Total Synthesis of Natural HDAC Inhibitors and Derivatives Thereof

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„Das Leben ist wert, gelebt zu werden, sagt die Kunst, die schönste Verführerin;
das Leben ist wert, erkannt zu werden, sagt die Wissenschaft.“

Friedrich Nietzsche

Meiner Mutter

Kurzfassung

Diese Arbeit beschäftigt sich mit der Totalsynthese makrocyclischer Histondeacetylase-inhibitoren (HDACi), welche interessante Zielstrukturen zur Behandlung von Krebs und anderen schweren Erkrankungen darstellen. Diese Inhibitoren spielen eine zentrale Rolle bei der Untersuchung epigenetischer Prozesse und tragen entscheidend zum Wissen über histonmodifizierende Enzyme bei.

In der vorliegenden Arbeit wird die Synthese der natürlich vorkommenden HDACi Trapoxin A und Cyl-1 beschrieben. Diese wurden aufgrund ihrer außergewöhnlichen Struktur als interessante Zielverbindungen ausgewählt. Als Schlüsselschritte können der stereoselektive Aufbau der nicht-proteinogenen Aminosäuren wie etwa (2*S*,9*S*)-2-Amino-9,10-epoxy-8-oxodecansäure (Aoe) sowie die Makrocyclisierung zum 12-gliedrigen Ringsystem betrachtet werden. Die stereoselektive Einführung der α-Epoxyketonseitenkette erfolgte mittels Peptidmodifizierungen wie beispielsweise Palladium-katalysierter allylischer Alkylierung im Falle von Trapoxin A und Esterenolat-Claisenumlagerung bei Cyl-1. Letztere erlaubte neben der Synthese des Naturstoffes auch den Zugang zu Derivaten hiervon durch Variation der eingesetzten Allylester. Die so erhaltenen Derivate wurden u.a. durch Thiol-En Klickreaktionen weiter modifiziert.

Abstract

This work aims to develop a synthetic approach towards macrocyclic histone deacetylase inhibitors (HDACi), which show extraordinary activities against several cancer cell lines and are potential candidates for the treatment of severe diseases. They play a crucial role in the study of epigenetic functions and contribute to the field of histone-modifying enzymes.

This dissertation describes the synthesis of trapoxin A and Cyl-1. They were found to be challenging targets due to their extraordinary structure. A peptide modification approach utilizing palladium-catalyzed allylic alkylation and ester enolate Claisen rearrangement was envisioned to be suitable to introduce the non-proteinogenic (2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid (Aoe) side chain. Furthermore, a synthetic access to pipecolinic acid-containing dipeptides was realized and methods to perform the challenging macrolactamization were evaluated. The peptide modification approach also allowed for the construction of Cyl-1 derivatives through esterification of different allylic alcohols with a common precursor. The obtained derivatives were further modified through thiol-ene click and other reactions.

Table of Contents:

List of abbreviations and conventions:

4-DMAP	4-dimethylaminopyridine
Ac	acetyl
acac	acetylacetone
A-domain	adenylation domain
Ala	alanine
Aoda	(*S*)-2-amino-8-oxo-decanoic acid
Aoe	(2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid
Aoh	(2*S*,9*R*)-2-amino-9-hydroxy-8-oxodecanoic acid
APS	apicidin synthetase gene
b	branched
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate
Bz	benzoyl
cat.	catalytic
Cbz	carboxybenzyl
C-domain	condensation domain
CM	cross metathesis
CoA	coenzyme A
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethyl-cyclopentadiene
Cy	cyclohexyl
Cy-domain	heterocyclization domain
DAST	diethylaminosulfur trifluoride
DB	double bond
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIAD	di-*iso*-propyl azodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DIPEA	*N*,*N*-di-*iso*-propylethylamine
DKR	dynamic kinetic resolution
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
ds	diastereoselectivity
EDC	3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine
E-domain	epimerization domain
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
FAS	fatty acid synthase
FDA	Food and Drug Administration
Fmoc	fluorenylmethyloxycarbonyl
GC	gas chromatography
GI_{50}	half maximal inhibitory concentration

Gly	glycine
Grubbs I	Benzylidene-bis(tricyclohexylphosphino)-dichlororuthenium
Grubbs II	[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphino)ruthenium
HAT	histone acetyltransferase
HCT-116	human colon cancer cell line
HDAC	histone deacetylase
HDACi	histone deacetylase inhibitor(s)
HDLP	HDAC-like protein
HeLa	Henrietta Lacks cells
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HOBt	benzotriazol-1-ol
HPLC	high-performance liquid chromatography
HSQCed	heteronuclear single quantum coherence spectroscopy, phase-sensitive
IBCF	*iso*-butyl chloroformate
IC_{50}	half maximal inhibitory concentration of a specific target
Ile	isoleucine
ImH	1*H*-imidazole
*i*Pr	*iso*-propyl
k	kilo
KB 3.1	human endocervical adenocarcinoma cell line
l	linear
LCMS	liquid chromatography mass-spectrometry
LDA	lithium di-*iso*-propylamide
Leu	leucine
LG	leaving group
LHMDS	lithium hexamethyldisilazide
Lys(Boc)	ε-*N*-Boc lysine
M	concentration in mol per litre
Me	methyl
Met	methionine
MTT	3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide
NAD	nicotinamide adenine dinucleotide
n-Bu	*n*-butyl
NHS	*N*-hydroxysuccinimide
NIH3T3	fibroblast cell line
nm	nanometer
NMM	4-methylmorpholine
NMR	nuclear magnetic resonance
N-Mt-domain	*N*-methylation domain
NRPS	non-ribosomal peptide synthetase
Ox-domain	oxidation domain
OXYMA	ethyl cyanohydroxyiminoacetate
P6C	Δ^1-pyrroline-6-carboxylate
PCP	peptidyl carrier protein
Pfp	pentafluorophenyl
PfTU	Pentafluorphenol-tetramethyluronium hexafluorophosphate
PG	protective group
Ph	phenyl
Phe	phenylalanine
Pip	pipecolinic acid

PKS	polyketide synthase
PLE	pig liver esterase
ppan	phosphopantetheine
PP_i	pyrophosphate
Pr	propyl
Pro	proline
Py	pyridine
PyBOP	(Benzotriazol-1-yl-oxy)tripyrrolidinophosphonium hexafluorophosphate
RCM	ring closing metathesis
R-domain	reduction domain
rt	room temperature
SAHA	suberanilohydroxamic acid
SAM	*S*-adenosyl methionine
SAR	structure-activity relationship
Ser(BOM)	*O*-benzyloxymethyl serine
Ser(TBDPS)	*O*-*tert*-butyldiphenylsilyl serine
sis	*sis*-gene
SM	starting material
SOMO	singly occupied molecular orbital
T	temperature
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
t-Bu	*tert*-butyl
T-domain	thiolation domain
TDS	thexyldimethylsilyl
TE-domain	thioesterase domain
Tf	trifluoromethansulfonyl
TFA	trifluoroacetic acid
TFA	trifluoroacetyl
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
Tle	*tert*-leucine
TM	transition metal
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine
TMS	trimethylsilyl
Tos	tosyl
TSA	trichostatin A
Tyr(Me)	*O*-methyl tyrosine
U-2 OS	human osteosarcoma cell line
UV	ultraviolet
µW	microwave
Val	valine
WHO	World Health Organization
Y	yield

In the present work, the geometry of ester enolates was determined according to the priorities given by the CIP-rules. Therefore, the determined ester enolate geometry is dependent on the metal species present in the ester enolate. For instance, Li-enolates were given lower priority then the esterified alcohol, while Zn-enolates obtained higher priority due to their position on the periodic table of elements.

1. Introduction

The search for new efficient treatments against severe diseases is a race against time. Scientific research makes key contributions to provide humanity with enhanced therapies to tackle these diseases. For instance, the fight against cancer involves many research fields that complement each other. Although advances have been made to address this serious health issue, the fight is not over. The World Health Organization (WHO) lists cancer as second most common cause of death worldwide, resulting in a total of 8.8 million deaths in 2015.[1] The most abundant cancers are those of lung (~ 1.7 million deaths per year), liver (~ 790 k), colorectal (~ 775 k), stomach (~ 750 k) and breast (~ 570 k). Besides the appallingly high mortality rate, cancer is an immense economic factor with annual costs of $ 1.16 trillion in 2010. New chemical entities to treat acute diseases are needed to improve the living conditions of many people around the world. Efforts to achieve this goal are made throughout academia and industry. On this account, natural products have always played a major role in the drug discovery and development process, a large number of anticancer drugs are natural products or natural product derived structures.[2] They often serve as lead structures for the discovery of new drugs and inspire the drug development process.[3] Nevertheless, many actual natural products are approved as anticancer agents like paclitaxel (marketed as Taxol), romidepsin and doxorubicin (figure 1.1).

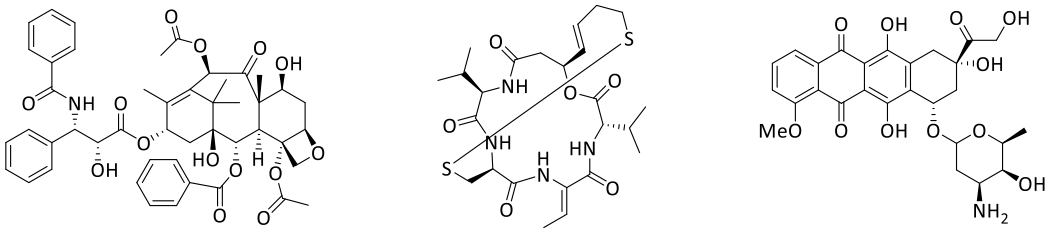


Figure 1.1: Natural products approved as anticancer drugs.[2]

The exceptional structure of paclitaxel has been the focus of many total synthesis efforts, culminating in nine reported total syntheses so far. In general, natural products have always tempted synthetic chemists as challenging targets to develop and assess new chemical methods. Many natural products have been in the spotlight of intensive synthetic studies, which led to remarkable achievements in the field of organic chemistry. Famous examples are Woodward's first total synthesis of strychnine,[4] an alkaloid from *Strychnos nux-vomica*, reported in 1954 or Nicolaou's synthesis of the cyclic polyether brevetoxin B in 123 steps.[5] Other stunning natural products like vitamin B12 and epothilone A have also been in the spotlight of total synthesis approaches (figure 1.2).[6] These contributions clearly paved the way for a variety of remarkable synthetic approaches. Total synthesis has emerged as key research area to develop and evaluate new synthetic methods. Besides providing material for exhaustive biological testing, since the isolated amounts are often not sufficient for this purpose, total synthesis contributes to structure elucidation

and verification of a given natural product. Furthermore, total synthesis facilitates access to several derivatives of a natural product, for e.g. structure-activity relationship studies, through chemical synthesis from a common precursor.[7]

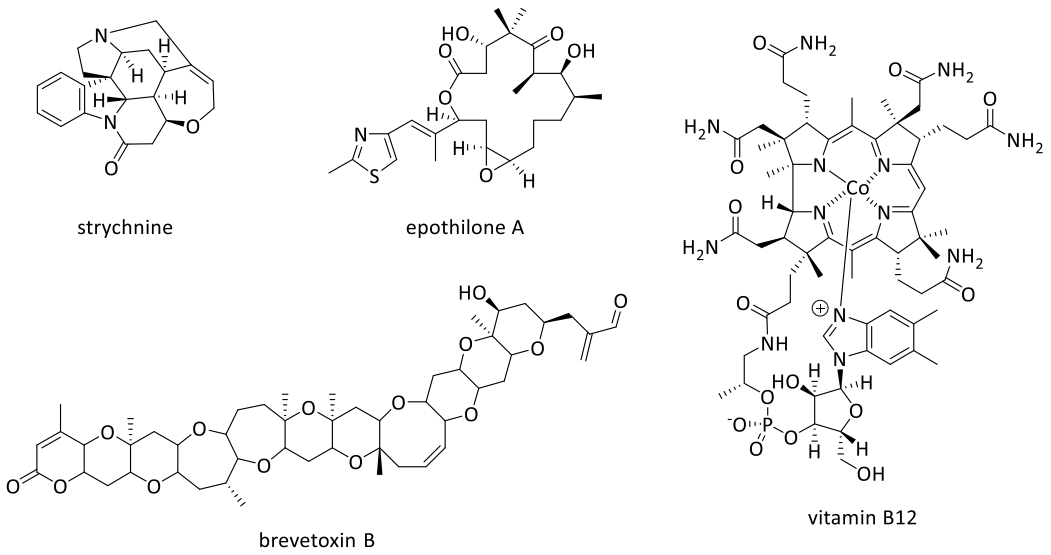


Figure 1.2: Natural products as total synthesis targets.

Among natural products, peptidic structures have entered the limelight due to their extraordinary biological activities.[8] Often found as secondary metabolites for self-defense in different microorganisms, peptidic natural products are assembled by non-ribosomal peptide synthetases (NRPS).[9] Incorporation of non-proteinogenic and unusual amino acids makes them compelling targets for synthetic approaches. Macrocyclic peptides are pervasive throughout this class of natural products and often show improved stability against proteolytic digest and metabolic processes.[10] Furthermore, cyclization generally helps to fix the active conformation of a peptide needed to interact with the respective cellular target. Besides peptidic structures like trapoxin B (figure 1.3), depsipeptides account for a large number of biologically active secondary metabolites. They are generally synthesized *via* a combination of NRPS and polyketide synthases (PKS). For example, the cyclic depsipeptide chondramide C shows strong binding to F-actin and has been the target of several total synthesis.[11,12] The structure of peptidic natural products can further be altered through modifying enzymes as seen for vancomycin. This antibiotic peptide inhibits bacterial cell wall synthesis and undergoes several modifications including glycosylation and cross-linking.[13]

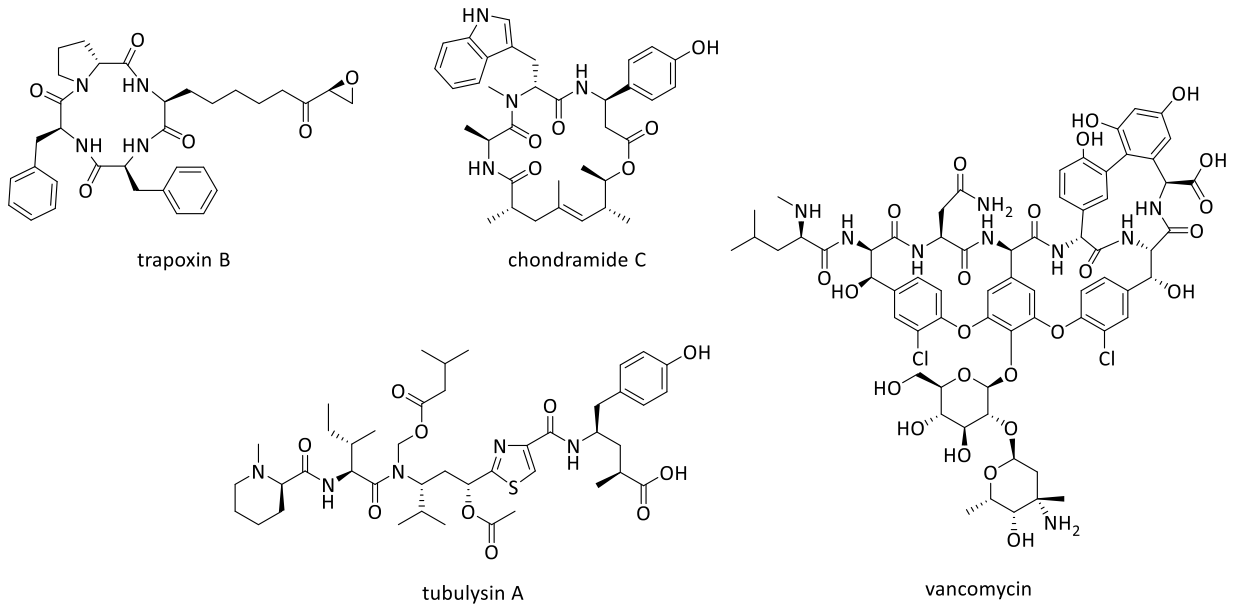


Figure 1.3: Structure of (depsi)peptidic natural products.

Our group is interested in the synthesis of biologically active peptides. Especially structures with antibiotic and antitumor activities have been in the focus of recent studies. Secondary metabolites from myxobacteria like chondramides[14] and pretubulysin[15] were targets of total synthesis approaches. Natural histone deacetylase inhibitors (HDACi) like trapoxins have aroused our interest as potential synthetic targets due to their chemical structure and their ability to affect cancer cells by epigenetic regulation. Naturally occurring macrocyclic HDACi show high structure analogy, which makes them interesting targets for both natural product synthesis and the development of synthetic derivatives through peptide modification reactions developed in our group like chelate enolate Claisen rearrangement and transition metal catalyzed allylic substitutions.

2. State of Knowledge

2.1 HDACs and HDAC inhibitors

Histones are proteins found in eukaryotic cells which are responsible for packaging of DNA into nucleosomes. Two of each histone protein H2A, H2B, H3 and H4 form an octameric structure and the DNA double strand is wrapped around this octamer to built a nucleosome core, which gets further packed into higher-ordered chromatin (figure 2.1).[16] Histones contain many basic residues like e.g. lysine. These basic proteins are protonated within the cytosol and therefore strongly interact with the negatively charged DNA backbone.[17] Packaging of DNA into chromatin limits access of transcription factors and is responsible for transcriptional regulation. Consequently, histones and histone-modifying enzymes play a vital role in gene expression and are involved in epigenetic processes.[18]

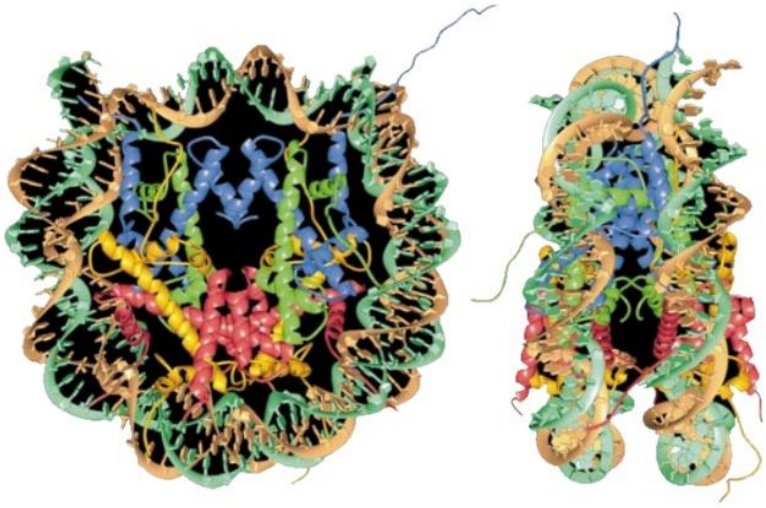


Figure 2.1: Crystal structure of the nucleosome core.[16]

2.1.1 Epigenetic background

Epigenetics is derived from the ancient Greek words “epi” (= above, upon) and “genesis” (= origin). Introduced by Conrad Waddington in the 1940s, epigenetics studies the regulation of genes and their effects on the phenotype.[19] Epigenetics refers to changes in the genome beyond the base sequence of the DNA. The DNA sequence acts as a blueprint for the proteins that are decoded by a particular gene. Epigenetics on the other hand is responsible for regulation of gene expression. During the cell cycle, different genes need activation to maintain the cell’s function. DNA is packed with histones into chromatin.[20] Generally, two types of chromatin are distinguished: 1) transcriptionally active and lightly packed euchromatin and 2) heterochromatin, tightly packed and not transcripted. The process of making DNA accessible for transcription factors, which are responsible for transcription of DNA into RNA, is called chromatin remodeling.[18] It occurs through different covalent modifications to the histone core. Acetylation of lysine residues

within the *N*-terminal histone tails proceeds through the action of histone acetylases (HATs) and interrupts the interaction between histones and DNA.[17] The unwrapped DNA can be accessed by transcription factors and is transcriptionally active. Acetylation of lysine residues is not limited to histones but is an important posttranslational modification and an essential epigenetic tool.[21] Enzymes that install a covalent group to histones are generally called "writers". Their cellular counterparts, the histone deacetylases (HDACs or generally "erasers"), are in charge of restoring the DNA-histone interaction by deacetylation of histone lysines once transcription is completed. As pointed out for HATs, histone deacetylases act not only on histones but on many non-histone targets including transcription factors and proteins that regulate cell proliferation, migration and death.[22,23] Bromodomains, or "readers", recognize acetylated lysine residues and complement the epigenetic toolbox. Together they are involved in active gene regulation and transcriptional control. Malfunction of HDAC activity is linked to several diseases including cancer. Aberrant HDAC expression is found in leukemias, lymphomas and solid tumors.[22–24] Therewith, HDACs are important pharmocological targets for the treatment of several diseases.

2.1.2 Classes of HDACs and mode of action

Eighteen different HDAC enzymes are known so far, and they are divided into four classes based on structural homology with yeast proteins (table 2.1).[25] Class I and II enzymes differ in terms of catalytic domain, size and location within the cell.[20,26] While class I enzymes are ubiquitously expressed and confined to the nucleus, the multidomain class II enzymes undergo tissue-selective expression and are further divided into class IIa and IIb. While the active site is highly conserved in the HDAC family, class IIa enzymes show a tyrosine to histidine mutation.[27,28] They are less active on standard acetylated substrates since histidine differs structurally too much from tyrosine for efficient substrate binding (figure 2.2). Class III enzymes are known as sirtuins due to their homology to Sir2 enzymes found in yeast.[29] While class I, II and IV enzymes contain Zn^{2+} within the active site, sirtuins (class III) are NAD^{+}-dependent and are therefore not affected by typical Zn^{2+}-binding HDAC inhibitors (HDACi).

Table 2.1: Classes of histone deacetylase enzymes.[25]

classification	enzymes	mode of action
class I	HDAC1, -2, -3, -8	Zn^{2+}-dependent
class IIa	HDAC4, -5, -7, -9	Zn^{2+}-dependent
class IIb	HDAC6, -10	Zn^{2+}-dependent
class III	sirtuins 1-7	NAD^{+}-dependent
class IV	HDAC11	Zn^{2+}-dependent

The mode of action of HDAC enzymes was explained based on the crystal structure of HDLP (HDAC-like protein), solved by Pavletich *et al*. in 1999.[30] HDLP shares sequence homology with human HDAC1 and shows identity within the active site. The central Zn^{2+}-cation is coordinated by two asparaginic acid residues, a histidine and one molecule of water. Cocrystallization with the natural HDACi trichostatin A (figure 2.3) gave insight into the mechanism of Zn^{2+}-dependent HDACs (figure 2.2).[31,32]

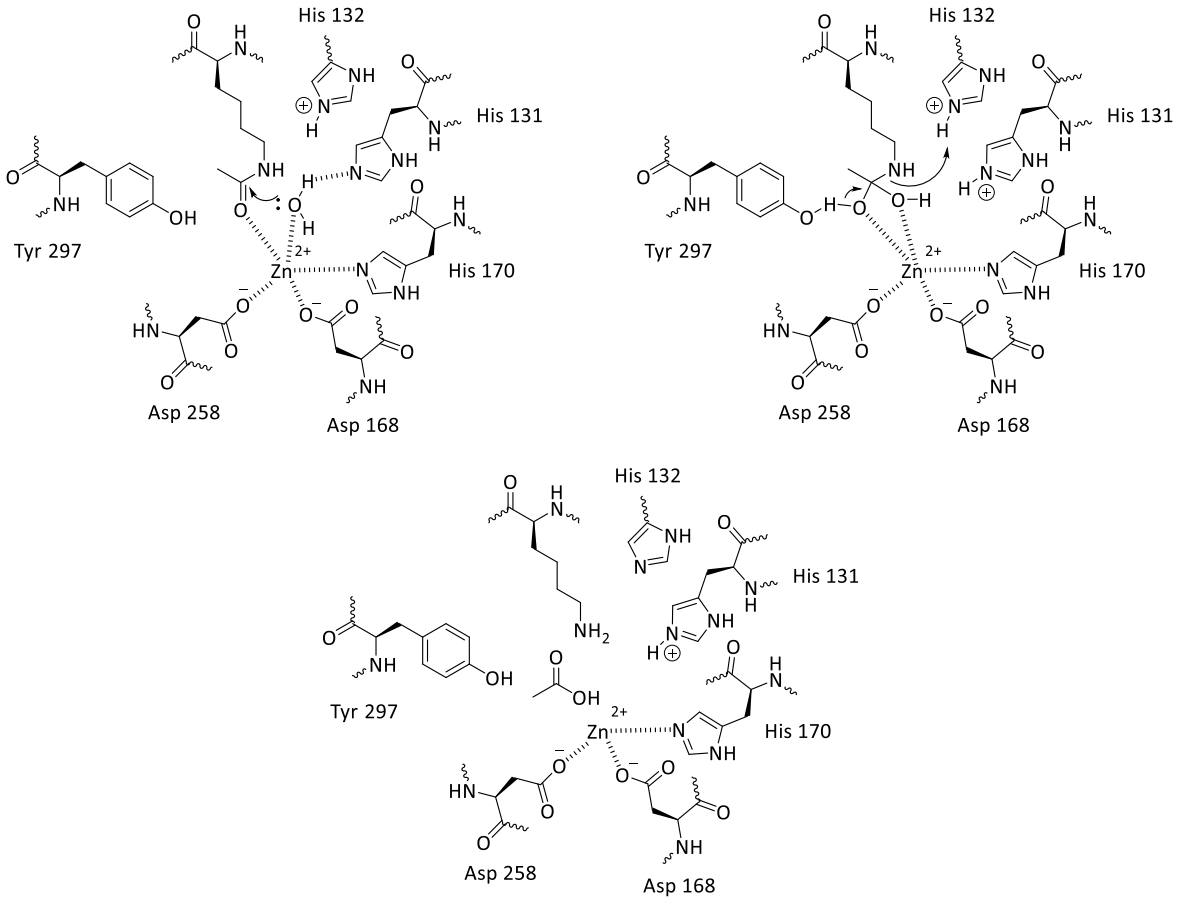


Figure 2.2: Mode of action of Zn^{2+}-dependent HDACs.[30,32]

Acetylated lysine entering the cavity of the active site gets coordinated to Zn^{2+} and subsequently attacked by water to form a tetrahedral intermediate. This intermediate is stabilized by Tyr 297, underlining its importance to maintain catalytic activity. Dissociation of the intermediate liberates lysine and one molecule of acetic acid.

Most HDAC inhibitors act as substrate mimics and contain a zinc-binding motif. They competitively interact with the HDACs to form stable intermediates and therewith block the active site. In fact, the first HDAC enzyme was isolated by affinity chromatography with a HDAC inhibitor, trapoxin, immobilized on a stationary phase by Schreiber and co-workers.[33] The isolated enzyme from human Jurkat T cells was called HDAC1 and these findings emphasize the importance of HDAC inhibitors for the development of this research area.

2.1.3 Natural HDAC inhibitors

Many naturally occurring HDAC inhibitors are known to date.[34] Acyclic molecules like trichostatin A (TSA, figure 2.3) were among the first isolated HDAC inhibitors. Isolated in 1976 from *Streptomyces hygroscopicus* by Tsuji *et al*.,[35] TSA played an important role in rationalizing the mode of action of HDACs.[30] Trichostatin contains a hydroxamic acid as zinc-binding motif, what inspired the design of several synthetic HDACi. It shares the common pharmacophores found in most natural HDAC inhibitors (figure 2.3). The essential Zn^{2+}-binding group is attached to a non-polar linker, delivering it inside the cavity through a narrow channel. The cap region is responsible for interactions with residues on the rim of the active site.[31] The length of the linker is important to attain biological activity. It was shown for derivatives of natural HDACi that 5-6 methylene units are most beneficial.[17] The cap region of acyclic HDAC inhibitors is generally small, resulting in non-specific interactions with the different HDAC isoforms. It is understandable that larger cap groups would be needed to reach selectivity towards the different enzyme classes. Therefore, macrocyclic HDAC inhibitors have more and more become the focus of attention.

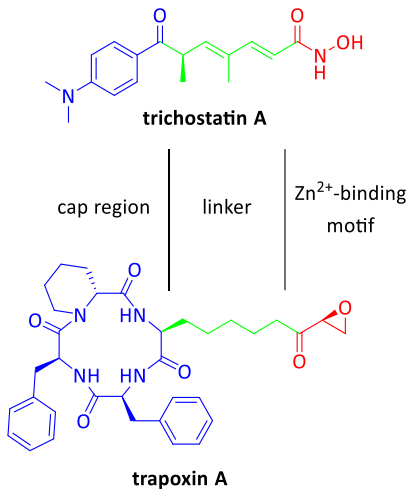


Figure 2.3: Common pharmacophore model of acyclic and macrocyclic HDACi.

More diverse cap regions are found in macrocyclic HDAC inhibitors (figure 2.4). They contain a peptidic or depsipeptidic backbone and generally show higher biological activities and greater selectivities between the different isoforms than acyclic inhibitors.[36] Macrocyclic HDACi also reveal more distinct zinc-binding motifs. The first isolated natural macrocyclic HDACi was HC-toxin, produced by *Helminthosporium carbonum*.[37] Its peptidic backbone contains both (*S*)- and (*R*)-alanine, (*R*)-proline and a non-proteinogenic amino acid, (2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid (Aoe). This combination of at least one D-configured and one cyclic amino acid is found in most of the natural macrocyclic HDACi. Many of them also contain one aromatic amino acid residue. The unusual Aoe with its α-epoxyketone motif is wide-spread among this compound class, as it is present in the trapoxins, Cyl-1 & -2, chlamydocin and many others.[34] The α-epoxyketone is isosteric to an acetylated lysine residue, which makes it a mimic of HDACs

natural substrate.[17] Although α-epoxyketones and hydroxamic acids show high affinities towards Zn^{2+}, other chelating groups are also found in natural products including ketones (apicidin, microsporin A), carboxylic acids (azumamide C,E), α-hydroxy ketones (FR235222) or thioesters (largazole). In fact, many naturally occurring HDACi contain sulfur moieties like e.g. disulfides or thioesters. They seem to lack a decent zinc-chelating group at first sight. However, the disulfide or thioester acts as a prodrug and is reduced *in vivo* to liberate the free thiol, a strong Zn-binding group.[38,39] Romidepsin contains a disulfide bridge and has been the subject of many clinical trials for the treatment of lymphoma and other cancers.[40] Other well established inhibitors are largazole and its derivatives, which helped to gain detailed insight into the binding mode and to assess the influence of the spacer on biological activity. They will be discussed in the section about HDACi derivatives (chapter 2.1.6).

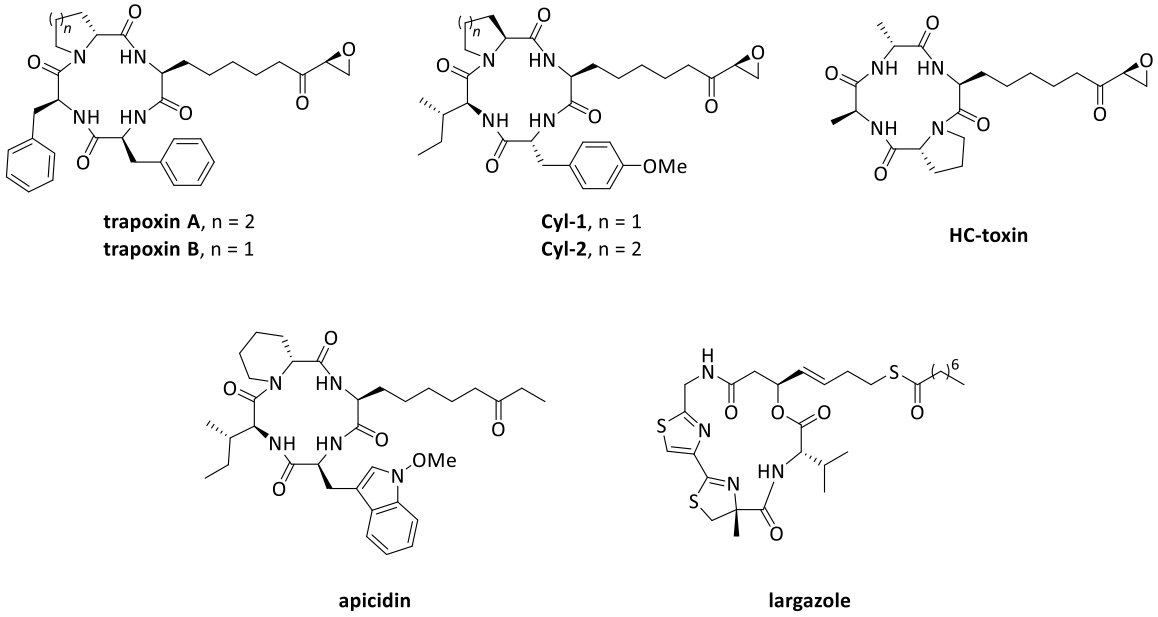


Figure 2.4: Structure of macrocyclic HDAC inhibitors.

Trapoxin A and B were first isolated in 1990 by Itazaki *et al*. from *Helicoma ambiens* RF-1023 strains.[41] The natural products differ only in their peptidic backbone with trapoxin A having a (*R*)-configured pipecolinic acid incorporated while trapoxin B has (*R*)-proline as cyclic amino acid component. (2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid (Aoe) delivers the essential zinc-binding motif, as found in many other natural HDACi like WF3161, HC-toxin and phoenistatin. Analogues of trapoxin B played an important role in the isolation of the first human HDAC enzyme.[33] Both natural products show detransformation activity against *sis* oncogene-transformed NIH3T3 fibroblast cells while having no effect on human red blood cell even at higher concentrations (figure 2.5).[41] It is a general observation for HDACi that they selectively induce cell death in cancer cells at concentrations that do not affect normal cells.[42] Reduction of the epoxide in trapoxin A diminished the transformation activity drastically, leading to the conclusion that the α-epoxyketone is crucial to retain biological activity. Trapoxin A shows irreversible

inhibition of mammalian histone deacetylases, in contrast to other HDACi like trichostatin A, which is a reversible inhibitor under the same conditions.[43,44] Irreversible inhibition of HDAC1 and -8 led to the hypothesis that trapoxin A alkylates the HDACs through attack at the reactive epoxy group.[44,45] Porter and Christianson recently resolved the structure of a trapoxin A-HDAC8 cocrystal (figure 2.6).[46] They could show that trapoxin A is an irreversible inhibitor of this class I enzyme and acts as a substrate mimic. Nucleophilic attack of water at the ketone forms a geminal diol that mimics the tetrahedral intermediate of the natural substrate. The epoxy group was shown to be intact in the cocrystal, ruling out a covalent inhibition. Nevertheless, the epoxy group is essential for irreversible inhibition. Apicidin, which lacks this group, shows reversible inhibition of HDAC8. In contrast, trapoxin A shows reversible inhibition of HDAC6, which can be rationalized by an energetically unfavored conformation of the epoxide as seen for the HC-toxin-HDAC6 cocrystal. The different binding modes of trapoxin A, together with the high selectivity towards class I enzymes over class IIb enzymes (table 2.5),[45] makes it a promising pharmaceutical compound for the treatment of cancer and other diseases.

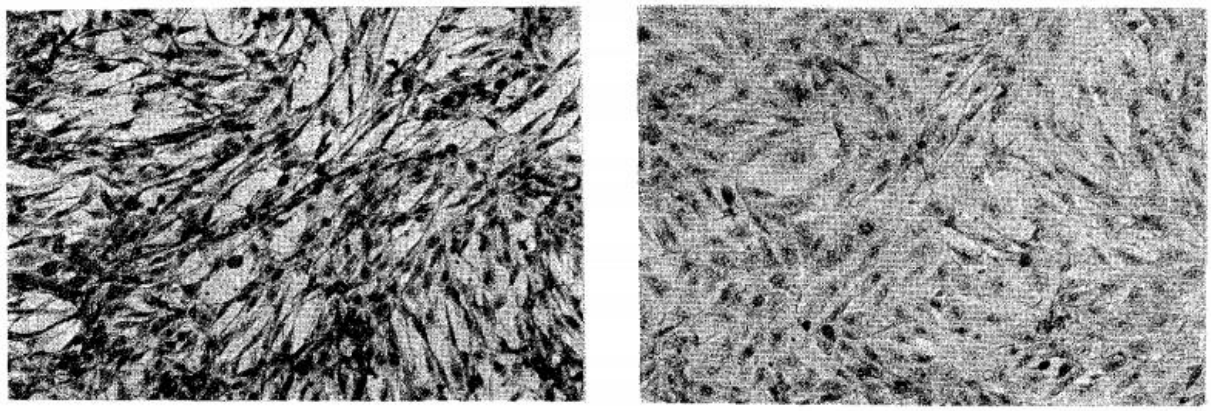


Figure 2.5: Effect of trapoxin A on *sis* oncogene-transformed NIH3T3 cells. On the left: cells after treatment with trapoxin A. On the right: untreated cells.[41]

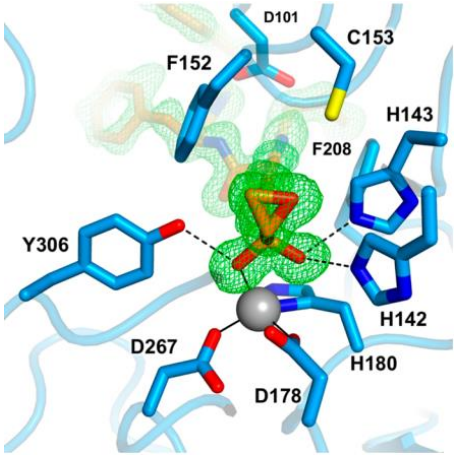


Figure 2.6: Co-crystal structure and binding mode of trapoxin A and HDAC8.[46]

Cyl-1 and -2 have been first reported by Suzuki and co-workers in 1973 and 1984, respectively.[47,48] Isolated from *Cylindrocladium scoparium*, both natural products show inhibitory activity on root growth of lettuce seedlings. Structure elucidation revealed the presence of an α-epoxyketone moiety along with a (*R*)-configured *O*-methylated tyrosine. Cyl-2 has been reported to have excellent selectivity towards class I HDACs over class IIb enzymes with up to 57.000-fold higher activity against HDAC1 in comparison to HDAC6 (table 2.5).[45] Although Cyl-1 is generally referred to as HDACi, no biological activities of the natural product have been reported so far. The classification as HDAC inhibitor can be substantiated due to the structural similarity to several known inhibitors. Anyway, several derivatives of Cyl were synthesized with regard to altered peptide backbone configurations and zinc-binding motifs (see chapter 2.1.6). The high selectivities seen for Cyl-2 and the fact that little is known about the natural Cyl-1 makes the Cyl family an interesting target for both natural product synthesis and derivatization efforts.

Both natural and synthetic HDAC inhibitors play an important role in the development of new drugs for the treatment of cancer and other diseases including sickle cell anemia[49] and rheumatoid arthritis.[50] Four HDAC inhibitors are currently approved by the FDA as anticancer drugs (figure 2.7). SAHA (suberanilohydroxamic acid) was developed by Breslow and Marks and showed therapeutical benefit in the treatment of cutaneous T cell lymphoma.[25,51] It has excellent selectivity towards malignant over normal cells resulting in little to no toxicity. It contains a hydroxamic acid as zinc-binding moiety, a functional group often considered as undruggable due to low stability and potential toxicity.[17,52] Along with belinostat[53] and panobinostat[54], they are synthetic panHDAC inhibitors. In contrast, romidepsin is a macrocyclic natural HDACi, isolated from *Chromobacterium violaceum*.[55,56] It acts as a prodrug, allowing stability for use *in vivo*, and shows selectivity towards class I HDACs.

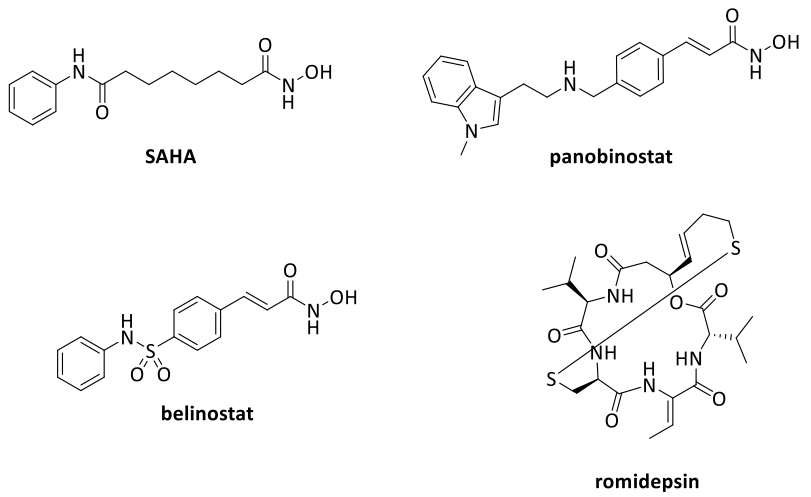


Figure 2.7: FDA-approved HDAC inhibitors.

2.1.4 Biosynthesis of natural HDAC inhibitors

Non-ribosomal peptides, produced by microbes as secondary metabolites, account for a variety of natural products including important pharmaceuticals like cyclosporin[57] or epothilone.[58] Structural diversity is achieved by incorporation of hundreds of unusual building blocks, in comparison to the 20 proteinogenic amino acids used in ribosomal peptide synthesis. Although structurally diversified, non-ribosomally produced peptides share a common mode of synthesis.[10,59] Non-ribosomal peptide synthetases (NRPSs), assembly lines for non-ribosomal peptides, show a modular organization. Each module is responsible for the incorporation of an amino acid and is further divided into different domains. Each domain catalyzes a certain reaction leading to the formation of structurally diverse peptides:

♦ Adenylation domain (A-domain): The A-domain (specifically) recognizes and activates an amino acid by catalyzing the condensation reaction of the carboxylic acid of the amino acid with Mg^{2+}-ATP. This forms an adenylated amino acid and PP_i. The activated amino acid then undergoes nucleophilic attack by a free thiol of an adjacent thiolation domain.

♦ Thiolation domain (T-domain or PCP): The thiolation domain is responsible for the transport of an activated amino acid to the catalytic centers. Binding of the adenylated amino acid to a cysteamine residue of its ppan (4'-phosphopantetheinyl) cofactor leads to formation of an amino acid thioester bound to the peptidyl carrier protein (PCP).

♦ Condensation domain (C-domain): Nucleophilic attack of a downstream-bound amino acid at the PCP-bound thioester of an upstream-bound amino acid leads to formation of a peptide bond and is catalyzed by the C-domain.

The combination of CAT forms an elongation module and is crucial for the subsequent growth of the peptide chain. To increase diversity of the natural product, additional editing domains are integrated in the assembly line:

♦ Epimerization domain (E-domain): Since almost every NRPS synthesized peptide contains D-amino acids, epimerization domains play an important part in the production of non-ribosomal peptides. Epimerization occurs at the α-center of the PCP-bound amino acid or peptide. Alternatively, L-amino acids get epimerized by external racemases or epimerases and get recognized and activated by the A-domain.

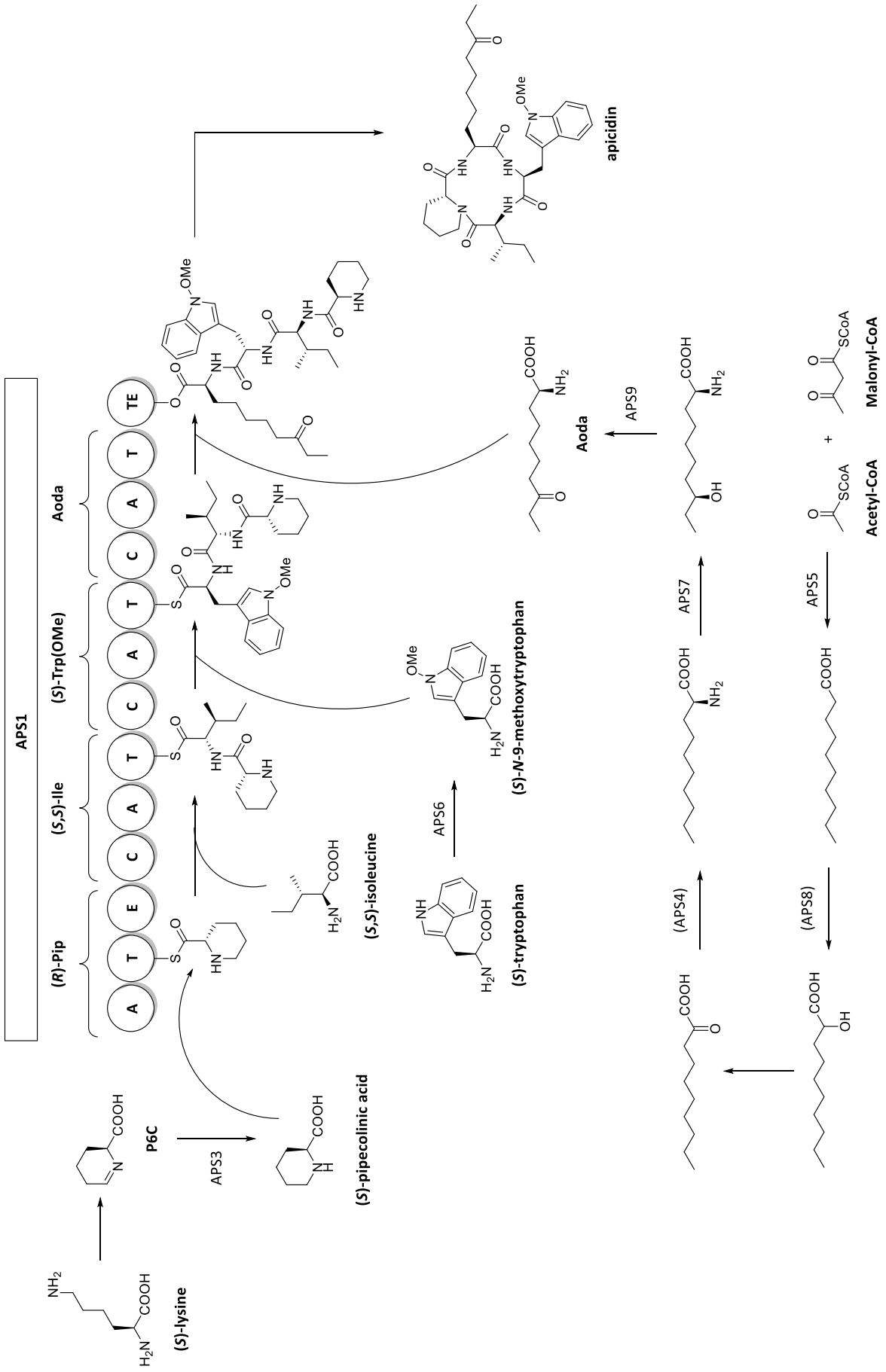
♦ *N*-Methylation domain (N-Mt-domain): *N*-methylation of the α-amino group of the PCP-bound thioester increases the stability of the secondary metabolite against proteolytic digest. Methylation is performed by transfer of a methyl group from *S*-adenosyl methionine (SAM).

Other domains present in NRPSs perform oxidations (Ox-domain), reductions (R-domain) or heterocyclizations (Cy-domain). To liberate the final product from the NRPS complex, cleavage of the thioester is required:

♦ Thioesterase domain (TE-domain): The thioesterase domain is located in the termination module and terminates the peptide elongation by nucleophilic attack of a serine residue at the thioester to form an acylated enzyme. Subsequent hydrolysis or intramolecular attack releases a linear or cyclic

peptide. Cyclization often occurs to fix the biologically active conformation of a peptide. Cleavage can also occur reductively to release an aldehyde- or alcohol-containing natural product.

The biosynthesis of the natural HDAC inhibitor apicidin was studied in great detail and will be discussed exemplarily for the synthesis of other macrocyclic HDACi.[60] The gene that encodes the non-ribosomal peptide synthetase responsible for the biosynthesis of apicidin was called apicidin synthetase gene 1 (APS1). It is located in a 63 kb region and is surrounded by other genes involved in the synthesis of apicidin. The function of every gene was determined by individual depletion and examination of their role in the biosynthesis. The proposed biosynthesis of apicidin is shown in scheme 2.1. The NRPS encoded by APS1 assembles the tetrapeptidic backbone and catalyzes the macrocyclization to form the 12-membered ring. The only proteinogenic amino acid in apicidin is (*S*,*S*)-isoleucine. (*S*)-tryptophan is oxidized and converted to (*S*)-9-*N*-methoxytryptophan by an *O*-methyltransferase encoded by APS6. The pipecolinic acid moiety present in apicidin is synthesized from (*S*)-lysine.[61,62] Cyclization to Δ^1-pyrroline-6-carboxylate (P6C) and subsequent reduction to (*S*)-pipecolinic acid is catalyzed by a reductase encoded from APS3. The presence of (*R*)-pipecolinic acid in apicidin suggested the incorporation of an epimerase domain in APS1. In contrast, an external racemase was found in the biosynthesis of HC-toxin that epimerizes (*S*)-alanine.[63] The unusual amino acid (*S*)-2-amino-8-oxo-decanoic acid (Aoda) is build up by a fatty acid synthase (FAS) encoded by APS5. Decanoic acid is formed from Acetyl-CoA and Malonyl-CoA. Hydroxylation to 2-hydroxydecanoic acid and subsequent oxidation gives a β-keto ester. An aminotransferase converts the β-keto ester into (*S*)-2-amino-decanoic acid. APS7 converts it to (2*S*,8*S*)-2-amino-8-hydroxydecanoic acid and APS9 further oxidizes it to Aoda. APS1 shows low substrate specificity, therefore, Aoda is recognized and activated by an A-domain of the NRPS encoded by APS1. The modular peptide synthesis starts with activation of (*S*)-pipecolinic acid, which gets epimerized by an E-domain on the NRPS complex. Subsequent condensations with the downstream bound amino acids gives a linear tetrapeptide. After binding to the TE-domain *via* serine, intramolecular cyclization leads to liberation of the cyclic apicidin.

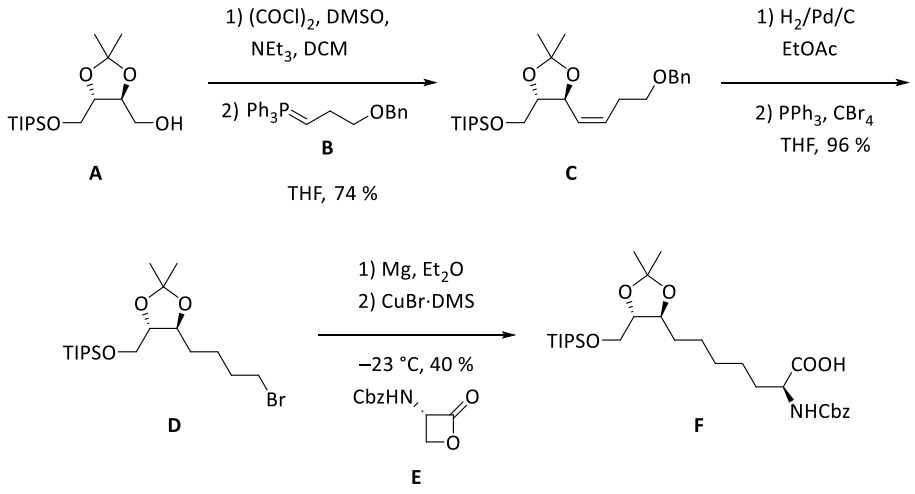


Scheme 2.1: Biosynthesis pathway of apicidin.[60]

2.1.5 Synthesis of natural HDAC inhibitors

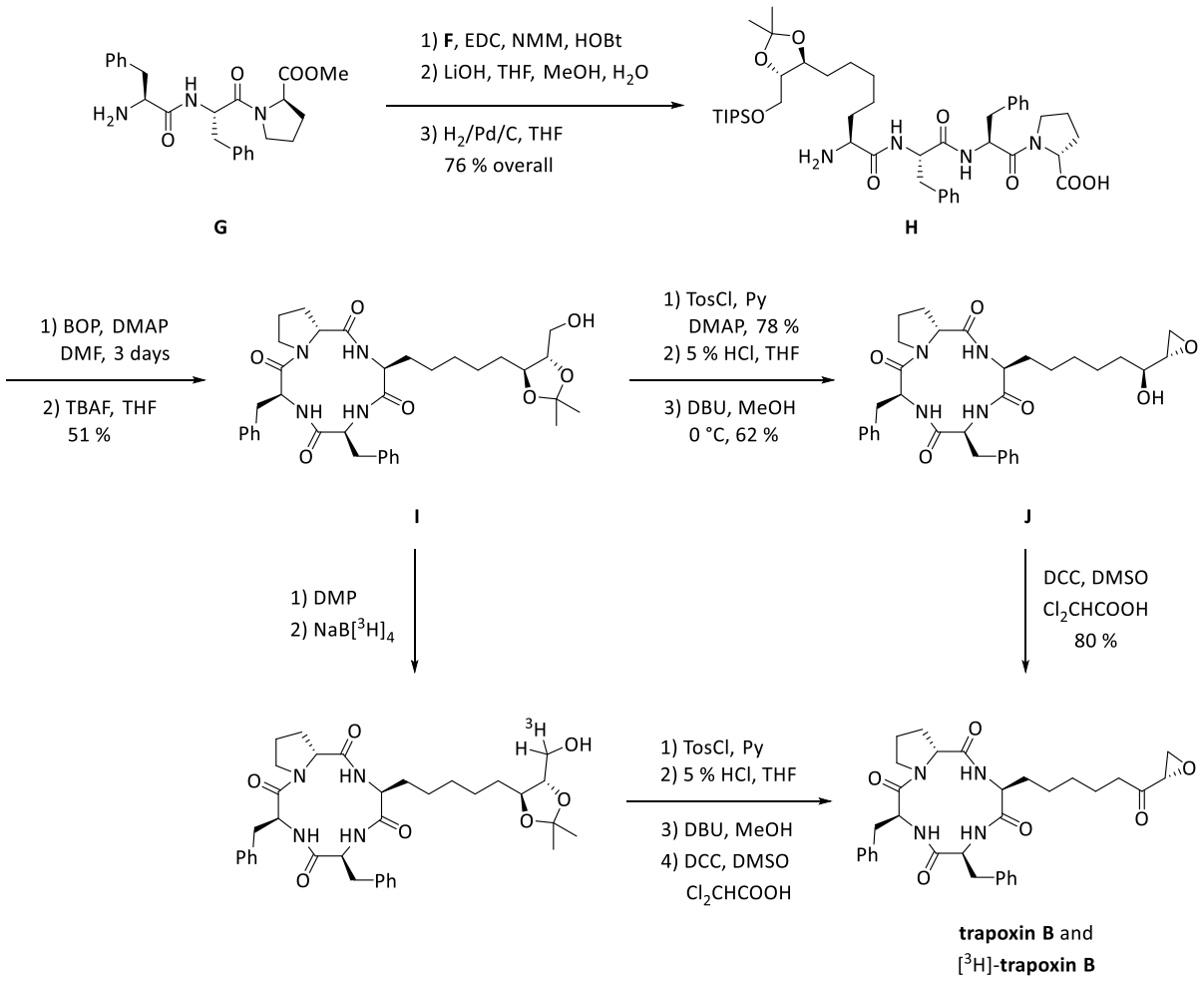
Several total syntheses of natural HDAC inhibitors have been accomplished so far. Olsen *et al.* published a comprehensive review on the synthesis of naturally occurring and synthetic HDACi.[34] In general, construction of the non-proteinogenic amino acid (2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid (Aoe) is one of the main challenges regarding this compound class. Several attempts were made towards this interesting amino acid scaffold including enzymatic resolution,[64] Sharpless epoxidation,[65] radical reactions[66] and epoxidation/oxidation.[67] As reported in the synthesis of several macrocyclic HDACi, the macrolactamization to form the 12-membered ring is the key challenge to access these natural products. Different cyclization methods were evaluated including activation as Pfp ester,[68] NHS-active ester[65] or use of diphenyl phosphoryl azide.[69] Besides that, choosing a proper position to perform ring closure is crucial to obtain the macrocycle in reasonable yield and without severe epimerization, as impressively pointed out by Schmidt *et al*. in their synthesis of WF-3161.[68] They synthesized a model tetrapeptide and alternated the ring closing position. While 70 % yield were obtained at the optimal position, the yield dropped significantly (down to no product formation at all) and epimerization was observed for other macrolactamization positions.

Schreiber *et al.* published their synthesis of trapoxin B in 1996 along with derivatives used to identify the molecular target of HDACi.[67] Their analogues of trapoxin B played a major role in the isolation and characterization of the first HDAC enzyme.[33] The total synthesis of trapoxin B starts with TIPS-protected 2,3-*O*-isopropylidine-L-threitol **A**, which was oxidized under Swern conditions and subsequently treated with Wittig's ylide **B** to give compound **C** in 74 % yield over two steps (scheme 2.2). Hydrogenation of the double bond in **C** and benzyl ether cleavage gave the free alcohol, which was brominated using Appel's protocol to access **D**. Formation of Grignard reagent, transmetalation to copper with CuBr·DMS and addition to β-lactone **E** gave Aoe precursor **F** in 40 % yield. This approach was inspired by Vederas' method to construct α-chiral amino acids using this β-lactone.[70]



Scheme 2.2: Schreiber's synthesis of Aoe precursor **F**.[67]

With Aoe precursor **F** at hand, coupling to tripeptide **G** and full deprotection gave the linear tetrapeptide **H**, which was used for cyclization (scheme 2.3). Several cyclization methods were tested including Schmidt's Pfp ester method utilized in the synthesis of chlamydocin.[71] While this method failed in the synthesis of trapoxin B, performing the macrocyclization with BOP and DMAP in DMF under high dilution afforded the cyclic tetrapeptide **I** in 51 % yield after TIPS-deprotection with TBAF. Macrocycle **I** was used to finish the synthesis of trapoxin B through installation of the epoxide *via* the tosylated intermediate and subsequent Moffatt oxidation with DCC/DMSO. [^{3}H]-labeled trapoxin B was synthesized through oxidation of **I** with DMP and reduction with NaB[^{3}H]$_4$. The labeled natural product was liberated after the same reaction cascade as described for trapoxin B.



Scheme 2.3: Synthesis of trapoxin B and [^{3}H]-labeled trapoxin B.[67]

By replacing the phenylalanine residue adjacent to Aoe with lysine, Schreiber *et al.* were able to immobilize this trapoxin B analogue and identify the molecular target of this HDAC inhibitor through affinity chromatography. The target was later recognized as the first isolated human histone deacetylase, which was therefore called HDAC1.[33]

Ma and coworkers reported the first total synthesis of FR235222 (figure 2.8), a cyclic HDACi containing several interesting amino acid moieties including 4-methylproline, isovaline and (2*S*,9*R*)-2-amino-9-hydroxy-8-oxodecanoic acid (Aoh).[72] The major challenges are the construction of the *trans*-4-methylproline residue as well as the synthesis of the non-proteinogenic Aoh.

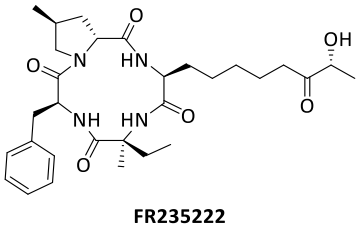
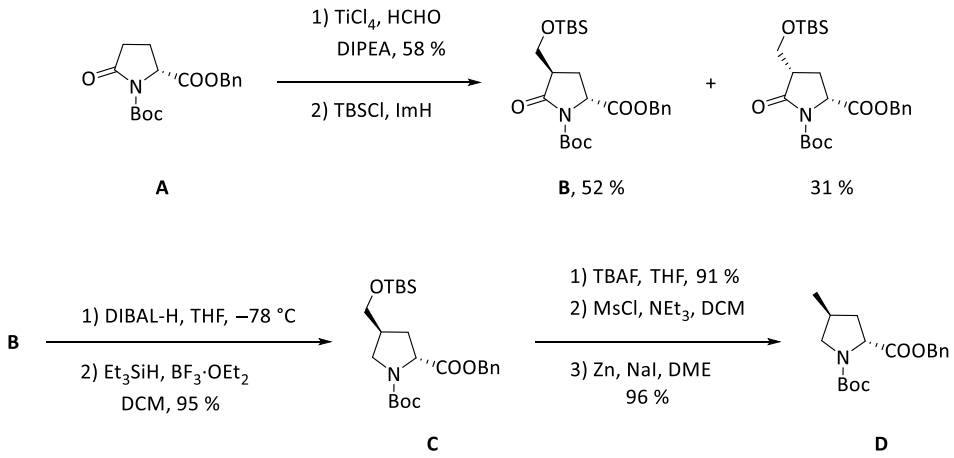


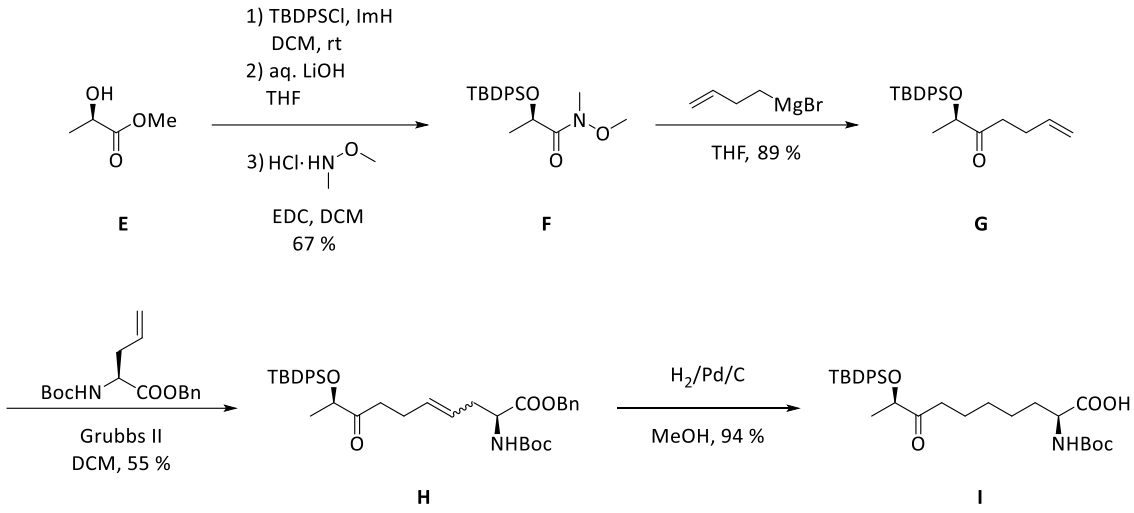
Figure 2.8: Structure of the macrocyclic HDACi FR235222.

The unusual (2*R*,4*S*)-4-methylproline was synthesized starting from (*R*)-pyroglutamic acid **A** (scheme 2.4). $TiCl_4$-mediated aldol addition of **A** to formaldehyde and subsequent TBS-protection gave compound **B** along with a separable diastereomer. The (2*R*,4*R*)-diastereomer was reduced with DIBAL-H and Et_3SiH/BF_3 to afford pyrrolidine **C**. TBS-deprotection with TBAF, mesylation and subsequent defunctionalization with Zn/NaI gave (2*R*,4*S*)-4-methylproline **D** in excellent yield.



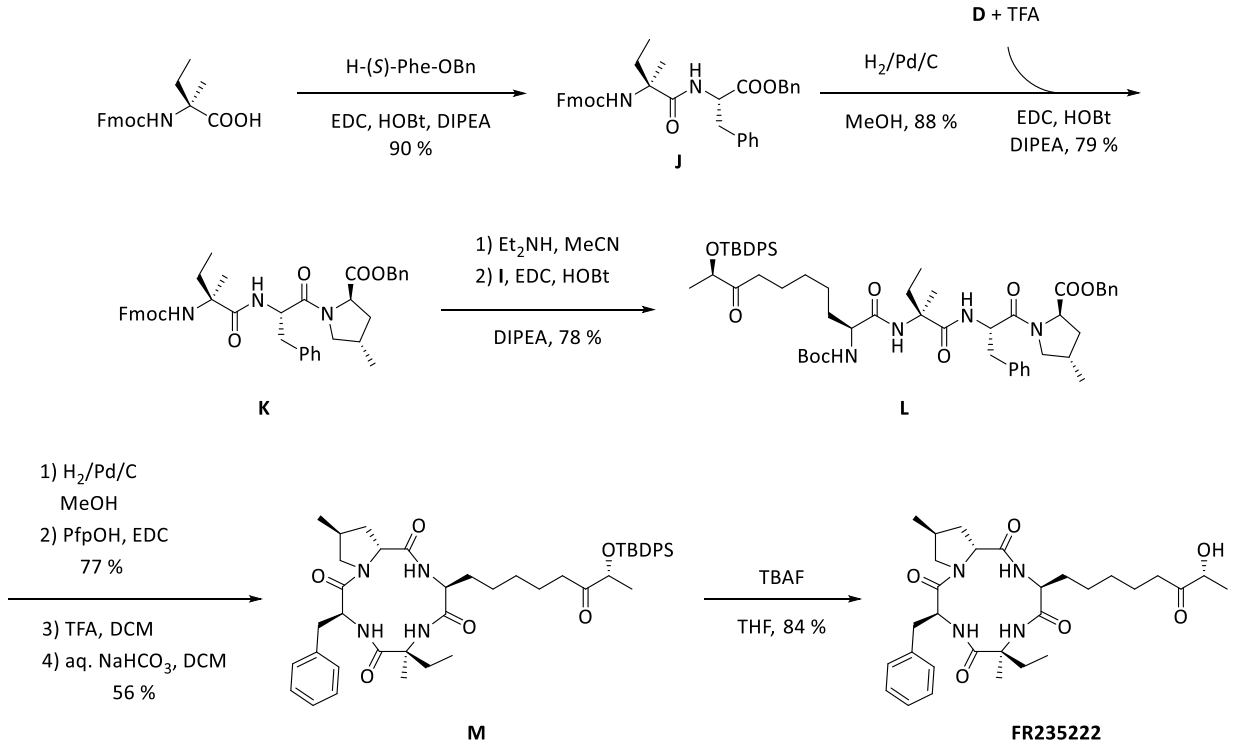
Scheme 2.4: Synthesis of (2*R*,4*S*)-4-methylproline by Ma and coworkers.[72]

Construction of the Aoh moiety was accomplished by TBDPS-protection of methyl (*R*)-lactate **E**, followed by ester saponification and formation of Weinreb's amide **F** with *N*,*O*-dimethylhydroxylamine and EDC (scheme 2.5). Addition of 3-butenylmagnesium bromide gave ketone **G,** which was subjected to olefin cross metathesis using Grubbs II catalyst. Hydrogenation of the newly formed double bond in **H** gave Aoh precursor **I** in 94 % yield.



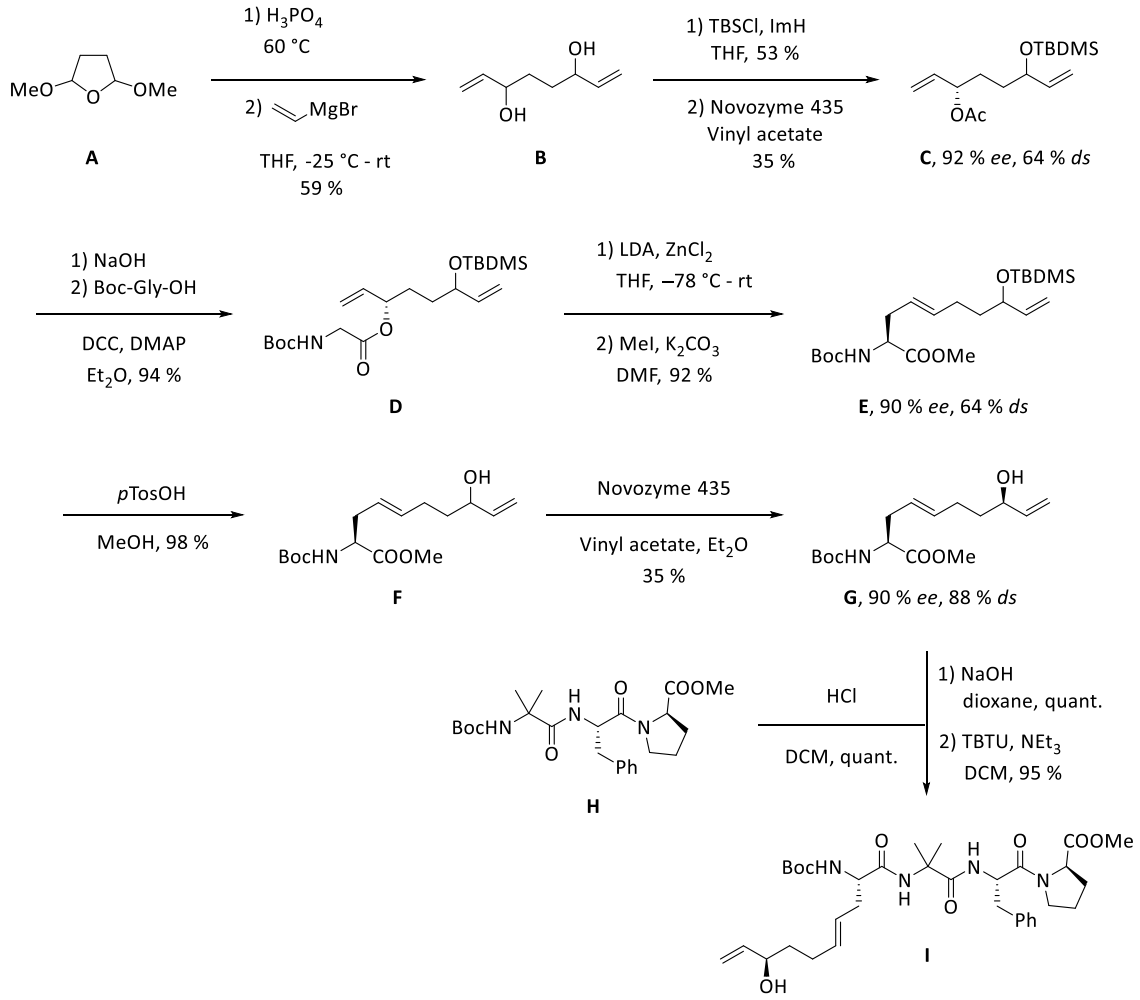
Scheme 2.5: Synthesis of Aoh precursor **I**.[72]

The synthesis of FR235222 was completed by coupling of Fmoc-protected isovaline with H-(*S*)-Phe-OBn using EDC/HOBt (scheme 2.6). Dipeptide **J** was hydrogenated and coupled with Boc-deprotected **D** in 79 % yield. Fmoc-deprotection in **K** and coupling to Aoh precursor **I** gave a linear tetrapeptide **L** suitable for macrolactamization. Removal of the benzyl ester in **L**, followed by activation of the carboxylic acid as Pfp ester and Boc-deprotection gave 56 % of cyclic **M** after biphasic ring closure. Finally, TBDPS-deprotection with TBAF liberated the natural product in 84 % yield.



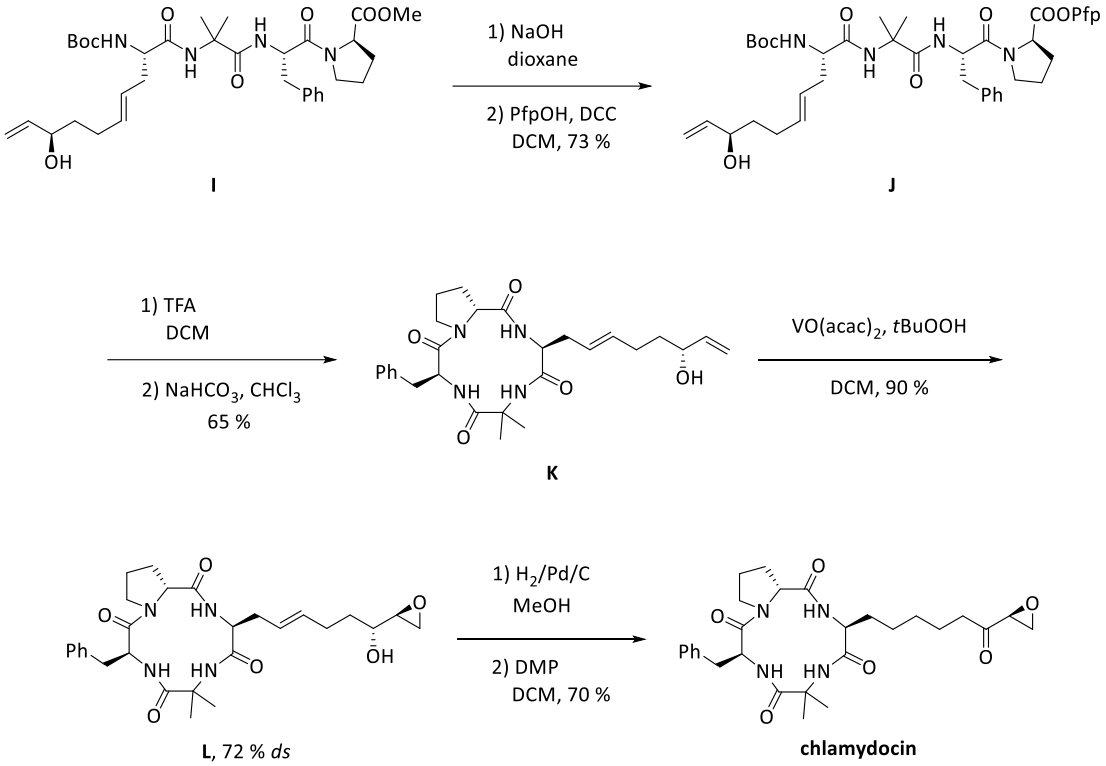
Scheme 2.6: Synthesis of FR235222.[72]

Quirin and Kazmaier accomplished the total synthesis of chlamydocin.[64] Although several synthetic routes towards this interesting natural product have been reported earlier, their approach is based on a chelated ester enolate Claisen rearrangement to build up the Aoe scaffold present in chlamydocin. The synthesis starts with THF-derivative **A**, which was treated with phosphoric acid to obtain the corresponding linear dialdehyde. Subsequent addition of vinylmagnesium bromide afforded diallylic alcohol **B** (scheme 2.7). Mono-protection with TBSCl, followed by enzymatic kinetic resolution gave enantiomerically enriched acetate **C** with good stereoselectivities. Saponification of **C** and esterification with Boc-Gly-OH gave allyl ester **D**, which was used to perform the key step of the synthesis: a chelated ester enolate Claisen rearrangement of amino acid ester **D**. Subsequent methylation of the rearranged acid gave Aoe precursor **E** in 92 % yield and 90 % *ee*. TBS-deprotection with *p*TosOH in **E** gave allylic alcohol **F**, which was again subjected to enzymatic kinetic resolution with Novozyme 435, a lipase from *Candida antarctica*. The resolved allylic alcohol **G** was saponified and coupled with the corresponding tripeptide **H** in 95 % yield. Linear tetrapeptide **I** was a suitable precursor for cyclization.



Scheme 2.7: Synthesis of the linear tetrapeptide of chlamydocin *via* ester enolate Claisen rearrangement.[64]

The synthesis of chlamydocin was finished by saponification of **I**, followed by activation of the carboxylic acid as Pfp ester **J** (scheme 2.8). Boc-deprotection under standard conditions and subsequent cyclization under biphasic conditions afforded cyclic peptide **K** in 65 % yield. Vanadium catalyzed epoxidation gave the desired epoxyalcohol in 90 % yield and 72 % *ds*, while no product formation was observed under Sharpless conditions, even after prolonged reaction times. Hydrogenation of the double bond in **L** and subsequent Dess-Martin oxidation gave chlamydocin in 70 % yield.



Scheme 2.8: Synthesis of chlamydocin by Quirin and Kazmaier.[64]

Although many other total synthesis of naturally occurring HDAC inhibitors have been published over the last decades, containing many striking synthetic approaches towards this compound class, the selected total syntheses underline the synthetic efforts made towards these natural scaffolds.

2.1.6. Derivatives of natural HDAC inhibitors

Natural HDAC inhibitors were isolated from a variety of different organisms and were the subject of many total synthesis approaches. Nevertheless, intensive studies towards derivatives of these naturally occurring inhibitors were undertaken. Derivatization was performed in order to improve the selectivity of a given HDACi towards the different isoforms, to introduce new zinc-binding motifs or to examine structure-activity relationships (SAR). The zinc-binding motifs found in natural inhibitors often fail in *in vivo* studies either due to rapid inactivation (α-epoxyketone)[73]

or toxicity (hydroxamic acid)[17,52]. Introduction of new zinc-binding motifs could therefore improve both pharmacokinetics and toxicity profiles of established HDACi.

Intensive SAR studies were performed for the sulfur-containing macrocyclic depsipeptide largazole (figure 2.4). Not only has it been target of 13 stunning total syntheses (so far) but also the lead compound for the development of several derivatives with altered zinc-binding motifs,[74] spacer lengths[75] or amino acid backbones.[74] It was shown for largazole that the thioester acts as a prodrug and that the thiol is the active zinc-binder. Luesch *et al*. provided inhibitory data against HDAC1 (class I) and HDAC6 (class IIb) for both largazole and the unveiled thiol (table 2.2).[76] These data impressively demonstrate not only the selectivity towards the different isoforms but the effect of thiol as active zinc-binding motif.

Table 2.2: Comparison between largazole and largazole thiol as HDACi.[76]

	K_i [nM]	
compound	HDAC1	HDAC6
largazole	25	5700
largazole thiol	2.5	380

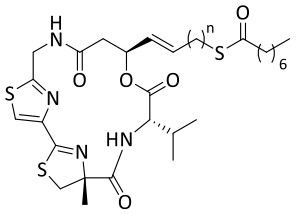
Further studies confirmed the hypothesis that largazole acts as a prodrug and gets reduced within the cytosol. When both compounds were applied to malign melanoma cell lines, largazole showed superior inhibitory activities due to better cell permeability.[77] The impact of the peptide configuration on the biological activity was rationalized by the synthesis of several epimers. Bradner and co-workers compared the inhibitory activities of largazole thiol with both the C-2 epimer (valine) and the enantiomer (table 2.3).[74] While the activity dropped by the factor 10 for the C-2 epimer, the enantiomer showed 1000-fold higher IC_{50}-values. These results underline the importance of a certain peptide configuration and therewith conformation to attain biological activity.

Table 2.3: Influence of the peptide backbone configuration on inhibitory activity of largazole.[74]

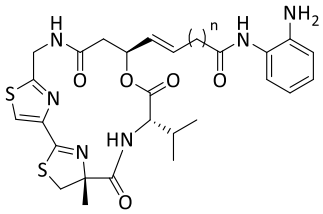
	IC_{50} [nM]			
compound	HDAC1	HDAC2	HDAC3	HDAC6
largazole thiol	1.2	3.5	3.4	49
C-2 epimer	30	82	84	680
enantiomer	1200	3100	1900	2200

The linker in largazole was found to be ideally composed of four atoms between the peptide backbone and the thiol moiety. Modifying the linker length led to reduced activities against HDAC as well as reduced inhibition of HCT-116 cell growth (human colon carcinoma).[75] Substitution of the thioester by an anilide or thioacetamide moiety did not improve activity, but the selectivity profile changed significantly.[74] While the anilide selectively inhibited class I enzymes, thioacetamide **IIIb** showed high selectivity towards HDAC6 (table 2.4).

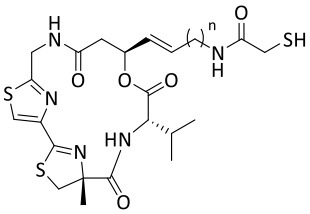
Table 2.4: Largazole derivatives with modified linkers and zinc-binding motifs.[74,75]



Ia: n = 1
Ib: n = 3
Ic: n = 4



IIa: n = 2
IIb: n = 3



IIIa: n = 1
IIIb: n = 2

	IC_{50} [nM]			GI_{50} [nM]
Compound	HDAC1	HDAC6	HeLa	HCT-116
largazole	7.6	1800	32	6.8
Ia	-	-	> 20000	> 10000
Ib	690	> 10000	7600	620
Ic	1900	> 10000	4100	2500

	IC_{50} [nM]			
Compound	HDAC1	HDAC2	HDAC3	HDAC6
IIa	270	4100	4100	> 30000
IIb	23000	29000	14000	> 30000
IIIa	670	1600	960	700
IIIb	1000	1900	1500	240

Similar investigations were undertaken for cyclic tetrapeptide analogues derived from trapoxin, chlamydocin, Cyl-1 &-2. The focus of these works was on replacing the α-epoxyketone by a hydroxamic acid moiety. While the inhibitory activity against class I enzymes was not significantly affected by this modification, the selectivity towards the different isoforms decreased immensely (table 2.5).[45]

Komatsu and co-workers developed derivatives of several natural HDACi by altering the amino acid sequence along with replacement of the α-epoxyketone motif and epimerization of

different amino acid residues (table 2.6).[78] It is worth noting that derivatives with two D-amino acids incorporated showed similar or even better inhibition of HDAC than the natural backbone. Additionally, epimerization of proline in the Cyl-1 derivatives seemed to have no impact on the biological activity of these compounds. These results are somehow in contrast to what was observed from the above presented largazole derivatives, where the epimeric compound revealed significantly lower biological activity. Substitution of isoleucine with alanine also seemed to have no influence as had depletion of the methyl ether in the tyrosine residue.

Table 2.5: Hydroxamic acid-containing natural product derivatives.[45]

compound	Zn^{2+}-binding motif	IC_{50} [nM]		selectivity (HDAC6/HDAC1)
		HDAC1	HDAC6	
trapoxin A	α-epoxyketone	0.82	524	640
trapoxin B	α-epoxyketone	0.11	360	3300
Cyl-2	α-epoxyketone	0.70	40000	57000
chlamydocin	α-epoxyketone	0.15	11000	7300
trapoxin A deriv.	hydroxamic acid	6.1	150	25
trapoxin B deriv.	hydroxamic acid	1.9	19	10
Cyl-1 deriv.	hydroxamic acid	4.4	110	25
Cyl-2 deriv.	hydroxamic acid	1.2	36	30
chlamydocin deriv.	hydroxamic acid	0.44	38	86

Table 2.6: Biological activities of derivatives of natural HDACi.[78]

derivative of	sequence	HDAC* IC_{50} [nM]
trapoxin A	*cyclo*((*S*)-Asu(NHOH)-(*R*)-Phe-(*S*)-Phe-(*R*)-Pip)	2.91
trapoxin A	*cyclo*((*S*)-Asu(NHOH)-(*S*)-Phe-(*S*)-Phe-(*R*)-Pip)	4.78
trapoxin A	*cyclo*((*S*)-Asu(NHOH)- *R*)-Phe-(*S*)-Phe-(*S*)-Pip)	4.18
Cyl-1	*cyclo*((*S*)-Asu(NHOH)-(*R*)-Tyr(Me)-(*S,S*)-Ile-(*S*)-Pro)	3.31
Cyl-1	*cyclo*((*S*)-Asu(NHOH)-(*R*)-Tyr(Me)-(*S,S*)-Ile-(*R*)-Pro)	3.32
Cyl-1	*cyclo*((*S*)-Asu(NHOH)-(*R*)-Tyr(Me)-(*S*)-Ala-(*R*)-Pro)	3.38
Cyl-1	*cyclo*((*S*)-Asu(NHOH)-(*R*)-Tyr-(*S,S*)-Ile-(*R*)-Pro)	3.38

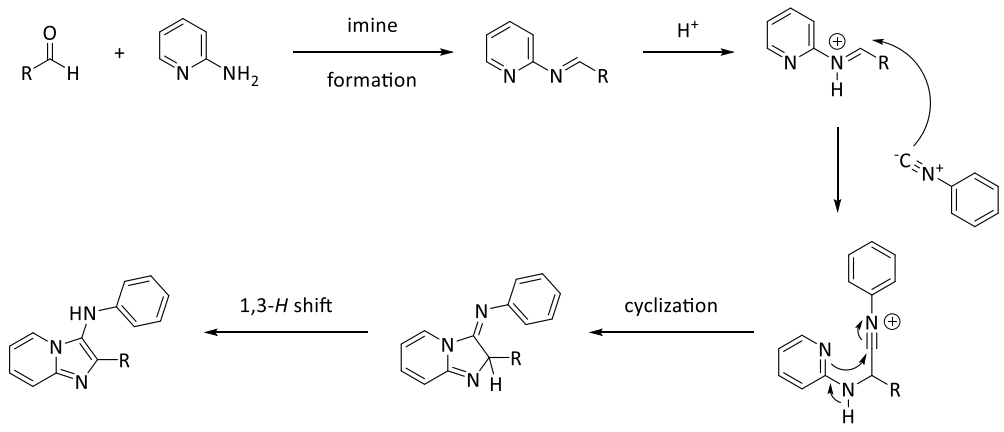
*prepared from B16/BL6 cells.

