $H_2O$ layer extracted with $Et_2O$ (2 × 100 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give aldehyde **8-8** (1.92 g, 78%) as a colorless oil. $\mathbf{R_f}$ = 0.38 (petroleum ether/EtOAc, 4:1);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.69 (dt, *J* = 6.1, 1.8 Hz, 2H, C*H*$_2$CHO), 3.81 (t, *J* = 6.1 Hz, 2H, BnOC*H*$_2$), 4.53 (s, 2H, PhC*H*$_2$O), 7.27–7.37 (m, 5H, ar H of Ph), 9.79 (t, *J* = 1.8 Hz, 1H, C*H*O);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 43.8 (*C*H$_2$CHO), 63.8 (BnO*C*H$_2$), 73.2 (Ph*C*H$_2$O), 127.7, 127.7, 128.4, 137.8 (C of Ph), 201.1 (*C*HO).

### (3*R*)-1-(Benzyloxy)hex-5-en-3-ol (8-26)



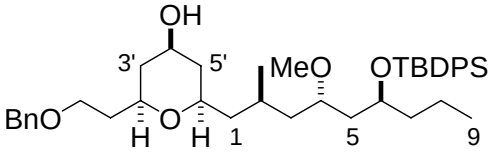

To a cooled (–20 °C) solution of (*S*,*S*)-**6-82** (1.18 g, 2.19 mmol, 1.06 equiv) in $CH_2Cl_2$ (11 mL) was added aldehyde **8-8** (340 mg, 2.07 mmol, 1.0 equiv). The reaction mixture was then placed into a freezer (–10 °C) and maintained at that temperature for 24 h (without stirring). The reaction was quenched, while still cold, with 1N HCl (10 mL) and EtOAc (10 mL) and the mixture was vigorously stirred at room temperature for 15 min. The obtained white precipitate of (*S*,*S*)-*N*,*N*'-bis-(4-bromo-benzyl)-cyclohexane-1,2-diamine dihydrochloride was filtered off, washed with $Et_2O$ (3 × 10 mL) and dried in vacuo (recovered 1.06 g, 92% of (*S*,*S*)-diamine dihydrochloride). The combined filtrates were poured into a separating funnel, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with $H_2O$ (40 mL), saturated NaCl solution (40 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 2:1) to give homoallylic alcohol **8-26** (358 mg, 84%) as a colorless oil. $\mathbf{R_f}$ = 0.42 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = −4.2 (*c* 1.3, $CH_2Cl_2$), lit.[270] $[\alpha]^{20}_D$ = −4.8 (c 2.31, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.65–1.73 (m, 2H, 2-H), 2.14–2.20 (m, 2H, 4-H), 2.78 (d, *J* = 3.0 Hz, 1H, OH), 3.53–3.67 (m, 2H, 1-H), 3.75–3.85 (m, 1H, 3-H), 4.44 (s, 2H, PhC*H*$_2$O), 4.99–5.06 (m, 2H, 6-H), 5.70–5.82 (m, 1H, 5-H), 7.18–7.30 (m, 5H, ar H of Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 35.8 (C-2), 41.9 (C-4), 68.9 (C-1), 70.3 (C-3), 73.3 (Ph*C*H$_2$O), 117.5 (C-6), 127.6, 127.7, 128.4 (C of Ph), 134.8 (C-5), 137.9 (C of Ph);
**HRMS** (ESI): calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$: 229.11990, found 229.11982.

### Trifluoroacetate 8-27




Trifluoroacetic acid (0.85 mL, 8.9 mmol) was added to a solution of alcohol **8-26** (330 mg, 1.6 mmol) and aldehyde **8-24** (404 mg, 0.89 mmol) in $CH_2Cl_2$ (8 mL) at –5 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at this temperature before saturated aqueous $NaHCO_3$ solution (10 mL) was added dropwise. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 10:1) to afford trifluoroacetate **8-27** as a colorless oil (485 mg, 72%). $\mathbf{R_f}$ = 0.69 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]^{20}_D}$ = –3.5 (*c* 2.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.83 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 0.87–0.99 (m, 1H, 8-H), 1.05 (s, 9H, Si(C($CH_3$)$_3$)), 1.08–1.14 (m, 1H, 8-H), 1.16–1.41 (m, 7H, 7-H, 5'-H, 1-H, BnOCH$_2$C*H*$_2$), 1.45–1.70 (m, 3H, BnOCH$_2$C*H*$_2$, 3-H), 1.73–1.88 (m, 3H, 5-H, 2-H), 1.95–2.08 (m, 2H, 3'-H), 3.09 (s, 3H, $OCH_3$), 3.29–3.44 (m, 2H, 6'-H, 2'-H), 3.51–3.66 (m, 3H, 4-H, BnOC*H*$_2$CH$_2$), 3.85–3.92 (m, 1H, 6-H), 4.48 (s, 2H, PhC$H_2$O), 5.04–5.14 (m, 1H, 4'-H), 7.27–7.44 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.66–7.73 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.8 (C-8), 19.4 (Si(*C*(C$H_3$)$_3$)), 19.5 (2-$CH_3$), 25.7 (C-2), 26.5, 27.1 (Si(C(*C*$H_3$)$_3$)), 36.1 (BnOCH$_2$*C*H$_2$), 36.7 (C-3'), 37.2 (C-3), 39.6 (C-5'), 42.1 (C-5), 43.5 (C-1), 55.8 ($OCH_3$), 66.4 (BnO*C*H$_2$CH$_2$), 70.4 (C-6), 71.9 (C-4), 72.6 (C-6'), 73.2 (Ph*C*H$_2$O), 75.4 (C-4'), 75.5 (C-2'), 114.5 (q, *J* = 286 Hz, *C*$F_3$), 127.4, 127.4, 127.6, 127.6, 127.7, 128.4, 129.5, 129.6, 134.4, 134.7, 134.8, 135.9, 136.0, 138.4 (C of $SiPh_2$ and Ph of Bn), 156.9 (q, J = 42 Hz, *C*O$CF_3$); **HRMS** (ESI): calcd for $C_{43}H_{59}F_3NaO_6Si$ $[M+Na]^+$: 779.39252, found 779.39261.

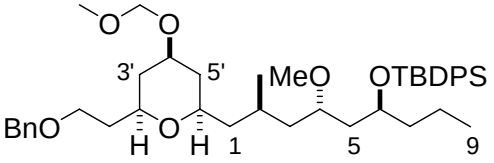
## Tetrahydropyran 8-28[271]




To a solution of triflouroacetate **8-27** (452 mg, 0.60 mmol) in methanol (6 mL) was added $K_2CO_3$ (166 mg, 1.2 mmol) and water (0.3 mL). The reaction mixture was stirred at room temperature for 30 min, then diluted with water (5 mL) and extracted with $Et_2O$ (3 × 40 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 3:1 to 2:1) provided alcohol **8-28** (361 mg, 91% yield) as a colorless oil. $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –7.0 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.83 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 0.87–0.98 (m, 1H, 8-H), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.07–1.31 (m, 4H, 7-H, 8-H, BnOCH$_2$C*H*$_2$), 1.32–1.41 (m, 3H, 5'-H, 1-H), 1.46–1.57 (m, 3H, 1-H, 5-H), 1.59–1.66 (m, 1H, 5-H), 1.71–1.82 (m, 3H,

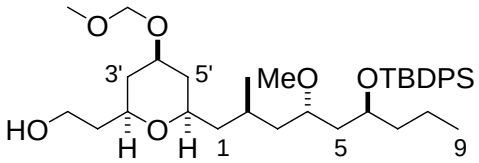
2-H, BnOCH$_2$C$H_2$), 1.82–1.95 (m, 2H, 3'-H), 3.08 (s, 3H, OCH$_3$), 3.26–3.37 (m, 2H, 6'-H, 4-H), 3.43–3.47 (m, 1H, 2'-H), 3.53–3.65 (m, 2H, BnOC$H_2$CH$_2$), 3.72–3.83 (m, 1H, 4'-H), 3.85–3.91 (m, 1H, 6-H), 4.48 (s, 2H, PhCH$_2$O), 7.26–7.43 (m, 11H, *m*CH, *p*CH ar SiPh$_2$, Ph of Bn), 7.65–7.71 (m, 4H, *o*CH ar SiPh$_2$); **$^{13}$C NMR** (100 MHz, CDCl$_3$): δ = 14.0 (8-CH$_3$), 17.7 (C-8), 19.4 (Si(*C*(CH$_3$)$_3$)), 19.6 (2-CH$_3$), 25.8 (C-2), 27.1 (Si(C(*C*H$_3$)$_3$)), 36.2 (BnOCH$_2$*C*H$_2$), 39.6 (C-3), 41.4 (C-3'), 41.8 (C-5'), 42.1 (C-7), 42.2 (C-5), 43.6 (C-1), 55.8 (OCH$_3$), 66.8 (BnO*C*H$_2$CH$_2$), 68.3 (C-6), 70.4 (C-4'), 72.2 (C-4), 73.0 (C-6'), 73.1 (Ph*C*H$_2$O), 75.5 (C-2'), 127.4, 127.4, 127.5, 127.6, 128.3, 129.4, 134.4, 134.8, 135.9, 136.0, 138.5 (C of SiPh$_2$ and Ph of Bn);
**HRMS** (ESI): calcd for C$_{41}$H$_{60}$NaO$_5$Si [M+Na]$^+$: 683.41022, found 683.41020.

**Methoxy-methyl ether 8-29**[272]



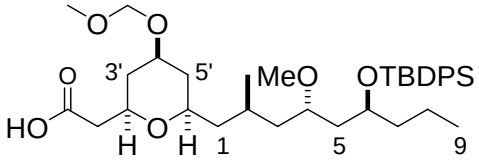

To a stirred, cooled (0 °C) solution of alcohol **8-28** (350 mg, 0.53 mmol) in DMF (3 mL) were added *N*,*N*-diisopropylethylamine (0.91 mL, 5.3 mmol), chloromethylmethyl ether[273] (250 μL, 3.2 mmol), and tetrabutylammonium iodide (20 mg, 0.05 mmol). The reaction mixture was warmed to room temperature. After stirring for 5 h, saturated aqueous NaHCO$_3$ solution (5 mL) was added followed by Et$_2$O (20 mL). After separation of the layers, the aqueous phase was extracted with Et$_2$O (3 × 30 mL). The combined organic extracts were washed with saturated NaHCO$_3$, saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 5:1) afforded MOM ether **8-29** (423 mg, 99% yield) as a colorless oil. **R$_f$** = 0.70 (petroleum ether/EtOAc, 2:1); **[α]$^{20}_D$** = –4.3 (*c* 2.3, CH$_2$Cl$_2$); **$^1$H NMR** (400 MHz, CDCl$_3$): δ = 0.69 (t, *J* = 7.3 Hz, 3H, 8-CH$_3$), 0.83 (d, *J* = 6.6 Hz, 3H, 2-CH$_3$), 0.88–0.99 (m, 1H, 8-H), 1.04 (s, 9H, Si(C(CH$_3$)$_3$)), 1.07–1.41 (m, 8H, 7-H, 8-H, 5'-H, 1-H, BnOCH$_2$C$H_2$), 1.47–1.67 (m, 3H, 1-H, BnOCH$_2$C$H_2$, 3-H) 1.73–1.85 (m, 3H, 5-H, 2-H), 1.87–1.98 (m, 2H, 3'-H), 3.08 (s, 3H, CHOC$H_3$), 3.28–3.39 (m, 5H, 6'-H, 4-H, CH$_2$OC$H_3$), 3.41–3.51 (m, 1H, 2'-H), 3.52–3.66 (m, 2H, BnOC$H_2$CH$_2$), 3.67–3.77 (m, 1H, 4'-H), 3.84–3.92 (m, 1H, 6-H), 4.48 (s, 2H, PhCH$_2$O), 4.68 (s, 2H, C$H_2$OCH$_3$), 7.26–7.43 (m, 11H, *m*CH, *p*CH ar SiPh$_2$, Ph of Bn), 7.66–7.71 (m, 4H, *o*CH ar SiPh$_2$); **$^{13}$C NMR** (100 MHz, CDCl$_3$): δ = 14.0 (8-CH$_3$), 17.7 (C-8), 19.4 (Si(*C*(CH$_3$)$_3$)), 19.6 (2-CH$_3$), 25.8 (C-2), 27.1 (Si(C(*C*H$_3$)$_3$)), 36.3 (BnOCH$_2$*C*H$_2$), 38.7 (C-3'), 39.2 (C-3), 39.6 (C-5'), 42.1 (C-7), 42.1 (C-5), 43.8 (C-1), 55.2 (CH$_2$O*C*H$_3$), 55.7 (CHO*C*H$_3$), 66.8 (BnO*C*H$_2$CH$_2$), 70.4 (C-6), 72.3 (C-4), 73.0 (C-6'), 73.1 (Ph*C*H$_2$O), 73.2 (C-4'), 75.5 (C-2'), 94.4 (*C*H$_2$OCH$_3$), 127.4, 127.4, 127.5, 127.6, 128.3, 129.4, 129.4, 134.4, 134.8, 135.9, 136.0, 138.6 (C of SiPh$_2$ and Ph of Bn);
**HRMS** (ESI): calcd for C$_{43}$H$_{64}$NaO$_6$Si [M+Na]$^+$: 727.43644, found 727.43653.

**Alcohol 8-30**




A hydrogenation vessel was charged with MOM ether **8-29** (371 mg, 0.53 mmol), Pd/C (110 mg), ethanol (20 mL), and attached to a hydrogen source. Hydrogen was introduced into the reaction vessel until the pressure gauge indicated 2 atm. The pressure was carefully released to 1 atm by opening the stop valve. This procedure was repeated three times, and finally hydrogen was pressurized to 5 atm. The reaction mixture was vigorously shaken at room temperature for 10 h during which time the hydrogen cylinder was kept connected. After the stop valve was opened, excess hydrogen was carefully bled off, and the apparatus was disassembled. The catalyst was filtered off through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give the alcohol **8-30** (304 mg, 92%) as a colorless oil. $\mathbf{R_f}$ = 0.30 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –1.6 (*c* 1.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.69 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.82 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 0.86–0.96 (m, 1-H, 8-H), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.08–1.40 (m, 8H, 7-H, 8-H, 5'-H, $HOCH_2CH_2$, 3-H), 1.41–1.59 (m, 2H, 1-H), 1.61–1.81 (m, 4H, 5-H, 2-H, $HOCH_2CH_2$), 1.87–1.97 (m, 2H, 3'-H), 2.55 (br s, 1H, OH), 3.09 (s, 3H, $CHOCH_3$), 3.27–3.41 (m, 5H, 6'-H, 4-H, $CH_2OCH_3$), 3.47–3.56 (m, 1H, 2'-H), 3.65–3.87 (m, 4H, $HOCH_2CH_2$, 4'-H, 6-H), 4.68 (s, 2H, $CH_2OCH_3$), 7.32–7.43 (m, 6H, *m*CH, *p*CH ar $SiPh_2$), 7.65–7.71 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.8 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 19.6 (2-$CH_3$), 26.1 (C-2), 27.1 (Si(C(*C*$H_3$)$_3$)), 37.9 (C-3'), 38.6 (C-3), 38.9 ($CH_2CH_2OH$), 39.5 (C-5'), 42.1 (C-7), 42.3 (C-5), 43.6 (C-1), 55.3 ($CH_2OCH_3$), 55.5 ($CHOCH_3$), 61.2 ($HOCH_2CH_2$), 70.5 (C-6), 72.8 (C-4'), 73.8 (C-4), 75.6 (C-6'), 75.8 (C-2'), 94.4 ($CH_2OCH_3$), 127.4, 127.4, 129.4, 129.4, 134.4, 134.7, 136.0 (C of $SiPh_2$);
**HRMS** (ESI): calcd for $C_{36}H_{58}NaO_6Si$ $[M+Na]^+$: 637.38949, found 637.38973.

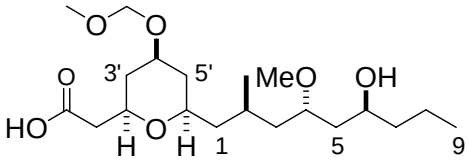
**Acid 8-31**




**a) Preparation of aldehyde:** To a cooled (0 °C) solution of alcohol **8-30** (260 mg, 0.42 mmol) in $CH_2Cl_2$ (4 mL) was added a solution of Dess-Martin periodinane (15% wt, 1.5 mL, 0.71 mmol). After stirring for 0.5 h at 0 °C and for 1.5 h at room temperature, the reaction mixture was concentrated, loaded on a flash silica gel column, and eluted with petroleum ether/EtOAc, 4:1 to give 253 mg (96%) of the corresponding aldehyde, which was used directly in the next reaction. TLC (petroleum ether/EtOAc, 2:1): $R_f$ = 0.64.
**b) Acid (152):**[257] The obtained aldehyde (250 mg, 0.41 mmol) was dissolved in *t*BuOH (4 mL) and 2,3-dimethyl-2-butene (1.4 mL). A solution of $NaClO_2$ (140 mg, 1.23 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (620 mg, 3.7 mmol) in water (3 mL) was added slowly at 0 °C. After stirring for 30 min at room temperature, the mixture was diluted with water (5 mL), extracted with

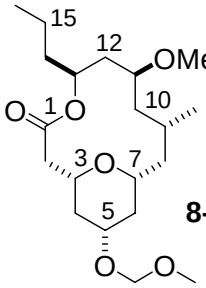
EtOAc (4 x 20 mL), washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1:0.01 to 1:1:0.01) provided acid **8-31** (253 mg, 98% yield) as a colorless oil. $\mathbf{R_f}$ = 0.43 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –3.3 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.69 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.81 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 0.86–0.96 (m, 1H, 8-H), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.08–1.41 (m, 8H, 7-H, 8-H, 5'-H, 1-H, 2-H), 1.42–1.58 (m, 2H, 3-H), 1.59–1.78 (m, 2H, 5-H), 1.89–1.98 (m, 1H, 3'-H), 1.99–2.07 (m, 1H, 3'-H), 2.44–2.62 (m, 2H, C*H*$_2$COOH), 3.09 (s, 3H, CHOC*H*$_3$), 3.29–3.44 (m, 5H, 6'-H, 4-H, $CH_2$OC*H*$_3$), 3.68–3.78 (m, 2H, 2'-H, 4'-H), 3.81–3.89 (m, 1H, 6-H), 4.68 (s, 2H, C*H*$_2$OCH$_3$), 7.31–7.43 (m, 6H, *m*CH, *p*CH ar $SiPh_2$), 7.65–7.70 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.8 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 19.6 (2-$CH_3$), 25.9 (C-2), 27.1 (Si(C(*C*$H_3$)$_3$)), 38.0 (C-3'), 38.7 (C-3), 39.5 (C-5'), 40.8 (C-7), 42.0 (*C*$H_2$COOH), 42.1 (C-5), 43.5 (C-1), 55.3 ($CH_2$O*C*$H_3$), 55.8 (CHO*C*$H_3$), 70.5 (C-6), 72.0 (C-4'), 72.6 (C-2'), 74.0 (C-6'), 75.6 (C-4), 94.5 (*C*$H_2$OCH$_3$), 127.4, 127.5, 129.4, 129.5, 134.4, 134.7, 136.0, 136.0 (C of $SiPh_2$), 174.1 (*C*OOH);
**HRMS** (ESI): calcd for $C_{36}H_{56}NaO_7Si$ $[M+Na]^+$: 651.36875, found 651.36843.

**Seco-acid 8-32**

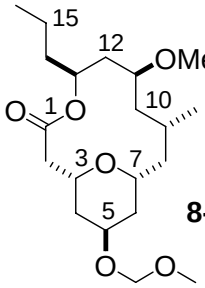



To a solution of acid **8-31** (214 mg, 0.34 mmol) in THF (1.5 mL) was added TBAF·3$H_2O$ (1.07 g, 3.40 mmol) at room temperature. The reaction mixture was stirred for 36 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (10 ml), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc/HOAc, 1:1:0.01 to 0:1:0.01) afforded seco-acid **8-32** (134 mg, 99% yield) as a colorless oil. $\mathbf{R_f}$ = 0.3 (petroleum ether/EtOAc/HOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +8.1 (*c* 1.8, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.86–0.94 (m, 6H, 8-$CH_3$, 2-$CH_3$), 1.03–1.14 (m, 1-H, 8-H), 1.18–1.58 (m, 9H, 7-H, 8-H, 5'-H, 1-H, 3-H), 1.70–1.82 (m, 2H, 5-H), 1.86–1.95 (m, 2H, 3'-H, 2-H), 1.97–2.04 (m, 1H, 3'-H), 2.42–2.53 (m, 2H, C*H*$_2$COOH), 3.31–3.45 (m, 7H, CHOC*H*$_3$, 6'-H, $CH_2$OC*H*$_3$), 3.48–3.55 (m, 1H, 4-H), 3.68–3.80 (m, 2H, 2'-H, 4'-H), 3.93–4.00 (m, 1H, 6-H), 4.67 (s, 2H, C*H*$_2$OCH$_3$), 6.52 (br s, 2H, O*H*, COO*H*);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 (8-$CH_3$), 18.6 (C-8), 20.7 (2-$CH_3$), 27.8 (C-2), 38.0 (C-3'), 38.6 (C-3), 39.1 (C-5'), 40.0 (C-7), 40.6 (*C*$H_2$COOH), 41.2 (C-5), 43.7 (C-1), 55.3 ($CH_2$O*C*$H_3$), 56.8 (CHO*C*$H_3$), 68.8 (C-4'), 72.5 (C-6), 72.8 (C-4), 75.4 (C-6'), 78.2 (C-2'), 94.5 (*C*$H_2$OCH$_3$), 173.6 (*C*OOH);
**HRMS** (ESI): calcd for $C_{20}H_{38}NaO_7$ $[M+Na]^+$: 413.25097, found 413.25082.

**Macrolactone 8-33a and 8-33b**




**8-33a**



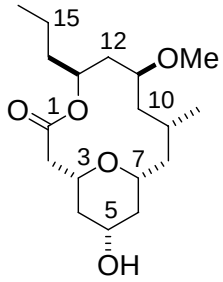

**8-33b**

To an ice-cooled solution of seco-acid **8-32** (102 mg, 0.26 mmol, 1.0 equiv) in THF (2.5 mL) was added $Et_3N$ (236 µl, 1.56 mmol, 6.0 equiv) followed by 2,4,6-trichlorobenzoyl chloride (203 µl, 1.3 mmol, 5.0 equiv). The mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temperature, whereupon toluene (7.0 mL) was added. This solution was added over 8 h by syringe pump to a solution of DMAP (793 mg, 6.5 mmol, 25 equiv) in toluene (200 mL). Upon complete addition, stirring was continued for additional 2 h. The mixture was concentrated to dryness and filtered over silica gel (using petroleum ether /EtOAc 2:1 as eluant). The filtrate was concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded lactone **8-33a** (81 mg, 83% yield) and its 5-epi isomer **8-33b** (8.7 mg, 9% yield).

Macrolactone **8-33a**:
**$R_f$** = 0.26 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = +19.4 (*c* 1.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3H, 15-$CH_3$), 0.96 (d, *J* = 6.8 Hz, 3H, 9-$CH_3$), 1.07–1.15 (m, 1H, 6-H), 1.17–1.61 (m, 11H, 6-H, 10-H, 12-H, 8-H, 14-H, 15-H, 9-H), 1.80–1.90 (m, 2H, 4-H, 12-H), 1.94–2.01 (m, 1H, 4-H), 2.37–2.45 (m, 1H, 2-H), 2.56–2.63 (m, 1H, 2-H), 3.11–3.19 (m, 1H, 7-H), 3.30 (s, 3H, CHOC$H_3$), 3.35 (s, 3H, $CH_2OCH_3$), 3.51–3.60 (m, 1H, 11-H), 3.65–3.76 (m, 2H, 3-H, 5-H), 4.67 (s, 2H, C$H_2$OCH$_3$), 5.09–5.18 (m, 1H, 13-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (15-$CH_3$), 19.0 (C-15), 25.5 (9-$CH_3$), 31.2 (C-9), 36.9 (C-4), 38.1 (C-14), 39.2 (C-6), 40.0 (C-10), 42.2 (C-2), 42.3 (C-12), 44.1 (C-8), 55.3 ($CH_2OCH_3$), 56.3 (CHO$CH_3$), 72.4 (C-3), 73.0 (C-5), 73.2 (C-13), 75.5 (C-11), 78.7 (C-7), 94.5 ($CH_2OCH_3$), 170.8 (C-1);
**HRMS** (ESI): calcd for $C_{20}H_{36}NaO_6$ $[M+Na]^+$: 395.24041, found 395.24064.

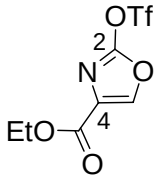
Macrolactone **8-33b**:
**$R_f$** = 0.20 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = +7.1 (*c* 0.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.84–0.93 (m, 6H, 15-$CH_3$, 9-$CH_3$), 1.08–1.43 (m, 9H, 6-H, 10-H, 8-H, 15-H, 9-H), 1.44–1.56 (m, 2H, 14-H), 1.57–2.05 (m, 4H, 4-H, 12-H), 2.32–2.39 (m, 1H, 2-H), 2.42–2.50 (m, 1H, 2-H), 2.98–3.07 (m, 1H, 7-H), 3.30 (s, 3H, CHOC$H_3$), 3.33–3.45 (m, 4H, $CH_2OCH_3$, 11-H), 3.55 (apt, *J* = 11.0, 1H, 3-H), 3.69–3.80 (m, 1H, 5-H), 4.67 (s, 2H, C$H_2$OCH$_3$), 5.02–5.10 (m, 1H, 13-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (15-$CH_3$), 18.9 (C-15), 24.3 (9-$CH_3$), 24.4 (C-9), 36.8 (C-4), 38.3 (C-14), 39.3 (C-6), 39.3 (C-12), 39.7 (C-10), 42.4 (C-2), 45.2 (C-8), 55.3 ($CH_2OCH_3$), 57.0 (CHO$CH_3$), 72.8 (C-3), 72.9 (C-5), 74.1 (C-13), 74.9 (C-11), 76.8 (C-7), 94.5 ($CH_2OCH_3$), 172.7 (C-1);
**HRMS** (ESI): calcd for $C_{20}H_{36}NaO_6$ $[M+Na]^+$: 395.24041, found 395.24030.

**Neopeltolide core 6-14**



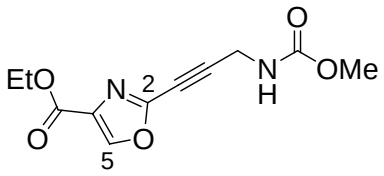

To a cooled (0 °C) solution of compound **8-33a** (73.0 mg, 0.196 mmol) in MeOH (3 mL) was added concentrated HCI (100 μL). After stirring for 0.5 h at 0 °C and for 24 h at ambient temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with EtOAc (4 × 20 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1 to 1:1) afforded neopeltolide macrolactone **6-14** (62.4 mg, 97% yield) as a colorless oil. $\mathbf{R_f}$ = 0.20 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = +18.4 (*c* 0.1, $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3H, 15-$CH_3$), 0.97 (d, *J* = 6.8 Hz, 3H, 9-$CH_3$), 1.08–1.25 (m, 3H, 6-H, 8-H), 1.26–1.73 (m, 10H, 10-H, 8-H, 9-H, 12-H, 14-H, 15-H, OH), 1.80–1.88 (m, 2H, 14-H, 4-H), 1.92–1.98 (m, 1H, 4H), 2.41 (dd, *J* = 14.4, 10.9 Hz, 1H, 2-H), 2.60 (dd, *J* = 14.6, 4.2 Hz, 1H, 2-H), 3.16 (apt, *J* = 10.1 Hz, 1H, 11-H), 3.30 (s, 3H, CHOC*H*$_3$), 3.56 (apt, *J* = 10.1 Hz, 1H, 7-H), 3.68–3.84 (m, 2H, 3-H, 5-H), 5.09–5.18 (m, 1H, 13-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (15-$CH_3$), 19.0 (C-15), 25.5 (9-$CH_3$), 31.2 (C-9), 36.9 (C-4), 40.0 (C-14), 40.7 (C-6), 41.9 (C-12), 42.2 (C-2), 42.2 (C-10), 44.1 (C-8), 56.2 (CHO*C*H$_3$), 68.0 (C-5), 72.3 (C-13), 73.3 (C-3), 75.6 (C-11), 78.6 (C-7), 170.8 (C-1); **HRMS** (ESI): calcd for $C_{18}H_{32}NaO_5$ $[M+Na]^+$: 351.21420, found 351.21414.

### Ethyl 2-{[(trifluoromethyl)sulfonyl]oxy}-1,3-oxazole-4-carboxylate (8-12)



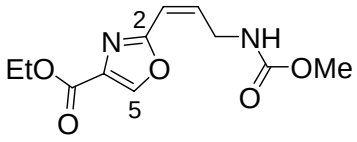

A solution of oxazolone **8-14**[251] (2.01 g, 12.8 mmol, 1 equiv) in $CH_2Cl_2$ (70 mL) was cooled to –80 °C, before 2,6-Lutidine (3.0 mL, 25.6 mmol, 2 equiv) was added via syringe followed by the addition of $Tf_2O$ (3.21 mL, 19.2 mmol, 1.5 equiv). The reaction mixture was then allowed to warm to ambient temperature with stirring for 40 min. The reaction was diluted with water (150 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give 3.30 g of **8-12** (88%) as a slightly yellow amorphous solid. Triflate **8-12** was used immediately after preparation. $\mathbf{R_f}$ = 0.52 (petroleum ether/EtOAc, 4:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3H, $CH_3$), 4.33 (q, *J* = 7.2 Hz, 2H, $CH_2$), 8.09 (s, 1H, 5-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 ($CH_3$), 61.7 ($CH_2$), 118.3 (q, *J* = 322.0 Hz, $CF_3$), 133.8 (C-4), 142.9 (C-5), 150.0 (C-2), 159.4 (*C*$O_2$Et).

**Ethyl 2-{3-[(methoxycarbonyl)amino]prop-1-ynyl}-1,3-oxazole-4-carboxylate (8-11)**



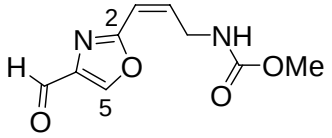
Triflate **8-12** (3.25 g, 11.1 mmol) and 2,6-lutidine (6.3 mL, 54.4 mmol) were dissolved in degased 1,4-dioxane (45.0 mL) and alkyne **8-13** (2.51 g, 22.2 mmol), $Pd(PPh_3)_4$ (1.27 g, 1.11 mmol), and CuI (422 mg, 2.22 mmol) were added. The reaction mixture was stirred at ambient temperature for 12 h, diluted with EtOAc (200 mL), filtered through a thin pad of $SiO_2$ and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 7:3→1:1) afforded alkyne **8-11** (2.21 g, 79% yield) as a slightly yellow oil which was crystallized upon standing in the fridge (–20 °C). $\mathbf{R_f}$ = 0.35 ($CH_2Cl_2$/EtOAc, 85:15); **m.p.** = 76–78 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$), 3.66 (s, 3H, $OCH_3$), 4.19 (d, *J* = 5.6 Hz, 2H, $CH_2NH$), 4.33 (q, *J* = 7.2 Hz, 2H, $CH_2CH_3$), 5.36 (br s, 1H, NH), 8.14 (s, 1H, 5-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CH_2CH_3$), 31.1 ($CH_2NH$), 52.5 ($OCH_3$), 61.4 ($CH_2CH_3$), 70.1 ($C{\equiv}CCH_2$), 89.7 ($C{\equiv}CCH_2$), 134.1 (C-4), 144.2 (C-5), 146.3 (C-2), 156.5 ($CO_2CH_3$), 160.3 ($CO_2Et$);
**HRMS** (ESI): calcd for $C_{11}H_{12}NaN_2O_5$ $[M+Na]^+$: 275.06384, found 275.06386.

**Ethyl 2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazole-4-carboxylate (8-10)**



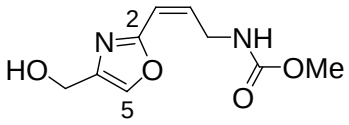
Alkyne **8-11** (1.21 g, 4.8 mmol, 1 equiv) and quinoline (0.94 mL, 7.7 mmol, 1.6 equiv) were dissolved in EtOAc (280 mL), which was followed by the addition of Lindlar's catalyst (5 wt% Pd on $CaCO_3$, posioned with lead (Fluka, № 62145), 940 mg, 100 wt%). The reaction was placed under $H_2$ atmosphere and stirred until HPLC-MS analysis showed complete consumption of the starting material (ca. 5–6 h). The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. Obtained oil was triturated with hexane (50 mL), resulting in the crystalization of product. Hexane was decanted and this procedure was repeated one more time. Flash chromatography of the obtained residue ($CH_2Cl_2$/EtOAc, 9:1→85:15→4:1) afforded ester **8-10** (1.085 g, 89% yield) as a slightly yellow solid. $\mathbf{R_f}$ = 0.36 ($CH_2Cl_2$/EtOAc, 85:15); **m.p.** = 92–93 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 3.62 (s, 3H, $OCH_3$), 4.28–4.37 (m, 4H, $CH_2NH$, $CH_2CH_3$), 5.47 (br s, 1H, NH), 6.10–6.19 (m, 1H, $HC{=}CHCH_2$), 6.30 (d, *J* = 11.9 Hz, 1H, $HC{=}CHCH_2$), 8.14 (s, 1H, 5-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CH_2CH_3$), 39.6 ($CH_2NH$), 52.1 ($OCH_3$), 61.2 ($CH_2CH_3$), 115.2 ($HC{=}CHCH_2$), 134.3 (C-4), 139.3 ($HC{=}CHCH_2$), 143.1 (C-5), 157.1 ($CO_2CH_3$), 160.6 ($CO_2Et$), 161.0 (C-2);
**HRMS** (ESI): calcd for $C_{11}H_{14}NaN_2O_5$ $[M+Na]^+$: 277.07949, found 277.07937.

**Methyl (2*Z*)-3-(4-formyl-1,3-oxazol-2-yl)prop-2-enylcarbamate (8-34)**



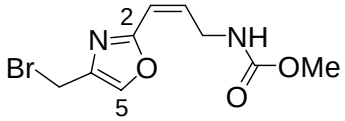

To a solution of ester **8-10** (0.72 g, 2.83 mmol) in dry $CH_2Cl_2$ (15 mL), at –80 °C, was added dropwise Dibal-H (1M in hexanes, 7.1 mL, 7.1 mmol, 2.5 equiv). The solution was stirred at –80 °C for 90 min, quenched with saturated aqueous $NH_4Cl$ solution and warmed up to room temperature. It was then treated with saturated potassium and sodium tartrate (Rochelle salt)/EtOAc (100:100 mL) and the mixture was vigorously stirred for 10 min. After the layers were separated, the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue ($CH_2Cl_2$/MeOH, 97:3→95:5) afforded aldehyde **8-34** (415 mg, 70% yield) as a colorless solid. Besides aldehyde **8-34** some overreducted alcohol **8-35** (85 mg, 14%) was isolated. $\mathbf{R_f}$ = 0.61 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 75–76 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.66 (s, 3H, $OCH_3$), 4.32–4.42 (m, 2H, C*H*$_2$NH), 5.39 (br s, 1H, NH), 6.20–6.29 (m, 1H, HC=C*H*$CH_2$), 6.33 (d, *J* = 11.6 Hz, 1H, *H*C=$CHCH_2$), 8.21 (s, 1H, 5-H), 9.93 (s, 1H, C*H*O); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.7 ($CH_2NH$), 52.2 ($OCH_3$), 115.0 (H*C*=$CHCH_2$), 140.4 (C-4), 141.5 (HC=*C*H$CH_2$), 143.5 (C-5), 157.1 (*C*$O_2CH_3$), 161.1 (C-2), 184.1 (*C*HO).

**Methyl (2*Z*)-3-[4-(hydroxymethyl)-1,3-oxazol-2-yl]prop-2-enylcarbamate (8-35)**



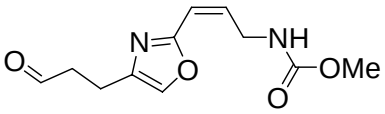

To a cooled (0 °C) solution of aldehyde **8-34** (380 mg, 1.81 mmol) in the mixture of THF/MeOH (6:2 mL) was added sodium borohydride (87 mg, 2.35 mmol) and the reaction mixture was stirred at this temperature for 1 h. Then it was treated with saturated $NH_4Cl$ solution and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL), and the combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5) afforded alcohol **8-35** (364 mg, 95% yield) as a colorless solid. $\mathbf{R_f}$ = 0.42 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 125–126 °C, Lit.[146a] m.p. = 124–125 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.53 (s, 3H, $OCH_3$), 4.16–4.22 (m, 2H, C*H*$_2$NH), 4.38 (d, *J* = 5.1 Hz, 2H, C*H*$_2$OH), 5.21 (t, *J* = 5.1 Hz, 1H, OH), 5.92–6.01 (m, 1H, HC=C*H*$CH_2$), 6.28 (dt, *J* = 11.9, 2.0 Hz, 1H, *H*C=$CHCH_2$), 7.46 (t, *J* = 5.2 Hz, 1H, NH), 7.89 (s, 1H, 5-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.8 (*C*$H_2$NH), 51.4 ($OCH_3$), 55.7(*C*$H_2$OH), 114.5 (H*C*=$CHCH_2$), 135.3 (C-4), 138.4 (HC=*C*H$CH_2$), 142.7 (C-5), 156.8 (*C*$O_2CH_3$), 159.6 (C-2);
**HRMS** (ESI): calcd for $C_{11}H_{14}NaN_2O_5$ $[M+Na]^+$: 235.06948, found 235.06952.

