(–)-Disorazole C_1 and New Analogs: Total Synthesis and Biological Evaluation

Dissertation

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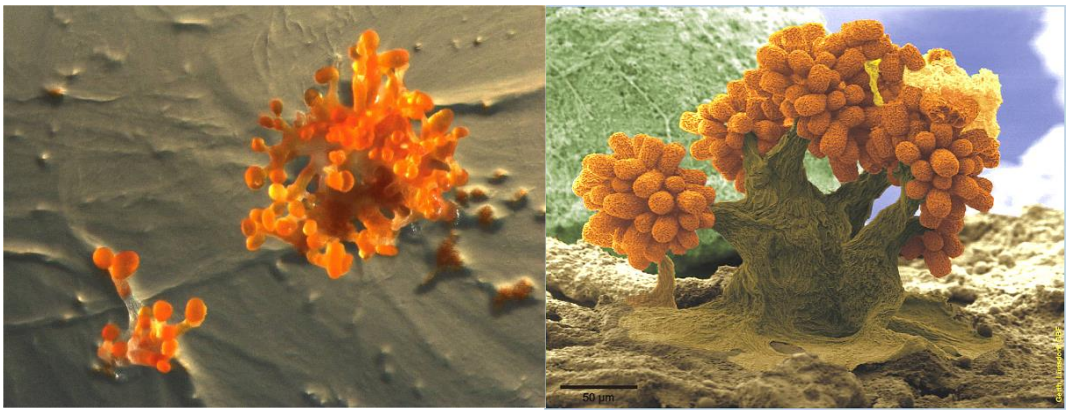
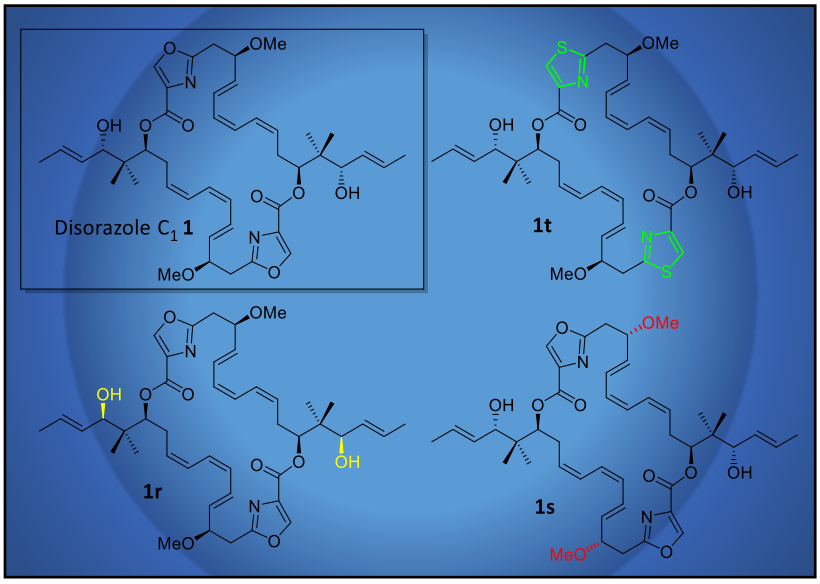
Abstract

The disorazoles represent a family of powerful cytotoxic natural products isolated in 1994 from the myxobaterium *Sorangium cellulosum* So ce12. They show a very potent antitubulin activity and a suitable biological profile to be considered as possible candidates for targeted cancer therapy.

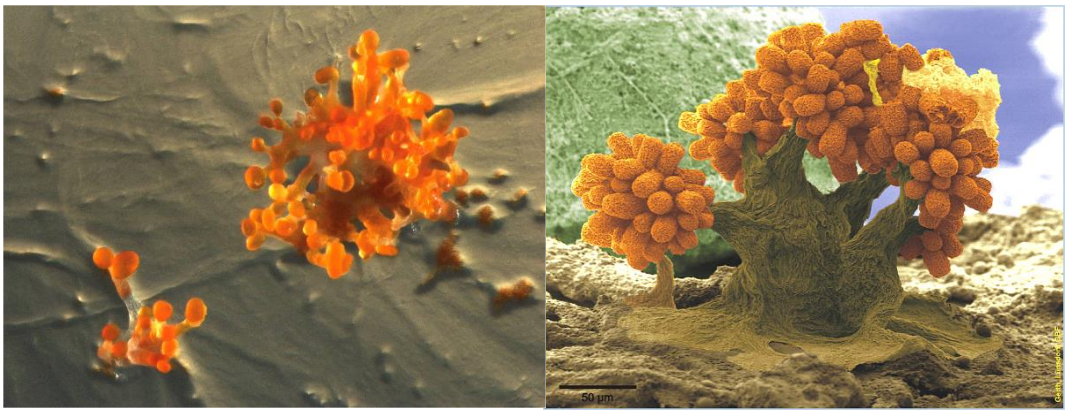


This work, after a brief description of cancer and its treatment, will be focused on this class of compounds. At first, their biological activities and possible therapeutic use will be discussed, followed by a review of previous synthetic efforts. The main section will report a detailed description of a new synthesis of disorazole C_1 **1**, which is based on a key intermediate of epothilone A synthesis in order to solve one of the major stereochemical issues. The convergent strategy was also employed to produce three novel derivatives (**1t**, **1r** and **1s**), and the final section will discuss the results of preliminary biological evaluations of these analogs and future perspective.

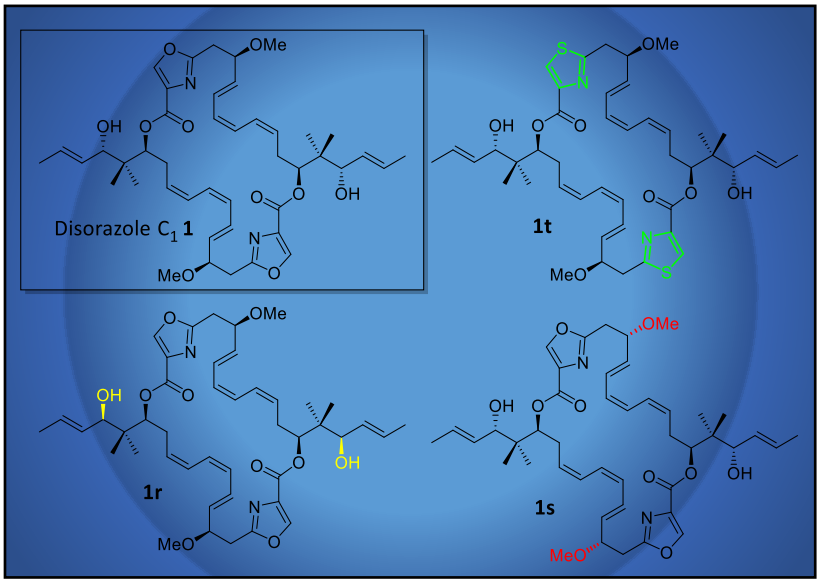


Zusammenfassung

Die Disorazole stellen eine Familie stark zytotoxischer Naturstoffe dar, die 1994 aus dem Myxobaterium *Sorangium cellulosum* So ce12 isoliert wurden. Sie zeigen eine sehr starke Antitubulin-Aktivität und ein geeignetes biologisches Profil, um als mögliche Kandidaten für eine zielgerichtete Krebstherapie in Betracht gezogen zu werden.



Diese Arbeit konzentriert sich, nach einer kurzen Beschreibung von Krebs und seiner Behandlung, auf diese Klasse von Molekülen. Zuerst werden ihre biologischen Aktivitäten und mögliche therapeutische Verwendung diskutiert, gefolgt von einem Überblick über frühere Syntheseversuche. Der Hauptabschnitt enthält eine detaillierte Beschreibung einer neuen Synthese von Disorazol C_1 **1**, die auf einem Schlüsselintermediat der Epothilon A Synthese basiert, um eines der wichtigsten stereochemischen Probleme zu lösen. Die konvergente Strategie wird auch eingesetzt, um drei neue Derivate (**1t**, **1r** und **1s**) herzustellen. Im letzten Abschnitt werden die Ergebnisse vorläufiger biologischer Untersuchungen dieser Analoga bewertet und die Zukunftsperspektive diskutiert.



List of Abbreviations

$(COCl)_2$	oxalyl chloride
AcCl	acetyl chloride
AcOH	acetic acid
ADC	antibody-drug conjugate
$AgNO_3$	silver nitrate
AllylMgBr	allylmagnesium bromide
Aq	aqueous
$B(OMe)_3$	trimethyl borate
$Ba(OH)_2$	bariumhydroxid
BCR	B cell receptor
$BH_3{\cdot}SMe_2$	borane dimethylsulfide
BINOL	1,1'-bi-2-naphthol
Bp	boiling point
$BrCCl_3$	bromotrichloromethane
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
$CHCl_3$	chloroform
$ClCO_2Et$	ethyl chloroformate
CSA	camphorsulfonic acid
$Cu(OAc)_2$	copper acetate
$Cu(OTf)_2$	copper trifluoromethanesulfonate
CuI	copper iodide
$CuSO_4$	copper sulfate
DAST	diethylaminosulfurtrifluoride
DBU	1,8-diazabiciclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCU	1,3-dicyclohexylurea
DDQ	2,2-dichlor-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-mimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
EC_{50}	half-maximal effective concentration
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron ionisation
er	enantiomeric ratio
ERM	Ezrin-Radixin-Moesin
ESI	electrospray ionization
Et_2O	diethylether

EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
FW	formula weight
GAS	group A *Streptococcus*
H_2SiF_6	hexafluorosilicic acid
H_2SO_4	sulfuric acid
HBr	hydrogen bromide
HCl	hydrogen chloride
HCOOH	formic acid
HF	hydrogen fuoride
HOBT	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HYTRA	2-hydroxy-1,2,2-triphenylethylacetate
IC_{50}	half-maximal inhibitory concentration
ICH_2PPh_3I	iodomethyltriphenylphosphonium iodide
$Ipc_2BAllyl$	allyldiisopinocampheylborane
Ipc_2BH	diisopinocampheylborane
Ipc_2BOMe	methoxydiisopinocampheylborane
IR	infrared spectroscopy
K_2CO_3	potassium carbonate
KCN	potassium cyanide
KHMDS	potassium bis(trimethylsilyl)amide
LAH = $LiAlH_4$	lithium aluminum hydride
LC-MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
$LiBF_4$	lithium tetrafluoroborate
LiHMDS	lithium bis(trimethylsilyl)amide
LiOH	lithium hydroxide
M	molar
mAbs	monoclonal antibodies
mdr	multi-drug resistant
Me_3OBF_4	trimethyloxonium tetrafluoroborate
MeMgBr	methylmagnesium bromide
MeOH	methanol
Mg	magnesium
MIC	minimum inhibitory concentration
mL	milliliter
mM	millimolar
mmol	millimol
MOM	methoxymethyl
MOMCl	methoxymethyl chloride
Mp	melting point
MS	mass spectrometry or molecular sieves
MTPA-Cl	α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate

NaHMDS	sodium bis(trimethylsilyl)amide
$NaHSO_4$	sodium hydrogen sulfate
NaOH	sodium hydroxide
NBS	*N*-bromosuccinimide
***n*-Bu_3SnH**	tributyltin hydride
***n*-Bu_4NHSO_4**	tetra-*n*-butylammonium hydrogen sulfate
***n*-BuLi**	*n*-butyl lithium
NEt_3	trimethylamine
NH_4Cl	ammonium chloride
$Ni(acac)_2$	nickel acetylacetonate
nM	nanomolar
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
***n*-PrSH**	*n*-propanethiol
O_2	oxygen
O_3	ozone
P_4O_{10}	phosphorus pentoxide
$PdCl_2(CH_3CN)_2$	bis(acetonitrile)palladium dichloride
$PdCl_2(PPh_3)_2$	bis(triphenylphosphine)palladium chloride
Pgp	P-glycoprotein
PhMgBr	phenylmagnesium bromide
Pin	pinacolato
pM	picomolar
PMB	*para*-methoxybenzyl
$POCl_3$	phosphorus oxychloride
PPh_3	triphenylphosphine
PPTS	pyridinium *para*-toluenesulfonate
***p*TsOH**	*para*-toluenesulfonic acid
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
R_f	retention factor
RNA	ribonucleic acid
rt	room temperature
SARs	structure-activity relationships
$Sc(OTf)_3$	scandium trifluoromethanesulfonate
SerOMe·HCl	serine methyl ester hydrochloride
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
***t*BuOK**	*tert*-butoxide
TCBC	2,4,6-trichlorobenzoyl chloride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
Tf_2NPh	*N*-phenyl-bis(trifluoromethanesulfonate)
Tf_2O	triflic anhydride
TFFH	tetramethylfluoroformamidinium hexafluorophosphate
THF	tetrahydrofuran
Ti(O*i*Pr)$_4$	titanium tetraisopropoxide
TiF_4	titanium tetrafluoride

TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
TMS	trimethylsilyl
TMSBr	bromotrimethylsilane
TMSCl	trimethylsilyl chloride
TMSI	iodotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Triflate	trifluoromethanesulfonate
TFAA	trifluoroacetic anhydride
$ZnBr_2$	zinc bromide
µL	microliter

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1. Introduction

Cancer is the second leading cause of death in Europe and in the United States, right after cardiovascular diseases, with 158.3 deaths every 100,000 people per year and an incidence of 442.2 every 100,000 people per year (based on 2013–2017 in the US).[1] In 2020, there were 19.3 million new cases and 9.9 million cancer-related deaths worldwide and the numbers are expected to increase in 20 years. Fortunately, the overall cancer death rates have decreased since the early 1990s by 1.8% per year among men and 1.4% among women,[2] thanks to the recent progress made after several years of research in the field of oncology.

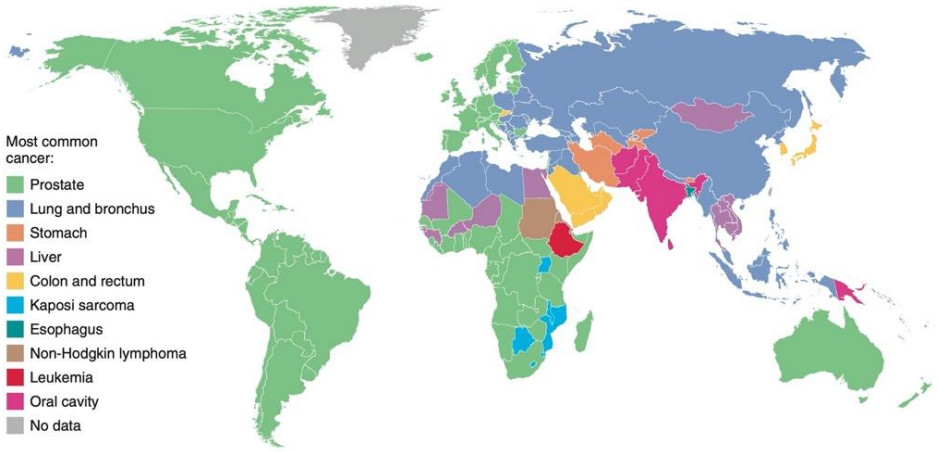


Figure 1.1: Worldwide variation of cancer incidence in males.[3]

Besides the statistics, neoplastic diseases represent an important cause of physical and mental suffering, in spite of the development of new chemotherapeutic schemes with reduced side effects. Moreover, similarly to what happens for the antimicrobial therapy, neoplastic cells may also develop a resistance to antitumor drugs, which leads to a constant search for new molecules with biological activity against cancer. For this reason, the disorazole family,[4] a group of 31 macrodiolides isolated from the fermentation broth of myxobacteria strain *Sorangium cellulosum* So ce12,[5] has always been of great interest since its discovery, because of the high cytotoxicity of these compounds.

1.1. Background

1.1.1. Definition and Classification of Tumors

A tumor or *neoplasia* can be defined as a disorder of cell growth triggered by a series of acquired mutations affecting a single cell and its clonal progeny.[3] Human cells normally receive specific signals telling them to grow and multiply (cell division) or to die (*apoptosis*: programmed cell death), sometimes this process fails and abnormal or damaged cells grow uncontrollably.

Tumors are classified as *benign* when they do not spread into nearby tissues, whilst *malignant* tumors can invade surrounding structures and disseminate to distant sites, forming *metastasis*. *Benign* tumors remain localized and are considered relatively innocent, but they can still cause serious symptoms and be life threatening.

Malignant tumors are generally referred to as cancers (derived from the Latin word for crab) and the most common types of cancer are breast, prostate, lung and colorectal cancer, but cancer can start in every part of the human body, since the cell is the fundamental element of every organ and tissue. **Figure 1.1** shows the worldwide incidence of the most common cancers in males.

1.1.2. Development of Cancer

In the last decades, huge steps have been made towards the comprehension of the basis of cancer. Nevertheless, cancer is not a single disease, but a group of disorders with different molecular origins and therefore different responses to treatment.

Despite the complexity of the disease, there is a common starting point: cancer results from a genetic damage (mutation), which may be caused by environmental exposure, such as with chemical substances, radiations or viruses, may be inherited or some of them can also be spontaneous. Our system normally kills cells with damaged DNA, but when a damaged cell is able to avoid *apoptosis*, it turns into a cancerous cell. Thus, a tumor derives from the clonal expansion of a single damaged cell.[3]

The genetic mutations that contribute to develop a cancer tend to affect four classes of regulatory genes:

- **Proto-oncogenes:** growth-promoting genes. Alterations in these genes result in excessive functions of the cell, included growing and surviving when they are

supposed to die. The affected gene may become in this case a cancer-causing gene or *oncogene*.

- **Tumor suppressor genes:** growth-inhibiting genes. Mutations affecting tumor suppressor genes can cause a loss of function and consequent uncontrolled division.
- ***Apoptosis*-regulating genes:** genes regulating programmed cell death. They may acquire mutations generating enhanced survival of the cell.
- **DNA repair genes:** Altering these genes implies impairing the ability of the cell to recognize and repair genetic damage in other genes, resulting in a genomic instability.

The occurrence of a mutation in the gene is just the first step for the formation of a cancer, but the carcinogenesis is a multiphasic process, resulting from the accumulation of consecutive mutations. The first mutation is called *initiating mutation* and it is maintained in all of the cancerous cells, but many other mutations occur in the initiated cells, contributing to the development of the *neoplasia*. Hence, although most of the tumors have a monoclonal origin, they become very heterogeneous and progressively more aggressive over time.

1.1.3. Characteristics of a Cancerous Cell

What happens to the cells after they become cancerous? Since numerous mutations can occur after the initiating one, it is very difficult to answer this question, because every tumor presents different features. However, there are some fundamental changes in the physiology of a cancerous cell (**Figure 1.3**):[1,3]

- **Self-sufficiency in growth signals:** normal cells only grow in the presence of a signal telling them to grow; cancerous cells are able to grow without external stimuli.
- **Insensitivity to inhibitory signals:** they ignore signals of *apoptosis* or other signals that stop proliferation.
- **Warburg effect:** tumor cells usually rely on aerobic glycolysis, which enables a more rapid cell growth.
- **Sustained angiogenesis:** tumors induce the growth of blood vessels in order to increase the oxygen supply (**Figure 1.2**).

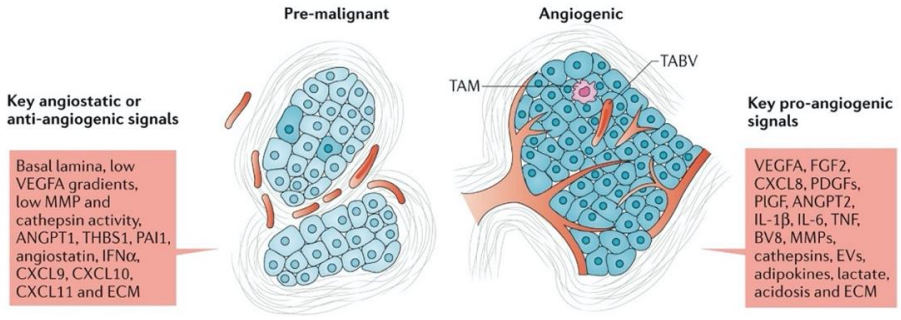


Figure 1.2*:* Representation of tumor-induced angiogenesis. [6]

- **Invasion:** cancerous cells spread into other tissues forming metastasis.
- **Immune evasion:** immune system eliminates damaged cells, but cancer cells hide from the immune response and they can even trick the immune system in protecting the tumor.
- **Immortality:** cancerous cells present stem-like properties that allow them to have limitless proliferative capacity.

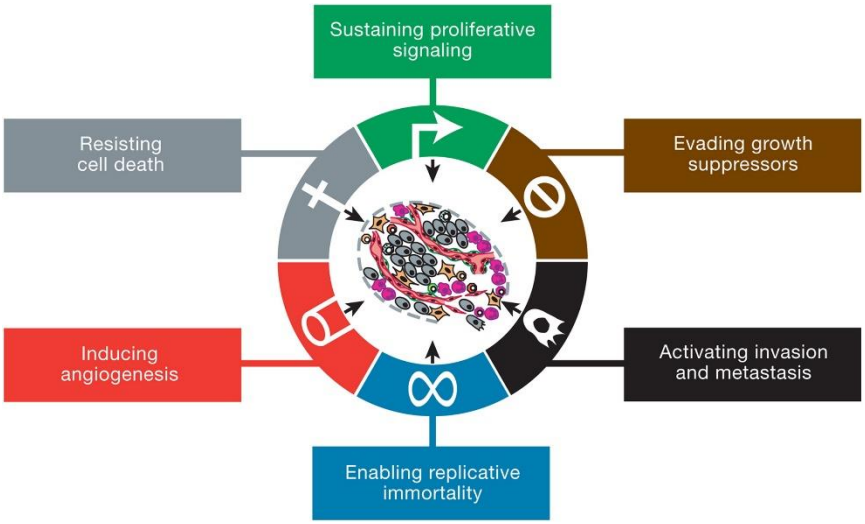


Figure 1.3: Illustration of the main hallmarks of cancer.[7]

1.1.4. Current Treatments in Oncology

As previously mentioned, cancer is a very complex and heterogeneous disease. The symptoms are a result of the different mutations accumulating in the neoplastic cells and they can vary widely, as well as the therapy.

The treatment plan depends on a variety of factors, such as the kind of tumor, the location, the stage (how far the cancer has spread in the body) and the presence or absence of metastasis. Sometimes the goal of the treatment is to eradicate the cancer completely, other times it is to shrink it or stop it from spreading further and prolong the patient's life. Most of

the therapeutic plans include a “palliative care”, which is meant to reduce the side effects of other treatments.

The most common types of cancer treatments are surgery, radiotherapy and pharmacological therapy:

- **Surgery:** Before the discovery of the radiotherapy in the 1920s and chemotherapy in the 1950s, surgical excision was the only option for oncologic patients. Surgery consists in the removal of solid tumors or part of them. It may also be used for diagnostic purpose, because the best way to know the kind of cancer is by taking a small piece of tissue and testing it; this procedure is called biopsy. Surgery is sometimes useful to determine the extension (staging) of the cancer, providing important information for future treatments.[1]

  In case surgery is used to treat cancer, the amount of tumor being removed will depend on the size and the location; if the mass is localized and with distinct margins, surgery can be the main treatment. However, in most cases surgery is used along with other treatments and sometimes it is only able to debulk the cancer, especially when the tumor is located very close to important tissues and the removal of the entire mass would cause too much damage.

- **Radiotherapy:** radiation therapy uses high-energy particles or waves that destroy cancer cell by making small breaks in their DNA; when the DNA is damaged beyond repair, the cells stop dividing or die.[1] The radiations may consist in electromagnetic waves, such as X-rays and gamma rays, or particle beams, such as protons, electrons, heavy ions and radioisotopes. Radiotherapy is also classified as external or internal, based on the source of the radiation: external radiation employs a machine that aims a certain part of the body; while in the internal radiation, the source is put inside the body. The choice of the source and type of radiation also depends on the characteristics of the tumor.

- **Pharmacological therapy:** the possibility to treat cancer through a pharmacological approach, referred to as chemotherapy, has officially begun in 1942, when poisonous compounds used during Second World War, called nitrogen mustards, were found to exhibit therapeutic potential on leukemia.[8] Nevertheless, the initial results were disappointing, showing only a short-term success of the therapy. The subsequent discovery of several other antineoplastic compounds with different

mechanisms of action led to the development of polychemotherapeutic protocols with reduced side effects and higher success rates.[9]

The traditional chemotherapy is based on the cytotoxic effect, which can derive from the interaction with the DNA (alkylation, covalent bonding, oxidative damage), inhibition of the synthesis of DNA and RNA or alteration of the cell cycle and the result is always the death of the cell. Naturally, the cytotoxicity affects not only cancerous cells, but every cell in active proliferation, leading to severe adverse effects.

The recent progress in the comprehension of the molecular basis of cancer has allowed the identification of new molecules having selective targets and potentially decreased side effects. This new pharmacological approach includes hormone therapy, targeted therapy and immunotherapy.

Hormone therapy is the oldest of the three and it is employed for hormone-dependent tumors, such as prostate and breast cancer.

Targeted therapy is referred to treatments that target specific molecules controlling cell growth and division, often using monoclonal antibodies.

Immunotherapy is an emerging treatment that helps the immune system fight the tumor. It has been widely demonstrated the involvement of the immune system in the regulation of tumors and the fact that neoplastic cells have the capability to evade the immune response. Immunotherapy can improve the activity of the immune system against the cancer.

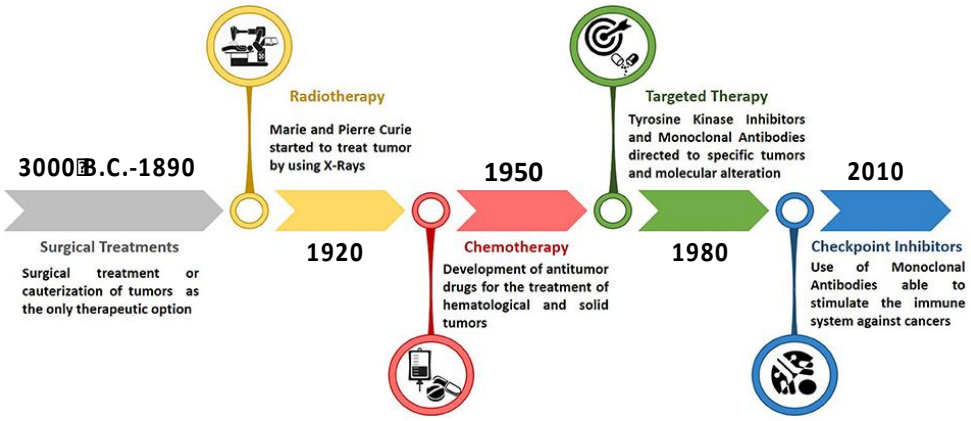


Figure 1.4: Timeline of turning points in cancer therapy. Adapted from reference 10.[10]

Figure 1.4 illustrates the evolution of cancer therapy from the first treatment ever until the last century.

Although some kind of cancer may be treated with only one of the aforementioned therapies, in most cases a combination of two or more treatments is required.

1.2. Cancer Immunotherapy – The Challenges Ahead

Nearly 75% of all FDA-approved small molecule anti-cancer drugs are derived from natural products.[11] However, the pharmaceutical industry has deemphasized natural product research in favor of high-throughput screening of fully synthetic compound libraries to discover novel anti-cancer drugs. Natural products have several advantages over fully synthetic compounds, such as production by large scale fermentation; they have evolved to interact with biomolecules and, therefore, are privileged structures for new medicines. Success stories, such as the discovery and development of Taxol®[12] or the epothilones[13] also provided new insights into fundamental biological processes like tubulin polymerization.[14] Natural products are also known to regulate the immune system[15] and have great potential as leading structures for drug discovery in cancer immunotherapy.

1.2.1. Immunotherapy and Checkpoint Inhibitors

The recent clinical success of new cancer immunotherapies has reinvigorated oncologists and created optimism that cancer can be effectively controlled by the immune system.[16] In spite of this enthusiasm, the reality is that durable clinical benefit still eludes many patients receiving this new class of anti-cancer agents. The ability to engage the immune system in cancer treatment has manifested a need for novel combination approaches that can target immune resistance mechanisms.

Immune evasion is a defining event in tumorigenesis and progression. Tumors evade the immune system via both intrinsic and micro environmental mechanisms that avert effector lymphocyte-mediated cytotoxicity.[17] Cancer immunotherapy stimulates the immune response so that it is able to find and attack cancer cells. A very important class of immunotherapeutic drugs is represented by the “immune checkpoint inhibitors”, which act targeting the immune checkpoints, molecules that ensure that the immune response is not constantly activated. These checkpoints are mostly T-cell receptors binding to ligands on cells in the surrounding environment, forming synapses which then regulate the functions of the T-cell.[16] Checkpoint inhibitors block these receptors from binding their partner, allowing the T-cells to destroy cancer cells (**Figure 1.5**).

The unexpected clinical success of immune checkpoint inhibitors revealed that tumors rely on certain primary mechanisms to avoid lymphocyte-cytotoxicity. Cancerous cells elaborate cytokines that recruit immune suppressive cells (e.g. MDSC, Treg) that dampen immune

responses and impede T cell infiltration (CAF). Emerging evidence suggests that tumor cells resistant to immunotherapy display characteristics of acquired drug resistance to other anti-cancer agents, implicating common resistance mechanisms to targeted agents and immune checkpoint inhibitors (e.g. anti-PD-1 and anti-PD-L1). This involves tumor cell co-option of stem cell phenotypic plasticity that is characteristic of regenerative homeostasis, paradoxically used to protect tissues from inflammation. Surprisingly, tumor cell phenotypic plasticity directly thwarts lymphocyte-mediated cytotoxicity by altering the formation and dynamics of the immune synapse, a fundamental prerequisite for all immunotherapies.[18] Understanding how cancer cells exploit stem cell-like phenotypic plasticity to resist lymphocyte-mediated cytotoxicity is a fundamental biological question and clinical challenge. Effectively addressing this emergent problem will require a multi-disciplinary approach that captures the complexity of tumor-immune cell interactions and applies novel drug discovery principles.

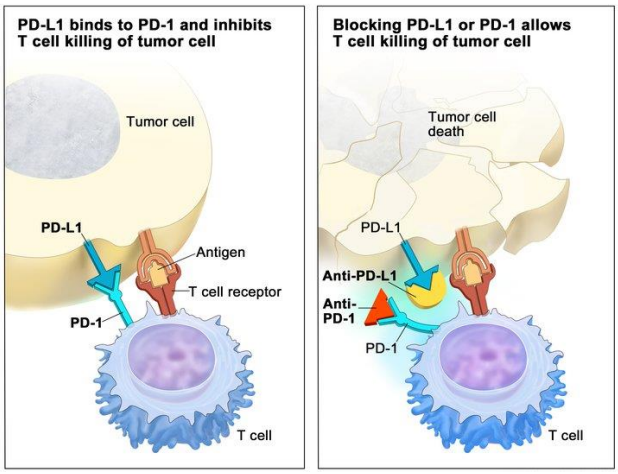


Figure 1.5: Mechanism of immune checkpoint inhibitors.[1]

1.2.2. New Immunotherapeutic Approaches with Natural Products

The complexity of the tumor microenvironment implicates a multitude of new therapeutic targets. New immunotherapeutic combinations will require compounds with low toxicity, high specificity and excellent pharmacological properties. Natural products are endowed with innately well-suited attributes for combination immunotherapy. Many natural products have evolved as important immune modulators with unique access to the immune cell compartment. Members of the disorazole family target cancer cells by inhibiting tubulin polymerization and destabilizing microtubules.[19] In addition, two members of this family may activate dendritic cells and increase the immune effector lymphocyte activity by affecting the dynamic phosphorylation of ezrin,[20] a key mediator of immune receptor activity.[21] Ezrin

regulates B and T cell receptor activation and downstream signaling. Ezrin is also a key driver of tumor progression and spread, and ezrin-targeting compounds have been shown to block metastasis.[22] Hence ezrin lies uniquely at the tumor-immune interface providing a novel targeting opportunity for immune-oncology. Disorazoles are accessible by both fermentation and synthetic approaches and, therefore, represent an ideal starting point for drug discovery in immuno-oncology. The symmetry of the target molecules allows efficient access to diverse key building blocks with simplified or modified molecular architecture, in order to optimise tumor cytotoxic effects and T cell activation.

Natural products allow early cell-based structure-activity relationship screening approaches, which are not possible with synthetic compound screening campaigns. In particular, natural product drug discovery can be conducted in cell culture settings comprising relevant cell mixtures necessary to address critical tumor-immune interactions, such as human tumor-effector cell (NK, CTL) co-cultures and in vitro immune tumor cell cultures with dissociated whole spleens. The favorable pharmacology of natural products further facilitates evaluation in intact animal settings required to validate immunotherapeutic effects.

1.2.3. Ezrin: Physiological Function and Pharmacological Perspective

Ezrin belongs to the Ezrin-Radixin-Moesin (ERM) family of plasma membrane-actin cytoskeleton crosslinking proteins, which regulate receptor signaling through spatial organization. It is the first ERM protein identified and the most studied, originally isolated from chicken intestinal epithelial brush borders as a component of microvilli.[23] Ezrin consists of 585 amino acids with an N-terminal domain, which is able to bind membrane proteins, an extended α-helical domain, a poly-proline region and a C-terminal domain, which binds F-actin.[24] Activation of ERM proteins is reliant on phosphorylation of a C-terminus threonine residue (T567 in ezrin): inactive ezrin resides in the cytosol, phosphorylation of the threonine residue by a process involving phosphatidyl 4,5-bisphosphate (PIP_2) leads to activation of the protein, which binds numerous membrane proteins by its N-terminal domain and F-actin via the C-terminal domain.[25] Serving as an intermediate between the plasma membrane and the actin cytoskeleton, it plays a key role in cell surface structure, adhesion, migration and organization, besides being one of the major regulators of microvilli.

Another important function of ezrin involves the regulation of B and T cells activation and migration. In order to become activated to produce antibodies, B cells must first recognize antigen through the B cell receptor (BCR), which induces rapid reorganization of B cell

cytoskeleton, leading to the initiation of intracellular signaling.[26] Ezrin is present in an open active conformation in resting B cells and associates with lipid rafts through Csk-binding protein. In response to BCR stimulation by antigen, ezrin undergoes rapid and transient dephosphorylation at the critical threonine residue (T567), which results in a closed structure that is incapable of binding to actin and lipid rafts, leading to breakdown of plasma membrane-actin cytoskeletal boundaries, association of BCRs with lipid rafts and lipid raft coalescence, increasing BCR diffusion and antigen-receptor microclustering. Continuous antigen stimulation causes rephosphoryation of ezrin, reinstatement of the membrane-cytoskeletal connections, which traps and immobilizes the raft-localized BCR clusters and signal transduction (**Figure 1.6**).[21] Surprisingly, recent studies have shown that loss of ezrin leads to enhanced activation of BCR and proximal signaling molecules, such as Igα, Syk and PLCγ, suggesting that ezrin acts as a limiting agent in antigen-induced BCR clustering and signaling.[27]

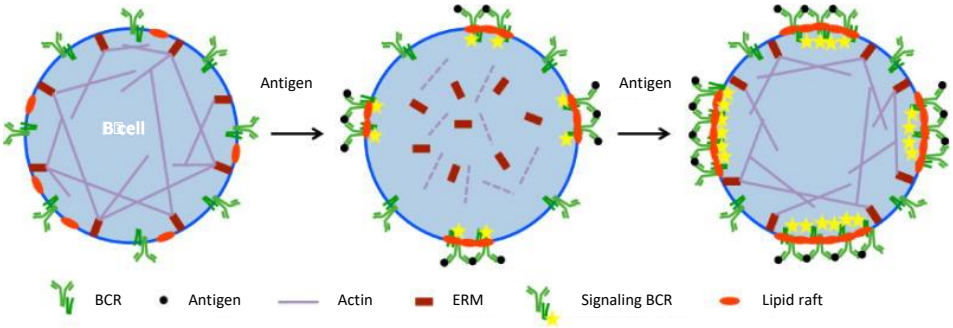


Figure 1.6: Ezrin dynamics in B cell activation.[21]

Since ezrin regulates both B and T cell activation and migration, it may play an important role in disease processes involving dysregulated lymphocyte activity and modulation of the tumor microenvironment and its inhibition may offer a novel strategy to improve therapy against B cell malignancies. It is already demonstrated its crucial involvement in tumor metastasis: studies on pediatric tumors rhabdomyosarcoma[28] and osteosarcoma[29] cell lines have shown that *Vil2*, the encoding gene for ezrin is overexpressed in metastatically capable clones and transfer of *Vil2* into low-metastatic cell lines dramatically increased the ability of these cell lines to form macroscopic pulmonary lesions in experimental metastasis assays, demonstrating that ezrin overexpression is sufficient to confer metastatic capacity. More importantly, using dominant-negative mutants, antisense RNA or RNA interference (RNAi), both groups demonstrated that ezrin overexpression is necessary for metastatic progression. This theory is corroborated by the fact that suppression of ezrin expression or disruption of its function led to significant inhibition of lung metastasis in vivo in murine model of

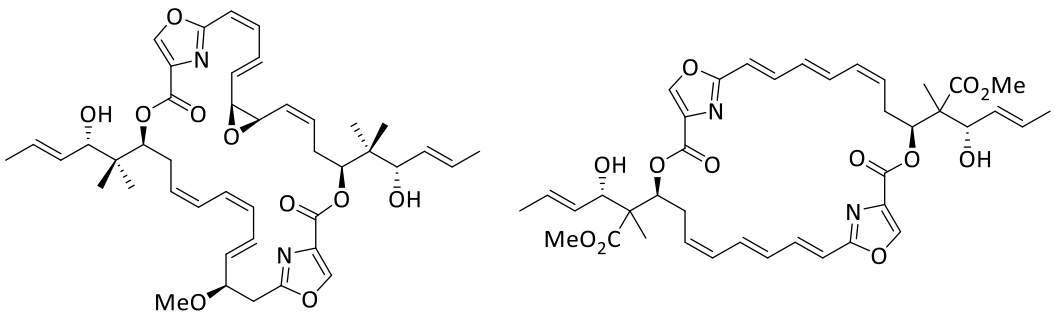
osteosarcoma.[22] It remains to understand if the role of ezrin in metastasis is limited to these two types of cancer or also in other tumors, but it is now clear that targeting ezrin would be an interesting strategy to improve the therapy against many malignancies.

1.2.4. Disorazoles Target Ezrin

Müller *et al.* demonstrated for the first time in 2017 that disorazoles, in particular disorazole A_1 **2** and Z **3** (**Figure 1.7**) are able to target ezrin.[20] They first observed their inhibition of GAS invasion adding disorazole A_1 and Z to cells prior to infection with GAS strain A8; upon treatment with 2.5 µg/mL of disorazoles, streptococci were only found extracellularly. Further investigation have shown that not only disorazoles bind Ezrin, but they also enhance the amount of phosphorylated ezrin.[30]

As a result of all the described processes in which Ezrin is involved, in combination with the well-known antimitotic activity, it is evident that the potential therapeutic value of the disorazoles is enormous. Although a big amount of work is still required to uncover the complexity and function that ezrin has in cell biology, a new target and new pathways and molecular interactions have been revealed in the search for ways to effectively improve the therapy against cancer and maybe infectious diseases.

Disorazole C_1 has not been tested so far because of lack of material, since it is a minor component of the fermentation broth (0.3%). Based on the results of this thesis, the situation may change in the immediate future, as more synthetic disorazole C_1 would be available.



Disorazole A_1 (**2**) Disorazole Z (**3**)

Figure 1.7: Chemical structures of Ezrin-binding disorazoles.

1.3. Antibody-Drug Conjugates (ADCs)

In 1906, Paul Ehrlich developed a derivative of an arsenic compound, which was found to be effective against malaria without producing any toxic effect on the host.[31] Later on, the compound, which Ehrlich code-named Compound 606 (representing the series of all his tested compounds), revealed to be capable of curing also syphilis with a single dose, again with no side effects. Ehrlich referred to this agent as "Magic Bullet", representing a single bullet fired from a gun to hit a specific target.

From this concept originated the approach to targeted chemotherapy, according to which the drug must be guided and released into the tumor site through association with ligands that are overexpressed or selectively expressed in the tumor. The discovery of monoclonal antibodies (mAbs) has permitted practical applications of this idea, since they can be linked to cytotoxic compounds, combining the highly desirable pharmacokinetic profile and targetability of monoclonal antibodies with the potent cancer-killing ability of the drug. The conjugation of a mAb with an anticancer agent is called Antibody-Drug Conjugate (ADC)[32] and such a combination potentially aims to limit systemic toxicity and maximize the desired therapeutic effects. To date, twelve ADCs have been approved by the FDA and more than 100 are currently in different stages of clinical development.[33]

1.3.1. Composition of ADCs

An ADC is composed of three elements (**Figure 1.8**): the first two are the monoclonal antibody and the cytotoxic payload; the third one is the linker, which connects the first two components.

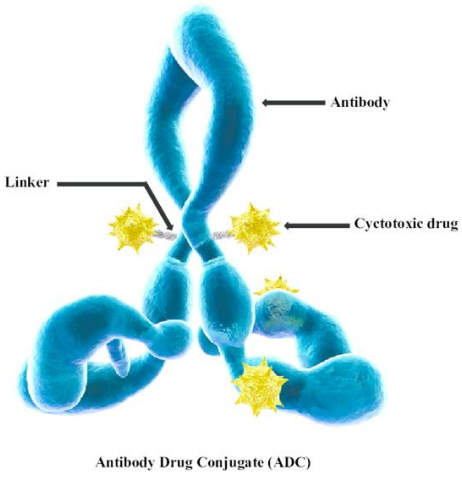


Figure 1.8: Illustration of the structure of an Antibody-Drug Conjugate.[34]

The mAbs are usually chimeric antibodies,[35] which means they contain two different sets of DNA, in particular mouse and human DNA, because the use of murine antibodies alone generated a strong production of anti-human antibodies resulting in reduced efficacy. The mAbs must be very target specific, in order to differentiate between cancer cells and healthy cells. The choice of the antibody is based on the antigens that are overexpressed in the tumor and have possibly low or even no expression in normal cells. Several antigens have been reported to be overexpressed in cancer tissues.[36] Another important characteristic of the antibody is the binding affinity for the target to ensure a rapid internalization in the cell.

The cytotoxic payload should have sufficient solubility in aqueous environment, allowing easy conjugation to the antibody and stability under physiological conditions, and a very high cytotoxicity, preferably subnanomolar half-maximal inhibitory concentration (IC_{50}). The chemical structure of the molecule is also important, because it should possess a functional group that facilitates the conjugation to the linker.

The choice of linker of the ADC is as crucial as the other two components: besides having chemical affinity for the antibody and the drug, it needs to be stable enough in a biological environment to avoid the release of the cytotoxic drug in the blood system, but it must be able to release it upon internalization.

1.3.2. Disorazoles as Payloads for ADCs

The disorazoles possess all the basic criteria to be exploited in targeted chemotherapy: they are very potent cytotoxic compounds showing an up to picomolar IC_{50}[4] and their free alcohol functionalities confer them a sufficient solubility and allow easy conjugation to the linker. Many potent drugs lack chemical groups that are necessary for conjugation, and modification to incorporate such moieties can have deleterious effects on drug action; hence, the disorazoles represent the perfect candidates for the development of an antibody-drug conjugate.

1.4. Disorazoles

The disorazoles comprise a family of 31 macrodiolides isolated for the first time in 1994 from the fermentation broth of the gliding bacteria (myxobacteria) strain *Sorangium cellulosum* So ce12,[5] except for disorazole Z and Z-epoxide, which were discovered 13 years later.[37] Myxobacteria (**Figure 1.9**) exhibit features of both unicellular and multicellular organisms and have a history of producing a rich collection of biologically active secondary metabolites, including the epothilones,[38] sorangicin A[39] and tubulysins.[40] These ''slime bacteria'' travel by gliding or creeping in waves across the surface of a host and are found in soil, rotting plant material, animal dung and on the bark of living and dead trees.[41]

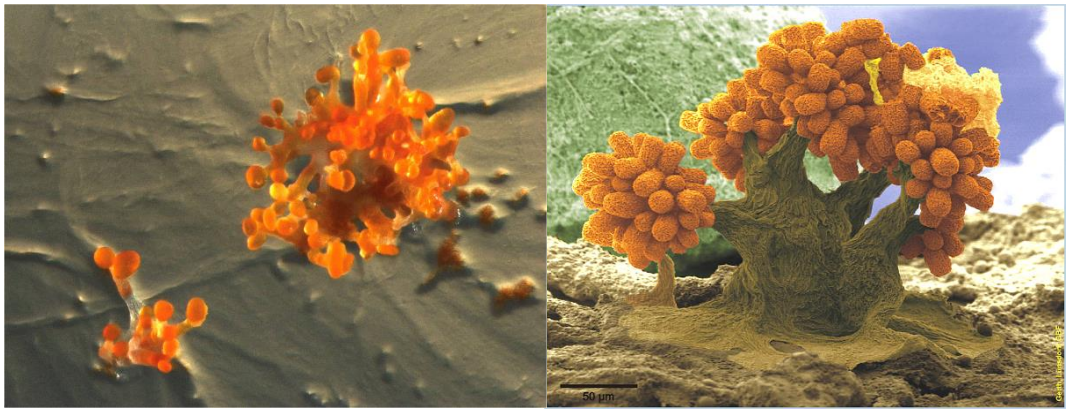
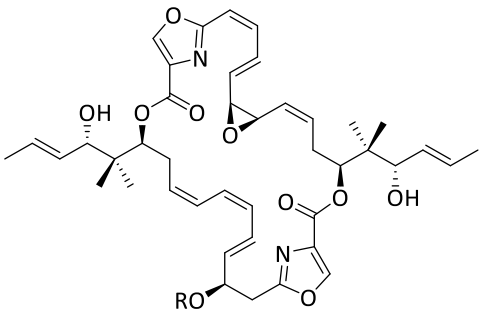


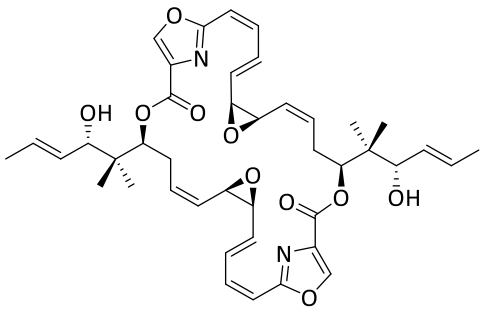
Figure 1.9: Fruiting bodies of Myxobacteria *Sorangium Cellulosum*. Pictures courtesy of Prof. Rolf Müller (Helmholtz Institute for Pharmaceutical Research Saarland).

The disorazoles were isolated from the original fermentation broth by solvent partition and chromatographic separation. Disorazole A_1 was identified as the major component, comprising 69.8% of the relative mass amount compared to the remaining disorazoles (**Figure 1.10**). Disorazole A_1 was also used as the basis for the structure elucidation of the disorazoles. Its molecular formula was determined by negative and positive ion FAB mass spectrometry, high-resolution mass spectrometry, and elemental analysis. Major structural subunit determinations and further structure refinements were achieved using 1D and 2D NMR techniques.

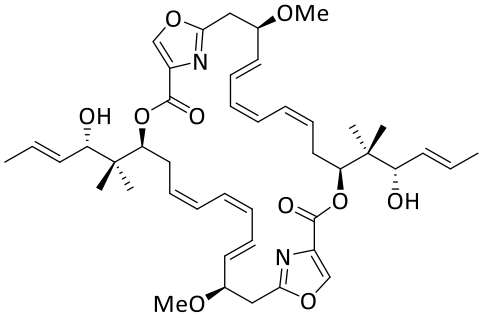
The disorazoles display a fascinating macrocyclic structure containing very sensitive unsaturated polyene units including epoxides. The structural diversity is high and spans from 24-membered macrocycles (disorazole Z **3**) to the C2-symmetric 30-membered macrocycle disorazole C_1 **1** with the very delicate (*Z*,*Z*,*E*)-triene core. **Figure 1.10** shows the structure of the most studied natural disorazoles and their relative abundance.



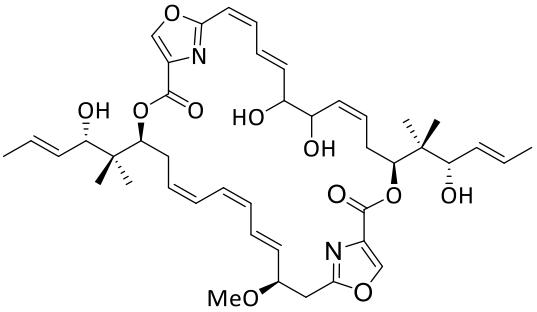
Disorazole A_1(**2**) 69.8%, (R=Me)
Disorazole A_2(**4**) 0.9%, (R=H)



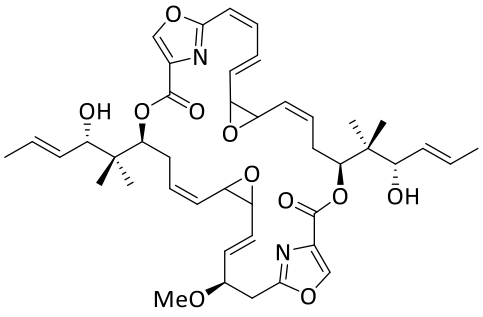
Disorazole B_1(**5**) 3.3%



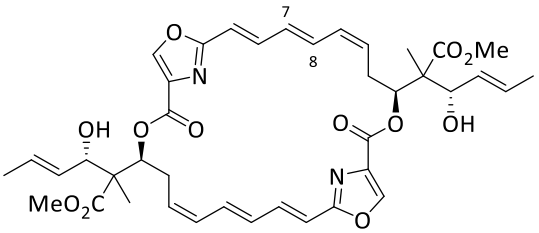
Disorazole C_1(**1**) 0.3%



Disorazole D_1(**6**) 1.4%



Disorazole E_1(**7**) 8.7%



Disorazole Z (**3**)
Disorazole Z-epoxide (**8**) (7,8-epoxide)

Figure 1.10: Selected members of the disorazole family. The percentages correspond to the relative abundance from the initial isolation from *Sorangium cellulosum* So ce12. No data has been reported for disorazole Z (**3**) and Z-epoxide (**8**). The absolute stereochemistry of disorazole D_1 (**6**) and E_1 (**7**) is not yet defined. The other members of the family show these typical characteristics in different variations.

1.4.1. Biological Activity and Mechanism of Action of the Disorazoles

Disorazoles have shown an exceptional cytotoxicity, antifungal activity and recently also antibacterial effects. Disorazole A_1 **2** is the most studied member because of its large natural abundance. It is well established that their antimitotic activity derives from an inhibitory effect on tubulin polymerization. Tubulin is the basic structural component of the microtubules, which are cytoskeletal structures playing a key role in cellular events, including cell division.

During mitosis, there are dramatic changes in microtubule network and compounds interacting with the tubulin are able to interfere with the cell cycle and stop cell division.

Tubulin-binding drugs are classified as microtubule-stabilizing, such as taxanes and epothilones, and microtubule-destabilizing agents, such as the vinca alkaloids (**Figure 1.11**). Disorazoles share a mechanism of action with the vinca alkaloids, binding to or near the vinca domain.[42–44] This process results in an irreversible perturbation of the microtubule network and cell cycle arrest at the G_2/M checkpoint, triggering the apoptotic cascade.

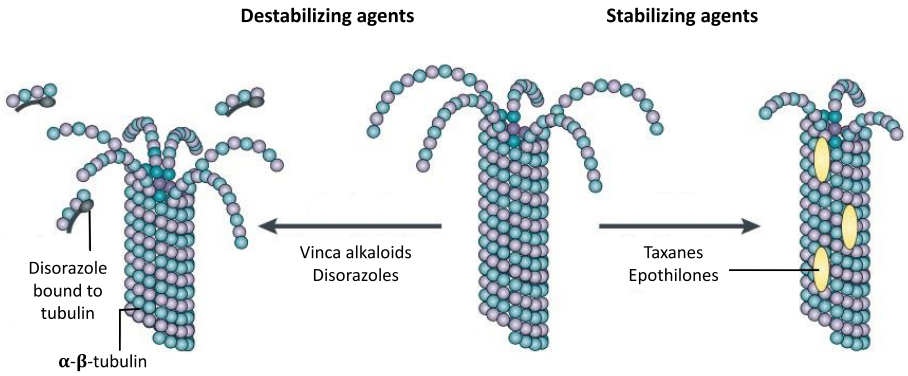


Figure 1.11: Interaction of anti-cancer agents with the tubulin. Adapted from reference 45.[45]

The antimitotic activity of disorazole A_1 is so potent that picomolar concentrations are sufficient for destabilizing microtubule assembling and inducing *apoptosis*.[43] Studies on a variety of human cancer cell lines have shown a concentration-dependent growth inhibition and, compared to epothilone B and vinblastine, an antiproliferative efficacy superior in all cell-based studies. Remarkably, disorazole A_1 seems to maintain its activity also against the multi-drug resistant (mdr) cell line KB-V1, which overexpresses the P-glycoprotein (Pgp) efflux pump.

Table 1.1 compares the biological activity of disorazole A_1, epothilone B and vinblastine against many cancer cell lines.

Disorazole A_1 has also been proven to be active against many filamentous fungi, but not against yeasts; it has shown fungicidal effect with MIC (minimum inhibitory concentration) values ranged from 0.1 to 1µg/mL.[46] Although disorazoles have not a direct action against bacteria, it has been observed that they block invasion of group A *Streptococcus* (GAS) into human epithelial cells.[20]

The mechanism of this effect is due to the fact that disorazoles target ezrin, a host protein involved in the process of membrane ruffling and co-opting host-cell caveolae,[47,48] two of the

main invasion mechanisms of GAS. Targeting ezrin leads to inhibition of GAS invasion and may potentially help their eradication as they are no longer able to invade epithelial cells.

Cell Line	Origin	IC_{50} (nM) Disorazole A_1	IC_{50} (nM) Epothilone B	IC_{50} (nM) Vinblastine
A549	Human lung carcinoma	0.0023±0.0005	0.26±0.14	5.9±0.5
PC-3	Human prostate adenocarcinoma	0.0071±0.0012	2.0±0.3	0.82±0.06
SK-OV-3	Human ovary adenocarcinoma	0.0049±0.0001	0.64±0.07	1.4±0.1
A-498	Human kidney carcinoma	0.016±0.004	4.3±3.6	46±12
U-937	Human histiocystic lymphoma	0.002±0.001	0.09±0.01	0.43±0.13
K-562	Human myelogenous leukemia	0.006±0.001	0.69±0.03	8.7±1.8
KB-3.1	Human cervix carcinoma	0.0025±0.0003	1.6±0.6	8.6±0.3
KB-V1	Human cervix carcinoma (mdr)	0.042±0.008	0.57±0.03	114±31
L929	Mouse fibroblasts	0.0038±0.0002	1.3±0.6	28±7
A549	Human lung carcinoma	0.0023±0.0005	0.26±0.14	5.9±0.5

Table 1.1: Activity comparison of disorazole A_1, epothilone B and vinblastine. Data taken from reference 4.[4]

Targeting ezrin could be significant in cancer treatment as well, because recent studies have identified ezrin as a crucial molecule in the dissemination of certain pediatric tumors, in particular rhabdomyosarcoma[28] and osteosarcoma;[29] in addition, ezrin is able to regulate the activation of B and T cells, playing a key role during the immune response.[21,27]

1.4.2. Disorazole C_1: The Ideal Starting Point for New Analogs

The antimitotic activity of disorazole A_1 was initially believed to be strictly related to the divinyl oxirane moiety, but in vitro studies on disorazole C_1 **1**, which bears a triene system instead of the divinyl oxirane, revealed a comparable cytotoxic activity for this compound. Disorazole C_1 is a minor component of the fermentation broth, representing only 0.3% of the relative mass amount. Its difficult accessibility by fermentation alongside its dimeric structure makes this molecule very attractive for synthetic chemists.

Regarding the biological activity, Wipf *et al.*[49,50] have tested disorazole C_1 against numerous cancer cell lines, such as human lung carcinoma, prostate adenocarcinoma, breast and ovarian carcinoma. The results are shown in **Table 1.2**, with IC_{50} values ranging from 1.1 to 6.9 nM. Remarkably, head and neck cancer cell lines were particularly sensitive to disorazole C_1, with an average IC_{50} value of 358 pM.[42] When quiescent WI-38 fibroblasts were exposed to disorazole C_1, no change in cell number or morphology was observed; in contrast, proliferating

WI-38 cells were sensitive to the compound, indicating that active cell division is important for the cytotoxic effects of disorazole C_1. This characteristic could be promising for future therapeutic applications, as it may imply a selectivity for cancerous cells.

Cell Line	Origin	IC_{50} (nM) Disorazole C_1	IC_{50} (nM) Vinblastine
A549	Human lung carcinoma	2.21±0.23	1.52±0.09
PC-3	Human prostate adenocarcinoma	1.57±0.10	0.86±0.08
MDA-MB-231	Breast epithelial adenocarcinoma	3.53±0.19	1.34±0.21
2008	Human ovarian carcinoma	1.91±0.23	2.24±0.16
UPCI:SSC104	Oral squamous carcinoma	6.87±0.54	1.13±0.18
WI-38 proliferating	Human fibroblasts	1.74±0.78	1.54±0.13
WI-38 quiescent	Human fibroblasts	>100	>100
HCT-116	Human colorectal carcinoma	1.09±0.41	1.40±0.07
PCI-15A	Head and neck squamous carcinoma	0.26±0.03	1.86±0.14

Table 1.2: Antiproliferative activity of Disorazole C_1. Data taken from reference 42.[42]

Chemically, disorazole C_1 is a symmetrical homodimer featuring six stereocenters, conjugated and unconjugated double bonds and a 30-membered macrocyclic structure. Each monomer represents the southern half of disorazole A_1 and contains a 2,4-disubstituted oxazole, a methoxy group connected to the very sensitive (*Z*,*Z*,*E*)-triene system and a 1-hydroxy-2-butenyl side chain linked through a gem-dimethyl unit, forming the distinctive 1,3-*anti* diol (**Figure 1.12**).

Disorazole C_1 is the simplest of the currently known members of the family and it probably represents the minimum pharmacophore of the disorazoles. Thus, it is a perfect starting point for the design of new analogs with specific modifications, in order to find more effective compounds for pharmaceutical applications.

1.4.3. Structure-Activity Relationships (SARs) of Disorazole C_1

Information on the structure-activity relationships (SARs) of the disorazoles derives from the biological studies performed on the natural members or their synthetic derivatives. The first studies were conducted by Wipf's research group,[50] which tried to evaluate the importance of the allylic alcohol side chain and the backbone functionality in the pharmacological activity of disorazole C_1 **1** (**Figure 1.12**). The results revealed a decreased

activity for all their analogs, indicating that the interaction with the biological target requires the correct orientation.

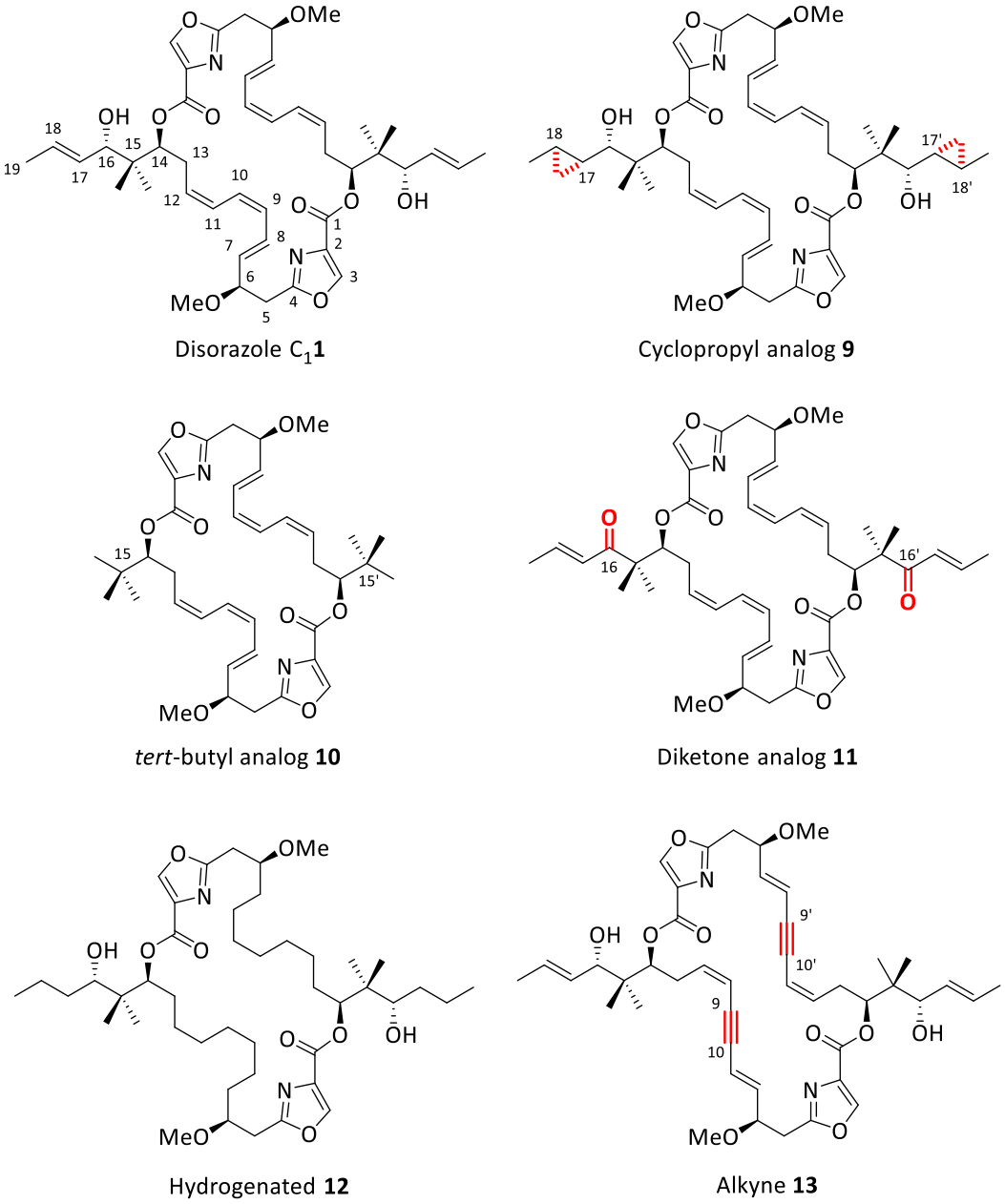


Figure 1.12: Illustration of analogs synthesized by Wipf *et al*.

A simplified side chain, in particular a cyclopropyl **9**, a *tert*-butyl **10** and an oxidized side chain **11**, led to inactive derivatives, as well as the completely hydrogenated natural product **12**. Truncated and acyclic analogs and even the alkyne precursor **13** were inactive, whereas a demethoxy compound was too unstable to be isolated.

Considering the other natural members, the high cytotoxicity of disorazoles A_1 **2**, D_1 **6** and E_1 **7**,[51] all showing an EC_{50} (half-maximal effective concentration) between 0.09 and 0.27 nM, suggests that the divinyl epoxide (or diol) moiety inserted at the C9-C10 position increases the

activity; but a cyclopropane in the same position is less effective, since the (–)-CP_2-disorazole C_1 **14** synthesized by Wipf had an IC_{50} of 35.27 nM (**Figure 1.13**).[52] Slight modifications in the configuration of the triene framework are tolerated, since the recently discovered disorazole Z **3**[37] and Kalesse's synthetic analog **15**[53] characterized by a (*Z*,*E*,*E*)-triene are still greatly potent, but the (*E*,*E*,*E*)-simplified disorazole **16** is 26 times less potent than disorazole C_1.[53] Interestingly, these compounds (**3**, **15** and **16**) lack the methoxy group at C6, but unlike the unstable Wipf's demethoxy analog, the triene core is directly conjugated with the heterocycle; disorazole Z features a methyl ester at C13 instead of the gem-dimethyl unit, which is quite an unusual variation.

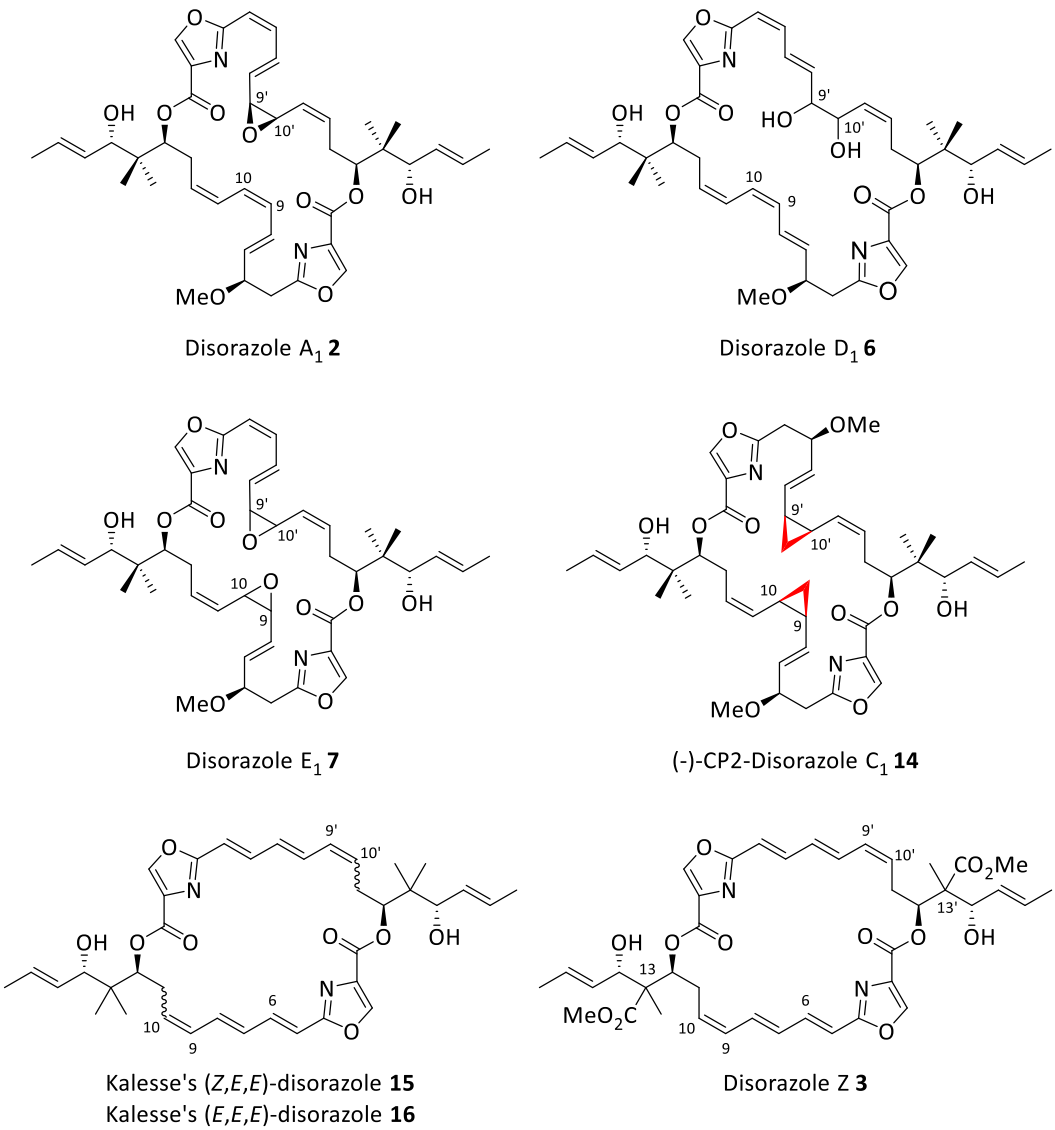


Figure 1.13: Variations of the central core of the disorazoles.

More recent studies by Nicolaou *et al*. have focused on disorazole B_1 **5**[54] and its analogs (**Figure 1.14**).[55,56] Disorazole B_1 is the homodimer of the northern half of disorazole A_1 and its high potency confirms the impact of the divinyl oxirane moiety, even though a bis-cyclopropyl

derivative **17** retained a good activity. Nicolaou's group extended the SARs of the side chain, revealing that oxygenation of the terminal carbon 19 is only partially tolerated, because a free alcohol in compound **18** destroys all activity, but a PMB ether in derivative **19** shows nanomolar IC_{50}. Analogs characterized by a lactam macrocycle, namely compounds **20** and **21**, are active and they also seem to tolerate the replacement of the oxazole-conjugated olefin with an alkyne (derivative **21**), which was detrimental at the C9-C10 position in Wipf's precursor **13**.

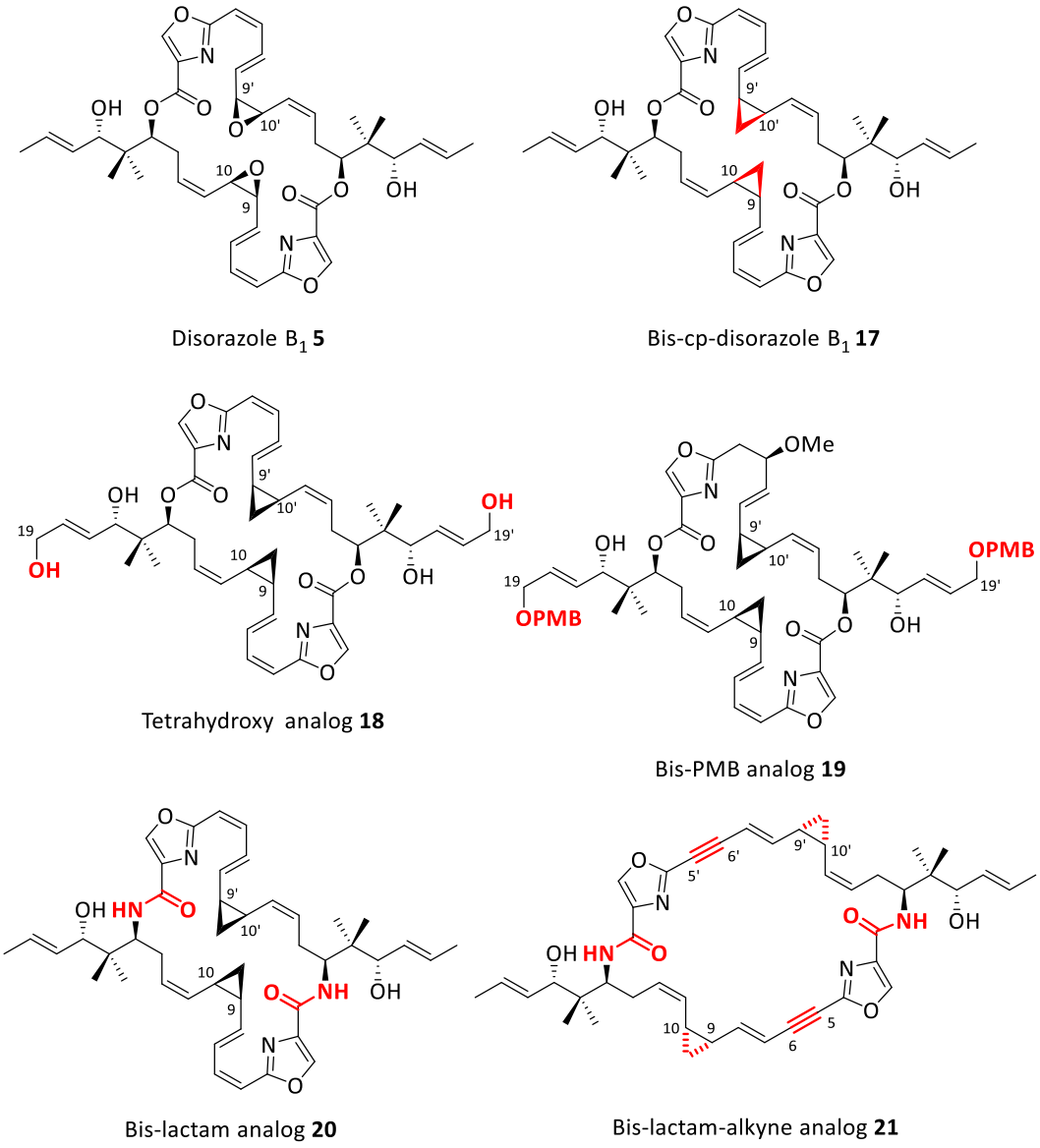


Figure 1.14: Structure of some of the analogs synthesized by Nicolaou *et al*.

Figure **1.15** summarizes the SARs of the disorazole family, using disorazole C_1 as a model and comparing it with the other natural members and synthetic analogs.

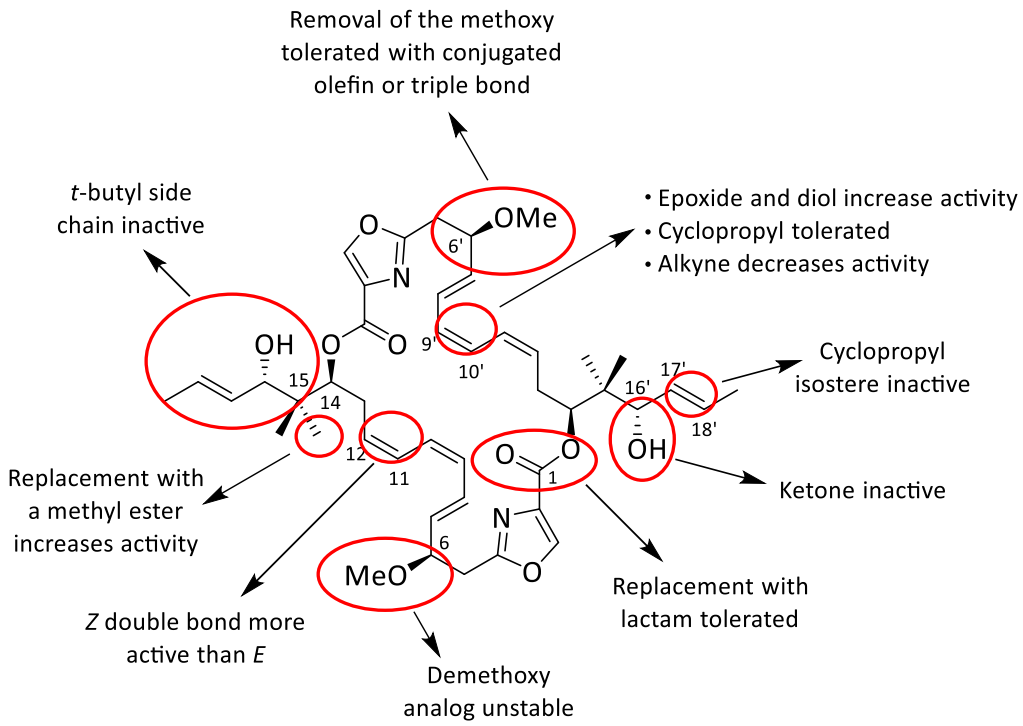


Figure 1.15: Summary of the structure-activity relationships (SARs) of disorazole C_1.

1.4.4. Aims of the Work

The goal of this research work is to develop a new synthetic route to the natural product disorazole C_1, which may provide access for the discovery of novel derivatives with anti-tumor activity. The synthesis of these analogs also intends to further extend the structure-activity relationships of the disorazoles, especially addressing modifications to the oxazole and the stereochemistry. Over the last years, a tremendous work has been made to elucidate the SARs of the disorazoles, but not much is known about the role of the heterocycle in the activity of these molecules; moreover, every analog that has been synthesized so far exhibits no variation in the six chiral centers. The synthesis of new derivatives with such modifications could finally give a complete picture of the SARs of these cytotoxic compounds.

The natural product along with its analogs will be then tested in conjugation with antibodies, in order to develop a suitable payload for ADCs. The need of new anti-cancer agent is becoming an increasing problem, because the tumors are developing new mechanisms of resistance to many drugs, and the discovery of novel therapies is the first step in the battle against cancer.

1.5. Previous Syntheses of (–)-Disorazole C_1

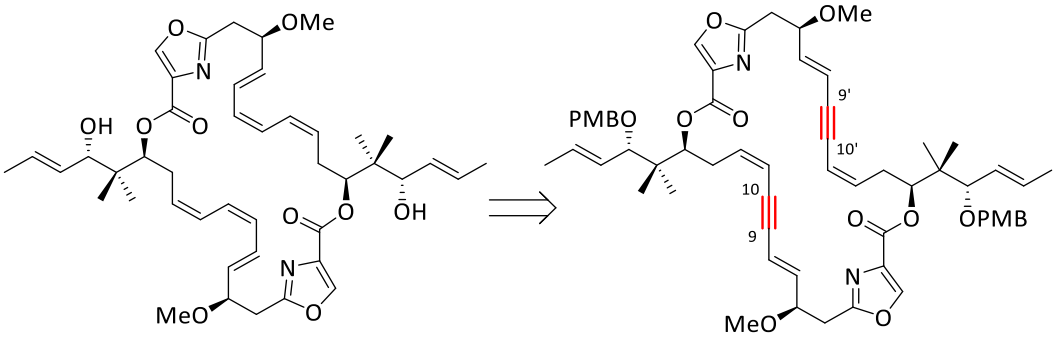
Given their high cytotoxic activity and possible pharmaceutical applications, the disorazoles became very soon an interesting target for synthetic chemists. The presence of the heterocyclic fragment and the labile polyene systems inserted into the macrocyclic structure represented (and still represent nowadays) synthetic intriguing challenges.