In summary, derivatization of natural HDACi can be performed in manifold ways and can improve potency, selectivity or (*in vivo*) stability of a given natural compound. The insights from these derivatizations clearly influenced the development of synthetic HDACi.

2.1.7 Synthetic HDAC inhibitors

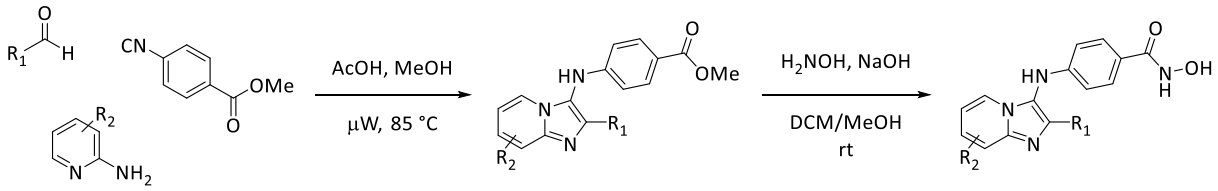
Over the past decades, several synthetic HDAC inhibitors have been developed. Among the most famous is SAHA, which was developed by Ronald Breslow and Paul Marks. They published a review article about the stunning development of SAHA, a FDA-approved drug for the treatment of cutaneous T-cell lymphoma.[25] SAHA shows structural similarity to trichostatin A, one of the first reported natural HDACi. One of the main advantages of SAHA over other therapeutics is its low toxicity along with high selectivity towards transformed cells over non-transformed ones. While growth arrest is observed for both cell types, cell death is only noticed for the transformed cells.[42] The track record of SAHA clearly influenced the development of other synthetic HDAC inhibitors that show the common features shared by all HDACi. In general, these synthetic HDACi are simplified structures that can be regarded more druggable. Manal *et al*. summarized the efforts made so far towards these analogues.[79] Noteworthy, even macrocyclic compounds which do not fit the pharmacophore model of common HDACi were shown to act as inhibitors including macrolides[80] and cyclodextrins.[81]

Hansen and co-workers were able to develop HDAC6 selective inhibitors by a multicomponent synthesis approach.[82] The design of selective inhibitors was rationalized by recent insights into the characteristics of HDAC6 in comparison to other enzymes of this class. Structural disparities of HDAC6 allow for bulky cap groups, and a specific substrate recognition mechanism makes the development of selective inhibitors attractive.[83] They synthesized a library of potential HDACi *via* the three compound Groebke-Blackburn-Bienayme reaction. The mechanism of the reaction is displayed in scheme 2.9.[84] Condensation of an aldehyde with 2-aminopyridine forms an imine, which undergoes protonation and nucleophilic attack by an isonitrile. Subsequent intramolecular cyclization of the intermediate leads to formation of a dihydroimidazo[1,2-*a*]pyridine, which undergoes 1,3-*H* shift to give the imidazo[1,2-*a*]pyridine core.



Scheme 2.9: Mechanism of the Groebke-Blackburn-Bienayme reaction.[84]

The authors demonstrated the synthesis of 13 imidazo[1,2-*a*]pyridines and reported their inhibitory activities against HDAC1 and -6, respectively (scheme 2.10 and table 2.7). The selectivities towards inhibition of HDAC6 over HDAC1 are remarkable given the structural simplicity and straightforward synthesis of these synthetic HDACi.



Scheme 2.10: Synthesis of imidazo[1,2-*a*]pyridine-based HDACi.[82]

Table 2.7: Biological activities and selectivities of imidazo[1,2-*a*]pyridine-based HDACi.[82]

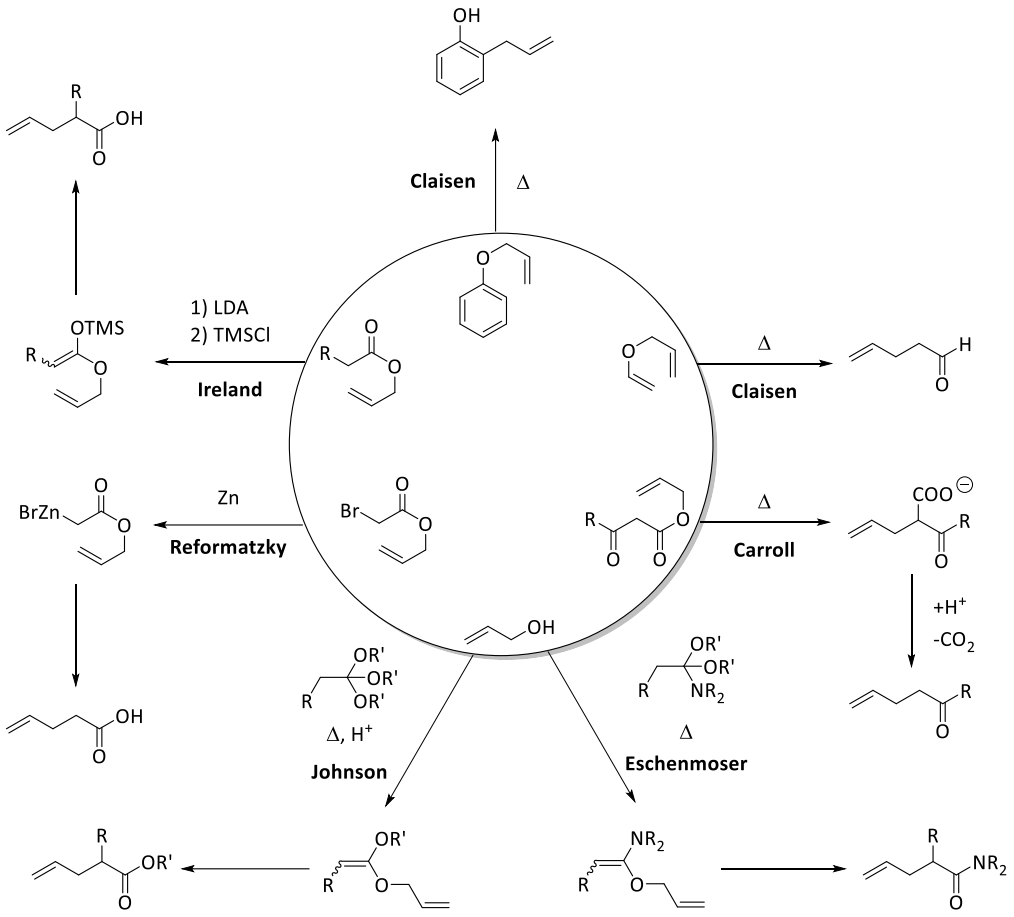
		IC_{50} [µM]		
R_1	R_2	HDAC1	HDAC6	selectivity HDAC1/HDAC6
p-NMe_2-Ph-	H	0.13	0.050	3
Ph-	H	0.89	0.074	12
p-F-Ph-	H	0.51	0.051	10
3,5-*t*Bu-Ph-	H	> 3.333	1.33	> 3
H	H	0.84	0.076	11
H	7-Me	1.01	0.069	15
nC_3H_7-	H	2.20	0.058	38

2.2 Amino acid and peptide modifications

Amino acids and the peptides they form are ubiquitously found in all biological systems. While the 20 proteinogenic amino acids account for ribosomally produced peptides and proteins, many non-proteinogenic amino acids are widespread among living systems and often show interesting biological activities. The latter are incorporated in secondary metabolites of microorganisms by the action of non-ribosomal peptide synthetases, e.g. in the biosynthesis of apicidin (section 2.1.4). Almost all naturally occurring HDACi contain at least one unusual amino acid residue, which needs to be addressed in the synthesis of these compounds. Furthermore, derivatization of a given natural product is unthinkable without the application of certain peptide modification reactions. To address this issue of adding non-proteinogenic amino acids to the synthetic toolbox, various methods for the construction and modification of unusual amino acids and peptide moieties have been developed over the last decades. In the context of this work, modified Claisen rearrangements, transition metal catalyzed allylic substitutions and thiol-ene click reactions were chosen as representative examples of these modification reactions.

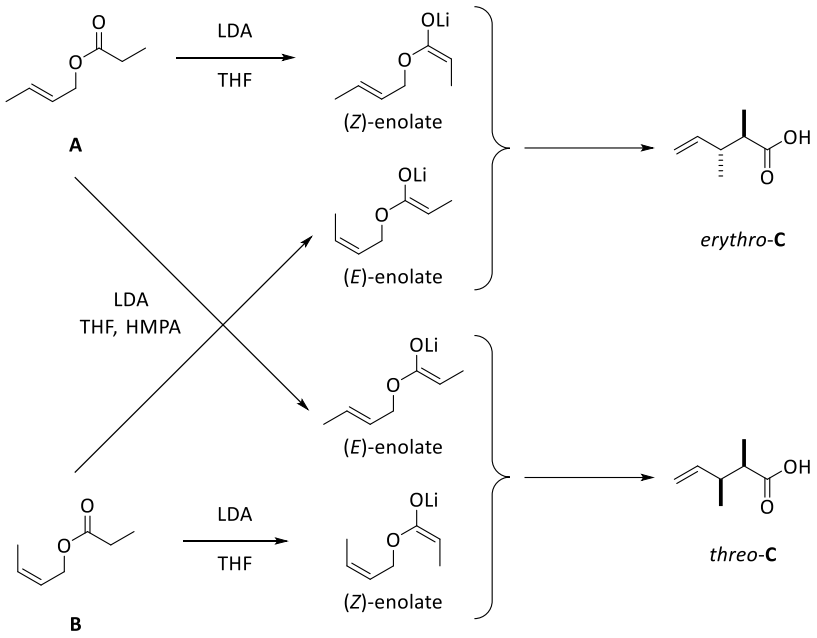
2.2.1 Ester enolate Claisen rearrangements

The [3,3]-sigmatropic rearrangement of allyl aryl and allyl vinyl ethers was first discovered by Ludwig Claisen in 1912.[85] Thermal rearrangement of allyl phenyl ethers gave *C*-allyl phenols, while allyl vinyl ethers afforded γ,δ-unsaturated carbonyls. Since its seminal publication, several versions of the latter transformation have been development with altered reaction conditions. Carroll reported the thermal rearrangement of *in situ* generated β-keto esters, which subsequently underwent decarboxylation to afford γ,δ-unsaturated ketones.[86] Application of this transformation is limited due to the harsh reaction conditions. Similarly, addition of allylic and benzylic alcohols to *N*,*N*-dimethylacetamide diethyl acetal and following rearrangement afforded unsaturated amides as reported by Eschenmoser and co-workers.[87,88] Utilization of orthoesters in this reaction gave rise to unsaturated esters and is referred to as Johnson-Claisen rearrangement.[89] In contrast to Eschenmoser's version, Johnson rearrangement needs the addition of catalytic amounts of acids to proceed readily.[90] The use of allyl esters in this reaction has been reported by Ireland[91] and Baldwin,[92] respectively. Ireland *et al.* generated ester enolates through α-deprotonation to form Li-enolates. Subsequent reaction with TMSCl formed silyl ketene acetals, which readily underwent rearrangement upon heating. In contrast, Baldwin used α-halo esters to generate Zn-enolates after zinc insertion in the C-X bond, wherefore this version is referred to as Reformatsky Claisen rearrangement. Both rearrangements proceed under mild basic to neutral conditions and generate γ,δ-unsaturated carboxylic acids. An overview of the discussed Claisen rearrangements is given in scheme 2.11.



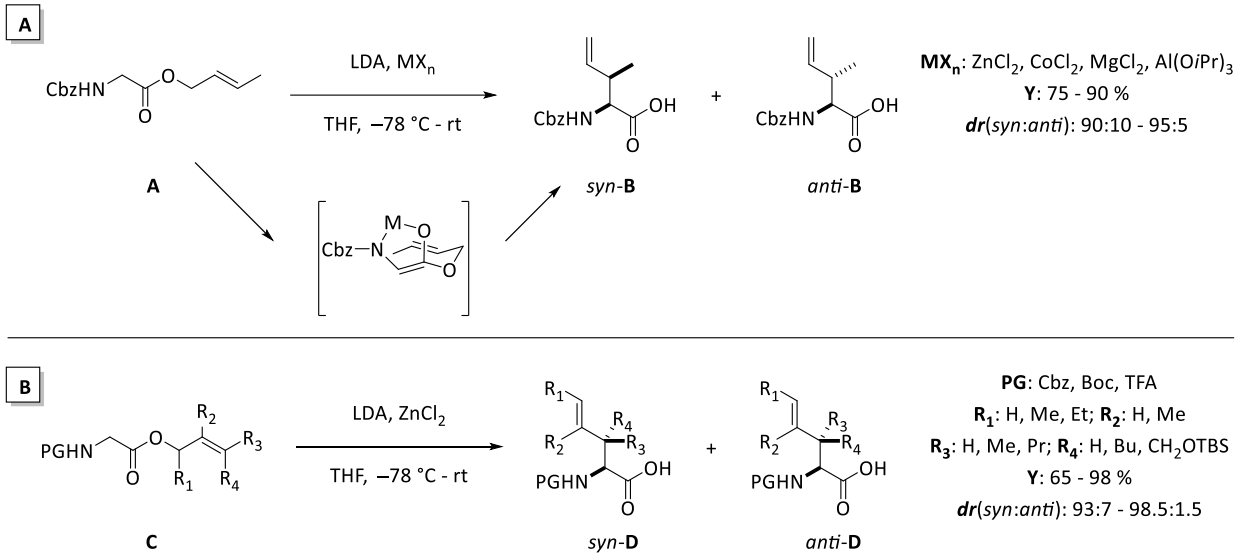
Scheme 2.11: The Claisen rearrangement and its versions.[85–87,89,91,92]

The reaction is generally considered to proceed *via* a chair-like transition state.[93] The stereochemical outcome of the rearranged product depends on the double bond geometry in both the allyl and vinyl fragment.[94,95] Detailed mechanistic studies were carried out by Ireland *et al.* for the rearrangement of ester enolates and silyl ketene acetals.[94] The two isomeric crotyl esters **A** and **B** were treated with LDA in either THF or THF/HMPA to selectively form the (*Z*)- or (*E*)-enolate (scheme 2.12). In THF, Li is coordinated to the carbonyl group and deprotonation presumably proceeds *via* a chair-like transition state to form the (*Z*)-enolate selectively. In contrast, addition of HMPA results in chelation of Li and generation of a stronger amide base. Therefore, an acyclic transition state is preferred to give the corresponding (*E*)-enolate. Upon rearrangement, either *erythro*- or *threo*-**C** were obtained in moderate selectivity. In most cases, rearrangement of the silyl ketene acetals proceeded more readily and with higher yields. This results could be rationalized given the tendency of unstabilized ester enolates to undergo condensation reactions above –78 °C.[91,96]



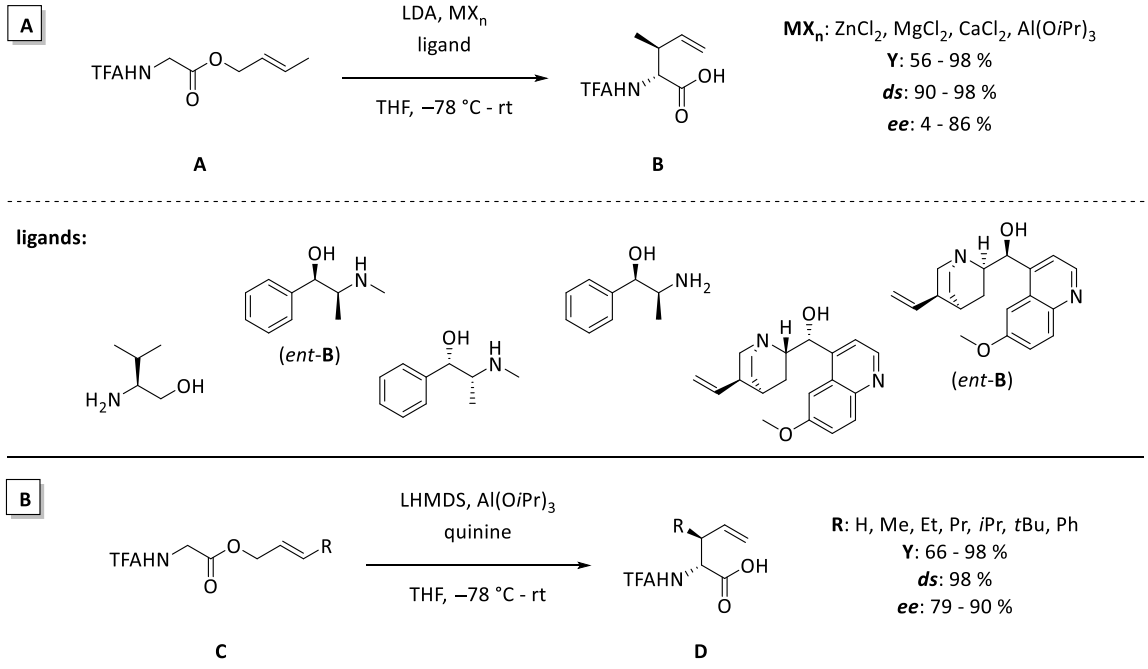
Scheme 2.12: Influence of the olefin and enolate geometry on the rearrangement of allyl esters.[94]

A different method to stabilize ester enolates which subsequently underwent [3,3]-sigmatropic rearrangement has been reported by Kazmaier.[97] Utilization of glycine allyl esters in the reaction should allow for the construction of γ,δ-unsaturated amino acids. While the corresponding Li-enolates derived from crotyl ester **A** only gave decomposition products upon warming to room temperature, several chelating metals provided the rearranged product **B** in good yield and high diastereoselectivity (scheme 2.13, A). The driving force was speculated to be the formation of a chelate enolate, which is stable at temperatures needed to facilitate rearrangement. The best results were generally obtained with zinc chloride as chelating agent. Consequently, this metal salt was used to study the influence of the olefin geometry and the degree of substitution on the stereochemical outcome of the reaction. Glycine esters **C** were treated with LDA and $ZnCl_2$ at –78 °C to form the corresponding (*Z*)-enolates, which then underwent rearrangement upon warming to room temperature. It was shown that (*E*)-configured olefins preferably afforded *syn*-**D**, while (*Z*)-olefins gave *anti*-**D** selectively (scheme 2.13, B). The high diastereoselectivity was a result of the fixed enolate geometry through chelation. The (*Z*)-enolate formed rearranged *via* a chair-like transition state to afford the product in a diastereoselective manner. However, the NH-function was found to be crucial for chelation and subsequent rearrangement since substrates without this function failed to give the rearranged product.



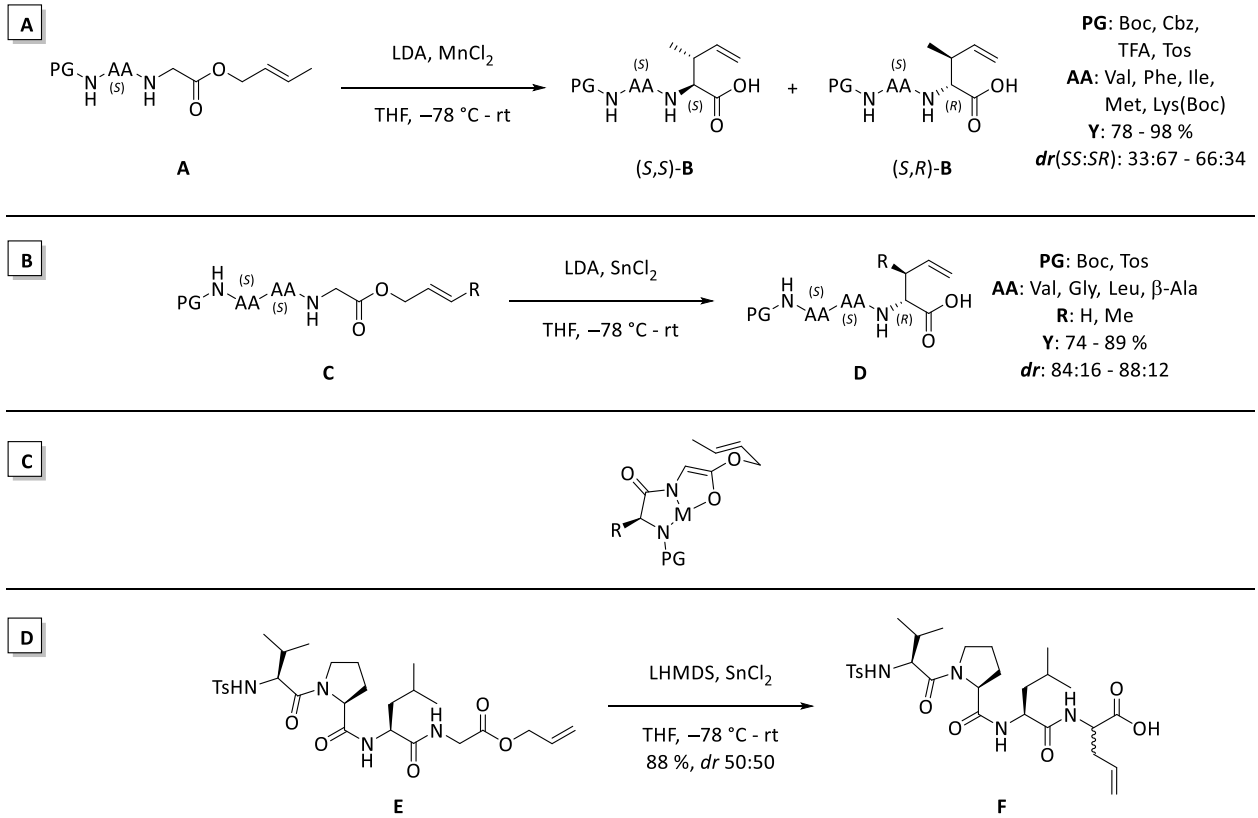
Scheme 2.13: Chelate enolate rearrangement developed by Kazmaier.[97]

Addition of chiral ligands to the chelate enolate solution enabled an asymmetric version of this rearrangement.[98] The rearrangement of TFA-protected glycine crotyl ester **A** in presence of different chiral ligands and metal salts was investigated (scheme 2.14, A). Bidentate ligands in combination with Al(O*i*Pr)$_3$ have proven beneficial, while the best results were obtained with the cinchona alkaloids quinine and quinidine. The chiral ligand presumably shields one side of the ester enolate, resulting in rearrangement *via* one of the two enantiomeric chair-like transition states preferably. Different glycine allyl esters **C** were exploited in this transformation under optimized conditions to afford the corresponding γ,δ-rearranged amino acids **D** with good enantio- and excellent diastereoselectivity (scheme 2.14, B).



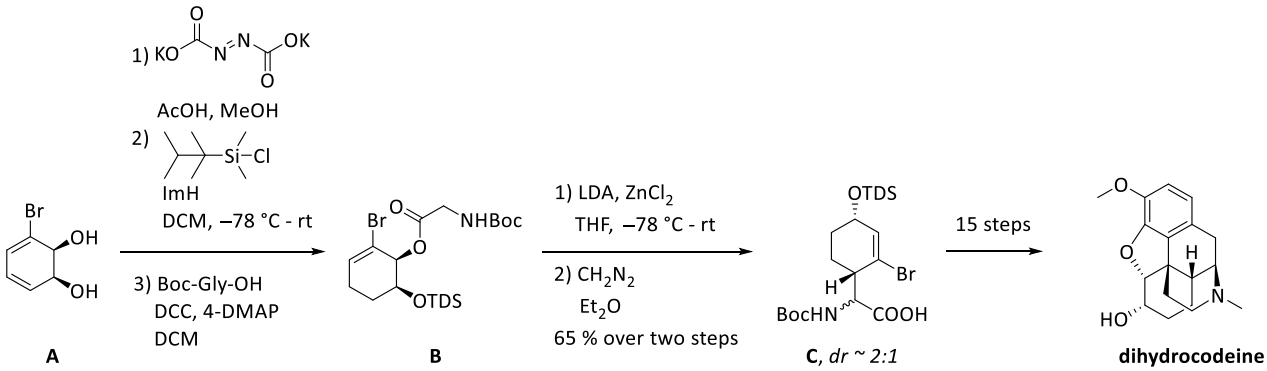
Scheme 2.14: Asymmetric chelate enolate Claisen rearrangement.[98]

The chelation concept is not limited to ester enolates derived from amino acids but can also be utilized for peptide ester enolates. With further amino acids attached to the chelate enolate, chiral complexes are formed and the stereochemical outcome of the newly formed α-center can in general be controlled by the peptide backbone. Kazmaier and Maier reported the rearrangement of dipeptide crotyl esters **A** in presence of manganese salts. The corresponding γ,δ-unsaturated dipeptide acids **B** were afforded in good yields, albeit modest diastereoselectivities (scheme 2.15, A).[99] Improved results were obtained with other metal salts like $NiCl_2$ or $SnCl_2$ (**C** → **D**, scheme 2.15, B).[100] Noteworthy, Tos-protected peptides gave the best results both in terms of yield and diastereoselectivity and even allowed for the rearrangement of Li-enolates. Di-, tri- and even tetrapeptides were shown to rearrange readily and with *unlike* diastereoselectivity, meaning that (*S*)-configured amino acids adjacent to the chelate enolate control the new stereogenic center in favor of the (*R*)-isomer.[100] This could be envisioned by formation of a chiral chelate complex where the amino acid side chains shield one side of the ester enolate. Rearrangement then takes place from the *unlike* side preferably (scheme 2.15, C). While no influence of the number of adjacent amino acids in the peptide chain on the diastereoselectivity was observed, rearrangement of tetrapeptides containing a secondary amine or sarcosine subunit resulted in epimeric mixtures of the newly formed α-stereocenter. For instance, rearrangement of tetrapeptide allyl ester **E** with tin chloride afforded **F** as a 1:1 diastereomeric mixture (scheme 2.15, D). This effect probably resulted from an interrupted chelation of the peptide backbone due to the missing NH-functionality of the proline residue.



Scheme 2.15: Chelate enolate Claisen rearrangement of peptide enolates.[99,100]

Chelate enolate Claisen rearrangements have been reported to be powerful tools in the construction of non-proteinogenic and unusual amino acids. Varghese and Hudlicky utilized this transformation in their total synthesis of dihydrocodeine and hydrocodone.[101] Reduction of diol **A**, followed by silyl protection and esterification with Boc-protected glycine gave cyclic allyl ester **B** in moderate yield (scheme 2.16). Subsequent ester enolate Claisen rearrangement afforded amino acid ester **C** after methylation in 65 % yield as a 2:1 mixture of diastereomers. The modest diastereoselectivity was speculated to result from rearrangement *via* both chair- and boat-like transition states as reported by Ireland *et al*. for cyclohexenyl derivatives.[102] The targeted dihydrocodeine was obtained from **C** after 15 consecutive steps.

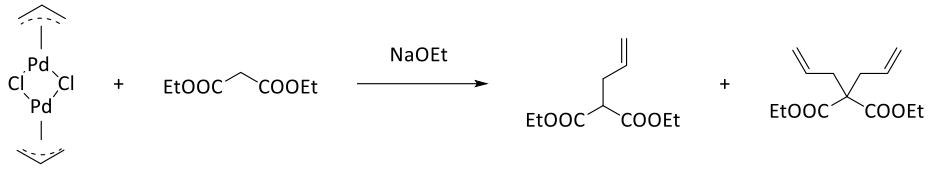


Scheme 2.16: Chelate enolate Claisen rearrangement in the synthesis of dihydrocodeine.[101]

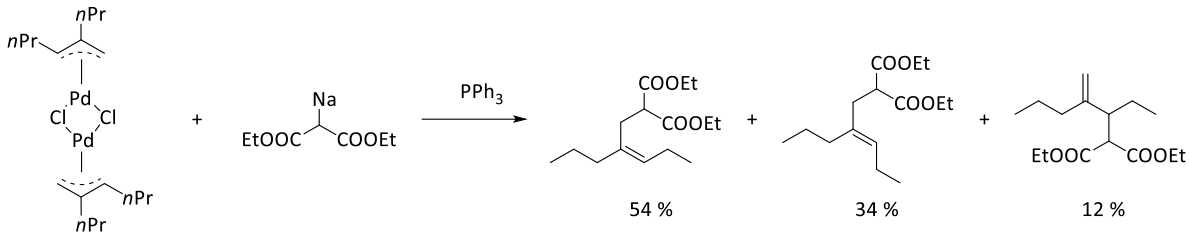
2.2.2 Transition metal catalyzed allylic alkylations

Allylic substitutions catalyzed by transition metals are of outstanding importance to the construction of C-C, C-N and even C-O bonds. While it has been known that palladium-olefin complexes undergo nucleophilic attack by hydroxide anion[103], amines[104] or acetate anion[105], studies undertaken by Tsuji *et al*. in 1965 found that malonates react with palladium-π-allyl chloride to form mono- and dialkylated products (scheme 2.17).[106,107] Trost and co-workers expanded the scope of the reaction tremendously by introducing phosphine ligands.[108] Reactions of preformed Pd-π-allyl complexes with malonates did occur readily upon addition of triphenylphosphine to afford a mixture of regioisomeric allylation products (scheme 2.17). Furthermore, addition of phosphines triggered the development of stereoselective versions of this reaction by utilizing chiral ligands.[109] Synthetical importance was gained through development of a catalytic version of the allylic substitution by employing olefins bearing a leaving group in allyl position.[110] These substrates react spontaneously with Pd(0) to form the crucial Pd-π-allyl complex and allow the intermediately formed Pd(0) species to reenter the catalytic cycle through oxidative addition. The transition metal catalyzed allylic alkylation is nowadays referred to as Tsuji-Trost reaction.

Tsuji 1965:



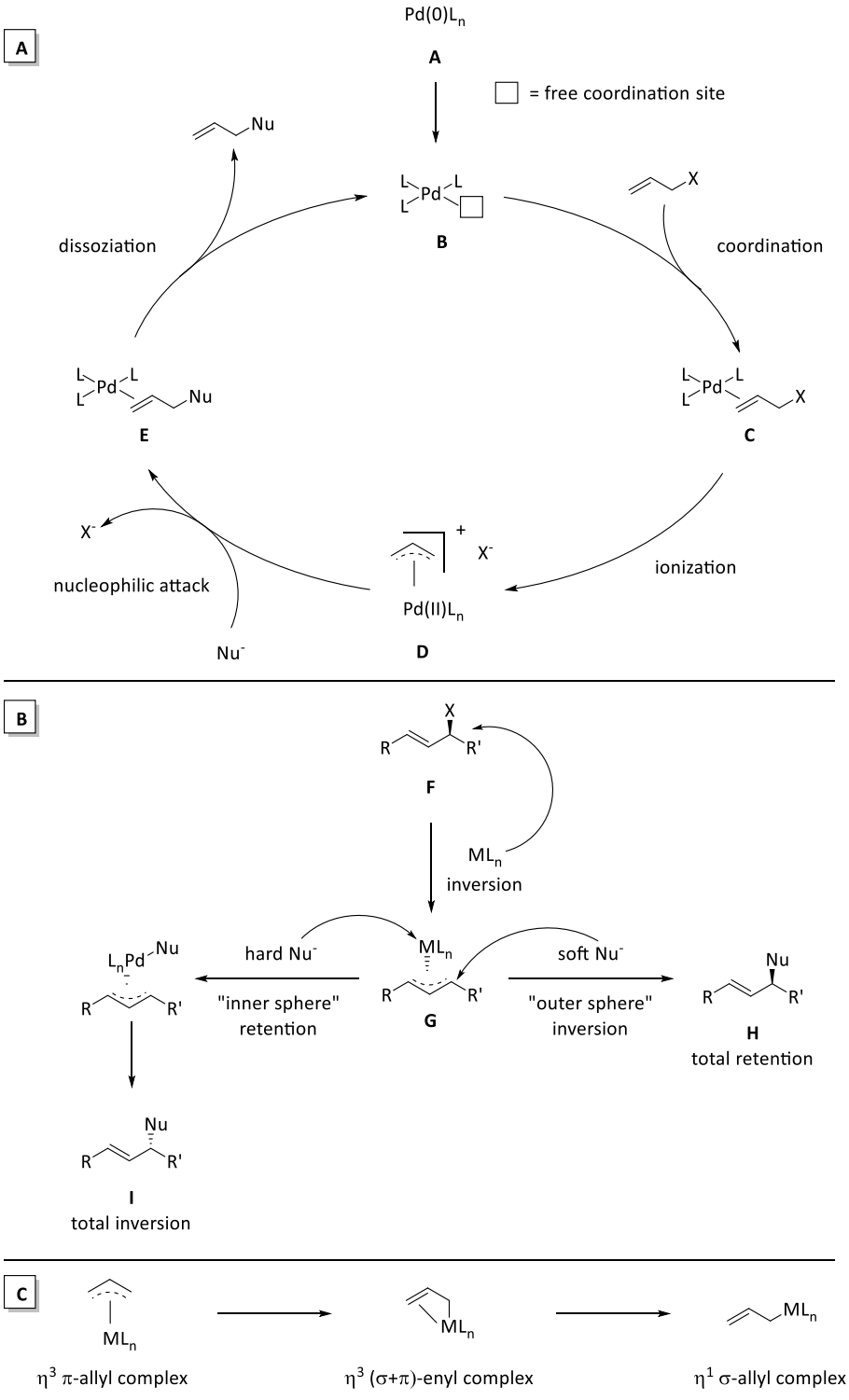
Trost 1973:



Scheme 2.17: Allylic substitutions developed by Tsuji[107] and Trost[108].

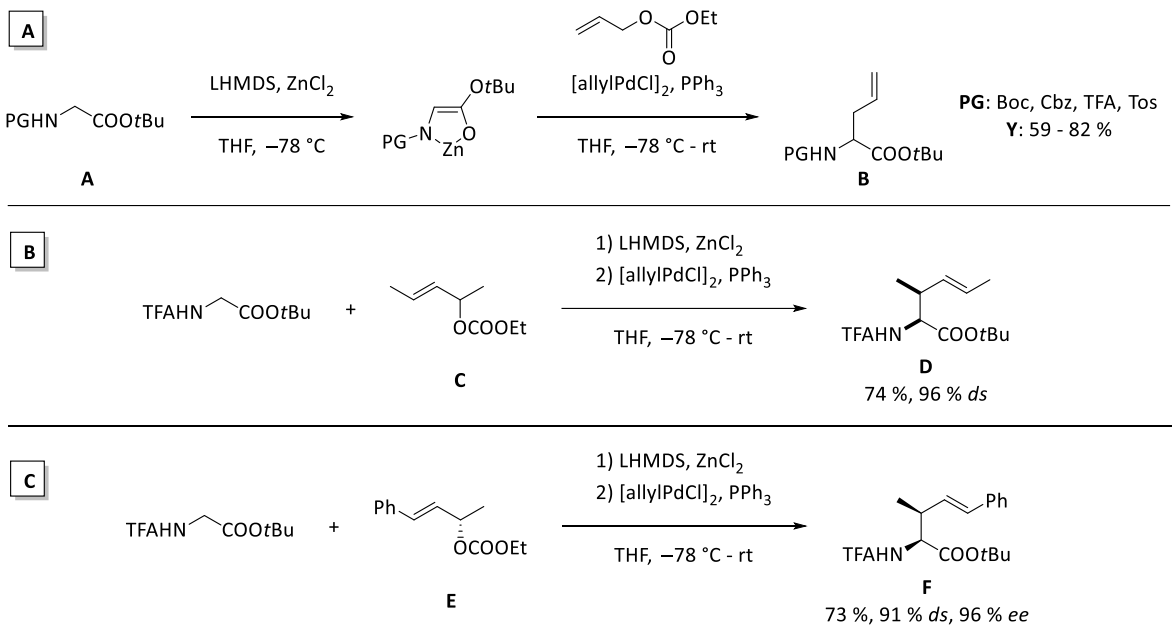
Detailed mechanistic studies were conducted in the last decades to rationalize the (stereochemical) outcome of the reaction. The course of the reaction can be depicted using a catalytic cycle (scheme 2.18, A).[111] A suitable Pd(0) precursor **A** undergoes dissociative ligand exchange under formation of a catalytically active $16e^-$ complex **B**, which allows for coordination of an olefinic substrate. The coordinated Pd complex **C** undergoes ionization to form Pd-π-allyl complex **D**, which subsequently undergoes nucleophilic attack by either a C-, N-, O- or another nucleophile. Dissociation of the newly formed olefin from complex **E** liberates the allylated product and simultaneously regenerates the active catalyst **B**. The stereochemical outcome can be envisioned utilizing chiral allylic substrates **F**, which undergo nucleophilic attack of the TM species under stereoinversion (scheme 2.18, B).[112] The newly formed TM-π-allyl complex **G** can then undergo nucleophilic attack in two different ways; soft nucleophiles (pK_a-value of corresponding acid < 25) directly attack at the allyl scaffold of complex **G** ("outer sphere"), while hard nucleophiles (pK_a-value of corresponding acid > 25) initially attack the transition metal center and form the product after reductive elimination ("inner sphere"). Attack of soft nucleophiles happens from the opposite side than the transition metal is located and with double inversion of the stereogenic center. The allylation product **H** shows total retention, meaning that the conformation of both starting material and product is the same. In contrast, an inner sphere mechanism performed by hard nucleophiles results in total stereoinversion (**F** → **I**) since reductive elimination proceeds under stereoretention from the same side than the transition metal. Another effect that was shown to influence the stereochemical outcome of the Tsuji-Trost reaction is π-σ-π isomerization of the TM-allyl complex (scheme 2.18, C). The η^3 π-allyl complex formed after ionization can change its hapticity under formation of a η^3 (σ+π)-enyl complex and finally a η^1 σ-allyl complex, which allows free rotation around the C-M bond. This can have drastic consequences for the regio- and stereoselectivity of the reaction and influences the double bond geometry of the allylation product. The tendency to undergo π-σ-π isomerizations depends on the transition metal employed in the reaction. Palladium is known to rapidly isomerize and undergo nucleophilic attack preferably at the

sterically less hindered position of the Pd-π-allyl complex. Other transition metals like Rh,[113] Ru[114] and Ir[115,116] have also been reported to perform allylic substitutions and generally show different stereochemical courses of the reaction. For instance, allylic substitutions catalyzed by Wilkinson's catalyst were shown to proceed under preservation of absolute configuration *via* a (σ+π)-enyl complex.[117]



Scheme 2.18: Mechanistic and stereochemical considerations of the transition metal catalyzed allylic substitution.[111,112]

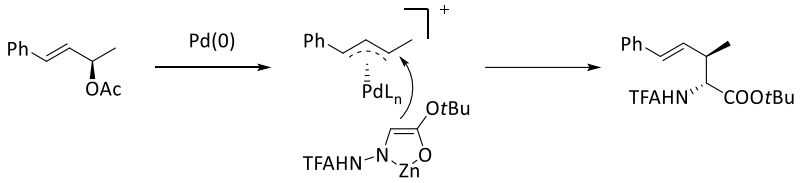
The Tsuji-Trost reaction proved to be a powerful tool in the modification of glycine and peptide enolates. Kazmaier and Zumpe reported the use of chelated glycine ester enolates in Pd-catalyzed allylic substitutions.[118] Differently *N*-protected glycine *tert*-butyl esters **A** were deprotonated with LHMDS and treated with zinc chloride to form a chelate enolate complex (as seen for ester enolate Claisen rearrangements). These enolates performed nucleophilic attack on a Pd-π-allyl complex formed *in situ* from allyl ethyl carbonate and $[allylPdCl]_2$. The reaction proceeded readily at –78°C to afford α-allylated glycine esters **B** (scheme 2.19, A). Furthermore, utilization of 1,3-disubstituted allyl carbonate **C** showed that the allylic alkylation of chelated glycine esters proceeded in a highly diastereoselective manner (scheme 2.19, B). In contrast to reflections about the stereochemical outcome of the ester enolate Claisen rearrangement, Pd-catalyzed allylic substitution gave rise to the *anti*-diastereomer **D** with excellent diastereoselectivity. Therewith, TM-catalyzed allylic substitutions and ester enolate Claisen rearrangements complement each other in terms of diastereoselective formation of γ,δ-unsaturated amino acid esters. Employing chiral allylic carbonate **E** in the reaction afforded the allylated amino acid **F** not only with high diastereoselectivity but also excellent enantioselectivity (scheme 2.19, C). The stereogenic information was transfer from the allylic substrate *via* a Pd-π-allyl complex.



Scheme 2.19: Chelated glycine enolates in the Pd-catalyzed allylic alkylation.[118]

These initial studies revealed that the stereogenic information of chiral 1,3-disubstituted allylic substrates could be transferred to the allylation product effectively.[118] The reason for the observed regio- and stereoselectivity can be rationalized by a chiral Pd-π-allyl complex that undergoes nucleophilic attack from the chelate enolate in such a way, that the bulky *tert*-butyl group stands *trans* to the larger substituent at the allyl fragment. Furthermore, nucleophilic attack preferably occurs from the opposite side than the Pd coordination (outer sphere) and at the least

hindered allylic position, leading to the formation of the corresponding allylation product with high regio- and stereoselectivity (scheme 2.20).

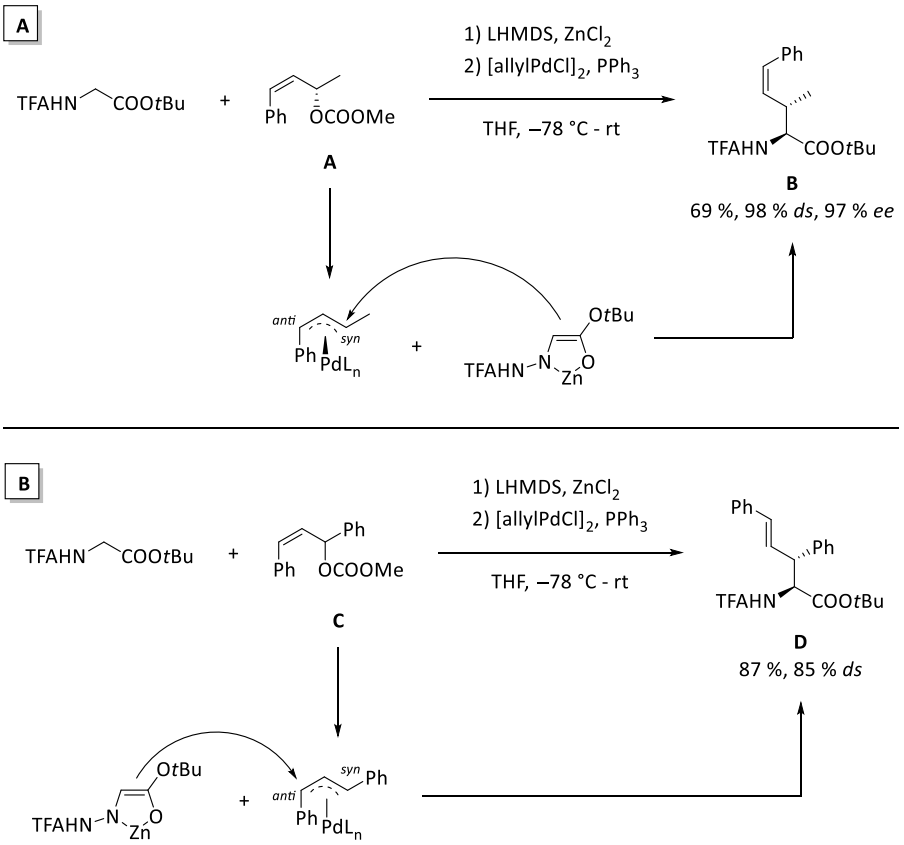


Scheme 2.20: Proposed mechanism for the allylic alkylation of chelated glycine enolates.[118]

As pointed out in the mechanistic reflections (scheme 2.18), π-σ-π isomerization can have a dramatic influence on the stereochemical outcome of the reaction. The stereogenic information of enantiomerically pure allylic substrates generally cannot be transferred *via* a terminal Pd-π-allyl complex due to rapid isomerization and therewith racemization *via* the σ-allyl complex.[119] However, chelated glycine enolates were shown to be very reactive nucleophiles, allowing transformations at low temperatures (–78 °C), where π-σ-π isomerization seemed to be suppressed. These findings resulted in the observation of unusual allylation products.[119] Kazmaier and Zumpe showed that (*Z*)-configured allylic substrate **A** could be transformed into the corresponding allylation product **B** bearing a (*Z*)-double bond (scheme 2.21, A). It was hypothesized that suppressed π-σ-π isomerization of the intermediately formed *anti*/*syn* complex led to formation of the observed product. The obtained regioselectivity was in accordance to previously reported results (see scheme 2.20). Moreover, symmetrically substituted (*Z*)-configured allylic substrate **C** was used to determine the relative reactivity of the *syn*- and *anti*-position to undergo nucleophilic attack (scheme 2.21, B). By ruling out the influence of sterics on the product formation, the attained product **D** allowed for conclusions about the intrinsic reactivity of the respective positions. The obtained results clearly indicated that the *anti*-position is more reactive in symmetrically substituted π-allyl complexes since only the (*E*)-configured product **D** was observed.

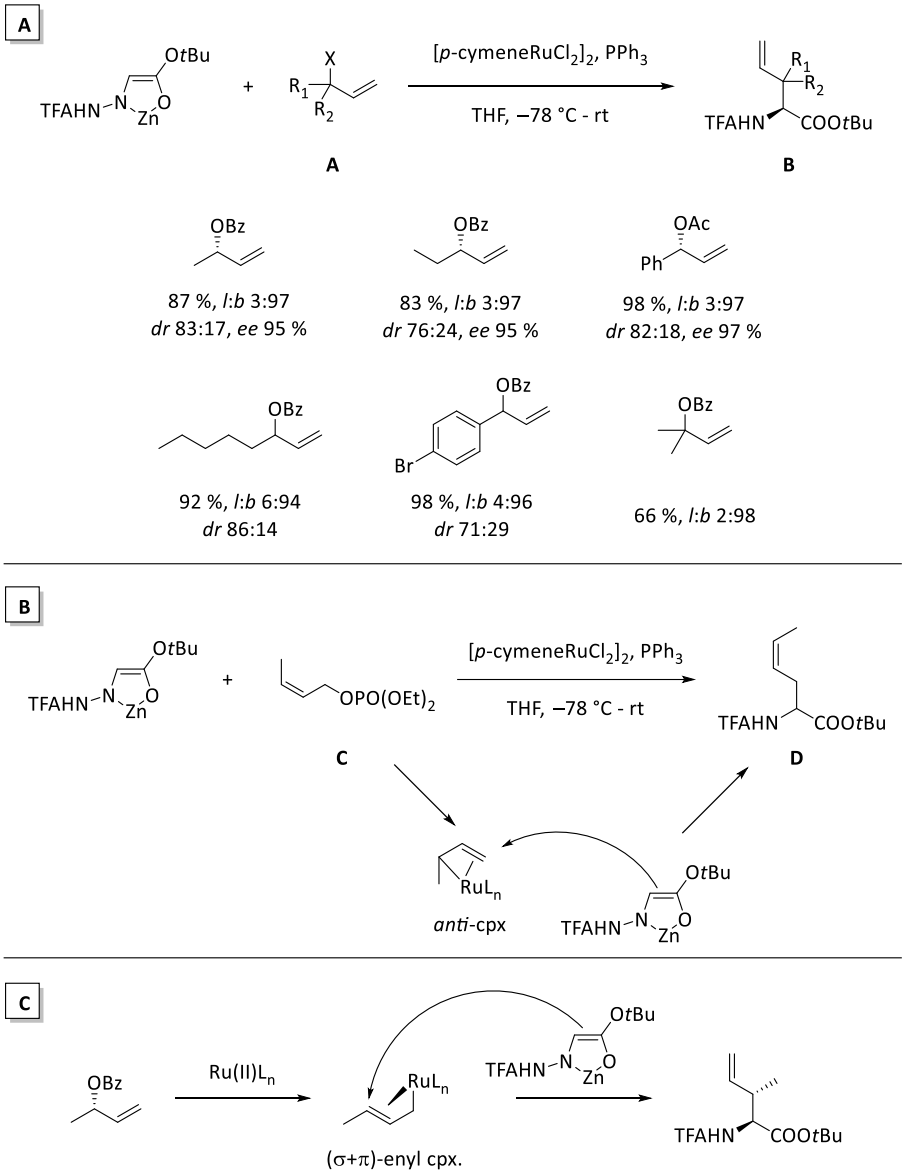
A characteristic of the Pd-catalyzed allylic substitution is that nucleophilic attack preferably occurs at the sterically less hindered position of the allyl moiety. Consequently, a terminal Pd-π-allyl complex gives rise to the linear allylation product with high selectivity. Luckily, this transformation is not limited to Pd-catalysis, but also other transition metals have been reported to effectively facilitate the allylic substitution. Ruthenium-catalyzed reactions have gained ground since their initial discovery by Tsuji and co-workers.[114] The observed regioselectivity in the Ru-catalyzed process depends more on the metal's ligand system than on the utilized allylic substrate.[120] This led to the development of catalysts with selectivities for either linear[121] or branched[120,122] products, regardless of the starting allylic substrate. On the contrary, Kawatsura *et al*. reported allylic substitutions under regioretention, meaning that branched allylic substrates afforded the branched products preferably, while linear allylic substrates gave the corresponding linear products.[121,123] The observed "memory effect" with the utilized [*p*-cymeneRuCl$_2$]$_2$ complex

could be rationalized *via* formation of a (σ+π)-enyl complex, as discussed for the Rh-catalyzed process.[117]



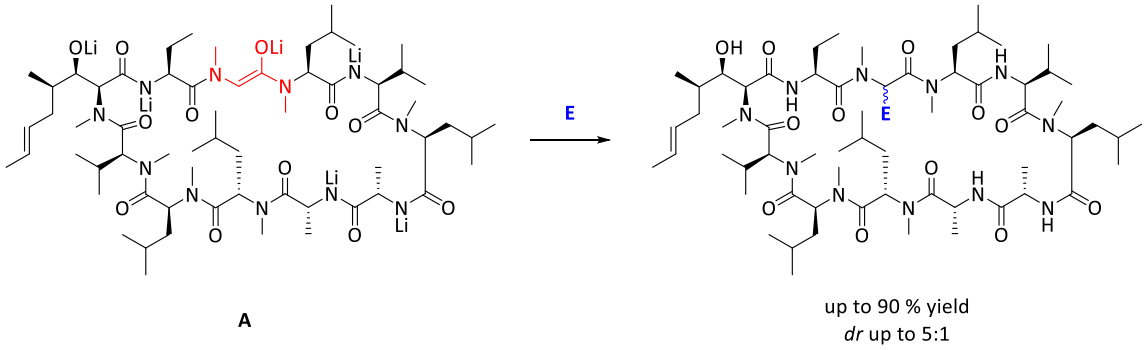
Scheme 2.21: Utilization of (*Z*)-configured allylic substrates in isomerization-free allylic substitutions.[119]

Outstanding results with the [*p*-cymeneRuCl$_2$]$_2$/PPh$_3$ catalyst system were obtained by Bayer and Kazmaier.[124,125] The memory effect of the utilized Ru-complex was exploited to synthesize branched glycine allyl esters **B** from the corresponding allylic substrates **A** bearing a terminal olefin (scheme 2.22, A). Thus, Ru-catalyzed allylic alkylation supplements the scope of the Pd-catalyzed reaction in terms of the employed allylic substrates as well as the attained products. Another peculiarity of this catalyst system was the observed lack of π-σ-π isomerization. When (*Z*)-configured allylic substrate **C** was used, the obtained product **D** also contained a (*Z*)-double bond, indicating the configurational stability of the intermediately formed *anti*-complex (scheme 2.22, B). These observations, together with the fact that the stereogenic information can be transferred *via* a terminal allyl complex, underlined the hypothesis of an intermediate (σ+π)-enyl complex (scheme 2.22, C).



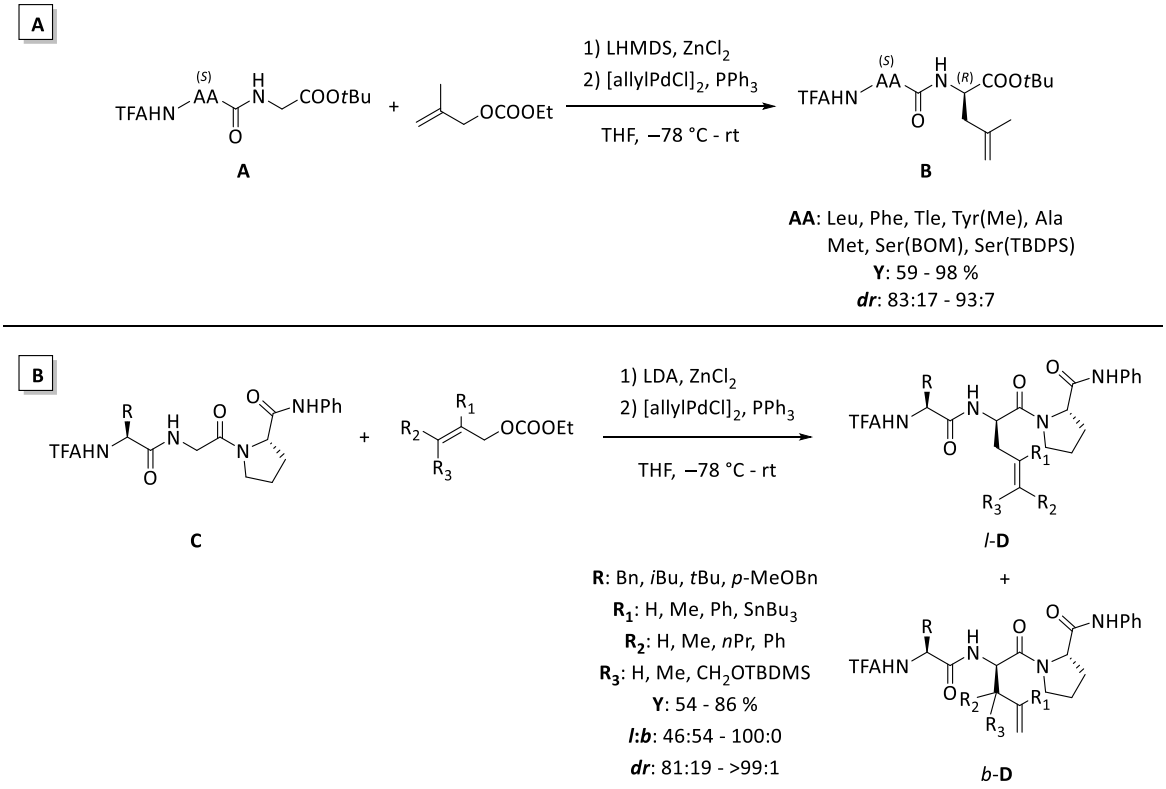
Scheme 2.22: Ru-catalyzed allylic alkylations of chelated glycine enolates.[124,125]

Seebach and co-workers reported the regio- and stereoselective modification of linear[126] and cyclic peptides[127] that underwent substitution with various electrophiles at glycine or sarcosine subunits. The observed regioselectivity could be rationalized by the lithiation state of a given peptide. While peptidic NH-groups prevented an adjacent amino acid's α-H from deprotonation, glycines or sarcosines next to secondary or *N*-Me amino acids could be modified. Seebach *et al*. impressively demonstrated the regio- and stereoselective modification of cyclosporin A, a cyclic undecapeptide (scheme 2.23). Treatment of cyclosporin A with LDA presumably afforded the hexalithiated compound **A**, which readily underwent nucleophilic substitution with methyl iodide or other suitable electrophiles. The stereochemical outcome of the reaction was controlled by the peptide backbone.



Scheme 2.23: Regio- and stereoselective modification of cyclosporin A.[127]

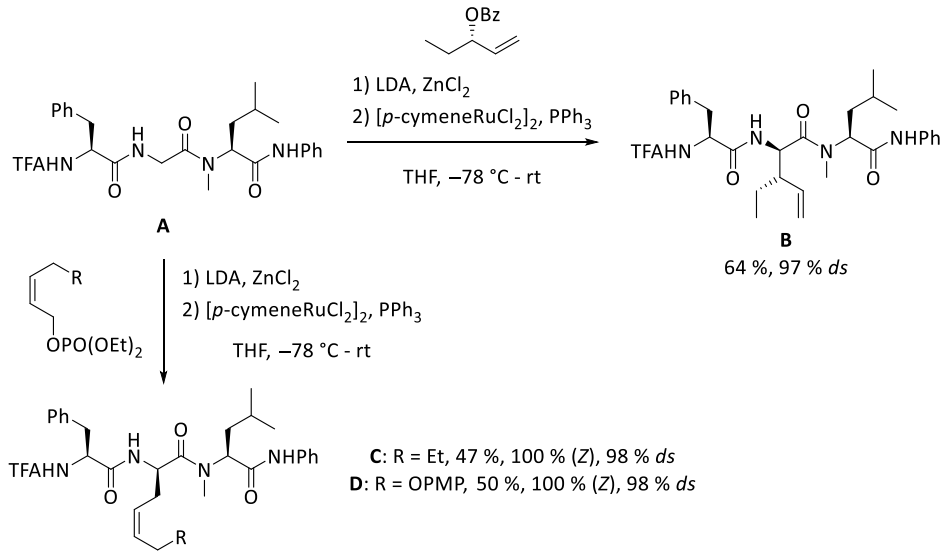
The concept of selective peptide modifications could be expanded to transition metal catalyzed allylic alkylations of chelated peptide enolates. Kazmaier and co-workers reported the diastereoselective allylic alkylation of dipeptides under Pd-catalysis[128]. These initial studies focused on modifications of *C*-terminal glycine moieties. Deprotonation of **A** with LHMDS and chelation with $ZnCl_2$ afforded stabilized dipeptide enolates, that performed nucleophilic attack at Pd-π-allyl complexes derived from allylic carbonates (scheme 2.24, A). Remarkably, the adjacent amino acid was able to control the stereochemical outcome of the newly formed α-stereogenic center in **B**. In accordance to reflections about the stereocontrol during peptide ester enolate Claisen rearrangement, the already present side chain shielded one side of the nucleophile and delivered the product with high selectivities for the (*S*,*R*)-diastereomer.



Scheme 2.24: Pd-catalyzed allylic alkylation of chelated peptide enolates.[128]

Interestingly, even internal peptide enolates could be successfully transformed *via* the aforementioned peptide modification reaction. To guarantee effective α-deprotonation and chelation, the modified glycine must contain a secondary amine in *C*-direction as seen in the selective modification of cyclosporin A. Proline-containing tripeptides **C** were shown to effectively undergo Pd-catalyzed allylic substitutions (scheme 2.24, B).

The selective modification of internal tripeptide enolates is not restricted to Pd-catalyzed allylic alkylations. Transformations of these substrates under Ru-catalysis were shown to proceed quite effectively and in a highly regio- and stereoselective manner.[129] Furthermore, *N*-methylated amino acids could also be utilized to achieve selective enolization of adjacent glycine residues and (*Z*)-configured allylic substrates allowed the introduction of the corresponding (*Z*)-olefins into a given peptide chain (scheme 2.25). These results demonstrated the synthetic usefulness of transition metal catalyzed allylic substitutions for the selective modification of amino acids and peptides.



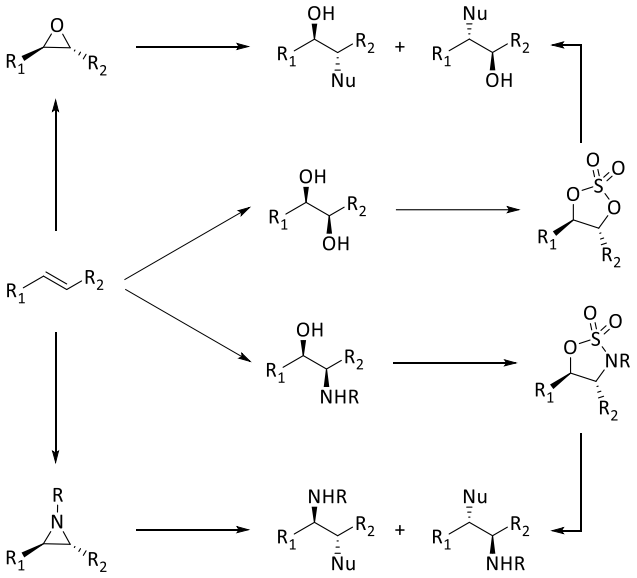
Scheme 2.25: Ru-catalyzed selective peptide modifications.[129]

2.2.3 Thiol-ene click reactions

The allylic side chain introduced by either ester enolate Claisen rearrangement or transition metal catalyzed allylic alkylation allows for a range of diverse modifications of the olefin moiety. Olefins are among the most versatile starting materials to introduce new functional groups into a given structure. Several transformations involving olefins have been developed over the past decades including Sharpless' asymmetric dihydroxylation,[130,131] Brown hydroboration,[132] Heck reaction,[133] and so on. Applying the developed methods to functionalized amino acids and peptides should allow for the construction of highly complex biomolecules with interesting properties.

Sharpless and co-workers have made great contributions to the field of olefin modifications by introducing the "click chemistry" concept. They envisioned that nature has a preference for making C-X bonds over C-C bonds.[134] Base of this concept was to provide a set of powerful and

reliable chemical transformations to perform C-X bond formations in a selective manner and to focus on the function of a synthesized molecule instead of its chemical structure. Sharpless *et al*. defined the parameters that a reaction has to meet in order to be considered a "click reaction". This includes high yields, simple reaction conditions, no or mild solvents and simple product isolations as key requirements. Furthermore, high thermodynamic driving forces are demanded in order to give full and rapid conversion of the starting materials. They initially focused their work on generation and opening of small ring electrophiles like epoxides and aziridines (scheme 2.26)

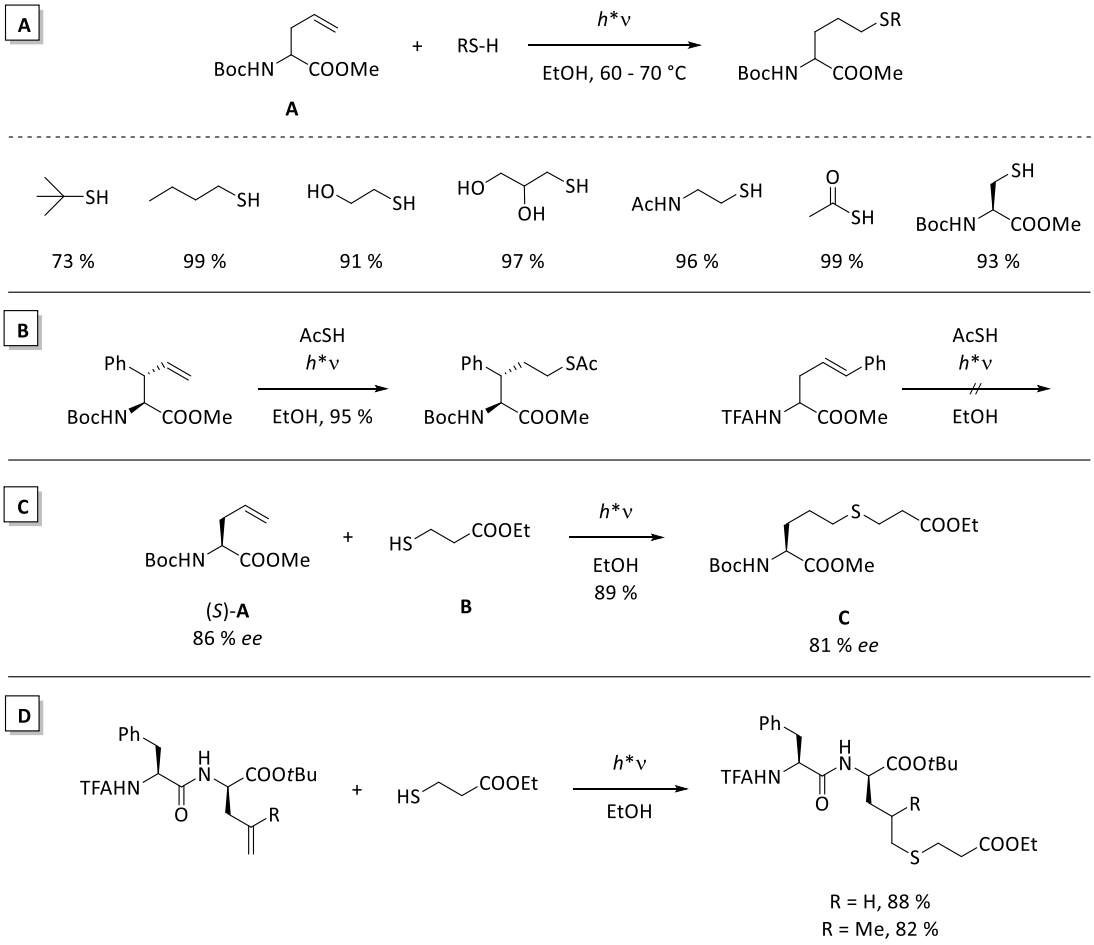


Scheme 2.26: "Click chemistry" as developed by Sharpless and co-workers.[134]

The click concept was expanded to further transformations involving olefins under formation of C-X bonds. The addition of thiols to olefins has been known for over a century and was resurrected in the light of these new developments.[135] The radical reaction of thiols with terminal olefins was found to meet the criteria of a classical click reaction. Hoyle and Bowman described the addition of thiols to alkenes as high yielding, simple to execute and rapidly proceeding without formation of side products.[136] Radical formation can be initiated by light and the reaction tolerates a large scope of olefin substrates and thiols. Thiol-ene click reactions can generally be conducted in presence of air and moisture and proceed with nearly quantitative formation of the corresponding thioether in a regioselective manner.[137] The radical thiol-ene click reaction was broadly applied to polymer and material synthesis by performing post-polymerization modifications or surface modification reactions.[136,137]

Due to the neutral reaction conditions, the reaction was shown to perform well in modification reactions of carbohydrates[138,139] and amino acids.[138,140] However, intramolecular H-radical shift led to racemization of the α-center of amino acids in some cases.[141] Karmann and Kazmaier reported the thiol-ene click reaction of allylglycine and unsaturated peptides containing terminal alkenes.[142] Boc-protected allylglycine **A** reacted with a series of different thiols under irradiation in good to excellent yields (scheme 2.27, A). While terminal olefins underwent radical

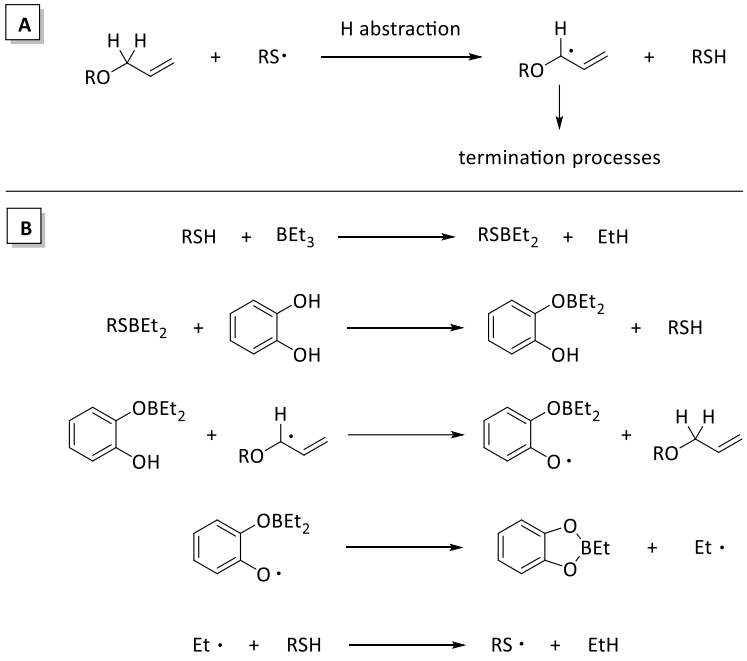
thiol addition rapidly, utilization of internal alkenes failed, meaning that no reaction was observed (scheme 2.27, B). Besides steric aspects, the addition of thiols to olefins is a reversible process and product formation is observed preferably with terminal alkenes.[143] Epimerization *via* internal radical 1,3-H shift was observed with Boc-protected allylglycine (*S*)-**A**. Addition of thiol **B** led to a slight drop in enantiomeric excess (scheme 2.27, C). These findings were in accordance to the above-mentioned observations by Broxterman and co-workers.[141] Interestingly, even unsaturated peptides could successfully be employed in the reaction giving the desired thioethers in good yield and most notably without epimerization of the α-center (scheme 2.27, D).



Scheme 2.27: Light-induced thiol-ene click reaction of amino acids and peptides.[142]

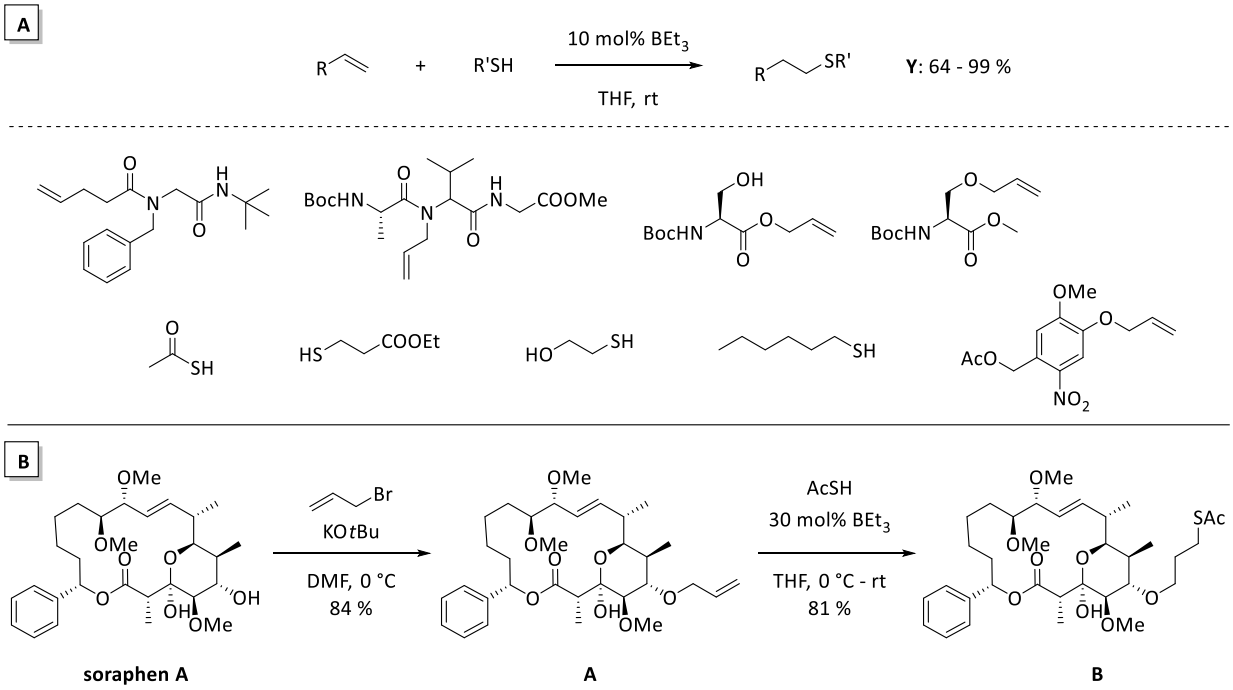
Although radical thiol-ene additions normally occur rapidly and with high yields of the desired product, rise of side reactions and moderate yields were observed with substrates bearing *O*-allyl and *O*-benzyl moieties.[144,145] The *in situ* formed thiyl radicals can cause H-abstraction in allyl- or benzyl position, resulting in undesired side reaction and chain termination processes (scheme 2.28, A).[146] Furthermore, large excess of thiol was needed in some cases to afford the addition products with these substrates.[147,148] To overcome these limitations, Renaud *et al*. reported an improved protocol for the radical thiol-ene click reaction with anomeric *O*-allyl sugar derivatives.[146] They found that a combination of triethylborane and catechol is suitable to "repair"

the radical chain process. Triethylborane is known to form ethyl radicals through reaction with oxygen and its use as radical initiator has been reported.[149,150] Addition of catechol leads to formation of a borinic ester, which is able to transfer H-radicals to *O*-allyl and *O*-benzyl radicals and therewith prevents termination processes (scheme 2.28, B).



Scheme 2.28: "Repair" mechanism in the BEt_3-mediated thiol-ene click reaction.[146]

While stochiometric amounts of both triethylborane and catechol were required in the aforementioned thiol-ene modification of sugar derivatives, Gorges and Kazmaier could show that catalytic amounts of BEt_3 are sufficient to efficiently perform the addition of thiols to amino acids and peptide derivatives (scheme 2.29, A).[151] Moreover, BEt_3-initiated thiol-ene click reaction proved to be an improvement of the light-induced version due to the fact that no large excess of thiol was needed and even photolabile substrates could be transformed under the reaction conditions used. *O*-allyl ethers were employed in the reaction to evaluate the presence of a H-abstraction mechanism. Interestingly, high yields were obtained for all kinds of substrate including *O*-allyl ethers and esters as well as *N*-allyl amides. Most striking was the selective modification of the natural product soraphen A, a cyclic polyketide from *Sorangium cellulosum*.[152] Treatment of soraphen A with allyl bromide afforded allyl ether **A**. Subsequent addition of thioacetic acid gave the desired thioester **B** in 81 % yield (scheme 2.29, B).



Scheme 2.29: BEt_3-initiated thiol-ene click reactions of unsaturated compounds.[151]

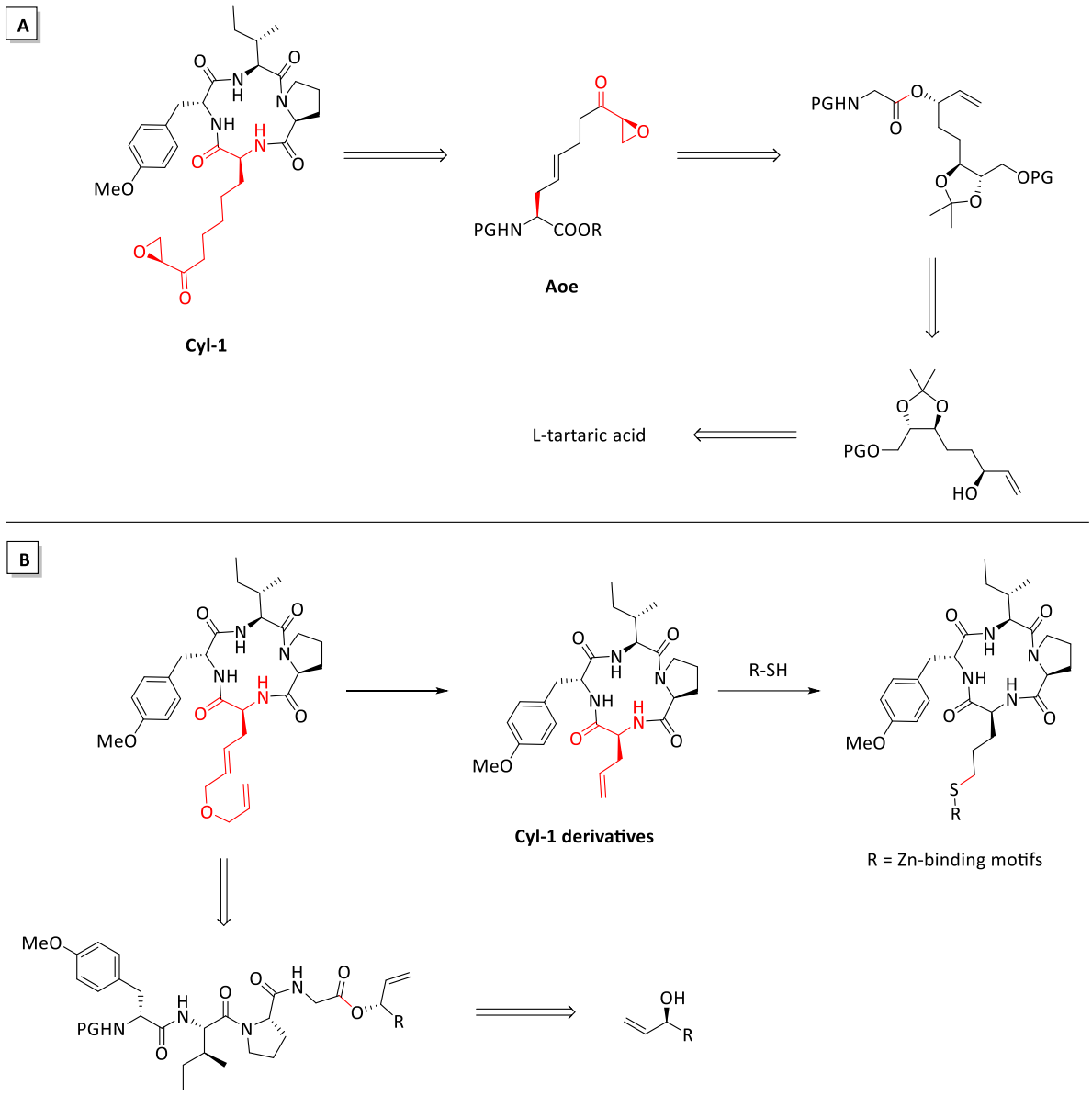
In conclusion, selective modifications of amino acids and peptides are powerful tools for the construction of unusual, non-proteinogenic amino acid residues, which are often incorporated in biologically active compounds. This large toolbox furthermore triggers the development of natural product derivatives essential for the study of biological function and evaluation of structure-activity relationships.

3. Aim of this work

The main goal of this dissertation was to synthesize natural HDAC inhibitors and develop a flexible protocol to get access to both the natural products and derivatives thereof. For this purpose, Cyl-1 and trapoxin A were identified as striking targets. The first natural HDACi, Cyl-1, was isolated from *Cylindrocladium scoparium* and was recognized as a HDACi due to its chemical structure.[47] However, no biological activities have been reported so far for Cyl-1, which made it an attractive goal for total synthesis. Together with the fact that its structural analogue Cyl-2 shows extraordinary selectivity towards the different HDAC isoforms (see chapter 2.1.6), Cyl-1 was noted as a promising core structure for the development of several derivatives. The second natural product, trapoxin A, was first isolated from *Helicoma ambiens* RF-1023 in 1990.[41] While trapoxin B, a structural analogue, was the target of a total synthesis shortly after its isolation, no synthetic access towards trapoxin A has been accomplished yet. Furthermore, trapoxin A evinced a peptide backbone which was found to be ideal to demonstrate the power of peptide modification reactions to incorporate unusual amino acids into a given peptide chain.

To establish a straightforward protocol for the synthesis of Cyl-1, construction of the non-proteinogenic (2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid (Aoe) was crucial. Therefore, the main goal in the synthesis of Cyl-1 was to exploit an elegant access towards the Aoe scaffold. This amino acid should be accessible through ester enolate Claisen rearrangement of a suitable precursor. These rearrangements generally proceed with high yield and excellent transfer of stereogenic information to the newly formed α-stereocenter. The stereogenic information of the corresponding allylic ester should be derived from natural sources, e.g. tartaric acid (scheme 3.1, A).

The synthesis of derivatives of Cyl-1 should be accomplished by incorporation of an allylglycine into the macrocyclic core structure. This would allow for manifold derivatization reaction like thiol-ene click reactions in order to introduce new zinc-binding motifs. This strategy was chosen since the Cyl-core structure already shows high isoform selectivity (determined by the peptidic backbone) and introduction of new zinc-binders should alter the pharmacological properties (especially pharmacokinetics). While the focus of this work clearly lied on the derivatization of this allylglycine moiety, access towards this non-proteinogenic amino acid containing macrocycle was essential. Thus, a flexible synthetic route was needed that would allow for the incorporation of other side chains through peptide modification reactions (scheme 3.1, B).

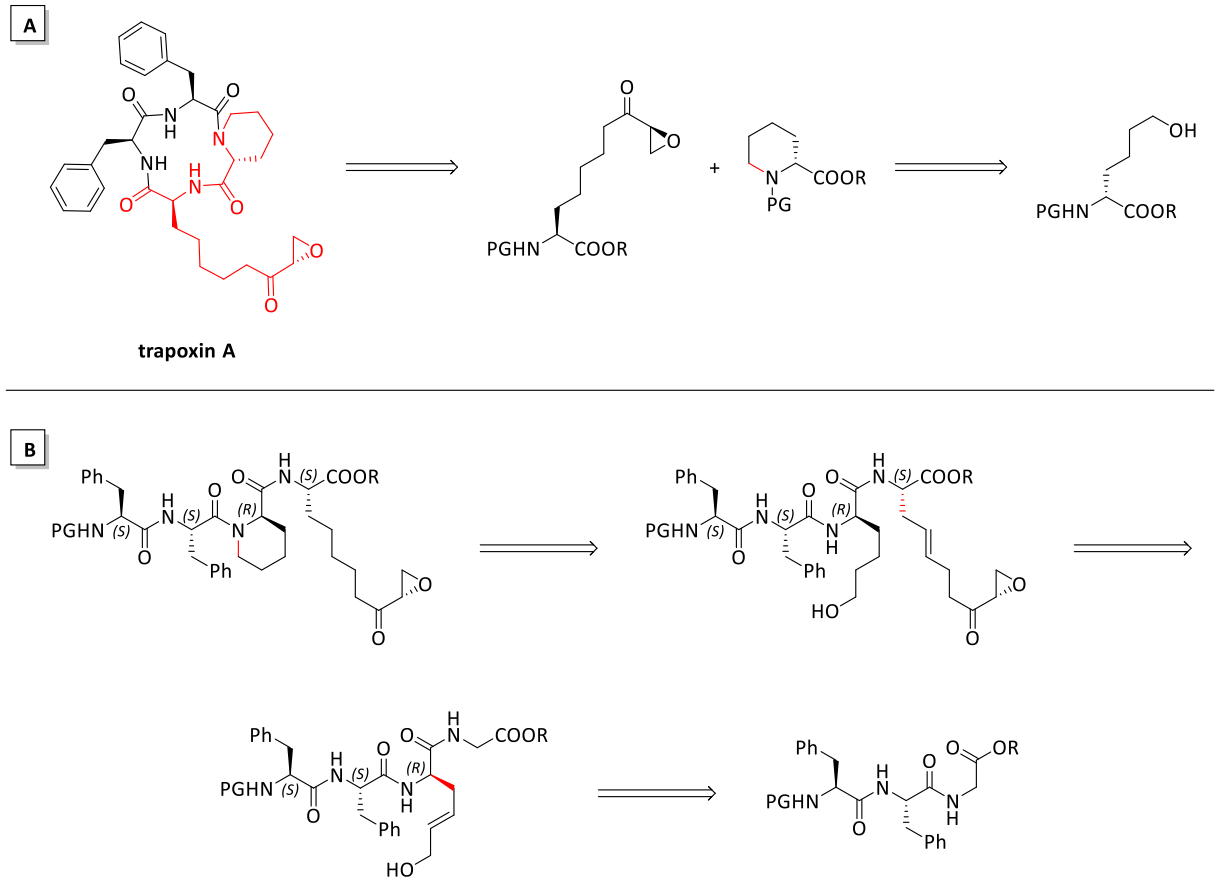


Scheme 3.1: Synthesis of Cyl-1 and its derivatives.