**Methyl (2*Z*)-3-[4-(bromomethyl)-1,3-oxazol-2-yl]prop-2-enylcarbamate (8-39)**[265]



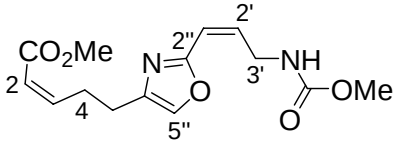
A solution of alcohol **8-35** (62 mg, 0.29 mmol) and $PPh_3$ (152 mg, 0.58 mmol) in $CH_3CN$ (3 mL) was treated with 2,6-lutidine (17 mL, 0.15 mmol) and $CBr_4$ (Fluka, № 86770) (192 mg, 0.58 mmol). After 1 h the reaction mixture was partioned between 5% solution of $NaHCO_3$ (10 mL) and $Et_2O$ (20 mL). The organic layer was separated and the aqueous layer extracted with $Et_2O$ (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc:hexane = 2:1→1:1→1:2) to give bromide **8-39** (64 mg, 81%) as a white solid. $\mathbf{R_f}$ = 0.62 (hexane:EtOAc, 1:2); **m.p.** = 85–86 °C, Lit.[146a] **m.p.** = 86–87 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.67 (s, 3H, $OCH_3$), 4.28–4.36 (m, 2H, C*H*$_2$NH), 4.37 (s, 2H, $CH_2Br$), 5.42 (br s, 1H, NH), 6.10–6.20 (m, 1H, HC=C*H*$CH_2$), 6.29 (d, *J* = 11.6 Hz, 1H, *H*C=$CHCH_2$), 7.60 (s, 1H, 5-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.8 ($CH_2NH$), 51.4 ($OCH_3$), 55.7 ($CH_2OH$), 114.5 (H*C*=$CHCH_2$), 135.3 (C-4), 138.4 (HC=*C*$HCH_2$), 142.7 (C-5), 156.8 (*C*$O_2CH_3$), 159.6 (C-2);
**HRMS** (ESI): calcd for $C_9H_{11}BrNaN_2O_3$ $[M+Na]^+$: 296.98453, found 296.98477.

### Methyl (2*Z*)-3-[4-(3-oxopropyl)-1,3-oxazol-2-yl]prop-2-enylcarbamate (8-9)[146d]



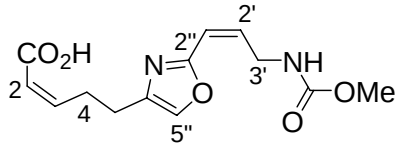
A solution of diethylamine (52.4 μL, 0.51 mmol, 2.2 equiv) in THF (0.5 mL) was cooled to –78 °C, and treated with *n*BuLi (2.5M solution in hexane, 204.0 μL, 0.51 mmol, 2.2 equiv). After 15 min, a solution of imine **8-40**[264] (66.1 mg, 0.53 mmol, 2.3 equiv) in THF (0.5 mL) was added to the reaction mixture, immediately followed by HMPA (68.2 mL, 0.393 mmol). The reaction was warmed to 0 °C, stirred for 10 min and then cooled to –78 °C. The resulting yellow solution of the enolate was transferred via canula over a period of 5 min into a stirring solution of bromide **8-39** (63 mg, 0.23 mmol) in THF (0.5 mL) at –30 °C. After 20 min at –30 °C, the reaction was quenched with 10% solution of tartaric acid (2 mL), and allowed to warm to room temperature. After the mixture was extracted with EtOAc (3 × 25 mL), the combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 98:2→95:5) afforded aldehyde **8-9** (43 mg, 78% yield) which was used immediately in the next step. TLC ($CH_2Cl_2$/MeOH, 9:1): $R_f$ = 0.48.

### Methyl (2*Z*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)pent-2-enoate (8-42)[267]



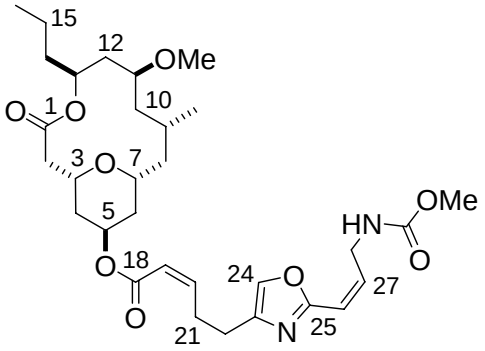
A solution of 18-crown-6, freshly recrystallized from acetonitrile, (269 mg, 1.02 mmol, 6 equiv) and bis(2,2,2-trifluoroethyl)(metoxycarbonylmethyl) phosphonate (**8-41**)[267] (86 µL, 0.41 mmol, 2.4 equiv) in THF (2.5 mL) was cooled to –78 °C, and treated with KHMDS (0.5M solution in toluene, 0.75 mL, 0.37 mmol, 2.2 equiv). After 1 h, the solution of aldehyde **8-9** (41 mg, 0.17 mmol, 1 equiv) in THF (0.5 mL) was added over a period of 5 min. After 1 h, TLC indicated complete consumption of aldehyde; the reaction was quenched with saturated $NH_4Cl$ and warmed to room temperature. After the mixture was extracted with EtOAc (3 × 20 mL), the combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 98:2) afforded ester **8-42** (32 mg, 65% yield, 11:1 mixture of *Z*:*E* isomers by $^1$H NMR analysis) as a colorless oil. $\mathbf{R_f}$ = 0.55 ($CH_2Cl_2$/MeOH, 9:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.68 (t, *J* = 7.2 Hz, 2H, 5-H), 2.96–3.03 (m, 2H, 4-H), 3.66 (s, 3H, OC*H*$_3$), 3.69 (s, 3H, $CCO_2CH_3$), 4.25–4.32 (m, 2H, 3'-H), 5.59 (br s, 1H, NH), 5.80 (d, *J* = 11.6 Hz, 1H, 2-H), 6.03–6.13 (m, 1H, 2'-H), 6.21–6.30 (m, 2H, 3-H, 1'-H), 7.36 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 25.6 (C-5), 27.5 (C-4), 39.3 (C-3'), 51.1 (O*C*H$_3$), 52.1 (O*C*H$_3$), 116.7 (C-1'), 120.2 (C-2), 133.9 (C-5''), 136.2 (C-4''), 141.1 (C-2'), 148.9 (C-5''), 157.1 ($CO_2CH_3$), 159.9 (C-2''), 166.7 (C-1);
**HRMS** (ESI): calcd for $C_{14}H_{18}NaN_2O_5$ $[M+Na]^+$: 317.11079, found 317.11086.

**Acid 6-15**



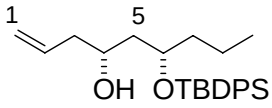

A solution of ester **8-42** (15 mg, 0.05 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.5 mL, 0.5 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 7 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.5 mL, 0.5 mmol). After the mixture was extracted with EtOAc (4 × 20 mL), the combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5→9:1) afforded acid **6-15** (12.7 mg, 91% yield) as a colorless oil. $\mathbf{R_f}$ = 0.36 ($CH_2Cl_2$/MeOH, 9:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.69 (t, *J* = 7.3 Hz, 2H, 5-H), 2.98 (m, 2H, 4-H), 3.66 (s, 3H, OC*H*$_3$), 4.25–4.32 (m, 2H, 3'-H), 5.52 (br s, 1H, NH), 5.81 (d, *J* = 11.5 Hz, 1H, 2-H), 6.03–6.10 (m, 1H, 2'-H), 6.25–6.32 (m, 2H, 3-H, 1'-H), 7.34 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 25.5 (C-5), 27.4 (C-4), 39.3 (C-3'), 52.1 (O*C*H$_3$), 116.6 (C-1'), 120.2 (C-2), 133.9 (C-5''), 136.4 (C-4''), 141.0 (C-2'), 148.9 (C-5''), 157.1 ($CO_2CH_3$), 159.9 (C-2''), 166.7 (C-1);
**HRMS** (ESI): calcd for $C_{13}H_{16}NaN_2O_5$ $[M+Na]^+$: 303.09514, found 303.09511.

**Neopeltolide (5-1)**




To a solution of alcohol **6-14** (8.3 mg, 0.025 mmol, 1 equiv), acid **6-15** (11.2 mg, 0.04 mmol, 1.6 equiv) and $PPh_3$ (11.5 mg, 0.044 mmol, 1.76 equiv) in absolute benzene (1 mL) was added diisopropyl azodicarboxylate (88 μL of 0.5M solution in benzene, 0.044 mmol, 1.76 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1→1:1→1:2) to afford neopeltolide **(5-1)** (12.0 mg, 80%) as a colorless oil. $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +23.8 (*c* 0.24, MeOH); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.96 (d, *J* = 6.6 Hz, 3H, 17-H), 1.06–1.14 (m, 1H, 10-H), 1.20–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.45–1.60 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.63–1.75 (m, 2H, 6-H, 14-H), 1.78–1.89 (m, 2H, 4-H, 12-H), 2.28 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.65–2.74 (m, 3H, 2-H, 22-H), 2.96–3.04 (m, 2H, 21-H), 3.27 (s, 3H, 11-$OCH_3$), 3.55 (apt, *J* = 9.9 Hz, 1H, 7-H), 3.62–3.70 (m, 4H, 29-$OCH_3$, 11-H), 4.02–4.11 (m, 1H, 3-H), 4.29 (d, *J* = 4.6 Hz, 2H, 28-H), 5.12–5.21 (m, 2H, 13-H, 5-H), 5.87 (d, *J* = 11.4 Hz, 1H, 19-H), 5.98–6.07 (m, 1H, 27-H), 6.26 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.36 (dt, *J* = 11.6, 7.4 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 26.4 (C-22), 29.0 (C-21), 32.6 (C-9), 36.2 (C-4), 37.4 (C-6), 37.9 (C-14), 41.0 (C-12), 43.2 (C-2), 43.5 (C-10), 45.2 (C-8), 52.6 (29-$OCH_3$), 56.4 (11-$OCH_3$), 69.2 (C-5), 71.3 (C-3), 73.9 (C-13), 77.0 (C-7), 77.1 (C-11), 115.9 (C-26), 121.7 (C-19), 135.9 (C-24), 139.2 (C-27), 142.3 (C-23), 150.0 (C-20), 159.6 (C-29), 161.9 (C-25), 166.9 (C-18), 173.0 (C-1);
**HRMS** (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+Na]^+$: 613.30955, found 613.31039.

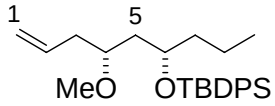
**(4*R*,6*S*)-6-{[*tert*-Butyl(diphenyl)silyl]oxy}non-1-en-4-ol (8-43)**




To a cooled (–20 °C) solution of (*S*,*S*)-**6-82** (22.3 g, 40.4 mmol, 1.1 equiv) in $CH_2Cl_2$ (190 mL) was added aldehyde **8-17** (13.0 g, 36.7 mmol, 1.0 equiv). The reaction mixture was then placed into a freezer (–10 °C) and maintained at that temperature for 24 h (without stirring). The reaction was quenched while cold with 1N HCl (100 mL) and EtOAc (100 mL) and the mixture was vigorously stirred at room temperature for 15 min. The obtained white precipitate of (*S*,*S*)-*N*,*N*'-bis-(4-bromo-benzyl)-cyclohexane-1,2-diamine dihydrochloride was filtered, washed with $Et_2O$ (3 × 50 mL) and dried in vacuo (recovered 18.6 g, 91% of (*S*,*S*)-diamine dihydrochloride). The filtrate layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were washed with $H_2O$ (100 mL),

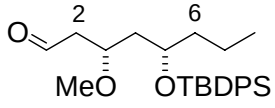
saturated NaCl solution (100 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash chromatography (petroleum ether/EtOAc, 20:1→10:1) to give homoallylic alcohol **8-43** (12.30 g, 85%) as a colorless oil. $\mathbf{R_f}$ = 0.41 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = +6.7 (*c* 3.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.62 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 1.06 (s, 9H, Si(C($CH_3$)$_3$)), 1.13–1.45 (m, 4H, 7-H, 8-H), 1.59–1.67 (m, 2H, 5-H), 2.08–2.21 (m, 2H, 3-H), 2.66 (d, *J* = 3.0 Hz, 1H, OH), 3.80–3.90 (m, 1H, 4-H), 3.93–4.02 (m, 1H, 6-H), 5.03–5.07 (m, 1H, 1-H), 5.08–5.10 (m, 1H, 1-H), 5.70–5.84 (m, 1H, 2-H), 7.35–7.47 (m, 6H, *m*CH, *p*CH ar Ph), 7.69–7.74 (m, 4H, *o*CH ar Ph);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 (8-$CH_3$), 18.0 (C-8), 19.3 (Si(*C*($CH_3$)$_3$)), 27.0 (Si(C(*C*$H_3$)$_3$)), 39.4 (C-7), 42.0 (C-3), 42.6 (C-5), 69.4 (C-4), 73.3 (C-6), 117.6 (C-1), 127.5, 127.6, 129.6, 129.7, 133.7, 134.4 (C of $SiPh_2$), 134.7 (C-2), 134.8, 135.9 (C of $SiPh_2$);
**HRMS** (ESI): calcd for $C_{25}H_{36}NaO_2Si$ $[M+Na]^+$: 419.23768, found 419.23758.

### *tert*-Butyl{[(1*S*,3*R*)-3-methoxy-1-propylhex-5-enyl]oxy}diphenylsilane (8-44)




To a solution of alcohol **8-43** (8.51 g, 21.4 mmol) in $CH_2Cl_2$ (220 mL) in the dark at room temperature was added $Me_3OBF_4$ (11.1 g, 74.9 mmol) and proton sponge (22.9 g, 107 mmol) and the mixture was allowed to stir for 48 h. After complete reaction (monitoring by TLC) $H_2O$ was added (50 mL) and the mixture extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 40:1→20:1) afforded methyl ether **8-44** (7.64 g, 87% yield) as a colorless oil. $\mathbf{R_f}$ = 0.57 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –7.9 (*c* 2.1, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 1.08 (s, 9H, Si(C($CH_3$)$_3$)), 1.15–1.36 (m, 2H, 8-H), 1.37–1.60 (m, 3H, 7-H, 5-H), 1.74–1.82 (m, 1H, 5-H), 1.99–2.08 (m, 1H, 3-H), 2.10–2.19 (m, 1H, 3-H), 3.23 (s, 3H, $OCH_3$), 3.34–3.42 (m, 1H, 4-H), 3.81–3.89 (m, 1H, 6-H), 4.92–5.02 (m. 2H, 1-H), 5.64–5.77 (m, 1H, 2-H), 7.35–7.46 (m, 6H, *m*CH, *p*CH ar Ph), 7.68–7.74 (m, 4H, *o*CH ar Ph);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.9 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 27.1 (Si(C(*C*$H_3$)$_3$)), 37.6 (C-3), 39.1 (C-7), 40.1 (C-5), 56.0 ($OCH_3$), 70.6 (C-6), 77.2 (C-4), 116.8 (C-1), 127.4, 127.5, 129.4, 129.5, 134.4, 134.6 (C of $SiPh_2$), 134.7 (C-2), 135.9 (C of $SiPh_2$);
**HRMS** (ESI): calcd for $C_{26}H_{38}NaO_2Si$ $[M+Na]^+$: 433.25333, found 433.25335.

### (3*S*,5*S*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-methoxyoctanal (8-45)



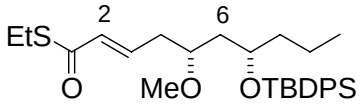

To a solution of methyl ether **8-44** (6.50 g, 15.9 mmol) in a mixture of THF/*t*BuOH (200/40 mL) was added 4-methyl-morpholine-N-oxide (4.30 g, 31.8 mmol) and an aqueous solution of $OsO_4$ (10 mL of a 0.032 M solution, 0.32 mmol, 2 mol%, prepared from $K_2OsO_4 \cdot 2H_2O$ (118

mg, 0.32 mmol)) at 0 ºC. After being stirred at room temperature for 20 h, 10% $Na_2S_2O_3$ solution (50 mL) was added to the mixture. After 30 min, the diol was extracted with EtOAc and the combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel followed by rinsing the pad with EtOAc. Removal of the solvent from the combined filtrate gave the crude diol.

$NaIO_4$ (5.1 g, 24.0 mmol, 1.5 equiv) was added to a solution of crude diol in 90% MeOH (200 mL). After stirring at room temperature for 1 h, most of the methanol was removed in vacuo and the residue extracted with $Et_2O$ (3 × 150 mL). The combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, and filtered. After concentration, the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1→5:1) to give aldehyde **8-45** as a colorless oil (6.11 g, 93% for 2 steps). $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –3.6 (*c* 1.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.3 Hz, 3H, 7-$CH_3$), 1.05 (s, 9H, Si(C($CH_3$)$_3$)), 1.14–1.33 (m, 2H, 7-H), 1.38–1.60 (m, 3H, 6-H, 4-H), 1.86–1.94 (m, 1H, 4-H), 2.15–2.30 (m, 2H, 2-H), 3.21 (s, 3H, $OCH_3$), 3.72–3.82 (m, 2H, 3-H, 5-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.63–7.69 (m, 4H, *o*CH ar Ph), 9.54–9.57 (m, 1H, C*H*O); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (7-$CH_3$), 17.9 (C-7), 19.3 (Si(*C*($CH_3$)$_3$)), 27.1 (Si(C(*C*$H_3$)$_3$)), 39.2 (C-6), 40.1 (C-4), 47.9 (C-2), 56.3 ($OCH_3$), 70.2 (C-5), 73.5 (C-3), 127.5, 127.6, 129.6, 129.7, 134.0, 134.3, 135.9, 135.9 (C of $SiPh_2$), 201.5 (C-1);

**HRMS** (ESI): calcd for $C_{25}H_{36}NaO_3Si$ $[M+Na]^+$: 435.23259, found 435.23257.

### *S*-Ethyl (2*E*,5*R*,7*S*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-5-methoxydec-2-enethioate (8-46)

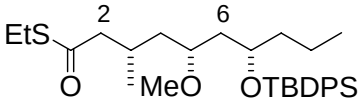



A solution of the aldehyde **8-45** (6.10 g, 14.8 mmol) and ylide **8-21** (22.2 mmol, 8.1 g) in $CH_2Cl_2$ (250 mL) was heated at reflux for 10 h. The solution was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 40:1→20:1) to afford the desired α,β-unsaturated thioester **8-46** as a colorless oil (6.71 g, 91% ). $\mathbf{R_f}$ = 0.51 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –22.3 (*c* 3.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.3 Hz, 3H, 9-$CH_3$), 1.05 (s, 9H, Si(C($CH_3$)$_3$)), 1.14–1.33 (m, 5H, 9-H, $SCH_2CH_3$), 1.38–1.52 (m, 3H, 6-H, 8-H), 1.76–1.84 (m, 1H, 6-H), 1.99–2.08 (m, 1H, 4-H), 1.99–2.08 (m, 1H, 4-H), 2.13–2.20 (m, 1H, 4-H), 2.93 (q, *J* = 14.7 Hz, 2H, $SCH_2CH_3$), 3.21 (s, 3H, $OCH_3$), 3.37–3.43 (m, 1H, 5-H), 3.75–3.80 (m, 1H, 7-H), 5.96 (d, *J* = 15.7 Hz, 1H, 2-H), 6.70–6.79 (m, 1H, 3-H), 7.34–7.46 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.70 (m, 4H, *o*CH ar Ph);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (9-$CH_3$), 14.8 ($SCH_2CH_3$), 18.0 (C-9), 19.3 (Si(*C*($CH_3$)$_3$)), 23.0 ($SCH_2CH_3$), 27.1 (Si(C(*C*$H_3$)$_3$)), 36.2 (C-4), 39.2 (C-8), 40.3 (C-6), 56.3 ($OCH_3$), 70.3 (C-7), 76.5 (C-5), 127.4, 127.6, 129.5, 129.7 (C of $SiPh_2$), 130.5 (C-2), 134.1, 134.4, 135.9 (C of $SiPh_2$), 141.3 (C-3), 189.8 (C-1);

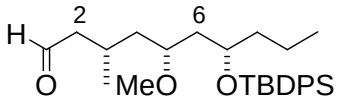
**HRMS** (ESI): calcd for $C_{29}H_{42}NaO_3SSi$ $[M+Na]^+$: 521.25161, found 521.25170.

### *S*-Ethyl (3*S*,5*R*,7*S*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-5-methoxy-3-methyldecanethioate (8-47)



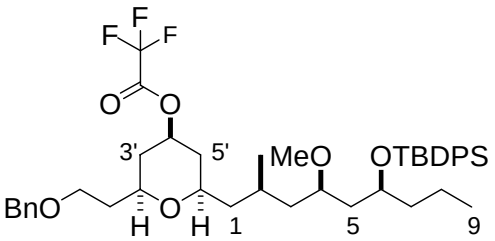

$CuBr{\cdot}Me_2S$ (7.1 mg, 0.034 mmol, 3 mol%) and (*S,R*)-Josiphos ***ent*-6-87** (26.0 mg, 0.04 mmol, 3.6 mol%) were dissolved in *t*BuOMe (10 mL) and stirred at room temperature for 30 min under nitrogen. The mixture was cooled to –75 °C and MeMgBr (3M solution in $Et_2O$, 465 µL, 1.4 mmol, 1.2 equiv) was added dropwise. After stirring for 10 min, a solution of thioester **8-46** (572 mg, 1.15 mmol, 1 equiv) in *t*BuOMe (1.2 mL) was added via a syringe pump over 2 h. The reaction mixture was stirred at –75 °C for 12 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous $NH_4Cl$ solution was then added, the phases were separated and the aqueous layer extracted with $Et_2O$ (2 × 50 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 30:1→20:1) to afford the desired 1,4-addition adduct **8-47** as a colorless oil (501 mg, 85%). $\mathbf{R_f}$ = 0.57 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –6.8 (*c* 1.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.3 Hz, 3H, 9-$CH_3$), 0.86 (d, *J* = 6.6 Hz, 3H, 3-$CH_3$), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.14–1.31 (m, 7H, 4-H, 9-H, $SCH_2CH_3$), 1.34–1.53 (m, 3H, 6-H, 8-H), 1.72–1.81 (m, 1H, 6-H), 2.00–2.12 (m, 1H, 3-H), 2.13–2.21 (m, 1H, 2-H), 2.48 (dd, *J* = 14.4, 4.8 Hz, 1H, 2-H), 2.86 (q, *J* = 14.9 Hz, 2H, $SCH_2CH_3$), 3.16 (s, 3H, $OCH_3$), 3.24–3.30 (m, 1H, 5-H), 3.76–3.82 (m, 1H, 7-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.69 (m, 4H, *o*CH ar Ph); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (9-$CH_3$), 14.8 ($SCH_2CH_3$), 17.9 (C-9), 19.4 (Si(*C*($CH_3$)$_3$)), 20.2 (3-$CH_3$), 23.2 ($SCH_2CH_3$), 27.1 (Si(C(*C*$H_3$)$_3$)), 27.8 (C-3), 39.0 (C-8), 40.6 (C-6), 41.2 (C-4), 50.8 (C-2), 55.7 ($OCH_3$), 70.6 (C-7), 75.9 (C-5), 127.4, 127.5, 129.5, 129.5, 134.3, 134.6, 136.0 (C of $SiPh_2$), 199.0 (C-1);
**HRMS** (ESI): calcd for $C_{30}H_{46}NaO_3SSi$ $[M+Na]^+$: 537.28291, found 537.28327.

**(3*S*,5*R*,7*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-5-methoxy-3-methyldecanal (8-48)**



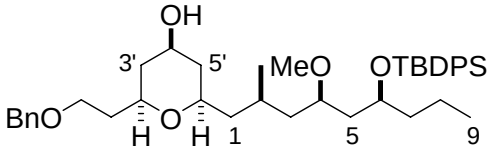

To a stirred mixture of the thioester **8-47** (470 mg, 0.92 mmol) and Pd-C (47.0 mg, 10% wt) in $CH_2Cl_2$ (5 mL) was added $Et_3SiH$ (438 µL, 2.76 mmol, 3 equiv) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 30 min. The catalyst was filtered off through a pad of celite and washed with $CH_2Cl_2$. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 10:1→5:1) to give the pure aldehyde **8-48** (397 mg, 95%). $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 10:1); $\mathbf{[\alpha]^{20}_D}$ = –3.0 (*c* 1, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.3 Hz, 3H, 9-$CH_3$), 0.87 (d, *J* = 6.3 Hz, 3H, 3-$CH_3$), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.14–1.30 (m, 4H, 4-H, 9-H), 1.37–1.52 (m, 3H, 6-H, 8-H), 1.73–1.83 (m, 1H, 6-H), 1.98–2.09 (m, 2H, 2-H, 3-H), 2.25–2.32 (m, 1H, 2-H), 3.14 (s, 3H, $OCH_3$), 3.25–3.32 (m, 1H, 5-H), 3.76–3.81 (m, 1H, 7-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.70 (m, 4H, *o*CH ar Ph), 9.61–9.64 (m, 1H, C*H*O);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (9-$CH_3$), 18.0 (C-9), 19.4 (Si(*C*($CH_3$)$_3$)), 20.8 (3-$CH_3$), 24.7 (C-3), 27.1 (Si(C(*C*$H_3$)$_3$)), 39.2 (C-8), 40.3 (C-6), 41.1 (C-4), 50.5 (C-2), 55.4 ($OCH_3$), 70.6 (C-7), 75.7 (C-5), 127.4, 127.5, 129.5, 129.6, 134.3, 134.5, 136.0 (C of $SiPh_2$), 202.9 (C-1);
**HRMS** (ESI): calcd for $C_{28}H_{42}NaO_3Si$ $[M+Na]^+$: 477.28009, found 477.27978.

**Trifluoroacetate 8-49**




Trifluoroacetic acid (0.78 ml, 8.2 mmol, 10 equiv) was added to a solution of alcohol **8-26** (220 mg, 1.07 mmol, 1.3 equiv) and aldehyde **8-48** (372 mg, 0.82 mmol) in $CH_2Cl_2$ (8 mL) at –5 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at this temperature and then saturated aqueous $NaHCO_3$ solution (10 mL) was added dropwise. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated in vacuo and purified by column flash chromatography (petroleum ether/EtOAc, 15:1→10:1) to afford trifluoracetate **8-49** as a colorless oil (437 mg, 71%). $\mathbf{R_f}$ = 0.75 (petroleum ether/EtOAc, 4:1);
$\mathbf{[\alpha]^{20}_D}$ = –2.7 (*c* 3.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.65 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.76 (d, *J* = 6.8 Hz, 3H, 2-$CH_3$), 0.98 (s, 9H, Si(C($CH_3$)$_3$)), 1.03–1.54 (m, 12H, 7-H, 8-H, 5'-H, 1-H, BnOCH$_2$C*H*$_2$, 3-H), 1.64–1.82 (m, 3H, 5-H, 2-H), 1.84–2.00 (m, 2H, 3'-H), 3.10 (s, 3H, $OCH_3$), 3.19–3.37 (m, 2H, 6'-H, 2'-H), 3.41–3.60 (m, 3H, 4-H, BnOC*H*$_2$CH$_2$), 3.70–3.79 (m, 1H, 6-H), 4.40 (s, 2H, PhC$H_2$O), 4.96–5.07 (m, 1H, 4'-H), 7.18–7.37 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.59–7.67 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.9 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 19.9 (2-$CH_3$), 25.6 (C-2), 26.5, 27.1 (Si(C(*C*$H_3$)$_3$)), 36.1 (BnOCH$_2$*C*H$_2$), 36.7 (C-3'), 37.3 (C-3), 39.0 (C-5'), 40.9 (C-7), 42.3 (C-5), 42.9 (C-1), 55.7 ($OCH_3$), 66.4 (BnO*C*H$_2$CH$_2$), 70.6 (C-6), 71.9 (C-4), 72.5 (C-6'), 73.1 (Ph*C*H$_2$O), 75.4 (C-4'), 76.0 (C-2'), 114.5 (q, *J* = 286 Hz, *C*$F_3$), 127.4, 127.4, 127.6, 127.6, 127.7, 128.4, 129.5, 129.6, 134.4, 134.5, 135.9, 138.3 (C of $SiPh_2$ and Ph of Bn), 156.9 (q, J = 42 Hz, *C*O$CF_3$);
**HRMS** (ESI): calcd for $C_{43}H_{59}F_3NaO_6Si$ $[M+Na]^+$: 779.39252, found 779.39261.

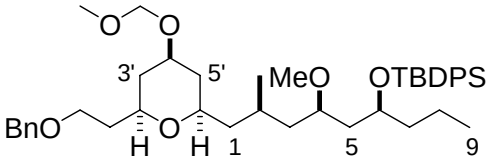
**Tetrahydropyran 8-50**




To a solution of trifluoracetate **8-49** (360 mg, 0.476 mmol) in methanol (5 mL) was added $K_2CO_3$ (131 mg, 0.95 mmol) and water (0.2 ml). The reaction mixture was stirred at room temperature for 1 h, then diluted with water (5 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 3:1→2:1) provided alcohol **8-50** (290 mg, 92% yield) as a colorless oil. $\mathbf{R_f}$ = 0.30 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –19.1 (*c* 1.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz,

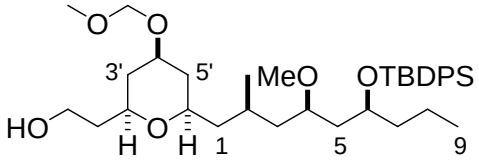
$CDCl_3$): δ = 0.65 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.76 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 0.98 (s, 9H, Si(C($CH_3$)$_3$)), 1.02–1.54 (m, 12H, 7-H, 8-H, 5'-H, 1-H, BnOCH$_2$C*H*$_2$, 3-H), 1.62–1.80 (m, 5H, 5-H, 2-H, 3'-H, BnOCH$_2$C*H*$_2$), 1.83–1.89 (m, 1H, 3'-H), 3.10 (s, 3H, $OCH_3$), 3.20–3.30 (m, 2H, 6'-H, 4-H), 3.34–3.42 (m, 1H, 2'-H), 3.47–3.58 (m, 2H, BnOC*H*$_2$CH$_2$), 3.64–3.81 (m, 2H, 4'-H, 6-H), 4.41 (s, 2H, PhC$H_2$O), 7.18–7.34 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.59–7.64 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.8 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 19.9 (2-$CH_3$), 25.8 (C-2), 27.1 (Si(C(*C*$H_3$)$_3$)), 36.2 (BnOCH$_2$*C*H$_2$), 38.9 (C-3), 41.0 (C-3'), 41.4 (C-5'), 41.9 (C-7), 42.4 (C-5), 43.2 (C-1), 55.7 ($OCH_3$), 66.8 (BnO*C*H$_2$CH$_2$), 68.3 (C-6), 70.7 (C-4'), 72.2 (C-4), 72.9 (C-6'), 73.1 (Ph*C*H$_2$O), 76.1 (C-2'), 127.4, 127.4, 127.5, 127.6, 128.3, 129.4, 129.4, 134.4, 134.6, 135.9, 135.9, 138.5 (C of $SiPh_2$ and Ph of Bn);
**HRMS** (ESI): calcd for $C_{41}H_{60}NaO_5Si$ $[M+Na]^+$: 683.41022, found 683.41103.

**Methoxy-methyl ether 8-51**



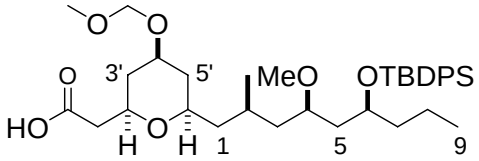

To a stirred, cooled (0 °C) solution of alcohol **8-50** (278 mg, 0.44 mmol) in DMF (2 mL) were added *N*,*N*-diisopropylethylamine (0.68 mL, 4.0 mmol), chloromethylmethyl ether (182 µL, 2.4 mmol), and tetrabutylammonium iodide (15 mg, 0.04 mmol). The reaction mixture was warmed to room temperature. After stirring for 4 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added followed by $Et_2O$ (20 mL). After separation of the layers, the aqueous phase was extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 5:1) afforded MOM ether **8-51** (304 mg, 98% yield) as a colorless oil. **$R_f$** = 0.58 (petroleum ether/EtOAc, 4:1); **$[\alpha]^{20}_D$** = –6.5 (*c* 3.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.65 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.76 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 0.99 (s, 9H, Si(C($CH_3$)$_3$)), 1.03–1.55 (m, 11H, 7-H, 8-H, 5'-H, 1-H, BnOCH$_2$C*H*$_2$, 3-H), 1.64–1.94 (m, 6H, 5-H, 2-H, 3'-H, BnOCH$_2$C*H*$_2$), 3.10 (s, 3H, CHOC*H*$_3$), 3.20–3.28 (m, 2H, 6'-H, 4-H), 3.31 (s, 3H, CH$_2$OC*H*$_3$), 3.35–3.43 (m, 1H, 2'-H), 3.46–3.59 (m, 2H, BnOC*H*$_2$CH$_2$), 3.61–3.71 (m, 1H, 4'-H), 3.73–3.81 (m, 1H, 6-H), 4.41 (s, 2H, PhC$H_2$O), 4.63 (s, 2H, C*H*$_2$OCH$_3$), 7.17–7.37 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.57–7.65 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.8 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 19.9 (2-$CH_3$), 25.8 (C-2), 27.1 (Si(C(*C*$H_3$)$_3$)), 36.3 (BnOCH$_2$*C*H$_2$), 38.7 (C-3'), 38.9 (C-3), 39.3 (C-5'), 41.0 (C-7), 42.5 (C-5), 43.3 (C-1), 55.2 (CH$_2$O*C*H$_3$), 55.8 (CHO*C*H$_3$), 66.8 (BnO*C*H$_2$CH$_2$), 70.7 (C-6), 72.3 (C-4), 72.9 (C-6'), 73.1 (Ph*C*H$_2$O), 73.2 (C-4'), 76.1 (C-2'), 94.3 (*C*H$_2$OCH$_3$), 127.4, 127.4, 127.5, 127.6, 128.3, 129.4, 129.4, 134.4, 134.7, 135.9, 138.5 (C of $SiPh_2$ and Ph of Bn);
**HRMS** (ESI): calcd for $C_{43}H_{64}NaO_6Si$ $[M+Na]^+$: 727.43644, found 727.43571.

**Alcohol 8-52**




The Parr hydrogenation vessel was charged with MOM ether **8-51** (195 mg, 0.276 mmol), Pd-C (20 mg), methanol (20 mL), attached to a hydrogen source and hydrogen was introduced into the reaction vessel until the pressure gauge indicates 2 atm. The pressure was carefully released to 1 atm by opening the stop valve. This procedure was repeated three times, and finally hydrogen was pressurized to 5 atm. The reaction mixture was vigorously shaked at room temperature for 10 h during which time the hydrogen cylinder was kept connected. After the stop valve was opened, excess hydrogen was carefully bled off, and the apparatus was disassembled. The catalyst was filtered off through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give the alcohol **8-52** (158 mg, 93%). $\mathbf{R_f}$ = 0.27 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = +6.0 (*c* 2.0, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.82 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.06–1.60 (m, 11H, 7-H, 8-H, 5'-H, 1-H, HOCH$_2$C*H*$_2$, 3-H), 1.65–1.80 (m, 4H, 5-H, 2-H, HOCH$_2$C*H*$_2$), 1.84–1.97 (m, 2H, 3'-H), 2.58 (br s, 1H, OH), 3.14 (s, 3H, CHOC*H*$_3$), 3.26–3.40 (m, 5H, 6'-H, 4-H, CH$_2$OC*H*$_3$), 3.46–3.55 (m, 1H, 2'-H), 3.65–3.84 (m, 4H, HOC*H*$_2$CH$_2$, 4'-H, 6-H), 4.69 (s, 2H, C*H*$_2$OCH$_3$), 7.31–7.43 (m, 6H, *m*CH, *p*CH ar SiPh$_2$), 7.64–7.70 (m, 4H, *o*CH ar SiPh$_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.9 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 20.1 (2-$CH_3$), 25.8 (C-2), 27.1 (Si(C(*C*$H_3$)$_3$)), 37.9 (C-3'), 38.6 (C-3), 39.0 (*C*H$_2$CH$_2$OH), 39.0 (C-5'), 40.8 (C-7), 42.4 (C-5), 43.0 (C-1), 55.3 (CH$_2$O*C*H$_3$), 55.5 (CHO*C*H$_3$), 61.3 (HO*C*H$_2$CH$_2$), 70.7 (C-6), 72.9 (C-4'), 73.6 (C-4), 75.7 (C-6'), 75.9 (C-2'), 94.4 (*C*H$_2$OCH$_3$), 127.4, 127.4, 129.4, 129.5, 134.4, 134.6, 135.9 (C of SiPh$_2$);
**HRMS** (ESI): calcd for $C_{36}H_{58}NaO_6Si$ $[M+Na]^+$: 637.38949, found 637.38926.

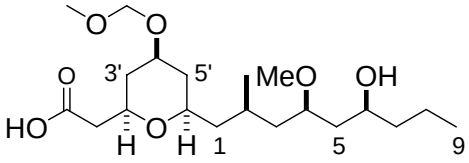
**Acid 8-53**




**a) Preparation of aldehyde:** To a cooled (0 °C) solution of alcohol **8-52** (155 mg, 0.25 mmol) in $CH_2Cl_2$ (3 mL) was added a solution of Dess-Martin periodinane (15% wt, 0.83 mL, 0.4 mmol). After stirring for 0.5 h at 0 °C and for 2 h at room temperature, the reaction mixture was concentrated, loaded on a flash silica gel column, and eluted with petroleum ether/EtOAc, 4:1 to give 147 mg (96%) of the corresponding aldehyde, which was used directly in the next reaction. TLC (petroleum ether/EtOAc, 4:1): $R_f$ = 0.76
**b) Acid 180:** The aldehyde obtained in the previous step (147 mg, 0.24 mmol) was dissolved in *t*BuOH (4 mL) and 2,3-dimethyl-2-butene (0.8 mL). A solution of $NaClO_2$ (65 mg, 0.72 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (336 mg, 2.16 mmol) in water (3 mL) was added slowly at 0 °C. After stirring for 30 min at room temperature the mixture was diluted with water (5 mL), extracted with EtOAc (4 × 20 mL), washed with saturated NaCl solution, dried ($Na_2SO_4$)

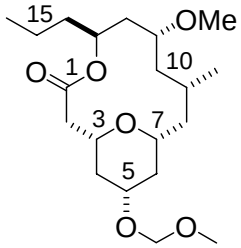
and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1:0.01→1:1:0.01) provided acid **8-53** (151 mg, 98% yield) as a colorless oil. $\mathbf{R_f}$ = 0.54 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = –2.3 (*c* 1.3, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): 0.70 (t, *J* = 7.3 Hz, 3H, 8-$CH_3$), 0.80 (d, *J* = 6.6 Hz, 3H, 2-$CH_3$), 1.04 (s, 9H, Si(C($CH_3$)$_3$)), 1.06–1.60 (m, 12H, 7-H, 8-H, 5'-H, 1-H, 2-H, 3-H), 1.69–1.81 (m, 2H, 5-H), 1.85–1.93 (m, 1H, 3'-H), 2.01–2.08 (m, 1H, 3'-H), 2.42–2.62 (m, 2H, C*H*$_2$COOH), 3.15 (s, 3H, CHOC*H*$_3$), 3.26–3.43 (m, 5H, 6'-H, 4-H, $CH_2$OC*H*$_3$), 3.66–3.84 (m, 3H, 2'-H, 4'-H, 6-H), 4.69 (s, 2H, C*H*$_2$OCH$_3$), 7.31–7.43 (m, 6H, *m*CH, *p*CH ar $SiPh_2$), 7.65–7.70 (m, 4H, *o*CH ar $SiPh_2$); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 (8-$CH_3$), 17.9 (C-8), 19.4 (Si(*C*($CH_3$)$_3$)), 20.1 (2-$CH_3$), 25.7 (C-2), 27.1 (Si(C(*C*H$_3$)$_3$)), 37.9 (C-3'), 38.9 (C-3), 39.0 (C-5'), 40.8 (C-7), 40.9 (*C*H$_2$COOH), 42.3 (C-5), 42.9 (C-1), 55.3 ($CH_2$O*C*H$_3$), 55.7 (CHO*C*H$_3$), 70.7 (C-6), 71.9 (C-4'), 72.7 (C-2'), 73.7 (C-6'), 76.0 (C-4), 94.5 (*C*H$_2$OCH$_3$), 127.4, 127.5, 129.4, 129.5, 134.4, 134.6, 135.9 (C of $SiPh_2$), 174.5 (*C*OOH);
**HRMS** (ESI): calcd for $C_{36}H_{56}NaO_7Si$ $[M+Na]^+$: 651.36875, found 651.36884.