The first synthetic efforts were conducted by Meyers group in 2000[57,58] toward the synthesis of disorazole C_1, when the relative and absolute stereochemistry was not known. In 2000, degradation studies of disorazole A_1[59] assigned the stereochemistry and two years later Hoffmann and co-workers were able to report the synthesis of a masked fragment of disorazole C_1[60] with the correct configuration at all sterecenters, followed by a synthesis of a tetradehydro-disorazole C_1 in 2006.[61]

Hereinafter, this section will focus on the three total syntheses of disorazole C_1 that had been published prior to this work. A more comprehensive review addressing the synthesis of the fragments, including the works performed by Meyers and Hoffmann, is available in the literature.[4]

1.5.1. Total synthesis by Wipf

Wipf and Graham achieved the first total synthesis of disorazole C_1 in 2004.[62] Pioneering work by Meyers and Hoffmann had been significant in revealing important information about the construction of the macrocycle and the instability of the triene unit.



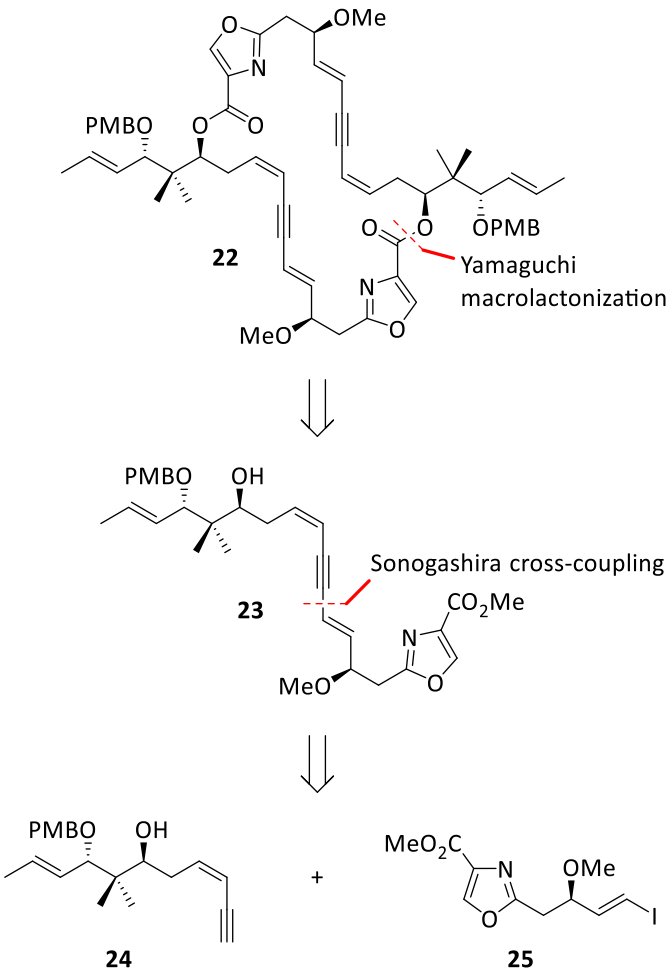
Disorazole C_1 **1** Alkyne **22**

Scheme 1.1: Masked alkene used by Wipf and Graham.

Probably, the most successful strategy employed by Wipf was to mask one of the (*Z*)-alkene of the triene system as an alkyne; they chose the central C9-C10 alkene (**Scheme 1.1**), because of the difficulty that Meyers had encountered adopting the C11-C12. PMB (*p*-methoxybenzyl)

was chosen as protecting group for its relatively neutral removal conditions. Retrosynthetic analysis led to the monomer **23**, which would be derived from building blocks **24** and **25**, as depicted in **Scheme 1.2**.

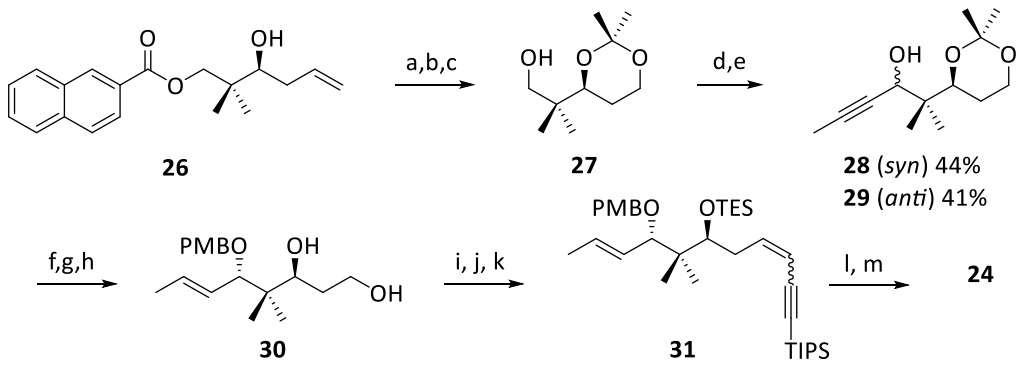
The two key fragments **24** and **25** would be coupled through a Sonogashira[63] condensation and the ring would be closed using Yamaguchi macrolactonization.[64]



Scheme 1.2: Retrosynthesis of (–)-disorazole C_1 conceived by Wipf and Graham.

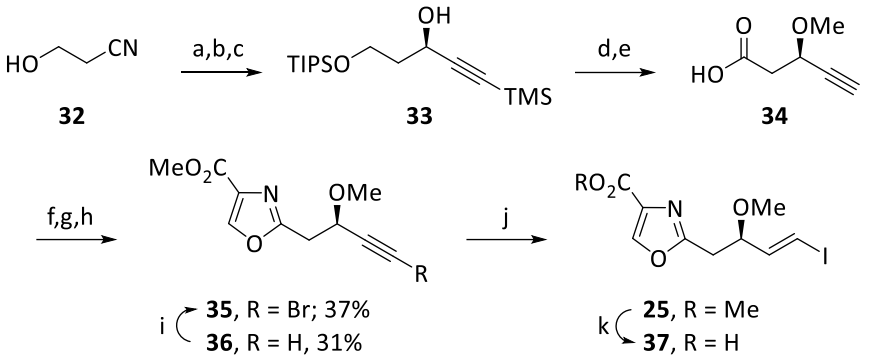
The synthesis of the enyne fragment **24** commenced from the known homoallylic alcohol **26**,[65] which was available in 91% yield and 92% *ee*. Ozonolysis of the terminal olefin and reductive work-up afforded the corresponding primary alcohol; protection of the 1,3-diol and saponification of the naphthyl ester afforded acetonide **27**. Then, oxidation of the primary alcohol and treatment with propynyllithium resulted in a 1.1:1 mixture of separable *syn* (**28**) and *anti* (**29**) diastereomers. Reduction using Red-Al, followed by PMB protection of the allylic alcohol and subsequent cleavage of the acetonide provided the corresponding 1,3-diol **30**. Protection of both free alcohols as triethylsilyl (TES) ethers and selective Swern oxidation[66] of the primary TES ether produced the aldehyde, which was exposed to lithiated 1,3-bis-

(triisopropylsilyl)propyne[67] to give enyne **31** as a 8:1 separable mixture of *Z* and *E* isomers. Final removal of the TES ether and TIPS deprotection afforded the desired enyne fragment **24** (**Scheme 1.3**).



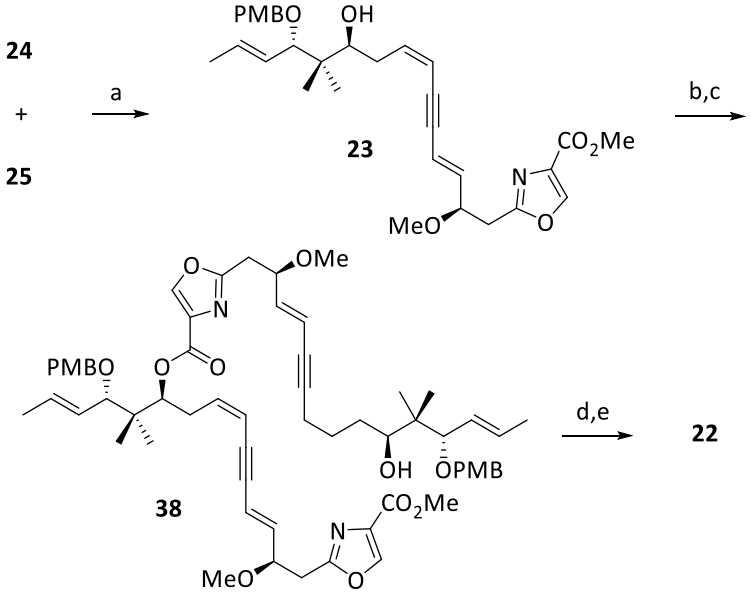
Scheme 1.3: Wipf's synthesis of the key fragment **24**. *Reagents and conditions*: (a) O_3/O_2, Sudan III, $MeOH/CH_2Cl_2$, –78 °C then $NaBH_4$, –78 °C to rt, 88%; (b) 2,2-dimethoxypropane, PPTS, THF, 0 °C to rt, 36 h, 97%; (c) 1 M LiOH, THF, MeOH, 0 °C to rt, 20 h, 82%; (d) Swern; (e) propyne, *n*-BuLi, THF, –78 °C to 0 °C, 1.5 h; (f) Red-Al, THF (degassed), 70–75 °C, 25 h, 83%; (g) PMB-Br, NEt_3, KHMDS, THF, –78 °C, 1 h, then rt, 2 h; (h) $AcOH/THF/H_2O$ 4:1:1, 60 °C, 12 h, 84% (2 steps); (i) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min; (j) Swern, 75% (2 steps); (k) 1,3-bis(TIPS)propyne, *n*-BuLi, THF, –78 °C, 30 min; (l) chloroacetic acid, $MeOH/CH_2Cl_2$, rt, 14 h; (m) TBAF, THF, 0 °C to rt, 14 h, 94%.

The oxazole fragment was synthesized starting from hydroxy nitrile **32**, which was protected with triisopropylsilyl (TIPS) chloride, and reduction with diisobutylaluminum hydride (DIBAL-H) gave the corresponding aldehyde. The transformation to the propargylic alcohol **33** was performed under Pu's conditions[68] and proceeded in 66% yield and 92% *ee*. Methylation of the secondary alcohol under phase-transfer conditions took place in 95% yield with concomitant removal of the trimethylsilyl (TMS) group. Deprotection of the primary alcohol and subsequent oxidation to carboxylic acid using Merck protocol[69] provided compound **34**. Condensation with serine methyl ester, followed by cyclodehydration with diethylaminosulfurtrifluoride (DAST) and oxidation with DBU and $BrCCl_3$[70] afforded oxazoles **35** and **36**. The terminal alkyne **36** was further converted to the alkynyl bromide **35** and the required vinyl iodide **25** was obtained through a palladium-catalyzed hydrostannylation[71] and subsequent treatment with iodine in 92% yield. Finally, hydrolysis of the methyl ester gave the carboxylic acid **37**, as shown in **Scheme 1.4**.



Scheme 1.4: Wipf's Synthesis of the key fragment **25**. *Reagents and conditions*: (a) TIPSCl, imidazole, DMF, rt, 16 h; (b) DIBAL-H, CH_2Cl_2, –10 °C, 50 min, 78% (2 steps); (c) TMS-acetylene, Et_2Zn, toluene, reflux, 1 h, then (*S*)-Binol, Ti(O*i*-Pr)$_4$, rt, 20 h, 66%; (d) Dimethyl sulfate, *n*-Bu_4NHSO_4, NaOH, toluene/H_2O, 0 °C to rt, 3.5 h, 95%; (e) HF, CH_3CN, rt, 24 h, then $NaClO_2$, TEMPO, CH_3CN, phosphate buffer (pH 6.7), 45 °C, 18 h, 99%; (f) SerOMe·HCl, EDC, HOBT, NMM, CH_2Cl_2, 0 °C to rt, 16 h, 55%; (g) DAST, CH_2Cl_2, –78 °C, 1 h, then K_2CO_3, –78 °C to rt, 40 min; (h) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C to 4 °C, 20 h; (i) NBS, $AgNO_3$, acetone, rt, 1 h, 54%; (j) *n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, – 78 °C to rt, 3 h, then I_2, 0 °C, 45 min, 92%; (k) 1 M LiOH, THF, rt, 12 h, 97%.

At this point, Wipf and Graham decided to use both fragments (**24** and **25**) twice and they chose to form the lactone ring in two different esterifications, because neither Meyers nor Hoffmann had succeeded in the construction of the macrocycle in one pot.

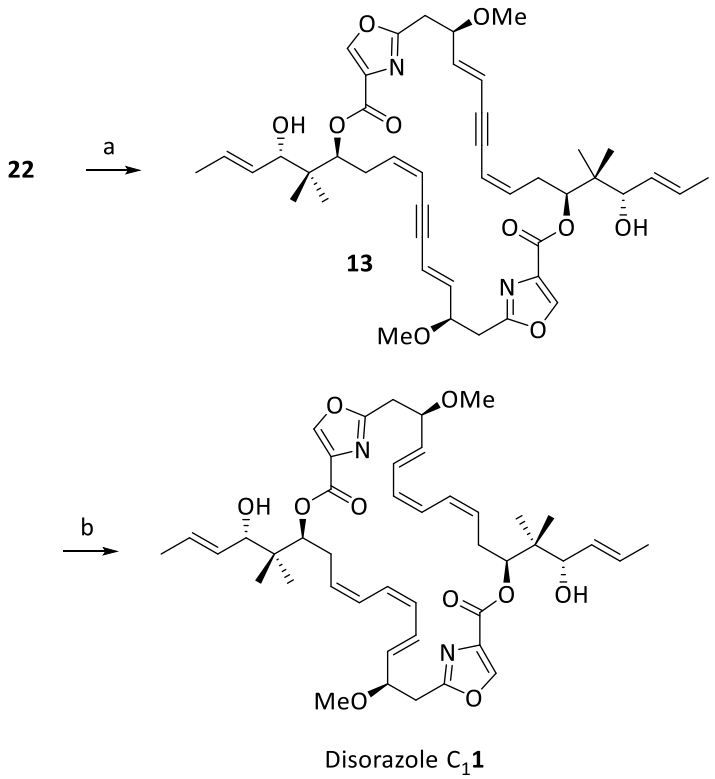


Scheme 1.5: Wipf's strategy for the construction of the macrocycle. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –20 °C to rt, 75 min, 94%; (b) **37**, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 14 h, 80%; (c) **24**, $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –20 °C to rt, 75 min, 94%; (d) 1 M LiOH, THF, rt, 13.5 h, 98%; (e) 2,4,6-trichlorobenzoyl chloride, NEt_3, THF, rt, 2 h, then DMAP, toluene, rt, 16 h, 79%.

Therefore, enyne **24** was coupled to the oxazole fragment **25** using a Sonogashira cross-coupling,[63] to form the monomer **23** in 94% yield. The formation of the (bis)dienyne **38** was achieved using a Steglich esterification[72] with carboxylic acid **37**, followed by a second

Sonogashira coupling with enyne **24**. Final saponification of the methyl ester and Yamaguchi lactonization[64] led to the protected tetradehydro-disorazole C_1 **22** (**Scheme 1.5**).

As expected, given the high sensitivity of the lactone, the endgame required extensive optimization of the reaction conditions to avoid decomposition of the macrodiolide. The best results for the cleavage of the PMB ethers were found with DDQ (2,2-dichlor-5,6-dicyano-1,4-benzoquinone) under buffered conditions, delivering diol **13** in 61% yield. Final hydrogenation of the triple bonds with Lindlar catalyst[73] produced the natural product **1** after HPLC purification (**Scheme 1.6**).



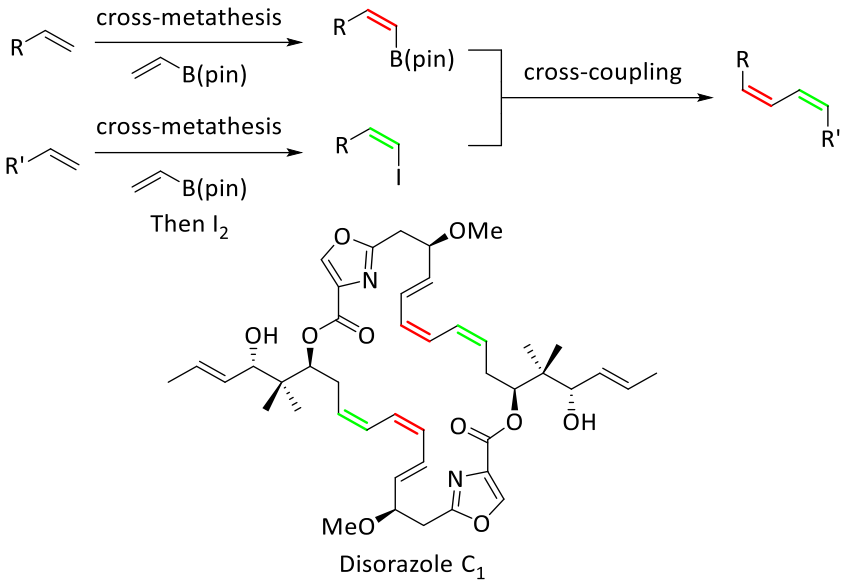
Scheme 1.6: Wipf's final steps in the synthesis of disorazole C_1. *Reagents and conditions*: (a) DDQ, phosphate buffer, CH_2Cl_2, rt, 15 min, 61%; (b) H_2, Lindlar catalyst, quinoline, EtOAc, rt, 1 h, 57%.

Wipf and Graham were able to complete the first total synthesis of a member of the disorazole family in 20 steps and 1.5% yield for the longest linear sequence, ten years after their isolation.

1.5.2. Total synthesis by Hoyveda

The second total synthesis of disorazole C_1 was published by Hoyveda and co-workers.[74] In 2013, Hoyveda's research group developed a new methodology for the preparation of *Z*-(Pinacolato)alkenylboron compounds through stereoselective catalytic cross-metathesis,

which could be combined with catalytic cross-coupling to obtain *Z*-alkenes and (*Z*,*Z*)-1,3-dienes.[75]

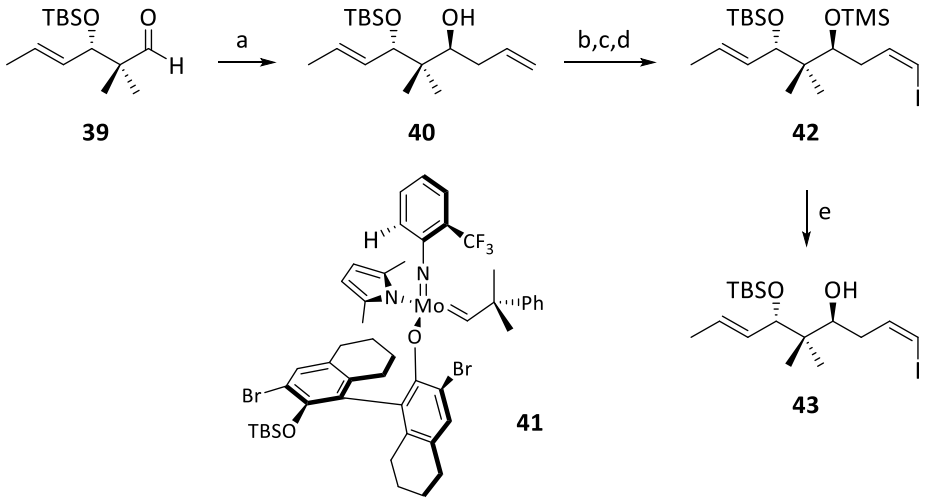


Scheme 1.7: General method for *Z*-selective cross-metathesis developed by Hoyveda and its application in the synthesis of disorazole C_1. Pin = pinacolato.

Accordingly, they decided to employ their method in the synthesis of disorazole C_1 and in particular for accessing the (*Z*,*Z*,*E*)-triene unit (**Scheme 1.7**). The strategy required the identification of two coupling partners, corresponding to the oxazole fragment and the lateral chain of the natural product. The lateral chain was synthesized starting from aldehyde **39**,[53] which had been reported by Kalesse *et al*. in the synthesis of novel disorazoles, and it was available in two steps.

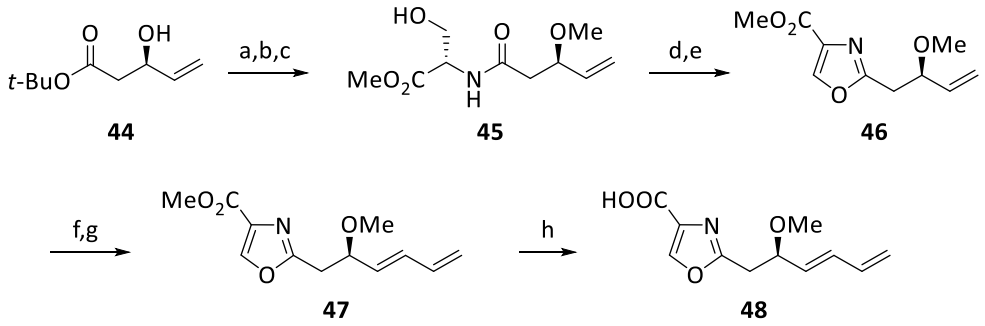
A stereoselective Leighton allylation[76,77] furnished homoallylic alcohol **40** in 91:9 diastereomeric ratio (*dr*) and set the stereochemistry of the 1,3-diol unit. It was at this point that Hoyveda put his cross-metathesis into practice: after protection of the secondary alcohol as a TMS ether, a *Z*-selective cross metathesis with vinyl– B(pin) using molybdenum complex **41** as catalyst, and subsequent conversion to vinyl iodide gave **42** in 79% yield. Final deprotection of the TMS ether delivered the *Z*-alkenyl iodide **43**, as depicted in **Scheme 1.8**.

B(pin) using molybdenum complex **41** as catalyst, and subsequent conversion to vinyl iodide gave **42** in 79% yield. Final deprotection of the TMS ether delivered the *Z*-alkenyl iodide **43**, as depicted in **Scheme 1.8**.



Scheme 1.8: Hoyveda's synthesis of fragment **42**. *Reagents and conditions*: (a) (*R*,*R*)-Leighton reagent, 5.0 mol% $Sc(Otf)_3$, CH_2Cl_2, –10 °C, 3 h, >98% (91:9 dr); (b) TMSCl, DIPEA, DMAP, CH_2Cl_2, 0 °C, 3 h, 92%; (c) vinyl B(pin), 3.0 mol% **41**, benzene, 100 torr, rt, 20 h, 72% (>92:8 *Z*:*E*); (d) I_2, 3 M NaOH, THF, rt, 10 h, 79%; (e) PPTS, CH_2Cl_2/MeOH 1:1, rt, 10 min, 85%.

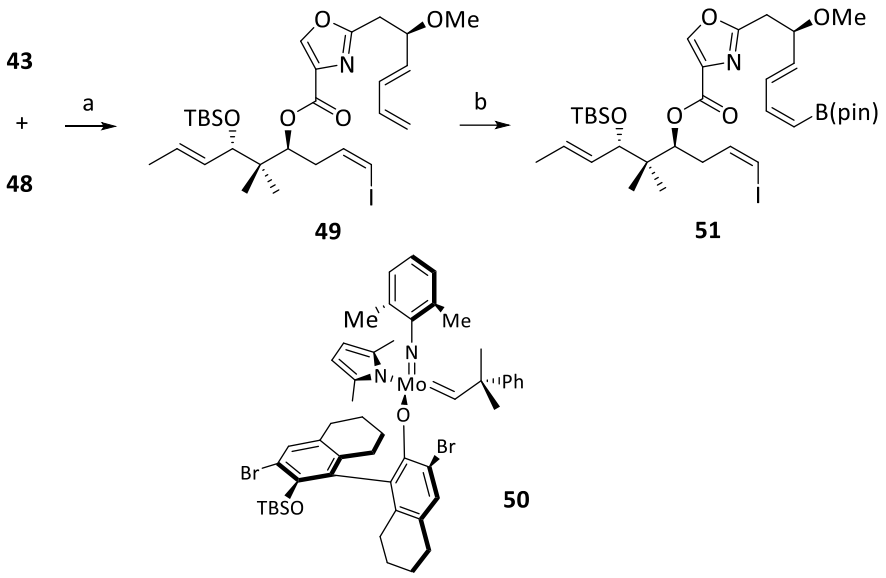
For the synthesis of the other coupling partner (**Scheme 1.9**), Hoyveda and co-workers used the enantiomerically enriched alcohol **44**, derived from the enzymatic resolution of the corresponding racemic β-hydroxyester.[78] Methylation of the allylic alcohol, followed by hydrolysis of the *t*-butyl ester and reaction with serine methyl ester hydrochloride afforded amide **45**.



Scheme 1.9: Hoyveda's synthesis of fragment **48**. *Reagents and conditions*: (a) Me_3OBF_4, Proton Sponge, CH_2Cl_2, rt, 3 h, 79%; (b) HCOOH, rt, 2.5 h, 93%; (c) DIPEA, TFFH, THF, rt, 2 h, then SerOMe·HCl, rt, 3 h, 83%; (d) DAST, CH_2Cl_2, –78 °C, 3 h, then K_2CO_3, –78 °C to rt, 45 min; (e) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C, 16 h, 58% (2 steps); (f) 4-bromo-1-butene, 5.0 mol% Hoyveda-Grubbs II, toluene, 70 °C, 18 h, 81% (95:5 *E*:*Z*); (g) DBU, EtOAc, rt, 7 h, 91%; (h) $Ba(OH)_2{\cdot}8H_2O$, H_2O/THF 1:1, rt, 1.5 h.

Cyclization with DAST and subsequent oxidation with with DBU and $BrCCl_3$[70] gave exclusively oxazole **46** in 58% yield, while Wipf's terminal alkyne had produced a mixture of two products (**35** and **36** in **Scheme 1.4**). Cross-metathesis between **46** and 4-bromo-1-butene using Grubbs-Hoyveda II catalyst[79] produced the terminal alkyl bromide, which was eliminated with DBU affording diene **47**. Hydrolysis of the methyl ester gave the carboxylic acid **48**.

Similarly to Wipf's experience, the final steps resulted to be extremely challenging, also because the conjugated double bonds were not masked in this case. After testing several approaches, satisfactory conditions were found forming the ester bond between alcohol **43** and carboxylic acid **48** and later cross-metathesis with vinyl B(pin).

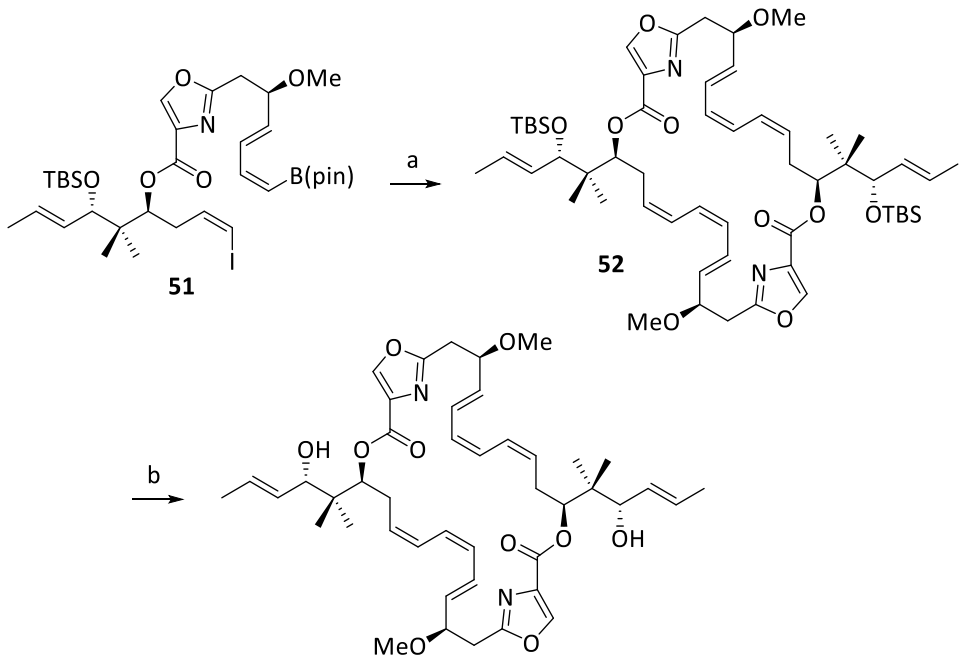


Scheme 1.10: Hoyveda's ester bond formation in the synthesis of disorazole C_1. *Reagents and conditions*: (a) DCC, DMAP, DMAP·HCl, $CDCl_3$, rt, 18 h, 83%; (b) vinyl B(pin), 10 mol% **50**, benzene, 100 torr, rt, 4 h, 91% (>98:2 *Z*:*E*).

Inverting the order of the reactions led to considerably lower yields, and attempts to form the macrocycle directly from a monomeric unit were unsuccessful. Cross-metathesis between **49** and vinyl B(pin) gave better results using molybdenum complex **50**, delivering (*Z*,*E*)-dienyl−B(pin) **51** in 91% yield (**Scheme 1.10**).

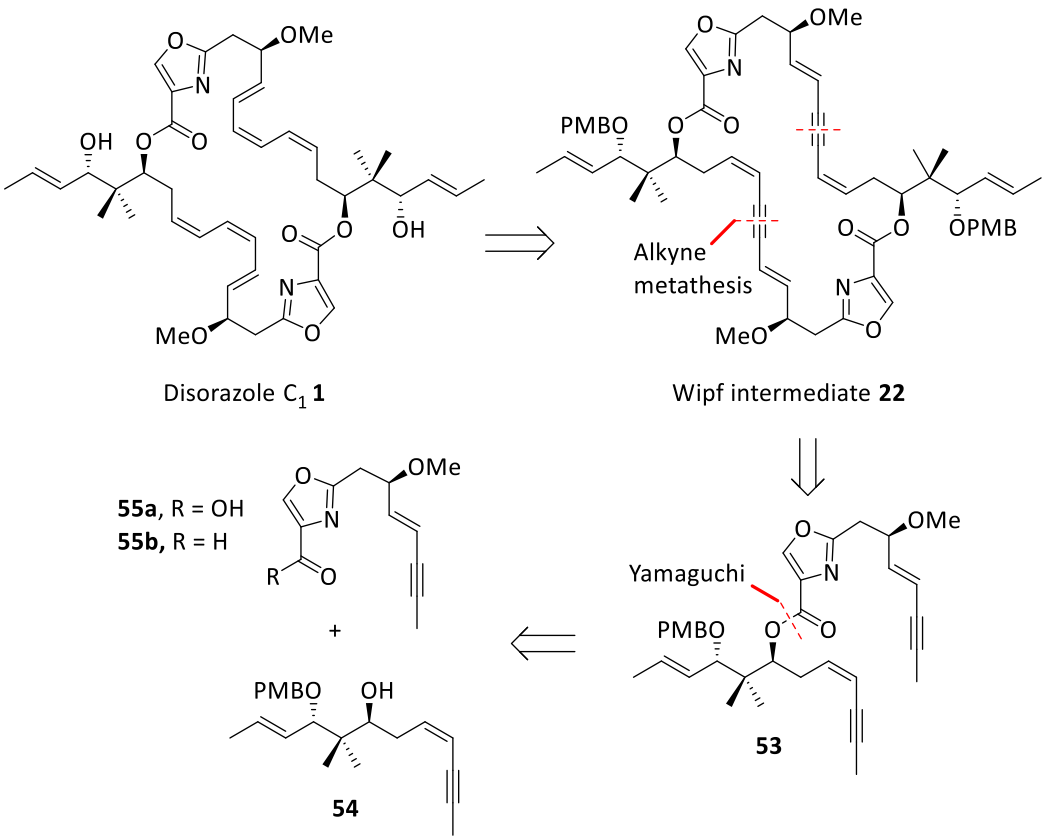
After extensive investigations, the inter- and intramolecular cross-coupling of **51** proceeded in the glovebox in 60% yield with $Pd[(o\text{-tol})_3P]_2$ as catalyst, affording dimer **52**. Finally, deprotection of the TBS (*t*-butyldimethylsilyl) groups with aqueous H_2SiF_6 afforded disorazole C_1 **1** in 68% yield, as shown in **Scheme 1.11**.

With this study, Hoyveda and co-workers provided an innovative strategy for the synthesis of this natural product and they demonstrated that a combination of catalytic cross-metathesis and cross-coupling reactions can be a useful tool in the synthesis of complex molecules. Thus, disorazole C_1 was synthesized in 12 steps and 8.0% yield for the longest linear sequence.



Scheme 1.11: Hoyveda's final strategy for the synthesis of disorazole C_1. *Reagents and conditions*: (a) 5.0 mol% Pd[(*o*-tol)$_3$P]$_2$, Cs_2CO_3, MeOH, rt, 12 h, 60%; (b) aq. H_2SiF_6, MeOH, 4 °C, 72 h, 68%.

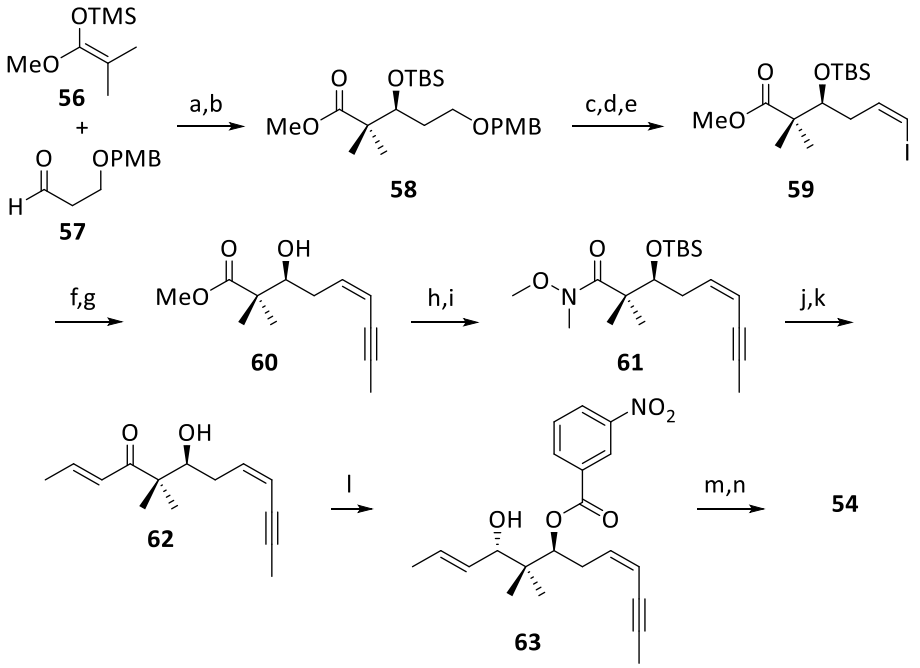
1.5.2. Total synthesis by Hulme



Scheme 1.12: Hulme's retrosynthetic analysis of disorazole C_1 and intersection with Wipf's intermediate.

One year after Hoyveda's total synthesis of disorazole C_1, Hulme *et al*. published a third approach to the synthesis of this molecule,[80] which was based on an alkyne metathesis homodimerization strategy and crossed Wipf's route at the tetradehydro intermediate **22** (**Scheme 1.12**). For the construction of the macrocycle, Hulme and co-workers made use of a combination of alkyne cross-metathesis and ring-closing alkyne metathesis on compound **53**, which was formed through an esterification reaction between alcohol **54** and carboxylic acid **55a**.

The synthesis of the first enyne fragment **54** started with an organoborane-mediated Mukaiyama aldol reaction[81,82] between the silyl ketene acetal **56** and aldehyde **57**, which proceeded in 85% yield and 89% *ee* (**Scheme 1.13**).

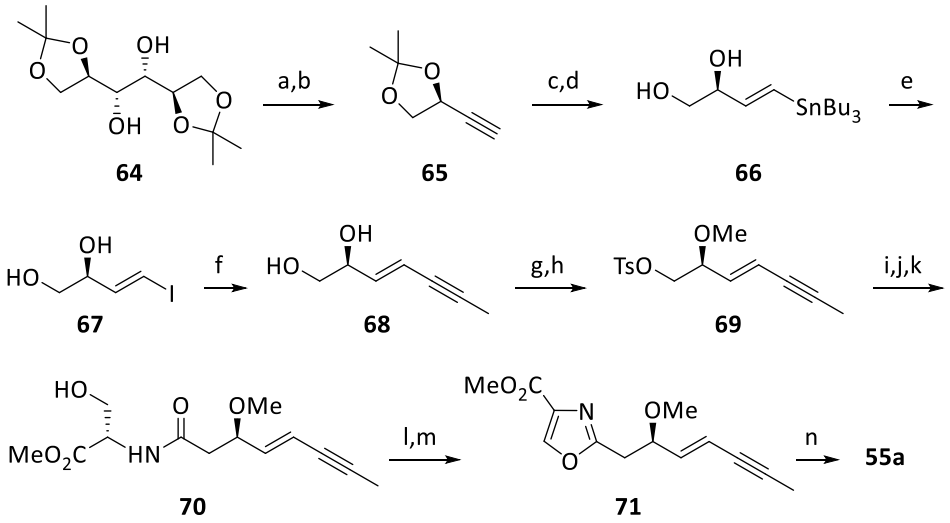


Scheme 1.13: Hulme's synthesis of the enyne fragment **54**. *Reagents and conditions*: (a) *N*-Ts-D-Valine, BH_3·THF, CH_2Cl_2, –78 °C, 5 h, then HCl, THF/H_2O 1:1, 85% (89% *ee*); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 2.5 h, 94%; (c) DDQ, CH_2Cl_2/H_2O 18:1, rt, 1.5 h; (d) Swern, 95%; (e) ICH_2PPh_3I, NaHMDS, HMPA, THF, –78 °C, 2 h, 75%; (f) $BrMgC{\equiv}CCH_3$, $ZnCl_2$, $PdCl_2(PPh_3)_2$, THF, 0 °C to rt, 16 h, 92%; (g) HF (40% aq.), CH_3CN, 0 °C to rt, 1 h, 99%; (h) HNMe(OMe)·HCl, *n*-BuLi, THF/hexane 1:1, –78 °C to rt, 1.5 h, 82%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to rt, 2 h, 96%; (j) 1. allyl-MgBr, Et_2O, –20 °C to –78 °C, 2 h, 2. DBU, NEt_3, 50 °C, 18 h, 81%; (k) HF (40% aq.), CH_3CN, 0 °C to rt, 45 min, 85%; (l) 3-nitrobenzaldehyde, SmI_2, THF, –20 °C, 4 h, 94% (>95:5 dr); (m) PMB-TCA, $Sc(OTf)_3$, toluene, 0 °C to rt, 1 h, 79%; (n) LiOH, MeOH/H_2O 10:1, reflux, 18 h, 91%.

TBS-protection of the resulting secondary alcohol afforded compound **58**. Then, deprotection of the PMB ether, followed by Swern oxidation[66] of the primary alcohol and a Stork-Zhao olefination[83] on the resulting aldehyde gave the *Z*-vinyl iodide **59**. A Negishi coupling[84] with propynylmagnesium bromide furnished the desired enyne portion. The

subsequent conversion to the Weinreb amide[85] gave better results with the free alcohol, so the enyne was first deprotected, and then reprotected to give compound **61**. Afterwards, addition of allyl Grignard and isomerization with DBU, followed by another deprotection of the TBS ether gave the β-hydroxyketone **62**. The initial plan was to perform a direct Evans-Tishchenko reaction[86] between **62** and aldehyde **55b**, but model studies suggested that the use of electron-rich aldehydes gave poor results.[87] Therefore, the authors decided to pursue a different strategy: the β-hydroxyketone **62** was further functionalized and the Evans-Tishchenko reaction was performed with 3-nitrobenzaldehyde, setting the stereochemistry of the 1,3-*anti* diol in **63**. The free alcohol was protected with PMB and hydrolysis of the ester delivered alcohol **54**.

For the synthesis of the oxazole fragment, mannitol derivative **64** was chosen as a starting point, and it was first converted to an aldehyde by periodate cleavage and then to alkyne **65** by Seyferth-Gilbert homologation[88] with the Ohira–Bestmann reagent.[89] Then acetal hydrolysis and palladium-catalyzed hydrostannylation[71] afforded compound **66**, which was treated with iodine to furnish vinyl iodide **67** in 92% yield.

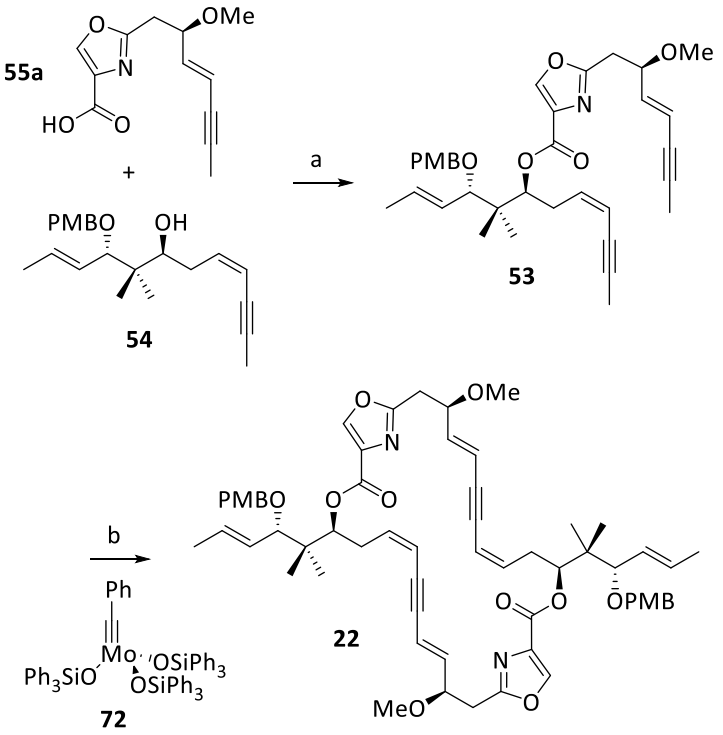


Scheme 1.14: Hulme's synthesis of the oxazole fragment **55a**. *Reagents and conditions*: (a) $NaIO_4$, aq. $NaHCO_3$, $MgSO_4$, CH_2Cl_2, 0 °C to rt, 2 h 20 min, 88%; (b) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 0 °C to rt, 17 h; (c) conc. HCl, MeOH, Et_2O, THF, 6 h 15 min, 66% (2 steps); (d) $PdCl_2(PPh_3)_2$, Bu_3SnH, Et_2O, –30 °C, 30 min, 60%; (e) I_2, Et_2O, 0 °C, 5 min, 92%; (f) $BrMgC{\equiv}CCH_3$, $ZnCl_2$, $PdCl_2(PPh_3)_2$, THF, 0 °C to rt, 25 h, 92%; (g) Bu_2SnO, TsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 11 h, 60% (2 steps); (h) Me_3OBF_4, Proton Sponge, 2 h; (i) KCN, Bu_4NI, $NaHCO_3$, DMSO, 60 °C to 70 °C, 4 h, 63% (2 steps); (j) H_2O_2, $LiOH{\cdot}H_2O$, EtOH, rt, 34 h, 75%; (k) HBTU, DIPEA, SerOMe·HCl, CH_3CN, 0 °C to rt, 10 h, 82%; l) XtalFluor-E, K_2CO_3, CH_2Cl_2, –78 °C to 0 °C, 50 min; (m) $BrCCl_3$, DBU, –20 °C to rt, 4 h 45 min, 76% (2 steps); (n) 1 M LiOH, THF, rt, 8 h, 96%.

A Negishi coupling[84] with propynylmagnesium bromide was performed also for this piece giving the enyne **68**, and then monotosylation of the primary alcohol[90] and methylation of the secondary one delivered tosylate **69**. The tosylate was converted to amide **70** by cyanide displacement, hydrolysis to give the acid, and reaction with serine methyl ester hydrochloride. The usual sequence cyclization-oxidation gave oxazole **71** in 76% yield. Saponification of the methyl ester afforded the desired carboxylic acid **55a**, as depicted in **Scheme 1.14**. Otherwise, DIBAL-H reduction would have given aldehyde **55b** for a direct Evans-Tishchenko reaction, a strategy that was not pursued.

At this point, the coupling between **54** and **55a** was accomplished through a Yamaguchi esterification,[64] producing the starting material for the alkyne cross-metathesis and ring-closing alkyne metathesis combination.

The optimum conditions for the head-to-tail coupling of **53** were found in the glovebox with the use of the molybdenum catalyst **72**,[91] delivering PMB-protected tetradehydro- disorazole C_1 **22** in 51% yield, along with 11% of the head-to-head coupled product (**Scheme 1.15**). Attempts to perform the metathesis with the deprotected **53** led to a complex mixture of products.



Scheme 1.15: Hulme's alkyne cross-metathesis process for the construction of the macrocycle. *Reagents and conditions*: (a) 1. 2,4,6-trichlorobenzoyl chloride, NEt_3, **55a**, toluene, rt, 30 min, added portionwise to **54** (0.05 M in toluene), DMAP, 40 °C, 30 min each addition, 2. 40 °C, 18 h 71%; (b) 1. 4 Å/5 Å MS (1:1), toluene, rt, 20 min; 2. **72** (20 mol%), rt, 16 h, 51%.

Theoretically, intermediate **22** could be transformed in two steps into disorazole C_1 using the procedures reported by Wipf, namely deprotection of the PMB ethers with DDQ and reduction of the triple bonds with Lindlar catalyst. However, although the deprotecton worked as described, the last step of the synthesis proved to be more troublesome. The hydrogenation of the triple bonds was tested on 1.8 mg of tetradehydro-disorazole C_1 **13**, but the result was unexpectedly disappointing, as after HPLC purification, they obtained 0.8 mg of starting material, a peak corresponding to partial reduction of the alkyne, and only 0.2 mg of product. Hulme and co-workers addressed the lower yield to the quality of the Lindlar catalyst, a problem encountered previously by others.

Even though the work carried out by Hulme resulted in a very small amount of natural product, it provided a novel approach to the synthesis of this complex molecule, and in general to the synthesis of macrocyclic structures. Indeed, such a self-assembly approach exploiting alkyne metathesis had not yet been explored in the synthesis of natural products.

In summary, these three syntheses offer different strategies to access disorazole C_1 and they also identified fundamental issues for eventual future syntheses, such as the importance of the protecting groups or the fact that avoiding a direct dimerization of a fully formed *seco*-acid seems to be the most successful approach, though a less direct one. Hoffmann and Meyers had attempted a homodimerization approach, but neither of them had been able to obtain the desired dimer, because of the competing intramolecular cyclization. Thereafter, turning to a stepwise formation of the macrolactone was one of the key changes that led to the completion of the synthesis.

2. Theoretical Section

The first task of the project was to synthetize disorazole C_1 **1**; after completing the total synthesis, we focused on the design of the analogs using the same strategy. In order to achieve this goal, the strategy had to be highly modular with a potential for late stage functionalization, in order to guarantee the maximum output of diversified structures for biological testing.

2.1. Total Synthesis of Disorazole C_1

Our retrosynthetic analysis of disorazole C_1 **1** identified two main fragments in the molecule: the heterocyclic part with the methoxy group, and the lateral chain with the 1,3-*anti* diol. The two fragments are connected through the triene system. Examining the lateral chain, we found some similarities with another natural product, epothilone A **73** (**Figure 2.1**), which is curiously another secondary metabolite of the myxobacteria *Sorangium Cellulosum*.[92,93] In particular, we were attracted by the gem-dimethyl unit, a structural feature frequently found in many natural products. Unlike the disorazoles, in which this moiety divides the 1,3-diol, in epothilone A it is in the middle of a secondary alcohol and a ketone; in spite of this difference, we still thought that we could take advantage of this similarity.

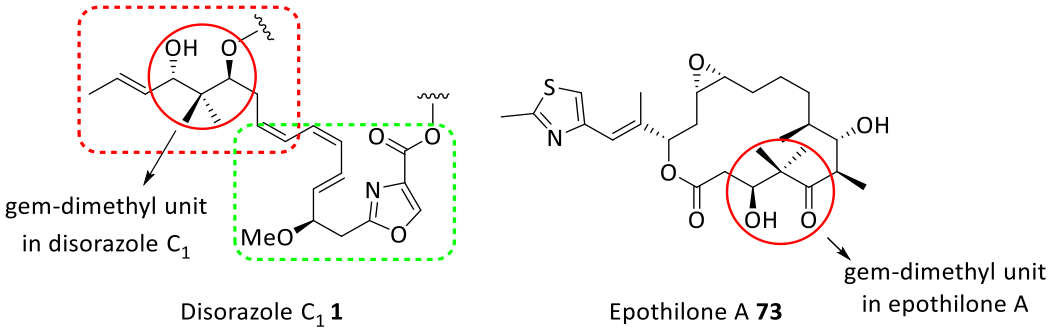
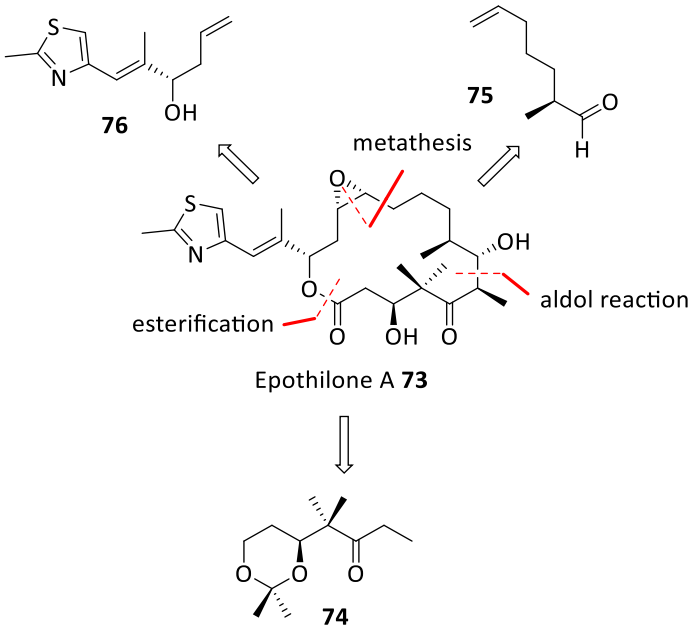


Figure 2.1: Comparison of the gem-dimethyl unit in disorazole C_1 and epothilone A.

2.1.1. From Epothilone to Disorazole

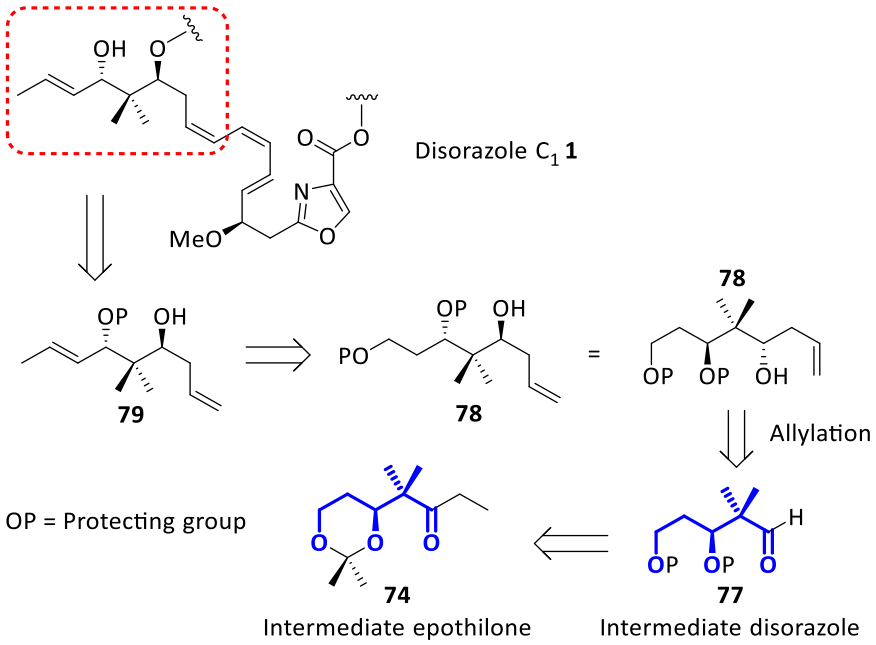
In 1997, our research group published a total synthesis of epothilone A.[94,95] The retrosynthesis of epothilone A made by Schinzer *et al.* gave three main precursors (**Scheme 2.1**): ethyl ketone fragment **74**, aldehyde **75** and thiazole fragment **76**, which were assembled in a convergent manner. Etyhl ketone **74** and aldehyde **75** were coupled in an aldol reaction and the thiazole building block **76** was added by esterification. Final olefin-metathesis reaction

and subsequent epoxidation led to epothilone A **73**. The ethyl ketone fragment **74** was then produced on large scale thanks to a robust sequence of steps.



Scheme 2.1: Retrosyntesis of epothilone A by Schinzer *et al*.

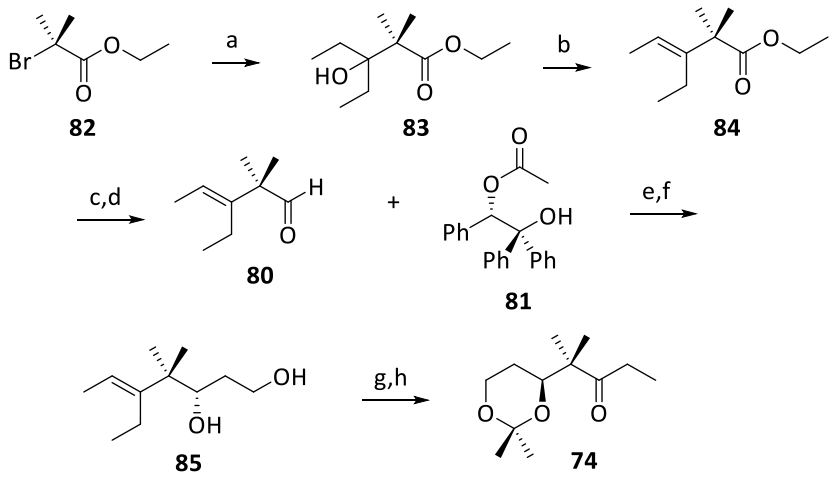
Hence, we decided to use this building block as a starting point of the synthesis of the lateral chain, making the required modifications in order to obtain the 1,3-diol instead of the ketone, as shown in **Scheme 2.2**.



Scheme 2.2: Retrosynthetic analysis of the lateral chain of disorazole C_1.

The only change required to further functionalize fragment **74** was to substitute the ketone with an aldehyde, leading to aldehyde **77**, since an asymmetric allylation reaction could deliver

the desired 1,3-*anti* diol in compound **78**. Thus, aldehyde **77** represented the key intermediate in the synthesis of the lateral chain and it would provide a new access for the synthesis of the disorazoles. Development of alcohol **78** would lead to the construction of the allylic alcohol side chain **79**. In the synthesis of epothilone A, the ethyl ketone **74** was prepared through a diastereoselective aldol reaction between aldehyde **80** and the chiral (*S*)-(–)-HYTRA (2-hydroxy-1,2,2-triphenylethylacetate) **81**, a very powerful tool for diastereoselective additions to chiral as well as achiral aldehydes, which had been reported for the first time by Braun *et al*.[96,97] Aldehyde **80** required for the aldol reaction was synthesized starting from a Reformatsky reaction[98,99] between α-bromo ester **82** and 3-pentanone, giving β-hydroxyester **83**. Dehydration with Sicapent® (P_4O_{10} on silicate carrier) furnished ester **84** and final reduction with lithium aluminum hydride (LAH) and subsequent Swern oxidation[66] gave the desired aldehyde **80**. After the aldol reaction with (*S*)-(–)-HYTRA **81**, removal of the chiral auxiliary produced diol **85**, which was protected as acetonide. Finally, ozonolysis of the double bond produced the key ethyl ketone **74** (**Scheme 2.3**).



Scheme 2.3: Synthesis of the ethyl ketone fragment **74** by Schinzer *et al*. *Reagents and conditions*: (a) Zn dust, 3-pentanone, THF/$B(OMe)_3$ 1:1, reflux, 2 h, then rt, 20 h, 65%; (b) Sicapent®, cyclohexane, reflux, 20 min, 80%; (c) LAH, THF, reflux, 2 h; (d) Swern, 63% (2 steps); (e) LDA, THF, 0 °C, 1 h, then **80**, –78 °C, 1.5 h, 75%; (f) LAH, Et_2O, reflux, 2.5 h, 90 %; (g) acetone, $CuSO_4$, *p*$TsOH{\cdot}H_2O$, pyridine, rt, 24 h, 90%; (h) O_3/O_2, CH_2Cl_2, –78 °C, then PPh_3, rt, 4 h, 85%.

As previously mentioned, the key intermediate for the synthesis of the lateral chain of disorazole C_1 was aldehyde **77**, which means that the substrate for the ozonolysis had to be without the ethyl substituent at C5. Therefore, the modification was to be conceived in aldehyde **80**, which was replaced with aldehyde **86**, as shown in **Figure 2.2**.

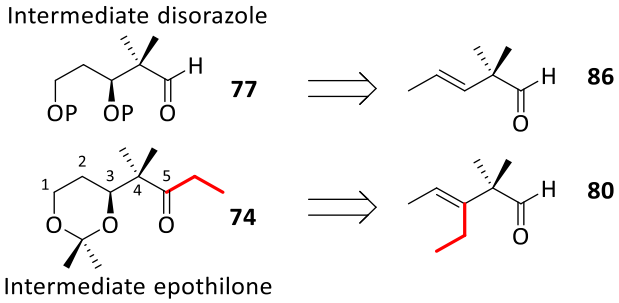


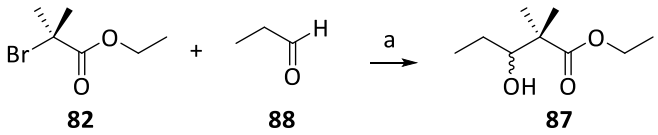
Figure 2.2: Selection of the aldehyde for the aldol reaction with (*S*)-(–)-HYTRA.

2.1.2. Synthesis of the Lateral Chain

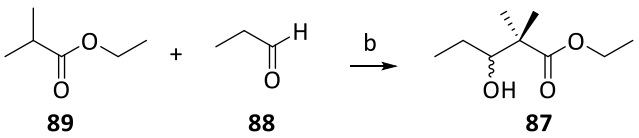
2.1.2.1. Synthesis of Aldehyde 86

Once the first target of the synthesis had been set, we began to explore the first reaction to get the β-hydroxyester **87** (**Scheme 2.4**). The Reformatsky reaction[98,99] was initially tested, using the same α-bromo ester **82** employed for the epothilone synthesis, but this time our target was a secondary alcohol instead of a tertiary one (**83** in **Scheme 2.3**); hence, propionaldehyde **88** was chosen as the second partner in the reaction. After some optimization, we were able to obtain β-hydroxyester **87** in good yield (75%); however, the reaction was not easily reproducible, as the protocol required activation of the zinc dust with trimethylsilyl chloride (TMSCl) and 1,2-dibromoethane, and subsequent dropwise addition of the two reactants **82** and **88** to a refluxing solution of the activated zinc dust. The activation required high temperatures, and once the reaction started, it was very exothermic and hard to control, leading to variable outcomes.

a) First approach: Reformatsky reaction



b) Second approach: aldol reaction

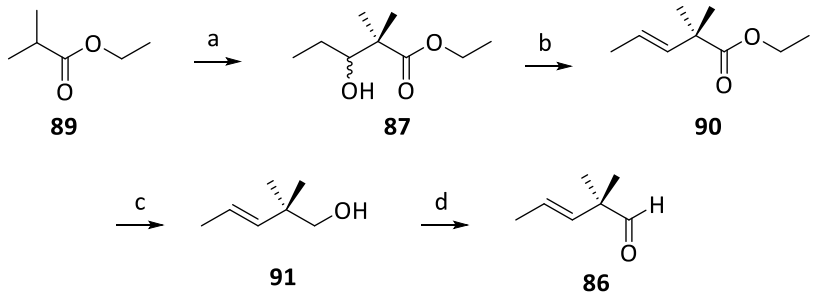


Scheme 2.4: Optimization of the synthesis of β-hydroxyester **87**. *Reagents and conditions*: (a) Zn dust, TMSCl, 1,3-dibromoethane, THF/$B(OMe)_3$ 1:1, reflux, 2 h, then rt, 20 h, 50-75%; (b) LDA, THF, –78 °C, 1 h, then **88**, –50 °C to –10 °C, 30 min, 93%.

Therefore, we decided to search for a more reliable method to produce **87**, and we were pleased to observe that an aldol reaction between ester **89** (ethyl isobutyrate) and propionaldehyde **88** proceeded very smoothly in 93% yield using LDA (lithium diisopropylamide) as a base. This procedure allowed us to produce **87** on large scale (up to 100 grams) and provided us enough material to optimize the following reactions.

The β-hydroxyester **87** was subjected to dehydration with Sicapent®; as expected, the secondary alcohol was found to be slightly less reactive than the tertiary (**83** in **Scheme 2.3**) in the elimination, but the yield was still satisfactory. Only the *E* isomer was detected by ^{1}H and ^{13}C NMR spectroscopy. Reduction of the ester with lithium aluminum hydride afforded the primary alcohol **91**, which was oxidized without purification using a Swern oxidation,[66] and giving the desired aldehyde **86**. At first, we could only reach 60% yield in the oxidation, and we thought that the problem might be the purification: the similar boiling point of triethylamine (used in excess during the Swern oxidation) and the product made the distillation quite difficult. Fortunately, a simple washing with 1 M HCl (1 molar hydrochloric acid) removed most of the triethylamine and raised the yield to 90%.

The synthesis of aldehyde **86** is very straightforward, with a total yield of 51.2%, and it does not require any chromatography, because all the compounds are relatively low boiling liquids, and they can be purified by distillation. The sequence is summarized in **Scheme 2.5**.

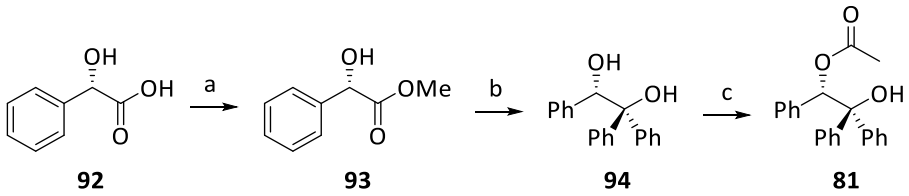


Scheme 2.5: Synthesis of aldehyde **86**. *Reagents and conditions*: (a) LDA, THF, –78 °C, 1 h, then **88**, –50 °C to –10 °C, 30 min, 93%. (b) Sicapent®, cyclohexane, reflux, 30 min, 68%; (c) LAH, THF, reflux, 2 h, 90%; (d) Swern, 90%.

2.1.2.2. Synthesis of (*S*)-(–)-2-hydroxy-1,2,2-triphenylethylacetate 81

While working on the synthesis of aldehyde **86**, we also focused on the other piece for the aldol reaction, (*S*)-(–)-HYTRA **81**, which was synthesized using the procedure reported by Braun.[97] The starting point was (*S*)-(+)-mandelic acid **92** (**Scheme 2.6**), an inexpensive chiral reagent, which was methylated with methanol and catalytic sulphuric acid giving (*S*)-(+)-

methyl mandelate **93** in 88% yield. A Grignard reaction[100] with excess of phenylmagnesium bromide (PhMgBr) produced diol **94**.



92 **93** **94** **81**

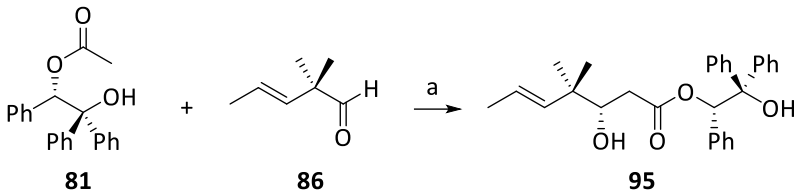
Scheme 2.6: Synthesis of (*S*)-(–)-HYTRA **81**. *Reagents and conditions*: (a) conc. H_2SO_4, MeOH, reflux 4 h, 88%; (b) 3 M PhMgBr, Et_2O/THF, 0 °C to rt, overnight, then reflux, 1 h, 69%; (c) Ac_2O, $Sc(OTf)_3$, CH_3CN, rt, 3 h, 84%.

At this point, the protocol developed by Braun and co-workers contemplated the acetylation of the less hindered alcohol using acetyl chloride and pyridine, a reaction that worked quite well (90%), but the work up was tedious and time consuming. Indeed, the reaction mixture had to be quenched with water and, after removing the solvent (CH_2Cl_2) under reduced pressure, the resulting solid was filtered and dissolved in hot toluene. Then, an azeotropic distillation was used to remove the remaining water, and finally the product was filtered from the solvent. Hence, we decided to employ a different procedure for the acetylation of the secondary alcohol, and we found a very easy and efficient protocol in the literature.[101,102] Diol **94** was treated with acetic anhydride and catalytic amount of scandium (III) triflate (trifluoromethanesulfonate) in acetonitrile at room temperature, giving (*S*)-(–)-HYTRA **81** in 84% yield after a simple filtration of the reaction mixture.

As well as the synthesis of aldehyde **86**, the sequence to get (*S*)-(–)-HYTRA **81** has no chromatography, since the three compounds (**93**, **94** and **81**) are crystalline solids and they are easily purified by crystallization; plus, HYTRA is a recyclable auxiliary, as explained in the next section. This allows the production of big amounts of the two coupling partners needed for the aldol reaction.

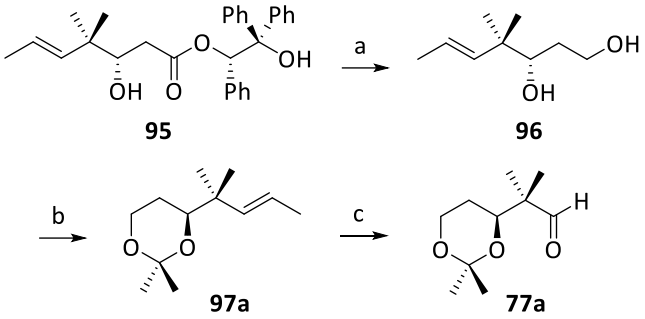
2.1.2.3. Synthesis of the Key Intermediate Aldehyde 77

Aldehyde **86** and (*S*)-(–)-HYTRA **81** were coupled in a diasteroselective aldol reaction (**Scheme 2.7**), in which (*S*)-(–)-HYTRA was doubly deprotonated with two equivalents of LDA in THF, and then the addition of the aldehyde at –78 °C resulted in the formation of crystalline β-hydroxyester **95** in 77% yield and excellent diastereoselectivity (96% *de*, by HPLC).



Scheme 2.7: Diasteroselective aldol reaction between **81** and **86**. *Reagents and conditions*: (a) LDA, THF, – 78 °C to 0 °C, 1 h, then **86**, –78 °C, 2.5 h, 77% (96% *de*).

This procedure sets the first stereocenter of the molecule and the peculiar gem-dimethyl unit as well, two of the most challenging chemical features of the disorazoles.

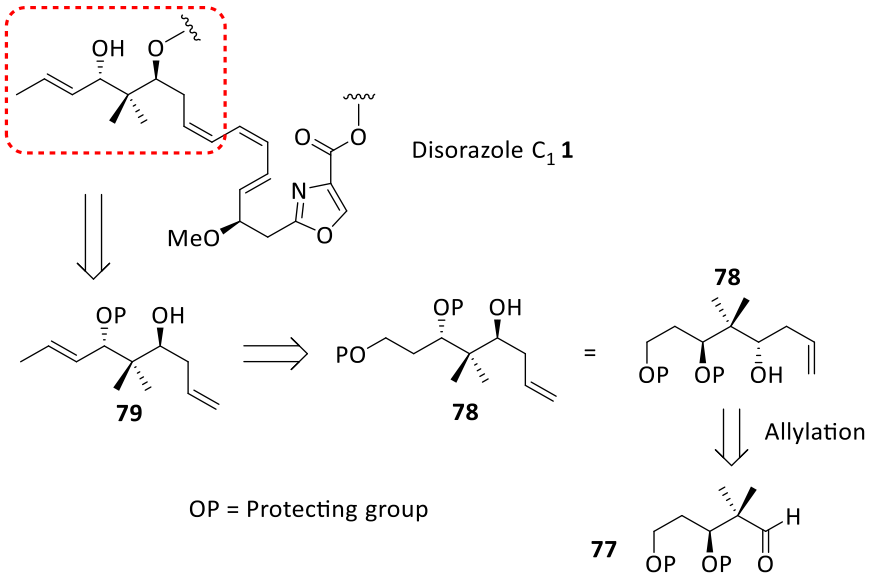


Scheme 2.8: Synthesis of Aldehyde **77a**. *Reagents and conditions*: (a) LAH, Et_2O, reflux, 2.5 h, 90%; (b) acetone, $CuSO_4$, *p*TsOH·H_2O, pyridine, rt, 24 h, 90%; (c) O_3/O_2, CH_2Cl_2, –78 °C, then PPh_3, rt, 4 h, 85%.

Next, the auxiliary was easily removed by LAH reduction in refluxing Et_2O, leading to diol **96** in 90% yield and (*S*)-(–)-1,1,2-triphenyl-1,2-ethandiol **94**, which may be recovered and used to produce HYTRA **81** again. With diol **96** in hand, a decision had to be taken regarding the protecting group for the two free alcohols. Initially, we decided to use the acetonide as for the epothilone, so that we could check the feasibility of the sequence to get aldehyde **77** and test the following reactions. However, the evolution of the route to the lateral chain led us to change the protecting groups more than once. **Scheme 2.9** summarizes the last steps of the synthesis of aldehyde **77**. The protection of the diol as the 1,3-dioxolane **97a** worked as expected, and the ozonolysis of the double bond afforded the desired aldehyde **77a** in 85% yield.

2.1.2.4. Investigation of the Allylation Reaction

To complete the scaffold of the lateral chain from aldehyde **77**, another stereocenter had to be established, along with a homoallylic unit. Thus, we imagined that an asymmetric allylation could be the right reaction to get the 1,3-diol in compound **78** (**Scheme 2.9**).

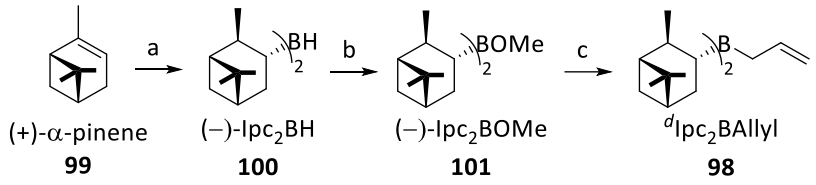


Scheme 2.9: Retrosynthesis of the lateral chain and reason behind the choice of the allylation.

Therefore, we began to explore the addition of the homoallylic unit with a Brown stereoselective allylboration.[103] The general procedure developed by Brown relies on the condensation of an aldehyde with the chiral ligand $Ipc_2BAllyl$ **98** (allyldiisopinocampheylborane) at low temperatures (–100 °C to –78 °C), to furnish the corresponding secondary homoallylic alcohol in great enantiomeric excess (83-96% *ee*), after alkaline (3 M NaOH) hydrogen peroxide work up (**Scheme 2.10**).[103] $^{l}Ipc_2BAllyl$ and $^{d}Ipc_2BAllyl$ **98** can be prepared in three steps from the cheap (+) or (–)-α-pinene, respectively: for instance, $^{d}Ipc_2B(allyl)$ **98** is prepared starting from the hydroboration of (+)-α-pinene **99** with borane dimethylsulfide ($BH_3{\cdot}SMe_2$), and equilibration for one day, during which the symmetrical dimer (–)-Ipc_2BH (diisopinocampheylborane) **100** crystallizes preferentially.

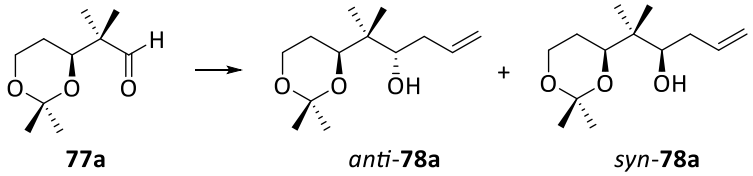
Scheme 2.10: General procedure of the Brown allylation. *Reagents and conditions*: (a) Et_2O, –100 °C to –78 °C, then 3 M NaOH, H_2O_2, rt.

Then, methanolysis of **100** proceeds cleanly to give (–)-Ipc_2BOMe (methoxydiisopinocampheylborane) **101**, and final treatment with allylmagnesium bromide (allylMgBr) provides $^{d}Ipc_2BAllyl$ **98**, as depicted in **Scheme 2.11**. This reagent is not stable under normal atmosphere and it is generally prepared *in situ* and used directly, without prior isolation.



Scheme 2.11: Preparation of Brown's reagent **98**. *Reagents and conditions*: (a) $BH_3{\cdot}SMe_2$, THF, 0 °C, 24 h, 72%; (b) MeOH, Et_2O, 0 °C, 1 h, 100%; (c) AllylMgBr, Et_2O, 0 °C to rt, 1 h.

We began exploring the Brown allylboration on our aldehyde **77a**, hoping to get the desired 1,3-*anti* diol **78a** (**Scheme 1.12**) in acceptable yield and stereoselectivity. Nevertheless, the first attempts were rather disappointing.

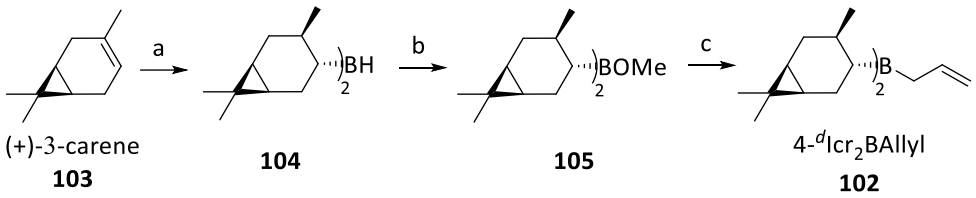


Scheme 1.12: Allylation on aldehyde **77a** using Brown's conditions.

After preparing the reagent, we tested the condensation *in situ* at –100 °C, but no reaction occurred in either Et_2O or THF. Therefore, we decided to raise the temperature to –78 °C, and in this case the condensation did take place, but with almost no chiral induction, with the *anti*/*syn* ratio being 1.2:1 (9.1% *de*). Several attempts to improve the reaction only managed to reach a good yield (80%), but no improvements were made in the selectivity.

Since the reaction did not occur at –100 °C, we thought that the presence of magnesium (Mg^{2+}) salts could decrease the rate of the reaction. In fact, it is established that during the last step of the preparation of the reagent, MgBrOMe salt is formed, and it can complex with the boron atom of the reagent, causing the reaction to slow down. The resulting complex becomes more stable at lower temperatures.[104] For this reason, we tried the reaction after filtration of the magnesium salts, as described by Brown *et al*. Unfortunately, there was no reaction even under salt-free conditions at –100 °C, and no improvements in the *anti*/*syn* ratio were observed at –78 °C.

Given the poor outcome of the reaction using reagent **98**, we turned our attention to reagent **102**, B-Allylbis(4-isocaranyl)borane (4-^{d}Icr$_2$BAllyl), which had been reported to give better enantioselectivities (87-99% *ee*).[105] Reagent **102** is prepared from (+)-3-carene **103** using the exact same conditions described for reagent **98**: hydroboration with $BH_3{\cdot}SMe_2$, methanolysis and treatment with AllylMgBr (**Scheme 2.13**).