For trapoxin A, synthetic routes towards the two non-proteinogenic amino acids Aoe and (*R*)-pipecolinic acid needed to be developed. While Aoe was also targeted in the synthesis of Cyl-1, the pipecolinic acid moiety should be accessible through Mitsunobu cyclization of a suitable precursor. With this amino acids in hand, the natural product should by accessible by gradual peptide coupling and following macrolactamization (scheme 3.2, A).

On the other hand, the structure of trapoxin A was compelling in terms of peptide modification reactions. Performing the macrolactamization between Aoe and Phe should leave a linear tetrapeptide backbone with a (*S*)-(*S*)-(*R*)-(*S*)-combination that would allow for subsequent introduction of both the pipecolinic acid precursor as well as the Aoe precursor *via* transition metal catalyzed allylic alkylations. Finally, Mitsunobu cyclization within the peptide chain and subsequent macrolactamization should give the natural product. This synthetic protocol should also

allow access to several derivatives through altering the allylic substrates in the allylic alkylation step (scheme 3.2, B).



Scheme 3.2: Synthesis of trapoxin A.

As outlined before, macrolactamization to form the 12-membered ring system was always a crucial step in the synthesis of these natural compounds and the optimal ring closing position needed evaluation in most cases. Consequently, a highly flexible approach towards these natural HDACi and their derivatives was needed that would allow for the straightforward synthesis of regioisomeric tetrapeptides with the developed methods.

4. Results and Discussion

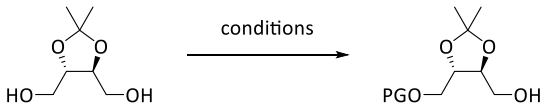
4.1 Synthesis of Cyl-1

The key steps in the synthesis of the macrocyclic HDAC inhibitor Cyl-1 were the construction of the non-proteinogenic Aoe moiety and the challenging macrolactamization to form the 12-membered ring system. From a retrosynthetical point of view, the α-epoxyketone present in Cyl-1 should be accessible through epoxidation and oxidation (scheme 4.1).[67] Macrolactamization between proline and Aoe should give a linear tetrapeptide that could further be disjointed into an Aoe precursor and a tripeptide. The carboxylic acid **A** should be directly accessible through ester enolate Claisen rearrangement of allyl ester **B** without further modifications. The corresponding allylic alcohol **C** needed for esterification with *N*-protected glycine should be derived from a suitable precursor through olefination. This precursor **D** could be synthesized *via* McMurry homocoupling of aldehydes, whose stereogenic information were obtained from L-tartaric acid. The outlined strategy is straightforward in terms of step count since no further derivatization of the rearranged carboxylic acid **A** is required before incorporation into the linear tetrapeptide. Subsequent cyclization and construction of the α-epoxyketone moiety should access the natural product Cyl-1.

4.1.1 Synthesis of the Aoe precursor

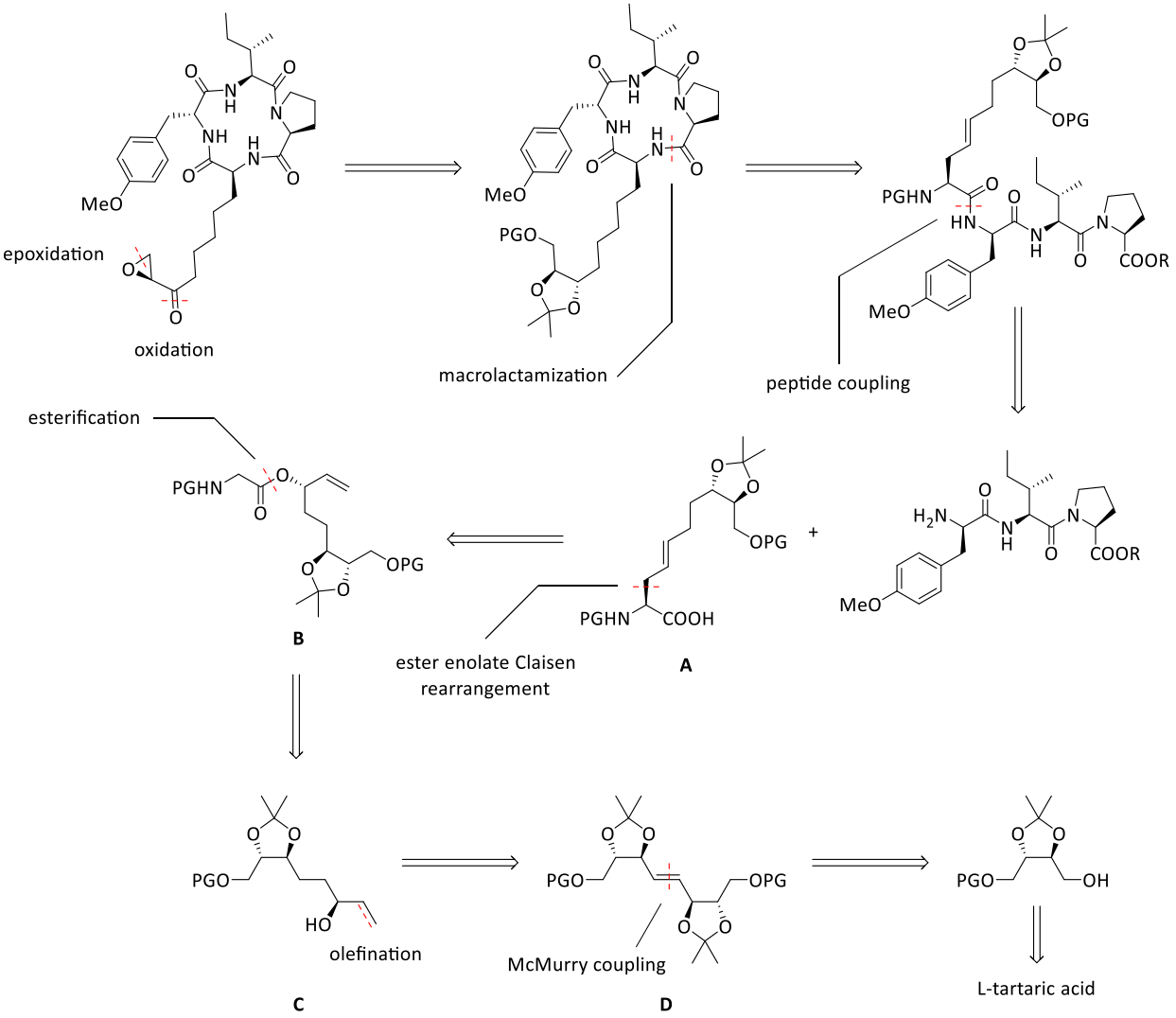
The stereogenic information for the construction of Aoe precursor **A** should be derived from naturally occurring, chiral starting materials like tartaric acids. This so called chiral pool synthesis allows for the construction of various natural products and is well described in literature.[153,154] 2,3-*O*-isopropylidene-L-threitol was synthesized following literature procedure[155] and monoprotection of the L-threitol derivative gave alcohols **1a-c** (table 4.1).[67,156] While **1a** and **1b** were obtained along with the corresponding double-protected compounds, alcohol **1c** was formed in 99 % yield when 0.9 eq. TIPSCl were used in the reaction.

Table 4.1: Monoprotection of 2,3-*O*-isopropylidene-L-threitol.



1a-c

entry	**1**	PG	conditions	Y
1	**a**	Bz	NaH, BzCl, THF, 0 °C – rt	62 %
2	**b**	Bn	NaH, BnBr, DMF, –40 °C – rt	71 %
3	**c**	TIPS	NaH, TIPSCl, THF, 0 °C	99 %

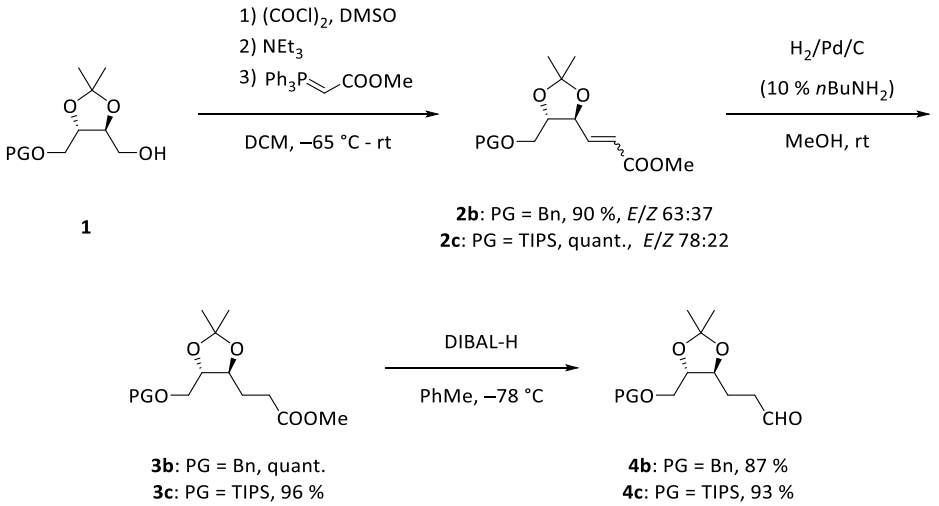


Scheme 4.1: Retrosynthetical analysis of Cyl-1.

Alcohols **1a-c** were then oxidized under Swern conditions to the corresponding aldehydes.[157] These aldehydes proved to be unstable and sensitive towards epimerization of the α-stereogenic center. The isolated aldehydes decomposed quickly even when stored at –20 °C. Therefore, crude aldehydes were immediately subjected to Mukaiyama/McMurry conditions to undergo subsequent homocoupling.[158,159] In general, $TiCl_4$ was dissolved in a solvent, treated with zinc dust and heated to reflux for up to two hours. The crude aldehydes were then added at temperatures ranging from –45 °C to 85 °C and reflux was continued. Latter reflux was required to eliminate TiO_2 from the intermediately formed pinacol.[158] Performing the reaction with aldehyde derived from **1a** in THF gave no olefinic product, although TLC control of the reaction mixture showed full consumption of the aldehyde. Instead, reduction to the corresponding alcohol was observed. In order to increase the temperature during $TiCl_4$ reduction and aldehyde coupling, DME was used rather than THF. However, only decomposition products were formed in DME during the course of the reaction. Switching the protective group from benzoyl to benzyl yielded only undefined decomposition products. The use of zinc-copper couple has been reported by McMurry *et al.* to

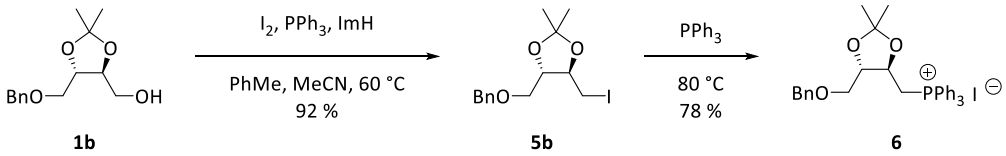
efficiently improve both yield and reproducibility of the coupling.[160] Unfortunately, only ketal cleavage was observed with aldehyde derived from **1b**. To avoid side reactions of the acid-labile groups initiated by partial hydrolysis of $TiCl_4$, pyridine was added to the reaction mixture. Lenoir described the use of $TiCl_4$/Zn/Py for efficient ketone coupling.[161] However, neither benzyl- nor TIPS-protected substrates gave any product. Since $TiCl_4$ was rather difficult to handle under anhydrous conditions, commercially available $TiCl_4$·2THF complex was used instead. This complex was used for successful McMurry coupling of an aldehyde containing a ketal, although not in adjacency to the affected aldehyde.[162] Analysis of the crude product indicated ketal cleavage but no formation of olefinic product. The less Lewis-acidic tin (IV) chloride has been reported to perform McMurry type couplings after reduction.[163] Subjecting alcohol **1b** in the oxidation/McMurry cascade with $SnCl_4$/Zn in THF led to reisolation of the intermediate aldehyde.

Considering that no olefinic product was formed under any reaction conditions tested gave rise to questions about the general eligibility of aldehydes with potential leaving groups in α-position. Although McMurry couplings have been used in the literature to build up complex natural products,[164] almost no examples of aldehydes with leaving groups in near proximity have been reported.[165] To prove this hypothesis, C_2-prolonged aldehydes were synthesized starting from **1c** (scheme 4.2). Oxidation under Swern conditions gave crude aldehydes, which were transformed with the corresponding Wittig ylide into the α,β-unsaturated ester **2c** in an one-pot protocol.[166,167] Despite the NMR spectra of **2c** appeared clean after column chromatography, a second chromatographic purification was needed before subsequent hydrogenation. Formation of elemental sulfur was sometimes observed during hydrogenation if the starting material was only purified once. However, hydrogenation of **2c** under 10 bar of H_2 with palladium on carbon gave saturated ester **3c** in 96 % yield. Ester **3c** was reduced with DIBAL-H in toluene at –78 °C to the corresponding aldehyde **4c**, which was then subjected to McMurry conditions. But as described before, only ketal cleavage and consumption of the aldehyde was observed, and no olefinic product was obtained. Alcohol **1b** was subjected to the same transformations as described for **1c**. Hydrogenation of the α,β-unsaturated ester **2b** was performed in the presence of 10 mol% *n*-$BuNH_2$ to prevent benzyl ether cleavage.[168] Various amines were shown to prevent *O*-debenzylation from occurring under hydrogenolysis conditions.[169] Subsequent reduction of **3b** with DIBAL-H gave aldehyde **4b**, which was utilized at a later stage of the synthesis.



Scheme 4.2: Synthesis of C_2-prolonged aldehydes **4**.

Since the McMurry approach provided no improvable results, other methods to derivatize the previously prepared aldehydes were tested. Alcohol **1b** was transformed into the corresponding iodide **5b** and subsequently heated with PPh_3 to 80 °C to form the corresponding Wittig salt **6** (scheme 4.3).[170] This phosphonium salt was treated with different bases (LHMDS, LDA, *n*-BuLi) in a variety of solvents (THF, DME, PhME) to form the corresponding Wittig ylene. Subsequent addition of aldehydes derived from **1a-c** led to no product formation under any reaction conditions tested. To rule out steric hinderance of the Wittig ylene, benzaldehyde was added to the *in situ* formed ylene. However, no product was observed from this reaction either. It was therefore speculated that deprotonation of the Wittig salt led to rapid decomposition of the substrate. The observation of various side reactions in both the McMurry approach as well as the Wittig approach called for another synthetic strategy to construct a suitable allylic alcohol **C** for introduction of the Aoe side chain.

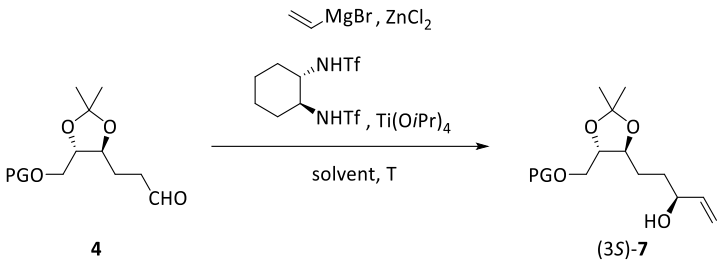


Scheme 4.3: Synthesis of Wittig salt **6**.

The stereogenic center in allylic alcohol **C** (scheme 4.1) could either be controlled during the addition of organometallic reagents to aldehydes **4**, or the allylic alcohol could be enzymatically resolved afterwards. Knochel *et al.* developed methods for the synthesis of diorganozinc compounds[171] and reported catalytic, enantioselective additions of these zinc organyls to aldehydes in the presence of chiral bissulfonamides and Ti(O*i*Pr)$_4$.[172] A similar approach was utilized to access chiral allylic alcohols **7** (table 4.2). Unfortunately, the reaction typically showed no full conversion (entry 1) or poor diastereoselectivities (entries 2-4). While Knochel *et al.* only used

dialkylzinc reagents, divinylzinc is required to access allylic alcohols through stereoselective carbonyl addition. The preparation and purification of divinylzinc proved to be challenging. While literature procedures are available for the preparation of divinylzinc, obtaining the product in pure form and avoiding extremely hazardous materials (e. g. mercury organyls) was difficult.[173] The poor diastereoselectivities probably resulted from incomplete separation of magnesium salts and -organyls.

Table 4.2: Stereoselective addition of divinylzinc to aldehydes **4**.

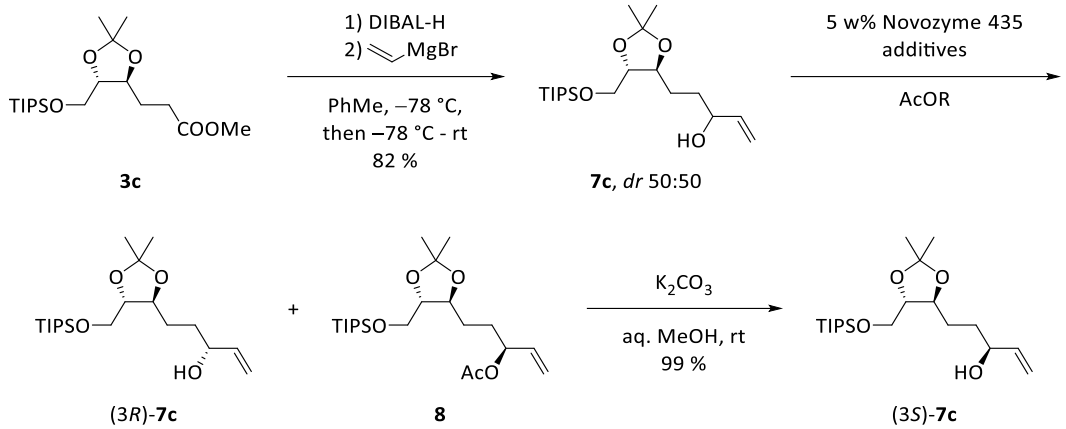


entry	PG	**4**	solvent	T	Y	*dr*[*]
1	Bn	**b**	PhMe	–40 °C - –25 °C	11 %	> 99:1
2	TIPS	**c**	PhMe	–40 °C - –25 °C	56 %	60:40
3	TIPS	**c**	PhMe	–40 °C - 0 °C	33 %	60:40
4	TIPS	**c**	THF	–78 °C - rt	54 %	70:30

[*]determined by ^{1}H-NMR

Since the stereoselective carbonyl addition of divinylzinc proved to be a non-trivial issue, enzymatic resolution of alcohol **7c** seemed to be the more convenient choice to access diastereomerically pure (3*S*)-**7c**. Enzymatic dynamic kinetic resolutions (DKR) were found to be an elegant way to gain access to the corresponding acetate. During the course of the reaction, the allylic alcohol is epimerized by a Ru(II) complex, while one epimer is permanently removed from the equilibrium through the action of the lipase. Several catalysts, like Shvo's catalyst,[174] are known to effectively perform this racemization reaction. Bäckvall *et al.* developed several enzymatic dynamic kinetic resolutions of simple alcohols utilizing $(Ph_5Cp)Ru(CO)_2Cl$ and other Ru complexes.[175,176] Racemization of the alcohol proceeds through Ru-catalyzed dehydrogenation, leaving a carbonyl and a Ru-hydride species. Subsequent re-addition of Ru-H leads to racemization of the alcohol.[177] Unfortunately, utilizing the reported reaction conditions for $(Ph_5Cp)Ru(CO)_2Cl$ with allylic alcohol **7c** as substrate failed (table 4.3, entries 1-2). While enzymatic resolution proceeded readily to give acetate **8**, epimerization of the allylic alcohol seemed not to occur. Therewith, both acetate **8** and alcohol (3*R*)-**7c** were obtained in good yields and excellent diastereoselectivities. The absolute configuration of acetate **8** and the remaining alcohol (3*R*)-**7c** can be rationalized by the Kazlauskas rule for lipases.[178]

Table 4.3: Enzymatic (dynamic) kinetic resolution of **7c**.



3c **7c**, *dr* 50:50 (3*R*)-**7c** **8** (3*S*)-**7c**

entry	additives	R	t	Y ((3*R*)-**7c**)	Y (**8**)	*dr** ((3*R*)-**7c**)	*dr** (**8**)
1	$(Ph_5Cp)Ru(CO)_2Cl$ Na_2CO_3, KO*t*Bu	vinyl	64.5 h	45 %	41 %	> 99:1	> 99:1
2	$(Ph_5Cp)Ru(CO)_2Cl$ Na_2CO_3, KO*t*Bu	isopro-penyl	22 h	50 %[c]	50 %[c]	> 99:1	> 99:1
3	-	vinyl	24 h	81 %	15 %	60:40	> 99:1
4	-	vinyl	40 h	65 %	34 %	73:27	> 99:1
5	-	vinyl	66 h	62 %	33 %	75:25	> 99:1
6	Na_2CO_3	vinyl	24 h	49 %	50 %	> 99:1	> 99:1
7	KO*t*Bu	vinyl	24 h	47 %	49 %	> 99:1	> 99:1
8	Na_2CO_3	vinyl	6 h	49 %	46 %	> 99:1	> 99:1

c: conversion, *determined by ^{1}H-NMR.

Since no epimerization seemed to proceed under DKR-conditions, substrate **7c** was subjected to an enzymatic kinetic resolution under standard conditions. Allylic alcohol **7c** was therefore dissolved in vinyl acetate at room temperature and treated with 5 w% Novozyme 435 (Lipase from *Candida antarctica*) for several hours. After 24 h, only 15 % of the corresponding acetate was obtained, although with excellent diastereoselectivity (table 4.3, entry 3). Performing the reaction for 40 h increased the yield of acetate **8** to 34 % (entry 4). However, further prolonged reaction times neither changed conversion nor diastereoselectivity, indicating the termination of the reaction. Since full conversion was achieved in the dynamic kinetic resolution, the role of the added base was examined. Checking the literature revealed that addition of base can accelerate enzymatic kinetic resolutions through deprotonation of acylated enzyme intermediates.[179,180] Therefore, 1.0 eq. sodium carbonate or 5 mol% KO*t*Bu were added to the reaction mixture (entries

6 and 7). Almost quantitative yields of both acetate and alcohol were obtained after 24 h. Sodium carbonate was preferred over KO*t*Bu since it can be removed from the reaction mixture through simple filtration. The reaction was further adjusted to give 46 % of acetate **8** and 49 % alcohol (3*R*)-**7c** with excellent diastereoselectivities after only 6 h. For the construction of (*S*)-configured Aoe *via* ester enolate Claisen rearrangement, allylic alcohol (3*S*)-**7c** was needed. Transesterification of acetate **8** with potassium carbonate in aq. MeOH gave the corresponding alcohol.

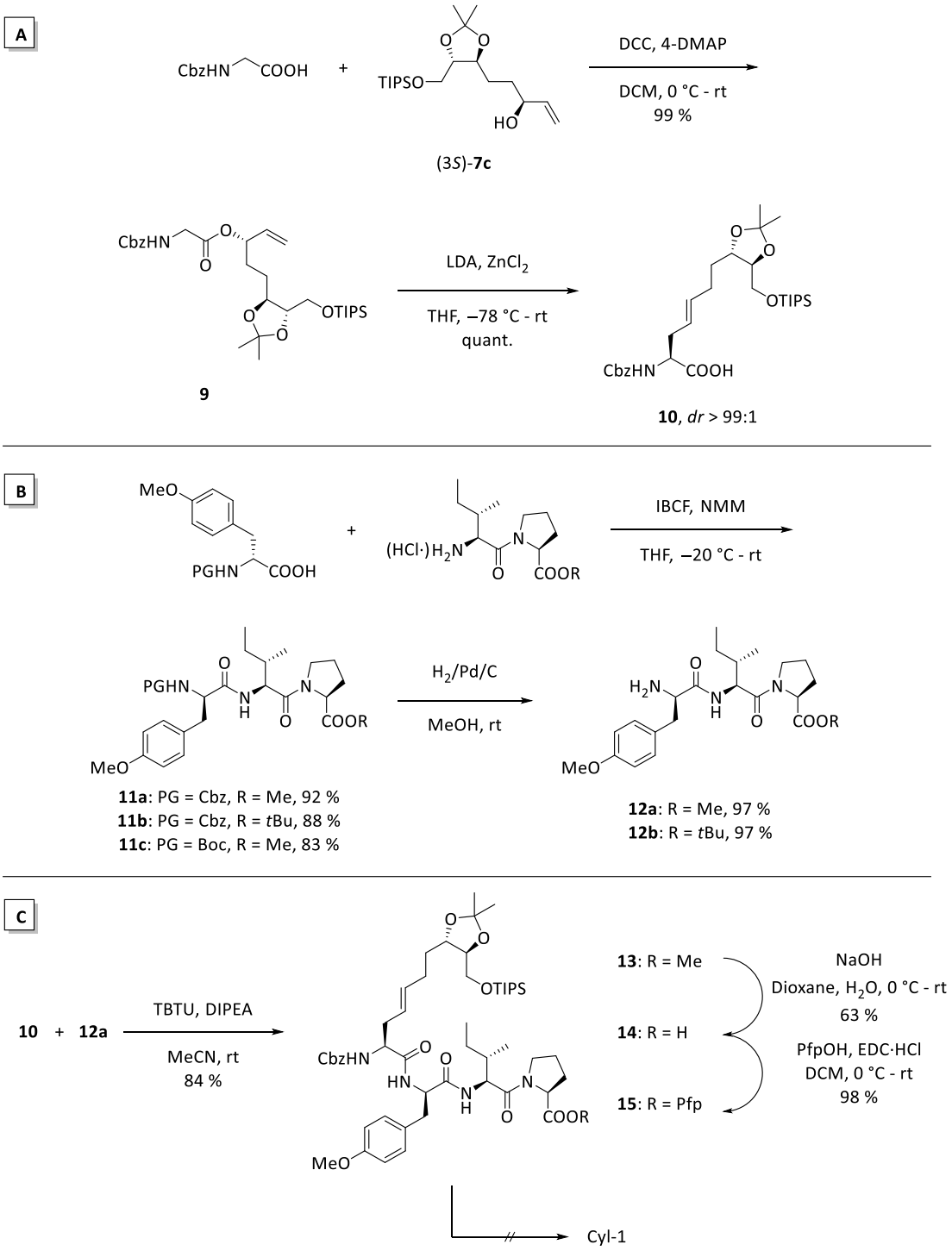
Other acyl donors were also exploited in the enzymatic kinetic resolution of **7c**. Using glycine esters as acyl donors would directly access glycine allyl esters, which could be subjected to ester enolate Claisen rearrangement. Although methods for the synthesis of amino acid vinyl esters are available,[181,182] *p*-Cl-phenol esters could easily be synthesized and have been used in DKR reactions before.[183] Furthermore, esterifications of *p*-nitro-phenol and trifluoroethanol with Cbz-Gly-OH were performed to alter the reactivity of the acyl donor.[184,185] With these active esters in hand, enzymatic kinetic resolutions were performed under optimized conditions and in toluene as solvent. At room temperature and with glycine *p*-Cl-phenol ester, only 17 % conversion to the corresponding glycine allyl ester was observed. Increasing the reaction temperature to 40 °C gave 34 % conversion. Similar results were obtained with the *p*-NO_2-phenol ester and the trifluoroethanol ester. Although the diastereomeric ratios were excellent, separation of the newly formed glycine allyl ester and alcohol **7c** couldn't be accomplished. Additionally, *p*-NO_2-phenol, formed as byproduct during the reaction, could not be removed from the reaction mixture. The obtained results clearly demonstrated the general applicability of other acyl donors in enzymatic kinetic resolutions. Due to difficulties regarding separation of the products, this approach was not continued further.

4.1.2 Synthesis of a linear tetrapeptide and cyclization

With allylic alcohol (3*S*)-**7c** in hand, Steglich esterification[186] with Cbz-protected glycine gave the corresponding allyl ester **9**, which was then subjected to ester enolate Claisen rearrangement (scheme 4.4, A). These rearrangements were shown to proceed with excellent yield and transfer of stereogenic information *via* a chair-like transition state. The enolate geometry is fixed by formation of a five-membered chelate complex and therefore, excellent transfer of stereogenic information from the allyl ester to the α-center of the amino acid is achieved. Indeed, chelate enolate Claisen rearrangement of allyl ester **9** afforded carboxylic acid **10** in excellent yield and as a single diastereomer. This Aoe precursor should subsequently be coupled to tripeptides to obtain linear tetrapeptides suitable for cyclization towards the Cyl-1 scaffold.

Coupling of PG-(*R*)-Tyr(Me)-OH with (HCl) H-(*S*,*S*)-Ile-(*S*)-Pro-OR to tripeptides **11** proceeded well and without side reaction for both methyl and *tert*-butyl esters (scheme 4.4, B). The use of *tert*-butyl esters in this coupling was exploited since preliminary results with proline dipeptide methyl esters indicated formation of side products. Luckily, this drawback was overcome by performing the coupling with the hydrochloride salt and IBCF at –20 °C. Hydrogenative cleavage of the Cbz-group in **11** gave amines **12**. Carboxylic acid **10** was then coupled with **12a** using TBTU

(scheme 4.4, C). Unfortunately, saponification of methyl ester **13** lacked from full conversion and gave the free carboxylic acid **14** in only moderate yield along with unreacted starting material. Subsequent activation of carboxylic acid **14** as Pfp ester gave compound **15** with almost full conversion.



Scheme 4.4: Synthesis of linear tetrapeptide **14** and activation as Pfp ester.

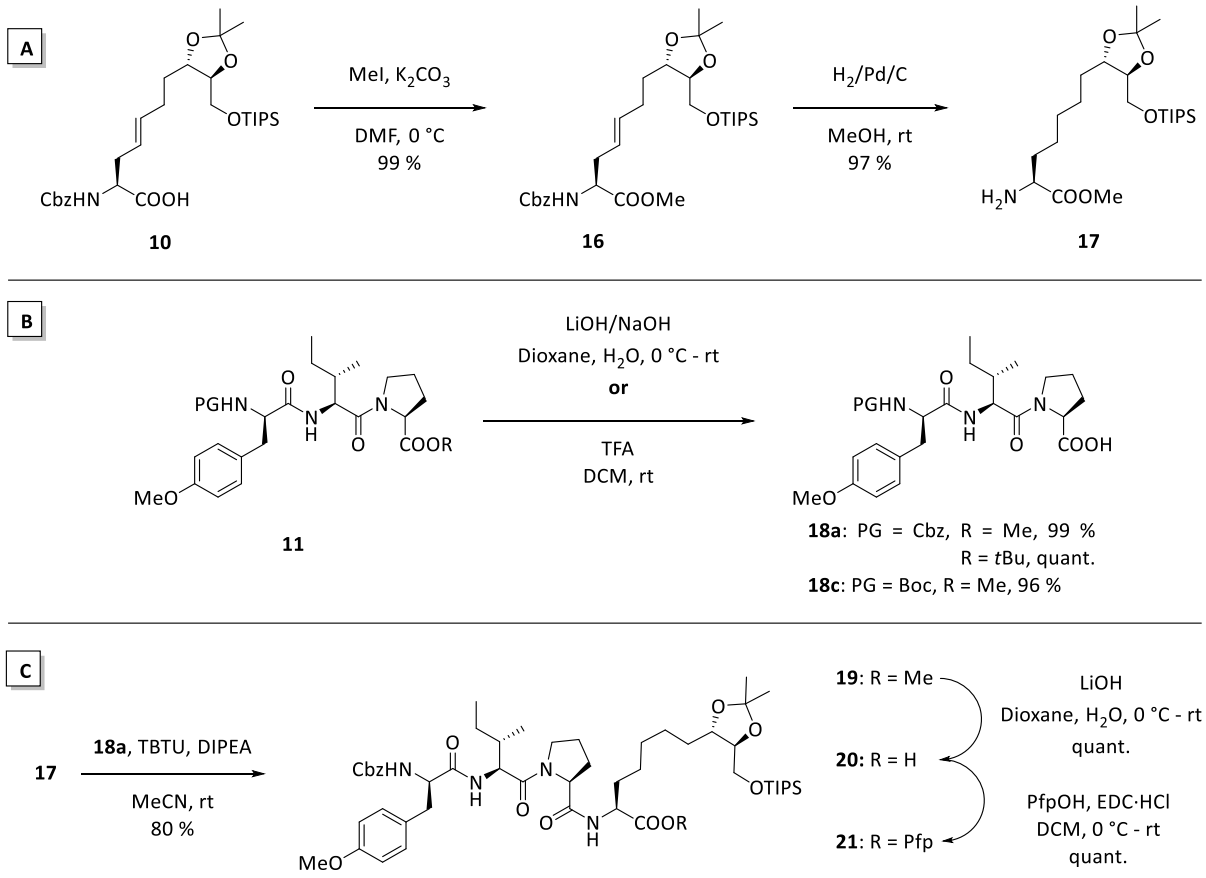
Amine **12b** was also coupled with carboxylic acid **10** to investigate the selective cleavage of *tert*-butyl esters in the presence of acid labile groups. Unfortunately, cleavage of the *tert*-butyl ester in this linear tetrapeptide under standard conditions (TFA, DCM) resulted in the cleavage of the silyl ether and ketal group, respectively. Subjecting this ester to basic conditions with KO*t*Bu in THF led to decomposition of the tetrapeptide.[187] Esterases from porcine liver (PLE) are known to cleave esters in various substrates.[188] Performing the reaction in phosphate buffer at rt showed no conversion of the starting material. Finally, heating in acetonitrile with $CeCl_3$ and NaI led to ketal cleavage rather than *tert*-butyl ester cleavage.[189] The results of these investigations were important for the synthesis of trapoxin A and are discussed in detail there.

To access the macrocyclic scaffold of Cyl-1, Pfp ester **15** was subjected to macrolactamization under hydrogenative conditions in THF with Pd on carbon as catalyst. Interestingly, even at 10 bar H_2 pressure, Cbz-deprotection seemed to occur very slowly. No product was formed after 24 h and the starting material could be reisolated. At 80 °C in dioxane, Cbz-cleavage occurred, but no cyclized product was found in the crude reaction mixture. These results led to the conclusion that the conformation of **15** apparently did not allow for rapid Cbz-cleavage and subsequent cyclization.

4.1.3 Synthesis of a regioisomeric tetrapeptide and synthesis of Cyl-1

Several total synthesis of natural macrocyclic HDAC inhibitors revealed that the ring closing position can have a dramatic effect on the overall yield and epimerization rate during cyclization.[68,190] Since macrocyclization of **15** failed under any reaction conditions tested, the construction of a regioisomeric tetrapeptide was required. Therefore, it was important to develop a synthetic strategy that would allow for rapid changes in the ring closing position.

With such a strategy at hand, the synthesis of a regioisomer of **15** was performed rapidly and with high yields. Methylation of carboxylic acid **10** and hydrogenative cleavage of the Cbz-group made amine **17** available (scheme 4.5, A). The tripeptide building block needed was derived from protected tripeptide esters **11** after saponification and *tert*-butyl ester cleavage, respectively (scheme 4.5, B). Similar to the synthesis of tetrapeptide **13**, the free amine **17** was coupled with **18a** using TBTU to get tetrapeptide **19** in excellent yield as a single diastereomer (scheme 4.5, C). Saponification of the methyl ester and activation as Pfp ester gave the desired substrate for macrolactamization. Noteworthy, Pfp ester **21** formed two stable rotamers (rotameric ratio ~ 3:1) which could be separated on an analytical column (Phenomenex Luna). NMR spectra recorded at elevated temperature (DMSO-d_6, 100 °C) excluded severe epimerization of the Pfp ester and the diastereomeric ratio was analyzed to be 97:3.

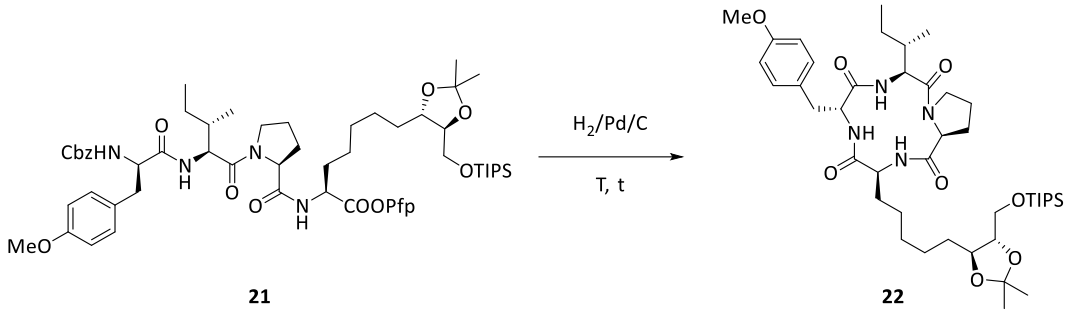


Scheme 4.5: Synthesis of a regioisomeric linear tetrapeptide for Cyl-1.

Tetrapeptide **21** was treated with H_2/Pd/C in THF with alternation of H_2 pressure and dilution (table 4.4). Applying 20 bar H_2 pressure and addition of HOAc to the reaction mixture yielded 27 % of macrocycle **22** with a diastereomeric ratio of 95:5 (entry 1). Interestingly, acetic acid apparently did not lead to ammonium salt formation as the free amine cyclized readily. At atmospheric pressure, longer reaction times were required, which gave slightly higher yield albeit with more epimerization (entry 2). Higher dilution under otherwise same conditions gave better yields but surprisingly also more epimerization (entries 3-6). When the reaction was performed at 80 °C in dioxane with a continuous H_2 passage through the reaction mixture,[191] 75 % of the desired macrocycle were obtained but with severe epimerization (entry 7). In summary, prolonged reaction times and high temperatures led to progressive epimerization of the activated Pfp ester.

Due to the fact that Pfp esters were prone to epimerize under the reaction conditions, other cyclization methods were evaluated. Since epimerization of the Pfp ester **21** was caused by long reaction times during hydrogenative cleavage of the Cbz-group, utilizing the free tetrapeptide for macrocyclization should remedy this drawback. Consequently, hydrogenation of carboxylic acid **20** at 20 bar H_2 pressure gave the free tetrapeptide, which was then subjected to diverse ring closing conditions. Using a literature protocol (PyBOP, DIPEA, DMF) for the construction of 12-membered ring systems developed by Schreiber *et al.*,[67] macrocycle **22** was obtained in 66 % yield containing several impurities. Irritatingly, these impurities could not be separated by any means to access the pure product.

Table 4.4: Optimization of the macrocyclization of **21**.



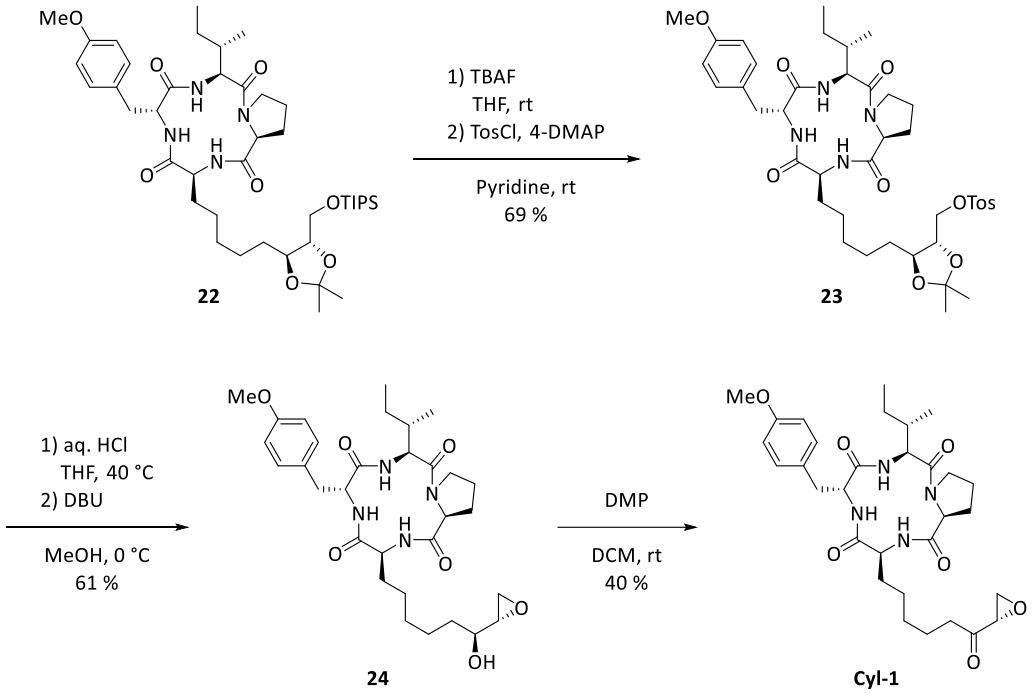
21 **22**

entry	conditions	Y	*dr*[*]
1	20 bar, HOAc, THF (50 mM), rt, 18 h	27 %	95:5
2	1 bar, THF (1 mM), rt, 48 h	32 %	85:15
3	5 bar, THF (50 mM), rt, 40 h	21 %	> 99:1
4	5 bar, THF (10 mM), rt, 40 h	28 %	94:6
5	10 bar, THF (1 mM), rt, 23 h	32 %	88:12
6	10 bar, THF (10 mM), rt, 24 h	16 %	93:7
7	continuous H_2 passage, dioxane (1 mM), 80 °C, 5.5 h	75 %	68:32

[*]determined by ^{1}H-NMR and LCMS

Furthermore, treatment of the free tetrapeptide with PfTU under different reaction conditions afforded only minor amounts of product or a complex mixture of compounds. PfTU should react with the carboxylic acid to form an intermediate Pfp ester, which should then readily undergo nucleophilic attack from the free amine. Apparently, PfTU was not suitable for this challenging macrocyclization, although it performed well in standard peptide couplings of test substrates. It was easily synthesized in two steps from tetramethylurea.[192]

With macrocycle **22** at hand, attempts to complete the total synthesis of natural Cyl-1 were undertaken Deprotection of silyl ether and following treatment with TosCl gave tosylate **23** (scheme 4.6). Cleavage of the ketal proceeded readily at 40 °C and the corresponding diol was further treated with DBU in MeOH to give epoxyalcohol **24**. Final oxidation with Dess-Martin periodinane in DCM gave natural Cyl-1 in 40 % yield. The epimers formed during Pfp ester activation and cyclization could be partially separated in all steps, so the natural product was isolated as a single diastereomer along with a diastereomeric mixture. The recorded NMR spectra were in accordance to previously reported data (see appendix).[47] Unfortunately, no complete data set or spectra were published for Cyl-1.

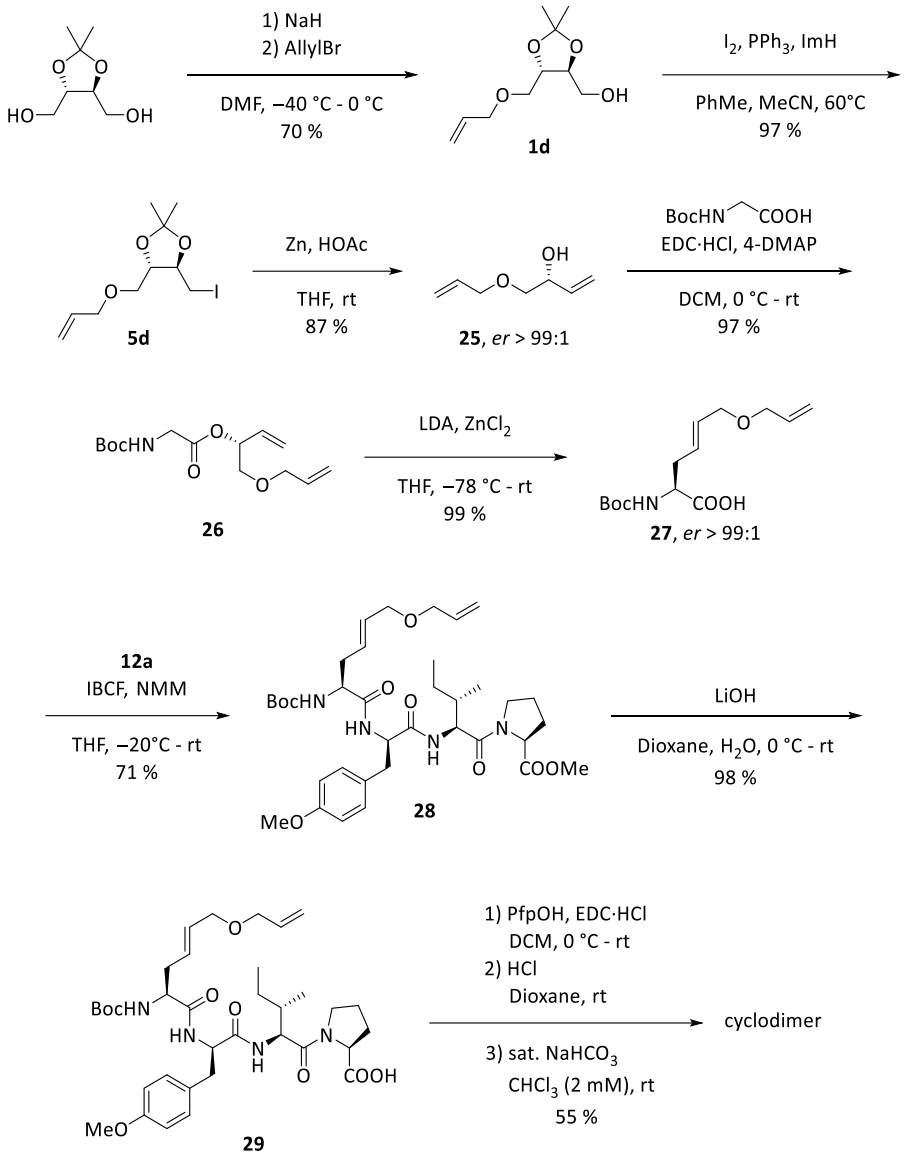


Scheme 4.6: Synthesis of Cyl-1.

4.2 Synthesis of Cyl-1 derivatives

With a straightforward synthesis of Cyl-1 accomplished, efforts towards derivatives of this natural product were undertaken. Consequently, the synthesis started with the construction of a suitable allylglycine precursor to be incorporated into linear tetrapeptides fit for subsequent cyclization.

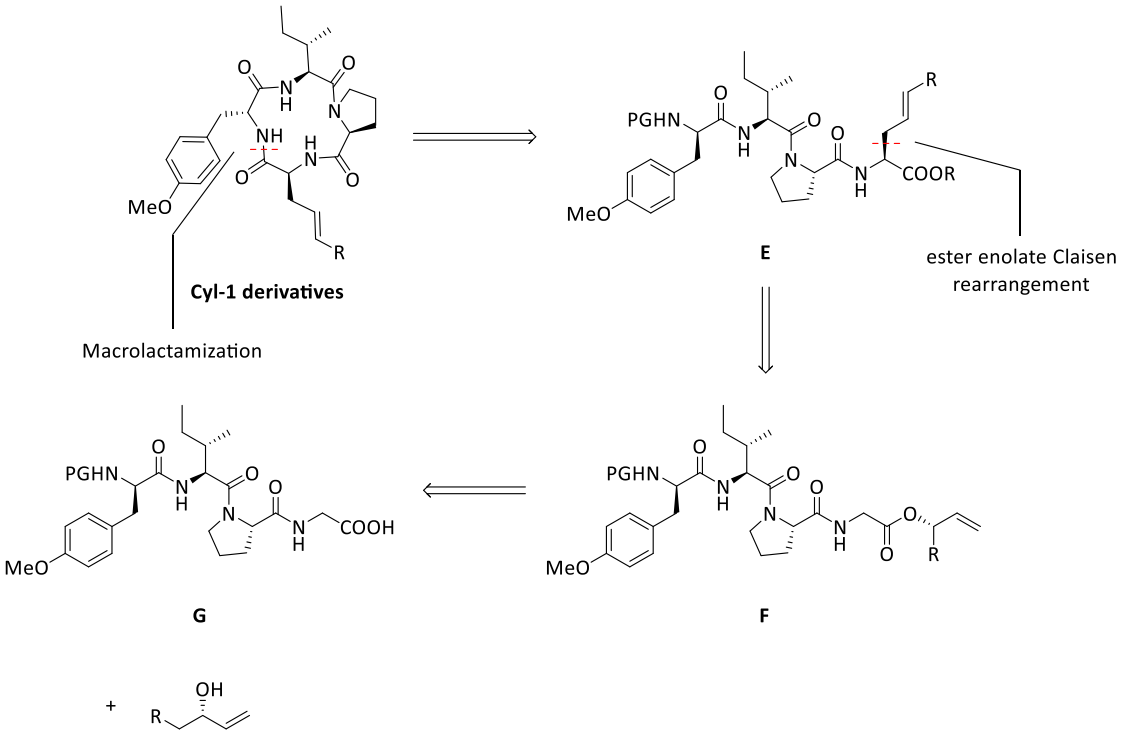
The stereogenic information for this allylglycine moiety was again derived from L-tartaric acid. Thus, mono-*O*-allylation of the L-threitol derivative under similar conditions as reported before for monobenzylation gave alcohol **1d** (scheme 4.7). Iodination and subsequent elimination of the iodide with zinc dust and acetic acid in THF gave allylic alcohol **25** as a single enantiomer. Esterification of this alcohol with Boc-protected glycine gave allyl ester **26**, which was rearranged *via* a chelated ester enolate to give carboxylic acid **27** in 99 % yield. Noteworthy, the rearranged product was obtained as a single enantiomer and was then coupled with tripeptide amine **12a** *via* mixed anhydride. Linear tetrapeptide **28** was saponified and subsequently activated as Pfp ester. Boc-deprotection gave a crude ammonium salt, which was subjected to a biphasic ring closure.[64] Although acceptable yield was obtained, the product appeared to be the corresponding cyclodimer, which consisted of two tetrapeptides forming a 24-membered ring. This indicated that ring closure between proline and the allylglycine precursor was not apt for the construction of the desired cyclic tetrapeptide. As discussed for tetrapeptide **15**, the conformation of this derivative apparently prevented cyclization.



Scheme 4.7: Attempts towards derivatives of Cyl-1.

4.2.1 Ester enolate Claisen rearrangement of linear tetrapeptides

The obtained results underlined previous observations made in the synthesis of Cyl-1. Furthermore, the effect of the ring closing position on the obtained product and the yield/epimerization rate during the reaction was emphasized. As a result, a different approach was tested, that would allow not only for the synthesis of derivatives but also the natural product from a common precursor (scheme 4.8). Macrolactamization between allylglycine and (*R*)-Tyr(Me) should leave a linear tetrapeptide **E**. The side chain of the *C*-terminal amino acid should be introduced *via* ester enolate Claisen rearrangement of a chelated tetrapeptide. The corresponding allyl ester **F** needed for this transformation should be accessible through esterification of a linear tetrapeptide **G** with suitable allylic alcohols. This would allow for the incorporation of different side chains at a late stage of the synthesis. In general, allylic alcohols (3*S*)-**7c** or **25** could be introduced to either access the natural product or its derivatives.

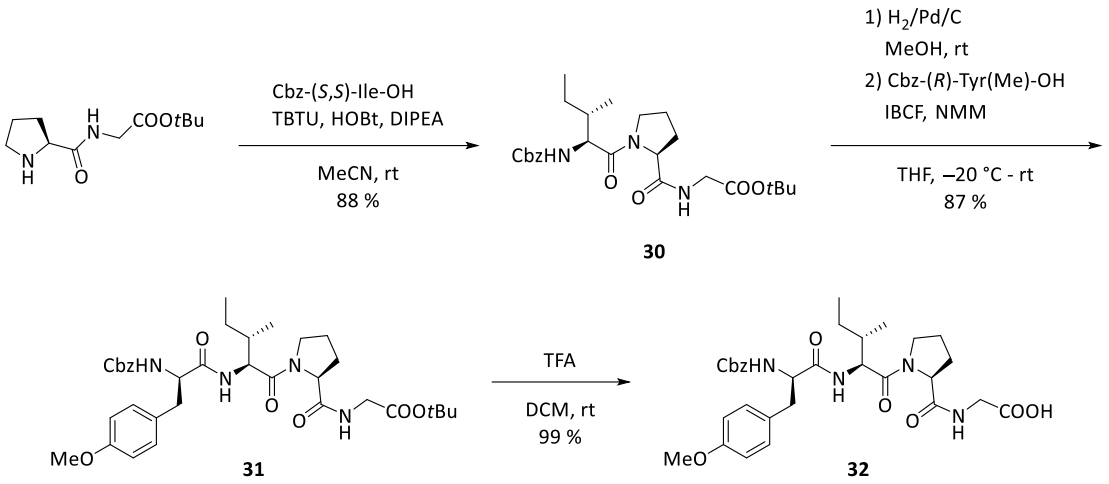


Scheme 4.8: Retrosynthetical analysis of Cyl-1 derivatives.

An effortless approach towards such a linear tetrapeptide **G** arose from the coupling of two dipeptides. Unfortunately, coupling of Cbz-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-OH with HCl·H-(*S*)-Pro-Gly-OMe failed by any means. Either no conversion was observed, or the product could not be purified or showed severe epimerization of the isoleucine residue. Therewith, stepwise coupling of the four amino acids seemed to be the more advantageous approach. Cbz-(*S*,*S*)-Ile-OH was coupled with H-(*S*)-Pro-Gly-O*t*Bu using TBTU as coupling reagent (scheme 4.9). In general, TBTU was the preferred coupling reagent for proline since the latter is known to form urethanes when coupled *via* mixed anhydrides and is generally prone to form diketopiperazines.[193,194] In addition, the use of *tert*-butyl esters could suppress diketopiperazine formation in proline-containing dipeptides.[195] The resulting tripeptide **30** was hydrogenated and coupled with Cbz-(*R*)-Tyr(Me)-OH to give linear tetrapeptide **31** in good yields. Cleavage of the *tert*-butyl ester gave carboxylic acid **32**, which should then be coupled with allylic alcohols. The resulting tetrapeptide allyl esters could then be transformed further *via* ester enolate Claisen rearrangements.

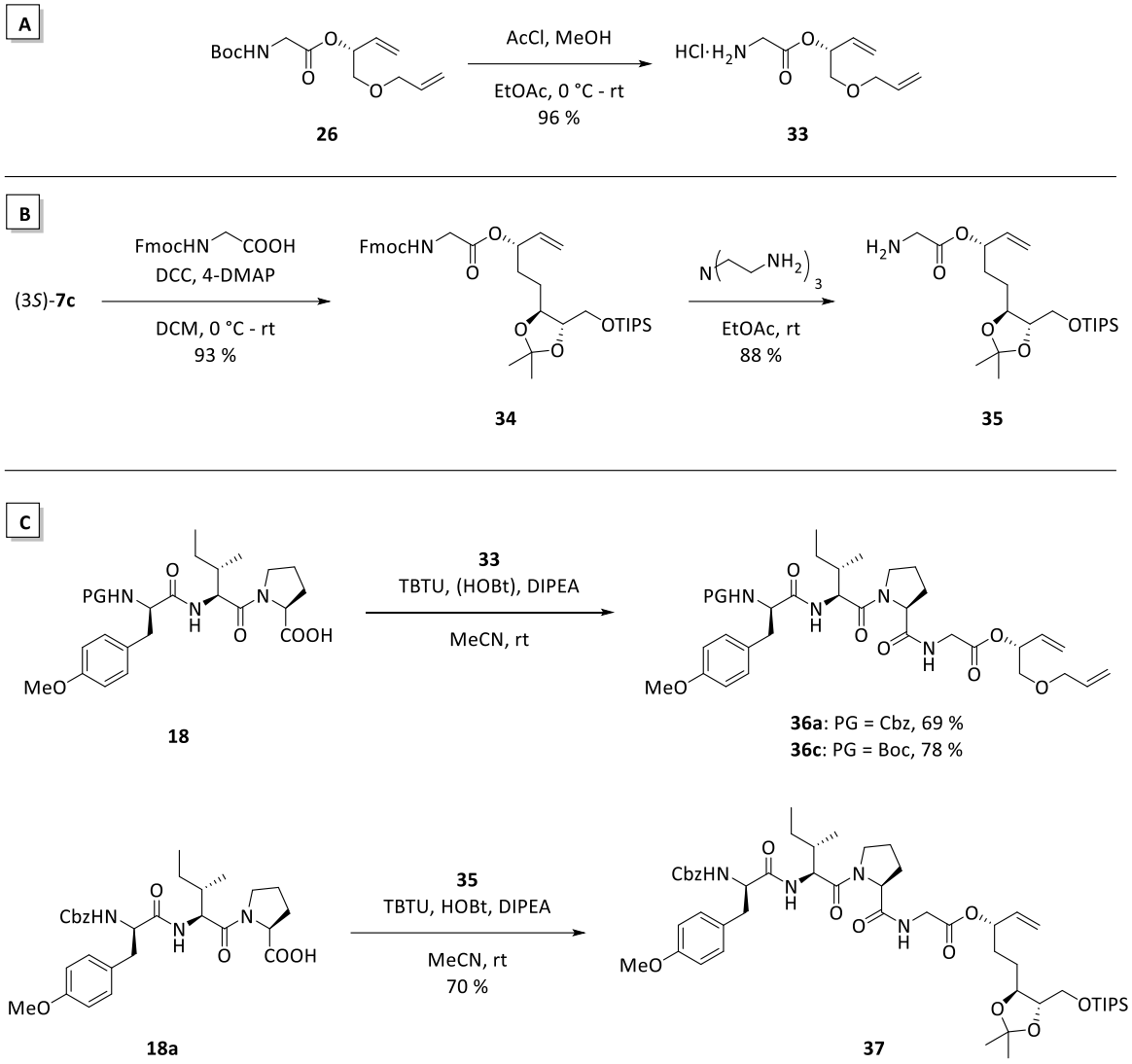
However, esterification of **32** with allylic alcohol **25** proved to be rather challenging. Under standard conditions (EDC, DMAP), only 30 % conversion was observed. Activation of **32** as acid chloride led to complete decomposition. Addition of DIPEA to the EDC coupling slightly increased conversion and with DCC under Steglich conditions, 49 % of the desired product were obtained. Nevertheless, the obtained ester was contaminated with the corresponding *N*-acyl urea formed during the reaction. This clearly indicated that addition of alcohol **25** to the activated carboxylic acid was restricted. Additionally, activation as acid fluoride with DAST resulted in no conversion at all. Performing the reaction in DMF with TBTU and DBU has been described in

literature for challenging esterifications,[196] but no conversion was observed either. EDC coupling in DMF revealed the formation of multiple side products, which weren't characterized further. Since low conversions and poor yields for a simple esterification were not acceptable at this stage of the synthesis, a different approach towards the tetrapeptidic allyl esters for Cyl-1 and its derivatives was chosen.



Scheme 4.9: Stepwise synthesis of a linear tetrapeptide for Cyl-1 derivatives.

Incorporation of an allylglycine moiety in the linear tetrapeptide required a different synthetic strategy. Since esterification of the linear tetrapeptide **32** was not an option, different glycine allyl esters were synthesized and subsequently coupled with linear tripeptides to the corresponding tetrapeptide allyl esters. Therefore, glycine allyl ester **26** was Boc-deprotected to give amine **33** as hydrochloride salt using a protocol developed by Nudelman *et al*. (scheme 4.10, A).[197] Steglich esterification of allylic alcohol (3*S*)-**7c** with Fmoc-Gly-OH was achieved in excellent yield (scheme 4.10, B).[186] Subsequent Fmoc-deprotection with Tris(2-aminoethyl)amine gave the free amine **35** for incorporation into linear tetrapeptides.[198] The previously synthesized tripeptides **18** were then coupled with the different amines **33** and **35** to give the desired tetrapeptidic allyl esters **36a**, **36c** and **37** in good to excellent yields (scheme 4.10, C). Tetrapeptide **36** was synthesized with two different *N*-protective groups, which both could be cleaved orthogonally to the side chain functional groups. Coupling with TBTU proved to be very effective and usually occurred without epimerization.[199] Occasionally, 1-2 % of an epimer were found after the reaction, which was acceptable given the presence of an activated tripeptide intermediate.



Scheme 4.10: Synthesis of linear tetrapeptide allyl esters.

The different tetrapeptide allyl esters **36** and **37** were subjected to the key step of the synthesis; ester enolate Claisen rearrangement should provide suitable precursors for cyclization to access Cyl-1 and its derivatives. Although some efforts were made towards peptide Claisen rearrangements, application of this synthetically useful reaction in the synthesis of natural products hasn't been accomplished yet. The peptidic backbone was shown to be able to control the stereochemical outcome of the newly formed C-C bond.[100] On the other hand, proline-containing peptides have also been reported to give epimeric mixtures. This effect is presumably caused by interrupted chelation (figure 4.1). To overcome these limitations, diastereomerically pure tetrapeptide allyl esters were used in the synthesis of Cyl-1 and its derivatives to control the stereochemical outcome *via* the configuration of the esterified allylic alcohol.

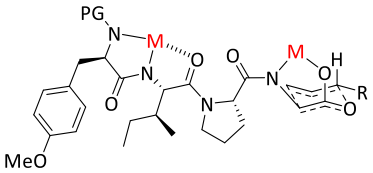
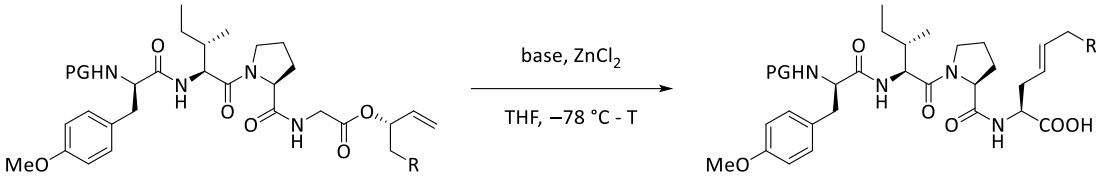


Figure 4.1: Potential transition state for ester enolate Claisen rearrangement of tetrapeptides.

Subjecting allyl ester **36a** to the conditions of an ester enolate Claisen rearrangement with zinc chloride as chelating metal gave the rearranged product in 33 % yield and a diastereomeric ratio of 93:7 (table 4.5, entry 1). The reaction was kept at –45 °C overnight to suppress potential epimerization of the peptide. Generally, epimerization is prevented through deprotonation of amide NH-bonds, as argued by Seebach for Li-enolates.[200] Nevertheless, isoleucine was prone to epimerize under the reaction conditions due to its vicinity to proline and therewith lack of "protecting" NH-groups. Since no full conversion was observed in this first attempt, LDA was replaced with LHMDS and the reaction was allowed to warm to rt overnight (entry 2). LHMDS is a slightly weaker base than LDA and should not deprotonate α-substituted amino acids. However, no full conversion was observed either and both yield and diastereomeric ratio were similar to the reaction with LDA. Afterwards, allyl ester **37** was subjected to the same reaction conditions as **36a** before (entries 3-4). Interestingly, no conversion at all was observed for this allylic ester. Starting material could be isolated after the reaction and the only byproduct formed was allylic alcohol (3*S*)-**7c**. Elimination of alcohol from the ester enolate can occur with allylic substrates that undergo rearrangement too slowly and partially form ketenes.[201] Boc-protected ester **36c** was then treated with LHMDS under the evaluated reaction conditions (entry 5). Surprisingly, also no conversion was observed for this substrate. Switching the base to LDA gave similar results than for **36a** (entry 6). Since the reaction seemed to stop after 30-40 % conversion, it was speculated that ester enolate chelate complex formation was incomplete due to consumption of the base. For instance, deprotonation of tyrosine residues in benzyl position has been reported in the derivatization of miuraenamides and called for an additional equivalent of base.[202] Therefore, the reaction was repeated with 5.5 eq. LDA (entry 7). The rearranged acid was obtained in quantitative yields as crude product without the formation of byproducts. Strikingly, the diastereomeric ratios were generally high (up to >99:1). The reaction was performed several times giving similar results. Only prolonged reaction times (> 18 h) led to epimerization of the rearranged peptide. The rearranged carboxylic acid derived from **36c** was suitable for cyclization towards Cyl-1 derivatives. Finally, ester **37** was subjected to the same reaction conditions (entry 8). Even with 5.5 eq. LDA, no rearranged product was obtained. Thus, ester enolate Claisen rearrangement proved to be suitable to incorporate an allylglycine precursor but not to access the natural product Cyl-1.

Table 4.5: Ester enolate Claisen rearrangements of tetrapeptide allyl esters.

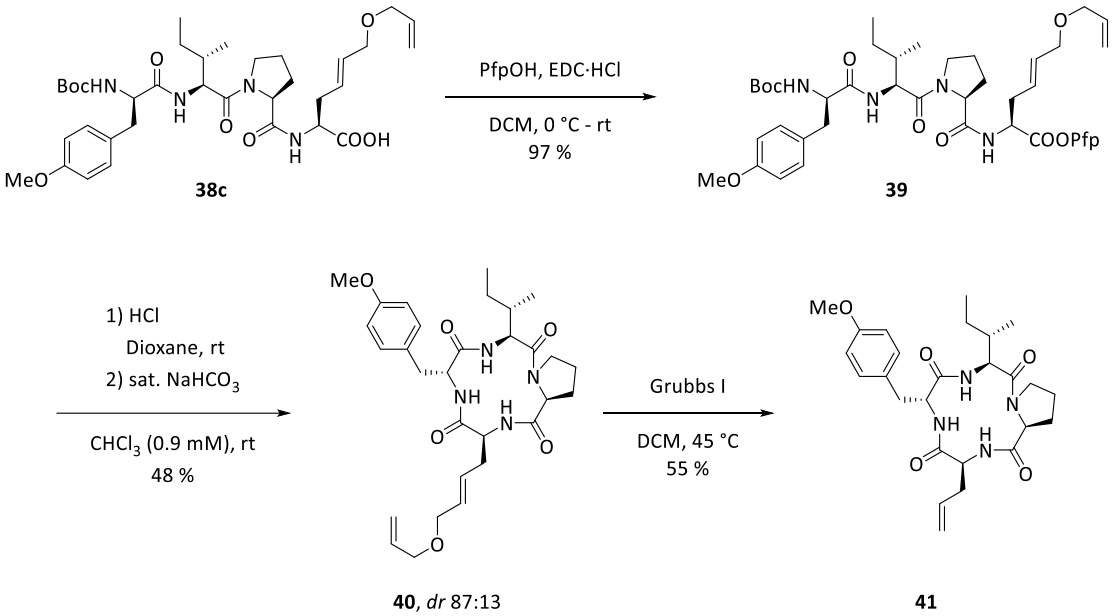


entry	ester	base	T	Y	*dr*	comment
1	**36a**	4.8 eq. LDA	–45 °C	33 %	93:7[a]	no full conversion
2	**36a**	4.8 eq. LHMDS	rt	37 %	~ 95:5[a]	no full conversion
3	**37**	4.5 eq. LHMDS	rt	-	-	no conversion
4	**37**	4.5 eq. LDA	rt	-	-	no conversion
5	**36c**	4.5 eq. LHMDS	rt	-	-	no conversion
6	**36c**	4.5 eq. LDA	rt	34 %	95:5[a]	no full conversion
7	**36c**	5.5 eq. LDA	rt	quant.	> 99:1[b]	-
8	**37**	5.5 eq. LDA	rt	-	-	no conversion

a: determined by ^{1}H-NMR, b: determined by HPLC of the corresponding methyl ester

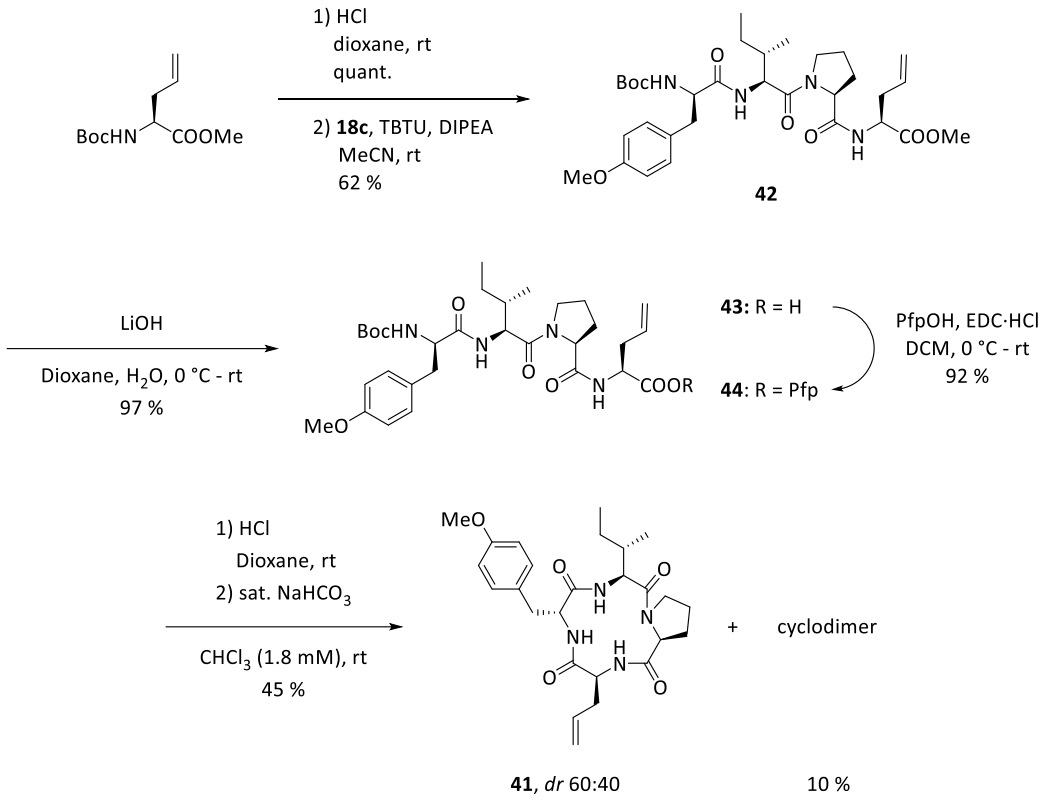
4.2.2 Cyclization and derivatization

With rearranged tetrapeptide **38c** in hand, esterification with PfpOH gave Pfp ester **39**, which should readily cyclize after Boc-deprotection (scheme 4.11). Treatment with HCl in dioxane gave the crude ammonium salt, which was subjected to biphasic ring closure.[64] The hydrochloride salt was therefore added dropwise to an emulsion of a saturated $NaHCO_3$ solution in chloroform. Macrocycle **40** was obtained in acceptable yield as a diastereomeric mixture (*dr* 87:13). The diastereomers of **40** could partially be separated by column chromatography. To access the allylglycine motif for further derivatization, cycle **40** was subjected to Grubbs I catalyst in DCM at 45 °C to get the desired product **41**. While the reaction proceeded well with the cyclic tetrapeptide, compound **41** proved to be highly insoluble, which complicated its purification. This fact also undermined later transformations of **41** (*vide infra*). The removal of Ru-impurities was crucial in order to obtain pure derivatives for further transformations and biological testing. An acknowledged method for the removal of metathesis catalysts is the formation of Ru-DMSO complexes, which do not eluate from a silica column.[203] Additionally, providing sophisticated NMR spectra of **41** turned out to be a non-trivial issue. The majority of commercially available deuterated solvents were tested in order to get good NMR spectra of **41**. Recording the NMR spectra in tetrachloroethane-d_2 at elevated temperatures (100 °C) led to a clear solution and hence clean NMR spectra.



Scheme 4.11: Synthesis of Cyl-1 derivatives.

It was not clear from the beginning whether the metathesis reaction to obtain the allylglycine moiety works well with the cyclic peptide. To optimize the synthesis of Cyl-1 derivatives and minimize the number of steps with the cyclic peptide, Boc-protected allylglycine was treated with HCl in dioxane and the hydrochloride salt was coupled with tripeptide **18c** using TBTU (scheme 4.12). Saponification of the obtained tetrapeptide **42** and activation as Pfp ester **44** was performed for subsequent macrocyclization. To access allylglycine-containing cycle **41** directly after cyclization, the corresponding linear tetrapeptide **44** was Boc-deprotected and cyclized in a biphasic ring closure. Unfortunately, only 45 % of the cyclic compound was obtained and with nearly complete epimerization of the intermediate Pfp ester. Compound **41** still contained 10 % of the corresponding cyclodimer, which could not be separated from the desired product. *In situ* activation of the corresponding free peptide (derived after Boc-deprotection in **43**) with PfTU and cyclization under the same conditions as before also gave no improved results. Macrocycle **41** was obtained as a mixture of diastereomers (*dr* 56:44) along with 15 % of the cyclodimer.



Scheme 4.12: Direct cyclization to allylglycine-containing macrocycle **41**.

In order to attach several zinc-binding motifs to Cyl-1's macrocyclic core, different derivatization reactions were tested. A convenient and powerful method to derivatize terminal alkenes as present in **41** is the thiol-ene click reaction. Several investigations into this reaction were undertaken in our group and it was shown that this reaction is in general suitable for complex substrates.[142,151] With this in mind, compound **41** was treated with *N*-acetylcysteamine in THF. When BEt_3 and air were used as radical starters, approximately 50 % conversion of the starting material was achieved. However, separation of the product from unreacted starting material could not be accomplished on a preparative scale. With 2-mercaptoacetic acid, no conversion was observed under the reaction conditions. Initiation of radical reactions involving thiols could also be performed with visible light. Therefore, compound **41** was treated again with *N*-acetylcysteamine, suspended in DCM, MeCN or DMF and irradiated. Unfortunately, no conversion of the terminal alkene was observed under any of the conditions tested. Finally, a method developed by Renaud *et al.* that utilized catechol to "repair" the thiol-ene click reaction was tested in order to achieve full conversion.[146] However, even after 24 h and repeated addition of BEt_3, only 10 % conversion of the starting material was obtained.

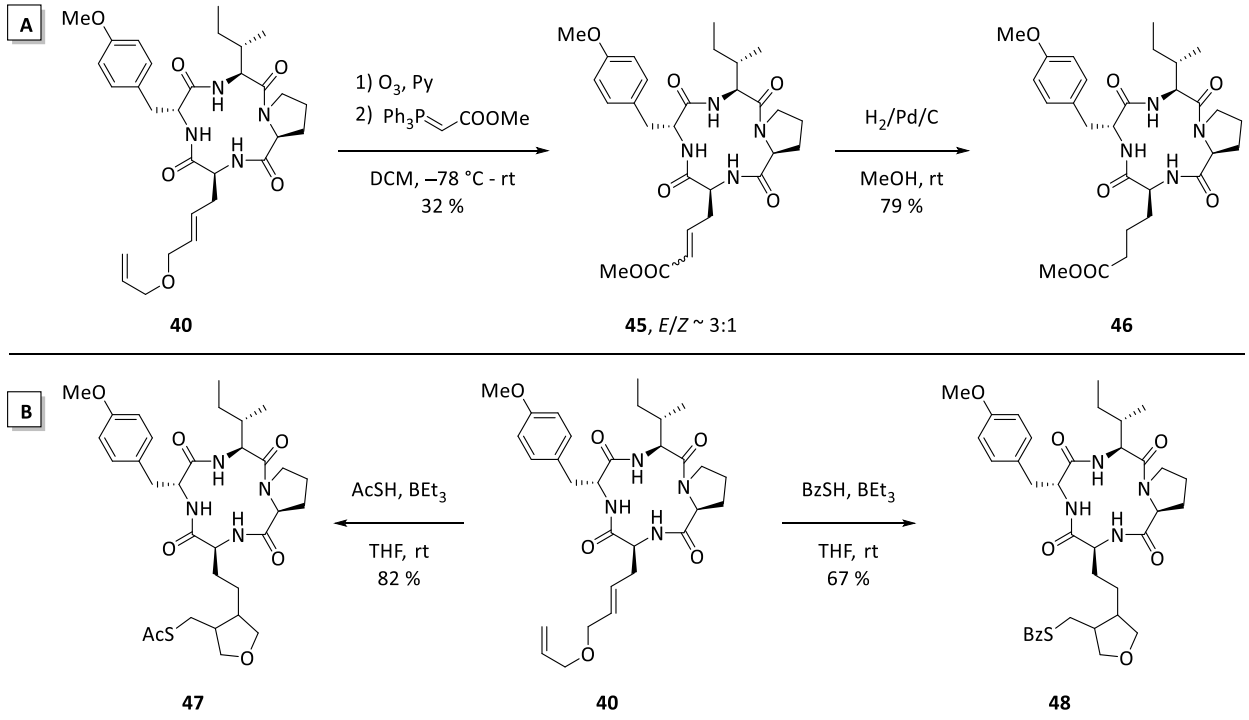
Since thiol-ene click reactions with macrocycle **41** failed, probably due to its low solubility, another access to derivatives of Cyl-1 was envisioned by olefin cross metathesis (CM reaction). Previous results demonstrated that **40** reacts readily with either Grubbs I or Grubbs II catalyst in an intramolecular ring closing metathesis (RCM) to give allylglycine derivative **41**. Consequently, addition of a second alkene to the reaction mixture should give rise to the corresponding CM

product. Grubbs *et al*. have developed a general model for selectivity in cross metathesis reactions.[204] Unlike RCM, no entropic driving force is present in cross metathesis. Homodimerization of alkenes and consumption of CM products generally lead to side products in cross metathesis. Acrylates are among the best alkenes for cross metathesis since they don't show homodimerization and the products formed from CM are stable towards further metathesis reactions. Thus, RCM/CM reactions were performed both with compound **40** and **41** in combination with different acrylates. Compound **40** was used preferably to overcome the limitations resulting from the poor solubility of **41**. Treatment of cycle **40** with ethyl acrylate and Grubbs II in DCM at 45 °C in a sealed vessel showed the formation of allylglycine derivative **41** but no cross metathesis product. Repetition of the experiment in an open vessel under Ar gave a 2:1 mixture of **41** and the desired product. Utilization of benzyl acrylate with Grubbs I in a sealed or open vessel only gave allylglycine derivative **41**. Using **40** or **41** and Grubbs II in degassed DCM also led to no improvement. Bubbling argon through the reaction mixture for several hours to expel the forming ethylene gave a conversion of 50-60 %. Unfortunately, separation of the CM product from **41** was a non-trivial issue and could not be accomplished on a preparative scale. The low solubility of **41** seemed to be the key problem in these transformations, preventing full conversion and therewith simple purification. Formation of allylglycine cycle **40** from **41** proceeded readily, clearly demonstrating the activity of the metathesis catalyst under the reaction conditions. Although large excess of acrylates (up to 10 eq.) were used in the reaction, the formation of allylglycine derivative **41** seemed to be preferred over the formation of CM product. In particular, precipitation of **41** from the reaction mixture undermined further transformations. While the general applicability of CM reactions for these substrates was indicated by the displayed results and literature reports,[205] the low solubility in combination with incomplete conversion restricted the synthetic use of these transformations.

With the so far obtained results at hand, other derivatization reactions were exploited. Due to the low solubility of **41** and the better accessibility of **40**, the latter was preferred for further derivatization. Hence, macrocycle **40** was subjected to an ozonolysis with subsequent Wittig reaction in an one-pot manner (scheme 4.13, A). Performing the ozonolysis in presence of pyridine led to immediate reduction of the primary ozonide formed during the reaction.[206] Consequently, no PPh_3 or Me_2S was needed to obtain the crude aldehyde. Subsequent addition of a Wittig ylide gave access to macrocycle **42**. Unsurprisingly, the newly formed double bond exhibited an *E*/*Z*-ratio of 3:1, which was in accordance to previously performed reactions with this ylide. Compound **45** contained approximately 30 w% of triphenylphosphine oxide as impurity, which could not be separated from the product. Although methods have been developed to remove triphenylphosphine oxide from polar compounds using $ZnCl_2$ in EtOH, application of these conditions to the potential zinc-binder **45** afforded no separation.[207] Hydrogenation of **45** proceeded readily and gave macrocycle **46** in good yield. However, the impurity could not be separated at this stage either. Due to the low yield of the ozonolysis/Wittig reaction and the inseparable $OPPh_3$ impurity, no further efforts were made towards this derivatization. Unfortunately, using a corresponding phosphonate

in a Horner-Wadsworth-Emmons reaction yielded no α,β-unsaturated ester at all. No reaction between the intermediately formed aldehyde and the phosphonate was observed.

Further efforts towards the thiol-ene click reaction were undertaken since solely the low solubility of **41** seemed to prevent full conversion. Consequently, compound **40** was used as a substrate in thiol-ene click reactions. Since the length of the side chain containing the zinc-binding motif is important to retain biological activity,[208] other thiols than before were evaluated. Thioacetic acid was treated with **40** and BEt_3/air in THF to give 82 % of the thiol-ene click product (scheme 4.13, B). Careful analysis of the NMR spectra revealed that the intermediately formed radical cyclized in an intramolecular 5-*exo* trig fashion with the internal double bond to form a tetrahydrofuran cycle **47**. In contrast, previous efforts to undertake thiol-ene click reactions in combination with intramolecular cyclizations to form pipecolinic acid derivatives failed and solely addition to the external double bond was observed. The formation of the 5-membered ring system seemed to be the driving force for this reaction and could be speculated from research done by Beckwith and Schiesser, who showed that 5-*exo* cyclizations are favored over 6-*endo*.[209] They argued that an efficient overlap of the SOMO with the π*-orbital of the alkene in the transition state accounts for the selective formation of 5-membered over 6-membered rings. Beckwith *et al.* also developed guidelines to predict the regioselectivity of radical cyclizations.[210] Furthermore, Renaud *et al*. have also reported thiol-ene click addition-cyclization reactions with simple substrates.[146] In the present case, the formation of four diastereomers made a detailed analysis of the constitution *via* NMR spectroscopy impossible. However, performing the reaction with thiobenzoic acid likewise gave the expected thiol-ene click product with subsequent cyclization to form compound **48** in 67 % yield.