**Seco-acid 8-54**



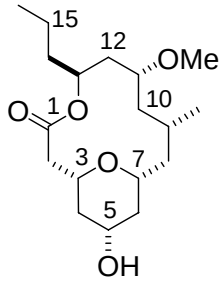

To a solution of acid **8-53** (149 mg, 0.237 mmol) in THF (1 mL) was added TBAF·3$H_2O$ (450 mg, 1.44 mmol) at room temperature. The reaction mixture was stirred for 48 h. After addition of saturated $NH_4Cl$ solution the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (10 ml), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc/HOAc, 1:1:0.01→0:1:0.01) afforded seco-acid **8-54** (92 mg, 99% yield) as a colorless oil. $\mathbf{R_f}$ = 0.2 (petroleum ether/EtOAc/HOAc, 2:1:0.01); $\mathbf{[\alpha]^{20}_D}$ = –18.8 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.84–0.94 (m, 6H, 8-$CH_3$, 2-$CH_3$), 1.12–1.75 (m, 14H, 7-H, 8-H, 5'-H, 1-H, 2-H, 3-H, 5-H), 1.86–1.94 (m, 1H, 3'-H), 2.00–2.07 (m, 1H, 3'-H), 2.42–2.60 (m, 2H, C*H*$_2$COOH), 3.31–3.47 (m, 8H, CHOC*H*$_3$, 6'-H, 4-H, $CH_2$OC*H*$_3$), 3.68–3.83 (m, 3H, 2'-H, 4'-H, 6-H), 4.67 (s, 2H, C*H*$_2$OCH$_3$), 6.42 (br s, 2H, O*H*, COO*H*); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 (8-$CH_3$), 18.6 (C-8), 19.6 (2-$CH_3$), 26.3 (C-2), 38.0 (C-3'), 38.8 (C-3), 39.7 (C-5'), 40.8 (C-7), 40.9 (*C*H$_2$COOH), 41.3 (C-5), 43.8 (C-1), 55.3 ($CH_2$O*C*H$_3$), 56.1 (CHO*C*H$_3$), 71.4 (C-4'), 72.1 (C-6), 72.7 (C-4), 74.0 (C-6'), 80.5 (C-2'), 94.5 (*C*H$_2$OCH$_3$), 174.4 (*C*OOH);
**HRMS** (ESI): calcd for $C_{20}H_{38}NaO_7$ $[M+Na]^+$: 413.25097, found 413.25110.

**Macrolactone 8-55**



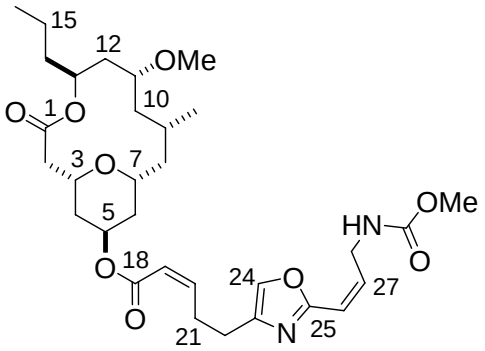
To an ice-cooled solution of seco-acid **8-54** (85 mg, 0.21 mmol, 1.0 equiv) in THF (2.5 mL) was added $Et_3N$ (177 μL, 1.26 mmol, 6.0 equiv) followed by 2,4,6-trichlorobenzoyl chloride (164 μL, 1.05 mmol, 5.0 equiv). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature, whereupon toluene (7.5 mL) was added. This solution was added over 8 h by syringe pump to a solution of DMAP (51 mg, 4.2 mmol, 20 equiv) in toluene (150 mL). Upon completion, stirring was maintained for an additional 2 h. The mixture was concentrated to dryness and filtered over silica gel (using petroleum ether/EtOAc 2:1 as eluant). The filtrate was concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded lactone **8-55** (69 mg, 85% yield) and its 5-epi isomer (7.0 mg, 9% yield). $\mathbf{R_f}$ = 0.33 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = +10.8 (*c* 1.2, $CH_2Cl_2$); **$^1$H NMR** (600 MHz, $CDCl_3$): δ = 0.84–0.90 (m, 6H, 15-$CH_3$, 9-$CH_3$), 1.07 (t, *J* = 11.7 Hz, 1H, 6-H), 1.14–1.50 (m, 8H, 6-H, 10-H, 12-H, 8-H, 14-H, 15-H), 1.56–1.64 (m, 1H, 14-H), 1.77–1.89 (m, 3H, 4-H, 8-H, 9-H), 1.96–2.01 (m, 1H, 4-H), 2.01–2.07 (m, 1H, 12-H), 2.31–2.38 (m, 1H, 2-H), 2.58–2.63 (m, 1H, 2-H), 3.18–3.25 (m, 1H, 7-H), 3.28–3.36 (m, 7H, 11-H, CHOC$H_3$, $CH_2OCH_3$), 3.63–3.73 (m, 2H, 3-H, 5-H), 4.65 (s, 2H, $CH_2OCH_3$), 4.86–4.94 (m, 1H, 13-H); **$^{13}$C NMR** (150 MHz, $CDCl_3$): δ = 14.0 (15-$CH_3$), 18.4 (C-15), 24.6 (9-$CH_3$), 28.9 (C-9), 37.2 (C-4), 37.9 (C-14), 38.1 (C-6), 39.3 (C-12), 40.2 (C-10), 42.6 (C-2), 44.2 (C-8), 55.2 ($CH_2OCH_3$), 56.1 (CHO$CH_3$), 71.3 (C-13), 71.5 (C-5), 72.7 (C-3), 76.7 (C-11), 77.0 (C-7), 94.4 ($CH_2OCH_3$), 170.2 (C-1);
**HRMS** (ESI): calcd for $C_{20}H_{36}NaO_6$ $[M+Na]^+$: 395.24041, found 395.24036.

**Deprotected macrolactone 8-56**



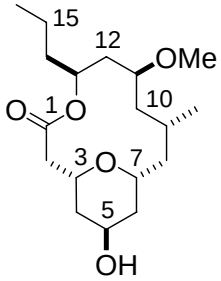

To a cooled (0 °C) solution of MOM-ether **8-55** (57.4 mg, 0.154 mmol) in MeOH (3 mL) was added concentrated HCl (100 μL). After stirring for 0.5 h at 0 °C and for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with EtOAc (4 × 20 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1→1:1) provided alcohol **8-56** (48.6 mg, 96% yield) as a colorless oil. $\mathbf{R_f}$ = 0.24 (petroleum ether/EtOAc, 2:1); $\mathbf{[\alpha]^{20}_D}$ = +9.1 (*c* 0.8, $CH_2Cl_2$); **$^1$H NMR** (600 MHz, $CD_3OD$): δ = 0.82–0.89 (m, 6H, 15-$CH_3$, 9-$CH_3$), 0.94–1.14 (m, 3H, 6-H, 8-H), 1.17–1.33 (m, 3H, 10-H, 9-H), 1.36–1.61 (m, 4H, 12-H, 14-H, 15-H), 1.69–1.86 (m, 3H, 14-H, 8-H, 4-H), 1.86–1.95 (m, 1H, 4H), 1.97–2.07 (m, 1H, 12-H), 2.16–2.24 (m, 1H, 2-H), 2.64–2.71 (m, 1H, 2-H), 3.23–3.35 (m, 5H, 7-H, 11-H, CHOC$H_3$), 3.61–3.72 (m, 2H, 3-H, 5-H), 4.83–4.93 (m, 1H, 13-H); **$^{13}$C NMR** (150 MHz, $CD_3OD$): δ = 14.4 (15-$CH_3$), 19.5 (C-15), 24.9 (9-$CH_3$), 30.5 (C-9), 38.1 (C-4), 39.1 (C-14), 41.3 (C-6), 41.6 (C-12), 42.9 (C-2), 43.5 (C-10), 45.4 (C-8), 56.5 (CHO$CH_3$), 68.4 (C-5), 72.3 (C-13), 72.9 (C-3), 78.2 (C-11), 78.5 (C-7), 172.5 (C-1);
**HRMS** (ESI): calcd for $C_{18}H_{32}NaO_5$ $[M+Na]^+$: 351.21420, found 351.21413.

**11-*epi* neopeltolide (8-57)**




To a solution of alcohol **8-56** (7.6 mg, 0.023 mmol, 1 equiv), acid **6-15** (10.3 mg, 0.037 mmol, 1.6 equiv) and $PPh_3$ (10.5 mg, 0.040 mmol, 1.74 equiv) in absolute benzene (1 mL) was added diisopropyl azodicarboxylate (80 µL of 0.5M solution in benzene, 0.040 mmol, 1.74 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (hexane/EtOAC, 2:1→1:1→1:2) to afford 11-*epi* neopeltolide **(8-57)** (11.7 mg, 86%) as a colorless oil. $\mathbf{R_f}$ = 0.5 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +19.4 (*c* 0.8, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.88 (d, *J* = 6.8 Hz, 3H, 17-H), 0.92 (t, *J* = 7.3 Hz, 3H, 16-H), 1.02–1.10 (m, 1H, 10-H), 1.20–1.42 (m, 5H, 8-H, 9-H, 15-H), 1.43–1.70 (m, 7H, 10-H, 4-H, 6-H, 14-H), 1.75–1.93 (m, 3H, 4-H, 14-H, 12-H), 2.06 (ddd, *J* = 14.1, 10.9, 3.0 Hz, 1H, 12-H), 2.21 (dd, *J* = 14.4, 11.1 Hz, 1H, 2-H), 2.66–2.73 (m, 3H, 2-H, 22-H), 2.96–3.04 (m, 2H, 21-H), 3.32–3.40 (m, 4H, 11-$OCH_3$, 7-H), 3.64 (s, 3H, 29-$OCH_3$), 3.75 (apt, *J* = 9.9 Hz, 1H, 11-H), 3.98–4.08 (m, 1H, 3-H), 4.29 (d, *J* = 5.1 Hz, 2H, 28-H), 4.90–4.98 (m, 1H, 13-H), 5.17–5.21 (m, 1H, 5-H), 5.85 (d, *J* = 11.4 Hz, 1H, 19-H), 5.98–6.07 (m, 1H, 27-H), 6.27 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.36 (dt, *J* = 11.5, 7.6 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.3 (C-16), 19.5 (C-15), 24.8 (C-17), 26.4 (C-22), 29.0 (C-21), 30.5 (C-9), 36.2 (C-4), 37.3 (C-6), 38.1 (C-14), 39.1 (C-10), 41.2 (C-12), 43.5 (C-2), 45.1 (C-8), 52.6 (29-$OCH_3$), 56.4 (11-$OCH_3$), 69.2 (C-5), 70.4 (C-3), 72.4 (C-13), 75.1 (C-7), 78.5 (C-11), 115.9 (C-26), 121.6 (C-19), 135.9 (C-24), 139.2 (C-27), 142.3 (C-23), 150.1 (C-20), 159.6 (C-29), 161.9 (C-25), 166.8 (C-18), 172.6 (C-1);
**HRMS** (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+Na]^+$: 613.30955, found 613.30863.

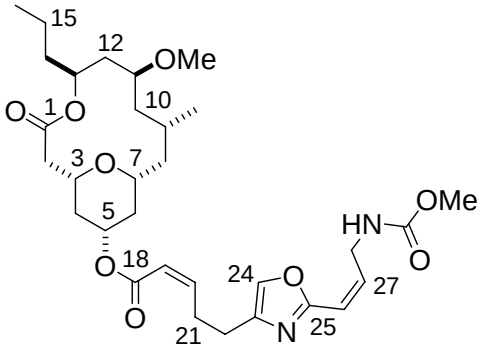
**Deprotected macrolactone 8-58**




To a cooled (0 °C) solution of MOM-ether **8-33b** (6.8 mg, 0.018 mmol) in MeOH (2 mL) was added concentrated HCl (70 µL). After stirring for 0.5 h at 0 °C and for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5

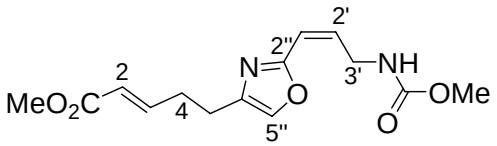
mL), extracted with EtOAc (4 × 10 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1→1:1) provided alcohol **8-58** (5.2 mg, 88% yield) as a colorless oil. $\mathbf{R_f}$ = 0.31 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +7.2 (*c* 0.5, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.87–0.94 (m, 6H, 15-$CH_3$, 9-$CH_3$), 1.11–1.22 (m, 3H, 6-H, 8-H), 1.23–1.44 (m, 6H, 10-H, 12-H, 8-H, 9-H), 1.45–1.80 (m, 6H, 10-H, 12-H, 14-H, 15-H, OH), 1.84–1.92 (m, 1H, 14-H), 1.92–2.02 (m, 2H, 4-H), 2.36 (dd, *J* = 12.1, 2.0 Hz, 1H, 2-H), 2.47 (dd, *J* = 12.1 Hz, 1H, 2-H), 3.00–3.07 (m, 1H, 11-H), 3.30 (s, 3H, CHOC*H*$_3$), 3.35–3.44 (m, 1H, 7-H), 3.55 (apt, *J* = 10.9 Hz, 1H, 3-H), 3.78–3.89 (m, 1H, 5-H), 5.04–5.12 (m, 1H, 13-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (15-$CH_3$), 18.9 (C-15), 24.3 (9-$CH_3$), 24.4 (C-9), 36.9 (C-4), 39.3 (C-14), 39.7 (C-6), 40.8 (C-12), 42.0 (C-2), 42.4 (C-10), 45.1 (C-8), 56.9 (CHO*C*H$_3$), 67.9 (C-5), 72.8 (C-13), 74.1 (C-3), 74.8 (C-11), 76.9 (C-7), 172.7 (C-1);
**HRMS** (ESI): calcd for $C_{18}H_{32}NaO_5$ $[M+Na]^+$: 351.21420, found 351.21429.

**5-*epi* neopeltolide (8-59)**



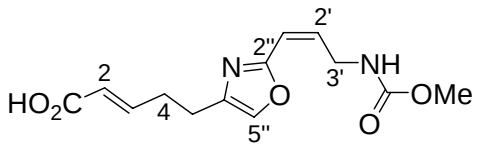

To a solution of alcohol **8-58** (4.0 mg, 0.012 mmol, 1 equiv), acid **6-15** (5.4 mg, 0.019 mmol, 1.6 equiv) and $PPh_3$ (5.5 mg, 0.021 mmol, 1.75 equiv) in absolute benzene (0.7 mL) was added diisopropyl azodicarboxylate (42 μL of 0.5M solution in benzene, 0.021 mmol, 1.75 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (hexane/EtOAC, 2:1→1:1→1:2) to afford 5-*epi* neopeltolide (**8-59**) (5.4 mg, 76%) as a colorless oil. $\mathbf{R_f}$ = 0.57 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = –3.3 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.90–0.96 (m, 6H, 16-H, 17-H), 1.11 (apt, *J* = 12.1 Hz, 1H, 10-H), 1.24–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.57 (m, 3H, 10-H, 4-H, 14-H), 1.57–1.93 (m, 8H, 6-H, 14-H, 4-H, 12-H), 2.28–2.37 (m, 2H, 2-H), 2.69 (t, *J* = 7.3 Hz, 2H, 22-H), 2.94–3.02 (m, 2H, 21-H), 3.12–3.20 (m, 1H, 11-H), 3.64 (s, 3H, 29-$OCH_3$), 3.71–3.81 (m, 1H, 7-H), 3.89–4.01 (m, 1H, 3-H), 4.29 (d, *J* = 4.6 Hz, 2H, 28-H), 4.95–5.03 (m, 1H, 13-H), 5.19–5.23 (m, 1H, 5-H), 5.82 (d, *J* = 11.6 Hz, 1H, 19-H), 5.99–6.07 (m, 1H, 27-H), 6.27 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.34 (dt, *J* = 11.6, 7.3 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.2 (C-16), 20.0 (C-15), 24.6 (C-17), 25.4 (C-9), 26.4 (C-22), 29.0 (C-21), 36.5 (C-4), 37.5 (C-6), 37.9 (C-14), 40.4 (C-12), 40.6, (C-10), 43.2 (C-2), 46.4 (C-8), 52.6 (29-$OCH_3$), 57.2 (11-$OCH_3$), 69.0 (C-5), 71.2 (C-3), 73.4 (C-13), 75.4 (C-7), 78.3 (C-11), 116.0 (C-26), 121.5 (C-19), 136.0 (C-24), 139.1 (C-27), 142.2 (C-23), 150.2 (C-20), 161.9 (C-29), 166.8 (C-18), 174.8 (C-1);
**HRMS** (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+H]^+$: 591.32761, found 591.32815.

**Methyl (2*E*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)pent-2-enoate (8-60)**



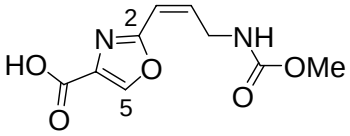

To a solution of aldehyde **8-9** (7 mg, 0.029 mmol, 1 equiv) in $CH_2Cl_2$ (1 mL) at ambient temperature was added (methoxycarbonylmethylene)triphenylphosphorane (**8-36**) (19.4 mg, 0.058 mmol, 2 equiv). The reaction mixture was stirred for 2 h, concentrated in vacuo and purified by flash column chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford unsaturated ester **8-60** (7.9 mg, 93%) as a colorless oil. $\mathbf{R_f}$ = 0.57 ($CH_2Cl_2$/MeOH, 9:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.57 (q, *J* = 7.4 Hz, 2H, 4-H), 2.70 (t, *J* = 7.3 Hz, 2H, 5-H), 3.67 (s, 3H, $OCH_3$), 3.71 (s, 3H, $CCO_2CH_3$), 4.30 (d, *J* = 4.3 Hz, 2H, 3'-H), 5.52 (br s, 1H, NH), 5.86 (d, *J* = 15.7 Hz, 1H, 2-H), 6.05–6.14 (m, 1H, 2'-H), 6.29 (d, *J* = 11.6 Hz, 1H, 1'-H), 6.97 (dt, *J* = 15.7, 6.8 Hz, 1H, 3-H), 7.35 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 24.8 (C-5), 30.7 (C-4), 39.4 (C-3'), 51.5 ($OCH_3$), 52.2 ($OCH_3$), 116.6 (C-1'), 121.8 (C-2), 133.9 (C-5''), 136.5 (C-4''), 140.6 (C-2'), 147.8 (C-5''), 157.2 ($CO_2CH_3$), 160.1 (C-2''), 166.9 (C-1);
**HRMS** (ESI): calcd for $C_{14}H_{18}NaN_2O_5$ $[M+Na]^+$: 317.11079, found 317.11064.

**(2*E*)-5-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)pent-2-enoic acid (8-61)**



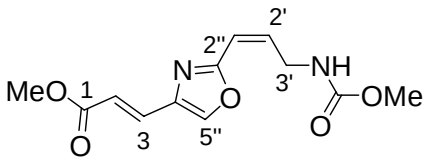

A solution of ester **8-60** (6.5 mg, 0.022 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.22 mL, 0.22 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 6 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.22 mL, 0.22 mmol). After the mixture was extracted with EtOAc (4 × 10 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5→9:1) afforded acid **8-61** (5.7 mg, 92% yield) as a white solid. $\mathbf{R_f}$ = 0.38 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 108–110 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.60 (q, *J* = 7.2 Hz, 2H, 4-H), 2.72 (t, *J* = 7.1 Hz, 2H, 5-H), 3.67 (s, 3H, $OCH_3$), 4.26–4.34 (m, 2H, 3'-H), 5.51 (br s, 1H, NH), 5.87 (d, *J* = 15.7 Hz, 1H, 2-H), 6.05-6.14 (m, 1H, 2'-H), 6.29 (d, *J* = 11.9 Hz, 1H, 1'-H), 7.08 (dt, *J* = 15.5, 6.8 Hz, 1H, 3-H), 7.36 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 24.6 (C-5), 30.9 (C-4), 39.4 (C-3'), 52.2 ($OCH_3$), 116.5 (C-1'), 121.4 (C-2), 133.9 (C-5''), 136.5 (C-4''), 140.5 (C-2'), 150.1 (C-5''), 157.2 ($CO_2CH_3$), 160.1 (C-2''), 170.4 (C-1);
**HRMS** (ESI): calcd for $C_{14}H_{18}NaN_2O_5$ $[M+Na]^+$: 303.09514, found 303.09516.

**2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazole-4-carboxylic acid (8-62)**



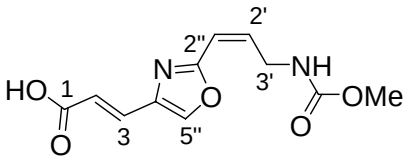
A solution of ester **8-10** (21 mg, 0.08 mmol) in MeOH (1 mL) was treated with LiOH (1N solution in water, 0.8 mL, 0.8 mmol) at ambient temperature and the reaction mixture was stirred until TLC indicated complete consumption of the starting material (ca. 2 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.8 mL, 0.8 mmol). After the mixture was extracted with EtOAc (4 × 20 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford acid **8-62** (18 mg, 94%) as a slightly yellow solid. $\mathbf{R_f}$ = 0.2 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 153–155 °C; **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 3.64 (s, 3H, $OCH_3$), 4.32 (d, *J* = 4.8 Hz, 2H, C*H*$_2$NH), 6.12–6.22 (m, 1H, HC=C*H*$CH_2$), 6.34 (d, *J* = 11.9 Hz, 1H, *H*C=$CHCH_2$), 8.47 (s, 1H, 5-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 40.9 ($CH_2NH$), 52.6 ($OCH_3$), 115.3 (H*C*=$CHCH_2$), 135.5 (C-4), 141.6 (HC=*C*$HCH_2$), 145.4 (C-5), 159.6 (*C*$O_2CH_3$), 162.4 (C-2), 164.0 (*C*$O_2$H);
**HRMS** (ESI): calcd for $C_9H_{10}NaN_2O_5$ $[M+Na]^+$: 249.04819, found 249.04838.

**Methyl (2*E*)-3-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)acrylate (8-37)**



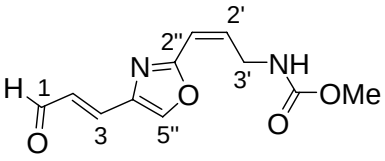
To a solution of aldehyde **8-34** (67 mg, 0.32 mmol, 1 equiv) in $CH_2Cl_2$ (5 mL) at ambient temperature was added (methoxycarbonylmethylene)triphenylphosphorane (**8-36**) (213.8 mg, 0.64 mmol, 2 equiv). The reaction mixture was stirred for 3 h, concentrated in vacuo and purified by flash column chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford unsaturated ester **8-37** (78.3 mg, 92%) as a colorless solid. $\mathbf{R_f}$ = 0.59 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 117–118 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.67 (s, 3H, 4'-$OCH_3$), 3.71 (s, 3H, 1-$OCH_3$), 4.33–4.40 (m, 2H, 3'-H), 5.49 (br s, 1H, NH), 6.13–6.24 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.63 (d, *J* = 15.4 Hz, 1H, 2-H), 7.48 (d, *J* = 15.4 Hz, 1H, 3-H), 7.72 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.4 (C-3'), 51.7 ($OCH_3$), 52.2 ($OCH_3$), 115.6 (C-1'), 120.0 (C-2), 132.1 (C-5''), 138.1 (C-4''), 138.5 (C-3), 139.0 (C-2'), 157.2 (*C*$O_2CH_3$), 160.7 (C-2''), 167.1 (C-1);
**HRMS** (ESI): calcd for $C_{12}H_{14}NaN_2O_5$ $[M+Na]^+$: 289.07949, found 289.07953.

**(2*E*)-3-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)acrylic acid (8-63)**



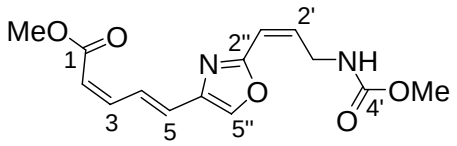
A solution of ester **8-37** (16.0 mg, 0.06 mmol) in THF (0.6 mL) was treated with LiOH (1N solution in water, 0.6 mL, 0.6 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca 7 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.6 mL, 0.6 mmol). After the mixture was extracted with EtOAc (4 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5→9:1) afforded acid **8-63** (14.4 mg, 92% yield) as a colorless solid. $\mathbf{R_f}$ = 0.30 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 134–136 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.65 (s, 3H, $OCH_3$), 4.36 (d, *J* = 4.3 Hz, 2H, 3'-H), 6.10–6.18 (m, 1H, 2'-H), 6.32 (dt, *J* = 11.9, 2.0 Hz, 1H, 1'-H), 6.56 (d, *J* = 15.4 Hz, 1H, 2-H), 7.52 (d, *J* = 15.4 Hz, 1H, 3-H), 8.10 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 41.1 (C-3'), 52.6 ($OCH_3$), 115.4 (C-1'), 121.4 (C-2), 133.9 (C-5''), 139.4 (C-4''), 140.9 (C-3), 141.2 (C-2'), 159.7 ($CO_2CH_3$), 162.5 (C-2''), 170.0 (C-1);
**HRMS** (ESI): calcd for $C_{11}H_{12}NaN_2O_5$ $[M+Na]^+$: 275.06384, found 275.06377.

**Methyl (2*Z*)-3-{4-[(1*E*)-3-oxoprop-1-enyl]-1,3-oxazol-2-yl}prop-2-enylcarbamate (8-64)**



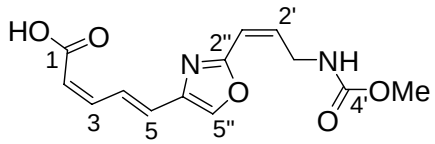

**a) Reduction to alcohol:** To a solution of ester **8-37** (46 mg, 0.17 mmol) in $CH_2Cl_2$ (3 mL), at –78 °C, was added dropwise Dibal-H (1M in hexanes, 0.43 mL, 0.43 mmol, 2.5 equiv). The reaction was stirred at –78 °C for 1 h, quenched with saturated aqueous $NH_4Cl$ solution and warmed up to room temperature. It was then treated with saturated potassium and sodium tartrate (Rochelle salt)/EtOAc (20:20 mL) and the mixture was vigorously stirred for 10 min. After the layers were separated, water layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue ($CH_2Cl_2$/MeOH, 97:3→95:5) afforded corresponding alcohol (37.2 mg, 92% yield) which was subjected to Dess-Martin periodinane oxidation. TLC ($CH_2Cl_2$/MeOH, 9:1): $R_f$ = 0.38.
**b) Preparation of aldehyde 8-64:** To a cooled (0 °C) solution of alcohol obtained in the previous step (37.2 mg, 0.16 mmol) in the mixture $CH_2Cl_2$ (2 mL) and $CH_3CN$ (0.8 mL) was added a solution of Dess-Martin periodinane (15% wt, 0.66 mL, 0.32 mmol), followed by addition of pyridine (26 μL, 0.32 mmol). After stirring for 10 min at 0 °C and for 1.5 h at room temperature, the reaction mixture was concentrated, loaded on a flash silica gel column, and eluted with petroleum ether/EtOAc, 4:1 to give 34 mg (93%) of aldehyde **8-64**, which was used directly in the next reaction. $\mathbf{R_f}$ = 0.47 ($CH_2Cl_2$/MeOH, 9:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.67 (s, 3H, $OCH_3$), 4.37 (dd, *J* = 5.9 Hz, 2H, 3'-H), 5.45 (br s, 1H, NH), 6.18–6.27 (m, 1H, 2'-H), 6.32 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.86 (dd, *J* = 15.5 Hz, 8.0 Hz, 1H, 2-H), 7.31 (d, *J* = 15.6 Hz, 1H, 3-H), 7.85 (s, 1H, 5''-H), 9.68 (d, *J* = 7.8 Hz, 1H, C*H*O); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.6 (C-3'), 52.2 ($OCH_3$), 115.4 (C-1'), 125.9 (C-2), 130.3 (C-5''), 135.1 (C-4''), 139.1 (C-3), 139.3 (C-2'), 157.1 ($CO_2CH_3$), 161.0 (C-2''), 193.0 (C-1).

**Methyl (2*Z*,4*E*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoate (8-65)**




A solution of 18-crown-6, freshly recrystallized from acetonitrile, (100 mg, 0.38 mmol, 6 equiv) and bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (**8-41**) (32 µL, 0.15 mmol, 2.4 equiv) in THF (2.0 mL) was cooled to –78 °C, and treated with KHMDS (0.5M solution in toluene, 260 µL, 0.13 mmol, 2.2 equiv). After 1 h, the solution of aldehyde **8-64** (15 mg, 0.063 mmol, 1 equiv) in THF (0.5 mL) was added over a period of 5 min. After 1 h, TLC indicated complete consumption of aldehyde; the reaction was quenched with saturated $NH_4Cl$ and warmed to room temperature. After the mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 98:2) afforded ester **8-65** (12.6 mg, 68% yield) as a colorless oil. $\mathbf{R_f}$ = 0.65 ($CH_2Cl_2$/MeOH, 9:1); **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H, 4'-$OCH_3$), 3.75 (s, 3H, 1-$OCH_3$), 4.37 (dd, *J* = 5.9 Hz, 2H, 3'-H), 5.55 (br s, 1H, NH), 5.74 (d, *J* = 11.1 Hz, 1H, 2-H), 6.14–6.23 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.61–6.72 (m, 2H, 3-H, 5-H), 7.67 (s, 1H, 5''-H), 8.13 (dd, *J* = 15.4, 11.9 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.4 (C-3'), 51.3 (1-$OCH_3$), 52.2 (4'-$OCH_3$), 116.1 (C-1'), 118.2 (C-5), 127.0 (C-2), 128.5 (C-4), 136.4 (C-5''), 138.1 (C-4''), 139.7 (C-2'), 143.7 (C-3), 157.2 (C-4'), 160.4 (C-2''), 166.7 (C-1);
**HRMS** (ESI): calcd for $C_{14}H_{16}NaN_2O_5$ $[M+Na]^+$: 315.09514, found 315.09542.

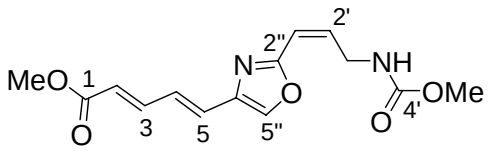
**(2*Z*,4*E*)-5-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoic acid (8-67)**




A solution of ester **8-65** (11.2 mg, 0.038 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.5 mL, 0.5 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 8 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.5 mL, 0.5 mmol). After the mixture was extracted with EtOAc (4 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5→9:1) afforded acid **8-67** (9.8 mg, 93% yield) as a colorless solid. $\mathbf{R_f}$ = 0.47 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 158–160 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.64 (s, 3H, 4'-$OCH_3$), 4.36 (d, *J* = 5.8 Hz, 2H, 3'-H), 5.72 (d, *J* = 11.4 Hz, 1H, 2-H), 6.06–6.14 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.72–6.80 (m, 2H, 3-H, 5-H), 7.95 (s, 1H, 5''-H), 8.13 (dd, *J* = 15.4, 11.9 Hz, 1H, 4-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 41.1 (C-3'), 52.6 (4'-$OCH_3$), 115.6 (C-1'), 119.9 (C-5), 128.1 (C-2), 129.3 (C-4), 138.9 (C-5''), 140.6 (C-2'), 141.0 (C-4''), 144.9 (C-3), 159.7 (C-4'), 162.3 (C-2''), 170.0 (C-1);

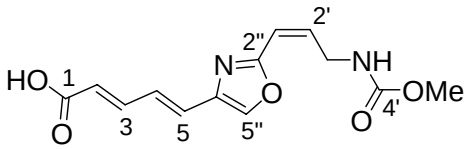
**HRMS** (ESI): calcd for $C_{13}H_{14}NaN_2O_5$ $[M+Na]^+$: 301.07949, found 301.07988.

**Methyl (2*E*,4*E*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoate (8-66)**



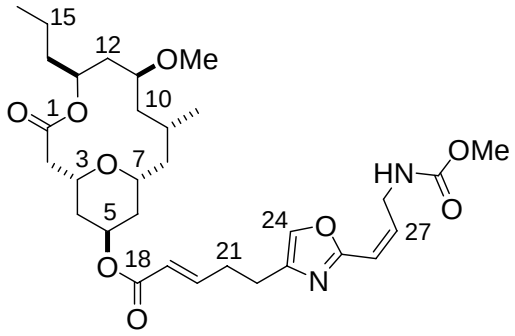

To a solution of aldehyde **8-64** (14.2 mg, 0.06 mmol, 1 equiv) in $CH_2Cl_2$ (1 mL) at ambient temperature was added (methoxycarbonylmethylene)triphenylphosphorane (**8-36**) (40.0 mg, 0.12 mmol, 2 equiv). The reaction mixture was stirred for 4 h, concentrated in vacuo and purified by flash chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford unsaturated ester **8-66** (15.2 mg, 87%) as a colorless solid. $\mathbf{R_f}$ = 0.67 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 132–134 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H, 4'-$OCH_3$), 3.75 (s, 3H, 1-$OCH_3$), 4.35–4.42 (m, 2H, 3'-H), 5.47 (br s, 1H, NH), 6.02 (d, *J* = 15.4 Hz, 1H, 2-H), 6.12–6.20 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.69 (d, *J* = 15.2 Hz, 1H, 5-H), 7.04 (dd, *J* = 15.2, 11.6 Hz, 1H, 4-H), 7.38 (dd, *J* = 15.2, 11.5 Hz, 1H, 3-H) 7.62 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 39.6 (C-3'), 51.6 (1-$OCH_3$), 52.2 (4'-$OCH_3$), 115.9 (C-1'), 121.8 (C-5), 127.3 (C-4), 128.3 (C-2), 136.6 (C-5''), 138.3 (C-4''), 139.4 (C-2'), 143.9 (C-3), 157.2 (C-4'), 160.5 (C-2''), 167.4 (C-1);
**HRMS** (ESI): calcd for $C_{14}H_{16}NaN_2O_5$ $[M+Na]^+$: 315.09514, found 315.09519.

**(2*E*,4*E*)-5-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoic acid (8-68)**



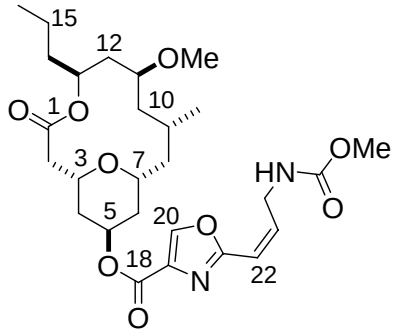

A solution of ester **8-66** (12.1 mg, 0.04 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.5 mL, 0.5 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 7 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.5 mL, 0.5 mmol). After the mixture was extracted with EtOAc (4 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$/MeOH, 95:5→9:1) afforded acid **8-68** (10.2 mg, 92% yield) as a colorless solid. $\mathbf{R_f}$ = 0.51 ($CH_2Cl_2$/MeOH, 9:1); **m.p.** = 177–179 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.65 (s, 3H, 4'-$OCH_3$), 4.37 (d, *J* = 5.3 Hz, 2H, 3'-H), 6.01 (d, *J* = 15.4 Hz, 1H, 2-H), 6.07–6.15 (m, 1H, 2'-H), 6.31 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.85 (d, *J* = 15.2 Hz, 1H, 5-H), 7.08 (dd, *J* = 15.2, 11.4 Hz, 1H, 4-H), 7.40 (dd, *J* = 15.0, 11.2 Hz, 1H, 3-H), 7.96 (s, 1H, 5''-H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 41.1 (C-3'), 52.6 (4'-$OCH_3$), 115.5 (C-1'), 123.3 (C-5), 129.0 (C-4), 129.3 (C-2), 139.0 (C-5''), 140.7 (C-2'), 145.7 (C-3), 159.7 (C-4'), 162.3 (C-2''), 170.4 (C-1);
**HRMS** (ESI): calcd for $C_{13}H_{14}NaN_2O_5$ $[M+Na]^+$: 279.09755, found 279.09812.