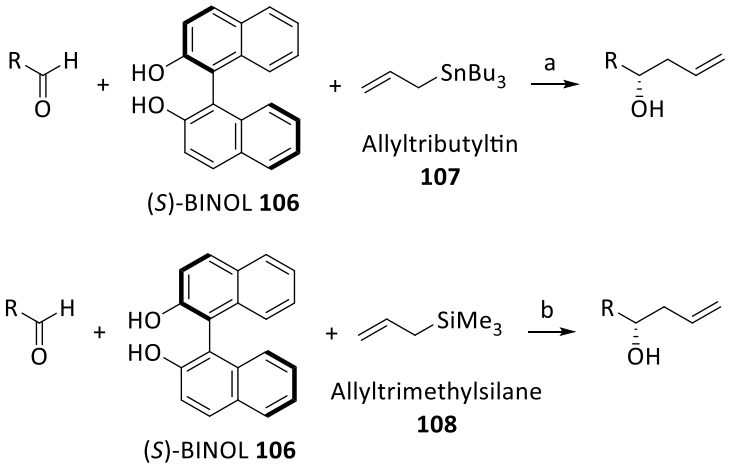


Scheme 2.13: Preparation of reagent **102**. *Reagents and conditions*: (a) $BH_3{\cdot}SMe_2$, THF, 0 °C, 24 h, 72%; (b) MeOH, Et_2O, 0 °C, 1 h, 100%; (c) AllylMgBr, Et_2O, 0 °C to rt, 1 h.

Indeed, aldehyde **77a** underwent condensation with **102** furnishing alcohol **78a** in outstanding diastereoselectivity (89% *de*), though the yield was not great (54%).

In spite of the good result obtained with $Icr_2BAllyl$, we decided not to pursue this path, because the starting material for this reagent, (+)-3-carene **103**, is very expensive and it would not be exploitable on large scale.

We started to explore completely different reagents, beginning with the chiral (*S*)-BINOL **106**. The first attempt was a Keck allylation,[106] which involves the Lewis acid-promoted addition of allyltributyltin **107** to the aldehyde, in the presence of the chiral ligand **106**. The Lewis acid is generally Ti(O*i*Pr)$_4$ (titanium tetraisopropoxide), as shown in **Scheme 2.14**.



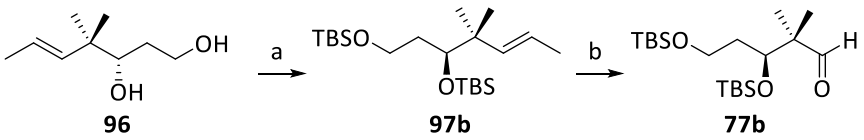
Scheme 2.14: General procedure of the Keck allylation. *Reagents and conditions*: (a) Ti(O*i*Pr)$_4$, 4Å MS, CH_2Cl_2, –78 °C to –20 °C; (b) TiF_4, CH_2Cl_2/CH_3CN, 0 °C.

An alternative procedure employs TiF_4 (titanium tetrafluoride) as Lewis acid and allyltrimethylsilane **108** as the allylic source; this procedure was also used by Wipf in the synthesis of disorazole C_1.[62,65] Unfortunately, none of these reactions gave the desired product, even at room temperature. Considering that Hoyveda *et al*. used the Leighton reagent **109**[76] for the allylation of a similar hindered aldehyde (**39** in **Scheme 1.8**) in the synthesis of disorazole C_1,[107] we decided to try this reagent, but once again we had no success. **Table 2.1** summarizes all the reagents tested for the allylation on aldehyde **77a**.

Reagent	Temperature	Conditions	Yield	*anti*:*syn* (*de*)
Ipc$_2$BAllyl (98)	–100 °C	Mg^{2+} salts present	No reacton	-
Ipc$_2$BAllyl (98)	–78 °C	Mg^{2+} salts present	80%	1.2:1 (9.1%)
Ipc$_2$BAllyl (98)	–100 °C	Mg^{2+} salts absent	No reaction	-
Ipc$_2$BAllyl (98)	–78 °C	Mg^{2+} salts absent	80%	1.2:1 (9.1%)
Icr$_2$BAllyl (103)	–78 °C	Mg^{2+} salts present	54%	18:1 (89%)
(*S*)-Binol/Allyltributyltin	–78 °C to rt	4Å MS	No reaction	-
(*S*)-Binol/Allyltrimethylsilane	0 °C to rt	-	No reaction	-
Leighton reagent (109)	-15 °C to rt	-	No reaction	-

Table 2.1: Conditions tried for the allylation on aldehyde **77a**.

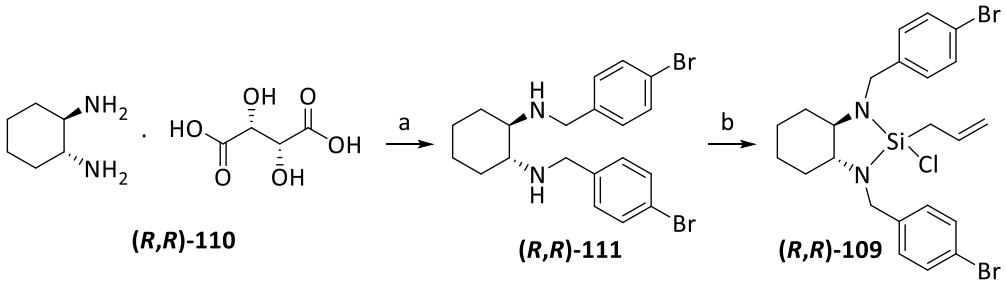
After all these failures, we speculated that a change in the protecting groups could perhaps give a different outcome, since the substrate resulted particularly hindered, and the protecting groups could influence the reactivity. Two TBS group were chosen for the protection of the diol, and **96** was converted quantitatively in compound **97b**, which was subjected to ozonolysis affording aldehyde **77b**, as shown in **Scheme 2.15**.



96 **97b** **77b**

Scheme 2.15: Synthesis of aldehyde **77b**. *Reagents and conditions*: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min, then 0 °C, 3 h, 99%; (b) O_3/O_2, CH_2Cl_2, –78 °C, then PPh_3, rt, 4 h, 78%.

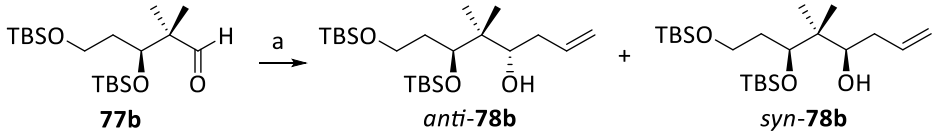
With aldehyde **77b**, we decided to try the Leighton allylation. The reagent **(*R*,*R*)-109** (**Scheme 2.16**) can be prepared in two steps from the chiral (1*R*,2*R*)-(+)-1,2-diaminocyclohexane·L-tartrate **(*R*,*R*)-110**, which upon condensation with 4-bromobenzaldehyde affords the diamine **(*R*,*R*)-111**, after reduction with sodium borohydride ($NaBH_4$).



(*R*,*R*)-110 **(*R*,*R*)-111** **(*R*,*R*)-109**

Scheme 2.16: Preparation of the Leighton reagent **(*R*,*R*)-109**. *Reagents and conditions*: (a) 1. 4-bromobenzaldehyde, K_2CO_3, methanesulfonic acid, H_2O/CH_2Cl_2/EtOH 2:2:1, rt, 12 h, then reflux, 1 h, 2. $NaBH_4$, MeOH, reflux, 1 h, 83%; (b) Allyltrichlorosilane, DBU, CH_2Cl_2, 0 °C, 2 h, then rt, 13 h, 88%.

The diamine is then treated with allyltrichlorosilane in the presence of DBU to give the active reagent **(*R*,*R*)-109**.[76] Unlike the Brown's reagent, **109** is more stable and it may be stored in a freezer under nitrogen, and used when needed. The scandium-catalyzed reaction between aldehyde **77b** and reagent **(*R*,*R*)-109** (**Scheme 2.17**) was slow at –15 °C, but it went to completion, leading to the disappearance of the starting material after 48 hours. However, after acid work up (1 M HCl) employed to remove the diamine **111** generated during the reaction, the primary TBS was not stable and the final yield of the desired **78b** was only 51%. Fortunately, an alternative work up with TBAF (tetrabutylammonium fluoride),[77] resulted in TBS retention and 90% yield. Analysis by ^{1}H and ^{13}C NMR showed a 10:1 mixture of *anti* and *syn* diastereomers (83% *de*).



77b *anti*-**78b** *syn*-**78b**

Scheme 2.17: Leighton allylation on aldehyde **77b**. *Reagents and conditions*: (a) **(*R*,*R*)-109**, $Sc(OTf)_3$, CH_2Cl_2, – 15 °C, 48 h, then TBAF, rt, 30 min, 90% (83% *de*).

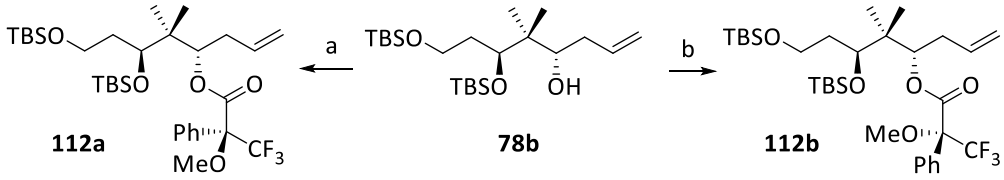
Raising the temperature to 0 °C did not increase the rate of the reaction, and warming to ambient temperature did reduce the reaction time to 24 hours, but it also led to a dramatic drop of the diastereomeric ratio (4:1 instead of 10:1).

2.1.2.5. Configuration of the New Stereocenter after the Allylation

After the allylation from aldehyde **77b** to **78b**, a new stereocenter was formed, and we believed that the Mosher's method[108] was a suitable way to assign the configuration of the newly formed secondary alcohol in **78b**. Nevertheless, the results of this analysis were misleading, which was rather surprising, but in agreement with Mosher's warning about the application of his methodology to molecules containing other chiral centers, heteroatoms or conformational restraint.

Following the reported procedures, the analysis was conducted treating alcohol **78b** with (*R*)-(–)- and (*S*)-(+)-MTPA-Cl in the presence of triethylamine and DMAP (4-dimethylaminopyridine), in two separate experiments, affording (*S*)-ester **112a** and (*R*)-ester **112b** respectively (note the change in the relative priority of the groups), as shown in **Scheme 2.18**.

The Mosher's method is based on the major conformation of the esters, which is shown in **Figure 2.3**. The CF_3 group, the O–CO bond and the methine proton of the secondary alcohol are coplanar.



Scheme 2.18: Synthesis of esters **112a** and **112b**. *Reagents and conditions*: (a) (*R*)-(–)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, rt, overnight, 98%; (b) (*S*)-(+)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, rt, overnight, 83%.

According to this conformation, which should be the one that dominates the spectroscopic characteristics of the MPTA esters, the phenyl substituent has an anisotropic effect on the proximal protons, resulting in a more upfield chemical shift of the affected protons in the NMR spectra. In the case of the (*S*)-Mosher ester, the affected protons belong to R_2, while for the (*R*)-Moher ester they belong to R_1. As a result, the difference in chemical shifts for analogous pair in the two Mosher esters (defined as $\Delta\delta^{SR}$) will be positive for all the protons residing in R_1 and negative for protons residing in R_2.

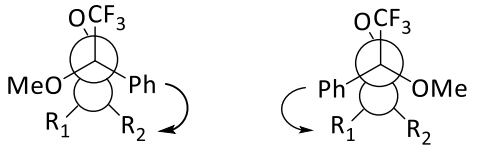


Figure 2.3: Major conformation of the Mosher esters.

In order to assign which protons belong to R_1 and which protons to R_2, a 3D model was built, revealing that the protons of the homoallylic chain are part of R_1, and the rest reside within R_2. **Figure 2.4** shows a PyMOL[109] model of the two Mosher esters **112a** and **112b**, and **Figure 2.5** indicates R_1 and R_2 based on the conformations displayed in the models.

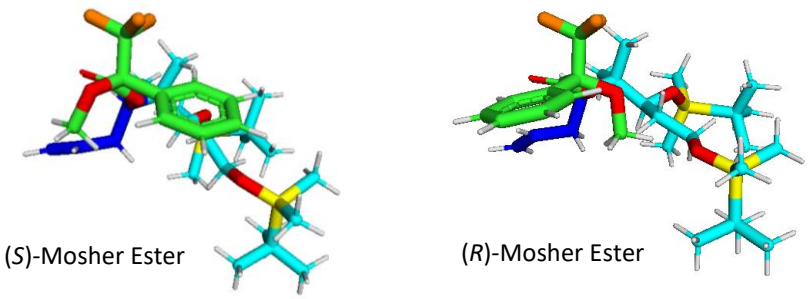
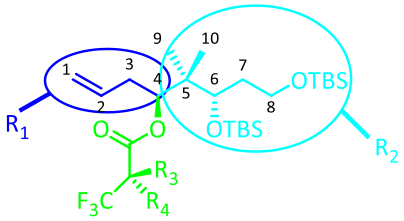


Figure 2.4: PyMOL model of **112a** and **112b**.



112a: R_3 = Ph, R_4 = OMe
112b: R_3 = OMe, R_4 = Ph

Figure 2.5: Assignment of R_1 and R_2 for **112**.

The $\Delta\delta^{SR}$ values are summarized in **Table 2.2**. Unfortunately, the measurements were in disagreement with the predicted data, as all the $\Delta\delta^{SR}$ for R_1 were negative, and all the $\Delta\delta^{SR}$ for R_2 were positive, leading us to think that we had the wrong diastereomer of **78b** (*syn*-diol instead of *anti*).

Protons	*δ (S)-Ester (ppm)*	$\Delta\delta^{SR}(\delta_S - \delta_R)$	*δ (R)-Ester (ppm)*	
1 (2H)	4.96	–0.06	5.02	R_1
2 (1H)	5.65	–0.06	5.71	
3a (1H) **3b (1H)**	2.45 2.24	–0.04 –0.05	2.49 2.29	
4 (1H)	5.24	–0.02	5.26	
6 (1H)	3.66	+0.01	3.65	R_2
7a (1H) **7b (1H)**	1.76 1.53	+0.02 +0.01	1.74 1.52	
8 (2H)	3.71-3.59	+0.02	3.69-3.57	
9 (3H)	0.84	+0.08	0.76	
10 (3H)	0.91	+0.04	0.87	
TBSa (18H) **TBSb (12H)**	0.90 0.06	+0.01 0.00	0.89 0.06	

Table 2.2: NMR data and $\Delta\delta^{SR}$ for the Mosher esters **112a** and **112b**.

On the contrary, another analysis proved that the configuration of the diol was *anti*. Indeed, since the new secondary alcohol formed a 1,3-diol, we could apply the method developed by Rychnovsky *et al*. to determine the relative stereochemistry of 1,3-diols.[110,111] The analysis relies on the conformational properties of the acetonides derived from the 1,3-diols: the *syn*-acetonides exist in the expected chair conformation with the two alkyl substituents in equatorial positions; while the *anti*-acetonides adopt a twist-boat conformation to avoid the 1,3-diaxial interactions, which would be present in a chair conformation (**Figure 2.6**).

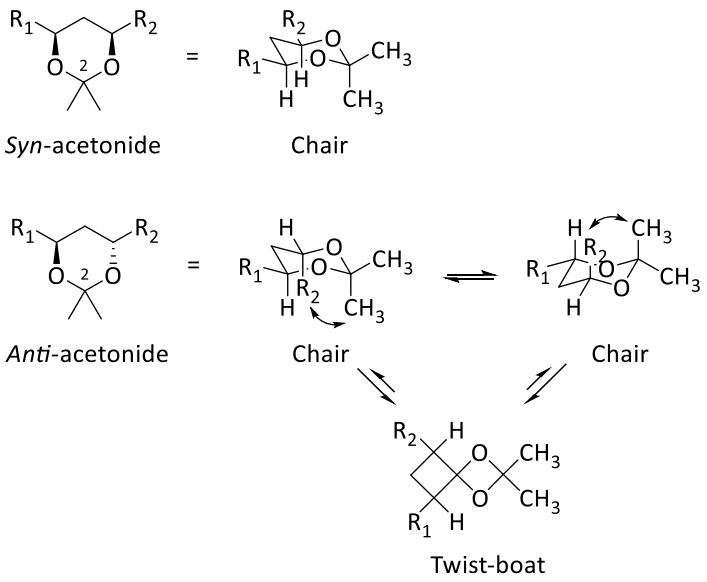
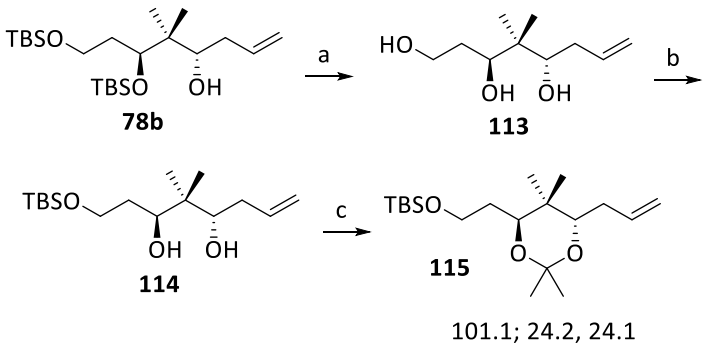


Figure 2.6: Conformation of *syn*- and *anti*-acetonides derived from 1,3-diols.

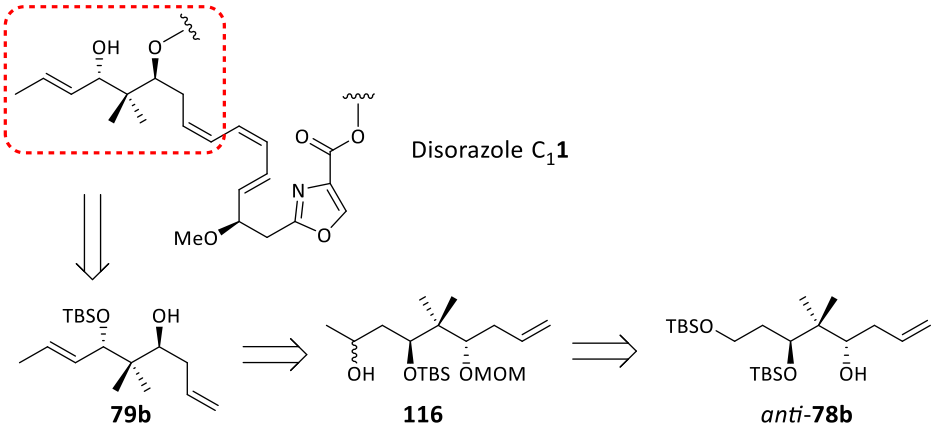
This difference in conformation can be distinguished by ^{13}C NMR, as the two methyl groups and the C2 central carbon of the acetonide follow a regular pattern: *syn*-acetonides show the axial methyl group around 30 ppm and the equatorial at 19 ppm, whereas *anti*-acetonides have both methyl groups at 25 ppm. Moreover, the C2 acetal carbon is typically found around 98.5 for *syn* and 100 for *anti*-acetonides. The application of this method to our molecule required a couple of steps: removal of both TBS groups by TBAF, selective protection of the primary alcohol with TBSCl, and final acetonide formation using dimethoxypropane (**Scheme 2.19**); the use of acetone and $CuSO_4$ did not work, probably due to steric hinderance.



Scheme 2.19: Synthesis of acetonide **115**. *Reagents and conditions*: (a) TBAF, THF, rt, overnight; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h; (c) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 1 h, 69% (3 steps).

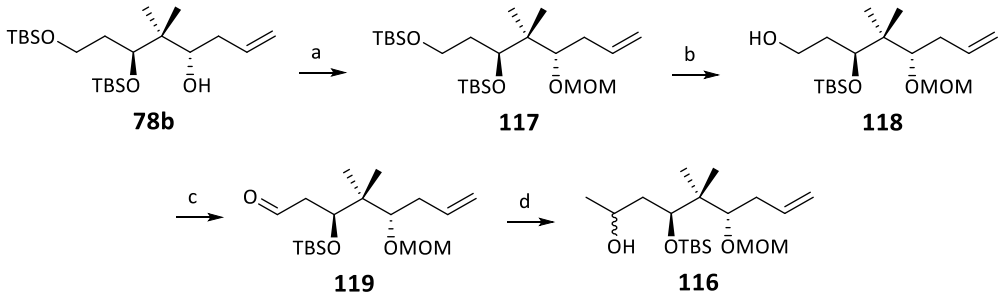
Compound **115** showed the typical signals of an *anti*-acetonide with the acetal carbon at 101.1 and the two methyl groups at 24.2 and 24.1, confirming the correct configuration of the new stereocenter.

2.1.2.6. Completion of the Lateral Chain: First Approach



Scheme 2.20: First approach to the synthesis of the lateral chain.

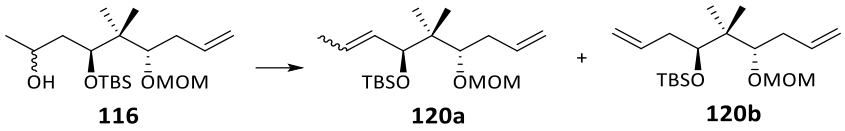
Satisfied of the outcome of Leighton allylation that had set the 1,3-*anti* diol, we envisioned that **78b** could be transformed in alcohol **116** by protection of the free alcohol, and subsequent selective deprotection of the primary TBS group, followed by oxidation of the resulting alcohol and addition of the methyl Grignard reagent to the aldehyde. Afterwards, elimination of the free alcohol would give the complete scaffold of the lateral chain in **79b**, as depicted in **Scheme 2.20**.



Scheme 2.21: Synthesis of alcohol **116**. *Reagents and conditions*: (a) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to 50 °C, 92%; (b) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 5 h; (c) Swern, 83% (2 steps); (d) MeMgBr, Et_2O, 0 °C, 1 h, 85%.

Homoallylic alcohol **78b** was protected as MOM (methoxymethyl) ether furnishing compound **117** in high yield (92%), and the primary TBS group was removed using CSA (camphorsulfonic acid) at 0 °C. Oxidation using Swern[66] conditions gave aldehyde **119**, and reaction with methylmagnesium bromide (MeMgBr) afforded racemic alcohol **116** in 85% yield (**Scheme 2.21**).

Unfortunately, the elimination of the secondary alcohol (**Scheme 2.22**) proved to be more complicated than expected. Various conditions were tested, but none of them resulted in the formation of **120a** in a satisfactory yield. First, we hoped to get the desired product using the same conditions we employed for alcohol **87** (described in **Scheme 2.5**).



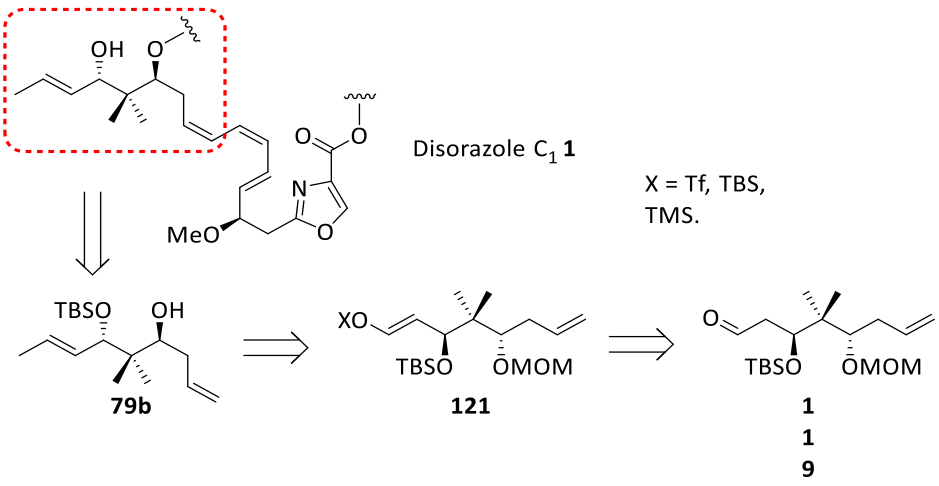
Scheme 2.22: Elimination of the secondary alcohol from **116**.

Yet, treatment of **116** with Sicapent® led to a complex mixture of products. Better results were obtained with $POCl_3$ (phosphorus oxychloride) and pyridine, since the elimination occurred, but a 1:1 mixture of regioisomers **120a** and **120b** was isolated. Comparable results were observed with the use of $Cu(OTf)_2$ (copper trifluoromethanesulfonate);[112] whereas reaction with methyl *p*-toluenesulfonyl chloride and subsequent elimination of the more reactive tosylate with sodium methoxide in methanol[113] produced the right regioisomer **120a**, but in low yield (45%). In all of the cases, the *E*-isomer was predominant when **120a** was formed, but despite the efforts, we could not improve the yields of these eliminations. **Table 2.3** shows the reagents tested for the synthesis of **120a**.

Reagent	Temperature	Yield	120a:120b
$POCl_3$/pyridine	0 °C to 100 °C	70%	1:1
$Cu(OTf)_2$	100 °C	72%	1.5:1
TosylCl-MeONa/MeOH	70 °C	45%	Only **120a**

Table 2.3: List of reagents tested for the synthesis of **120a**.

2.1.2.7. Completion of the Lateral Chain: Second Approach

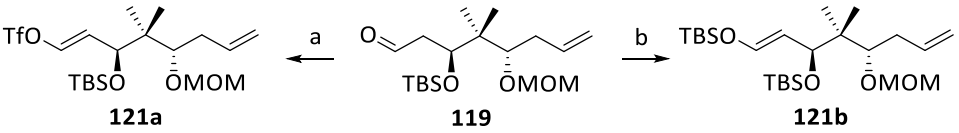


Scheme 2.23: Second approach to the synthesis of the lateral chain.

While working at the first approach to finish the lateral chain, we also tried a different strategy, which involved the trapping of the enolate derived from aldehyde **119**, in order to get the double bond in the right position. The enolate could be trapped as a silyl enol ether or

a vinyl triflate (compound **121**, **Scheme 2.23**). Then, a cross-coupling reaction with a methyl organometallic compound would give the desired olefin.

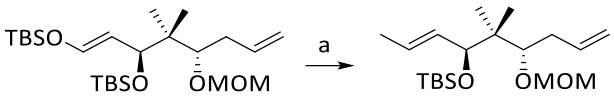
We began testing the transformation of aldehyde **119** in the corresponding vinyl triflate **121a**, which we believed was more reactive than a silyl enol ether in a cross-coupling reaction. However, treatment of aldehyde **119** with triflic anhydride (Tf_2O) in the presence of the sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine[114] afforded an unidentified mixture of products. Enolate formation using a strong base, such as LDA or potassium bis(trimethylsilyl)amide (KHMDS), and subsequent trapping with phenyl triflimide[115] (Tf_2NPh) or Comins' reagent[116] led to poor yields of the desired product **121a** (not more than 10%).



121a **119** **121b**

Scheme 2.24: Transformation of aldehyde **119** in the corresponding vinyl triflate **121a** and silyl enol ether **121b**. *Reagents and conditions*: (a) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, 1,2-DCE or KHMDS/LDA, Comins' reagent/Tf_2NPh, THF, 10%; (b) TBSCl, DBU, CH_2Cl_2, 35 °C, 78% (*E*:*Z* > 95/5).

Hence, we turned our attention to the silyl enol ether formation, determined to test a nickel-catalyzed cross coupling of silyl enol ethers with Grignard reagents, a procedure described by Kumada *et al*.[117] The use of TBSCl and DBU at 35 °C[118] furnished the thermodynamic *E*-product **121b** in 78% yield, as depicted in **Scheme 2.24**. The use of TMSCl instead of TBSCl was possible, but the resulting TMS enol ether was unstable on chromatographic column, and the crude material was not pure enough to be employed in the next step. Though the cross-coupling was reported for TMS enol ethers, we attempted to get compound **122** from the TBS enol ether **121b** (**Scheme 2.25**). Reaction of **121b** with methyl magnesium bromide (MeMgBr) in the presence of catalytic amounts of $Ni(acac)_2$ (nickel acetylacetonate) was very slow, and even at high temperatures for several days, the amount of starting material converted was not more than 20%.



121b **122**

Scheme 2.25: Cross-coupling reaction. *Reagents and conditions*: (a) 10% mol $Ni(acac)_2$, MeMgBr, touene, MW, 120 °C, 40 min, 45%.

A slight improvement could be made performing the reaction in a microwave at 120 °C for 40 minutes, raising the yield to 45%. Higher temperatures or longer reaction times led to decomposition of the material.

2.1.2.8. Completion of the Lateral Chain: Third Approach

Although we were able to synthesize **122**, which represented the complete scaffold of the lateral chain, we were not satisfied by the yield of the last step. Besides, the plan was now to transform the terminal olefin of **122** into a *Z*-vinyl iodide, in order to have a coupling partner ready for a future cross-coupling with the rest of the molecule, but this was not an easy task. One possibility was to employ Hoyveda's cross-metathesis with vinyl–B(pin) and subsequent reaction with iodine.[74,75] While considering the best strategy, we realized that **122** had a center of symmetry, and so did every compound from **78b**.

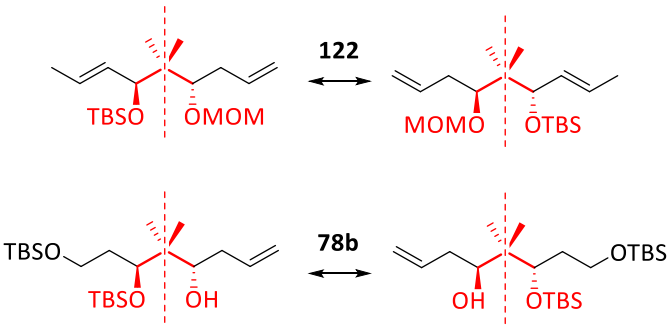


Figure 2.7: Symmetry of the lateral chain.

As shown in **Figure 2.7**, this symmetry implied that rotating the molecule, the stereochemistry of the chiral centers did not change, allowing us to develop the external parts of the structure in a different way. As depicted in **Figure 2.8**, we imagined that a simple isomerization of the terminal olefin in **78b** or **117** could produce the allylic side of **122**, avoiding the complicated enolate trapping and cross-coupling sequence.

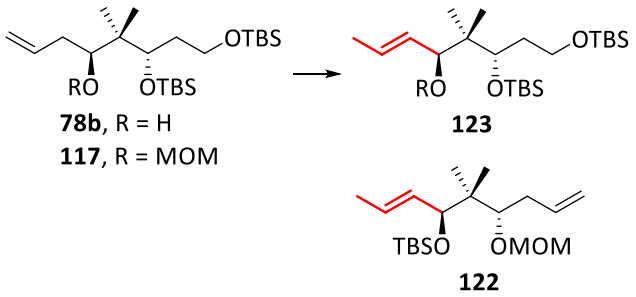
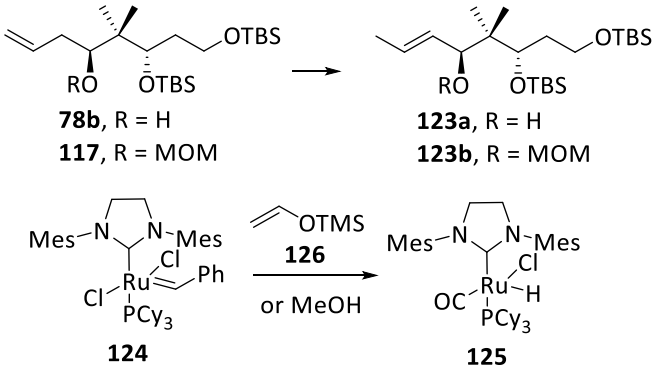


Figure 2.8: Comparison of **122** and isomerization product **123**.

Thus, we tested the isomerization on both compounds, **78b** and **117**. The first attempt was unsuccessful, as exposure of **78b** to catalytic $PdCl_2(CH_3CN)_2$[119] produced many side products. Better results were obtained with the use of Grubbs second-generation catalyst **124**, which had been reported to decompose into the corresponding ruthenium hydride **125** in the presence of vinyloxy-trimethylsilane **126**, and catalyze isomerization reactions (**Scheme 2.26**).[120] This procedure resulted in quantitative amounts of **123a**, as an inseparable 7:1 mixture of *E* and *Z* isomers. The reaction required 10 equivalents of **126**, in order to transform the ruthenium carbene **124** into the ruthenium hydride **125**.

Since the same reaction had been also reported to occur with methanol as solvent[121] and in absence of **126**, we decided to try this alternative. Heating a solution of **78b** and Grubbs II **124** in methanol at 60 °C for 24 hours produced a 1:1 mixture of starting material and product. Fortunately, the same conditions on compound **117** generated **123b** in 90% yield as a mixture of 12:1 *E*/*Z* isomers.



Scheme 2.26: Isomerization of the terminal olefin in **78b** or **117**.

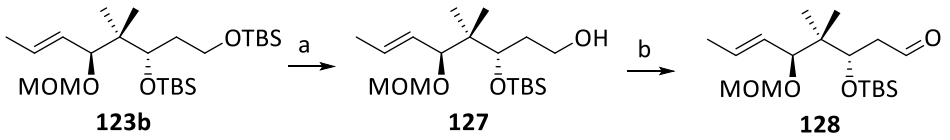
Table 2.4 summarizes the outcomes of the isomerization reactions. The yield using **126** was higher (100%), but the combination Grubbs II-MeOH on **117** was much more scalable and with a better *E*/*Z* selectivity; therefore, we decided to choose this procedure.

Starting	Reagent	Temperature	Yield	*E*/*Z* ratio
78b	**$PdCl_2(CH_3CN)_2$**	100 °C	No product	-
78b	**Grubbs II (124) / 126**	100 °C	100%	7:1
78b	**Grubbs II (124) / MeOH**	60 °C	50%	10:1
117	**Grubbs II (124) / MeOH**	60 °C	90%	12:1

Table 2.4: Optimization of the reaction conditions for the isomerization.

From **123b**, we could get aldehyde **128** exploiting the same selective deprotection-oxidation sequence that we previously employed: treatment of **123b** with CSA at 0 °C led to

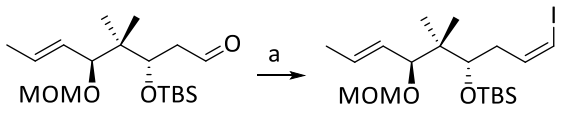
alcohol **127**, which was oxidized using Swern conditions affording aldehyde **128**, as shown in **Scheme 2.27**.



123b **127** **128**

Scheme 2.27: Synthesis of aldehyde **128**. *Reagents and conditions*: (a) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 5 h; (b) Swern, 83% (2 steps).

Aldehyde **128** could be transformed in vinyl iodide **129** via a Stork-Zhao olefination,[83] a reaction employed also by other groups in the synthesis of the disorazoles.[122–125] Accordingly, reaction of aldehyde **128** at –78 °C with 1.5 equivalents of iodomethyltriphenylphosphonium iodide (ICH_2PPh_3I), previously deprotonated by sodium hexamethyldisilazide (NaHMDS) to form the ylide, delivered exclusively the *Z*-vinyl iodide **129** in 65% yield (**Scheme 2.28**).

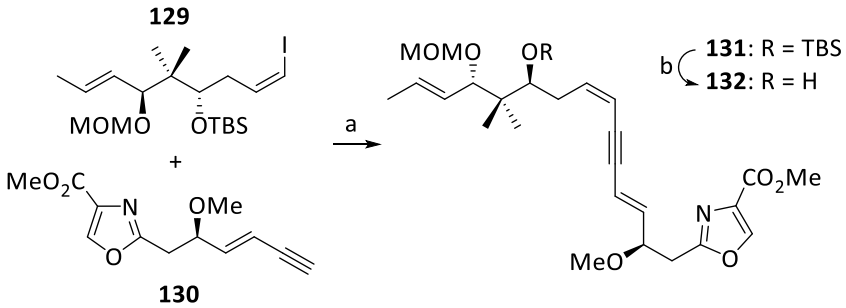


128 **129**

Scheme 2.28: Olefination of aldehyde **128**. *Reagents and conditions*: (a) ICH_2PPh_3I, NaHMDS, DMPU, THF, – 78 °C, 1 h, 65%.

2.1.2.9. Completion of the Lateral Chain: Change in the Protecting Groups

With iodide **129** in hand, the next steps involved a Sonogashira reaction[63] to couple **129** with the oxazole fragment **130** (its synthesis will be described in the next section **2.1.3**), and then deprotection of the TBS ether to get monomer **132** (**Scheme 2.29**).



130

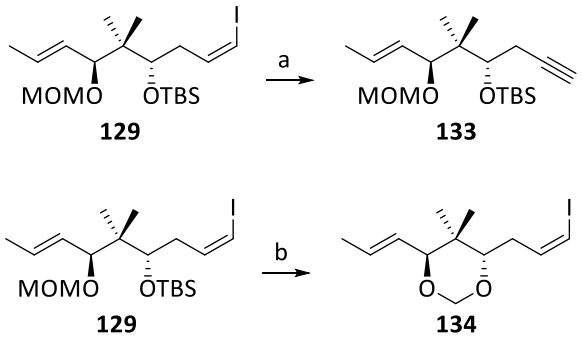
Scheme 2.29: Planned strategy for the synthesis of **132**. *Reagents and conditions*: (a) Sonogashira; (b) 1. TBAF, THF, rt to 70 °C, no reaction, or 2. TASF, H_20, DMF, 45 °C, 3 days, 50%.

Unfortunately, the TBS group resulted very difficult to remove: monomer **132** was completely inert to TBAF, whereas the use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[126] did manage to remove the protecting group, but the

reaction was very slow and did not go to completion, resulting in 50% yield, even after three days at 45 °C. Acidic reagents were avoided for the concomitant presence of the acid sensitive MOM group.

Next, we tested the deprotection of the TBS at the vinyl iodide stage (**Scheme 2.30**). However, treatment of **129** with TBAF induced a dehydroiodination of the vinyl iodide, generating the terminal acetylene **133**, without removing the TBS group. Another unexpected reaction occurred when **129** was exposed to hydrogen fluoride/pyridine complex (70% HF·pyridine): the TBS was removed, but the free alcohol reacted with the MOM group forming dioxane **134**.

Upon treatment with TASF, **129** behaved similarly to the monomer **131**, with a slow reaction rate and incomplete conversion.

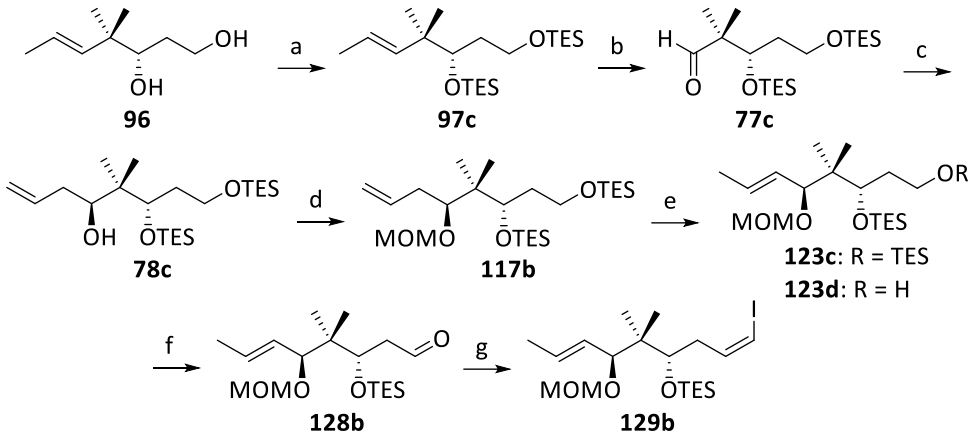


Scheme 2.30: Attempts at deprotecting TBS on **129**. *Reagents and conditions*: (a) TBAF, THF, rt, 48 h; (b) 70% HF·pyridine, THF, 0 °C to rt, 48 h.

The problems encountered in the deprotection of the TBS group suggested that the gem-dimethyl function rendered the adjacent positions particularly hindered. Therefore, we considered replacing the TBS with a less bulky group; and we imagined that the use of the TES group allowed an easier deprotection, while maintaining the same strategy.

Scheme 2.31 describes the final route to the vinyl iodide **129b**: diol **96** was quantitatively protected with a double TES, and subsequent ozonolysis afforded aldehyde **77c**. This step gave a lower yield with the TES, probably because part of the primary silyl ether was deprotected during the reaction, but 67% was still acceptable. The Leighton allylation worked in comparable yield and slightly better diastereoselectivity, with 11:1 *dr* (84% *de*). After MOM protection, the double bond was subjected to the isomerization. Once again, the primary TES proved to be very labile, as the isomerization conditions led to 15% of **123c** and 80% of **123d**, most likely due to the formation of HCl during the transformation of the Grubbs II catalyst **124** in the ruthenium hydride **125**.[127] Naturally, the partial loss of the primary TES was not an issue,

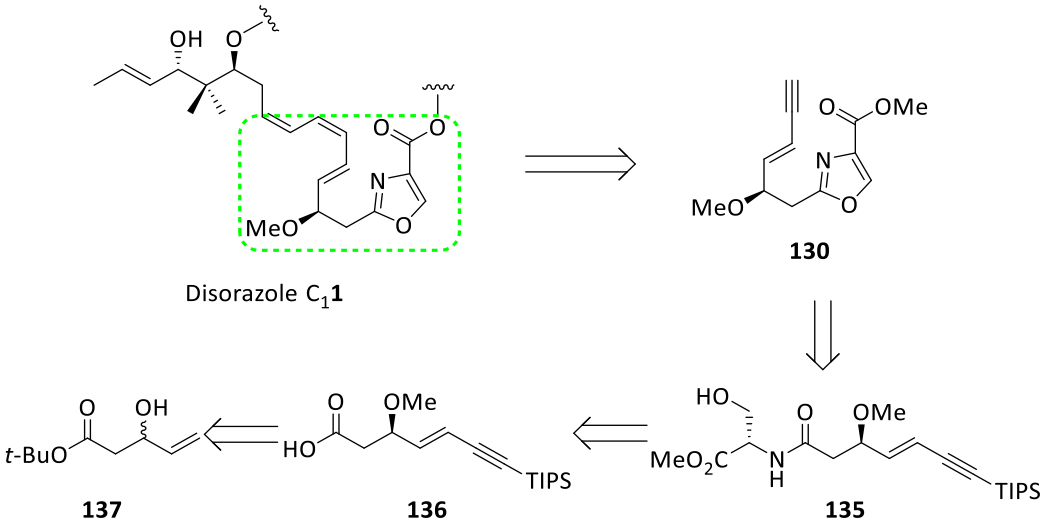
as the following step was the oxidation; the crude material was used without purification, because we expected that TES protected **123c** would also react under the Swern conditions, as reported by Godfroid and co-workers.[128] Indeed, **128b** was obtained in 77% yield over two steps, and the final olefination worked in 67% yield delivering the *Z*-vinyl iodide **129b**.



Scheme 2.31: Synthesis of vinyl iodide **129b**. *Reagents and conditions*: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min, then 0 °C, 1 h, 99%; (b) O_3/O_2, CH_2Cl_2, –78 °C, then PPh_3, rt, 4 h, 67%; (c) **(*R*,*R*)-109**, $Sc(OTf)_3$, CH_2Cl_2, – 15 °C, 48 h, then TBAF, rt, 30 min, 85% (84% *de*); (d) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to 50 °C, 92%; (e) Grubbs II, MeOH, 60 °C, 22 h; (f) Swern, 77% (2 steps); (g) ICH_2PPh_3I, NaHMDS, DMPU, THF, –78 °C, 1 h, 67%.

2.1.3. Synthesis of the Oxazole Fragment

As previously mentioned, the strategy for the construction of the monomeric unit was based on a Sonogashira coupling, which normally requires a vinyl halide and a terminal acetylene.[63] Having the vinyl iodide on **129b**, we needed a triple bond on the other coupling partner, and this led us to the design of **130** as the final oxazole segment (**Scheme 2.32**).

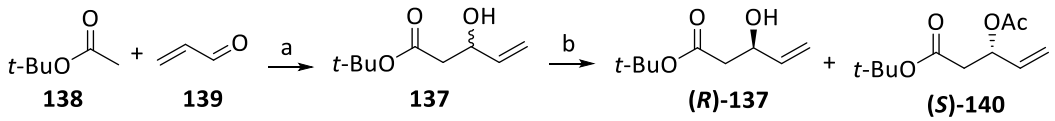


Scheme 2.32: Retrosynthetic analysis of the oxazole fragment of disorazole C_1.

The synthetic route for accessing 2,4-disubsituted oxazoles is quite general and it requires the condensation of a carboxylic acid with the amino acid serine; hence, we conceived the retrosynthesis of our oxazole **130** from compound **135**, which would be derived from the condensation of the amino acid with carboxylic acid **136**.

The two peculiar features of **136** were the chiral methoxy group and the *E*-enyne function. We planned to obtain the enyne moiety through a Wittig reaction;[129] while regarding the methoxy group, we chose to employ the same strategy as Hoyveda,[107] which involved the enzymatic resolution of β-hydroxyester **137**.

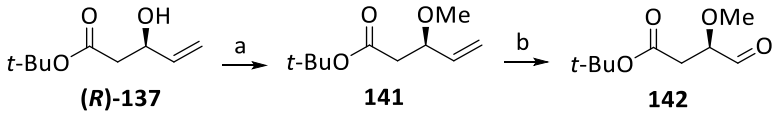
Thus, the synthesis of the oxazole fragment commenced from racemic **137**, which is commercially available or it may be synthesized via aldol reaction of the lithium enolate of *tert*-butyl acetate **138** with acrolein **139**, as depicted in **Scheme 2.33**. β-hydroxyester **137** was subjected to an enzymatic resolution, incubating a solution of the ester and vinyl acetate with molecular sieves and Amano Lipase PS in pentane at 30 °C for 24 h.



Scheme 2.33: Enzymatic resolution of β-hydroxyester **137**. *Reagents and conditions*: (a) LDA, THF, –78 °C, 1 h, 80%; (b) Amano Lipase PS, vinyl acetate, 4 Å MS, pentane, 30 °C, 24 h, 47% **(*R*)-137** (99:1 *er*) and 48% **(*S*)-140**.

Selective acetylation of (*S*)-alcohol enabled chromatographic separation of the two isomers in excellent enantiomeric purity (99:1 enantiomeric ratio).[78] The (*R*)-alcohol was the one bearing the right configuration for the synthesis of disorazole C_1, and it was isolated in 47% yield. Methylation of the free alcohol was achieved with Meerwein's salt (Me_3OBF_4) in the presence of 1,8-bis-(dimethylamino)-naphthalene (Proton Sponge), as described by Hoyveda,[107] yielding 77% of **141**.

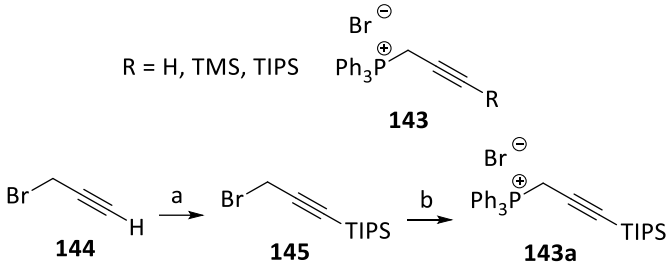
At this point, we needed to extend the terminal olefin to an enyne to have the skeleton of acid **136**. We established that a Wittig reaction with the ylide derived from propargyl triphenylphosphonium bromide **143** was a rapid and efficient way to produce the enyne. Of course, the double bond of **141** had to be transformed in an aldehyde, the common starting material for a Wittig reaction. This task was easily accomplished by ozonolysis, which delivered aldehyde **142** in high yield, as shown in **Scheme 2.34**.



(*R*)-137 141 142

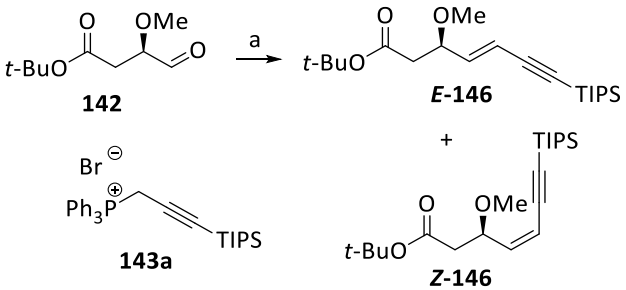
Scheme 2.34: Synthesis of aldehyde **141**. *Reagents and conditions*: (a) Me_3OBF_4, Proton Sponge, CH_2Cl_2, rt, 3 h, 77%; (b) O_3/O_2, CH_2Cl_2/MeOH 5:1, –78 °C, then PPh_3, rt, 2 h, 89%.

Regarding reagent **143**, the terminal acetylene could be protected with TMS or TIPS, and we opted for the more stable TIPS, because we assumed that the labile TMS could have been unstable under the conditions required to produce the final oxazole ring, namely the presence of a fluoride source and potassium carbonate, both used during the cyclization reaction (described later in this section). **143** was readily available in two steps, starting from the commercially available propargyl bromide **144**, which was protected with TIPSCl, after deprotonation of the acetylene using *n*-BuLi as a base. Reaction of **145** with triphenylphosphine at room temperature afforded the phosphonium salt **143a** (**Scheme 2.35**).[130]



Scheme 2.35: Synthesis of the Wittig reagent **143a**. *Reagents and conditions*: (a) *n*-BuLi, TIPSCl, THF, –78 °C to rt, 63%; (b) PPh_3, toluene, 0 °C to rt, 24 h, 59%.

We began to investigate the Wittig reaction between **142** and **143a** (**Scheme 2.36**). For the first attempt, we used *n*-BuLi to form the ylide at –78 °C, and then the addition was performed at –40 °C in THF. These conditions resulted in 82% overall yield and a 2:1 ratio of *E* and *Z* isomers. Fortunately, the two isomers could be easily separated by flash chromatography, allowing us to obtain ***E*-146** in satisfying purity.



Scheme 2.36: Wittig reaction with phosphonium salt **143a**. *Reagents and conditions*: (a) **143a**, *n*-BuLi, THF, – 78 °C to 0 °C, 30 min, then **142**, 0 °C to rt, 30 min, 60% ***E*-146**, 22% ***Z*-146** (2.7:1 *E*/*Z*).

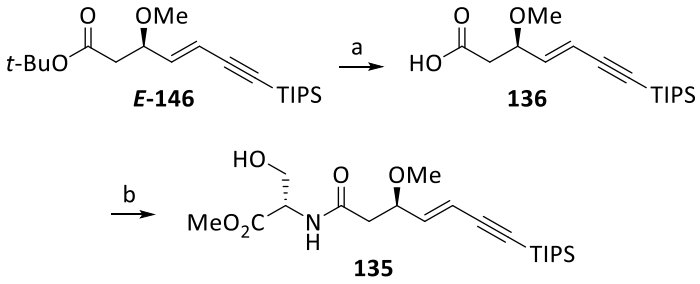
Changing the solvent to a mixture of THF/toluene decreased the total yield to 64%. In order to improve the *E*/*Z* ratio, we raised the temperature to 0 °C, which led to a 2.5:1 mixture of the two isomers and a comparable yield. Next, we explored the use of other bases, such as potassium *tert*-butoxide (*t*BuOK) or lithium and potassium hexamethyldisilazide (Li or KHMDS), but none of them were able to increase the amount of the *E*-enyne. Finally, a slight excess of base delivered the desired ***E*-146** in 60% yield, along with 22% of ***Z*-146**.

Although 60% was not an excellent yield, we were able to increase the ratio from 2:1 to 2.7:1, which was a good achievement, considering the complexity of the Wittig reaction with semi-stabilized ylides. **Table 2.5** summarizes all the conditions tested for this Wittig reaction.

Base	Solvent	Temperature	Overall yield	*E*/*Z* ratio	Yield *E*-146
***n*-BuLi**	THF	–40 °C	82%	2:1	54%
***n*-BuLi**	THF/toluene	–40 °C	64%	2:1	43%
***n*-BuLi**	THF	0 °C	80%	2.5:1	57%
***t*BuOK**	THF	0 °C	79%	2.5:1	56%
Li or KHMDS	THF	0 °C	80%	2.5:1	57%
***n*-BuLi**	THF	0 °C	82%	2.7:1	60%

Table 2.5: Optimization of the Wittig reaction with **143a**.

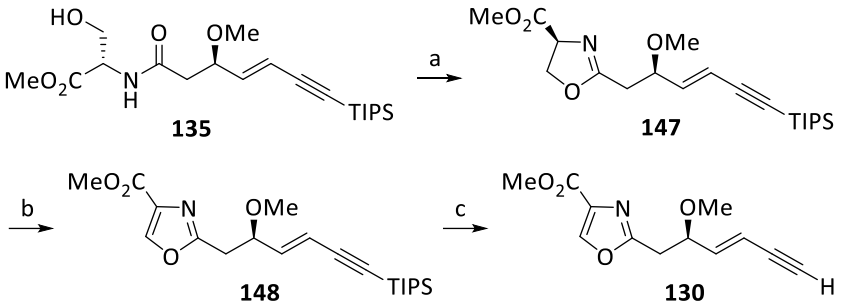
From ***E*-146**, the next target was carboxylic acid **136**, which was synthesized through acid hydrolysis of the *tert*-butyl ester with formic acid (HCOOH). Condensation of **136** with L-serine methyl ester hydrochloride generated hydroxy amide **135** in high yield (**Scheme 2.37**).



Scheme 2.37: Synthesis of hydroxy amide **135**. *Reagents and conditions*: (a) HCOOH, rt, overnight, 99%; (b) DIPEA, TFFH, THF, rt, 2 h, then SerOMe·HCl, rt, 3 h, 90%.

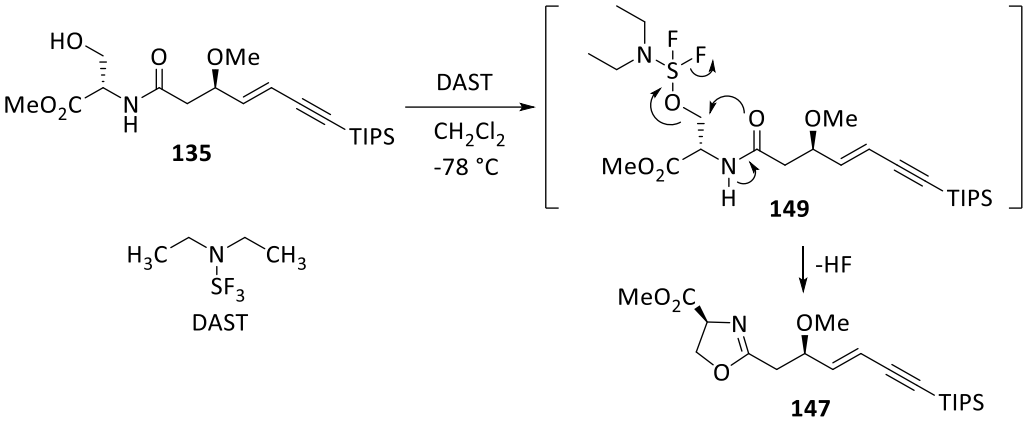
The 2,4-disubsituted oxazole was constructed via a cyclization-oxidation sequence: treatment of **135** with diethylaminosulfur trifluoride (DAST)[70] at –78 °C, followed by addition of potassium carbonate, led to the formation of oxazoline **147**; then oxidation initiated by DBU and bromotrichloromethane ($BrCCl_3$)[131] furnished TIPS-protected oxazole **148**. Performing the reaction at 0 °C resulted in 56% yield, but a slight improvement could be achieved at room

temperature, raising the yield to 62%. Finally, removal of TIPS through the action of TBAF afforded the desired oxazole fragment **130** in 81% yield, as depicted in **Scheme 2.38**.



Scheme 2.38: Completion of the oxazole fragment **130**. *Reagents and conditions*: (a) DAST, CH_2Cl_2, –78 °C, 2 h, then K_2CO_3, rt, 1 h; (b) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C to rt, 16 h, 62% (2 steps); (c) TBAF, THF, 0 °C to rt, 30 min, 81%.

As described above, TMS was avoided in the protection of the triple bond, and the reason behind this choice was mainly the cyclization step. **Scheme 2.39** displays the proposed mechanism for this reaction, consisting in an S_N2-like ring closing, after the conversion of the alcohol into the activated spiecies **149**.[132] Intramolecular attack of the carbonyl group to the activated alcohol (with inversion of configuration, S_N2) results in HF formation, and that was the first possible risk for a TMS group, besides DAST itself, which is a powerful fluorinating agent. Moreover, the reaction was quenched with potassium carbonate, in order to minimize the possible ring opening mediated by HF, and this was another reason to avoid TMS, since this protecting group is labile to the presence of K_2CO_3.

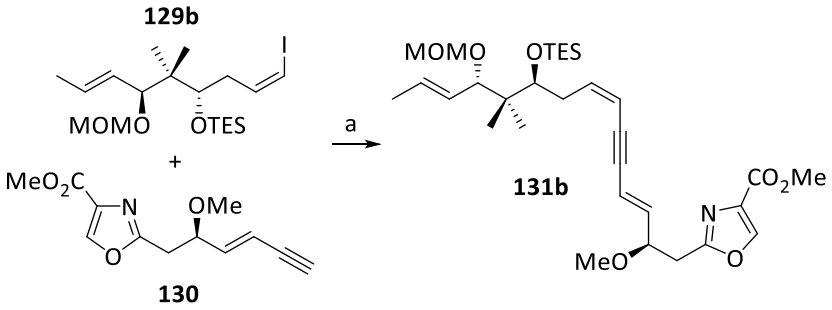


Scheme 2.39: Proposed mechanism for the cyclization of hydroxy amide **135**.

2.1.4. Final Strategy for the Total Synthesis of Disorazole C_1

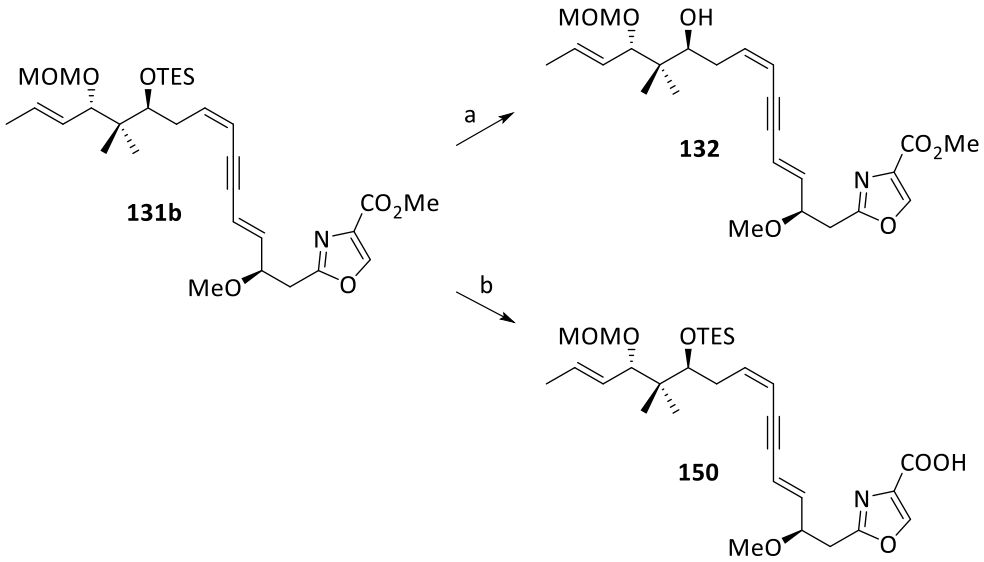
With both fragments in hand, we could begin the final part of the synthesis. The first step was the formation of the monomer, which was accomplished through a Sonogashira

coupling[63] between iodide **129b** and enyne **130**, as shown in **Scheme 2.40**. The first attempt was not successful though, as mixing the two fragments with the catalyst, triethylamine and copper iodide did not generate any reaction; whereas adding the base and the enyne **130** to a degassed solution of the iodide **129b**, the catalyst and copper iodide in acetonitrile delivered monomer **131b** in 85% yield. Acetonitrile proved to be the best solvent, while the use of DMF (*N*,*N*-dimethylformamide) resulted in a slightly lower yield (68%).



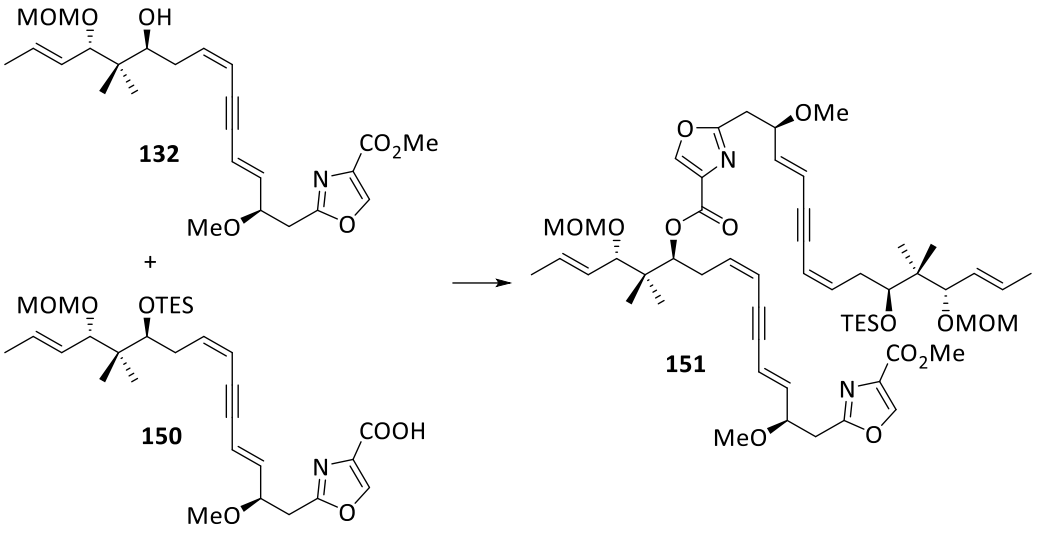
Scheme 2.40: Synthesis of the monomer **131b**. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, 15 °C to rt, 1 h, 85%.

From the monomer **131b**, we could take advantage of the C2-symmetry of target molecule and synthesize alcohol **132** and carboxylic acid **150**, both from the same starting material. The deprotection of the TES ether was achieved using the same conditions that we used to remove the primary TBS in **123b** (**Scheme 2.27**, **Section 2.1.2.8**). Indeed, CSA removed the secondary TES in 1 hour almost quantitatively; 1 M HCl in THF gave comparable results and reaction times. The hydrolysis of the methyl ester was performed treating monomer **131b** with aqueous lithium hydroxide for 3 hours, affording acid **150** (**Scheme 2.41**).



Scheme 2.41: Synthesis of the starting materials for the esterification. *Reagents and conditions*: (a) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 95%; (b) 1 M LiOH, THF, rt, 3 h, 99%.

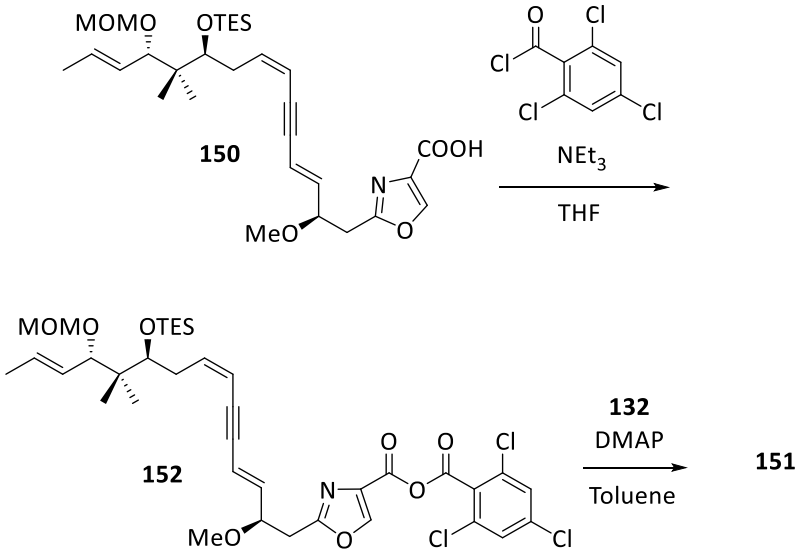
Compounds **132** and **150** represented the starting materials for the esterification needed to get the full skeleton of disorazole C_1 (**Scheme 2.42**).



Scheme 2.42: Esterification reaction between alcohol **132** and acid **150**.

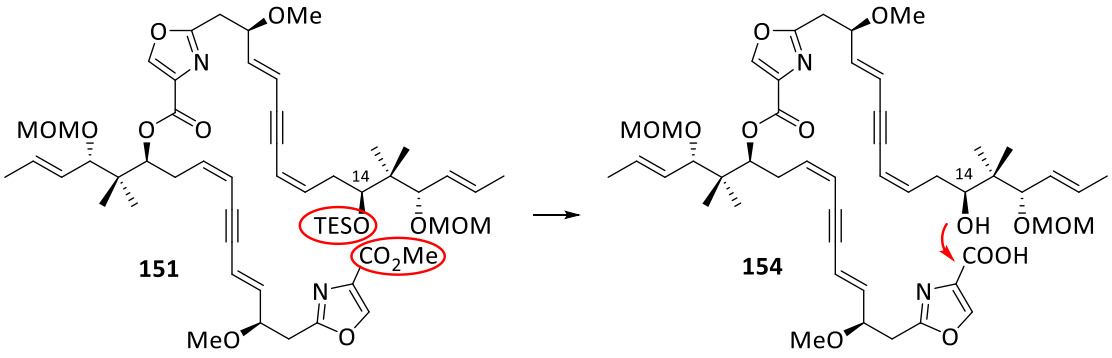
At first, we tested a classical Steglich esterification,[133] adding DCC (*N*,*N*'-dicyclohexylcarbodiimide) and DMAP to a solution of the two starting materials in CH_2Cl_2 at 0 °C, and then warming to room temperature, but no reaction occurred under these conditions.

Next, we tried the Yamaguchi esterification,[64] but again mixing the two starting materials with 2,4,6-trichlorobenzoyl chloride (TCBC), triethylamine and DMAP in toluene did not produce any reaction. Therefore, we decided to activate the acid first, and then add it to a solution of alcohol and DMAP. Carboxylic acid **150** reacted in 2 hours with TCBC in the presence of the base, forming the mixed anhydride **152** (**Scheme 2.43**).



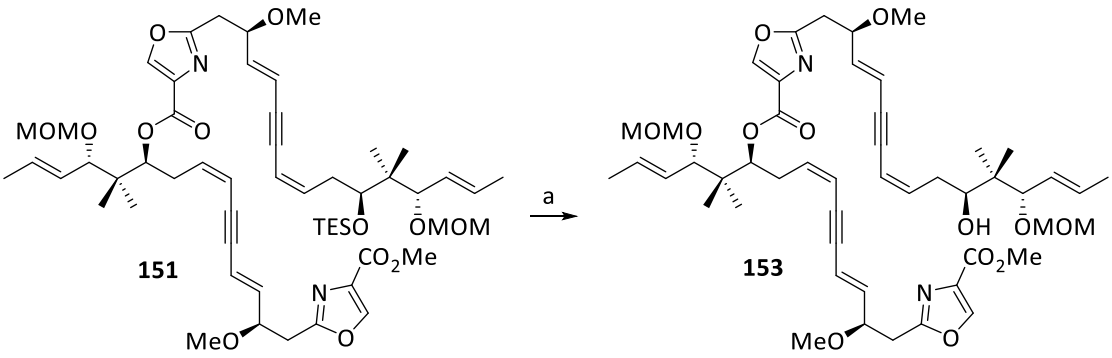
Scheme 2.43: Activation of the carboxylic acid **150** to form the mixed anhydride and subsequent reaction with alcohol **132**.

After the addition of the activated acid to alcohol **132** and DMAP, the reaction was complete in 16 hours at room temperature, affording **151** in 75% yield. The next goal was now to obtain the macrocycle, but before trying the cyclization, the TES ether and the remaining methyl ester had to be hydrolyzed, in order to get the free alcohol at C14 and the carboxylic acid, which could react in an intramolecular esterification and form the 30-membered ring, as shown in **Scheme 2.44**.



Scheme 2.44: Preparation to the macrolactonization.

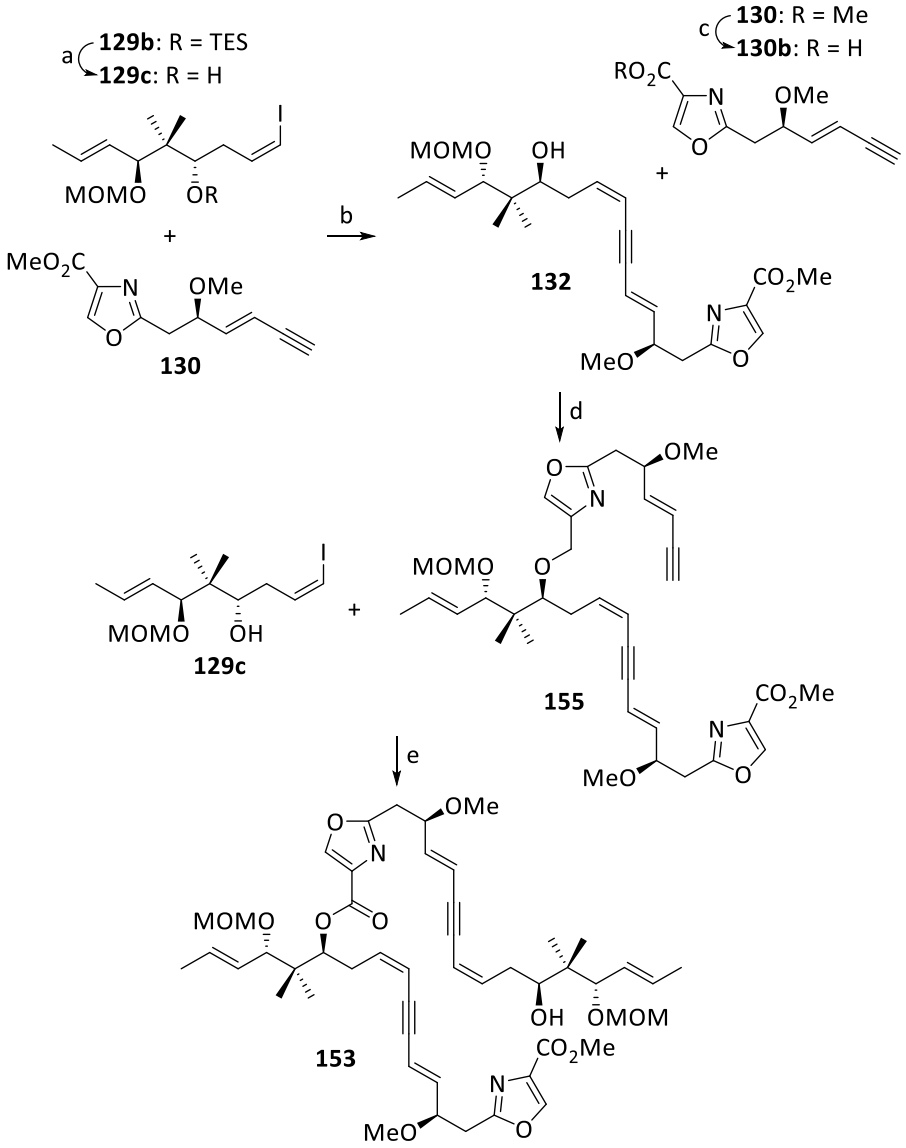
The deprotection of the TES ether proceeded smoothly under the same conditions used for the deprotection of the monomer: CSA at 0 °C gave the corresponding alcohol **154** in 1 hour, as depicted in **Scheme 2.45**.



Scheme 2.45: Deprotection of the TES ether to synthesize alcohol **154**. *Reagents and conditions*: (a) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 95%.

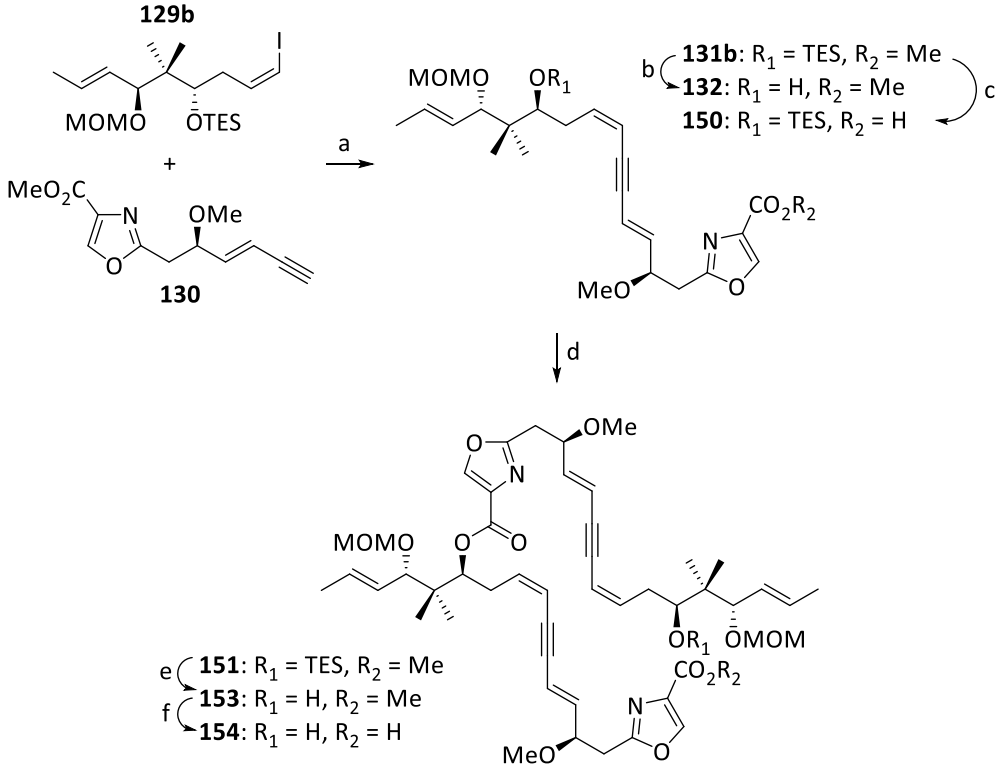
An alternative route that we tested to arrive at alcohol **153** was more similar to Wipf's strategy[62] and involved the Sonogashira coupling between the oxazole **130** and the deprotected iodide **129c**, as shown in **Scheme 2.46**. In fact, the deprotection of TES worked on iodide **129b** in 86% yield, proving once again the great difference in the stability of TBS compared to the smaller counterpart, since we had not been able to remove the bulky TBS group on **129b**. The Sonogashira gave directly the deprotected monomer **132**, which was transformed in ester **155** upon reaction with carboxylic acid **130b**, derived from oxazole **130**.

Interestingly, the use of DCC/DMAP for the esterification with the oxazole fragment proved successful, and the resulting enyne **155** was subjected to another Sonogashira, furnishing compound **153**. However, the DCU (1,3-dicyclohexylurea) generated during the esterification was very hard to remove, even after several steps, causing lack of purity in all the final compounds.



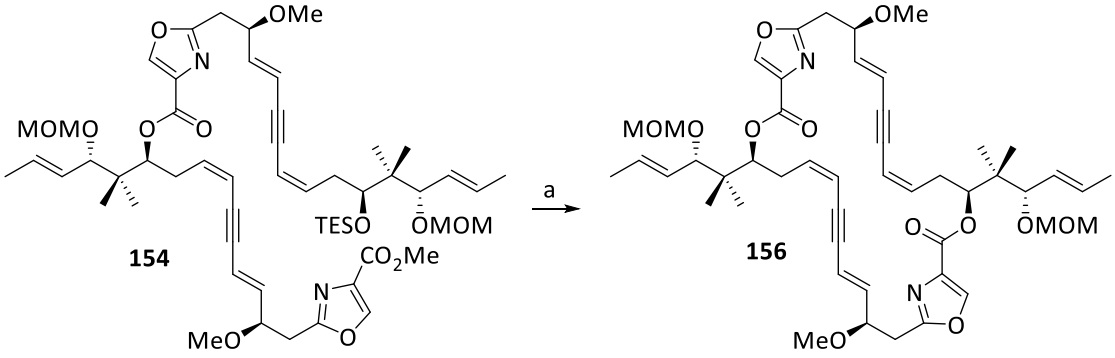
Scheme 2.46: Alternative strategy for the synthesis of alcohol **154**. *Reagents and conditions*: (a) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 86%; (b) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –15 °C to rt, 1 h, 90%; (c) 1 M LiOH, THF, rt, 2 h, 99%; (d) DCC, DMAP, CH_2Cl_2, rt, overnight; (e) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –15 °C to rt, 1 h, 82% (2 steps).

As mentioned at the end of **Chapter 1**, a direct dimerization was avoided, seeing all the failed attempts made in the past by other research groups. Thus, after carefully evaluating the two possible routes, we chose to continue with the first one, which we believed was convergent and more efficient. **Scheme 2.47** summarizes the selected strategy for the construction of the full skeleton of disorazole C_1.