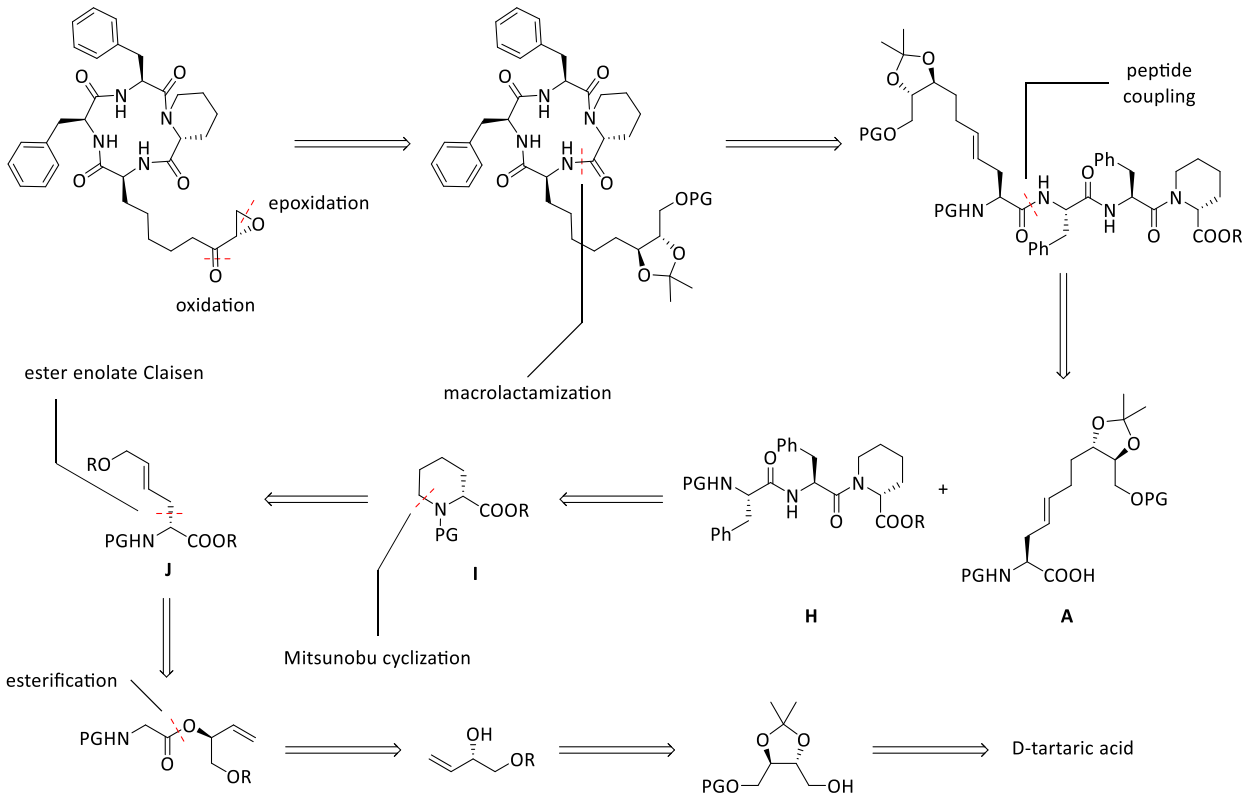


Scheme 4.13: Ozonolysis/Wittig reaction and thiol-ene click reactions of macrocycle **40**.

In conclusion, formation of thiol-ene click products **47** and **48** substantiated the hypothesis that the insolubility of **41** limited its synthetic applicability. The fact that **40** underwent rapid intramolecular cyclization after thiol addition could render further investigations into thiol-ene click initiated cyclization reactions with complex substrates. The chain length in **47** and **48** should generally be suitable for effective HDAC inhibition and the thioester moiety might act as a prodrug as seen for the natural HDACi largazole (see state of knowledge).

4.3 Synthesis of trapoxin A

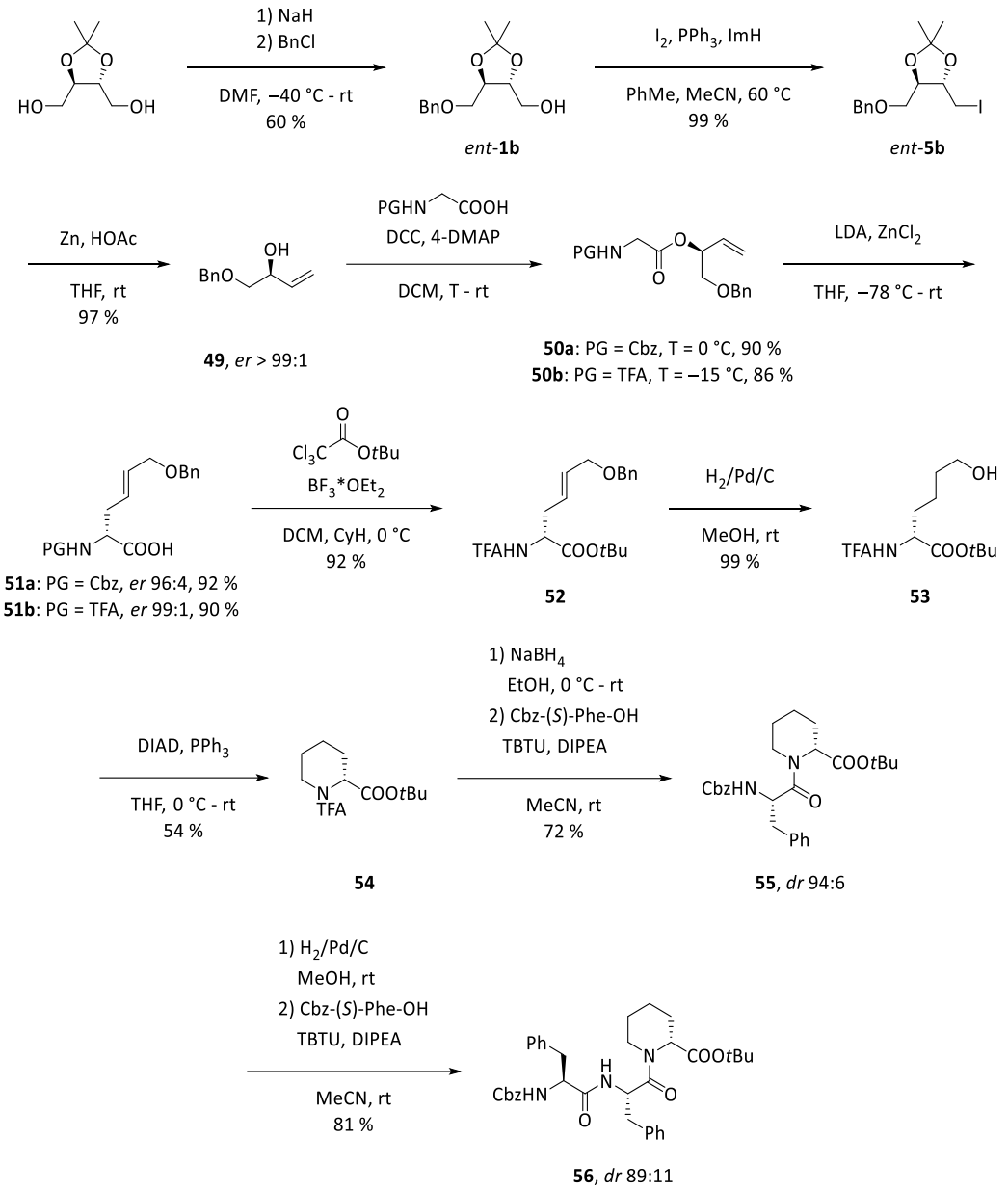
A straightforward approach towards the macrocyclic HDACi trapoxin A should arise from similar building blocks as used for the synthesis of Cyl-1. As outlined there, epoxidation and oxidation should liberate the natural product from a suitable precursor (scheme 4.14). Macrolactamization between Pip and Aoe should leave a linear tetrapeptide, which could be further divided into Aoe precursor **A** and tripeptide **H**. Although the corresponding position prevented successful cyclization in the synthesis of Cyl-1, the respective position proved beneficial in the synthesis of trapoxin B.[67] Tripeptide **H** could be build up through peptide coupling of phenylalanine and (*R*)-pipecolinic acid **I**. This non-proteinogenic amino acid should be accessible through Mitsunobu cyclization of a suitable alcohol **J**, which in turn could be obtained through ester enolate Claisen rearrangement. The stereogenic information should again come from the chiral pool, in this case from D-tartaric acid.



Scheme 4.14: Retrosynthetical analysis of trapoxin A.

4.3.1 Synthesis of a (*R*)-pipecolinic acid-containing tetrapeptide

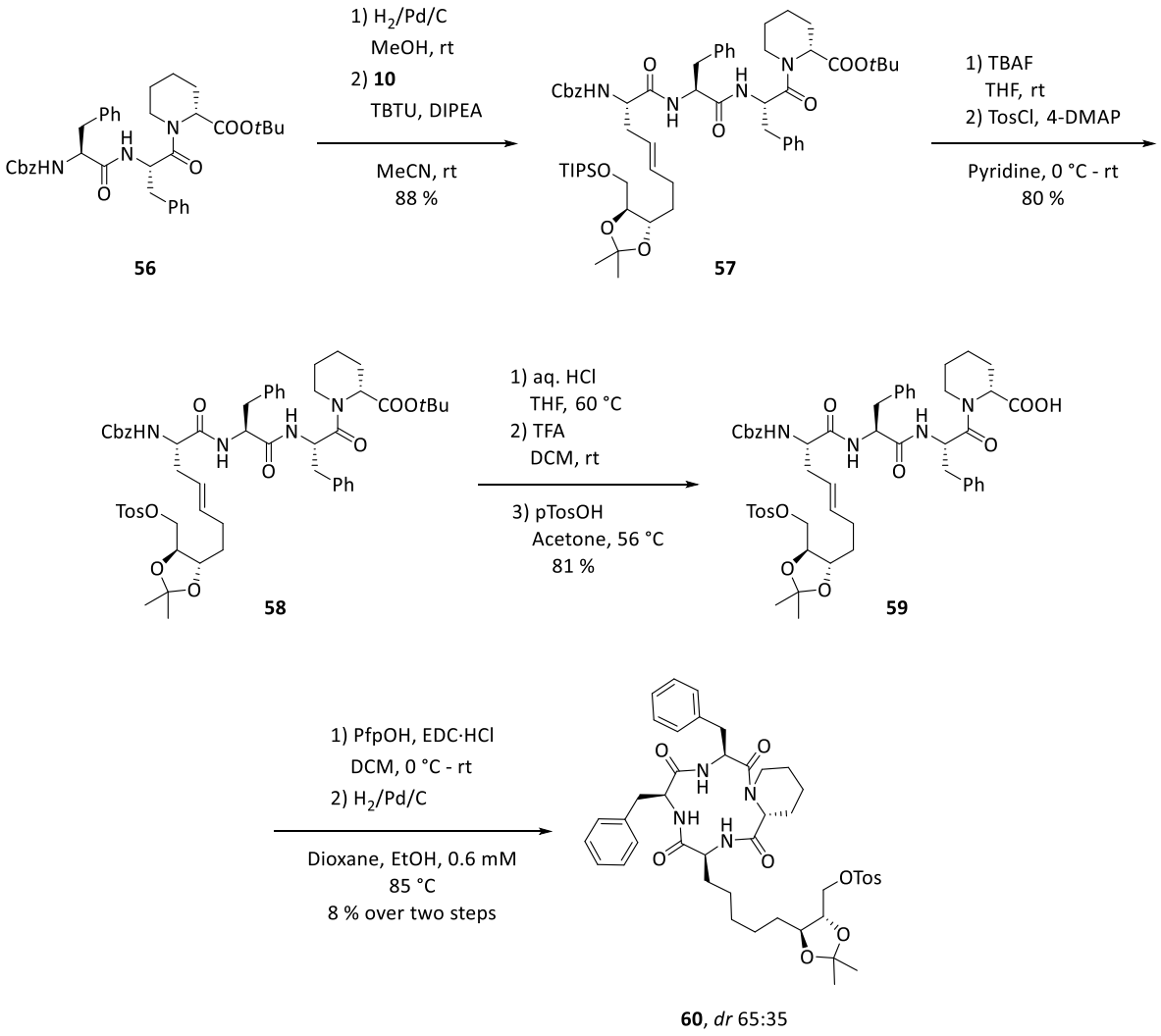
To target the non-proteinogenic (*R*)-pipecolinic acid moiety in trapoxin A *via* ester enolate Claisen rearrangement and subsequent Mitsunobu cyclization, a fitting allylic alcohol was needed. Starting from D-tartaric acid, 2,3-*O*-isopropylidene-D-threitol can be obtained in two steps following literature procedure.[155] Monobenzylation of this threitol derivative needed optimization to access **1** in reasonable yield. Following a literature protocol using sodium hydride and benzyl bromide in DMF gave 50 % of *ent*-**1b**, together with the corresponding dibenzylated product.[156] While altering solvent and/or temperature didn't yield better results, replacement of benzyl bromide with benzyl chloride gave an improved yield of 60 % (scheme 4.15). Alcohol *ent*-**1b** was further transformed into iodide *ent*-**5b** in a modified Appel reaction[211] and was then treated with zinc dust and acetic acid in THF to form allylic alcohol **49**.[212] The enantiomeric ratio in **49** was shown to be > 99:1, clearly demonstrating the power of a chiral pool synthesis approach. Esterifications with *N*-protected glycines gave allyl esters **50**. Choosing a proper solvent for esterification under Steglich conditions was crucial in terms of yield. While diethyl ether would allow for quantitative removal of urea byproducts by simple filtration, the yields were significantly worse compared to the yields obtained in DCM. To introduce the (*R*)-configured pipecolinic acid moiety, esters **50** were subjected to ester enolate Claisen rearrangements, which proceeded readily with both esters **50a** and **50b** and afforded carboxylic acids **51** in good yields and good to excellent enantioselectivities. Towards the synthesis of the pipecolinic acid scaffold, the TFA-protected carboxylic acid **51b** was transformed into *tert*-butyl ester **52** with *tert*-butyl trichloroacetimidate in 92 % yield.[213] The combination of TFA- and *tert*-butyl protected amino acid was chosen since good results were obtained with these protective groups in previous studies.[214] Hydrogenation of this amino acid ester and subsequent Mitsunobu cyclization then gave pipecolinic acid **54** in moderate yields. High dilutions were mandatory for this latter step to form the six-membered ring. Nevertheless, elimination of the activated hydroxy group to the corresponding olefin was observed even at dilutions as low as 12 mM. Removal of the TFA group was performed with a method developed by Weygand and Frauendorfer using sodium borohydride in ethanol.[215] Coupling of the crude amine with Cbz-(*S*)-Phe-OH accessed dipeptide **55** with slight epimerization (*dr* 94:6). Further hydrogenation of **55** and coupling with Cbz-(*S*)-Phe-OH yielded 82 % of tripeptide **56**, which was then derivatized to give the linear tetrapeptide. The diastereomeric ratio of tripeptide **56** was analyzed to be 89:11. The observed epimerization was surprising since the combination of TBTU and DIPEA usually performed well in similar couplings. No further investigations into the origin of these diastereomers were undertaken at this point of the synthesis since the optimal ring closing position needed to be evaluated first.



Scheme 4.15: Synthesis of Pip-containing tripeptide **56**.

Tripeptide **56** was hydrogenated under typical conditions (H_2/Pd/C) and coupled with Aoe precursor **10** to gain access to linear tetrapeptide **57** (scheme 4.16). TBTU proved to be by far the most useful reagent to perform this kind of couplings due to the mild reaction conditions. Selective cleavage of *tert*-butyl esters in presence of acid-labile groups has previously been investigated in the synthesis of Cyl-1 (see chapter 4.1.2). Careful analysis of the course of the reaction under acidic conditions revealed that decomposition started with cleavage of the TIPS group. However, several literature reports were found that utilized TMSOTf or TESOTf for mild cleavage of *tert*-butyl esters in complex structures and natural product synthesis.[216] With this in mind, tetrapeptide **57** was treated with TMSOTf to give a complex mixture of starting material, product, and TIPS-deprotected compounds. As a result, the silyl ether in **57** was replaced by a tosylate to give tetrapeptide **58** and a more convenient and robust three-step protocol for the selective *tert*-butyl

ester cleavage was developed. Ketal cleavage with aq. HCl at 60 °C led to the corresponding diol, which was treated with TFA in DCM to obtain the free carboxylic acid. Reinstallation of the ketal with *p*TosOH in boiling acetone gave access to carboxylic acid **59** in 81 % yield without intermediate purification steps. Subsequent activation of **59** as Pfp ester did not proceed as readily as observed for other substrates, meaning that no full conversion was attained. Following hydrogenative ring closure in dioxane/EtOH at 85 °C afforded the cyclic tetrapeptide **60** in poor yield and with almost full epimerization. However, no starting material was reisolated from the reaction mixture, indicating that Cbz-cleavage did occur, but the conformation of the macrocycle seemed to undermine a successful cyclization.

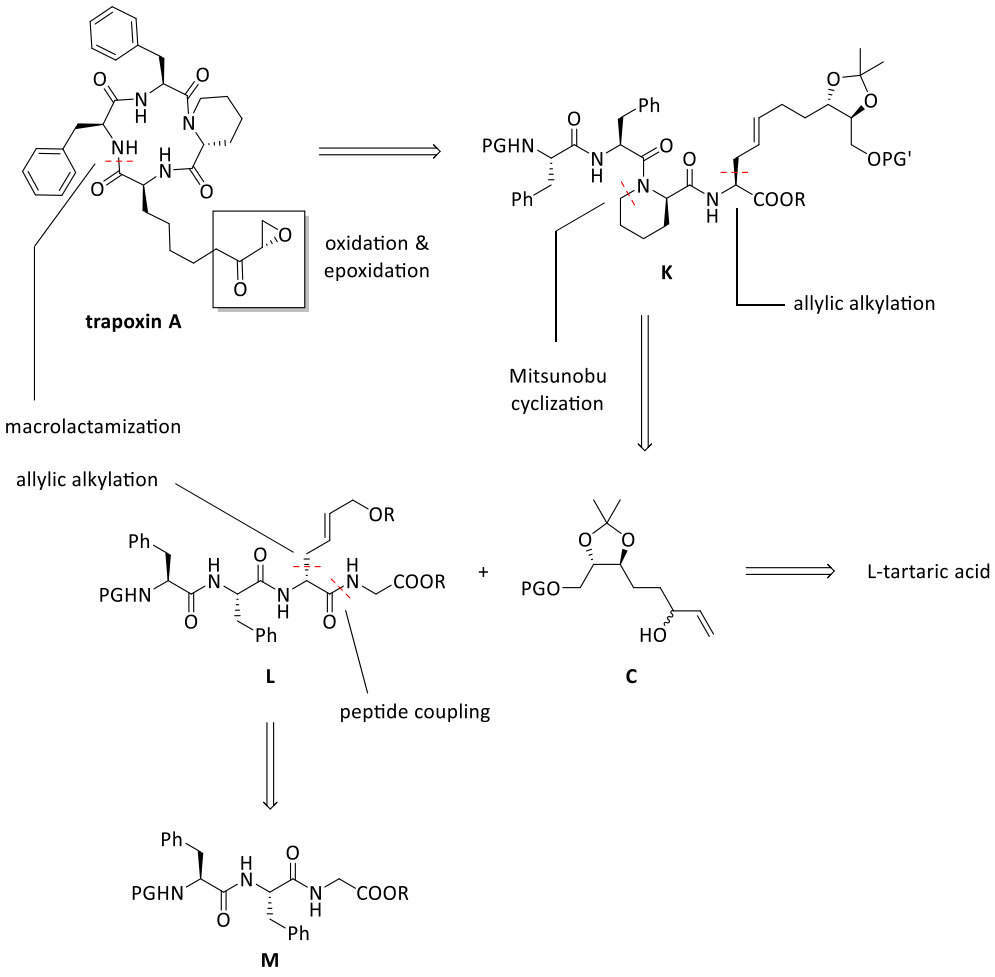


Scheme 4.16: Synthesis of linear tetrapeptide **59** and macrocyclization.

4.3.2 Synthesis of trapoxin A *via* peptide backbone modifications

Macrolactamization between Pip and Aoe failed to afford the macrocyclic core structure of trapoxin A in acceptable yield. Consequently, a different approach towards the natural product was desired. As envisioned earlier, the structure of trapoxin A should allow for several peptide

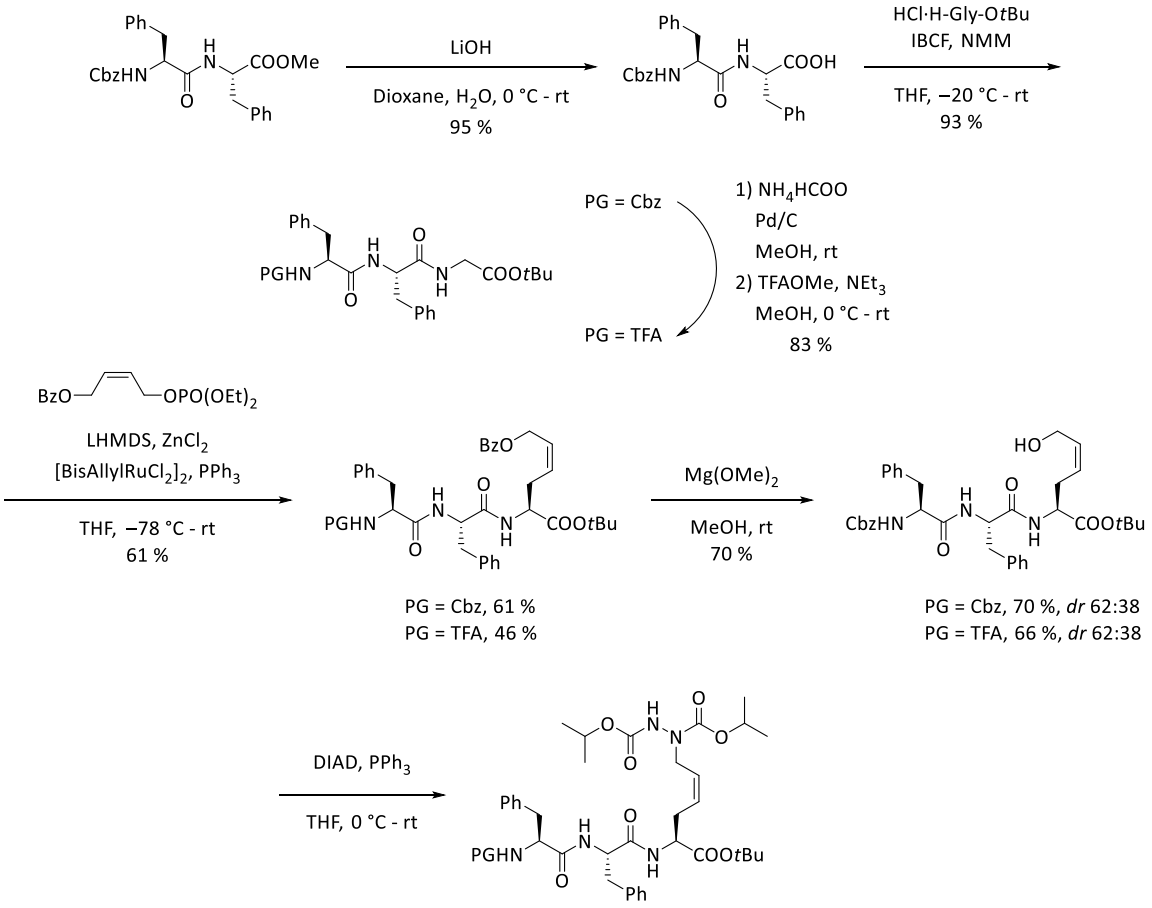
backbone modification reactions, as outlined in the retrosynthetical analysis (scheme 4.17). Macrocyclization between Aoe and phenylalanine should give a linear tetrapeptide **K**, which could be further disjointed by various peptide modifications. Mitsunobu cyclization to construct the pipecolinic acid moiety, together with transition metal catalyzed allylic alkylation to introduce the Aoe side chain, were powerful transformations to be considered in the synthesis of natural HDAC inhibitors. Linear tetrapeptide **K** contains a combination of (*S*)-(*S*)-(*R*)-(*S*)-configured amino acids. The (*S*)-configured Aoe side chain should be introduced *via* transition metal catalyzed allylic alkylation, controlled by the (*R*)-configured pipecolinic acid precursor in **L**. Allylic alcohol **C** should be synthesized starting from L-tartaric acid as outlined for Cyl-1. The Pip precursor itself can be introduced in a second TM-catalyzed allylic alkylation of tripeptide **M**, while the adjacent (*S*)-phenylalanine should control the stereochemical outcome of the C-C bond formation in favor of the (*R*)-isomer.



Scheme 4.17: Retrosynthesis of trapoxin A using peptide modifications.

Following the retrosynthetical analysis, glycine-containing tripeptides were synthesized starting from Cbz-(*S*)-Phe-(*S*)-Phe-OMe (scheme 4.18). Both the Cbz- and TFA-protected tripeptides were subjected to ruthenium catalyzed allylic alkylations to introduce (*Z*)-configured allyl

side chains. Subsequent transesterification of benzoates formed allylic alcohols in acceptable yields.[217] These (*Z*)-configured allylic alcohols should allow for rapid cyclization and would leave a double bond in the six-membered baikiain derivative for further modifications.[214] The utilized $[BisAllylRuCl_2]_2$ complex (= $[(\eta^3{:}\eta^3\text{-}2,7\text{-Dimethylocta-2,6-diene-1,8-diyl})RuCl_2]$) was discovered in earlier works to efficiently catalyze allylic alkylations of glycine enolates.[218] Nevertheless, the diastereomeric ratios obtained in the allylation step were not outstanding and could only be determined after transesterification. Before further efforts were made to evaluate other reaction conditions or catalysts to remedy this drawback, attempts towards the Mitsunobu cyclization of these derivatives were undertaken.[219] While cyclizations of *N*-terminal amino acids bearing electron-withdrawing groups under Mitsunobu conditions have been described in literature,[214,220] the utilization of internal or *C*-terminal amino acids in peptides for this purpose has not. Therefore, the previously synthesized allylic alcohols were subjected to Mitsunobu conditions (scheme 4.18). Unfortunately, in all reactions performed, only substitution of the activated alcohol with hydrazine was observed. This led to the conclusion that the pK_a-value of peptidic amides was not feasible for successful cyclization under the reaction conditions used.

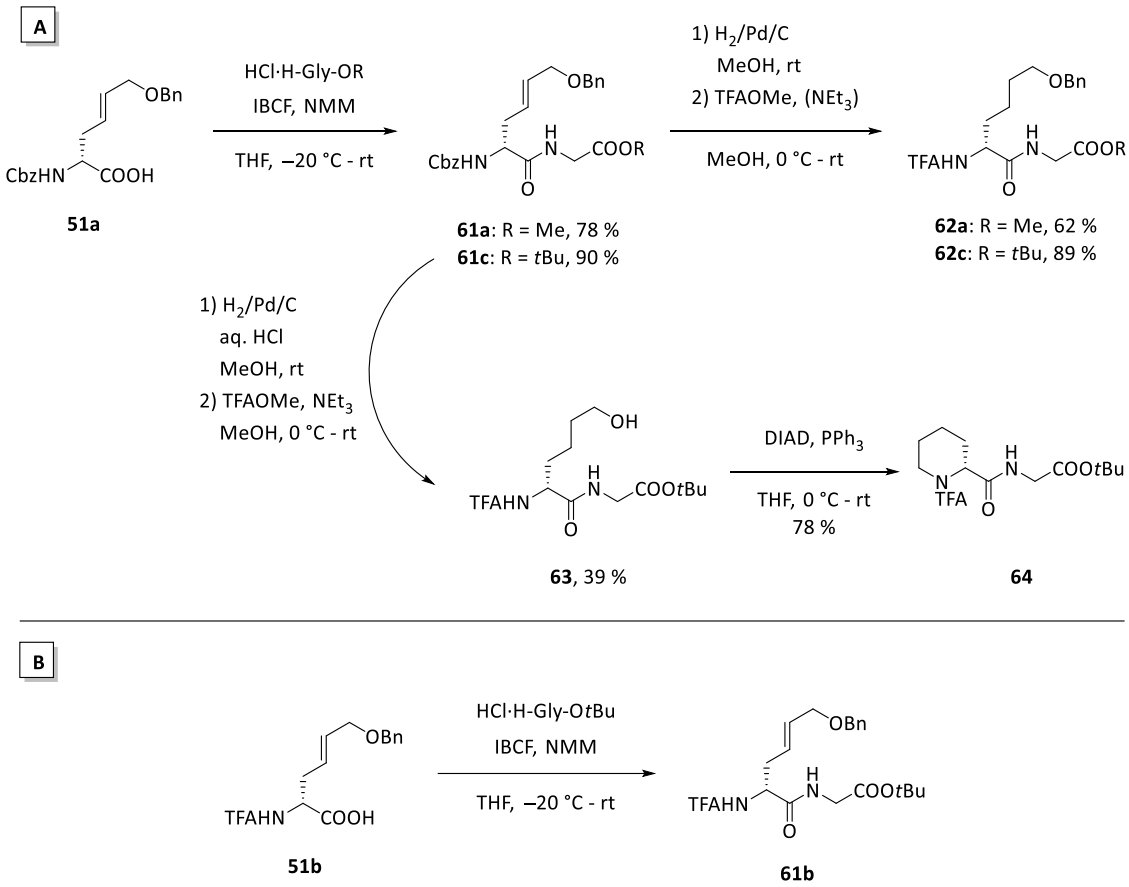


Scheme 4.18: Ru-catalyzed allylic alkylation of tripeptides.

These results clearly indicated that another synthetic strategy was needed to construct the pipecolinic acid scaffold present in trapoxin A. The requirement of *N*-terminal amides for successful Mitsunobu cyclization called for a different protocol to introduce the (*R*)-configured side chain. The stereogenic center in the Pip moiety could be introduced *via* ester enolate Claisen rearrangement as presented earlier (scheme 4.15). Coupling to glycine would give a dipeptide, whose (*R*)-configured residue could be used to introduce the (*S*)-configured Aoe side chain through allylic alkylation of a chelated dipeptide enolate. Subsequent Mitsunobu cyclization of the *N*-terminal amino acid should afford a Pip-containing dipeptide.

Consequently, carboxylic acid **51a** was activated with IBCF and coupled with glycine esters to afford dipeptides **61** (scheme 4.19, A). The Cbz-group in **61** was replaced by TFA through hydrogenation and subsequent treatment with TFAOMe.[221,222] The obtained dipeptides **61** and **62** were used to determine the optimal combination of *N*-protective group and ester for Pd-catalyzed allylic alkylation in terms of yield and diastereoselectivity (*vide infra*). Dipeptide **61c** was also hydrogenated in presence of aq. HCl and treated with TFAOMe to give the TFA-protected dipeptide **63** with a free hydroxy group. Addition of acid to the hydrogenation mixture was crucial since the initially formed amine prevented cleavage of the benzyl ether. Under these conditions, 22 % of the dehydroxylation product were isolated as side product. Transformation of the desired alcohol **63** under Mitsunobu conditions gave rise to the pipecolinic acid-containing dipeptide **64** in good yields, proving the applicability of this synthetic strategy (proof of concept).

The call for dipeptides with electron-withdrawing *N*-protective groups for successful Mitsunobu cyclization made switching of protective groups necessary. To omit these steps, carboxyl acid **51b** was coupled with HCl·H-Gly-O*t*Bu under diverse reaction conditions. In general, TFA-protected amino acids are known to epimerize after activation and during peptide coupling. Epimerization proceeds *via* intramolecular cyclization of the TFA-amide with the activated carboxylic acid and subsequent racemization of the azlactone formed. However, some examples have been described in literature to successfully couple TFA-protected amino acids.[223] Activation of **51b** with IBCF to form the mixed anhydride at –20 °C gave dipeptide **61b** in 58 % yield and 92 % *ee* (scheme 4.19, B). To improve the yield of the coupling, the reaction was repeated with EDC·HCl, HOBt and DIPEA. Under these conditions, 86 % of the dipeptide were obtained. However, severe epimerization of the activated amino acid (*er* 76:24) was observed. Repetition of the reaction under exact same conditions gave an enantiomeric ratio of 85:15, demonstrating the poor reproducibility of the reaction. Omitting the additional base and increasing the equivalents of EDC·HCl was also of no advantage. Utilization of other coupling reagents and additives also fell short compared to the first attempt. Surprisingly, performing the IBCF coupling at –40 °C gave even worse *er* values than at –20 °C. Thus, the synthetic route *via* the Cbz-protected dipeptides was by far the best choice to construct TFA-protected dipeptides in terms of yields and epimerization rates.



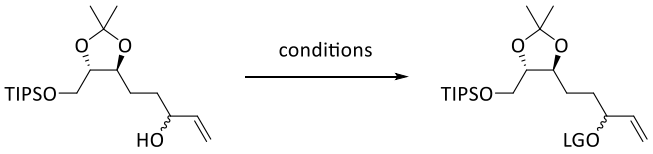
Scheme 4.19: Synthesis of dipeptides for Pd-catalyzed allylic alkylation.

With different suitable dipeptides in hand, the next step in the synthesis towards trapoxin A was the introduction of the Aoe side chain. As mentioned above, (*R*)-configured amino acids control the stereochemical outcome of the new stereogenic center formed during allylic alkylation in favor of the (*S*)-configured amino acid (and *vice versa*).[128] One side of the chelated dipeptide ester enolate complex is shielded by the side chain of the *N*-terminal amino acid and attack of the dipeptide nucleophile at the Pd-π-allyl complex takes place from the unshielded side preferably. This diastereoselective peptide modification reaction was therefore particularly useful for the construction of the peptide backbone present in trapoxin A. To determine the optimal conditions to introduce the Aoe side chain, the above prepared dipeptides were reacted with different allylic substrates under Pd-catalysis to form the linear allylation products.

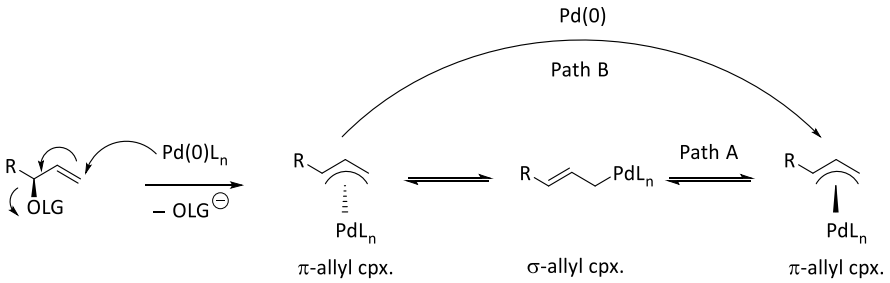
Allylic substrates for the allylic alkylation bearing different leaving groups were derived from allylic alcohol **7c** (table 4.6). Since a terminal Pd-π-allyl complex was formed in the course of the allylation reaction, the stereogenic information from these substrates could not be transferred due to rapid π-σ-π isomerization of the Pd-allyl complex (scheme 4.20, path A) or displacement of Pd(0), as suggested by Bäckvall *et al.* (path B).[224] This was no synthetic disadvantage because the newly formed stereogenic center should be controlled by the chiral, chelated dipeptide enolate complex, anyway. Due to this rapid isomerization, alcohol (3*R*)-**7c** could also be utilized in the transformation after introduction of a suitable leaving group. Therewith, both diastereomers of

alcohol **7c**, derived from enzymatic kinetic resolution, could be employed for the synthesis of the Aoe scaffold *via* either ester enolate Claisen rearrangement or Pd-catalyzed allylic alkylation.

Table 4.6: Synthesis of different allylic substrates for Pd-catalyzed allylic alkylation.



entry	SM	conditions	Y	LG	product
1	**7c**	MeOCOCl, Py, 0 °C	94 %	-COOMe	**65**
2	**7c**	EtOCOCl, Py, 0 °C - rt	91 %	-COOEt	**66**
3	**7c**	$(EtO)_2POCl$, Py, 4-DMAP, DCM, 0 °C – rt	75 %	$-PO(OEt)_2$	**67**
4	**7c**	BzCl, Py, 0 °C	99 %	-Bz	**68**
5	(3*R*)-7**c**	EtOCOCl, Py, 0 °C - rt	93 %	-COOEt	(3*R*)-**66**

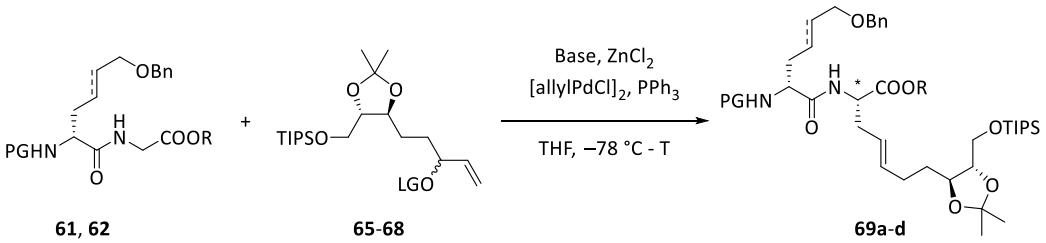


Scheme 4.20: Racemization of terminal Pd-π-allyl complexes.

The investigations into Pd-catalyzed allylic alkylation started with Cbz-protected dipeptides **61a** and **61c**, which gave the desired allylated products but usually lacked full conversion of the allylic substrate **65** (table 4.7, entries 1-2). Since TFA-protective groups were needed anyway for further transformations (Mitsunobu cyclization), the allylations were in the following performed with the corresponding TFA-protected dipeptides **61b** and **62c**. Use of LHMDS as base for the formation of chelated enolates in combination with methyl- and ethyl chloroformates gave the allylation product **69c** in 62 % and 80 % yield, respectively (entries 3-4). Afterwards, different leaving groups in the allylic substrate were tested in combination with different temperature profiles according to their general reactivity (entries 5-8). While incomplete conversion was observed for all leaving groups tested, the phosphate group in **67** seemed to be by far the most reactive. Benzoate **68** on the other hand gave the best diastereoselectivities. This matched previous results since more reactive leaving groups generally tended to give poorer selectivities.[225] Ethyl carbonate **66** was further utilized in combination with LDA to give allylation product **69d** in 66 %

yield (entry 9). Noteworthy, allylations performed with LDA generally showed better reproducibility. Furthermore, reisolation of unreacted dipeptide from the reaction mixture and determination of diastereomeric ratios revealed no epimerization of the α-center of the *N*-terminal amino acid. Later experiments with the diastereomerically enriched allylic substrate (3*R*)-**66** in combination with dipeptide **61b** (entry 10) or **62c** (entry 11) gave similar results in terms of yield (87 % and 85 %) and diastereoselectivity (*dr* ~ 80:20). These results demonstrated that the presence of a double bond in the dipeptide had no effect on the stereochemical outcome of the reaction.

Table 4.7: Pd-catalyzed allylic alkylations of dipeptides to introduce the Aoe side chain.



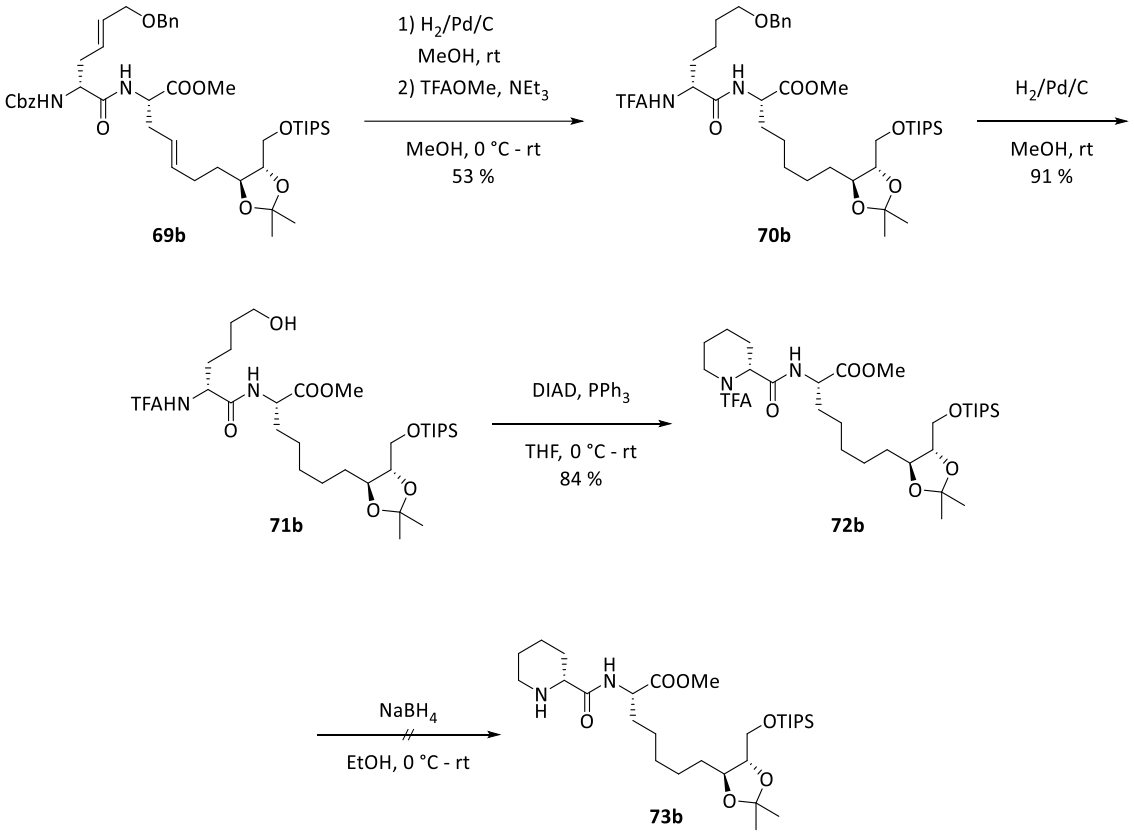
61, 62 **65-68** **69a-d**

		allylic substrate		conditions		product		
entry	**61/62**	LG	**65-68**	base	T	Y	**69**	*dr*
1	**61c**	COOMe	**65**	LHMDS	rt	18 %	**a**	77:23[a]
2	**61a**	COOMe	**65**	LHMDS	rt	65 %	**b**	75:25[b]
3	**62c**	COOMe	**65**	LHMDS	rt	62 %	**c**	84:16[b]
4	**62c**	COOEt	**66**	LHMDS	rt	80 %	**c**	89:11[a]
5	**61b**	COOEt	**66**	LHMDS	rt	55 %	**d**	86:14[c]
6	**61b**	$PO(OEt)_2$	**67**	LHMDS	–65 °C	62 %	**d**	74:26[a]
7	**61b**	COOEt	**66**	LHMDS	–60 °C	24 %	**d**	84:16[a]
8	**61b**	Bz	**68**	LHMDS	rt	29 %	**d**	92:8[a]
9	**61b**	COOEt	**66**	LDA	rt	66 %	**d**	89:11[c]
10	**61b**	COOEt	(3*R*)-**66**	LDA	rt	87 %	**d**	79:21[b]
11	**62c**	COOEt	(3*R*)-**66**	LDA	rt	85 %	**c**	80:20[b]

a: determined by ^{1}H-NMR, b: determined by HPLC, c: determined by ^{13}C-NMR

The next step in the synthesis was the construction of the pipecolinic acid since this has to be accomplished with the *N*-terminal amino acid residue (as discussed above). The use of methyl esters in the synthesis of trapoxin A was exploited, in order to avoid issues later in the synthesis during *tert*-butyl ester cleavage as seen before. Therefore, methyl ester **69b** was transformed into

the pipecolinic acid-containing dipeptide **72b** (scheme 4.21). Hydrogenation of **69b** and subsequent TFA-protection gave the corresponding dipeptide **70b**. To prevent deoxygenation during hydrogenation under acidic conditions, the benzyl ether in **70b** was cleaved in a second reaction to give alcohol **71b**, suitable for Mitsunobu cyclization. Luckily, cyclization proceeded well to form the Pip-dipeptide **72b** in 84 % yield. All attempts to remove the TFA group under basic conditions failed, meaning that the crude amine couldn't be isolated from the reaction mixture. Reducing the TFA-group in **72b** with $NaBH_4$ gave the corresponding amine. Unfortunately, the ^{1}H-NMR spectrum revealed additional cleavage of the methyl ester. These findings have also been reported by Weygand and Frauendorfer, who stated the incompatibility of their method in presence of methyl esters.[215] Therefore, the use of *tert*-butyl esters to construct the pipecolinic acid moiety and reduce the TFA-group was obligatory.

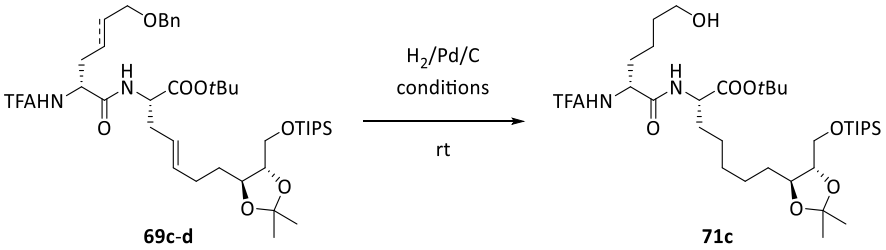


Scheme 4.21: Transformation of **69b** to Pip-containing dipeptide **72b**.

The reactions were then optimized for the TFA-protected dipeptide *tert*-butyl esters. Dipeptides **69c-d** were hydrogenated to reduce the double bond(s) and cleave the benzyl ether (table 4.8). Under standard conditions (1 bar H_2/Pd/C, MeOH, rt), neither reduction of the double bond nor the benzyl ether was observed (entry 1). Instead, partial cleavage of the ketal in **69c** was detected. Changing the solvent to ethyl acetate and rising the pressure to 2 bar led to hydrogenation of the double bond, but no benzyl ether cleavage was observed. Subsequent performance of the reaction at 20 bar gave 85 % of the desired product **71c** (entry 2). In contrast, repeating the reaction

with dipeptide **69d** showed less reactivity resulting in incomplete double bond hydrogenation at 3 bar (entry 3) and no benzyl cleavage at 20 bar (entry 4). However, at pressures as high as 50 bar, **71c** was obtained in quantitative yields (entry 5). The solvent was switched to THF, which generally showed the highest reactivities for benzyl ether cleavage.[226] Indeed, hydrogenation of **69c** in THF at 20 bar for 24 h gave 82 % of **71c**, along with an unknown side product (entry 6). The reaction was repeated and no benzyl ether cleavage was observed after 18 h at 20 bar. Catalytic amounts of acetic acid were added to facilitate benzyl ether hydrogenolysis and the pressure was increased to 30 bar to obtain 99 % of pure **71c** (entry 7). Performing the reaction immediately at 30 bar with catalytic HOAc lowered the yield slightly (entry 8).

Table 4.8: Optimization of the hydrogenation of **69c-d**.

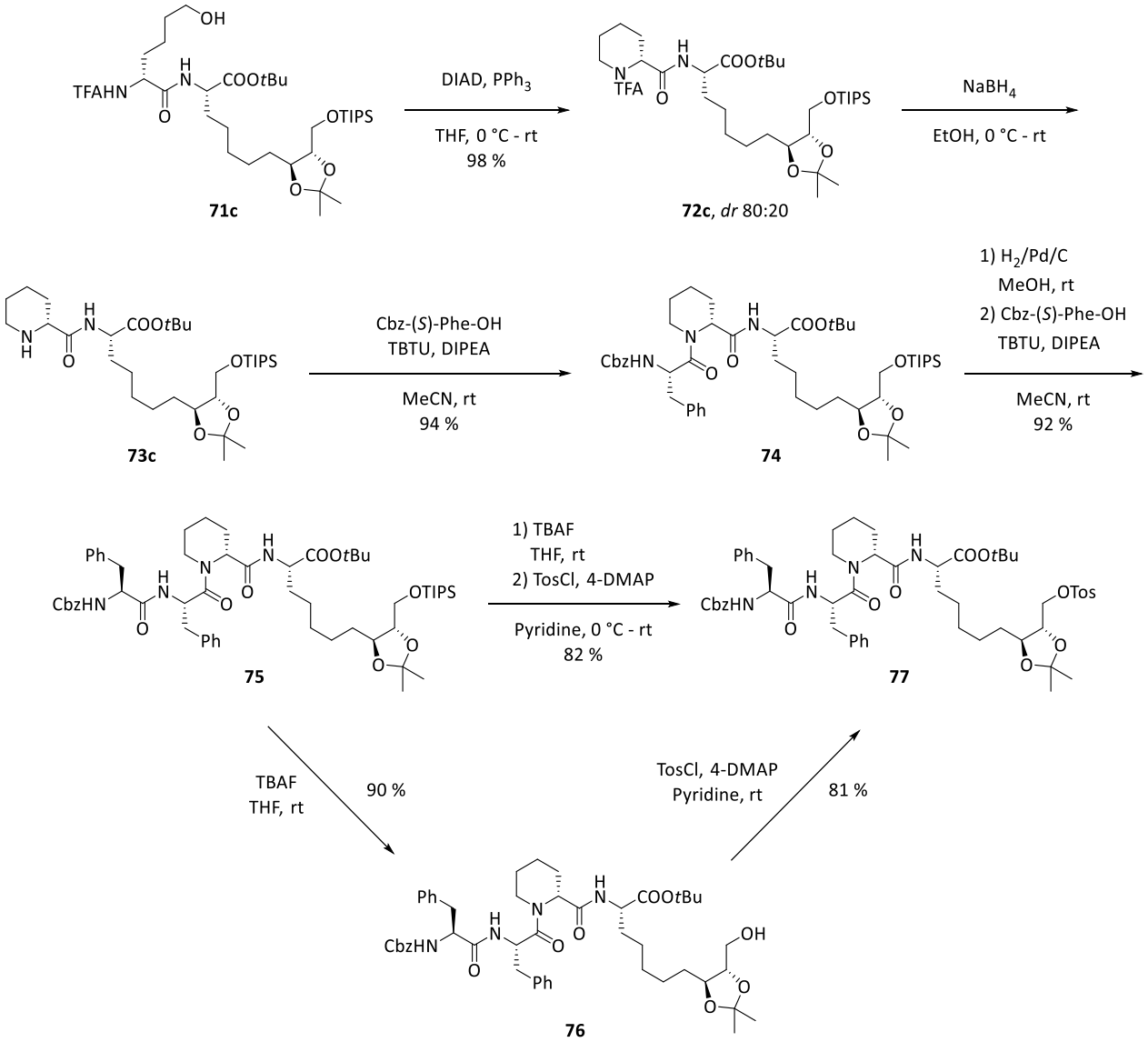


entry	DB	conditions	Y	comment
1	×	1 bar, MeOH, 21 h	-	partial ketal cleavage
2	×	2 bar, EtOAc, 3 h, then 20 bar, EtOAc, 20 h	85 %	no benzyl deprotection at 2 bar
3	✓	3 bar, EtOAc, 6 h	-	partial DB hydrogenation
4	✓	20 bar, EtOAc, 4 h	71 %	no benzyl deprotection
5	×	50 bar, EtOAc, 24 h	quant.	-
6	×	20 bar, THF, 24 h	82 %	unknown side product
7	×	20 bar, THF, 18 h, then cat. HOAc, 30 bar, THF, 22 h	99 %	-
8	×	30 bar, cat. HOAc, THF, 24 h	91 %	-

Having dipeptide **71c** at hand, attempts towards the crucial Mitsunobu reaction were undertaken. Under the previously described conditions, Pip-containing dipeptide **72c** was obtained in excellent yield and the diastereomeric ratio was not influenced by the reaction (scheme 4.22). Subsequent reduction of **72c** with $NaBH_4$ gave crude amine **73c**, leaving the *tert*-butyl ester unaffected. Unfortunately, coupling with Cbz-(*S*)-Phe-(*S*)-Phe-OH and TBTU failed and did not lead to formation of the corresponding tetrapeptide **75**. Stepwise coupling of amine **73c** with

Cbz-(*S*)-Phe-OH to tripeptide **74**, followed by hydrogenolysis and immediate second coupling with Cbz-(*S*)-Phe-OH gave the desired tetrapeptide **75** in excellent yield.

As speculated above, the selective cleavage of *tert*-butyl esters in presence of acid-sensitive groups in **75** was again a non-trivial issue. Performing the reaction under standard conditions (HCl, dioxane, rt) as well as at low temperatures (TFA, DCM, –40 °C) gave only decomposition products. Other methods to selectively cleave the *tert*-butyl ester were examined in the synthesis of Cyl-1 and gave no improved results. As pointed out before, decomposition was found to start with TIPS-cleavage. Consequently, the silyl ether in **75** was again replaced by a tosylate to give tetrapeptide **77** (scheme 4.22). The substitution could either be performed in two steps, with isolation of alcohol **76**, or in two subsequent steps without intermediate purification of the alcohol. The yields were in a similar range (73 % and 82 % respectively).



Scheme 4.22: Mitsunobu cyclization and synthesis of tetrapeptide **77**.

Noteworthy, tripeptide **74** crystallized spontaneously after column chromatography from a mixture of petroleum ether/ethyl acetate. Therefore, the relative configuration of the stereocenters in **74** was determined by X-ray diffraction (figure 4.2). Conclusions about the absolute configuration were drawn from the known stereogenic centers derived from starting materials (Cbz-(*S*)-Phe-OH and L-tartaric acid). The assumption about stereocontrol during Pd-catalyzed allylic alkylation was proven correct since the configuration of the main diastereomer met the expectations.

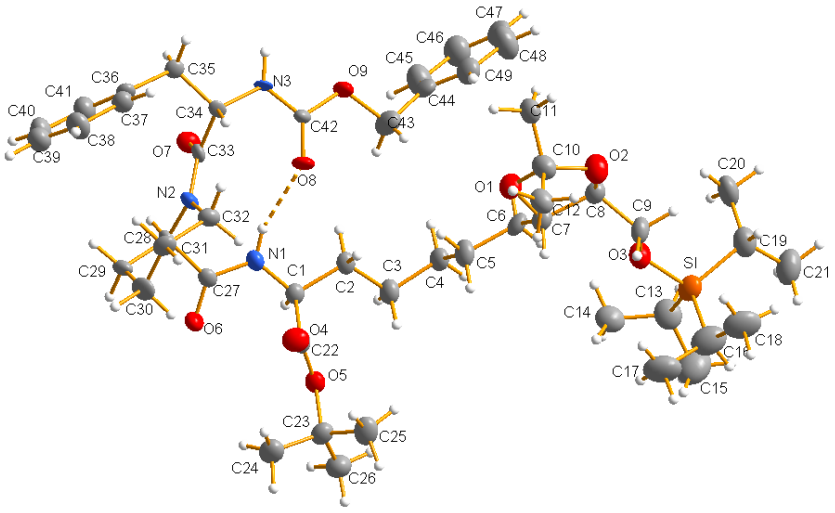
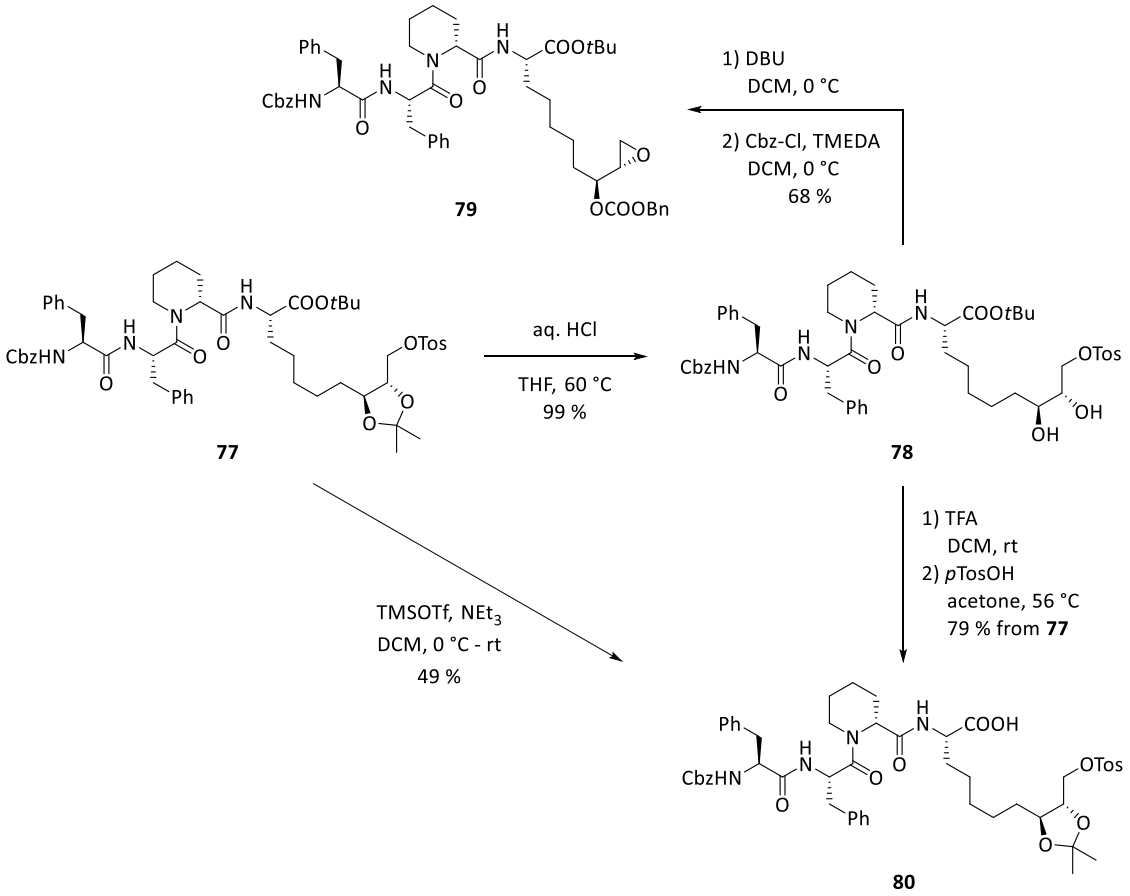


Figure 4.2: X-ray structure of the major diastereomer of tripeptide **74**.

In order to avoid side reaction of the labile ketal in **77** during *tert*-butyl ester cleavage, acid hydrolysis with aq. HCl in THF was attempted to give diol **78** (scheme 4.23). Interestingly, very slow conversion of the ketal was observed at room temperature. Thus, hydrolysis was performed at 60 °C to afford the free diol in almost quantitative yield. Diol **78** was typically obtained along with 10 % of the corresponding carboxylic acid. Further methods were evaluated to suppress this side reaction. While Amberlyst 15 has been reported to selectively cleave acetonides in acid-sensitive substrates,[227,228] no conversion of the starting material was observed under the reported conditions, not even at 50 °C. Diol **78** was then subjected to a variety of transformations as highlighted in scheme 4.22. Due to the fact that the Aoe side chain already needed alteration to cleave the *tert*-butyl ester (switching from -TIPS to -Tos), some attempts were undertaken to install a precursor of the α-epoxyketone at this stage of the synthesis. This would account for fewer transformations of the cyclic peptide later in the synthesis. Thus, diol **78** was treated with DBU to form the epoxyalcohol under similar conditions than reported in the synthesis of trapoxin B.[67] To suppress side reactions of this epoxyalcohol during acidic *tert*-butyl ester cleavage, like Payne rearrangement or epoxide opening, the alcohol function was directly protected as benzyl carbonate **79**. The Cbz-group could potentially be cleaved during hydrogenative ring closure to give a direct precursor of trapoxin A after cyclization. Unfortunately, treatment of carbonate **79** with TFA in DCM gave solely decomposition products. Consequently, further options to selectively cleave the

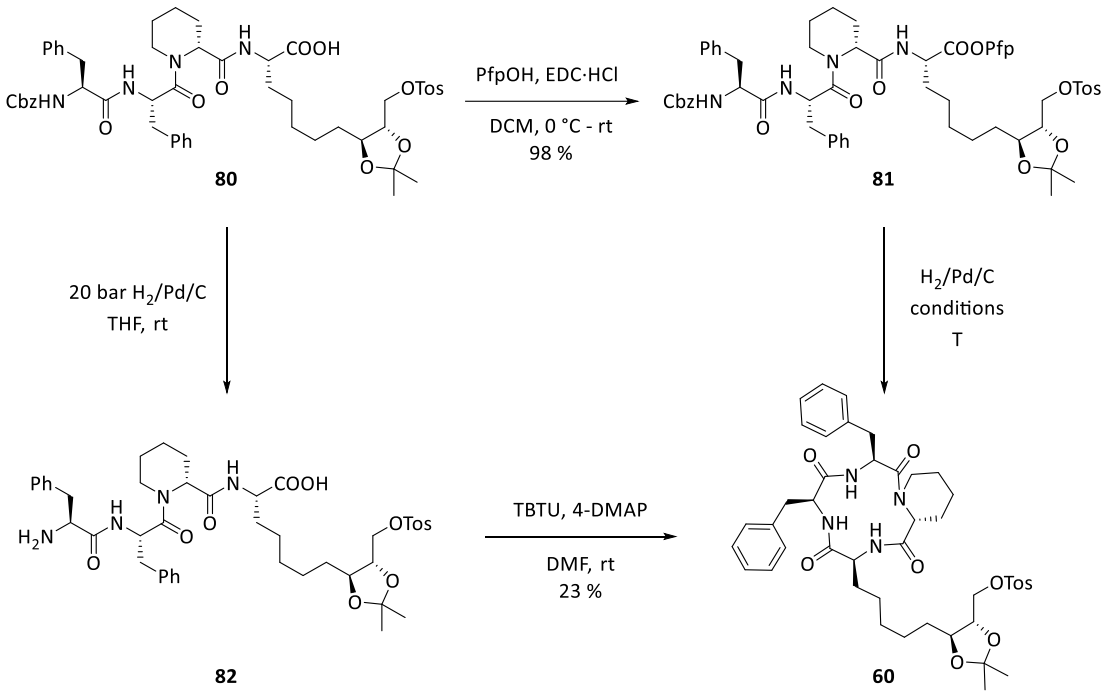
tert-butyl ester in **77** were tested. As discussed before, TMSOTf was used to transform tetrapeptide **77** into the corresponding carboxylic acid **80**. Even though 49 % of the carboxylic acid was obtained, the reaction suffered from poor reproducibility and the results could not get improved. Reactions with TESOTf and **77** gave none of the desired product. As a result, the beforehand developed three-step protocol was utilized. Diol **38** was treated with TFA to give the free carboxylic acid and subsequent reinstallation of the ketal with *p*TosOH in acetone gave tetrapeptide **80** in 79 % yield without intermediate purification. This linear tetrapeptide **80** was then used for cyclizations to the macrocyclic core of trapoxin A.



Scheme 4.23: Transformations of *tert*-butyl ester **77** and diol **78**.

With tetrapeptide **80** at hand, intensive investigations into the macrocyclization step were undertaken. Activation of linear tetrapeptide **80** was performed with pentafluorophenol. The corresponding Pfp ester **81** was cyclized under hydrogenative conditions to form the cyclic peptide **60** (scheme 4.24 and table 4.9). Performing the reaction under elevated pressure with or without additional acid showed no conversion (entries 1-4). Addition of acid was thought to suppress catalyst inactivation from gradually formed amine and the ammonium salt should then be cyclized in a subsequent step. However, Cbz-deprotection seemed not to occur as the activated Pfp ester **81** was reisolated from the reaction mixture. Since higher temperatures were sometimes required for successful macrolactamization of these derivatives, a solution of Pfp ester **81** was added slowly to

a vigorously stirred suspension of Pd/C in dioxane at 80 °C. During the addition, H_2 was continuously passed through the reaction mixture. Utilizing this method developed by Schmidt *et al.* gave 28 % of macrocycle **60** as a single diastereomer after purification (entry 5).[191] Carboxylic acid **80** was also hydrogenated at 20 bar H_2 pressure to give free peptide **82**, which was subsequently cyclized according to Schreiber's trapoxin B synthesis.[67] Herein, similar results were observed compared to the hydrogenative ring closure, although with slightly worse diastereoselectivities (*dr* ~ 90:10).



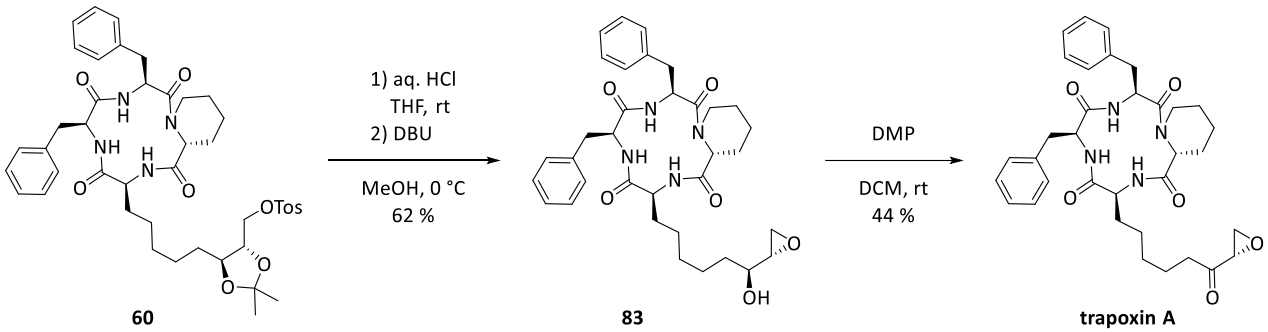
Scheme 4.24: Macrocyclization with tetrapeptide **80**.

Table 4.9: Optimization of the hydrogenative ring closure of **81**.

entry	conditions	T	Y	*dr**	comment
1	5 bar, THF (5 mM), 18 h, then 20 bar, 24 h	rt	-	-	almost no conversion
2	5 bar, THF (5 mM), 24 h, then 20 bar, 20 h	rt	-	-	1 % cyclic product
3	20 bar, HCl/dioxane, THF (14 mM), Pd/C + $Pd(OH)_2$/C, 63 h	rt	-	-	no product detected
4	5 bar, THF (5 mM), 18 h, then 20 bar, cat. HOAc, 24 h	rt	-	-	no product detected
5	continuous H_2 induction, dioxane (0.6 mM), EtOH	80 °C	28 %	> 99:1	-

*determined by ^{1}H-NMR and LCMS

To accomplish the first total synthesis of trapoxin A, macrocycle **60** was transformed similarly to literature procedures described for trapoxin B (scheme 4.25).[67] Ketal cleavage in **60** with aq. HCl proceeded smoothly at rt and subsequent treatment with DBU in MeOH gave epoxyalcohol **83**. Finally, this alcohol was oxidized with DMP in DCM to give rise to trapoxin A as a single diastereomer. The NMR spectra recorded were in accordance to previously reported data of the isolated natural product (see appendix).[41]



Scheme 4.25: Synthesis of trapoxin A.

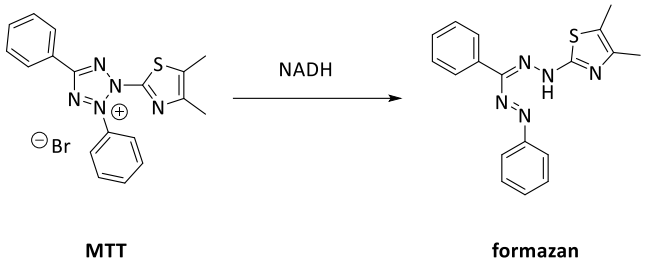
In conclusion, the described peptide modification approach towards the natural product trapoxin A proved to be a powerful tool in the construction of both the (*R*)-configured pipecolinic acid and the Aoe scaffold. Allyl alkylation of chelated dipeptides should in general be suitable for the synthesis of various derivatives through altering the allylic substrate. Although *tert*-butyl ester cleavage proved to be difficult without altering the initial Aoe side chain precursor, robust methods to accomplish this task were developed and could be used in other natural product synthesis.

4.4 Biological evaluation

The synthesized natural products, together with their epoxyalcohol precursors and derivatives, were surveyed with regard to their cytotoxicity. Biological testing was performed in cooperation with Prof. Dr. R. Müller at Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken and the experiments were conducted by Viktoria Schmitt and Dr. Jennifer Herrmann. The synthesized compounds were incubated with different cancer cell lines in order to determine their influence on cell proliferation and viability. Quantification of the concentration-dependent inhibition of cell growth was achieved using an MTT assay.[229,230]

This quantitative colorimetric assay is based on the NADH-dependent transformation of the tetrazolium salt MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide) to formazan (scheme 4.26). Cell-dependent reduction of the pale yellow MTT leads to formation of dark blue formazan, which segregates from the assay medium. Formazan is then dissolved with acidified *iso*-propanol and colorimetrically quantified at a wavelength of 570 nm. The concentration-

dependent absorption of formazan is proportional to the number of living cells since only these can reduce MTT effectively.



Scheme 4.26: NADH-dependent reduction of MTT to formazan.

To determine the biological activity of the synthesized compounds, incubation with different cancer cell lines was performed for five days before MTT was added. Afterwards, the amount of produced formazan was measured, which allowed conclusions about the number of living cells present after treatment with the substances. The obtained IC_{50} values are summarized in table 4.10 and are given in µg/mL and µmol/L, respectively.

Table 4.10: Biological activity of the natural HDACi and their derivatives.

	IC_{50} [µg/mL]			IC_{50} [µM]		
compound	HCT-116	KB-3.1	U-2 OS	HCT-116	KB-3.1	U-2 OS
24	19.1	-	7.2	32.6	-	12.3
Cyl-1*	0.007	-	0.0002	0.01197	-	0.00034
41*	> 50	> 50	-	> 103.2	>103.2	-
46*,a	> 50	> 50	-	> 91.8	>91.8	-
47	12.3	44.6	-	19.5	70.7	-
48	> 50	> 50	-	> 72.2	>72.2	-
83	1.4	10.1	-	2.3	16.7	-
trapoxin A	0.00024	0.052	-	0.00040	0.08627	-

*not completely soluble; a: triphenylphosphine oxide impurity; HCT-116: human colon cancer cells; KB-3.1: human endocervical adenocarcinoma cells; U-2 OS: human osteosarcoma cells

Direct comparison between the natural product Cyl-1 and its epoxyalcohol precursor **24** underlined the importance of the epoxyketone functionality to attain biological activity. An increase in inhibitory activity by 4-5 orders of magnitude was noted after oxidation to the natural product. Furthermore, Cyl-1 exhibited a 35-fold higher activity against U-2 OS cells compared to the HCT-116 cell line.

Unsurprisingly, the derivatives of Cyl-1 (**41**, **46**, **47** and **48**) showed significantly lower activity due to their rather simple side chain functionalities. However, thioacetate **47** inhibited cellular growth in the µM range, while the corresponding benzoate revealed less pronounced inhibitory activity. Since these two compounds only differ in their esterified acid moiety, further investigations whether a prodrug mechanism is in place need to be undertaken.

Outstanding results were obtained for trapoxin A. Similar to Cyl-1, the epoxyalcohol precursor **83** showed significantly lower activity due to the missing epoxyketone group. However, the natural product showed IC_{50} values in the low nM range with a 215-fold selectivity in favor of HCT-116 over KB-3.1. The origin of this high selectivity towards a certain cancer cell line needs further assessment.

In summary, the natural HDACi were shown to effectively inhibit cellular growth in the nM range. The importance of the ketone functionality for the biological activity was underlined. Further zinc-binding motifs were evaluated, while interesting results were obtained for the two thioesters **47** and **48**. The distinguished selectivity of trapoxin A in favor of one cancer cell line over another triggered further investigations. Moreover, inhibition of isolated HDAC enzymes needs to be evaluated to allow conclusions about their HDACi-activity and -selectivity profiles.

5. Experimental section

5.1 General remarks

All **chemicals** and **solvents** were ordered from *"Zentrales Chemikalienlager"* at Saarland University and were occasionally purified and dried using standard techniques.

Thin layer chromatography was performed with precoated silica gel plates from *Sigma-Aldrich*. Visualization was accomplished with a 254 nm UV lamp, an iodine chamber, a $KMnO_4$ bath, a ninhydrin bath or a Ce(IV) bath.

Column chromatography was done with silica gel (*60 Å, 63-200 µm, technical*) from *Macherey-Nagel* and a *Reveleris® Flash Chromatography System* from *Grace* with *RediSep® Rf* columns from *Teledyne Isco*.

^{1}H-NMR spectra were recorded on a 400 MHz *Bruker AC II 400* or a 500 MHz *Bruker AV 500* spectrometer. Chemical shifts are reported in ppm relative to TMS, and the NMR solvent was used as internal standard. Analysis of the spectra was performed with *NMR Processor Academic Edition 12.01* from *ACD*.

^{13}C-NMR spectra were also recorded on a 400 MHz *Bruker AC II 400* or a 500 MHz *Bruker AV 500* spectrometer. The spectra were proton decoupled. The theoretical couplings between C and H and the actual couplings between C and F, P are given. Chemical shifts are reported in ppm relative to TMS, and the NMR solvent was used as internal standard. Analysis of the spectra was performed with *NMR Processor Academic Edition 12.01* from *ACD*.

Optical rotations were measured on a *PerkinElmer Model 341* in a tempered (20 ± 0.1 °C, unless otherwise stated) 1 dm cuvette. A sodium vapor lamp (λ = 589 nm) was used as light source and the optical rotation was calculated from the device as function of the concentration.

HRMS were recorded with a *MAT 95Q* from *Finnigan* or a *maXis 4G hr-ToF* from *Bruker Daltonics*.

For **gas chromatography**, a *Shimadzu* (*GC-2010*, autoinjector *AOC-20i*, FID-detector) with a *Varian* capillary column *CP-Chirasil-Dex CB* (25 m x 0.25 mm, 0.25 µm ID) with nitrogen as carrier gas was used.

HPLC analyses were performed on a *Merck Hitachi D-7000* with a *Diode Array detector L-7455*.

LCMS analyses were accomplished on a *Shimadzu* (*LC-10At*, autoinjector *SCL-6B*, mass spectrometer *LCMS-2020*). A *Phenomenex Luna C18(2)* column (50 x 4.6 mm, grain size 3 µm) was used as the column.

Melting points were measured uncorrected in open glass capillaries with an *IA 9100* device from *Electrothermal*.

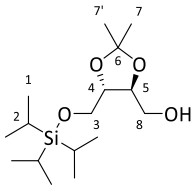
For **lyophilisation**, a lyophilisator *Alpha* from *Christ* was used.

5.2 Synthesis of compounds

((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)methanol (1c)[67]

To a suspension of 2.40 g (60.0 mmol) Sodium hydride (60 w% in paraffin) in 350 mL THF abs. was added dropwise a solution of 8.92 g (55.0 mmol) (+)-2,3-O-Isopropylidene-L-threitol in 35 mL THF abs. at 0 °C. The cooling bath was removed and the reaction was stirred at rt for 1 h. After cooling to 0 °C, a solution of 10.8 mL (9.84 g, 50 mmol) TIPSCl in 35 mL THF abs. was added slowly and the reaction was stirred for 1 h. The reaction was concentrated *in vacuo*, the residue was redissolved in Et_2O and water was added. The layers were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the crude product was purified by column chromatography (silica gel, PE:EA 80:20, 50:50) to yield 15.8 g (49.6 mmol, 99 %) of compound **1c** as a slightly yellow oil.

R_f (1c) = 0.39 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.16 (m, 21 H, 1-H, 2-H), 1.40 (s, 3 H, 7-H), 1.42 (s, 3 H, 7'-H), 2.45 (br s, 1 H, OH), 3.71 – 3.76 (m, 2 H, 3-H_a, 8-H_a), 3.79 (dd, $^2J_{8b,8a}$ = 11.5 Hz, $^3J_{8b,5}$ = 4.8 Hz, 1 H, 8-H_b), 3.90 (dt, $^3J_{5,8}$ = 7.7 Hz, $^3J_{5,4}$ = 3.8 Hz, 1 H, 5-H), 3.97 (dd, $^2J_{3a,3b}$ = 9.8 Hz, $^3J_{3a,4}$ = 4.0 Hz, 1 H, 3-H_b), 4.03 (dt, $^3J_{4,3}$ = 7.9 Hz, $^3J_{4,5}$ = 4.6 Hz, 1 H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.0 (q, C-7'), 62.8 (t, C-8), 64.2 (t, C-3), 78.2 (d, C-5), 80.5 (d, C-4), 109.1 (s, C-6).

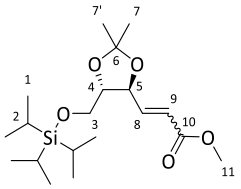
Optical rotation: $[\alpha]_D^{20}$ = +13.0° (c = 1.0, $CHCl_3$)

Methyl 3-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)acrylate (2c)

To a solution of 2.70 mL (4.05 g, 31.9 mmol) oxalyl chloride in 75 mL DCM abs. was added a solution of 4.30 mL (4.73 g, 60.5 mmol) DMSO abs. in 15 mL DCM abs. in such a way that the temperature stayed between –71 °C and –66 °C. After complete addition, the reaction was stirred for 5 min before a solution of 6.37 g (20.0 mmol) **1c** in 40 mL DCM abs. were added dropwise (the temperature must not exceed –65 °C). The reaction was then stirred at –66 °C for 30 min before 14.0 mL (10.2 g, 101 mmol) triethylamine were added slowly (T < –60 °C). The cooling bath was replaced by an ice bath and the reaction was allowed to warm to 0 °C within 1 h. Afterwards, a solution of 7.07 g (21.2 mmol) methyl 2-(triphenyl-λ^5-phosphaneylidene)acetate in 20 mL DCM abs. was added dropwise and the cooling bath was removed. The reaction was stirred

for 1 h at rt. For workup, water was added and the layers were separated. The aqueous phase was extracted three times with DCM and the combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified twice by column chromatography (silica gel, *n*-pentane:Et_2O 80:20). 7.45 g (20.0 mmol, *E*/*Z* 78:22, quant.) of product **2c** were obtained as a slightly yellow oil.

R_f(2c) = 0.57 (silica gel, PE:EA 70:30)



E-Isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04 – 1.16 (m, 21 H, 1-H, 2-H), 1.42 (s, 3 H, 7-H), 1.43 (s, 3 H, 7'-H), 3.74 (s, 3 H, 11-H), 3.83 (m, 1 H, 3-H_a), 3.87 (m, 1 H, 4-H), 3.93 (m, 1 H, 3-H_b), 4.58 (ddd, $^3J_{5,4}$ = 7.4 Hz, $^3J_{5,8}$ = 5.0 Hz, $^4J_{5,9}$ = 1.4 Hz, 1 H, 5-H), 6.14 (dd, $^3J_{9,8}$ = 15.7 Hz, $^4J_{9,5}$ = 1.6 Hz, 1 H, 9-H), 6.99 (dd, $^3J_{8,9}$ = 15.8 Hz, $^3J_{8,5}$ = 5.0 Hz, 1 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.8 (q, C-7), 26.9 (q, C-7'), 51.6 (q, C-11), 63.3 (t, C-3), 78.0 (d, C-5), 80.8 (d, C-4), 109.9 (s, C-6), 121.2 (d, C-9), 145.2 (d, C-8), 166.6 (s, C-10).

Z-Isomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, 7-H), 3.71 (s, 3 H, 11-H), 5.44 (ddd, $^3J_{5,4} \approx {}^3J_{5,8}$ = 8.1 Hz, $^4J_{5,9}$ = 0.9 Hz, 1 H, 5-H), 5.93 (dd, $^3J_{9,8}$ = 11.7 Hz, $^4J_{9,5}$ = 1.1 Hz, 1 H, 9-H), 6.20 (dd, $^3J_{8,9}$ = 11.8 Hz, $^3J_{8,5}$ = 8.8 Hz, 1 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 27.1 (q, C-7), 27.2 (q, C-7'), 51.4 (q, C-11), 64.0 (t, C-3), 73.7 (d, C-5), 82.3 (d, C-4), 110.0 (s, C-6), 122.4 (d, C-9), 145.7 (d, C-8), 165.7 (s, C-10).

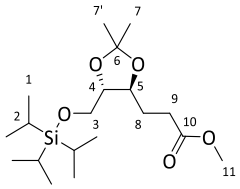
HRMS (CI):	calculated	found
$C_{19}H_{37}O_5Si$ $[M+H]^+$	373.2405	373.2447

Optical rotation: $[\alpha]_D^{20}$ = +5.2° (c = 1.0, $CHCl_3$)

Methyl 3-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)propanoate (3c)

A solution of 7.45 g (20.0 mmol) **2c** in 40 mL MeOH was treated with 748 mg palladium on charcoal (10 w% Pd) and hydrogenated at 10 bar for 3.5 h. The reaction was then filtrated through a pad of Celite® and washed with Et_2O. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, PE:EA 80:20) to give 7.18 g (19.2 mmol, 96 %) of product **3c** as a colourless oil.

R_f (3c) = 0.49 (silica gel, PE:EA 80:20)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.15 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.86 (m, 1 H, 8-H_a), 2.07 (m, 1 H, 8-H_b), 2.44 (ddd, $^2J_{9a,9b}$ = 16.1 Hz, $^3J_{9a,8a}$ = 9.3 Hz, $^3J_{9a,8b}$ = 6.6 Hz, 1 H, 9-H_a), 2.54 (ddd, $^2J_{9b,9a}$ = 16.1 Hz, $^3J_{9b,8a}$ = 9.7 Hz, $^3J_{9b,8b}$ = 5.9 Hz, 1 H, 9-H_b), 3.67 (s, 3 H, 11-H), 3.69 – 3.77 (m, 2 H, 4-H, 3-H_a), 3.88 (m, 1 H, 3-H_b), 3.96 (td, $^3J_{5,8}$ = 7.8 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 17.9 (q, C-1), 27.0 (q, C-7), 27.3 (q, C-7'), 28.6 (t, C-8 o. C-9), 30.5 (t, C-8 o. C-9), 51.5 (q, C-11), 64.1 (t, C-3), 78.2 (d, C-5), 80.7 (d, C-4), 108.7 (s, C-6), 173.7 (s, C-10).

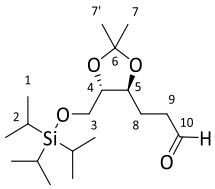
HRMS (CI):	calculated	found
$C_{19}H_{39}O_5Si$ $[M+H]^+$	375.2561	375.2542

Optical rotation: $[\alpha]_D^{20}$ = –10.0° (c = 1.0, $CHCl_3$)

3-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)propanal (4c)

380 mg (0.997 mmol) **3c** were dissolved in 10 mL toluene abs. and cooled to –78 °C. 1.40 mL (1.40 mmol) DIBAL-H (1.0 M in toluene) were added dropwise within 30 min. The reaction was stirred for further 15 min at this temperature. The reaction was diluted with DCM at –78 °C and hydrolyzed with sat. K-Na-tartrate solution. The reaction was allowed to warm to rt and the layers were separated. The aqueous phase was extracted three times with DCM, washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10) to yield 318 mg (0.923 mmol, 93 %) aldehyde **4c** as a colourless oil.

R_f (4c) = 0.50 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04 – 1.15 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.86 (dtd, $^2J_{8a,8b}$ = 14.4 Hz, $^3J_{8a,9}$ = 8.1 Hz, $^3J_{8a,5}$ = 6.4 Hz, 1 H, 8-H_a), 2.09 (dddd, $^2J_{8b,8a}$ = 14.5 Hz, $^3J_{8b,5}$ = 10.4 Hz, $^3J_{8b,9a}$ = 6.6 Hz, $^3J_{8b,9b}$ = 3.5 Hz, 1 H, 8-H_b), 2.62 (m, 2 H, 9-H), 3.72 (m, 1 H, 3-H_a), 3.74 (dd, $^2J_{3b,3a}$ = 14.1 Hz, $^3J_{3ba,4}$ = 6.3 Hz, 1 H, 3-H_b), 3.90 (m, 1 H, 4-H), 3.97 (ddd, $^3J_{5,8b}$ = 11.3 Hz, $^3J_{5,8a}$ = 5.5 Hz, $^3J_{5,4}$ = 3.5 Hz, 1 H, 5-H), 9.80 (t, $^3J_{10,9}$ = 1.5 Hz, 1 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 17.9 (q, C-1), 25.8 (t, C-8), 27.0 (q, C-7), 27.3 (q, C-7'), 40.4 (t, C-9), 64.1 (t, C-3), 78.4 (d, C-5), 80.6 (d, C-4), 108.7 (s, C-6), 201.9 (s, C-10).