**19-*trans* Neopeltolide 8-69**



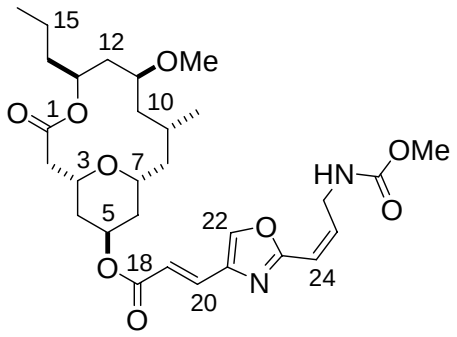

To a solution of alcohol **6-14** (4.1 mg, 0.0125 mmol, 1 equiv), acid **8-61** (5.6 mg, 0.02 mmol, 1.6 equiv) and $PPh_3$ (5.8 mg, 0.022 mmol, 1.76 equiv) in absolute benzene (0.7 mL) was added diisopropyl azodicarboxylate (44 μL of 0.5M solution in benzene, 0.022 mmol, 1.76 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1→1:1→1:2) to afford 19-*trans* neopeltolide (**8-69**) (5.6 mg, 76%) as a colorless oil. $\mathbf{R_f}$ = 0.44 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +31.0 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.8 Hz, 3H, 17-H), 1.08–1.15 (m, 1H, 10-H), 1.23–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.62 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.64–1.76 (m, 2H, 6-H, 14-H), 1.78–1.93 (m, 2H, 4-H, 12-H), 2.28 (dd, *J* = 14.9, 11.1 Hz, 1H, 2-H), 2.60 (q, *J* = 7.2 Hz, 2H, 21-H), 2.66–2.77 (m, 3H, 2-H, 22-H), 3.27 (s, 3H, 11-$OCH_3$), 3.58 (apt, *J* = 10.0 Hz, 1H, 7-H), 3.62–3.72 (m, 4H, 29-$OCH_3$, 11-H), 4.03–4.12 (m, 1H, 3-H), 4.30 (d, *J* = 4.6 Hz, 2H, 28-H), 5.13–5.21 (m, 2H, 13-H, 5-H), 5.95 (d, *J* = 15.7 Hz, 1H, 19-H), 5.99–6.07 (m, 1H, 27-H), 6.28 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 7.03 (dt, *J* = 15.5, 6.8 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.1 (C-16), 20.0 (C-15), 25.5 (C-22), 26.0 (C-17), 31.8 (C-21), 32.6 (C-9), 36.2 (C-4), 37.4 (C-6), 38.0 (C-14), 41.1 (C-12), 43.2 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (29-$OCH_3$), 56.4 (11-$OCH_3$), 69.4 (C-5), 71.2 (C-3), 74.0 (C-13), 77.1 (C-7), 77.1 (C-11), 115.9 (C-26), 123.2 (C-19), 136.1 (C-24), 139.3 (C-27), 141.9 (C-23), 149.7 (C-20), 161.9 (C-25), 167.2 (C-18), 173.1 (C-1);
**HRMS** (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+Na]^+$: 613.30955, found 613.31007.

**Neopeltolide analogue 8-70**



To a solution of alcohol **6-14** (5.3 mg, 0.016 mmol, 1 equiv), acid **8-62** (7.7 mg, 0.032 mmol, 2.0 equiv) and $PPh_3$ (9.2 mg, 0.035 mmol, 2.2 equiv) in a mixture of absolute benzene (0.8 mL) and THF (1.5 mL) was added diisopropyl azodicarboxylate (70 μL of 0.5M solution in benzene, 0.035 mmol, 2.2 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1→1.5:1→1:1) to afford neopeltolide analogue **8-70** (7.5 mg, 88%) as a colorless oil. $\mathbf{R_f}$ = 0.58 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +28.8 (*c* 0.7, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.6 Hz, 3H, 17-H), 1.08–1.16 (m, 1H, 10-H), 1.22–1.44 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.45–1.64 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.65–1.83 (m, 2H, 6-H, 14-H), 1.86–1.97 (m, 2H, 4-H, 12-H), 2.31 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.73 (dd, *J* = 14.7, 4.3 Hz, 1H, 2-H), 3.28 (s, 3H, 11-$OCH_3$), 3.59–3.75 (m, 5H, 7-H, 29-$OCH_3$, 11-H), 4.15–4.24 (m, 1H, 3-H), 4.34 (d, *J* = 4.8 Hz, 2H, 24-H), 5.14–5.22 (m, 1H, 13-H), 5.36–5.41 (m, 1H, 5-H), 6.15–6.23 (m, 1H, 23-H), 6.37 (dt, *J* = 11.9, 2.0 Hz, 1H, 22-H), 8.62 (s, 1H, 20-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 32.5 (C-9), 36.2 (C-4), 37.4 (C-6), 37.9 (C-14), 41.1 (C-12), 43.2 (C-2), 43.6 (C-10), 45.3 (C-8), 52.6 (25-$OCH_3$), 56.4 (11-$OCH_3$), 70.7 (C-5), 71.2 (C-3), 73.9 (C-13), 76.9 (C-7), 77.1 (C-11), 115.2 (C-22), 135.2 (C-20), 141.9 (C-23), 145.8 (C-19), 159.6 (C-25), 161.8 (C-21), 162.5 (C-18), 173.1 (C-1);
**HRMS** (ESI): calcd for $C_{27}H_{40}NaN_2O_9$ $[M+Na]^+$: 559.26260, found 559.26265.

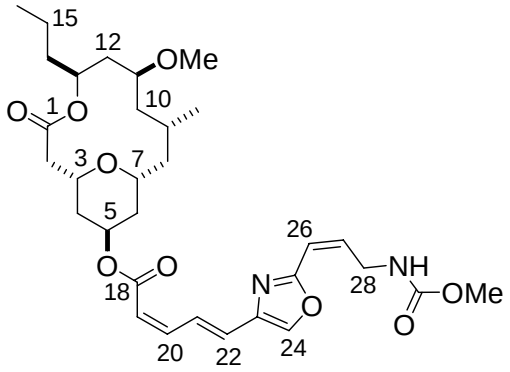
**Neopeltolide analogue 8-71**




To a solution of alcohol **6-14** (4.1 mg, 0.0125 mmol, 1 equiv), acid **8-63** (5.6 mg, 0.02 mmol, 1.6 equiv) and $PPh_3$ (5.8 mg, 0.022 mmol, 1.76 equiv) in absolute benzene (0.7 mL) was added diisopropyl azodicarboxylate (44 μL of 0.5M solution in benzene, 0.022 mmol, 1.76 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1→1:1→1:2) to afford neopeltolide analogue **8-71** (5.6 mg, 76%) as a colorless oil. $\mathbf{R_f}$ = 0.57 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +20.5 (*c* 0.4, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.6 Hz, 3H, 17-H), 1.07–1.14 (m, 1H, 10-H), 1.21–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.61 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.67–1.79 (m, 2H, 6-H, 14-H), 1.84–1.95 (m, 2H, 4-H, 12-H), 2.31 (dd, *J* = 14.7, 10.9 Hz, 1H, 2-H), 2.72 (dd, *J* = 14.7, 4.3 Hz, 1H, 2-H), 3.28 (s, 3H, 11-$OCH_3$), 3.62–3.74 m, 5H, 7-H, 27-$OCH_3$, 11-H), 4.10–4.19 (m, 1H, 3-H), 4.38 (d, *J* = 4.6 Hz, 2H, 26-H), 5.14–5.22 (m, 1H, 13-H), 5.23–5.28 (m, 1H, 5-H), 6.11–6.19 (m, 1H, 25-H), 6.34 (dt, *J* = 11.9, 2.0 Hz, 1H, 24-H), 6.65 (d, *J* = 15.7 Hz, 1H, 19-H), 7.59 (d, *J* = 15.4 Hz, 1H, 20-H), 8.15 (s, 1H, 22-H); **$^{13}$C NMR** (100

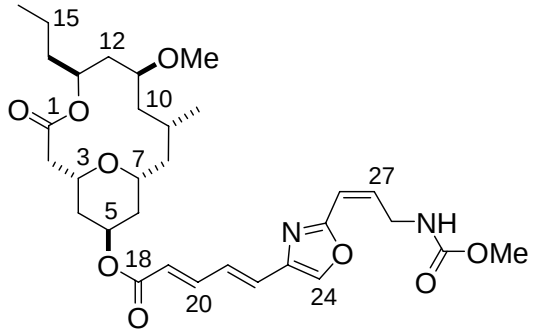
MHz, $CD_3OD$): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 32.5 (C-9), 36.3 (C-4), 37.4 (C-6), 37.9 (C-14), 41.1 (C-12), 43.3 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (27-$OCH_3$), 56.4 (11-$OCH_3$), 69.8 (C-5), 71.3 (C-3), 74.0 (C-13), 77.1 (C-7), 77.1 (C-11), 115.3 (C-24), 121.0 (C-19), 134.1 (C-22), 139.3 (C-25), 141.2 (C-20), 141.3 (C-21), 159.7 (C-27), 162.5 (C-23), 167.4 (C-18), 173.1 (C-1);
**HRMS** (ESI): calcd for $C_{29}H_{42}NaN_2O_9$ $[M+Na]^+$: 585.27825, found 585.27827.

**Neopeltolide analogue 8-72**




To a solution of alcohol **6-14** (4.6 mg, 0.014 mmol, 1 equiv), acid **8-67** (7.8 mg, 0.028 mmol, 2.0 equiv) and $PPh_3$ (8.1 mg, 0.031 mmol, 2.2 equiv) in a mixture of absolute benzene (1.0 mL) and THF (1.0 mL) was added diisopropyl azodicarboxylate (62 μL of 0.5M solution in benzene, 0.031 mmol, 2.2 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1→1.5:1→1:1) to afford neopeltolide analog **8-72** (7.0 mg, 85%) as a colorless oil. $\mathbf{R_f}$ = 0.61 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +30.5 (*c* 0.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.92 (t, *J* = 7.3 Hz, 3H, 16-H), 0.97 (d, *J* = 6.8 Hz, 3H, 17-H), 1.08–1.15 (m, 1H, 10-H), 1.26–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.62 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.63–1.76 (m, 2H, 6-H, 14-H), 1.84–1.92 (m, 2H, 4-H, 12-H), 2.30 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.71 (dd, *J* = 14.8, 4.2 Hz, 1H, 2-H), 3.27 (s, 3H, 11-$OCH_3$), 3.56–3.72 (m, *5*H, 7-H, 29-$OCH_3$, 11-H), 4.07–4.16 (m, 1H, 3-H), 4.36 (dd, *J* = 4.6 Hz, 2H, 28-H), 5.12–5.20 (m, 1H, 13-H), 5.21–5.25 (m, 1H, 5-H), 5.81 (d, *J* = 11.4 Hz, 1H, 19-H), 6.06–6.14 (m, 1H, 27-H), 6.32 (d, *J* = 11.9 Hz, 1H, 26-H), 6.77–6.87 (m, 2H, 20-H, 22-H), 7.98 (s, 1H, 24-H), 8.15 (dd, *J* = 15.5, 11.8 Hz, 1H, 21-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.1 (C-16), 20.0 (C-15), 25.9 (C-17), 32.5 (C-9), 36.3 (C-4), 37.4 (C-6), 37.9 (C-14), 41.0 (C-12), 43.2 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (29-$OCH_3$), 56.4 (11-$OCH_3$), 69.2 (C-5), 71.3 (C-3), 74.0 (C-13), 77.0 (C-7), 77.1 (C-11), 115.7 (C-26), 119.1 (C-22), 127.8 (C-19), 130.1 (C-24), 139.1 (C-27), 140.6 (C-23), 141.0 (C-21), 145.6 (C-20), 159.7 (C-29), 162.3 (C-25), 167.0 (C-18), 173.1 (C-1);
**HRMS** (ESI): calcd for $C_{31}H_{44}NaN_2O_9$ $[M+Na]^+$: 611.29390, found 611.29403.

**Neopeltolide analogue 8-73**

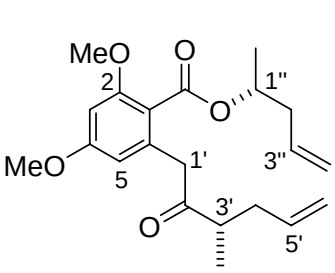



To a solution of alcohol **6-14** (4.4 mg, 0.013 mmol, 1 equiv), acid **8-68** (7.2 mg, 0.026 mmol, 2.0 equiv) and $PPh_3$ (7.6 mg, 0.029 mmol, 2.2 equiv) in a mixture of absolute benzene (1.0 mL) and THF (1.0 mL) was added diisopropyl azodicarboxylate (58 µL of 0.5M solution in benzene, 0.029 mmol, 2.2 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1→1.5:1→1:1) to afford neopeltolide analogue **8-73** (6.6 mg, 86%) as a colorless oil. $\mathbf{R_f}$ = 0.64 (petroleum ether/EtOAc, 1:1); $\mathbf{[\alpha]^{20}_D}$ = +47.5 (*c* 0.6, $CH_2Cl_2$); **$^1$H NMR** (400 MHz, $CD_3OD$): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.6 Hz, 3H, 17-H), 1.08–1.17 (m, 1H, 10-H), 1.26–1.43 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.45–1.62 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.67–1.77 (m, 2H, 6-H, 14-H), 1.83–1.95 (m, 2H, 4-H, 12-H), 2.30 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.71 (dd, *J* = 14.9, 4.3 Hz, 1H, 2-H), 3.28 (s, 3H, 11-$OCH_3$), 3.59–3.72 (m, 5H, 7-H, 29-$OCH_3$, 11-H), 4.07–4.16 (m, 1H, 3-H), 4.38 (d, *J* = 4.6 Hz, 2H, 28-H), 5.14–5.24 (m, 2H, 13-H, 5-H), 6.07–6.16 (m, 2H, 19-H, 27-H), 6.31 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.91 (d, *J* = 15.2 Hz, 1H, 22-H), 7.11 (dd, *J* = 15.2, 11.4 Hz, 1H, 21-H), 7.46 (dd, *J* = 15.2, 11.1 Hz, 1H, 20-H), 7.97 (s, 1H, 24-H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 32.5 (C-9), 36.3 (C-4), 37.4 (C-6), 38.0 (C-14), 41.1 (C-12), 43.3 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (29-$OCH_3$), 56.4 (11-$OCH_3$), 69.6 (C-5), 71.2 (C-3), 74.0 (C-13), 77.0 (C-7), 77.1 (C-11), 115.5 (C-26), 122.9 (C-22), 129.2 (C-21), 129.5 (C-19), 139.2 (C-24), 140.7 (C-27), 140.7 (C-23), 145.8 (C-20), 159.7 (C-29), 162.3 (C-25), 167.8 (C-18), 173.1 (C-1);
**HRMS** (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+H]^+$: 589.31196, found 589.31195.

# 11 Appendix

## 11.1 NMR-Spectra for important compounds

Additional spectra are included in the supporting information of the published papers from this work and are available free of charge via Internet at http://pubs.acs.org, http://www.angewandte.org and http://www.chemeurj.org.


MeO
O
2
1''
O
MeO
1'
3''
5
3'
O
5'

**3-11**


Chloroform-d
7.0
6.5
6.0
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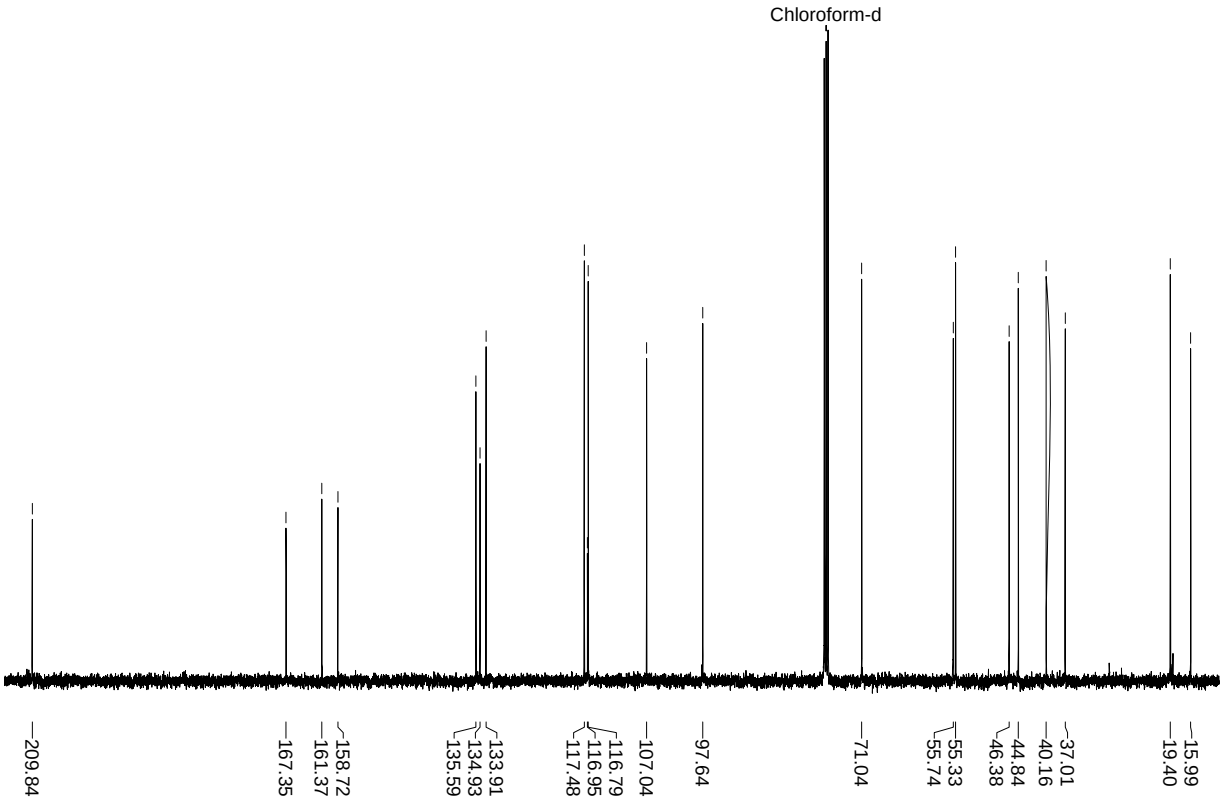
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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161.37
158.72
135.59
134.93
133.91
117.48
116.95
116.79
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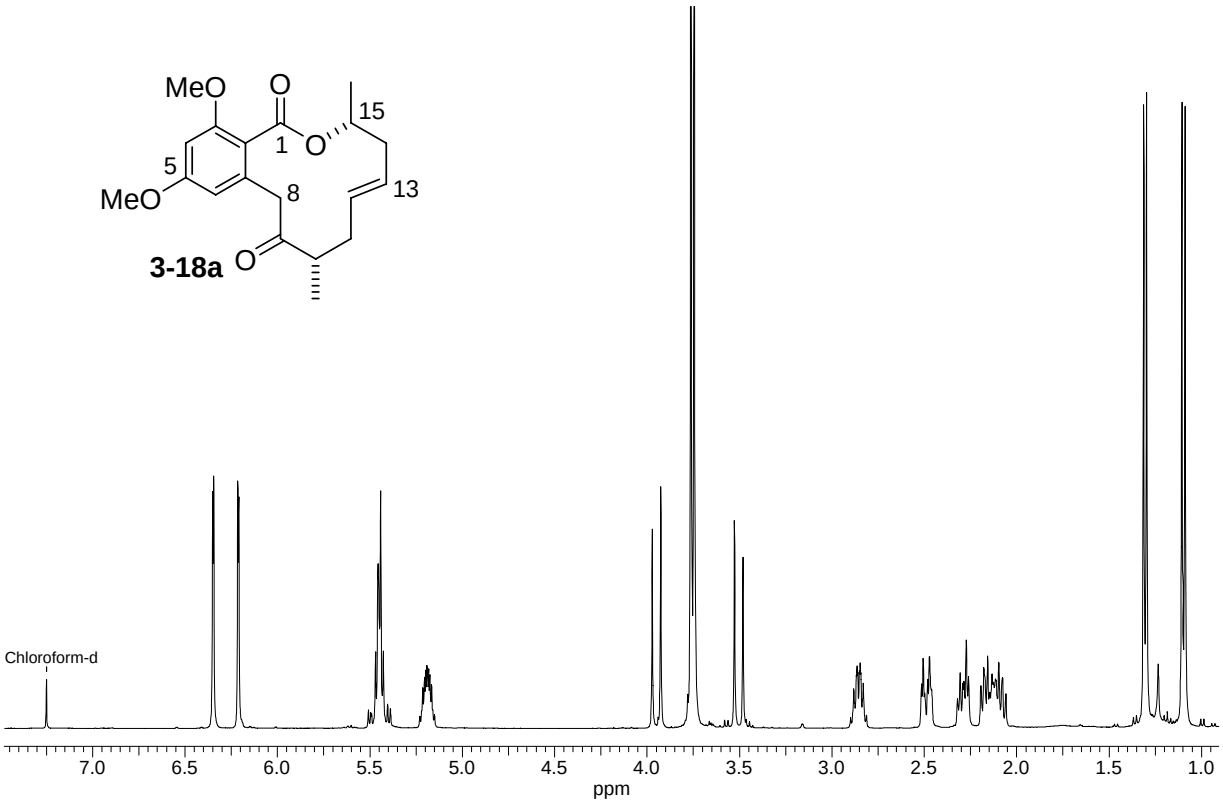
46.38
44.84
40.16
37.01
19.40
15.99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O
15
1
O
5
8
13
MeO
O
3-18a
Chloroform-d
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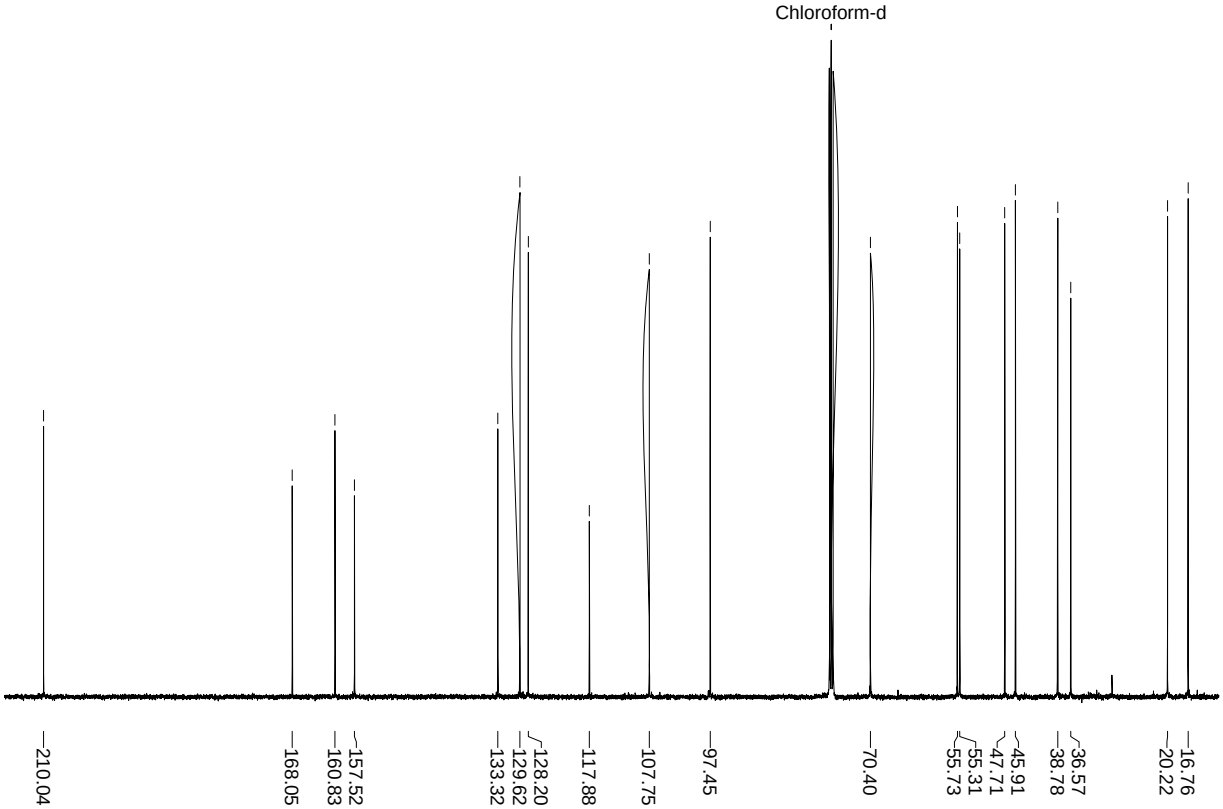
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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168.05
160.83
157.52
133.32
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117.88
107.75
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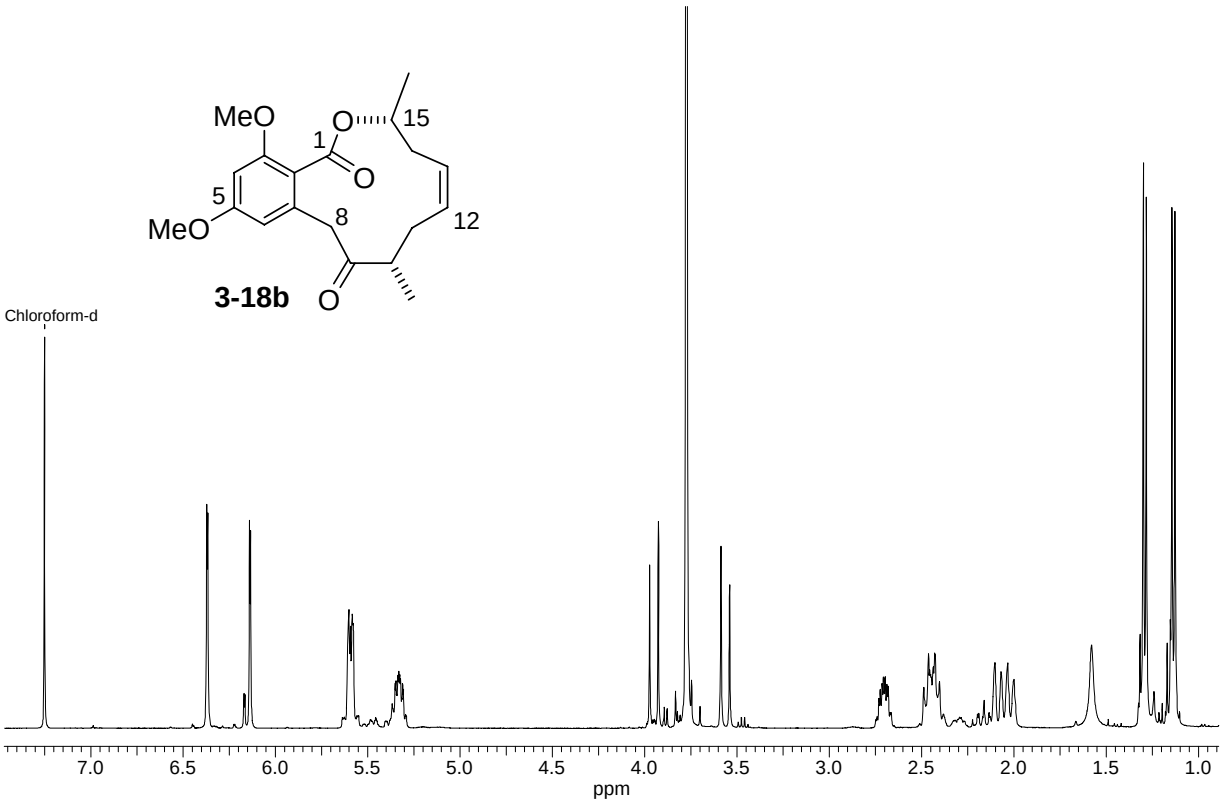
47.71
45.91
38.78
36.57
20.22
16.76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O
5
8
12
MeO
O
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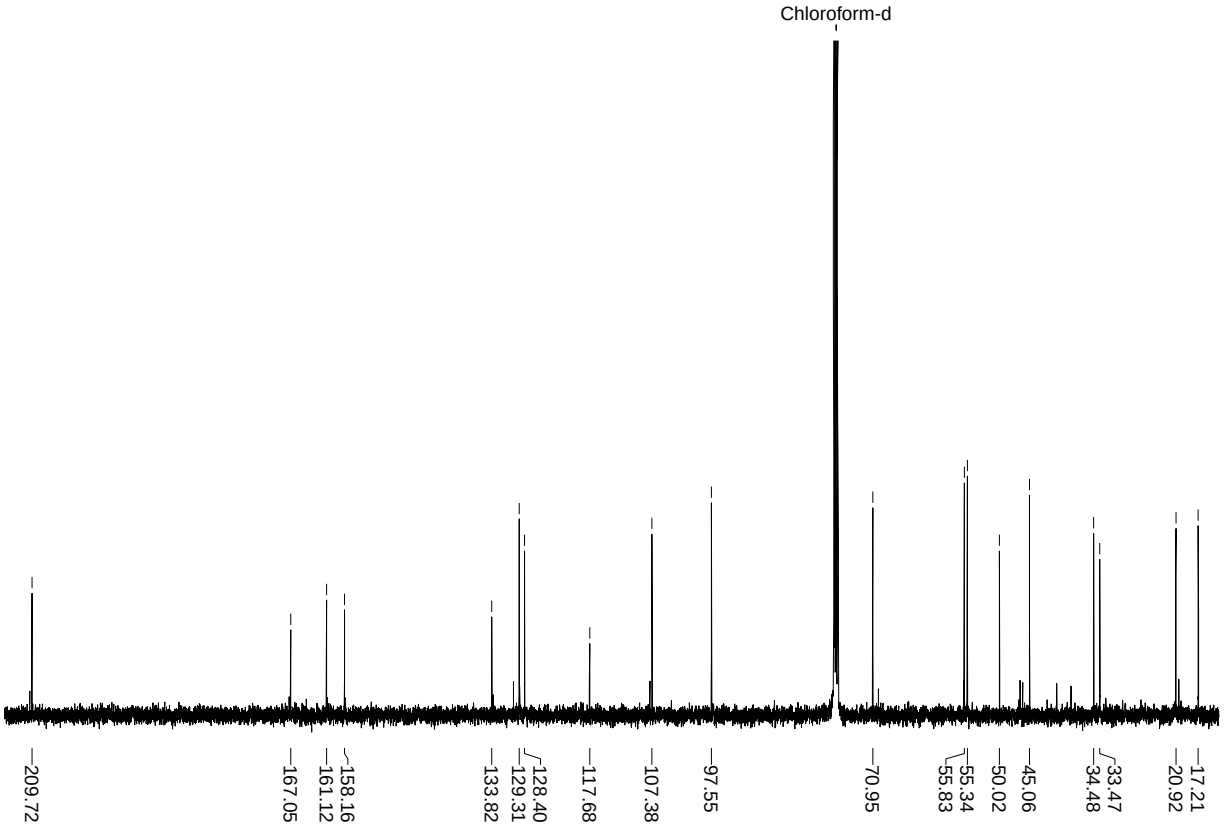
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
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161.12
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133.82
129.31
128.40
117.68
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97.55
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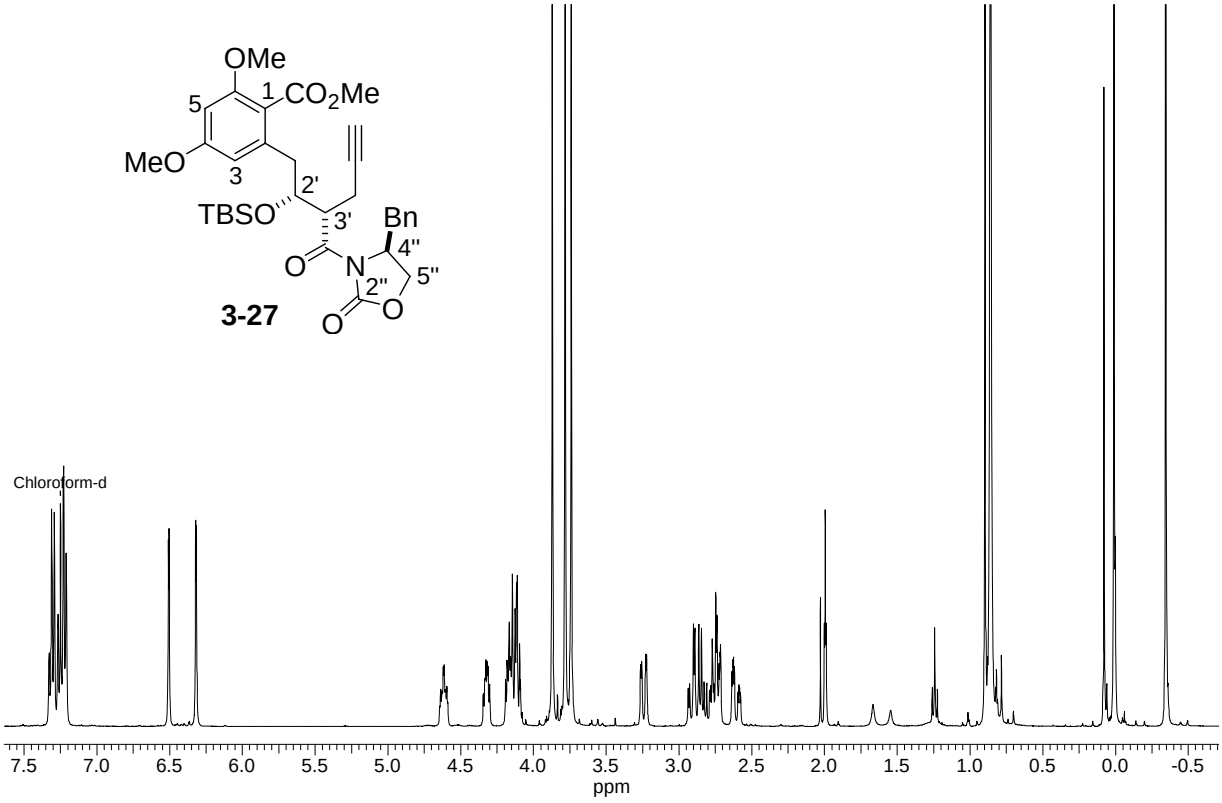
50.02
45.06
34.48
33.47
20.92
17.21


OMe
1
CO2Me
5
MeO
3
2'
TBSO
3'
Bn
4"
5"
2"
O
N
O
O
3-27
Chloroform-d
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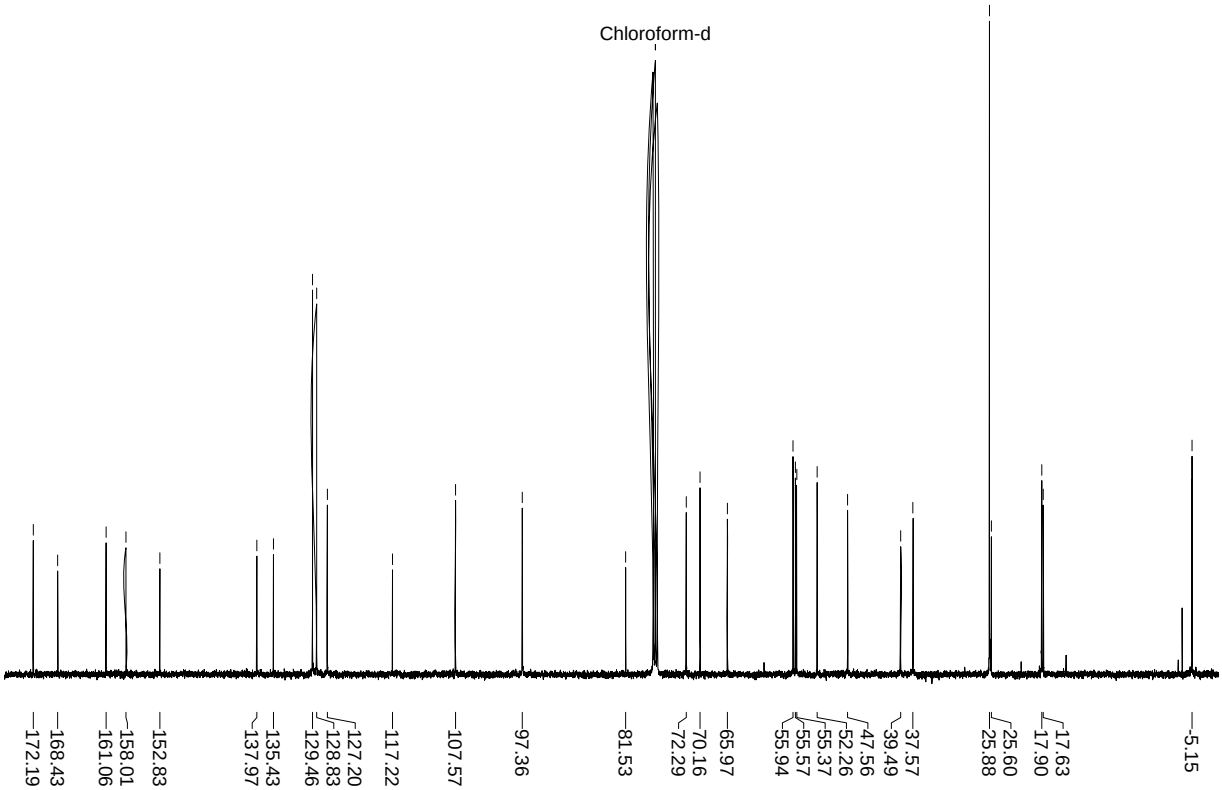
ppm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152.83
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128.83
127.20
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107.57
97.36
81.53
72.29
70.16
65.97
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55.57
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52.26
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25.88
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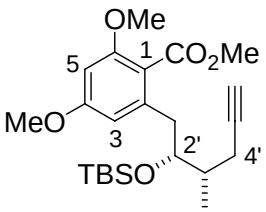
-5.15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MeO
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2'
4'
TBSO