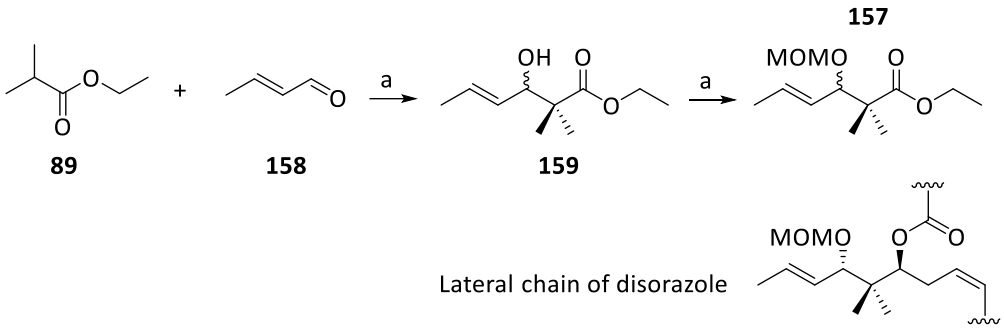
Scheme 2.47: Selected route to compound **154**. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –15 °C to rt, 1 h, 85%; (b) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 95%; (c) 1 M LiOH, THF, rt, 3 h, 99%; (d) **150**, TCBC, NEt_3, THF, rt, 2 h, then **132**, DMAP, toluene, rt, 16 h, 75%; (e) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 95%; (f) 1 M LiOH, THF, rt, overnight, 99%.

After saponification of the methyl ester, the final macrolactonization to produce the macrocycle was achieved under Yamaguchi conditions:[64] the *seco*-acid **154** was treated with TCBC and triethylamine in THF, and then added to a highly diluted solution of DMAP in toluene (0.8 mM), affording dimer **156** in 78% yield after 16 hours. Alternatively, from TES-protected **151**, we tried to get **156** without purifying the intermediates **153** and **154**. This sequence resulted in 70% yield over three steps, as depicted in **Scheme 2.48**.



Scheme 2.48: Synthesis of the macrolactone **156**. *Reagents and conditions*: (a) 1. CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h; 2. 1 M LiOH, THF, rt, overnight; 3. TCBC, NEt_3, THF, rt, 2 h, then DMAP, toluene, rt, 16 h, 70% (3 steps).

From **156**, we were only two steps away from the final molecule, namely deprotection of the MOM ethers and hydrogenation of the triple bonds. Nevertheless, the polyunsaturated macrocycle proved to be very sensitive and many reagents caused decomposition of the material. Before misusing big amounts of **156**, we decided to test some deprotection reactions of the MOM group on a model system.



Scheme 2.49: Preparation of the model system for the deprotection of MOM. *Reagents and conditions*: (a) LDA, THF, –78 °C, 1 h, 85%; MOMCl, DIPEA, DMAP, CH_2Cl_2, rt, overnight, 90%.

Compound **157** was chosen as a model, because we considered it to be closely related to our structure, for the presence of the gem-dimethyl, the allylic alcohol and the adjacent carbonyl group.

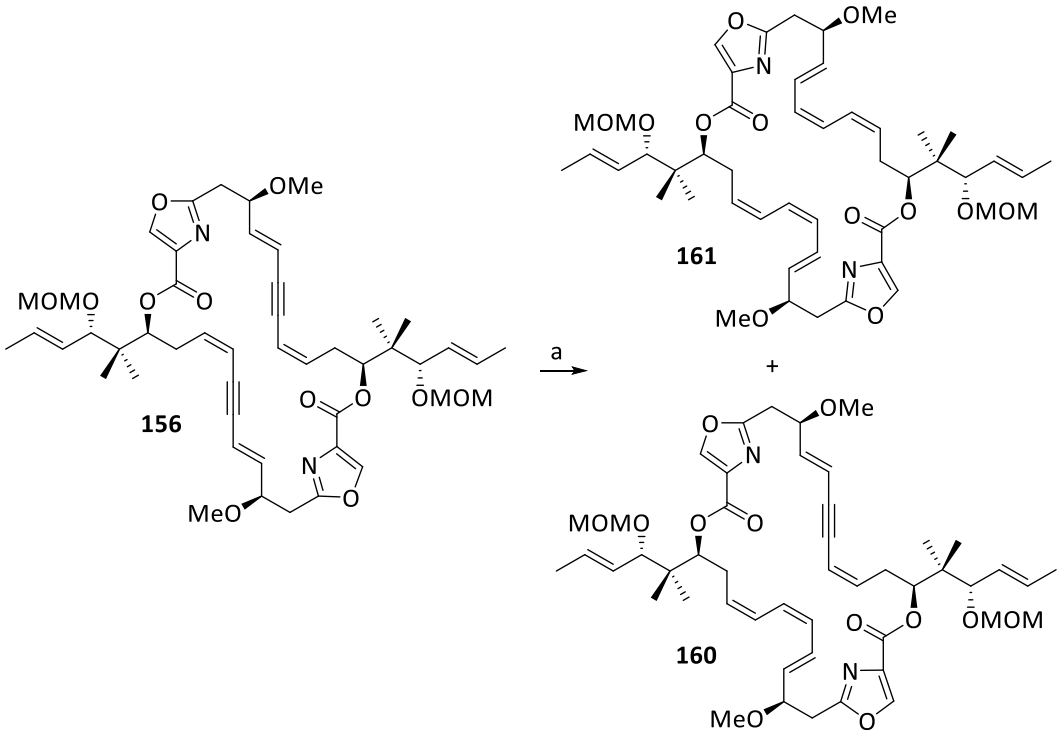
Reagent	Model System **157**	Macrocycle **156**
HCl (2 M, 6 M or conc.)	rt: quantitative	0 °C or rt: no reaction 50 °C: slow decomposition
48% aq. HBr in MeOH	rt: quantitative	0 °C or rt: no reaction 50 °C: slow decomposition
Bromocatecholborane	0 °C: 70%	–78°C to –40 °C: no reaction 0 °C: decomposition
4 M H_2SO_4	rt: quantitative	rt: slow decomposition
AcCl/MeOH	0 °C: quantitative	0 °C: no reaction
$ZnBr_2$/*n*-PrSH	50%	No reaction
Dowex resin	70 °C: 70%	70 °C: slow decomposition
TMSOTf/bipyridil	30%	No reaction
CSA/MeOH	40 °C: quantitative	rt: no reaction 40 °C: slow decomposition
pTSA/MeOH	rt: quantitative	rt: no reaction 40 °C: slow decomposition
$LiBF_4$	not tried	slow decomposition
TMSBr/TMSI	not tried	0 °C: decomposition –78 °C: too fast reaction (5 min)

Table 2.6: List of reagents tested for the deprotection of MOM.

157 was readily synthesized through an aldol reaction between ethyl isobutyrate **89** and crotonaldehyde **158**, followed by protection of the free alcohol with MOMCl, as shown in

Scheme 2.49. However, compound **157** was easily converted to the corresponding alcohol **159** with many reagents, such as HCl, HBr, bromocatecholborane or acetyl chloride in MeOH; whereas compound **156** either did not react or decomposed under the same conditions. **Table 2.6** compares all the reagents tested for the deprotection of **157** and **156**.

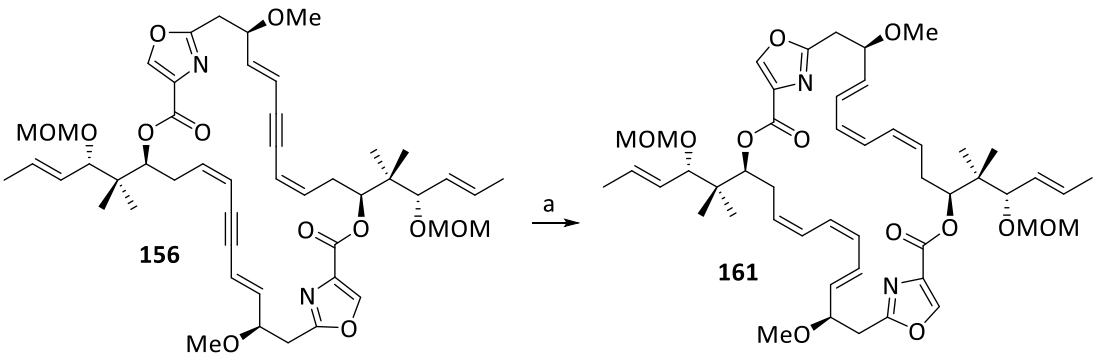
After losing a substantial amount of material, we chose to invert the order of the reactions, and we turned our attention to the hydrogenation of the alkynes. Unfortunately, classical reduction using Lindlar conditions[73] resulted in a mixture of starting material **156**, compound **160** (corresponding to a partial reduction) and the desired product **161** (**Scheme 2.50**). The progress of the reaction was followed by LC-MS, but the three compounds could not be isolated in satisfying purity. Similar results were obtained by Hulme and co-workers,[123] and they addressed the failure to the quality of the catalyst.



Scheme 2.50: Hydrogenation of the triple bonds under Lindlar conditions. *Reagents and conditions*: (a) Lindlar catalyst, quinoline, EtOAc, overnight.

Hence, we searched for a different kind of reduction of the triple bonds, and we found that exposure of **156** to zinc dust, previously activated by $Cu(OAc)_2$ (copper acetate) and $AgNO_3$ (silver nitrate), following the procedure reported by Boland,[134,135] delivered MOM-protected disorazole C_1 **161** in 65% yield, as shown in **Scheme 2.51**.

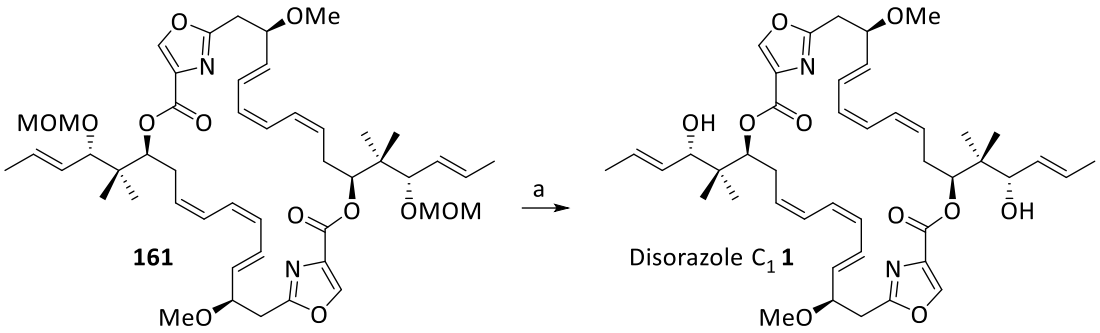
Although only one reaction was required to accomplish the total synthesis, we were extremely concerned, due to the numerous failures experienced attempting the deprotection of **156**.



Scheme 2.51: Hydrogenation of the triple bonds under Boland conditions. *Reagents and conditions*: (a) Zn (Ag/Cu), MeOH/H_2O 1:1, 50 °C, 24 h, 65%.

In order to avoid waste of material, which would have been very discouraging at this stage of the synthesis, and considering that the model system did not provide the desired guidance, we started to test the deprotection with very small amount of **161** (~1 mg). When attempting the deprotection of **156**, the only reagents that had been able to deliver some traces of product (at least according to LC-MS) had been TMSBr (trimethylsilylbromide) or TMSI (trimethylsilyliodide). Consequently, these were the first reagents that we tested on **161**, but the reaction was too fast to isolate the pure product, even at –78 °C. Yet, we could identify the right spot on TLC, which facilitated the following experiments. Next, we tried bromocatecholborane, which had given no reaction at –78 °C or –40 °C when used to deprotect **156**, but fast decomposition at 0 °C. Thus, we decided to perform the reaction at –15 °C, hoping to find a window in which the molecule was stable. However, fast decomposition occurred at this temperature as well.

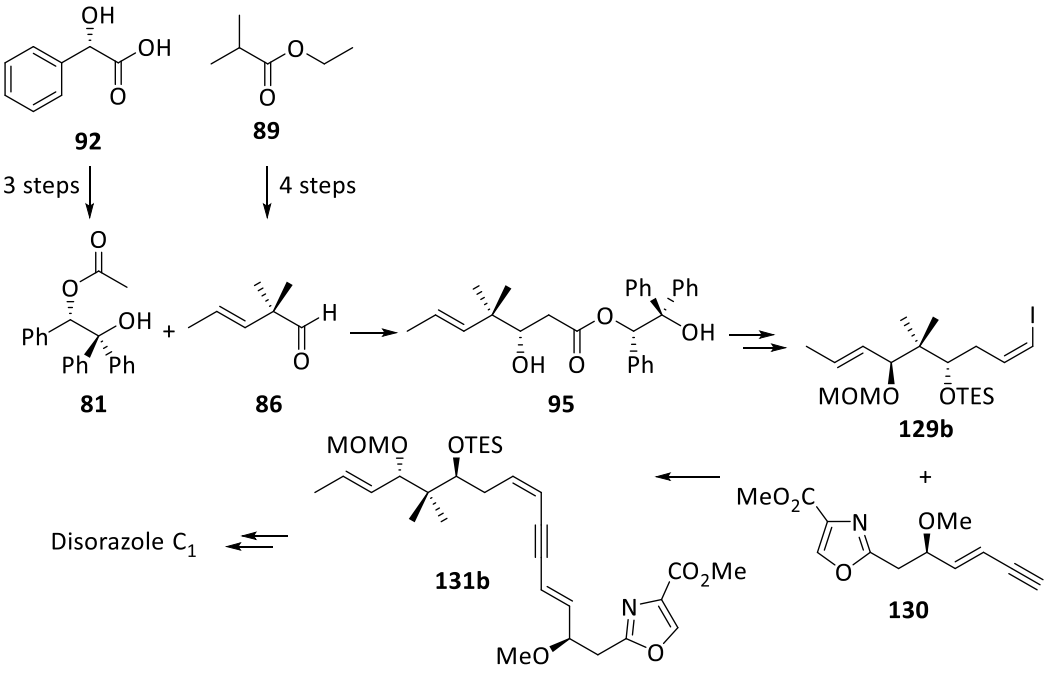
Surprisingly, when we were about to lose hope and run out of material, a drop of aqueous HBr in acetonitrile at 0 °C was able to remove both MOM groups and provided disorazole C_1. After one hour, the starting material was gone, but some mono-MOM-protected disorazole C_1 was still present. Unfortunately, longer reaction times resulted in decomposition of the product; therefore, we decided to stop the reaction after one hour, and column chromatography of the crude material delivered pure disorazole C_1 **1** in 56% yield, as depicted in **Scheme 2.52**.



Scheme 2.52: Deprotection of the MOM ethers and synthesis of disorazole C_1. *Reagents and conditions*: (a) 48% aq. HBr, CH_3CN, 0 °C, 1 h, 56%.

2.1.5. Summary

We have demonstrated that disorazole C_1 can be synthesized in 17 steps and 2.9% overall yield for the longest linear sequence, starting from a stereoselective aldol reaction of the commercially available (*S*)-(–)-HYTRA **81** and aldehyde **86**, as shown in **Scheme 2.53**. We also provided an efficient synthesis of the two starting materials **81** and **86**, which would permit to begin the synthesis from big amount of material at low cost. Disorazole C_1 was obtained in very high purity, which was a difficult task considering the sensitivity of the compound and the complexity of the last steps. Furthermore, 11 mg is the largest amount of disorazole C_1 that has been synthesized so far, based on our knowledge.



Scheme 2.53: Summary of the synthesis of disorazole C_1.

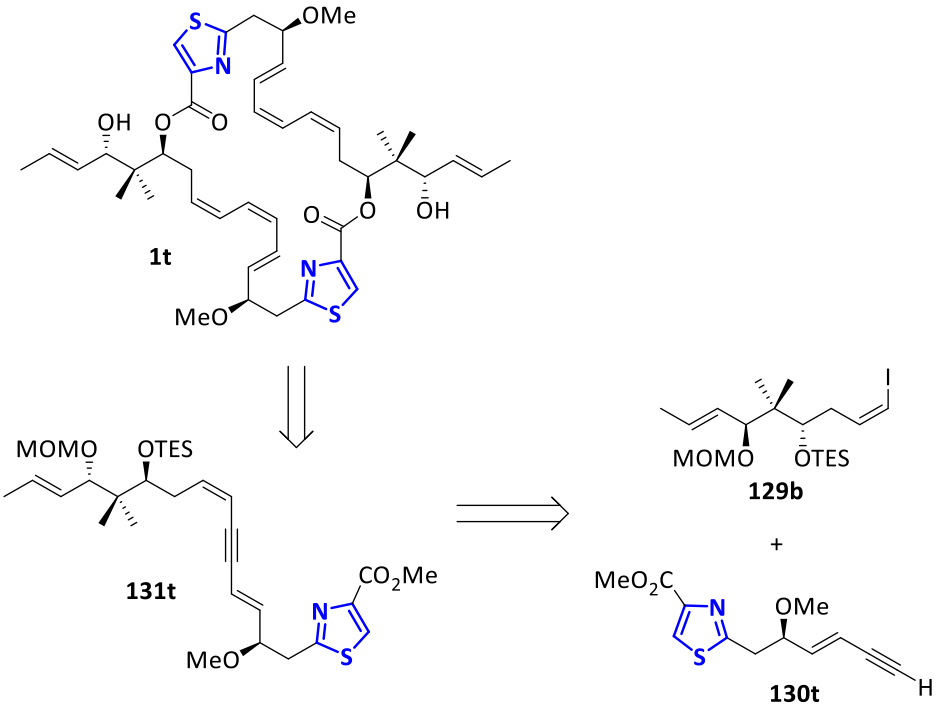
In addition, the synthesis of the natural product provides a broad entry to construct a large number of analogs, some of them have already been synthesized and will be described in the next chapter.

2.2. Synthesis of Analogs of Disorazole C_1

After completing the total synthesis of the natural product, we focused on the design of new analogs that could have a biological activity. The biological evaluation of the derivative could also produce new information on the structure-activity relationships of the disorazole family; for this reason, we decided to explore modifications on the heterocyclic motif and the chiral centers of the molecule, two parts of the structure whose role in the activity was still partly unknown.

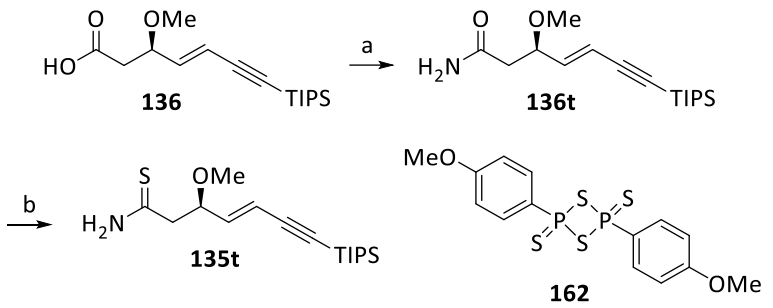
2.2.1. Synthesis of the Thiazole Analog

The first derivative that was selected as target featured a thiazole ring instead of the oxazole moiety. As depicted in **Scheme 2.54**, the synthesis of **1t** required the coupling of our previously synthesized vinyl iodide **129b** with the thiazole fragment **130t**, which replaced the oxazole piece **130**.



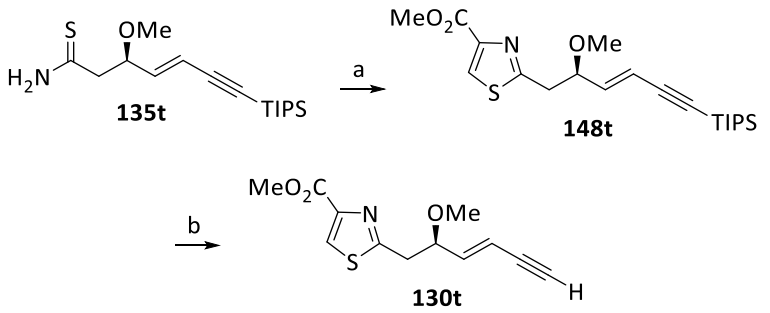
Scheme 2.54: Retrosynthetic analysis of the thiazole derivative **1t**.

The synthesis of **130t** commenced from the carboxylic acid **136**, which was transformed in the corresponding amide **136t** by reaction with ethyl chloroformate and triethylamine, followed by addition of aqueous ammonium hydroxide. The crude amide was then treated with Lawesson's reagent[136] **162** to furnish thioamide **135t** in 80% yield (**Scheme 2.55**).



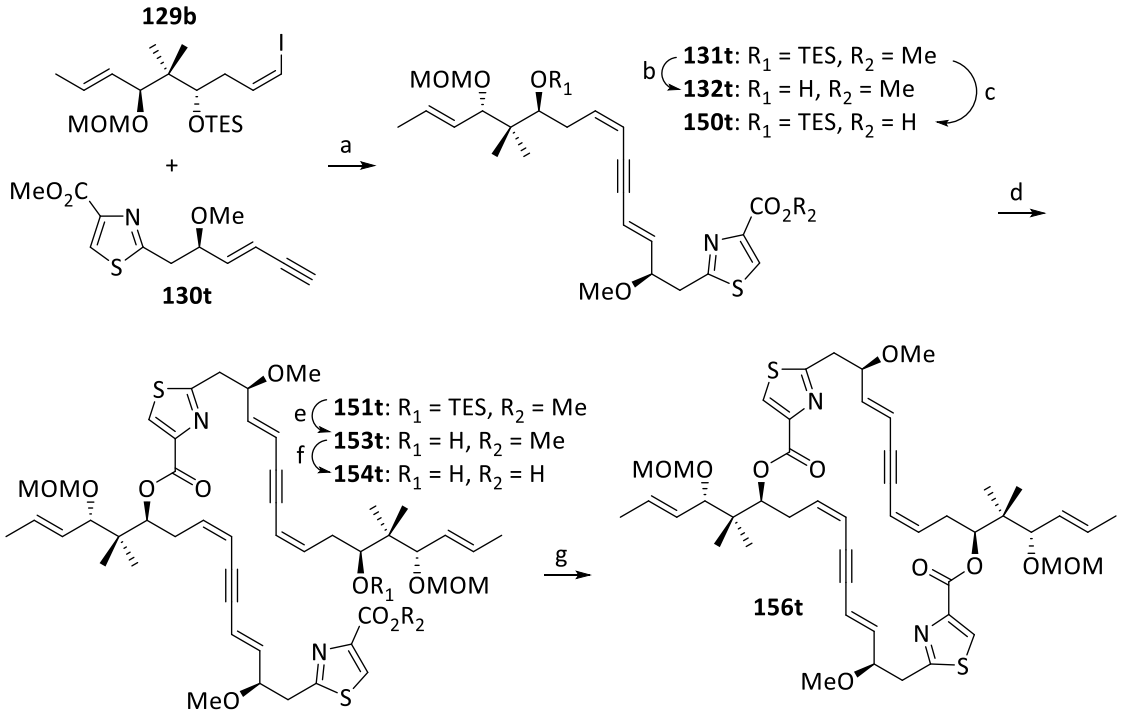
Scheme 2.55: Synthesis of thioamide **135t**. *Reagents and conditions*: (a) $ClCO_2Et$, NEt_3, THF, 0 °C, 30 min, then 25% NH_4OH, 0 °C to rt, 1 h; (b) Lawesson's reagent **162**, CH_2Cl_2, rt, 30 min, 80% (2 steps).

The thiazole ring was constructed using Hantzsch's methodology.[137] Accordingly, thioamide **135t** was treated with methyl bromopyruvate in the presence of $NaHCO_3$ at 0 °C to form the thiazoline intermediate, subsequent addition of trifluoroacetic anhydride (TFAA) and pyridine at –30 °C delivered the desired thiazole **148t** in 83% yield. Final removal of the TIPS group with TBAF provided the complete piece **130t** in 80% yield, as depicted in **Scheme 2.56**.



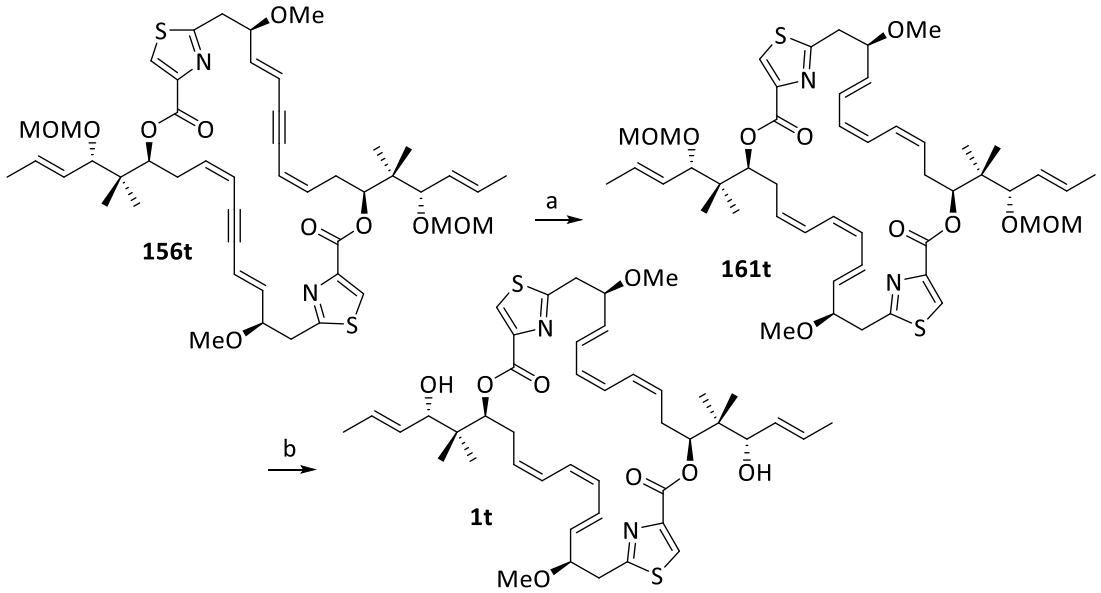
Scheme 2.56: Synthesis of the thiazole fragment **130t**. *Reagents and conditions*: (a) Methyl bromopyruvate, $NaHCO_3$, THF, 0 °C, 1 h, then TFAA, pyridine, –30 °C, 1 h, 83%; (b) TBAF, THF, 0 °C to rt, 30 min, 80%.

The final strategy was the same employed for the synthesis of disorazole C_1 and it is shown in **Scheme 2.57**: a Sonogashira[63] coupling between iodide **129b** and the thiazole segment **130t** afforded monomer **131t** in 75% yield; **131t** was used to produce alcohol **132t** and carboxylic acid **150t**, which were coupled together under Yamaguchi conditions[64] furnishing compound **151t** in 77% yield. The TES ether was deprotected through the action of CSA giving alcohol **153t**, and saponification of the methyl ester produced *seco*-acid **154t**. The final macrolactonization gave the dimer **156t**, though in lower yield than the oxazole-containing **156** (45% in 3 steps instead of 70%).



Scheme 2.57: Strategy for the construction of the macrocycle **156t**. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –15 °C to rt, 1 h, 75%; (b) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 95%; (c) 1 M LiOH, THF, rt, 3 h, 99%; (d) **150t**, TCBC, NEt_3, THF, rt, 2 h, then **132t**, DMAP, toluene, rt, 16 h, 77%; (e) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h; (f) 1 M LiOH, THF, rt, overnight; (g) TCBC, NEt_3, THF, rt, 2 h, then DMAP, toluene, rt, 16 h, 45% (3 steps).

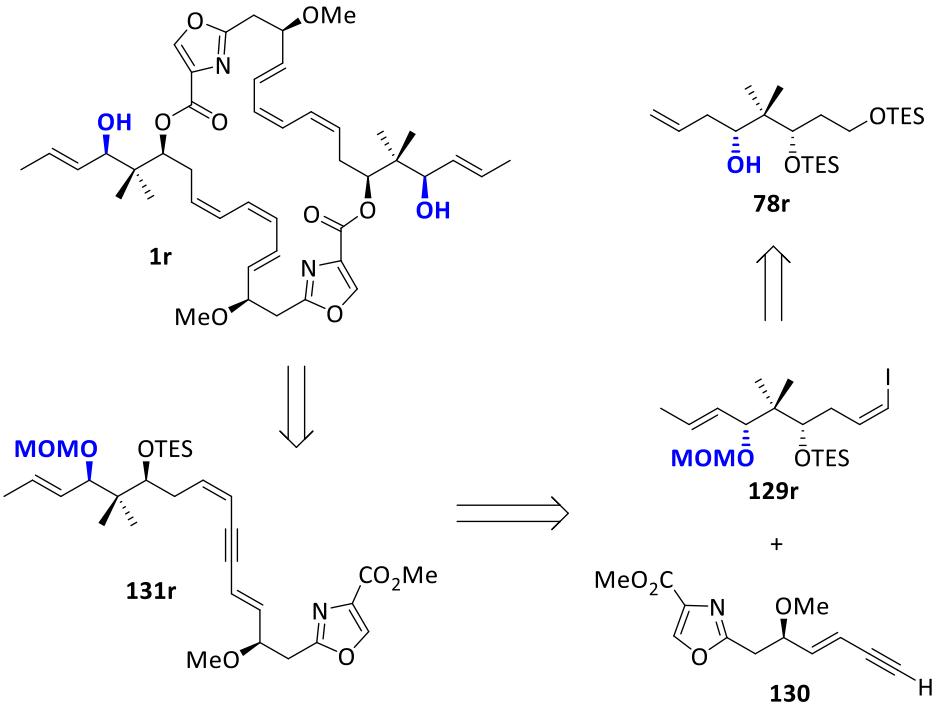
Luckily, the last two steps worked as expected and we were able to synthesize the first derivative: the Boland reduction[134,135] afforded the MOM-protected **161t** in 60% yield, and aqueous HBr removed the two MOM groups delivering the final thiazole analog **1t** in 56% yield, as shown in **Scheme 2.58**.



Scheme 2.58: Synthesis of the thiazole analog **1t**. *Reagents and conditions*: (a) Zn (Ag/Cu), MeOH/H_2O 1:1, 50 °C, 24 h, 60%; (b) 48% aq. HBr, CH_3CN, 0 °C, 1 h, 56%.

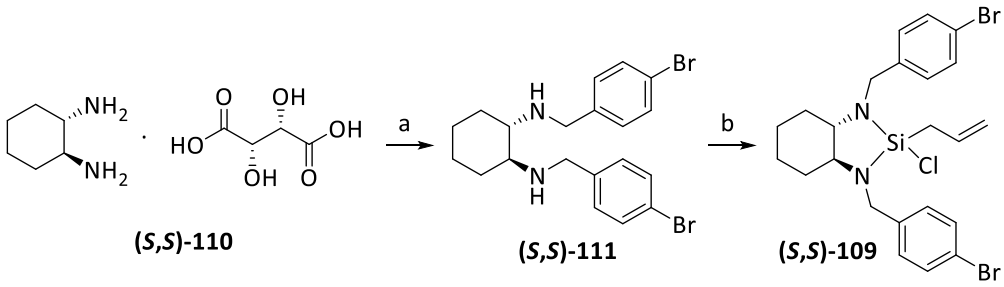
2.2.2. Synthesis of (16*R*,16'*R*)-Disorazole C_1

The second synthesized analog was **1r**, which is characterized by the opposite chirality of the two free alcohols of the lateral chain (C16 and C16'), resulting in 1,3-*syn* diols. The stereochemistry at C16 and C16' is set by the Leighton allylation (**Section 2.1.2.4**), and thus the use of the opposite diastereomer of the Leighton reagent enabled the preparation of **78r**, which was the main precursor of the monomer for this analog, as displayed in **Scheme 2.59**.



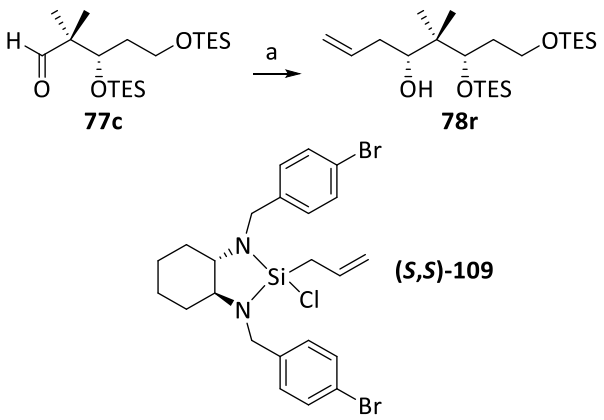
Scheme 2.59: Retrosynthesis of analog **1r**.

Hence, the first step of the synthesis of **1r** was the Leighton allylation between aldehyde **77c** and **(*S*,*S*)-109**, which was prepared according to the standard procedure but starting from (1*S*,2*S*)-(–)-1,2-diaminocyclohexane·D-tartrate **(*S*,*S*)-110**, as shown in **Scheme 2.60**.



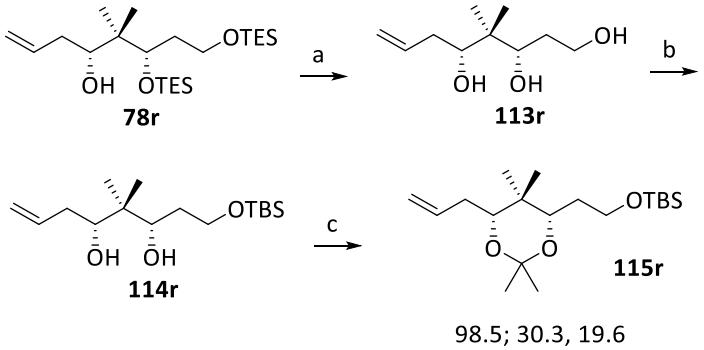
Scheme 2.60: Preparation of the Leighton reagent **(*S*,*S*)-109**. *Reagents and conditions*: (a) 1. 4-bromobenzaldehyde, K_2CO_3, methanesulfonic acid, H_2O/CH_2Cl_2/EtOH 2:2:1, rt, 12 h, then reflux, 1 h, 2. $NaBH_4$, MeOH, reflux, 1 h, 83%; (b) Allyltrichlorosilane, DBU, CH_2Cl_2, 0 °C, 2 h, then rt, 13 h, 88%.

Surprisingly, the allylation with **(*S*,*S*)-109** was more diastereoselective than the reaction with the corresponding (*R*,*R*)-reagent, resulting in a 13:1 mixture of *syn* and *anti* diastereomers (86% *de*), as shown in **Scheme 2.61**. Even at room temperature, no significant change in the selectivity was observed, and the reaction was complete after 24 h.



Scheme 2.61: Leighton allylation with **(*S*,*S*)-109**. *Reagents and conditions*: (a) **(*S*,*S*)-109**, $Sc(OTf)_3$, CH_2Cl_2, rt, 24 h, then TBAF, rt, 30 min, 87% (86% *de*).

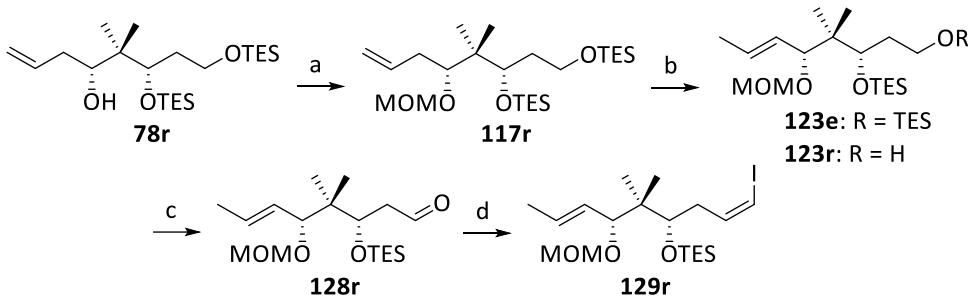
The ambiguity of the Mosher's method[108] performed on **78c** (**Section 2.1.2.5**) prompted us to directly apply Rychnovsky's protocol[110,111] to assign the relative stereochemistry of **78r**. Acetonide **115r** was prepared through the same sequence employed for **115**: removal of both silyl groups (this time with CSA instead of TBAF, given the more lability of TES compared to TBS), selective TBS protection of the primary alcohol and acetonide formation with dimethoxypropane, as depicted in **Scheme 2.62**. ^{13}C NMR of **115r** showed the typical signals of the *syn*-acetonides with the two methyl groups at 30.3 and 19.6 and the acetal carbon at 98.5, confirming the relative stereochemistry of **78r**.



Scheme 2.62: Synthesis of acetonide **115r**. *Reagents and conditions*: (a) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 2 h; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h; (c) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 1 h, 70% (3 steps).

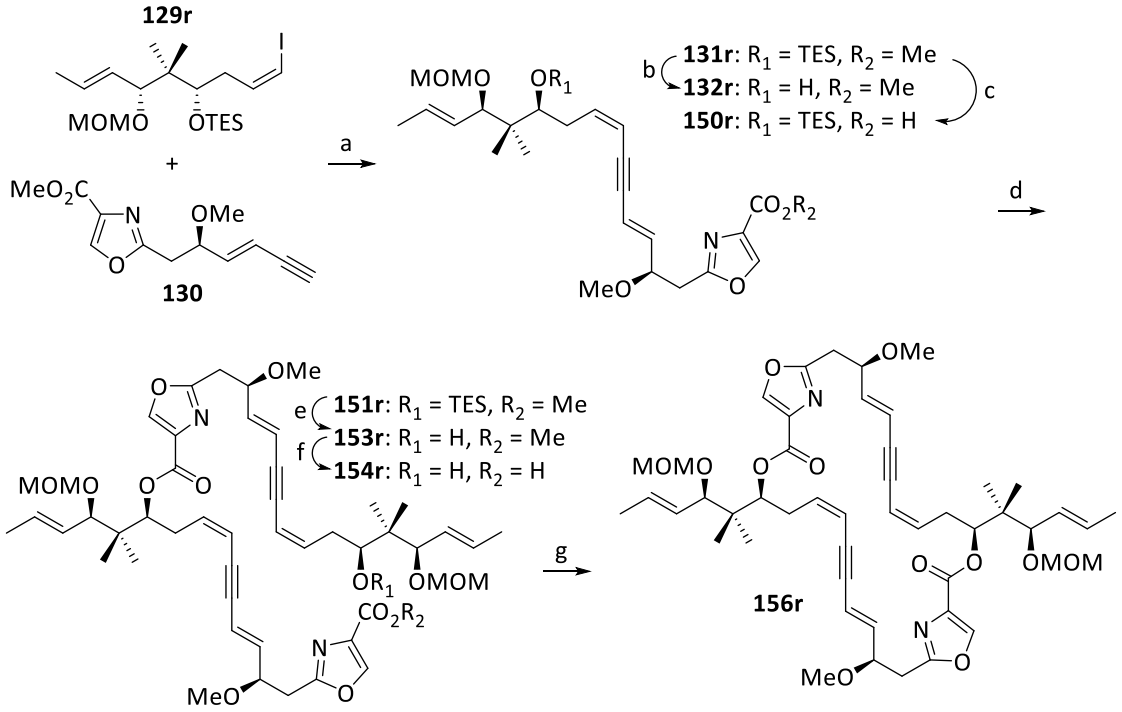
After building the 1,3-diol, the development of the lateral chain followed the established route (**Scheme 2.63**), with MOM protection of the secondary alcohol leading to compound

117r, isomerization of the double bond and subsequent Swern oxidation,[66] which produced aldehyde **128r**, and final Stork-Zhao olefination[83] to deliver vinyl iodide **129r**.



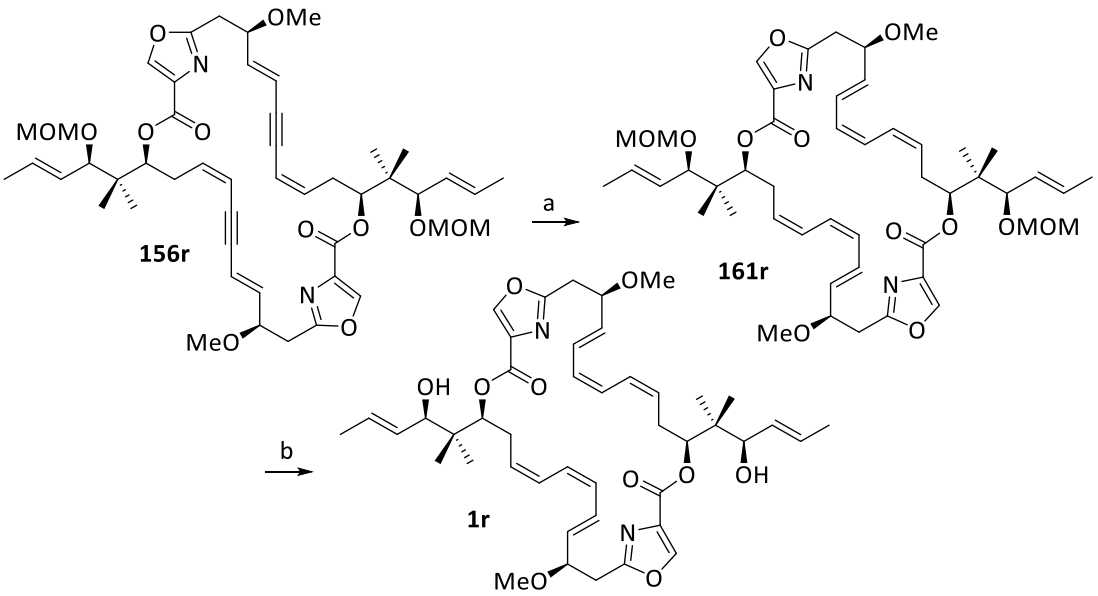
Scheme 2.63: Synthesis of vinyl iodide **129r**. *Reagents and conditions*: (a) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to 50 °C, 92%; (b) Grubbs II, MeOH, 60 °C, 22 h; (c) Swern, 77% (2 steps); (d) ICH_2PPh_3I, NaHMDS, DMPU, THF, – 78 °C, 1 h, 67%.

129r was coupled with oxazole **130** via Sonogashira reaction, which afforded monomer **131r** in 85% yield. Alcohol **132r** and carboxylic acid **150r** were both synthesized from **131r** and coupled in a Yamaguchi esterification, giving compound **151r**. Desilylation, saponification and macrolactonization led to homodimer **156r** in 70% yield, as depicted in **Scheme 2.64**.



Scheme 2.64: Strategy for the construction of the macrocycle **156r**. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –15 °C to rt, 1 h, 85%; (b) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 95%; (c) 1 M LiOH, THF, rt, 3 h, 99%; (d) **150r**, TCBC, NEt_3, THF, rt, 2 h, then **132r**, DMAP, toluene, rt, 16 h, 75%; (e) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h; (f) 1 M LiOH, THF, rt, overnight; (g) TCBC, NEt_3, THF, rt, 2 h, then DMAP, toluene, rt, 16 h, 70% (3 steps).

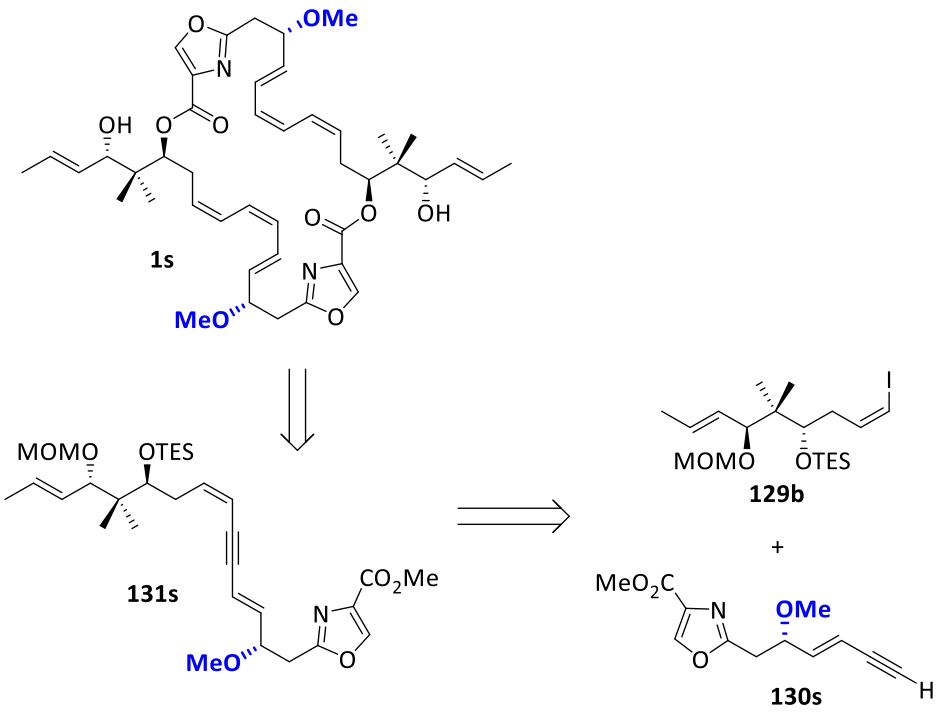
Finally, hydrogenation of the triple bonds furnished **161r** in 65% yield, and deprotection of the MOM ethers using aqueous HBr gave analog **1r** in 56% yield.



Scheme 2.65: Synthesis of analog **1r**. *Reagents and conditions*: (a) Zn (Ag/Cu), MeOH/H_2O 1:1, 50 °C, 24 h, 65%; (b) 48% aq. HBr, CH_3CN, 0 °C, 1 h, 56%.

2.2.3. Synthesis of (6*S*,6'*S*)-Disorazole C_1

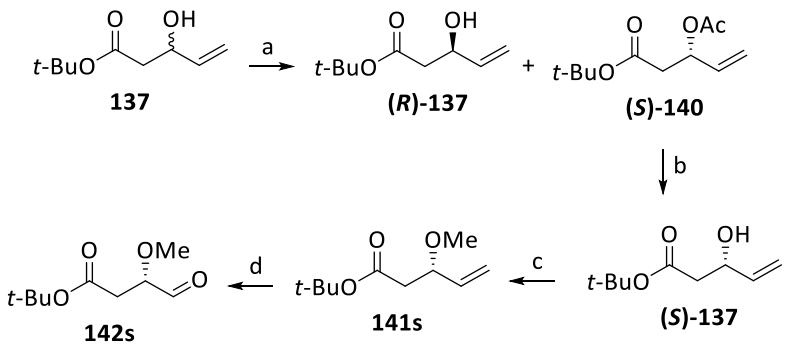
The last analog that was chosen as synthetic target was **1s**, which is distinguished by the change in the configuration of the C6-methoxy group. As suggested in **Scheme 2.66**, the synthesis of **1s** demanded oxazole **130s**, bearing the (*S*)-configuration of the methoxy group.



Scheme 2.66: Retrosynthetic analysis of derivative **1s**.

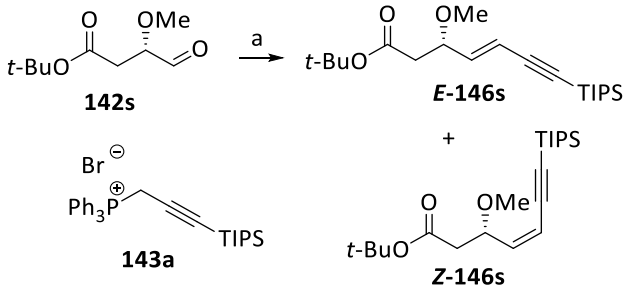
Consequently, the synthesis of the oxazole piece **130s** was accomplished using acetate **(*S*)-140** (**Scheme 2.67**), derived from the enzymatic resolution of racemic **137**. **(*S*)-140** was

deacetylated by potassium carbonate in methanol furnishing alcohol **(*S*)-137**. From **(*S*)-137**, the known sequence led to oxazole **130s**: methylation of the secondary alcohol formed compound **141s**, which was subjected to ozonolysis to give aldehyde **142s** in 92% yield.



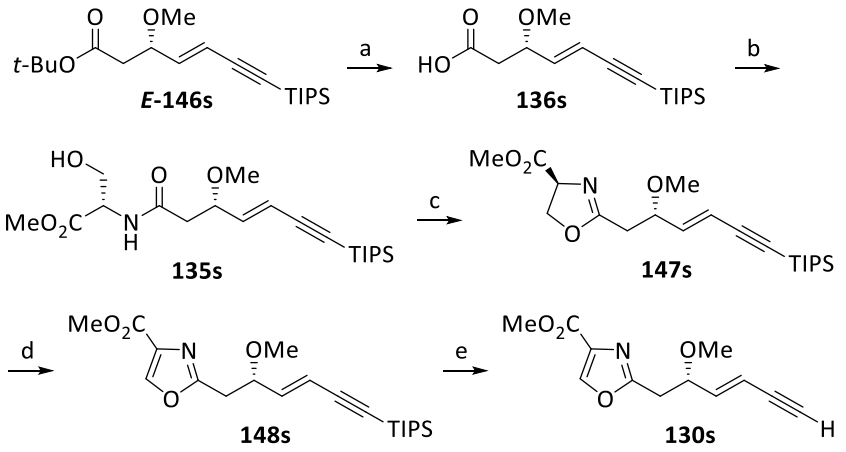
Scheme 2.67: Enzymatic resolution of β-hydroxyester **137** and synthesis of aldehyde **142s**. *Reagents and conditions*: (a) Amano Lipase PS, vinyl acetate, 4 Å MS, pentane, 30 °C, 24 h, 47% **(*R*)-137** and 48% **(*S*)-140**; (b) K_2CO_3, MeOH, 0 °C, 30 min, 80%; (c) Me_3OBF_4, Proton Sponge, CH_2Cl_2, rt, 3 h, 72%; (d) O_3/O_2, CH_2Cl_2/MeOH 5:1, –78 °C, then PPh_3, rt, 2 h, 92%;

As well as the (*R*)-counterpart, the Wittig reaction with phosphonium salt **143s** resulted in 60% of ***E*-146s**, alongside 22% of ***Z*-146s**, as shown in **Scheme 2.68**.



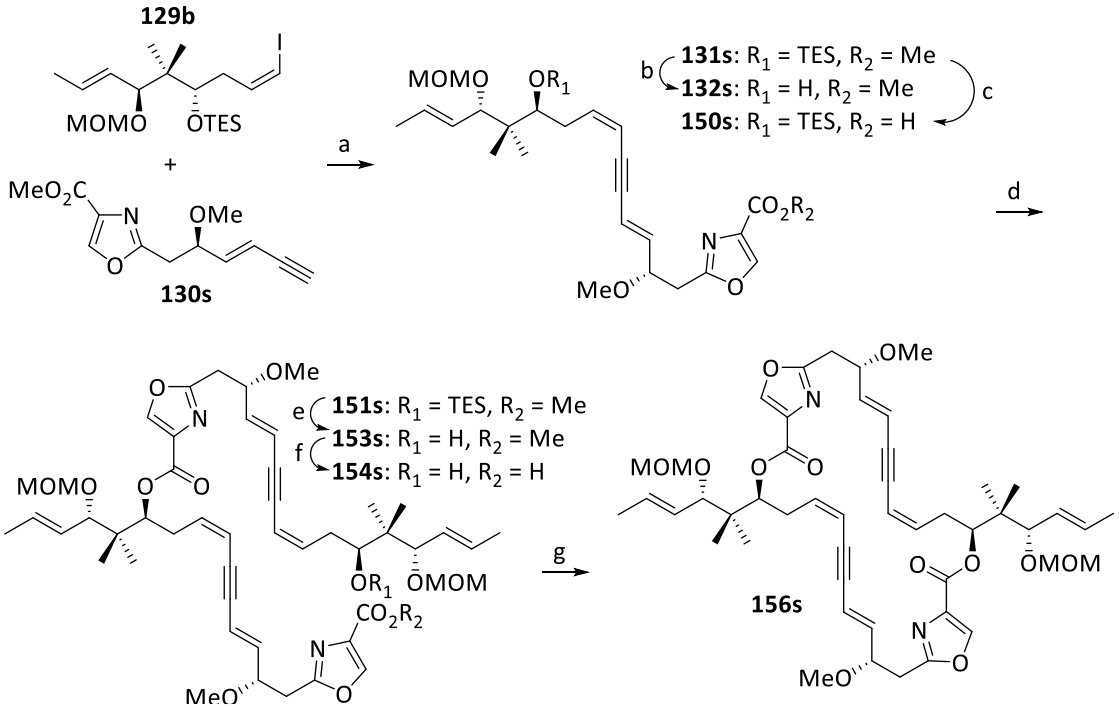
Scheme 2.68: Wittig reaction with phosphonium salt **143a**. *Reagents and conditions*: (a) **143a**, *n*-BuLi, THF, – 78 °C to 0 °C, 30 min, then **142s**, 0 °C to rt, 30 min, 60% ***E*-146s**, 22% ***Z*-146s**.

Enyne ***E*-146s** was transformed in the corresponding carboxylic acid **136s** under acidic conditions, and condensation with serine methyl ester hydrochloride afforded hydroxy amide **135s** in 82% yield. Cyclization with DAST and oxidation with DBU and $BrCCl_3$ generated TIPS-protected oxazole **148s**, and final deprotection of the terminal acetylene delivered the desired oxazole fragment **130s** in 70% yield, as depicted in **Scheme 2.69**.



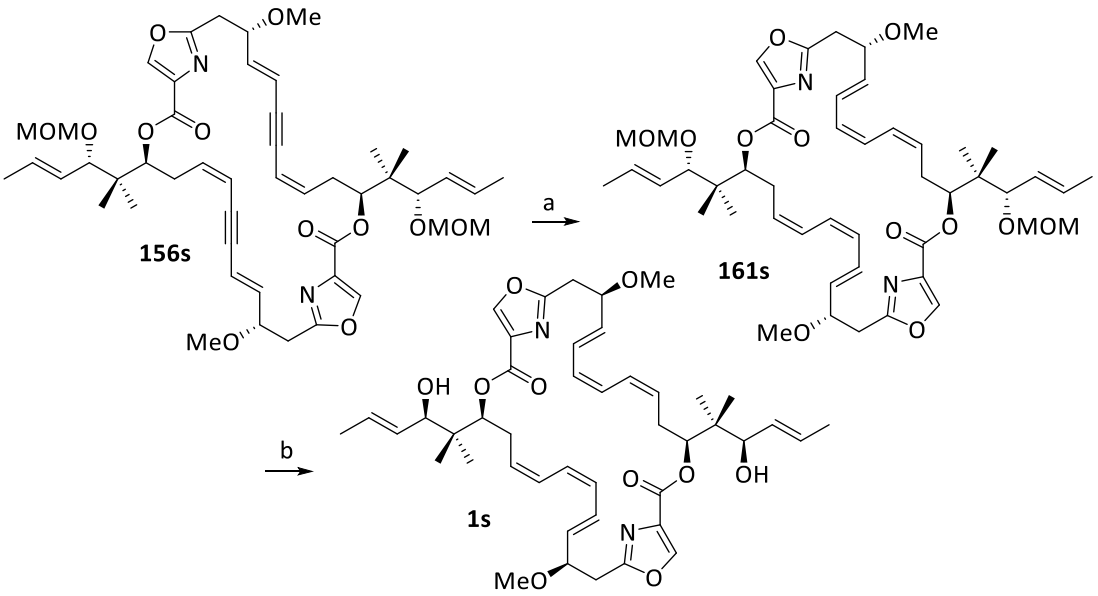
Scheme 2.69: Completion of the oxazole fragment **130**. *Reagents and conditions*: (a) HCOOH, rt, overnight, 99%; (b) DIPEA, TFFH, THF, rt, 2 h, then SerOMe·HCl, rt, 3 h, 82%; (c) DAST, CH_2Cl_2, –78 °C, 2 h, then K_2CO_3, rt, 1 h; (d) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C to rt, 16 h, 62% (2 steps); (e) TBAF, THF, 0 °C to rt, 30 min, 70%.

Sonogashira coupling[63] of **130s** and vinyl iodide **129b** worked in 75% yield, giving monomer **131s**. Deprotection of the TES ether produced alcohol **132s** in 97% yield, and hydrolysis of the methyl ester afforded acid **150s**. Esterification between **132s** and **150s** generated the full skeleton of the molecule, then desilylation, saponification of the methyl ester and Yamaguchi[64] macrolactonization delivered macrocycle **156s** in 60% yield over three steps (**Scheme 2.70**).



Scheme 2.70: Strategy for the synthesis of macrocycle **156s**. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, CH_3CN, –15 °C to rt, 1 h, 75%; (b) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h, 97%; (c) 1 M LiOH, THF, rt, 3 h, 99%; (d) **150s**, TCBC, NEt_3, THF, rt, 2 h, then **132s**, DMAP, toluene, rt, 16 h, 72%; (e) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 1 h; (f) 1 M LiOH, THF, rt, overnight; (g) TCBC, NEt_3, THF, rt, 2 h, then DMAP, toluene, rt, 16 h, 60% (3 steps).

Next, Boland reduction[134,135] worked in 60% yield furnishing MOM-protected **161s**, and removal of the MOM groups completed the synthesis of the last analog **1s**.



Scheme 2.65: Completion of the synthesis of analog **1s**. *Reagents and conditions*: (a) Zn (Ag/Cu), MeOH/H_2O 1:1, 50 °C, 24 h, 60%; (b) 48% aq. HBr, CH_3CN, 0 °C, 1 h, 56%.

2.2.4. Summary

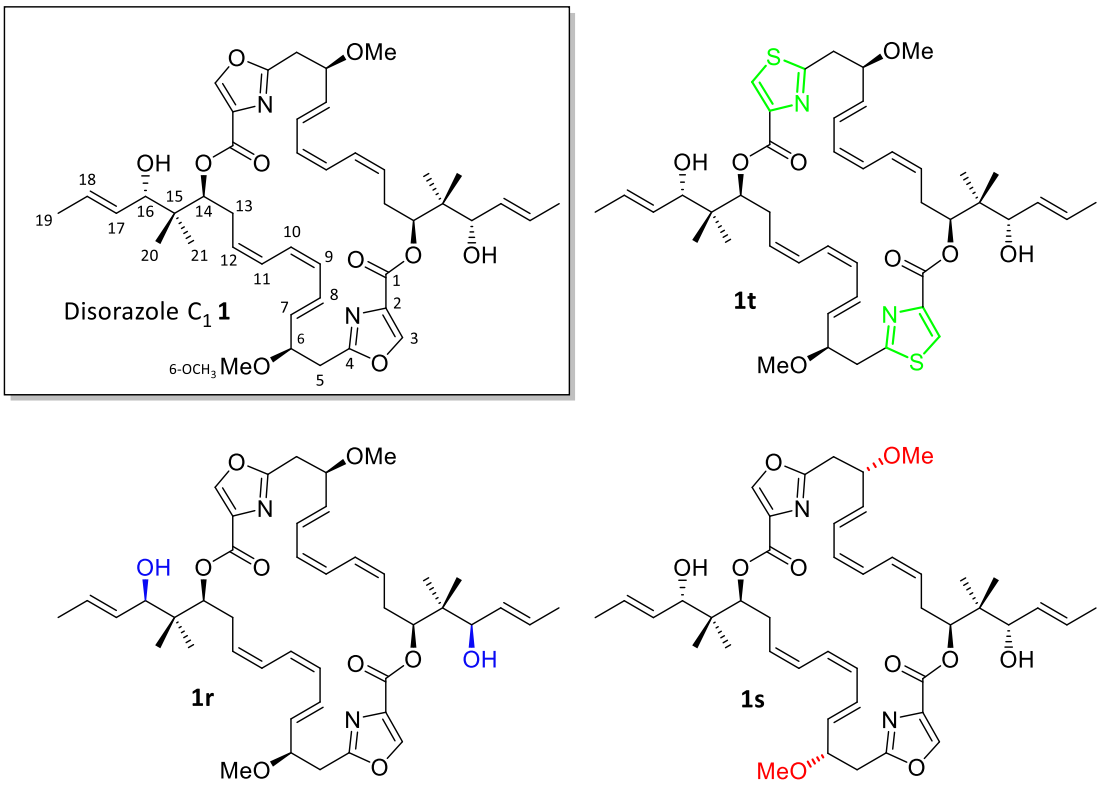


Figure 2.8: Structure of disorazole C_1 and its analogs.

The results of this work were interesting also from an analytical point of view: we expected a considerable difference in the chemical shifts in the NMR spectra of the analogs. On the

contrary, excluding a few signals (for example the aromatic proton in the thiazole analog), most of the differences in chemical shift were almost imperceptible, ranging from 0.01 to 0.07 for ^{1}H NMR and from 0.08 to 0.60 for ^{13}C NMR. **Table 2.7** compares the ^{1}H NMR chemical shifts of disorazole C_1 with the analogs.

	1	1t	1r	1s	
Proton	**δ [ppm]**	**δ [ppm]**	**δ [ppm]**	**δ [ppm]**	**$\Delta\delta_{max}$**
3-H	8.24	8.11	8.23	8.33	0.22
5-Ha	3.00	3.20	2.99	3.00	0.21
5-Hb	2.77	3.01	2.75	2.77	0.26
6-H	4.13	4.13	4.13	4.13	-
7-H	5.54	5.51	5.53	5.53	0.03
8-H	6.50	6.49	6.51	6.48	0.03
9-H	5.91	5.85	5.91	5.94	0.03
10-H	6.28	6.27	6.29	6.35	0.08
11-H	6.40	6.39	6.41	6.43	0.04
12-H	5.48	5.51	5.48	5.50	0.03
13-Ha	2.69	2.69	2.71	2.69	0.02
13-Hb	2.39	2.46	2.45	2.39	0.07
14-H	5.26	5.26	5.29	5.28	0.03
16-H	3.84	3.86	3.91	3.84	0.07
17-H	5.58	5.59	5.57	5.58	0.02
18-H	5.67	5.67	5.64	5.67	0.03
19-H3	1.70	1.69	1.71	1.70	0.02
20-H3	1.01	1.03	0.99	1.01	0.04
21-H3	0.95	0.97	0.95	0.95	0.02
6-OCH_3	3.21	3.20	3.21	3.21	0.01
16-OH	-	-	-	-	-
16-OH	-	-	-	-	-

Table 2.7: Comparison of ^{1}H NMR spectra of disorazole C_1 and its analogs. **$\Delta\delta_{max}$** refers to the maximal difference in the chemical shift for the selected proton.

While **Table 2.8** shows the ^{13}C NMR signals for the four compounds.

	1	1t	1r	1s	
Carbon	**δ [ppm]**	**δ [ppm]**	**δ [ppm]**	**δ [ppm]**	**$\Delta\delta_{max}$**
1	162.24	162.28	162.27	162.34	0.10
2	134.07	129.04	134.06	133.48	5.03
3	145.83	147.47	145.80	146.35	1.67
4	164.11	169.01	164.15	164.04	4.97
5	35.98	40.45	36.02	34.79	5.66
6	80.56	81.77	80.45	80.02	1.75
7	134.15	133.93	134.08	134.53	0.60
8	129.96	130.05	129.98	129.45	0.60
9	129.29	129.25	129.21	129.26	0.08
10	126.80	126.62	126.90	126.53	0.37
11	127.36	127.17	127.43	127.32	0.26
12	130.88	130.61	131.05	130.39	0.66
13	29.24	29.15	29.16	29.14	0.10
14	78.73	79.16	79.20	78.95	0.47
15	42.70	42.84	42.74	42.80	0.14
16	77.83	77.92	78.01	77.79	0.22
17	131.67	131.67	131.50	131.63	0.17
18	129.63	129.65	129.56	129.61	0.09
19	18.05	18.03	18.02	18.04	0.03
20	19.41	19.47	19.71	19.53	0.30
21	19.32	19.42	19.69	19.29	0.40
6-OCH_3	56.83	56.86	56.82	56.78	0.08

Table 2.8: Comparison of ^{13}C NMR spectra of disorazole C_1 and its analogs. **$\Delta\delta_{max}$** refers to the maximal difference in the chemical shift for the selected carbon.

In conclusion, a stereoselective synthesis of disorazole C_1 **1** was successfully accomplished, and the convergent strategy allowed for the synthesis of three new analogs, displayed in **Figure 2.8**. The synthetic route was efficiently applied to the synthesis of compounds **1t**, **1r** and **1s**, demonstrating the robustness of the reactions involved and the reliability of the strategy, which may offer the possibility of generate substantial amounts of the natural product and its analogs for *in vitro* and *in vivo* testing.

2.3. Biological Activity of Disorazole C_1 Analogs

Immediately after completing their synthesis, the analogs were submitted for biological evaluation at the HZI (Helmholtz Center for Infection Research) in Braunschweig. Professor Marc Stadler and his team tested the biological activities of compounds **1t**, **1r** and **1s** along with some intermediates against a variety of animal and human cancerous cells. The results are summarized in **Table 2.9** and **2.10**, and **Figure 2.9** shows the structures of the compounds discussed below.

Cell Line	Origin	IC_{50} (ng/mL) Disorazole A_1	IC_{50} (ng/mL) Disorazole C_1	IC_{50} (ng/mL) 1s	IC_{50} (ng/mL) MOM-1s	IC_{50} (ng/mL) 154s	IC_{50} (ng/mL) 153s
L929	Mouse fibroblasts	0.026	0.25	100	6800	n.a.	n.a.
KB-3.1	Human cervix carcinoma	0.014	0.23	18	4000	14000	9500
A549	Human lung carcinoma	0.053	0.32	13	3700	n.d.	n.d.
PC-3	Human prostate carcinoma	0.092	0.60	65	4600	n.d.	n.d.
MCF-7	Human breast adenocarcinoma	0.015	0.11	18	3500	n.d.	n.d.
SKOV-3	Human ovarian adenocarcinoma	0.023	0.28	12	4400	n.d.	n.d.

Table 2.9: Biological activities of disorazole C_1, analog **1s** and some intermediates. Disorazole A_1 was used as internal reference. Abbreviations: n.a. = no activity, n.d. = not done.

Synthetic disorazole C_1 was also tested (**Table 2.9**) and it proved to be once again highly active against all the selected cells, with IC_{50} between 0.11 and 0.60 ng/mL. The biological evaluation of the analogs indicated that any attempted modification to disorazole C_1 led to decreased cytotoxic activity. Nonetheless, the three analogs maintained a certain activity: the thiazole analog **1t** and analog **1s** were the most active, showing IC_{50} ranging from 12 to 180 ng/mL, while derivative **1r** showed IC_{50} values of 5400 ng/mL or more. The lower cytotoxicity of **1r** suggests that the free alcohol at C16 could have a bigger role in the interaction with the active site than the methoxy group at C6 and the heterocyclic motif.

Intermediates with protected alcohol such as **161t** or the monoprotected **MOM-1s** (derived from the partial deprotection of **161s**) exhibited similar IC_{50} to **1r**, indicating that the free alcohol functionality is as important as the spatial configuration.

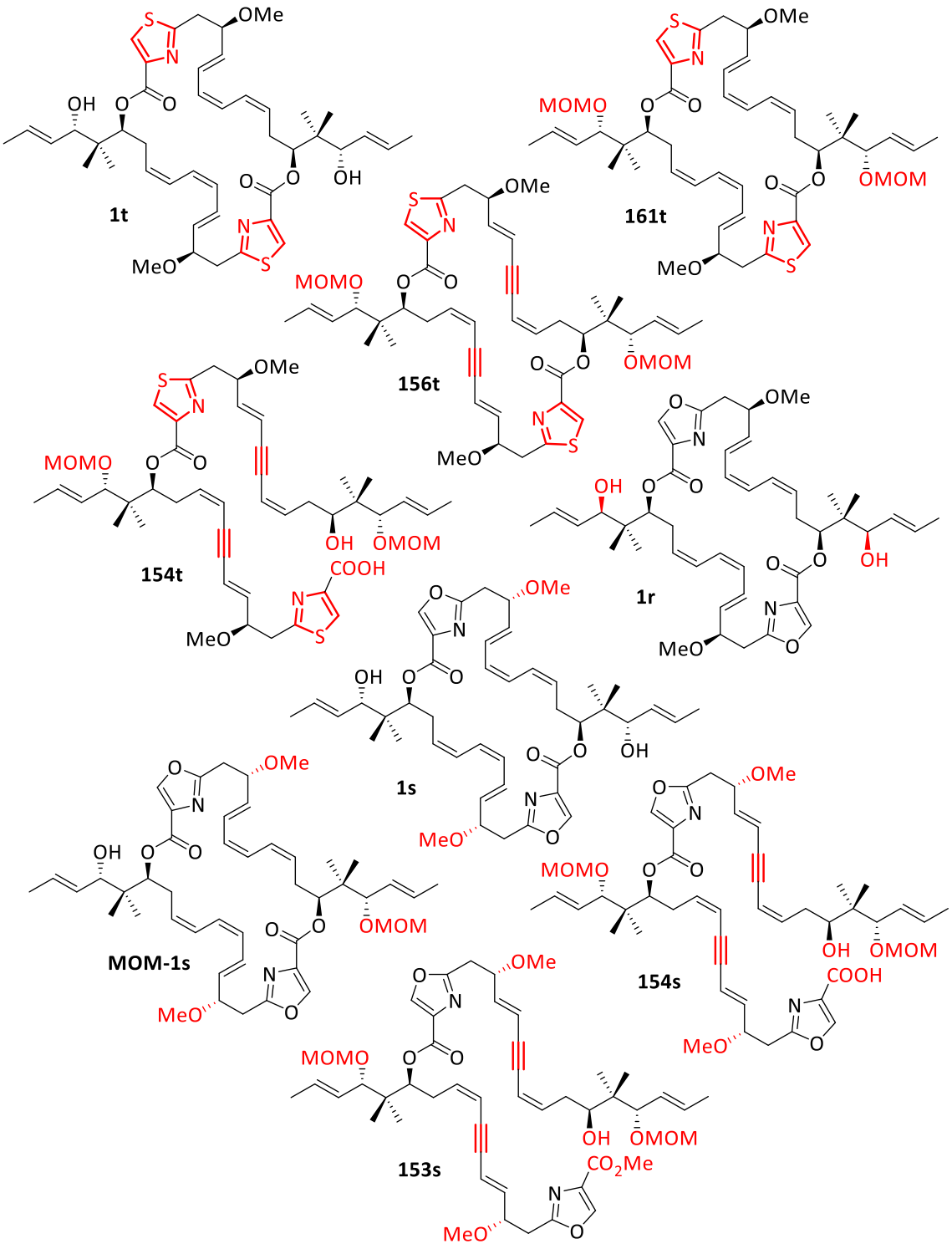


Figure 2.9: Structures of the compounds that were submitted for biological evaluation. In red the differences with the natural product.

The alkyne precursor **156t** was inactive and all the open form intermediates (**153s**, **154s** and **154t**) had very low activity, confirming that the macrocyclic structure and the conformation of the lactone are essential for the activity of the disorazoles, as already observed by Wipf and Graham.[50]

Cell Line	Origin	IC_{50} (ng/mL) Epothilone B	IC_{50} (ng/mL) 1t	IC_{50} (ng/mL) 161t	IC_{50} (ng/mL) 156t	IC_{50} (ng/mL) 154t	IC_{50} (ng/mL) 1r
L929	Mouse fibroblasts	0.24	180	n.a.	n.a.	n.a.	8600
KB-3.1	Human cervix carcinoma	0.017	85	2800	n.a.	3300	7200
A431	Human squamous carcinoma	0.026	82	7000	n.d.	4600	14000
A549	Human lung carcinoma	0.034	86	8300	n.d.	13000	9000
PC-3	Human prostate carcinoma	0.048	120	1200	n.d.	2900	7500
MCF-7	Human breast adenocarcinoma	0.015	91	6300	n.d.	3900	5400

Table 2.10: Biological activities of analogs **1t** and **1r** and some intermediates. Epothilone B was used as internal reference. Abbreviations: n.a. = no activity, n.d. = not done.

Interestingly, our synthetic disorazole C_1 exhibited approximately one order of magnitude higher potency, compared to the data reported on similar cell lines by Wipf *et al.*[42] (discussed in **Section 1.4.2**). The superior antiproliferative efficacy may suggest a better purity of our synthetic material.

2.3.1. Conclusion and Future Perspective

In summary, disorazole C_1 and a number of synthetic analogs and precursors have been tested against several cancerous cell lines, revealing two moderately active compounds (**1t** and **1s**) and extending the knowledge on the structure-activity relationships (SARs) of the family of disorazoles.

The future application of these cytotoxic compounds is strictly connected to targeted cancer therapy, which has been discussed at the beginning of this work (**Section 1.3**). The possible relation between disorazoles and ezrin (described in **Section 1.2**) will require an extensive multi-disciplinary investigation that will probably last many years. The possible interaction of disorazole C_1 with ezrin has never been tested due to lack of material, but our new route for the synthesis of this natural product could finally provide sufficient material to start the investigation. On the other hand, the conjugation of these molecules with antibodies and their consequent use in targeted therapy may be achieved in shorter times. In this regard, our research group has already begun a new project for the synthesis of new linkers for the production of ADCs (Antibody-Drug Conjugates). The goal of the project is to connect disorazole C_1 or one of the analogs to antibodies through the synthesized linker, and finally test the possible application of these highly active molecules.

Hopefully, these compounds could represent a new tool in the fight against cancer and the increasing phenomenon of drug-resistance, giving a solid alternative to the existing drugs on the market.

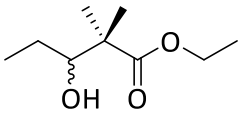
3. Experimental Procedures and Analytical Data

3.1. General Methods

Solvents were dried by standard procedures and redistilled under N_2 atmosphere prior to use. All reactions were run under nitrogen unless otherwise stated. For reactions that require heating, an oil bath was used. The products were purified by flash chromatography on Merck silica gel 60 (40-63 µm). POLYGRAM SIL G/UV$_{254}$ prefabricated TLC plates with fluorescent indicator from Macherey-Nagel have been used for the analytical thin layer chromatography (TLC). The separated substances were detected by irradiation with UV light with a wavelength of 254 nm or staining with vanillin or potassium permanganate reagent and subsequent warming with a heat gun. Electrospray ionization (ESI) and electron ionisation (EI) mass spectra were recorded on Finnigan MAT 95 and Waters Xevo G2-TOF spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVIII 400 and Bruker AVI 600 spectrometers. Chemical shifts (δ) are reported in ppm from tetramethylsilane, referenced to the solvent resonance resulting from incomplete deuteration (^{1}H NMR = $CDCl_3$: δ 7.26, CD_3OD: δ 3.31; ^{13}C NMR = $CDCl_3$: δ 77.16, CD_3OD: δ 49.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, app = apparent), coupling constants (Hz) and integration. Optical rotations were recorded on Perkin-Elmer 341 and Anton Paar MCP150 polarimeters. Infrared (IR) spectra were recorded on Bruker Vertex 70v. Bands are characterized as strong (s), medium (m), weak (w) or broad (br).

3.2. Total Synthesis of Disorazole C_1

3.2.1. Ethyl 3-hydroxy-2,2-dimethylpentanoate (87)



87

n-BuLi (2.5 M solution in hexane, 133 mL, 332.38 mmol, 1.1 eq) was added dropwise at – 78 °C to a solution of diisopropylamine (46.5 mL, 332.37 mmol, 1.1 eq) in THF (300 mL). This LDA solution was stirred for 30 min at 0 °C and then cooled to –78 °C. Ethyl isobutyrate **89** (40.6 mL, 302.16 mmol, 1 eq) dissolved in THF (58 mL) was added dropwise and the mixture was stirred for 1 h at –78 °C. Propionaldehyde **88** (23.8 mL, 332.38 mmol, 1.1 eq) was added dropwise at –78 °C and then the bath was removed and the mixture was stirred for 30 min

between –50 °C and –10 °C. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution (300 mL), the organic layer was separated and the aqueous phase was extracted with Et_2O (3x200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by vacuum distillation through a short Vigreux column afforded β-hydroxyester **87** (48.97 g, 281.25 mmol, 93%) as a colorless liquid.

General Data: $C_9H_{18}O_3$; FW: 174.13; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (–); Vanillin: light blue; bp: 105 °C (5 mbar).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.14 (qd, *J* = 14.2, 7.2, 1.1 Hz, 2H, OC*H*$_2$CH$_3$); 3.49 (dd, *J* = 10.6, 2.1 Hz, 1H, C*H*OH); 2.35 (s, 1H, CHO*H*); 1.54-1.46 (m, 1H, 1C*H*$_2$CH$_3$); 1.29-1.20 (m, 1H, 1C*H*$_2$CH$_3$); 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); 1.17 (s, 3H, C*H*$_3$); 1.15 (s, 3H, C*H*$_3$); 1.01 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$).

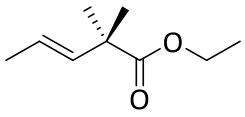
^{13}C-NMR (151MHz, $CDCl_3$): δ (ppm): 177.9 (C=O); 78.5 (CH); 60.8 (CH_2); 47.1 (C); 24.7 (CH_2); 22.5 (CH_3); 20.5 (CH_3); 14.3 (CH_3); 11.4 (CH_3).