HRMS (CI):	calculated	found
$C_{18}H_{35}O_4Si$ $[M+H]^+$	345.2299	345.2306

Optical rotation: $[\alpha]_D^{20}$ = –6.0° (c = 1.0, $CHCl_3$)

5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-ol (7c)

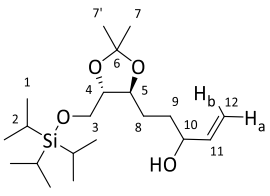
From compound **4c**:

To a solution of 1.07 g (3.11 mmol) aldehyde **4c** in 30 mL THF abs. were added 4.70 mL (4.70 mmol) vinylmagnesium bromide (1.0 M in THF) dropwise at –78 °C. The reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with Et_2O and water was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20) yielded 804 mg (2.16 mmol, *dr* 50:50, 69 %) allylic alcohol **7c** as a slightly yellow oil.

From compound **3c**:

A solution of 1.87 g (5.0 mmol) ester **3c** in 50 mL toluene abs. was cooled to –78 °C before 5.25 mL (5.25 mmol) DIBAL-H (1.0 M in toluene) were added *via* syringe pump within 50 min. The reaction was stirred for further 10 min at this temperature before 6.25 mL (6.25 mmol) vinylmagnesium bromide (1.0 M in THF) were added slowly. The reaction was allowed to warm to rt overnight. The reaction was diluted with Et_2O and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10). 1.52 g (4.08 mmol, *dr* 50:50, 82 %) of allylic alcohol **7c** were obtained as a colourless oil.

R_f (7c) = 0.41 (silica gel, PE:EA 70:30)



(3*S*)-Diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.16 (m, 21 H, 1-H, 2-H), 1.38 (s, 3 H, 7-H), 1.41 (s, 3 H, 7'-H), 1.62 – 1.79 (m, 3 H, 8-H_a, 9-H), 1.85 (m, 1 H, 8-H_b), 2.45 (br s, 1 H, OH), 3.72 (m, 1 H, 4-H), 3.75 (m, 1 H, 3-H_a), 3.89 (dd, $^2J_{3b,3a}$ = 9.8 Hz, $^3J_{3b,4}$ = 3.5 Hz, 1 H, 3-H_b), 3.97 (m, 1 H, 5-

H), 4.16 (m, 1 H, 10-H), 5.10 (ddd, $^{3}J_{12a,11}$ = 10.5 Hz, $^{2}J_{12a,12b} \approx {}^{4}J_{12a,10}$ = 1.4 Hz, 1 H, 12-H_a), 5.24 (ddd, $^{3}J_{12b,11}$ = 17.1 Hz, $^{2}J_{12b,12a} \approx {}^{4}J_{12b,10}$ = 1.6 Hz, 1 H, 12-H_b), 5.87 (ddd, $^{3}J_{11,12b}$ = 16.6 Hz, $^{3}J_{11,12a}$ = 10.5 Hz, $^{3}J_{11,10}$ = 6.0 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 17.9 (q, C-1), 27.0 (q, C-7), 27.3 (q, C-7'), 29.8 (t, C-8), 34.0 (t, C-9), 64.1 (t, C-3), 73.0 (d, C-10), 79.4 (d, C-5), 80.9 (d, C-4), 108.6 (s, C-6), 114.5 (d, C-11), 140.9 (t, C-12).

(3*R*)-Diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.19 (br s, 1 H, OH), 3.87 (dd, $^{2}J_{3b,3a}$ = 10.3 Hz, $^{3}J_{3b,4}$ = 3.8 Hz, 1 H, 3-H_b), 5.10 (ddd, $^{3}J_{12a,11}$ = 10.4 Hz, $^{2}J_{12a,12b} \approx {}^{4}J_{12a,10}$ = 1.6 Hz, 1 H, 12-H_a), 5.24 (ddd, $^{3}J_{12b,11}$ = 17.2 Hz, $^{2}J_{12b,12a} \approx {}^{4}J_{12b,10}$ = 1.6 Hz, 1 H, 12-H_b), 5.88 (ddd, $^{3}J_{11,12b}$ = 16.3 Hz, $^{3}J_{11,12a}$ = 10.5 Hz, $^{3}J_{11,10}$ = 5.8 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.9 (t, C-8), 33.6 (t, C-9), 64.0 (t, C-3), 72.4 (d, C-10), 79.3 (d, C-5), 80.9 (d, C-4), 108.6 (s, C-6), 140.8 (t, C-12).

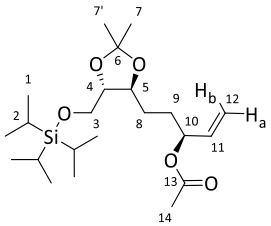
HRMS (CI):	calculated	found
$C_{20}H_{41}O_4Si$ $[M+H]^+$	373.2769	373.2792

(*S*)-5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl acetate (8) and **(*R*)-5-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-ol ((3*R*)-7c)**

4.45 g (11.9 mmol) **7c** were dissolved in 5.6 mL (5.23 g, 60.8 mmol) vinyl acetate at rt before 1.26 g (11.9 mmol) Na_2CO_3 and 221 mg Novozyme 435 were added. The reaction was shaken for 6 h at ambient temperature. For workup, the reaction mixture was filtrated. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10). 2.27 g (5.47 mmol, *dr* > 99:1, 46 %) acetate **8** were obtained as a colourless oil and 2.17 g (5.82 mmol, *dr* > 99:1, 49 %) alcohol (3*R*)-**7c** were obtained as a colourless oil.

R_f (8) = 0.28 (silica gel, PE:EA 90:10)

R_f ((3*R*)-7c) = 0.08 (silica gel, PE:EA 90:10)



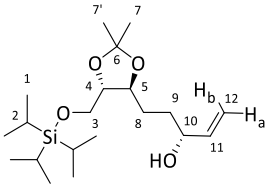
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.15 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.61 (m, 1 H, 8-H_a), 1.72 (m, 2 H, 9-H), 1.87 (m, 1 H, 8-H_b), 2.05 (s, 3 H, 14-H), 3.70 (m, 1 H, 4-H), 3.72 (dd, $^{2}J_{3a,3b}$ = 9.5 Hz, $^{3}J_{3a,4}$ = 6.2 Hz, 1 H, 3-H_a), 3.89 (dd, $^{2}J_{3b,3a}$ = 9.6 Hz, $^{3}J_{3b,4}$

= 3.5 Hz, 1 H, 3-H_b), 3.93 (td, $^3J_{5,8}$ = 7.5 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H), 5.17 (d, $^3J_{12a,11}$ = 10.5 Hz, 1 H, 12-H_a), 5.24 (d, $^3J_{12b,11}$ = 17.2 Hz, 1 H, 12-H_b), 5.27 (dt, $^3J_{10,11} \approx {}^3J_{10,9}$ = 6.2 Hz, 1 H, 10-H), 5.76 (ddd, $^3J_{11,12b}$ = 17.1 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.4 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 21.2 (q, C-14), 27.0 (q, C-7), 27.4 (q, C-7'), 28.9 (t, C-8), 30.6 (t, C-9), 64.3 (t, C-3), 74.5 (d, C-10), 79.2 (d, C-5), 80.8 (d, C-4), 108.5 (s, C-6), 116.9 (d, C-11), 136.2 (t, C-12), 170.2 (s, C-13).

HRMS (CI):	calculated	found
$C_{22}H_{43}O_5Si$ $[M+H]^+$	415.2874	415.2908

Optical rotation: $[\alpha]_D^{20}$ = –5.1° (c = 1.0, $CHCl_3$)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.15 (m, 21 H, 1-H, 2-H), 1.37 (s, 3 H, 7-H), 1.40 (s, 3 H, 7'-H), 1.60 – 1.90 (m, 4 H, 8-H, 9-H), 2.19 (br s, 1 H, OH), 3.72 (m, 1 H, 4-H), 3.75 (dd, $^2J_{3a,3b}$ = 10.1 Hz, $^3J_{3a,4}$ = 6.1 Hz, 1 H, 3-H_a), 3.88 (dd, $^2J_{3b,3a}$ = 10.0 Hz, $^3J_{3b,4}$ = 3.8 Hz, 1 H, 3-H_b), 3.96 (td, $^3J_{5,8}$ = 7.8 Hz, $^3J_{5,4}$ = 3.0 Hz, 1 H, 5-H), 4.18 (dt, $^3J_{10,11} \approx {}^3J_{10,9}$ = 5.5 Hz, 1 H, 10-H), 5.11 (d, $^3J_{12a,11}$ = 10.5 Hz, 1 H, 12-H_a), 5.24 (d, $^3J_{12b,11}$ = 17.2 Hz, 1 H, 12-H_b), 5.88 (ddd, $^3J_{11,12b}$ = 16.7 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 5.8 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 17.9 (q, C-1), 27.0 (q, C-7), 27.3 (q, C-7'), 28.9 (t, C-8), 33.6 (t, C-9), 64.1 (t, C-3), 72.4 (d, C-10), 79.3 (d, C-5), 80.9 (d, C-4), 108.6 (s, C-6), 114.5 (d, C-11), 140.8 (t, C-12).

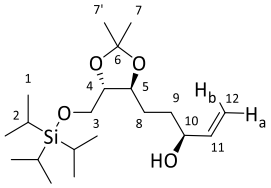
HRMS (CI):	calculated	found
$C_{20}H_{41}O_4Si$ $[M+H]^+$	373.2769	373.2766

Optical rotation: $[\alpha]_D^{20}$ = –4.7° (c = 1.0, $CHCl_3$)

(*S*)-5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-ol ((3*S*)-7c)

To a solution of 725 mg (1.75 mmol) **8** in 15.5 mL MeOH and 2.0 mL H_2O were added 267 mg (1.93 mmol) K_2CO_3 at rt. The reaction was stirred for 2.5 h. For workup, the reaction was diluted with DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to obtain 646 mg (1.73 mmol, 99 %) alcohol (3*S*)-**7c** as a colourless oil.

R_f((3*S*)-7c) = 0.11 (silica gel, PE:EA 90:10)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04 – 1.15 (m, 21 H, 1-H, 2-H), 1.38 (s, 3 H, 7-H), 1.41 (s, 3 H, 7'-H), 1.66 (m, 1 H, 8-H_a), 1.71 (m, 2 H, 9-H), 1.85 (m, 1 H, 8-H_b), 2.44 (br s, 1 H, OH), 3.72 (m, 1 H, 4-H), 3.75 (dd, $^{2}J_{3a,3b}$ = 9.9 Hz, $^{3}J_{3a,4}$ = 6.1 Hz, 1 H, 3-H_a), 3.89 (dd, $^{2}J_{3b,3a}$ = 9.8 Hz, $^{3}J_{3b,4}$ = 3.6 Hz, 1 H, 3-H_b), 3.97 (td, $^{3}J_{5,8}$ = 7.9 Hz, $^{3}J_{5,4}$ = 3.0 Hz, 1 H, 5-H), 4.14 (dt, $^{3}J_{10,11} \approx {}^{3}J_{10,9}$ = 6.0 Hz, 1 H, 10-H), 5.10 (d, $^{3}J_{12a,11}$ = 10.4 Hz, 1 H, 12-H_a), 5.25 (d, $^{3}J_{12b,11}$ = 17.2 Hz, 1 H, 12-H_b), 5.87 (ddd, $^{3}J_{11,12b}$ = 16.8 Hz, $^{3}J_{11,12a}$ = 10.4 Hz, $^{3}J_{11,10}$ = 5.9 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.3 (q, C-7'), 29.7 (t, C-8), 34.0 (t, C-9), 64.1 (t, C-3), 73.0 (d, C-10), 79.4 (d, C-5), 80.9 (d, C-4), 108.6 (s, C-6), 114.5 (d, C-11), 140.9 (t, C-12).

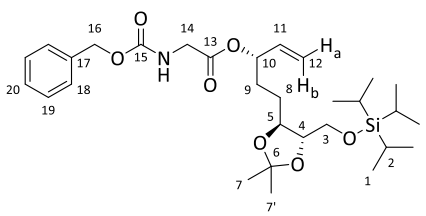
HRMS (CI):	calculated	found
$C_{20}H_{41}O_4Si$ $[M+H]^+$	373.2769	373.2772

Optical rotation: $[\alpha]_D^{20}$ = –3.4° (c = 1.0, $CHCl_3$)

(*S*)-5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl ((benzyloxy)carbonyl)glycinate (9)

535 mg (2.56 mmol) Cbz-Gly-OH and 635 mg (1.70 mmol) (3*S*)-**7c** were dissolved in 17 mL DCM abs. and cooled to 0 °C. 23.5 mg (0.192 mmol) 4-DMAP and 534 mg (2.59 mmol) DCC were added subsequently. The reaction was allowed to warm to rt overnight. For workup, the reaction was filtrated through a pad of Celite® and washed with DCM. The filtrate was concentrated *in vacuo*. The residue was redissolved in DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10). 947 mg (1.68 mmol, 99 %) **9** were obtained as a colourless oil.

R_f (9) = 0.34 (silica gel, PE:EA 80:20).



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.14 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.57 (m, 1 H, 8-H_a), 1.67 – 1.78 (m, 2 H, 8-H_b, 9-H_a), 1.91 (m, 1 H, 9-H_b), 3.69 (m, 1 H,

4-H), 3.72 (m, 1 H, 3-H_a), 3.88 (dd, $^2J_{3b,3a}$ = 9.6 Hz, $^3J_{3b,4}$ = 3.2 Hz, 1 H, 3-H_b), 3.92 (td, $^3J_{5,8}$ = 7.4 Hz, $^3J_{5,4}$ = 3.0 Hz, 1 H, 5-H), 3.98 (d, $^3J_{14,NH}$ = 5.4 Hz, 2 H, 14-H), 5.13 (s, 2 H, 16-H), 5.20 (d, $^3J_{12a,11}$ = 10.5 Hz, 1 H, 12-H_a), 5.24 (br s, 1 H, NH), 5.26 (d, $^3J_{12b,11}$ = 17.2 Hz, 1 H, 12-H_b), 5.32 (dt, $^3J_{10,11} \approx {}^3J_{10,9}$ = 6.4 Hz, 1 H, 10-H), 5.75 (ddd, $^3J_{11,12b}$ = 17.2 Hz, $^3J_{11,12a}$ = 10.4 Hz, $^3J_{11,10}$ = 6.7 Hz, 1 H, 11-H), 7.29 – 7.37 (m, 5 H, 18-H, 19-H, 20-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.3 (q, C-7'), 28.8 (t, C-8), 30.6 (t, C-9), 42.9 (t, C-14), 64.2 (t, C-3), 67.1 (t, C-16), 76.1 (d, C-10), 79.1 (d, C-5), 80.7 (d, C-4), 108.5 (s, C-6), 117.9 (t, C-12), 128.1 (d, C-18 o. C-20), 128.2 (d, C-18 o. C-20), 128.5 (d, C-19), 135.4 (d, C-11), 136.2 (s, C-17), 156.1 (s, C-15), 169.2 (s, C-13).

HRMS (CI):	calculated	found
$C_{30}H_{50}NO_7Si$ $[M+H]^+$	564.3351	564.3381

Optical rotation: $[\alpha]_D^{20}$ = –4.3° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 90:10, 1 mL/min, 20 °C:

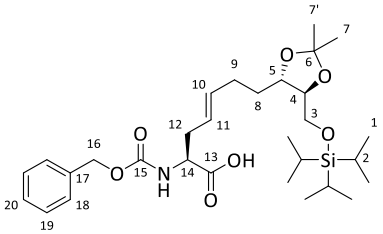
(3*S*)-**9**: t_R = 25.9 min (> 99 %).

(*S*,*E*)-2-(((Benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)-methyl)-1,3-dioxolan-4-yl)hept-4-enoic acid (10)

0.21 mL (149 mg, 1.47 mmol) Di-*iso*-propylamine were dissolved in 1.5 mL THF abs. before 0.88 mL (1.41 mmol) *n*-BuLi (1.6 M in hexanes) were added dropwise at –78 °C. The cooling bath was removed and the reaction was stirred at rt for 15 min.

A solution of 93 mg (0.682 mmol) vacuum-dried zinc chloride in 0.5 mL THF abs. were added to a solution of 282 mg (0.500 mmol) **9** in 2.0 mL THF abs. at rt. After cooling to –78 °C, the freshly prepared LDA solution was transferred to the amino acid ester/ zinc chloride solution carefully. Remaining dry ice was removed from the cooling bath and the reaction was allowed to warm to rt overnight. The reaction was diluted with Et_2O and NH_4OAc/HOAc buffer sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dried by lyophilisation. 281 mg (0.499 mmol, quant.) of acid **10** were obtained as a yellow oil.

R_f (10) = 0.34 (silica gel, PE:EA 50:50 + 1 % HOAc)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.15 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.68 (m, 2 H, 8-H), 2.17 (m, 2 H, 9-H), 2.53 (dd, $^3J_{12,11} \approx {}^3J_{12,14}$ = 5.5 Hz, 2 H, 12-H), 3.71 (m, 1 H, 4-H), 3.75 (dd, $^2J_{3a,3b}$ = 10.2 Hz, $^3J_{3a,4}$ = 6.2 Hz, 1 H, 3-H_a), 3.87 (dd, $^2J_{3b,3a}$ = 10.2 Hz, $^3J_{3b,4}$ = 4.0 Hz, 1 H, 3-H_b), 3.93 (td, $^3J_{5,8}$ = 7.8 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H), 4.44 (dt, $^3J_{14,NH}$ = 7.2 Hz, $^3J_{14,12}$ = 5.5 Hz, 1 H, 14-H), 5.12 (s, 2 H, 16-H), 5.28 (d, $^3J_{NH,14}$ = 7.8 Hz, 1 H, NH), 5.35 (dt, $^3J_{11,10}$ = 14.9 Hz, $^3J_{11,12}$ = 7.4 Hz, 1 H, 11-H), 5.58 (dt, $^3J_{10,11}$ = 14.5 Hz, $^3J_{10,9}$ = 7.1 Hz, 1 H, 10-H), 7.29 – 7.36 (m, 5 H, 18-H, 19-H, 20-H). The signal of -COOH wasn't observed in the ^{1}H-NMR spectrum.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.3 (q, C-7'), 29.0 (t, C-9), 33.0 (t, C-8), 35.2 (t, C-12), 53.3 (d, C-14), 64.2 (t, C-3), 67.1 (t, C-16), 78.6 (d, C-5), 80.7 (d, C-4), 108.6 (s, C-6), 123.5 (d, C-11), 128.2 (d, C-18 o. C-20), 128.2 (d, C-18 o. C-20), 128.5 (d, C-19), 135.4 (d, C-10), 136.1 (s, C-17), 155.9 (s, C-15), 175.3 (s, C-13).

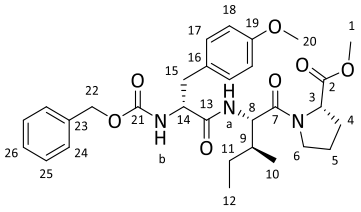
HRMS (CI):	calculated	found
$C_{30}H_{50}NO_7Si$ $[M+H]^+$	564.3351	564.3354

Optical rotation: $[\propto]_D^{20}$ = +10.2° (c = 1.0, $CHCl_3$)

Cbz-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-OMe (11a)

494 mg (1.5 mmol) Cbz-(*R*)-Tyr(Me)-OH were dissolved in 15 mL THF abs. and 0.185 mL (170 mg, 1.65 mmol) NMM were added. The reaction was cooled to –20 °C and 0.22 mL (230 mg, 1.65 mmol) IBCF were added. After 10 min, further 0.185 mL (170 mg, 1.65 mmol) NMM and 450 mg (1.50 mmol) HCl·H-(*S*,*S*)-Ile-(*S*)-Pro-OMe were added and the reaction was allowed to warm to rt overnight. For workup, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo*. The residue was redissolved in EA and water was added. The layers were separated and the aqueous phase was extracted three times with EA. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 70:30, 50:50) to obtain 764 mg (1.38 mmol, *dr* ~ 94:6, 92 %) tripeptide **11a** as an off-white solid.

R_f (11a) = 0.25 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, $^3J_{12,11}$ = 6.5 Hz, 3 H, 12-H), 0.87 (m, 1 H, 11-H_a), 0.91 (d, $^3J_{10,9}$ = 6.9 Hz, 3 H, 10-H), 1.32 (m, 1 H, 11-H_b), 1.69 (m, 1 H, 9-H), 1.92 – 2.09 (m, 3 H, 4-

H_a, 5-H), 2.21 (m, 1 H, 4-H_b), 2.99 (d, $^3J_{15,14}$ = 6.9 Hz, 2 H, 15-H), 3.64 (dt, $^2J_{6a,6b}$ = 9.7 Hz, $^3J_{6a,5}$ = 6.9 Hz, 1 H, 6-H_a), 3.70 (s, 3 H, 1-H), 3.77 (s, 3 H, 20-H), 3.82 (dt, $^2J_{6b,6a}$ = 9.5 Hz, $^3J_{6b,5}$ = 6.4 Hz, 1 H, 6-H_b), 4.40 (m, 1 H, 14-H), 4.48 (dd, $^3J_{3,4a}$ = 8.4 Hz, $^3J_{3,4b}$ = 4.7 Hz, 1 H, 3-H), 4.55 (dd, $^3J_{8,9}$ = 8.6 Hz, $^3J_{8,NH}$ = 7.6 Hz, 1 H, 8-H), 5.05 (s, 2 H, 22-H), 5.30 (d, $^3J_{NH,14}$ = 7.8 Hz, 1 H, NH_b), 6.47 (d, $^3J_{NH,8}$ = 7.7 Hz, 1 H, NH_a), 6.79 (d, $^3J_{18,17}$ = 8.4 Hz, 2 H, 18-H), 7.09 (d, $^3J_{17,18}$ = 7.8 Hz, 2 H, 17-H), 7.27 – 7.36 (m, 5 H, 24-H, 25-H, 26-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.1 (q, C-12), 15.0 (q, C-10), 24.0 (t, C-11), 24.9 (t, C-5), 29.0 (t, C-4), 37.7 (d, C-9), 38.1 (t, C-15), 47.3 (t, C-6), 52.1 (q, C-1), 54.9 (d, C-8), 55.2 (q, C-20), 56.4 (d, C-14), 58.9 (d, C-3), 66.9 (t, C-22), 114.1 (d, C-18), 128.0 (d, C-24), 128.1 (s, C-16), 128.2 (d, C-25 o. C-26), 128.5 (d, C-25 o. C-26), 130.2 (d, C-17), 136.2 (s, C-23), 155.6 (s, C-21), 158.6 (s, C-19), 170.4 (s, C-13), 170.6 (s, C-7), 172.3 (s, C-2).

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.67 (d, $^3J_{18,17}$ = 8.3 Hz, 2 H, 18-H), 6.95 (d, $^3J_{17,18}$ = 8.3 Hz, 2 H, 17-H).

HRMS (CI):	calculated	found
$C_{30}H_{40}N_3O_7$ $[M+H]^+$	554.2861	554.2858

Melting point: 56 °C

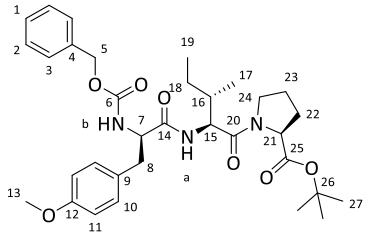
Optical rotation: $[\alpha]_D^{20}$ = –43.2° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 9.41 min ($[M+H]^+$ = 554).

Cbz-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-O*t*Bu (11b)

1.07 g (3.25 mmol) Cbz-(*R*)-Tyr(Me)-OH were dissolved in 32.5 mL THF abs. and cooled to –20 °C before 0.39 mL (359 mg, 3.55 mmol) NMM and 0.47 mL (492 mg, 3.60 mmol) IBCF were added subsequently. After 10 min at this temperature, a solution of 930 mg (3.27 mmol) H-(*S*,*S*)-Ile-(*S*)-Pro-O*t*Bu in 6.5 mL THF abs. was added slowly. The reaction was allowed to warm to rt overnight, filtrated and washed with Et_2O. The filtrate was concentrated *in vacuo*, the residue was redissolved in EA and water was added. The layers were separated and the aqueous phase was extracted three times with EA. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50) to give 1.71 g (2.87 mmol, *dr* 98:2, 88 %) of tripeptide **11b** as an off-white solid.

R_f (11b) = 0.05 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, $^{3}J_{19,18}$ = 7.0 Hz, 3 H, 19-H), 0.82 – 0.90 (m, 1 H, 18-H_a), 0.92 (d, $^{3}J_{13,12}$ = 6.8 Hz, 3 H, 17-H), 1.35 (m, 1 H, 18-H_b), 1.43 (s, 9 H, 27-H), 1.69 (m, 1 H, 16-H), 1.87 – 1.97 (m, 2 H, 22-H_a, 23-H_a), 2.03 (m, 1 H, 23-H_b), 2.18 (m, 1 H, 22-H_b), 2.99 (m, 2 H, 8-H), 3.61 (dt, $^{2}J_{24a,24b}$ = 9.8 Hz, $^{3}J_{24a,23}$ = 6.8 Hz, 1 H, 24-H_a), 3.77 (s, 3 H, 13-H), 3.80 (dt, $^{2}J_{24b,24a}$ = 9.8 Hz, $^{3}J_{24b,23}$ = 6.4 Hz, 1 H, 24-H_b), 4.34 (dd, $^{3}J_{21,22a}$ = 8.2 Hz, $^{3}J_{21,22b}$ = 4.9 Hz, 1 H, 21-H), 4.41 (m, 1 H, 7-H), 4.54 (dd, $^{3}J_{15,NH} \approx {}^{3}J_{15,16}$ = 8.0 Hz, 1 H, 15-H), 5.05 (s, 2 H, 5-H), 5.29 (d, $^{3}J_{NH,7}$ = 7.5 Hz, 1 H, NH_b), 6.52 (d, $^{3}J_{NH,7}$ = 8.3 Hz, 1 H, NH_a), 6.79 (d, $^{3}J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.08 (d, $^{3}J_{10,11}$ = 7.8 Hz, 2 H, 10-H), 7.27 – 7.36 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.1 (q, C-19), 15.2 (q, C-17), 24.1 (t, C-18), 24.8 (t, C-23), 27.9 (q, C-27), 29.1 (t, C-22), 37.7 (d, C-16), 38.1 (t, C-8), 47.4 (t, C-24), 54.8 (d, C-15), 55.2 (q, C-13), 56.4 (d, C-7), 59.8 (d, C-21), 66.9 (t, C-5), 81.3 (s, C-26), 114.1 (d, C-11), 128.0 (d, C-1 o. C-3), 128.1 (d, C-1 o. C-3), 128.2 (s, C-9), 128.5 (d, C-2), 130.2 (d, C-10), 136.2 (s, C-4), 155,6 (s, C-6), 158,6 (s, C-12), 170,2 (s, C-14 o. C-20 o. C-25), 170,6 (s, C-14 o. C-20 o. C-25), 171,1 (s, C-14 o. C-20 o. C-25).

HRMS (CI):	calculated	found
$C_{33}H_{46}N_3O_7$ $[M+H]^+$	596.3330	596.3340

Melting point: 53-56 °C

Optical rotation: $[\propto]_D^{20}$ = –44.2° (c = 1.0, $CHCl_3$)

HPLC: Chiralcel OD-H, *n*-hexane:*i*PrOH 80:20, 1 mL/min, 20 °C:

t_{R1} = 6.37 min (2 %),

t_{R2} = 7.69 min (98 %).

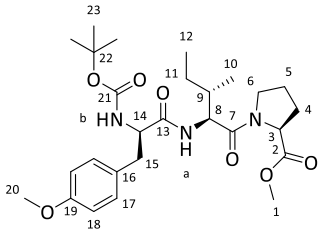
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 14.5 min ($[M+Na]^+$ = 618).

Boc-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-OMe (11c)

1.51 g (5.11 mmol) Boc-(*R*)-Tyr(Me)-OH were dissolved in 50.0 mL THF abs. and cooled to –20 °C before 0.62 mL (570 mg , 5.64 mmol) NMM and 0.74 mL (775 mg, 5-67 mmol) IBCF were added slowly. After 10 min at this temperature, 1.42 g (5.09 mmol) HCl·H-(*S*,*S*)-Ile-(*S*)-Pro-OMe and further 0.62 mL (570 mg, 5.64 mmol) NMM were added slowly. The reaction was allowed to warm to rt overnight. For workup, the reaction mixture was filtrated and washed with Et_2O. The

filtrate was concentrated *in vacuo* and the residue was redissolved in EA. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with EA, the combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 70:30, 50:50) to give 2.24 g (4.31 mmol, 85 %) product **11c** (containing 2 % *iso*-butylcarbonate at tyrosine residue) as an off-white solid.

R_f (11c) = 0.19 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, $^3J_{12,11}$ = 7.0 Hz, 3 H, 12-H), 0.91 (m, 1 H, 11-H_a), 0.93 (d, $^3J_{10,9}$ = 6.8 Hz, 3 H, 10-H), 1.37 (m, 1 H, 11-H_b), 1.38 (s, 9 H, 23-H), 1.71 (m, 1 H, 9-H), 2.00 (m, 3 H, 4-H_a, 5-H), 2.23 (m, 1 H, 4-H_b), 2.93 (dd, $^2J_{15a,15b}$ = 13.9 Hz, $^3J_{15a,14}$ = 6.8 Hz, 1 H, 15-H_a), 3.00 (dd, $^2J_{15b,15a}$ = 13.9 Hz, $^3J_{15b,14}$ = 6.8 Hz, 1 H, 15-H_b), 3.65 (m, 1 H, 6-H_a), 3.70 (s, 3 H, 1-H), 3.77 (s, 3 H, 20-H), 3.84 (m, 1 H, 6-H_b), 4.32 (m, 1 H, 14-H), 4.47 (dd, $^3J_{3,4a}$ = 8.7 Hz, $^3J_{3,4b}$ = 5.2 Hz, 1 H, 3-H), 4.56 (dd, $^3J_{8,9} \approx {}^3J_{8,NH}$ = 8.3 Hz, 1 H, 8-H), 4.93 (d, $^3J_{NH,14}$ = 7.5 Hz, 1 H, NH_b), 6.50 (d, $^3J_{NH,8}$ = 8.0 Hz, 1 H, NH_a), 6.80 (d, $^3J_{18,17}$ = 8.5 Hz, 2 H, 18-H), 7.08 (d, $^3J_{17,18}$ = 8.5 Hz, 2 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.1 (q, C-12), 15.0 (q, C-10), 24.0 (t, C-11), 24.9 (t, C-5), 28.2 (q, C-23), 29.1 (t, C-4), 37.7 (d, C-9), 37.7 (t, C-15), 47.3 (t, C-6), 52.2 (q, C-1), 54.8 (d, C-8), 55.2 (q, C-20), 56.0 (d, C-14), 58.9 (d, C-3), 80.0 (s, C-22), 114.0 (d, C-18), 128.4 (s, C-16), 130.1 (d, C-17), 155.1 (s, C-21), 158.5 (s, C-19), 170.4 (s, C-7), 171.0 (s, C-13), 172.3 (s, C-2).

HRMS (CI):	calculated	found
$C_{27}H_{42}N_3O_7$ $[M+H]^+$	520.3017	520.3021

Melting point: 64 °C

Optical rotation: $[\alpha]_D^{20}$ = –38.6° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 80:20, 1 mL/min, 20 °C:

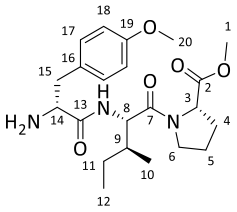
t_R = 25.4 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 7.49 min (98 %, $[M+Na]^+$ = 542), t_{R2} = 13.4 min (2 %, $[M+Na]^+$ = 628).

H-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-OMe (12a)

To a solution of 179 mg (0.323 mmol) **11a** in 1.6 mL MeOH were added 19 mg palladium on charcoal (10 w% Pd) at rt. The reaction was set under a H_2-atmossphere and hydrogenated for 2 h. The reaction mixture was filtrated through a pad of Celite® and washed with MeOH. The filtrate was concentrated *in vacuo*. After lyophilisation, 132 mg (0.315 mmol, *dr* ~ 92:8, 97 %) of amine **12a** were obtained as a colourless resin.

R_f (12a) = 0.05 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{12,11}$ = 7.3 Hz, 3 H, 12-H), 1.00 (d, $^3J_{10,9}$ = 6.7 Hz, 3 H, 10-H), 1.07 (m, 1 H, 11-H_a), 1.46 (br s, 2 H, NH_2), 1.50 (m, 1 H, 11-H_b), 1.83 (m, 1 H, 9-H), 1.93 – 2.10 (m, 3 H, 4-H_a, 5-H), 2.23 (m, 1 H, 4-H_b), 2.58 (dd, $^2J_{15a,15b}$ = 13.8 Hz, $^3J_{15a,14}$ = 9.5 Hz, 1 H, 15-H_a), 3.17 (dd, $^2J_{15b,15a}$ = 13.8 Hz, $^3J_{15b,14}$ = 4.4 Hz, 1 H, 15-H_b), 3.54 (dd, $^3J_{14,15a}$ = 9.5 Hz, $^3J_{14,15b}$ = 4.4 Hz, 1 H, 14-H), 3.69 (m, 1 H, 6-H_a), 3.72 (s, 3 H, C-1), 3.78 (s, 3 H, C-20), 3.88 (m, 1 H, 6-H_b), 4.49 (dd, $^3J_{3,4a}$ = 8.4 Hz, $^3J_{3,4b}$ = 5.1 Hz, 1 H, 3-H), 4.59 (dd, $^3J_{8,NH}$ = 9.0 Hz, $^3J_{8,9}$ = 7.9 Hz, 1 H, 8-H), 6.83 (d, $^3J_{18,17}$ = 8.6 Hz, 2 H, 18-H), 7.10 (d, $^3J_{17,18}$ = 8.6 Hz, 2 H, 17-H), 7.62 (d, $^3J_{NH,8}$ = 9.2 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.1 (q, C-12), 15.2 (q, C-10), 24.4 (t, C-11), 25.0 (t, C-5), 29.1 (t, C-4), 37.7 (d, C-9), 40.2 (t, C-15), 47.3 (t, C-6), 52.1 (q, C-1), 54.6 (d, C-8), 55.2 (q, C-20), 56.8 (d, C-14), 58.9 (d, C-3), 114.1 (d, C-18), 130.0 (s, C-16), 130.1 (d, C-17), 158.4 (s, C-19), 170.8 (s, C-7 o. C-13), 172.4 (s, C-2), 174.2 (s, C-7 o. C-13).

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, $^3J_{12,11}$ = 7.2 Hz, 3 H, 12-H), 3.06 (dd, $^2J_{15b,15a}$ = 14.3 Hz, $^3J_{15b,14}$ = 4.5 Hz, 1 H, 15-H_b), 4.34 – 4.42 (m, 2 H, 3-H, 8-H), 7.54 (d, $^3J_{NH,8}$ = 9.2 Hz, 1 H, NH).

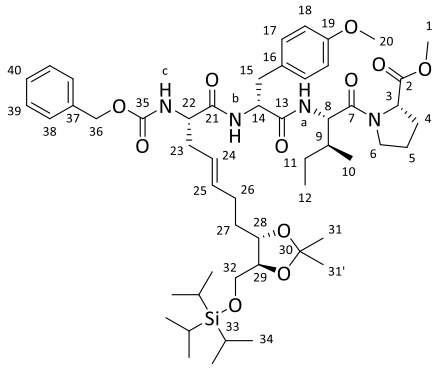
HRMS (CI):	calculated	found
$C_{22}H_{34}N_3O_5$ $[M+H]^+$	420.2493	420.2496

Optical rotation: $[\alpha]_D^{20}$ = –35.7° (c = 1.0, $CHCl_3$)

Methyl ((*R*)-2-((*S*,*E*)-2-(((benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enamido)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl-L-prolinate (13)

A solution of 318 mg (0.564 mmol) **10** and 265 mg (0.582 mmol) **HCl·12a** in 4.5 mL MeCN was treated with 181 mg (0.563 mmol) TBTU at rt. Afterwards, 0.21 mL (155 mg, 1.20 mmol) DIPEA were added dropwise and the reaction was stirred for 4.5 h. The reaction mixture was then concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM, the combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50) gave 456 mg (0.472 mmol, *dr* > 99:1, 84 %) tetrapeptide **13** as an off-white solid.

R_f (13) = 0.30 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, $^3J_{12,11}$= 6.9 Hz, 3 H, 12-H), 0.90 (m, 1 H, 11-H_a), 0.91 (d, $^3J_{10,9}$= 6.9 Hz, 3 H, 10-H), 1.01 – 1.13 (m, 21 H, 33-H, 34-H), 1.34 (m, 1 H, 11-H_b), 1.35 (s, 3 H, 31-H), 1.38 (s, 3 H, 31'-H), 1.59 (m, 1 H, 27-H_a), 1.66 – 1.75 (m, 2 H, 9-H, 27-H_b), 1.92 – 2.11 (m, 4 H, 5-H, 26-H), 2.18 (m, 2 H, 4-H), 2.30 (ddd, $^2J_{23a,23b}$ = 14.2 Hz, $^3J_{23a,22} \approx {}^3J_{23a,24}$ = 7.3 Hz, 1 H, 23-H_a), 2.42 (ddd, $^2J_{23b,23a}$ = 14.1 Hz, $^3J_{23b,22} \approx {}^3J_{23b,24}$ = 6.4 Hz, 1 H, 23-H_b), 2.97 (m, 2 H, 15-H), 3.61 – 3.71 (m, 2 H, 29-H, 32-H_a), 3.68 (s, 3 H, 1-H), 3.72 (m, 1 H, 6-H_a), 3.75 (s, 3 H, 20-H), 3.82 (m, 1 H, 6-H_b), 3.84 (dd, $^2J_{32a,32b}$= 10.1 Hz, $^3J_{32a,29}$ = 3.9 Hz, 1 H, 32-H_b), 3.91 (td, $^3J_{28,27}$ = 7.8 Hz, $^3J_{28,29}$ = 3.3 Hz, 1 H, 28-H), 4.08 (dt, $^3J_{22,23} \approx {}^3J_{22,NH}$ = 6.6 Hz, 1 H, 22-H), 4.48 – 4.53 (m, 2 H, 3-H, 8-H), 4.67 (m, 1 H, 14-H), 5.06 (d, $^2J_{36a,36b}$= 12.1 Hz, 1 H, 36-H_a), 5.11 (d, $^2J_{36b,36a}$= 12.0 Hz, 1 H, 36-H_b), 5.28 (dt, $^3J_{24,25}$= 14.8 Hz, $^3J_{24,23}$ = 7.3 Hz, 1 H, 24-H), 5.37 (d, $^3J_{NH,22}$ = 6.1 Hz, 1 H, NH_c), 5.51 (dt, $^3J_{25,24}$= 14.6 Hz, $^3J_{25,26}$ = 7.1 Hz, 1 H, 25-H), 6.56 (br s, 1 H, NH_a), 6.57 (d, $^3J_{NH,14}$ = 7.7 Hz, 1 H, NH_b), 6.79 (d, $^3J_{18,17}$ = 8.4 Hz, 2 H, 18-H), 7.09 (d, $^3J_{17,18}$ = 8.1 Hz, 2 H, 17-H), 7.28 – 7.37 (m, 5 H, 38-H, 39-H, 40-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.0 (q, C-12), 11.8 (d, C-33), 15.0 (q, C-10), 17.9 (q, C-34), 24.1 (t, C-11), 24.9 (t, C-5), 27.0 (q, C-31), 27.4 (q, C-31'), 29.0 (t, C-4 o. C-26), 29.1 (t, C-4 o. C-26), 33.1 (t, C-27), 35.5 (t, C-23), 37.5 (d, C-9), 37.6 (t, C-15), 47.3 (t, C-6), 52.1 (q, C-1), 54.4 (d, C-14), 54.7 (d, C-22), 55.0 (d, C-8), 55.2 (q, C-20), 58.8 (d, C-3), 64.1 (t, C-32), 67.1 (t, C-36), 78.6 (d, C-28), 80.8 (d, C-29), 108.4 (s, C-30), 114.1 (d, C-18), 124.4 (d, C-24), 128.1 (d, C-38 o.

C-39 o. C-40), 128.1 (d, C-38 o. C-39 o. C-40), 128.3 (s, C-16), 128.5 (d, C-38 o. C-39 o. C-40), 130.2 (d, C-17), 134.7 (d, C-25), 136.2 (s, C-37), 158.6 (s, C-19), 170.4 (s, C-7 o. C-13), 170.4 (s, C-7 o. C-13), 170.8 (s, C-21), 172.3 (s, C-2). The signal of C-35 wasn't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{52}H_{81}N_4O_{11}Si$ $[M+H]^+$	965.5666	965.5679

Melting point: 66 °C

Optical rotation: $[\propto]_D^{20}$ = –25.3° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 50:50, 1 mL/min, 20 °C:

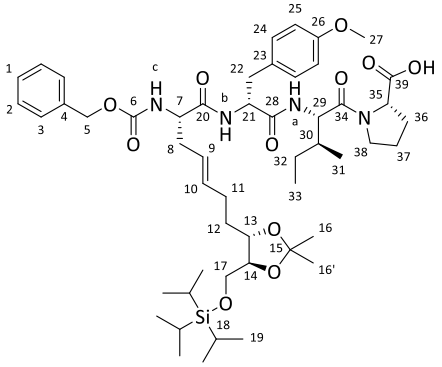
t_R = 22.6 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 21.7 min ($[M+H]^+$ = 966).

((*R*)-2-((*S*,*E*)-2-(((benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enamido)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl-L-proline (14)

453 mg (0.469 mmol) **13** were dissolved in 4.7 mL dioxane and treated with 516 µL (0.516 mmol) NaOH (1 M in H_2O) at 0 °C. The cooling bath was removed and the reaction was stirred for 23 h. The reaction mixture was concentrated *in vacuo* and the residue was redissolved in Et_2O. Water was added and the layers were separated. The etheric phase was discarded and the aqueous phase was acidified with 1 M HCl sol. and extracted three times with ethyl acetate. The crude product was again dissolved in 2 mL dioxane and treated with 500 µL (0.500 mmol) NaOH (1 M in H_2O) at rt and the reaction was stirred overnight. For workup, the reaction was diluted with DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over Na_2SO_4. Purification by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) afforded 283 mg (0.297 mmol, 63 %) of acid **14** as an off-white solid along with 61.9 mg (64.1 µmol, 14 %) of educt **13**.

R_f (14) = 0.10 (silica gel, DCM:MeOH 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, $^3J_{33,32}$= 7.2 Hz, 3 H, 33-H), 0.90 (m, 1 H, 32-H_a), 0.92 (d, $^3J_{31,30}$= 6.7 Hz, 3 H, 31-H), 1.02 – 1.13 (m, 21 H, 18-H, 19-H), 1.26 (m, 1 H, 32-H_b), 1.35 (s, 3 H, 16-H), 1.38 (s, 3 H, 16'-H), 1.60 (m, 1 H, 12-H_a), 1.65 – 1.77 (m, 2 H, 12-H_b, 30-H), 1.97 (m, 1 H, 37-H_a), 2.05 – 2.21 (m, 5 H, 11-H, 36-H, 37-H_b), 2.33 (m, 2 H, 8-H), 2.91 (m, 1 H, 22-H_a), 3.04 (dd, $^2J_{22a,22b}$= 13.7 Hz, $^3J_{22a,21}$ = 7.1 Hz, 1 H, 22-H_b), 3.63 – 3.75 (m, 3 H, 14-H, 17-H_a, 38-H_a), 3.73 (s, 3 H, 27-H), 3.84 (dd, $^2J_{17b,17a}$= 10.2 Hz, $^3J_{17b,14}$ = 3.9 Hz, 1 H, 17-H_b), 3.88 (m, 1 H, 38-H_b), 3.92 (td, $^3J_{13,12}$ = 7.7 Hz, $^3J_{13,14}$ = 3.4 Hz, 1 H, 13-H), 4.22 (m, 1 H, 7-H), 4.46 (t, $^3J_{35,36}$ = 6.7 Hz, 1 H, 35-H), 4.49 (m, 1 H, 29-H), 4.82 (m, 1 H, 21-H), 5.06 (d, $^2J_{5a,5b}$= 11.9 Hz, 1 H, 5-H_a), 5.12 (d, $^2J_{5b,5a}$= 12.2 Hz, 1 H, 5-H_b), 5.28 (dt, $^3J_{9,10}$= 14.6 Hz, $^3J_{9,8}$ = 7.2 Hz, 1 H, 9-H), 5.44 – 5.52 (m, 2 H, 10-H, NH_c), 6.76 (d, $^3J_{25,24}$ = 8.3 Hz, 2 H, 25-H), 6.93 (br s, 1 H, NH_b), 7.06 (d, $^3J_{24,25}$ = 8.3 Hz, 2 H, 24-H), 7.28 – 7.36 (m, 5 H, 1-H, 2-H, 3-H), 7.72 (br s, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.7 (q, C-33), 11.8 (d, C-18), 15.0 (q, C-31), 17.9 (q, C-19), 24.4 (t, C-32), 25.0 (t, C-37), 27.0 (q, C-16), 27.3 (q, C-16'), 28.5 (t, C-11 o. C-36), 29.1 (t, C-11 o. C-36), 33.1 (t, C-12), 35.9 (t, C-8), 37.3 (d, C-30), 37.5 (t, C-22), 47.8 (t, C-38), 55.1 (d, C-29), 55.1 (q, C-27), 59.6 (d, C-35), 64.1 (t, C-17), 67.1 (t, C-5), 78.6 (d, C-13), 80.9 (d, C-14), 108.5 (s, C-15), 113.8 (d, C-25), 124.2 (d, C-9), 128.1 (d, C-1 o. C-2 o. C-3), 128.2 (s, C-23), 128.5 (d, C-1 o. C-2 o. C-3), 130.4 (d, C-24), 134.7 (d, C-10), 136.1 (s, C-4), 158.5 (s, C-26), 170.1 (s, C-20 o. C-28 o. C-34 o. C-39), 170.9 (s, C-20 o. C-28 o. C-34 o. C-39), 171.3 (s, C-20 o. C-28 o. C-34 o. C-39), 171.6 (s, C-20 o. C-28 o. C-34 o. C-39). The signals of C-6, C-7 and C-21 weren't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{51}H_{79}N_4O_{11}Si$ $[M+H]^+$	951.5509	951.5525

Melting point: 85 °C

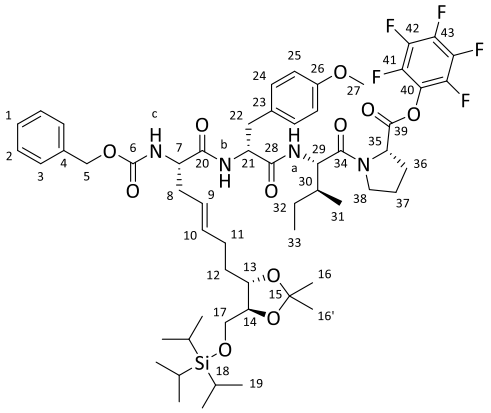
Optical rotation: $[\propto]_D^{20}$ = –25.8° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 19.2 min ($[M+H]^+$ = 952).

Perfluorophenyl ((*R*)-2-((*S*,*E*)-2-(((benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enamido)-3-(4-methoxyphenyl)-propanoyl)-L-isoleucyl-L-prolinate (15)

A solution of 266 mg (0.280 mmol) **14** in 2.8 mL DCM abs. was cooled to 0 °C before 66 mg (0.359 mmol) pentafluorophenol and 61 mg (0.319 mmol) EDC·HCl were added. The reaction was allowed to warm to rt overnight and diluted with DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. 305 mg (0.273 mmol, 98 %) of Pfp ester **15** were obtained as an off-white solid after lyophilisation.

R_f (15) = 0.43 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, $^3J_{33,32}$= 7.2 Hz, 3 H, 33-H), 0.86 (d, $^3J_{31,30}$= 6.7 Hz, 3 H, 31-H), 0.89 (m, 1 H, 32-H_a), 1.02 – 1.13 (m, 21 H, 18-H, 19-H), 1.32 (m, 1 H, 32-H_b), 1.35 (s, 3 H, 16-H), 1.38 (s, 3 H, 16'-H), 1.60 (m, 1 H, 12-H_a), 1.66 – 1.75 (m, 2 H, 12-H_b, 30-H), 2.05 – 2.22 (m, 5 H, 11-H, 36-H_a, 37-H), 2.29 (m, 1 H, 8-H_a), 2.36 – 2.47 (m, 2 H, 8-H_b, 36-H_a), 2.98 (d, $^3J_{22,21}$ = 5.8 Hz, 2 H, 22-H), 3.65 – 3.75 (m, 3 H, 14-H, 17-H_a, 38-H_a), 3.73 (s, 3 H, 27-H), 3.84 (dd, $^2J_{17b,17a}$= 10.2 Hz, $^3J_{17b,14}$ = 3.9 Hz, 1 H, 17-H_b), 3.91 (td, $^3J_{13,12}$ = 7.9 Hz, $^3J_{13,14}$ = 3.5 Hz, 1 H, 13-H), 3.95 (m, 1 H, 38-H_b), 4.12 (dt, $^3J_{7,8} \approx {}^3J_{7,NH}$ = 6.9 Hz, 1 H, 7-H), 4.48 (t, $^3J_{29,30} \approx {}^3J_{29,NH}$ = 8.3 Hz, 1 H, 29-H), 4.73 (m, 1 H, 21-H), 4.84 (m, 1 H, 35-H), 5.05 (d, $^2J_{5a,5b}$= 12.1 Hz, 1 H, 5-H_a), 5.11 (d, $^2J_{5b,5a}$= 12.0 Hz, 1 H, 5-H_b), 5.30 (dt, $^3J_{9,10}$= 14.7 Hz, $^3J_{9,8}$ = 7.2 Hz, 1 H, 9-H), 5.47 – 5.54 (m, 2 H, 10-H, NH_c), 6.70 (br s, 1 H, NH_b), 6.77 (d, $^3J_{25,24}$ = 8.7 Hz, 2 H, 25-H), 6.92 (br s, 1 H, NH_a), 7.09 (d, $^3J_{24,25}$ = 8.3 Hz, 2 H, 24-H), 7.29 – 7.36 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-33), 11.8 (d, C-18), 14.9 (q, C-31), 17.9 (q, C-19), 24.2 (t, C-32), 25.1 (t, C-37), 26.9 (q, C-16), 27.4 (q, C-16'), 29.1 (t, C-11), 29.3 (t, C-36), 33.1 (t, C-12), 35.6 (t, C-8), 37.3 (d, C-30), 37.7 (t, C-22), 47.4 (t, C-38), 54.2 (d, C-21), 54.6 (d, C-7), 55.0 (d, C-29), 55.1 (q, C-27), 58.4 (d, C-35), 64.1 (t, C-17), 67.1 (t, C-5), 78.6 (d, C-13), 80.8 (d, C-14), 108.4 (s, C-15), 114.0 (d, C-25), 124.5 (d, C-9), 128.1 (d, C-1 o. C-2 o. C-3), 128.2 (d, C-1 o. C-2 o. C-3), 128.3 (s, C-23), 128.4 (d, C-1 o. C-2 o. C-3), 130.2 (d, C-24), 134.5 (d, C-10), 136.2 (s, C-4), 158.5 (s, C-26), 168.2 (s, C-20 o. C-28 o. C-34 o. C-39), 170.5 (s, C-20 o. C-28 o. C-34 o. C-39), 170.9 (s, C-20 o. C-28 o. C-34 o. C-39). The signals of C-6, C-40 to C-43 as well as the signal of one of the carbonyls weren't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{57}H_{78}F_5N_4O_{11}Si$ $[M+H]^+$	1117.5351	1117.5353

Melting point: 62 °C

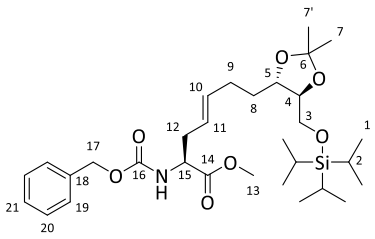
Optical rotation: $[\alpha]_D^{20}$ = –32.0° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH90:10, 0.6 mL/min, t_R = 17.6 min ($[M+Na]^+$ = 1140).

Methyl (*S*,*E*)-2-(((benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propyl-silyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enoate (16)

To a solution of 2.75 g (4.87 mmol) acid **10** in 20.0 mL DMF were added 809 mg (5.85 mmol) K_2CO_3 at rt. After cooling to 0 °C, 0.91 mL (2.07 g, 14.6 mmol) methyl iodide were added and the reaction was stirred for 2 h at this temperature. For workup, the reaction mixture was poured into 15 mL sat. NH_4Cl sol. and 80 mL water at rt. After stirring for 30 min, the layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with brine trice and dried over Na_2SO_4. After purification by column chromatography (silica gel, PE:EA 100:0, 90:10), 2.79 g (4.83 mmol, *dr* > 99:1, 99 %) **16** were obtained as a colourless oil.

R_f (16) = 0.30 (silica gel, PE:EA 80:20)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.14 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.63 (m, 1 H, 8-H_a), 1.71 (m, 1 H, 8-H_b), 2.15 (m, 2 H, 9-H), 2.48 (dd, $^3J_{12,11} \approx {}^3J_{12,15}$ = 6.1 Hz, 2 H, 12-H), 3.66 – 3.76 (m, 2 H, 3-H_a, 4-H), 3.73 (s, 3 H, 13-H), 3.87 (dd, $^2J_{3b,3a}$ = 10.0 Hz, $^3J_{3b,4}$ = 3.7 Hz, 1 H, 3-H_b), 3.91 (td, $^3J_{5,8}$ = 7.7 Hz, $^3J_{5,4}$ = 3.6 Hz, 1 H, 5-H), 4.41 (dt, $^3J_{15,NH}$ = 7.7 Hz, $^3J_{15,12}$ = 5.7 Hz, 1 H, 15-H), 5.11 (s, 2 H, 17-H), 5.27 (br s, 1 H, NH), 5.31 (dt, $^3J_{11,10}$ = 15.7 Hz, $^3J_{11,12}$ = 7.3 Hz, 1 H, 11-H), 5.54 (dt, $^3J_{10,11}$ = 14.6 Hz, $^3J_{10,9}$ = 7.1 Hz, 1 H, 10-H), 7.30 – 7.36 (m, 5 H, 19-H, 20-H, 21-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.4 (q, C-7'), 29.1 (t, C-9), 33.0 (t, C-8), 35.4 (t, C-12), 52.3 (q, C-13), 53.5 (d, C-15), 64.2 (t, C-3), 67.0 (t, C-17), 78.7 (d, C-5), 80.8 (d, C-4), 108.4 (s, C-6), 123.5 (d, C-11), 128.1 (d, C-19 o. C-21), 128.2 (d, C-19 o. C-21), 128.5 (d, C-20), 135.0 (d, C-10), 136.2 (s, C-18), 155.7 (s, C-16), 172.3 (s, C-14).

HRMS (CI):	calculated	found
$C_{31}H_{52}NO_7Si$ $[M+H]^+$	578.3508	578.3523

Optical rotation: $[\alpha]_D^{20}$ = +6.9° (c = 1.0, $CHCl_3$)

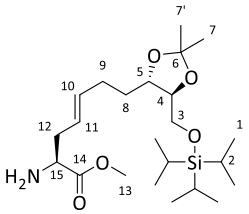
HPLC: Reprosil, *n*-hexane:*i*PrOH 90:10, 1 mL/min, 20 °C:

(*S*)-**16**: t_R = 29.9 min (> 99 %).

Methyl (*S*)-2-amino-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxo-lan -4-yl)heptanoate (17)

201 mg (0.348 mmol) amino acid ester **16** were dissolved in 1.75 mL MeOH at rt before 21.1 mg palladium on charcoal (10 w% Pd) were added and the reaction mixture was stirred under H_2 atmosphere for 18 h. The reaction was filtrated through a pad of Celite® and washed with MeOH. The filtrate was concentrated *in vacuo*. 151 mg (0.339 mmol, 97 %) of amine **17** were obtained as a colourless oil after lyophilisation.

R_f (17) = 0.18 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04 – 1.15 (m, 21 H, 1-H, 2-H), 1.32 – 1.43 (m, 5 H, 9-H, 10-H_a/10-H_b, 11-H_a/11-H_b), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.47 – 1.60 (m, 3 H, 8-H_a, 10-H_a/10-H_b/11-H_a/11-H_b, 12-H_a), 1.57 (m, 2 H, NH_2), 1.62 – 1.75 (m, 2 H, 8-H_b, 12-H_b), 3.43 (dd, $^3J_{15,12/NH}$ = 7.4 Hz, $^3J_{15,12/NH}$ = 5.6 Hz, 1 H, 15-H), 3.69 (m, 1 H, 4-H), 3.71 (s, 3 H, 13-H), 3.75 (dd, $^2J_{3a,3b}$ = 10.3 Hz, $^3J_{3a,4}$ = 6.0 Hz, 1 H, 3-H_a), 3.86 (dd, $^2J_{3b,3a}$ = 10.3 Hz, $^3J_{3b,4}$ = 4.0 Hz, 1 H, 3-H_b), 3.93 (td, $^3J_{5,8}$ = 7.7 Hz, $^3J_{5,4}$ = 3.7 Hz, 1 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 17.9 (q, C-1), 25.6 (q, C-7), 26.0 (q, C-7'), 27.0 (t, C-10 o. C-11), 27.4 (t, C-10 o. C-11), 29.5 (t, C-9), 33.5 (t, C-8), 34.9 (t, C-12), 51.9 (q, C-13), 54.4 (d, C-15), 64.2 (t, C-3), 79.1 (d, C-5), 81.0 (d, C-4), 108.3 (s, C-6), 176.7 (s, C-14).

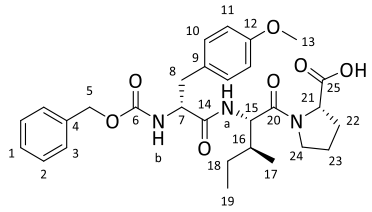
HRMS (CI):	calculated	found
$C_{23}H_{48}NO_5Si$ $[M+H]^+$	446.3296	446.3296

Optical rotation: $[\alpha]_D^{20}$ = –5.1° (c = 1.0, $CHCl_3$)

Cbz-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-OH (18a)

A solution of 1.99 g (3.59 mmol) ester **11a** in 35 mL 1,4-dioxane was treated with 3.94 mL (3.94 mmol) NaOH (1.0 M in H_2O) at 0 °C. The cooling bath was removed and the reaction was stirred at rt overnight. The reaction was then concentrated *in vacuo* and the residue was redissolved in EA. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with EA. The combined organic phases were dried over Na_2SO_4. 1.93 g (3.58 mmol, 99 %) of acid **18a** were obtained as an off-white solid after lyophilisation.

R_f (18a) = 0.22 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, $^{3}J_{19,18}$ = 6.9 Hz, 3 H, 19-H), 0.85 (m, 1 H, 18-H_a), 0.89 (d, $^{3}J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 1.23 (m, 1 H, 18-H_b), 1.68 (m, 1 H, 16-H), 1.97 (m, 1 H, 23-H_a), 2.04 – 2.21 (m, 3 H, 22-H, 23-H_b), 2.92 (dd, $^{2}J_{8a,8b}$ = 13.6 Hz, $^{3}J_{8a,7}$ = 5.9 Hz, 1 H, 8-H_a), 3.00 (dd, $^{2}J_{8b,8a}$ = 13.8 Hz, $^{3}J_{8b,7}$ = 7.1 Hz, 1 H, 8-H_b), 3.65 (m, 1 H, 24-H_a), 3.75 (s, 3 H, 13-H), 3.88 (m, 1 H, 24-H_b), 4.48 (dd, $^{3}J_{21,22a}$ = 7.5 Hz, $^{3}J_{21,22b}$ = 5.5 Hz, 1 H, 21-H), 4.53 (dd, $^{3}J_{15,NH}$ = 8.9 Hz, $^{3}J_{15,16}$ = 8.9 Hz, 1 H, 15-H), 4.56 (m, 1 H, 7-H), 5.05 (m, 2 H, 5-H), 5.66 (d, $^{3}J_{NH,7}$ = 7.6 Hz, 1 H, NH_b), 6.76 (d, $^{3}J_{11,10}$ = 8.6 Hz, 2 H, 11-H), 7.07 (d, $^{3}J_{10,11}$ = 8.6 Hz, 2 H, 10-H), 7.23 – 7.36 (m, 5 H, 1-H, 2-H, 3-H), 7.50 (d, $^{3}J_{NH,15}$ = 7.2 Hz, 1 H, NH_a), 9.75 (br s, 1 H, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.8 (q, C-19), 14.9 (q, C-17), 24.3 (t, C-18), 24.9 (t, C-23), 28.6 (t, C-22), 37.4 (d, C-16), 38.3 (t, C-8), 47.8 (t, C-24), 54.8 (d, C-15), 55.1 (q, C-13), 55.7 (d, C-7), 59.3 (d, C-21), 67.0 (t, C-5), 113.9 (d, C-11), 128.0 (d, C-3), 128.1 (s, C-9), 128.4 (d, C-1 o. C-2), 128.5 (d, C-1 o. C-2), 130.4 (d, C-10), 136.2 (s, C-4), 156.0 (s, C-6), 158.5 (s, C-12), 171.1 (s, C-14), 171.6 (s, C-20), 173.7 (s, C-25).

HRMS (CI):	calculated	found
$C_{29}H_{38}N_3O_7$ $[M+H]^+$	540.2704	540.2695

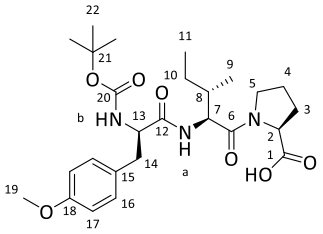
Melting point: 92 °C

Optical rotation: $[\propto]_D^{20}$ = –45.9° (c = 0.5, $CHCl_3$)

Boc-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-OH (18c)

A solution of 2.14 g (4.12 mmol) **11c** in 34 mL dioxane was treated with a solution of 264 mg (6.17 mmol) $LiOH \cdot H_2O$ in 7 mL water at 0 °C. The reaction was allowed to warm to rt within 7.5 h. The reaction mixture was then concentrated *in vacuo* and the residue was redissolved in water. The aqueous phase was extracted with EA and the organic phase was discarded. The aqueous phase was then acidified with 1 M HCl sol. and extracted three times with EA. The combined organic layers of this latter extraction were dried over Na_2SO_4. After lyophilisation, 2.03 g (4.01 mmol, 99 %) of acid **18c** (containing 3 % *iso*-Butylcarbonate at tyrosine residue) were obtained as an off-white solid.

R_f (18c) = 0.17 (silica gel, PE:EA 50:50 + 1 % HOAc)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, $^{3}J_{11,10}$ = 7.0 Hz, 3 H, 11-H), 0.88 (m, 1 H, 10-H_a), 0.91 (d, $^{3}J_{9,8}$ = 6.8 Hz, 3 H, 9-H), 1.27 (m, 1 H, 10-H_b), 1.39 (s, 9 H, 22-H), 1.70 (m, 1 H, 8-H), 2.01 (m, 1 H, 4-H_a), 2.15 (m, 3 H, 3-H, 4-H_b), 2.89 (dd, $^{2}J_{14a,14b}$ = 14.0 Hz, $^{3}J_{14a,13}$ = 5.0 Hz, 1 H, 14-H_a), 3.05 (dd, $^{2}J_{14b,14a}$ = 13.6 Hz, $^{3}J_{14b,13}$ = 7.1 Hz, 1 H, 14-H_b), 3.69 (m, 1 H, 5-H_a), 3.76 (s, 3 H, 19-H), 3.91 (m, 1 H, 5-H_b), 4.52 (m, 3 H, 2-H, 7-H, 13-H), 5.31 (d, $^{3}J_{NH,13}$ = 6.1 Hz, 1 H, NH_b), 6.78 (d, $^{3}J_{17,16}$ = 8.6 Hz, 2 H, 17-H), 7.08 (d, $^{3}J_{16,17}$ = 8.6 Hz, 2 H, 16-H), 7.54 (br s, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.8 (q, C-11), 14.9 (q, C-9), 24.3 (t, C-10), 24.9 (t, C-4), 28.2 (q, C-22), 28.6 (t, C-3), 37.6 (d, C-8), 38.2 (t, C-14), 47.8 (t, C-5), 54.8 (d, C-7), 55.1 (q, C-19), 59.4 (d, C-2 o. C-13), 60.4 (d, C-2 o. C-13), 80.3 (s, C-21), 113.8 (d, C-17), 128.3 (s, C-15), 130.4 (d, C-16), 155.6 (s, C-20), 158.5 (s, C-18), 171.4 (s, C-6), 171.6 (s, C-12), 173.6 (s, C-1).

HRMS (CI):	calculated	found
$C_{26}H_{40}N_3O_7$ $[M+H]^+$	506.2861	506.2864

Melting point: 98 °C

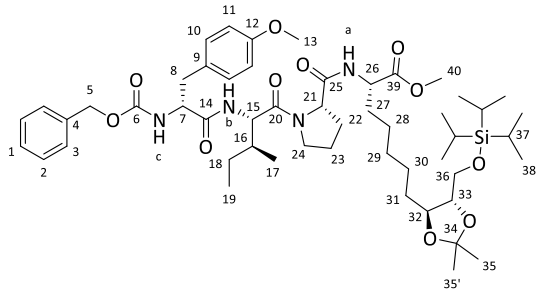
Optical rotation: $[\propto]_D^{20}$ = –48.9° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.6 mL/min, t_{R1} = 16.5 min (95 %, $[M+H]^+$ = 506), t_{R2} = 18.6 min (3 %, $[M+Na]^+$ = 614).

Methyl (*S*)-2-((*S*)-1-(((*R*)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)-oxy)-methyl)-1,3-dioxolan-4-yl)heptanoate (19)

1.87 g (3.47 mmol) **18a** were dissolved in 28 mL MeCN and 1.56 g (3.50 mmol) **17** were added. Afterwards, 1.14 g (3.55 mmol) TBTU and 642 µL (475 mg, 3.68 mmol) DIPEA were added and the reaction was stirred at rt overnight. The reaction was then concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 50:50 + 1 % HOAc) yielded 2.70 g (2.79 mmol, *dr* > 99:1, 80 %) tetrapeptide **19** as an off-white solid.

R_f (19) = 0.36 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.75 (t, $^{3}J_{19,18}$ = 6.9 Hz, 3 H, 19-H), 0.85 (d, $^{3}J_{17,16}$ = 6.7 Hz, 3 H, 17-H), 0.86 (m, 1 H, 18-H_a), 1.03 – 1.14 (m, 21 H, 37-H, 38-H), 1.20 – 1.33 (m, 6 H, 18-H_b, 28-H_a/28-H_b, 29-H_a/29-H_b, 30-H_a/30-H_b), 1.35 (s, 3 H, 35-H), 1.37 (m, 1 H, 28-H_a/28-H_b/29-H_a/29-H_b/30-H_a/30-H_b), 1.38 (s, 3 H, 35'-H), 1.50 (m, 1 H, 31-H_a), 1.57 – 1.67 (m, 3 H, 16-H, 31-H_b, 27-H_a), 1.72 (m, 1 H, 27-Hb), 1.87 – 2.02 (m, 2 H, 22-H_a, 23-H_a), 2.10 (m, 1 H, 23-H_b), 2.30 (m, 1 H, 22-H_b), 2.99 (d, $^{3}J_{8,7}$ = 6.6 Hz, 2 H, 8-H), 3.59 – 3.68 (m, 2 H, 24-H_a, 33-H), 3.71 (s, 3 H, 40-H), 3.73 (m, 1 H, 36-H_a), 3.76 (s, 3 H, 13-H), 3.83 (m, 1 H, 24-H_b), 3.85 (dd, $^{2}J_{36b,36a}$ = 10.3 Hz, $^{3}J_{36b,33}$ = 4.1 Hz, 1 H, 36-H_b), 3.90 (td, $^{3}J_{32,31}$ = 7.9 Hz, $^{3}J_{32,33}$ = 3.5 Hz, 1 H, 32-H), 4.44 (dt, $^{3}J_{26,27} \approx {}^{3}J_{26,NH}$ = 6.6 Hz, 1 H, 26-H), 4.49 (m, 1 H, 15-H), 4.52 (t, $^{3}J_{7,8/NH}$ = 8.4 Hz, 2 H, 7-H), 4.61 (d, $^{3}J_{21,22a}$ = 6.5 Hz, 1 H, 21-H), 5.07 (s, 2 H, 5-H), 5.34 (d, $^{3}J_{NH,7}$ = 7.0 Hz, 1 H, NH_c), 6.70 (br s, 1 H, NH_b), 6.78 (d, $^{3}J_{11,10}$ = 8.4 Hz, 2 H, 11-H), 7.08 (d, $^{3}J_{10,11}$ = 7.6 Hz, 2 H, 10-H), 7.27 – 7.37 (m, 6 H, 1-H, 2-H, 3-H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-19), 11.8 (d, C-37), 15.2 (q, C-17), 17.9 (q, C-38), 24.1 (t, C-18), 24.9 (t, C-23), 25.3 (t, C-28 o. C-29 o. C-30), 26.0 (t, C-28 o. C-29 o. C-30), 27.0 (q, C-35), 27.4 (q, C-35'), 27.5 (t, C-22), 29.3 (t, C-28 o. C-29 o. C-30), 32.2 (t, C-27), 33.5 (t, C-31), 37.6 (d, C-16), 38.3 (t, C-8), 47.8 (t, C-24), 52.5 (q, C-40), 52.5 (d, C-26), 54.9 (d, C-7), 55.1 (q, C-13), 56.2 (d, C-15), 59.7 (d, C-21), 64.2 (t, C-36), 67.0 (t, C-5), 79.0 (d, C-32), 81.0 (d, C-33), 108.3 (s, C-34), 114.0 (d, C-11), 128.0 (d, C-3), 128.1 (d, C-1 o. C-2), 128.1 (s, C-9), 128.5 (d, C-1 o. C-2), 130.2 (d, C-10), 136.2 (s, C-4), 155.6 (s, C-6), 158.6 (s, C-12), 170.7 (s, C-14), 170.9 (s, C-20 o. C-25), 171.6 (s, C-20 o. C-25), 172.7 (s, C-39).

HRMS (CI):	calculated	found
$C_{52}H_{83}N_4O_{11}Si$ $[M+H]^+$	967.5822	967.5840

Melting point: 56 °C

Optical rotation: $[\alpha]_D^{20}$ = –42.6° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 50:50, 1 mL/min, 20 °C:

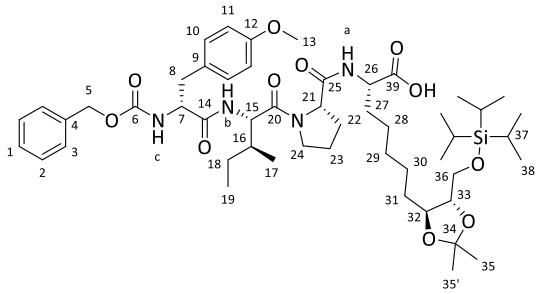
t_R = 31.4 min (> 99 %, broad).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 24.5 min ($[M+H]^+$ = 968).

(*S*)-2-((*S*)-1-(((*R*)-2-(((Benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)-oxy)methyl)-1,3-dioxolan-4-yl)heptanoic acid (20)

A solution of 2.67 g (2.76 mmol) ester **19** in 25 mL 1,4-dioxane was treated with 3 mL (3.37 mmol) LiOH (1.12 M in H_2O) at 0 °C. The cooling bath was removed and the reaction was stirred at rt for 8 h. For workup, the reaction was concentrated *in vacuo* and the residue was redissolved in EA. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with EA and the combined organic phases were dried over Na_2SO_4. After lyophilisation, 2.62 g (2.75 mmol, *dr* 95:5, quant.) of product **20** were obtained as an off-white solid.

R_f (20) = 0.10 (silica gel, PE:EA 50:50 + 1 % HOAc)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, $^3J_{19,18}$ = 6.8 Hz, 3 H, 19-H), 0.87 (d, $^3J_{17,16}$ = 6.7 Hz, 3 H, 17-H), 0.96 (m, 1 H, 18-H_a), 1.02 – 1.13 (m, 21 H, 37-H, 38-H), 1.24 – 1.39 (m, 6 H, 18-H_b, 28-H_a/28-H_b, 29-H_a/29-H_b, 30-H_a/30-H_b), 1.34 (s, 3 H, 35-H), 1.37 (s, 3 H, 35'-H), 1.44 (m, 1 H, 28-H_a/28-H_b/29-H_a/29-H_b/30-H_a/30-H_b), 1.51 (m, 1 H, 31-H_a), 1.57 – 1.72 (m, 3 H, 16-H, 27-H_a, 31-H_b), 1.78 (m, 1 H, 27-H_b), 1.87 (m, 1 H, 22-H_a), 2.06 (m, 2 H, 23-H), 2.50 (m, 1 H, 22-H_b), 2.99 (d, $^3J_{8,7}$ = 5.9 Hz, 2 H, 8-H), 3.60 – 3.68 (m, 2 H, 24-H_a, 33-H), 3.72 (m, 1 H, 36-H_a), 3.75 (s, 3 H, 13-H), 3.84 (dd, $^2J_{36b,36a}$ = 10.3 Hz, $^3J_{36b,33}$ = 4.0 Hz, 1 H, 36-H_b), 3.89 (td, $^3J_{32,31}$ = 7.9 Hz, $^3J_{32,33}$ = 3.4 Hz, 1 H, 32-H), 3.94 (m, 1 H, 24-H_b), 4.44 – 4.53 (m, 3 H, 7-H, 15-H, 26-H), 4.70 (d, $^3J_{21,22a/b}$ = 7.3 Hz, 1 H, 21-H), 5.05 (s, 2 H, 5-H), 5.48 (d, $^3J_{NH,7}$ = 8.2 Hz, 1 H, NH_c), 6.78 (d, $^3J_{11,10}$ = 8.4 Hz, 2 H, 11-H), 7.08 (d, $^3J_{10,11}$ = 8.6 Hz, 2 H, 10-H), 7.27 – 7.35 (m, 5 H, 1-H, 2-H, 3-H), 7.63 (d, $^3J_{NH,15}$ = 8.7 Hz, 1 H, NH_b), 7.83 (d, $^3J_{NH,26}$ = 6.6 Hz, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.7 (q, C-19), 11.8 (d, C-37), 15.0 (q, C-17), 17.9 (q, C-38), 24.6 (t, C-18), 25.0 (t, C-23), 25.5 (t, C-28 o. C-29 o. C-30), 26.1 (t, C-28 o. C-29 o. C-30), 26.5 (t, C-22), 27.0 (q, C-35), 27.4 (q, C-35'), 29.5 (t, C-28 o. C-29 o. C-30), 33.0 (t, C-27), 33.6 (t, C-31), 37.1 (d, C-16), 38.1 (t, C-8), 48.4 (t, C-24), 53.0 (d, C-26), 55.0 (d, C-7 o. C-15), 55.2 (q, C-13), 56.0 (d, C-7 o. C-15), 60.4 (d, C-21), 64.1 (t, C-36), 66.7 (t, C-5), 79.0 (d, C-32), 81.0 (d, C-33), 108.3 (s, C-34), 113.9 (d, C-11), 127.8 (d, C-3), 128.0 (d, C-1 o. C-2), 128.1 (s, C-9), 128.4 (d, C-1 o. C-2), 130.3 (d, C-10), 136.4 (s, C-4), 155.7 (s, C-6), 158.6 (s, C-12), 169.8 (s, C-25), 171.7 (s, C-14), 173.4 (s, C-20), 174.1 (s, C-39).

HRMS (CI):	calculated	found
$C_{51}H_{81}N_4O_{11}Si$ $[M+H]^+$	953.5666	953.5685

Melting point: 55-57 °C

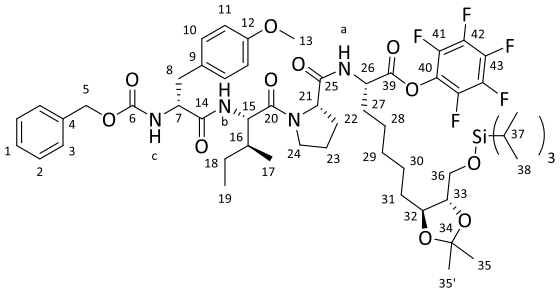
Optical rotation: $[\propto]_D^{20}$ = –37.5° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 17.9 min (95 %, $[M+Na]^+$ = 976) t_{R2} = 18.5 min (5 %, $[M+Na]^+$ = 976).

Perfluorophenyl (*S*)-2-((*S*)-1-(((*R*)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)-propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)heptanoate (21)

To a solution of 102 mg (0.107 mmol) acid **20** in 1.1 mL DCM abs. were added 27 mg (0.147 mmol) pentafluorophenol and 24.1 mg (0.126 mmol) EDC·HCl at 0 °C. The reaction was allowed to warm to rt overnight and diluted with DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM and the combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. 120 mg (0.107 mmol, *dr* ~ 97:3, quant.) **21** were obtained as an off-white solid after lyophilisation.

R_f (21) = 0.31 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (500 MHz, 373K, DMSO-d_6): δ = 0.80 (t, $^3J_{19,18}$ = 7.4 Hz, 3 H, 19-H), 0.88 (m, 3 H, 17-H), 0.88 (m, 1 H, 18-H_a), 1.02 – 1.14 (m, 21 H, 37-H, 38-H), 1.27 – 1.46 (m, 7 H, 18-H_b, 28-H_a, 28-H_b, 29-H_a, 29-H_b, 30-H_a, 30-H_b), 1.30 (s, 3 H, 35-H), 1.32 (s, 3 H, 35'-H), 1.53 (m, 1 H, 31-H_a), 1.57 – 1.65 (m, 2 H, 16-H, 31-H_b), 1.71 – 1.86 (m, 3 H, 22-H_a, 27-H), 1.88 – 2.06 (m, 3 H, 22-H_b, 23-H), 2.76 (dd, $^2J_{8a,8b}$ = 13.4 Hz, $^3J_{8a,7}$ = 9.6 Hz, 1 H, 8-H_a), 2.95 (dd, $^2J_{8b,8a}$ = 13.4 Hz, $^3J_{8b,7}$ = 9.6 Hz, 1 H, 8-H_b), 3.56 (m, 1 H, 24-H_a), 3.65 (ddd, $^3J_{33,36a}$ = 7.7 Hz, $^3J_{33,36b} \approx {}^3J_{33,32}$ = 4.7 Hz, 1 H, 33-H), 3.74 (s, 3 H, 13-H), 3.76 (m, 1 H, 24-H_b), 3.77 (dd, $^2J_{36a,36b}$ = 10.8 Hz, $^3J_{36a,33}$ = 4.9 Hz, 1 H, 36-H_a), 3.81 (dd, $^2J_{36b,36a}$ = 10.7 Hz, $^3J_{36b,33}$ = 4.4 Hz, 1 H, 36-H_b), 3.87 (m, 1 H, 32-H), 4.24 (m, 1 H, 15-H/26-H), 4.33 (m, 1 H, 7-H), 4.41 – 4.49 (m, 2 H, 15-H/26-H, 21-H), 4.96 (d, $^2J_{5a,5b}$ = 13.2 Hz, 1 H, 5-H_a), 4.99 (d, $^2J_{5b,5a}$ = 13.2 Hz, 1 H, 5-H_b), 6.80 (d, $^3J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 6.93 (br s, 1 H, NH_c), 7.16 (d, $^3J_{10,11}$ = 8.5 Hz, 2 H, 10-H), 7.25 – 7.34 (m, 5 H, 1-H, 2-H, 3-H), 7.62 (br s, 1 H, NH), 7.71 (br s, 1 H, NH).

^{13}C-NMR (125 MHz, 373K, DMSO-d_6): δ = 10.1 (q, C-19), 11.1 (d, C-37), 14.7 (q, C-17), 17.2 (q, C-38), 23.5 (t, C-18), 24.5 (t, C-23), 24.5 (t, C-28 o. C-29 o. C-30), 24.8 (t, C-28 o. C-29 o. C-

30), 26.4 (q, C-35), 26.8 (q, C-35'), 28.1 (t, C-22), 30.9 (t, C-28 o. C-29 o. C-30), 31.1 (t, C-27), 32.4 (t, C-31), 36.2 (d, C-16), 36.7 (t, C-8), 46.7 (t, C-24), 51.5 (d, C-21), 53.9 (d, C-15 o. C-26), 54.6 (q, C-13), 56.0 (d, C-7), 58.8 (d, C-15 o. C-26), 63.4 (t, C-36), 64.9 (t, C-5), 77.3 (d, C-32), 80.6 (d, C-33), 107.2 (s, C-34), 113.2 (d, C-11), 126.8 (d, C-1 o. C-2 o. C-3), 127.0 (d, C-1 o. C-2 o. C-3), 127.6 (d, C-1 o. C-2 o. C-3), 129.2 (s, C-9), 129.6 (d, C-10), 136.6 (s, C-4), 155.0 (s, C-6), 157.6 (s, C-12), 170.5 (s, C-14 o. C-20 o. C-25 o. C-39), 172.4 (s, C-14 o. C-20 o. C-25 o. C-39), 172.6 (s, C-14 o. C-20 o. C-25 o. C-39).

Minor diastereomer:

^{1}H-NMR (500 MHz, 373K, DMSO-d_6): δ = 1.27 (s, 3 H, 35-H), 4.70 – 4.75 (m, 2 H, 15-H/26-H, 21-H), 6.65 (d, $^{3}J_{11,10}$ = 8.2 Hz, 2 H, 11-H), 7.03 (d, $^{3}J_{10,11}$ = 8.5 Hz, 2 H, 10-H), 7.52 (br s, 1 H, NH), 7.83 (br s, 1 H, NH).

^{13}C-NMR (125 MHz, 373K, DMSO-d_6): δ = 14.6 (q, C-17), 28.2 (t, C-22), 32.3 (t, C-31), 51.3 (d, C-21), 54.1 (d, C-15 o. C-26), 59.1 (d, C-15 o. C-26), 77.3 (d, C-32).