**3-30**


Chloroform-d
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6.0
5.5
5.0
4.5
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3.5
3.0
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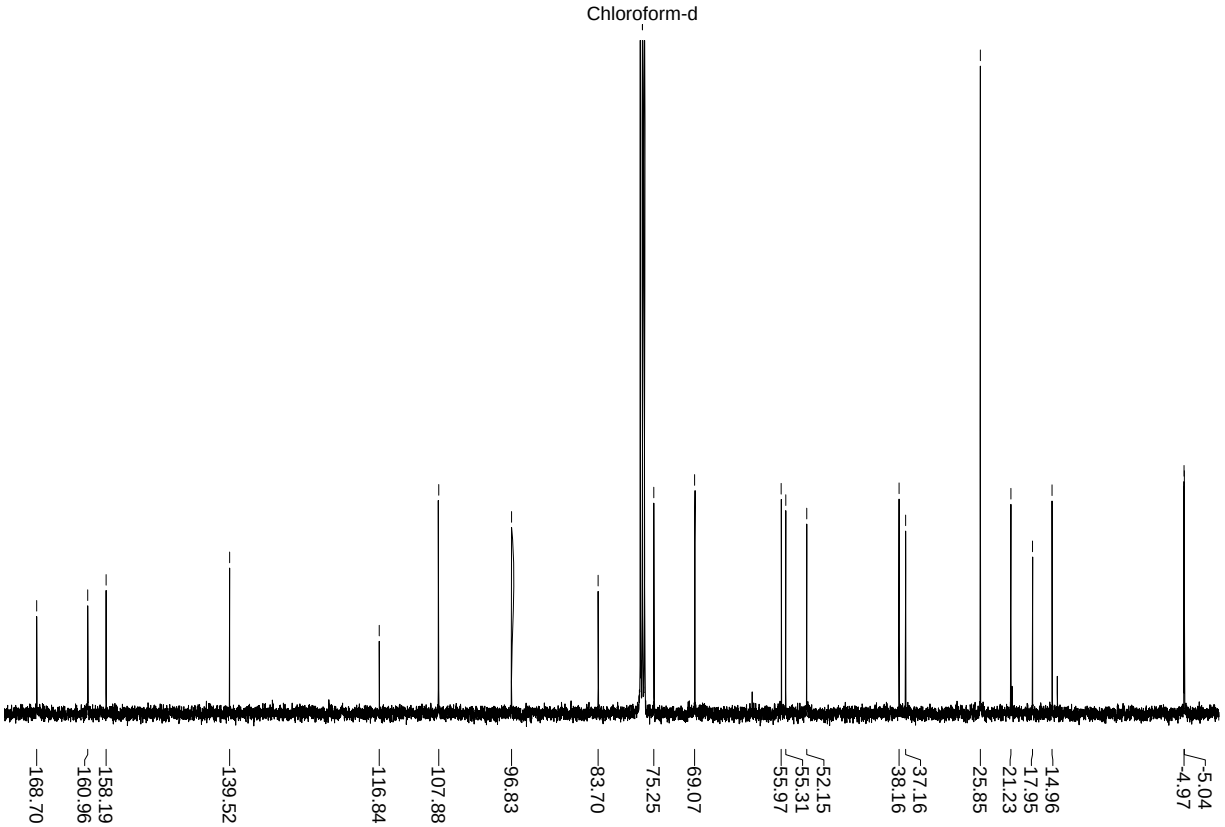
2.0
1.5
1.0
0.5
0.0
-0.5
ppm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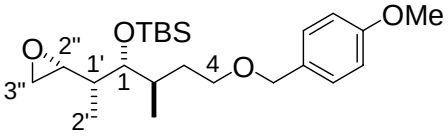
21.23
17.95
14.96
-4.97
-5.04


OMe
OTBS
O
2"
1'
1
4
O
3"
2'

**3-42**


Chloroform-d
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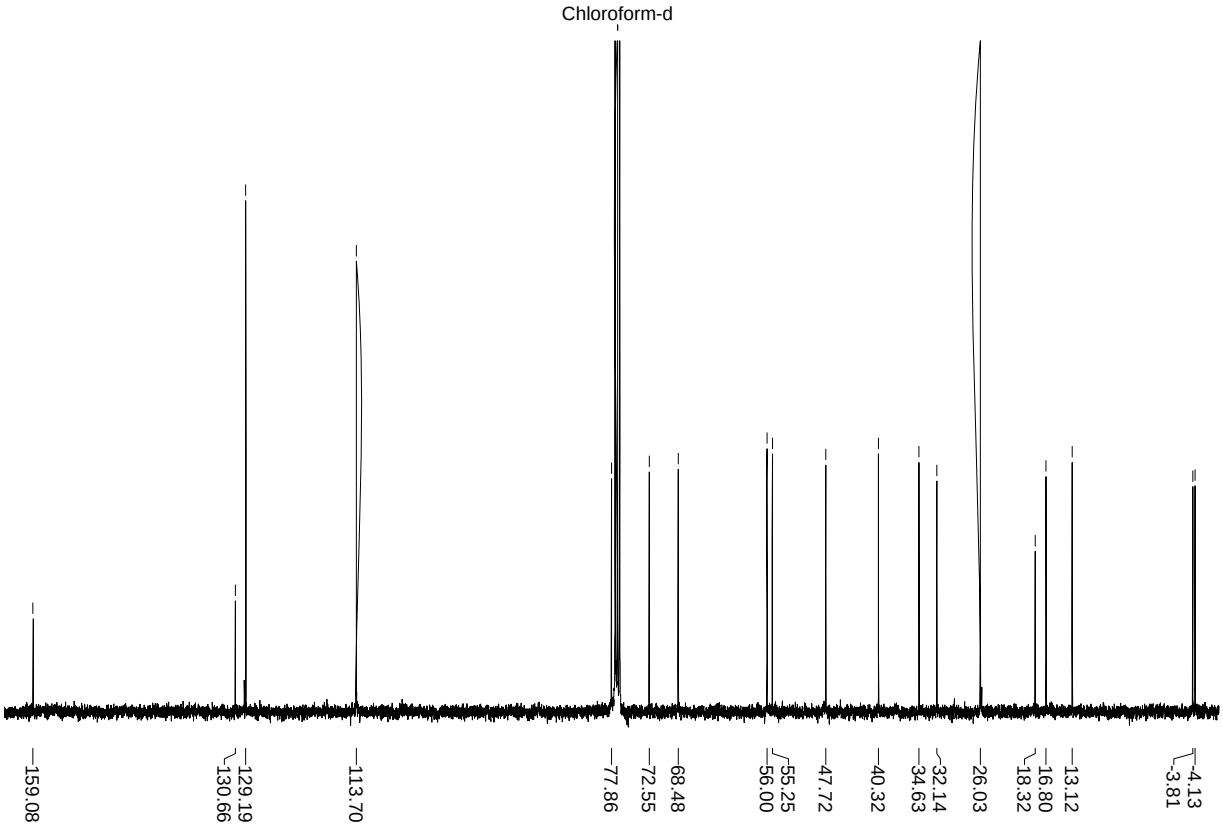
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


Chloroform-d
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129.19
113.70
77.86
72.55
68.48
56.00
55.25
47.72
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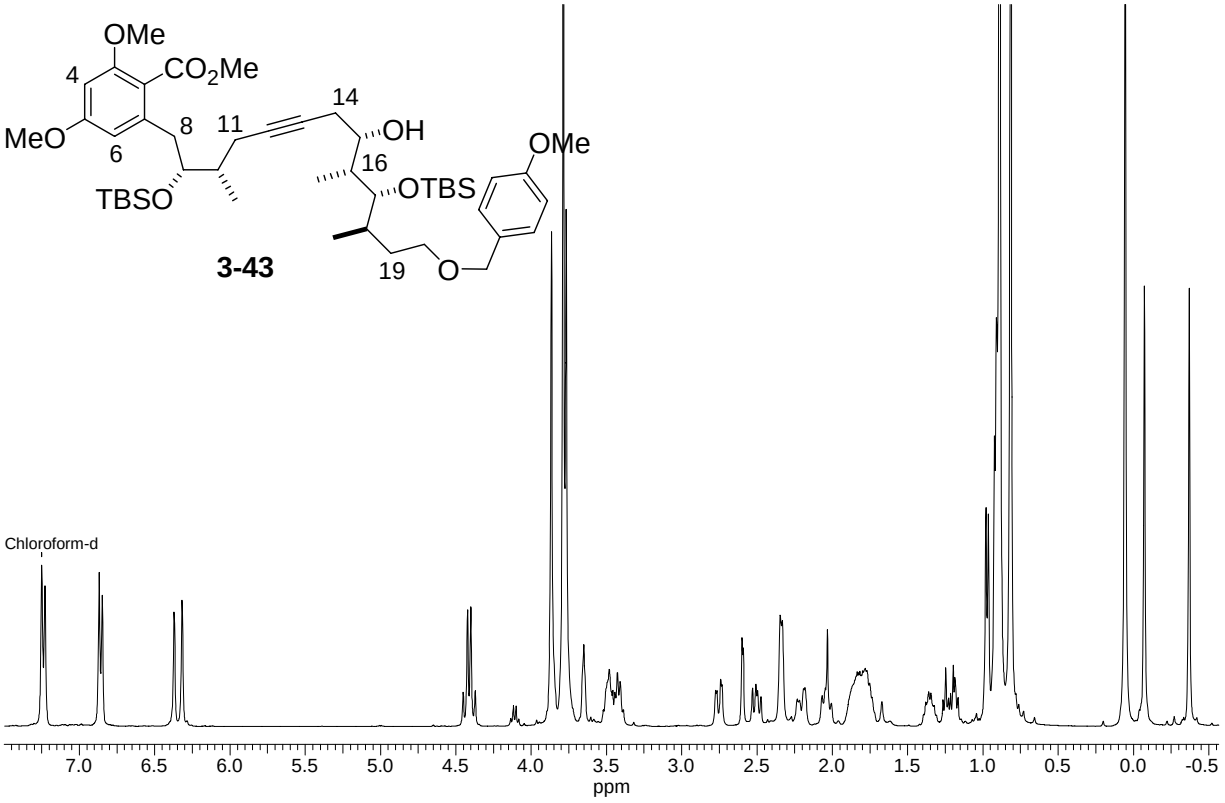
26.03
18.32
16.80
13.12
4.13
3.81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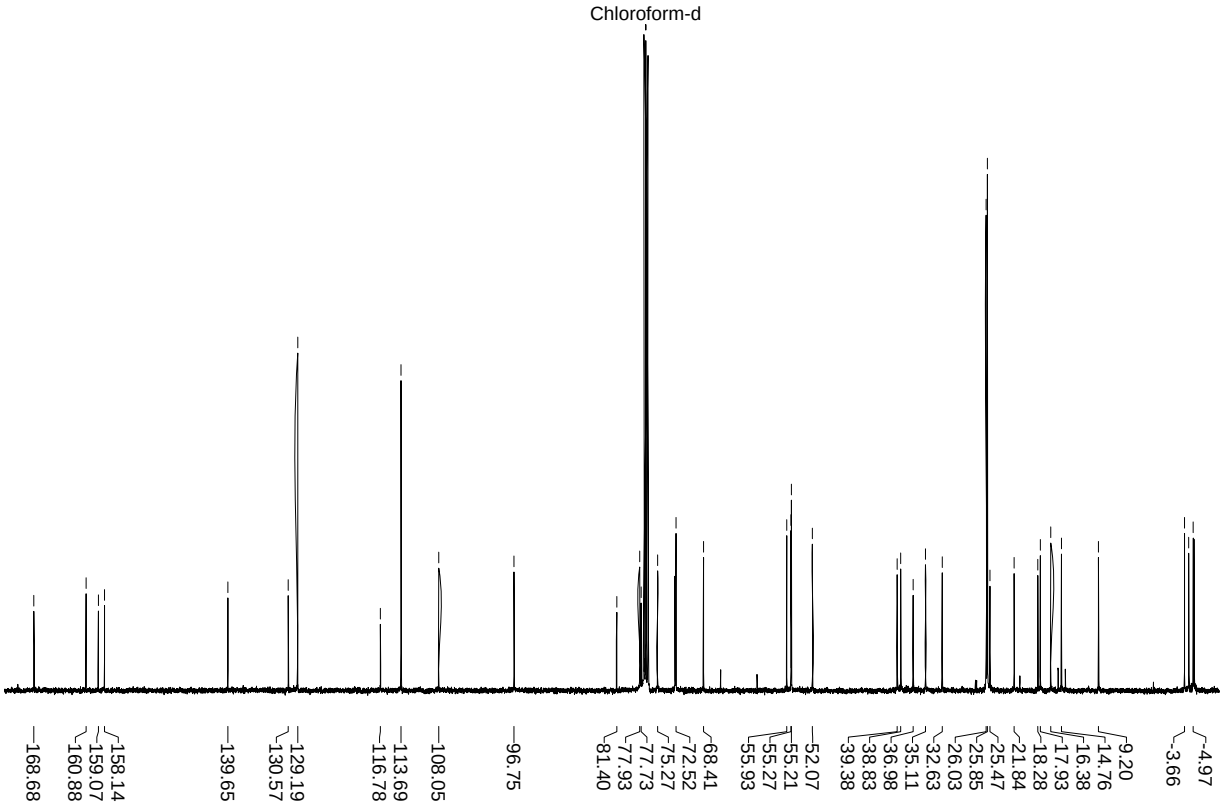
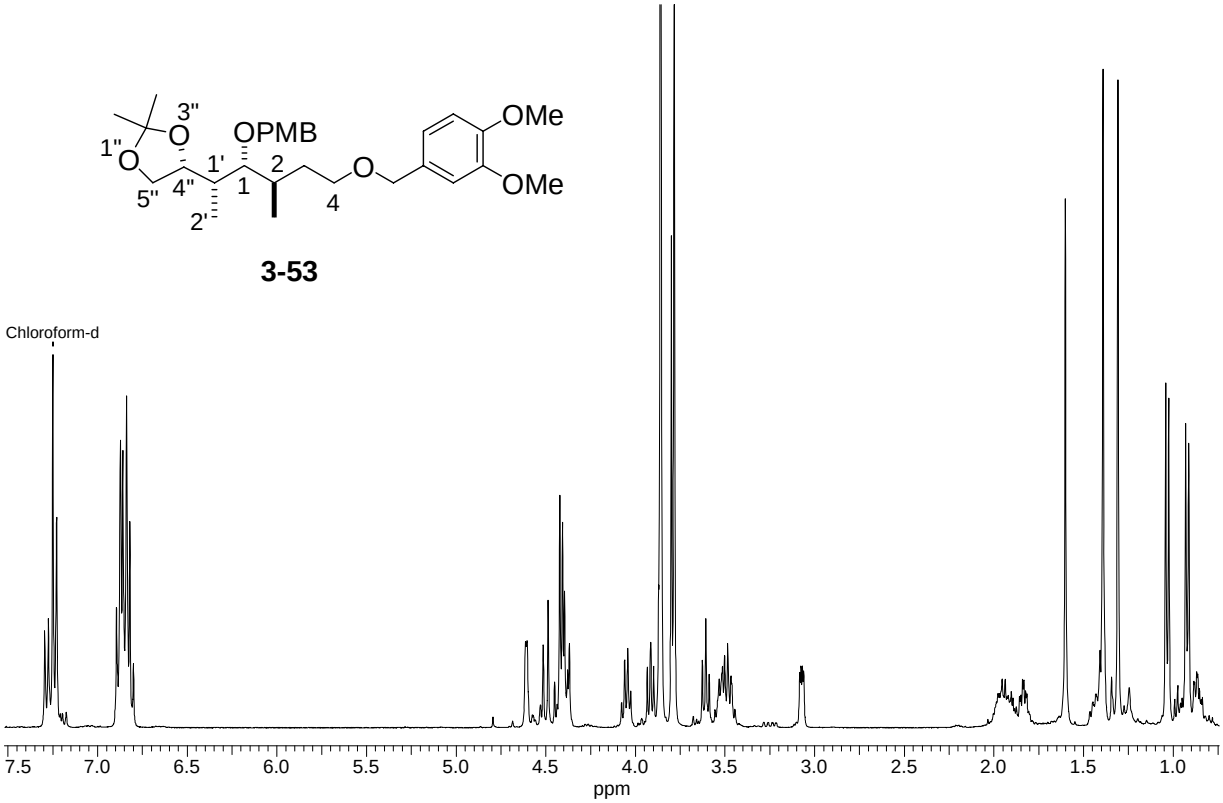
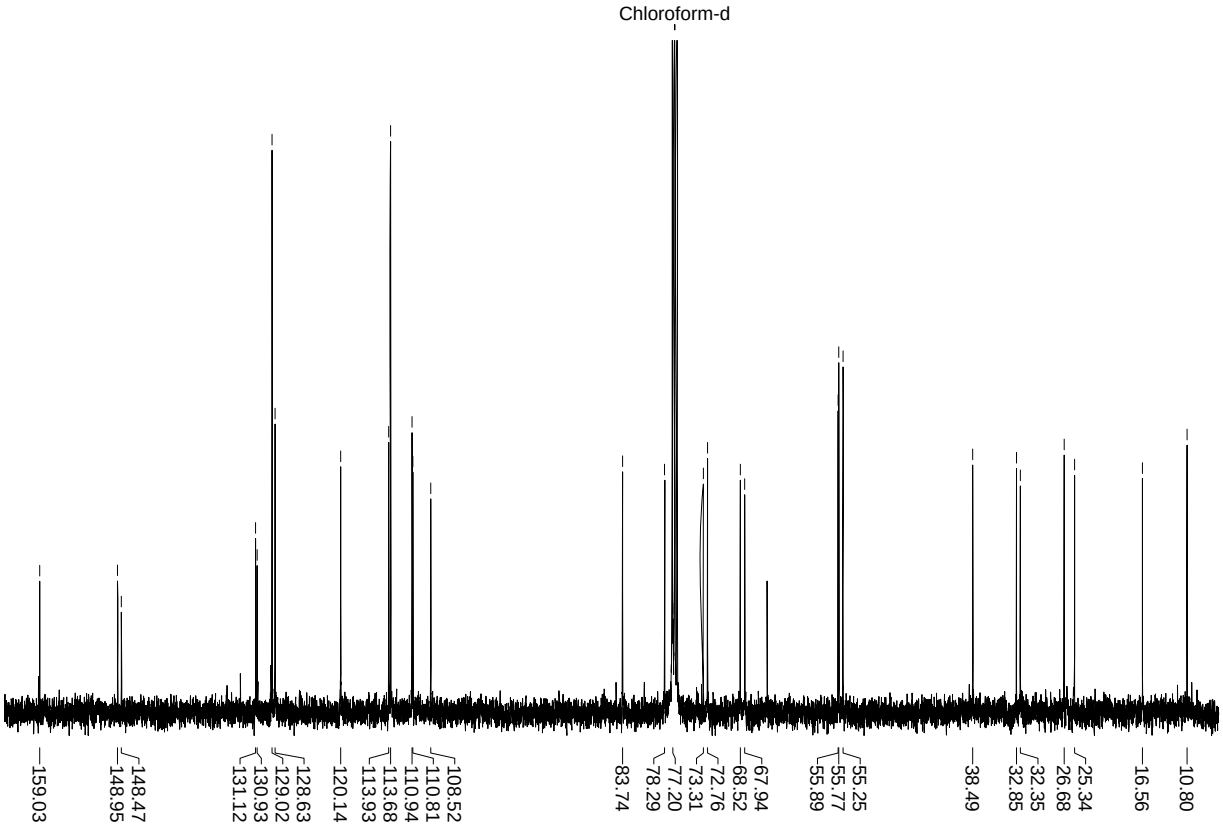
MeO
6
8
11
14
OH
16
OTBS
OMe
TBSO
19
O
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

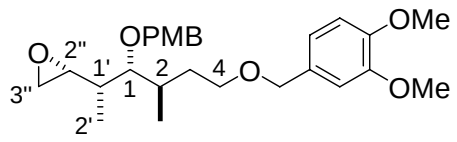
**3-43**


Chloroform-d
168.68
160.88
159.07
158.14
139.65
130.57
129.19
116.78
113.69
108.05
96.75
81.40
77.93
77.73
75.27
72.52
68.41
55.93
55.27
55.21
52.07
39.38
38.83
36.98
35.11
32.63
26.03
25.85
25.47
21.84
18.28
17.93
16.38
14.76
9.20
-3.66
-4.97


3"
1"
O
O
OPMB
1'
2
1
O
OMe
OMe
5"
4"
2'
4
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

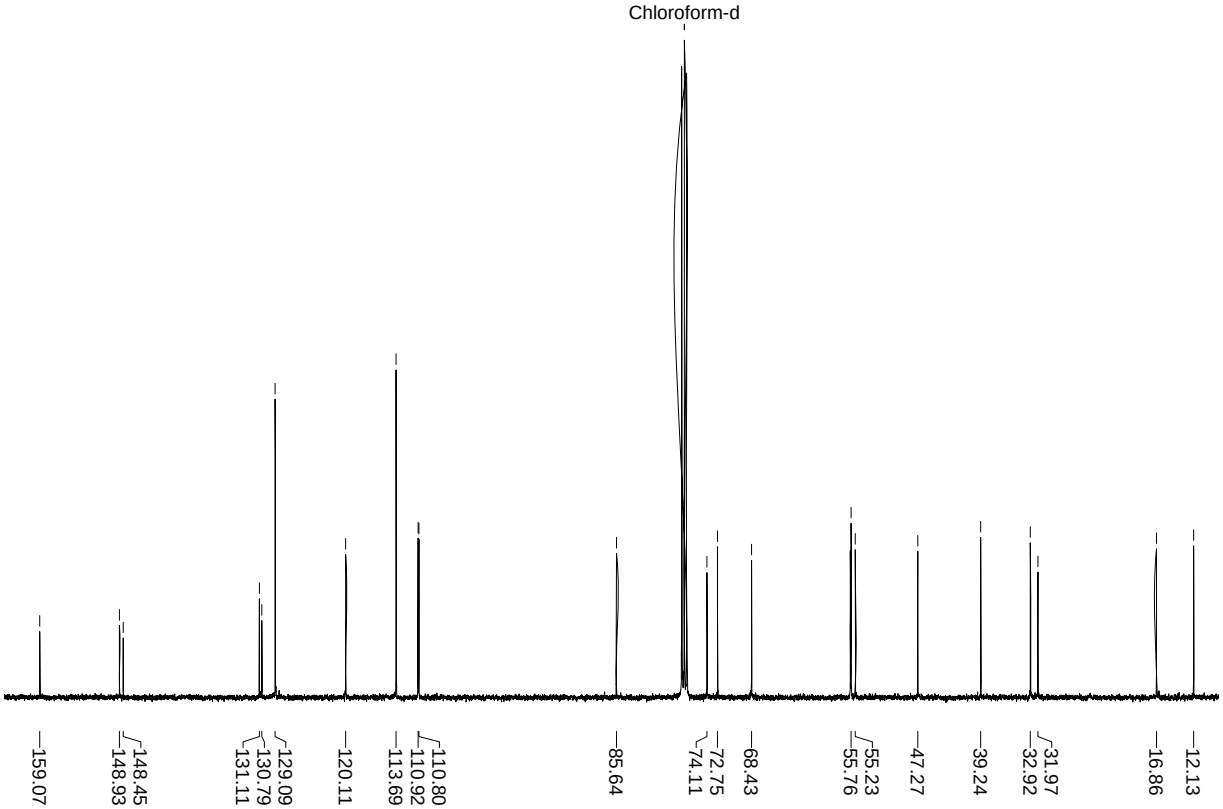
**3-53**

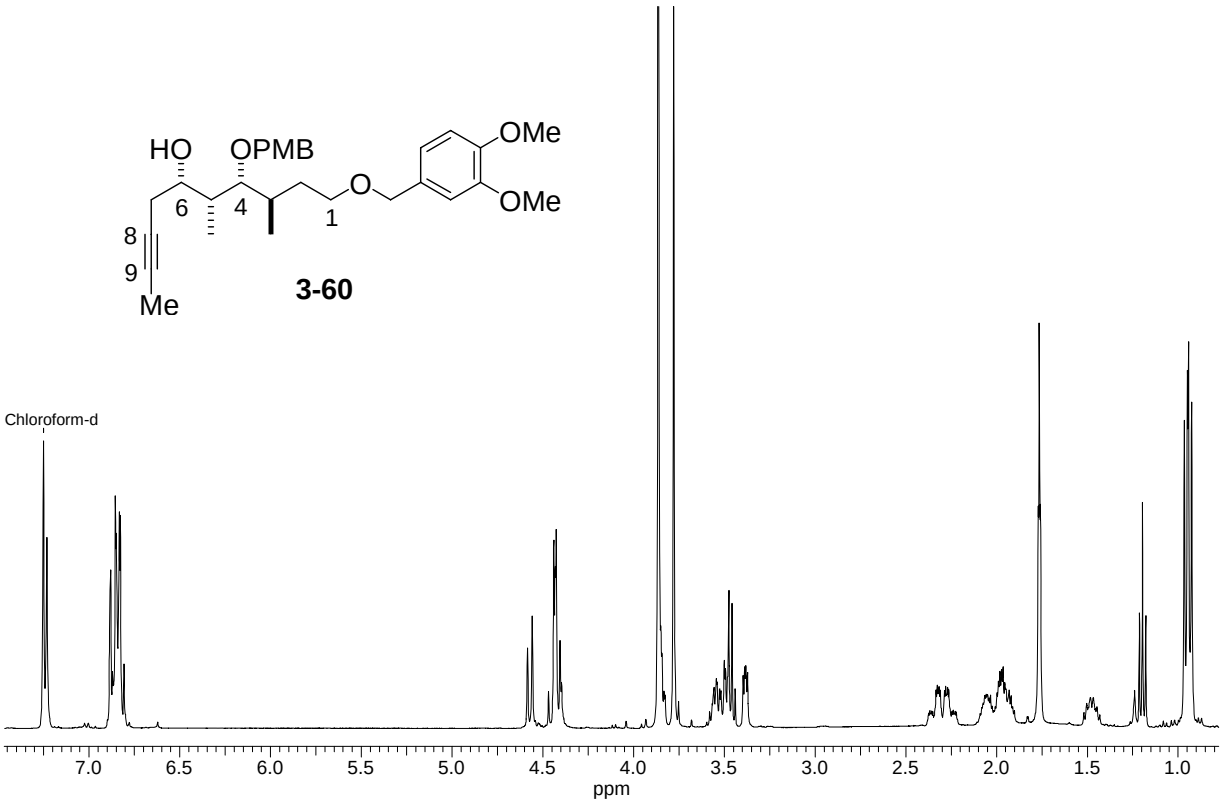

Chloroform-d
159.03
148.95
148.47
131.12
130.93
129.02
128.63
120.14
113.93
113.68
110.94
110.81
108.52
83.74
78.29
77.20
73.31
72.76
68.52
67.94
55.89
55.77
55.25
38.49
32.85
32.35
26.68
25.34
16.56
10.80

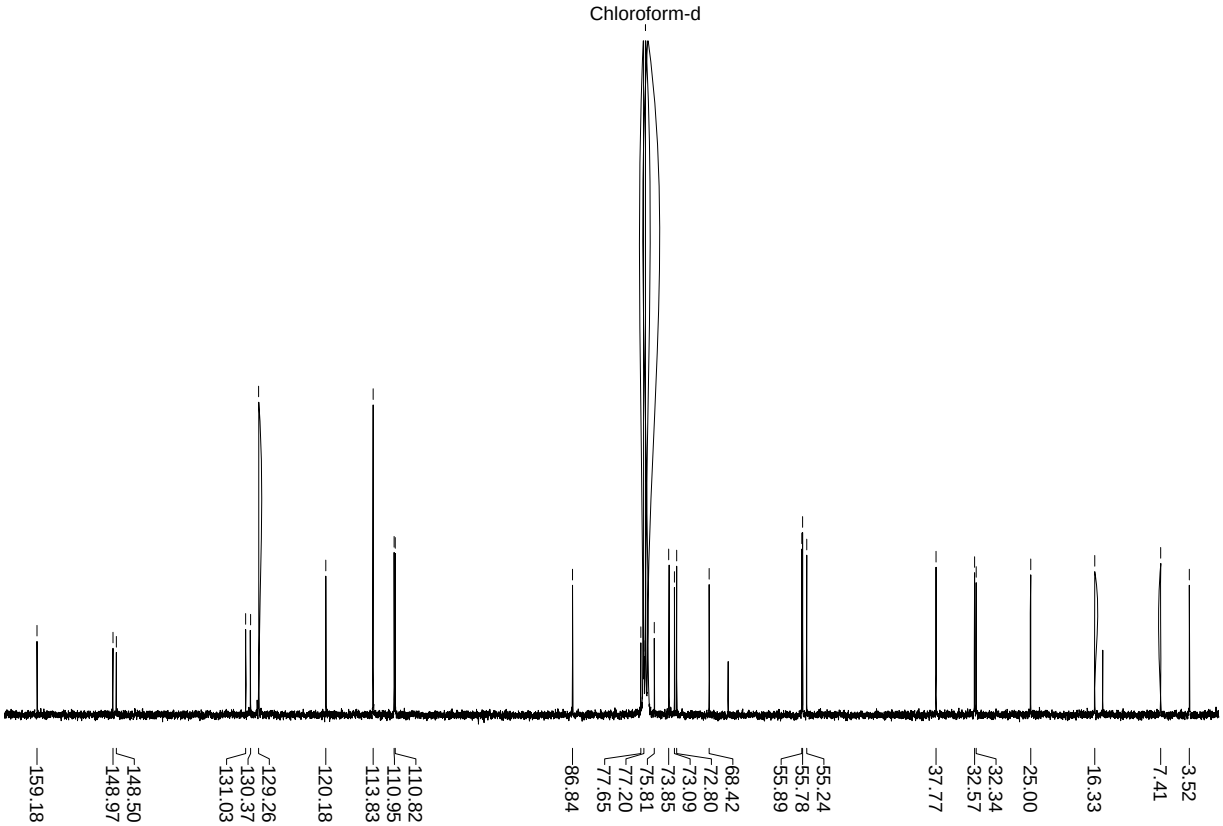

OPMB
OMe
OMe
O
2"
1'
2
4
O
3"
1
2'

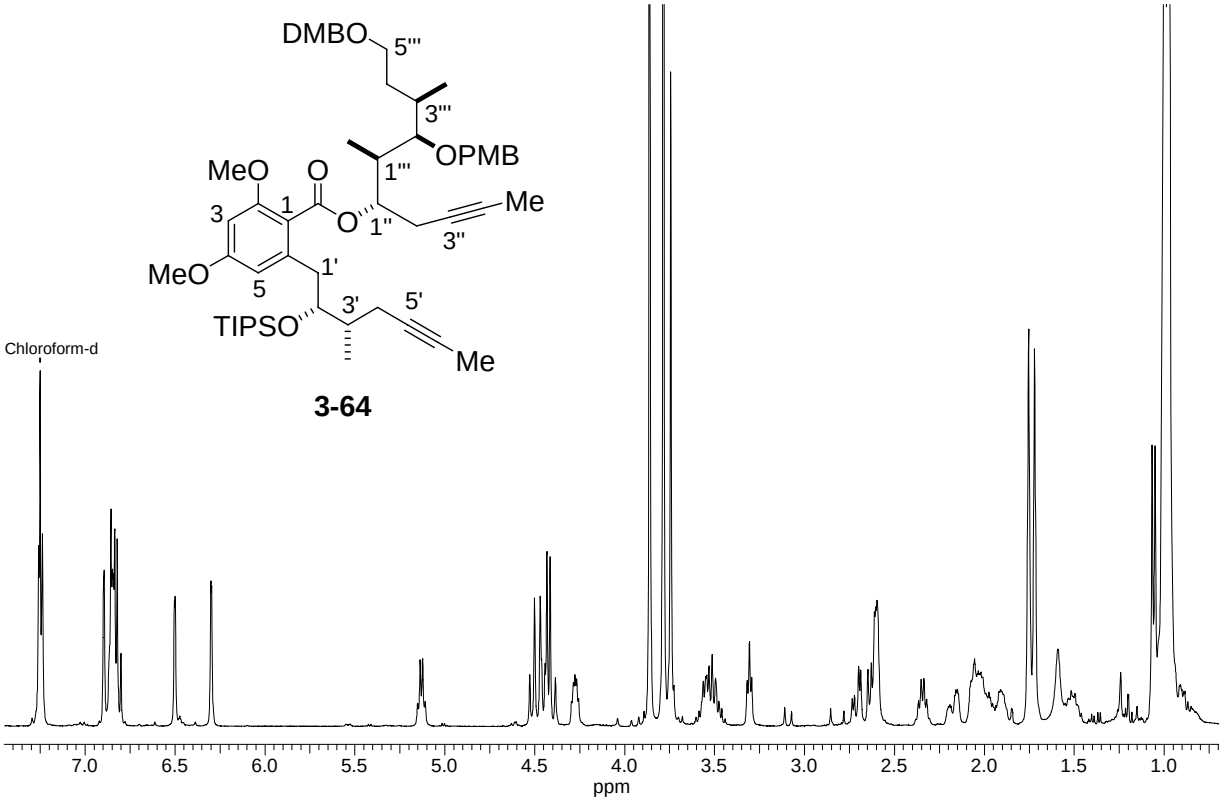
**3-55**


Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

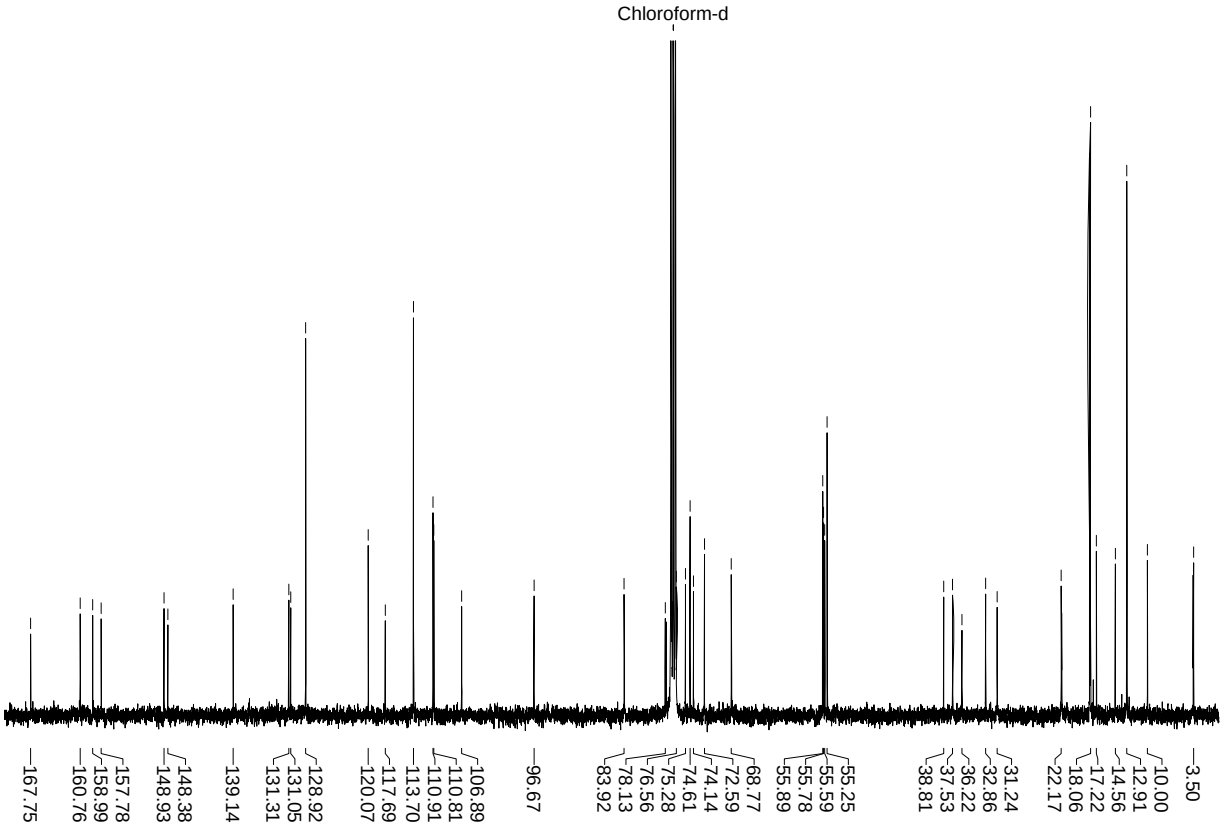

Chloroform-d
159.07
148.45
148.93
131.11
130.79
129.09
120.11
113.69
110.92
110.80
85.64
74.11
72.75
68.43
55.23
55.76
47.27
39.24
32.92
31.97
16.86
12.13

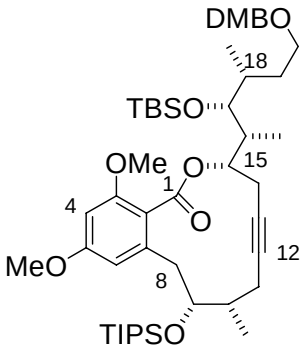

HO
OPMB
OMe
OMe
O
6
4
1
8
9
Me
3-60
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
159.18
148.97
148.50
131.03
130.37
129.26
120.18
113.83
110.95
110.82
86.84
77.65
77.20
75.81
73.85
73.09
72.80
68.42
55.89
55.78
55.24
37.77
32.57
32.34
25.00
16.33
7.41
3.52


DMBO
5'''
3'''
OPMB
1'''
MeO
O
1
3
O
1''
Me
3''
MeO
5
1'
3'
5'
TIPSO
Me
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