IR (neat): 3464 (br); 2977 (m); 2938 (m); 2978 (m); 1712 (s); 1466 (m); 1366 (m); 1264 (s); 1139 (s); 1094 (s); 1024 (m); 975 (s); 861 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 175.13 (100) [*M*+H]$^+$, 197.11 (72) [*M*+Na]$^+$, 173.06 (68), 170.05 (26), 169.04 (22).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_9H_{19}O_3$: 175.1329; found: 175.1329.

3.2.2. Ethyl (*E*)-2,2-dimethyl-3-pentenoate (90)



90

β-hydroxyester **87** (48.97 g, 281.25 mmol) was refluxed with Sicapent® (70 g) in cyclohexane (250 mL) for 30 min. The solvent was removed by atmospheric distillation and the residue was distilled under vacuum to afford ester **90** (29.85 g, 191.25 mmol, 68%) as a colorless liquid.

General Data: $C_9H_{16}O_2$; FW: 156.11; TLC: R_f = 0.75 (pentane/Et_2O 2:1); UV (–); bp: 55-60 °C (10 mbar).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.61 (dq, *J* = 15.6, 1.5 Hz, 1H, C*H*=CH); 5.53-5.45 (m, 1H, CH=C*H*); 4.10 (q, *J* = 7.3 Hz, 2H, OCH_2CH$_3$); 1.67 (dd, *J* = 6.3, 1.4 Hz, 3H, OCH$_2$CH_3), 1.25 (s, 6H, 2CH_3); 1.23 (t, *J* = 7.1 Hz, 3H, CHCH_3).

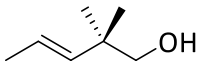
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 176.9 (C=O); 135.7 (CH); 123.4 (CH); 60.7 (CH_2); 44.1 (C); 25.2 (CH_3); 18.2 (CH_3); 14.3 (CH_3).

IR (neat): 2980 (s); 2921 (m); 2329 (w); 1632 (w); 1383 (m); 1252 (m); 1152 (m); 1073 (m); 954; 814 (w); 606 (w) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%): 156.07 (100) [*M*]$^+$, 141.05 (77), 116.03 (54), 110.02 (21).

HRMS (EI, 70 eV) *m*/*z*: [*M*]$^+$ Calcd for $C_9H_{16}O_2$: 156.1145; found: 156.1145.

3.2.3. (*E*)-2,2-dimethyl-3-penten-1-ol (91)



91

To a solution of ester **90** (16.37 g, 104.94 mmol, 1 eq) in THF (150 mL), $LiAlH_4$ (7.98 g, 209.87 mmol, 2 eq) was added and the mixture was refluxed for 2 h. After cooling to 0 °C, Et_2O (100 mL) was added and the reaction was quenched by dropwise addition of water (10 mL). The mixture was stirred for 30 min at room temperature until a white precipitate was formed, which was filtered off by suction through Celite and washed with Et_2O (3x200 mL). The filtrate and the washings were combined and concentrated in vacuo to furnish crude alcohol **91** (10.77 g, 94.45 mmol, 90%) as a colorless liquid, which was used for the preparation of aldehyde **86** without further purification. In case it was not used immediately, it was stored in the freezer.

General Data: $C_7H_{14}O$; FW: 114.10; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (–); Vanillin: dark blue; bp: 152-160 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.50-5.43 (m, 1H, C*H*=CH); 5.35 (dd, *J* = 15.6, 1.3 Hz, 1H, CH=C*H*); 3.27 (s, 2H, CH_2OH); 1.69 (dd, *J* = 6.5, 1.2 Hz, 3H, CHCH_3); 0.977 (s, 6H, 2CH_3).

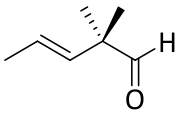
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 137.9 (CH); 124.3 (CH); 71.7 (CH_2); 38.5 (C); 24.1 (CH_3); 18.4 (CH_3).

IR (neat): 3366 (br); 3027 (w); 2960 (m); 2930 (m); 2869 (m); 1723 (w); 1450 (m); 1378 (m); 1248 (m); 1158 (w); 1044 (m); 970 (m); 894 (w); 697 (w); 610 (w) cm^{-1}.

MS (ESI): *m/z* (%): 175.13 (100), 115.11 (58) [*M*+H]$^+$, 141.05 (77), 116.03 (54), 110.02 (21).

HRMS (ESI) *m/z*: [*M*+H]$^+$ Calcd for $C_7H_{15}O$: 115.1123; found: 115.1119.

3.2.4. (*E*)-2,2-dimethyl-3-pentenal (86)



86

DMSO (11.2 mL, 157.4 mmol, 2 eq) in CH_2Cl_2 (45 mL) was added dropwise at –78 °C to a stirred solution of $(COCl)_2$ (8.1 mL, 94.44 mmol, 1.2 eq) in CH_2Cl_2 (210 mL). The mixture was stirred for 10 min at –78 °C. The crude (*E*)-2,2-dimethyl-3-penten-1-ol **91** (8.97 g, 78.7 mmol, 1 eq) dissolved in CH_2Cl_2 (60 mL) was added dropwise at –78 °C and the mixture was stirred for 1 h at –78 °C. The reaction was quenched by dropwise addition of NEt_3 (54.6 mL, 393.5 mmol, 5 eq) and the mixture was warmed to room temperature over 45 min. Water was added (250 mL) and the mixture was stirred for 10 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3x150 mL). The combined organic extracts were washed with 1M HCl (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Vacuum distillation of the residue afforded aldehyde **86** (7.9 g, 70.83 mmol, 90%) as a colorless liquid, which was stored in the freezer.

General Data: $C_7H_{12}O$; FW: 112.09; TLC: R_f = 0.80 (pentane/Et_2O 5:1); UV (–); bp: 127-128 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.32 (s, 1 H, C*H*O); 5.57-5.49 (m, 1H, C*H*=CH); 5.36 (dd, *J* = 15.7, 1.6 Hz, 1H, CH=C*H*); 1.71 (dd, *J* = 6.4, 1.5 Hz, 3H, CHCH_3); 1.14 (s, 6H, 2CH_3).

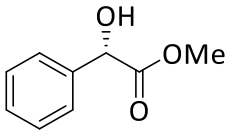
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 203.0 (C=O); 132.6 (CH); 127.2 (CH); 48.6 (C); 21.6 (CH_3); 18.5 (CH_3).

IR ($CDCl_3$): 3014 (m); 2935 (m); 2349 (w); 2328 (w); 2256 (w); 1723 (s); 1651 (w); 1466 (w); 1309 (w); 1213 (w); 1035 (w); 906 (s); 728 (s); 649 (m) cm^{-1}.

MS (ESI): *m/z* (%): 109.10 (100), 111.08 (35), 112.11 (30), 195.08 (31), 107.08 (21), 113.09 (4) [*M*+H]$^+$.

HRMS (ESI) *m/z*: [*M*+H]$^+$ Calcd for $C_7H_{13}O$: 113.0966; found: 113.0976.

3.2.5. (*S*)-(+)-Mandelic acid methyl ester (93)



93

To a solution of (*S*)-(+)-Mandelic acid **92** (57.13 g, 376 mmol, 1 eq) in MeOH (300 mL), concentrated sulfuric acid (600 µL, 11.3 mmol, 0.03 eq) was added and the mixture was refluxed for 4 h. The reaction was quenched with K_2CO_3 (1.04 g, 7.52 mmol, 0.02 eq) in 1.2 mL of water and the MeOH was evaporated in vacuo. Then Et_2O (300 mL) was added and the solid was filtered off; the filtrate was concentrated and crystallized from hexane (75 mL) to furnish ester **93** (54.9 g, 330.72 mmol, 88%) as a white solid.

General Data: $C_9H_{10}O_3$; FW: 166.06; TLC: R_f = 0.35 (pentane/Et_2O 1:1); UV (+); Vanillin: yellow; mp: 56-58 °C; $[\alpha]_D^{20}$ = +144.0 (*c* = 1.0, MeOH).

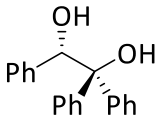
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.43-7.40 (m, 2H, Ar-*H*); 7.39-7.35 (m, 2H, Ar-*H*); 7.35-7.31 (m, 1H, Ar-*H*); 5.18 (s, 1H, C*H*OH), 3.76 (s, 3H, OCH_3).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 174.3 (C=O); 138.3 (ArC); 128.8 (ArCH); 128.7 (ArCH); 126.7 (ArCH); 73.00 (CH); 53.2 (OCH_3).

MS (ESI): *m*/*z* (%): 184.09 (100) $[M+NH_4]^+$, 189.05 (87) $[M+Na]^+$, 149.06 (72).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_9H_{10}O_3Na$: 189.0528; found: 189.0538.

3.2.6. (*S*)-(–)-1,1,2-Triphenyl-1,2-ethandiol (94)



94

To a solution of Phenylmagnesium bromide 3 M in Et_2O (200 mL, 600 mmol, 5 eq), ester **93** (20 g, 120.36 mmol, 1 eq) in Et_2O (120 mL) and THF (12 mL) was added dropwise at 0 °C at such a rate that the temperature does not rise above 10 °C (90 min required). The mixture was allowed to slowly warm to room temperature overnight and then refluxed for 1 h. After cooling to room temperature, the mixture was carefully poured into ice (200 g) and 2 M HCl (~300mL) was added dropwise to adjust the pH value to 4. The mixture was stirred for 1 h at room temperature and then the organic layer was separated. The aqueous phase was

extracted with CH_2Cl_2 (3x200 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated in vacuo. Crystallization of the residue from methanol (70 mL) afforded diol **94** (24.1 g, 83 mmol, 69%) as a white needle-shaped solid, which was dried under vacuum for several hours to remove all traces of methanol.

General Data: $C_{20}H_{18}O_2$; FW: 290.13; TLC: R_f = 0.25 (pentane/Et_2O 2:1); UV (+); mp: 123-127 °C; $[\alpha]_D^{20}$ = –125.5 (*c* = 1.0, $CHCl_3$).

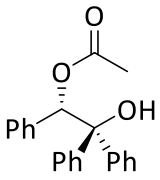
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.73-7.64 (m, 2H, Ar-*H*); 7.46-7.36 (m, 2H, Ar-*H*); 7.35-7.28 (m, 1H, Ar-*H*); 7.20-7.02 (m, 10H, Ar-*H*); 5.61 (s, 1H, C*H*OH); 3.15 (s, 1H, Ph_2CO*H*); 2.47 (s, 1H, PhCHO*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 145.2 (ArC); 143.5 (ArC); 138.9 (ArC); 128.6 (ArCH); 128.2 (ArCH); 127.8 (ArCH); 127.7 (ArCH); 127.6 (ArCH); 127.5 (ArCH); 127.1 (ArCH); 126.9 (ArCH); 126.3 (ArCH); 80.9 (CH); 78.1 (C).

MS (ESI): *m*/*z* (%): 273.12 (100), 308.16 (38) $[M+NH_4]^+$, 195.08 (14).

HRMS (ESI) *m*/*z*: $[M+NH_4]^+$ Calcd for $C_{20}H_{22}NO_2$: 308.1651; found: 308.1654.

3.2.7. (*S*)-(–)-2-Hydroxy-1,2,2-triphenylethylacetate [(*S*)-HYTRA] (81)



81

$Sc(OTf)_3$ (817 mg, 1.66 mmol, 0.02 eq) in CH_3CN (80 mL) was added dropwise at room temperature to a solution of diol **94** (24.1 g, 83 mmol, 1 eq) and acetic anhydride (11.77 mL, 124.5 mmol, 1.5 eq) in CH_3CN (340 mL). The mixture was stirred for 3 h at room temperature and then the solid was filtered, washed with in CH_3CN (2x20 mL) and dried under vacuum to furnish (*S*)-HYTRA **81** (23.2 g, 69.8 mmol, 84%) as a white solid.

General Data: $C_{22}H_{20}O_3$; FW: 332.14; TLC: R_f = 0.50 (pentane/Et_2O 2:1); UV (+); mp: 249-251 °C; $[\alpha]_D^{20}$ = –215.5 (*c* = 1.0, Pyridine).

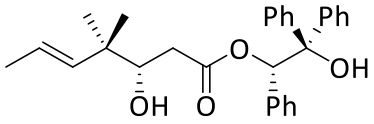
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.57-7.53 (m, 2H, Ar-*H*); 7.39-7.33 (m, 2H, Ar-*H*); 7.30-7.26 (m, 1H, Ar-*H*); 7.19-7.03 (m, 10H, Ar-*H*); 6.68 (s, 1H, PhC*H*); 2.82 (s, 1H, Ph_2CO*H*); 1.98 (s, 3H, CH_3CO_2CH).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 169.8 (C=O); 144.9 (ArC); 142.8 (ArC); 135.9 (ArC); 128.6 (ArCH); 128.5 (ArCH); 128.0 (ArCH); 127.9 (ArCH); 127.6 (ArCH); 127.5 (ArCH); 127.1 (ArCH); 126.4 (ArCH); 126.3 (ArCH); 80.4 (C); 78.6 (CH); 21.3 (CH_3).

MS (ESI): *m*/*z* (%): 274.27 (100), 280.26 (42), 355.13 (38) [*M*+Na]$^+$.

HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ Calcd for $C_{22}H_{20}O_3Na$: 355.1310; found: 355.1359.

3.2.8. (1*S*)-2-Hydoxy-1,2,2-triphenylethl (3*S*,5*E*)-3hydoxy-4,4-dimethyl-5-heptenoate (95)



95

n-BuLi (2.5 M solution in hexane, 22.5 mL, 56.32 mmol, 2.2 eq) was added dropwise at – 78 °C to a solution of diisopropylamine (7.9 mL, 56.32 mmol, 2.2 eq) in THF (80 mL). This LDA solution was stirred for 30 min at 0 °C and then added dropwise to a solution of (*S*)-HYTRA **81** (8.5 g, 25.6 mmol, 1 eq) in THF (150 mL) at –78 °C. The mixture was stirred for 1 h at 0 °C. The resulting yellow-orange solution was cooled to –78 °C and a solution of aldehyde **86** (3.44 g, 30.7 mmol, 1.2 eq) in THF (7 mL) was added dropwise. The mixture was stirred for 2 h 30 min at –78 °C The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution (150 mL) and the mixture was allowed to warm to room temperature over 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3x100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 3:1) afforded β-hydroxyester **95** (8.75 g, 19.71 mmol, 77%, 96% *de*) as a colorless solid.

General Data: $C_{29}H_{32}O_4$; FW: 444.23; TLC: R_f = 0.45 (pentane/Et_2O 2:1); UV (+); Vanillin: green; mp: 120-126 °C; $[\alpha]_D^{20}$ = –167.8 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.61-7.53 (m, 2H, Ar-*H*); 7.41-7.33 (m, 2H, Ar-*H*); 7.31-7.26 (m, 1H, Ar-*H*); 7.22-7.09 (m, 8H, Ar-*H*); 7.08-7.05 (m, 2H, Ar-*H*); 6.71 (s, 1H, C*H*Ph); 5.45-5.34 (m, 1H, C*H*=CH); 5.31 (dd, *J* = 15.9, 1.1 Hz, 1H, CH=C*H*); 3.51 (dd, *J* = 10.4, 2.2 Hz, 1H, C*H*OH); 2.86 (s, 1H, CHO*H*); 2.36 (dd, *J* = 15.8, 2.2 Hz, 1H, 1COCH_2); 2.24 (dd, *J* = 15.8, 10.3 Hz, 1H, 1COCH_2); 1.65 (dd, *J* = 5.8, 1.0 Hz, 3H, CHCH_3); 0.923 (s, 3H, 1CCH_3); 0.916 (s, 3H, 1CCH_3).

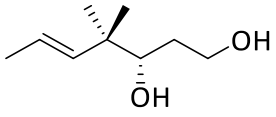
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 172.4 (C=O); 144.8 (ArC); 142.7 (ArC); 137.1 (CH); 135.6 (ArC); 128.5 (ArCH); 128.5 (ArCH); 128.1 (ArCH); 127.9 (ArCH); 127.7 (ArCH); 127.5 (ArCH); 127.2 (ArCH); 126.4 (ArCH); 126.3 (ArCH); 123.9 (CH); 80.5 (*C*HPh); 79.1 (*C*Ph_2OH); 74.9 (*C*HOH); 40.2 (C); 37.5 (CH_2); 23.8 (CH_3); 22.9 (CH_3); 18.4 (CH_3).

IR (neat): 3536 (br); 3029 (w); 2965 (w); 2876 (w); 1718 (m); 1600 (w); 1493 (m); 1447 (m); 1323 (m); 1247 (m); 1150 (m); 1033 (m); 974 (m); 891 (m); 752 (m); 695 (s); 612 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 273.13 (100), 467.22 (97) $[M+Na]^+$, 911.45 (40) $[2M+Na]^+$, 195.08 (31), 255.12 (18), 444.23 (<0.4) $[M]^+$.

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{29}H_{32}O_4Na$: 467.2098; found: 467.2198.

3.2.9. (3*S*,5*E*)-4,4-dimethyl-5-heptene-1,3-diol (96)



96

$LiAlH_4$ (5.2 g, 137.97 mmol, 7 eq) was added portionwise to a refluxing solution of β-hydroxyester **95** (8.75 g, 19.71 mmol, 1 eq) in Et_2O (210 mL) during a period of 2 h. Refluxing was continued for 30 min. After cooling to 0 °C, the reaction was quenched by dropwise addition of water (10 mL). Then Et_2O (150 mL) was added and the mixture was stirred for 30 min at room temperature until a white precipitate has formed. The precipitate was filtered off by suction through Celite and washed with Et_2O (4x100 mL). The filtrate and the washings were combined and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1 then pure Et_2O) afforded diol **96** (2.8 g, 17.74 mmol, 90%) as a colorless oil and (*S*)-(–)-1,1,2-triphenyl-1,2-ethandiol **94** (5.1 g, 17.74 mmol, 90%).

General Data: $C_9H_{18}O_2$; FW: 158.13; TLC: R_f = 0.30 (Et_2O); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –7.28 (*c* = 0.7, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.52-5.43 (m, 1 H, CH=C*H*); 5.38 (dq, *J* = 15.6, 1.3 Hz, 1H, C*H*=CH); 3.86-3.76 (m, 2H, CH_2OH); 3.47 (dd, *J* = 10.7, 2.2 Hz, 1H, C*H*OH); 2.42 (s, 2H, 2O*H*); 1.74-1.66 (m, 1H, 1C$H_2$$CH_2$OH); 1.69 (dd, *J* = 6.0, 1.3 Hz, 3H, CHCH_3); 1.62-1.52 (m, 1H, 1C$H_2$$CH_2$OH); 0.980 (s, 6H, 2CC$H_3$).

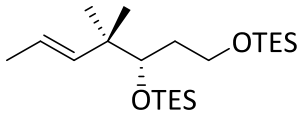
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 137.8 (CH); 124.6 (CH); 79.0 (CH); 62.7 (CH_2); 40.8 (C); 32.8 (CH_2); 23.8 (CH_3); 22.3 (CH_3); 18.4 (CH_3).

IR (neat): 3336 (br); 3025 (w); 2961 (m); 2932 (m); 2876 (m); 1668 (w); 1468 (m); 1447 (m); 1382 (m); 1320 (m); 1192 (w); 1049 (s); 971 (s); 878 (m); 832 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 181.1207 (100) $[M+Na]^+$, 123.12 (42), 158.13 (<0.4) $[M]^+$.

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_9H_{18}O_2Na$: 181.1205; found: 181.1207.

3.2.10. (*S,E*)-3,3,9,9-tetraethyl-5-(2-methylpent-3-en-2-yl)-4,8-dioxa-3,9-disilaundecane (97c)



97c

To a solution of diol **96** (1.96 g, 12.4 mmol, 1 eq) in CH_2Cl_2 (120 mL), 2,6-Lutidine (4.3 mL, 37.2 mmol, 3 eq) and TESOTf (5.9 mL, 26.0 mmol, 2.1 eq) were sequentially added dropwise at –78 °C. The mixture was stirred for 30 min at –78 °C and for 1 h at 0 °C. Saturated aqueous $NaHCO_3$ solution (100 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x80 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane) furnished compound **97c** (4.74 g, 12.28 mmol, 99%) as a colorless liquid.

General Data: $C_{21}H_{46}O_2Si_2$; FW: 386.3; TLC: R_f = 0.20 (pentane); UV (–); Vanillin: black; $[\alpha]_D^{20}$ = –15.00 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.43 (dq, *J* = 15.6, 1.2 Hz, 1H, C*H*=CH); 5.38-5.30 (m, 1H, CH=C*H*); 3.71-3.62 (m, 1H, 1C*H*$_2$OSi); 3.61-3.53 (m, 1H, 1C*H*$_2$OSi); 3.46 (dd, *J* = 8.4, 2.8 Hz, 1H, C*H*OSi); 1.77-1.67 (m, 1H, 1C*H*$_2$CH$_2$O); 1.65 (dd, *J* = 6.2, 1.3 Hz, 3H, CHC*H*$_3$); 1.53-1.43 (m, 1H, 1C*H*$_2$CH$_2$O); 1.00-0.89 (m, 18H, 2OSi(CH$_2$C*H*$_3$)$_3$); 0.969 (s, 3H, 1CC*H*$_3$); 0.940 (s, 3H, 1CC*H*$_3$); 0.654-0.552 (m, 12H, 2OSi(C*H*$_2$CH$_3$)$_3$).

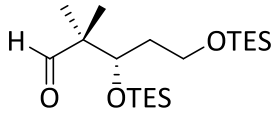
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 139.4 (CH); 121.6 (CH); 77.0 (CH); 61.0 (CH_2); 41.2 (C); 36.8 (CH_2); 24.7 (CH_3); 23.0 (CH_3); 18.4 (CH_3); 7.3 (CH_3); 6.9 (CH_3); 5.6 (CH_2); 4.6 (CH_2).

IR (neat): 2954 (m); 2915 (m); 2876 (m); 1632 (w); 1536 (w); 1460 (m); 1379 (m); 1238 (m); 1099 (s); 1006 (s); 800 (w); 725 (s); 674 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 506.53 (100), 156.12 (3), 449.34 (2), 387.31 (<0.4) $[M+H]^+$.

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{21}H_{47}O_2Si_2$: 387.3115; found: 387.3111.

3.2.11. (*S*)-2,2-dimethyl-3,5-bis((triethylsilyl)oxy)pentanal (77c)



77c

A stream of ozone in oxygen was bubbled through a solution of compound **97c** (4.74 g, 12.28 mmol, 1 eq) in CH_2Cl_2 (400 mL) at –78 °C until the blue color of the solution persisted. Then oxygen was bubbled for 10 min to remove excess of ozone and PPh_3 (3.86 g, 14.73 mmol, 1.2 eq) was added at –78 °C. The mixture was warmed to room temperature and stirred for 3 h. The crude solution was concentrated in vacuo, then pentane (300 mL) was added (to precipitate triphenylphosphine oxide) and the mixture was filtered through paper, with additional pentane washes. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 100:1 to 50:1) to furnish aldehyde **77c** (3.08 g, 8.22 mmol, 67%) as a colorless liquid, which was stored in the freezer.

General Data: $C_{19}H_{42}O_3Si_2$; FW: 374.27; TLC: R_f = 0.35 (pentane/Et_2O 50:1); UV (–); Vanillin: violet; $[\alpha]_D^{20}$ = +10.11 (*c* = 0.9, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 9.57 (s, 1H, C*H*O); 3.99 (dd, *J* = 8.2, 3.0 Hz, 1H, C*H*OSi); 3.71-3.58 (m, 2H, CH_2OSi); 1.74-1.64 (m, 1H, 1CH_2CH$_2$O); 1.62-1.52 (m, 1H, 1CH_2CH$_2$O); 1.04 (s, 3H, 1CCH_3); 1.00 (s, 3H, 1CCH_3); 0.984-0.908 (m, 18H, 2OSi(CH$_2$CH_3)$_3$); 0.659-0.519 (m, 12H, 2OSi(CH_2CH$_3$)$_3$).

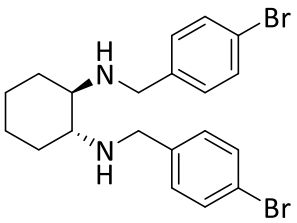
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 206.6 (C=O); 73.4 (CH); 59.8 (CH_2); 51.3 (C); 36.6 (CH_2); 19.1 (CH_3); 17.6 (CH_3); 7.1 (CH_3); 6.9 (CH_3); 5.5 (CH_2); 4.6 (CH_2).

IR (neat): 2955 (s); 2932 (m); 2877 (s); 2731 (w); 1730 (m); 1671 (w); 1460 (m); 1415 (m); 1378 (m); 1238 (m); 1085 (s); 1006 (s); 962 (m); 918 (m); 821 (m); 725 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 243.17 (100), 259.17 (5), 156.12 (4), 503.35 (2), 375.27 (<0.4) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{19}H_{43}O_3Si_2$: 375.2751; found: 375.2743.

3.2.12. (*R,R*)-*N,N*'-bis-(4-bromo-benzyl)-cyclohexane-1,2-diamine [(*R,R*)-111)]



(*R,R*)-111

To a suspension of (1*R*,2*R*)-(+)-1,2-diaminocyclohexane·L-tartrate **(*R,R*)-110** (5 g, 18.92 mmol, 1 eq) in H_2O (90 mL), K_2CO_3 (5.23 g, 37.84 mmol, 2 eq) was added, followed by EtOH (45 mL). To the resulting mixture was added a solution of 4-bromobenzaldehyde (7 g, 37.84 mmol, 2 eq) and methanesulfonic acid (0.148 mL, 2.27 mmol, 0.12 eq) in CH_2Cl_2 (90 mL). The mixture was stirred for 12 h at room temperature and 1 h at reflux. The mixture was concentrated, diluted with water and filtered. The collected solid was suspended in MeOH (25 mL), cooled to 0 °C and then $NaBH_4$ (1.6 g, 42.38 mmol, 2.24 eq) was added. The mixture was refluxed for 1 h and concentrated again. A 1:1 mixture of hexane and EtOAc (100 mL) was added, followed by 1 M NaOH (100 mL). The layers were separated and the aqueous phase was extracted with hexane/EtOAc 1:1 (3x80 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 4:1 then hexane/EtOAc/NEt_3 1:1:0.1) to afford the diamine **(*R,R*)-111** (7.08 g, 15.74 mmol, 83%) as a slightly yellow paste.

General Data: $C_{20}H_{24}Br_2N_2$; FW: 450.04; TLC: R_f = 0.45 (hexane/EtOAc/NEt_3 1:1:0.1); UV (+); Vanillin: white.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.42 (d, *J* = 8.3 Hz, 4H, Ar-*H*); 7.17 (d, *J* = 8.3 Hz, 4H, Ar-*H*); 3.84 (d, *J* = 13.4 Hz, 2H, ArC*H*$_2$N); 3.59 (d, *J* = 13.4 Hz, 2H, ArC*H*$_2$N); 2.25-2.18 (m, 2H, 2C*H*N); 2.16-2.08 (m, 2H, Cy); 2.00 (s, 2H, N*H*); 1.77-1.66 (m, 2H, Cy); 1.29-1.16 (m, 2H, Cy); 1.09-0.940 (m, 2H, Cy).

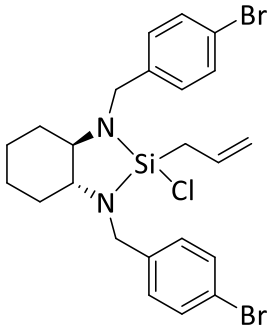
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 140.0 (ArC); 131.6 (ArCH); 129.9 (ArCH); 120.7 (ArC); 60.9 (CH); 50.3 (CH_2); 31.6 (CH_2); 25.1 (CH_2).

IR (neat): 3298 (s); 3020 (m); 2926 (s); 2864 (w); 1895 (m); 1738 (w); 1590 (m); 1497 (m); 1368 (m); 1238 (m); 1115 (s); 1061 (s); 798 (m); 725 (s) cm^{-1}.

MS (ESI): *m/z* (%): 453.04 (100), 451.04 (49) $[M+H]^+$, 456.04 (14), 156.05 (12).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{20}H_{25}Br_2N_2$: 451.0384; found: 451.0369.

3.2.13. (*R,R*)-Leighton reagent [(*R,R*)-109]



(*R,R*)-109

(*R,R*)-111 (7.05 g, 15.6 mmol, 1 eq) dissolved in CH_2Cl_2 (20 mL) was added dropwise to a solution of DBU (5.6 mL, 37.44 mmol, 2.4 eq) and allyltrichlorosilane (2.73 mL, 18.8 mmol, 1.2 eq) in CH_2Cl_2 (55 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and 13 h at room temperature. The solvent was removed in vacuo and then Et_2O (60 mL) was added, causing the formation of a white precipitate. The suspension was stirred for 1 h and then the supernatant was transferred by syringe into another flask. The mixture was concentrated again affording **(*R,R*)-109** (7.32 g, 13.26 mmol, 85%) as a yellow oil, which solidified upon standing in the freezer.

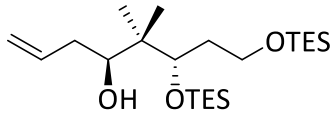
General Data: $C_{23}H_{27}Br_2ClN_2Si$; FW: 552.0.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.43 (d, *J* = 8.5 Hz, 2H, Ar-*H*); 7.42 (d, *J* = 8.5 Hz, 2H, Ar-*H*); 7.29 (d, *J* = 8.3 Hz, 2H, Ar-*H*); 7.25 (d, *J* = 2.0 Hz, 1H, Ar-*H*); 7.18 (d, *J* = 7.4 Hz, 1H, Ar-*H*); 5.67-5.58 (m, 1H, C*H*=CH_2); 4.94-4.88 (m, 2H, CH=C*H*$_2$); 4.14 (d, *J* = 16.1 Hz, 1H, 1ArC*H*$_2$N); 3.98 (d, *J* = 14.9 Hz, 1H, 1ArC*H*$_2$N); 3.84 (d, *J* = 15.7 Hz, 2H, ArC*H*$_2$N); 2.81-2.67 (m, 2H, 2C*H*N); 1.84-1.72 (m, 2H, Cy); 1.68-1.62 (m, 2H, Cy); 1.62-1.56 (m, 2H, SiC*H*$_2$CH=CH_2); 1.20-1.05 (m, 2H, Cy); 1.04-0.869 (m, 2H, Cy).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 141.2 (ArC); 140.3 (ArC); 131.3 (CH); 131.1 (ArCH); 130.0 (ArC); 129.2 (ArCH); 129.1 (ArCH); 128.3 (ArCH); 125.4 (ArCH); 120.7 (ArC); 120.4 (ArC); 116.4 (CH_2); 66.4 (CH); 65.5 (CH); 48.0 (CH_2); 47.3 (CH_2); 30.8 (CH_2); 30.4 (CH_2); 24.9 (CH_2); 24.8 (CH_2); 24.7 (CH_2).

IR (neat): 3062 (s); 3030 (m); 2936 (s); 2864 (w); 1895 (m); 1812 (w); 1590 (m); 1497 (m); 1368 (m); 1238 (m); 1115 (s); 1061 (s); 798 (m); 725 (s) cm^{-1}.

3.2.14. (4*S*,6*S*)-5,5-dimethyl-6,8-bis((triethylsilyl)oxy)oct-1-en-4-ol (78c)



78c

A solution of aldehyde **77c** (2.23 g, 5.96 mmol, 1 eq) in CH_2Cl_2 (10 mL) was added to a solution of **(*R*,*R*)-109** (3.95 g, 7.15 mmol, 1.2 eq) in CH_2Cl_2 (50 mL) at –15 °C (ice/acetone bath). Then $Sc(OTf)_3$ (147 mg, 0.298 mmol, 0.05 eq) was added, the flask was sealed under nitrogen, transferred into a freezer (–15 °C) and stirred for 48 h. TBAF trihydrate (1.88 g, 5.96 mmol, 1 eq) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated and the residue was purified by flash chromatography (pentane/Et_2O 50:1, then hexane/EtOAc/NEt_3 1:1:0.1) to furnish the allylic alcohol **78c** (2.1 g, 5.06 mmol, 85%, 84% *de*) as a colorless liquid and the recovered diamine **(*R*,*R*)-111** (3.64 g, 8.08 mmol, 87%) as a yellow paste. Analysis by ^1H and ^{13}C NMR showed a 11:1 mixture of *anti* and *syn* diastereoisomers.

General Data: $C_{22}H_{48}O_3Si_2$; FW: 416.31; TLC: R_f = 0.2 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –38.00 (*c* = 0.45, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.97-5.89 (m, 1H, C*H*=CH_2); 5.13-5.03 (m, 2H, CH=C*H*$_2$); 4.28 (s, 1H, CHO*H*); 3.78 (dd, *J* = 9.5, 3.2 Hz, 1H, C*H*OH); 3.73 (m, 1H, 1C*H*$_2$OSi); 3.69 (dd, *J* = 8.6, 2.2 Hz, 1H, C*H*OSi); 3.63 (m, 1H, 1C*H*$_2$OSi); 2.16-2.06 (m, 2H, C*H*$_2$CH); 1.90-1.83 (m, 1H, 1C*H*$_2$CH$_2$O); 1.74-1.65 (m, 1H, 1C*H*$_2$CH$_2$O); 1.01 (s, 3H, 1CC*H*$_3$); 0.991-0.931 (m, 18H, 2OSi(CH$_2$C*H*$_3$)$_3$); 0.755 (s, 3H, 1CC*H*$_3$); 0.663 (qd, *J* = 7.7, 1.3 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$); 0.590 (q, *J* = 8.0 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

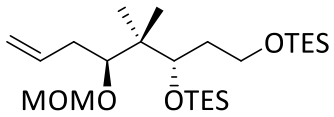
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 137.1 (CH); 116.3 (CH_2); 80.5 (CH); 75.5 (CH); 60.2 (CH_2); 40.6 (C); 36.6 (CH_2); 35.9 (CH_2); 23.3 (CH_3); 20.2 (CH_3); 7.1 (CH_3); 6.9 (CH_3); 5.4 (CH_2); 4.6 (CH_2).

IR (neat): 3488 (br); 2955 (m); 2913 (m); 2876 (m); 1677 (w); 1640 (w); 1461 (m); 1415 (m); 1381 (m); 1238 (m); 1085 (s); 1004 (s); 908 (w); 782 (m); 725 (s); 672 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 153.13 (100), 303.23 (62), 285.22 (40), 254.24 (38), 325.21 (4), 417.32 (2) $[M+H]^+$.

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{22}H_{48}O_3Si_2$: 417.3220; found: 417.3270.

3.2.15. (5*S*,7*S*)-5-allyl-11,11-diethyl-6,6-dimethyl-7-((triethylsilyl)oxy)-2,4,10-trioxa-11-silatridecane (117b)



117b

MOMCl (1.3 mL, 17 mmol, 3 eq) was added dropwise at 0 °C to a solution of allylic alcohol **78c** (2.36 g, 5.67 mmol, 1 eq), DIPEA (3 mL, 17 mmol, 3 eq) and DMAP (207 mg, 1.7 mmol, 0.3 eq) in CH_2Cl_2 (60 mL). The mixture was stirred for 16 h at 50 °C and then filtered on a pad of silica (pentane/Et_2O 10:1). The filtrate was concentrated in vacuo, the residue was again dissolved in CH_2Cl_2 (60 mL) and treated with DIPEA (3 mL, 17 mmol, 3 eq) and DMAP (207 mg, 1.7 mmol, 0.3 eq). The mixture was cooled to 0 °C, MOMCl (1.3 mL, 17 mmol, 3 eq) was added dropwise and then the mixture was stirred for 20 h at 50 °C. Evaporation of the solvent and purification of the residue by flash chromatography (pentane/Et_2O 60:1) afforded the protected triol **117b** (2.4 g, 5.21 mmol, 92%) as a colorless liquid.

General Data: $C_{24}H_{52}O_4Si_2$; FW: 460.34; TLC: R_f = 0.5 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –20.0 (*c* = 0.9, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.94-5.84 (m, 1H, C*H*=CH_2); 5.10-4.96 (m, 2H, CH=C*H*$_2$); 4.64 (dd, *J* = 17.3, 6.7 Hz, 2H, OC*H*$_2$OCH$_3$); 3.72 (d, *J* = 9.0 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.71-3.65 (m, 1H, 1C*H*$_2$OSi); 3.64-3.57 (m, 1H, 1C*H*$_2$OSi); 3.40 (dd, *J* = 8.4, 2.5 Hz 1H, C*H*OSi); 3.37 (s, 3H, OC*H*$_3$); 2.35-2.26 (m, 1H, 1C*H*$_2$CH); 2.23-2.14 (m, 1H, 1C*H*$_2$CH); 1.72-1.60 (m, 1H, 1C*H*$_2$CH$_2$O); 1.55-1.45 (m, 1H, 1C*H*$_2$CH$_2$O); 1.00-0.923 (m, 18H, 2OSi(CH$_2$C*H*$_3$)$_3$); 0.883(s, 6H, C(C*H*$_3$)$_2$); 0.674-0.544 (m, 12H, 2OSi(C*H*$_2$CH$_3$)$_3$).

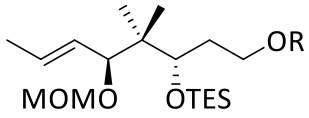
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 137.0 (CH); 116.2 (CH_2); 98.2 (CH_2); 83.9 (CH); 73.9 (CH); 60.4 (CH_2); 56.2 (CH_3); 43.7 (C); 35.9 (CH_2); 35.7 (CH_2); 19.9 (CH_3); 19.4 (CH_3); 7.3 (CH_3); 6.9 (CH_3); 5.8 (CH_2); 4.6 (CH_2).

IR (neat): 2954 (m); 2911 (m); 2876 (m); 1640 (w); 1459 (m); 1415 (m); 1386 (m); 1238 (m); 1090 (s); 1036 (s); 1004 (s); 912 (m); 726 (s); 673 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 506.52 (100), 243.17 (23), 457.33 (4), 461.34 (<1) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{24}H_{52}O_4Si_2$: 461.3438; found: 461.3460.

3.2.16. (3*S*,5*S*,*E*)-5-(methoxymethoxy)-4,4-dimethyl-3-((triethylsilyl)oxy)non-7-en-1-ol (123d)



123c: R = TES
123d: R = H

A solution of protected triol **117b** (2.3 g, 5 mmol, 1 eq) and Grubbs II (212 mg, 0.250 mmol, 0.05 eq) in MeOH was stirred for 22 h at 60 °C. The mixture was then concentrated in vacuo and the residue was filtered on a pad of silica gel (pentane/Et_2O 1:1). The filtrate was concentrated in vacuo affording a mixture of **123d** (80%) and **123c** (15%) as a colorless liquid, which was used in the next step without further purification. A small amount was further purified by flash chromatography (pentane/Et_2O 60:1 to 3:1) for analytical purpose.

General Data (123c): $C_{24}H_{52}O_4Si_2$; FW: 460.34; TLC: R_f = 0.5 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = +7.8 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (123c) (400 MHz, $CDCl_3$): δ (ppm): 5.64-5.53 (m, 1H, C*H*=CH); 5.36-5.27 (m, 1H, CH=C*H*); 4.66 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.46 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 3.79 (d, *J* = 8.9 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.75-3.66 (m, 1H, 1C*H*$_2$OSi); 3.63 (dd, *J* = 9.1, 2.2 Hz, 1H, C*H*OSi); 3.60-3.51 (m, 1H, 1C*H*$_2$OSi); 3.35 (s, 3H, OC*H*$_3$); 1.78-1.65 (m, 1H, 1C*H*$_2$CH$_2$O); 1.71 (dd, *J* = 6.4, 1.5 Hz, 3H, CHC*H*$_3$); 1.61-1.48 (m, 1H, 1C*H*$_2$CH$_2$O); 0.994-0.929 (m, 18H, 2OSi(CH$_2$C*H*$_3$)$_3$); 0.899 (s, 3H, 1CC*H*$_3$); 0.848 (s, 3H, 1CC*H*$_3$); 0.664-0.547 (m, 12H, 2OSi(C*H*$_2$CH$_3$)$_3$).

^{13}C-NMR (123c) (100 MHz, $CDCl_3$): δ (ppm): 130.7 (CH); 128.0 (CH); 93.5 (CH_2); 81.5 (CH); 74.0 (CH); 60.9 (CH_2); 55.7 (CH_3); 42.7 (C); 36.0 (CH_2); 19.8 (CH_3); 19.4 (CH_3); 17.9 (CH_3); 7.3 (CH_3); 6.9 (CH_3); 5.8 (CH_2); 4.6 (CH_2).

IR (neat) (123c): 2954 (m); 2918 (m); 2877 (m); 1730 (w); 1671 (w); 1632 (w); 1461 (m); 1415 (m); 1379 (m); 1239 (m); 1095 (s); 1033 (s); 973 (m); 922 (m); 823 (m); 726 (s) cm^{-1}.

MS (ESI) **(123c)**: *m*/*z* (%): 156.11 (100), 506.52 (75), 303.21 (25), 369.23 (18), 461.34 (<1) [*M*+H]$^+$.

HRMS (ESI) *m*/*z* **(123c)**: [*M*+H]$^+$ Calcd for $C_{24}H_{53}O_4Si_2$: 461.3482; found: 461.3445.

General Data (123d): $C_{18}H_{38}O_4Si$; FW: 346.25; TLC: R_f= 0.3 (pentane/Et_2O 3:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = +24.8 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (123d) (400 MHz, $CDCl_3$): δ (ppm): 5.65-5.54 (m, 1H, C*H*=CH); 5.37-5.28 (m, 1H, CH=C*H*); 4.66 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.46 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$OCH$_3$); 3.78 (d, *J* = 9.1 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.78-3.71 (m, 1H, 1C*H*$_2$OSi); 3.68 (dd, *J* = 8.7, 2.6 Hz, 1H, C*H*OSi); 3.66-3.59 (m, 1H, 1C*H*$_2$OSi); 3.35 (s, 3H, OC*H*$_3$); 1.84-1.60 (m, 1H, 1C*H*$_2$CH$_2$O); 1.72 (dd, *J* = 6.4, 1.6 Hz, 3H, CHC*H*$_3$); 1.66-1.55 (m, 1H, 1C*H*$_2$CH$_2$O); 0.963 (t, *J* = 7.9 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.915 (s, 3H, 1CC*H*$_3$); 0.867 (s, 3H, 1CC*H*$_3$); 0.630 (q, 6H, *J* = 8.0 Hz, OSi(C*H*$_2$CH$_3$)$_3$).

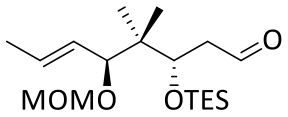
^{13}C-NMR (123d) (100 MHz, $CDCl_3$): δ (ppm): 131.1 (CH); 127.9 (CH); 93.5 (CH_2); 81.7 (CH); 74.6 (CH); 61.1 (CH_2); 55.8 (CH_3); 42.6 (C); 35.7 (CH_2); 20.0 (CH_3); 19.3 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat) (123d): 3386 (br); 2954 (m); 2877 (m); 1669 (w); 1465 (m); 1415 (m); 1382 (m); 1238 (m); 1146 (m); 1091 (m); 1033 (s); 972 (m); 921 (m); 840 (m); 727 (s) cm^{-1}.

MS (ESI) **(123d)**: *m*/*z* (%): 156.11 (100), 158.09 (48), 369.24 (42) [*M*+Na]$^+$, 189.12 (28), 506.25 (5), 347.26 (<1) [*M*+H]$^+$.

HRMS (ESI) *m*/*z* **(123d)**: [*M*+H]$^+$ Calcd for $C_{18}H_{39}O_4Si$: 347.2618; found: 347.2570.

3.2.17. (3*S*,5*S*,*E*)-5-(methoxymethoxy)-4,4-dimethyl-3-((triethylsilyl)oxy)oct-6-enal (128b)



128b

DMSO (0.780 mL, 11 mmol, 2 eq) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $(COCl)_2$ (0.644 mL, 7.5 mmol, 1.5 eq) in CH_2Cl_2 (20 mL) at –78 °C. The mixture was stirred for 10 min at –78 °C and then the crude **123c** + **123d** dissolved in CH_2Cl_2 (5 mL) was added dropwise. The reaction was stirred for 1 h at –78 °C, quenched by dropwise addition of NEt_3 (3.5 mL, 25 mmol, 5 eq) and then warmed to room temperature over 45 min. H_2O (30 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 10:1) afforded aldehyde **128b** (1.33 g, 3.86 mmol, 77%, from **117b**) as a colorless liquid.

General Data: $C_{18}H_{36}O_4Si$; FW: 344.24; TLC: R_f = 0.3 (pentane/Et_2O 10:1); UV (–); Vanillin: grey; $[\alpha]_D^{20}$ = +33.10 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.80 (dd, *J* = 3.0, 1.4 Hz, 1H, C*H*O); 5.59-5.52 (m, 1H, C*H*=CH); 5.38-5.32 (m, 1H, CH=C*H*); 4.65 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.45 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.18 (dd, *J* = 6.8, 3.8 Hz, 1H, C*H*OSi); 3.73 (d, *J* = 9.3 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.34 (s, 3H, OC*H*$_3$); 2.62 (ddd, *J* = 16.7, 3.9, 1.4 Hz, 1H, 1C*H*$_2$CO); 2.54 (ddd, *J* = 16.7, 6.9, 3.0 Hz, 1H, 1C*H*$_2$CO); 1.72 (dd, *J* = 6.4, 1.6 Hz, 3H, CHC*H*$_3$); 0.943 (t, *J* = 7.9 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.895 (s, 3H, 1CC*H*$_3$); 0.865 (s, 3H, 1CC*H*$_3$); 0.592 (q, *J* = 8.0 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

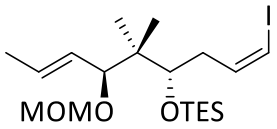
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 202.5 (C=O); 131.4 (CH); 127.9 (CH); 93.5 (CH_2); 81.9 (CH); 72.2 (CH); 55.8 (CH_3); 48.2 (CH_2); 42.6 (C); 20.3 (CH_3); 19.8 (CH_3); 17.9 (CH_3); 7.1 (CH_3); 5.5 (CH_2).

IR (neat): 3075 (w); 2955 (m); 2913 (m); 2876 (m); 1677 (m); 1640 (m); 1461 (m); 1415 (m); 1381 (w); 1238 (m); 1085 (s); 1004 (s); 974 (m); 908 (m); 782 (m); 725 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 362.27 (100) [*M*+Na]$^+$, 367.22 (76), 345.24 (28) [*M*+H]$^+$, 369.24 (16), 285.22 (7).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{18}H_{36}O_4Si$: 345.2461; found: 345.2436.

3.2.18. (5*S*,7*S*)-9,9-diethyl-7-((*Z*)-3-iodoallyl)-6,6-dimethyl-5-((*E*)-prop-1-en-1-yl)-2,4,8-trioxa-9-silaundecane (129b)



129b

NaHMDS (1 M in THF, 4.2 mL, 4.2 mmol, 1.5 eq) was added dropwise at 0 °C to a solution of ICH_2PPh_3I (2.22 g, 4.2 mmol, 1.5 eq) in THF (30 mL). The red solution was stirred for 10 min at room temperature and then cooled to –78 °C. DMPU (2.5 mL, 20.93 mmol, 7.5 eq) was added dropwise, followed by aldehyde **128b** (960 mg, 2.79 mmol, 1 eq) in THF (7 mL). The mixture was stirred for 1 h at –78 °C and 30 min at room temperature. Saturated NH_4Cl solution (30 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 100:1) giving the *Z* Iodide **129b** (875 mg, 1.87 mmol, 67%) as a slightly yellow liquid.

General Data: $C_{19}H_{37}IO_3Si$; FW: 468.16; TLC: R_f = 0.25 (pentane/Et_2O 100:1); UV (–); Vanillin: black; $[\alpha]_D^{20}$ = +7.8 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.32 (q, *J* = 6.8 Hz, 1H, C*H*=CHI); 6.22 (m, 1H, CH=C*H*I); 5.72-5.63 (m, 1H, C*H*=CH); 5.38-5.29 (m, 1H, CH=C*H*); 4.68 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.48 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$OCH$_3$); 3.82 (d, *J* = 9.1 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.72 (dd, *J* = 6.7, 4.1 Hz, 1H, C*H*OSi); 3.36 (s, 3H, OC*H*$_3$); 2.38-2.21 (m, 2H, C*H*$_2$CH); 1.73 (dd, *J* = 6.1, 1.4 Hz, 3H, CHC*H*$_3$); 0.957 (t, 9H, *J* = 8.0, OSi(CH$_2$C*H*$_3$)$_3$); 0.929 (s, 3H, 1CC*H*$_3$); 0.867 (s, 3H, 1CC*H*$_3$); 0.599 (q, *J* = 8.0 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

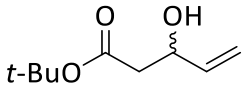
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 140.2 (CH); 131.4 (CH); 127.8 (CH); 93.6 (CH_2); 82.8 (CH); 81.7 (CH); 75.7 (CH); 55.8 (CH_3); 43.1 (C); 38.8 (CH_2); 19.9 (CH_3); 19.6 (CH_3); 18.1 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 3069 (w); 2980 (s); 2884 (m); 1668 (w); 1462 (m); 1382 (m); 1240 (m); 1147 (m); 1088 (s); 1036 (s); 970 (m); 922 (m); 820 (w); 724 (s); 572 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 506.53 (100), 507.53 (45), 504.51 (22), 469.16 (8) [*M*+H]$^+$, 457.16 (5), 396.31 (4).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{19}H_{38}IO_3Si$: 469.1635; found: 469.1682.

3.2.19. *tert*-Butyl 3-hydroxypent-4-enoate (137)



137

n-BuLi (2.5 M in hexane, 40 mL, 100 mmol, 1.1 eq) was added dropwise at –78 °C to a solution of diisopropylamine (14.02 mL, 100 mmol, 1.1 eq) in THF (60 mL). The mixture was stirred for 30 min at 0 °C and then cooled back to –78 °C. *t*-Butyl acetate **138** (12.18 mL, 90.9 mmol, 1 eq) in THF (30 mL) was added dropwise and the mixture was stirred for 1 h at – 78 °C. Acrolein (6.68 ml, 100 mmol, 1.1 eq) was added dropwise and the mixture was stirred for an additional hour at –78 °C and quenched with saturated aqueous NH_4Cl solution (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x60 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to afford **137** (12.52 g, 72.72 mmol, 80%) as a colorless liquid.

General Data: $C_9H_{16}O_3$; FW: 172.11; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (–); Vanillin: light blue.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.89-5.80 (m, 1H, C*H*=CH_2); 5.29 (dt, *J* = 17.2, 1.5 Hz, 1H, 1CH=C*H*$_2$); 5.13 (dt, *J* = 10.5, 1.4 Hz, 1H, 1CH=C*H*$_2$); 4.49-4.43 (m, 1H, C*H*OH); 2.89 (s, 1H, CHO*H*); 2.50 (dd, *J* = 16.1, 4.0 Hz, 1H, 1C*H*$_2$CH); 2.41 (dd, *J* = 16.1, 8.2 Hz, 1H, 1C*H*$_2$CH); 1.45 (s, 9H, OC(C*H*$_3$)$_3$)).

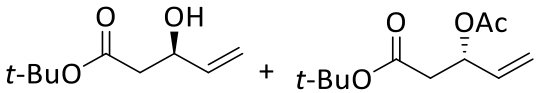
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.8 (C=O); 139.0 (CH); 115.3 (CH_2); 81.6 (C); 69.2 (CH); 42.2 (CH_2); 28.2 (C(*C*H$_3$)$_3$).

IR (neat): 3438 (br); 2980 (m); 2933 (w); 1726 (s); 1367 (m); 1152 (s); 922 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 173.12 (100) [*M*+H]$^+$, 117.05 (96), 190.14 (43) [*M*+Na]$^+$, 195.10 (23), 367.21 (18).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_9H_{17}O_3$: 173.1178; found: 173.1183.

3.2.20. *tert*-Butyl (*R*)-3-hydroxypent-4-enoate ((*R*)-137)



(*R*)-137 **(*S*)-140**

Vinyl acetate (16 mL, 174.18 mmol, 3 eq) was added to a solution of racemic *tert*-Butyl 3-hydroxypent-4-enoate **137** (10 g, 58.06 mmol, 1 eq) in pentane (200 mL). Then Amano Lipase PS (6 g) and 4Å molecular sieves (9.5 g) were added and the mixture was stirred for 24 h at 30 °C. The solids were filtered on paper and washed with Et_2O; the filtrate was concentrated in vacuo and the residue purified by flash chromatography (pentane/Et_2O 6:1 to 2:1) to afford **(*R*)-137** (4.71 g, 27.35 mmol, 47%, 99:1 *er*) and **(*S*)-140** (6.04 g, 28.22 mmol, 48%) as colorless liquids.

General Data: $C_9H_{16}O_3$; FW: 172.11; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (–); Vanillin: light blue; $[\alpha]_D^{20}$ = +8.9 (*c* = 0.55, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.89-5.80 (m, 1H, C*H*=CH_2); 5.29 (dt, *J* = 17.2, 1.5 Hz, 1H, 1CH=C*H*$_2$); 5.13 (dt, *J* = 10.5, 1.4 Hz, 1H, 1CH=C*H*$_2$); 4.49-4.43 (m, 1H, C*H*OH); 2.89 (s, 1H, CHO*H*); 2.50 (dd, *J* = 16.1, 4.0 Hz, 1H, 1C*H*$_2$CH); 2.41 (dd, *J* = 16.1, 8.2 Hz, 1H, 1C*H*$_2$CH); 1.45 (s, 9H, OC(C*H*$_3$)$_3$)).

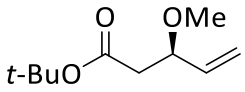
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.8 (C=O); 139.0 (CH); 115.3 (CH_2); 81.6 (C); 69.2 (CH); 42.2 (CH_2); 28.2 ($C(CH_3)_3$).

IR (neat): 3438 (br); 2980 (m); 2933 (w); 1726 (s); 1367 (m); 1152 (s); 922 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 173.12 (100) $[M+H]^+$, 117.05 (96), 190.14 (43) $[M+Na]^+$, 195.10 (23), 367.21 (18).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_9H_{17}O_3$: 173.1178; found: 173.1183.

3.2.21. *tert*-Butyl (*R*)-3-methoxypent-4-enoate (141)



141

Proton Sponge® (17.5 g, 81.86 mmol, 3 eq) and trimethyloxonium tetrafluoroborate (8.08 g, 54.58 mmol, 2 eq) were added to a solution of **(*R*)-137** (4.7 g, 27.29 mmol, 1 eq) in CH_2Cl_2 (115 mL) and the mixture was stirred for 3 h at room temperature. The reaction mixture was then filtered through a pad of Celite and the filtrate was washed with saturated aqueous solution of $NaHSO_4$ to remove Proton Sponge. The aqueous phase was extracted with CH_2Cl_2 and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (pentane/Et_2O 20:1, then 2:1) to give **141** (3.91 g, 21.03 mmol, 77%) as a colorless liquid and unreacted alcohol **(*R*)-137** (517 mg, 3.00 mmol, 11%).

General Data: $C_{10}H_{18}O_3$; FW: 186.13; TLC: R_f = 0.30 (pentane/Et_2O 20:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = +1.1 (*c* = 0.55, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.72-5.65 (m, 1H, C*H*=CH_2); 5.27 (dt, *J* = 17.1, 1.4 Hz, 1H, 1CH=C*H*$_2$); 5.21 (dt, *J* = 10.5, 1.2 Hz, 1H, 1CH=C*H*$_2$); 4.00-3.93 (m, 1H, C*H*OCH_3); 3.28 (s, 3H, OC*H*$_3$); 2.51 (dd, *J* = 15.0, 8.1 Hz, 1H, 1C*H*$_2$CH); 2.36 (dd, *J* = 15.0, 5.7 Hz, 1H, 1C*H*$_2$CH); 1.44 (s, 9H, OC(C*H*$_3$)$_3$)).

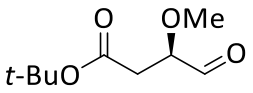
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.3 (C=O); 137.3 (CH); 117.8 (CH_2); 80.7 (C); 79.5 (CH); 56.6 (CH_3); 42.3 (CH_2); 28.2 ($C(CH_3)_3$).

IR (neat): 2979 (m); 2927 (m); 1732 (s); 1457 (m); 1392 (m); 1367 (m); 1280 (m); 1254 (m); 1156 (s); 1102 (s); 1018 (w); 991 (m); 928 (m); 845 (m); 765 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 131.07 (100), 113.06 (25), 279.17 (15), 187.13 (9) $[M+H]^+$, 252.23 (6)

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{10}H_{19}O_3$: 187.1334; found: 187.1336.

3.2.22. *tert*-Butyl (*R*)-3-methoxy-4-oxobutanoate (142)



142

A stream of O_3 in O_2 was bubbled through a solution of **141** (3.23 g, 17.37 mmol, 1 eq) in CH_2Cl_2 (75 mL) and MeOH (15 mL) at –78 °C until the blue color of the solution persisted. Then O_2 was bubbled for 10 min and PPh_3 (5.47 g, 20.84 mmol, 1.2 eq) was added. The mixture was warmed to room temperature and stirred for 2 h. The solvents were removed in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 2:1) to afford aldehyde **142** (2.91 g, 15.5 mmol, 89%) as a colorless liquid.

General Data: $C_9H_{16}O_4$; FW: 188.10; TLC: R_f = 0.25 (pentane/Et_2O 2:1); UV (–); Vanillin: yellow; $[\alpha]_D^{20}$ = +30.08 (*c* = 1.25, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.76 (s, 1H, C*H*O); 3.93-3.89 (m, 1H, C*H*OCH_3); 3.50 (s, 3H, OC*H*$_3$); 2.69 (dd, *J* = 16.2, 4.8 Hz, 1H, 1C*H*$_2$CH); 2.60 (dd, *J* = 16.1, 6.6 Hz, 1H, 1C*H*$_2$CH); 1.44 (s, 9H, OC(C*H*$_3$)$_3$)).

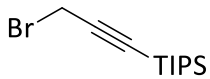
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 202.1 (CHO); 169.3 (C=O); 82.2 (C); 81.8 (CH); 58.8 (CH_3); 37.1 (CH_2); 28.2 (C(*C*H_3)$_3$).

IR (neat): 2979 (m); 2933 (m); 2832 (w); 1729 (s); 1456 (w); 1368 (m); 1256 (m); 1113 (s); 1076 (m); 953 (w); 846 (w) cm^{-1}.

MS (EI, 70eV): *m*/*z* (%): 189.11 (100) [*M*+H]$^+$, 187.10 (23), 188.10 (23) [*M*]$^+$, 190.09 (22).

HRMS (EI, 70eV) *m*/*z*: [*M*+H]$^+$ Calcd for $C_9H_{17}O_4$: 189.1121; found: 189.1116.

3.2.23. 3-Bromo-1-(triisopropylsilyl)-1-propyne (145)



145

n-BuLi (2.5 M solution in hexane, 40 mL, 100 mmol, 1 eq) was added dropwise at –78 °C to a solution of propargyl bromide **144** (80% in toluene, 10.87 mL, 100 mmol, 1 eq) in THF (200 mL). The mixture was stirred for 10 min and then TIPSCl (21.4 mL, 100 mmol, 1 eq) was added dropwise. Stirring was continued for 30 min at –78 °C and 2 h at room temperature. Saturated aqueous NH_4Cl solution was added (150 mL) and the layers were separated. The aqueous

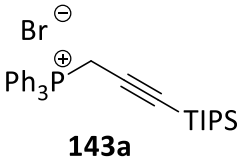
phase was extracted with Et_2O (3x100 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude by flash chromatography (pentane) furnished **145** (14.16 g, 62.61 mmol, 63%) as a colorless liquid.

General Data: $C_{12}H_{23}BrSi$; FW: 274.08; TLC: R_f = 0.5 (pentane); UV (+).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 3.94 (s, 2H, BrC*H*$_2$C); 1.07 (s, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 102.0 (C); 89.3 (C); 18.7 (C(*C*H$_3$)$_3$); 17.8 (CH_2); 11.3 (CH).

3.2.24. Phosphonium-triphenyl-(3-(tris-(1-methylethyl)silyl)-2-propyn-1-yl)-bromide (143a)



143a

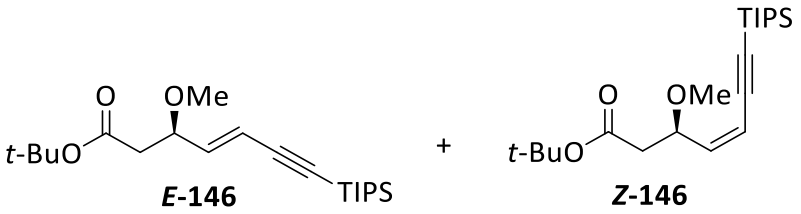
To a solution of PPh_3 (16.14 g, 61.55 mmol, 1 eq) in toluene (25 mL) at 0 °C, **145** was added via syringe. The mixture was stirred for 24 h at room temperature and then filtered. The product **143a** (19.55 g, 36.31 mmol, 59%) was collected on the filter and washed with cold pentane (10 mL).

General Data: $C_{30}H_{38}BrPSi$; FW: 536.17.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.95-7.86 (m, 6H, Ar-*H*); 7.82-7.75 (m, 3H, Ar-*H*); 7.70-7.62 (m, 6H, Ar-*H*); 5.12 (d, 2H, BrC*H*$_2$C); 0.853 (s, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 135.5 (ArC); 135.4 (ArC); 134.2 (ArCH); 134.1 (ArCH); 130.5 (ArCH); 130.3 (ArCH); 118.2 (ArC); 117.3 (ArC); 94.3 (C); 91.3 (C); 19.4 (CH_2); 18.5 (C(*C*H$_3$)$_3$); 11.0 (CH).

3.2.25. *tert*-Butyl (*R,E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynoate (*E*-146)



***E*-146** ***Z*-146**

n-BuLi (2.5 M solution in hexane, 8 mL, 20.05 mmol, 1.3 eq) was added dropwise to a suspension of TIPS propargyl triphenylphosphonium bromide **143a** (9.96 g, 18.5 mmol, 1.2 eq) in THF (100 mL) –78 °C. The red solution was stirred at 0 °C for 30 min and then aldehyde **142** (2.9 g, 15.42 mmol, 1 eq) in THF (20 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (100 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3x80 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 40:1 to 30:1) gave ***E*-146** (3.38 g, 9.25 mmol, 60%) and ***Z*-146** (1.25 g, 3.42 mmol, 22%).

General Data: $C_{21}H_{38}O_3Si$; FW: 366.26; TLC: R_f = 0.45 (pentane/Et_2O 20:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +8.2 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.01 (dd, *J* = 15.8, 7.2 Hz, 1H, C*H*=CH); 5.76 (dd, *J* = 15.9, 1.0 Hz, 1H, CH=C*H*); 4.04-3.98 (m, 1H, C*H*OCH_3); 3.30 (s, 3H, OC*H*$_3$); 2.50 (dd, *J* = 14.9, 7.9 Hz, 1H, 1C*H*$_2$CH); 2.37 (dd, *J* = 14.9, 5.6 Hz, 1H, 1C*H*$_2$CH); 1.44 (s, 9H, OC(C*H*$_3$)$_3$)); 1.07 (s, 21H, Si(C*H*(C*H*$_3$))$_3$).

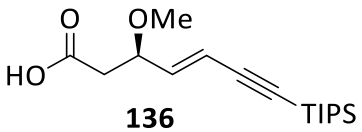
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 169.9 (C=O); 142.5 (CH); 112.9 (CH); 104.6 (C); 92.2 (C); 81.0 (C); 78.5 (CH); 57.1 (CH_3); 42.0 (CH_3); 28.2 (C(*C*H$_3$)$_3$); 18.7 (CH_3); 11.4 (CH).

IR (neat): 2942 (s); 2866 (s); 2148 (w); 1927 (w); 1732 (s); 1627 (w); 1463 (m); 1367 (m); 1244 (m); 1150 (s); 1102 (m); 996 (m); 882 (m); 673 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 279.18 (100), 311.20 (24), 384.29 (23), 367.26 (10) [*M*+H]$^+$, 219.12 (6), 172.11 (3).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{21}H_{39}O_3Si$: 367.2668; found: 367.2668.

3.2.26. (*R,E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynoic acid (136)



136

A solution of ***E*-146** (3.2 g, 8.74 mmol) in formic acid (13 mL) was stirred overnight at room temperature. The mixture was then concentrated in vacuo and azeotropically dried with toluene for 3 times to remove formic acid. Carboxylic acid **136** was obtained (2.68 g, 8.65 mmol, 99%) as a slightly yellow liquid.

General Data: $C_{17}H_{30}O_3Si$; FW: 310.20; TLC: R_f = 0.3 (pentane/Et_2O 5:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +10.22 (*c* = 0.45, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.02 (dd, *J* = 16.0, 7.4 Hz, 1H, C*H*=CH); 5.81 (dd, *J* = 16.0, 1.1 Hz, 1H, CH=C*H*); 4.11-4.04 (m, 1H, C*H*OCH_3); 3.33 (s, 3H, OC*H*$_3$); 2.62 (dd, *J* = 15.8, 8.5 Hz, 1H, 1C*H*$_2$CH); 2.54 (dd, *J* = 15.8, 4.7 Hz, 1H, 1C*H*$_2$CH); 1.07 (s, 21H, Si(C*H*(C*H*$_3$))$_3$).

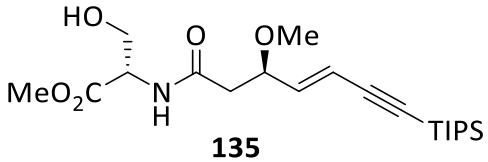
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 174.7 (C=O); 141.4 (CH); 113.8 (CH); 104.1 (C); 92.9 (C); 77.9 (CH); 57.2 (CH_3); 40.4 (CH_2); 18.8 (CH_3); 11.4 (CH).

IR (neat): 2921 (s); 2865 (s); 2142 (w); 1714 (s); 1641 (m); 1563 (w); 1462 (m); 1377 (w); 1240 (m); 1100 (s); 996 (m); 958 (m); 882 (m); 674 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 328.23 (100) [*M*+NH_4]$^+$, 279.17 (43), 638.42 (23), 311.20 (19) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{17}H_{31}O_3Si$: 311.2042; found: 311.2043.

3.2.27. Methyl ((*R,E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynoyl)-L-serinate (135)



135

DIPEA (3.5 mL, 20.1 mmol, 2.3 eq) and TFFH (2.54 g, 9.61 mmol, 1.1 eq) were added to a solution of carboxylic acid **136** (2.7 g, 8.74 mmol, 1 eq) in THF (30 mL) and the mixture was stirred for 2 h at room temperature. L-serine methyl ester hydrochloride (1.63 g, 10.49 mmol, 1.2 eq) was added and the mixture was stirred for 3 h. Et_2O (20 mL) was added and the solution was washed with 1 M HCl (40 mL). The aqueous phase was extracted with Et_2O (3x40 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O) afforded the serinate **135** (3.22 g, 7.82 mmol, 90%) as a yellow oil.

General Data: $C_{21}H_{37}NO_5Si$; FW: 411.24; TLC: R_f = 0.25 (Et_2O); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +28.42 (*c* = 1.2, $CHCl_3$).

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm): 6.05 (dd, *J* = 16.0, 7.2 Hz, 1H, C*H*=CH); 5.82 (dd, *J* = 16.0, 1.0 Hz, 1H, CH=C*H*); 4.51 (t, *J* = 4.4 Hz, 1H, COC*H*NH); 4.13-4.04 (m, 1H, C*H*OCH_3); 3.87 (dd, *J* = 11.2, 4.6 Hz, 1H, C*H*$_2$OH); 3.76 (dd, *J* = 11.2, 4.2 Hz, 1H, C*H*$_2$OH); 3.74 (s, 3H, COOC*H*$_3$);

3.30 (s, 3H, CHOCH_3); 2.56 (dd, *J* = 14.5, 8.1 Hz, 1H, 1CH_2CH); 2.41 (dd, *J* = 14.5, 5.0 Hz, 1H, 1CH_2CH); 1.08 (s, 21H, Si(CH(CH_3))$_3$).

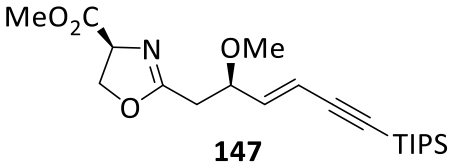
^{13}C-NMR (100 MHz, CD_3OD): δ (ppm): 172.7 (C=O); 172.2 (C=O); 144.0 (CH); 113.5 (CH); 106.0 (C); 92.4 (C); 79.6 (CH); 62.9 (CH_2); 57.3 (CH); 56.1 (CH_3); 52.8 (CH_3); 42.7 (CH_2); 19.0 (CH_3); 12.5 (CH).

IR (neat): 3343 (br); 2943 (m); 2865 (m); 2129 (w); 2048 (w); 1745 (m); 1650 (m); 1538 (m); 1462 (m); 1364 (w); 1213 (m); 1074 (m); 959 (w); 882 (m); 675 (m) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%): 411.24 (100) [*M*]$^+$, 396.22 (67), 412.25 (28), 397.22 (22), 393.24 (17).

HRMS (EI, 70eV) *m*/*z*: [*M*]$^+$ Calcd for $C_{21}H_{37}NO_5Si$: 411.2436; found: 411.2442.

3.2.28. Methyl (*S*)-2-((*R*,*E*)-2-methoxy-6-(triisopropylsilyl)hex-3-en-5-yn-1-yl)-4,5-dihydrooxazole-4-carboxylate (147)



147

DAST (1.13 mL, 8.56 mmol, 1.1 eq) was added dropwise to a solution of serinate **135** (3.2 g, 7.78 mmol, 1 eq) in CH_2Cl_2 (60 mL) at –78 °C and the mixture was stirred for 2 h at –78 °C. K_2CO_3 (2.15 g, 15.56 mmol, 2 eq) was added and the mixture was warmed to room temperature and stirred for 1 h. A saturated aqueous solution of NH_4Cl (50 mL) was carefully added and, after the gas evolution ceased, the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x50 mL) and the combined organic extracts were washed with Brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product **147** as a yellow oil, which was used for the next step without further purification.

General Data: $C_{21}H_{35}NO_4Si$; FW: 393.23; TLC: R_f = 0.5 (Et_2O); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +58.59 (*c* = 0.85, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.03 (dd, *J* = 16.0, 7.5 Hz, 1H, CH=CH); 5.77 (dd, *J* = 16.0, 1.0 Hz, 1H, CH=CH); 4.74 (dd, *J* = 10.5, 7.7 Hz, 1H, OCH_2CHCO); 4.50 (dd, *J* = 8.8, 7.8 Hz, 1H, 1OCH_2CHCO); 4.38 (dd, *J* = 10.5, 8.8 Hz, 1H, 1OCH_2CHCO); 4.07-3.99 (m, 1H, CHOCH$_3$); 3.77 (s, 3H, COOCH_3); 3.29 (s, 3H, CHOCH_3); 2.66 (dd, *J* = 14.9, 7.7 Hz, 1H, 1CH_2CH); 2.49 (dd, *J* = 14.9, 5.8 Hz, 1H, 1CH_2CH); 1.06 (s, 21H, Si(CH(CH_3))$_3$).

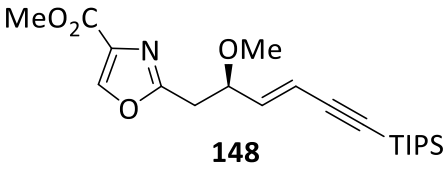
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.6 (C=N); 167.5 (C=O); 142.1 (CH); 113.3 (CH); 104.4 (C); 92.4 (C); 78.5 (CH); 69.5 (CH); 68.2 (CH_2); 57.1 (CH_3); 52.8 (CH_3); 34.4 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 3738 (w); 3649 (w); 2980 (s); 2890 (m); 2866 (m); 2328 (w); 2130 (w); 1743 (m); 1628 (w); 1462 (m); 1384 (m); 1250 (m); 1156 (m); 1073 (m); 994 (m); 956 (m); 882 (m); 664 (m) cm^{-1}.

MS (EI, 70eV): *m/z* (%): 350.16 (100), 337.22 (96), 361.18 (87), 393.23 (45) $[M]^+$, 368.17 (43), 362.19 (36), 351.17 (35).

HRMS (EI, 70eV) *m/z*: $[M]^+$ Calcd for $C_{21}H_{35}NO_4Si$: 393.2330; found: 393.2334.

3.2.29. Methyl (*R,E*)-2-(2-methoxy-6-(triisopropylsilyl)hex-3-en-5-yn-1-yl)oxazole-4-carboxylate (148)



148

The crude material **147** was dissolved in CH_2Cl_2 (60 mL), cooled to 0 °C and protected from light with aluminium foil. DBU (2.24 mL, 15.56 mmol, 2 eq) and $BrCCl_3$ (1.53 mL, 15.56 mmol, 2 eq) were sequentially added dropwise, then the bath was removed and the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x100 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1) afforded oxazole **148** (1.77 g, 4.51 mmol, 62% from **135**) as a yellow oil.

General Data: $C_{21}H_{33}NO_4Si$; FW: 391.22; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = –17.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.04 (dd, *J* = 15.8, 7.4 Hz, 1H, C*H*=CH); 5.77 (dd, *J* = 15.9, 1.0 Hz, 1H, CH=C*H*); 4.18-4.11 (m, 1H, C*H*OCH_3); 3.90 (s, 3H, COOCH_3); 3.26 (s, 3H, CHOCH_3); 3.08 (dd, *J* = 15.1, 8.1 Hz, 1H, 1CH_2CH); 2.99 (dd, *J* = 15.1, 5.3 Hz, 1H, 1CH_2CH); 1.07 (s, 21H, Si(C*H*(CH_3))$_3$).

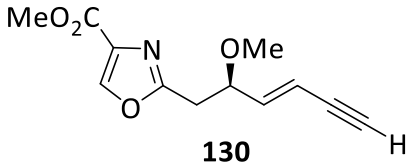
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 141.7 (CH); 133.5 (C); 113.8 (CH); 104.1 (C); 92.9 (C); 79.3 (CH); 57.1 (CH_3); 52.3 (CH_3); 34.6 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 3867 (w); 3738 (w); 3649 (w); 2980 (s); 2866 (m); 2328 (w); 2137 (w); 1747 (m); 1584 (m); 1462 (m); 1384 (m); 1323 (m); 1239 (m); 1165 (m); 1107 (m); 997 (m); 956 (m); 882 (m); 763 (m); 664 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 360.20 (100), 392.22 (65) $[M+H]^+$, 414.20 (20) $[M+Na]^+$, 805.42 (4)

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{21}H_{34}NO_4Si$: 392.2257; found: 392.2259.

3.2.30. Methyl (*R,E*)-2-(2-methoxyhex-3-en-5-yn-1-yl)oxazole-4-carboxylate (130)



130

TBAF (1 M in THF, 4.21 mL, 4.21 mmol, 1.1 eq) was added dropwise at 0 °C to a solution of TIPS oxazole **148** (1.5 g, 3.83 mmol, 1 eq) in THF (40 mL). The mixture was stirred for 30 min at room temperature and then quenched with water (30 mL). The aqueous phase was extracted with Et_2O (3x20 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1 to 1:1) afforded oxazole **130** (729 mg, 3.1 mmol, 81%) as a yellow oil.

General Data: $C_{12}H_{13}NO_4$; FW: 235.08; TLC: R_f = 0.30 (pentane/Et_2O 1:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = –26.89 (*c* = 0.45, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.10 (ddd, *J* = 16.0, 7.4, 0.5 Hz, 1H, C*H*=CH); 5.70 (ddd, *J* = 16.0, 2.3, 1.0 Hz, 1H, CH=C*H*); 4.19-4.12 (m, 1H, C*H*OCH_3); 3.89 (s, 3H, COOCH_3); 3.26 (s, 3H, CHOCH_3); 3.08 (dd, *J* = 15.1, 7.8 Hz, 1H, 1CH_2CH); 2.98 (dd, *J* = 15.0, 5.8 Hz, 1H, 1CH_2CH); 2.92 (d, *J* = 2.3 Hz, 1H, CC*H*).

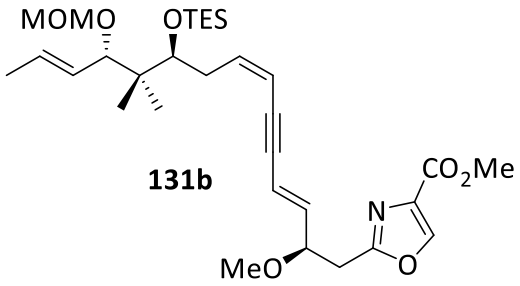
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.4 (C=O); 161.7 (C=N); 144.1 (CH); 143.1 (CH); 133.5 (C); 112.4 (CH); 80.9 (C); 79.1 (CH); 79.0 (CH); 57.1 (CH_3); 52.3 (CH_3); 34.5 (CH_2).