HRMS (CI):	calculated	found
$C_{57}H_{80}F_5N_4O_{11}Si$ $[M+H]^+$	1119.5508	1119.5509

Melting point: 57 °C

Optical rotation: $[\alpha]_D^{20}$ = –40.8° (c = 1.0, $CHCl_3$)

(3*S*,6*R*,9*S*,14a*S*)-9-((*S*)-*sec*-Butyl)-3-(5-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)-methyl)-1,3-dioxolan-4-yl)pentyl)-6-(4-methoxybenzyl)decahydropyrrolo[1,2-a][1,4,7,10]-tetraazacyclododecine-1,4,7,10-tetraone (22)

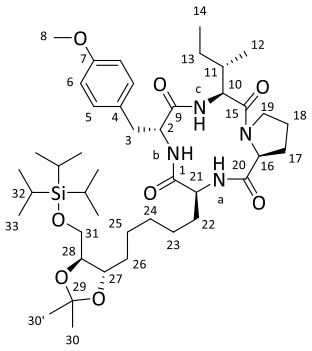
Method A:

58 mg (51.8 µmol) **21** were dissolved in 50 mL THF and 5.6 mg palladium on charcoal (10 w% Pd) were added. The reaction was hydrogenated under atmospheric pressure for 48 h. The reaction mixture was filtrated through a pad of Celite and washed with Et_2O. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50). 13.1 mg (16.4 µmol, *dr* 85:15, 32 %) of the cyclic tetrapeptide **22** were obtained as an off-white solid.

Method B:

To a solution of 56 mg (50.0 µmol) **21** in 5 mL THF were added 5.6 mg palladium on charcoal (10 w% Pd) at rt. The reaction was set under 5 bar H_2 and hydrogenated for 40 h at rt. The reaction mixture was filtrated through a pad of Celite and washed with Et_2O. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50). 11.3 mg (14.1 µmol, *dr* 94:6, 28 %) of the cyclic tetrapeptide **22** were obtained as an off-white solid.

R_f (22) = 0.27 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.70 (t, $^3J_{14,13}$ = 6.9 Hz, 3 H, 14-H), 0.80 (d, $^3J_{12,11}$ = 6.4 Hz, 3 H, 12-H), 0.80 (m, 1 H, 13-H_a), 1.03 (m, 1 H, 13-H_b), 1.03 – 1.15 (m, 21 H, 32-H, 33-H), 1.29 – 1.41 (m, 5 H, 23-H_a/23-H_b, 24-H_a/24-H_b, 25-H_a/25-H_b), 1.36 (s, 3 H, 30-H), 1.39 (s, 3 H, 30'-H), 1.46 – 1.58 (m, 2 H, 23-H_a/23-H_b/24-H_a/24-H_b/25-H_a/25-H_b, 26-H_a), 1.60 – 1.69 (m, 2 H, 22-H_a, 26-H_b), 1.82 – 1.92 (m, 3 H, 11-H, 18-H_a, 22-H_b), 1.98 (m, 1 H, 18-H_b), 2.16 (m, 1 H, 17-H_a), 2.24 (m, 1 H, 17-H_b), 2.83 (dd, $^2J_{3a,3b}$ = 13.5 Hz, $^3J_{3a,2}$ = 5.3 Hz, 1 H, 3-H_a), 3.21 (dd, $^2J_{3b,3a}$ = 13.0 Hz, $^3J_{3b,2}$ = 10.8 Hz, 1 H, 3-H_b), 3.61 – 3.70 (m, 2 H, 19-H_a, 28-H), 3.69 (s, 3 H, 8-H), 3.72 – 3.78 (m, 2 H, 19-H_b, 31-H_a), 3.86 (dd, $^2J_{31b,31a}$ = 10.4 Hz, $^3J_{31b,28}$ = 4.0 Hz, 1 H, 31-H_b), 3.91 (dt, $^3J_{27,26}$ = 7.5 Hz, $^3J_{27,28}$ = 3.4 Hz, 1 H, 27-H), 4.52 (dd, $^3J_{10,11} \approx {}^3J_{10,NH}$ = 9.8 Hz, 1 H, 10-H), 4.57 (dt, $^3J_{21,22/NH}$ = 9.3 Hz, $^3J_{21,22/NH}$ = 7.5 Hz, 1 H, 21-H), 4.63 (ddd, $^3J_{2,3b}$ = 10.3 Hz, $^3J_{2,3a} \approx {}^3J_{2,NH}$ = 5.4 Hz, 1 H, 2-H), 4.93 (d, $^3J_{16,17}$ = 7.0 Hz, 1 H, 16-H), 6.22 (br s, 1 H, NH_a), 6.58 (br s, 1 H, NH_c), 6.65 (d, $^3J_{6,5}$ = 8.2 Hz, 2 H, 6-H), 6.85 (m, 1 H, NH_b), 7.01 (d, $^3J_{5,6}$ = 8.1 Hz, 2 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 11.9 (d, C-32), 15.9 (q, C-12), 18.0 (q, C-33), 21.9 (t, C-18), 24.1 (t, C-13), 25.8 (t, C-23 o. C-24 o. C-25), 26.1 (t, C-23 o. C-24 o. C-25), 27.0 (q, C-30), 27.4 (q, C-30'), 28.2 (t, C-22), 29.5 (t, C-23 o. C-24 o. C-25), 31.6 (t, C-17), 33.4 (t, C-26), 34.6 (t, C-3), 36.2 (d, C-11), 47.0 (t, C-19), 54.0 (d, C-21), 55.0 (q, C-8), 55.7 (d, C-10), 57.2 (d, C-2), 61.0 (d, C-16), 64.2 (t, C-31), 79.2 (d, C-27), 81.0 (d, C-28), 108.3 (s, C-29), 113.7 (d, C-6), 128.7 (s, C-4), 130.5 (d, C-5), 158.3 (s, C-7), 170.1 (s, C-9), 170.6 (s, C-15), 174.0 (s, C-1 o. C-20), 174.6 (s, C-1 o. C-20).

Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ =2.93 (m, 1 H, 3-H_a), 3.12 (m, 1 H, 3-H_b).

HRMS (CI):	calculated	found
$C_{43}H_{73}N_4O_8Si$ $[M+H]^+$	801.5192	801.5192

Melting point: 198 °C

Optical rotation: $[\propto]_D^{20}$ = –56.6° (c = 0.5, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 50:50, 1 mL/min, 20 °C:

t_{R1} = 7.0 min (minor),

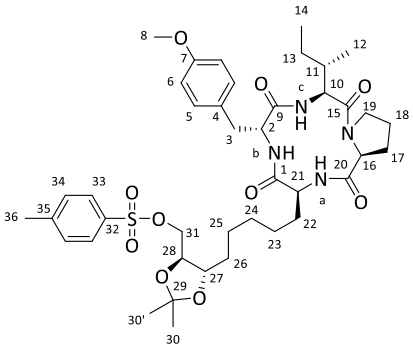
t_{R2} = 13.7 min (major).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 20.1 min ($[M+Na]^+$ = 824).

((4*S*,5*S*)-5-(5-((3*S*,6*R*,9*S*,14a*S*)-9-((*S*)-*sec*-Butyl)-6-(4-methoxybenzyl)-1,4,7,10-tetraoxo-tetra-decahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (23)

To a solution of 122 mg (152 µmol) **22** in 1.5 mL THF were added 228 µL (228 µmol) TBAF (1.0 M in THF) at rt. The reaction was stirred for 1.5 h and concentrated *in vacuo*. The residue was redissolved in DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4. The crude product was dissolved in 3.0 mL pyridine abs. and 3.8 mg (31.1 µmol) 4-DMAP were added. Afterwards, 64 mg (336 µmol) tosyl chloride were added and the reaction was stirred at rt over-night before further 23 mg (121 µmol) tosyl chloride were added. Stirring was continued for 4 h and the reaction was concentrated *in vacuo*. The crude product was either purified by preparative TLC (silica gel, EA/MeOH 99:1) or reversed phase column chromatography (silica gel C-18, H_2O:MeCN 50:50, Gradient 10:90) to obtain 5.8 mg (7.26 µmol, 5 % over two steps) of the pure tosylate **23** as an off-white solid and 78 mg (97.6 µmol, *dr* 91:9, 64 % over two steps) of an epi-meric mixture as an off-white solid.

R_f (23) = 0.26 (silica gel, PE:EA 50:50)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.71 (t, $^3J_{14,13}$ = 7.3 Hz, 3 H, 14-H), 0.80 (d, $^3J_{12,11}$ = 6.6 Hz, 3 H, 12-H), 0.82 (m, 1 H, 13-H_a), 1.05 (m, 1 H, 13-H_b), 1.25 – 1.36 (m, 5 H, 23-H_a/23-H_b, 24-H_a/24-H_b, 25-H_a/25-H_b), 1.29 (s, 3 H, 30-H), 1.35 (s, 3 H, 30'-H), 1.43 (m, 1 H, 23-H_a/23-H_b/24-H_a/24-H_b/25-H_a/25-H_b), 1.51 – 1.55 (m, 2 H, 26-H), 1.67 (m, 1 H, 22-H_a), 1.84 – 1.93 (m, 3 H, 11-H, 18-H_a, 22-H_b), 1.96 (m, 1 H, 18-H_b), 2.16 (m, 1 H, 17-H_a), 2.24 (m, 1 H, 17-H_b), 2.45 (s, 3 H, 36-H), 2.83 (dd, $^2J_{3a,3b}$ = 13.4 Hz, $^3J_{3a,2}$ = 5.5 Hz, 1 H, 3-H_a), 3.20 (dd, $^2J_{3b,3a}$ = 13.6 Hz, $^3J_{3b,2}$ = 10.1 Hz, 1 H, 3-H_b), 3.62 (m, 1 H, 19-H_a), 3.70 (s, 3 H, 8-H), 3.74 – 3.83 (m, 3 H, 19-H_b, 27-H, 28-H), 4.05

(dd, $^{2}J_{31a,31b}$ = 10.7 Hz, $^{3}J_{31a,28}$ = 4.4 Hz, 1 H, 31-H_a), 4.10 (dd, $^{2}J_{31b,31a}$ = 10.6 Hz, $^{3}J_{31b,28}$ = 4.3 Hz, 1 H, 31-H_b), 4.52 (dd, $^{3}J_{10,11} \approx {}^{3}J_{10,NH}$ = 9.8 Hz, 1 H, 10-H), 4.57 (dt, $^{3}J_{21,22/NH}$ = 9.8 Hz, $^{3}J_{21,22/NH}$ = 7.9 Hz, 1 H, 21-H), 4.63 (ddd, $^{3}J_{2,3b}$ = 10.4 Hz, $^{3}J_{2,3a} \approx {}^{3}J_{2,NH}$ = 5.7 Hz, 1 H, 2-H), 4.92 (d, $^{3}J_{16,17}$ = 7.3 Hz, 1 H, 16-H), 6.24 (br s, 1 H, NH_a), 6.50 (br s, 1 H, NH_c), 6.66 (d, $^{3}J_{6,5}$ = 8.5 Hz, 2 H, 6-H), 6.83 (d, 1 H, NH_b), 7.02 (d, $^{3}J_{5,6}$ = 8.5 Hz, 2 H, 5-H), 7.35 (d, $^{3}J_{34,33}$ = 8.2 Hz, 2 H, 34-H), 7.79 (d, $^{3}J_{33,34}$ = 8.2 Hz, 2 H, 33-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 21.7 (q, C-36), 21.9 (t, C-18), 24.1 (t, C-13), 25.6 (t, C-23 o. C-24 o. C-25), 25.7 (t, C-23 o. C-24 o. C-25), 26.7 (q, C-30), 27.3 (q, C-30'), 28.1 (t, C-22), 29.2 (t, C-23 o. C-24 o. C-25), 31.6 (t, C-17), 32.8 (t, C-26), 34.5 (t, C-3), 36.3 (d, C-11), 47.0 (t, C-19), 53.9 (d, C-21), 55.0 (q, C-8), 55.7 (d, C-10), 57.2 (d, C-2), 61.0 (d, C-16), 69.1 (t, C-31), 77.8 (d, C-27 o. C-28), 78.1 (d, C-27 o. C-28), 109.3 (s, C-29), 113.7 (d, C-6), 128.0 (d, C-33), 128.7 (s, C-4), 129.9 (d, C-34), 130.5 (d, C-5), 132.7 (s, C-32), 145.0 (s, C-35), 158.3 (s, C-7), 170.1 (s, C-9), 170.6 (s, C-15), 173.9 (s, C-1 o. C-20), 174.6 (s, C-1 o. C-20).

HRMS (CI):	calculated	found
$C_{41}H_{59}N_4O_{10}S$ $[M+H]^+$	799.3946	799.3963

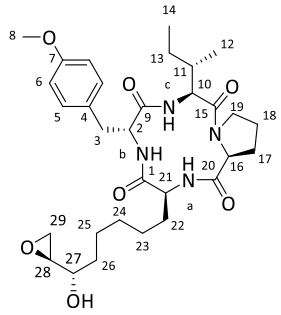
Melting point: 205 °C

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 10.3 min (minor, $[M+H]^+$ = 799), t_{R2} = 11.5 min (major, $[M+H]^+$ = 799).

(3*S*,6*R*,9*S*,14a*S*)-9-((*S*)-sec-butyl)-3-((*S*)-6-Hydroxy-6-((*S*)-oxiran-2-yl)hexyl)-6-(4-methoxybenzyl)decahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetraone (24)

A solution of 14.7 mg (18.4 µmol) tosylate **23** in 1 mL THF was treated with 1.0 mL HCl (5 w% in H_2O) at rt and the reaction was heated to 40 °C for 8 h. Stirring was continued at ambient temperature for 1.5 h and the reaction was concentrated in *high vacuo*. The residue was redissolved in DCM and brine was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4. The crude product was dissolved in 3.6 mL MeOH abs. before 14.0 µL (14.1 µg, 92.6 µmol) DBU were added at 0 °C. The reaction was allowed to warm to rt within 8.5 h. The reaction mixture was filtrated through a pad of silica gel and washed with EA:MeOH 90:10. The filtrate was concentrated *in vacuo* and the crude product was purified by reversed phase column chromatography (silica gel C-18, H_2O:MeCN 90:10, Gradient 10:90). 6.6 mg (11.2 µmol, 61 % over two steps) of epoxyalcohol **24** were obtained as an off-white solid.

R_f (24) = 0.46 (silica gel, EA:MeOH 95:5)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.71 (t, $^{3}J_{14,13}$ = 7.2 Hz, 3 H, 14-H), 0.80 (d, $^{3}J_{12,11}$ = 6.3 Hz, 3 H, 12-H), 0.82 (m, 1 H, 13-H_a), 1.06 (m, 1 H, 13-H_b), 1.28 – 1.37 (m, 4 H, 23-H, 25-H), 1.40 (m, 1 H, 24-H_a), 1.49 (m, 1 H, 24-H_b), 1.57 (m, 2 H, 26-H), 1.67 (m, 1 H, 22-H_a), 1.71 (br s, 1 H, OH), 1.83 – 1.94 (m, 3 H, 11-H, 18-H_a, 22-H_b), 1.98 (m, 1 H, 18-H_b), 2.16 (m, 1 H, 17-H_a), 2.24 (m, 1 H, 17-H_b), 2.71 (dd, $^{2}J_{29a,29b}$= 5.0 Hz, $^{3}J_{29a,28}$ = 2.8 Hz, 1 H, 29-H_a), 2.81 (dd, $^{2}J_{29b,29a}$= 4.7 Hz, $^{3}J_{29b,28}$ = 4.0 Hz, 1 H, 29-H_b), 2.84 (dd, $^{2}J_{3a,3b}$ = 13.8 Hz, $^{3}J_{3a,2}$ = 5.7 Hz, 1 H, 3-H_a), 2.97 (ddd, $^{3}J_{28,27}$ = 7.2 Hz, $^{3}J_{28,29b}$ = 4.4 Hz, $^{3}J_{28,29a}$ = 2.8 Hz, 1 H, 28-H), 3.21 (dd, $^{2}J_{3b,3a}$ = 13.2 Hz, $^{3}J_{3b,2}$ = 10.4 Hz, 1 H, 3-H_b), 3.44 (dt, $^{3}J_{27,28} \approx {}^{3}J_{27,26}$ = 5.9 Hz, 1 H, 27 H), 3.63 (m, 1 H, 19-H_a), 3.70 (s, 3 H, 8-H), 3.77 (m, 1 H, 19-H_b), 4.52 (t, $^{3}J_{10,11} \approx {}^{3}J_{10,NH}$ = 9.7 Hz, 1 H, 10-H), 4.58 (m, 1 H, 21-H), 4.64 (ddd, $^{3}J_{2,3b}$ = 10.4 Hz, $^{3}J_{2,3a} \approx {}^{3}J_{2,NH}$ = 5.8 Hz, 1 H, 2-H), 4.95 (d, $^{3}J_{16,17a/b}$ = 6.9 Hz, 1 H, 16-H), 6.25 (br s, 1 H, NH_a), 6.61 (br s, 1 H, NH_c), 6.65 (d, $^{3}J_{6,5}$ = 8.5 Hz, 2 H, 6-H), 6.86 (br s, 1 H, NH_b), 7.01 (d, $^{3}J_{5,6}$ = 8.5 Hz, 2 H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 21.9 (t, C-18), 24.1 (t, C-13), 25.2 (t, C-24), 25.8 (t, C-23 o. C-25), 28.2 (t, C-22), 29.4 (t, C-23 o. C-25), 31.6 (t, C-17), 34.3 (t, C-26), 34.6 (t, C-3), 36.3 (d, C-11), 45.0 (t, C-29), 47.0 (t, C-19), 54.0 (d, C-21), 55.1 (q, C-8), 55.3 (d, C-28), 55.7 (d, C-10), 57.3 (d, C-2), 61.0 (d, C-16), 71.2 (d, C-27), 113.7 (d, C-6), 128.7 (s, C-4), 130.5 (d, C-5), 158.3 (s, C-7), 170.2 (s, C-9), 170.6 (s, C-15), 173.9 (s, C-1 o. C-20), 174.6 (s, C-1 o. C-20).

HRMS (CI):	calculated	found
$C_{31}H_{47}N_4O_7$ $[M+H]^+$	587.3439	587.3423

Melting point: 230 °C (decomposition)

Optical rotation: $[\propto]_D^{20}$ = –79° (c = 0.1, $CHCl_3$)

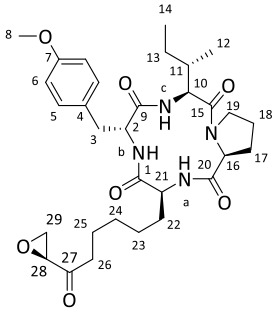
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.6 mL/min, t_{R1} = 14.9 min (minor, $[M+H]^+$ = 587), t_{R2} = 15.5 min (major, $[M+H]^+$ = 587).

Cyl-1[47]

To a solution of 9.6 mg (16.4 µmol) **24** in 2.0 mL DCM abs. was added 14.3 mg (33.7 µmol) DMP at rt and the reaction was stirred for 3 h. The reaction mixture was then filtrated through a pad of Celite® and washed with DCM. The filtrate was concentrated *in vacuo* and the crude product was

purified by column chromatography (silica gel C-18, H_2O:MeCN 90:10, Gradient 10:90). 1.8 mg (3.08 µmol, 19 %) pure Cyl-1 and 2.0 mg (3.42 µmol, *dr* 81:19, 21 %) of an epimeric mixture of Cyl-1 were obtained as off-white solids.

R_f (Cyl-1) = 0.18 (silica gel, EA)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.71 (t, $^3J_{14,13}$ = 6.8 Hz, 3 H, 14-H), 0.80 (d, $^3J_{12,11}$ = 6.5 Hz, 3 H, 12-H), 0.85 (m, 1 H, 13-H_a), 1.05 (m, 1 H, 13-H_b), 1.24 – 1.33 (m, 4 H, 23-H, 24-H), 1.50 – 1.66 (m, 3 H, 22-H_a, 25-H), 1.81 – 1.92 (m, 3 H, 11-H, 18-H_a, 22-H_b), 1.99 (m, 1 H, 18-H_b), 2.18 (m, 2 H, 17-H), 2.25 (m, 1 H, 26-H_a), 2.42 (m, 1 H, 26-H_b), 2.83 (dd, $^2J_{3a,3b}$ = 13.8 Hz, $^3J_{3a,2}$ = 5.8 Hz, 1 H, 3-H_a), 2.86 (dd, $^2J_{29a,29b}$= 5.8 Hz, $^3J_{29a,28}$ = 2.5 Hz, 1 H, 29-H_a), 2.99 (dd, $^2J_{29b,29a}$= 5.8 Hz, $^3J_{29b,28}$ = 4.8 Hz, 1 H, 29-H_b), 3.20 (dd, $^2J_{3b,3a}$ = 13.5 Hz, $^3J_{3b,2}$ = 10.2 Hz, 1 H, 3-H_b), 3.41 (dd, $^3J_{28,29b}$ = 4.5 Hz, $^3J_{28,29a}$ = 2.5 Hz, 1 H, 28-H), 3.62 (m, 1 H, 19-H_a), 3.71 (s, 3 H, 8-H), 3.74 (m, 1 H, 19-H_b), 4.51 (dd, $^3J_{10,11} \approx {}^3J_{10,NH}$ = 9.8 Hz, 1 H, 10-H), 4.52 (m, 1 H, 21-H), 4.61 (ddd, $^3J_{2,3b}$ = 10.4 Hz, $^3J_{2,3a} \approx {}^3J_{2,NH}$ = 5.5 Hz, 1 H, 2-H), 4.88 (d, $^3J_{16,17a/b}$ = 6.9 Hz, 1 H, 16-H), 6.16 (br s, 1 H, NH_a), 6.43 (br s, 1 H, NH_c), 6.68 (d, $^3J_{6,5}$ = 8.5 Hz, 2 H, 6-H), 6.76 (br s, 1 H, NH_b), 7.04 (d, $^3J_{5,6}$ = 7.8 Hz, 2 H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 21.9 (t, C-18), 22.8 (t, C-25), 24.1 (t, C-13), 25.6 (t, C-23 o. C-24), 27.9 (t, C-22), 28.7 (t, C-23 o. C-24), 31.6 (t, C-17), 34.5 (t, C-3), 36.2 (t, C-26), 36.3 (d, C-11), 46.1 (t, C-29), 47.1 (t, C-19), 53.4 (d, C-28), 53.9 (d, C-21), 55.1 (q, C-8), 55.7 (d, C-10), 57.1 (d, C-2), 61.1 (d, C-16), 113.7 (d, C-6), 128.7 (s, C-4), 130.4 (d, C-5), 158.3 (s, C-7), 170.1 (s, C-9), 170.5 (s, C-15), 173.1 (s, C-1 o. C-20), 174.7 (s, C-1 o. C-20), 207.5 (s, C-27).

HRMS (CI):	calculated	found
$C_{31}H_{45}N_4O_7$ $[M+H]^+$	585.3283	585.3293

Melting point: 220 °C (decomposition)

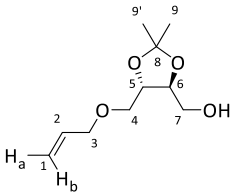
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 15.6 min (minor, $[M+H]^+$ = 585), t_{R2} = 16.3 min (major, $[M+H]^+$ = 585).

((4*S*,5*S*)-5-((Allyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (1d)

2.20 g (55.0 mmol) Sodium hydride (60 w% in paraffin) was placed in a three-necked flask and 10 mL *n*-pentane were added. After stirring for a few minutes, the sodium hydride was allowed to segregate and the solvent was removed *via* syringe. The procedure was repeated two times and the oil-free NaH was dried *in high-vacuo*.

The free sodium hydride was suspended in 35 mL DMF abs. and cooled to –40 °C. A solution of 8.15 g (50.3 mmol) (+)-2,3-O-Isopropylidene-L-threitol in 45 mL DMF abs. was added carefully within 50 min. Afterwards, a solution of 4.46 mL (6.24 g, 51.6 mmol) allyl bromide in 45 mL DMF abs. was added dropwise within 20 min at –40 °C and the reaction was allowed to warm to 0 °C slowly. The solvent was then distilled off *in vacuo* (0.43 mbar, 30-50 °C oil bath). The residue was dissolved in DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 80:20, 70:30). 7.12 g (35.2 mmol, 70 %) of compound **1d** were obtained as a colourless oil.

R_f (1d) = 0.32 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 6 H, 9-H, 9-H'), 2.28 (dd, $^3J_{OH,\ 7a}$ = 8.2 Hz, $^3J_{OH,7b}$ = 4.6 Hz, 1 H, OH), 3.52 (dd, $^2J_{4a,4b}$ = 9.9 Hz, $^3J_{4a,5}$ = 5.6 Hz, 1 H, 4-H_a), 3.65 (dd, $^2J_{4b,4a}$ = 9.9 Hz, $^3J_{4b,5}$ = 5.1 Hz, 1 H, 4-H_b), 3.71 (ddd, $^2J_{7a,7b}$ = 11.9 Hz, $^3J_{7a,OH}$ = 8.2 Hz, $^3J_{7a,6}$ = 4.2 Hz, 1 H, 7-H_a), 3.78 (ddd, $^2J_{7b,7a}$ = 11.6 Hz, $^3J_{7b,OH} \approx {}^3J_{7b,6}$ = 4.5 Hz, 1 H, 7-H_b), 3.93 (dt, $^3J_{6,5}$ = 8.4 Hz, $^3J_{6,7}$ = 4.2 Hz, 1 H, 6-H), 4.02 (m, 1 H, 5-H), 4.04 (d, $^3J_{3,2}$ = 5.5 Hz, 2 H, 3-H), 5.20 (ddt, $^3J_{1a,2}$ = 10.4 Hz, $^2J_{1a,1b} \approx {}^4J_{1a,3}$ = 1.3 Hz, 1 H, 1-H_a), 5.27 (ddt, $^3J_{1b,2}$ = 17.2 Hz, $^2J_{1b,1a} \approx {}^4J_{1b,3}$ = 1.6 Hz, 1 H, 1-H_b), 5.89 (dddd, $^3J_{2,1b}$ = 17.1 Hz, $^3J_{2,1a}$ = 10.4 Hz, $^3J_{2,3a}$ = 5.8 Hz, $^3J_{2,3b}$ = 5.5 Hz, 1 H, 2-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.9 (q, C-9), 26.9 (q, C-9'), 62.4 (t, C-7), 70.4 (t, C-4), 72.6 (t, C-3), 76.6 (d, C-5), 79.6 (d, C-6), 109.3 (s, C-8), 117.6 (t, C-1), 134.1 (d, C-2).

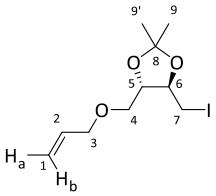
HRMS (CI):	calculated	found
$C_{10}H_{19}O_4$ $[M+H]^+$	203.1278	203.1283
Optical rotation:	$[\alpha]_D^{20}$ = +3.5° (c = 1.0, $CHCl_3$)	

(4*S*,5*R*)-4-((Allyloxy)methyl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane (5d)

To a solution of 7.01 g (34.7 mmol) **1d** in 100 mL toluene abs. and 20 mL MeCN abs. was added 2.95 g (43.3 mmol) imidazole, 9.55 g (36.4 mmol) PPh_3 and 9.23 g (36.4 mmol) iodine carefully

at rt. The reaction was heated to 60 °C for 2 h. For workup, the reaction was diluted with Et_2O and washed with sat. $Na_2S_2O_3$ sol., water and brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, *n*-pentane:Et_2O 2:1) afforded 10.5 g (33.6 mmol, 97 %) of iodide **5d** as a colourless liquid.

R_f (5d) = 0.25 (silica gel, PE:EA 90:10)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, ˉ, 3 H, 9-H), 1.47 (s, ˉ, 3 H, 9'-H), 3.29 (dd, $^2J_{7a,7b}$ = 10.5 Hz, $^3J_{7a,6}$ = 5.3 Hz, 1 H, 7-H_a), 3.36 (dd, $^2J_{7b,7a}$ = 10.5 Hz, $^3J_{7b,6}$ = 5.3 Hz, 1 H, 7-H_b), 3.60 (dd, $^2J_{4a,4b}$ = 10.3 Hz, $^3J_{4a,5}$ = 4.9 Hz, 1 H, 4-H_a), 3.64 (dd, $^2J_{4b,4a}$ = 10.3 Hz, $^3J_{4b,5}$ = 5.3 Hz, 1 H, 4-H_b), 3.85 (dt, $^3J_{6,5}$ = 7.5 Hz, $^3J_{6,7}$ = 5.3 Hz, 1 H, 6-H), 3.95 (dt, $^3J_{5,6}$ = 7.5 Hz, $^3J_{5,4}$ = 5.3 Hz, 1 H, 5-H), 4.05 (d, $^3J_{3,2}$ = 5.6 Hz, 2 H, 3-H), 5.20 (ddt, $^3J_{1a,2}$ = 10.4 Hz, $^2J_{1a,1b}$ = 2.9 Hz, $^4J_{1a,3}$ = 1.3 Hz, 1 H, 1-H_a), 5.28 (ddt, $^3J_{1b,2}$ = 17.2 Hz, $^2J_{1b,1a}$ = 3.3 Hz, $^4J_{1b,3}$ = 1.6 Hz, 1 H, 1-H_b), 5.90 (dddd, $^3J_{2,1b}$ = 17.3 Hz, $^3J_{2,1a}$ = 10.5 Hz, $^3J_{2,3a}$ = 5.8 Hz, $^3J_{2,3b}$ = 5.5 Hz, 1 H, 2-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 6.3 (t, C-7), 27.3 (q, C-9), 27.3 (q, C-9'), 70.6 (t, C-4), 72.6 (t, C-3), 77.6 (d, C-6), 80.1 (d, C-5), 109.8 (s, C-8), 117.4 (t, C-1), 134.3 (d, C-2).

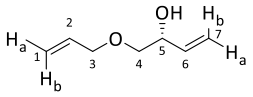
HRMS (CI):	calculated	found
$C_{10}H_{18}IO_3$ $[M+H]^+$	313.0295	313.0312

Optical rotation: $[\alpha]_D^{20}$ = –11.6° (c = 1.0, $CHCl_3$)

(*R*)-1-(Allyloxy)but-3-en-2-ol (25)

A solution of 10.5 g (33.6 mmol) **5d** in 135 mL THF abs. was treated with 8.78 g (134 mmol) zinc dust and 9.60 mL (10.1 g, 168 mmol) acetic acid at rt and the reaction was stirred for 3 h. The reaction mixture was filtrated through a pad of Celite® and washed with Et_2O. The filtrate was concentrated *in vacuo* and the residue was dissolved in Et_2O. Sat. $NaHCO_3$ sol. was added and the layers were separated. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 80:20, 70:30) gave 3.76 g (29.3 mmol, *er* > 99:1, 87 %) allylic alcohol **25** as a slightly yellow liquid.

R_f (25) = 0.21 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.65 (br s, 1 H, OH), 3.34 (dd, $^2J_{4a,4b}$ = 9.7 Hz, $^3J_{4a,5}$ = 7.9 Hz, 1 H, 4-H_a), 3.51 (dd, $^2J_{4b,4a}$ = 9.7 Hz, $^3J_{4b,5}$ = 3.4 Hz, 1 H, 4-H_b), 4.04 (ddd, $^3J_{3,2}$ = 5.8 Hz, $^4J_{3,1a} \approx {}^4J_{3,1b}$ = 1.3 Hz, 2 H, 3-H), 4.33 (m, 1 H, 5-H), 5.20 (m, 2 H, 1-H_a, 7-H_a), 5.28 (ddt, $^3J_{1b,2}$ = 17.3 Hz, $^2J_{1b,1a}$ = 1.8 Hz, $^4J_{1b,3}$ = 1.5 Hz, 1 H, 1-H_b), 5.36 (ddd, $^3J_{7b,6}$ = 17.3 Hz, $^2J_{7b,7a} \approx {}^4J_{7b,5}$ = 1.5 Hz, 1 H, 7-H_b), 5.84 (ddd, $^3J_{6,7b}$ = 17.2 Hz, $^3J_{6,7a}$ = 10.5 Hz, $^3J_{6,5}$ = 5.5 Hz, 1 H, 6-H), 5.91 (dddd, $^3J_{2,1b}$ = 17.3 Hz, $^3J_{2,1a}$ = 10.5 Hz, $^3J_{2,3a}$ = 5.8 Hz, $^3J_{2,3b}$ = 5.5 Hz, 1 H, 2-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 71.5 (d, C-5), 72.2 (t, C-3), 73.9 (t, C-4), 116.4 (t, C-7), 117.4 (t, C-1), 134.3 (d, C-2), 136.5 (d, C-6).

HRMS (CI):	calculated	found
$C_7H_{13}O_2$ $[M+H]^+$	129.0910	129.0908

Optical rotation: $[\propto]_D^{20}$ = –1.6° (c = 1.0, $CHCl_3$)

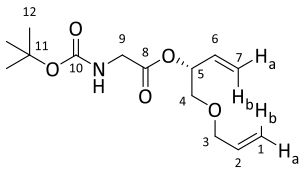
GC: CP-Chirasil-Dex CB, column flow 1.25 mL/min, injector 250 °C; 60 °C (5 min), 80 °C (1 °C/min), 5 min, 170 °C (6 °C/min), 10 min:

(*R*)-**25**: t_R = 31.51 min (> 99 %).

(*R*)-1-(Allyloxy)but-3-en-2-yl (*tert*-butoxycarbonyl)glycinate (26)

990 mg (5.65 mmol) Boc-Gly-OH and 658 mg (5.13 mmol) **25** were dissolved in 20.0 mL DCM abs. before 62.4 mg (0.511 mmol) 4-DMAP and 1.18 g (6.16 mmol) EDC·HCl were added at 0 °C. The reaction was stirred at this temperature for 1 h and afterwards at rt for 30 min. For workup, the reaction was diluted with DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol., dried over Na_2SO_4 and concentrated *in vacuo*. 1.42 g (4.98 mmol, 97 %) of ester **26** were obtained as a colourless oil.

R_f (26) = 0.43 (silica gel, PE:EA 60:40)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 12-H), 3.55 (m, 2 H, 4-H), 3.96 (d, $^3J_{9,NH}$ = 5.3 Hz, 2 H, 9-H), 4.01 (m, 2 H, 3-H), 5.00 (br s, 1 H, NH), 5.19 (ddt, $^3J_{1a,2}$ = 10.5 Hz, $^2J_{1a,1b}$ = 1.5 Hz, $^4J_{1a,3}$ = 1.3 Hz, 1 H, 1-H_a), 5.27 (m, 2 H, 1-H_b, 7-H_a), 5.34 (ddd, $^3J_{7b,6}$ = 17.3 Hz, $^2J_{7b,7a} \approx {}^4J_{7b,5}$ = 1.3 Hz, 1 H, 7-H_b), 5.50 (dt, $^3J_{5,6}$ = 6.0 Hz, $^3J_{5,4}$ = 5.0 Hz, 1 H, 5-H), 5.82 (ddd, $^3J_{6,7b}$ = 16.8 Hz, $^3J_{6,7a}$ = 10.5 Hz, $^3J_{6,5}$ = 6.3 Hz, 1 H, 6-H), 5.87 (ddt, $^3J_{2,1b}$ = 17.3 Hz, $^3J_{2,1a}$ = 10.3 Hz, $^3J_{2,3}$ = 5.5 Hz, 1 H, 2-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.3 (q, C-12), 42.5 (t, C-9), 71.0 (t, C-4), 72.2 (t, C-3), 74.3 (d, C-5), 79.9 (s, C-11), 117.4 (t, C-1), 118.6 (t, C-7), 132.7 (d, C-6), 134.3 (d, C-2), 155.6 (s, C-10), 169.6 (s, C-8).

HRMS (CI):	calculated	found
$C_{14}H_{24}NO_5$ $[M+H]^+$	286.1649	286.1652

Optical rotation: $[\alpha]_D^{20}$ = –3.8° (c = 1.0, $CHCl_3$)

GC: CP-Chirasil-Dex CB, column flow 1.50 mL/min, injector 250 °C; 130 °C, 175 °C (1 °C/min), 200 °C (5 °C/min), 10 min:

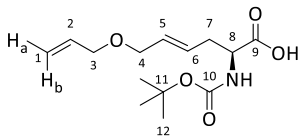
(*R*)-**26**: t_R = 39.27 min (> 99 %).

(*S*,*E*)-6-(Allyloxy)-2-((*tert*-butoxycarbonyl)amino)hex-4-enoic acid (27)

1.00 mL (710 mg, 7.02 mmol) Di-*iso*-propylamine was dissolved in 7.0 mL THF abs. and cooled to –78 °C before 4.00 mL (6.4 mmol) *n*-BuLi (1.6 M in hexanes) were added dropwise. The cooling bath was removed and the LDA solution was stirred at rt for 15 min.

A solution of 571 mg (2.00 mmol) **26** in 10.0 mL THF abs. was added to 330 mg (2.42 mmol) zinc chloride (dried *in high-vacuo*) and the mixture was cooled to –78 °C. The freshly prepared LDA solution was added slowly to the amino acid ester/ zinc chloride solution at –78 °C. After complete addition, the remaining dry ice was removed from the cooling bath and the reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with Et_2O and 1 M $KHSO_4$ sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. 569 mg (1.99 mmol, *er* > 99:1, 99 %) of acid **27** were obtained as a yellow oil.

R_f (27) = 0.07 (silica gel, PE:EA 60:40)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, 12-H), 2.57 (m, 2 H, 7-H), 3.95 – 3.98 (m, 4 H, 3-H, 4-H), 4.39 (m, 1 H, 8-H), 5.05 (d, $^3J_{NH,8}$ = 7.1 Hz, 1 H, NH), 5.18 (d, $^3J_{1a,2}$ = 10.3 Hz, 1 H, 1-H_a), 5.27 (dd, $^3J_{1b,2}$ = 17.3 Hz, $^2J_{1b,1a}$ = 1.6 Hz, 1 H, 1-H_b), 5.59 – 5.74 (m, 2 H, 5-H, 6-H), 5.90 (ddt, $^3J_{2,1b}$ = 17.1 Hz, $^3J_{2,1a}$ = 10.4 Hz, $^3J_{2,3}$ = 5.8 Hz, 1 H, 2 H), 9.33 (br s, 1 H, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.3 (q, C-12), 34.9 (t, C-7), 52.8 (d, C-8), 70.2 (t, C-3 o. C-4), 71.0 (d, C-3 o. C-4), 80.4 (s, C-11), 117.3 (t, C-1), 127.3 (t, C-6), 131.1 (d, C-7), 134.5 (d, C-2), 155.6 (s, C-10), 175.7 (s, C-9).

HRMS (CI):	calculated	found
$C_{14}H_{24}NO_5$ $[M+H]^+$	286.1649	286.1654

Optical rotation: $[\propto]_D^{20}$ = +26.4° (c = 1.0, $CHCl_3$)

GC: A small amount was derivatized using TMS-diazomethane for GC-analysis. CP-Chirasil-Dex CB, column flow 1.50 mL/min, injector 250 °C; 145 °C, 5 min, 180 °C (1 °C/min), 15 min, 200 °C (20 °C/min), 5 min:

t_{R1} = 28.2 min (< 1 %),

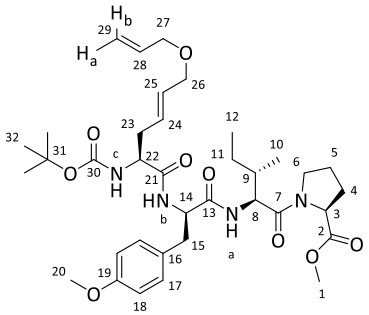
t_{R2} = 28.95 min (> 99 %),

t_{R3} = 29.55 min (< 1 %).

Methyl ((*R*)-2-((*S*,*E*)-6-(allyloxy)-2-((tert-butoxycarbonyl)amino)hex-4-enamido)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl-L-prolinate (28)

To a solution of 137 mg (0.480 mmol) **27** in 10.0 mL THF abs. were added 0.06 mL (55 mg, 0.544 mmol) NMM and 0.07 mL (73 mg, 0.535 mmol) IBCF at –20 °C. After stirring for 10 min at this temperature, 195 mg (0.465 mmol) **12a**,dissolved in 2.0 mL THF abs., were added dropwise and the reaction was allowed to warm to rt overnight. The reaction mixture was then filtrated and washed with diethyl ether. The filtrate was concentrated *in vacuo*, the residue was redissolved in EA and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with EA. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 70:30, 50:50) gave 228 mg (0.332 mmol, *dr* > 99:1, 71 %) of tetrapeptide **28** as an off-white solid.

R_f (28) = 0.06 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.76 – 0.87 (m, 4 H, 11-H_a, 12-H), 0.90 (d, $^3J_{10,9}$ = 6.7 Hz, 3 H, 10-H), 1.30 (m, 1 H, 11-H_b), 1.42 (s, 9 H, 32-H), 1.68 (m, 1 H, 9-H), 1.91 – 2.05 (m, 3 H, 4-H_a, 5-H), 2.22 (m, 1 H, 4-H_b), 2.35 (ddd, $^2J_{23a,23b}$ = 14.1 Hz, $^3J_{23a,22} \approx {}^3J_{23a,24}$ = 7.0 Hz, 1 H, 23-H_a), 2.49 (ddd, $^2J_{23b,23a}$ = 13.6 Hz, $^3J_{23b,22} \approx {}^3J_{23b,24}$ = 6.5 Hz, 1 H, 23-H_b), 2.94 (dd, $^2J_{15a,15b}$ = 14.1 Hz, $^3J_{15a,14}$ = 8.0 Hz, 1 H, 15-H_a), 3.00 (dd, $^2J_{15b,15a}$ = 13.9 Hz, $^3J_{15b,14}$ = 6.4 Hz, 1 H, 15-H_b), 3.63 (m, 1 H, 6-H_a), 3.69 (s, 3 H, 1-H), 3.75 (s, 3 H, 20-H), 3.82 (m, 1 H, 6-H_b), 3.90 (d, $^3J_{26,25}$ = 5.4 Hz, 2 H, 26-H), 3.92 (d, $^3J_{27,28}$ = 5.6 Hz, 2 H, 27-H), 4.12 (br s, 1 H, 22-H), 4.46 – 4.53 (m, 2 H, 3-H, 8-H),

4.66 (dt, $^3J_{14,15} \approx {}^3J_{14,NH}$ = 7.3 Hz, 1 H, 14-H), 5.13 (m, 1 H, NH_c), 5.15 (dd, $^3J_{29a,28}$ = 10.5 Hz, $^2J_{29a,29b}$ = 1.0 Hz, 1 H, 29-H_a), 5.25 (dd, $^3J_{29b,28}$ = 17.2 Hz, $^2J_{29b,29a}$ = 1.5 Hz, 1 H, 29-H_b), 5.54 (dt, $^3J_{24,25}$ = 14.7 Hz, $^3J_{24,23}$ = 7.4 Hz, 1 H, 24-H), 5.62 (dt, $^3J_{25,24}$ = 15.5 Hz, $^3J_{25,26}$ = 5.6 Hz, 1 H, 25-H), 5.88 (ddd, $^3J_{28,29b}$ = 16.1 Hz, $^3J_{28,29a}$ = 10.8 Hz, $^3J_{28,27}$ = 5.7 Hz, 1 H, 28-H), 6.52 (br s, 1 H, NH_a), 6.65 (d, $^3J_{NH,14}$ = 7.8 Hz, 1 H, NH_b), 6.83 (d, $^3J_{18,17}$ = 8.6 Hz, 2 H, 18-H), 7.10 (d, $^3J_{17,18}$ = 8.4 Hz, 2 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.0 (q, C-12), 15.0 (q, C-10), 24.1 (t, C-11), 24.9 (t, C-5), 28.3 (q, C-32), 29.0 (t, C-4), 35.5 (t, C-23), 37.5 (d, C-9), 37.8 (t, C-15), 47.3 (t, C-6), 52.1 (q, C-1), 53.8 (d, C-22), 54.4 (d, C-14), 55.0 (d, C-3 o. C-8), 55.1 (q, C-20), 58.8 (d, C-3 o. C-8), 70.3 (t, C-26), 70.9 (t, C-27), 80.0 (s, C-31), 114.0 (d, C-18), 117.0 (t, C-29), 128.2 (d, C-24), 128.3 (s, C-16), 130.2 (d, C-17), 130.8 (d, C-25), 134.7 (d, C-28), 158.6 (s, C-19), 170.3 (s, C-7), 170.4 (s, C-13), 171.0 (s, C-21), 172.3 (s, C-2). The signal of C-30 wasn't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{36}H_{55}N_4O_9$ $[M+H]^+$	687.3964	687.3971

Melting point: 92 °C

Optical rotation: $[\propto]_D^{20}$ = –26.9° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 70:30, 1 mL/min, 20 °C:

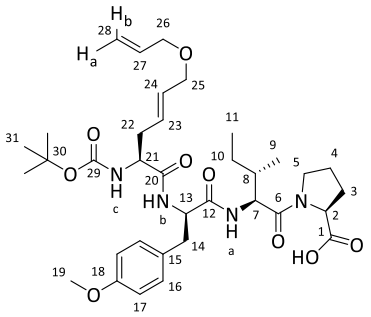
t_R = 33.3 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 11.0 min ($[M+Na]^+$ = 710).

((*R*)-2-((*S*,*E*)-6-(Allyloxy)-2-((*tert*-butoxycarbonyl)amino)hex-4-enamido)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl-L-proline (29)

192 mg (0.280 mmol) **28** were dissolved in 2.5 mL dioxane and cooled to 0 °C before a solution of 19 mg (0.444 mmol) LiOH·H_2O in 0.5 mL water was added. The cooling bath was removed and the reaction was stirred at rt for 3 h. For workup, the reaction mixture was concentrated *in vacuo* and the residue was redissolved in water. The aqueous phase was acidified with 1 M HCl sol. and the aqueous phase was extracted three times with EA. The combined organic phases were dried over Na_2SO_4 and the crude product was dried by lyophilisation to afford 185 mg (0.275 mmol, 98 %) of compound **29** as an off-white solid.

R_f (29) = 0.08 (silica gel, PE:EA 50:50 + 1 % HOAc)



Major rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, $^3J_{11,10}$ = 7.1 Hz, 3 H, 11-H), 0.88 (m, 1 H, 10-H_a), 0.92 (d, $^3J_{9,8}$ = 6.5 Hz, 3 H, 9-H), 1.26 (m, 1 H, 10-H_b), 1.41 (s, 9 H, 31-H), 1.72 (m, 1 H, 8-H), 2.01 (m, 1 H, 4-H_a), 2.08 – 2.26 (m, 3 H, 3-H, 4-H_b), 2.33 (ddd, $^2J_{22a,22b}$ = 14.0 Hz, $^3J_{22a,21} \approx {}^3J_{22a,23}$ = 7.0 Hz, 1 H, 22-H_a), 2.46 (m, 1 H, 22-H_b), 2.91 (m, 1 H, 14-H_a), 3.07 (m, 1 H, 14-H_b), 3.69 (m, 1 H, 5-H_a), 3.74 (s, 3 H, 19-H), 3.90 (m, 1 H, 5-H_b), 3.90 (d, $^3J_{25,24}$ = 5.1Hz, 2 H, 25-H), 3.94 (d, $^3J_{26,27}$ = 5.6 Hz, 2 H, 26-H), 4.20 (br s, 1 H, 21-H), 4.46 (m, 1 H, 2-H), 4.51 (dd, $^3J_{7,8} \approx {}^3J_{7,NH}$ = 8.7 Hz, 1 H, 7-H), 4.83 (dt, $^3J_{13,14} \approx {}^3J_{13,NH}$ = 6.6 Hz, 1 H, 13-H), 5.16 (m, 1 H, NH_c), 5.16 (d, $^3J_{28a,27}$ = 10.2 Hz, 1 H, 28-H_a), 5.25 (dd, $^3J_{28b,27}$ = 17.2 Hz, $^2J_{28b,28a}$ = 1.5 Hz, 1 H, 28-H_b), 5.45 – 5.67 (m, 2 H, 23-H, 24-H), 5.88 (ddd, $^3J_{27,28b}$ = 16.0 Hz, $^3J_{27,28a}$ = 10.8 Hz, $^3J_{27,26}$ = 5.6 Hz, 1 H, 27-H), 6.77 (d, $^3J_{17,16}$ = 8.6 Hz, 2 H, 17-H), 6.96 (d, $^3J_{NH,13}$ = 7.3 Hz, 1 H, NH_b), 7.08 (d, $^3J_{16,17}$ = 8.0 Hz, 2 H, 16-H), 7.81 (br s, 1 H, NH_a). The signal of -COOH wasn't observed in the ^{1}H-NMR spectrum.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.8 (q, C-11), 14.9 (q, C-9), 24.4 (t, C-10), 25.1 (t, C-4), 28.3 (q, C-31), 28.7 (t, C-3), 35.7 (t, C-22), 37.4 (d, C-8), 37.7 (t, C-14), 47.9 (t, C-5), 53.7 (d, C-21), 53.9 (d, C-13), 55.0 (d, C-7), 55.1 (q, C-19), 59.6 (d, C-2), 70.3 (t, C-25), 71.0 (t, C-26), 80.1 (s, C-30), 113.8 (d, C-17), 117.2 (t, C-28), 128.1 (d, C-23), 130.3 (s, C-15), 130.5 (d, C-16), 130.7 (d, C-24), 134.6 (d, C-27), 155.5 (s, C-29), 158.5 (s, C-18), 171.5 (s, C-1 o. C-6 o. C-12 o. C-20), 173.2 (s, C-1 o. C-6 o. C-12 o. C-20). The signal of C-1/C-6/C-12/C-20 wasn't observed in the ^{13}C-NMR spectrum.

Minor rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, 31-H), 3.78 (s, 3 H, 19-H), 7.12 (d, $^3J_{16,17}$ = 8.6 Hz, 2 H, 16-H).

HRMS (CI):	calculated	found
$C_{35}H_{53}N_4O_9$ $[M+H]^+$	673.3807	673.3809

Melting point: 82 °C

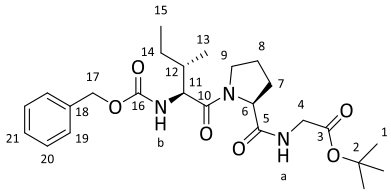
Optical rotation: $[\propto]_D^{20}$ = –30.9° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.6 mL/min, t_R = 17.8 min ($[M+Na]^+$ = 695).

Cbz-(*S*,*S*)-Ile-(*S*)-Pro-Gly-O*t*Bu (30)

275 mg (1.04 mmol) Cbz-(*S*,*S*)-Ile-OH were dissolved in 10.0 mL acetonitrile abs. and 333 mg (1.04 mmol) TBTU, 168 mg (1.10 mmol) HOBt and 0.23 mL (170 mg, 1.32 mmol) DIPEA were added at rt. Afterwards, a solution of 240 mg (1.05 mmol) H-(*S*)-Pro-Gly-O*t*Bu in 2.0 mL acetonitrile abs. was added dropwise and the reaction was stirred overnight. The reaction mixture was diluted with Et_2O and 1 M $KHSO_4$ sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 70:30, 50:50) yielded 437 mg (0.919 mmol, *dr* > 99:1, 88 %) tripeptide **30** as a colourless oil.

R_f (30) = 0.13 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{15,14}$ = 7.4 Hz, 3 H, 15-H), 0.97 (d, $^3J_{13,12}$ = 6.8 Hz, 3 H, 13-H), 1.14 (m, 1 H, 14-H_a), 1.45 (s, 9 H, 1-H), 1.60 (m, 1 H, 14-H_b), 1.78 (m, 1 H, 12-H), 1.87 – 2.03 (m, 2 H, 7-H_a, 8-H_a), 2.11 (m, 1 H, 8-H_b), 2.37 (m, 1 H, 7-H_b), 3.63 (dt, $^2J_{9a,9b}$ = 8.7 Hz, $^3J_{9a,8}$ = 3.8 Hz, 1 H, 9-H_a), 3.76 (dt, $^2J_{9b,9a} \approx {}^3J_{9b,8}$ = 8.3 Hz, 1 H, 9-H_b), 3.85 (dd, $^2J_{4a,4b}$ = 18.6 Hz, $^3J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 3.91 (dd, $^2J_{4b,4a}$ = 18.6 Hz, $^3J_{4b,NH}$ = 5.5 Hz, 1 H, 4-H_b), 4.37 (dd, $^3J_{11,NH}$ = 9.2 Hz, $^3J_{11,12}$ = 7.4 Hz, 1 H, 11-H), 4.63 (dd, $^3J_{6,7a}$ = 7.9 Hz, $^3J_{6,7b}$ = 2.6 Hz, 1 H, 6-H), 5.06 (d, $^2J_{17a,17b}$ = 12.3 Hz, 1 H, 17-H_a), 5.11 (d, $^2J_{17b,17a}$ = 12.3 Hz, 1 H, 17-H_b), 5.44 (d, $^3J_{NH,11}$ = 9.3 Hz, 1 H, NH_b), 7.14 (dd, $^3J_{NH,4a} \approx {}^3J_{NH,4b}$ = 4.6 Hz, 1 H, NH_a), 7.29 – 7.38 (m, 5 H, 19-H, 20-H, 21-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.1 (q, C-15), 15.4 (q, C-13), 24.2 (t, C-14), 25.0 (t, C-8), 27.2 (t, C-7), 28.0 (q, C-1), 37.9 (d, C-12), 42.1 (t, C-4), 47.7 (t, C-9), 56.8 (d, C-11), 59.7 (d, C-6), 66.9 (t, C-17), 82.0 (s, C-2), 128.0 (d, C-19), 128.1 (d, C-21), 128.5 (d, C-20), 136.3 (s, C-18), 156.3 (s, C-16), 168.5 (s, C-3), 170.9 (s, C-5 o. C-10), 172.4 (s, C-5 o. C-10).

HRMS (CI):	calculated	found
$C_{25}H_{38}N_3O_6$ $[M+H]^+$	476.2755	476.2752

Optical rotation: $[\alpha]_D^{20}$ = –77.1° (c = 1.0, $CHCl_3$)

HPLC: Chiralcel OD-H, *n*-hexane:*i*PrOH 80:20, 1 mL/min, 20 °C:

t_R = 10.8 min (> 99 %).

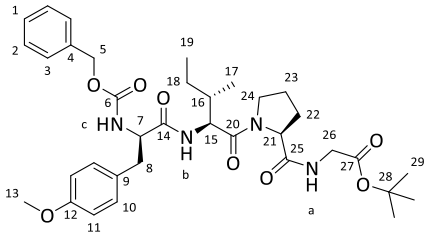
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 5.17 min ($[M+Na]^+$ = 498).

Cbz-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-Gly-O*t*Bu (31)

1.56 g (3.28 mmol) **30** were dissolved in 33 mL MeOH and treated with 153 mg palladium on charcoal (10 w% Pd) at rt. The reaction was set under a H_2-atmossphere and hydrogenated overnight. The reaction mixture was filtrated through a pad of Celite® and the filtrate was concentrated *in vacuo*.

To a solution of 961 mg (2.92 mmol) Cbz-(*R*)-Tyr(Me)-OH in 29 mL THF abs. were added 0.35 mL (322 mg, 3.18 mmol) NMM and the reaction was cooled to –20 °C. 0.42 mL (440 mg, 3.22 mmol) IBCF were added dropwise and the reaction was stirred for 10 min at this temperature before 991 mg (2.90 mmol) of the above prepared H-(*S*,*S*)-Ile-(*S*)-Pro-Gly-O*t*Bu in 6 mL THF abs. were added slowly and the reaction was allowed to warm to rt overnight. The reaction mixture was filtrated and the filtrate was concentrated *in vacuo*. The residue was redissolved in EA and water was added. The layers were separated and the aqueous phase was extracted three times with EA. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 70:30, 50:50) gave 1.65 g (2.53 mmol, *dr* ~ 94:6, 87 %) of compound **31** as an off-white solid.

R_f (31) = 0.05 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.64 – 0.76 (m, 4 H, 19-H, 18-H_a), 0.88 (d, $^3J_{17,16}$ = 6.8 Hz, 3 H, 17-H), 0.97 (m, 1 H, 18-H_b), 1.43 (s, 9 H, 29-H), 1.59 (m, 1 H, 16-H), 1.94 – 2.06 (m, 2 H, 22-H_a, 23-H_a), 2.13 (m, 1 H, 23-H_b), 2.24 (m, 1 H, 22-H_b), 2.95 (m, 2 H, 8-H), 3.59 – 3.72 (m, 2 H, 24-H_a, 26-H_a), 3.74 (s, 3 H, 13-H), 3.87 (m, 1 H, 24-H_b), 4.01 (dd, $^2J_{26b,26a}$ = 18.2 Hz, $^3J_{26b,NH}$ = 5.6 Hz, 1 H, 26-H_b), 4.51 (dd, $^3J_{15,16} \approx {}^3J_{15,NH}$ = 8.8 Hz, 1 H, 15-H), 4.66 – 4.75 (m, 2 H, 7-H, 21-H), 5.08 (m, 2 H, 5-H), 5.50 (d, $^3J_{NH,7}$ = 7.5 Hz, 1 H, NH_c), 6.75 (d, $^3J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.06 (d, $^3J_{10,11}$ = 8.3 Hz, 2 H, 10-H), 7.28 – 7.38 (m, 6 H, 1-H, 2-H, 3-H, NH_b), 7.53 (br s, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-19), 15.2 (q, C-17), 23.9 (t, C-18), 24.7 (t, C-23), 28.0 (q, C-29), 28.4 (t, C-22), 37.4 (d, C-16), 38.8 (t, C-8), 42.0 (t, C-26), 47.9 (t, C-24), 54.8 (d, C-15), 55.1 (q, C-13), 55.6 (d, C-7), 59.6 (d, C-21), 67.0 (t, C-5), 81.9 (s, C-28), 113.9 (d, C-11), 128.1 (s, C-9), 128.1 (d, C-1), 128.1 (d, C-3), 128.5 (d, C-2), 130.2 (d, C-10), 136.2 (s, C-4), 155.7 (s, C-6), 158.5 (s, C-12), 168.7 (s, C-27). The signals of C-14, C-20 and C-25 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, $^{3}J_{17,16}$ = 6.8 Hz, 3 H, 17-H), 1.44 (s, 9 H, 29-H), 3.77 (s, 3 H, 13-H), 5.31 (d, $^{3}J_{NH,7}$ = 7.8 Hz, 1 H, NH_c).

HRMS (CI):	calculated	found
$C_{35}H_{49}N_4O_8$ $[M+H]^+$	653.3545	653.3559

Melting point: 68 °C

Optical rotation: $[\alpha]_D^{20}$ = –68.0° (c = 1.0, $CHCl_3$)

HPLC: Chiralcel OD-H, *n*-hexane:*i*PrOH 80:20, 1 mL/min, 20 °C:

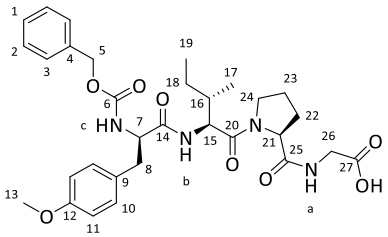
t_R = 10.7 min (> 99 %, broad).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 8.53 min ($[M+Na]^+$ = 676).

Cbz-(*R*)-Tyr(Me)-(*S*,*S*)-Ile-(*S*)-Pro-Gly-OH (32)

A solution of 652 mg (0.999 mmol) **31** in 5.0 mL DCM abs. was treated with 5.0 mL (7.40 g, 64.9 mmol) Trifluoroacetic acid at rt. The reaction was stirred for 1 h, concentrated *in vacuo* and dried by lyophilisation. 592 mg (0.993 mmol, 99 %) of acid **32** were obtained as an off-white solid.

R_f (32) = 0.04 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, $^{3}J_{19,18}$ = 7.2 Hz, 3 H, 19-H), 0.78 – 0.94 (m, 1 H, 18-H_a), 0.84 (d, $^{3}J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 1.23 (m, 1 H, 18-H_b), 1.65 (m, 1 H, 16-H), 1.96 – 2.07 (m, 2 H, 22-H_a, 23-H_a), 2.10 – 2.28 (m, 2 H, 22-H_b, 23-H_b), 2.96 (m, 2 H, 8-H), 3.65 (m, 1 H, 24-H_a), 3.76 (s, 3 H, 13-H), 3.87 (dd, $^{2}J_{26a,26b}$ = 18.6 Hz, $^{3}J_{26a,NH}$ = 4.0 Hz, 1 H, 26-H_a), 3.97 (m, 1 H, 24-H_b), 4.16 (dd, $^{2}J_{26b,26a}$ = 18.4 Hz, $^{3}J_{26b,NH}$ = 5.9 Hz, 1 H, 26-H_b), 4.39 – 4.55 (m, 2 H, 7-H, 21-H), 4.46 (dd, $^{3}J_{15,16} \approx {}^{3}J_{15,NH}$ = 9.3 Hz, 1 H, 15-H), 5.01 (d, $^{2}J_{5a,5b}$ = 12.1 Hz, 1 H, 5-H_a), 5.06 (d,

$^{2}J_{5b,5a}$ = 12.6 Hz, 1 H, 5-H_b), 5.56 (d, $^{3}J_{NH,7}$ = 8.5 Hz, 1 H, NH_c), 6.78 (d, $^{3}J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.07 (d, $^{3}J_{10,11}$ = 8.3 Hz, 2 H, 10-H), 7.20 – 7.35 (m, 6 H, 1-H, 2-H, 3-H, NH_b), 7.99 (d, $^{3}J_{NH,26a/b}$ = 8.3 Hz, 1 H, NH_a), 9.47 (br s, 1 H, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.6 (q, C-19), 14.7 (q, C-17), 24.6 (t, C-18), 25.0 (t, C-23), 27.9 (t, C-22), 37.0 (d, C-16), 38.2 (t, C-8), 41.8 (t, C-26), 48.4 (t, C-24), 55.2 (d, q, C-15, C-13), 55.9 (d, C-7), 60.4 (d, C-21), 66.9 (t, C-5), 114.0 (d, C-11), 127.8 (s, C-9), 127.9 (d, C-1), 128.1 (d, C-3), 128.5 (d, C-2), 130.3 (d, C-10), 136.2 (s, C-4), 155.8 (s, C-6), 158.5 (s, C-12), 170.9 (s, C-14 o. C-20 o. C-25), 172.2 (s, C-14 o. C-20 o. C-25), 172,6 (s, C-14 o. C-20 o. C-25). The signal of C-27 wasn't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{31}H_{41}N_4O_8$ $[M+H]^+$	597.2919	597.2947

Melting point: 81 °C

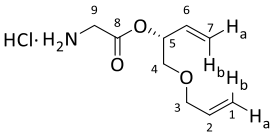
Optical rotation: $[\alpha]_D^{20}$ = –39.8° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 2.79 min ($[M+Na]^+$ = 619).

(*R*)-1-(Allyloxy)but-3-en-2-yl glycinate hydrochloride (33)

To a solution of 2.1 mL (1.66 g, 51.8 mmol) methanol in 8.8 mL ethyl acetate were added 3.6 mL (3.96 g, 50.4 mmol) acetyl chloride at 0 °C and the reaction was stirred for 30 min. The resulting HCl sol. was then transferred to 1.47 g (5.16 mmol) **26** at rt and the reaction was stirred for 1 h. The reaction mixture was concentrated *in vacuo* and the crude product was dried by lyophilisation. 1.10 g (4.96 mmol, 96 %) of hydrochloride salt **33** were obtained as an off-white solid.

R_f (33) = starting point (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.56 (d, $^{3}J_{4,5}$ = 5.3 Hz, 2 H, 4-H), 4.00 (m, 4 H, 3-H, 9-H), 5.18 (dd, $^{3}J_{7a,6}$ = 10.3 Hz, $^{2}J_{7a,7b}$ = 1.3 Hz, 1 H, 7-H_a), 5.26 (m, 2 H, 1-H_a, 1-H_b), 5.39 (d, $^{3}J_{7b,6}$ = 17.3 Hz, 1 H, 7-H_b), 5.52 (dt, $^{3}J_{5,6}$ = 5.5 Hz, $^{3}J_{5,4}$ = 5.5 Hz, 1 H, 5-H), 5.82 (ddd, $^{3}J_{6,7b}$ = 17.1 Hz, $^{3}J_{6,7a}$ = 10.8 Hz, $^{3}J_{6,5}$ = 6.3 Hz, 1 H, 6-H), 5.86 (ddt, $^{3}J_{2,1b}$ = 17.3 Hz, $^{3}J_{2,1a}$ = 10.8 Hz, $^{3}J_{2,3}$ = 5.5 Hz, 1 H, 2-H), 8.56 (br s, 3 H, NH_3).

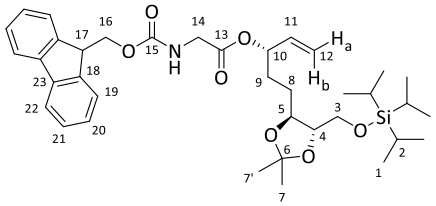
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 40.7 (t, C-9), 70.8 (t, C-4), 72.3 (t, C-3), 75.7 (d, C-5), 117.6 (t, C-1), 119.2 (t, C-7), 132.3 (d, C-6), 134.3 (d, C-2), 167.1 (s, C-8).

HRMS (CI):	calculated	found
$C_9H_{16}NO_3$ $[M+H]^+$	186.1125	186.1130
Melting point:	53 °C	
Optical rotation:	$[\alpha]_D^{20}$ = –6.5° (c = 1.0, $CHCl_3$)	

(*S*)-5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl (((9H-fluoren-9-yl)methoxy)carbonyl)glycinate (34)

A mixture of 187 mg (0.629 mmol) Fmoc-Gly-OH and 213 mg (0.572 mmol) (3*S*)-**7c** in 6.0 mL DCM abs. was cooled to 0 °C before 136 mg (0.659 mmol) DCC and 7.9 mg (64.7 µmol) 4-DMAP were added. The reaction was allowed to warm to rt overnight. Afterwards, further 68 mg (0.229 mmol) Fmoc-Gly-OH and 48 mg (0.233 mmol) DCC were added and stirring was continued for 4.5 h. For workup, the reaction was filtrated through a pad of Celite® and washed with DCM. The filtrate was treated with water and the layers were separated. The aqueous phase was extracted three times with DCM, the combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20) to yield 346 mg (0.531 mmol, 93 %) of ester **34** as a colourless oil.

R_f (34) = 0.17 (silica gel, PE:EA 80:20)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.17 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.60 (m, 1 H, 8-H_a), 1.69 – 1.77 (m, 2 H, 8-H_b, 9-H_a), 1.93 (m, 1 H, 9-H_b), 3.67 – 3.75 (m, 2 H, 3-H_a, 4-H), 3.89 (dd, $^2J_{3b,3a}$ = 9.5 Hz, $^3J_{3b,4}$ = 3.3 Hz, 1 H, 3-H_b), 3.93 (td, $^3J_{5,8}$ = 7.7 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H), 4.00 (d, $^3J_{14,NH}$ = 5.3 Hz, 2 H, 14-H), 4.24 (t, $^3J_{17,16}$ = 7.0 Hz, 1 H, 17-H), 4.40 (d, $^3J_{16,17}$ = 7.3 Hz, 2 H, 16-H), 5.21 (d, $^3J_{12a,11}$ = 10.3 Hz, 1 H, 12-H_a), 5.28 (d, $^3J_{12b,11}$ = 17.3 Hz, 1 H, 12-H_b), 5.28 (m, 1 H, NH), 5.34 (td, $^3J_{10,9} \approx {}^3J_{10,11}$ = 6.5 Hz, 1 H, 10-H), 5.77 (ddd, $^3J_{11,12b}$ = 17.3 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.8 Hz, 1 H, 11-H), 7.31 (ddd, $^3J_{21,20} \approx {}^3J_{21,22}$ = 7.5 Hz, $^4J_{21,19}$ = 0.9 Hz, 2 H, 21-H), 7.40 (dd, $^3J_{20,19}$ = 7.5 Hz, $^3J_{20,21}$ = 7.3 Hz, 2 H, 20-H), 7.60 (d, $^3J_{22,21}$ = 7.3 Hz, 2 H, 22-H), 7.77 (d, $^3J_{19,20}$ = 7.5 Hz, 2 H, 19-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 18.0 (q, C-1), 26.9 (q, C-7), 27.4 (q, C-7'), 28.9 (t, C-8), 30.6 (t, C-9), 42.9 (t, C-14), 47.1 (d, C-17), 64.2 (t, C-3), 67.2 (t, C-16), 76.2 (d, C-10), 79.1 (d, C-5), 80.7 (d, C-4), 108.6 (s, C-6), 117.9 (t, C-12), 120.0 (d, C-19), 125.1 (d, C-22), 127.1 (d, C-21), 127.7 (d, C-20), 135.5 (d, C-11), 141.3 (s, C-23), 143.8 (s, C-18). The signals of C-13 and C-15 weren't observed in the ^{13}C-NMR spectrum.

HRMS (CI): calculated found

$C_{37}H_{54}NO_7Si$ $[M+H]^+$ 652.3664 652.3668

Optical rotation: $[\propto]_D^{20}$ = –3.0° (c = 1.0, $CHCl_3$)

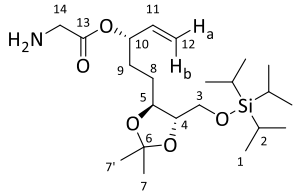
HPLC: Chiralcel OD-H, *n*-hexane:*i*PrOH 80:20, 0.8 mL/min, 20 °C:

(3*S*)-**34**: t_R = 25.8 min (> 99 %).

(*S*)-5-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl glycinate (35)

To a solution of 156 mg (0.239 mmol) **34** in 2.0 mL ethyl acetate was added 0.25 mL (245 mg, 1.68 mmol) Tris(2-aminoethyl)amine and the reaction was stirred at rt for 1 h. For workup, the reaction was diluted with EA and sat. $NaHCO_3$ sol. was added. The layers were separated, the organic phase was washed two times with sat. $NaHCO_3$ sol. and dried over Na_2SO_4.The crude product was purified by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) to yield 90.6 mg (0.211 mmol, 88 %) of amine **35** as a colourless oil.

R_f (35) = 0.18 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.14 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.50 (br s, 2 H, NH_2), 1.60 (m, 1 H, 8-H_a), 1.67 – 1.78 (m, 2 H, 8-H_b, 9-H_a), 1.89 (m, 1 H, 9-H_b), 3.41 (s, 2 H, 14-H), 3.66 – 3.74 (m, 2 H, 3-H_a, 4-H), 3.88 (dd, $^2J_{3b,3a}$ = 9.0 Hz, $^3J_{3b,4}$ = 3.0 Hz, 1 H, 3-H_b), 3.92 (td, $^3J_{5,8}$ = 7.6 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H), 5.18 (d, $^3J_{12a,11}$ = 10.5 Hz, 1 H, 12-H_a), 5.25 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a} \approx {}^4J_{12b,10}$ = 1.1 Hz, 1 H, 12-H_b), 5.31 (td, $^3J_{10,9} \approx {}^3J_{10,11}$ = 6.4 Hz, 1 H, 10-H), 5.76 (ddd, $^3J_{11,12b}$ = 17.2 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.5 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.3 (q, C-7'), 28.9 (t, C-8), 30.6 (t, C-9), 44.1 (t, C-14), 64.2 (t, C-3), 75.3 (d, C-10), 79.2 (d, C-5), 80.7 (d, C-4), 108.5 (s, C-6), 117.4 (t, C-12), 135.9 (d, C-11), 173.6 (s, C-13).

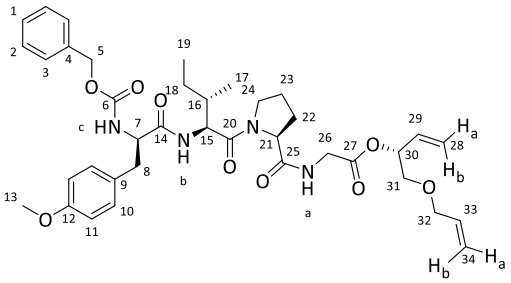
HRMS (CI): calculated found

$C_{22}H_{44}NO_5Si$ $[M+H]^+$ 430.2983 430.2980

(*R*)-1-(Allyloxy)but-3-en-2-yl ((*R*)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)-propanoyl)-L-isoleucyl-L-prolylglycinate (36a)

888 mg (1.65 mmol) **18a** and 332 mg (1.50 mmol) **33** were dissolved in 15.0 mL MeCN abs. before 528 mg (1.64 mmol) TBTU, 249 mg (1.63 mmol) HOBt and 588 µL (435 mg, 3.37 mmol) DIPEA were added subsequently at rt. The reaction was stirred at rt overnight and concentrated *in vacuo*. The residue was redissolved in DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine, sat. $NaHCO_3$ sol. and dried over Na_2SO_4. After purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50), 727 mg (1.03 mmol, *dr* ~ 90:10, 69 %) of tetrapeptide **36a** were obtained as an off-white solid.

R_f (36a) = 0.04 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.61 – 0.72 (m, 4 H, 18-H_a, 19-H), 0.80 – 0.97 (m, 1 H, 18-H_b), 0.88 (d, $^3J_{13,12}$ = 6.5 Hz, 3 H, 17-H), 1.57 (m, 1 H, 16-H), 1.92 – 2.07 (m, 2 H, 22-H_a, 23-H_a), 2.13 (m, 1 H, 23-H_b), 2.24 (m, 1 H, 22-H_b), 2.93 (m, 2 H, 8-H), 3.52 (d, $^3J_{31,30}$ = 5.3 Hz, 2 H, 31-H), 3.65 – 3.81 (m, 2 H, 24-H_a, 26-H_a), 3.74 (s, 3 H, 13-H), 3.87 (dt, $^2J_{24b,24a}$ = 9.5 Hz, $^3J_{24b,23}$ = 7.5 Hz, 1 H, 24-H_b), 3.98 (m, 2 H, 32-H), 4.18 (dd, $^2J_{26b,26a}$ = 18.4 Hz, $^3J_{26b,NH}$ = 5.6 Hz, 1 H, 26-H_b), 4.50 (dd, $^3J_{15,NH} \approx {}^3J_{15,16}$ = 9.0 Hz, 1 H, 15-H), 4.66 – 4.76 (m, 2 H, 7-H, 21-H), 5.08 (s, 2 H, 5-H), 5.17 (ddd, $^3J_{34a,33}$ = 10.5 Hz, $^2J_{34a,34b} \approx {}^4J_{34a,32}$ = 1.3 Hz, 1 H, 34-H_a), 5.20 – 5.33 (m, 3 H, 28-H, 34-H_b), 5.44 (dt, $^3J_{30,29} \approx {}^3J_{30,31}$ = 5.7 Hz, 1 H, 30-H), 5.48 (m, 1 H, NH_c), 5.74 – 5.90 (m, 2 H, 29-H, 33-H), 6.76 (d, $^3J_{11,10}$ = 8.8 Hz, 2 H, 11-H), 7.05 (d, $^3J_{10,11}$ = 8.3 Hz, 2 H, 10-H), 7.27 – 7.36 (m, 6 H, 1-H, 2-H, 3-H, NH_b), 7.67 (br s, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-19), 15.2 (q, C-17), 23.9 (t, C-18), 24.7 (t, C-23), 28.4 (t, C-22), 37.4 (d, C-16), 38.8 (t, C-8), 41.4 (t, C-26), 47.9 (t, C-24), 54.8 (d, C-15), 55.1 (q, C-13), 55.5 (d, C-7), 59.6 (d, C-21), 67.0 (t, C-5), 71.0 (t, C-31), 72.2 (t, C-32), 74.3 (d, C-30), 113.9 (d, C-11), 117.4 (t, C-34), 118.5 (t, C-28), 128.0 (s o. d, C-1 o. C-3 o. C-9), 128.1 (s o. d, C-1 o. C-3 o. C-9), 128.2 (s o. d, C-1 o. C-3 o. C-9), 128.5 (d, C-2), 130.2 (d, C-10), 132.8 (d, C-29), 134.3 (d, C-33), 136.2 (s, C-4), 155.7 (s, C-6), 158.5 (s, C-12), 168.8 (s, C-14 o. C-20 o. C-27). The signal of C-14/C-20/C-25/C-27 wasn't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

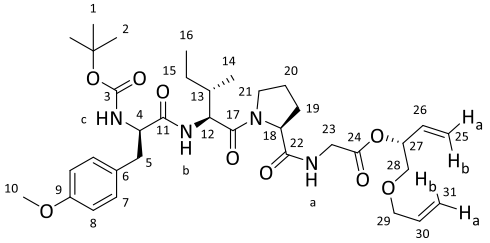
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, $^3J_{17,16}$ = 6.8 Hz, 3 H, 17-H), 6.80 (d, $^3J_{11,10}$ = 8.3 Hz, 2 H, 11-H).

HRMS (CI):	calculated	found
$C_{38}H_{51}N_4O_9$ $[M+H]^+$	707.3651	707.3642
Melting point:	47-48 °C	
Optical rotation:	$[\propto]_D^{20}$ = –64.7° (c = 0.5, $CHCl_3$)	

(*R*)-1-(Allyloxy)but-3-en-2-yl ((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-propanoyl)-L-isoleucyl-L-prolylglycinate (36c)

To a solution of 1.19 g (2.35 mmol) **18c** and 525 mg (2.37 mmol) **33** in 19 mL acetonitrile were added 757 mg (2.36 mmol) TBTU. Afterwards, 0.84 mL (622 mg, 4.81 mmol) DIPEA were added dropwise and the reaction was stirred at rt for 5 h. For workup, the reaction was concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM, the combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50) to give 1.24 g (1.84 mmol, *dr* > 99:1, 78 %) of tetrapeptide **36c** as an off-white solid.

R_f (36c) = 0.08 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.71 (m, 3 H, 16-H), 0.80 (m, 1 H, 15-H_a), 0.89 (d, $^3J_{14,13}$ = 6.4 Hz, 3 H, 14-H), 1.06 (m, 1 H, 15-H_b), 1.40 (s, 9 H, 1-H), 1.62 (m, 1H, 13-H), 1.99 (m, 2 H, 19-H_a, 20-H_a), 2.13 (m, 1 H, 20-H_b), 2.25 (m, 1 H, 19-H_b), 2.93 (m, 2 H, 5-H), 3.51 (d, $^3J_{28,27}$ = 5.5 Hz, 2 H, 28-H), 3.68 (m, 1 H, 21-H_a), 3.75 (s, 3 H, 10-H), 3.84 (m, 1 H, 23-H_a), 3.88 (m, 1 H, 21-H_b), 3.98 (m, 2 H, 29-H), 4.16 (dd, $^2J_{23b,23a}$ = 18.3 Hz, $^3J_{23b,NH}$ = 5.5 Hz, 1 H, 23-H_b), 4.51 (dd, $^3J_{12,13} \approx {}^3J_{12,NH}$ = 8.8 Hz, 1 H, 12-H), 4.63 (m, 1 H, 4-H), 4.68 (m, 1 H, 18-H), 5.14 (m, 1 H, NH_c), 5.22 (m, 4 H, 25-H, 31-H), 5.43 (dt, $^3J_{27,26}$ = 5.8 Hz, $^3J_{27,28}$ = 5.5 Hz, 1 H, 27-H), 5.82 (m, 2 H, 26-H, 30-H), 6.78 (d, $^3J_{8,7}$ = 8.5 Hz, 2 H, 8-H), 7.07 (d, $^3J_{7,8}$ = 8.5 Hz, 2 H, 7-H), 7.21 (m, 1 H, NH_b), 7.66 (m, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-16), 15.2 (q, C-14), 24.1 (t, C-15), 24.8 (t, C-20), 27.7 (t, C-19), 28.3 (q, C-1), 37.5 (d, C-13), 38.4 (t, C-5), 41.3 (t, C-23), 47.8 (t, C-21), 54.8 (d,

C-12), 55.1 (q, C-10), 55.2 (d, C-4), 59.6 (d, C-18), 71.0 (t, C-28), 72.2 (t, C-29), 74.3 (d, C-27), 80.1 (s, C-2), 113.9 (d, C-8), 117.4 (t, C-25 o. C-31), 118.5 (t, C-25 o. C-31), 130.2 (t, C-7), 132.7 (d, C-26 o. C-30), 134.2 (d, C-26 o. C-30), 155.2 (s, C-3 o. C-6), 158.5 (s, C-9), 168.8 (s, C-24), 171.1 (s, C-17 o. C-22), 171.5 (s, C-11), 171.8 (s, C-17 o. C-22).

HRMS (CI):	calculated	found
$C_{35}H_{53}N_4O_9$ $[M+H]^+$	673.3807	673.3814

Melting point: 53 °C

Optical rotation: $[\alpha]_D^{20}$ = –61.2° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 70:30, 1 mL/min, 20 °C:

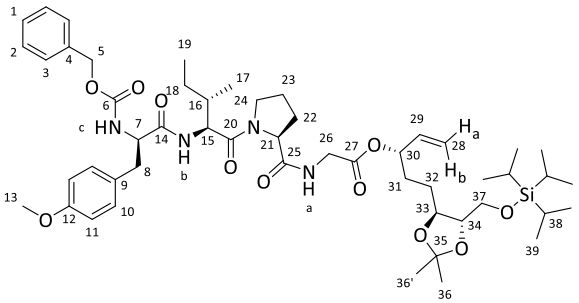
t_R = 27.7 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 9.67 min ($[M+H]^+$ = 673).

(*S*)-5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl ((*R*)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl-L-prolylglycinate (37)

A solution of 85.5 mg (0.158 mmol) **18a** in 1.5 mL MeCN abs. was treated with 61.9 mg (0.144 mmol) **35**, 51 mg (0.159 mmol) TBTU, 23 mg (0.150 mmol) HOBt and 31 µL (22.9 mg, 0.177 mmol) DIPEA subsequently at rt. The reaction was stirred overnight concentrated *in vacuo*. The residue was redissolved in DCM and water was added. The aqueous phase was extracted three times with DCM, the combined organic layers were washed with brine and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 70:30, 50:50) yielded 96.3 mg (0.101 mmol, 70 %) tetrapeptide **37** as an off-white solid.