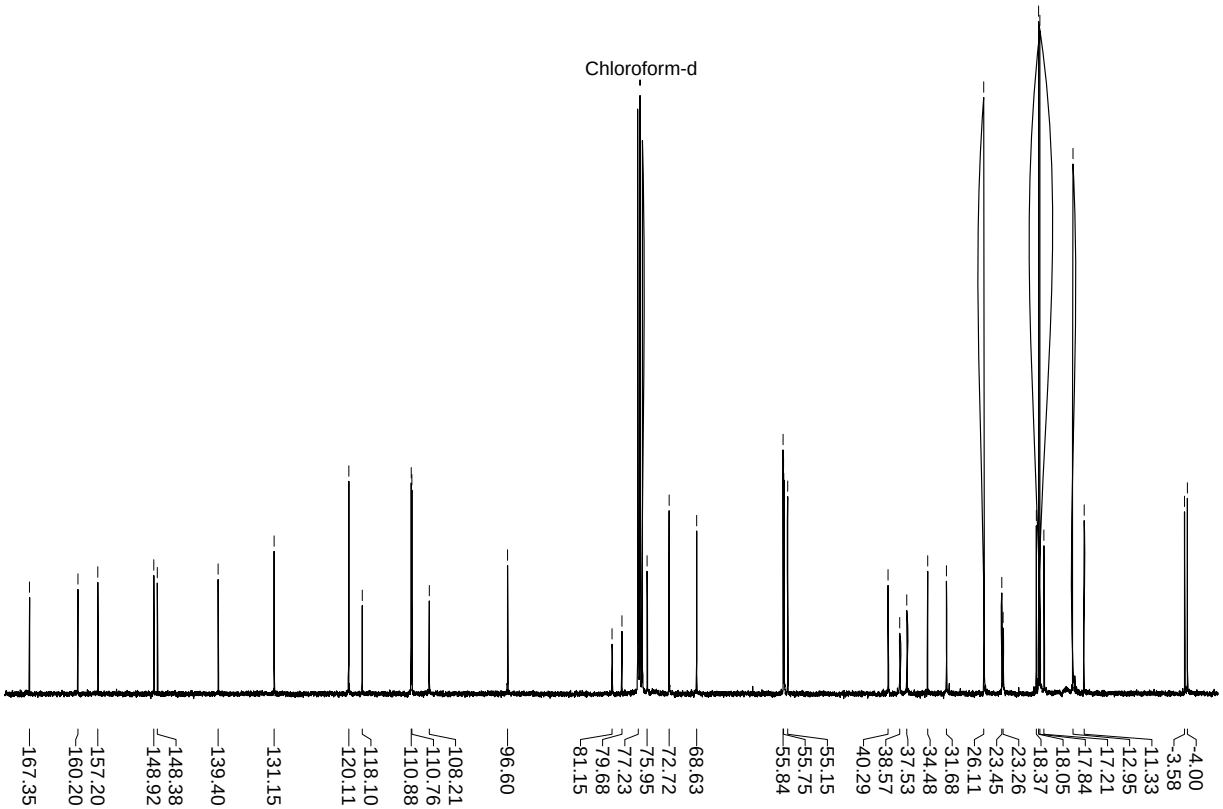
**3-64**

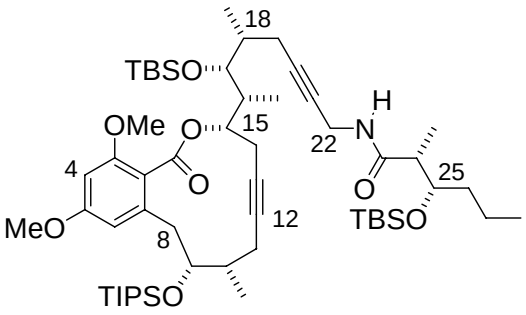

Chloroform-d
167.75
160.76
158.99
157.78
148.93
148.38
139.14
131.31
131.05
128.92
120.07
117.69
113.70
110.91
110.81
106.89
96.67
83.92
78.13
76.56
75.28
74.61
74.14
72.59
68.77
55.89
55.78
55.59
55.25
38.81
37.53
36.22
32.86
31.24
22.17
18.06
17.22
14.56
12.91
10.00
3.50


DMBO
18
TBSO
15
OMe
O
1
4
O
12
MeO
8
TIPSO

**3-74**

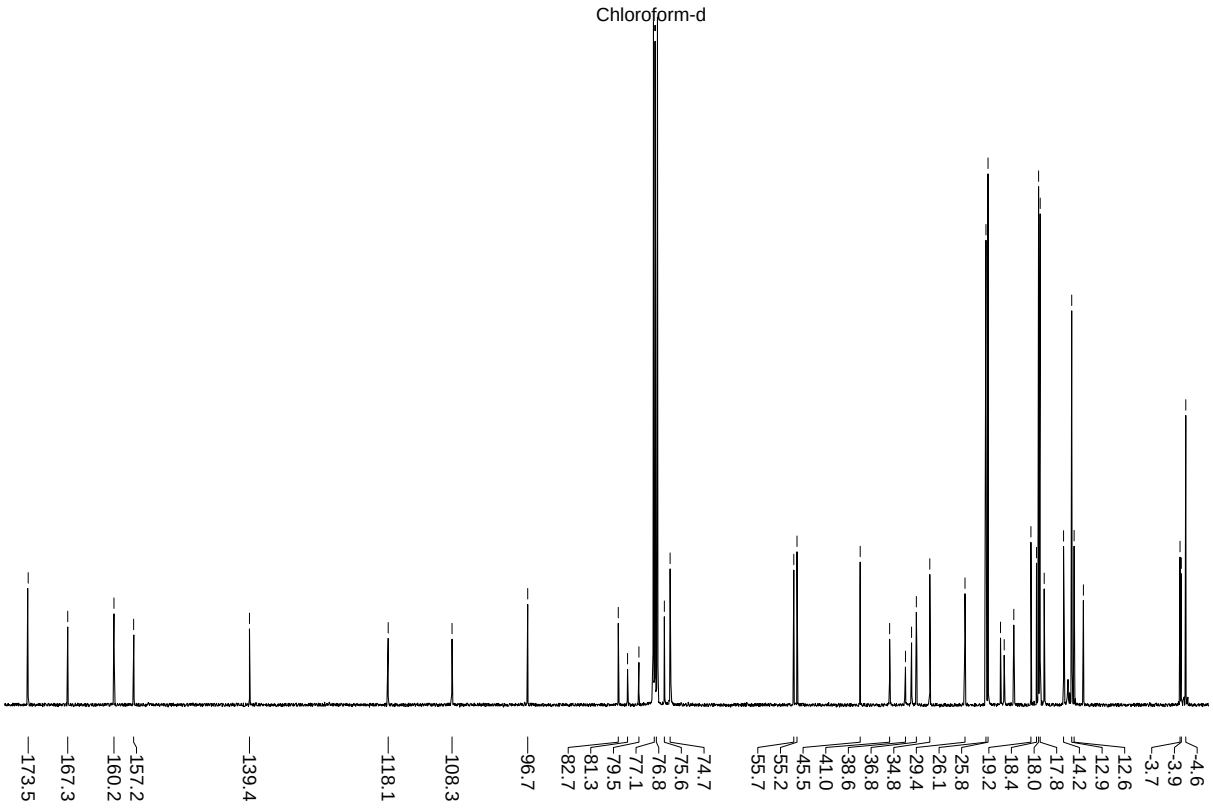

Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

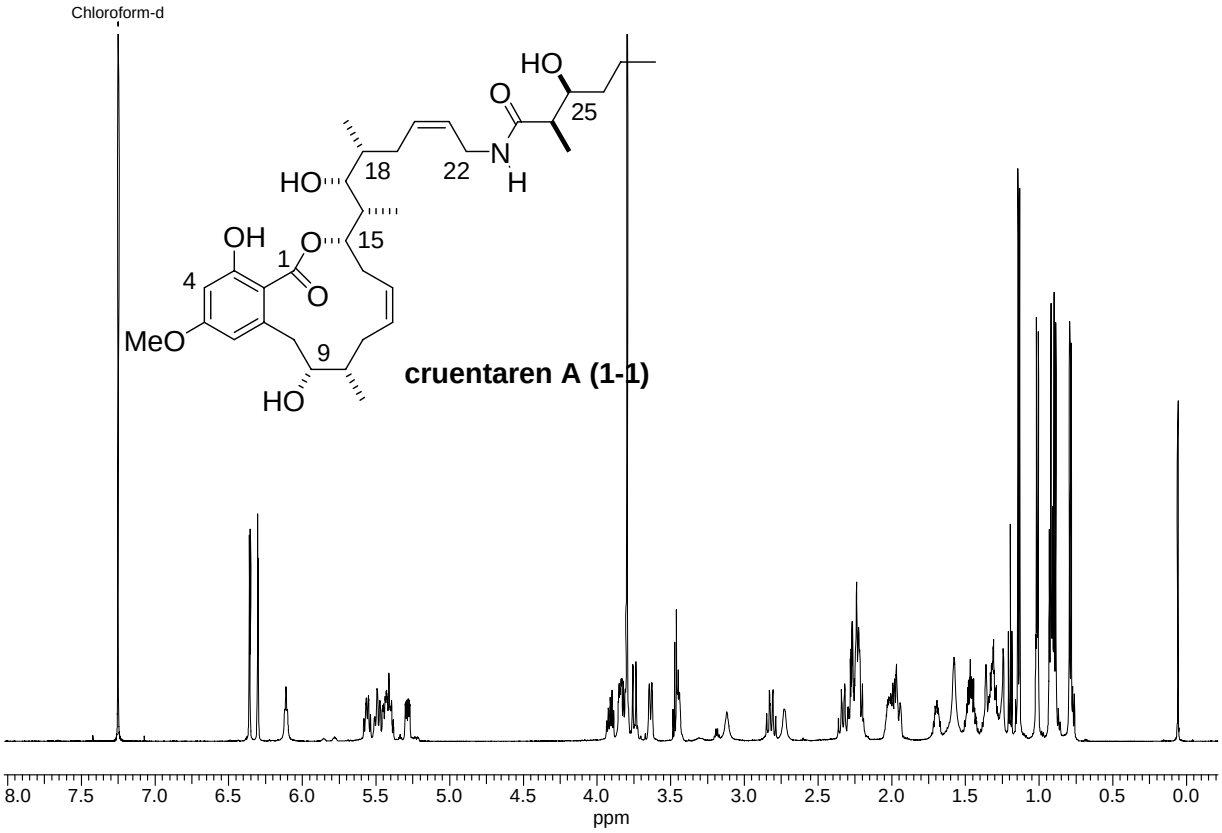

Chloroform-d
167.35
160.20
157.20
148.92
148.38
139.40
131.15
120.11
118.10
110.88
110.76
108.21
96.60
81.15
79.68
77.23
75.95
72.72
68.63
55.84
55.75
55.15
40.29
38.57
37.53
34.48
31.68
26.11
23.45
23.26
18.37
18.05
17.84
17.21
12.95
11.33
3.58
-4.00

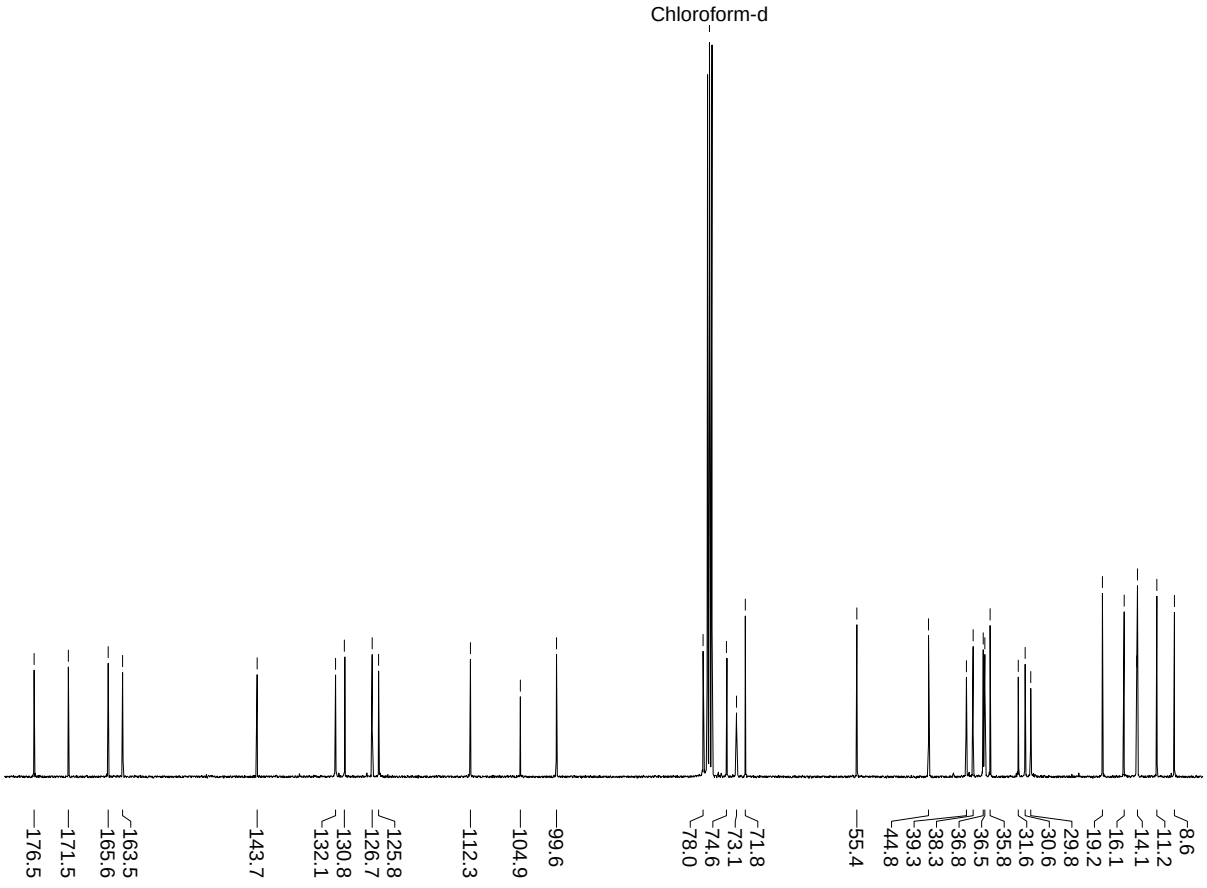

18
TBSO
OMe
O
15
22
N
H
4
O
25
O
TBSO
MeO
8
12
TIPSO

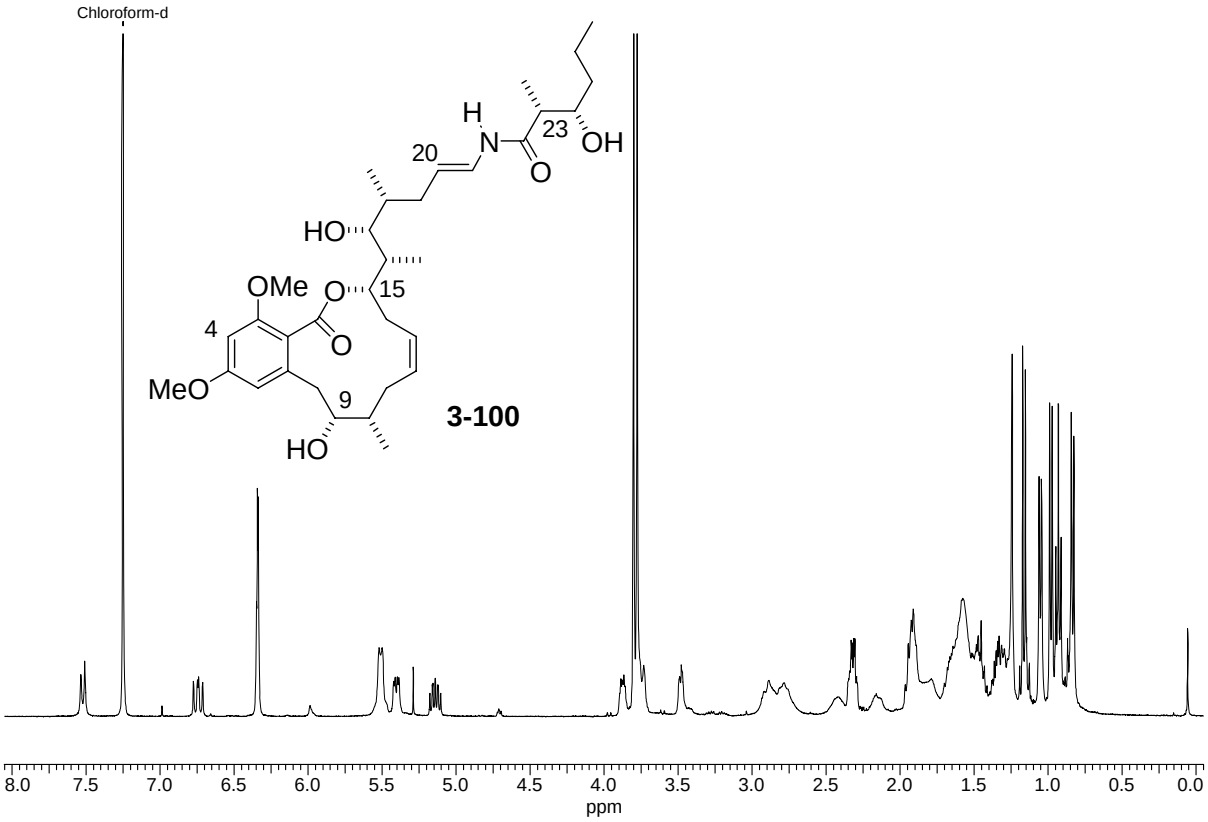
**3-84**

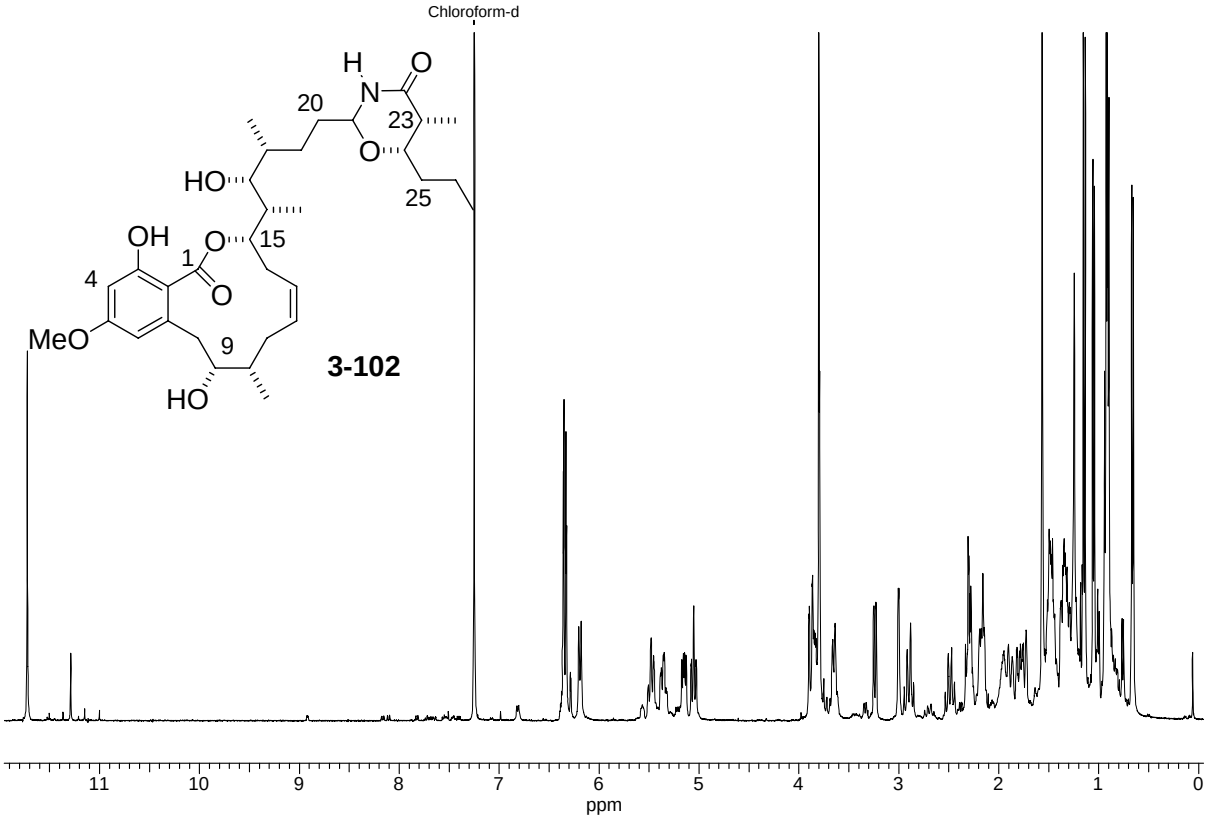

Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

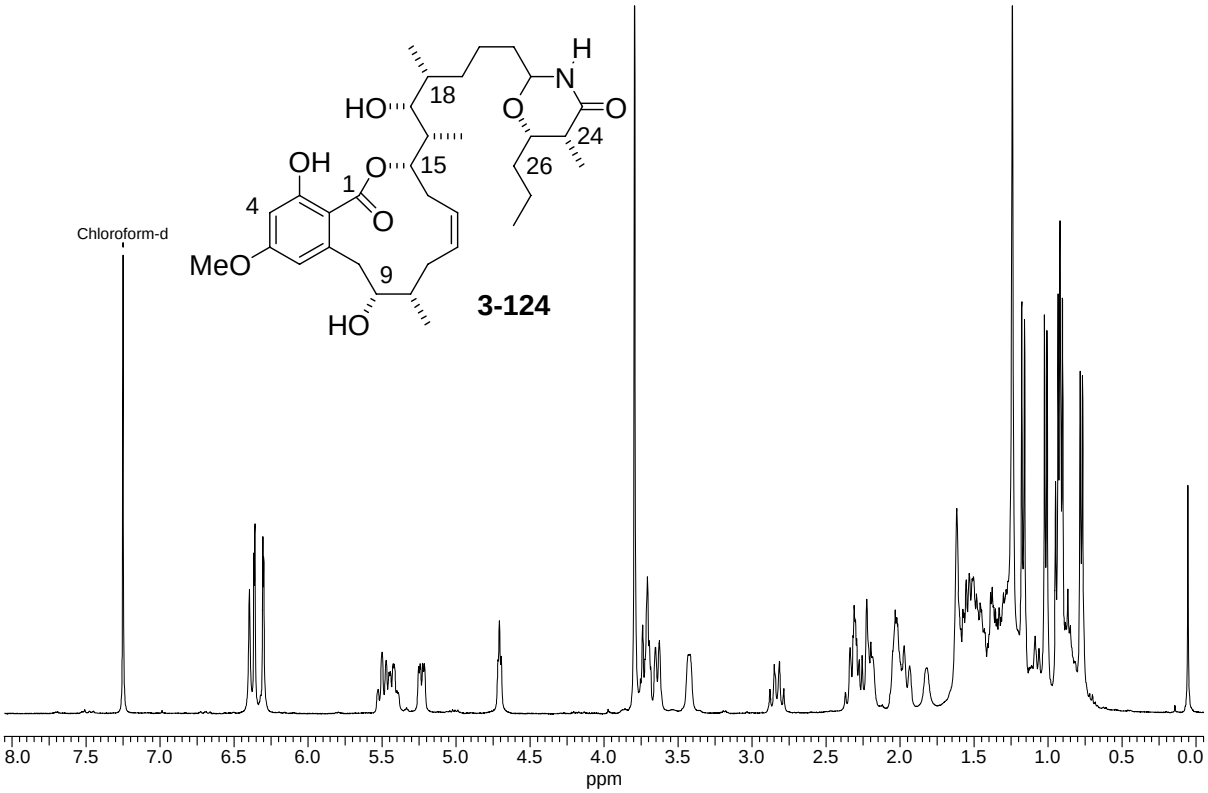

Chloroform-d
173.5
167.3
160.2
157.2
139.4
118.1
108.3
96.7
82.7
81.3
79.5
77.1
76.8
75.6
74.7
55.7
55.2
45.5
41.0
38.6
36.8
34.8
29.4
26.1
25.8
19.2
18.4
18.0
17.8
14.2
12.9
12.6
-3.7
-3.9
-4.6

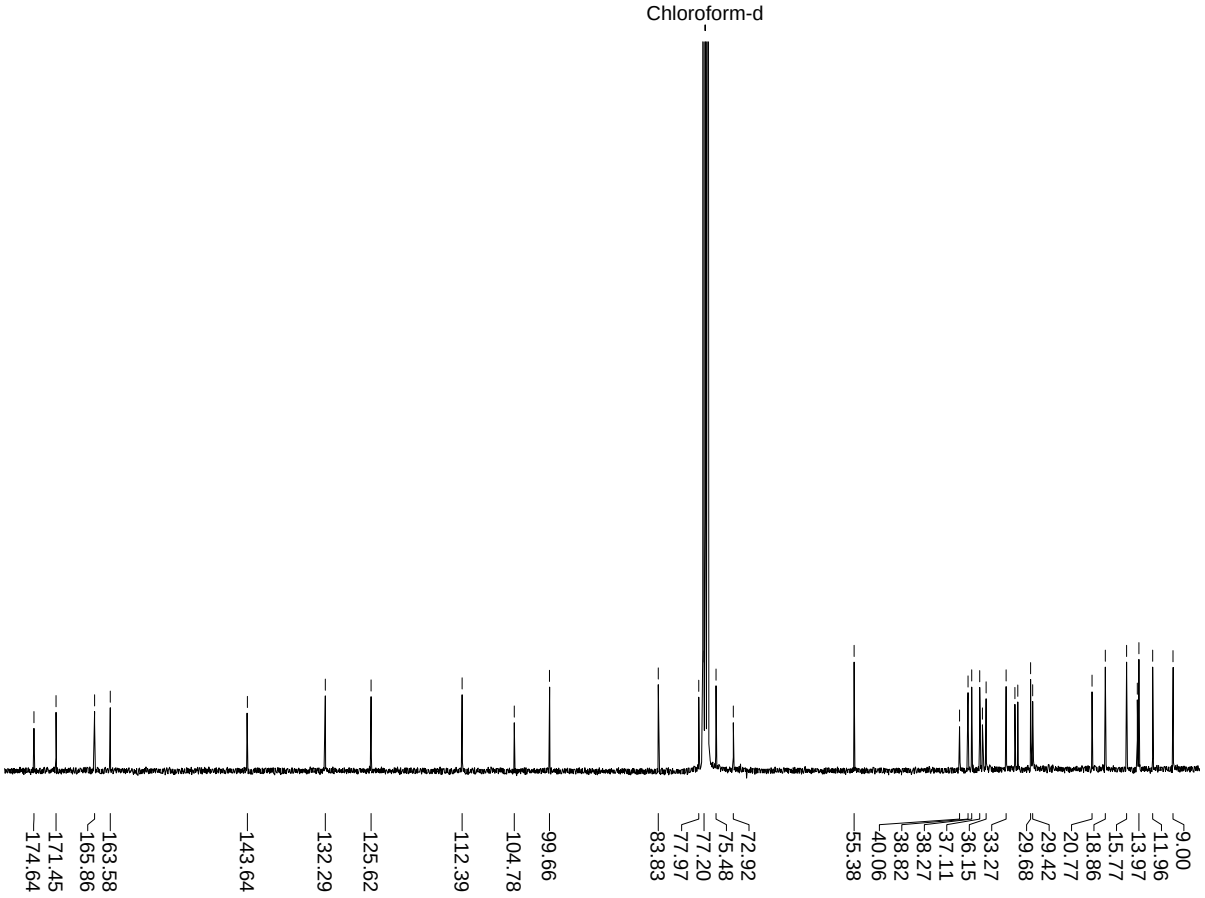

Chloroform-d
HO
O
25
N
H
22
18
HO
OH
O
15
1
O
4
MeO
9
HO
cruentaren A (1-1)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

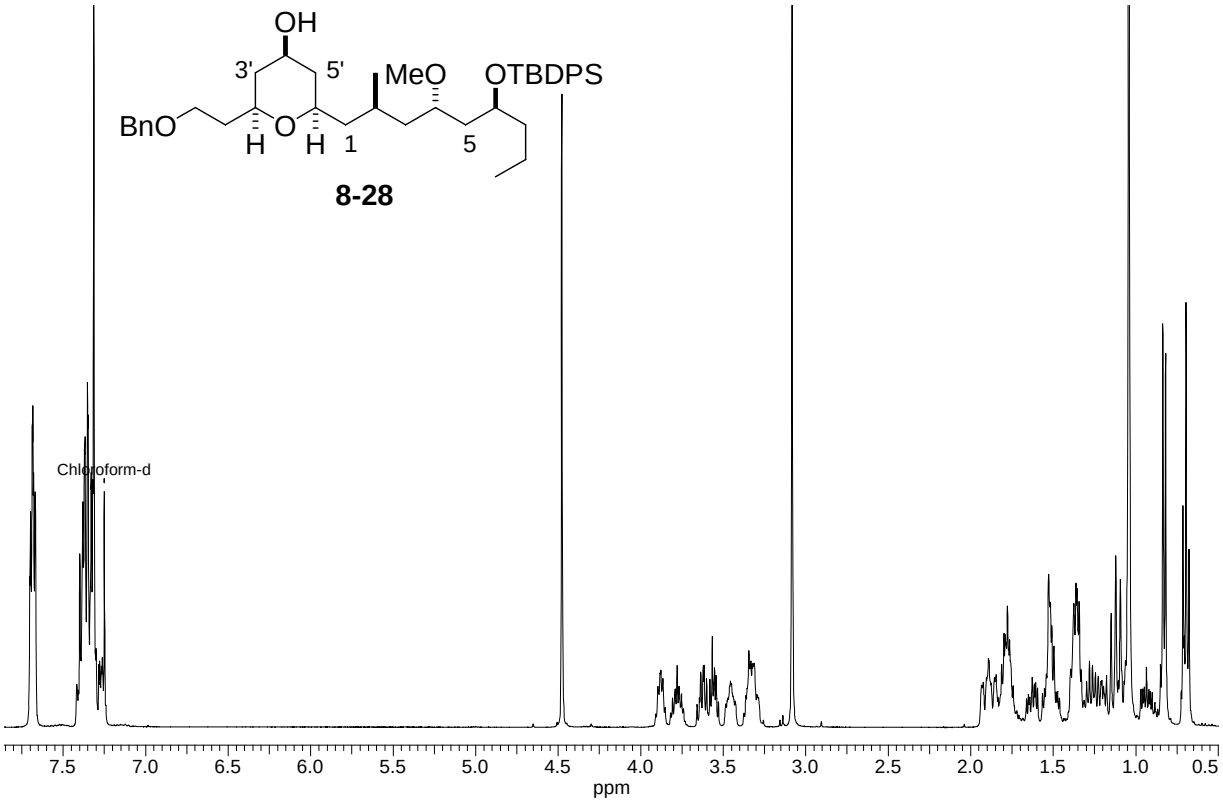

Chloroform-d
176.5
171.5
165.6
163.5
143.7
132.1
130.8
126.7
125.8
112.3
104.9
99.6
78.0
74.6
73.1
71.8
55.4
44.8
39.3
38.3
36.8
36.5
35.8
31.6
30.6
29.8
19.2
16.1
14.1
11.2
8.6


Chloroform-d
H
N
O
23
OH
20
HO
OMe
O
15
4
O
MeO
9
HO
3-100
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

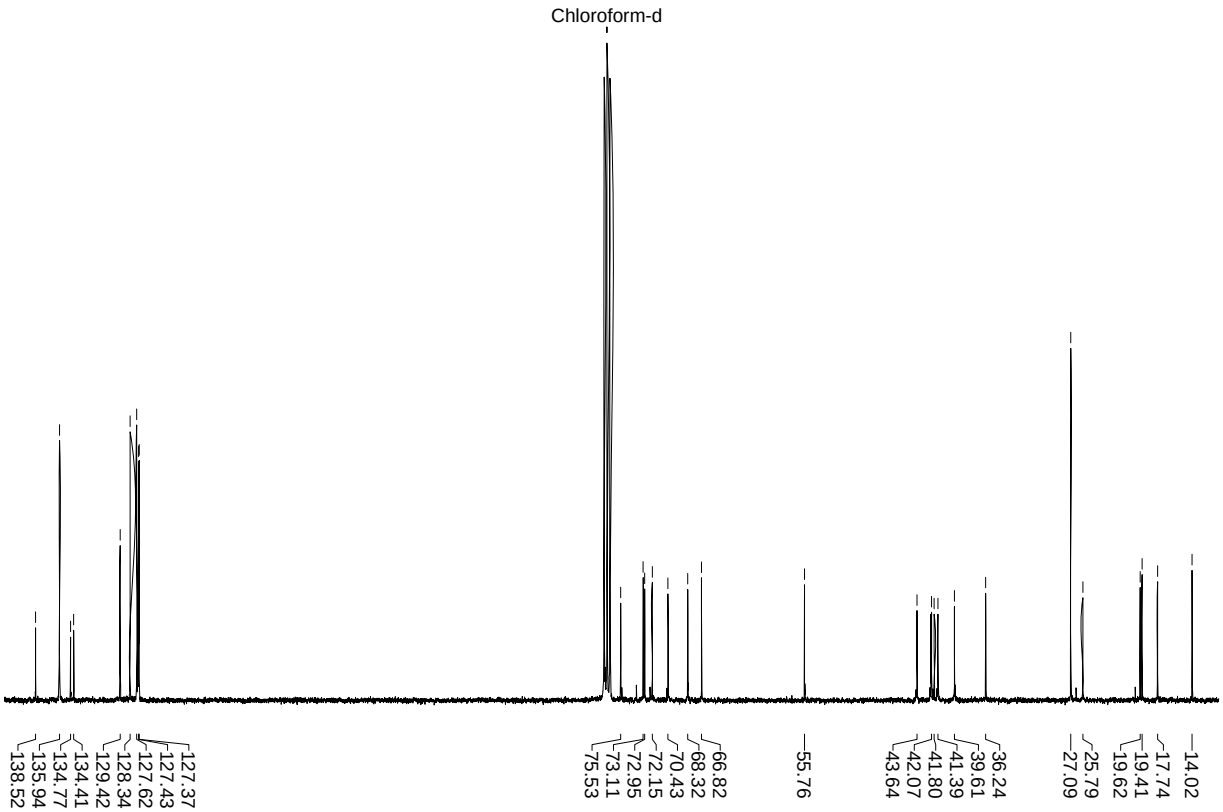

Chloroform-d
H
N
O
O
20
23
HO
25
OH
O
15
1
4
O
MeO
9
HO
3-102
11
10
9
8
7
6
5
4
3
2
1
0
ppm

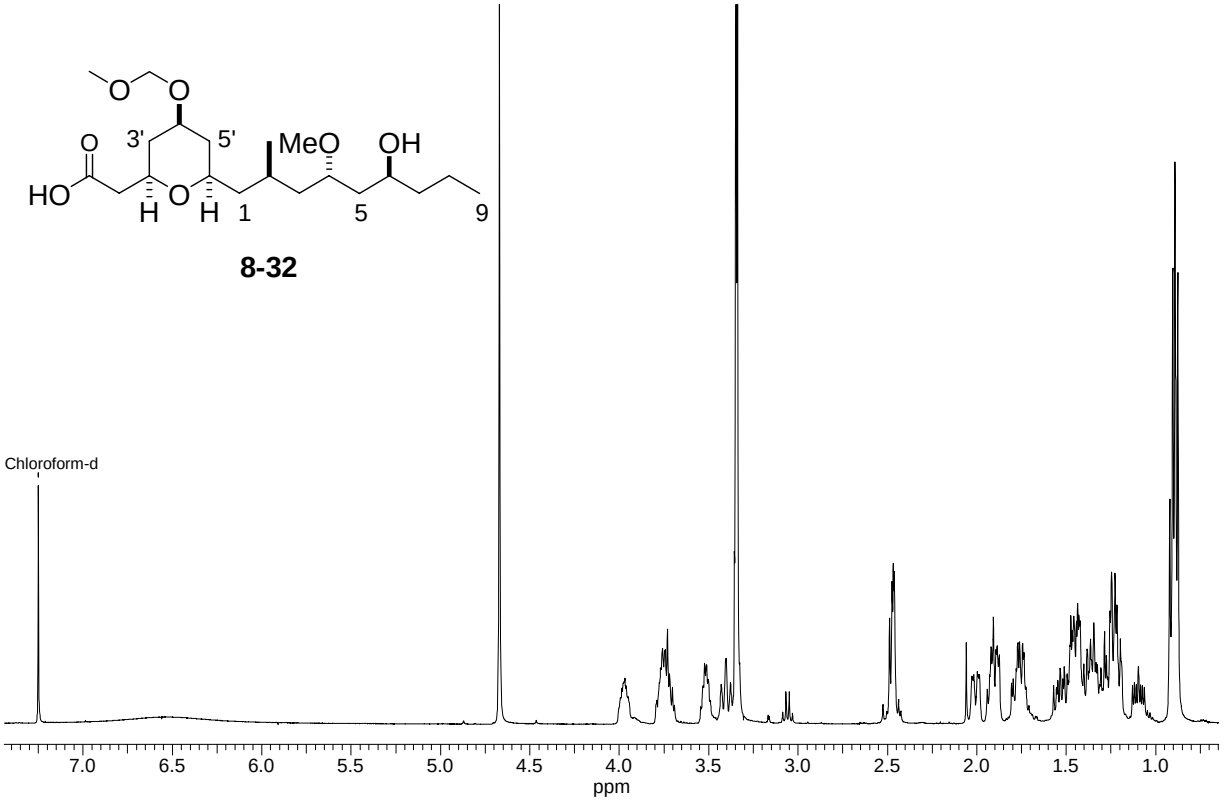

Chloroform-d
HO
18
H
N
O
O
24
26
OH
1
O
15
4
O
MeO
9
HO
3-124
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


Chloroform-d
174.64
171.45
165.86
163.58
143.64
132.29
125.62
112.39
104.78
99.66
83.83
77.97
77.20
75.48
72.92
55.38
40.06
38.82
38.27
37.11
36.15
33.27
29.68
29.42
20.77
18.86
15.77
13.97
11.96
9.00

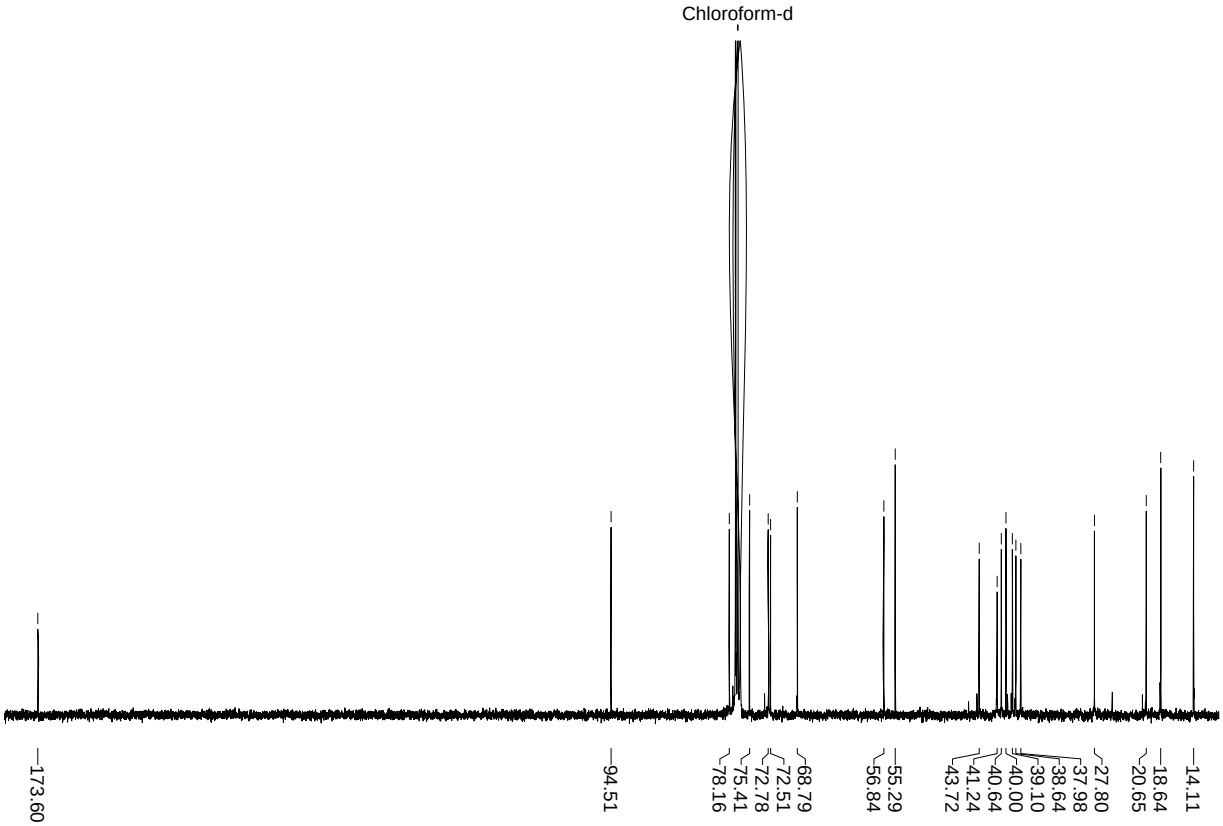

OH
3'
5'
MeO
OTBDPS
BnO
O
H
H
1
5
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