IR (neat): 3251 (m); 3119 (w); 2941 (w); 2882 (w); 2826 (w); 1712 (s); 1582 (s); 1437 (m); 1323 (s); 1231 (m); 1200 (m); 1163 (m); 1095 (s); 1006 (m); 970 (m); 940 (m); 810 (m); 768 (m); 679 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 204.06 (100), 236.09 (97) $[M+H]^+$, 156.12 (55), 486.19 (32), 469.16 (28), 279.18 (22), 311.03 (19).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{12}H_{14}NO_4$: 236.0923; found: 236.0935.

3.2.31. Methyl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (131b)



The vinyl iodide **129b** (397 mg, 0.847 mmol, 1 eq) was dissolved in degassed CH_3CN (5 mL) and CuI (39 mg, 0.254 mmol, 0.3 eq) and $PdCl_2(PPh_3)_2$ (60 mg, 0.0847 mmol, 0.1 eq) were added. The mixture was degassed by freeze-pump-thaw (2 cycles) and then cooled to –15 °C (ice/acetone bath). NEt_3 (0.706 mL, 5.08 mmol, 6 eq) was added, followed by a slow addition of the enyne **130** (240 mg, 1.02 mmol, 1.2 eq) in degassed CH_3CN (3 mL). The solution became red and after 15 min the bath was removed. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to give the monomer **131b** (414 mg, 0.720 mmol, 85%) as a yellow oil.

General Data: $C_{31}H_{49}NO_7Si$; FW: 575.33; TLC: R_f = 0.20 (pentane/Et_2O 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –28.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.10-6.02 (m, 1H, CH_2CH=CH); 5.99 (dd, *J* = 15.9, 7.5 Hz, 1H, CC*H*=CHCH); 5.89 (dd, *J* = 15.9, 2.2 Hz, 1H, CC*H*=$CHCH_2$); 5.66-5.54 (m, 2H, $CH(OCH_3)CH$=CH, C*H*=$CHCH_3$); 5.37-5.28 (m, 1H, CH=C*H*CH_3); 4.66 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.46 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.21-4.13 (m, 1H, C*H*OCH_3); 3.90 (s, 3H, $COOCH_3$); 3.84 (d, *J* = 9.3 Hz, 1H, C*H*OCH_2OCH_3); 3.67 (dd, *J* = 7.1, 3.8 Hz, 1H, CH_2CHOTES);

3.35 (s, 3H, CHOCH_3); 3.27 (s, 3H, CHOCH$_2$OCH_3); 3.10 (dd, *J* = 12.6, 5.6 Hz, 1H, 1CH_2CHOCH$_3$); 2.99 (dd, *J* = 15.0, 5.5 Hz, 1H, 1CH_2CHOCH$_3$); 2.62-2.53 (m, 1H, 1CH_2CH=CH); 2.45-2.37 (m, 1H, 1CH_2CH=CH); 1.71 (dd, *J* = 6.4, 1.6 Hz, 3H, CH=CHCH_3); 0.952 (app t, *J* = 8.0 Hz, 9H, OSi(CH$_2$CH_3)$_3$); 0.922 (s, 3H, CCH_3); 0.849 (s, 3H, CCH_3); 0.599 (q, *J* = 8.0 Hz, 6H, OSi(CH_2CH$_3$)$_3$).

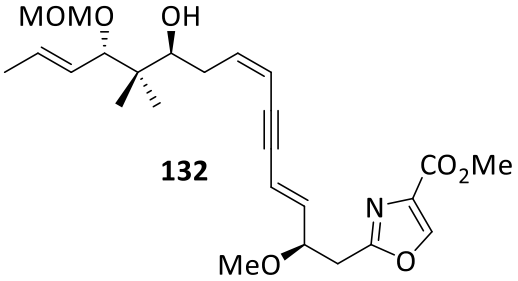
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 143.2 (CH); 140.4 (CH); 133.5 (C); 131.0 (CH); 128.0 (CH); 113.9 (CH); 109.5 (CH); 93.6 (CH_2); 91.2 (C); 88.5 (C); 81.6 (CH); 79.4 (CH); 76.5 (CH); 56.9 (CH_3); 55.7 (CH_3); 52.3 (CH_3); 43.1 (C); 34.7 (CH_2); 34.5 (CH_2); 19.8 (CH_3); 19.4 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 3656 (w); 2980 (s); 2884 (m); 1749 (m); 1585 (m); 1461 (m); 1382 (m); 1238 (m); 1142 (m); 1091 (s); 1036 (s); 1004 (s); 956 (s); 923 (m); 727 (s); 678 (m); 604 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 418.20 (100), 514.29 (81), 598.31 (22), 593.36 (18) [*M*+NH_4]$^+$, 350.17 (8), 482.27 (6), 576.33 (<1) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{31}H_{50}NO_7Si$: 576.3357; found: 576.3363.

3.2.32. Methyl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (132)



CSA (10 mg, 0.0444 mmol, 0.2 eq) was added at 0 °C to a solution of TES protected monomer **131b** (128 mg, 0.222 mmol, 1 eq) in CH_2Cl_2 (6 mL) and MeOH (6 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated aqueous $NaHCO_3$ solution (15 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 2:1) giving deprotected monomer **132** (97 mg, 0.210 mmol, 95%) as a slightly yellow oil.

General Data: $C_{25}H_{35}NO_7$; FW: 461.24; TLC: R_f = 0.25 (Et_2O/Pentane 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –36.11 (*c* = 1.75, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.24-6.15 (m, 1H, CH_2C*H*=CH); 5.96 (dd, *J* = 15.8, 7.5 Hz, 1H, CC*H*=CHCH); 5.87 (d, *J* = 15.9 Hz, 1H, CC*H*=$CHCH_2$); 5.71-5.61 (m, 2H, $CH(OCH_3)$C*H*=CH, C*H*=$CHCH_3$); 5.43-5.36 (m, 1H, CH=C*H*CH_3); 4.65 (d, *J* = 6.5 Hz, 1H, $1OCH_2OCH_3$); 4.47 (d, *J* = 6.5 Hz, 1H, $1OCH_2OCH_3$); 4.21-4.12 (m, 1H, C*H*OCH_3); 3.90 (s, 3H, $COOCH_3$); 3.89 (m, 1H, CH_2CHOH); 3.68 (d, *J* = 10.0 Hz, 1H, C*H*OCH_2OCH_3); 3.38 (s, 3H, $CHOCH_3$); 3.26 (s, 3H, $CHOCH_2OCH_3$); 3.09 (dd, *J* = 15.1, 7.9 Hz, 1H, $1CH_2CHOCH_3$); 2.99 (dd, *J* = 14.9, 5.3 Hz, 1H, $1CH_2CHOCH_3$); 2.54 (dd, *J* = 14.3, 7.6 Hz, 1H, $1CH_2CH$=CH); 2.37-2.28 (m, 1H, $1CH_2CH$=CH); 1.75 (d, *J* = 6.3 Hz, 3H, CH=$CHCH_3$); 0.917 (s, 3H, CCH_3); 0.867 (s, 3H, CCH_3).

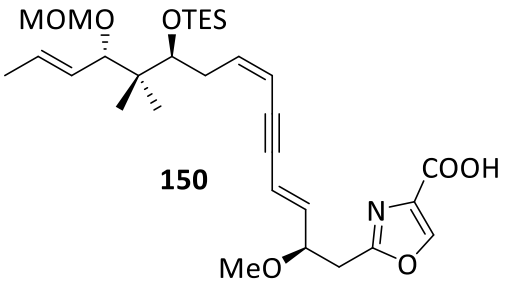
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 143.3 (CH); 140.3 (CH); 133.5 (C); 132.0 (CH); 126.9 (CH); 114.0 (CH); 109.8 (CH); 93.8 (CH_2); 91.1 (C); 88.3 (C); 84.7 (CH); 79.4 (CH); 76.1 (CH); 56.9 (CH_3); 56.2 (CH_3); 52.3 (CH_3); 41.0 (C); 34.7 (CH_2); 32.8 (CH_2); 21.1 (CH_3); 17.7 (CH_3); 18.0 (CH_3).

IR (neat): 3483 (br); 3164 (w); 2934 (m); 2826 (w); 2249 (w); 1734 (m); 1585 (m); 1438 (m); 1322 (m); 1166 (m); 1101 (s); 1030 (s); 927 (m); 917 (m); 731 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 304.11 (100), 400.21 (48), 479.27 (20) $[M+NH_4]^+$, 272.09 (19), 430.22 (15), 462.24 (12) $[M+H]^+$, 209.13 (3).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{25}H_{36}NO_7$: 462.2492; found: 462.2473.

3.2.33. 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylic acid (150)



150

131b (150 mg, 0.261 mmol, 1 eq) was dissolved in THF (5 mL) and treated at room temperature with LiOH (1 M in H_2O, 0.783 mL, 0.783 mmol, 3 eq). The mixture was stirred for 3 h at room temperature and neutralized with 1 M HCl (~2 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give acid **150** (146 mg, 0.259 mmol, 99%) as a yellow oil, which was used for the next step without further purification.

General Data: $C_{30}H_{47}NO_7Si$; FW: 561.31; TLC: UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –36.9 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.24 (s, 1H, NC=C*H*); 6.09-6.02 (m, 1H, CH_2C*H*=CH); 6.00 (dd, *J* = 15.6, 7.5 Hz, 1H, CC*H*=CHCH); 5.89 (d, *J* = 15.9 Hz, 1H, CC*H*=CHCH$_2$); 5.69-5.55 (m, 2H, CH(OCH_3)C*H*=CH, C*H*=CHCH$_3$); 5.37-5.28 (m, 1H, CH=C*H*CH$_3$); 4.68 (d, *J* = 6.4 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.48 (d, *J* = 6.4 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.23-4.13 (m, 1H, C*H*OCH$_3$); 3.84 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.65 (dd, *J* = 6.8, 3.5 Hz, 1H, C*H*OTES); 3.36 (s, 3H, CHOC*H*$_3$); 3.28 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.13 (dd, *J* = 15.0, 7.4 Hz, 1H, 1C*H*$_2$CHOCH$_3$); 3.03 (dd, *J* = 15.0, 4.2 Hz, 1H, 1C*H*$_2$CHOCH$_3$); 2.59-2.51 (m, 1H, 1C*H*$_2$CH=CH); 2.45-2.36 (m, 1H, 1C*H*$_2$CH=CH); 1.72 (d, *J* = 5.9, Hz, 3H, CH=CHC*H*$_3$); 0.951 (t, *J* = 7.8 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.925 (s, 3H, CC*H*$_3$); 0.853 (s, 3H, CC*H*$_3$); 0.598 (q, *J* = 7.9 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

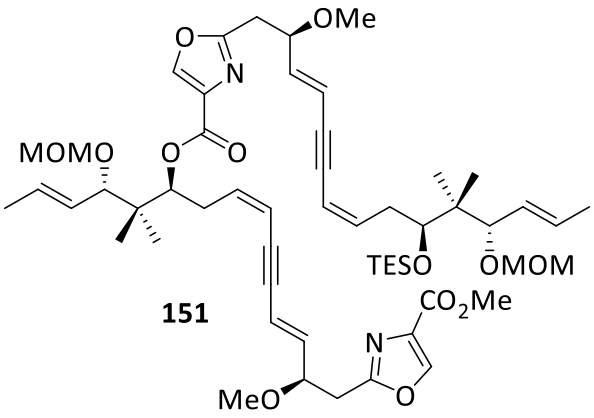
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 164.4 (C=O); 162.8 (C=N); 145.0 (CH); 143.2 (CH); 140.2 (CH); 133.0 (C); 131.1 (CH); 127.9 (CH); 114.0 (CH); 109.5 (CH); 93.6 (CH_2); 91.2 (C); 88.5 (C); 81.8 (CH); 79.3 (CH); 76.5 (CH); 56.9 (CH_3); 55.7 (CH_3); 43.2 (C); 34.4 (CH_2); 30.5 (CH_2); 19.8 (CH_3); 19.4 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 2953 (m); 2912 (m); 2877 (m); 1716 (m); 1587 (m); 1440 (m); 1359 (w); 1234 (w); 1144 (m); 1090 (s); 1036 (s); 957 (m); 921 (m); 826 (m); 726 (s); 542 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 404.18 (100), 579.34 (78) [*M*+NH_4]$^+$, 500.28 (51), 372.16 (27), 468.25 (10), 336.15 (8), 562.32 (3) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{30}H_{48}NO_7Si$: 562.3200; found: 562.3188.

3.2.34. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (151)



The crude acid **150** (91 mg, 0.162 mmol, 1.5 eq) was dissolved in THF (5 mL) and treated at room temperature with NEt_3 (90 µL, 0.648 mmol, 6 eq) and 2,4,6-trichlorobenzoyl chloride (68 µL, 0.432 mmol, 4 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (3 mL) and added dropwise to a solution of alcohol **132** (50 mg, 0.108 mmol, 1 eq) and DMAP (79 mg, 0.648 mmol, 6 eq) in toluene (5 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with EtOAc (3x10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to afford the dimer **151** (81 mg, 0.0813 mmol, 75%) as a slightly yellow oil.

General Data: $C_{55}H_{80}N_2O_{13}Si$; FW: 1004.54; TLC: R_f = 0.30 (Et_2O/pentane 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +29.65 (*c* = 1.75, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.18 (s, 1H, NC=C*H*); 8.06 (s, 1H, NC=C*H*); 6.10-5.94 (m, 4H, C*H*=CH); 5.93-5.84 (m, 2H, CH=CH); 5.70-5.52 (m, 4H, CH=CH); 5.42-5.28 (m, 2H, CH=CH); 5.25 (app dd, *J* = 7.6, 5.5 Hz, 1H, C*H*OC=O); 4.65 (dd, *J* = 6.5, 3.0 Hz, 2H, OCH_2OCH$_3$); 4.46 (d, *J* = 6.6 Hz, 1H, 1OCH_2OCH$_3$); 4.39 (d, *J* = 6.6 Hz, 1H, 1OCH_2OCH$_3$); 4.23-4.13 (m, 2H, C*H*OCH$_3$); 3.90 (s, 3H, COOCH_3); 3.84 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.76 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.66 (dd, *J* = 7.0, 3.8 Hz, 1H, CH$_2$C*H*OTES); 3.34 (s, 3H, CHOCH_3); 3.32 (s, 3H, CHOCH_3); 3.28 (s, 3H, CHOCH$_2$OCH_3); 3.27 (s, 3H, CHOCH$_2$OCH_3); 3.15-2.93 (m, 4H,

C*H*$_2$CHOCH$_3$); 2.72-2.62 (m, 2H, C*H*$_2$CH=CH); 2.60-2.51 (m, 1H, 1C*H*$_2$CH=CH); 2.46-2.36 (m, 1H, 1C*H*$_2$CH=CH); 1.71 (dt, *J* = 6.4, 1.5 Hz, 6H, CH=CHC*H*$_3$); 1.03 (s, 3H, CC*H*$_3$); 0.966 (s, 3H, CC*H*$_3$); 0.945 (app t, *J* = 7.9 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.918 (s, 3H, CC*H*$_3$); 0.844 (s, 3H, CC*H*$_3$); 0.591 (q, *J* = 8.0 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

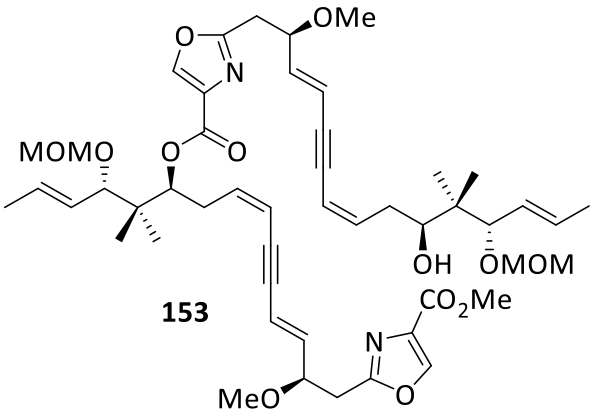
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 162.5 (C=O); 161.8 (C=N); 160.8 (C=N); 144.2 (CH); 143.6 (CH); 143.2 (CH); 140.6 (CH); 140.5 (CH); 133.6 (C); 133.5 (C); 132.1 (CH); 131.0 (CH); 128.0 (CH); 127.1 (CH); 125.6 (CH); 113.8 (CH); 113.7 (CH); 111.1 (CH); 109.5 (CH); 93.6 (CH_2); 93.6 (CH_2); 91.4 (C); 91.2 (C); 88.4 (C); 88.0 (C); 81.6 (CH); 81.6 (CH); 79.3 (CH); 77.4 (CH); 77.0 (CH); 76.4 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.1 (CH_3); 55.7 (CH_3); 52.3 (CH_3); 43.2 (C); 41.8 (C); 34.7 (CH_2); 34.5 (CH_2); 31.4 (CH_2); 30.4 (CH_2); 19.9 (CH_3); 19.8 (CH_3); 19.5 (CH_3); 19.4 (CH_3); 18.1 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 2953 (m); 2879 (m); 2284 (w); 1737 (m); 1583 (m); 1439 (m); 1318 (m); 1168 (m); 1099 (s); 1033 (s); 911 (s); 807 (m); 728 (s); 647 (m); 551 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 1005.55 (100) [*M*+H]$^+$, 1022.56 (760) [*M*+NH_4]$^+$, 943.52 (45), 973.53 (28), 847.43 (8).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{55}H_{81}N_2O_{13}Si$: 1005.5508; found: 1005.5594.

3.2.35. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (153)



153

CSA (3 mg, 0.0132 mmol, 0.2 eq) was added at 0 °C to a solution TES protected dimer **151** (67 mg, 0.0661 mmol, 1 eq) in CH_2Cl_2 (2 mL) and MeOH (2 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated $NaHCO_3$ solution (10 mL) was added and the

layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo giving the deprotected alcohol **153** as a slightly yellow oil, which was used in the next step without further purification.

General Data: $C_{49}H_{66}N_2O_{13}$; FW: 890.46; TLC: R_f = 0.30 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +24.93 (*c* = 1.4, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.18 (s, 1H, NC=C*H*); 8.06 (s, 1H, NC=C*H*); 6.24-6.14 (m, 1H, CH_2C*H*=CH); 6.03-5.92 (m, 3H, CH=CH); 5.88 (ddd, *J* = 15.9, 4.8, 2.0 Hz, 2H, CH=CH); 5.72-5.60 (m, 3H, CH=CH); 5.56 (d, *J* = 10.1 Hz, 1H, CH=CH); 5.44-5.32 (m, 2H, CH=CH); 5.25 (dd, *J* = 8.0, 5.2 Hz, 1H, C*H*OC=O); 4.67 (dd, *J* = 15.0, 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.66 (dd, *J* = 6.5, 1.8 Hz, 1H, CHOC*H*$_2$OCH$_3$); 4.47 (d, *J* = 6.6 Hz, 1H, CHOC*H*$_2$OCH$_3$); 4.39 (d, *J* = 6.6 Hz, 1H, CHOC*H*$_2$OCH$_3$); 4.23-4.13 (m, 2H, C*H*OCH$_3$); 3.90 (s, 3H, COOC*H*$_3$); 3.89 (m, 1H, C*H*OCH$_2$OCH$_3$); 3.76 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.68 (dd, *J* = 10.3, 2.4 Hz, 1H, C*H*OH); 3.38 (s, 3H, CHOC*H*$_3$); 3.32 (s, 3H, CHOC*H*$_3$); 3.28 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.27 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.15-2.94 (m, 4H, C*H*$_2$CHOCH$_3$); 2.72-2.62 (m, 2H, C*H*$_2$CH=CH); 2.58-2.48 (m, 1H, 1C*H*$_2$CH=CH); 2.39-2.28 (m, 1H, 1C*H*$_2$CH=CH); 1.74 (dd, *J* = 6.5, 1.4 Hz, 3H, CH=CHC*H*$_3$); 1.71 (dd, *J* = 6.5, 1.4 Hz, 3H, CH=CHC*H*$_3$); 1.03 (s, 3H, CC*H*$_3$); 0.968 (s, 3H, CC*H*$_3$); 0.921 (s, 3H, CC*H*$_3$); 0.868 (s, 3H, CC*H*$_3$).

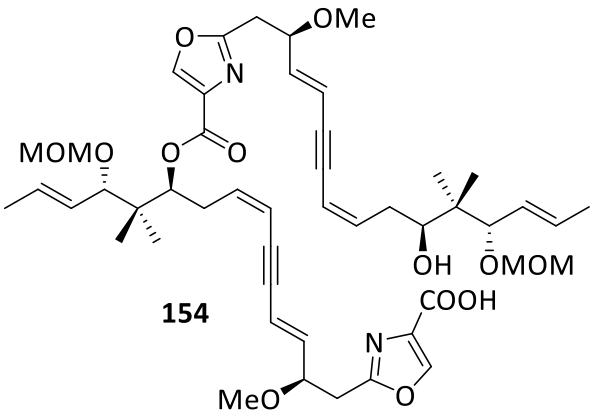
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 162.5 (C=O); 161.8 (C=N); 160.8 (C=N); 144.2 (CH); 143.6 (CH); 143.2 (CH); 140.6 (CH); 140.4 (CH); 140.4 (CH); 133.6 (C); 133.5 (C); 132.1 (CH); 132.0 (CH); 127.1 (CH); 126.8 (CH); 113.9 (CH); 113.7 (CH); 111.1 (CH); 109.8 (CH); 93.8 (CH_2); 93.6 (CH_2); 91.4 (C); 91.2 (C); 88.3 (C); 88.0 (C); 84.7 (CH); 81.4 (CH); 79.3 (CH); 77.4 (CH); 77.0 (CH); 76.1 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.2 (CH_3); 56.1 (CH_3); 52.3 (CH_3); 41.8 (C); 41.0 (C); 34.7 (CH_2); 34.7 (CH_2); 32.8 (CH_2); 31.4 (CH_2); 21.1 (CH_3); 19.9 (CH_3); 19.8 (CH_3); 19.5 (CH_3); 18.1 (CH_3); 18.0 (CH_3).

IR (neat): 3658 (br); 2980 (s); 2890 (m); 1737 (m); 1584 (m); 1463 (m); 1380 (m); 1258 (m); 1143 (s); 1098 (s); 1031 (s); 969 (m); 919 (m); 805 (m); 732 (m); 542 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 908.49 (100) [*M*+NH_4]$^+$, 891.46 (98) [*M*+H]$^+$, 859.44 (35), 733.33 (7), 829.43 (5).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{49}H_{67}N_2O_{13}$: 891.4643; found: 891.4644.

3.2.36. 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-((2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carbonyl)oxy)-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylic acid (154)



154

The crude deprotected alcohol **153** was dissolved in THF (1.5 mL) and treated at room temperature with LiOH (1 M in H_2O, 0.165 mL, 0.165 mmol, 2.5 eq). The mixture was stirred overnight at room temperature and neutralized with 1 M HCl (~1 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give the *seco*-acid **154** as a yellow wax, which was used without further purification.

General Data: $C_{48}H_{64}N_2O_{13}$; FW: 876.44; TLC: UV (+); Vanillin: grey; $[\alpha]_D^{20}$ = +17.4 (*c* = 1.3, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.24 (s, 1H, NC=C*H*); 8.07 (s, 1H, NC=C*H*); 6.24-6.14 (m, 1H, CH_2CH=CH); 6.04-5.93 (m, 3H, CH=CH); 5.93-5.81 (m, 2H, CH=CH); 5.73-5.60 (m, 3H, CH=CH); 5.55 (d, *J* = 10.5 Hz, 1H, CH=CH); 5.44-5.32 (m, 2H, CH=CH); 5.25 (dd, *J* = 8.6, 4.3 Hz, 1H, C*H*OC=O); 4.67 (d, *J* = 6.6 Hz, 2H, OCH_2OCH_3); 4.49 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.41 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.23-4.14 (m, 2H, $CHOCH_3$); 3.92 (d, *J* = 8.8 Hz, 1H, $CHOCH_2OCH_3$); 3.76 (d, *J* = 9.1 Hz, 1H, $CHOCH_2OCH_3$); 3.70 (dd, *J* = 10.3, 2.6 Hz, 1H, C*H*OH); 3.39 (s, 3H, $CHOCH_3$); 3.34 (s, 3H, $CHOCH_3$); 3.30 (s, 3H, $CHOCH_2OCH_3$); 3.27 (s, 3H, $CHOCH_2OCH_3$); 3.19-2.94 (m, 4H, CH_2CHOCH_3); 2.75-2.61 (m, 2H, CH_2CH=CH); 2.59-2.49 (m, 1H, $1CH_2CH$=CH); 2.42-2.29 (m, 1H, $1CH_2CH$=CH); 1.74 (dd, *J* = 6.5, 1.4 Hz, 3H, CH=CHCH_3); 1.71 (dd, *J* = 6.5, 1.4 Hz, 3H, CH=CHCH_3); 1.03 (s, 3H, CCH_3); 0.975 (s, 3H, CCH_3); 0.927 (s, 3H, CCH_3); 0.877 (s, 3H, CCH_3).

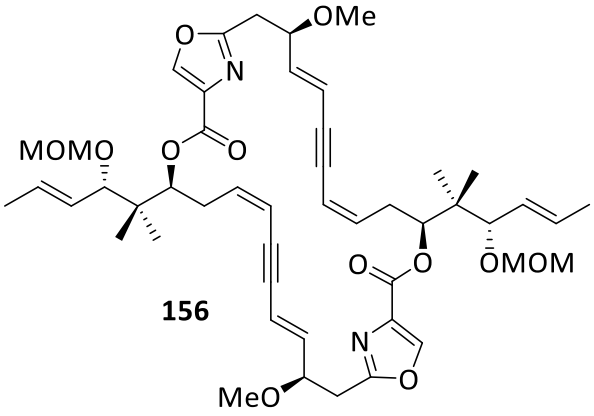
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 163.7 (C=O); 162.6 (C=O); 162.5 (C=N); 160.7 (C=N); 144.8 (CH); 143.7 (CH); 143.1 (CH); 140.5 (CH); 140.3 (CH); 133.5 (C); 133.2 (C); 132.2 (CH); 132.1 (CH); 127.1 (CH); 126.8 (CH); 125.7 (CH); 113.9 (CH); 113.8 (CH); 111.2 (CH); 109.9 (CH); 93.8 (CH_3); 93.5 (CH_3); 91.4 (C); 91.2 (C); 88.3 (C); 88.0 (C); 84.7 (CH); 81.6 (CH); 79.4 (CH); 79.3 (CH); 77.4 (CH); 76.3 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.2 (CH_3); 56.1 (CH_3); 41.8 (C); 41.0 (C); 34.6 (CH_2); 34.5 (CH_2); 30.5 (CH_2); 29.8 (CH_2); 21.1 (CH_3); 19.9 (CH_3); 19.9 (CH_3); 19.4 (CH_3); 18.1 (CH_3); 18.1 (CH_3).

IR (neat): 3658 (br); 2980 (s); 2923 (s); 2328 (w); 1719 (m); 1584 (m); 1461 (m); 1377 (m); 1251 (m); 1146 (m); 1098 (s); 1032 (s); 969 (s); 909 (m); 818 (w); 734 (s); 542 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 877.44 (100) $[M+H]^+$, 894.47 (77) $[M+NH_4]^+$, 845.42 (49), 719.31 (30), 783.38 (23).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{48}H_{65}N_2O_{13}$: 877.4487; found: 877.4473.

3.2.37. (16,16')-Bis(methoxymethyl)-(9,10,9',10')-tetradehydridodisorazole C_1 (156)



The crude *seco*-acid **154** was dissolved in THF (5 mL) and treated at room temperature with NEt_3 (184 µL, 1.32 mmol, 20 eq) and 2,4,6-trichlorobenzoyl chloride (103 µL, 0.661 mmol, 10 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (3 mL) and added dropwise to a solution of DMAP (323 mg, 2.64 mmol, 40 eq) in toluene (80 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (20 mL) and water (20 mL) and the aqueous phase was extracted with EtOAc (3x40 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to afford the macrocycle **156** (40 mg, 0.0462 mmol, 70% from **151**) as a slightly yellow oil.

General Data: $C_{48}H_{62}N_2O_{12}$; FW: 858.43; TLC: R_f = 0.50 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +140.2 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.04 (s, 2H, NC=C*H*); 6.02-5.90 (m, 4H, CH=CH); 5.70-5.60 (m, 4H, CH=CH); 5.51 (d, *J* = 10.3 Hz, 2H, CH=CH); 5.44-5.36 (m, 2H, CH=CH); 5.34 (dd, *J* = 11.0, 2.3 Hz, 2H, C*H*OC=O); 4.67 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.42 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.17-4.08 (m, 2H, C*H*OCH$_3$); 3.73 (d, *J* = 9.2 Hz, 2H, C*H*OCH$_2$OCH$_3$); 3.36 (s, 6H, CHOC*H*$_3$); 3.34 (s, 6H, CHOCH$_2$OC*H*$_3$); 3.32-3.26 (m, 2H, C*H*$_2$CH=CH); 3.06-2.88 (m, 4H, C*H*$_2$CHOCH$_3$); 2.43-2.35 (m, 2H, C*H*$_2$CH=CH); 1.74 (dd, *J* = 6.1, 1.2 Hz, 6H, CH=CHC*H*$_3$); 1.04 (s, 6H, CC*H*$_3$); 1.00 (s, 6H, CC*H*$_3$).

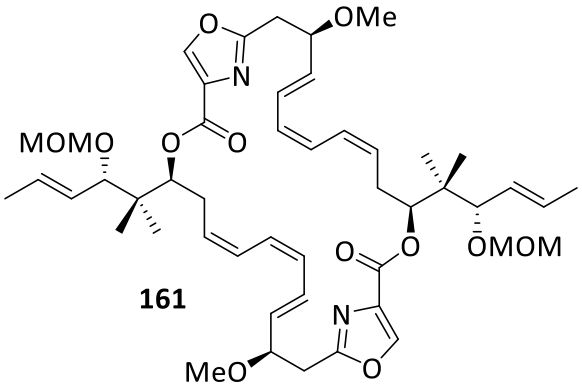
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 161.8 (C=O); 160.7 (C=N); 143.4 (CH); 141.3 (CH); 140.4 (CH); 133.8 (C); 132.0 (CH); 127.2 (CH); 113.7 (CH); 112.2 (CH); 93.8 (CH_2); 91.0 (C); 87.9 (C); 81.5 (CH); 79.7 (CH); 76.4 (CH); 57.0 (CH_3); 56.2 (CH_3); 41.6 (C); 34.5 (CH_2); 31.5 (CH_2); 19.9 (CH_3); 19.6 (CH_3); 18.1 (CH_3).

IR (neat): 3172 (w); 3180 (w); 2930 (m); 2855 (m); 1736 (m); 1649 (m); 1584 (m); 1450 (m); 1368 (m); 1216 (m); 1140 (m); 1103 (s); 1031 (s); 973 (m); 921 (m); 830 (m); 752 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 859.44 (100) [*M*+H]$^+$, 876.46 (42) [*M*+NH$_4$]$^+$, 797.40 (16), 735.36 (3).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{48}H_{65}N_2O_{13}$: 859.4381; found: 859.4464.

3.2.38. (16,16')-Bis(methoxymethyl)-disorazole C_1 (161)



161

Nitrogen was bubbled for 15 min through a suspension of zinc dust (5 g, 45.88 mmol) in H_2O (30 mL) and then $Cu(OAc)_2 \cdot H_2O$ (500 mg, 2.5 mmol) was added at room temperature and after 15 min $AgNO_3$ (500 mg, 2.94 mmol) was added (exothermic reaction). The mixture was stirred for 30 min at room temperature, filtered by suction and washed with H_2O (40 mL), MeOH (30 mL), acetone (30 mL) and Et_2O (30 mL). This activated zinc solids were added to a solution of **156** (40 mg, 0.0466 mmol) in MeOH/H_2O 1:1 (20 mL). The mixture was stirred for

24 h at 50 °C, then filtered on a pad of silica with MeOH washes. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 70:1) to afford **161** (26 mg, 0.0302, 65%) as a colorless wax.

General Data: $C_{48}H_{66}N_2O_{12}$; FW: 862.46; TLC: R_f = 0.40 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –1.2 (*c* = 0.55, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.89 (s, 2H, NC=C*H*); 6.42 (dd, *J* = 15.3, 11.4 Hz, 2H, CH(OCH3)CH=C*H*); 6.32 (app t, *J* = 11.3 Hz, 2H, CH2CH=C*H*); 6.18 (dd, *J* = 11.4, 11.1 Hz, 2H, CHC*H*=CHCH); 5.90 (dd, *J* = 11.2, 11.0 Hz, 2H, CHCH=C*H*CH); 5.63 (dd, *J* = 15.4, 6.5 Hz, 2H, CH3C*H*=CH); 5.53 (dd, *J* = 15.1, 8.5 Hz, 2H, CH3CH=C*H*); 5.51 (dd, *J* = 16.6, 8.9 Hz, 2H, C*H*OC=O); 5.37 (ddd, *J* = 15.4, 9.1, 1.5 Hz, 2H, CH(OCH3)C*H*=CH); 5.26 (dd, *J* = 11.2, 2.2 Hz, 2H, CH2C*H*=CH); 4.65 (d, *J* = 6.7 Hz, 2H, 1OCH_2OCH$_3$); 4.39 (d, *J* = 6.7 Hz, 2H, 1OCH_2OCH$_3$); 4.13 (ddd, *J* = 12.8, 7.0, 5.0 Hz, 2H, C*H*OCH3); 3.71 (d, *J* = 9.0 Hz, 2H, C*H*OH); 3.33 (s, 6H, CHOCH$_2$OCH_3); 3.26 (s, 6H, CHOCH_3); 3.13 (dd, *J* = 13.8, 5.9 Hz, 2H, CH_2CHOCH$_3$); 2.79 (dd, *J* = 14.6, 7.5 Hz, 2H, CH_2CHOCH$_3$); 2.57 (ddd, *J* = 14.7, 10.1, 5.1 Hz, CH_2CH=CH); 2.43 (dd, *J* = 14.9, 6.3 Hz, 2H, CH_2CH=CH); 1.72 (dd, *J* = 6.3, 1.3 Hz, 3H, CH=CHCH_3); 1.01 (s, 6H, CCH_3); 0.946 (s, 6H, CCH_3).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.3 (C=O); 160.7 (C=N); 143.3 (CH); 133.5 (C); 133.3 (CH); 132.1 (CH); 130.0 (CH); 129.1 (CH); 128.2 (CH); 127.2 (CH); 125.7 (CH); 125.5 (CH); 93.6 (CH_2); 81.7 (CH); 80.0 (CH); 77.4* (CH); 56.7 (CH_3); 56.1 (CH_3); 41.7 (C); 35.2 (CH_2); 29.9 (CH_2); 20.1 (CH_3); 19.8 (CH_3); 18.1 (CH_3).

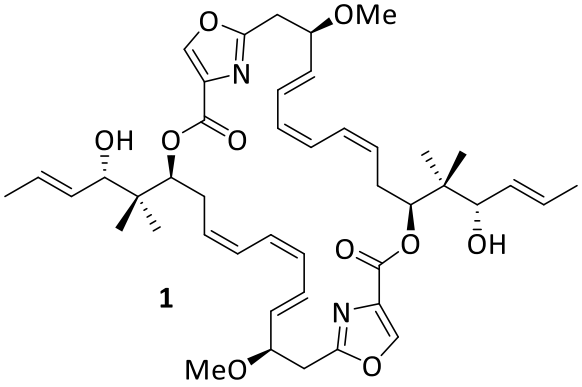
*obscured by $CDCl_3$

IR (neat): 2927 (m); 2855 (m); 1727 (m); 1583 (m); 1442 (w); 1370 (w); 1315 (w); 1262 (w); 1104 (s); 1012 (m); 805 (m); 757 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 863.47 (100) [*M*+H]$^+$, 880.50 (15) [*M*+NH$_4$]$^+$, 282.28 (3).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{48}H_{67}N_2O_{12}$: 863.4694; found 863.4758.

3.2.39. Disorazole C_1 (1)



MOM protected disorazole C_1 **161** (22 mg, 25.5 µmol) was dissolved in CH_3CN (1.5 mL) and cooled to 0 °C. 2 drops of HBr (48% in H_2O) were slowly added and then the mixture was stirred for 1 h at 0 °C. The mixture was diluted with EtOAc (4 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous phase was extracted with EtOAc (3x5 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 50:1) to give Disorazole C_1 **1** (11 mg, 14.2 µmol, 56%) as a colorless wax.

General Data: $C_{44}H_{58}N_2O_{10}$; FW: 774.41; TLC: R_f = 0.20 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –125.11 (*c* = 0.45, MeOH), lit. $[\alpha]_D^{22}$ = –124.8 (*c* = 0.6, MeOH).

^{1}H-NMR (600 MHz, CD_3OD): δ (ppm): 8.24 (s, 2H, NC=C*H*); 6.50 (dd, *J* = 15.1, 11.3 Hz, 2H, CH(OCH_3)CH=C*H*); 6.40 (app t, *J* = 11.2 Hz, 2H, CH2CH=C*H*); 6.28 (dd, *J* = 11.3, 11.1 Hz, 2H, CHC*H*=CHCH); 5.91 (dd, *J* = 11.3, 11.0 Hz, 2H, CHCH=C*H*CH); 5.67 (dq, *J* = 15.2, 6.2 Hz, 2H, CH3C*H*=CH); 5.58 (ddd, *J* = 15.4, 7.7, 1.4 Hz, 2H, CH3CH=C*H*); 5.54 (dd, *J* = 15.1, 8.4 Hz, 2H, CH(OCH3)C*H*=CH); 5.48 (app dt, *J* = 10.2, 6.4 Hz, 2H, CH2C*H*=CH); 5.26 (dd, *J* = 11.3, 2.2 Hz, 2H, C*H*OC=O); 4.13 (ddd, *J* = 7.9, 7.2, 5.3 Hz, 2H, C*H*OCH3); 3.84 (d, *J* = 7.5 Hz, 2H, C*H*OH); 3.21 (s, 6H, CHOC*H*$_3$); 3.00 (dd, *J* = 15.4, 7.4 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.77 (dd, *J* = 15.4, 7.2 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.69 (ddd, *J* = 13.8, 10.9, 10.2 Hz, 2H, C*H*$_2$CH=CH); 2.39 (dd, *J* = 13.6, 6.2 Hz, 2H, C*H*$_2$CH=CH); 1.70 (dd, *J* = 6.3, 1.1 Hz, 6H, CH=CHC*H*$_3$); 1.01 (s, 6H, CC*H*$_3$); 0.954 (s, 6H, CC*H*$_3$).

^{13}C-NMR (151 MHz, CD_3OD): δ (ppm): 164.1 (C=O); 162.2 (C=N); 145.8 (CH); 134.2 (C); 134.1 (CH); 131.7 (CH); 130.9 (CH); 130.0 (CH); 129.6 (CH); 129.3 (CH); 127.4 (CH); 126.8 (CH); 80.6 (CH); 78.7 (CH); 77.8 (CH); 56.8 (CH_3); 42.7 (C); 36.0 (CH_2); 29.2 (CH_2); 19.4 (CH_3); 19.3 (CH_3); 18.1 (CH_3).

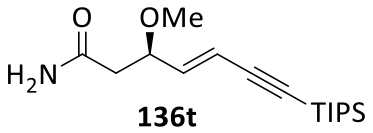
IR (neat): 3419 (br); 2924 (m); 2854 (m); 1723 (m); 1583 (m); 1447 (w); 1367 (w); 1312 (w); 1261 (w); 1101 (s); 1010 (m); 803 (m); 758 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 775.41 (100) $[M+H]^+$, 792.44 (28) $[M+NH_4]^+$, 797.40 (6); 757.40 (5).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{44}H_{59}N_2O_{10}$: 775.4170; found 775.4198.

3.3. Synthesis of Bis(thiazolyl)-Disorazole C_1 (1t)

3.3.1. (*R*,*E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynamide (136t)



136t

Carboxilyic acid **136** (2.3 g, 7.41 mmol, 1 eq) was dissolved in THF (40 mL), cooled to 0 °C and ethyl chloroformate (0.917 mL, 9.63 mmol, 1.3 eq) was added dropwise, followed by NEt_3 (1.44 mL, 10.37 mmol, 1.4 eq). The mixture was stirred for 30 min at 0 °C and then 25% aqueous NH_4OH solution (3 mL) was added. The mixture was stirred for 30 min at 0 °C and 1 h at room temperature. The solution was washed with H_2O (30 mL) and the aqueous phase was extracted with EtOAc (3x25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude amide **136t** as a yellow oil, which was used for the next step without further purification.

General Data: $C_{17}H_{31}NO_2Si$; FW: 309.21; TLC: R_f = 0.2 (Et_2O); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +24.4 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.01 (dd, *J* = 16.0, 7.4 Hz, 1H, C*H*=CH); 5.80 (dd, *J* = 15.9, 1.0 Hz, 1H, CH=C*H*); 4.06-4.01 (m, 1H, C*H*OCH_3); 3.33 (s, 3H, OCH_3); 2.49-2.44 (m, 2H, CH_2CH); 1.07 (s, 21H, Si(C*H*(CH_3))$_3$).

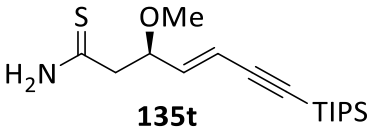
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 173.4 (C=O); 141.4 (CH); 113.6 (CH); 104.1 (C); 93.0 (C); 78.3 (CH); 57.1 (CH_3); 41.8 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 2921 (s); 3339 (br); 2942 (s); 2865 (s); 2134 (w); 1667 (s); 1462 (m); 1385 (m); 1241 (w); 1093 (s); 996 (m); 957 (m); 882 (s); 662 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 278.19 (100), 332.20 (10) [*M*+Na]$^+$., 619.43 (8), 310.22 (4) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{17}H_{32}NO_2Si$: 310.2202; found: 310.2206.

3.3.2. (*R*,*E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynethioamide (135t)



135t

Lawesson‘s reagent **162** (2.1 g, 5.19 mmol, 0.7 eq) was added to a solution of crude **136t** in THF (65 mL) and the mixture was stirred for 30 min at room temperature. The solution was

washed with Brine (100 mL) and the aqueous phase was extracted with Et_2O (3x70 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/EtOAc 4:1) afforded **135t** (1.92 g, 5.93 mmol, 80%, from **136**) as an orange oil.

General Data: $C_{17}H_{31}NOSSi$; FW: 325.19; TLC: R_f = 0.25 (pentane/Et_2O 3:2); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +7.0 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.00 (dd, *J* = 15.9, 7.2 Hz, 1H, C*H*=CH); 5.81 (dd, *J* = 15.9, 0.9 Hz, 1H, CH=C*H*); 4.11-4.03 (m, 1H, C*H*OCH_3); 3.34 (s, 3H, OCH_3); 2.97 (dd, *J* = 15.1, 3.1 Hz, 1H, 1CH_2CH); 2.87 (dd, *J* = 15.1, 8.1 Hz, 1H, 1CH_2CH); 1.07 (s, 21H, Si(C*H*(CH_3))$_3$).

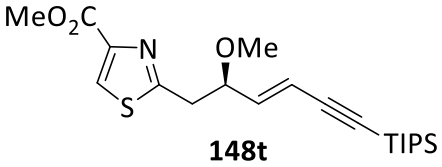
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 206.3 (C=S); 140.8 (CH); 113.9 (CH); 104.0 (C); 93.2 (C); 80.4 (CH); 57.2 (CH_3); 50.4 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 3658 (m); 3313 (m); 3173 (m); 2970 (s); 2865 (s); 2327 (w); 1626 (m); 1461 (m); 1384 (m); 1256 (m); 1073 (s); 951 (s); 882 (m); 664 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 294.17 (100), 112.02 (9), 638.42 (23), 326.19 (7) [*M*+H]$^+$,250.10 (6).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{17}H_{32}NOSSi$: 326.1974; found: 326.1943.

3.3.3. Methyl (*R*,*E*)-2-(2-methoxy-6-(triisopropylsilyl)hex-3-en-5-yn-1-yl)thiazole-4-carboxylate (148t)



148t

$NaHCO_3$ (2.3 g, 27.05 mmol, 5 eq) was added portionwise to a solution of **135t** (1.76 g, 5.41 mmol, 1 eq) in THF (45 mL) at 0 °C, followed by a dropwise addition of methyl bromopyruvate (1.73 mL, 16.23 mmol, 3 eq). The mixture was stirred for 1 h at 0 °C, then the reaction was cooled to –30 °C and pyridine (3.06 mL, 37.87 mmol, 7 eq) and TFAA (3 mL, 21.64 mmol, 4 eq) were sequentially added dropwise. The mixture was stirred for 1 h at –30 °C and then quenched with Brine (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x40 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 5.1 to 4:1) to give thiazole **148t** (1.83 g, 4.49 mmol, 83%) as a yellow oil.

General Data: $C_{21}H_{33}NO_3SSi$; FW: 407.20; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +1.76 (*c* = 0.85, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.11 (s, 1H, C=C*H*); 6.04 (dd, *J* = 16.0, 7.2 Hz, 1H, C*H*=CH); 5.78 (dd, *J* = 16.0, 0.9 Hz, 1H, CH=C*H*); 4.02-3.92 (m, 1H, C*H*OCH_3); 3.97-3.88 (m, 1H, 1CH_2CH); 3.95 (s, 3H, COOCH_3); 3.31 (s, 3H, CHOCH_3); 3.20 (dd, *J* = 15.0, 8.8 Hz, 1H, 1CH_2CH); 1.08 (s, 21H, Si(C*H*(CH_3))$_3$).

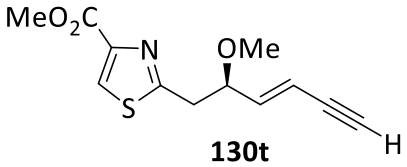
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 167.8 (C=O); 162.0 (C=N); 145.9 (C); 141.6 (CH); 128.5 (CH); 113.7 (CH); 104.2 (C); 93.0 (C); 80.3 (CH); 57.1 (CH_3); 52.6 (CH_3); 39.5 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 3118 (w); 2926 (m); 2325 (m); 2130 (w); 1725 (s); 1462 (m); 1324 (m); 1238 (s); 1093 (s); 995 (m); 883 (m); 754 (m); 675 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 376.18 (100), 408.21 (88) [*M*+H]$^+$, 430.18 (22), 194.02 (6).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{21}H_{34}NO_3SSi$: 408.2029; found: 408.2067.

3.3.4. Methyl (*R*,*E*)-2-(2-methoxyhex-3-en-5-yn-1-yl)thiazole-4-carboxylate (130t)



130t

TIPS thiazole **148t** (1.4 g, 3.44 mmol, 1 eq) was carefully dried under high vacuum, dissoved in THF (35 mL) and cooled to 0 °C. TBAF (1 M in THF, 3.78 mL, 3.78 mmol, 1.1 eq) was added dropwise and the mixture was stirred for 30 min at room temperature and then quenched with water (30 mL). The aqueous phase was extracted with Et_2O (3x20 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1 to 1:1) afforded thiazole **130t** (691 mg, 2.75 mmol, 80%) as a yellow oil.

General Data: $C_{12}H_{13}NO_3S$; FW: 251.06; TLC: R_f = 0.30 (pentane/Et_2O 1:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +12.2 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.11 (s, 1H, NC=C*H*); 6.12 (dd, *J* = 16.1, 7.1, 1H, C*H*=CH); 5.72 (ddd, *J* = 15.9, 2.1, 0.9 Hz, 1H, CH=C*H*); 4.04-3.96 (m, 1H, C*H*OCH_3); 3.95 (s, 3H, COOCH_3);

3.36-2.27 (m, 1H, 1C*H*$_2$CH); 3.31 (s, 3H, CHOC*H*$_3$); 3.21 (dd, *J* = 15.1, 8.5 Hz, 1H, 1C*H*$_2$CH); 2.94 (d, *J* = 2.2 Hz, 1H, CC*H*).

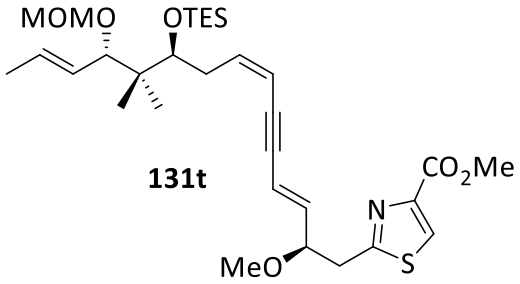
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 167.4 (C=O); 162.0 (C=N); 146.1 (C); 143.1 (CH); 128.5 (CH); 112.3 (CH); 81.1 (C); 80.1 (CH); 79.0 (CH); 57.1 (CH_3); 52.6 (CH_3); 39.4 (CH_2).

IR (neat): 3626 (w); 3219 (m); 3126 (m); 2953 (m); 2836 (w); 1719 (s); 1482 (s); 1319 (m); 1236 (s); 1194 (s); 1091 (s); 983 (s); 915 (m); 782 (m); 672 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 252.07 (100) [*M*+H]$^+$, 220.04 (95), 274.05 (34) [*M*+Na]$^+$, 206.03 (13), 194.03 (8).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{12}H_{14}NO_3S$: 252.0694; found: 252.0711.

3.3.5. Methyl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)thiazole-4-carboxylate (131t)



131t

The vinyl iodide **129b** (595 mg, 1.27 mmol, 1 eq) was dissolved in degassed CH_3CN (12 mL) and CuI (57 mg, 0.381 mmol, 0.3 eq) and $PdCl_2(PPh_3)_2$ (89 mg, 0.127 mmol, 0.1 eq) were added. The mixture was degassed by freeze-pump-thaw (2 cycles) and then cooled to –15 °C (ice/acetone bath). NEt_3 (1.06 mL, 7.62 mmol, 6 eq) was added, followed by a slow addition of the enyne **130t** (383 mg, 1.52 mmol, 1.2 eq) in degassed CH_3CN (3 mL). The solution became green and after 15 min the bath was removed. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with Et_2O (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to give the monomer **131t** (563 mg, 0.952 mmol, 75%) as a yellow oil.

General Data: $C_{31}H_{49}NO_6SSi$; FW: 591.31; TLC: R_f = 0.20 (pentane/Et_2O 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –8.5 (*c* = 0.85, $CHCl_3$).

^{1}H-NMR (600 MHz, CD_3OD): δ (ppm): 8.29 (s, 1H, NC=C*H*); 6.11-6.04 (m, 1H, CH_2CH=CH); 6.03-5.94 (m, 2H, C*H*=CH); 5.71-5.60 (m, 2H, $CH(OCH_3)CH$=CH, C*H*=$CHCH_3$); 5.40-5.33 (m, 1H, CH=C*H*CH_3); 4.65 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.46 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.11-4.06 (m, 1H, C*H*OCH_3); 3.91 (s, 3H, $COOCH_3$); 3.89 (d, *J* = 9.2 Hz, 1H, C*H*OCH_2OCH_3); 3.71 (dd, *J* = 7.2, 3.8 Hz, 1H, CH_2CHOTES); 3.34 (s, 3H, $CHOCH_3$); 3.32 (s, 3H, $CHOCH_2OCH_3$); 3.26 (dd, *J* = 14.5, 4.6 Hz, 2H, CH_2CHOCH_3); 2.63-2.56 (m, 1H, $1CH_2CH$=CH); 2.46-2.38 (m, 1H, $1CH_2CH$=CH); 1.72 (dd, *J* = 6.6, 1.7 Hz, 3H, CH=$CHCH_3$); 0.984 (app t, *J* = 7.9 Hz, 9H, $OSi(CH_2CH_3)_3$); 0.934 (s, 3H, CCH_3); 0.871 (s, 3H, CCH_3); 0.638 (q, *J* = 8.0 Hz, 6H, $OSi(CH_2CH_3)_3$).

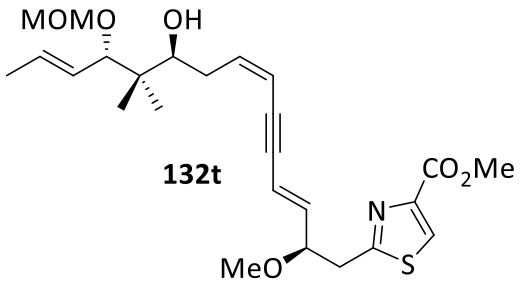
^{13}C-NMR (151 MHz, CD_3OD): δ (ppm): 169.7 (C=O); 163.0 (C=N); 146.6 (C); 143.6 (CH); 141.7 (CH); 132.3 (CH); 129.9 (CH); 129.2 (CH); 114.7 (CH); 110.8 (CH); 94.5 (CH_2); 92.5 (C); 88.9 (C); 82.7 (CH); 81.3 (CH); 77.9 (CH); 57.1 (CH_3); 55.9 (CH_3); 52.7 (CH_3); 44.2 (C); 39.8 (CH_2); 35.5 (CH_2); 20.4 (CH_3); 19.9 (CH_3); 18.0 (CH_3); 7.5 (CH_3); 6.5 (CH_2).

IR (neat): 3120 (w); 2953 (m); 2877 (m); 1724 (m); 1464 (m); 1325 (m); 1238 (m); 1210 (m); 1089 (s); 1036 (s); 957 (m); 919 (m); 739 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 530.28 (100), 434.18 (97), 614.29 (22), 366.15 (16), 498.25 (18), 592.31 (<1) $[M+H]^+$.

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{31}H_{50}NO_6SSi$: 592.3128; found: 592.3130.

3.3.6. Methyl 2-((*2R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)thiazole-4-carboxylate (132t)



CSA (18 mg, 0.0744 mmol, 0.2 eq) was added at 0 °C to a solution of TES protected monomer **131t** (220 mg, 0.372 mmol, 1 eq) in CH_2Cl_2 (9 mL) and MeOH (9 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated aqueous $NaHCO_3$ solution (20 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and

concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 2:1) giving deprotected monomer **132t** (168 mg, 0.353 mmol, 95%) as a slightly yellow oil.

General Data: $C_{25}H_{35}NO_6S$; FW: 477.22; TLC: R_f = 0.25 (Et_2O/Pentane 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –18.0 (*c* = 1.8, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.10 (s, 1H, NC=C*H*); 6.22-6.16 (m, 1H, CH_2C*H*=CH); 5.96 (dd, *J* = 15.9, 7.1 Hz, 1H, CC*H*=CHCH); 5.87 (dd, *J* = 15.8, 1.8 Hz, 1H, CC*H*=CHCH_2); 5.70-5.62 (m, 2H, CH(OCH_3)C*H*=CH, C*H*=CHCH_3); 5.42-5.35 (m, 1H, CH=C*H*CH_3); 4.65 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH_3); 4.47 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH_3); 4.02-3.95 (m, 1H, C*H*OCH_3); 3.93 (s, 3H, COOC*H*$_3$); 3.90 (d, *J* = 8.7 Hz, 1H, CH_2C*H*OH); 3.67 (dd, *J* = 10.2, 2.5 Hz, 1H, C*H*O$CH_2O CH_3$); 3.37 (s, 3H, CHOC*H*$_3$); 3.32-3.27 (m, 1H, 1C*H*$_2$CHOCH_3); 3.29 (s, 3H, CHOCH_2OC*H*$_3$); 3.21 (dd, *J* = 15.1, 8.7 Hz, 1H, 1C*H*$_2$CHOCH_3); 2.59-2.51 (m, 1H, 1C*H*$_2$CH=CH); 2.37-2.28 (m, 1H, 1C*H*$_2$CH=CH); 1.74 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHC*H*$_3$); 0.913 (s, 3H, CC*H*$_3$); 0.863 (s, 3H, CC*H*$_3$).

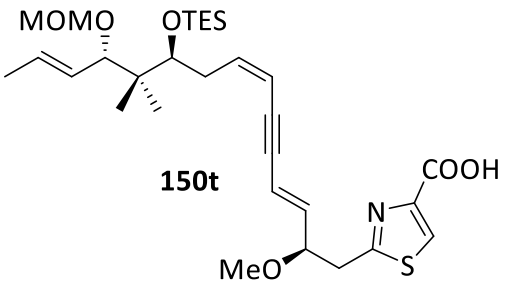
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 167.6 (C=O); 162.0 (C=N); 146.0 (C); 143.2 (CH); 140.2 (CH); 132.0 (CH); 128.4 (CH); 126.9 (CH); 113.8 (CH); 109.8 (CH); 93.8 (CH_2); 91.2 (C); 88.3 (C); 84.7 (CH); 80.4 (CH); 76.1 (CH); 56.9 (CH_3); 56.2 (CH_3); 52.5 (CH_3); 41.0 (C); 39.6 (CH_2); 32.8 (CH_2); 21.1 (CH_3); 19.7 (CH_3); 18.0 (CH_3).

IR (neat): 3657 (w); 3452 (br); 2972 (s); 2888 (m); 2326 (w); 1722 (s); 1603 (m); 1440 (m); 1339 (m); 1256 (m); 1146 (m); 1091 (s); 1033 (s); 954 (s); 922 (m); 753 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 320.10 (100), 384.16 (56), 416.19 (52), 446.20 (45), 228.07 (29), 500.20 (22), 478.23 (12) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{25}H_{36}NO_6S$: 478.2263; found: 478.2257.

3.3.7. 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)thiazole-4-carboxylic acid (150t)



150t

LiOH (1 M in H_2O, 0.777 mL, 0.777 mmol, 3 eq) was added to a solution of **131t** (153 mg, 0.259 mmol, 1 eq) in THF (3.5 mL). The mixture was stirred for 3 h at room temperature and neutralized with 1 M HCl (~2 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give acid **150t** (148 mg, 0.256 mmol, 99%) as a yellow oil, which was used for the next step without further purification.

General Data: $C_{30}H_{47}NO_6SSi$; FW: 577.29; TLC: UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +36.9 (*c* = 0.55, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.25 (s, 1H, NC=C*H*); 6.11-6.04 (m, 1H, CH_2CH=CH); 6.03-5.94 (m, 2H, CC*H*=CHCH); 5.72-5.60 (m, 2H, $CH(OCH_3)CH$=CH, C*H*=$CHCH_3$); 5.40-5.33 (m, 1H, CH=C*H*CH_3); 4.65 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.46 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.13-4.04 (m, 1H, C*H*OCH_3); 3.92-3.87 (m, 1H, C*H*OTES); 3.71 (dd, *J* = 7.2, 3.7 Hz, 1H, $CHOCH_2OCH_3$); 3.34 (s, 3H, $CHOCH_3$); 3.32 (s, 3H, $CHOCH_2OCH_3$); 3.26 (dd, *J* = 13.7, 4.6 Hz, 2H, CH_2CHOCH_3); 2.63-2.56 (m, 1H, $1CH_2CH$=CH); 2.46-2.38 (m, 1H, $1CH_2CH$=CH); 1.72 (dd, *J* = 6.4, 1.6 Hz, 3H, CH=CHCH_3); 1.01-0.959 (m, 9H, $OSi(CH_2CH_3)_3$); 0.937 (s, 3H, CCH_3); 0.873 (s, 3H, CCH_3); 0.638 (q, *J* = 8.0 Hz, 6H, $OSi(CH_2CH_3)_3$).

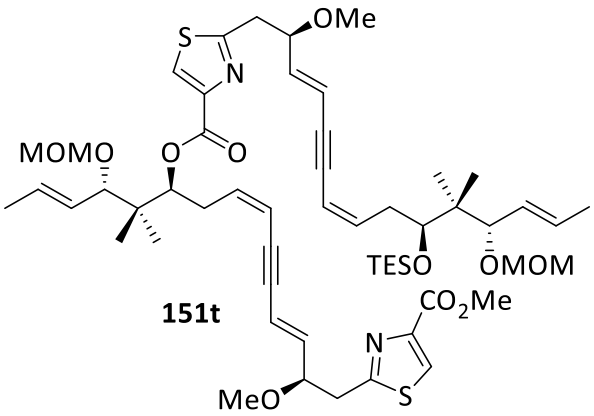
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 164.4 (C=O); 162.8 (C=N); 145.0 (CH); 143.2 (CH); 140.2 (CH); 133.0 (C); 131.1 (CH); 127.9 (CH); 114.0 (CH); 109.5 (CH); 93.6 (CH_2); 91.2 (C); 88.5 (C); 81.8 (CH); 79.3 (CH); 76.5 (CH); 56.9 (CH_3); 55.7 (CH_3); 43.2 (C); 34.4 (CH_2); 30.5 (CH_2); 19.8 (CH_3); 19.4 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 3495 (w); 2952 (m); 2877 (m); 1715 (m); 1468 (m); 1415 (w); 1192 (m); 1091 (s); 1033 (s); 956 (m); 921 (m); 825 (m); 723 (s); 542 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 420.17 (100), 516.26 (77), 600.28 (49), 546.27 (24), 388.14 (17), 352.14 (8), 306.08 (4), 578.27 (<1) $[M+H]^+$.

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{30}H_{48}NO_6SSi$: 578.2972; found: 578.2963.

3.3.8. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)thiazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)thiazole-4-carboxylate (151t)



The crude acid **150t** (140 mg, 0.243 mmol, 1.2 eq) was dissolved in THF (4 mL) and treated at room temperature with NEt_3 (0.175 mL, 1.25 mmol, 6 eq) and 2,4,6-trichlorobenzoyl chloride (0.130 mL, 0.836 mmol, 4 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (2 mL) and added dropwise to a solution of alcohol **132t** (100 mg, 0.209 mmol, 1 eq) and DMAP (153 mg, 1.25 mmol, 6 eq) in toluene (5 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with EtOAc (3x15 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 2:1) to afford **151t** (168 mg, 0.162 mmol, 77%) as a slightly yellow oil.

General Data: $C_{55}H_{80}N_2O_{11}S_2Si$; FW: 1036.50; TLC: R_f = 0.45 (hexane/EtOAc 1:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +26.7 (*c* = 1.25, $CHCl_3$).

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm): 8.30 (s, 1H, NC=C*H*); 8.23 (s, 1H, NC=C*H*); 6.12-6.03 (m, 2H, C*H*=CH); 6.025.92 (m, 4H, CH=CH); 5.76-5.55 (m, 4H, CH=CH); 5.48-5.31 (m, 2H, CH=CH); 5.24 (app dd, *J* = 6.7, 6.0 Hz, 1H, C*H*OC=O); 4.64 (dd, *J* = 8.9, 6.5 Hz, 2H, OCH_2OCH$_3$); 4.46 (d, *J* = 6.6 Hz, 1H, 1OCH_2OCH$_3$); 4.40 (d, *J* = 6.6 Hz, 1H, 1OCH_2OCH$_3$); 4.14-4.06 (m, 2H, C*H*OCH$_3$); 3.91-3.87 (m, 1H, C*H*OCH$_2$OCH$_3$);3.90 (s, 3H, COOCH_3); 3.83 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.71 (dd, *J* = 7.0, 3.7 Hz, 1H, CH$_2$C*H*OTES); 3.34 (s, 3H, CHOCH_3); 3.33 (s, 3H, CHOCH_3); 3.32 (s, 3H, CHOCH$_2$OCH_3); 3.29 (s, 3H, CHOCH$_2$OCH_3); 3.28-3.23 (m, 4H,

C*H*$_2$CHOCH$_3$); 2.73 (app dd, *J* = 6.9, 7.2 Hz, 2H, C*H*$_2$CH=CH); 2.65-2.55 (m, 1H, 1C*H*$_2$CH=CH); 2.47-2.37 (m, 1H, 1C*H*$_2$CH=CH); 1.712 (app d, *J* = 6.2 Hz, 6H, CH=CHC*H*$_3$); 1.06 (s, 3H, CC*H*$_3$); 1.01 (s, 3H, CC*H*$_3$); 0.982 (app t, *J* = 7.8 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.935 (s, 3H, CC*H*$_3$); 0.871 (s, 3H, CC*H*$_3$); 0.637 (q, *J* = 8.0 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

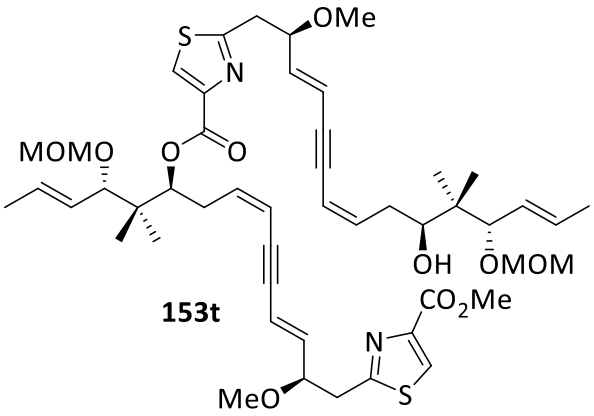
^{13}C-NMR (100 MHz, CD$_3$OD): δ (ppm): 169.6 (C=O); 169.5 (C=O); 163.0 (C=N); 162.2 (C=N); 147.1 (CH); 146.6 (CH); 143.6 (CH); 141.9 (CH); 141.8 (CH); 141.2 (C); 133.1 (C); 132.3 (CH); 130.0 (CH); 129.8 (CH); 129.2 (CH); 128.5 (CH); 114.7 (CH); 114.6 (CH); 112.1 (CH); 110.8 (CH); 94.6 (CH$_2$); 94.5 (CH$_2$); 92.6 (C); 92.5 (C); 88.9 (C); 88.5 (C); 82.8 (CH); 82.7 (CH); 81.4 (CH); 81.2 (CH); 78.6 (CH); 77.9 (CH); 57.1 (CH$_3$); 57.0 (CH$_3$); 56.3 (CH$_3$); 56.0 (CH$_3$); 52.7 (CH$_3$); 44.2 (C); 42.8 (C); 39.8 (CH$_2$); 39.7 (CH$_2$); 35.5 (CH$_2$); 32.4 (CH$_2$); 20.4 (CH$_3$); 20.3 (CH$_3$); 19.9 (CH$_3$); 19.7 (CH$_3$); 18.1 (CH$_3$); 18.0 (CH$_3$); 7.5 (CH$_3$); 6.5 (CH$_2$).

IR (neat): 2952 (m); 2879 (m); 2224 (w); 1736 (s); 1468 (m); 1371 (m); 1238 (s); 1206 (s); 1091 (s); 1033 (s); 956 (s); 918 (m); 736 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 1005.55 (100) [*M*+H]$^+$, 1022.56 (760) [*M*+NH$_4$]$^+$, 943.52 (45), 973.53 (28), 847.43 (8).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{55}H_{81}N_2O_{11}S_2Si$: 1036.4973; found: 1036.4981.

3.3.9. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)thiazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)thiazole-4-carboxylate (153t)



153t

CSA (8 mg, 0.0324 mmol, 0.2 eq) was added at 0 °C to a solution TES protected dimer **151t** (168 mg, 0.162 mmol, 1 eq) in CH_2Cl_2 (8 mL) and MeOH (8 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated $NaHCO_3$ solution (20 mL) was added and the

layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo giving the deprotected alcohol **153t** as a slightly yellow oil, which was used in the next step without further purification.

General Data: $C_{49}H_{66}N_2O_{11}S_2$; FW: 922.41; TLC: R_f = 0.30 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +36.9 (*c* = 0.55, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.11 (s, 1H, NC=C*H*); 7.99 (s, 1H, NC=C*H*); 6.27-6.12 (m, 1H, CH_2C*H*=CH); 6.05-5.93 (m, 3H, CH=CH); 5.89 (ddd, *J* = 16.0, 4.8, 2.5 Hz, 2H, CH=CH); 5.73-5.61 (m, 3H, CH=CH); 5.56 (d, *J* = 10.3 Hz, 1H, CH=CH); 5.45-5.33 (m, 2H, CH=CH); 5.28 (dd, *J* = 8.0, 4.8 Hz, 1H, C*H*OC=O); 4.66 (d, *J* = 6.6 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.48 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.40 (d, *J* = 6.7 Hz, 1H, CHOC*H*$_2$OCH$_3$); .4.06-3.96 (m, 2H, C*H*OCH$_3$); 3.94 (s, 3H, COOC*H*$_3$); 3.92 (m, 1H, C*H*OCH$_2$OCH$_3$); 3.79 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.69 (dd, *J* = 10.1, 2.2 Hz, 1H, C*H*OH); 3.38 (s, 3H, CHOC*H*$_3$); 3.32 (s, 3H, CHOC*H*$_3$); 3.31 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.35-2.29 (m, 2H, C*H*$_2$CHOCH$_3$); 23.30 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.26-2.18 (m, 2H, C*H*$_2$CHOCH$_3$); 2.80-2.66 (m, 2H, C*H*$_2$CH=CH); 2.61-2.50 (m, 1H, 1C*H*$_2$CH=CH); 2.40-2.28 (m, 1H, 1C*H*$_2$CH=CH); 1.75 (dd, *J* = 6.3, 1.3 Hz, 3H, CH=CHC*H*$_3$); 1.71 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHC*H*$_3$); 1.05 (s, 3H, CC*H*$_3$); 1.00 (s, 3H, CC*H*$_3$); 0.927 (s, 3H, CC*H*$_3$); 0.878 (s, 3H, CC*H*$_3$).

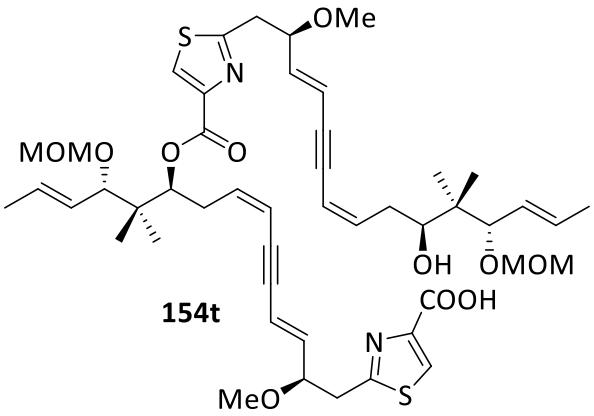
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 167.5 (C=O); 167.4 (C=O); 162.1 (C=N); 160.9 (C=N); 146.6 (CH); 146.1 (CH); 143.2 (CH); 140.5 (CH); 140.4 (CH); 132.0 (CH); 131.9 (CH); 128.5 (CH); 127.6 (C); 127.3 (C); 126.9 (CH); 125.7 (CH); 113.7 (CH); 113.6 (CH); 111.1 (CH); 109.8 (CH); 93.8 (CH_2); 93.7 (CH_2); 91.5 (C); 91.3 (C); 88.3 (C); 88.1 (C); 84.7 (CH); 81.6 (CH); 80.4 (CH); 80.4 (CH); 77.4 (CH); 76.2 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.2 (CH_3); 56.1 (CH_3); 52.6 (CH_3); 41.9 (C); 41.0 (C); 39.7 (CH_2); 32.9 (CH_2); 31.6 (CH_2); 30.4 (CH_2); 21.1 (CH_3); 20.0 (CH_3); 19.8 (CH_3); 19.6 (CH_3); 18.1 (CH_3); 18.0 (CH_3).

IR (neat): 3500 (br); 2934 (m); 2886 (m); 1723 (m); 1468 (m); 1345 (m); 1205 (s); 1092 (s); 1032 (s); 971 (s); 919 (m); 749 (m); 540 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 923.42 (100) [*M*+H]$^+$, 891.39 (10), 945.40 (6) [*M*+Na]$^+$, 765.29 (5).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{49}H_{67}N_2O_{11}S_2$: 923.4186; found: 923.4194.

3.3.10. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)thiazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)thiazole-4-carboxylate (154t)



154t

The crude deprotected alcohol **153t** was dissolved in THF (6 mL) and treated at room temperature with LiOH (1 M in H_2O, 0.486 mL, 0.486 mmol, 3 eq). The mixture was stirred overnight at room temperature and neutralized with 1 M HCl (~1.5 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give the *seco*-acid **154t** as a yellow wax, which was used without further purification.

General Data: $C_{48}H_{64}N_2O_{11}S_2$; FW: 908.40; TLC: UV (+); Vanillin: grey; $[\alpha]_D^{20}$ = +28.5 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.18 (s, 1H, NC=C*H*); 8.00 (s, 1H, NC=C*H*); 6.26-6.14 (m, 1H, CH_2CH=CH); 6.03-5.93 (m, 3H, CH=CH); 5.93-5.83 (m, 2H, CH=CH); 5.71-5.61 (m, 3H, CH=CH); 5.56 (d, *J* = 10.1 Hz, 1H, CH=CH); 5.44-5.33 (m, 2H, CH=CH); 5.28 (dd, *J* = 7.5, 5.8 Hz, 1H, C*H*OC=O); 4.67 (d, *J* = 6.6 Hz, 2H, OCH_2OCH_3); 4.48 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.41 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.08-3.97 (m, 2H, $CHOCH_3$); 3.91 (d, *J* = 8.6 Hz, 1H, $CHOCH_2OCH_3$); 3.79 (d, *J* = 9.0 Hz, 1H, $CHOCH_2OCH_3$); 3.70 (dd, *J* = 10.2, 2.0 Hz, 1H, C*H*OH); 3.39 (s, 3H, $CHOCH_3$); 3.35-3.28 (m, 2H, CH_2CHOCH_3); 3.33 (s, 3H, $CHOCH_3$); 3.32 (s, 3H, $CHOCH_2OCH_3$); 3.31 (s, 3H, $CHOCH_2OCH_3$); 3.27-3.16 (m, 2H, CH_2CHOCH_3); 2.76-2.66 (m, 2H, CH_2CH=CH); 2.60-2.50 (m, 1H, $1CH_2CH$=CH); 2.41-2.30 (m, 1H, $1CH_2CH$=CH); 1.75 (d, *J* = 6.3 Hz, 3H, CH=CHCH_3); 1.71 (d, *J* = 6.3, 1.4 Hz, 3H, CH=CHCH_3); 1.05 (s, 3H, CCH_3); 0.999 (s, 3H, CCH_3); 0.928 (s, 3H, CCH_3); 0.879 (s, 3H, CCH_3).

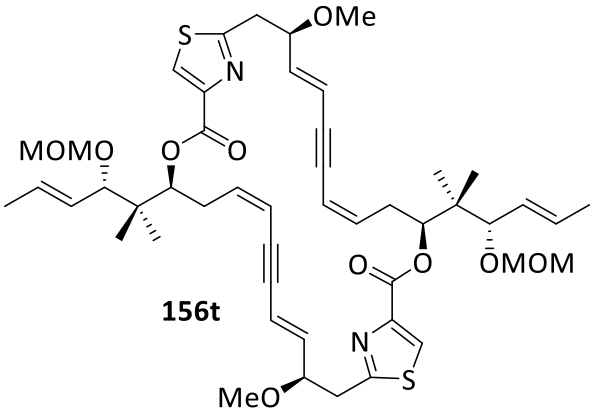
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 167.6 (C=O); 167.5 (C=O); 163.2 (C=N); 160.8 (C=N); 146.4 (CH); 145.8 (CH); 143.1 (CH); 140.6 (CH); 140.4 (C); 132.1 (CH); 129.2 (C); 129.1 (CH); 127.8 (CH); 127.2 (CH); 126.8 (CH); 125.6 (CH); 113.7 (CH); 111.0 (CH); 109.9 (CH); 109.8 (CH); 93.8 (CH_3); 93.6 (CH_3); 91.5 (C); 91.3 (C); 88.3 (C); 88.1 (C); 84.7 (CH); 81.6 (CH); 80.4 (CH); 80.2 (CH); 77.4 (CH); 76.3 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.2 (CH_3); 56.1 (CH_3); 41.9 (C); 41.0 (C); 32.8 (CH_2); 31.6 (CH_2); 30.5 (CH_2); 29.8 (CH_2); 21.1 (CH_3); 20.0 (CH_3); 19.8 (CH_3); 19.5 (CH_3); 18.1 (CH_3); 18.0 (CH_3).

IR (neat): 3507 (br); 2924 (m); 2826 (w); 1722 (s); 1469 (m); 1337 (m); 1200 (s); 1146 (m); 1093 (s); 1030 (s); 956 (s); 911 (s); 730 (s); 576 (w) cm^{-1}.

MS (ESI): *m/z* (%): 909.40 (100) $[M+H]^+$, 931.39 (18) $[M+Na]^+$, 897.40 (12), 847.36 (9).

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{48}H_{65}N_2O_{11}S_2$: 909.4030; found: 909.4003.