R_f (37) = 0.11 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.63 – 0.75 (m, 4 H, 18-H_a, 19-H), 0.75 – 0.88 (m, 1 H, 18-H_b), 0.86 (d, $^3J_{13,12}$ = 6.5 Hz, 3 H, 17-H), 0.99 – 1.13 (m, 21 H, 38-H, 39-H), 1.34 (s, 3 H, 36-H), 1.37 (s, 3 H, 36'-H), 1.53 – 1.62 (m, 2 H, 16-H, 32-H_a), 1.63 – 1.73 (m, 2 H, 32-H_b, 31-H_a), 1.87 (m, 1 H, 31-H_b), 1.92 – 2.05 (m, 2 H, 22-H_a, 23-H_a), 2.12 (m, 1 H, 23-H_b), 2.25 (m, 1 H, 22-H_b), 2.94 (m, 2 H, 8-H), 3.63 – 3.81 (m, 4 H, 24-H_a, 26-H_a, 34-H, 37-H_a), 3.75 (s, 3 H, 13-H), 3.82 – 3.90

(m, 1 H, 24-H_b), 3.86 (dd, $^2J_{37b,37a}$ = 9.7 Hz, $^3J_{37b,34}$ = 3.4 Hz, 1 H, 37-H_b), 3.89 (td, $^3J_{33,32}$ = 7.9 Hz, $^3J_{33,34}$ = 2.9 Hz, 1 H, 33-H), 4.09 (dd, $^2J_{26b,26a}$ = 18.2 Hz, $^3J_{26b,NH}$ = 5.6 Hz, 1 H, 26-H_b), 4.50 (dd, $^3J_{15,NH} \approx {}^3J_{15,16}$ = 8.8 Hz, 1 H, 15-H), 4.59 – 4.70 (m, 2 H, 7-H, 21-H), 5.07 (s, 2 H, 5-H), 5.16 (d, $^3J_{28a,29}$ = 10.5 Hz, 1 H, 28-H_a), 5.21 (d, $^3J_{28b,29}$ = 17.3 Hz, 1 H, 28-H_b), 5.26 (dt, $^3J_{30,29} \approx {}^3J_{30,31}$ = 6.3 Hz, 1 H, 30-H), 5.47 (d, $^3J_{NH,7}$ = 7.3 Hz, 1 H, NH_c), 5.71 (ddd, $^3J_{29,28b}$ = 17.2 Hz, $^3J_{29,28a}$ = 10.5 Hz, $^3J_{29,30}$ = 6.8 Hz, 1 H, 29-H), 6.76 (d, $^3J_{11,10}$ = 8.8 Hz, 2 H, 11-H), 7.06 (d, $^3J_{10,11}$ = 8.5 Hz, 2 H, 10-H), 7.20 (br s, 1 H, NH_b), 7.27 – 7.37 (m, 5 H, 1-H, 2-H, 3-H), 7.53 (br s, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-19), 11.8 (d, C-38), 15.2 (q, C-17), 17.9 (q, C-39), 24.0 (t, C-18), 24.8 (t, C-23), 26.9 (q, C-36), 27.3 (q, C-36'), 28.2 (t, C-22), 28.8 (t, C-32), 30.6 (t, C-31), 37.4 (d, C-16), 38.6 (t, C-8), 41.4 (t, C-26), 47.9 (t, C-24), 54.9 (d, C-15), 55.0 (d, C-7 o. C-21), 55.1 (q, C-13), 59.7 (d, C-7 o. C-21), 64.2 (t, C-37), 67.0 (t, C-5), 76.0 (d, C-30), 79.1 (d, C-33), 80.7 (d, C-34), 108.5 (s, C-35), 114.0 (d, C-11), 117.7 (t, C-28), 128.0 (s/d, C-1 o. C-3 o. C-9), 128.1 (s/d, C-1 o. C-3 o. C-9), 128.1 (s/d, C-1 o. C-3 o. C-9), 128.5 (d, C-2), 130.2 (d, C-10), 135.5 (d, C-29), 136.2 (s, C-4), 158.6 (s, C-6), 168.8 (s, C-14 o. C-20 o. C-25 o. C-27). The signals of C-12 and C-14/C-20/C-25/C-27 weren't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{51}H_{79}N_4O_{11}Si$ $[M+H]^+$	951.5509	951.5535

Melting point: 65 °C

Optical rotation: $[\alpha]_D^{20}$ = –48.9° (c = 1.0, $CHCl_3$)

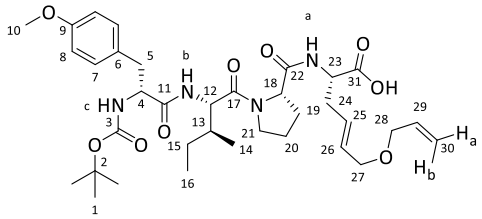
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 26.0 min ($[M+Na]^+$ = 974).

(*S*,*E*)-6-(Allyloxy)-2-((*S*)-1-(((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)hex-4-enoic acid (38c)

A solution of 0.91 mL (646 mg, 6.38 mmol) Di-*iso*-propylamine in 6.5 mL THF abs. was cooled to –78 °C before 3.6 mL (5.76 mmol) *n*-BuLi (1.6 M in hexanes) were added dropwise. The cooling bath was removed and the reaction was stirred at rt for 15 min.

435 mg (3.19 mmol) zinc chloride (dried *in high-vacuo*) was treated with a solution of 713 mg (1.06 mmol) **36c** in 13 mL THF abs. at rt. After cooling to –78 °C, the previously prepared LDA solution was added dropwise to the zinc chloride/tetrapeptide ester solution. Upon complete addition, the remaining dry ice was removed from the cooling bath and the reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with Et_2O and 1 M $KHSO_4$ sol. was added. The layers were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. After lyophilisation, 713 mg (1.06 mmol, *dr* > 99:1, quant.) of acid **38c** were obtained as a slightly yellow solid.

R_f (38c) = 0.02 (silica gel, PE:EA 50:50 + 1 % HOAc)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, $^3J_{16,15}$ = 7.4 Hz, 3 H, 16-H), 0.88 (d, $^3J_{14,13}$ = 6.5 Hz, 3 H, 14-H), 0.98 (m, 1 H, 15-H_a), 1.37 (s, 9 H, 1-H), 1.38 (m, 1 H, 15-H_b), 1.69 (m, 1 H, 13-H), 1.89 – 2.20 (m, 3 H, 19-H_a, 20-H), 2.40 (m, 1 H, 19-H_b), 2.49 (ddd, $^2J_{24a,24b}$ = 13.6 Hz, $^3J_{24a,23} \approx {}^3J_{24a,25}$ = 5.9 Hz, 1 H, 24-H_a), 2.61 (ddd, $^2J_{24b,24a}$ = 13.9 Hz, $^3J_{24b,23} \approx {}^3J_{24b,25}$ = 5.0 Hz, 1 H, 24-H_b), 2.96 (m, 2 H, 5-H), 3.64 (m, 1 H, 21-H_a), 3.76 (s, 3 H, 10-H), 3.86 (d, $^3J_{27,26}$ = 3.9 Hz, 2 H, 27-H), 3.91 (d, $^3J_{28,29}$ = 5.6 Hz, 2 H, 28-H), 3.94 (m, 1 H, 21-H_b), 4.40 (m, 1 H, 4-H), 4.49 (m, 1 H, 12-H), 4.53 (td, $^3J_{23,24} \approx {}^3J_{23,NH}$ = 6.4 Hz, 1 H, 23-H), 4.65 (d, $^3J_{18,19a/b}$ = 6.5 Hz, 1 H, 18-H), 5.15 (d, $^3J_{30a,29}$ = 10.2 Hz, 1 H, 30-H_a), 5.16 (m, 1 H, NH_c), 5.23 (dd, $^3J_{30b,29}$ = 17.2 Hz, $^2J_{30b,30a}$ = 1.6 Hz, 1 H, 30-H_b), 5.54 – 5.67 (m, 2 H, 25-H, 26-H), 5.86 (ddd, $^3J_{29,30b}$ = 16.0 Hz, $^3J_{29,30a}$ = 11.0 Hz, $^3J_{29,28}$ = 5.6 Hz, 1 H, 29-H), 6.97 (d, $^3J_{8,7}$ = 8.6 Hz, 2 H, 8-H), 7.07 (d, $^3J_{7,8}$ = 8.4 Hz, 2 H, 7-H), 7.52 (d, $^3J_{NH,12}$ = 8.4 Hz, 1 H, NH_b), 7.60 (m, 1 H, NH_a). The signal of -COOH wasn't observed in the ^{1}H-NMR spectrum.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.7 (q, C-16), 15.1 (q, C-14), 24.6 (t, C-15), 24.8 (t, C-20), 27.7 (t, C-19), 28.2 (q, C-1), 35.3 (t, C-24), 37.0 (d, C-13), 38.0 (t, C-5), 48.2 (t, C-21), 52.6 (d, C-23), 55.0 (d, C-12), 55.2 (q, C-10), 55.6 (d, C-4), 60.5 (d, C-18), 70.3 (t, C-27), 71.1 (t, C-28), 79.8 (s, C-2), 113.9 (d, C-8), 117.1 (t, C-30), 127.8 (d, C-25 o. C-26), 128.4 (a, C-6), 130.3 (d, C-7), 130.5 (d, C-25 o. C-26), 134.6 (d, C-29), 155.1 (s, C-3), 158.5 (s, C-9), 170.3 (s, C-22), 172.0 (s, C-11), 173.2 (s, C-31). The signal of C-17 wasn't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{35}H_{53}N_4O_9$ $[M+H]^+$	673.3807	673.3816

Melting point: 68 °C

Optical rotation: $[\propto]_D^{20}$ = –33.3° (c = 1.0, $CHCl_3$)

HPLC: A small sample was derivatized with TMS-diazomethane for HPLC analysis. Reprosil, *n*-hexane:*i*PrOH 70:30, 1 mL/min, 20 °C:

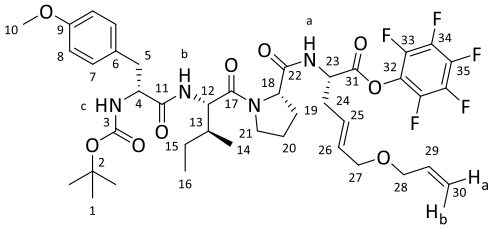
t_R = 32.3 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 17.6 min ($[M+Na]^+$ = 695).

Perfluorophenyl (*S*,*E*)-6-(allyloxy)-2-((*S*)-1-(((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)hex-4-enoate (39)

To a solution of 484 mg (0.705 mmol) **38c** in 7.0 mL DCM abs. were added 149 mg (0.809 mmol) pentafluorophenol and 149 mg (0.777 mmol) EDC·HCl at 0 °C. The reaction was allowed to warm to rt overnight. The reaction mixture was diluted with DCM and 1 M HCl sol. was added. The layers were separated, and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. 573 mg (0.683 mmol, *dr* ~ 96:4, 97 %) of Pfp ester **39** were obtained after lyophilisation.

R_f (39) = 0.16 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 0.81 (t, $^3J_{16,15}$ = 7.0 Hz, 3 H, 16-H), 0.88 (m, 1 H, 15-H_a), 0.89 (d, $^3J_{14,13}$ = 6.7 Hz, 3 H, 14-H), 1.05 (m, 1 H, 15-H_b), 1.34 (s, 9 H, 1-H), 1.44 (m, 1 H, 13-H), 1.73 – 2.06 (m, 5 H, 19-H, 20-H, 24-H_a), 2.40 (m, 1 H, 24-H_b), 2.73 (dd, $^2J_{5a,5b}$ = 13.9 Hz, $^3J_{5a,4}$ = 9.1 Hz, 1 H, 5-H_a), 2.91 (dd, $^2J_{5b,5a}$ = 13.9 Hz, $^3J_{5b,4}$ = 5.4 Hz, 1 H, 5-H_b), 3.57 (m, 1 H, 21-H_a), 3.74 (s, 3 H, 10-H), 3.88 – 3.94 (m, 5 H, 27-H, 28-H, 21-H_b), 4.20 (m, 1 H, 4-H), 4.31 (m, 1 H, 23-H), 4.41 (t, $^3J_{18,19}$ = 8.2 Hz, 1 H, 18-H), 4.47 (m, 1 H, 23-H), 5.13 (dd, $^3J_{30a,29}$ = 10.4 Hz, $^2J_{30a,30b}$ = 1.4 Hz, 1 H, 30-H_a), 5.24 (d, $^3J_{30b,29}$ = 17.4 Hz, 1 H, 30-H_b), 5.59 – 5.70 (m, 2 H, 25-H, 26-H), 5.89 (dddd, $^3J_{29,30b}$ = 15.9 Hz, $^3J_{29,30a}$ = 10.7 Hz, $^3J_{29,28a}$ = 5.4 Hz, $^3J_{29,28b}$ = 2.1 Hz, 1 H, 29-H), 6.38 (br s, 1 H, NH_c), 6.81 (d, $^3J_{8,7}$ = 8.6 Hz, 2 H, 8-H), 7.14 (d, $^3J_{7,8}$ = 8.4 Hz, 2 H, 7-H), 7.56 – 7.67 (m, 2 H, NH_a, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-16), 15.2 (q, C-14), 24.2 (t, C-15), 24.8 (t, C-20), 27.7 (t, C-19), 28.2 (q, C-1), 34.5 (t, C-24), 37.5 (d, C-13), 38.2 (t, C-5), 47.9 (t, C-21), 52.2 (d, C-23), 54.8 (d, C-4 o. C-12), 55.1 (q, C-10), 55.2 (d, C-4 o. C-12), 59.5 (d, C-18), 70.0 (t, C-27), 71.1 (t, C-28), 114.0 (d, C-8), 117.0 (t, C-30), 125.5 (d, C-25), 128.3 (s, C-6), 130.2 (d, C-7), 132.2 (d, C-26), 134.6 (d, C-29), 155.1 (s, C-3), 158.6 (s, C-9), 167.6 (s, C-31), 171.2 (s, C-11 o. C-17 o. C-22), 171.4 (s, C-11 o. C-17 o. C-22), 171.9 (s, C-11 o. C-17 o. C-22). The signals of C-2, C-32, C-33, C-34 and C-35 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 4.72 (m, 1 H, 23-H), 7.05 (d, $^3J_{8,7}$ = 8.5 Hz, 2 H, 8-H), 7.26 (d, $^3J_{7,8}$ = 8.7 Hz, 2 H, 7-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.8 (q, C-16), 15.0 (q, C-14), 34.7 (t, C-24), 52.3 (d, C-23), 114.0 (d, C-8), 125.5 (d, C-25), 132.3 (d, C-26), 134.6 (d, C-29).

HRMS (CI):	calculated	found
$C_{41}H_{52}F_5N_4O_9$ $[M+H]^+$	839.3649	839.3666

Melting point: 53 °C

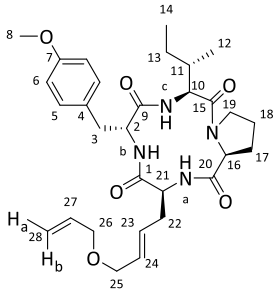
Optical rotation: $[\alpha]_D^{20}$ = –43.1° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.6 mL/min, t_R = 23.0 min ($[M+H]^+$ = 839).

(3*S*,6*R*,9*S*,14a*S*)-3-((*E*)-4-(Allyloxy)but-2-en-1-yl)-9-((*S*)-*sec*-butyl)-6-(4-methoxybenzyl)-decahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetraone (40)

A solution of 90.6 mg (0.108 mmol) **39** in 0.3 mL dioxane was treated with 0.54 mL (2.16 mmol) HCl (4 M in dioxane) at rt. The reaction was stirred for 1 h at rt and concentrated *in vacuo*. The residue was redissolved in 25 mL chloroform and added dropwise to a vigorously stirred emulsion of 50 mL chloroform in 50 mL sat. $NaHCO_3$ sol. at rt. The reaction was stirred for 4 h. The layers were then separated and the aqueous phase was extracted two times with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product was column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) afforded 29.0 mg (52.3 µmol, *dr* 87:13, 48 % over two steps) of cyclic peptide **40** as an off-white solid. A small sample was further purified by reversed phase column chromatography (silica gel C-18, MeCN:H_2O 10:90, Gradient 90:10) to partially separate the epimers and for analytical purposes.

R_f (40) = 0.30 (silica gel, DCM:MeOH 95:5)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.71 (t, $^3J_{14,13}$ = 7.4 Hz, 3 H, 14-H), 0.80 (d, $^3J_{12,11}$ = 6.3 Hz, 3 H, 12-H), 0.81 (m, 1 H, 13-H_a), 1.05 (m, 1 H, 13-H_b), 1.82 – 1.92 (m, 2 H, 11-H, 18-H_a), 1.96 (m, 1 H, 18-H_b), 2.14 (dd, $^2J_{17a,17b}$ = 12.8 Hz, $^3J_{17a,16}$ = 6.8 Hz, 1 H, 17-H_a), 2.23 (m, 1 H, 17-H_b), 2.49 (dt, $^2J_{22a,22b}$ = 13.9 Hz, $^3J_{22a,21} \approx {}^3J_{22a,23}$ = 7.3 Hz, 1 H, 22-H_a), 2.60 (dt, $^2J_{22b,22a}$ = 13.3 Hz, $^3J_{22b,21} \approx {}^3J_{22b,23}$ = 6.7 Hz, 1 H, 22-H_b), 2.84 (dd, $^2J_{3a,3b}$ = 13.6 Hz, $^3J_{3a,2}$ = 5.7 Hz, 1 H, 3-H_a), 3.19 (dd, $^2J_{3b,3a}$ = 13.6 Hz, $^3J_{3b,2}$ = 10.1 Hz, 1 H, 3-H_b), 3.61 (m, 1 H, 19-H_a), 3.69 (s, 3 H, 8-H), 3.76 (m, 1 H, 19-H_b), 3.98 (d, $^3J_{25,24}$ = 4.7 Hz, 2 H, 25-H), 3.93 (ddd, $^3J_{26,27}$ = 5.7 Hz, $^4J_{26,28a} \approx {}^4J_{26,28b}$ = 1.3 Hz, 2 H, 26-H), 4.52 (dd, $^3J_{10,11} \approx {}^3J_{10,NH}$ = 9.8 Hz, 1 H, 10-H), 4.63 (ddd, $^3J_{2,3b}$ = 10.4 Hz, $^3J_{2,3a} \approx$

$^{3}J_{2,NH}$ = 5.7 Hz, 1 H, 2-H), 4.67 (m, 1 H, 21-H), 4.95 (d, $^{3}J_{16,17a/b}$ = 8.8 Hz, 1 H, 16-H), 5.17 (ddt, $^{3}J_{28a,29}$ = 10.4 Hz, $^{2}J_{28a,28b}$ = 1.6 Hz, $^{4}J_{28a,26}$ = 1.3 Hz, 1 H, 28-H_a), 5.25 (ddt, $^{3}J_{28b,29}$ = 17.3 Hz, $^{2}J_{28b,28a} \approx {}^{4}J_{28b,26}$ = 1.6 Hz, 1 H, 28-H_b), 5.56 – 5.66 (m, 2 H, 23-H, 24-H), 5.88 (ddd, $^{3}J_{27,28b}$ = 16.6 Hz, $^{3}J_{27,28a}$ = 10.6 Hz, $^{3}J_{27,26}$ = 5.5 Hz, 1 H, 29-H), 6.22 (br s, 1 H, NH_a), 6.57 (br s, 1 H, NH_b), 6.65 (d, $^{3}J_{6,5}$ = 8.5 Hz, 2 H, 6-H), 6.86 (br s, 1 H, NH_c), 7.00 (d, $^{3}J_{5,6}$ = 8.5 Hz, 2 H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 21.8 (t, C-18), 24.1 (t, C-13), 31.1 (t, C-22), 31.6 (t, C-17), 34.6 (t, C-3), 36.3 (d, C-11), 47.0 (t, C-19), 53.3 (d, C-21), 55.0 (q, C-8), 55.8 (d, C-10), 57.4 (d, C-2), 61.0 (d, C-16), 70.3 (t, C-25), 71.0 (t, C-26), 113.7 (d, C-6), 117.0 (t, C-28), 127.9 (d, C-23), 128.6 (s, C-4), 130.3 (d, C-24), 130.5 (d, C-5), 134.7 (d, C-27), 158.3 (s, C-7), 170.2 (s, C-9), 170.6 (s, C-15), 173.5 (s, C-1), 174.5 (s, C-20).

HRMS (CI):	calculated	found
$C_{30}H_{43}N_4O_6$ $[M+H]^+$	555.3177	555.3169

Melting point: 250 °C (decomposition)

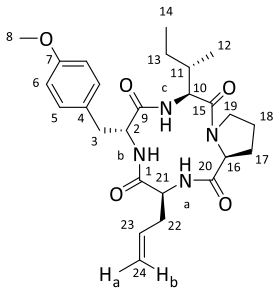
Optical rotation: $[\propto]_D^{20}$ = –76.6° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.6 mL/min, t_{R1} = 16.4 min (13 %, $[M+H]^+$ = 555), t_{R2} = 17.4 min (87 %, $[M+H]^+$ = 555).

(3*S*,6*R*,9*S*,14a*S*)-3-allyl-9-((*S*)-*sec*-butyl)-6-(4-methoxybenzyl)decahydropyrrolo[1,2-a]-[1,4,7,10]tetraazacyclododecine-1,4,7,10-tetraone (41)

26.5 mg (48.5 µ mol) **40** and 2.0 mg (2.39 µmol) Grubbs I were dissolved in 2.0 mL DCM abs. and heated to 45 °C in a sealed tube for 20 h. For workup, 8.5 µL (9.4 mg, 120 µmol) DMSO were added and stirring was continued for 24 h. The reaction was concentrated *in vacuo* and purified by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) to yield 13.0 mg (26.8 µmol, 55 %) of peptide **41** as an off-white solid.

R_f (41) = 0.40 (silica gel, DCM:MeOH 95:5)



^{1}H-NMR (500 MHz, 373 K, Tetrachloroethane-d_2): δ = 0.83 (t, $^{3}J_{14,13}$ = 7.4 Hz, 3 H, 14-H), 0.88 (d, $^{3}J_{12,11}$ = 6.6 Hz, 3 H, 12-H), 0.96 (m, 1 H, 13-H_a), 1.27 (m, 1 H, 13-H_b), 1.87 – 1.98 (m, 2 H, 11-H, 18-H_a), 2.01 (m, 1 H, 18-H_b), 2.18 (m, 1 H, 17-H_a), 2.28 (m, 1 H, 17-H_b), 2.48 (dt, $^{2}J_{22a,22b}$ = 14.8 Hz, $^{3}J_{22a,21} \approx {}^{3}J_{22a,23}$ = 7.4 Hz, 1 H, 22-H_a), 2.62 (dt, $^{2}J_{22b,22a}$ = 14.5 Hz, $^{3}J_{22b,21} \approx {}^{3}J_{22b,23}$ =

6.7 Hz, 1 H, 22-H_b), 2.88 (dd, $^2J_{3a,3b}$ = 14.1 Hz, $^3J_{3a,2}$ = 6.3 Hz, 1 H, 3-H_a), 3.25 (dd, $^2J_{3b,3a}$ = 14.1 Hz, $^3J_{3b,2}$ = 9.1 Hz, 1 H, 3-H_b), 3.68 (m, 2 H, 19-H), 3.81 (s, 3 H, 8-H), 4.54 (dd, $^3J_{10,11} \approx {}^3J_{10,NH}$ = 9.3 Hz, 1 H, 10-H), 4.54 (m, 1 H, 21-H), 4.63 (m, 1 H, 2-H), 4.68 (d, $^3J_{16,17a/b}$ = 8.8 Hz, 1 H, 16-H), 5.18 (m, 2 H, 24-H), 5.67 (d, $^3J_{NH,21}$ = 10.0 Hz, 1 H, NH_a), 5.82 (m, 1 H, 23-H), 5.87 (d, $^3J_{NH,10}$ = 10.0 Hz, 1 H, NH_c), 6.29 (d, $^3J_{NH,2}$ = 10.7 Hz, 1 H, NH_b), 6.84 (d, $^3J_{6,5}$ = 8.8 Hz, 2 H, 6-H), 7.16 (d, $^3J_{5,6}$ = 8.8 Hz, 2 H, 5-H).

^{13}C-NMR (125 MHz, 373 K, Tetrachloroethane-d_2): δ = 11.0 (q, C-14), 15.7 (q, C-12), 21.6 (t, C-18), 24.2 (t, C-13), 31.2 (t, C-17), 32.2 (t, C-22), 34.2 (t, C-3), 36.6 (d, C-11), 46.9 (t, C-19), 52.9 (d, C-21), 55.2 (q, C-8), 55.5 (d, C-10), 56.3 (d, C-2), 61.2 (d, C-16), 114.1 (d, C-6), 118.2 (t, C-24), 128.8 (s, C-4), 130.0 (d, C-5), 132.5 (d, C-23), 158.5 (s, C-7), 170.0 (s, C-9), 170.1 (s, C-15), 173.0 (s, C-1), 174.4 (s, C-20).

HRMS (CI):	calculated	found
$C_{26}H_{36}N_4O_5$ $[M]^+$	484.2686	484.2684

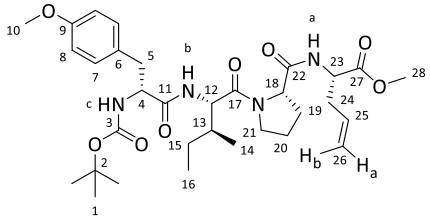
Melting point: 280 °C (decomposition)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.8 mL/min, t_R = 10.1 min ($[M+H]^+$ = 485).

Methyl (*S*)-2-((*S*)-1-(((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)pent-4-enoate (42)

To a solution of 1.11 g (2.20 mmol) **18c** and 365 mg (2.20 mmol) methyl (*S*)-2-aminopent-4-enoate hydrochloride in 11.0 mL acetonitrile abs. were added 709 mg (2.21 mmol) TBTU and 0.79 mL (585 mg, 4.53 mmol) DIPEA slowly at rt. The reaction was stirred at rt overnight and concentrated *in vacuo*. The residue was redissolved in DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50) to afford 847 mg (1.37 mmol, *dr* ~ 95:5, 62 %) of product **42** as an off-white solid.

R_f (42) = 0.12 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, $^3J_{16,15}$ = 7.0 Hz, 3 H, 16-H), 0.84 (m, 1 H, 15-H_a), 0.88 (d, $^3J_{14,13}$ = 6.7 Hz, 3 H, 14 H), 1.26 (m, 1 H, 15-H_b), 1.39 (s, 9 H, 1-H), 1.66 (m, 1 H, 13-H), 1.92

- 2.02 (m, 2 H, 19-H_a, 20-H_a), 2.10 (m, 1 H, 20-H_b), 2.28 (m, 1 H, 19-H_b), 2.47 (dd, $^3J_{24,23} \approx {}^3J_{24,25}$ = 6.0 Hz, 2 H, 24-H), 2.96 (m, 2 H, 5-H), 3.63 (m, 1 H, 21-H_a), 3.71 (s, 3 H, 28-H), 3.76 (s, 3 H, 10-H), 3.86 (m, 1 H, 21-H_b), 4.41 (m, 1 H, 4-H), 4.49 - 4.58 (m, 2 H, 12-H, 23-H), 4.61 (d, $^3J_{18,19a}$ = 5.3 Hz, 1 H, 18-H), 4.95 - 5.15 (m, 3 H, 26-H, NH_c), 5.66 (ddt, $^3J_{25,26b}$ = 16.9 Hz, $^3J_{25,26a}$ = 10.0 Hz, $^3J_{25,24}$ = 7.1 Hz, 1 H, 25-H), 6.79 (d, $^3J_{8,7}$ = 8.4 Hz, 2 H, 8-H), 6.80 (m, 1 H, NH_b), 7.08 (d, $^3J_{7,8}$ = 8.2 Hz, 2 H, 7-H), 7.32 (br s, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.9 (q, C-16), 15.2 (q, C-14), 24.1 (t, C-15), 24.9 (t, C-20), 27.7 (t, C-19), 28.2 (q, C-1), 36.2 (t, C-24), 37.6 (d, C-13), 38.0 (t, C-5), 47.8 (t, C-21), 52.2 (q, C-28), 52.2 (d, C-23), 54.8 (d, C-12), 55.2 (q, C-10), 55.7 (d, C-4), 59.8 (d, C-18), 80.0 (s, C-2), 114.0 (d, C-8), 118.9 (t, C-26), 128.4 (s, C-6), 130.2 (d, C-7), 132.2 (d, C-25), 155.1 (s, C-3), 158.5 (s, C-9), 171.0 (s, C-22), 171.7 (s, C-11 o. C-17), 171.9 (s, C-27). The signal of C-11/C-17 wasn't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, $^3J_{8,7}$ = 8.3 Hz, 2 H, 8-H), 6.97 (d, $^3J_{7,8}$ = 8.3 Hz, 2 H, 7-H).

HRMS (CI):	calculated	found
$C_{32}H_{49}N_4O_8$ $[M+H]^+$	617.3545	617.3554

Melting point: 44-46 °C

Optical rotation: $[\alpha]_D^{20}$ = –43.4° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 50:50, 1 mL/min, 20 °C:

t_{R1} = 9.53 min (11 %),

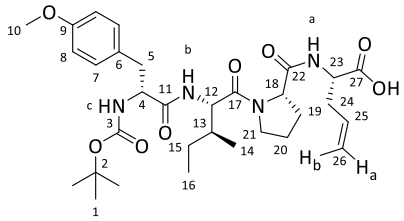
t_{R2} = 13.6 min (89 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 8.33 min ($[M+Na]^+$ = 639).

(*S*)-2-((*S*)-1-(((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-isoleucyl)pyrrolidine-2-carboxamido)pent-4-enoic acid (43)

841 mg (1.36 mmol) **42** were dissolved in 12.0 mL dioxane and cooled to 0 °C before a solution of 67.8 mg (1.59 mmol) $LiOH \cdot H_2O$ in 1.50 mL water was added slowly. The cooling bath was removed and the reaction was stirred for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was redissolved in EA. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with EA and the combined organic layers were dried over Na_2SO_4. After lyophilisation, 798 mg (1.32 mmol, 97 %) of acid **43** (containing 2 % *iso*-butylcarbonate at tyrosine residue) were obtained as an off-white solid.

R_f (43) = 0.03 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, $^3J_{16,15}$ = 7.3 Hz, 3 H, 16-H), 0.87 (d, $^3J_{14,13}$ = 6.2 Hz, 3 H, 14 H), 0.97 (m, 1 H, 15-H_a), 1.36 (m, 1 H, 15-H_b), 1.37 (s, 9 H, 1-H), 1.68 (m, 1 H, 13-H), 1.92 (m, 1 H, 19-H_a), 2.05 (m, 2 H, 20-H), 2.44 (m, 1 H, 19-H_b), 2.53 (ddd, $^2J_{24a,24b}$ = 13.9 Hz, $^3J_{24a,23} \approx {}^3J_{24a,25}$ = 6.8 Hz, 1 H, 24-H_a), 2.62 (ddd, $^2J_{24b,24a}$ = 13.7 Hz, $^3J_{24b,23} \approx {}^3J_{24b,25}$ = 6.7 Hz, 1 H, 24-H_b), 2.97 (m, 2 H, 5-H), 3.63 (m, 1 H, 21-H_a), 3.76 (s, 3 H, 10-H), 3.97 (dt, $^2J_{21a,21b}$ = 8.8 Hz, $^3J_{21a,20}$ = 8.6 Hz, 1 H, 21-H_b), 4.41 (m, 1 H, 4-H), 4.49 (dd, $^3J_{12,13} \approx {}^3J_{12,NH}$ = 7.9 Hz, 1 H, 12-H), 4.56 (dt, $^3J_{23,24} \approx {}^3J_{23,NH}$ = 5.7 Hz, 1 H, 23-H), 4.69 (d, $^3J_{18,19a}$ = 7.2 Hz, 1 H, 18-H), 5.02 (d, $^3J_{26a,25}$ = 10.8 Hz, 1 H, 26-H_a), 5.06 (d, $^3J_{26b,25}$ = 18.3 Hz, 1 H, 26-H_b), 5.20 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH_c), 5.66 (m, 1 H, 25-H), 6.79 (d, $^3J_{8,7}$ = 8.6 Hz, 2 H, 8-H), 7.07 (d, $^3J_{7,8}$ = 8.3 Hz, 2 H, 7-H), 7.62 (d, $^3J_{NH,12}$ = 8.6 Hz, 1 H, NH_b), 7.74 (d, $^3J_{NH,23}$ = 5.6 Hz, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.7 (q, C-16), 15.1 (q, C-14), 24.5 (t, C-15), 24.9 (t, C-20), 26.9 (t, C-19), 28.2 (q, C-1), 36.5 (t, C-24), 37.0 (d, C-13), 37.9 (t, C-5), 48.3 (t, C-21), 52.7 (d, C-23), 55.0 (d, C-12), 55.2 (q, C-10), 55.7 (d, C-4), 60.5 (d, C-18), 79.8 (s, C-2), 113.9 (d, C-8), 118.6 (t, C-26), 128.4 (s, C-6), 130.3 (d, C-7), 132.6 (d, C-25), 155.1 (s, C-3), 158.5 (s, C-9), 171.0 (s, C-17 o. C-22), 172.2 (s, C-11), 173.3 (s, C-27). The signal of C-17/C-22 wasn't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, 10-H), 6.73 (d, $^3J_{8,7}$ = 8.2 Hz, 2 H, 8-H), 6.93 (d, $^3J_{7,8}$ = 8.8 Hz, 2 H, 7-H).

HRMS (CI):	calculated	found
$C_{31}H_{47}N_4O_8$ $[M+H]^+$	603.3388	603.3380

Melting point: 90 °C

Optical rotation: $[\propto]_D^{20}$ = –41.4° (c = 1.0, $CHCl_3$)

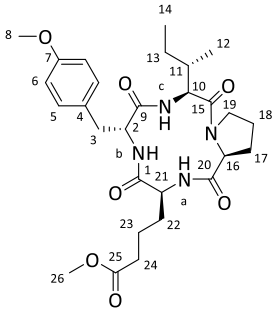
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.6 mL/min, t_R = 17.3 min (95 %, $[M+H]^+$ = 603), t_{R2} = 19.3 min (2 %, $[M+H]^+$ = 689).

Methyl 4-((3*S*,6*R*,9*S*,14a*S*)-9-((*S*)-*sec*-butyl)-6-(4-methoxybenzyl)-1,4,7,10-tetraoxotetradecahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)butanoate (46)

To a solution of 14.7 mg (26.5 µmol) **40** in 0.53 mL DCM abs. were added 6.44 µL pyridine and the reaction was cooled to –78 °C. The reaction was then treated with ozone until the mixture turned blue. The dissolved ozone was removed with oxygen and the reaction was allowed to warm to rt within 15 min. Afterwards, a solution of 35.4 mg (106 µmol) methyl 2-(triphenyl-λ^5-phosphaneylidene)acetate in 0.53 mL DCM abs. was added and stirring was continued for 3 h. For workup, the reaction was diluted with Et_2O and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) to give 6.8 mg (8.36 µmol, *E*/*Z* = 3:1, 32 %) of unsaturated ester **45**, which contained triphenylphosphine oxide as an impurity.

6.6 mg (8.15 µmol) of this ester were then dissolved in 1.0 mL MeOH at rt before 2.0 mg palladium on charcoal (10 w% Pd) were added. The reaction was hydrogenated for 6.5 h and filtrated through a pad of Celite®. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5). 5.0 mg (6.43 µmol, 70 % pure, 79 %) of ester **46** were obtained as an off-white solid. **46** still contained approximately 30 w% of triphenylphosphine oxide as an impurity.

R_f (46) = 0.30 (silica gel, DCM:MeOH 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, $^3J_{14,13}$ = 7.2 Hz, 3 H, 14-H), 0.81 (d, $^3J_{12,11}$ = 6.4 Hz, 3 H, 12-H), 0.87 (m, 1 H, 13-H_a), 1.06 (m, 1 H, 13-H_b), 1.57 – 1.78 (m, 3 H, 22-H_a, 23-H), 1.83 – 1.94 (m, 3 H, 11-H, 18-H_a, 22-H_b), 1.98 (m, 1 H, 18-H_b), 2.21 (m, 2 H, 17-H), 2.33 (m, 2 H, 24-H), 2.83 (dd, $^2J_{3a,3b}$ = 13.5 Hz, $^3J_{3a,2}$ = 5.6 Hz, 1 H, 3-H_a), 3.19 (dd, $^2J_{3b,3a}$ = 13.3 Hz, $^3J_{3b,2}$ = 10.0 Hz, 1 H, 3-H_b), 3.67 (m, 1 H, 19-H_{eq}), 3.65 (s, 3 H, 26-H), 3.70 (s, 3 H, 8-H), 3.78 (dd, $^2J_{19ax,19eq}$ ≈ $^3J_{19ax,18ax}$ = 10.2 Hz, 1 H, 19-H_{ax}), 4.52 (dd, $^3J_{10,11}$ ≈ $^3J_{10,NH}$ = 9.7 Hz, 1 H, 10-H), 4.58 (m, 1 H, 21-H), 4.63 (m, 1 H, 2-H), 4.95 (d, $^3J_{16,17a/b}$ = 8.4 Hz, 1 H, 16-H), 6.21 (br s, 1 H, NH_a), 6.54 (br s, 1 H, NH_c), 6.66 (d, $^3J_{6,5}$ = 8.6 Hz, 2 H, 6-H), 6.86 (m, 1 H, NH_b), 7.01 (d, $^3J_{5,6}$ = 8.3 Hz, 2 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 21.0 (t, C-23), 21.9 (t, C-18), 24.1 (t, C-13), 27.6 (t, C-22), 31.6 (t, C-17), 33.3 (t, C-24), 34.5 (t, C-3), 36.3 (d, C-11), 47.1 (t, C-19), 51.6 (q, C-26), 53.7 (d, C-21), 55.1 (q, C-8), 55.7 (d, C-10), 57.1 (d, C-2), 61.0 (d, C-16),

113.7 (d, C-6), 128.4 (s, C-4), 130.4 (d, C-5), 158.3 (s, C-7), 170.1 (s, C-9), 170.5 (s, C-15), 173.3 (s, C-25), 173.5 (s, C-1), 174.8 (s, C-20).

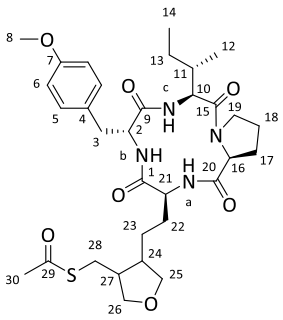
HRMS (CI):	calculated	found
$C_{28}H_{41}N_4O_7$ $[M]^+$	545.2970	545.2952

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.8 mL/min, t_{R1} = 9.47 min ($[M+H]^+$ = 545), t_{R2} = 9.71 min ($[M+H]^+$ = 279).

S-((4-(2-((3*S*,6*R*,9*S*,14a*S*)-9-((*S*)-*sec*-Butyl)-6-(4-methoxybenzyl)-1,4,7,10-tetraoxotetradeca-hydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)ethyl)tetrahydrofuran-3-yl)methyl) ethanethioate (47)

To a suspension of 10.2 mg (18.4 µmol) **40** in 0.5 mL THF were added 2.63 µL (2.80 mg, 36.8 µmol) thioacetic acid and 6.0 µL (6.0 µmol) BEt_3 (1 M in THF) at rt. 0.1 mL air were added and the reaction was stirred at rt overnight before further 2.0 µL (2.13 mg, 28.0 µ mol) thioacetic acid and 6.0 µL (6.0 µmol) BEt_3 (1 M in THF) were added. Stirring was continued for 3 h and the reaction was concentrated *in vacuo*. Purification by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) afforded 9.5 mg (15.1 µmol, 82 %) of compound **47** as an off-white solid.

R_f (47) = 0.19 (silica gel, DCM:MeOH 95:5)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.72 (m, 3 H, 14-H), 0.80 (d, $^3J_{12,13}$ = 6.2 Hz, 3 H, 12-H), 0.82 (m, 1 H, 13-H_a), 1.04 (m, 1 H, 13-H_b), 1.27 (m, 2 H, 23-H), 1.71 (m, 1 H, 22-H_a), 1.80 – 1.94 (m, 4 H, 11-H, 18-H_a, 22-H_b, 24-H), 2.01 (m, 2 H, 18-H_b, 27-H), 2.22 (m, 2 H, 17-H), 2.33 (s, 3 H, 30-H), 2.78 – 2.87 (m, 2 H, 3-H_a, 28-H_a), 3.03 (m, 1 H, 28-H_b), 3.21 (m, 1 H, 3-H_b), 3.45 (m, 1 H, 26-H_a), 3.57 – 3.79 (m, 4 H, 19-H, 25-H), 3.71 (s, 3 H, 8-H), 3.88 (dd, $^2J_{26b,26a} \approx {}^3J_{26b,24/27}$ = 9.3 Hz, 1 H, 26-H_b), 4.49 – 4.68 (m, 3 H, 2-H, 10-H, 21-H), 4.93 (m, 1 H, 16-H), 6.26 (m, 1 H, NH_c), 6.46 (br s, 1 H, NH_a), 6.66 (d, $^3J_{6,5}$ = 8.6 Hz, 2 H, 6-H), 6.86 (m, 1 H, NH_b), 7.02 (m, 2 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 21.9 (t, C-18), 24.1 (t, C-13), 27.7 (t, C-22), 29.3 (t, C-23), 30.6 (q, C-30), 31.6 (t, C-17), 31.7 (t, C-28), 34.5 (t, C-3), 36.3 (d, C-24), 44.5 (d, C-27), 47.1 (t, C-19), 54.0 (d, C-21), 55.1 (q, C-8), 55.7 (d, C-10), 57.2 (d, C-2),

61.1 (d, C-16), 72.0 (t, C-25 o. C-26), 72.6 (t, C-25 o. C-26), 113.7 (d, C-6), 128.6 (s, C-4), 130.4 (d, C-5), 158.3 (s, C-7), 170.1 (s, C-9), 170.6 (s, C-15), 195.5 (s, C-29). The signals of C-1, C-11 and C-20 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, 30-H), 2.64 (m, 1 H, 28-H_a), 3.36 (m, 1 H, 25-H_a), 3.69 (s, 3 H, 8-H), 3.70 (s, 3 H, 8-H), 3.82 (m, 1 H, 26-H_a), 3.97 (m, 1 H, 25-H_b), 6.65 (d, $^{3}J_{6,5}$ = 8.6 Hz, 2 H, 6-H), 6.67 (d, $^{3}J_{6,5}$ = 8.2 Hz, 2 H, 6-H), 6.68 (d, $^{3}J_{6,5}$ = 8.4 Hz, 2 H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 11.3 (q, C-14), 11.4 (q, C-14), 15.9 (q, C-12), 15.9 (q, C-12), 21.9 (t, C-18), 24.1 (t, C-13), 27.6 (t, C-22), 29.3 (t, C-23), 44.6 (d, C-27), 47.2 (t, C-19), 55.1 (q, C-8), 130.5 (d, C-5), 195.4 (s, C-29).

HRMS (CI):	calculated	found
$C_{32}H_{47}N_4O_7S$ $[M]^+$	631.3160	631.3118

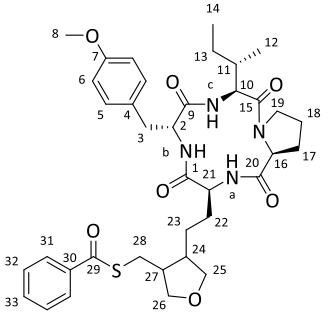
Melting point: 238 °C (decomposition)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.8 mL/min, t_R = 9.88 min ($[M+H]^+$ = 631).

S-((4-(2-((3*S*,6*R*,9*S*,14a*S*)-9-((*S*)-*sec*-Butyl)-6-(4-methoxybenzyl)-1,4,7,10-tetraoxotetra-deca-hydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)ethyl)tetrahydrofuran-3-yl)methyl) benzothioate (48)

A suspension of 10.2 mg (18.4 µmol) **40** in 0.5 mL THF was treated with 4.34 µL (5.10 mg, 36.9 µmol) thiobenzoic acid and 6.0 µL (6.0 µmol) BEt_3 (1 M in THF) at rt. 0.1 mL air were added and the reaction was stirred at rt overnight before further 6.0 µL (6.0 µmol) BEt_3 (1 M in THF) were added and stirring was continued for 4 h. The reaction was concentrated *in vacuo* and purified by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) to yield 8.6 mg (12.4 µmol, 67 %) of compound **48** as an off-white solid.

R_f (48) = 0.30 (silica gel, DCM:MeOH 95:5)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.71 (m, 3 H, 14-H), 0.80 (d, $^3J_{12,13}$ = 6.2 Hz, 3 H, 12-H), 0.83 (m, 1 H, 13-H_a), 1.04 (m, 1 H, 13-H_b), 1.31 (m, 1 H, 23-H_a), 1.58 (m, 1 H, 23-H_b), 1.76 (m, 1 H, 22-H_a), 1.82 – 2.04 (m, 5 H, 11-H, 18-H, 22-H_b, 28-H_a), 2.10 – 2.35 (m, 3 H, 17-H, 24-H), 2.47 (m, 1 H, 27-H), 2.85 (m, 1 H, 3-H_a), 3.14 – 3.27 (m, 2 H, 3-H_b, 28-H_b), 3.49 – 3.82 (m, 4 H, 19-H, 25-H_a, 26-H_a), 3.69 (s, 3 H, 8-H), 3.84 – 3.95 (m, 2 H, 25-H_b, 26-H_b), 4.49 – 4.71 (m, 3 H, 2-H, 10-H, 21-H), 5.00 (d, $^3J_{16,17a/b}$ = 6.4 Hz, 1 H, 16-H), 6.24 (m, 1 H, NH_a), 6.42 (m, 1 H, NH_c), 6.65 (d, $^3J_{6,5}$ = 7.0 Hz, 2 H, 6-H), 6.96 (m, 1 H, NH_b), 7.00 (d, $^3J_{5,6}$ = 7.7 Hz, 2 H, 5-H), 7.44 (dd, $^3J_{32,31} \approx {}^3J_{32,33}$ = 7.6 Hz, 2 H, 32-H), 7.57 (t, $^3J_{33,32}$ = 7.4 Hz, 1 H, 33-H), 7.93 (d, $^3J_{31,32}$ = 7.5 Hz, 2 H, 31-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.8 (q, C-12), 21.9 (t, C-18), 23.7 (t, C-22), 24.1 (t, C-13), 27.4 (t, C-28), 29.7 (t, C-23), 31.7 (t, C-17), 34.6 (t, C-3), 36.3 (d, C-11), 41.7 (d, C-27), 44.7 (d, C-24), 47.0 (t, C-19), 53.9 (d, C-21), 55.0 (q, C-8), 55.8 (d, C-10), 57.3 (d, C-2), 61.0 (d, C-16), 70.6 (t, C-26), 72.3 (t, C-25), 113.7 (d, C-6), 127.2 (d, C-31), 128.6 (s, C-4), 128.7 (d, C-32), 130.5 (d, C-5), 133.5 (d, C-33), 136.8 (s, C-30), 158.3 (s, C-7), 170.2 (s, C-9), 170.6 (s, C-15), 173.6 (s, C-1 o. C-20), 174.7 (s, C-1 o. C-20), 191.5 (s, C-29).

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.01 (m, 1 H, 28-H_b), 3.39 (m, 1 H, 25-H_a), 3.67 (s, 3 H, 8-H), 3.68 (s, 3 H, 8-H), 4.00 (dt, $^2J_{25b,25a}$ = 8.2 Hz, $^3J_{25b,24}$ = 7.5 Hz, 1 H, 25-H_b), 6.63 (d, $^3J_{6,5}$ = 6.0 Hz, 2 H, 6-H), 6.98 (d, $^3J_{5,6}$ = 6.1 Hz, 2 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.3 (q, C-14), 15.9 (q, C-12), 22.0 (t, C-18), 27.5 (t, C-28), 31.6 (t, C-17), 31.7 (t, C-17), 41.8 (d, C-27), 42.2 (d, C-27), 42.3 (d, C-27), 44.8 (d, C-24), 45.2 (d, C-24), 45.3 (d, C-24), 47.1 (t, C-19), 54.0 (d, C-21), 54.2 (d, C-21), 57.5 (d, C-2), 61.0 (d, C-16), 71.9 (d, C-25 o. C-26), 72.0 (d, C-25 o. C-26), 72.3 (t, C-25), 72.7 (d, C-25 o. C-26), 72.7 (d, C-25 o. C-26), 133.6 (d, C-33), 136.7 (s, C-30), 174.8 (s, C-1 o. C-20), 174.9 (s, C-1 o. C-20), 191.4 (s, C-29).

Melting point: 208 °C (decomposition)

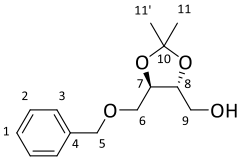
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.8 mL/min, t_R = 10.8 min ($[M+H]^+$ = 693).

((4*R*,5*R*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (*ent*-1b)[156]

2.99 g (74.8 mmol) Sodium hydride (60 w% in paraffin) were placed in a three-necked flask and 25 mL *n*-pentane were added. The suspension was stirred for few minutes and the NaH was allowed to segregate. The solvent was removed *via* syringe and the free NaH was dried *in high-vacuo*. Afterwards, 45 mL DMF abs. were added and the suspension was cooled to –40 °C. A solution of 11.0 g (67.8 mmol) (-)-2,3-*O*-Isopropylidene-D-threitol in 60 mL DMF abs. was added

within 1 h at this temperature. Afterwards, a solution of 8.1 mL (8.83 g , 69.8 mmol) benzyl chloride in 60 mL DMF abs. was added slowly within 35 min and the reaction was allowed to warm slowly to 0 °C. After stirring at 0 °C for 1 h, the reaction was allowed to warm to rt overnight. For workup, a few drops of water were added and the reaction was concentrated *in vacuo*. The residue was dissolved in DCM and water was added. The layers were separated, the aqueous phase was extracted three times with DCM, the combined organic phases were washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 70:30) to give 10.2 g (40.4 mmol, 60 %) of monobenzylated product *ent*-**1b** as a yellow oil.

R_f (*ent*-1b) = 0.30 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, 11-H), 1.42 (s, 3 H, 11'-H), 2.18 (br s, 1 H, OH), 3.56 (dd, $^2J_{6a,6b}$ = 9.8 Hz, $^3J_{6a,7}$ = 5.8 Hz, 1 H, 6-H_a), 3.66 – 3.71 (m, 2 H, 6-H_b, 9-H_a), 3.77 (dd, $^2J_{9b,9a}$ = 11.7 Hz, $^3J_{9b,8}$ = 4.4 Hz, 1 H, 9-H_b), 3.94 (dt, $^3J_{8,7}$ = 8.4 Hz, $^3J_{8,9}$ = 4.3 Hz, 1 H, 8-H), 4.06 (dt, $^3J_{7,8}$ = 8.2 Hz, $^3J_{7,6}$ = 5.4 Hz, 1 H, 7-H), 4.59 (s, 2 H, 5-H), 7.28 – 7.38 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.9 (q, C-11), 62.4 (t, C-9), 70.3 (t, C-6), 73.7 (t, C-5), 76.5 (d, C-7), 79.6 (d, C-8), 109.3 (s, C-10), 127.7 (d, C-3), 127.8 (d, C-1), 128.4 (d, C-2), 137.5 (s, C-4).

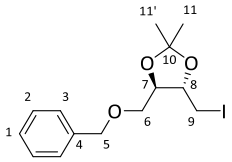
HRMS (CI):	calculated	found
$C_{14}H_{20}O_4$ $[M]^+$	252.1362	252.1363

Optical rotation: $[\alpha]_D^{20}$ = –7.6° (c = 1.0, $CHCl_3$)

(4*R*,5*S*)-4-((Benzyloxy)methyl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane (*ent*-5b)[211]

A solution of 1.03 g (4.08 mmol) alcohol *ent*-**1b** in 12 mL toluene abs. and 2.5 mL acetonitrile abs. was treated with 1.13 g (4.31 mmol) triphenylphosphine and 349 mg (5.12 mmol) imidazole at rt. Afterwards, 1.09 g (4.30 mmol) iodine were added carefully and the reaction was heated to 60 °C for 2 h. For workup, the reaction was diluted with Et_2O and washed with sat. $Na_2S_2O_3$, water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, *n*-pentane:Et_2O 2:1) to give 1.47 g (4.06 mmol, 99 %) of iodide *ent*-**5b** as a yellowish oil.

R_f (*ent*-5b) = 0.51 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, 11-H), 1.47 (s, 3 H, 11-H'), 3.28 (dd, $^2J_{9a,9b}$ = 10.5 Hz, $^3J_{9a,8}$ = 5.3 Hz, 1 H, 9-H_a), 3.36 (dd, $^2J_{9b,9a}$ = 10.5 Hz, $^3J_{9b,8}$ = 5.3 Hz, 1 H, 9-H_b), 3.64 (dd, $^2J_{6a,6b}$ = 10.0 Hz, $^3J_{6a,7}$ = 5.0 Hz, 1 H, 6-H_a), 3.67 (dd, $^2J_{6b,6a}$ = 10.0 Hz, $^3J_{6b,7}$ = 5.0 Hz, 1 H, 6-H_b), 3.87 (dt, $^3J_{8,7}$ = 7.3 Hz, $^3J_{8,9}$ = 5.3 Hz, 1 H, 8-H), 3.97 (dt, $^3J_{7,8}$ = 7.3 Hz, $^3J_{7,6}$ = 5.3 Hz, 1 H, 7-H), 4.60 (s, 2 H, 5-H), 7.24 – 7.38 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 6.4 (t, C-9), 27.3 (q, C-11), 27.4 (q, C-11'), 70.5 (t, C-6), 73.6 (t, C-5), 77.7 (d, C-8), 80.1 (d, C-7), 109.8 (s, C-10), 127.7 (d, C-2 o. C-3), 127.8 (d, C-1), 128.5 (d, C-2 o. C-3), 137.8 (s, C-4).

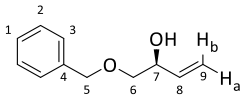
HRMS (CI):	calculated	found
$C_{14}H_{20}O_3I$ $[M+H]^+$	363.0452	363.0453

Optical rotation: $[\alpha]_D^{20}$ = +8.1° (c = 1.0, $CHCl_3$)

(*S*)-1-(Benzyloxy)but-3-en-2-ol (49)[212]

To a solution of 1.91 g (5.27 mmol) *ent*-**5b** in 26 mL THF abs. was added 1.38 g (21.1 mmol) zinc dust and 1.51 mL (1.58 g, 26.3 mmol) acetic acid at rt. The reaction was stirred for 2 h, filtrated through a pad of Celite® and washed with Et_2O. The filtrated was concentrated *in vacuo*, the residue was redissolved in Et_2O and sat. $NaHCO_3$ sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20) to yield 915 mg (5.13 mmol, *er* > 99:1, 97 %) allylic alcohol **49** as a slightly yellow liquid.

R_f (49) = 0.14 (silica gel, PE:EA 80:20)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.45 (d, $^3J_{OH,7}$ = 3.5 Hz, 1 H, OH), 3.39 (dd, $^2J_{6a,6b}$ = 9.7 Hz, $^3J_{6a,7}$ = 7.9 Hz, 1 H, 6-H_a), 3.55 (dd, $^2J_{6b,6a}$ = 9.7 Hz, $^3J_{6b,7}$ = 3.4 Hz, 1 H, 6-H_b), 4.36 (m, 1 H, 7-H), 4.58 (s, 2 H, 5-H), 5.20 (ddd, $^3J_{9a,8}$ = 10.5 Hz, $^2J_{9a,9b} \approx {}^4J_{9a,7}$ = 1.5 Hz, 1 H, 9-H_a), 5.37 (ddd, $^3J_{9b,8}$ = 17.3 Hz, $^2J_{9b,9a} \approx {}^4J_{9b,7}$ = 1.5 Hz, 1 H, 9-H_b), 5.84 (ddd, $^3J_{8,9b}$ = 17.3 Hz, $^3J_{8,9a}$ = 10.5 Hz, $^3J_{8,7}$ = 5.5 Hz, 1 H, 8-H), 7.29 – 7.39 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 71.5 (t, C-6), 73.4 (t, C-5), 74.0 (d, C-7), 116.5 (t, C-9), 127.8 (d, C-2 o. C-3), 127.8 (d, C-1), 128.5 (d, C-2 o. C-3), 136.5 (d, C-8), 137.8 (s, C-4).

HRMS (CI):	calculated	found
$C_{11}H_{14}O_2$ $[M]^+$	178.0994	178.0992

Optical rotation: $[\alpha]_D^{20}$ = –1.3° (c = 1.0, $CHCl_3$)

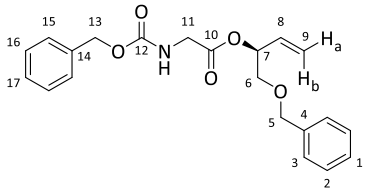
HPLC: Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

(*S*)-**49**: t_R = 8.60 min (> 99 %).

(*S*)-1-(Benzyloxy)but-3-en-2-yl ((benzyloxy)carbonyl)glycinate (50a)

230 mg (1.10 mmol) Cbz-Gly-OH and 178 mg (1.00 mmol) **49** were dissolved in 10.0 mL DCM abs. and cooled to 0 °C before 227 mg (1.10 mmol) DCC and 12.4 mg (0.101 mmol) 4-DMAP were added subsequently. The reaction was allowed to warm to rt overnight. For workup, the reaction was filtrated through a pad of Celite® and washed with DCM. The filtrate was concentrated *in vacuo*. Purification by column chromatography (silica gel, PE:EA 100:0, 80:20) afforded 331 mg (0.896 mmol, 90 %) of ester **50a** as an off-white solid.

R_f (50a) = 0.20 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.58 (d, $^3J_{6,7}$ = 5.5 Hz, 2 H, 6-H), 4.03 (d, $^3J_{11,NH}$ = 5.5 Hz, 2 H, 11-H), 4.52 (d, $^2J_{5a,5b}$ = 12.3 Hz, 1 H, 5-H_a), 4.58 (d, $^2J_{5b,5a}$ = 12.3 Hz, 1 H, 5-H_b), 5.13 (s, 2 H, 13-H), 5.24 (br s, 1 H, NH), 5.27 (d, $^3J_{9a,8}$ = 10.8 Hz, 1 H, 9-H_a), 5.34 (d, $^3J_{9b,8}$ = 17.3 Hz, 1 H, 9-H_b), 5.54 (dt, $^3J_{7,8}$ = 6.3 Hz, $^3J_{7,6}$ = 5.5 Hz, 1 H, 7-H), 5.82 (ddd, $^3J_{8,9b}$ = 17.3 Hz, $^3J_{8,9a}$ = 10.8 Hz, $^3J_{8,7}$ = 6.3 Hz, 1 H, 8-H), 7.27 – 7.38 (m, 10 H, 1-H, 2-H, 3H, 15-H, 16-H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 42.9 (t, C-11), 67.1 (t, C-13), 71.0 (t, C-6), 73.2 (t, C-5), 74.5 (d, C-7), 118.7 (t, C-9), 127.6 (d, C-2 o. C-3), 127.8 (d, C-1), 128.1 (d, C-15 o. C-16 o. C-17), 128.2 (d, C-15 o. C-16 o. C-17), 128.4 (d, C-15 o. C-16 o. C-17), 128.5 (d, C-2 o. C-3), 132.5 (d, C-8), 136.2 (s, C-14), 137.7 (s, C-4), 156.1 (s, C-12), 169.2 (s, C-10).

HRMS (CI):	calculated	found
$C_{21}H_{24}NO_5$ $[M+H]^+$	370.1649	370.1644

Melting point: 93-95 °C

Optical rotation: $[\alpha]_D^{20}$ = +2.7° (c = 1.0, $CHCl_3$)

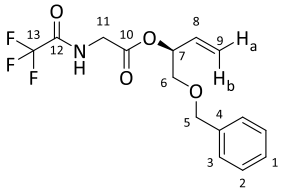
HPLC: Reprosil, *n*-hexane:*i*PrOH 80:20, 1.0 mL/min, 20 °C:

(*S*)-**50a**: t_R = 15.1 min (> 99 %).

(*S*)-1-(Benzyloxy)but-3-en-2-yl (2,2,2-trifluoroacetyl)glycinate (50b)

438 mg (2.56 mmol) TFA-Gly-OH and 457 mg (2.56 mmol) **49** were dissolved in 5.0 mL DCM abs. and cooled to –15 °C before a suspension of 530 mg (2.57 mmol) DCC and 31.7 mg (0.259 mmol) 4-DMAP in 4.0 mL DCM abs. was added slowly. The reaction was allowed to warm to rt overnight. The precipitated urea was removed by filtration through a pad of Celite® and washed with DCM. 1 M HCl sol. was added to the filtrate and the layers were separated. The aqueous phase was extracted three times with DCM and the combined organic layers were washed with sat. $NaHCO_3$ and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 90:10) afforded 731 mg (2.21 mmol, 86 %) of ester **50b** as a colourless oil.

R_f (50b) = 0.50 (silica gel, PE:EA 60:40)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.60 (d, $^3J_{6,7}$ = 5.5 Hz, 2 H, 6-H), 4.15 (d, $^3J_{11,NH}$ = 5.0 Hz, 2 H, 11-H), 4.53 (d, $^2J_{5a,5b}$ = 12.3 Hz, 1 H, 5-H_a), 4.58 (d, $^2J_{5b,5a}$ = 12.3 Hz, 1 H, 5-H_b), 5.30 (ddd, $^3J_{9a,8}$ = 10.8 Hz, $^2J_{9a,9b} \approx {}^4J_{9a,7}$ = 1.0 Hz, 1 H, 9-H_a), 5.36 (ddd, $^3J_{9b,8}$ = 17.3 Hz, $^2J_{9b,9a} \approx {}^4J_{9b,7}$ = 1.1 Hz, 1 H, 9-H_b), 5.57 (dt, $^3J_{7,8}$ = 6.5 Hz, $^3J_{7,6}$ = 5.4 Hz, 1 H, 7-H), 5.82 (ddd, $^3J_{8,9b}$ = 17.2 Hz, $^3J_{8,9a}$ = 10.7 Hz, $^3J_{8,7}$ = 6.4 Hz, 1 H, 8-H), 6.88 (br s, 1 H, NH), 7.28 – 7.39 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 41.4 (t, C-11), 70.9 (t, C-6), 73.3 (t, C-5), 75.4 (d, C-7), 115.6 (q, $^1J_{13,F}$ = 287 Hz, C-13), 119.4 (t, C-9), 127.7 (d, C-3), 127.9 (d, C-1), 128.5 (d, C-2), 132.0 (d, C-8), 137.5 (s, C-4), 157.1 (q, $^2J_{12,F}$ = 37 Hz, C-12), 167.6 (s, C-10).

HRMS (CI):	calculated	found
$C_{15}H_{17}F_3NO_4$ $[M+H]^+$	332.1104	332.1144

Optical rotation: $[\alpha]_D^{20}$ = +12.9° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 90:10, 1.0 mL/min, 20 °C:

(*S*)-**50b**: t_R = 15.3 min (> 99 %).

GC: CP-Chirasil-Dex CB, column flow 1.25 mL/min, injector 250 °C, 180 °C, 20 min, 220 °C (5 °C/min), 5 min:

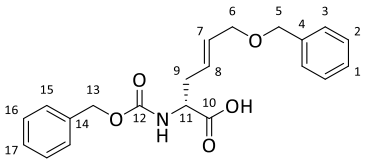
(*S*)-**50b**: t_R = 16.89 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 4.93 min ($[M+Na]^+$ = 354).

(*R*,*E*)-6-(Benzyloxy)-2-(((benzyloxy)carbonyl)amino)hex-4-enoic acid (51a)

2.50 mL (1.78 g, 17.6 mmol) Di-*iso*-propylamine were dissolved in 17.5 mL THF abs. and cooled to –78 °C before 9.4 mL (15.0 mmol) *n*-BuLi (1.6 M in hexanes) were added dropwise. The cooling bath was removed and the reaction was stirred for 10 min at rt. 822 mg (6.03 mmol) zinc chloride (dried in *high-vacuo*) were dissolved in 5.0 mL THF abs. and treated with a solution of 1.85 g (5.01 mmol) **50a** in 20 mL THF abs. at rt. The zinc chloride/ amino acid ester solution was cooled to –78 °C and treated with the above prepared LDA solution carefully. The remaining dry ice was removed and the reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with diethyl ether and 1 M $KHSO_4$ sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, DCM:MeOH 99:1, 98:2, 95:5) gave 302 mg (0.695 mmol, 14 %) of a mixture of product and allylic alcohol **3** and 1.44 g (3.90 mmol, *er* 96:4, 78 %) of acid **51a** as a slightly yellow oil.

R_f (51a) = 0.05 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.54 (ddd, $^2J_{9a,9b}$ = 13.9 Hz, $^3J_{9a,8}$ = 7.1 Hz, $^3J_{9a,11}$ = 6.5 Hz, 1 H, 9-H_a), 2.63 (ddd, $^2J_{9b,9a}$ = 13.9 Hz, $^3J_{9b,8}$ = 6.3 Hz, $^3J_{9b,11}$ = 5.8 Hz, 1 H, 9-H_b), 3.96 (m, 2 H, 6-H), 4.45 – 4.50 (m, 3 H, 5-H, 11-H), 5.10 (s, 2 H, 13-H), 5.34 (d, $^3J_{NH,11}$ = 8.0 Hz, 1 H, NH), 5.62 (dt, $^3J_{8,7}$ = 15.3 Hz, $^3J_{8,9}$ = 6.9 Hz, 1 H, 8-H), 5.71 (dt, $^3J_{7,8}$ = 15.3 Hz, $^3J_{7,6}$ = 5.5 Hz, 1 H, 7-H), 7.00 (br s, 1 H, COOH), 7.26 – 7.37 (m, 10 H, 1-H, 2-H, 3-H, 15-H, 16-H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 34.9 (t, C-9), 53.1 (d, C-11), 67.2 (t, C-13), 70.0 (t, C-6), 72.1 (t, C-5), 127.1 (d, C-8), 127.7 (d, C-17), 127.8 (d, C-1), 128.1 (d, C-3 o. C-15), 128.2 (d, C-3 o. C-15), 128.4 (d, C-2 o. C-16), 128.5 (d, C-2 o. C-16), 131.3 (d, C-7), 136.0 (s, C-14), 137.9 (s, C-4), 155.9 (s, C-12), 175.3 (s, C-10).

HRMS (CI):	calculated	found
$C_{21}H_{24}NO_5$ $[M+H]^+$	370.1649	370.1654

Optical rotation: $[\alpha]_D^{20}$ = –27.2° (c = 1.0, $CHCl_3$)

HPLC: A small sample was derivatized with TMS-diazomethane to obtain the corresponding methyl ester for HPLC analysis. Reprosil, *n*-hexane:*i*PrOH 60:40, 1.0 mL/min, 20 °C:

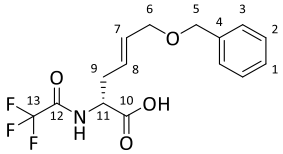
(*R*)-**51a**: t_R = 16.6 min (96 %),

(*S*)-**51a**: t_R = 22.2 min (4 %).

(*R*,*E*)-6-(Benzyloxy)-2-(2,2,2-trifluoroacetamido)hex-4-enoic acid (51b)

To a solution of 1.8 mL (1.28 g, 12.6 mmol) Di-*iso*-propylamine in 13.0 mL THF abs. were added 7.4 mL (11.8 mmol) *n*-BuLi (1.6 M in hexanes) dropwise at –20 °C. The cooling bath was removed and the reaction was stirred at rt for 15 min. A solution of 698 mg (5.12 mmol) zinc chloride (dried *in high-vacuo*) in 4.0 mL THF abs. was added to a solution of 1.41 g (4.26 mmol) **50b** at rt. The resulting solution was cooled to –78 °C and carefully treated with the above prepared LDA solution. The reaction was allowed to warm to rt overnight and diluted with Et_2O. 1 M $KHSO_4$ sol. was added and the layers were separated. The aqueous phase was extracted three times with diethyl ether and the combined organic phases were dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 70:30 + 1 % HOAc) to yield 269 mg (0.543 mmol, 13 %) of a mixture of product and allylic alcohol **49** and 1.09 g (3.29 mmol, *er* 99:1, rotameric ratio 86:14, 77 %) %) of acid **51b** as an off-white solid.

R_f (51b) = 0.45 (silica gel, PE:EA 50:50 + 1 % HOAc)



Major rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.68 (m, 2 H, 9-H), 4.02 (d, $^3J_{6,7}$ = 5.3 Hz, 2 H, 6-H), 4.54 (s, 2 H, 5-H), 4.73 (dt, $^3J_{11,NH}$ = 7.6 Hz, $^3J_{11,9}$ = 5.4 Hz, 1 H, 11-H), 5.60 (dt, $^3J_{8,7}$ = 15.1 Hz, $^3J_{8,9}$ = 7.5 Hz, 1 H, 8-H), 5.73 (dt, $^3J_{7,8}$ = 15.4 Hz, $^3J_{7,6}$ = 5.6 Hz, 1 H, 7-H), 7.11 (d, $^3J_{NH,11}$ = 7.6 Hz, 1 H, NH), 7.28 – 7.38 (m, 5 H, 1-H, 2-H, 3-H), 9.69 (br s, 1 H, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 34.1 (t, C-9), 51.8 (d, C-11), 69.7 (t, C-6), 72.3 (t, C-5), 115.6 (q, $^1J_{13,F}$ = 288 Hz, C-13), 125.9 (d, C-8), 127.9 (d, C-3), 128.0 (d, C-1), 128.5 (d, C-2), 131.8 (d, C-7), 137.2 (s, C-4), 156.9 (q, $^2J_{12,F}$ = 37 Hz, C-12), 172.9 (s, C-10).

Minor rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.52 (s, 2 H, 5-H), 6.95 (d, $^3J_{NH,11}$ = 6.9 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 34.2 (t, C-9), 51.9 (d, C-11), 69.8 (t, C-6), 72.3 (t, C-5), 125.7 (d, C-8), 127.9 (d, C-3), 127.9 (d, C-1), 128.5 (d, C-2), 132.1 (d, C-7), 137.4 (s, C-4), 173.3 (s, C-10).

HRMS (CI):	calculated	found
$C_{15}H_{17}F_3NO_4$ $[M+H]^+$	332.1104	332.1108

Melting point: 62 °C

Optical rotation: $[\alpha]_D^{20}$ = –61.6° (c = 1.0, $CHCl_3$)

HPLC: A small sample was derivatized with TMS-diazomethane for HPLC analysis. Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

(*S*)-**51b**: t_R = 9.16 min (1 %),

(*R*)-**51b**: t_R = 17.8 min (99 %).

GC: A small sample was derivatized with TMS-diazomethane for GC analysis. CP-Chirasil-Dex CB, column flow 1.50 mL/min, injector 250 °C, 145 °C, 2 min, 180 °C (1 °C/min), 5 min, 200 °C (20 °C/min), 5 min:

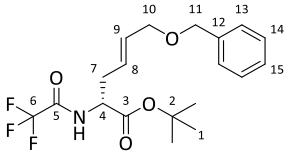
(*S*)-**51b**: t_R = 35.74 min (1 %),

(*R*)-**51b**: t_R = 37.45 min (99 %).

tert-Butyl (*R*,*E*)-6-(benzyloxy)-2-(2,2,2-trifluoroacetamido)hex-4-enoate (52)

1.56 g (4.71 mmol) **51b** were dissolved in 4.0 mL DCM abs. and cooled to 0 °C before a solution of 2.06 g (9.43 mmol) *tert*-Butyl trichloroacetimidate in 8.0 mL cyclohexane was added slowly within 10 min. Afterwards, 0.12 mL (134 mg (0.944 mmol) BF_3*OEt_2 were added dropwise and the reaction was stirred at 0 °C for 1 h. For workup, the reaction was diluted with ethyl acetate and sat. $NaHCO_3$ sol. was added. The layers were separated and the aqueous phase was extracted three times with EA. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, PE:EA 80:20) afforded 1.67 g (4.31 mmol, *er* 98:2, 92 %) of ester **52** as a slightly yellow oil.

R_f (52) = 0.53 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, 1-H), 2.57 (dt, $^2J_{7a,7b}$ = 13.8 Hz, $^3J_{7a,8}$ = 7.2 Hz, $^3J_{7a,4}$ = 6.2 Hz, 1 H, 7-H_a), 2.70 (dt, $^2J_{7b,7a}$ = 13.7 Hz, $^3J_{7b,8}$ = 7.2 Hz, $^3J_{7b,4}$ = 6.2 Hz, 1 H, 7-H_a), 3.98 (d, $^3J_{10,9}$ = 5.5 Hz, 2 H, 10-H), 4.49 (s, 2 H, 11-H), 4.54 (dt, $^3J_{4,NH}$ = 7.1 Hz, $^3J_{4,7}$ = 5.6 Hz, 1 H, 4-H), 5.57 (dt, $^3J_{8,9}$ = 15.1 Hz, $^3J_{8,7}$ = 7.5 Hz, 1 H, 8-H), 5.72 (dt, $^3J_{9,8}$ = 15.3 Hz, $^3J_{9,10}$ = 5.7 Hz, 1 H, 9-H), 6.91 (d, $^3J_{NH,4}$ = 6.0 Hz, 1 H, NH), 7.27 – 7.37 (m, 5 H, 13-H, 14-H, 15-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 34.6 (t, C-7), 52.6 (d, C-4), 69.9 (t, C-10), 72.1 (t, C-11), 83.6 (s, C-2), 115.6 (q, $^1J_{6,F}$ = 288 Hz, C-6), 125.6 (d, C-8), 127.6 (d, C-15), 127.6 (d, C-13), 128.4 (d, C-14), 132.0 (d, C-9), 138.1 (s, C-12), 156.5 (q, $^2J_{5,F}$ = 37 Hz, C-5), 169.2 (s, C-3).

HRMS (CI):	calculated	found
$C_{19}H_{25}F_3NO_4$ $[M+H]^+$	388.1730	388.1695

Optical rotation: $[\alpha]_D^{20}$ = –44.0° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

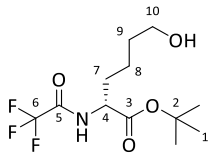
(*R*)-**52**: t_R = 13.0 min (98 %),

(*S*)-**52**: t_R = 26.6 min (2 %).

tert-Butyl (*R*)-6-Hydroxy-2-(2,2,2-trifluoroacetamido)hexanoate (53)

A solution of 1.63 g (4.21 mmol) **52** in 17 mL MeOH was treated with 165 mg palladium on charcoal (10 w% Pd) and hydrogenated for 7 h. The reaction mixture was filtrated through a pad of Celite® and washed with MeOH. The filtrate was concentrated *in vacuo* and the crude product was dried by lyophilisation. 1.25 g (4.18 mmol, rotameric ratio 66:34, 99 %) of compound **53** were obtained as a colourless oil. The compound contained an unknown side product.

R_f (53) = 0.19 (silica gel, PE:EA 70:30)



Major rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (m, 2 H, 8-H), 1.48 (s, 9 H, 1-H), 1.61 (m, 2 H, 9-H), 1.76 (m, 1 H, 7-H_a), 1.93 (m, 1 H, 7-H_b), 3.65 (t, $^3J_{10,9}$ = 6.3 Hz, 2 H, 10-H), 4.49 (dt, $^3J_{4,NH} \approx {}^3J_{4,7}$ = 6.5 Hz, 1 H, 4-H), 7.03 (br s, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.2 (t, C-8), 27.9 (q, C-1), 31.7 (t, C-7), 31.9 (t, C-9), 53.1 (d, C-4), 62.3 (t, C-10), 83.3 (s, C-2), 115.7 (q, $^1J_{6,F}$ = 288 Hz, C-6), 156.7 (q, $^2J_{5,F}$ = 38 Hz, C-5), 170.0 (s, C-3).

Minor rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.92 (br s, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.6 (t, C-7), 170.2 (s, C-3).

HRMS (CI):	calculated	found
$C_{12}H_{20}F_3NO_4$ $[M]^+$	299.1339	299.1336

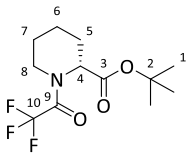
Optical rotation: $[\alpha]_D^{20}$ = –21.1° (c = 1.0, $CHCl_3$)

TFA-(*R*)-Pip-O*t*Bu (54)

To a solution of 1.28 g (4.88 mmol) PPh_3 in 175 mL THF abs. were added 0.96 mL (986 mg, 4.88 mmol) DIAD dropwise at 0 °C. Afterwards, a solution of 908 mg (3.03 mmol) **53** in 75 mL THF

abs. was added dropwise within 1 h and the reaction was allowed to warm to rt overnight. The reaction was concentrated *in vacuo* and purified by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20) to give 461 mg (1.64 mmol, rotameric ratio 74:26, 54 %) of amino acid ester **54** as a slightly yellow liquid. The product contained appr. 6 % of *tert*-butyl 2-(2,2,2-trifluoroacetamido)hex-5-enoate and an unknown side product.

R_f (54) = 0.62 (silica gel, PE:EA 70:30)



Major rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.31 – 1.53 (m, 2 H, 6-H_a, 7-H_a), 1.47 (s, 9 H, 1-H), 1.60 – 1.79 (m, 3 H, 5-H_a, 6-H_b, 7-H_b), 2.31 (d, $^{2/3}J_{5b,5a/6/4}$ = 13.9 Hz, 1 H, 5-H_b), 3.33 (ddd, $^2J_{8ax,8eq}$ = 13.4 Hz, $^3J_{8ax,7ax}$ = 13.4 Hz, $^3J_{8ax,7eq}$ = 2.8 Hz, 1 H, 8-H_{ax}), 3.91 (d, $^2J_{8eq,8ax}$ = 13.8 Hz, 1 H, 8-H_{eq}), 5.13 (d, $^3J_{4,5a}$ = 5.8 Hz, 1 H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.7 (t, C-6), 25.1 (t, C-7), 26.5 (t, C-5), 27.9 (q, C-1), 43.6 (qt, $^3J_{8,F}$ = 4 Hz, C-8), 53.9 (d, C-4), 82.4 (s, C-2), 116.5 (q, $^1J_{10,F}$ = 288 Hz, C-10), 156.9 (q, $^2J_{9,F}$ = 36 Hz, C-9), 168.6 (s, C-3).

Minor rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, 1-H), 2.98 (ddd, $^2J_{8ax,8eq}$ = 13.3 Hz, $^3J_{8ax,7ax}$ = 13.3 Hz, $^3J_{8ax,7eq}$ = 3.3 Hz, 1 H, 8-H_{ax}), 4.42 (d, $^2J_{8eq,8ax}$ = 13.5 Hz, 1 H, 8-H_{eq}), 4.58 (d, $^3J_{4,5a}$ = 5.1 Hz, 1 H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.5 (t, C-6), 24.3 (t, C-7), 26.7 (t, C-5), 27.9 (q, C-1), 41.1 (t, C-8), 56.5 (qd, $^3J_{4,F}$ = 4 Hz, C-4), 82.8 (s, C-2), 168.7 (s, C-3).

HRMS (CI):	calculated	found
$C_{12}H_{19}F_3NO_3$ $[M+H]^+$	282.1312	282.1333

Optical rotation: $[\alpha]_D^{20}$ = +47.7° (c = 1.0, $CHCl_3$)

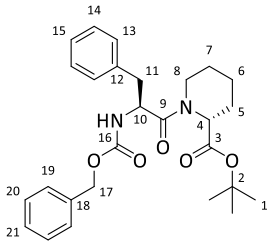
Cbz-(*S*)-Phe-(*R*)-Pip-O*t*Bu (55)

A solution of 420 mg (1.49 mmol) **54** in 7.5 mL EtOH was treated with 114 mg (3.01 mmol) $NaBH_4$ at 0 °C. The cooling bath was removed and the reaction was stirred at rt for 45 min. Acetone was added and stirring was continued for 15 min. The reaction was concentrated *in vacuo* and the residue was dissolved in DCM and 10 w% K_2CO_3 sol. was added. The layers were separated

and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*.

The crude product was redissolved in 12.0 mL MeCN and 491 mg (1.64 mmol) Cbz-(*S*)-Phe-OH were added at rt. Afterwards, 530 mg (1.65 mmol) TBTU and 300 µL (222 mg, 1.72 mmol) DIPEA were added slowly and the reaction was stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM, the combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20, 50:50) to yield 216 mg (0.463 mmol, *dr* 89:11, 31 % over two steps) of a diastereomeric mixture and 284 mg (0.609 mmol, *dr* 97:3, rotameric ratio 80:20, 41 % over two steps) of pure **55** as colourless oils.

R_f (55) = 0.55 (silica gel, PE:EA 50:50)



Major rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.61 (m, 1 H, 7-H_a), 1.22 (m, 1 H, 6-H_a), 1.31 – 1.45 (m, 2 H, 5-H_{eq}, 7-H_b), 1.42 (s, 9 H, 1-H), 1.55 (m, 1 H, 6-H_b), 2.16 (d, $^{2/3}J_{5ax,5eq/6ax/4}$ = 14.3 Hz, 1 H, 5-H_{ax}), 3.01 (m, 2 H, 11-H), 3.14 (ddd, $^2J_{8ax,8eq}$ = 13.2 Hz, $^3J_{8ax,7ax}$ = 13.2 Hz, $^3J_{8ax,7eq}$ = 2.9 Hz, 1 H, 8-H_{ax}), 3.56 (d, $^2J_{8eq,8ax}$ = 12.8 Hz, 1 H, 8-H_{eq}), 4.98 (dt, $^3J_{10,NH}$ = 8.0 Hz, $^3J_{10,11}$ = 6.4 Hz, 1 H, 10-H), 5.09 (m, 2 H, 17-H), 5.11 (m, 1 H, 4-H), 5.70 (d, $^3J_{NH,10}$ = 8.3 Hz, 1 H, NH), 7.13 – 7.37 (m, 10 H, 13-H, 14-H, 15-H, 19-H, 20-H, 21-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.5 (t, C-6), 24.4 (t, C-7), 26.5 (t, C-5), 28.0 (q, C-1), 40.4 (t, C-11), 43.6 (t, C-8), 51.5 (d, C-10), 52.9 (d, C-4), 66.7 (t, C-17), 81.6 (s, C-2), 126.9 (d, C-15), 127.9 (d, C-19), 128.0 (d, C-21), 128.5 (d, C-14 o. C-20), 128.5 (d, C-14 o. C-20), 129.6 (d, C-13), 136.2 (s, C-12), 136.5 (s, C-18), 155.4 (s, C-16), 169.7 (s, C-3), 171.0 (s, C-9).

Minor rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, 1-H), 1.71 (m, 1 H, 5-H_a), 2.27 (d, $^{2/3}J_{5b,5a/6/4}$ = 13.7 Hz, 1 H, 5-H_b), 2.76 (dd, $^2J_{11a,11b}$ = 13.9 Hz, $^3J_{11a,10}$ = 7.6 Hz, 1 H, 11-H_a), 2.86 (m, 1 H, 8-H_a), 4.56 (d, $^{2/3}J_{8b,8a/7}$ = 15.0 Hz, 1 H, 8-H_b), 4.80 (d, $^3J_{4,5a/b}$ = 5.0 Hz, 1 H, 4-H), 4.85 (m, 1 H, 10-H), 5.53 (d, $^3J_{NH,10}$ = 8.6 Hz, 1 H, NH (Phe)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.9 (t, C-6), 24.7 (t, C-7), 27.3 (t, C-5), 28.0 (q, C-1), 126.8 (d, C-15), 128.3 (d, C-14 o. C-20), 129.5 (d, C-13).

HRMS (CI):	calculated	found
$C_{27}H_{35}N_2O_5$ $[M+H]^+$	467.2540	467.2554

Optical rotation: $[\alpha]_D^{20}$ = +47.3° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 90:10, 1.0 mL/min, 20 °C:

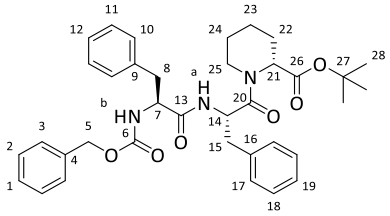
t_{R1} = 24.8 min (minor),

t_{R2} = 31.3 min (major).

Cbz-(*S*)-Phe-(*S*)-Phe-(*R*)-Pip-O*t*Bu (56)

To a solution of 451 mg (0.967 mmol) **55** in 7.75 mL MeOH was added 45 mg palladium on charcoal (10 w% Pd) at rt and the reaction was hydrogenated for 5.5 h. The mixture was then filtrated through a pad of Celite® and washed with MeOH. The filtrate was concentrated *in vacuo* and the crude product was redissolved in 7.75 mL MeCN. 319 mg (1.07 mmol) Cbz-Phe-OH, 343 mg (1.07 mmol) TBTU and 0.19 mL (141 mg, 1.09 mmol) DIPEA were added subsequently and the reaction was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added, the layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50) gave 479 mg (0.780 mmol, *dr* 89:11, rotameric ratio 79:21, 81 % over two steps) of tripeptide **56** as an off-white solid.