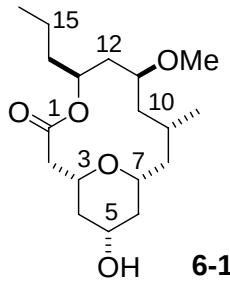
**8-28**


Chloroform-d
138.52
135.94
134.77
134.41
129.42
128.34
127.62
127.43
127.37
75.53
73.11
72.95
72.15
70.43
68.32
66.82
55.76
43.64
42.07
41.80
41.39
39.61
36.24
27.09
25.79
19.62
19.41
17.74
14.02


O
O
O
3'
5'
MeO
OH
HO
O
H
H
1
5
9
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

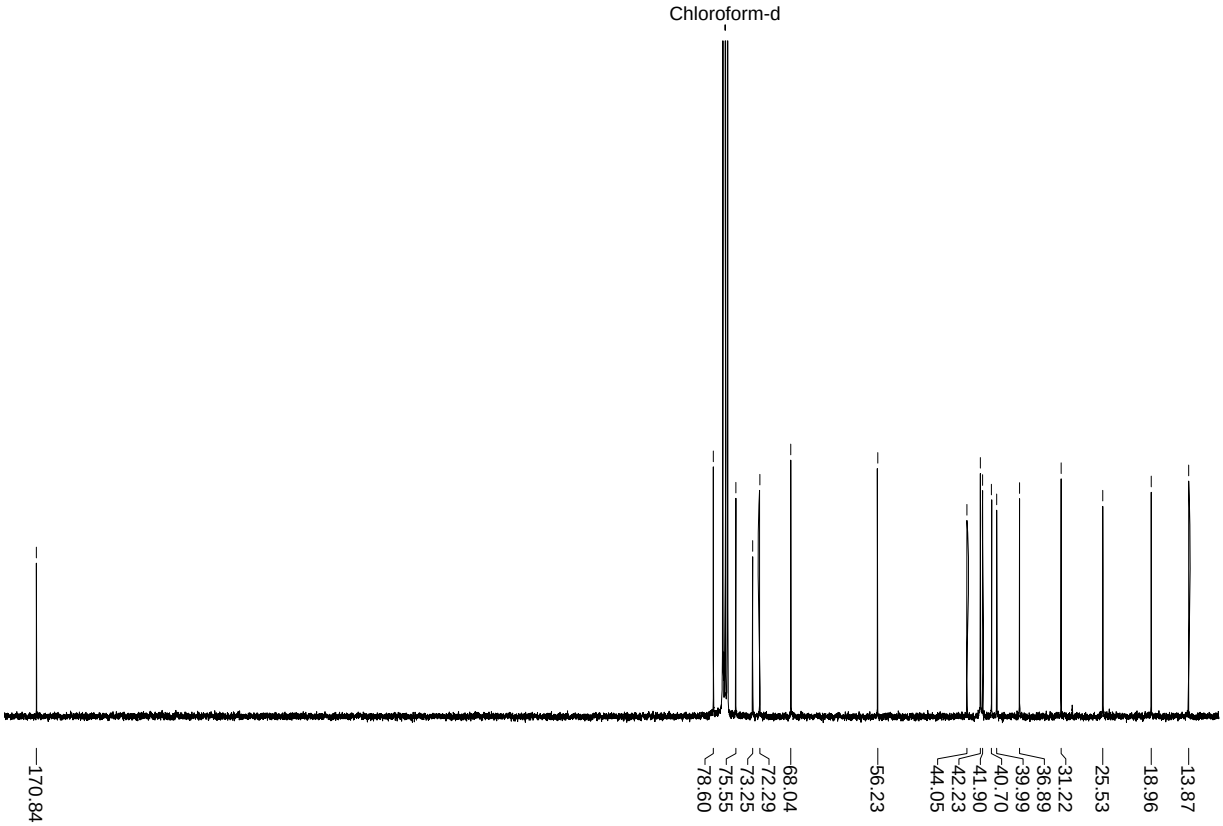
**8-32**

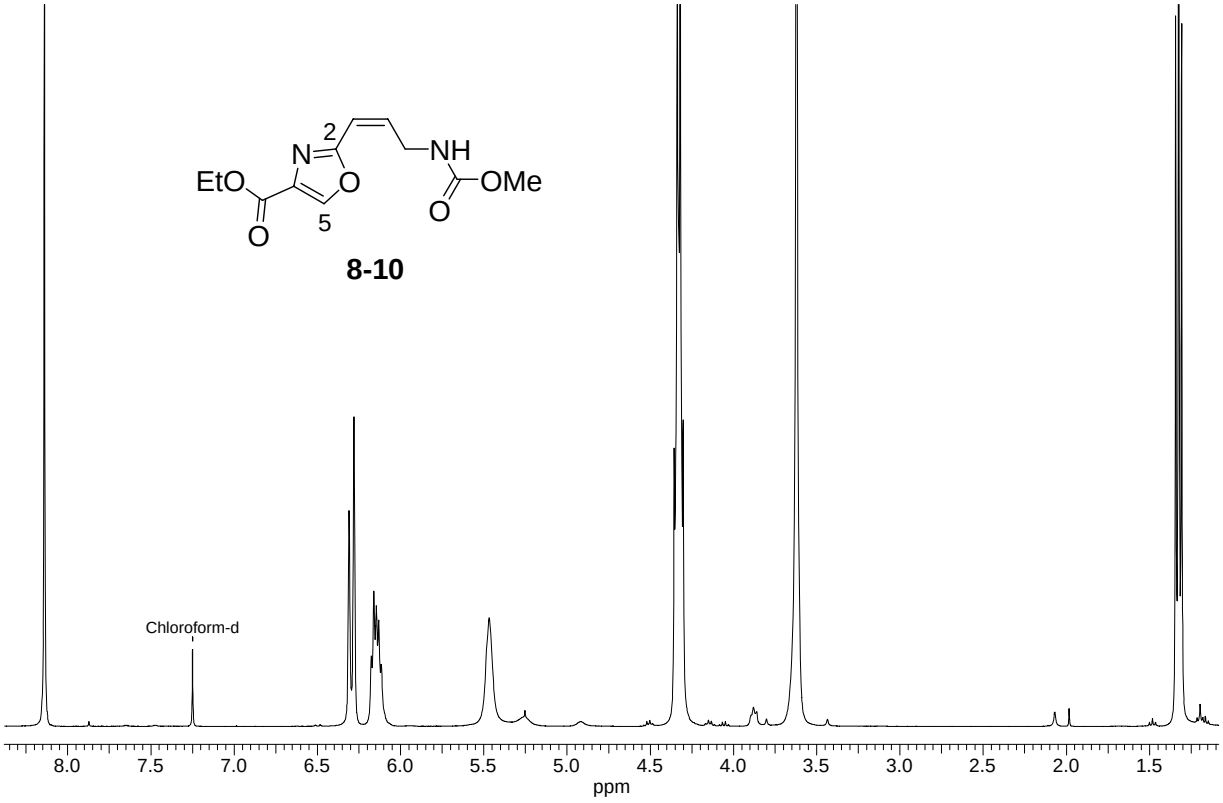

Chloroform-d
173.60
94.51
78.16
75.41
72.78
72.51
68.79
56.84
55.29
43.72
41.24
40.64
40.00
39.10
38.64
37.98
27.80
20.65
18.64
14.11


15
12
OMe
10
O
1
O
3
O
7
5
OH

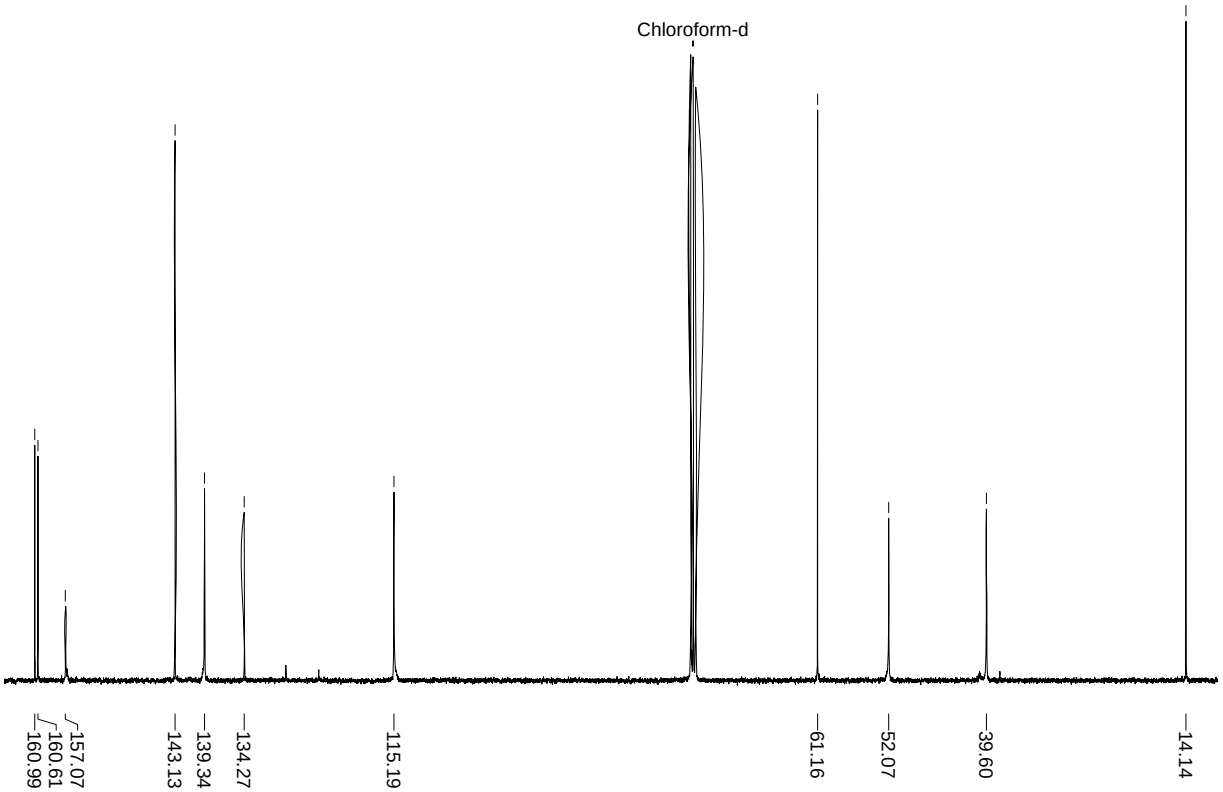
**6-14**

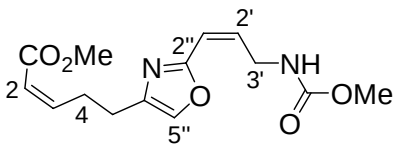

Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
170.84
78.60
75.55
73.25
72.29
68.04
56.23
44.05
42.23
41.90
40.70
39.99
36.89
31.22
25.53
18.96
13.87


2
N
NH
EtO
O
OMe
O
5
O
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

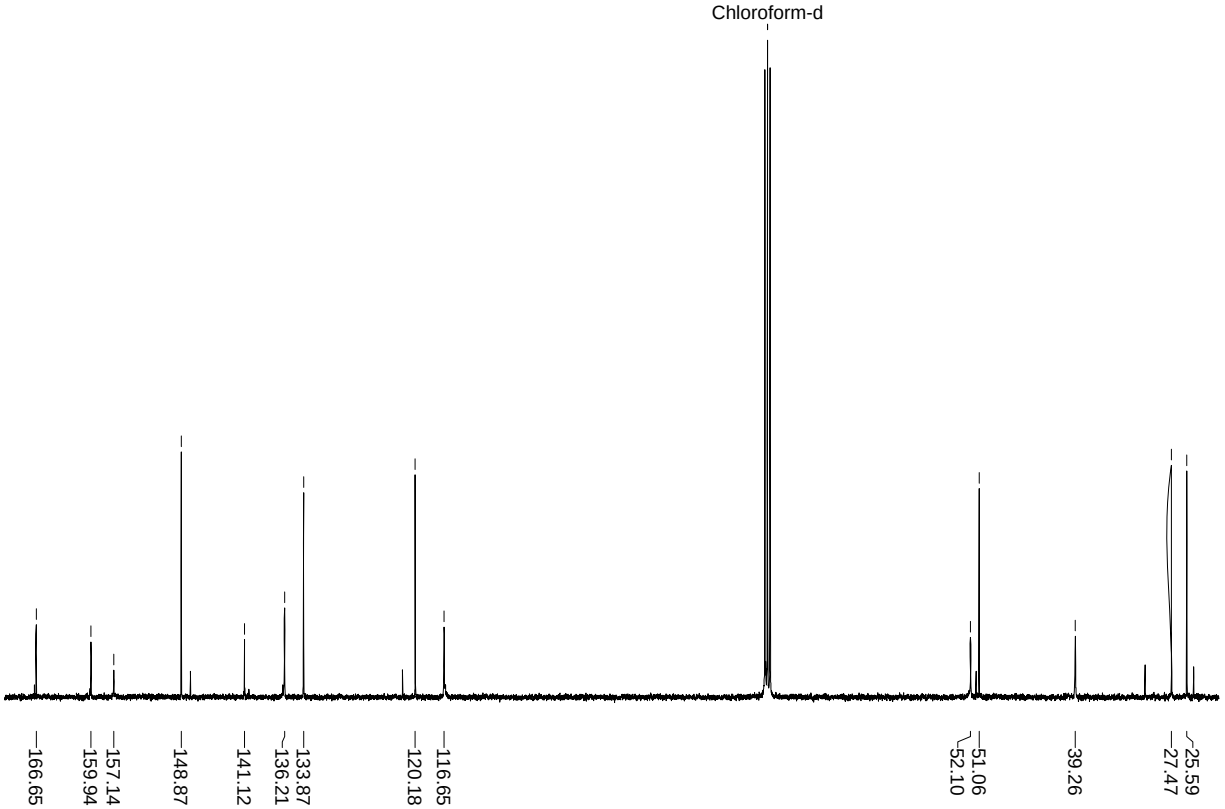
**8-10**

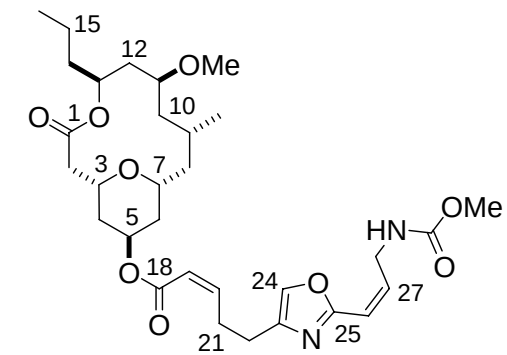

Chloroform-d
160.99
160.61
157.07
143.13
139.34
134.27
115.19
61.16
52.07
39.60
14.14


CO2Me
2
4
N
O
2'
2''
3'
NH
OMe
O
5''

**8-42**

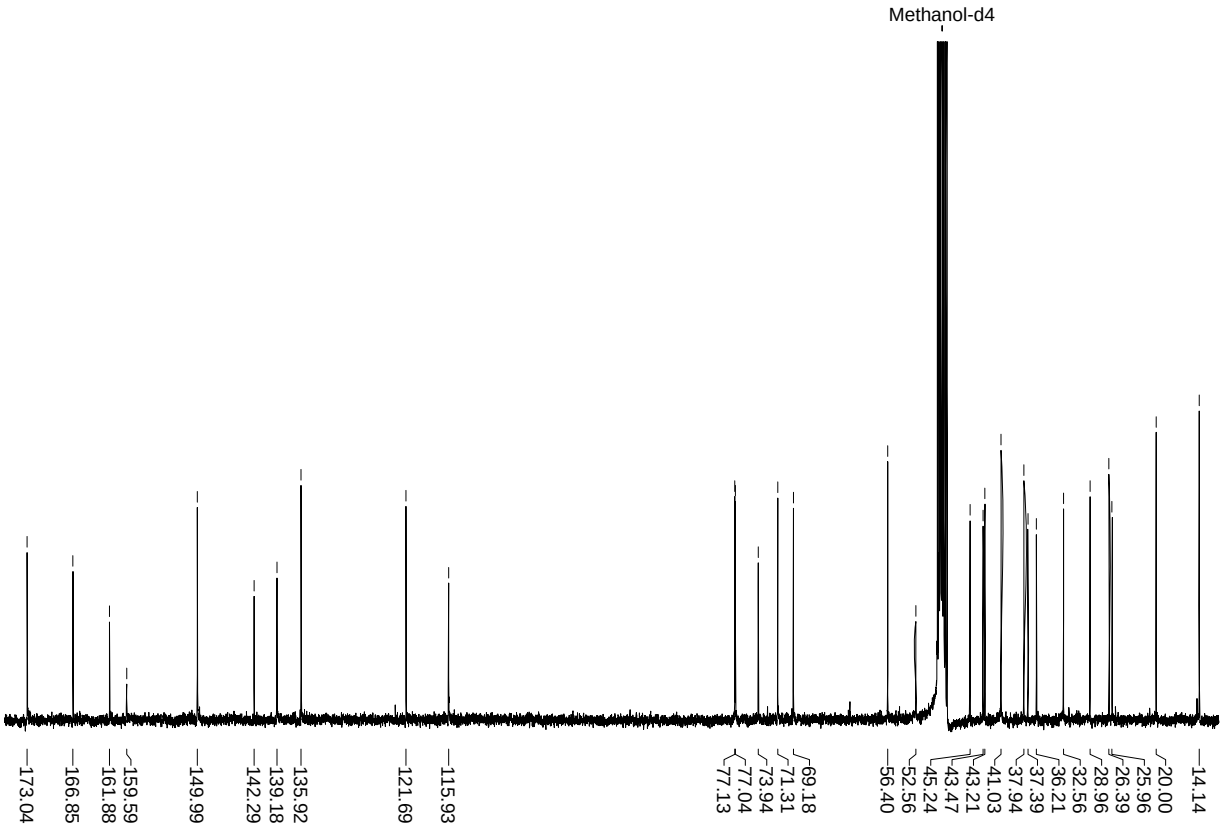

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

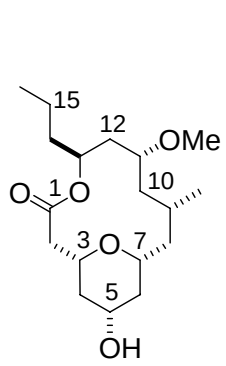

Chloroform-d
166.65
159.94
157.14
148.87
141.12
136.21
133.87
120.18
116.65
52.10
51.06
39.26
27.47
25.59




**Neopeltolide (5-1)**

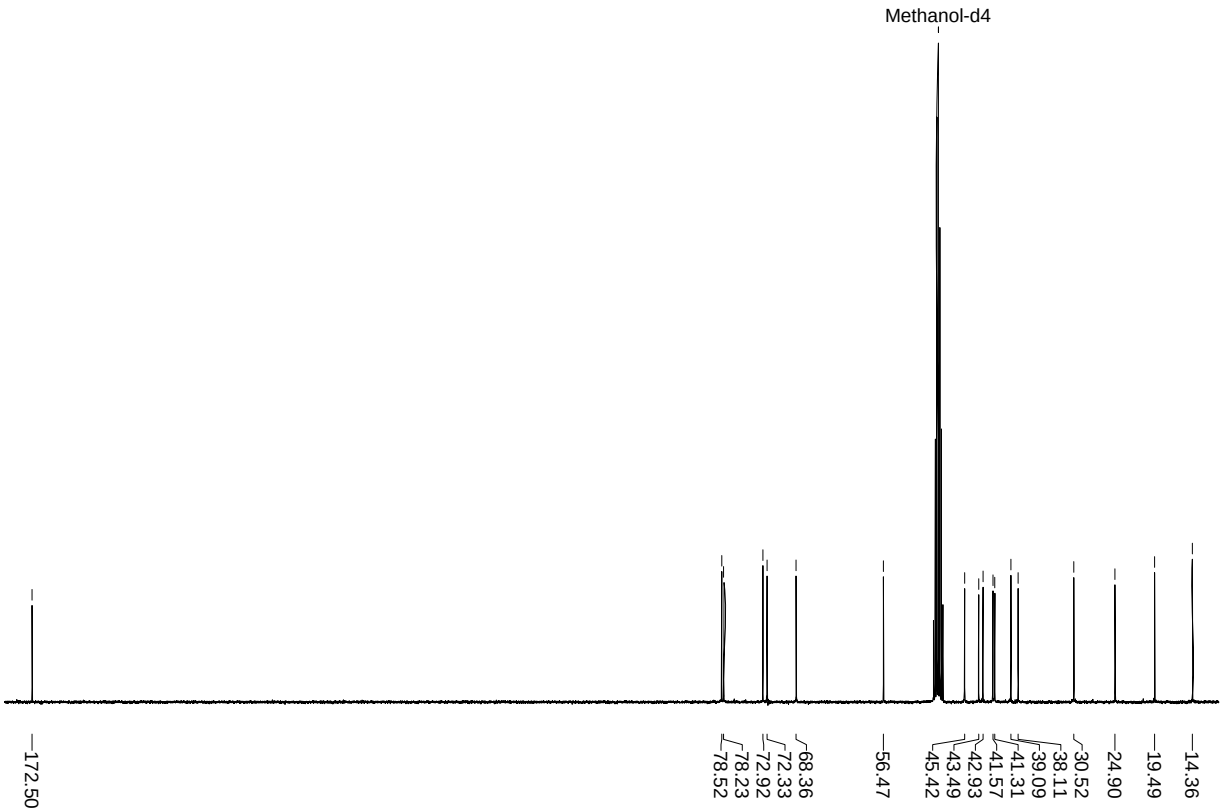


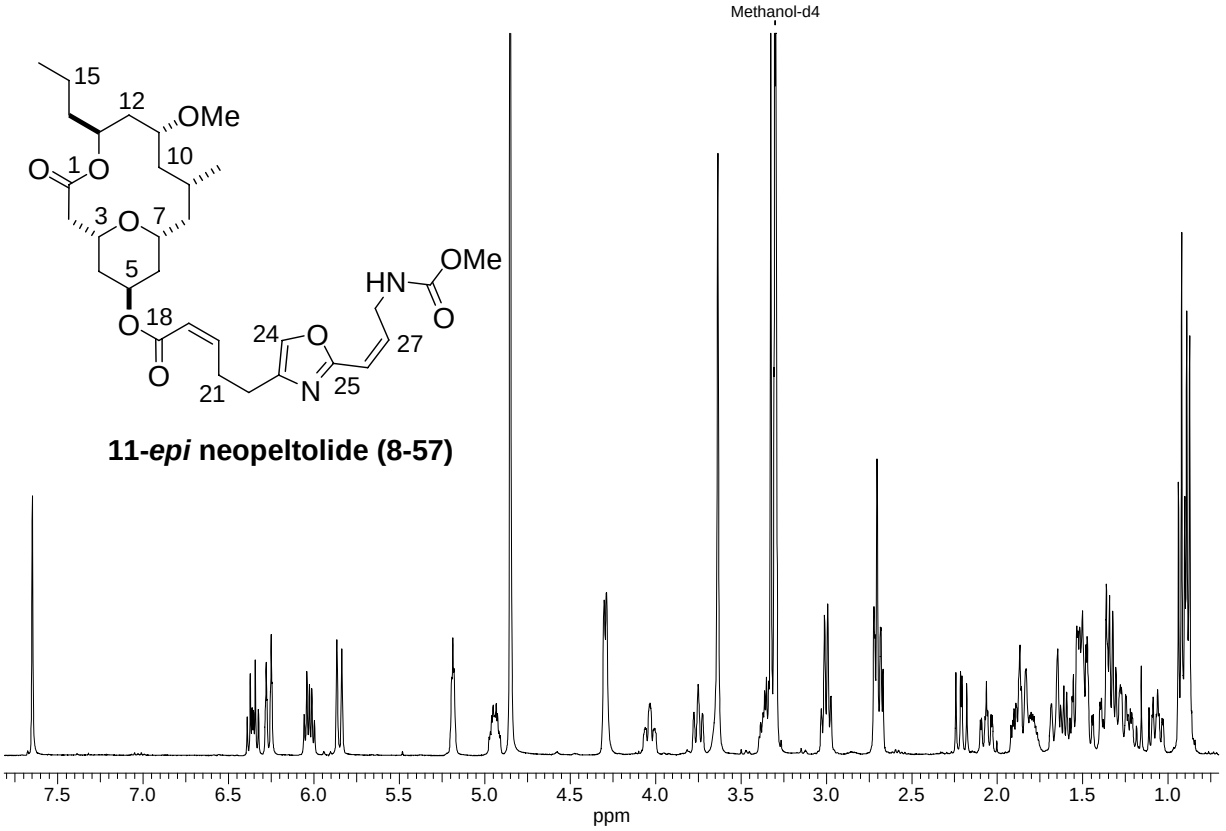




15
12
OMe
10
O
1
O
3
O
7
5
OH

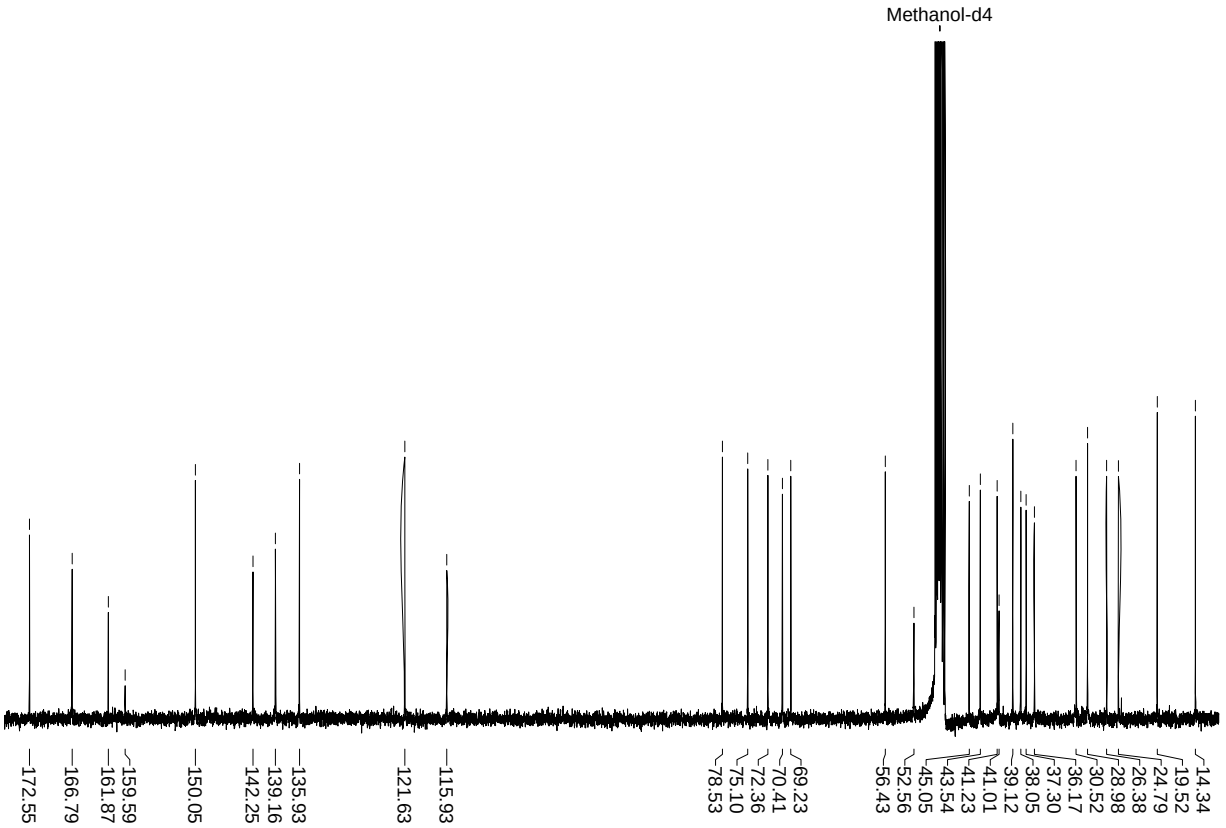
**8-56**

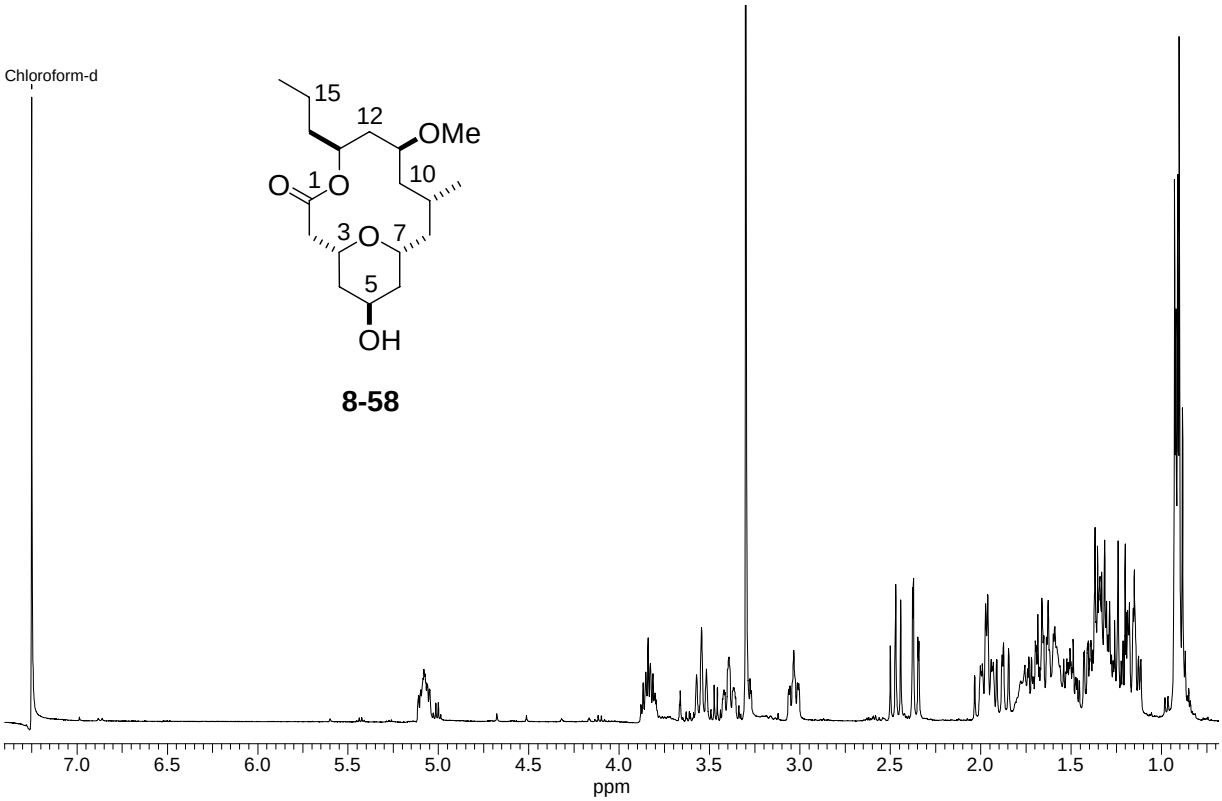

Methanol-d4
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Methanol-d4
172.50
78.52
78.23
72.92
72.33
68.36
56.47
45.42
43.49
42.93
41.57
41.31
39.09
38.11
30.52
24.90
19.49
14.36

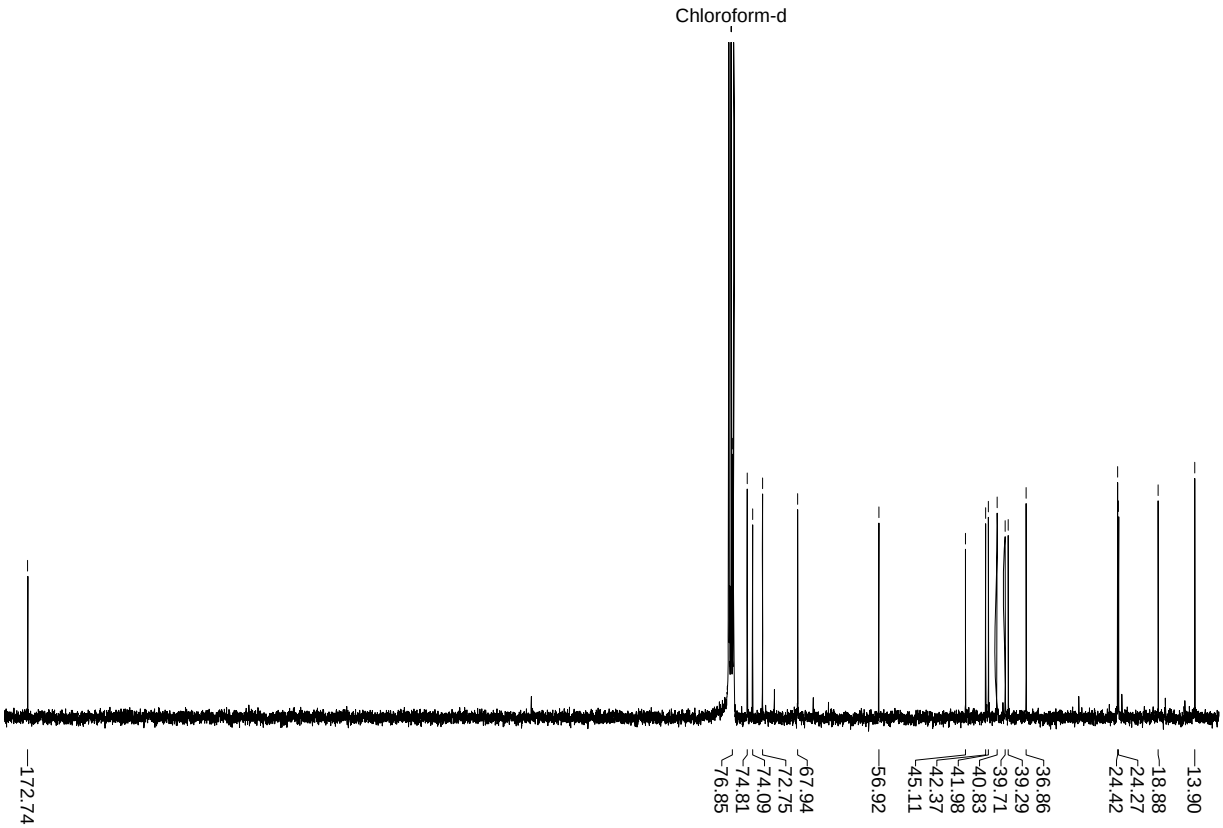


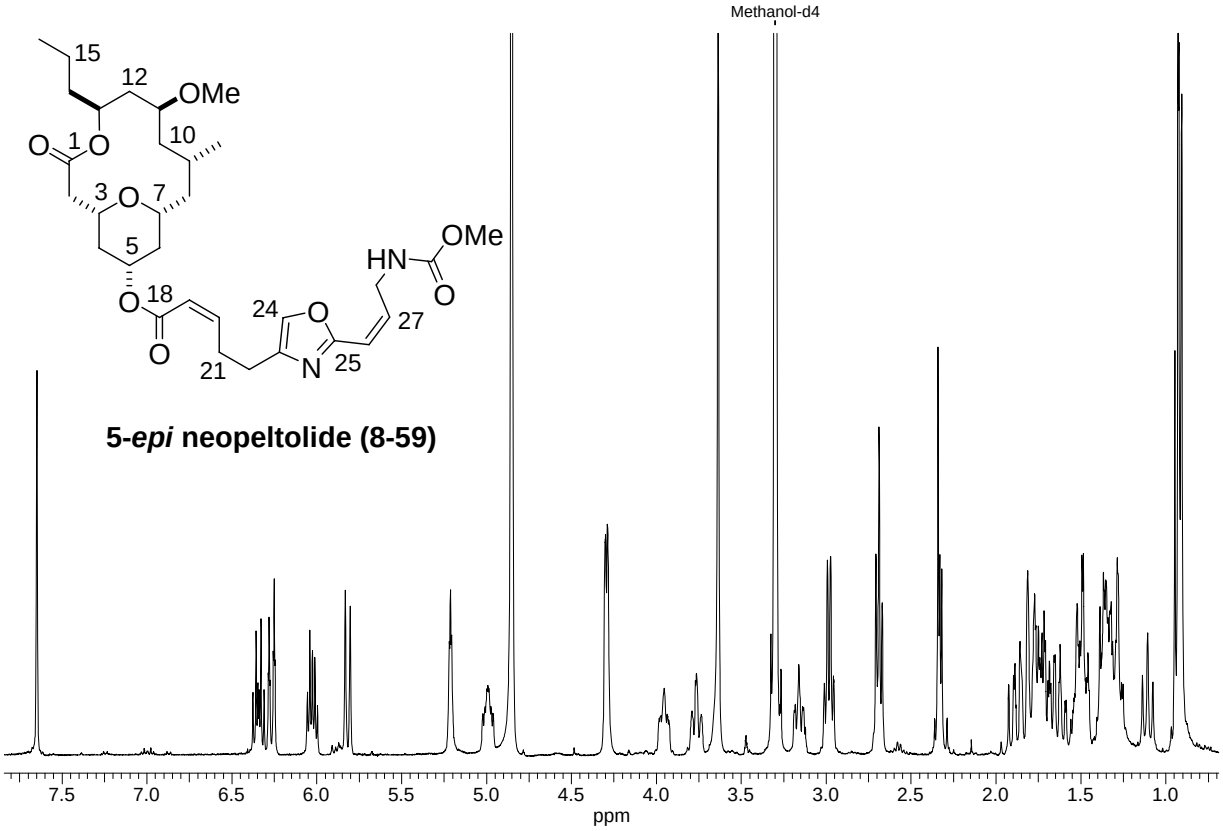

**11-*epi* neopeltolide (8-57)**



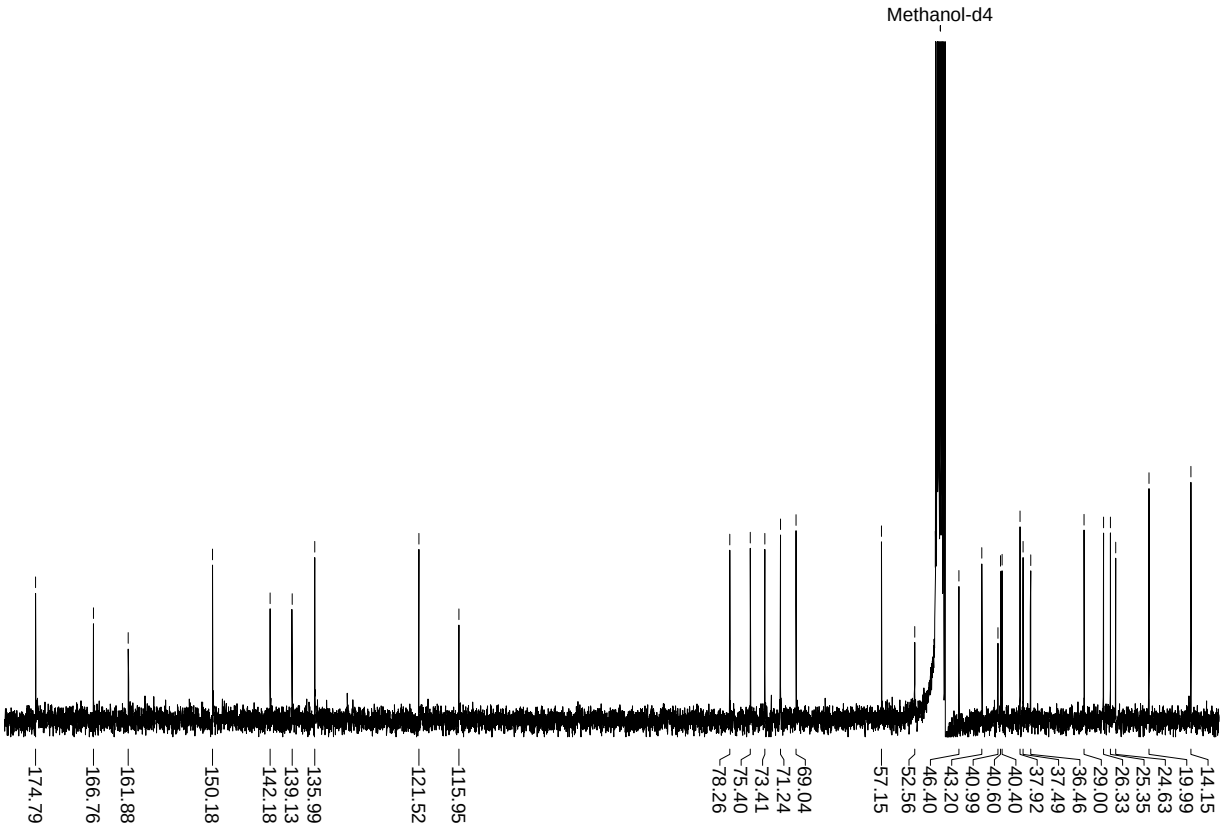

Chloroform-d
15
12
OMe
10
O
1
O
3
O
7
5
OH
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