3.3.11. Bis(thiazolyl)-(16,16')-bis(methoxymethyl)-(9,10,9',10')-tetradehydridodisorazole C_1 (156t)



156t

The crude *seco*-acid **154t** was dissolved in THF (10 mL) and treated at room temperature with NEt_3 (506 µL, 3.24 mmol, 20 eq) and 2,4,6-trichlorobenzoyl chloride (225 µL, 1.62 mmol, 10 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (3 mL) and added dropwise to a solution of DMAP (791 mg, 6.48 mmol, 40 eq) in toluene (80 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (20 mL) and water (20 mL) and the aqueous phase was extracted with EtOAc (3x40 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 2:1 to 1:1) to afford the macrocycle **156t** (65 mg, 0.0729 mmol, 45% from **151t**) as a slightly yellow wax.

General Data: $C_{48}H_{62}N_2O_{10}S_2$; FW: 890.38; TLC: R_f = 0.50 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +98.2 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.98 (s, 2H, NC=C*H*); 6.02-5.90 (m, 4H, CH=CH); 5.79 (dd, *J* = 15.8, 2.0 Hz, 2H, CH=CH); 5.66 (dd, *J* = 15.4, 6.5 Hz, 2H, CH=CH); 5.54 (d, *J* = 10.8 Hz, 2H, CH=CH); 5.46-5.37 (m, 2H, CH=CH); 5.32 (dd, *J* = 10.6, 2.8 Hz, 2H, C*H*OC=O); 4.67 (d, *J* = 6.6 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.42 (d, *J* = 6.6 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.15-4.07 (m, 2H, C*H*OCH$_3$); 3.77 (d, *J* = 8.9 Hz, 2H, C*H*OCH$_2$OCH$_3$); 3.53-3.46 (m, 2H, C*H*$_2$CH=CH); 3.37 (s, 6H, CHOC*H*$_3$); 3.34 (s, 6H, CHOCH$_2$OC*H*$_3$); 3.31-3.22 (m, 2H, C*H*$_2$CH=CH); 3.05-2.90 (m, 2H, C*H*$_2$CHOCH$_3$); 2.50-2.41 (m, 2H, C*H*$_2$CH=CH); 1.73 (dd, *J* = 6.4, 1.4 Hz, 6H, CH=CHC*H*$_3$); 1.07 (s, 6H, CC*H*$_3$); 1.03 (s, 6H, CC*H*$_3$).

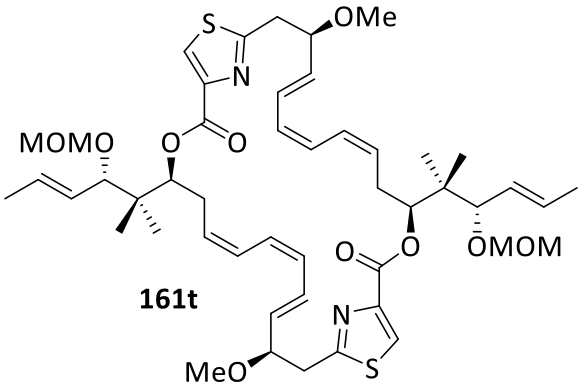
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 165.8 (C=O); 160.6 (C=N); 147.0 (CH); 140.5 (CH); 140.4 (CH); 131.9 (C); 128.4 (CH); 127.4 (CH); 114.5 (CH); 112.1 (CH); 93.8 (CH_2); 91.2 (C); 88.2 (C); 81.7 (CH); 79.9 (CH); 77.4 (CH); 56.9 (CH_3); 56.2 (CH_3); 41.7 (C); 39.1 (CH_2); 30.5 (CH_2); 20.1 (CH_3); 19.8 (CH_3); 18.1 (CH_3).

IR (neat): 3115 (w); 2925 (m); 2854 (m); 1730 (m); 1468 (m); 1368 (m); 1236 (s); 1192 (s); 1092 (s); 1031 (s); 960 (s); 921 (m); 824 (m); 747 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 891.39 (100) [*M*+H]$^+$, 829.35 (15), 913.37 (12) [*M*+Na]$^+$, 879.39 (9).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{48}H_{63}N_2O_{10}S_2$: 891.3924; found: 891.3915.

3.3.12. Bis(thiazolyl)-(16,16')-bis(methoxymethyl)-disorazole C_1 (161t)



161t

Nitrogen was bubbled for 15 min through a suspension of zinc dust (6 g, 91.77 mmol) in H_2O (30 mL) and then $Cu(OAc)_2 \cdot H_2O$ (600 mg, 3.00 mmol) was added at room temperature and after 15 min $AgNO_3$ (600 mg, 3.53 mmol) was added (exothermic reaction). The mixture was stirred for 30 min at room temperature, filtered by suction and washed with H_2O (40 mL), MeOH (30 mL), acetone (30 mL) and Et_2O (30 mL). This activated zinc solids were added to a solution of **156t** (50 mg, 0.0562 mmol) in MeOH/H_2O 1:1 (25 mL). The mixture was stirred for

24 h at 50 °C, then filtered on a pad of silica with MeOH washes. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 70:1) to afford **161t** (30 mg, 0.0335 mmol, 60%) as a colorless wax.

General Data: $C_{48}H_{66}N_2O_{10}S_2$; FW: 894.42; TLC: R_f = 0.40 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –52.8 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.82 (s, 2H, NC=C*H*); 6.43 (dd, *J* = 15.3, 11.6 Hz, 2H, CH(OCH3)CH=C*H*); 6.33 (app t, *J* = 11.3 Hz, 2H, CH2CH=C*H*); 6.19 (dd, *J* = 11.7, 11.0 Hz, 2H, CHC*H*=CHCH); 5.89 (dd, *J* = 11.2, 10.9 Hz, 2H, CHCH=C*H*CH); 5.63 (dd, *J* = 15.3, 6.5 Hz, 2H, CH3C*H*=CH); 5.50 (dd, *J* = 15.1, 8.7 Hz, 2H, CH3CH=C*H*); 5.40 (ddd, *J* = 15.2, 9.0, 1.5 Hz, 2H, CH(OCH3)C*H*=CH); 5.31 (dd, *J* = 11.2, 2.5 Hz, 2H, C*H*OC=O); 5.26 (dd, *J* = 11.2, 2.2 Hz, 2H, CH2C*H*=CH); 4.66 (d, *J* = 6.6 Hz, 2H, 1OCH_2OCH$_3$); 4.39 (d, *J* = 6.6 Hz, 2H, 1OCH_2OCH$_3$); 4.10 (ddd, *J* = 12.8, 7.0, 5.0 Hz, 2H, C*H*OCH$_3$); 3.74 (d, *J* = 9.0 Hz, 2H, C*H*OH); 3.43 (dd, *J* = 14.2, 5.3 Hz, 2H, CH_2CHOCH$_3$); 3.33 (s, 6H, CHOCH$_2$OCH_3); 3.28 (s, 6H, CHOCH_3); 3.01 (dd, *J* = 14.2, 8.0 Hz, 2H, CH_2CHOCH$_3$); 2.65-2.55 (m, 2H, CH_2CH=CH); 2.50 (dd, *J* = 15.3, 6.1 Hz, 2H, CH_2CH=CH); 1.72 (d, *J* = 6.1 Hz, 3H, CH=CHCH_3); 1.03 (s, 6H, CCH_3); 0.979 (s, 6H, CCH_3).

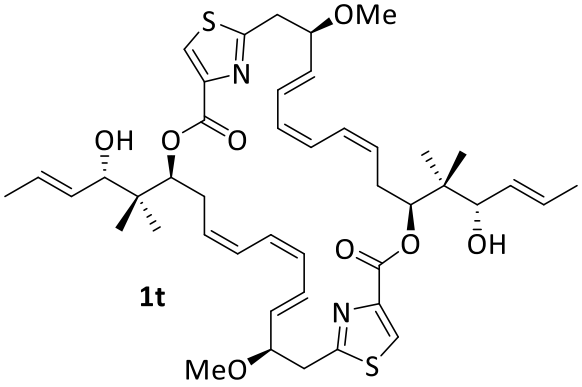
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 166.6 (C=O); 160.8 (C=N); 147.1 (CH); 132.9 (C); 132.0 (CH); 129.9 (CH); 128.1 (CH); 127.2 (CH); 126.8 (CH); 125.7 (CH); 125.6 (CH); 125.5 (CH); 93.6 (CH_2); 81.9 (CH); 81.2 (CH); 77.4 (CH); 56.6 (CH_3); 56.1 (CH_3); 41.8 (C); 30.5 (CH_2); 29.8 (CH_2); 20.3 (CH_3); 19.9 (CH_3); 18.1 (CH_3).

IR (neat): 2923 (s); 2853 (m); 1731 (m); 1466 (m); 1365 (w); 1194 (m); 1092 (s); 1032 (s); 973 (m); 920 (m); 731 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 895.42 (100) [*M*+H]$^+$, 917.40 (12) [*M*+Na]$^+$, 863.39 (5), 833.38 (4).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{48}H_{67}N_2O_{10}S_2$: 895.4237; found 895.4210.

3.3.13. Bis(thiazolyl)-Disorazole C_1 (1t)



MOM protected **161t** (12 mg, 13.4 µmol) was dissolved in CH_3CN (1.5 mL) and cooled to 0 °C. 2 drops of HBr (48% in H_2O) were slowly added and then the mixture was stirred for 1 h at 0 °C. The mixture was diluted with EtOAc (4 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous phase was extracted with EtOAc (3x5 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 50:1) to give Bis(thiazolyl)-disorazole C_1 **1t** (6 mg, 7.44 µmol, 56%) as a colorless wax.

General Data: $C_{44}H_{58}N_2O_8S_2$; FW: 806.36; TLC: R_f = 0.20 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –113.33 (*c* = 0.15, MeOH).

^{1}H-NMR (600 MHz, CD_3OD): δ (ppm): 8.11 (s, 2H, NC=C*H*); 6.49 (dd, *J* = 15.2, 11.4 Hz, 2H, CH(OCH_3)CH=C*H*); 6.39 (app t, *J* = 11.1 Hz, 2H, CH2CH=C*H*); 6.27 (dd, *J* = 11.2, 11.0 Hz, 2H, CHC*H*=CHCH); 5.85 (dd, *J* = 11.2, 11.1 Hz, 2H, CHCH=C*H*CH); 5.67 (dq, *J* = 15.3, 6.4 Hz, 2H, CH3C*H*=CH); 5.59 (ddd, *J* = 15.3, 7.9, 1.5 Hz, 2H, CH3CH=C*H*); 5.51 (dd, *J* = 15.4, 8.0 Hz, 4H, CH(OCH3)C*H*=CH); 5.26 (dd, *J* = 11.1, 2.2 Hz, 2H, C*H*OC=O); 4.13 (ddd, *J* = 7.9, 7.2, 5.3 Hz, 2H, C*H*OCH3); 3.86 (d, *J* = 7.9 Hz, 2H, C*H*OH); 3.25 (s, 6H, CHOCH_3); 3.20 (dd, *J* = 12.4, 7.3 Hz, 2H, CH_2CHOCH_3); 3.01 (dd, *J* = 14.9, 5.6 Hz, 2H, CH_2CHOCH_3); 2.69 (ddd, *J* = 13.8, 10.9, 10.2 Hz, 2H, CH_2CH=CH); 2.46 (dd, *J* = 14.1, 6.5 Hz, 2H, CH_2CH=CH); 1.69 (dd, *J* = 6.1, 1.1 Hz, 6H, CH=CHCH_3); 1.03 (s, 6H, CCH_3); 0.972 (s, 6H, CCH_3).

^{13}C-NMR (151 MHz, CD_3OD): δ (ppm): 169.0 (C=O); 162.3 (C=N); 147.5 (CH); 133.9 (C); 131.7 (CH); 130.6 (CH); 130.1 (CH); 129.7 (CH); 129.3 (CH); 129.0 (CH); 127.2 (CH); 126.6 (CH); 81.8 (CH); 79.2 (CH); 77.9 (CH); 56.9 (CH_3); 42.8 (C); 40.5 (CH_2); 29.2 (CH_2); 19.5 (CH_3); 19.4 (CH_3); 18.0 (CH_3).

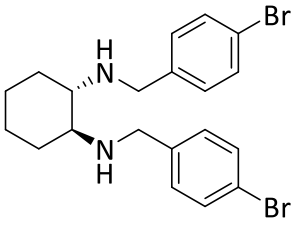
IR (neat): 3419 (br); 2924 (m); 2854 (m); 1723 (m); 1583 (m); 1447 (w); 1367 (w); 1312 (w); 1261 (w); 1101 (s); 1010 (m); 803 (m); 758 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 807.37 (100) $[M+H]^+$, 829.35 (34) $[M+Na]^+$, 172.13 (33); 155.11 (28), 659.52 (14), 798.36 (13).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{44}H_{59}N_2O_8S_2$: 807.3713; found 807.3704.

3.4. Synthesis of (16*R*,16'*R*)-Disorazole C_1 (1r)

3.4.1. (*S*,*S*)-*N*,*N*'-bis-(4-bromo-benzyl)-cyclohexane-1,2-diamine [(*S*,*S*)-111)]



111s

To a suspension of (1*S*,2*S*)-(–)-1,2-diaminocyclohexane·D-tartrate **(*S*,*S*)-110** (5 g, 18.92 mmol, 1 eq) in H_2O (90 mL), K_2CO_3 (5.23 g, 37.84 mmol, 2 eq) was added, followed by EtOH (45 mL). To the resulting mixture was added a solution of 4-bromobenzaldehyde (7 g, 37.84 mmol, 2 eq) and methanesulfonic acid (0.148 mL, 2.27 mmol, 0.12 eq) in CH_2Cl_2 (90 mL). The mixture was stirred for 12 h at room temperature and 1 h at reflux. The mixture was concentrated, diluted with water and filtered. The collected solid was suspended in MeOH (25 mL), cooled to 0 °C and then $NaBH_4$ (1.6 g, 42.38 mmol, 2.24 eq) was added. The mixture was refluxed for 1 h and concentrated again. A 1:1 mixture of hexane and EtOAc (100 mL) was added, followed by 1 M NaOH (100 mL). The layers were separated and the aqueous phase was extracted with hexane/EtOAc 1:1 (3x80 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 4:1 then hexane/EtOAc/NEt_3 1:1:0.1) to afford the diamine **(*S*,*S*)-111** (7.08 g, 15.74 mmol, 83%) as a slightly yellow paste.

General Data: $C_{20}H_{24}Br_2N_2$; FW: 450.04; TLC: R_f = 0.45 (hexane/EtOAc/NEt_3 1:1:0.1); UV (+); Vanillin: white.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.42 (d, *J* = 8.3 Hz, 4H, Ar-*H*); 7.17 (d, *J* = 8.3 Hz, 4H, Ar-*H*); 3.83 (dd, *J* = 13.4, 4.5 Hz, 2H, ArC*H*$_2$N); 3.59 (d, *J* = 13.4, 5.9 Hz, 2H, ArC*H*$_2$N); 2.25-2.17 (m, 2H, 2C*H*N); 2.16-2.08 (m, 2H, Cy); 1.79 (s, 2H, N*H*); 1.75-1.66 (m, 2H, Cy); 1.26-1.15 (m, 2H, Cy); 1.07-0.950 (m, 2H, Cy).

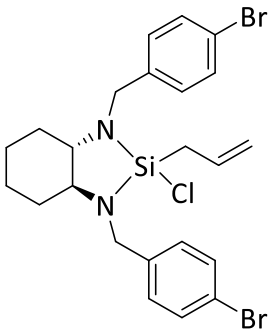
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 140.2 (ArC); 131.5 (ArCH); 129.9 (ArCH); 120.6 (ArC); 61.0 (CH); 50.4 (CH_2); 31.7 (CH_2); 25.1 (CH_2).

IR (neat): 3298 (s); 3020 (m); 2926 (s); 2864 (w); 1895 (m); 1738 (w); 1590 (m); 1497 (m); 1368 (m); 1238 (m); 1115 (s); 1061 (s); 798 (m); 725 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 453.04 (100), 451.04 (49) [*M*+H]$^+$, 456.04 (14), 156.05 (12).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{20}H_{25}Br_2N_2$: 451.0384; found: 451.0369.

3.4.2. (*S,S*)-Leighton reagent [(*S,S*)-109]



(*S,S*)-109

(*S,S*)-111 (7.05 g, 15.6 mmol, 1 eq) dissolved in CH_2Cl_2 (20 mL) was added dropwise to a solution of DBU (5.6 mL, 37.44 mmol, 2.4 eq) and allyltrichlorosilane (2.73 mL, 18.8 mmol, 1.2 eq) in CH_2Cl_2 (55 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and 13 h at room temperature. The solvent was removed in vacuo and then Et_2O (60 mL) was added, causing the formation of a white precipitate. The suspension was stirred for 1 h and then the supernatant was transferred by syringe into another flask. The mixture was concentrated again affording **(*S,S*)-109** (7.32 g, 13.26 mmol, 85%) as a yellow oil, which solidified upon standing in the freezer.

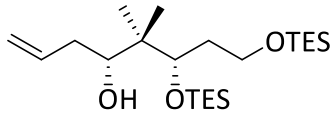
General Data: $C_{23}H_{27}Br_2ClN_2Si$; FW: 552.0.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.47 (d, *J* = 8.2 Hz, 1H, Ar-*H*); 7.45-7.36 (m, 4H, Ar-*H*); 7.20-7.30 (m, 3H, Ar-*H*); 5.68-5.54 (m, 1H, C*H*=CH_2); 4.94-4.84 (m, 2H, CH=C*H*$_2$); 4.13 (d, *J* = 16.1 Hz, 1H, 1ArC*H*$_2$N); 3.98 (d, *J* = 14.9 Hz, 1H, 1ArC*H*$_2$N); 3.82 (d, *J* = 15.8 Hz, 2H, ArC*H*$_2$N); 2.82-2.66 (m, 2H, 2C*H*N); 1.89-1.78 (m, 2H, Cy); 1.77-1.69 (m, 2H, Cy); 1.68-1.54 (m, 2H, SiC*H*$_2$CH=CH_2); 1.25-1.05 (m, 2H, Cy); 1.05-0.838 (m, 2H, Cy).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 141.2 (ArC); 140.3 (ArC); 132.0 (CH); 131.3 (ArCH); 131.1 (ArC); 130.0 (ArCH); 129.1 (ArCH); 120.7 (ArCH); 120.4 (ArC); 116.4 (CH_2); 66.4 (CH); 65.5 (CH); 48.0 (CH_2); 47.3 (CH_2); 30.8 (CH_2); 30.4 (CH_2); 24.9 (CH_2); 24.8 (CH_2); 24.7 (CH_2).

IR (neat): 3062 (s); 3030 (m); 2936 (s); 2864 (w); 1895 (m); 1812 (w); 1590 (m); 1497 (m); 1368 (m); 1238 (m); 1115 (s); 1061 (s); 798 (m); 725 (s) cm^{-1}.

3.4.3. (4*R*,6*S*)-5,5-dimethyl-6,8-bis((triethylsilyl)oxy)oct-1-en-4-ol (78r)



78r

A solution of **(*S*,*S*)-109** (4.74 g, 8.58 mmol, 1.2 eq) in CH_2Cl_2 (20 mL) was added to a solution of aldehyde **77c** (2.67 g, 7.15 mmol, 1 eq) in CH_2Cl_2 (50 mL) at room temperature. Then $Sc(OTf)_3$ (175 mg, 0.375 mmol, 0.05 eq) was added and the mixture was stirred for 24 h at room temperature. TBAF trihydrate (2.26 g, 7.15 mmol, 1 eq) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated and the residue was purified by flash chromatography (pentane/Et_2O 50:1, then pentane/EtOAc/NEt_3 1:1:0.1) to furnish the allylic alcohol **78r** (2.59 g, 6.22 mmol, 87%, 86% *de*) as a colorless liquid and the recovered diamine **(*S*,*S*)-111** (3.64 g, 8.08 mmol, 87%) as a yellow paste. Analysis by ^{1}H and ^{13}C NMR showed a 13:1 mixture *syn* and *anti* diastereoisomers.

General Data: $C_{22}H_{48}O_3Si_2$; FW: 416.31; TLC: R_f = 0.2 (Pentane/Et_2O 50:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –4.2 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.94-5.86 (m, 1H, C*H*=CH_2); 5.13-5.05 (m, 2H, CH=C*H*$_2$); 3.79 (dd, *J* = 6.5, 2.7 Hz, 1H, C*H*OH); 3.73 (m, 1H, 1C*H*$_2$OSi); 3.65 (m, 1H, 1C*H*$_2$OSi); 3.51 (dt, *J* = 10.5, 2.3 Hz, 1H, C*H*OSi); 2.74 (s, 1H, CHO*H*); 2.31-2.25 (m, 1H, 1C*H*$_2$CH); 2.1-2.02 (m, 1H, 1C*H*$_2$CH); 2.01-1.93 (m, 1H, 1C*H*$_2$CH$_2$O); 1.54-1.48 (m, 1H, 1C*H*$_2$CH$_2$O); 0.990-0.931 (m, 18H, 2OSi(CH_2C*H*_3)$_3$); 0.897 (s, 3H, 1CC*H*$_3$); 0.781 (s, 3H, 1CC*H*$_3$); 0.650-0.570 (m, 12H, 2OSi(C*H*$_2$CH$_3$)$_3$).

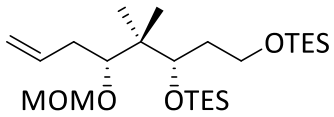
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 137.3 (CH); 116.7 (CH*2*); 75.8 (CH); 75.5 (CH); 61.2 (CH_2); 42.6 (C); 36.6 (CH_2); 36.5 (CH_2); 18.9 (*C*H$_3$); 18.6 (*C*H$_3$); 7.2 (CH_3); 6.9 (CH_3); 5.6 (CH_2); 4.4 (CH_2).

IR (neat): 3335 (br); 2955 (s); 2913 (s); 2877 (s); 1670 (w); 1642 (w); 1461 (m); 1415 (m); 1381 (m); 1238 (m); 1093 (s); 1056 (s); 1004 (s); 910 (m); 842 (m); 726 (s); 675 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 303.24 (100), 417.32 (23), 153.13 (16), 418.32 (8).

HRMS (ESI): calculated for $C_{22}H_{48}O_3Si_2$ [*M*+H]$^+$: 417.3220, found: 417.3227.

3.4.4. (5*R*,7*S*)-5-allyl-11,11-diethyl-6,6-dimethyl-7-((triethylsilyl)oxy)-2,4,10-trioxa-11-silatridecane (117r)



117r

MOMCl (1.3 mL, 17 mmol, 3 eq) was added dropwise at 0 °C to a solution of allylic alcohol **78r** (2.36 g, 5.67 mmol, 1 eq), DIPEA (3 mL, 17 mmol, 3 eq) and DMAP (207 mg, 1.7 mmol, 0.3 eq) in CH_2Cl_2 (60 mL). The mixture was stirred overnight at 45 °C. Evaporation of the solvent and purification of the residue by flash chromatography (pentane/Et_2O 60:1) afforded the protected triol **117r** (2.4 g, 5.21 mmol, 92%) as a colorless liquid.

General Data: $C_{24}H_{52}O_4Si_2$; FW: 460.34; TLC: R_f = 0.5 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –10.67 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.95-5.87 (m, 1H, C*H*=CH_2); 5.09-4.98 (m, 2H, CH=C*H*$_2$); 4.61 (q, *J* = 6.7 Hz, 2H, OC*H*$_2$OCH$_3$); 3.74-3.68 (m, 1H, 1C*H*$_2$OSi); 3.71 (dd, *J* = 8.6, 1.8 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.63.3.57 (m, 1H, 1C*H*$_2$OSi); 3.47 (dd, *J* = 8.6, 2.9 Hz 1H, C*H*OSi); 3.36 (s, 3H, OC*H*$_3$); 2.48-2.41 (m, 1H, 1C*H*$_2$CH); 2.23-2.14 (m, 1H, 1C*H*$_2$CH); 1.91-1.83 (m, 1H, 1C*H*$_2$CH$_2$O); 1.55-1.48 (m, 1H, 1C*H*$_2$CH$_2$O); 1.00-0.923 (m, 18H, 2OSi(CH$_2$C*H*$_3$)$_3$); 0.917 (s, 3H, 1CC*H*$_3$); 0.811 (s, 3H, 1CC*H*$_3$); 0.655-0.565 (m, 12H, 2OSi(C*H*$_2$CH$_3$)$_3$).

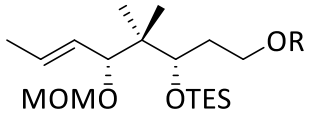
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 137.4 (CH); 116.1 (CH_2); 98.2 (CH_2); 83.6 (CH); 74.6 (CH); 60.9 (CH_2); 56.2 (CH_3); 43.4 (C); 36.4 (CH_2); 36.3 (CH_2); 21.0 (CH_3); 19.4 (CH_3); 7.3 (CH_3); 6.9 (CH_3); 5.8 (CH_2); 4.6 (CH_2).

IR (neat): 2954 (m); 2914 (m); 2877 (m); 1641 (w); 1461 (m); 1382 (m); 1238 (m); 1093 (s); 1035 (s); 1006 (s); 912 (m); 725 (s); 674 (m) cm^{-1}.

MS (EI, 70eV): *m*/*z* (%): 116.02 (100), 58.54 (64), 86.32 (50), 300.21 (45), 436.80 (9), 313.7 (6).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{24}H_{52}O_4Si_2$: 461.3438; found: 461.3460.

3.4.5. (3*S*,5*R*,*E*)-5-(methoxymethoxy)-4,4-dimethyl-3-((triethylsilyl)oxy)non-7-en-1-ol (123r)



123e: R = TES
123r: R = H

A solution of protected triol **117r** (2.3 g, 5 mmol, 1 eq) and Grubbs II (212 mg, 0.250 mmol, 0.05 eq) in MeOH was stirred for 20 h at 60 °C. The mixture was then concentrated in vacuo and the residue was filtered on a pad of silica gel (pentane/Et_2O 1:1). The filtrate was concentrated in vacuo affording a mixture of **123r** (80%) and **123e** (15%) as a colorless liquid, which was used in the next step without further purification. A small amount was further purified by flash chromatography (pentane/Et_2O 60:1 to 3:1) for analytical purpose. Analysis by ^{1}H and ^{13}C NMR showed a 14:1 mixture of *E* and *Z* isomers.

General Data (123e): $C_{24}H_{52}O_4Si_2$; FW: 460.34; TLC: R_f = 0.5 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –44.0 (*c* = 0.2, $CHCl_3$).

^{1}H-NMR (123e) (400 MHz, $CDCl_3$): δ (ppm): 5.64-5.54 (m, 1H, C*H*=CH); 5.31 (m, 1H, CH=C*H*); 4.66 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.43 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 3.86 (d, *J* = 8.7 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.75 (dd, *J* = 8.8, 2.4 Hz, 1H, C*H*OSi); 3.73-3.67 (m, 1H, 1C*H*$_2$OSi); 3.64-3.55 (m, 1H, 1C*H*$_2$OSi); 3.35 (s, 3H, OC*H*$_3$); 1.94-1.82 (m, 1H, 1C*H*$_2$CH$_2$O); 1.71 (dd, *J* = 6.4, 1.4 Hz, 3H, CHC*H*$_3$); 1.63-1.53 (m, 1H, 1C*H*$_2$CH$_2$O); 1.01-0.878 (m, 18H, 2OSi(CH$_2$C*H*$_3$)$_3$); 0.922 (s, 3H, 1CC*H*$_3$); 0.746 (s, 3H, 1CC*H*$_3$); 0.668-0.540 (m, 12H, 2OSi(C*H*$_2$CH$_3$)$_3$).

^{13}C-NMR (123e) (100 MHz, $CDCl_3$): δ (ppm): 130.8 (CH); 128.1 (CH); 93.5 (CH_2); 81.3 (CH); 74.5 (CH); 61.3 (CH_2); 55.9 (CH_3); 42.4 (C); 35.9 (CH_2); 20.3 (CH_3); 19.5 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 6.9 (CH_3); 5.8 (CH_2); 4.6 (CH_2).

IR (neat) (123e): 2954 (m); 2918 (m); 2877 (m); 1730 (w); 1671 (w); 1632 (w); 1461 (m); 1415 (m); 1379 (m); 1239 (m); 1095 (s); 1033 (s); 973 (m); 922 (m); 823 (m); 726 (s) cm^{-1}.

MS (EI, 70eV) **(123e)**: *m*/*z* (%): 116.02 (100), 58.54 (64), 86.32 (50), 300.21 (45), 436.80 (9), 313.7 (6).

HRMS (ESI) **(123e)**: *m*/*z* [*M*+H]$^+$ Calcd for $C_{24}H_{53}O_4Si_2$: 461.3482; found: 461.3445.

General Data (123r): $C_{18}H_{38}O_4Si$; FW: 346.25; TLC: R_f = 0.3 (Pentane/Et_2O 3:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –69.0 (*c* = 0.8, $CHCl_3$).

^{1}H-NMR (123r) (400 MHz, $CDCl_3$): δ (ppm): 5.64-5.54 (m, 1H, C*H*=CH); 5.31 (m, 1H, CH=C*H*); 4.62 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.43 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$OCH$_3$); 3.87 (dd, *J* = 8.7, 2.4 Hz, 1H, C*H*OSi); 3.81 (d, *J* = 8.5 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.79-3.72 (m, 1H, 1C*H*$_2$OSi); 3.71-3.62 (m, 1H, 1C*H*$_2$OSi); 3.33 (s, 3H, OC*H*$_3$); 1.95-1.84 (m, 1H, 1C*H*$_2$CH$_2$O); 1.71 (dd, *J* = 6.4, 1.5 Hz, 3H, CHC*H*$_3$); 1.67-1.57 (m, 1H, 1C*H*$_2$CH$_2$O); 1.00-0.932 (m, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.923 (s, 3H, 1CC*H*$_3$); 0.736 (s, 3H, 1CC*H*$_3$); 0.678-0.583 (m, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

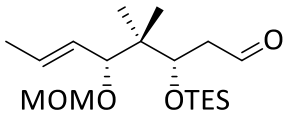
^{13}C-NMR (123r) (100 MHz, $CDCl_3$): δ (ppm): 131.0 (CH); 127.8 (CH); 93.7 (CH_2); 81.9 (CH); 74.6 (CH); 61.0 (CH_2); 55.8 (CH_3); 42.2 (C); 35.4 (CH_2); 20.2 (CH_3); 19.2 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat) (123r): 3386 (br); 2954 (m); 2877 (m); 1669 (w); 1465 (m); 1415 (m); 1382 (m); 1238 (m); 1146 (m); 1091 (m); 1033 (s); 972 (m); 921 (m); 840 (m); 727 (s) cm^{-1}.

MS (ESI) **(123r)**: *m*/*z* (%): 347.26 (100) [*M*+H]$^+$, 317.25 (31), 348.26 (28), 369.24 (16) [*M*+Na]$^+$, 285.22 (7).

HRMS (ESI) **(123r)**: calculated for $C_{18}H_{39}O_4Si$ [*M*+H]$^+$: 347.2618, found: 347.2620.

3.4.6. (3*S*,5*R*,*E*)-5-(methoxymethoxy)-4,4-dimethyl-3-((triethylsilyl)oxy)oct-6-enal (128r)



128b

DMSO (0.780 mL, 11 mmol, 2 eq) in CH_2Cl_2 (5 mL) was added dropwise to a solution of oxalyl chloride (0.644 mL, 7.5 mmol, 1.5 eq) in CH_2Cl_2 (20 mL) at –78 °C. The mixture was stirred for 10 min at –78 °C and then the crude isomerized material dissolved in CH_2Cl_2 (5 mL) was added dropwise. The reaction was stirred for 1 h at –78 °C, quenched by dropwise addition of NEt_3 (3.5 mL, 25 mmol, 5 eq) and then warmed to room temperature over 45 min. H_2O (30 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 10:1) afforded aldehyde **128r** (1.33 g, 3.86 mmol, 77% from **117r**) as a colorless liquid.

General Data: $C_{18}H_{36}O_4Si$; FW: 344.24; TLC: R_f = 0.3 (pentane/Et_2O 10:1); UV (–); Vanillin: grey; $[\alpha]_D^{20}$ = –54.87 (*c* = 0.8, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.84 (dd, *J* = 3.0, 1.2 Hz, 1H, C*H*O); 5.66-5.56 (m, 1H, C*H*=CH); 5.35-5.25 (m, 1H, CH=C*H*); 4.64 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.41 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.31 (dd, *J* = 7.2, 3.7 Hz, 1H, C*H*OSi); 3.78 (d, *J* = 8.7 Hz, 1H, C*H*OC*H*$_2$OCH$_3$); 3.33 (s, 3H, OC*H*$_3$); 2.75 (ddd, *J* = 16.7, 3.7, 1.3 Hz, 1H, 1C*H*$_2$CO); 2.58 (ddd, *J* = 16.7, 7.2, 3.0 Hz, 1H, 1C*H*$_2$CO); 1.72 (dd, *J* = 6.5, 1.6 Hz, 3H, CHC*H*$_3$); 0.973 (s, 3H, 1CC*H*$_3$); 0.986-0.912 (m, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.777 (s, 3H, 1CC*H*$_3$); 0.651-0.545 (m, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

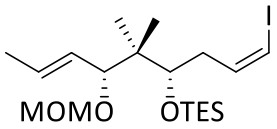
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 202.9 (C=O); 131.6 (CH); 127.4 (CH); 93.4 (CH_2); 81.5 (CH); 72.2 (CH); 56.1 (CH_3); 47.9 (CH_2); 42.3 (C); 20.2 (CH_3); 19.9 (CH_3); 18.0 (CH_3); 7.1 (CH_3); 5.5 (CH_2).

IR (neat): 3017 (w); 2952 (m); 2877 (m); 2716 (w); 1727 (s); 1464 (m); 1381 (w); 1238 (w); 1096 (s); 1074 (s); 1030 (s); 972 (m); 921 (m); 823 (m); 726 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 362.27 (100) [*M*+Na]$^+$, 367.22 (76), 345.24 (28) [*M*+H]$^+$, 369.24 (16), 285.22 (7).

HRMS (ESI): calculated for $C_{18}H_{36}O_4Si$ [*M*+H]$^+$: 345.2461, found: 345.2460.

3.4.7. (5*R*,7*S*)-9,9-diethyl-7-((*Z*)-3-iodoallyl)-6,6-dimethyl-5-((*E*)-prop-1-en-1-yl)-2,4,8-trioxa-9-silaundecane (14r)



129r

NaHMDS (1 M in THF, 4.2 mL, 4.2 mmol, 1.5 eq) was added dropwise at 0 °C to a solution of IMePPh$_3$I (2.22 g, 4.2 mmol, 1.5 eq) in THF (30 mL). The red solution was stirred for 10 min at room temperature and then cooled to –78 °C. DMPU (2.5 mL, 20.93 mmol, 7.5 eq) was added dropwise, followed by aldehyde **128r** (960 mg, 2.79 mmol, 1 eq) in THF (7 mL). The mixture was stirred for 1 h at –78 °C and 30 min at room temperature. Saturated NH_4Cl solution (30 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 100:1) giving the *Z* Iodide **129r** (875 mg, 1.87 mmol, 67%) as a slightly yellow liquid.

General Data: $C_{19}H_{37}IO_3Si$; FW: 468.16; TLC: R_f = 0.25 (pentane/Et_2O 100:1); UV (–); Vanillin: black; $[\alpha]_D^{20}$ = –30.13 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.36 (q, *J* = 7.3 Hz, 1H, C*H*=CHI); 6.21 (dt, *J* = 7.4, 1.7 Hz, 1H, CH=C*H*I); 5.69-5.58 (m, 1H, C*H*=CH); 5.33 (m, 1H, CH=C*H*); 4.68 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.45 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 3.90-3.84 (m, 2H, 2C*H*OR); 3.36 (s, 3H, OC*H*$_3$); 2.44-2.38 (m, 2H, C*H*$_2$CH); 1.73 (dd, *J* = 6.5, 1.6 Hz, 3H, CHC*H*$_3$); 1.02-0.922 (m, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.944 (s, 3H, 1CC*H*$_3$); 0.769 (s, 3H, 1CC*H*$_3$); 0.658-0.559 (m, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

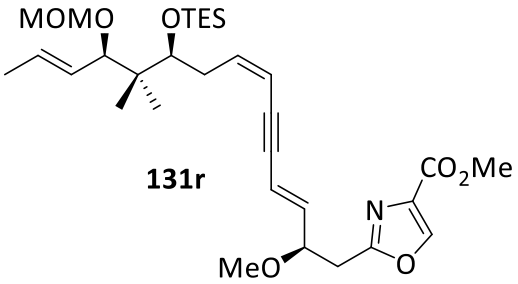
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 140.3 (CH); 131.2 (CH); 127.9 (CH); 93.6 (CH_2); 82.7 (CH); 81.6 (CH); 75.8 (CH); 56.0 (CH_3); 42.8 (C); 38.8 (CH_2); 20.3 (CH_3); 19.7 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 3016 (w); 2919 (m); 2876 (m); 1665 (w); 1465 (m); 1415 (m); 1381 (w); 1238 (m); 1093 (s); 1033 (s); 972 (m); 922 (m); 822 (w); 724 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 506.53 (100), 507.53 (45), 504.51 (22), 469.16 (8) [*M*+H]$^+$, 457.16 (5), 396.31 (4).

HRMS (ESI): calculated for $C_{19}H_{38}IO_3Si$ [*M*+H]$^+$: 469.1635, found: 469.1631.

3.4.8. Methyl 2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (131r)



131r

The vinyl iodide **129r** (397 mg, 0.847 mmol, 1 eq) was dissolved in degassed CH_3CN (5 mL) and CuI (39 mg, 0.254 mmol, 0.3 eq) and $PdCl_2(PPh_3)_2$ (60 mg, 0.0847 mmol, 0.1 eq) were added. The mixture was degassed by freeze-pump-thaw (2 cycles) and then cooled to –15 °C. NEt_3 (0.706 mL, 5.08 mmol, 6 eq) was added, followed by a slow addition of the enyne **130** (240 mg, 1.02 mmol, 1.2 eq) in degassed CH_3CN (3 mL). The solution became red and after 15 min the bath was removed. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted

with Et_2O (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to give the monomer **131r** (414 mg, 0.720 mmol, 85%) as a slightly yellow oil.

General Data: $C_{31}H_{49}NO_7Si$; FW: 575.33; TLC: R_f = 0.20 (pentane/Et_2O 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –13.00 (*c* = 0.8, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.15 (s, 1H, NC=C*H*); 6.14-6.05 (m, 1H, CH_2C*H*=CH); 5.99 (dd, *J* = 15.8, 7.4 Hz, 1H, CC*H*=CHCH); 5.88 (dd, *J* = 15.9, 2.1 Hz, 1H, CC*H*=$CHCH_2$); 5.66-5.54 (m, 2H, $CH(OCH_3)$C*H*=CH, C*H*=$CHCH_3$); 5.36-5.27 (m, 1H, CH=C*H*CH_3); 4.66 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$$OCH_3$); 4.43 (d, *J* = 6.7 Hz, 1H, 1OC*H*$_2$$OCH_3$); 4.20-4.13 (m, 1H, C*H*OCH_3); 3.90 (s, 3H, COOC*H*$_3$); 3.89 (app t, *J* = 6.2 Hz, 1H, C*H*OCH_2OCH_3); 3.82 (t, *J* = 5.3 Hz, 1H, CH_2C*H*OTES); 3.33 (s, 3H, CHOC*H*$_3$); 3.26 (s, 3H, $CHOCH_2$OC*H*$_3$); 3.10 (dd, *J* = 15.0, 7.9 Hz, 1H, 1C*H*$_2$$CHOCH_3$); 2.98 (dd, *J* = 15.0, 5.5 Hz, 1H, 1C*H*$_2$$CHOCH_3$); 2.62-2.54 (m, 2H, C*H*$_2$CH=CH); 1.71 (dd, *J* = 6.4, 1.5 Hz, 3H, CH=CHC*H*$_3$); 0.957 (app t, *J* = 8.0 Hz, 9H, $OSi(CH_2CH_3)_3$); 0.938 (s, 3H, CC*H*$_3$); 0.765 (s, 3H, CC*H*$_3$); 0.600 (q, *J* = 7.8 Hz, 6H, $OSi(CH_2CH_3)_3$).

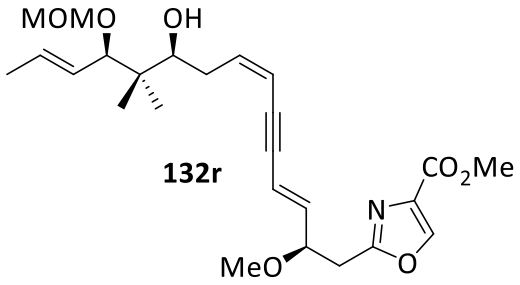
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 143.5 (CH); 140.3 (CH); 133.5 (C); 131.0 (CH); 128.0 (CH); 114.0 (CH); 109.4 (CH); 93.6 (CH_2); 91.3 (C); 88.5 (C); 81.5 (CH); 79.4 (CH); 76.5 (CH); 56.9 (CH_3); 55.9 (CH_3); 52.3 (CH_3); 42.9 (C); 34.7 (CH_2); 34.4 (CH_2); 20.2 (CH_3); 19.7 (CH_3); 18.0 (CH_3); 7.2 (CH_3); 5.7 (CH_2).

IR (neat): 3237 (m); 2954 (m); 2878 (m); 1750 (m); 1583 (m); 1536 (m); 1397 (s); 1238 (m); 1140 (m); 1093 (s); 1033 (s); 1006 (s); 956 (m); 922 (m); 725 (m); 670 (m); 609 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 593.36 (100) $[M+NH_4]^+$, 418.20 (54), 514.30 (48), 350.17 (8), 482.27 (6), 576.33 (2) $[M+H]^+$.

HRMS (ESI): calculated for $C_{31}H_{50}NO_7Si$ $[M+H]^+$: 576.3357, found: 576.3365.

3.4.9. Methyl 2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (132r)



CSA (13 mg, 0.0521 mmol, 0.2 eq) was added at 0 °C to a solution of TES protected monomer **131r** (150 mg, 0.261 mmol, 1 eq) in CH_2Cl_2 (7 mL) and MeOH (7 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated aqueous $NaHCO_3$ solution (15 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 2:1) giving deprotected monomer **132r** (114 mg, 0.248 mmol, 95%) as a slightly yellow oil.

General Data: $C_{25}H_{35}NO_7$; FW: 461.24; TLC: R_f = 0.25 (Et_2O/pentane 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –81.07 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.15 (s, 1H, NC=C*H*); 6.19-6.08 (m, 1H, CH_2CH=CH); 5.96 (dd, *J* = 15.8, 7.3 Hz, 1H, CC*H*=CHCH); 5.86 (dd, *J* = 15.9, 2.0 Hz, 1H, CC*H*=CHCH_2); 5.73-5.61 (m, 2H, CH(OCH_3)C*H*=CH, C*H*=CHCH_3); 5.37-5.27 (m, 1H, CH=C*H*CH_3); 4.71 (d, *J* = 6.7 Hz, 1H, 1OCH_2OCH_3); 4.46 (d, *J* = 6.7 Hz, 1H, 1OCH_2OCH_3); 4.21-4.11 (m, 1H, C*H*OCH_3); 3.90 (s, 3H, COOCH_3); 3.89 (app dd, *J* = 6.7, 2.0 Hz, 1H, C*H*OCH_2OCH_3); 3.62 (dd, *J* = 10.1, 2.8 Hz, 1H, CH_2CHOH); 3.37 (s, 3H, CHOCH_3); 3.26 (s, 3H, $CHOCH_2OCH_3$); 3.10 (dd, *J* = 14.9, 7.8 Hz, 1H, 1CH_2CHOCH_3); 2.99 (dd, *J* = 14.9, 5.6 Hz, 1H, 1CH_2CHOCH_3); 2.61-2.50 (m, 1H, 1CH_2CH=CH); 2.43-2.33 (m, 1H, 1CH_2CH=CH); 1.74 (dd, *J* = 6.5, 1.7 Hz, 3H, CH=CHCH_3); 0.973 (s, 3H, CCH_3); 0.807 (s, 3H, CCH_3).

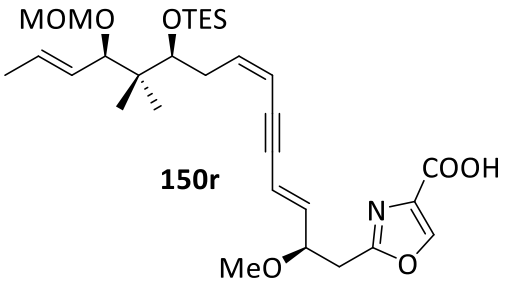
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.5 (C=O); 161.8 (C=N); 144.1 (CH); 142.7 (CH); 140.4 (CH); 133.5 (C); 132.5 (CH); 127.1 (CH); 113.9 (CH); 110.3 (CH); 93.2 (CH_2); 91.2 (C); 88.2 (C); 84.8 (CH); 79.4 (CH); 78.0 (CH); 57.0 (CH_3); 56.2 (CH_3); 52.3 (CH_3); 41.2 (C); 34.7 (CH_2); 33.0 (CH_2); 21.5 (CH_3); 18.0 (CH_3); 16.2 (CH_3).

IR (neat): 3489 (br); 3159 (w); 3020 (m); 2937 (m); 2826 (w); 2246 (w); 1737 (m); 1585 (m); 1438 (m); 1322 (m); 1221 (m); 1167 (m); 1098 (s); 1032 (s); 913 (s); 806 (m); 730 (s); 646 (m); 542 (w) cm^{-1}.

MS (ESI): *m/z* (%): 304.11 (100), 479.27 (80) $[M+NH_4]^+$, 272.09 (77), 400.21 (48), 430.22 (30), 462.24 (28) $[M+H]^+$, 368.18 (27), 209.13 (3).

HRMS (ESI): calculated for $C_{25}H_{36}NO_7$ $[M+H]^+$: 462.2492, found: 462.2482.

3.4.10. 2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylic acid (150r)



150r

131r (150 mg, 0.261 mmol, 1 eq) was dissolved in THF (5 mL) and treated at room temperature with LiOH (1 M in H_2O, 0.783 mL, 0.783 mmol, 3 eq). The mixture was stirred for 3 h at room temperature and neutralized with 1 M HCl (~2 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give acid **150r** (146 mg, 0.259 mmol, 99%) as a slightly yellow oil, which was used for the next step without further purification.

General Data: $C_{30}H_{47}NO_7Si$; FW: 561.31; TLC: UV (+); Vanillin: black.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.23 (s, 1H, NC=C*H*); 6.16-6.07 (m, 1H, CH_2CH=CH); 6.00 (dd, *J* = 15.7, 7.4 Hz, 1H, CC*H*=CHCH); 5.89 (dd, *J* = 15.8, 1.9 Hz, 1H, CC*H*=$CHCH_2$); 5.64-5.56 (m, 2H, $CH(OCH_3)CH$=CH, C*H*=$CHCH_3$); 5.35-5.29 (m, 1H, CH=C*H*CH_3); 4.67 (d, *J* = 6.7 Hz, 1H, $1OCH_2OCH_3$); 4.44 (d, *J* = 6.7 Hz, 1H, $1OCH_2OCH_3$); 4.20-4.15 (m, 1H, C*H*OCH_3); 3.89 (d, *J* = 8.9 Hz, 1H, C*H*OCH_2OCH_3); 3.82 (t, *J* = 5.2 Hz, 1H, C*H*OTES); 3.35 (s, 3H, $CHOCH_3$); 3.28 (s, 3H, $CHOCH_2OCH_3$); 3.12 (dd, *J* = 15.0, 7.8 Hz, 1H, $1CH_2CHOCH_3$); 3.02 (dd, *J* = 15.1, 5.6 Hz, 1H, $1CH_2CHOCH_3$); 2.62-2.54 (m, 2H, $1CH_2CH$=CH); 1.72 (dd, *J* = 6.5, 1.4 Hz, 3H, CH=$CHCH_3$); 0.959 (t, *J* = 8.0 Hz, 9H, $OSi(CH_2CH_3)_3$); 0.943 (s, 3H, CCH_3); 0.771 (s, 3H, CCH_3); 0.604 (q, *J* = 7.9 Hz, 6H, $OSi(CH_2CH_3)_3$).

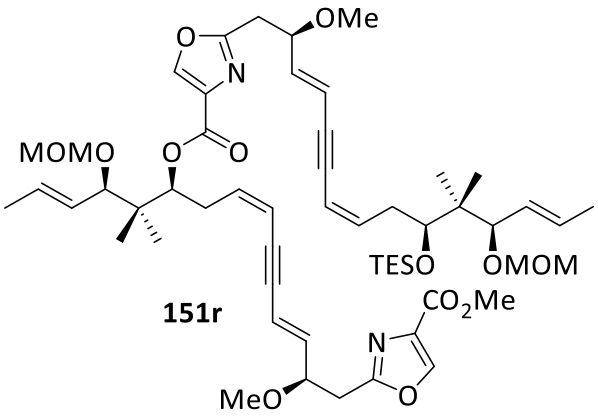
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 164.0 (C=O); 162.8 (C=N); 144.9 (CH); 143.5 (CH); 140.1 (CH); 132.9 (C); 131.0 (CH); 128.0 (CH); 114.1 (CH); 109.4 (CH); 93.5 (CH_2); 91.2 (C); 88.6 (C); 81.6 (CH); 79.3 (CH); 76.6 (CH); 56.9 (CH_3); 55.9 (CH_3); 42.9 (C); 34.4 (CH_2); 30.5 (CH_2); 20.3 (CH_3); 19.7 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 3026 (w); 2934 (br); 2876 (m); 1723 (m); 1586 (m); 1463 (m); 1360 (w); 1214 (w); 1143 (m); 1095 (s); 1033 (s); 973 (m); 921 (m); 766 (m); 6728 (s); 546 (w) cm^{-1}.

MS (ESI): *m/z* (%): 404.18 (100), 579.34 (78) $[M+NH_4]^+$, 500.28 (51), 372.16 (27), 468.25 (10), 336.15 (8), 562.32 (3) $[M+H]^+$.

HRMS (ESI): calculated for $C_{30}H_{48}NO_7Si$ $[M+H]^+$: 562.3200, found: 562.3199.

3.4.11. (2*E*,4*R*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (151r)



151r

The crude acid **150r** (91 mg, 0.162 mmol, 1.5 eq) was dissolved in THF (5 mL) treated at room temperature with NEt_3 (90 µL, 0.648 mmol, 6 eq) and 2,4,6-trichlorobenzoyl chloride (68 µL, 0.432 mmol, 4 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (3 mL) and added dropwise to a solution of alcohol **132r** (50 mg, 0.108 mmol, 1 eq) and DMAP (79 mg, 0.648 mmol, 6 eq) in toluene (5 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with EtOAc (3x10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash

chromatography (Et_2O/pentane 2:1) to afford the dimer **151r** (81 mg, 0.0813 mmol, 75%) as a slightly yellow oil.

General Data: $C_{55}H_{80}N_2O_{13}Si$; FW: 1004.54; TLC: R_f = 0.30 (Et_2O/pentane 2:1); UV (+); Vanillin: black.

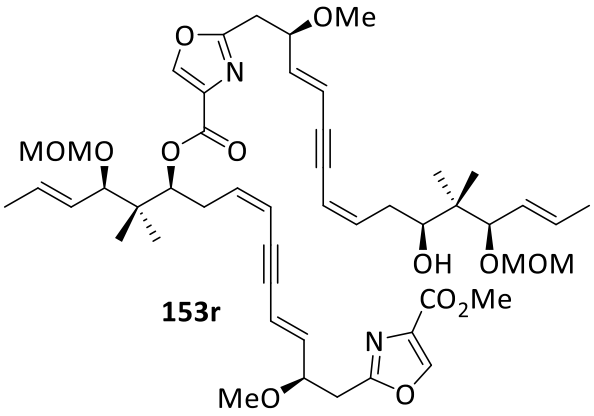
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.18 (s, 1H, NC=C*H*); 8.07 (s, 1H, NC=C*H*); 6.15-6.05 (m, 1H, CH_2CH=CH); 6.05-5.84 (m, 5H, CH=CH); 5.66-5.53 (m, 4H, CH=CH); 5.38-5.29 (m, 2H, CH=CH); 5.28 (app dd, *J* = 5.3, 1.7 Hz, 1H, C*H*OC=O); 4.68 (dd, *J* = 7.0, 6.7 Hz, 2H, $1OCH_2OCH_3$); 4.45 (dd, *J* = 6.9, 4.7 Hz, 2H, $1OCH_2OCH_3$); 4.24-4.14 (m, 2H, $CHOCH_3$); 3.90 (s, 3H, $COOCH_3$); 3.89 (app d, *J* = 7.8 Hz, 1H, $CH_2CHOTES$); 3.82 (m, 2H, $CHOCH_2OCH_3$); 3.38 (s, 3H, $CHOCH_3$); 3.34 (s, 3H, $CHOCH_3$); 3.29 (s, 3H, $CHOCH_2OCH_3$); 3.28 (s, 3H, $CHOCH_2OCH_3$); 3.17-2.98 (m, 4H, CH_2CHOCH_3); 2.76-2.69 (m, 2H, CH_2CH=CH); 2.62-2.56 (m, 2H, CH_2CH=CH); 1.71 (dd, *J* = 6.4, 1.3 Hz, 6H, CH=CHCH_3); 1.02 (s, 3H, CCH_3); 0.977 (s, 3H, CCH_3); 0.951 (app t, *J* = 5.6 Hz, 9H, $OSi(CH_2CH_3)_3$); 0.938 (s, 3H, CCH_3); 0.771 (s, 3H, CCH_3); 0.602 (q, *J* = 7.7 Hz, 6H, $OSi(CH_2CH_3)_3$).

IR (neat): 2953 (m); 2879 (m); 2284 (w); 1737 (m); 1583 (m); 1439 (m); 1318 (m); 1168 (m); 1099 (s); 1033 (s); 911 (s); 807 (m); 728 (s); 647 (m); 551 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 1005.55 (100) $[M+H]^+$, 1022.56 (760) $[M+NH_4]^+$, 943.52 (45), 973.53 (28), 847.43 (8).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{55}H_{81}N_2O_{13}Si$: 1005.5508; found: 1005.5594.

3.4.12. (2*E*,4*R*,6*S*,8*Z*,12*E*,14*R*)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (153r)



153r

CSA (3 mg, 0.0132 mmol, 0.2 eq) was added at 0 °C to a solution TES protected dimer **151r** (67 mg, 0.0661 mmol, 1 eq) in CH_2Cl_2 (2 mL) and MeOH (2 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated $NaHCO_3$ aqueous solution (10 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo giving the deprotected alcohol **153r** as a slightly yellow oil, which was used in the next step without further purification.

General Data: $C_{49}H_{66}N_2O_{13}$; FW: 890.46; TLC: R_f = 0.20 (CH_2Cl_2/MeOH 100:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = –22.83 (*c* = 0.6, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.17 (s, 1H, NC=C*H*); 8.05 (s, 1H, NC=C*H*); 6.19-6.09 (m, 1H, CH_2CH=CH); 6.03-5.83 (m, 5H, CH=CH); 5.70-5.51 (m, 4H, CH=CH); 5.37-5.25 (m, 2H, CH=CH); 5.28 (app dd, *J* = 5.3, 1.7 Hz, 1H, C*H*OC=O); 4.70 (dd, *J* = 15.0, 6.7 Hz, 2H, 1OCH_2OCH$_3$); 4.45 (t, *J* = 6.7 Hz, 2H, 1OCH_2OCH$_3$); 4.22-4.13 (m, 2H, C*H*OCH$_3$); 3.90 (s, 3H, COOCH_3); 3.89 (app d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.82 (d, *J* = 8.7 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.62 (dt, *J* = 10.0, 2.7 Hz, 1H, C*H*OH); 3.37 (s, 6H, CHOCH_3); 3.28 (s, 3H, CHOCH$_2$OCH_3); 3.27 (s, 3H, CHOCH$_2$OCH_3); 3.15-2.96 (m, 4H, CH_2CHOCH$_3$); 2.78-2.64 (m, 2H, CH_2CH=CH); 2.61-2.51 (m, 1H, 1CH_2CH=CH); 2.45-2.33 (m, 1H, 1CH_2CH=CH); 1.74 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHCH_3); 1.71 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHCH_3); 1.02 (s, 3H, CCH_3); 0.977 (s, 3H, CCH_3); 0.944 (s, 3H, CCH_3); 0.813 (s, 3H, CCH_3).

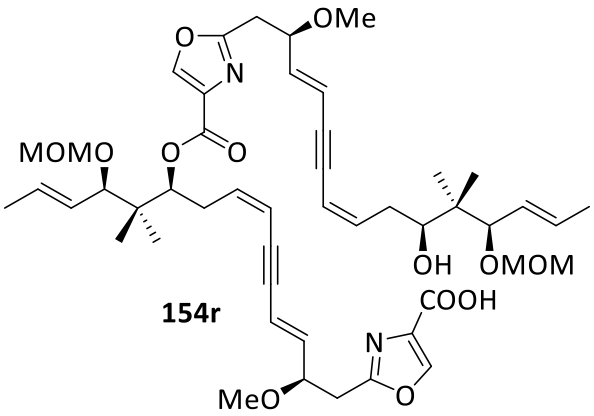
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 162.50 (C=O); 161.76 (C=N); 160.77 (C=N); 144.17 (CH); 143.64 (CH); 142.65 (CH); 140.62 (CH); 140.6 (CH); 133.6 (C); 133.5 (C); 132.5 (CH); 132.3 (CH); 127.1 (CH); 126.9 (CH); 125.6 (CH); 113.8 (CH); 113.7 (CH); 111.2 (CH); 110.3 (CH); 93.5 (CH_2); 93.2 (CH_2); 91.4 (C); 91.3 (C); 88.1 (C); 88.1 (C); 84.9 (CH); 81.5 (CH); 79.3 (CH); 78.0 (CH); 77.4 (CH); 57.0 (CH_3); 57.0 (CH_3); 56.2 (CH_3); 52.3 (CH_3); 41.8 (C); 41.2 (C); 34.7 (CH_2); 34.1 (CH_2); 33.0 (CH_2); 31.2 (CH_2); 21.5 (CH_3); 20.1 (CH_3); 19.6 (CH_3); 18.1 (CH_3); 18.0 (CH_3); 16.2 (CH_3).

IR (neat): 3327 (br); 3165 (w); 2928 (m); 2853 (m); 1736 (s); 1583 (m); 1439 (m); 1370 (m); 1314 (m); 1241 (m); 1143 (m); 1099 (s); 1031 (s); 972 (m); 920 (m); 883 (w); 762 (m); 724 (m); 542 (m) cm^{-1}.

MS (ESI): *m/z* (%): 908.49 (100) [*M*+NH_4]$^+$, 891.46 (83) [*M*+H]$^+$, 733.33 (41), 797.40 (25), 671.29 (7).

HRMS (ESI): calculated for $C_{49}H_{67}N_2O_{13}$ $[M+H]^+$: 891.4643, found: 891.4648.

3.4.13. 2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-10-((2-((2*R*,3*E*,7*Z*,10*S*,12*R*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carbonyl)oxy)-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylic acid (154r)



154r

The crude deprotected alcohol **153r** was dissolved in THF (1.5 mL) and treated at room temperature with LiOH (1 M in H_2O, 0.165 mL, 0.165 mmol, 2.5 eq). The mixture was stirred overnight at room temperature and neutralized with 1 M HCl (~1 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give the *seco*-acid **154r** as a yellow wax, which was used without further purification.

General Data: $C_{48}H_{64}N_2O_{13}$; FW: 876.44; TLC: UV (+); Vanillin: grey; $[\alpha]_D^{20}$ = –26.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.20 (s, 1H, NC=C*H*); 8.10 (s, 1H, NC=C*H*); 6.18-6.09 (m, 1H, CH_2CH=CH); 6.04-5.80 (m, 5H, CH=CH); 5.73-5.52 (m, 4H, CH=CH); 5.38-5.26 (m, 3H, CH=CH, C*H*OC=O); 4.71 (dd, *J* = 13.5, 6.8 Hz, 2H, $1OCH_2OCH_3$); 4.46 (dd, *J* = 6.7, 3.8 Hz, 2H, $1OCH_2OCH_3$); 4.24-4.13 (m, 2H, $CHOCH_3$); 3.90 (d, *J* = 9.1 Hz, 1H, $CHOCH_2OCH_3$); 3.83 (d, *J* = 8.7 Hz, 1H, $CHOCH_2OCH_3$); 3.64 (dd, *J* = 9.8, 2.8 Hz, 1H, C*H*OH); 3.39 (s, 3H, $CHOCH_3$); 3.38 (s, 3H, $CHOCH_3$); 3.30 (s, 3H, $CHOCH_2OCH_3$); 3.28 (s, 3H, $CHOCH_2OCH_3$); 3.18-2.94 (m, 4H, CH_2CHOCH_3); 2.82-2.51 (m, 3H, $3CH_2CH$=CH); 2.47-2.33 (m, 1H, $1CH_2CH$=CH); 1.74 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHCH_3); 1.71 (dd, *J* = 6.4, 1.3 Hz, 3H, CH=CHCH_3); 1.03 (s, 3H, CCH_3); 0.983 (s, 3H, CCH_3); 0.950 (s, 3H, CCH_3); 0.815 (s, 3H, CCH_3).

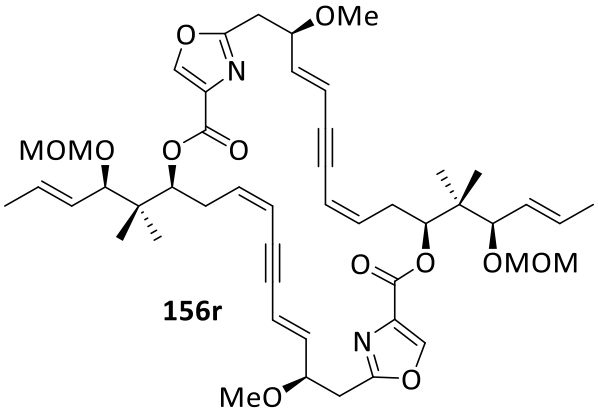
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 162.2 (C=O); 160.7 (C=N); 157.7 (C=N); 144.5 (CH); 143.9 (CH); 142.6 (CH); 140.6 (CH); 140.5 (CH); 133.6 (C); 133.5 (C); 132.6 (CH); 132.4 (CH); 127.0(CH); 126.8 (CH); 125.7 (CH); 113.9 (CH); 113.8 (CH); 111.4 (CH); 110.3 (CH); 93.5 (CH_3); 93.2 (CH_3); 91.4 (C); 91.3 (C); 88.1 (C); 88.1 (C); 84.9 (CH); 81.7 (CH); 79.5 (CH); 79.3 (CH); 78.1 (CH); 77.4 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.2 (CH_3); 56.1 (CH_3); 41.8 (C); 41.2 (C); 34.6 (CH_2); 33.0 (CH_2); 31.3 (CH_2); 29.8 (CH_2); 21.6 (CH_3); 20.0 (CH_3); 19.5 (CH_3); 18.1 (CH_3); 18.0 (CH_3); 16.2 (CH_3).

IR (neat): 3323 (br); 2929 (m); 2851 (m); 2249 (w); 1731 (m); 1583 (m); 1438 (m); 1364 (m); 1310 (m); 1143 (m); 1100 (s); 1030 (s); 972 (m); 910 (m); 837 (w); 730 (s); 646 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 877.44 (100) $[M+H]^+$, 894.47 (77) $[M+NH_4]^+$, 845.42 (49), 719.31 (30), 783.38 (23).

HRMS (ESI): calculated for $C_{48}H_{65}N_2O_{13}$ $[M+H]^+$: 877.4487, found: 877.4478.

3.4.14. (16*R*,16'*R*)-(16,16')-Bis(methoxymethyl))-(9,10,9',10')-tetradehydridodisorazole C_1 (156r)



The crude *seco*-acid **154r** was dissolved in THF (5 mL) and treated at room temperature with NEt_3 (184 µL, 1.32 mmol, 20 eq) and 2,4,6-trichlorobenzoyl chloride (103 µL, 0.661 mmol, 10 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (3 mL) and added dropwise to a solution of DMAP (323 mg, 2.64 mmol, 40 eq) in toluene (80 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (20 mL) and water (20 mL) and the aqueous phase was extracted with EtOAc (3x40 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to afford the macrocycle **156r** (40 mg, 0.0462 mmol, 70% from **151r**) as a slightly yellow oil.

General Data: $C_{48}H_{62}N_2O_{12}$; FW: 858.43; TLC: R_f = 0.50 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +53.7 (*c* = 1.00, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.04 (s, 2H, NC=C*H*); 6.03-5.88 (m, 4H, CH=CH); 5.70-5.47 (m, 6H, CH=CH); 5.44-5.23 (m, 2H, CH=CH); 5.40 (dd, *J* = 11.2, 2.4 Hz, 2H, C*H*OC=O); 4.69 (d, *J* = 7.0 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.45 (d, *J* = 7.0 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.17-3.99 (m, 2H, C*H*OCH$_3$); 3.81 (d, *J* = 8.8 Hz, 2H, C*H*OCH$_2$OCH$_3$); 3.38 (s, 6H, CHOC*H*$_3$); 3.36 (s, 6H, CHOCH$_2$OC*H*$_3$); 3.34-3.25 (m, 2H, C*H*$_2$CH=CH); 3.07-2.83 (m, 4H, C*H*$_2$CHOCH$_3$); 2.53-2.43 (m, 2H, C*H*$_2$CH=CH); 1.73 (dd, *J* = 6.3, 1.3 Hz, 6H, CH=CHC*H*$_3$); 1.03 (s, 6H, CC*H*$_3$); 0.962 (s, 6H, CC*H*$_3$).

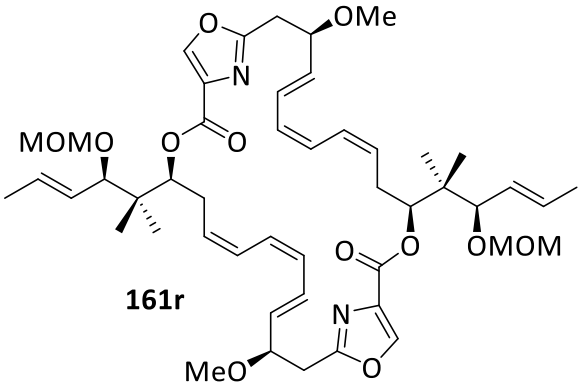
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 161.8 (C=O); 160.7 (C=N); 143.5 (CH); 141.3 (CH); 140.4 (CH); 133.7 (C); 132.5 (CH); 126.8 (CH); 113.6 (CH); 112.2 (CH); 93.5 (CH_2); 90.9 (C); 87.9 (C); 81.6 (CH); 79.7 (CH); 77.4 (CH); 57.0 (CH_3); 56.2 (CH_3); 41.6 (C); 34.5 (CH_2); 31.1 (CH_2); 20.0 (CH_3); 19.4 (CH_3); 18.1 (CH_3).

IR (neat): 3168 (w); 2933 (m); 2855 (m); 2249 (w); 1736 (m); 1690 (m); 1582 (m); 1441 (m); 1365 (m); 1308 (m); 1141 (m); 1099 (s); 1028 (s); 988 (m); 914 (m); 805 (m); 730 (s) cm^{-1}.

MS (ESI): *m/z* (%): 859.43 (100) [*M*+H]$^+$, 876.46 (32) [*M*+NH$_4$]$^+$, 797.40 (20), 735.36 (3).

HRMS (ESI): calculated for $C_{48}H_{65}N_2O_{13}$ [*M*+H]$^+$: 859.4381, found: 859.4366.

3.4.15. (16*R*,16'*R*)-(16,16')-Bis(methoxymethyl))-disorazole C$_1$ (161r)



161r

Nitrogen was bubbled for 15 min through a suspension of zinc dust (3 g, 45.88 mmol) in H_2O (18 mL) and then $Cu(OAc)_2 \cdot H_2O$ (300 mg, 1.50 mmol) was added at room temperature and after 15 min $AgNO_3$ (300 mg, 1.77 mmol) was added (exothermic reaction). The mixture was stirred for 30 min at room temperature, filtered by suction and washed with H_2O (30 mL), MeOH (20 mL), acetone (20 mL) and Et_2O (20 mL). This activated zinc solids were added to a solution of **156r** (20 mg, 0.0233 mmol) in MeOH/H_2O 1:1 (5 mL). The mixture was stirred for 24 h at 50 °C and then filtered on a pad of silica and washed with MeOH. The filtrate was

concentrated in vacuo and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 60:1) to afford **161r** (13 mg, 0.0151, 65%) as a colorless oil.

General Data: $C_{48}H_{66}N_2O_{12}$; FW: 862.46; TLC: R_f = 0.40 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –43.3 (*c* = 0.35, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.89 (s, 2H, NC=C*H*); 6.44 (dd, *J* = 15.2, 11.3 Hz, 2H, CH(OCH3)CH=C*H*); 6.34 (app t, *J* = 11.3 Hz, 2H, CH2CH=C*H*); 6.21 (dd, *J* = 11.5, 11.0 Hz, 2H, CHC*H*=CHCH); 5.90 (dd, *J* = 11.2, 11.0 Hz, 2H, CHCH=C*H*CH); 5.61 (dd, *J* = 15.4, 6.5 Hz, 2H, CH3C*H*=CH); 5.54 (dd, *J* = 15.1, 8.6 Hz, 2H, CH3CH=C*H*); 5.38 (dd, *J* = 10.8, 2.5 Hz, 2H, C*H*OC=O); 5.32 (dd, *J* = 8.8, 1.7 Hz, 2H, CH(OCH3)C*H*=CH); 5.29 (dd, *J* = 8.6, 1.5 Hz, 2H, CH2C*H*=CH); 4.68 (d, *J* = 6.9 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.43 (d, *J* = 6.9 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.15-4.10 (app q, *J* = 14.9, 6.7 Hz, 2H, C*H*OCH3); 3.81 (d, *J* = 8.7 Hz, 2H, C*H*OH); 3.36 (s, 6H, CHOCH$_2$OC*H*$_3$); 3.26 (s, 6H, CHOC*H*$_3$); 3.12 (dd, *J* = 14.8, 6.0 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.78 (dd, *J* = 14.8, 7.2 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.63-2.50 (m, 4H, C*H*$_2$CH=CH); 1.73 (dd, *J* = 6.5, 1.3 Hz, 3H, CH=CHC*H*$_3$); 0.984 (s, 6H, CC*H*$_3$); 0.919 (s, 6H, CC*H*$_3$).

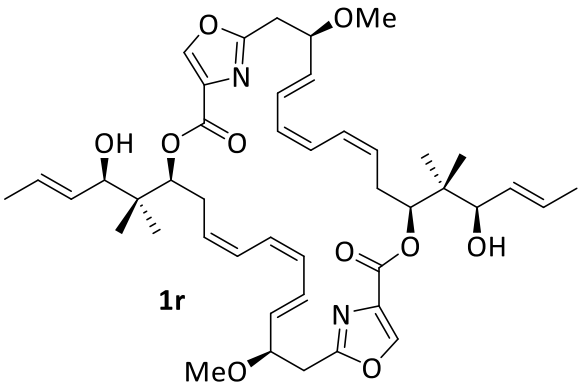
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.4 (C=O); 160.7 (C=N); 143.3 (CH); 133.5 (C); 133.2 (CH); 132.4 (CH); 130.3 (CH); 129.1 (CH); 128.1 (CH); 126.9 (CH); 125.7 (CH); 125.7 (CH); 93.4 (CH_2); 81.4 (CH); 79.9 (CH); 77.6 (CH); 56.7 (CH_3); 56.3 (CH_3); 41.6 (C); 35.2 (CH_2); 28.1 (CH_2); 20.1 (CH_3); 19.6 (CH_3); 18.1 (CH_3).

IR (neat): 2927 (m); 2855 (m); 1727 (m); 1583 (m); 1442 (w); 1370 (w); 1315 (w); 1262 (w); 1104 (s); 1012 (m); 805 (m); 757 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 861.46 (100) [*M*+H]$^+$, 282.28 (70), 880.49 (32) [*M*+NH_4]$^+$.

HRMS (ESI): calculated for $C_{48}H_{67}N_2O_{12}$ [*M*+H]$^+$: 863.4694, found 863.4672.

3.4.16. (16*R*,16'*R*)-Disorazole C_1 (1r)



1r

MOM protected **161r** (16 mg, 18.45 µmol) was dissolved in CH_3CN (2 mL) and cooled to 0 °C. 2 drops of HBr (48% in H_2O) were slowly added and then the mixture was stirred for 1 h at 0 °C. The mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with EtOAc (3x5 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 50:1) to give (14*R*,14'*R*)-Disorazole C_1 **1r** (8 mg, 12.9, 10.33 µmol, 56%) as a colorless wax.

General Data: $C_{44}H_{58}N_2O_{10}$; FW: 774.41; TLC: R_f = 0.20 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –42.6 (*c* = 0.15, MeOH).

^{1}H-NMR (600 MHz, CD_3OD): δ (ppm): 8.23 (s, 2H, NC=C*H*); 6.51 (dd, *J* = 14.9, 11.3 Hz, 2H, CH(OCH_3)CH=C*H*); 6.41 (app t, *J* = 11.2 Hz, 2H, CH2CH=C*H*); 6.29 (dd, *J* = 11.3, 11.1 Hz, 2H, CHC*H*=CHCH); 5.91 (dd, *J* = 11.3, 11.0 Hz, 2H, CHCH=C*H*CH); 5.64 (dq, *J* = 15.1, 6.3 Hz, 2H, CH3C*H*=CH); 5.57 (ddd, *J* = 15.4, 7.6, 1.5 Hz, 2H, CH3CH=C*H*); 5.53 (dd, *J* = 15.1, 8.3 Hz, 2H, CH(OCH3)C*H*=CH); 5.48 (app dt, *J* = 10.0, 6.7 Hz, 2H, CH2C*H*=CH); 5.29 (dd, *J* = 11.3, 2.1 Hz, 2H, C*H*OC=O); 4.13 (ddd, *J* = 7.9, 7.2, 5.1 Hz, 2H, C*H*OCH3); 3.91 (d, *J* = 7.3 Hz, 2H, C*H*OH); 3.21 (s, 6H, CHOC*H*$_3$); 2.99 (dd, *J* = 15.5, 7.3 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.75 (dd, *J* = 15.6, 5.0 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.71 (ddd, *J* = 13.8, 10.9, 10.1 Hz, 2H, C*H*$_2$CH=CH); 2.45 (dd, *J* = 13.1, 6.1 Hz, 2H, C*H*$_2$CH=CH); 1.71 (dd, *J* = 6.1, 1.1 Hz, 6H, CH=CHC*H*$_3$); 0.991 (s, 6H, CC*H*$_3$); 0.953 (s, 6H, CC*H*$_3$).

^{13}C-NMR (151 MHz, CD_3OD): δ (ppm): 164.1 (C=O); 162.3 (C=N); 145.8 (CH); 134.1 (C); 134.1 (CH); 131.5 (CH); 131.0 (CH); 130.0 (CH); 129.6 (CH); 129.2 (CH); 127.4 (CH); 126.9 (CH); 80.5 (CH); 79.2 (CH); 78.0 (CH); 56.8 (CH_3); 42.7 (C); 36.0 (CH_2); 29.2 (CH_2); 19.7 (CH_3); 19.7 (CH_3); 18.0 (CH_3).

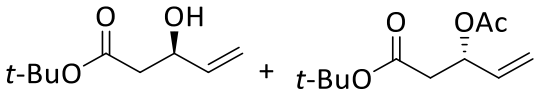
IR (neat): 3419 (br); 2924 (m); 2854 (m); 1723 (m); 1583 (m); 1447 (w); 1367 (w); 1312 (w); 1261 (w); 1101 (s); 1010 (m); 803 (m); 758 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 775.41 (100) $[M+H]^+$, 792.44 (48) $[M+NH_4]^+$, 757.40 (11), 771.36 (8), 693.35 (4).

HRMS (ESI): calculated for $C_{44}H_{59}N_2O_{10}$ $[M+H]^+$: 775.4170, found 775.4175.

3.5. Synthesis of (6*S*,6'*S*)-Disorazole C_1 (1s)

3.5.1. *tert*-Butyl (*S*)-3-acetoxypent-4-enoate [(*S*)-140]



(*R*)-137 **(*S*)-140**

Vinyl acetate (16 mL, 174.18 mmol, 3 eq) was added to a solution of racemic *tert*-Butyl 3-hydroxypent-4-enoate **137** (10 g, 58.06 mmol, 1 eq) in pentane (200 mL). Then Amano Lipase PS (6 g) and 4Å molecular sieves (9.5 g) were added and the mixture was stirred for 24 h at 30 °C. The solids were filtered on paper and washed with Et_2O; the filtrate was concentrated in vacuo and the residue purified by flash chromatography (pentane/Et_2O 6:1 to 2:1) to afford **(*R*)-137** (4.71 g, 27.35 mmol, 47%) and **(*S*)-140** (6.04 g, 28.22 mmol, 48%) as colorless liquids.