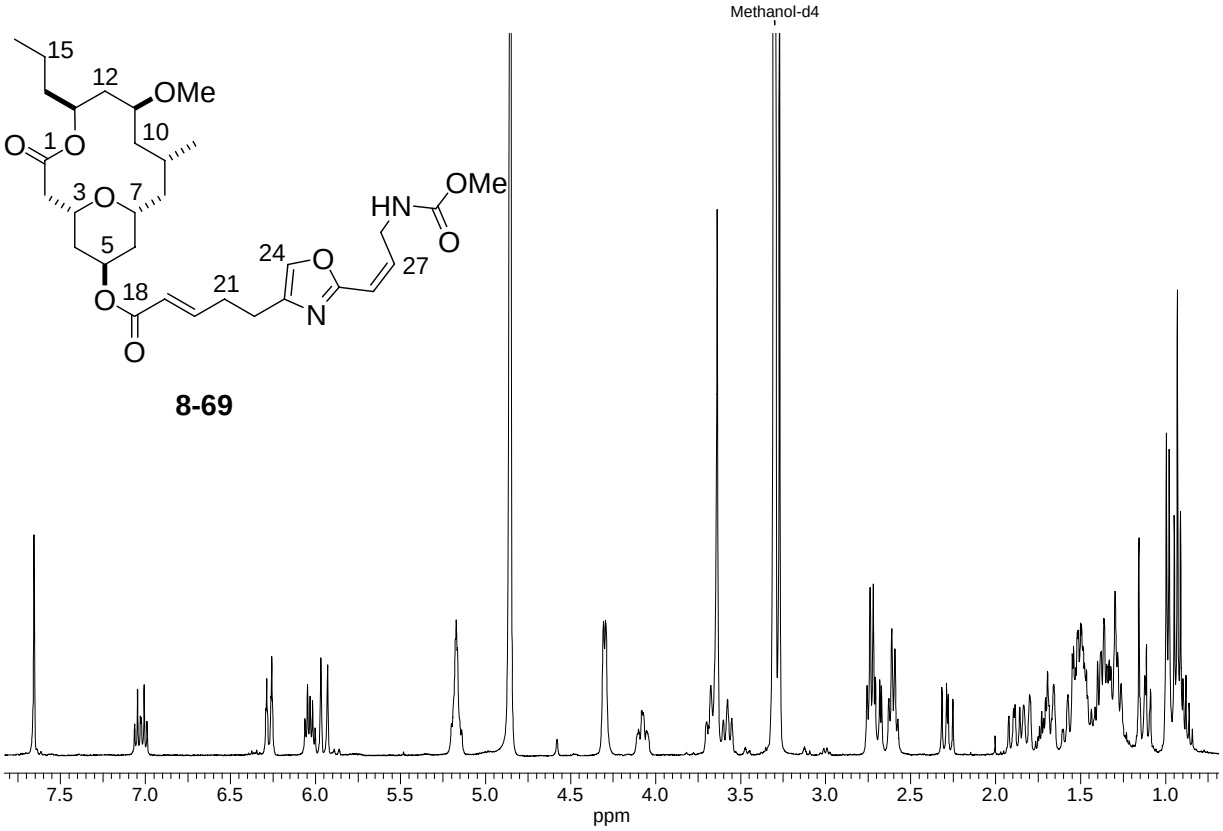
**8-58**


Chloroform-d
172.74
76.85
74.81
74.09
72.75
67.94
56.92
45.11
42.37
41.98
40.83
39.71
39.29
36.86
24.42
24.27
18.88
13.90

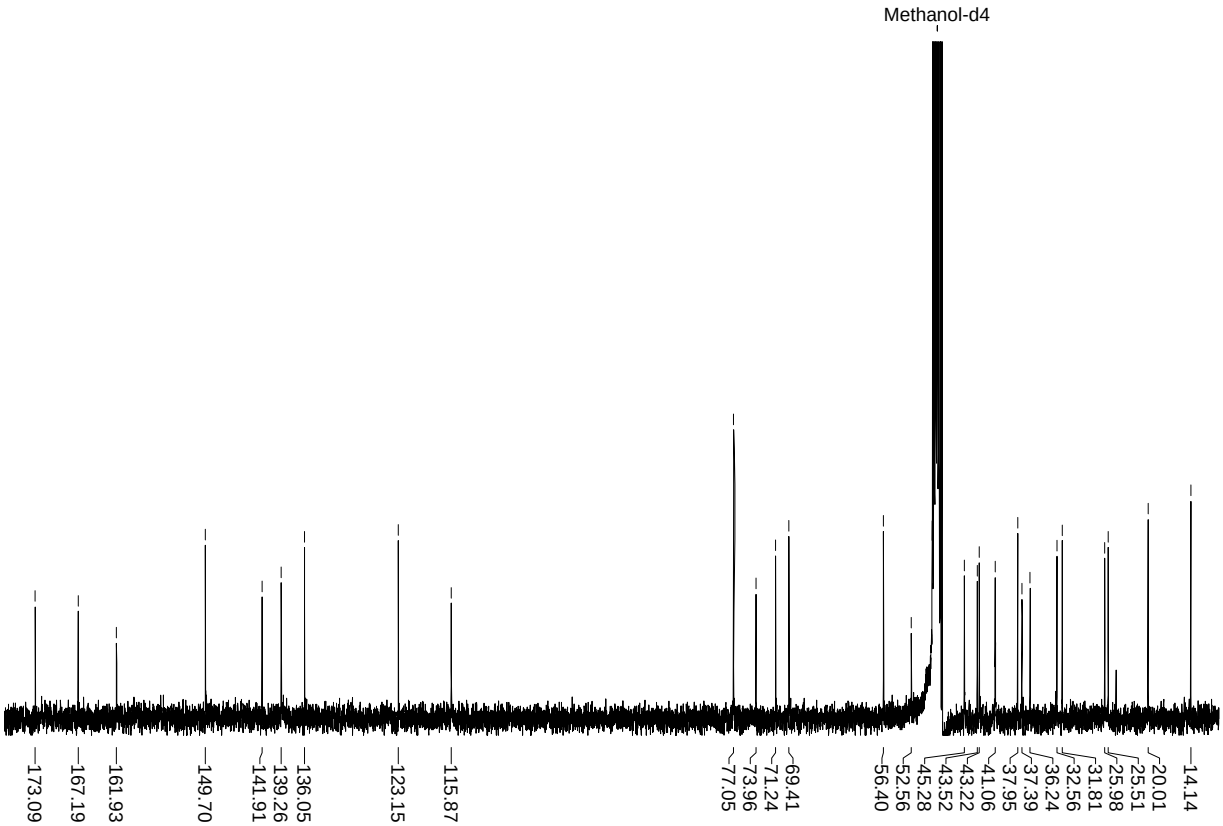


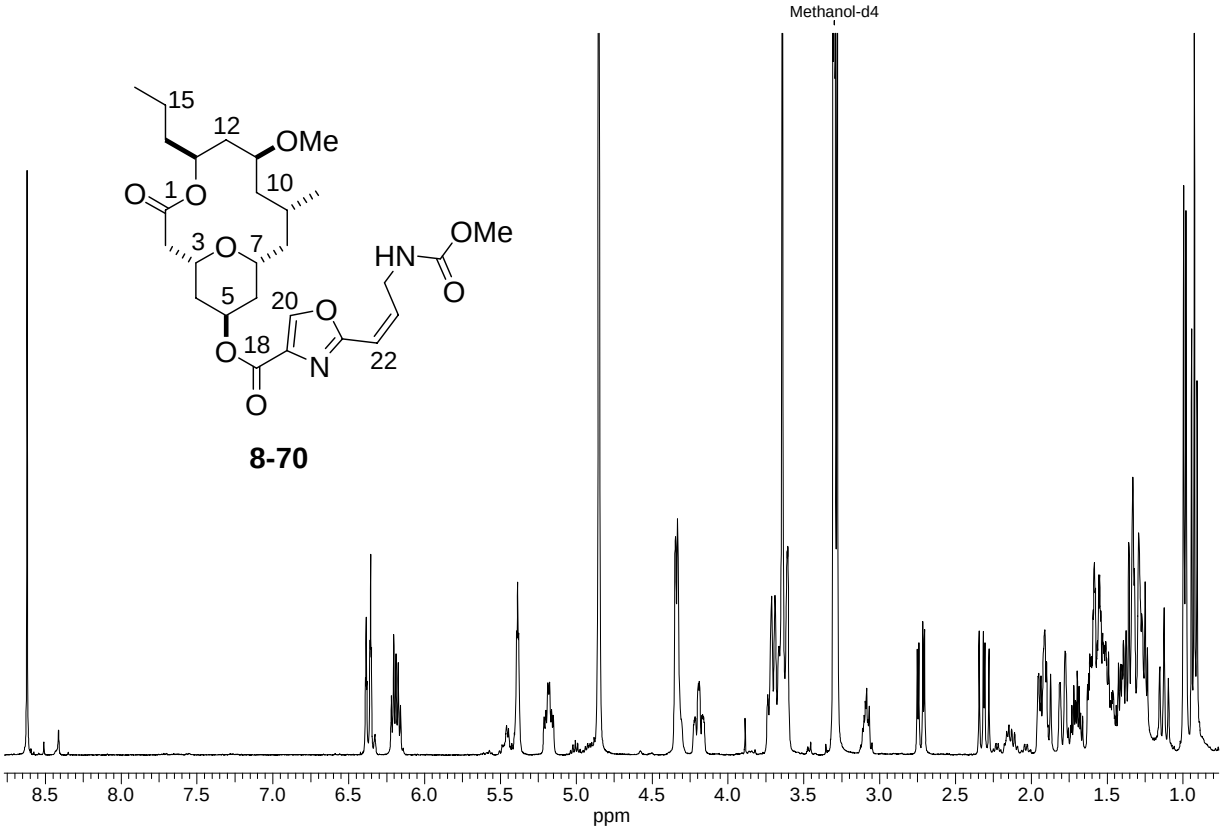

**5-*epi* neopeltolide (8-59)**



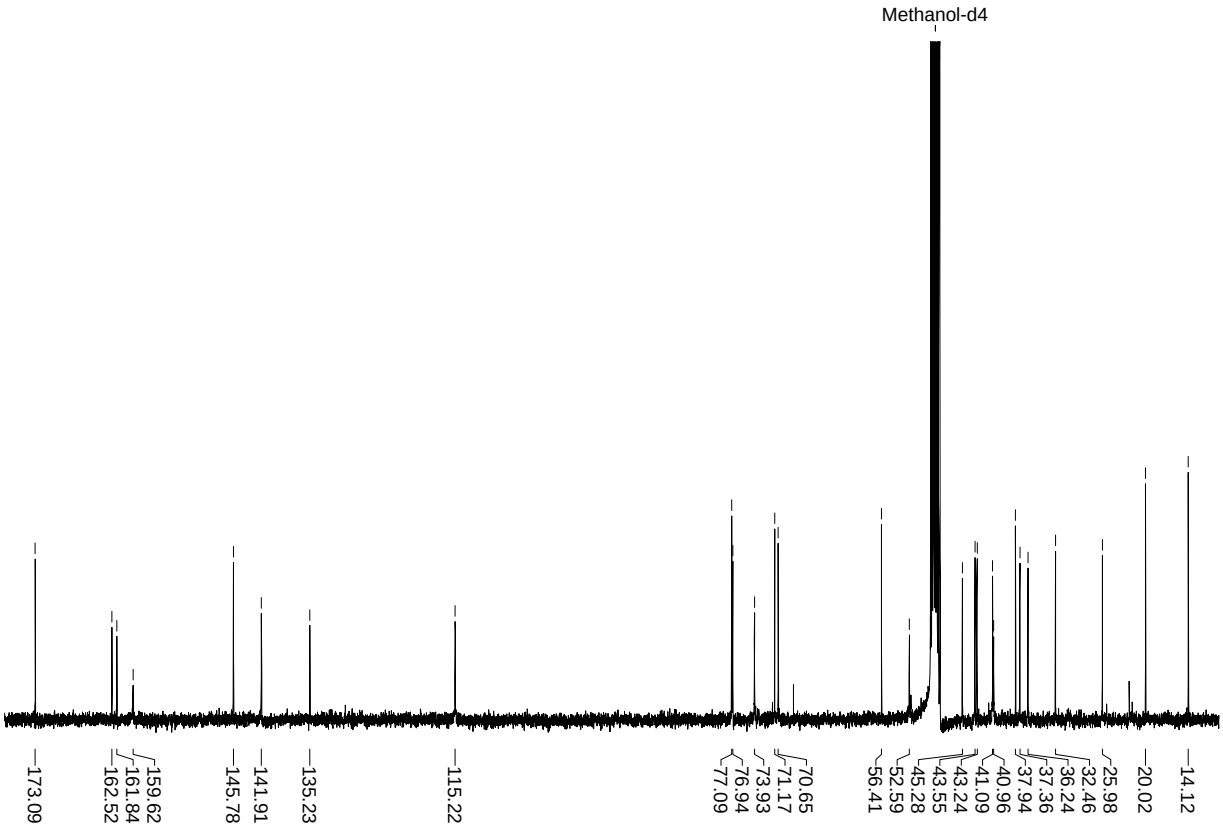

Methanol-d4
15
12
OMe
10
O
1
O
3
O
7
5
O
18
O
21
24
O
27
N
HN
OMe
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

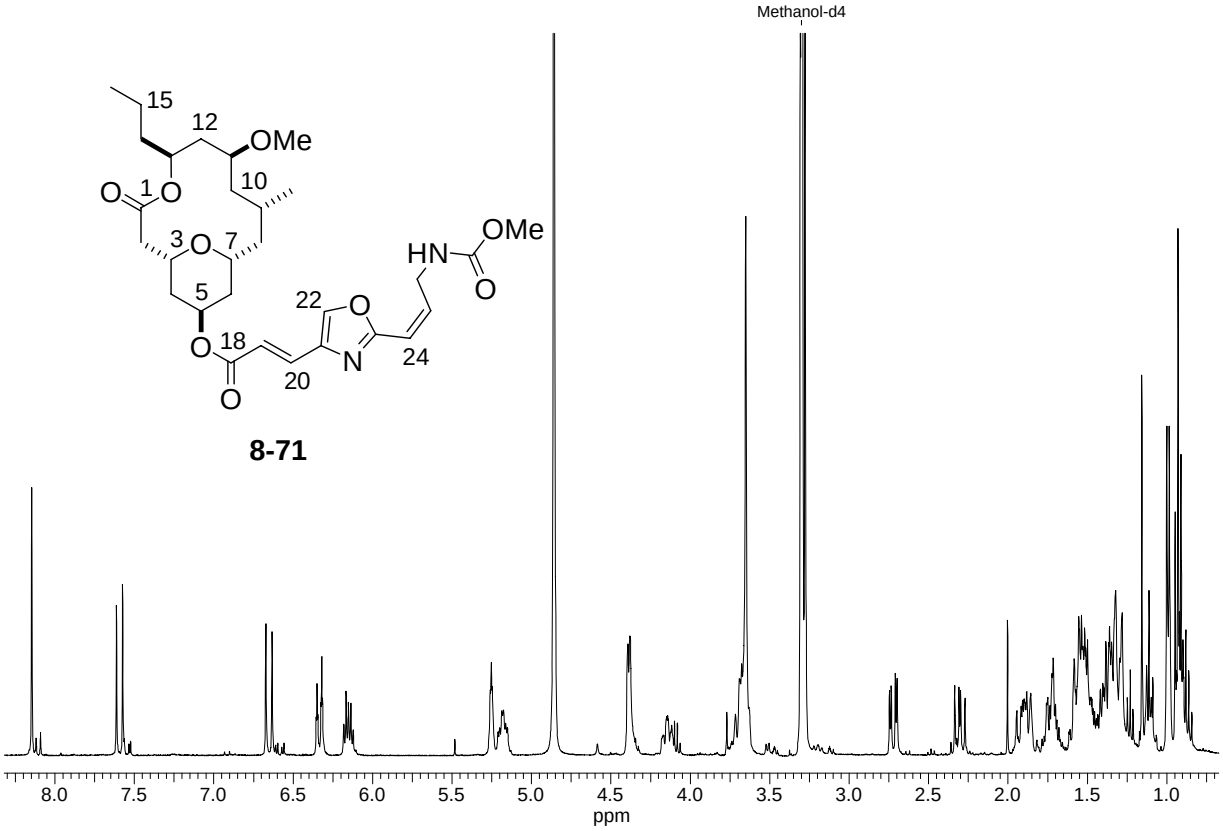
**8-69**


Methanol-d4
173.09
167.19
161.93
149.70
141.91
139.26
136.05
123.15
115.87
77.05
73.96
71.24
69.41
56.40
52.56
45.28
43.52
43.22
41.06
37.95
37.39
36.24
32.56
31.81
25.98
25.51
20.01
14.14

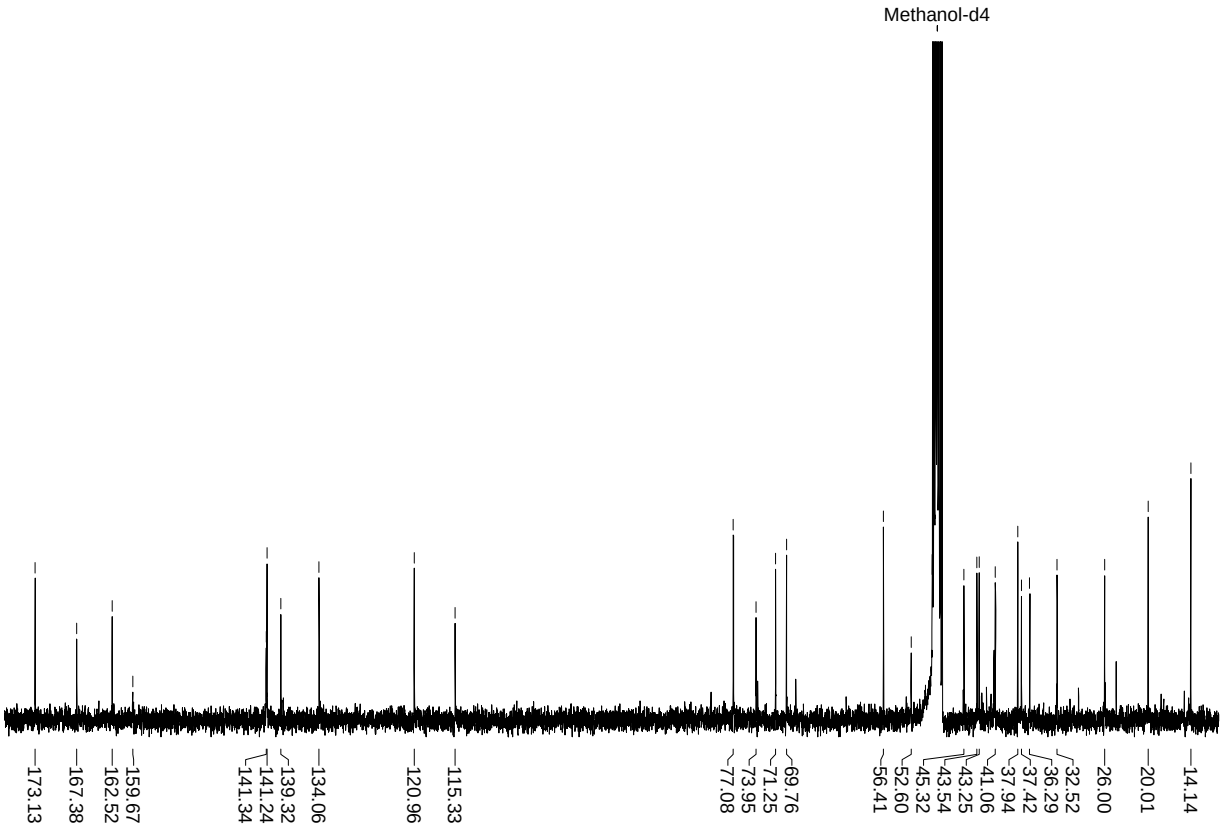

Methanol-d4
15
12
OMe
10
O 1 O
3 O 7
5
20 O
O 18
N
22
HN
OMe
O
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

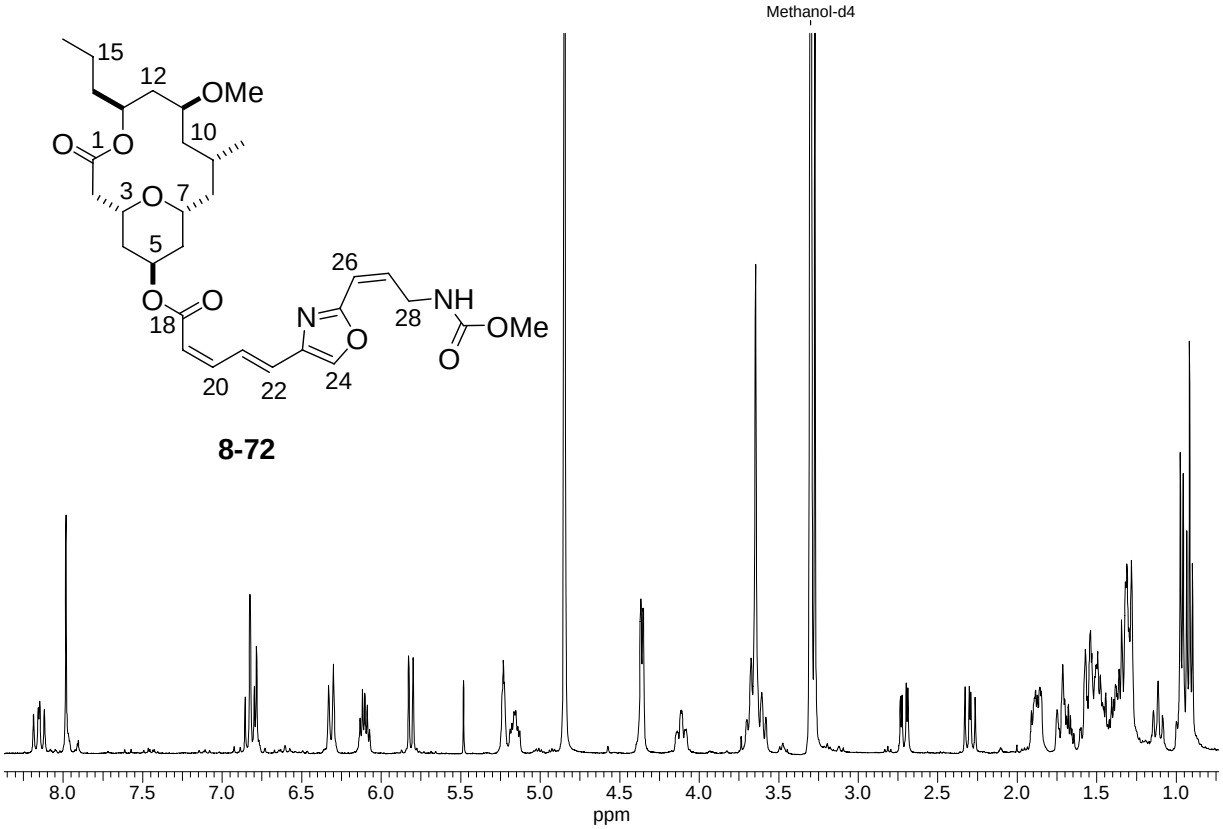
**8-70**


Methanol-d4
173.09
162.52
161.84
159.62
145.78
141.91
135.23
115.22
77.09
76.94
73.93
71.17
70.65
56.41
52.59
45.28
43.55
43.24
41.09
40.96
37.94
37.36
36.24
32.46
25.98
20.02
14.12

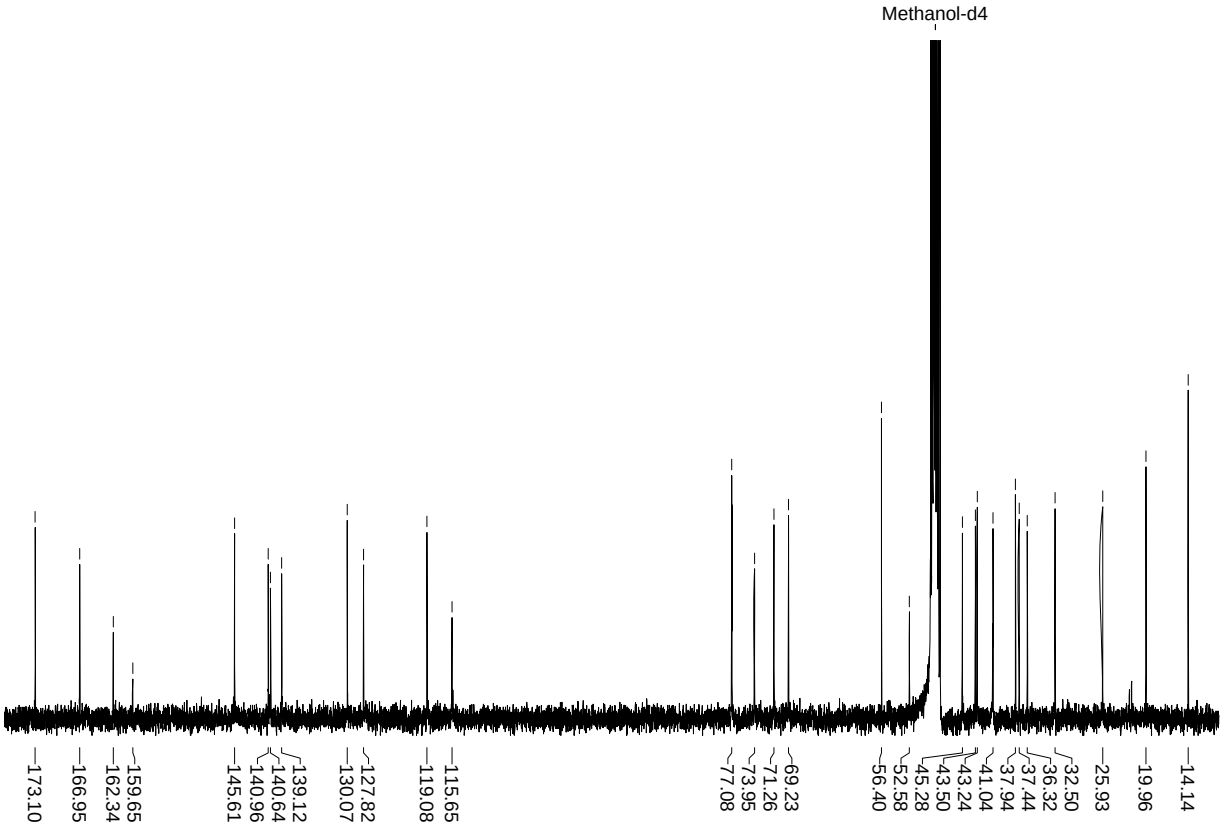

Methanol-d4
15
12
OMe
10
O
1
O
3
O
7
5
O
18
O
22
O
N
24
20
HN
OMe
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

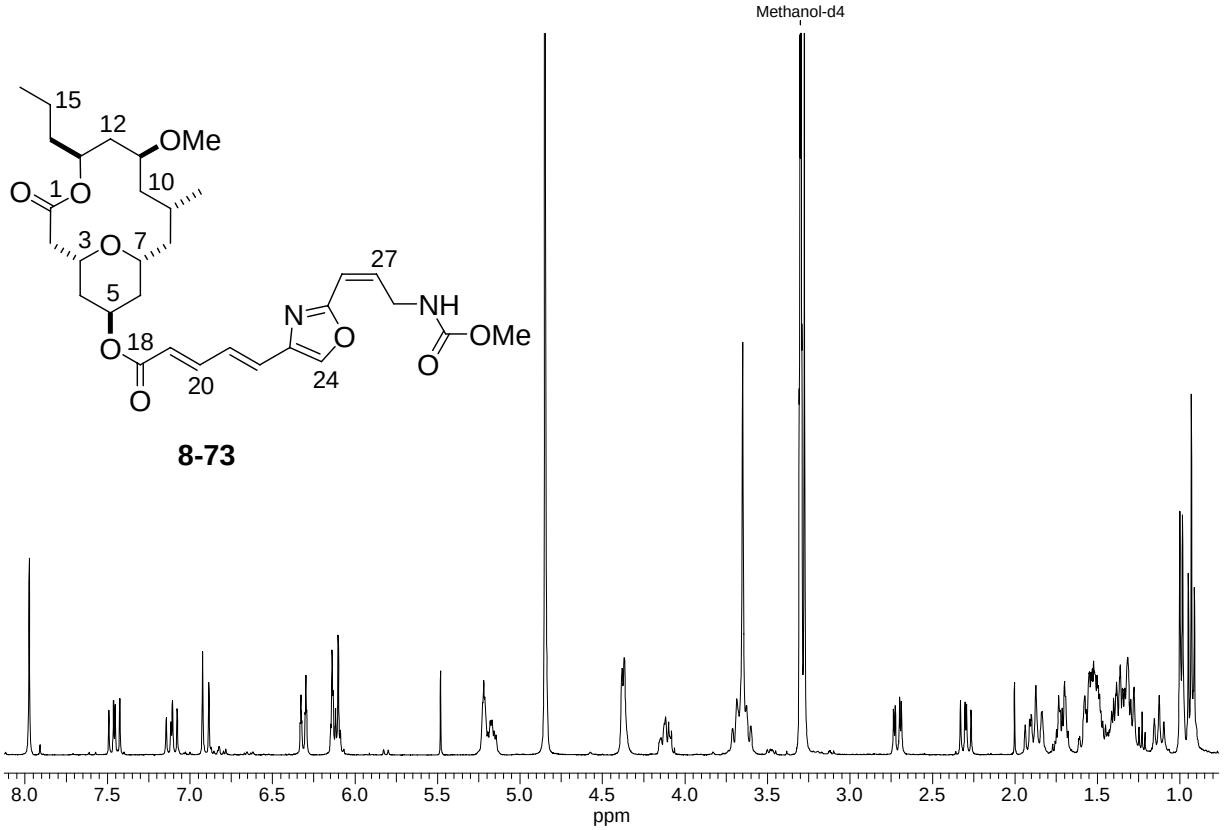
**8-71**


Methanol-d4
173.13
167.38
162.52
159.67
141.34
141.24
139.32
134.06
120.96
115.33
77.08
73.95
71.25
69.76
56.41
52.60
45.32
43.54
43.25
41.06
37.94
37.42
36.29
32.52
26.00
20.01
14.14

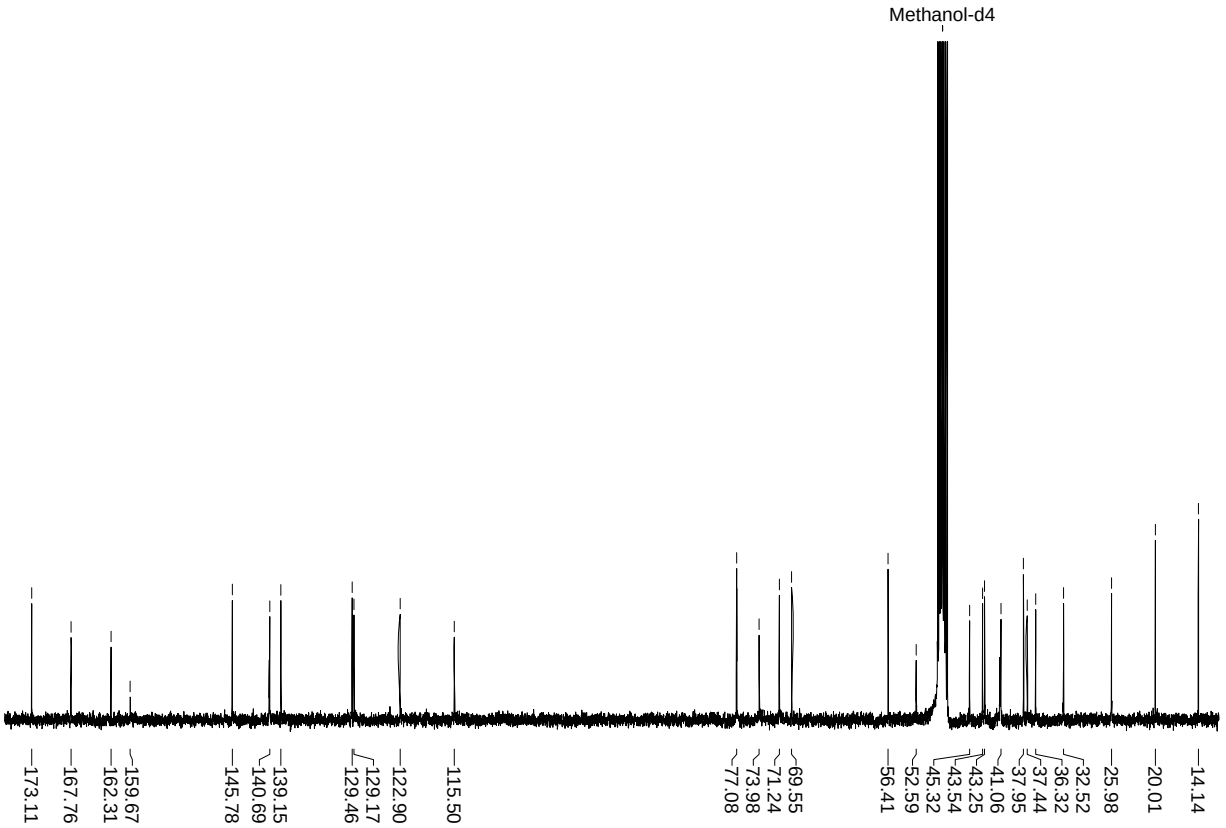

Methanol-d4
15
12
OMe
10
O
1
O
3
O
7
5
O
O
18
26
N
O
NH
28
OMe
O
20
22
24
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

**8-72**


Methanol-d4
173.10
166.95
162.34
159.65
145.61
140.96
140.64
139.12
130.07
127.82
119.08
115.65
77.08
73.95
71.26
69.23
56.40
52.58
45.28
43.50
43.24
41.04
37.94
37.44
36.32
32.50
25.93
19.96
14.14


Methanol-d4
15
12
OMe
10
O
1
O
3
O
7
5
O
18
O
20
24
N
O
27
NH
OMe
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

**8-73**


Methanol-d4
173.11
167.76
162.31
159.67
145.78
140.69
139.15
129.46
129.17
122.90
115.50
77.08
73.98
71.24
69.55
56.41
52.59
45.32
43.54
43.25
41.06
37.95
37.44
36.32
32.52
25.98
20.01
14.14

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