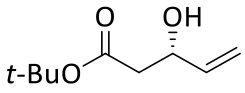
General Data: $C_{11}H_{18}O_4$; FW: 214.12; TLC: R_f = 0.20 (pentane/Et_2O 6:1); UV (–); Vanillin: blue; $[\alpha]_D^{20}$ = –4.8 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.87-5.76 (m, 1H, C*H*=CH_2); 5.63-5.55 (m, 1H, C*H*OAc); 5.29 (dt, *J* = 17.3, 1.2 Hz, 1H, 1CH=C*H*$_2$); 5.20 (dt, *J* = 10.5, 1.1 Hz, 1H, 1CH=C*H*$_2$); 2.89 (s, 1H, CHO*H*); 2.59 (dd, *J* = 15.3, 8.1 Hz, 1H, 1C*H*$_2$CH); 2.51 (dd, *J* = 15.3, 5.8 Hz, 1H, 1C*H*$_2$CH); 2.05 (s, 3H, C*H*$_3$CO); 1.43 (s, 9H, OC(C*H*$_3$)$_3$)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 169.9 (C=O); 169.1 (C=O); 135.3 (CH); 117.4 (CH_2); 81.2 (C); 71.2 (CH); 40.8 (CH_2); 28.1 (C(*C*H$_3$)$_3$); 21.2 (CO*C*H$_3$).

IR (neat): 2982 (m); 2930 (w); 1724 (s); 1369 (m); 1152 (s); 922 (m) cm^{-1}.

3.5.2. *tert*-Butyl (*S*)-3-hydroxypent-4-enoate [(*S*)-137]



(*S*)-137

K_2CO_3 (14 g, 100.93 mmol, 2 eq) was added to a solution of **(*S*)-140** (10.8 g, 50.47 mmol, 1 eq) in MeOH (100 mL) at 0 °C and the mixture was stirred for 30 min at 0 °C. Then the solid was filtered off on a paper filter and washed with Et_2O. The filtrate was washed with H_2O (50 mL) and Brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (pentane/Et_2O 2:1) affording **(*S*)-137** (6.95 g, 40.37 mmol, 80%) as a colorless liquid.

General Data: $C_9H_{16}O_3$; FW: 172.11; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (–); Vanillin: light blue; $[\alpha]_D^{20}$ = –8.7 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.89-5.80 (m, 1H, C*H*=CH_2); 5.29 (dt, *J* = 17.2, 1.5 Hz, 1H, 1CH=C*H*$_2$); 5.13 (dt, *J* = 10.5, 1.4 Hz, 1H, 1CH=C*H*$_2$); 4.49-4.43 (m, 1H, C*H*OH); 2.89 (s, 1H, CHO*H*); 2.50 (dd, *J* = 16.1, 4.0 Hz, 1H, 1C*H*$_2$CH); 2.41 (dd, *J* = 16.1, 8.2 Hz, 1H, 1C*H*$_2$CH); 1.45 (s, 9H, OC(C*H*$_3$)$_3$)).

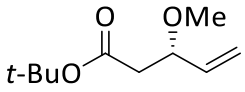
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.8 (C=O); 139.0 (CH); 115.3 (CH_2); 81.6 (C); 69.2 (CH); 42.2 (CH_2); 28.2 (C(*C*H_3)$_3$).

IR (neat): 3438 (br); 2980 (m); 2933 (w); 1726 (s); 1367 (m); 1152 (s); 922 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 173.12 (100) [*M*+H]$^+$, 117.05 (96), 190.14 (43) [*M*+Na]$^+$, 195.10 (23), 367.21 (18).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_9H_{17}O_3$: 173.1178; found: 173.1183.

3.5.3. *tert*-Butyl (*S*)-3-Methoxypent-4-enoate (141s)



141s

Proton Sponge® (22.4 g, 104.52 mmol, 3 eq) and trimethyloxonium tetrafluoroborate (10.3 g, 69.68 mmol, 2 eq) were added to a solution of **(*S*)-137** (6 g, 34.84 mmol, 1 eq) in CH_2Cl_2 (150 mL) and the mixture was stirred for 3 h at room temperature. The reaction mixture was then filtered through a pad of Celite and the filtrate was washed with saturated aqueous solution of $NaHSO_4$ to remove Proton Sponge. The aqueous phase was extracted with CH_2Cl_2 and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (pentane/Et_2O 20:1, then 2:1) to give **141s** (4.66 g, 25.08 mmol, 72%) as a colorless liquid and unreacted alcohol **(*S*)-137** (900 mg, 5.23 mmol, 15%).

General Data: $C_{10}H_{18}O_3$; FW: 186.13; TLC: R_f = 0.30 (pentane/Et_2O 20:1); UV (–); Vanillin: dark blue; $[\alpha]_D^{20}$ = –0.7 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.72-5.65 (m, 1H, C*H*=CH_2); 5.27 (dt, *J* = 17.1, 1.4 Hz, 1H, 1CH=C*H*$_2$); 5.21 (dt, *J* = 10.5, 1.2 Hz, 1H, 1CH=C*H*$_2$); 4.00-3.93 (m, 1H, C*H*OCH_3); 3.28 (s, 3H,

OC*H*$_3$); 2.51 (dd, *J* = 15.0, 8.1 Hz, 1H, 1C*H*$_2$CH); 2.36 (dd, *J* = 15.0, 5.7 Hz, 1H, 1C*H*$_2$CH); 1.44 (s, 9H, OC(C*H*$_3$)$_3$)).

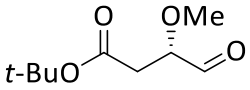
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.3 (C=O); 137.3 (CH); 117.8 (CH_2); 80.7 (C); 79.5 (CH); 56.6 (CH_3); 42.3 (CH_2); 28.2 (C(*C*H$_3$)$_3$).

IR (neat): 2979 (m); 2927 (m); 1732 (s); 1457 (m); 1392 (m); 1367 (m); 1280 (m); 1254 (m); 1156 (s); 1102 (s); 1018 (w); 991 (m); 928 (m); 845 (m); 765 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 131.07 (100), 113.06 (25), 279.17 (15), 187.13 (9) [*M*+H]$^+$, 252.23 (6)

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{10}H_{19}O_3$: 187.1334; found: 187.1336.

3.5.4. *tert*-Butyl (*S*)-3-methoxy-4-oxobutanoate (142s)



142s

A stream of O_3 in O_2 was bubbled through a solution of **141s** (3.73 g, 20.05 mmol, 1 eq) in CH_2Cl_2 (75 mL) and MeOH (15 mL) at –78 °C until the blue color of the solution persisted. Then O_2 was bubbled for 10 min and PPh_3 (6.3 g, 24.06 mmol, 1.2 eq) was added. The mixture was warmed to room temperature and stirred for 2 h. The solvents were removed in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 2:1) to afford aldehyde **142s** (3.47 g, 18.45 mmol, 92%) as a colorless liquid.

General Data: $C_9H_{16}O_4$; FW: 188.10; TLC: R_f = 0.25 (pentane/Et_2O 2:1); UV (–); Vanillin: yellow; $[\alpha]_D^{20}$ = –38.6 (*c* = 1.1, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.76 (s, 1H, C*H*O); 3.93-3.89 (m, 1H, C*H*OCH$_3$); 3.50 (s, 3H, OC*H*$_3$); 2.69 (dd, *J* = 16.2, 4.8 Hz, 1H, 1C*H*$_2$CH); 2.60 (dd, *J* = 16.1, 6.6 Hz, 1H, 1C*H*$_2$CH); 1.44 (s, 9H, OC(C*H*$_3$)$_3$)).

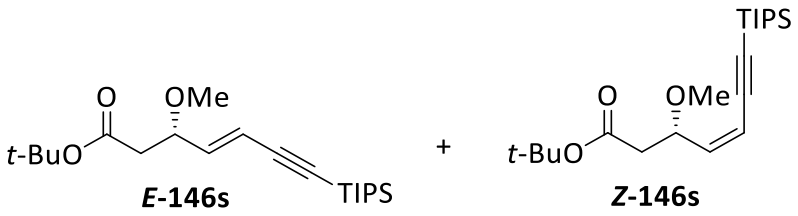
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 202.1 (CHO); 169.3 (C=O); 82.2 (C); 81.8 (CH); 58.8 (CH_3); 37.1 (CH_2); 28.2 (C(*C*H$_3$)$_3$).

IR (neat): 2979 (m); 2933 (m); 2832 (w); 1729 (s); 1456 (w); 1368 (m); 1256 (m); 1113 (s); 1076 (m); 953 (w); 846 (w) cm^{-1}.

MS (EI, 70eV): *m*/*z* (%): 189.11 (100) [*M*+H]$^+$, 187.10 (23), 188.10 (23) [*M*]$^+$, 190.09 (22).

HRMS (EI, 70eV) *m*/*z*: [*M*+H]$^+$ Calcd for $C_9H_{17}O_4$: 189.1121; found: 189.1116.

3.5.5. *tert*-Butyl (*S,E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynoate (*E*-146s)



***E*-146s** **Z-146s**

n-BuLi (2.5 M solution in hexane, 10.7 mL, 26.79 mmol, 1.4 eq) was added dropwise to a suspension of TIPS propargyl triphenylphosphonium bromide **143a** (12.3 g, 22.97 mmol, 1.2 eq) in THF (125 mL) at –78 °C. The red solution was stirred at 0 °C for 30 min and then aldehyde **142s** (3.6 g, 19.14 mmol, 1 eq) in THF (15 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (100 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3x80 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 40:1 to 30:1) gave ***E*-146s** (4.2 g, 11.48 mmol, 60%) and ***Z*-146s** (1.54 g, 4.21 mmol, 22%).

General Data: $C_{21}H_{38}O_3Si$; FW: 366.26; TLC: R_f = 0.45 (pentane/Et_2O 20:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = –6.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.01 (dd, *J* = 15.8, 7.2 Hz, 1H, C*H*=CH); 5.76 (dd, *J* = 15.9, 1.0 Hz, 1H, CH=C*H*); 4.04-3.98 (m, 1H, C*H*OCH_3); 3.30 (s, 3H, OC*H*$_3$); 2.50 (dd, *J* = 14.9, 7.9 Hz, 1H, 1C*H*$_2$CH); 2.37 (dd, *J* = 14.9, 5.6 Hz, 1H, 1C*H*$_2$CH); 1.44 (s, 9H, OC(C*H*$_3$)$_3$)); 1.07 (s, 21H, Si(C*H*(C*H*$_3$))$_3$).

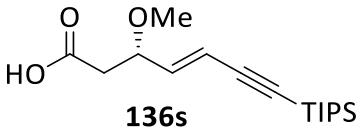
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 169.9 (C=O); 142.5 (CH); 112.9 (CH); 104.6 (C); 92.2 (C); 81.0 (C); 78.5 (CH); 57.1 (CH_3); 42.0 (CH_3); 28.2 (C(*C*H$_3$)$_3$); 18.7 (CH_3); 11.4 (CH).

IR (neat): 2942 (s); 2866 (s); 2148 (w); 1927 (w); 1732 (s); 1627 (w); 1463 (m); 1367 (m); 1244 (m); 1150 (s); 1102 (m); 996 (m); 882 (m); 673 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 279.18 (100), 311.20 (24), 384.29 (23), 367.26 (10) [*M*+H]$^+$, 219.12 (6), 172.11 (3).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{21}H_{39}O_3Si$: 367.2668; found: 367.2668.

3.5.6. (*S,E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynoic acid (136s)



136s

A solution of ***E*-146s** (3.84 g, 10.48 mmol) in formic acid (16 mL) was stirred overnight at room temperature. The mixture was then concentrated in vacuo and azeotropically dried with toluene for three times to remove formic acid. Crude carboxylic acid **136s** was used in the next step without further purification.

General Data: $C_{17}H_{30}O_3Si$; FW: 310.20; TLC: R_f = 0.3 (pentane/Et_2O 5:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = –9.2 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.02 (dd, *J* = 16.0, 7.4 Hz, 1H, C*H*=CH); 5.81 (dd, *J* = 16.0, 1.1 Hz, 1H, CH=C*H*); 4.11-4.04 (m, 1H, C*H*OCH_3); 3.33 (s, 3H, OC*H*$_3$); 2.62 (dd, *J* = 15.8, 8.5 Hz, 1H, 1C*H*$_2$CH); 2.54 (dd, *J* = 15.8, 4.7 Hz, 1H, 1C*H*$_2$CH); 1.07 (s, 21H, Si(C*H*(C*H*$_3$))$_3$).

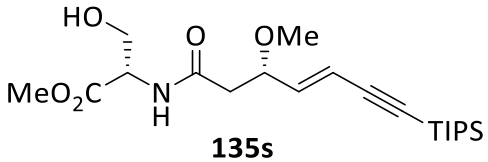
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 174.7 (C=O); 141.4 (CH); 113.8 (CH); 104.1 (C); 92.9 (C); 77.9 (CH); 57.2 (CH_3); 40.4 (CH_2); 18.8 (CH_3); 11.4 (CH).

IR (neat): 2921 (s); 2865 (s); 2142 (w); 1714 (s); 1641 (m); 1563 (w); 1462 (m); 1377 (w); 1240 (m); 1100 (s); 996 (m); 958 (m); 882 (m); 674 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 328.23 (100) [*M*+NH_4]$^+$, 279.17 (43), 638.42 (23), 311.20 (19) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{17}H_{31}O_3Si$: 311.2042; found: 311.2043.

3.5.7. Methyl ((*S,E*)-3-methoxy-7-(triisopropylsilyl)hept-4-en-6-ynoyl)-L-serinate (135s)



135s

DIPEA (3.4 mL, 19.32 mmol, 2.3 eq) and TFFH (2.44 g, 9.24 mmol, 1.1 eq) were added to a solution of the crude carboxylic acid **136s** (2.7 g, 8.74 mmol, 1 eq) in THF (30 mL) and the mixture was stirred for 2 h at room temperature. L-serine methyl ester hydrochloride (1.56 g, 10.08 mmol, 1.2 eq) was added and the mixture was stirred for 3 h. Et_2O (20 mL) was added and the solution was washed with 1 M HCl (40 mL). The aqueous phase was extracted with Et_2O (3x40 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in

vacuo. Purification of the residue by flash chromatography (Et_2O) afforded the serinate **135s** (2.82 g, 6.86 mmol, 82%) as a yellow oil.

General Data: $C_{21}H_{37}NO_5Si$; FW: 411.24; TLC: R_f = 0.25 (Et_2O); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = –15.0 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (600 MHz, CD_3OD): δ (ppm): 7.90 (s, 1H, N*H*); 6.09 (dd, *J* = 16.0, 7.1 Hz, 1H, C*H*=CH); 5.84 (dd, *J* = 16.0, 1.0 Hz, 1H, CH=C*H*); 4.53 (t, *J* = 4.5 Hz, 1H, COC*H*NH); 4.14-4.07 (m, 1H, C*H*OCH_3); 3.89 (dd, *J* = 11.2, 4.7 Hz, 1H, CH_2OH); 3.78 (dd, *J* = 11.2, 4.2 Hz, 1H, CH_2OH); 3.74 (s, 3H, COOCH_3); 3.31 (s, 3H, CHOCH_3); 2.55 (dd, *J* = 14.6, 8.1 Hz, 1H, 1CH_2CH); 2.46 (dd, *J* = 14.6, 5.1 Hz, 1H, 1CH_2CH); 1.10 (s, 21H, Si(C*H*(CH_3))$_3$).

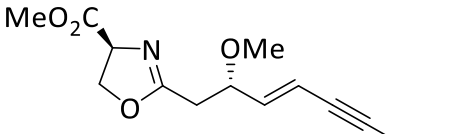
^{13}C-NMR (151 MHz, CD_3OD): δ (ppm): 172.7 (C=O); 172.2 (C=O); 144.0 (CH); 113.6 (CH); 106.1 (C); 92.5 (C); 79.6 (CH); 62.8 (CH_2); 57.3 (CH); 56.2 (CH_3); 52.8 (CH_3); 42.7 (CH_2); 19.0 (CH_3); 12.5 (CH).

IR (neat): 3343 (br); 2943 (m); 2865 (m); 2129 (w); 2048 (w); 1745 (m); 1650 (m); 1538 (m); 1462 (m); 1364 (w); 1213 (m); 1074 (m); 959 (w); 882 (m); 675 (m) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%): 411.24 (100) $[M]^+$, 396.22 (67), 412.25 (28), 397.22 (22), 393.24 (17).

HRMS (EI, 70eV) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{37}NO_5Si$: 411.2436; found: 411.2442.

3.5.7. Methyl (*S*)-2-((*S*,*E*)-2-methoxy-6-(triisopropylsilyl)hex-3-en-5-yn-1-yl)-4,5-dihydrooxazole-4-carboxylate (147s)



147s

DAST (0.980 mL, 7.41 mmol, 1.1 eq) was added dropwise to a solution of serinate **135s** (2.77 g, 6.74 mmol, 1 eq) in CH_2Cl_2 (60 mL) at –78 °C and the mixture was stirred for 2 h at – 78 °C. K_2CO_3 (1.86 g, 13.48 mmol, 2 eq) was added and the mixture was warmed to room temperature and stirred for 1 h. A saturated aqueous solution of NH_4Cl (50 mL) was carefully added and, after the gas evolution ceased, the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x50 mL) and the combined organic extracts were washed with brine,

dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product **147s** as a yellow oil, which was used for the next step without further purification.

General Data: $C_{21}H_{35}NO_4Si$; FW: 393.23; TLC: R_f = 0.5 (Et_2O); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +32.94 (*c* = 0.85, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.03 (dd, *J* = 15.8, 7.3 Hz, 1H, C*H*=CH); 5.78 (dd, *J* = 16.0, 1.0 Hz, 1H, CH=C*H*); 4.78-4.73 (m, 1H, OCH_2CHCO); 4.49 (dd, *J* = 8.8, 7.9 Hz, 1H, $1OCH_2CHCO$); 4.41 (dd, *J* = 10.6, 8.7 Hz, 1H, $1OCH_2CHCO$); 4.09-4.03 (m, 1H, $CHOCH_3$); 3.79 (s, 3H, $COOCH_3$); 3.30 (s, 3H, $CHOCH_3$); 2.65-2.60 (m, 1H, $1CH_2CH$); 2.55-5.47 (m, 1H, $1CH_2CH$); 1.07 (s, 21H, $Si(CH(CH_3))_3$).

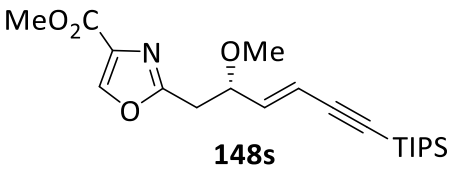
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.7 (C=N); 167.7 (C=O); 142.2 (CH); 113.3 (CH); 104.4 (C); 92.5 (C); 78.6 (CH); 69.6 (CH); 68.2 (CH_2); 57.1 (CH_3); 52.8 (CH_3); 34.4 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 3738 (w); 3649 (w); 2980 (s); 2890 (m); 2866 (m); 2328 (w); 2130 (w); 1743 (m); 1628 (w); 1462 (m); 1384 (m); 1250 (m); 1156 (m); 1073 (m); 994 (m); 956 (m); 882 (m); 664 (m) cm^{-1}.

MS (EI, 70eV): *m*/*z* (%): 350.16 (100), 337.22 (96), 361.18 (87), 393.23 (45) $[M]^+$, 368.17 (43), 362.19 (36), 351.17 (35).

HRMS (EI, 70eV) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{35}NO_4Si$: 393.2330; found: 393.2334.

3.5.8. Methyl (*S,E*)-2-(2-methoxy-6-(triisopropylsilyl)hex-3-en-5-yn-1-yl)oxazole-4-carboxylate (148s)



148s

The crude material **147s** was dissolved in CH_2Cl_2 (50 mL), cooled to 0 °C and protected from light with aluminium foil. DBU (1.94 mL, 12.94 mmol, 2 eq) and $BrCCl_3$ (1.28 mL, 12.94 mmol, 2 eq) were sequentially added dropwise, then the bath was removed and the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x100 mL) and the organic layers were dried over Na_2SO_4, filtered and

concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1) afforded oxazole **148s** (1.63 g, 4.17 mmol, 62% from **135s**) as a yellow oil.

General Data: $C_{21}H_{33}NO_4Si$; FW: 391.22; TLC: R_f = 0.35 (pentane/Et_2O 2:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +16.4 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.04 (dd, *J* = 15.8, 7.4 Hz, 1H, C*H*=CH); 5.77 (dd, *J* = 15.9, 1.0 Hz, 1H, CH=C*H*); 4.18-4.11 (m, 1H, C*H*OCH_3); 3.90 (s, 3H, COOC*H*$_3$); 3.26 (s, 3H, CHOC*H*$_3$); 3.08 (dd, *J* = 15.1, 8.1 Hz, 1H, 1C*H*$_2$CH); 2.99 (dd, *J* = 15.1, 5.3 Hz, 1H, 1C*H*$_2$CH); 1.07 (s, 21H, Si(C*H*(C*H*$_3$))$_3$).

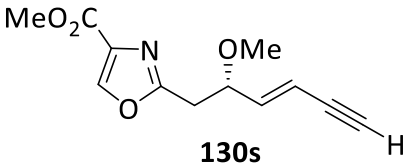
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 141.7 (CH); 133.5 (C); 113.8 (CH); 104.1 (C); 92.9 (C); 79.3 (CH); 57.1 (CH_3); 52.3 (CH_3); 34.6 (CH_2); 18.7 (CH_3); 11.4 (CH).

IR (neat): 3867 (w); 3738 (w); 3649 (w); 2980 (s); 2866 (m); 2328 (w); 2137 (w); 1747 (m); 1584 (m); 1462 (m); 1384 (m); 1323 (m); 1239 (m); 1165 (m); 1107 (m); 997 (m); 956 (m); 882 (m); 763 (m); 664 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 360.20 (100), 392.22 (65) [*M*+H]$^+$, 414.20 (20) [*M*+Na]$^+$, 805.42 (4)

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{21}H_{34}NO_4Si$: 392.2257; found: 392.2259.

3.5.9. Methyl (*S,E*)-2-(2-methoxyhex-3-en-5-yn-1-yl)oxazole-4-carboxylate (130s)



130s

TBAF (1 M in THF, 1.26 mL, 1.26 mmol, 1.1 eq) was added dropwise at 0 °C to a solution of TIPS oxazole **148s** (450 mg, 1.15 mmol, 1 eq) in THF (15 mL). The mixture was stirred for 30 min at room temperature and then quenched with water (15 mL). The aqueous phase was extracted with Et_2O (3x10 mL) and the organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1 to 1:1) afforded oxazole **130s** (190 mg, 0.808 mmol, 70%) as a yellow oil.

General Data: $C_{12}H_{13}NO_4$; FW: 235.08; TLC: R_f = 0.30 (pentane/Et_2O 1:1); UV (+); Vanillin: brown; $[\alpha]_D^{20}$ = +24.6 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.10 (ddd, *J* = 16.0, 7.4, 0.5 Hz, 1H, C*H*=CH); 5.70 (ddd, *J* = 16.0, 2.3, 1.0 Hz, 1H, CH=C*H*); 4.19-4.12 (m, 1H, C*H*OCH_3); 3.89 (s, 3H, COOC*H*$_3$); 3.26 (s, 3H, CHOC*H*$_3$); 3.08 (dd, *J* = 15.1, 7.8 Hz, 1H, 1C*H*$_2$CH); 2.98 (dd, *J* = 15.0, 5.8 Hz, 1H, 1C*H*$_2$CH); 2.92 (d, *J* = 2.3 Hz, 1H, CC*H*).

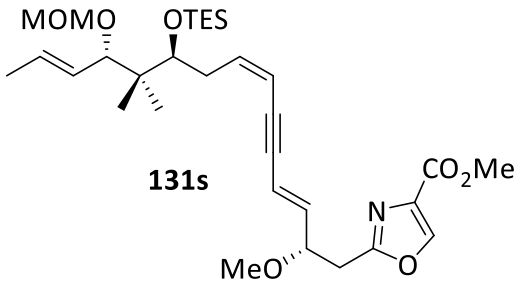
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.4 (C=O); 161.7 (C=N); 144.1 (CH); 143.1 (CH); 133.5 (C); 112.4 (CH); 80.9 (C); 79.1 (CH); 79.0 (CH); 57.1 (CH_3); 52.3 (CH_3); 34.5 (CH_2).

IR (neat): 3251 (m); 3119 (w); 2941 (w); 2882 (w); 2826 (w); 1712 (s); 1582 (s); 1437 (m); 1323 (s); 1231 (m); 1200 (m); 1163 (m); 1095 (s); 1006 (m); 970 (m); 940 (m); 810 (m); 768 (m); 679 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 204.06 (100), 236.09 (97) [*M*+H]$^+$, 156.12 (55), 486.19 (32), 469.16 (28), 279.18 (22), 311.03 (19).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{12}H_{14}NO_4$: 236.0923; found: 236.0935.

3.5.10. Methyl 2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (131s)



131s

The vinyl iodide **129b** (691 mg, 1.47 mmol, 1 eq) was dissolved in degassed CH_3CN (10 mL) and CuI (66 mg, 0.441 mmol, 0.3 eq) and $PdCl_2(PPh_3)_2$ (103 mg, 0.147 mmol, 0.1 eq) were added. The mixture was degassed by freeze-pump-thaw (2 cycles) and then cooled to –15 °C (ice/acetone bath). NEt_3 (1.22 mL, 8.82 mmol, 6 eq) was added, followed by a slow addition of the enyne **130s** (382 mg, 1.62 mmol, 1.1 eq) in degassed CH_3CN (5 mL). The solution became red and after 15 min the bath was removed. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (3x15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to give the monomer **131s** (634 mg, 1.10 mmol, 75%) as a yellow oil.

General Data: $C_{31}H_{49}NO_7Si$; FW: 575.33; TLC: R_f = 0.20 (pentane/Et_2O 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +12.0 (*c* = 0.6, $CHCl_3$).

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm): 8.46 (s, 1H, NC=C*H*); 6.13-6.01 (m, 1H, CH_2CH=CH); 6.01-5.92 (m, 2H, CC*H*=CHCH); 5.72-5.58 (m, 2H, CH(OCH_3)C*H*=CH, C*H*=$CHCH_3$); 5.42-5.31 (m, 1H, CH=C*H*CH_3); 4.66 (d, *J* = 6.6 Hz, 1H, 1OCH_2OCH_3); 4.46 (d, *J* = 6.6 Hz, 1H, 1OCH_2OCH_3); 4.24-4.16 (m, 1H, C*H*OCH_3); 3.87 (s, 3H, COOCH_3); 3.87 (m, 1H, C*H*O OCH_2OCH_3); 3.72 (dd, *J* = 7.0, 3.7 Hz, 1H, CH_2CHOTES); 3.34 (s, 3H, CHOCH_3); 3.28 (s, 3H, $CHOCH_2OCH_3$); 3.11-301 (m, 2H, CH_2CHOCH_3); 2.64-2.54 (m, 1H, 1CH_2CH=CH); 2.48-2.37 (m, 1H, 1CH_2CH=CH); 1.71 (dd, *J* = 6.4, 1.6 Hz, 3H, CH=CHCH_3); 0.985 (app t, *J* = 7.8Hz, 9H, OSi(CH_2CH_3)$_3$); 0.938 (s, 3H, CCH_3); 0.847 (s, 3H, CCH_3); 0.640 (q, *J* = 8.0 Hz, 6H, OSi(CH_2CH_3)$_3$).

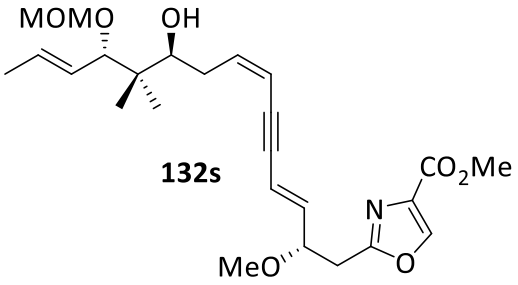
^{13}C-NMR (100 MHz, CD_3OD): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 143.2 (CH); 140.4 (CH); 133.5 (C); 131.0 (CH); 128.0 (CH); 113.9 (CH); 109.5 (CH); 93.6 (CH_2); 91.2 (C); 88.5 (C); 81.6 (CH); 79.4 (CH); 76.5 (CH); 56.9 (CH_3); 55.7 (CH_3); 52.3 (CH_3); 43.1 (C); 34.7 (CH_2); 34.5 (CH_2); 19.8 (CH_3); 19.4 (CH_3); 18.0 (CH_3); 7.3 (CH_3); 5.7 (CH_2).

IR (neat): 3656 (w); 2980 (s); 2884 (m); 1749 (m); 1585 (m); 1461 (m); 1382 (m); 1238 (m); 1142 (m); 1091 (s); 1036 (s); 1004 (s); 956 (s); 923 (m); 727 (s); 678 (m); 604 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 418.20 (100), 514.29 (81), 598.31 (22), 593.36 (18) [*M*+NH_4]$^+$, 350.17 (8), 482.27 (6), 576.33 (<1) [*M*+H]$^+$.

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{31}H_{50}NO_7Si$: 576.3357; found: 576.3363.

3.5.11. Methyl 2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (132s)



132s

CSA (23 mg, 0.0984 mmol, 0.2 eq) was added at 0 °C to a solution of TES protected monomer **131s** (283 mg, 0.492 mmol, 1 eq) in CH_2Cl_2 (12 mL) and MeOH (12 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated aqueous $NaHCO_3$ solution

(20 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 2:1) giving deprotected monomer **132s** (220 mg, 0.477 mmol, 97%) as a slightly yellow oil.

General Data: $C_{25}H_{35}NO_7$; FW: 461.24; TLC: R_f = 0.25 (Et_2O/pentane 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +6.53 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 8.16 (s, 1H, NC=C*H*); 6.23-6.17 (m, 1H, CH_2C*H*=CH); 5.96 (dd, *J* = 15.8, 7.4 Hz, 1H, CC*H*=CHCH); 5.87 (dd, *J* = 15.9, 2.0 Hz, 1H, CC*H*=CHCH_2); 5.71-5.62 (m, 2H, CH(OCH_3)C*H*=CH, C*H*=CHCH_3); 5.43-5.36 (m, 1H, CH=C*H*CH_3); 4.66 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$$OCH_3$); 4.48 (d, *J* = 6.5 Hz, 1H, 1OC*H*$_2$$OCH_3$); 4.20-4.12 (m, 1H, C*H*OCH_3); 3.91 (s, 3H, COOC*H*$_3$); 3.90 (m, 1H, CH_2C*H*OH); 3.68 (dd, *J* = 10.0, 1.9 Hz, 1H, C*H*OCH_2OCH_3); 3.38 (s, 3H, CHOC*H*$_3$); 3.27 (s, 3H, $CHOCH_2$OC*H*$_3$); 3.10 (dd, *J* = 15.0, 7.9 Hz, 1H, 1C*H*$_2$$CHOCH_3$); 2.99 (dd, *J* = 15.0, 5.6 Hz, 1H, 1C*H*$_2$$CHOCH_3$); 2.57-2.50 (m, 1H, 1C*H*$_2$CH=CH); 2.37-2.29 (m, 1H, 1C*H*$_2$CH=CH); 1.75 (dd, *J* = 6.4, 1.5 Hz, 3H, CH=CHC*H*$_3$); 0.921 (s, 3H, CC*H*$_3$); 0.870 (s, 3H, CC*H*$_3$).

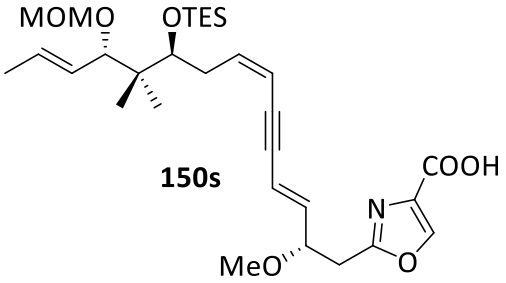
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 161.8 (C=N); 144.1 (CH); 143.3 (CH); 140.3 (CH); 133.5 (C); 132.0 (CH); 126.9 (CH); 114.0 (CH); 109.8 (CH); 93.8 (CH_2); 91.1 (C); 88.3 (C); 84.7 (CH); 79.4 (CH); 76.1 (CH); 57.0 (CH_3); 56.2 (CH_3); 52.3 (CH_3); 41.0 (C); 34.7 (CH_2); 32.8 (CH_2); 21.1 (CH_3); 19.7 (CH_3); 18.0 (CH_3).

IR (neat): 3483 (br); 3164 (w); 2934 (m); 2826 (w); 2249 (w); 1734 (m); 1585 (m); 1438 (m); 1322 (m); 1166 (m); 1101 (s); 1030 (s); 927 (m); 917 (m); 731 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 304.11 (100), 400.21 (48), 479.27 (20) [*M*+NH_4]$^+$, 272.09 (19), 430.22 (15), 462.24 (12) [*M*+H]$^+$, 209.13 (3).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{25}H_{36}NO_7$: 462.2492; found: 462.2473.

3.5.12. 2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylic acid (150s)



150s

131s (324 mg, 0.563 mmol, 1 eq) was dissolved in THF (6 mL) and treated at room temperature with LiOH (1 M in H_2O, 1.7 mL, 1.7 mmol, 3 eq). The mixture was stirred for 3 h at room temperature and neutralized with 1 M HCl (~2.5 mL) to adjust the pH value to 2. The aqueous phase was extracted with Et_2O (3x3 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give acid **150s** (313 mg, 0.557 mmol, 99%) as a yellow oil, which was used for the next step without further purification.

General Data: $C_{30}H_{47}NO_7Si$; FW: 561.31; TLC: UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +6.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm): 8.41 (s, 1H, NC=C*H*); 6.13-6.02 (m, 1H, CH_2CH=CH); 6.02-5.93 (m, 2H, CC*H*=CHCH); 5.73-5.59 (m, 2H, $CH(OCH_3)CH$=CH, C*H*=$CHCH_3$); 5.41-5.31 (m, 1H, CH=C*H*CH_3); 4.66 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.46 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.25-4.15 (m, 1H, C*H*OCH_3); 3.89 (d, *J* = 9.0 Hz, 1H, C*H*OCH_2OCH_3); 3.72 (dd, *J* = 6.7, 3.3 Hz, 1H, C*H*OTES); 3.34 (s, 3H, CHOC*H*$_3$); 3.28 (s, 3H, $CHOCH_2OCH_3$); 3.11-2.98 (m, 2H, CH_2CHOCH_3); 2.65-2.55 (m, 1H, $1CH_2CH$=CH); 2.47-2.37 (m, 1H, $1CH_2CH$=CH); 1.72 (dd, *J* = 6.4, 1.5, Hz, 3H, CH=CHC*H*$_3$); 0.986 (t, *J* = 7.9 Hz, 9H, $OSi(CH_2CH_3)_3$); 0.940 (s, 3H, CC*H*$_3$); 0.876 (s, 3H, CC*H*$_3$); 0.639 (q, *J* = 8.1 Hz, 6H, $OSi(CH_2CH_3)_3$).

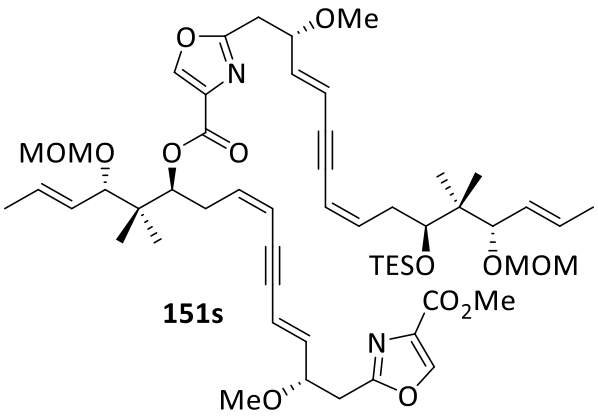
^{13}C-NMR (100 MHz, CD_3OD): δ (ppm): 164.2 (C=O); 163.8 (C=N); 145.9 (CH); 143.6 (CH); 141.8 (CH); 134.6 (C); 132.4 (CH); 129.1 (CH); 114.7 (CH); 110.8 (CH); 94.5 (CH_2); 92.4 (C); 88.9 (C); 82.8 (CH); 80.2 (CH); 77.9 (CH); 57.0 (CH_3); 55.9 (CH_3); 44.2 (C); 35.5 (CH_2); 35.1 (CH_2); 20.4 (CH_3); 19.9 (CH_3); 18.0 (CH_3); 7.5 (CH_3); 6.5 (CH_2).

IR (neat): 2953 (m); 2912 (m); 2877 (m); 1716 (m); 1587 (m); 1440 (m); 1359 (w); 1234 (w); 1144 (m); 1090 (s); 1036 (s); 957 (m); 921 (m); 826 (m); 726 (s); 542 (w) cm^{-1}.

MS (ESI): *m/z* (%): 404.18 (100), 579.34 (78) $[M+NH_4]^+$, 500.28 (51), 372.16 (27), 468.25 (10), 336.15 (8), 562.32 (3) $[M+H]^+$.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{48}NO_7Si$: 562.3200; found: 562.3188.

3.5.13. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*S*)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-2-methoxy-12-(methoxymethoxy)-11,11-dimethyl-10-((triethylsilyl)oxy)pentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (151s)



151s

The crude acid **150s** (316 mg, 0.563 mmol, 1.27 eq) was dissolved in THF (10 mL) and treated at room temperature with NEt_3 (369 µL, 265 mmol, 6 eq) and 2,4,6-trichlorobenzoyl chloride (276 µL, 1.77 mmol, 4 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (3 mL) and added dropwise to a solution of alcohol **132s** (204 mg, 0.442 mmol, 1 eq) and DMAP (324 mg, 2.65 mmol, 6 eq) in toluene (10 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with EtOAc (3x15 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 2:1) to afford **151s** (320 mg, 0.319 mmol, 72%) as a slightly yellow oil.

General Data: $C_{55}H_{80}N_2O_{13}Si$; FW: 1004.54; TLC: R_f = 0.30 (Et_2O/pentane 2:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +57.6 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm): 8.47 (s, 1H, NC=C*H*); 8.40 (s, 1H, NC=C*H*); 6.13-6.02 (m, 2H, C*H*=CH); 6.02-5.90 (m, 4H, CH=CH); 5.74-5.56 (m, 4H, CH=CH); 5.45-5.32 (m, 2H, CH=CH); 5.23 (app dd, *J* = 6.0, 6.9 Hz, 1H, C*H*OC=O); 4.64 (dd, *J* = 11.1, 6.6 Hz, 2H, OCH_2OCH$_3$);

4.46 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.40 (d, *J* = 6.6 Hz, 1H, 1OC*H*$_2$OCH$_3$); 4.25-4.16 (m, 2H, C*H*OCH$_3$); 3.87 (s, 3H, COOC*H*$_3$); 3.87 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.81 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.71 (dd, *J* = 7.1, 3.5 Hz, 1H, CH$_2$C*H*OTES); 3.34 (s, 3H, CHOC*H*$_3$); 3.31 (s, 3H, CHOC*H*$_3$); 3.29 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.28 (s, 3H, CHOCH$_2$OC*H*$_3$); 3.15-3.01 (m, 4H, C*H*$_2$CHOCH$_3$); 2.77-2.65 (m, 2H, C*H*$_2$CH=CH); 2.64-2.55 (m, 1H, 1C*H*$_2$CH=CH); 2.48-2.37 (m, 1H, 1C*H*$_2$CH=CH); 1.73 (dd, *J* = 2.9, 1.5 Hz, 3H, CH=CHC*H*$_3$); 1.72 (dd, *J* = 3.0, 1.6 Hz, 3H, CH=CHC*H*$_3$); 1.05 (s, 3H, CC*H*$_3$); 0.985 (app t, *J* = 7.9 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$); 0.972 (s, 3H, CC*H*$_3$); 0.939 (s, 3H, CC*H*$_3$); 0.874 (s, 3H, CC*H*$_3$); 0.639 (q, *J* = 7.9 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$).

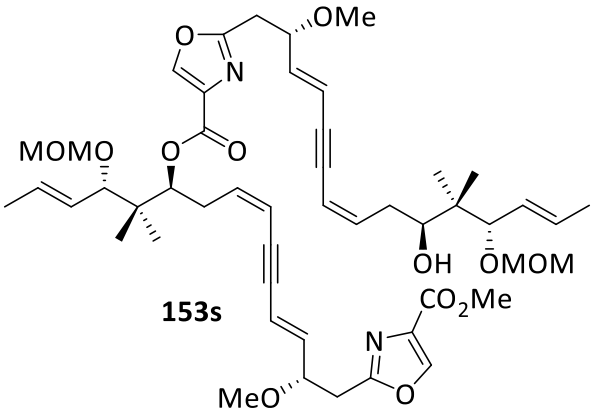
^{13}C-NMR (100 MHz, CD$_3$OD): δ (ppm): 164.4 (C=O); 164.3 (C=O); 162.9 (C=N); 162.2 (C=N); 146.1 (CH); 143.6 (CH); 142.0 (CH); 141.8 (CH); 141.1 (CH); 134.3 (C); 133.6 (C); 133.2 (CH); 132.4 (CH); 129.2 (CH); 129.1 (CH); 128.4 (CH); 114.8 (CH); 114.6 (CH); 112.1 (CH); 110.8 (CH); 94.6 (CH$_2$); 94.5 (CH$_2$); 92.5 (C); 92.4 (C); 88.9 (C); 88.5 (C); 82.8 (CH); 80.2 (CH); 80.1 (CH); 78.4 (CH); 77.9 (CH); 77.6 (CH); 57.1 (CH$_3$); 57.0 (CH$_3$); 56.3 (CH$_3$); 56.0 (CH$_3$); 52.5 (CH$_3$); 44.2 (C); 42.8 (C); 35.5 (CH$_2$); 35.1 (CH$_2$); 35.0 (CH$_2$); 32.3 (CH$_2$); 20.4 (CH$_3$); 20.2 (CH$_3$); 19.9 (CH$_3$); 19.6 (CH$_3$); 18.0 (CH$_3$); 7.5 (CH$_3$); 6.5 (CH$_2$).

IR (neat): 2953 (m); 2879 (m); 2284 (w); 1737 (m); 1583 (m); 1439 (m); 1318 (m); 1168 (m); 1099 (s); 1033 (s); 911 (s); 807 (m); 728 (s); 647 (m); 551 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 1005.55 (100) [*M*+H]$^+$, 1022.56 (760) [*M*+NH$_4$]$^+$, 943.52 (45), 973.53 (28), 847.43 (8).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for C$_{55}$H$_{81}$N$_2$O$_{13}$Si: 1005.5508; found: 1005.5594.

3.5.14. (2*E*,4*S*,6*S*,8*Z*,12*E*,14*S*)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-4-(methoxymethoxy)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylate (153s)



153s

CSA (14 mg, 0.0597 mmol, 0.2 eq) was added at 0 °C to a solution TES protected dimer **151s** (300 mg, 0.299 mmol, 1 eq) in CH_2Cl_2 (7.5 mL) and MeOH (7.5 mL). The mixture was stirred for 1 h at 0 °C under normal atmosphere. Saturated $NaHCO_3$ solution (15 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo, giving the deprotected alcohol **153s** as a slightly yellow oil, which was used in the next step without further purification.

General Data: $C_{49}H_{66}N_2O_{13}$; FW: 890.46; TLC: R_f = 0.30 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +58.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.17 (s, 1H, NC=C*H*); 8.06 (s, 1H, NC=C*H*); 6.24-6.15 (m, 1H, CH_2C*H*=CH); 6.03-5.93 (m, 3H, CH=CH); 5.89 (dt, *J* = 15.9, 2.5 Hz, 2H, CH=CH); 5.71-5.61 (m, 3H, CH=CH); 5.57 (dd, *J* = 10.8, 1.5 Hz, 1H, CH=CH); 5.44-5.32 (m, 2H, CH=CH); 5.26 (dd, *J* = 7.5, 5.4 Hz, 1H, C*H*OC=O); 4.67 (d, *J* = 2.8 Hz, 1H, 1OCH_2OCH$_3$); 4.65 (d, *J* = 2.8 Hz, 1H, 1OCH_2OCH$_3$); 4.48 (d, *J* = 6.5 Hz, 1H, CHOCH_2OCH$_3$); 4.40 (d, *J* = 6.6 Hz, 1H, CHOCH_2OCH$_3$); 4.23-4.14 (m, 2H, C*H*OCH$_3$); 3.91 (s, 3H, COOCH_3); 3.89 (m, 1H, C*H*OCH$_2$OCH$_3$); 3.76 (d, *J* = 9.0 Hz, 1H, C*H*OCH$_2$OCH$_3$); 3.69 (dd, *J* = 10.2, 2.2 Hz, 1H, C*H*OH); 3.38 (s, 3H, CHOCH_3); 3.33 (s, 3H, CHOCH_3); 3.29 (s, 3H, CHOCH$_2$OCH_3); 3.28 (s, 3H, CHOCH$_2$OCH_3); 3.16-2.94 (m, 4H, CH_2CHOCH$_3$); 2.73-2.64 (m, 2H, CH_2CH=CH); 2.58-2.49 (m, 1H, 1CH_2CH=CH); 2.39-2.28 (m, 1H, 1CH_2CH=CH); 1.75 (dd, *J* = 6.4, 1.5 Hz, 3H, CH=CHCH_3); 1.72 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHCH_3); 1.03 (s, 3H, CCH_3); 0.965 (s, 3H, CCH_3); 0.925 (s, 3H, CCH_3); 0.876 (s, 3H, CCH_3).

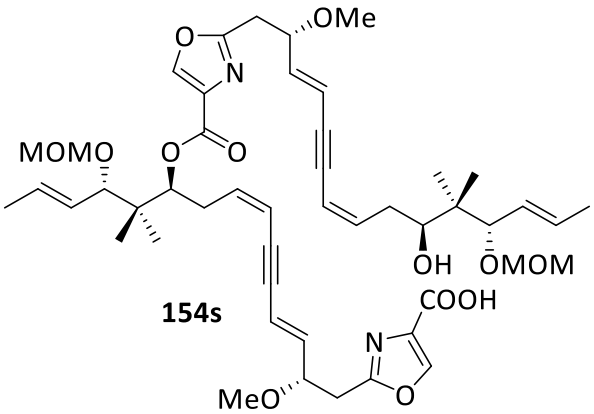
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.6 (C=O); 162.5 (C=O); 161.8 (C=N); 160.8 (C=N); 144.2 (CH); 143.6 (CH); 143.2 (CH); 140.7 (CH); 140.4 (CH); 140.4 (CH); 133.7 (C); 133.5 (C); 132.1 (CH); 132.0 (CH); 127.2 (CH); 126.9 (CH); 113.9 (CH); 113.8 (CH); 111.1 (CH); 109.8 (CH); 93.8 (CH_2); 93.6 (CH_2); 91.5 (C); 91.2 (C); 88.3 (C); 88.1 (C); 84.7 (CH); 81.5 (CH); 79.4 (CH); 79.3 (CH); 77.4 (CH); 76.1 (CH); 57.0 (CH_3); 57.0 (CH_3); 56.2 (CH_3); 56.1 (CH_3); 52.3 (CH_3); 41.8 (C); 41.1 (C); 34.8 (CH_2); 34.7 (CH_2); 32.8 (CH_2); 31.5 (CH_2); 21.1 (CH_3); 19.9 (CH_3); 19.8 (CH_3); 19.5 (CH_3); 18.1 (CH_3); 18.0 (CH_3).

IR (neat): 3658 (br); 2980 (s); 2890 (m); 1737 (m); 1584 (m); 1463 (m); 1380 (m); 1258 (m); 1143 (s); 1098 (s); 1031 (s); 969 (m); 919 (m); 805 (m); 732 (m); 542 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 908.49 (100) $[M+NH_4]^+$, 891.46 (98) $[M+H]^+$, 859.44 (35), 733.33 (7), 829.43 (5).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{49}H_{67}N_2O_{13}$: 891.4643; found: 891.4644.

3.5.15. 2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-((2-((2*S*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carbonyl)oxy)-2-methoxy-12-(methoxymethoxy)-11,11-dimethylpentadeca-3,7,13-trien-5-yn-1-yl)oxazole-4-carboxylic acid (154s)



154s

The crude deprotected alcohol **153s** was dissolved in THF (10 mL) and treated at room temperature with LiOH (1 M in H_2O, 0.897 mL, 0.897 mmol, 3 eq). The mixture was stirred overnight at room temperature and neutralized with 1 M HCl (~1.5 mL) to adjust the pH to a value of 2. The aqueous phase was extracted with Et_2O (3x5 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give the *seco*-acid **154s** as a yellow wax, which was used without further purification.

General Data: $C_{48}H_{64}N_2O_{13}$; FW: 876.44; TLC: UV (+); Vanillin: grey; $[\alpha]_D^{20}$ = +43.6 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.22 (s, 1H, NC=C*H*); 8.07 (s, 1H, NC=C*H*); 6.24-6.14 (m, 1H, CH_2CH=CH); 6.04-5.93 (m, 3H, CH=CH); 5.92-5.81 (m, 2H, CH=CH); 5.71-5.61 (m, 3H, CH=CH); 5.56 (d, *J* = 10.4 Hz, 1H, CH=CH); 5.44-5.32 (m, 2H, CH=CH); 5.24 (dd, *J* = 8.1, 5.1 Hz, 1H, C*H*OC=O); 4.67 (dd, *J* = 6.7, 3.0 Hz, 2H, OCH_2OCH_3); 4.49 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.42 (d, *J* = 6.6 Hz, 1H, $1OCH_2OCH_3$); 4.22-4.13 (m, 2H, $CHOCH_3$); 3.91 (d, *J* = 8.6 Hz, 1H, $CHOCH_2OCH_3$); 3.73 (m, 1H, $CHOCH_2OCH_3$); 3.69 (dd, *J* = 7.2, 2.9 Hz, 1H, C*H*OH); 3.39 (s, 3H, $CHOCH_3$); 3.34 (s, 3H, $CHOCH_3$); 3.31 (s, 3H, $CHOCH_2OCH_3$); 3.28 (s, 3H, $CHOCH_2OCH_3$); 3.16-2.96 (m, 4H, CH_2CHOCH_3); 2.71-2.62 (m, 1H, $1CH_2CH$=CH); 2.60-2.48 (m, 2H, $2CH_2CH$=CH); 2.41-2.29 (m, 1H, $1CH_2CH$=CH); 1.75 (dd, *J* = 6.5, 1.2 Hz, 3H, CH=CHCH_3); 1.72 (dd, *J* = 6.5, 1.2 Hz, 3H, CH=CHCH_3); 1.03 (s, 3H, CCH_3); 0.969 (s, 3H, CCH_3); 0.927 (s, 3H, CCH_3); 0.879 (s, 3H, CCH_3).

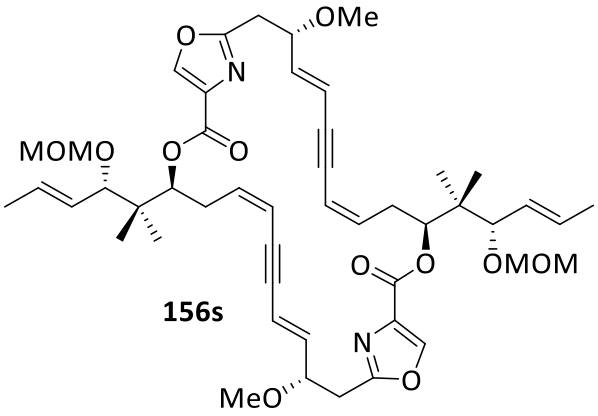
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 163.2 (C=O); 162.6 (C=O); 162.4 (C=N); 160.8 (C=N); 144.8 (CH); 144.7 (CH); 143.7 (CH); 140.6 (CH); 140.4 (CH); 133.6 (C); 133.3 (C); 132.2 (CH); 132.1 (CH); 127.1 (CH); 126.9 (CH); 126.8 (CH); 114.0 (CH); 113.8 (CH); 111.2 (CH); 109.9 (CH); 93.8 (CH_3); 93.5 (CH_3); 91.4 (C); 91.2 (C); 88.3 (C); 88.0 (C); 84.7 (CH); 81.6 (CH); 79.3 (CH); 79.3 (CH); 77.4 (CH); 76.3 (CH); 57.0 (CH_3); 56.9 (CH_3); 56.2 (CH_3); 56.0 (CH_3); 41.9 (C); 41.0 (C); 34.7 (CH_2); 34.5 (CH_2); 31.5 (CH_2); 30.5 (CH_2); 21.1 (CH_3); 20.0 (CH_3); 19.8 (CH_3); 19.4 (CH_3); 18.1 (CH_3); 18.0 (CH_3).

IR (neat): 3658 (br); 2980 (s); 2923 (s); 2328 (w); 1719 (m); 1584 (m); 1461 (m); 1377 (m); 1251 (m); 1146 (m); 1098 (s); 1032 (s); 969 (s); 909 (m); 818 (w); 734 (s); 542 (w) cm^{-1}.

MS (ESI): *m*/*z* (%): 877.44 (100) $[M+H]^+$, 894.47 (77) $[M+NH_4]^+$, 845.42 (49), 719.31 (30), 783.38 (23).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{48}H_{65}N_2O_{13}$: 877.4487; found: 877.4473.

3.5.16. (6*S*,6'*S*)-(16,16')-Bis(methoxymethyl)-(9,10,9',10')-tetradehydridodisorazole C_1 (156s)



The crude *seco*-acid **154s** was dissolved in THF (20 mL) and treated at room temperature with NEt_3 (831 µL, 5.98 mmol, 20 eq) and 2,4,6-trichlorobenzoyl chloride (467 µL, 2.99 mmol, 10 eq). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (10 mL) and added dropwise to a solution of DMAP (1.4 g, 11.96 mmol, 40 eq) in toluene (150 mL). The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl solution (50 mL) and water (50 mL) and the aqueous phase was extracted with EtOAc (3x80 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane 3:1) to afford the macrocycle **156s** (154 mg, 0.179 mmol, 60% from **151s**) as a slightly yellow oil.

General Data: $C_{48}H_{62}N_2O_{12}$; FW: 858.43; TLC: R_f = 0.50 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: black; $[\alpha]_D^{20}$ = +183.4 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.94 (s, 2H, NC=C*H*); 5.98 (dd, *J* = 16.0, 7.8 Hz, 2H, CH=CH); 5.89 (m, 2H, CH=CH); 5.79 (dd, *J* = 15.9, 1.9 Hz, 2H, CH=CH); 5.65 (dd, *J* = 15.5, 6.6 Hz, 2H, CH=CH); 5.52 (dd, *J* = 10.5, 2.1 Hz, 2H, CH=CH); 5.36 (ddd, *J* = 15.4, 9.0, 1.6 Hz, 2H, CH=CH); 5.21 (dd, *J* = 11.1, 2.3 Hz, 2H, C*H*OC=O); 4.67 (d, *J* = 6.7 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.43 (d, *J* = 6.7 Hz, 2H, 1OC*H*$_2$OCH$_3$); 4.13-4.05 (m, 2H, C*H*OCH$_3$); 3.73 (d, *J* = 8.9 Hz, 2H, C*H*OCH$_2$OCH$_3$); 3.41-3.35 (m, 2H, C*H*$_2$CHOCH$_3$); 3.35 (s, 6H, CHOC*H*$_3$); 3.34 (s, 6H, CHOCH$_2$OC*H*$_3$); 3.01 (dd, *J* = 14.1, 9.8 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.91-2.80 (m, 2H, C*H*$_2$CH=CH); 2.37-2.28 (m, 2H, C*H*$_2$CH=CH); 1.73 (dd, *J* = 6.2, 1.3 Hz, 6H, CH=CHC*H*$_3$); 0.989 (s, 6H, CC*H*$_3$); 0.938 (s, 6H, CC*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.1 (C=O); 160.6 (C=N); 143.6 (CH); 141.3 (CH); 140.1 (CH); 133.8 (C); 132.1 (CH); 127.0 (CH); 113.7 (CH); 112.5 (CH); 93.5 (CH_2); 91.1 (C); 88.2 (C);

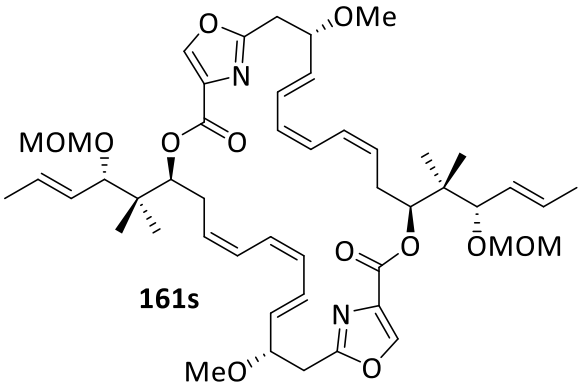
81.2 (CH); 79.8 (CH); 77.4 (CH); 56.9 (CH_3); 56.1 (CH_3); 41.7 (C); 34.7 (CH_2); 31.3 (CH_2); 19.7 (CH_3); 19.5 (CH_3); 18.1 (CH_3).

IR (neat): 3172 (w); 3180 (w); 2930 (m); 2855 (m); 1736 (m); 1649 (m); 1584 (m); 1450 (m); 1368 (m); 1216 (m); 1140 (m); 1103 (s); 1031 (s); 973 (m); 921 (m); 830 (m); 752 (s) cm^{-1}.

MS (ESI): *m*/*z* (%): 859.44 (100) $[M+H]^+$, 876.46 (42) $[M+NH_4]^+$, 797.40 (16), 735.36 (3).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{48}H_{65}N_2O_{13}$: 859.4381; found: 859.4464.

3.5.17. (6*S*,6'*S*)-(16,16')-Bis(methoxymethyl)-disorazole C_1 (161s)



161s

Nitrogen was bubbled for 15 min through a suspension of zinc dust (5 g, 45.88 mmol) in H_2O (30 mL) and then $Cu(OAc)_2 \cdot H_2O$ (500 mg, 2.5 mmol) was added at room temperature and after 15 min $AgNO_3$ (500 mg, 2.94 mmol) was added (exothermic reaction). The mixture was stirred for 30 min at room temperature, filtered by suction and washed with H_2O (40 mL), MeOH (30 mL), acetone (30 mL) and Et_2O (30 mL). This activated zinc solids were added to a solution of **156s** (33 mg, 0.0387 mmol) in MeOH/H_2O 1:1 (20 mL). The mixture was stirred for 24 h at 50 °C, then filtered on a pad of silica with MeOH washes. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 70:1) to afford **161s** (20 mg, 0.0232 mmol, 60%) as a colorless wax.

General Data: $C_{48}H_{66}N_2O_{12}$; FW: 862.46; TLC: R_f = 0.40 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = +24.2 (*c* = 0.5, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.01 (s, 2H, NC=C*H*); 6.40 (dd, *J* = 15.2, 11.3 Hz, 2H, CH(OCH3)CH=C*H*); 6.33 (app t, *J* = 10.3 Hz, 2H, CH2CH=C*H*); 6.26 (dd, *J* = 11.5, 10.5 Hz, 2H, CHC*H*=CHCH); 5.92 (dd, *J* = 11.0, 10.5 Hz, 2H, CHCH=C*H*CH); 5.65 (dd, *J* = 15.5, 6.5 Hz, 2H, CH3C*H*=CH); 5.59 (dd, *J* = 15.2, 7.0 Hz, 2H, CH3CH=C*H*); 5.52 (dd, *J* = 10.0, 5.1 Hz, 2H, C*H*OC=O); 5.41 (ddd, *J* = 15.4, 9.1, 1.5 Hz, 2H, CH(OCH3)C*H*=CH); 5.26 (dd, *J* = 10.6, 2.5 Hz, 2H,

CH2C*H*=CH); 4.65 (d, *J* = 6.7 Hz, 2H, 1OCH_2OCH$_3$); 4.39 (d, *J* = 6.7 Hz, 2H, 1OCH_2OCH$_3$); 4.13 (ddd, *J* = 12.8, 7.0, 5.0 Hz, 2H, C*H*OCH3); 3.71 (d, *J* = 9.0 Hz, 2H, C*H*OH); 3.33 (s, 6H, CHOCH$_2$OCH_3); 3.26 (s, 6H, CHOCH_3); 3.13 (dd, *J* = 13.8, 5.9 Hz, 2H, CH_2CHOCH$_3$); 2.79 (dd, *J* = 14.6, 7.5 Hz, 2H, CH_2CHOCH$_3$); 2.57 (ddd, *J* = 14.7, 10.1, 5.1 Hz, CH_2CH=CH); 2.43 (dd, *J* = 14.9, 6.3 Hz, 2H, CH_2CH=CH); 1.72 (dd, *J* = 6.3, 1.3 Hz, 3H, CH=CHCH_3); 1.01 (s, 6H, CCH_3); 0.946 (s, 6H, CCH_3).

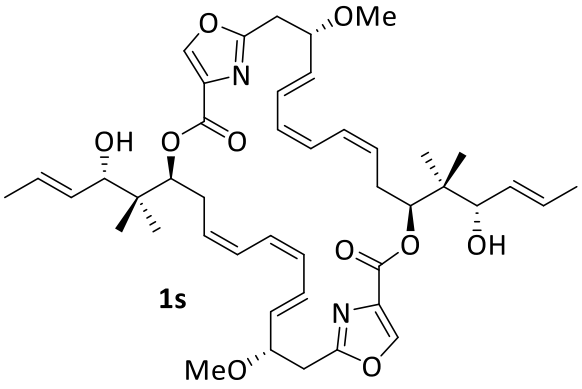
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 162.0 (C=O); 161.1 (C=N); 144.2 (CH); 133.8 (C); 132.4 (CH); 132.0 (CH); 131.6 (CH); 129.0 (CH); 128.4 (CH); 127.3 (CH); 126.2 (CH); 125.4 (CH); 93.7 (CH_2); 81.6 (CH); 80.0 (CH); 78.9 (CH); 56.7 (CH_3); 56.1 (CH_3); 41.7 (C); 34.4 (CH_2); 28.3 (CH_2); 20.0 (CH_3); 19.7 (CH_3); 18.1 (CH_3).

IR (neat): 2927 (m); 2855 (m); 1727 (m); 1583 (m); 1442 (w); 1370 (w); 1315 (w); 1262 (w); 1104 (s); 1012 (m); 805 (m); 757 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 863.47 (100) [*M*+H]$^+$, 880.50 (15) [*M*+NH_4]$^+$, 282.28 (3).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{48}H_{67}N_2O_{12}$: 863.4694; found 863.4672.

3.5.17. (6*S*,6'*S*)-Disorazole C_1 (1s)



1s

MOM protected **161s** (20 mg, 23.1 µmol) was dissolved in CH_3CN (1.5 mL) and cooled to – 15 °C (ice/acetone bath). 1 drop of HBr (48% in H_2O) was added and then the mixture was stirred for 2.5 h at –15 °C. The mixture was diluted with EtOAc (4 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous phase was extracted with EtOAc (3x5 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 50:1) to give **1s** (10 mg, 12.9 µmol, 56%) as a colorless wax.

General Data: $C_{44}H_{58}N_2O_{10}$; FW: 774.41; TLC: R_f = 0.20 (CH_2Cl_2/MeOH 50:1); UV (+); Vanillin: dark green; $[\alpha]_D^{20}$ = –14.5 (*c* = 0.4, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm): 8.33 (s, 2H, NC=C*H*); 6.48 (dd, *J* = 11.2, 10.0 Hz, 2H, CHC*H*=CHCH); 6.43 (dd, *J* = 15.2, 11.3 Hz, 2H, CH(OCH_3)CH=C*H*); 6.35 (dd, *J* = 5.2, 4.1 Hz, 2H, CH2CH=C*H*); 5.94 (dd, *J* = 10.5, 8.7 Hz, 2H, CHCH=C*H*CH); 5.67 (dq, *J* = 15.2, 6.2 Hz, 2H, CH3C*H*=CH); 5.58 (ddd, *J* = 14.4, 7.5, 1.2 Hz, 2H, CH3CH=C*H*); 5.53 (dd, *J* = 15.1, 7.5 Hz, 2H, CH(OCH3)C*H*=CH); 5.50 (app dt, *J* = 10.2, 6.4 Hz, 2H, CH2C*H*=CH); 5.28 (dd, *J* = 10.8, 2.0 Hz, 2H, C*H*OC=O); 4.13 (ddd, *J* = 7.9, 7.2, 5.3 Hz, 2H, C*H*OCH3); 3.84 (d, *J* = 7.5 Hz, 2H, C*H*OH); 3.21 (s, 6H, CHOC*H*$_3$); 3.00 (dd, *J* = 15.4, 7.4 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.77 (dd, *J* = 15.4, 7.2 Hz, 2H, C*H*$_2$CHOCH$_3$); 2.69 (ddd, *J* = 13.8, 10.9, 10.2 Hz, 2H, C*H*$_2$CH=CH); 2.39 (dd, *J* = 13.6, 6.2 Hz, 2H, C*H*$_2$CH=CH); 1.70 (dd, *J* = 6.3, 1.1 Hz, 6H, CH=CHC*H*$_3$); 1.01 (s, 6H, CC*H*$_3$); 0.954 (s, 6H, CC*H*$_3$).

^{13}C-NMR (100 MHz, CD_3OD): δ (ppm): 164.0 (C=O); 162.3 (C=N); 146.3 (CH); 134.5 (C); 133.5 (CH); 131.6 (CH); 130.4 (CH); 129.6 (CH); 129.5 (CH); 129.2 (CH); 127.3 (CH); 126.5 (CH); 80.0 (CH); 78.9 (CH); 77.8 (CH); 56.8 (CH_3); 42.8 (C); 34.8 (CH_2); 29.1 (CH_2); 19.5 (CH_3); 19.3 (CH_3); 18.0 (CH_3).

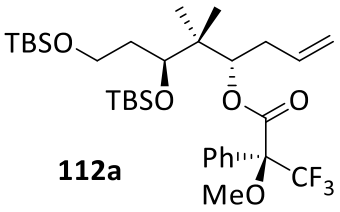
IR (neat): 3419 (br); 2924 (m); 2854 (m); 1723 (m); 1583 (m); 1447 (w); 1367 (w); 1312 (w); 1261 (w); 1101 (s); 1010 (m); 803 (m); 758 (m); 729 (m) cm^{-1}.

MS (ESI): *m*/*z* (%): 775.41 (100) [*M*+H]$^+$, 792.44 (28) [*M*+NH_4]$^+$, 797.40 (6); 757.40 (5).

HRMS (ESI) *m*/*z*: [*M*+H]$^+$ Calcd for $C_{44}H_{59}N_2O_{10}$: 775.4170; found 775.4198.

3.6. Assignment of the Relative Stereochemistry

3.6.1. (*S*)-Mosher Ester of 78b (112a)



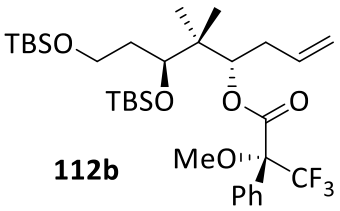
112a

DMAP (9 mg, 72.06 µmol, 1.5 eq), NEt_3 (34 µL, 0.240 mmol, 5 eq) and (*R*)-(–)-MTPA-Cl (14 µL, 72.06 µmol, 1.5 eq) were added to a solution of **78b** (20 mg, 48.08 µmol, 1 eq) in CH_2Cl_2 (1 mL) and the mixture was stirred overnight at room temperature. The solution was directly purified by flash chromatography (pentane/Et_2O 100:1) affording (*S*)-Mosher Ester **112a** (30 mg, 47.44 µmol, 98%) as a colorless liquid.

General Data: $C_{32}H_{55}O_5F_3Si_2$; FW: 632.35; TLC: R_f = 0.45 (pentane/Et_2O 100:1); UV (+); Vanillin: dark blue.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.60-7.57 (m, 2H, Ar-*H*); 7.42-4.35 (m, 3H, Ar-*H*); 5.65 (m, 1H, C*H*=CH_2); 5.24 (dd, *J* = 10.0, 2.5 Hz, 1H, C*H*OO); 4.96 (m, 2H, CH=CH_2); 3.71-3.59 (m, 2H, CH_2OSi); 3.66 (dd, *J* = 8.8, 2.7 Hz, 1H, C*H*OSi); 3.49 (s, 3H, OCH_3); 2.45 (m, 1H, 1CH_2CH); 2.24 (m, 1H, 1CH_2CH); 1.76 (m, 1H, 1C$H_2$$CH_2$O); 1.53 (m, 1H, 1C$H_2$$CH_2$O); 0.909 (s, 3H, 1CC$H_3$); 0.896 (d, *J* = 7.4 Hz, 18H, 2OSi(C(CH_3)$_3$); 0.837 (s, 3H, 1CCH_3); 0.064 (m, 12H, OSi(CH_3)$_2$).

3.6.2. (*R*)-Mosher Ester of 78b (112b)



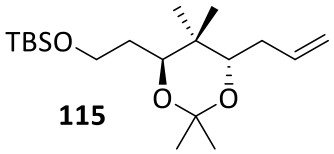
112b

DMAP (9 mg, 72.06 µmol, 1.5 eq), NEt_3 (34 µL, 0.240 mmol, 5 eq) and (*R*)-(–)-MTPA-Cl (14 µL, 72.06 µmol, 1.5 eq) were added to a solution of **78b** (20 mg, 48.08 µmol, 1 eq) in CH_2Cl_2 (1 mL) and the mixture was stirred overnight at room temperature. The solution was directly purified by flash chromatography (pentane/Et_2O 100:1) affording (*R*)-Mosher Ester **112b** (25 mg, 39.53 µmol, 83%) as a colorless liquid.

General Data: $C_{32}H_{55}O_5F_3Si_2$; FW: 632.35; TLC: R_f = 0.45 (pentane/Et_2O 100:1); UV (+); Vanillin: dark blue.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.61-7.56 (m, 2H, Ar-*H*); 7.41-4.34 (m, 3H, Ar-*H*); 5.71 (m, 1H, C*H*=CH_2); 5.26 (dd, *J* = 10.1, 2.3 Hz, 1H, C*H*OO); 5.02 (m, 2H, CH=C*H*$_2$); 3.69-3.58 (m, 2H, C*H*$_2$OSi); 3.65 (dd, *J* = 7.4, 1.7 Hz, 1H, C*H*OSi); 3.55 (s, 3H, OC*H*$_3$); 2.49 (m, 1H, 1C*H*$_2$CH); 2.29 (m, 1H, 1C*H*$_2$CH); 1.74 (m, 1H, 1C*H*$_2$CH$_2$O); 1.52 (m, 1H, 1C*H*$_2$CH$_2$O); 0.888 (d, *J* = 5.1 Hz, 18H, 2OSi(C(C*H*$_3$)$_3$); 0.870 (s, 3H, 1CC*H*$_3$); 0.764 (s, 3H, 1CC*H*$_3$); 0.059 (m, 12H, OSi(C*H*$_3$)$_2$).

3.6.3. (2-((4*S*,6*S*)-6-allyl-2,2,5,5-tetramethyl-1,3-dioxan-4-yl)ethoxy)(tert-butyl)dimethylsilane (115)



115

TBAF (1 M in THF, 2.4 mL, 2.40 mmol, 4 eq) was added dropwise to a solution of **78b** (250 mg, 0.601, 1 eq) in THF (15 mL) at 0 °C and the mixture was stirred overnight at room temperature. The reaction was quenched with H_2O (20 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3x15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo affording the crude triol **113**, which was used without further purification.

The crude **113** was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C, then imidazole (102 mg, 1.50 mmol, 2.5 eq) and TBSCl (100 mg, 0.661 mmol, 1.1 eq) were added. The mixture was stirred for 1 h at 0 °C and quenched with H_2O (15 mL). The layers were separated, the aqueous phase extracted with CH_2Cl_2 (3x10 mL) and the organic phase was dried over Na_2SO_4, filtered and concentrated to give **114** as a colorless liquid, which was used for the next step without further purification.

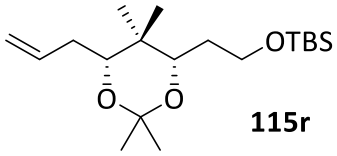
2,2-dimethoxypropane (0.148 mL, 1.20 mmol, 2 eq) was added to a solution of **114** in CH_2Cl_2 (10 mL), followed by CSA (28 mg, 0.120 mmol, 0.2 eq). The mixture was stirred for 1 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to furnish **115** (142 mg, 0.415 mmol, 69% from **78b**).

General Data: $C_{19}H_{38}O_3Si$; FW: 342.26; TLC: R_f = 0.3 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.91-5.79 (m, 1H, C*H*=CH_2); 5.13-4.98 (m, 2H, CH=C*H*$_2$); 3.74-3.59 (m, 2H, C*H*$_2$O); 3.57 (dd, *J* = 10.6, 2.1 Hz, 1H, C*H*OH); 3.37 (dd, *J* = 8.1, 5.3 Hz, 1H, CH_2C*H*O); 2.15-2.07 (m, 2H, C*H*$_2$CH); 1.58-1.44 (m, 2H, C*H*$_2$$CH_2$O); 1.33 (s, 3H, 1OCC*H*$_3$); 1.31 (s, 3H, 1OCC*H*$_3$); 0.886 (s, 9H, 2OSi(C(C*H*$_3$)$_3$); 0.783 (s, 3H, 1CC*H*$_3$); 0.770 (s, 3H, 1CC*H*$_3$); 0.038 (s, 6H, OSi(C*H*$_3$)$_2$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 136.7 (CH); 116.0 (CH_2); 101.1 (C); 76.3 (CH); 72.2 (CH); 59.8 (CH_2); 39.2 (C); 33.6 (CH_2); 32.3 (CH_2); 30.3 (CH_3); 26.0 (CH_3); 24.2 (CH_3); 24.1 (CH_3); 19.7 (CH_3); 19.3 (CH_3); –5.2 (CH_3).

3.6.3. (2-((4*S*,6*R*)-6-allyl-2,2,5,5-tetramethyl-1,3-dioxan-4-yl)ethoxy)(tert-butyl)dimethylsilane (115r)



115r

CSA (93 mg, 0.352, 0.4 eq) was added to a solution of **78r** (367 mg, 0.882, 1 eq) in CH_2Cl_2 (20 mL) and MeOH (20 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then quenched with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3x30 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford crude **113r**.

The crude **113r** was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C, then imidazole (102 mg, 1.50 mmol, 2.5 eq) and TBSCl (100 mg, 0.661 mmol, 1.1 eq) were added. The mixture was stirred for 1 h at 0 °C and quenched with H_2O (15 mL). The layers were separated, the aqueous phase extracted with CH_2Cl_2 (3x10 mL) and the organic phase was dried over Na_2SO_4, filtered and concentrated to give **114r** as a colorless liquid, which was used for the next step without further purification.

2,2-dimethoxypropane (0.217 mL, 1.76 mmol, 2 eq) was added to a solution of **114r** in CH_2Cl_2 (10 mL), followed by CSA (41 mg, 0.176 mmol, 0.2 eq). The mixture was stirred for 1 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to furnish **115r** (211 mg, 0.617 mmol, 70% from **78r**).

General Data: $C_{19}H_{38}O_3Si$; FW: 342.26; TLC: R_f = 0.3 (pentane/Et_2O 50:1); UV (–); Vanillin: dark blue.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.91-5.81 (m, 1H, C*H*=CH_2); 5.08-4.97 (m, 2H, CH=C*H*$_2$); 3.69-3.60 (m, 3H, C*H*$_2$O, CH_2C*H*O); 3.52 (dd, *J* = 9.9, 2.2 Hz, 1H, CH_2C*H*O); 2.24-2.17 (m, 1H, C*H*$_2$CH); 2.13-2.05 (m, 1H, C*H*$_2$CH); 1.71-1.64 (m, 1H, 1C*H*$_2$$CH_2$O); 1.60-1.53 (m, 1H, 1C*H*$_2$$CH_2$O); 1.40 (s, 3H, 1OCC*H*$_3$); 1.38 (s, 3H, 1OCC*H*$_3$); 0.893 (s, 9H, 2OSi(C(C*H*$_3$)$_3$); 0.856 (s, 3H, 1CC*H*$_3$); 0.753 (s, 3H, 1CC*H*$_3$); 0.042 (s, 6H, OSi(C*H*$_3$)$_2$).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 136.9 (CH); 115.6 (CH_2); 98.5 (C); 78.4 (CH); 74.2 (CH); 59.9 (CH_2); 35.5 (C); 33.8 (CH_2); 32.6 (CH_2); 30.3 (CH_3); 26.1 (CH_3); 20.8 (CH_3); 19.6 (CH_3); 13.0 (CH_3); –5.2 (CH_3).

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