R_f (56) = 0.42 (silica gel, PE:EA 50:50)



Major diastereomer/rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.63 (ddddd, $^3J_{24ax,23ax} \approx {}^3J_{24ax,25ax}$ = 13.1 Hz, $^2J_{24ax,24eq}$ = 13.0 Hz, $^3J_{24ax,23eq} \approx {}^3J_{24ax,25eq}$ = 4.1 Hz, 1 H, 24-H_{ax}), 1.22 (m, 1 H, 23-H_a), 1.32 - 1.46 (m, 2 H, 22-H_a, 24-H_{eq}), 1.43 (s, 9 H, 28-H), 1.55 (m, 1 H, 23-H_b), 2.15 (d, $^{2/3}J_{22b,22a/23/21}$ = 13.6 Hz, 1 H, 22-H_b), 2.95 (d, $^3J_{15,14}$ = 6.5 Hz, 2 H, 15-H), 3.04 (m, 2 H, 8-H), 3.13 (ddd, $^2J_{25ax,25eq} \approx {}^3J_{25ax,24ax}$ = 13.2 Hz, $^3J_{25ax,24eq}$ = 2.9 Hz, 1 H, 25-H_{ax}), 3.51 (d, $^2J_{25eq,25ax}$ = 12.5 Hz, 1 H, 25-H_{eq}), 4.44 (m, 1 H, 7-H), 5.00 - 5.12 (m, 3 H, 5-H, 21-H), 5.16 (td, $^3J_{14,15}$ = 7.4 Hz, $^3J_{14,NH}$ = 6.7 Hz, 1 H, 14-H), 5.26 (d, $^3J_{NH,7}$ = 7.6 Hz, 1 H, NH_b), 6.74 (d, $^3J_{NH,14}$ = 7.3 Hz, 1 H, NH_a), 7.08 - 7.17 (m, 4 H, 10-H, 17-H), 7.17 - 7.38 (m, 11 H, 1-H, 2-H, 3-H, 11-H, 12-H, 18-H, 19-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.5 (t, C-23), 24.4 (t, C-24), 26.6 (t, C-22), 28.0 (q, C-28), 38.4 (t, C-8), 39.8 (t, C-15), 43.5 (t, C-25), 50.0 (d, C-14), 52.9 (d, C-21), 55.9 (d, C-7), 66.9 (t, C-5), 81.6 (s, C-27), 127.0 (d, C-12, C-19), 128.0 (d, C-3), 128.1 (d, C-1), 128.4 (d, C-2 o. C-11 o. C-18), 128.5 (d, C-2 o. C-11 o. C-18), 128.6 (d, C-2 o. C-11 o. C-18), 129.4 (d, C-10 o. C-17), 129.6 (d, C-10 o. C-17), 136.0 (s, C-9), 136.0 (s, C-16), 136.1 (s, C-4), 155.7 (s, C-6), 169.5 (s, C-13), 169.8 (s, C-20), 170.4 (s, C-26).

Minor diastereomer/rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, 28-H), 1.49 (s, 9 H, 28-H), 1.71 (m, 1 H, 23-H_b), 2.27 (d, $^{2/3}J_{22b,22a/23/21}$ = 13.2 Hz, 1 H, 22-H_b), 2.74 (dd, $^{2}J_{15a,15b}$ = 14.2 Hz, $^{3}J_{15a,14}$ = 7.4 Hz, 1 H, 15-H_a), 4.36 (m, 1 H, 7-H), 4.52 (m, 1 H, 7-H), 4.64 (m, 1 H, 14-H), 4.79 (d, $^{3}J_{21,22a/b}$ = 4.8 Hz, 1 H, 21-H), 6.25 (br s, 1 H, Cbz-NH), 6.41 (d, $^{3}J_{NH,14}$ = 8.0 Hz, 1 H, NH (Phe)), 6.68 (d, $^{3}J_{NH,14}$ = 8.1 Hz, 1 H, NH (Phe)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-28), 128.3 (d, C-1), 128.8 (d, C-2 o. C-11 o. C-18), 129.2 (d, C-2 o. C-11 o. C-18), 129.3 (d, C-10 o. C-17), 129.6 (d, C-10 o. C-17).

HRMS (CI):	calculated	found
$C_{36}H_{44}N_3O_6$ $[M+H]^+$	614.3225	614.3230

Melting point: 66-67 °C

Optical rotation: $[\propto]_D^{20}$ = +22.1° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 60:40, 1.0 mL/min, 20 °C:

t_{R1} = 11.1 min (11 %),

t_{R2} = 13.8 min (89 %).

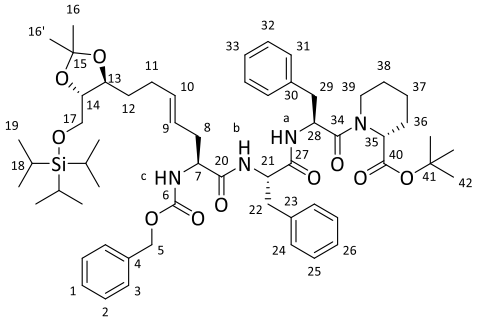
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.8 mL/min, t_R = 10.9 min ($[M+H]^+$ = 614).

tert-Butyl (*R*)-1-(((*S*,*E*)-2-(((benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enoyl)-L-phenylalanyl-L-phenylalanyl)-piperidine-2-carboxylate (57)

A solution of 245 mg (0.399 mmol) **56** in 2.0 mL MeOH was treated with 25 mg palladium on charcoal (10 w% Pd) and hydrogenated at rt for 5 h. The reaction mixture was filtrated through a pad of Celite® and washed with MeOH. The filtrate was concentrated *in vacuo* and the crude product was dissolved in 3.2 mL acetonitrile at rt. 225 mg (0.399 mmol) **10**, 128 mg (0.399 mmol) TBTU and 73 µL (54.0 mg, 0.418 mmol) DIPEA were added subsequently and the reaction was stirred at rt overnight. The reaction was concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added, the layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried

over Na_2SO_4. After purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50), 360 mg (0.351 mmol, *dr* ~ 80:20, 88 % over two steps) of tetrapeptide **57** were obtained as an off-white solid.

R_f (57) = 0.45 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.61 (m, 1 H, 38-H_a), 1.00 – 1.13 (m, 21 H, 18-H, 19-H), 1.33 – 1.48 (m, 2 H, 36-H_a, 38-H_b), 1.35 (s, 3 H, 16-H), 1.38 (s, 3 H, 16-H'), 1.44 (s, 9 H, 42-H), 1.50 – 1.76 (m, 4 H, 12-H, 37-H), 2.03 – 2.29 (m, 3 H, 11-H, 36-H_b), 2.39 (dd, $^3J_{8,7} \approx {}^3J_{8,9}$ = 6.0 Hz, 2 H, 8-H), 2.87 – 3.03 (m, 3 H, 22-H_a, 29-H), 3.07 (dd, $^2J_{22b,22a}$ = 14.1 Hz, $^3J_{22b,21}$ = 6.1 Hz, 1 H, 22-H_b), 3.15 (ddd, $^2J_{39ax,39eq} \approx {}^3J_{39ax,38ax}$ = 13.2 Hz, $^3J_{39ax,38eq}$ = 2.9 Hz, 1 H, 39-H_{ax}), 3.51 (d, $^2J_{39eq,39ax}$ = 13.5 Hz, 1 H, 39-H_{eq}), 3.68 (m, 1 H, 14-H), 3.73 (dd, $^2J_{17a,17b}$ = 10.1 Hz, $^3J_{17a,14}$ = 5.9 Hz, 1 H, 17-H_a), 3.85 (dd, $^2J_{17b,17a}$ = 10.1 Hz, $^3J_{17b,14}$ = 3.9 Hz, 1 H, 17-H_b), 3.90 (td, $^3J_{13,12}$ = 7.9 Hz, $^3J_{13,14}$ = 3.4 Hz, 1 H, 13-H), 4.15 (m, 1 H, 7-H), 4.64 (dt, $^3J_{21,NH}$ = 7.6 Hz, $^3J_{21,22}$ = 6.6 Hz, 1 H, 21-H), 5.04 – 5.13 (m, 4 H, 5-H, 35-H, NH_c), 5.15 (dt, $^3J_{28,NH} \approx {}^3J_{28,29}$ = 7.3 Hz, 1 H, 28-H), 5.26 (m, 1 H, 9-H), 5.51 (dt, $^3J_{10,9}$ = 14.7 Hz, $^3J_{10,11}$ = 7.2 Hz, 1 H, 10-H), 6.61 (d, $^3J_{NH,21}$ = 7.7 Hz, 1 H, NH_b), 6.68 (d, $^3J_{NH,28}$ = 7.5 Hz, 1 H, NH_a), 7.09 – 7.16 (m, 4 H, 24-H, 31-H), 7.18 – 7.28 (m, 6 H, 25-H, 26-H, 32-H, 33-H), 7.30 – 7.40 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-18), 17.9 (q, C-19), 20.5 (t, C-37), 24.4 (t, C-38), 26.7 (t, C-36), 27.0 (q, C-16), 27.4 (q, C-16'), 28.0 (q, C-42), 29.2 (t, C-11), 33.1 (t, C-12), 35.3 (t, C-8), 38.2 (t, C-22), 39.8 (t, C-29), 43.5 (t, C-39), 50.0 (d, C-28), 52.9 (d, C-35), 54.1 (d, C-7), 54.1 (d, C-21), 64.1 (t, C-17), 67.2 (t, C-5), 78.6 (d, C-13), 80.8 (d, C-14), 81.6 (s, C-41), 108.4 (s, C-15), 124.3 (d, C-9), 127.0 (d, C-26, C-33), 128.1 (d, C-3), 128.2 (d, C-1), 128.5 (d, C-2 o. C-25 o. C-32), 128.5 (d, C-2 o. C-25 o. C-32), 128.6 (d, C-2 o. C-25 o. C-32), 129.3 (d, C-24), 129.6 (d, C-31), 135.0 (d, C-10), 136.0 (s, C-4), 136.1 (s, C-23, C-30), 156.1 (s, C-6), 169.3 (s, C-27), 169.6 (s, C-40), 170.3 (s, C-34), 170.7 (s, C-20).

Minor diastereomer (selected signals):

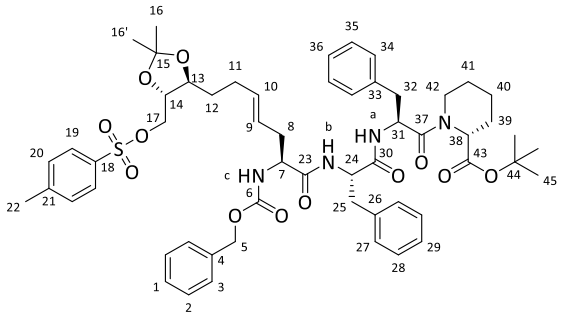
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, 42-H), 2.33 (dd, $^3J_{8,7} \approx {}^3J_{8,9}$ = 6.4 Hz, 2 H, 8-H), 2.77 (m, 1 H, 29-H_a), 4.07 (t, $^3J_{7,8}$ = 6.2 Hz, 1 H, 7-H), 4.36 (dt, $^3J_{21,NH}$ = 7.6 Hz, $^3J_{21,22}$ = 5.5 Hz, 1 H, 21-H), 4.52 (m, 1 H, 28-H), 4.78 (d, $^3J_{35,36a}$ = 4.9 Hz, 1 H, 35-H), 6.43 (d, $^3J_{NH,21}$ = 7.8 Hz, 1 H, NH_b), 6.52 (d, $^3J_{NH,28}$ = 7.1 Hz, 1 H, NH_a), 7.06 (m, 2 H, 24-H o. 31-H).

HRMS (CI):	calculated	found
$C_{58}H_{85}N_4O_{10}Si$ $[M+H]^+$	1025.6029	1025.6059
Melting point:	68 °C	
Optical rotation:	$[\alpha]_D^{20}$ = +9.5° (c = 1.0, $CHCl_3$)	

***tert*-Butyl (*R*)-1-(((*S*,*E*)-2-(((benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-((tosyloxy)methyl)-1,3-dioxolan-4-yl)hept-4-enoyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxylate (58)**

331 mg (0.323 mmol) **57** were dissolved in 3.2 mL THF and treated with 484 µL (0.484 mmol) TBAF (1 M in THF) at rt. The reaction was stirred for 1.5 h and concentrated *in vacuo*. The residue was redissolved in DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dissolved in 3.2 mL pyridine abs. and cooled to 0 °C. Afterwards, 5.0 mg (40.9 µmol) 4-DMAP and 96.0 mg (0.504 mmol) TosCl were added and the reaction was allowed to warm to rt overnight. Further 36 mg (0.189 mmol) TosCl were added and stirring was continued for 3.5 h. For workup, the reaction was diluted with Et_2O and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with 1 M HCl sol. three times and dried over Na_2SO_4. Purification of the crude product by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50) gave 264 mg (0.258 mmol, *dr* ~ 78:22, 80 % over two steps) of tosylate **58** as an off-white solid.

R_f (58) = 0.29 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.62 (m, 1 H, 41-H_a), 1.18 (m, 1 H, 40-H_a), 1.27 (s, 3 H, 16-H), 1.33 (s, 3 H, 16-H'), 1.37 – 1.48 (m, 2 H, 39-H_a, 41-H_b), 1.44 (s, 9 H, 45-H), 1.51 – 1.60 (m, 3 H, 12-H, 40-H_b), 1.96 – 2.18 (m, 3 H, 11-H, 39-H_b), 2.36 (m, 2 H, 8-H), 2.44 (s, 3 H, 22-H), 2.89 – 3.04 (m, 3 H, 25-H_a, 32-H), 3.08 (dd, $^2J_{25b,25a}$ = 13.9 Hz, $^3J_{25b,24}$ = 6.5 Hz, 1 H, 25-H_b), 3.15 (ddd, $^2J_{42ax,42eq} \approx {}^3J_{42ax,41ax}$ = 13.1 Hz, $^3J_{42ax,41eq}$ = 2.5 Hz, 1 H, 42-H_{ax}), 3.52 (d, $^2J_{42eq,42ax}$ = 13.3 Hz, 1 H, 42-H_{eq}), 3.72 – 3.82 (m, 2 H, 13-H, 14-H), 4.03 (dd, $^2J_{17a,17b}$ = 10.7 Hz, $^3J_{17a,14}$ = 4.3 Hz, 1 H,

17-H_a), 4.08 (dd, $^2J_{17b,17a}$ = 10.6 Hz, $^3J_{17b,14}$ = 4.1 Hz, 1 H, 17-H_b), 4.16 (m, 1 H, 7-H), 4.64 (dt, $^3J_{24,NH}$ = 7.5 Hz, $^3J_{24,25}$ = 6.6 Hz, 1 H, 24-H), 4.97 – 5.32 (m, 6 H, 5-H, 9-H, 31-H, 38-H, NH_c), 5.48 (dt, $^3J_{10,9}$ = 14.6 Hz, $^3J_{10,11}$ = 6.9 Hz, 1 H, 10-H), 6.59 (d, $^3J_{NH,24}$ = 7.5 Hz, 1 H, NH_b), 6.70 (d, $^3J_{NH,31}$ = 7.5 Hz, 1 H, NH_a), 7.05 – 7.16 (m, 4 H, 27-H, 34-H), 7.17 – 7.28 (m, 6 H, 28-H, 29-H, 35-H, 36-H), 7.29 – 7.39 (m, 7 H, 1-H, 2-H, 3-H, 20-H), 7.78 (d, $^3J_{19,20}$ = 8.2 Hz, 2 H, 19-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.5 (t, C-40), 21.6 (q, C-22), 24.4 (t, C-41), 26.7 (t, C-39), 26.7 (q, C-16), 27.2 (q, C-16'), 28.0 (q, C-45), 28.8 (t, C-11), 32.5 (t, C-12), 35.4 (t, C-8), 38.2 (t, C-25), 39.8 (t, C-32), 43.5 (t, C-42), 50.0 (d, C-31), 52.9 (d, C-38), 54.1 (d, C-7, 24), 67.1 (t, C-5), 69.1 (t, C-17), 77.2 (d, C-13), 77.9 (d, C-14), 81.6 (s, C-44), 109.4 (s, C-15), 124.9 (d, C-9), 127.0 (d, C-29), 127.0 (d, C-36), 128.0 (d, C-19), 128.2 (d, C-3), 128.2 (d, C-1), 128.5 (d, C-2 o. C-28 o. C-35), 128.5 (d, C-2 o. C-28 o. C-35), 128.6 (d, C-2 o. C-28 o. C-35), 129.4 (d, C-27 o. C-34), 129.6 (d, C-27 o. C-34), 129.9 (d, C-20), 132.7 (s, C-18), 134.2 (d, C-10), 136.0 (s, C-4), 136.1 (s, C-26), 136.1 (s, C-33), 145.0 (s, C-21), 169.3 (s, C-30), 169.6 (s, C-23), 170.3 (s, C-37), 170.7 (s, C-43). The signal of C-6 wasn't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, 45-H), 2.78 (m, 1 H, 32-H_a), 4.36 (dt, $^3J_{31,NH}$ = 7.3 Hz, $^3J_{31,32}$ = 5.5 Hz, 1 H, 31-H), 4.52 (m, 1 H, 24-H), 4.78 (m, 1 H, 38-H), 6.43 (d, $^3J_{NH,24}$ = 7.7 Hz, 1 H, NH_b), 6.54 (d, $^3J_{NH,31}$ = 6.7 Hz, 1 H, NH_a).

HRMS (CI):	calculated	found
$C_{56}H_{71}N_4O_{12}S$ $[M+H]^+$	1023.4784	1023.4785

Melting point: 60 °C

Optical rotation: $[\propto]_D^{20}$ = –2.8° (c = 1.0, $CHCl_3$)

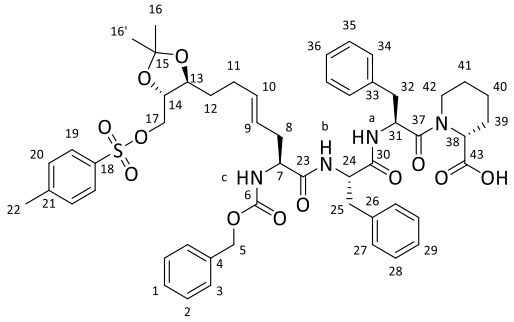
LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 15.6 min ($[M+H]^+$ = 1024).

(*R*)-1-(((*S*,*E*)-2-(((Benzyloxy)carbonyl)amino)-7-((4*S*,5*S*)-2,2-dimethyl-5-((tosyloxy)methyl)-1,3-dioxolan-4-yl)hept-4-enoyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxylic acid (59)

To a solution of 200 mg (0.195 mmol) **58** in 1.0 mL THF were added 1.0 mL HCl sol. (5 w% in H_2O) at rt and the reaction was heated to 60 °C overnight. For workup, the reaction was diluted with DCM and brine was added. The layers were separated, the aqueous phase was extracted three times with DCM and the combined organic layers were dried over Na_2SO_4. The crude product was dissolved in 1.0 mL DCM abs. before 1.0 mL (1.48 g, 13.0 mmol) TFA was added dropwise. The reaction was stirred for 2 h at rt and concentrated *in high-vacuo*. The crude product was dissolved in 2.5 mL acetone and 2.8 mg (14.7 µmol) *p*TosOH·H_2O were added. The reaction was heated to 60 °C overnight and the reaction was concentrated *in vacuo*. After purification by column

chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5), 152 mg (0.157 mmol, 81 % over three steps) of acid **59** (contaminated with educt **58**) were obtained as an off-white solid.

R_f (59) = 0.08 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.68 (m, 1 H, 41-H_a), 1.14 – 1.45 (m, 3 H, 39-H_a, 40-H_a, 41-H_b), 1.27 (s, 3 H, 16-H), 1.33 (s, 3 H, 16-H'), 1.47 – 1.62 (m, 3 H, 12-H, 40-H_b), 2.03 (m, 2 H, 11-H), 2.20 (d, $^{2/3}J_{39b,39a/38/40ax}$ = 12.7 Hz, 1 H, 39-H_b), 2.35 (m, 2 H, 8-H), 2.43 (s, 3 H, 22-H), 2.89 (dd, $^2J_{25a,25b}$ = 14.0 Hz, $^3J_{25a,24}$ = 7.3 Hz, 1 H, 25-H_a), 2.94 – 3.18 (m, 4 H, 25-H_b, 32-H, 42-H_{ax}), 3.56 (d, $^2J_{42eq,42ax}$ = 13.8 Hz, 1 H, 42-H_{eq}), 3.69 – 3.82 (m, 2 H, 13-H, 14-H), 4.02 (dd, $^2J_{17a,17b}$ = 10.7 Hz, $^3J_{17a,14}$ = 4.5 Hz, 1 H, 17-H_a), 4.07 (dd, $^2J_{17b,17a}$ = 10.6 Hz, $^3J_{17b,14}$ = 4.0 Hz, 1 H, 17-H_b), 4.17 (m, 1 H, 7-H), 4.80 (dt, $^3J_{24,NH}$ = 7.4 Hz, $^3J_{24,25}$ = 6.0 Hz, 1 H, 24-H), 4.98 – 5.27 (m, 4 H, 5-H, 9-H, 31-H, 38-H), 5.32 – 5.49 (m, 2 H, 10-H, NH_c), 6.86 (d, $^3J_{NH,24}$ = 7.5 Hz, 1 H, NH_b), 7.06 (d, $^3J_{27,28}$ = 7.0 Hz, 2 H, 27-H), 7.10 – 7.37 (m, 15 H, 1-H, 2-H, 3-H, 20-H, 28-H, 29-H, 34-H, 35-H, 36-H), 7.50 (d, $^3J_{NH,31}$ = 7.6 Hz, 1 H, NH_a), 7.77 (d, $^3J_{19,20}$ = 8.2 Hz, 2 H, 19-H). The signal of -COOH wasn't observed in the ^{13}C-NMR spectrum.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.4 (t, C-40), 21.6 (q, C-22), 24.3 (t, C-41), 26.0 (t, C-39), 26.6 (q, C-16), 27.2 (q, C-16'), 28.7 (t, C-11), 32.4 (t, C-12), 35.5 (t, C-8), 38.3 (t, C-25), 39.4 (t, C-32), 43.8 (t, C-42), 50.3 (d, C-31), 52.6 (d, C-38), 53.9 (d, C-24), 54.5 (d, C-7), 67.1 (t, C-5), 69.1 (t, C-17), 77.2 (d, C-13), 77.9 (d, C-14), 109.4 (s, C-15), 128.8 (d, C-9), 126.9 (d, C-29), 127.0 (d, C-36), 128.0 (d, C-19), 128.1 (d, C-3), 128.2 (d, C-1), 128.4 (d, C-2 o. C-28 o. C-35), 128.5 (d, C-2 o. C-28 o. C-35), 129.2 (d, C-2 o. C-28 o. C-35), 129.4 (d, C-27 o. C-34), 129.5 (d, C-27 o. C-34), 129.9 (d, C-20), 132.6 (s, C-18), 134.0 (d, C-10), 136.0 (s, C-4), 136.1 (s, C-26, C-33), 145.0 (s, C-21), 156.1 (s, C-6), 170.3 (s, C-30), 171.3 (s, C-23 o. C-37), 173.1 (s, C-43). The signal of C-23/C-37 wasn't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{52}H_{63}N_4O_{12}S$ $[M+H]^+$	967.4158	967.4185

Melting point: 73 °C

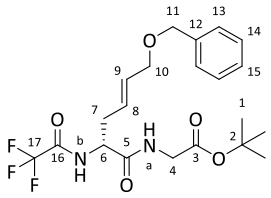
Optical rotation: $[\alpha]_D^{20}$ = –8.9° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.8 mL/min, t_{R1} = 10.4 min (23 %, $[M+H]^+$ = 1024), t_{R2} = 10.8 min (77 %, $[M+H]^+$ = 968).

***tert*-Butyl (*R*,*E*)-(6-(benzyloxy)-2-(2,2,2-trifluoroacetamido)hex-4-enoyl)glycinate (61b)**

To a solution of 1.46 g (4.41 mmol) **51b** in 20.0 mL DCM abs. were added 931 mg (4.86 mmol) EDC·HCl and 67.6 mg (0.441 mmol) HOBt at 0 °C. The reaction was stirred for 10 min at this temperature before 740 mg (4.42 mmol) HCl·H-Gly-O*t*Bu and 0.77 mL (570 mg, 4.41 mmol) DIPEA were added subsequently and the reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 90:10, 70:30) gave 1.79 g (3.78 mmol, 94 % pure, *er* 76:24, 86 %) of dipeptide **61b** as a yellow oil.

R_f (61b) = 0.25 (silica gel, PE:EA 70:30)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.55 (ddd, $^2J_{7a,7b}$ = 13.8 Hz, $^3J_{7a,6} \approx {}^3J_{7a,8}$ = 6.4 Hz, 1 H, 7-H_a), 2.64 (ddd, $^2J_{7b,7a}$ = 13.9 Hz, $^3J_{7b,6} \approx {}^3J_{7b,8}$ = 6.8 Hz, 1 H, 7-H_b), 3.90 (dd, $^2J_{4a,4b}$ = 18.1 Hz, $^3J_{4a,NH}$ = 5.0 Hz, 1 H, 4-H_a), 3.96 (dd, $^2J_{4b,4a}$ = 18.1 Hz, $^3J_{4b,NH}$ = 5.3 Hz, 1 H, 4-H_b), 3.97 (d, $^3J_{10,9}$ = 5.3 Hz, 2 H, 10-H), 4.48 (s, 2 H, 11-H), 4.57 (td, $^3J_{6,7} \approx {}^3J_{6,NH}$ = 6.9 Hz, 1 H, 6-H), 5.66 (dt, $^3J_{8,9}$ = 15.0 Hz, $^3J_{8,7}$ = 7.3 Hz, 1 H, 8-H), 5.77 (dt, $^3J_{9,8}$ = 15.5 Hz, $^3J_{9,10}$ = 5.5 Hz, 1 H, 9-H), 6.57 (br s, 1 H, NH_a), 7.27 – 7.34 (m, 5 H, 13-H, 14-H, 15-H), 7.42 (d, $^3J_{NH,6}$ = 7.8 Hz, 1 H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.9 (q, C-1), 35.4 (t, C-7), 42.1 (t, C-4), 52.8 (d, C-6), 70.0 (t, C-10), 72.1 (t, C-11), 82.8 (s, C-2), 115.6 (q, $^1J_{17,F}$ = 287 Hz, C-17), 126.3 (d, C-8), 127.6 (d, C-15), 127.7 (d, C-13), 128.4 (d, C-14), 132.1 (d, C-9), 138.1 (s, C-12), 156.8 (q, $^2J_{16,F}$ = 37 Hz, C-16), 168.3 (s, C-3 o. C-5), 169.3 (s, C-3 o. C-5).

HRMS (CI):	calculated	found
$C_{21}H_{28}F_3N_2O_5$ $[M]^+$	445.1945	445.1943

Optical rotation: $[\alpha]_D^{20}$ = –13.9° (*er* 96:4, c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

(*R*)-**61b**: t_R = 21.9 min (76 %),

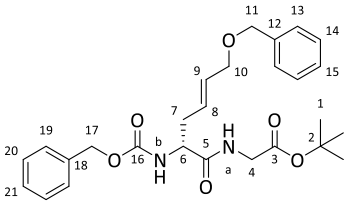
(*S*)-**61b**: t_R = 26.2 min (24 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 7.26 min ($[M+Na]^+$ = 467).

***tert*-Butyl (*R*,*E*)-(6-(benzyloxy)-2-(((benzyloxy)carbonyl)amino)hex-4-enoyl)glycinate (61c)**

To a solution of 2.10 g (5.68 mmol) **51a** in 55 mL THF abs. were added 0.64 mL (589 mg, 5.82 mmol) NMM before 0.75 mL (786 mg, 5.76 mmol) IBCF were added dropwise at –20 °C. The reaction was stirred for 10 min before 953 mg (5.69 mmol) HCl·H-Gly-O*t*Bu and further 0.64 mL (589 mg, 5.82 mmol) NMM were added and the reaction was allowed to warm to rt overnight. The reaction was then filtrated and washed with diethyl ether. The filtrate was concentrated *in vacuo* and redissolved in Et_2O. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 90:10, 70:30). 2.47 g (5.12 mmol, *er* > 99:1, 90 %) of **61c** were obtained as a slightly yellow oil.

R_f (61c) = 0.32 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.55 (m, 2 H, 7-H), 3.91 (m, 2 H, 4-H), 3.96 (m, 2 H, 10-H), 4.28 (m, 1 H, 6-H), 4.47 (s, 2 H, 11-H), 5.10 (s, 2 H, 17-H), 5.35 (d, $^3J_{NH,6}$ = 6.0 Hz, 1 H, NH_b), 5.62 – 5.75 (m, 2 H, 8-H, 9-H), 6.55 (br s, 1 H, NH_a), 7.26 – 7.35 (m, 10 H, 13-H, 14-H, 15-H, 19-H, 20-H, 21-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 35.4 (t, C-7), 42.0 (t, C-4), 54.2 (d, C-6), 67.2 (t, C-17), 70.2 (t, C-10), 72.1 (t, C-11), 82.4 (s, C-2), 127.6 (d, C-15 o. C-21), 127.8 (d, C-8), 127.8 (d, C-13), 128.1 (d, C-19), 128.2 (d, C-15 o. C-21), 128.4 (d, C-14 o. C-20), 128.5 (d, C-14 o. C-20), 131.3 (d, C-9), 136.0 (s, C-18), 138.1 (s, C-12), 156.0 (s, C-16), 168.6 (s, C-3), 170.9 (s, C-5).

HRMS (CI):	calculated	found
$C_{27}H_{35}N_2O_6$ $[M+H]^+$	483.2490	483.2493

Optical rotation: $[\alpha]_D^{20}$ = +0.8° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 80:20, 1.0 mL/min, 20 °C:

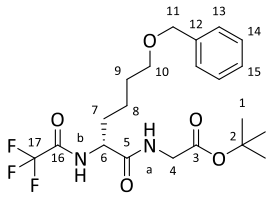
(*R*)-**61c**: t_R = 33.8 min (> 99 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 12.5 min ($[M+Na]^+$ = 505).

***tert*-Butyl (*R*)-(6-(benzyloxy)-2-(2,2,2-trifluoroacetamido)hexanoyl)glycinate (62c)**

To a solution of 1.60 g (3.32 mmol) **61c** in 15 mL MeOH were added 163 mg palladium on charcoal (10 w% Pd) at rt. The reaction was set under a H_2-atmossphere and hydrogenated for 4 h. Afterwards, the reaction was filtrated through a pad of Celite® and washed with MeOH. The filtrate was concentrated *in vacuo* and redissolved in 15 mL MeOH. 0.67 mL (853 mg, 6.66 mmol) TFA-OMe were added at 0 °C and the reaction was allowed to warm to rt overnight. The reaction mixture was concentrated and redissolved in Et_2O. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 70:30) gave 1.32 g (2.96 mmol, *er* 95:5, 89 %) dipeptide **62c** as a colourless oil.

R_f (62c) = 0.48 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, 1-H), 1.49 (m, 2 H, 8-H), 1.62 – 1.79 (m, 3 H, 7-H_a, 9-H), 1.94 (m, 1 H, 7-H_b), 3.48 (dt, $^2J_{10a,10b}$ = 9.4 Hz, $^3J_{10a,9}$ = 6.2 Hz, 1 H, 10-H_a), 3.53 (dt, $^2J_{10b,10a}$ = 9.5 Hz, $^3J_{10b,9}$ = 6.0 Hz, 1 H, 10-H_b), 3.73 (dd, $^2J_{4a,4b}$ = 18.3 Hz, $^3J_{4a,NH}$ = 4.8 Hz, 1 H, 4-H_a), 3.91 (dd, $^2J_{4b,4a}$ = 18.2 Hz, $^3J_{4b,NH}$ = 5.7 Hz, 1 H, 4-H_b), 4.49 (s, 2 H, 11-H), 4.50 (m, 1 H, 6-H), 6.36 (t, $^3J_{4,NH}$ = 4.9 Hz, 1 H, NH_a), 7.25 – 7.37 (m, 6 H, 13-H, 14-H, 15-H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.0 (t, C-8), 28.0 (q, C-1), 28.8 (t, C-9), 32.5 (t, C-7), 42.0 (t, C-4), 53.1 (d, C-6), 70.0 (t, C-10), 73.0 (t, C-11), 82.7 (s, C-2), 115.7 (q, $^1J_{17,F}$ = 288 Hz, C-17), 127.7 (d, C-15), 127.8 (d, C-13 o. C-14), 128.4 (d, C-13 o. C-14), 138.2 (s, C-12), 156.8 (q, $^2J_{16,F}$ = 37 Hz, C-16), 168.3 (s, C-3 o. C-5), 169.9 (s, C-3 o. C-5).

HRMS (CI):	calculated	found
$C_{21}H_{30}F_3N_2O_5$ $[M+H]^+$	447.2101	447.2104

Optical rotation: $[\alpha]_D^{20}$ = –2.1° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 90:10, 1.0 mL/min, 20 °C:

(*R*)-**62c**: t_R = 11.2 min (95 %),

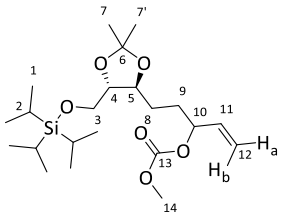
(*S*)-**62c**: t_R = 13.1 min (5 %).

5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl methyl carbonate (65)

To a solution of 732 mg (1.97 mmol) **7c** in 2.0 mL pyridine were added 0.31 mL (379 mg, 4.02 mmol) methyl chloroformate carefully at 0 °C. The reaction was allowed to warm to rt overnight

before further 0.46 mL (562 mg, 5.95 mmol) methyl chloroformate were added at 0 °C and stirring was continued for 3 h. For workup, water was added and the layers were separated. The aqueous phase was extracted three times with DCM and the combined organic layers were dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10) to give 795 mg (1.85 mmol, 94 %) **65** as a colourless liquid.

R_f (65) = 0.31 (silica gel, PE:EA 90:10)



Diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.14 (m, 21 H, 1-H, 2-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.62 (m, 1 H, 8-H_a), 1.70 – 1.99 (m, 3 H, 8-H_b, 9-H), 3.70 (m, 1 H, 4-H), 3.73 (dd, $^2J_{3a,3b}$ = 9.8 Hz, $^3J_{3a,4}$ = 6.5 Hz, 1 H, 3-H_a), 3.76 (s, 3 H, 14-H), 3.88 (m, 1 H, 3-H_b), 3.93 (m, 1 H, 5-H), 5.09 (dt, $^3J_{10,11} \approx {}^3J_{10,9}$ = 6.2 Hz, 1 H, 10-H), 5.21 (ddd, $^3J_{12a,11}$ = 10.5 Hz, $^2J_{12a,12b} \approx {}^4J_{12a,10}$ = 1.0 Hz, 1 H, 12-H_a), 5.30 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a} \approx {}^4J_{12b,10}$ = 1.1 Hz, 1 H, 12-H_b), 5.79 (ddd, $^3J_{11,12b}$ = 17.3 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 7.3 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.3 (q, C-7'), 28.7 (t, C-8), 30.6 (t, C-9), 54.6 (q, C-14), 64.2 (t, C-3), 78.8 (d, C-10), 79.0 (d, C-5), 80.8 (d, C-4), 108.5 (s, C-6), 117.5 (t, C-12), 135.7 (d, C-11), 155.2 (s, C-13).

Diastereomer 2 (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.22 (ddd, $^3J_{12a,11}$ = 10.5 Hz, $^2J_{12a,12b} \approx {}^4J_{12a,10}$ = 1.1 Hz, 1 H, 12-H_a), 5.31 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a} \approx {}^4J_{12b,10}$ = 1.1 Hz, 1 H, 12-H_b), 5.79 (ddd, $^3J_{11,12b}$ = 17.3 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.8 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 29.0 (t, C-8), 30.9 (t, C-9), 78.9 (d, C-10), 79.2 (d, C-5), 80.8 (d, C-4), 117.8 (t, C-12), 135.8 (d, C-11), 155.2 (s, C-13).

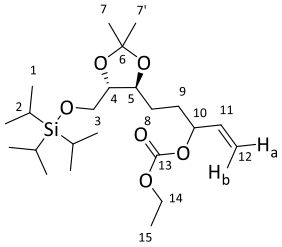
HRMS (CI):	calculated	found
$C_{22}H_{43}O_6Si$ $[M+H]^+$	431.2823	431.2796

5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl ethyl carbonate (66)

A solution of 396 mg (1.06 mmol) **7c** in 1.0 mL pyridine abs. was treated with 0.20 mL (226 mg, 2.08 mmol) ethyl chloroformate dropwise at 0 °C. The reaction was allowed to warm to rt over-night. For workup, the reaction was diluted with Et_2O and 1 M $CuSO_4$ sol. was added. The organic

phase was washed three times with 1 M $CuSO_4$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 90:10) gave 429 mg (0.965 mmol, 91 %) of carbonate **66** as a colourless oil.

R_f (66) = 0.40 (silica gel, PE:EA 90:10)



Diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.16 (m, 21 H, 1-H, 2-H), 1.30 (t, $^3J_{15,14}$ = 7.2 Hz, 3 H, 15-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.61 (m, 1 H, 8-H_a), 1.71 – 1.98 (m, 3 H, 8-H_b, 9-H), 3.70 (m, 1 H, 4-H), 3.73 (dd, $^2J_{3a,3b}$ = 9.8 Hz, $^3J_{3a,4}$ = 6.3 Hz, 1 H, 3-H_a), 3.88 (dd, $^2J_{3b,3a}$ = 9.5 Hz, $^3J_{3b,4}$ = 3.3 Hz, 1 H, 3-H_b), 3.93 (m, 1 H, 5-H), 4.18 (q, $^3J_{14,15}$ = 7.1 Hz, 2 H, 14-H), 5.08 (dt, $^3J_{10,11}$ ≈ $^3J_{10,9}$ = 6.0 Hz, 1 H, 10-H), 5.20 (ddd, $^3J_{12a,11}$ = 10.5 Hz, $^2J_{12a,12b}$ ≈ $^4J_{12a,10}$ = 1.0 Hz, 1 H, 12-H_a), 5.30 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a}$ ≈ $^4J_{12b,10}$ = 1.1 Hz, 1 H, 12-H_b), 5.79 (ddd, $^3J_{11,12b}$ = 17.3 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.8 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 14.2 (q, C-15), 18.0 (q, C-1), 27.0 (q, C-7), 27.4 (q, C-7'), 28.8 (t, C-8), 30.7 (t, C-9), 63.8 (t, C-14), 64.2 (t, C-3), 78.6 (d, C-10), 79.0 (d, C-5), 80.8 (d, C-4), 108.5 (s, C-6), 117.5 (t, C-12), 135.8 (d, C-11), 154.6 (s, C-13).

Diastereomer 2 (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.21 (ddd, $^3J_{12a,11}$ = 10.5 Hz, $^2J_{12a,12b}$ ≈ $^4J_{12a,10}$ = 1.0 Hz, 1 H, 12-H_a), 5.31 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a}$ ≈ $^4J_{12b,10}$ = 1.1 Hz, 1 H, 12-H_b), 5.80 (ddd, $^3J_{11,12b}$ = 17.3 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.8 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 29.1 (t, C-8), 30.9 (t, C-9), 78.7 (d, C-10), 79.2 (d, C-5), 80.9 (d, C-4), 110.0 (s, C-6), 117.7 (t, C-12), 135.9 (d, C-11), 154.6 (s, C-13).

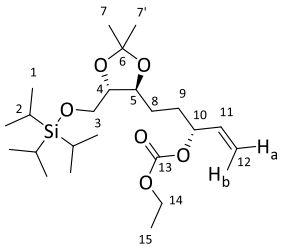
HRMS (CI):	calculated	found
$C_{23}H_{45}O_6Si$ $[M+H]^+$	445.2980	445.2978

(*R*)-5-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl ethyl carbonate ((3*R*)-66)

2.18 g (5.85 mmol) allylic alcohol (3*R*)-**7c** were dissolved in 7.5 mL pyridine abs. and cooled to 0 °C. Afterwards, 1.12 mL (1.27 g, 11.7 mmol) Ethyl chloroformate were added carefully and the

reaction was allowed to warm to rt within 5 h. For workup, the reaction mixture was diluted with Et_2O and 1 M $CuSO_4$ sol. was added. The layers were separated, the organic phase was washed three times with 1 M $CuSO_4$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 100:0, 90:10) afforded 2.41 g (5.42 mmol, 93 %) allylic carbonate (3*R*)-**66** as a colourless oil.

R_f ((3*R*)-66) = 0.39 (silica gel, PE:EA 90:10)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.14 (m, 21 H, 1-H, 2-H), 1.30 (t, $^3J_{15,14}$ = 7.2 Hz, 3 H, 15-H), 1.36 (s, 3 H, 7-H), 1.39 (s, 3 H, 7-H'), 1.59 (m, 1 H, 8-H_a), 1.75 – 1.93 (m, 3 H, 8-H_b, 9-H), 3.70 (m, 1 H, 4-H), 3.72 (dd, $^2J_{3a,3b}$ = 9.8 Hz, $^3J_{3a,4}$ = 6.4 Hz, 1 H, 3-H_a), 3.88 (dd, $^2J_{3b,3a}$ = 9.5 Hz, $^3J_{3b,4}$ = 3.2 Hz, 1 H, 3-H_b), 3.91 (m, 1 H, 5-H), 4.18 (q, $^3J_{14,15}$ = 7.2 Hz, 2 H, 14-H), 5.08 (dt, $^3J_{10,11} \approx {}^3J_{10,9}$ = 6.2 Hz, 1 H, 10-H), 5.20 (d, $^3J_{12a,11}$ = 10.5 Hz, 1 H, 12-H_a), 5.30 (d, $^3J_{12b,11}$ = 17.2 Hz, 1 H, 12-H_b), 5.80 (ddd, $^3J_{11,12b}$ = 17.2 Hz, $^3J_{11,12a}$ = 10.5 Hz, $^3J_{11,10}$ = 6.7 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 14.2 (q, C-15), 17.9 (q, C-1), 27.0 (q, C-7), 27.4 (q, C-7'), 29.1 (t, C-8), 30.9 (t, C-9), 63.8 (t, C-14), 64.2 (t, C-3), 78.6 (d, C-10), 79.2 (d, C-5), 80.9 (d, C-4), 108.5 (s, C-6), 117.5 (t, C-12), 135.9 (d, C-11), 154.6 (s, C-13).

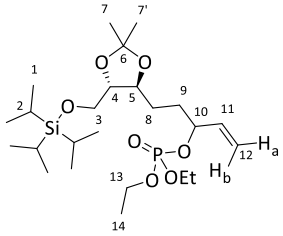
HRMS (CI):	calculated	found
$C_{23}H_{45}O_6Si$ $[M+H]^+$	445.2980	445.2990

Optical rotation: $[\alpha]_D^{20}$ = –3.5° (c = 1.0, $CHCl_3$)

5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl diethyl phosphate (67)

195 mg (0.523 mmol) **7c** were dissolved in 2.0 mL DCM abs. before 0.11 mL (108 mg, 1.37 mmol) pyridine and 7.4 mg (60.6 µmol) 4-DMAP were added. After cooling to 0 °C, 94 µL (113 mg, 0.655 mmol) diethyl chlorophosphate were added and the reaction was allowed to warm to rt overnight. Further 56 µL (67.2 mg, 0.389 mmol) diethyl chlorophosphate were added and stirring was continued for 4.5 h. For workup, the reaction was diluted with DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4. After purification by column chromatography (silica gel, PE:EA 100:0, 80:20, 70:30), 199 mg (0.391 mmol, 75 %) of **67** were obtained as a colourless oil.

R_f (67) = 0.14 (silica gel, PE:EA 70:30)



Diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 – 1.14 (m, 21 H, 1-H, 2-H), 1.31 (dt, $^3J_{14,13}$ = 7.0 Hz, $^4J_{14,P}$ = 4.8 Hz, 6 H, 14-H), 1.36 (s, 3 H, 7-H), 1.38 (s, 3 H, 7'-H), 1.50 – 2.05 (m, 4 H, 8-H, 9-H), 3.70 (m, 1 H, 4-H), 3.74 (m, 1 H, 3-H_a), 3.86 (m, 1 H, 3-H_b), 3.92 (dt, $^3J_{5,8}$ = 7.3 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H), 4.09 (m, 2 H, 13-H), 5.08 (ddt, $^3J_{10,P}$ = 12.9 Hz, $^3J_{10,11} \approx {}^3J_{10,9}$ = 6.5 Hz, 1 H, 10-H), 5.21 (dd, $^3J_{12a,11}$ = 10.5 Hz, 1 H, 12-H_a), 5.32 (ddd, $^3J_{12b,11}$ = 17.1 Hz, $^2J_{12b,12a} \approx {}^4J_{12b,10}$ = 1.3 Hz, 1 H, 12-H_b), 5.82 (ddd, $^3J_{11,12b}$ = 17.3 Hz, $^3J_{11,12a}$ = 10.3 Hz, $^3J_{11,10}$ = 70. Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 16.1 (dq, $^3J_{14,P}$ = 2 Hz, C-14), 17.9 (q, C-1), 27.0 (q, C-7), 27.4 (q, C-7'), 28.6 (t, C-8), 32.3 (dt, $^3J_{9,P}$ = 7 Hz, C-9), 63.5 (dt, $^2J_{13,P}$ = 3 Hz, C-13), 64.1 (t, C-3), 78.7 (d, C-5), 79.5 (dd, $^2J_{10,P}$ = 7 Hz, C-10), 80.9 (d, C-4), 108.5 (s, C-6), 117.4 (t, C-12), 135.6 (dd, $^3J_{11,P}$ = 3 Hz, C-11).

Diastereomer 2 (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.83 (ddd, $^3J_{11,12b}$ = 17.1 Hz, $^3J_{11,12a}$ = 10.3 Hz, $^3J_{11,10}$ = 6.8 Hz, 1 H, 11-H).

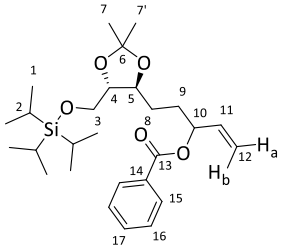
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.1 (dq, $^3J_{14,P}$ = 3 Hz, C-14), 27.4 (q, C-7'), 32.3 (dt, $^3J_{9,P}$ = 7 Hz, C-9), 63.6 (dt, $^2J_{13,P}$ = 3 Hz, C-13), 64.2 (t, C-3), 78.9 (d, C-5), 79.5 (dd, $^2J_{10,P}$ = 6 Hz, C-10), 81.0 (d, C-4), 117.6 (t, C-12), 136.7 (dd, $^3J_{11,P}$ = 3 Hz, C-11).

HRMS (CI):	calculated	found
$C_{24}H_{50}O_7PSi$ $[M+H]^+$	509.3058	509.3062

5-((4*S*,5*S*)-2,2-Dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)pent-1-en-3-yl benzoate (68)

To a solution of 372 mg (0.998 mmol) **7c** in 0.5 mL pyridine were added 0.23 mL (279 mg, 1.98 mmol) benzoyl chloride dropwise at 0 °C. The reaction was stirred for 2 h. For workup, 60 µL (60.7 mg, 0.993 mmol) ethanolamine and Et_2O were added and the reaction was stirred for 15 min. Afterwards, 1 M $CuSO_4$ sol. was added and the layers were separated. The aqueous phase was extracted three times with Et_2O and the combined organic layers were dried over Na_2SO_4. Purification of the crude product by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20) afforded 474 mg (0.994 mmol, 99 %) of benzoate **68** as a colourless oil.

R_f (68) = 0.46 (silica gel, PE:EA 80:20)



Diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 – 1.10 (m, 21 H, 1-H, 2-H), 1.37 (s, 3 H, 7-H), 1.39 (s, 3 H, 7'-H), 1.61 – 2.07 (m, 4 H, 8-H, 9-H), 3.70 (m, 1 H, 4-H), 3.72 (m, 1 H, 3-H_a), 3.88 (m, 1 H, 3-H_b), 3.96 (m, 1 H, 5-H), 5.20 (ddd, $^3J_{12a,11}$ = 10.5 Hz, $^2J_{12a,12b} \approx {}^4J_{12a,10}$ = 1.1 Hz, 1 H, 12-H_a), 5.33 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a} \approx {}^4J_{12b,10}$ = 1.3 Hz, 1 H, 12-H_b), 5.54 (dt, $^3J_{10,11} \approx {}^3J_{10,9}$ = 6.3 Hz, 1 H, 10-H), 5.90 (ddd, $^3J_{11,12b}$ = 17.1 Hz, $^3J_{11,12a}$ = 10.8 Hz, $^3J_{11,10}$ = 6.5 Hz, 1 H, 11-H), 7.43 (dd, $^3J_{16,15} \approx {}^3J_{16,17}$ = 7.7 Hz, 2 H, 16-H), 7.55 (tt, $^3J_{17,16}$ = 7.4 Hz, $^4J_{17,15}$ = 1.3 Hz, 1 H, 17-H), 8.05 (dd, $^3J_{15,16}$ = 7.0 Hz, $^4J_{15,17}$ = 1.5 Hz, 2 H, 15-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 17.9 (q, C-1), 26.9 (q, C-7), 27.4 (q, C-7'), 29.4 (t, C-8), 31.0 (t, C-9), 64.2 (t, C-3), 75.1 (d, C-10), 79.3 (d, C-5), 80.9 (d, C-4), 108.5 (s, C-6), 116.8 (t, C-12), 128.3 (d, C-16), 129.6 (d, C-15), 130.5 (s, C-14), 132.9 (d, C-17), 136.3 (d, C-11), 165.8 (s, C-13).

Diastereomer 2 (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, 7'-H), 5.21 (ddd, $^3J_{12a,11}$ = 10.5 Hz, $^2J_{12a,12b} \approx {}^4J_{12a,10}$ = 1.2 Hz, 1 H, 12-H_a), 5.34 (ddd, $^3J_{12b,11}$ = 17.3 Hz, $^2J_{12b,12a} \approx {}^4J_{12b,10}$ = 1.3 Hz, 1 H, 12-H_b), 5.89 (ddd, $^3J_{11,12b}$ = 17.1 Hz, $^3J_{11,12a}$ = 10.8 Hz, $^3J_{11,10}$ = 6.5 Hz, 1 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 29.0 (t, C-8), 30.8 (t, C-9), 75.0 (d, C-10), 79.0 (d, C-5), 80.9 (d, C-4), 117.0 (t, C-12), 136.2 (d, C-11).

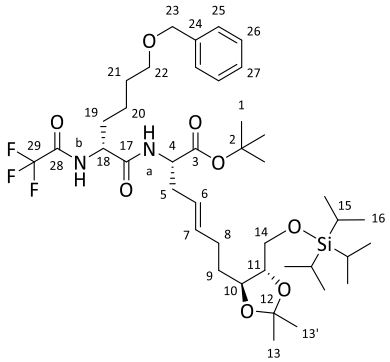
HRMS (CI):	calculated	found
$C_{27}H_{45}O_5Si$ $[M+H]^+$	477.3031	477.3024

tert-Butyl (*S*,*E*)-2-((*R*)-6-(benzyloxy)-2-(2,2,2-trifluoroacetamido)hexanamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enoate (69c)

A solution of 2.10 mL (1.49 g, 14.7 mmol) Di-*iso*-propylamine in 30.0 mL THF abs. was treated with 8.30 mL (13.3 mmol) *n*-BuLi (1.6 M in hexanes) at –78 °C. The cooling bath was removed and the reaction was stirred at rt for 15 min. 1.70 g (3.81 mmol) **62c** were dissolved in 30 mL THF abs. before 637 mg (4.67 mmol) zinc chloride (dried in *high-vacuo*) were added at rt. The resulting mixture was cooled to –78 °C and the above prepared LDA solution was added slowly at this temperature. The reaction was stirred at –78 °C for 30 min. 25.5 mg (69.7 µmol) $[AllylPdCl]_2$ and

60.4 mg (230 µmol) PPh_3 were dissolved in 7.50 mL THF abs. before 1.14 g (2.56 mmol) (3*R*)-**66** were added. The mixture was stirred at rt for 5 min. Afterwards, the catalyst/allylic substrate solution was transferred to the zinc enolate at –78 °C and the reaction was allowed to warm to rt overnight (remaining dry ice was removed from the cooling bath). For workup, the reaction was diluted with diethyl ether and NH_4OAc/HOAC-buffer was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20, 70:30, 50:50) to obtain 196 mg (0.245 mmol, *dr* 64:36, 10 %) and 1.55 g (1.93 mmol, *dr* 82:18, 75 %) **69c** as slightly yellow oils.

R_f (69c) = 0.11 (silica gel, PE:EA 80:20)



(2*S*,*R*)-diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.15 (m, 21 H, 15-H, 16-H), 1.36 (s, 3 H, 13-H), 1.39 (s, 3 H, 13-H'), 1.46 (s, 9 H, 1-H), 1.46 (m, 2 H, 20-H), 1.56 – 1.77 (m, 5 H, 9-H, 19-H_a, 21-H), 1.90 (m, 1 H, 19-H_b), 2.09 (m, 1 H, 8-H_a), 2.19 (m, 1 H, 8-H_b), 2.43 (dd, $^2J_{5a,5b}$ = 14.0 Hz, $^3J_{5a,6}$ = 6.2 Hz, 1 H, 5-H_a), 2.50 (dd, $^2J_{5b,5a}$ = 14.1 Hz, $^3J_{5b,6}$ = 6.4 Hz, 1 H, 5-H_b), 3.46 (m, 2 H, 22-H), 3.69 (m, 1 H, 11-H), 3.73 (dd, $^2J_{14a,14b}$ = 10.0 Hz, $^3J_{14a,11}$ = 6.0 Hz, 1 H, 14-H_a), 3.86 (dd, $^2J_{14b,14a}$ = 10.0 Hz, $^3J_{14b,11}$ = 3.9 Hz, 1 H, 14-H_b), 3.92 (td, $^3J_{10,9}$ = 7.7 Hz, $^3J_{10,11}$ = 3.4Hz, 1 H, 10-H), 4.44 – 4.54 (m, 2 H, 4-H, 18-H), 4.49 (s, 2 H, 23-H), 5.28 (dt, $^3J_{6,7}$ = 14.9 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 5.51 (dt, $^3J_{7,6}$ = 14.6 Hz, $^3J_{7,8}$ = 7.0 Hz, 1 H, 7-H), 6.33 (d, $^3J_{NH,4}$ = 7.5 Hz, 1 H, NH_a), 7.22 (d, $^3J_{NH,18}$ = 7.6 Hz, 1 H, NH_b), 7.27 – 7.36 (m, 5 H, 25-H, 26-H, 27-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-15), 17.9 (q, C-16), 21.9 (t, C-20), 27.0 (q, C-13), 27.4 (q, C-13'), 28.0 (q, C-1), 29.1 (t, C-8, C-9), 32.7 (t, C-21), 33.0 (t, C-19), 35.4 (t, C-5), 52.5 (d, C-4 o. C-18), 53.3 (d, C-4 o. C-18), 64.1 (t, C-14), 69.6 (t, C-22), 72.9 (t, C-23), 78.6 (d, C-10), 80.8 (d, C-11), 82.6 (s, C-2), 108.5 (s, C-12), 123.5 (d, C-6), 127.6 (d, C-27), 127.7 (d, C-25), 128.4 (d, C-26), 134.8 (d, C-7), 138.3 (s, C-24), 156.7 (q, $^2J_{28,F}$ = 37 Hz, C-28), 169.1 (s, C-3), 170.2 (s, C-17). The signal of C-29 wasn't observed in the ^{13}C-NMR spectrum.

(2*R*,*R*)-diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, 13-H), 1.46 (s, 9 H, 1-H), 2.56 (m, 2 H, 5-H), 5.09 (m, 1 H, 6-H o. 7-H), 6.37 (d, $^3J_{NH,4}$ = 7.2 Hz, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.9 (q, C-1).

HRMS (CI):	calculated	found
$C_{41}H_{68}F_3N_2O_8Si$ $[M+H]^+$	801.4692	801.4702

Optical rotation: $[\alpha]_D^{20}$ = +9.0° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

(2*R*,*R*)-**69c**: t_R = 16.1 min,

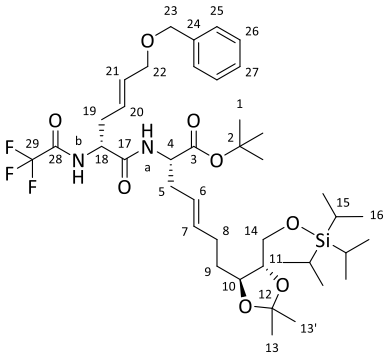
(2*S*,*R*)-**69c**: t_R = 17.9 min.

***tert*-Butyl (*S*,*E*)-2-((*R*,*E*)-6-(benzyloxy)-2-(2,2,2-trifluoroacetamido)hex-4-enamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)hept-4-enoate (69d)**

A solution of 1.51 mL (1.07 g, 10.6 mmol) Di-*iso*-propylamine in 20.0 mL THF abs. was cooled to –78 °C and 6.1 mL (9.76 mmol) *n*-BuLi (1.6 M in hexanes) were added dropwise. The cooling bath was removed and the reaction was stirred at rt for 15 min.

1.25 g (2.81 mmol, *er* 96:4) **61b** were added to a solution of 490 mg (3.60 mmol) zinc chloride (dried *in high-vacuo*) in 20.0 mL THF abs. at rt. The dipeptide/zinc chloride solution was added dropwise to the LDA solution at –78 °C and stirred for 30 min. 17.2 mg (47.0 µmol) $[AllylPdCl]_2$ and 44.6 mg (170 µmol) PPh_3 were dissolved in 5.0 mL THF abs. and stirred for 5 min before 830 mg (1.87 mmol) (3*R*)-**66** were added and the catalyst/allyl substrate solution was transferred slowly to the zinc enolate at –78 °C. The remaining dry ice was removed from the cooling bath and the reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with diethyl ether and NH_4OAc/HOAc-buffer was added and the layers were separated. The aqueous phase was extracted three times with Et_2O and the combined organic phases were dried over Na_2SO_4. After purification by column chromatography (silica gel, PE:EA 100:0, 90:10, 80:20, 70:30), 1.30 g (1.63 mmol, *dr* 79:21, 87 %) of allylated dipeptide **69d** were obtained as a slightly yellow oil.

R_f (69d) = 0.51 and 0.55 (silica gel, PE:EA 70:30)



(2*S*,*R*)-diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.15 (m, 21 H, 15-H, 16-H), 1.36 (s, 3 H, 13-H), 1.39 (s, 3 H, 13-H'), 1.46 (s, 9 H, 1-H), 1.65 (m, 2 H, 9-H), 2.16 (m, 2 H, 8-H), 2.47 (dd, $^3J_{5,4} \approx {}^3J_{5,6}$ = 6.1 Hz, 2 H, 5-H), 2.51 (dt, $^2J_{19a,19b}$ = 13.1 Hz, $^3J_{19a,18}$ = 6.5 Hz, 1 H, 19-H_a), 2.64 (dt, $^2J_{19b,19a}$ = 13.9 Hz, $^3J_{19b,18}$ = 6.8 Hz, 1 H, 19-H_b), 3.70 (m, 1 H, 11-H), 3.73 (dd, $^2J_{14a,14b}$ = 10.0 Hz, $^3J_{14a,11}$ = 6.0 Hz, 1 H, 14-H_a), 3.86 (dd, $^2J_{14b,14a}$ = 9.9 Hz, $^3J_{14b,11}$ = 3.9 Hz, 1 H, 14-H_b), 3.92 (td, $^3J_{10,9}$ = 7.8 Hz, $^3J_{10,11}$ = 3.4Hz, 1 H, 10-H), 3.98 (d, $^3J_{22,21}$ = 5.3 Hz, 2 H, 22-H), 4.44 – 4.58 (m, 2 H, 4-H, 18-H), 4.49 (s, 2 H, 23-H), 5.28 (dt, $^3J_{6,7}$ = 15.0 Hz, $^3J_{6,5}$ = 7.4 Hz, 1 H, 6-H), 5.53 (dt, $^3J_{7,6}$ = 14.6 Hz, $^3J_{7,8}$ = 7.2 Hz, 1 H, 7-H), 5.63 (dt, $^3J_{20,21}$ = 14.8 Hz, $^3J_{20,19}$ = 7.3 Hz, 1 H, 20-H), 5.73 (dt, $^3J_{21,20}$ = 15.4 Hz, $^3J_{21,22}$ = 5.6 Hz, 1 H, 21-H), 6.34 (d, $^3J_{NH,4}$ = 7.5 Hz, 1 H, NH_a), 7.22 (d, $^3J_{NH,18}$ = 7.3 Hz, 1 H, NH_b), 7.26 – 7.42 (m, 5 H, 25-H, 26-H, 27-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-15), 17.9 (q, C-16), 27.0 (q, C-13), 27.4 (q, C-13'), 28.0 (q, C-1), 29.2 (t, C-8), 33.1 (t, C-9), 35.4 (t, C-5), 35.7 (t, C-19), 52.6 (d, C-4 o. C-18), 52.7 (d, C-4 o. C-18), 64.1 (t, C-14), 69.9 (t, C-22), 72.2 (t, C-23), 78.6 (d, C-10), 80.8 (d, C-11), 82.7 (s, C-2), 108.5 (s, C-12), 123.5 (d, C-6), 126.0 (d, C-20), 127.6 (d, C-27), 127.7 (d, C-25), 128.4 (d, C-26), 132.2 (d, C-21), 134.9 (d, C-7), 138.1 (s, C-24), 168.4 (s, C-3), 170.2 (s, C-17).

(2*R*,*R*)-diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, 13-H), 1.46 (s, 9 H, 1-H), 3.83 (d, $^3J_{14b,11}$ = 3.8 Hz, 1 H, 14-H_b), 5.10 (m, 1 H, 6-H o. 7-H), 6.34 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH_a).

HRMS (CI):	calculated	found
$C_{37}H_{57}F_3N_2O_8Si$ $[M+H-t\text{Bu}]^+$	742.3831	742.3850

Optical rotation: $[\alpha]_D^{20}$ = –1.1° (c = 1.0, $CHCl_3$)

HPLC: Chiralcel OD-H, *n*-hexane:*i*PrOH 80:20, 1.0 mL/min, 20 °C:

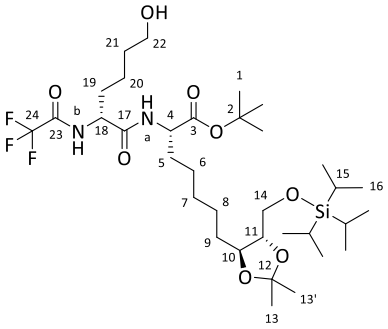
(2*S*,*R*)-**69d**: t_R = 3.75 min (79 %),

(2*R*,*R*)-**69d**: t_R = 5.45 min (21 %).

tert-Butyl (*S*)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)-2-((*R*)-6-Hydroxy-2-(2,2,2-trifluoroacetamido)hexanamido)heptanoate (71c)

To a solution of 1.52 g (1.90 mmol) **69c** in 15.0 mL THF were added 151 mg palladium on charcoal (10 w% Pd) at rt. The reaction was set under 20 bar H_2-atmosphere for 18 h and after addition of 5.4 µL (5.7 mg, 94.9 µmol) HOAc under 30 bar H_2-atmossphere for 22 h. The reaction was then filtrated through a pad of Celite® and washed with Et_2O. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, PE:EA 70:30, 50:50) to yield 885 mg (1.24 mmol, *dr* 81:19, 65 %) and 455 mg (0.638 mmol, *dr* 88:12, 34 %) alcohol **71c** as colourless oils.

R_f (71c) = 0.08 (silica gel, PE:EA 70:30)



(2*S*,*R*)-diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.16 (m, 21 H, 15-H, 16-H), 1.29 – 1.50 (m, 4 H, 7-H, 8-H, 9-H), 1.36 (s, 3 H, 13-H), 1.39 (s, 3 H, 13-H'), 1.46 (s, 9 H, 1-H), 1.51 – 1.77 (m, 8 H, 6-H, 9-H, 20-H, 21-H), 1.78 – 2.01 (m, 4 H, 5-H, 19-H), 3.60 – 3.70 (m, 3 H, 11-H, 22-H), 3.74 (dd, $^2J_{14a,14b}$ = 10.3 Hz, $^3J_{14a,11}$ = 5.9 Hz, 1 H, 14-H_a), 3.86 (dd, $^2J_{14b,14a}$ = 10.3 Hz, $^3J_{14b,11}$ = 4.0 Hz, 1 H, 14-H_b), 3.92 (td, $^3J_{10,9}$ = 7.9 Hz, $^3J_{10,11}$ = 3.4Hz, 1 H, 10-H), 4.46 (dt, $^3J_{4,NH}$ = 7.2 Hz, $^3J_{4,5}$ = 5.5 Hz, 1 H, 4-H), 4.52 (dt, $^3J_{18,19} \approx {}^3J_{18,NH}$ = 6.8 Hz, 1 H, 18-H), 6.54 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH_a), 7.33 (d, $^3J_{NH,18}$ = 7.2 Hz, 1 H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-15), 17.9 (q, C-16), 21.5 (t, C-20), 25.0 (t, C-6), 26.1 (t, C-7 o. C-8), 26.9 (q, C-13), 27.4 (q, C-13'), 28.0 (q, C-1), 29.4 (t, C-7 o. C-8), 31.7 (t, C-21), 32.3 (t, C-5), 32.7 (t, C-19), 33.4 (t, C-9), 52.9 (d, C-4), 53.2 (d, C-18), 62.1 (t, C-22), 64.1 (t, C-14), 79.1 (d, C-10), 81.0 (d, C-11), 82.6 (s, C-2), 108.4 (s, C-12), 115.7 (q, $^1J_{24,F}$ = 288 Hz, C-24), 156.7 (q, $^2J_{23,F}$ = 37 Hz, C-23), 169.3 (s, C-3), 170.0 (s, C-17).

(2*R*,*R*)-diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.46 (d, $^3J_{NH,4}$ = 8.0 Hz, 1 H, NH_a).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.0 (t, C-20), 25.9 (t, C-7 o. C-8), 53.1 (d, C-4).

HRMS (CI):	calculated	found
$C_{34}H_{64}F_3N_2O_8Si$ $[M+H]^+$	713.4379	713.4410

Optical rotation: $[\alpha]_D^{20}$ = +1.1° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

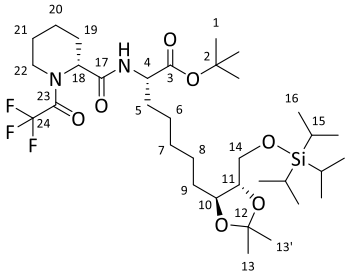
(2*R*,*R*)-**71c**: t_R = 13.7 min,

(2*S*,*R*)-**71c**: t_R = 16.9 min.

tert-Butyl (*S*)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)-2-((*R*)-1-(2,2,2-trifluoroacetyl)piperidine-2-carboxamido)heptanoate (72c)

To a solution of 553 mg (2.11 mmol) PPh_3 in 80 mL THF abs. were added 411 µL (427 mg, 2.11 mmol) DIAD at 0 °C. Afterwards, a solution of 941 mg (1.32 mmol) **71c** in 50 mL THF abs. was added dropwise and the reaction was allowed to warm to rt overnight. For workup, the reaction was concentrated *in vacuo* and the crude product was purified by column chromatography (silica gel, PE:EA 80:20). 902 mg (1.30 mmol, *dr* 80:20, rotameric ratio 80:20, 98 %) of dipeptide **72c** were obtained as a slightly yellow oil.

R_f (72c) = 0.54 (silica gel, PE:EA 70:30)



Major diastereomer/rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.16 (m, 21 H, 15-H, 16-H), 1.28 – 1.41 (m, 5 H, 6-H, 8-H, 19-H_a), 1.36 (s, 3 H, 13-H), 1.39 (s, 3 H, 13-H'), 1.45 (s, 9 H, 1-H), 1.50 – 1.86 (m, 10-H, 5-H, 7-H, 9-H, 20-H, 21-H), 2.31 (d, $^{2/3}J_{19b,19a/18/20}$ = 12.8 Hz, 1 H, 19-H_b), 3.35 (ddd, $^2J_{22ax,22eq}$ = 14.1 Hz, $^3J_{22ax,21ax}$ = 11.4 Hz, $^3J_{22ax,21eq}$ = 2.5 Hz, 1 H, 22-H_{ax}), 3.68 (m, 1 H, 11-H), 3.75 (dd, $^2J_{14a,14b}$ = 10.2 Hz, $^3J_{14a,11}$ = 5.9 Hz, 1 H, 14-H_a), 3.86 (dd, $^2J_{14b,14a}$ = 10.3 Hz, $^3J_{14b,11}$ = 4.0 Hz, 1 H, 14-H_b), 3.92 (m, 1 H, 10-H), 3.95 (m, 1 H, 22-H_{eq}), 4.43 (dt, $^3J_{4,NH}$ = 7.4 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 5.14 (d, $^3J_{18,19ax/19eq}$ = 5.0 Hz, 1 H, 18-H), 6.20 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-15), 17.9 (q, C-16), 21.5 (t, C-20), 25.0 (t, C-6), 26.1 (t, C-7 o. C-8), 26.9 (q, C-13), 27.4 (q, C-13'), 28.0 (q, C-1), 29.4 (t, C-7 o. C-8), 31.7 (t, C-21), 32.3 (t, C-5), 32.7 (t, C-19), 33.4 (t, C-9), 52.9 (d, C-4), 53.2 (d, C-18), 62.1 (t, C-22), 64.1 (t, C-14), 79.1 (d, C-10), 81.0 (d, C-11), 82.6 (s, C-2), 108.4 (s, C-12), 115.7 (q, $^1J_{24,F}$ = 288 Hz, C-24), 156.7 (q, $^2J_{23,F}$ = 37 Hz, C-23), 169.3 (s, C-3), 170.0 (s, C-17).

Minor diastereomer/rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, 13-H), 1.46 (s, 9 H, 1-H), 2.49 (d, $^{2/3}J_{19b,19a/18/20}$ = 12.8 Hz, 1 H, 19-H_b), 3.03 (m, 1 H, 22-H_{ax}), 4.48 (m, 1 H, 4-H), 4.55 (d, $^2J_{22eq,22ax}$ = 13.9 Hz, 1 H, 22-H_{eq}), 4.62 (m, 1 H, 4-H), 5.10 (m, 1 H, 18-H), 6.22 (m, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.0 (t, C-20), 25.9 (t, C-7 o. C-8), 53.1 (d, C-4).

HRMS (CI):	calculated	found
$C_{34}H_{62}F_3N_2O_7Si$ $[M+H]^+$	695.4273	695.4287

Optical rotation: $[\alpha]_D^{20}$ = +42.1° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 95:5, 1.0 mL/min, 20 °C:

(2*R*,*R*)-**72c**: t_R = 11.1 min (20 %),

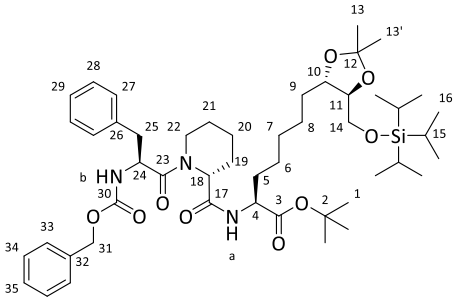
(2*S*,*R*)-**72c**: t_R = 17.2 min (80 %).

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 29.5 min (minor, $[M+Na]^+$ = 718), t_{R2} = 30.3 min (major, $[M+Na]^+$ = 718).

tert-Butyl (*S*)-2-((*R*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl)piperidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)heptanoate (74)

876 mg (1.26 mmol) **72c** were dissolved in 6.5 mL EtOH abs. and cooled to 0 °C before 97 mg (2.56 mmol) $NaBH_4$ were added slowly. The reaction was stirred at rt for 15 min before acetone was added and stirring was continued for 15 min. The reaction was concentrated *in vacuo* and the residue was redissolved in DCM. 10 w% K_2CO_3 sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM and the combined organic layers were dried over Na_2SO_4. The corresponding amine was then dissolved in 15.0 mL acetonitrile abs. at rt before 421 mg (1.41 mmol) Cbz-(*S*)-Phe-OH, 446 mg (1.39 mmol) TBTU and 256 µL (189 mg, 1.46 mmol) DIPEA were added subsequently. The reaction was stirred at rt overnight. For workup, the reaction was concentrated *in vacuo* and the residue was redissolved in DCM. 1 M HCl sol. was added and the layers were separated. The aqueous phase was extracted three times with DCM, the combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. Purification by column chromatography (silica gel, PE:EA 70:30) gave 1.05 g (1.19 mmol, *dr* 81:19, rotameric ratio 70:30, 94 % over two steps) **74** as an off-white solid.

R_f (74) = 0.30 (silica gel, PE:EA 70:30)



Major diastereomer/rotamer:

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 1.04 – 1.14 (m, 21 H, 15-H, 16-H), 1.25 – 1.35 (m, 7 H, 6-H, 8-H, 7-H/19-H_a/20-H, 21-H), 1.30 (s, 3 H, 13-H), 1.31 (s, 3 H, 13-H'), 1.37 – 1.44 (m, 4 H, 7-H/19-H_a/20-H, 21-H), 1.40 (s, 9 H, 1-H), 1.45 – 1.66 (m, 3 H, 5-H_a, 9-H), 1.71 (m, 1 H, 5-H_b), 2.16 (d, $^{2/3}J_{19b,19a/18}$ = 10.0 Hz, 1 H, 19-H_b), 2.94 (d, $^3J_{25,24}$ = 6.9 Hz, 2 H, 25-H), 2.98 (br s, 2 H, 22-H), 3.64 (m, 1 H, 11-H), 3.75 (dd, $^2J_{14a,14b}$ = 10.7 Hz, $^3J_{14a,11}$ = 4.8 Hz, 1 H, 14-H_a), 3.80 (dd, $^2J_{14b,14a}$ = 10.7 Hz, $^3J_{14b,11}$ = 4.5 Hz, 1 H, 14-H_b), 3.85 (td, $^3J_{10,9}$ = 7.6 Hz, $^3J_{10,11}$ = 4.3 Hz, 1 H, 10-

H), 4.17 (dt, $^3J_{4,NH} \approx {}^3J_{4,5}$ = 7.1 Hz, 1 H, 4-H), 4.72 (br s, 1 H, 24-H), 4.96 – 5.05 (m, 3 H, 18-H, 31-H), 7.19 – 7.36 (m, 11 H, 27-H, 28-H, 29-H, 33-H, 34-H, 35-H, NH_a). The signal of NH_b wasn't observed in the ^{1}H-NMR spectrum.

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 11.1 (d, C-15), 17.2 (q, C-16), 19.4 (t, C-20), 23.7 (t, C-6 o. C-8 o. C-21), 24.6 (t, C-6 o. C-8 o. C-21), 24.7 (t, C-6 o. C-8 o. C-21), 26.4 (q, C-13), 26.8 (q, C-13'), 27.2 (q, C-1), 28.0 (t, C-7), 30.4 (t, C-5), 32.3 (t, C-9), 37.1 (t, C-25), 51.4 (d, C-24), 52.4 (d, C-4), 63.4 (t, C-14), 65.1 (t, C-31), 77.3 (d, C-10), 80.0 (s, C-2), 80.6 (d, C-11), 107.2 (s, C-12), 125.9 (d, C-29), 126.9 (d, C-33), 127.2 (d, C-27), 127.6 (d, C-35), 127.7 (d, C-28), 128.8 (d, C-34), 136.4 (s, C-26 o. C-32), 170.4 (s, C-3 o. C-17 o. C-23). The signals of C-3/C-17/C-23, C-18, C-19, C-22, C-26/C-32 and C-30 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer/rotamer (selected signals):

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 1.79 (m, 1 H, 5-H_b), 3.10 (dd, $^2J_{25a,25b}$ = 14.1 Hz, $^3J_{25a,24}$ = 4.9 Hz, 1 H, 25-H_a), 4.27 (m, 1 H, 24-H), 4.40 (m, 1 H, 4-H).

HRMS (CI):	calculated	found
$C_{49}H_{78}N_3O_9Si$ $[M+H]^+$	880.5502	880.5510

Melting point: 122-124 °C

Optical rotation: $[\alpha]_D^{20}$ = +43.2° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 90:10, 1.0 mL/min, 20 °C:

(2*R*,*R*,*S*)-**74**: t_R = 21.6 min (5 %, minor rotamer),

(2*S*,*R*,*S*)-**74**: t_R = 25.2 min (25 %, minor rotamer),

(2*R*,*R*,*S*)-**74**: t_R = 30.7 min (14 %, major rotamer),

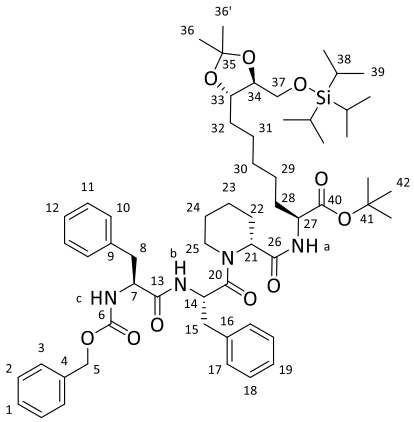
(2*S*,*R*,*S*)-**74**: t_R = 36.3 min (56 %, major rotamer).

tert-Butyl (*S*)-2-((*R*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-(((tri-*iso*-propylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)heptanoate (75)

A solution of 770 mg (0.875 mmol) **74** in 7.5 mL MeOH was treated with 77 mg palladium on charcoal (10 w% Pd) at rt. A small amount of DCM was added to guarantee stirring, the reaction was set under H_2 and hydrogenated for 22.5 h. The reaction was then filtrated through a pad of Celite® and washed with MeOH. The filtrated was concentrated *in vacuo* and the crude product was redissolved in 7.0 mL acetonitrile. Afterwards, 290 mg (0.969 mmol) Cbz-(*S*)-Phe-OH, 309 mg (0.962 mmol) TBTU and 176 µL (130 mg, 1.01 mmol) DIPEA were added subsequently at rt. The reaction was stirred overnight and concentrated *in vacuo*. The residue was redissolved in DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three

times with DCM. The combined organic layers were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50). 831 mg (0.808 mmol, *dr* 87:13, 92 % over two steps) of tetrapeptide **75** were obtained as an off-white solid.

R_f (75) = 0.46 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 – 1.14 (m, 21 H, 38-H, 39-H), 1.18 – 1.49 (m, 11 H, 22-H_a, 23-H, 24-H, 29-H, 30-H, 31-H), 1.34 (s, 3 H, 36-H), 1.37 (s, 3 H, 36-H'), 1.41 (s, 9 H, 42-H), 1.50 – 1.65 (m, 3 H, 28-H_a, 32-H), 1.77 (m, 1 H, 28-H_b), 2.30 (d, $^{2/3}J_{22b,22a/23/21}$ = 13.0 Hz, 1 H, 22-H_b), 2.88 (m, 1 H, 15-H_a), 2.96 – 3.08 (m, 3 H, 8-H, 15-H_b), 3.13 (dd, $^2J_{25ax,25eq} \approx {}^3J_{25ax,24ax}$ = 12.4 Hz, 1 H, 25-H_{ax}), 3.59 (d, $^2J_{25eq,25ax}$ = 14.0 Hz, 1 H, 25-H_{eq}), 3.64 (m, 1 H, 34-H), 3.73 (dd, $^2J_{37a,37b}$ = 10.4 Hz, $^3J_{37a,34}$ = 5.5 Hz, 1 H, 37-H_a), 3.83 (dd, $^2J_{37b,37a}$ = 10.3 Hz, $^3J_{37b,34}$ = 4.1 Hz, 1 H, 37-H_b), 3.89 (td, $^3J_{33,32}$ = 7.8 Hz, $^3J_{33,34}$ = 3.6 Hz, 1 H, 33-H), 4.35 (td, $^3J_{27,28}$ = 7.5 Hz, $^3J_{27,NH}$ = 6.5 Hz, 1 H, 27-H), 4.39 (m, 1 H, 7-H), 4.83 (dt, $^3J_{14,NH}$ = 7.5 Hz, $^3J_{14,15}$ = 6.3 Hz, 1 H, 14-H), 5.07 (s, 2 H, 5-H), 5.24 (d, $^3J_{21,22a}$ = 4.3 Hz, 1 H, 21-H), 5.42 (d, $^3J_{NH,7}$ = 7.0 Hz, 1 H, NH_c), 6.54 (br s, 1 H, NH_b), 6.92 (d, $^3J_{NH,27}$ = 7.6 Hz, 1 H, NH_a), 7.09 (d, $^3J_{10,11}$ = 7.6 Hz, 2 H, 10-H), 7.17 – 7.37 (m, 13 H, 1-H, 2-H, 3-H, 11-H, 12-H, 17-H, 18-H, 19-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-38), 17.9 (q, C-39), 20.2 (t, C-23), 24.7 (t, C-22), 25.2 (t, C-24 o. C-29 o. C-31), 25.5 (t, C-24 o. C-29 o. C-31), 26.1 (t, C-24 o. C-29 o. C-31), 26.9 (q, C-36), 27.4 (q, C-36'), 28.0 (q, C-42), 29.4 (t, C-30), 31.8 (t, C-28), 33.5 (t, C-32), 38.1 (t, C-8), 38.2 (t, C-15), 43.9 (t, C-25), 51.1 (d, C-14), 52.6 (d, C-21), 53.0 (d, C-27), 55.6 (d, C-7), 64.1 (t, C-37), 67.0 (t, C-5), 78.9 (d, C-33), 81.1 (s, C-41), 81.4 (d, C-34), 108.3 (s, C-35), 127.0 (d, C-19), 127.2 (d, C-12), 128.0 (d, C-3), 128.2 (d, C-1), 128.5 (d, C-17), 128.6 (d, C-11 o. C-18), 128.7 (d, C-11 o. C-18), 129.4 (d, C-10), 129.6 (d, C-2), 135.7 (s, C-16), 136.2 (s, C-4, C-9), 155.9 (s, C-6), 169.6 (s, C-26), 170.6 (s, C-20), 170.8 (s, C-13), 171.9 (s, C-40).

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 42-H), 4.67 (m, 1 H, 14-H), 5.20 (d, $^3J_{21,22a}$ = 6.2 Hz, 1 H, 21-H), 5.33 (d, $^3J_{NH,7}$ = 8.4 Hz, 1 H, NH_c), 6.64 (m, 1 H, NH_b), 6.83 (m, 1 H, NH_a).

HRMS (CI):	calculated	found
$C_{58}H_{87}N_4O_{10}Si$ $[M+H]^+$	1027.6186	1027.6199

Melting point: 56 °C

Optical rotation: $[\alpha]_D^{20}$ = +26.4° (c = 1.0, $CHCl_3$)

HPLC: Reprosil, *n*-hexane:*i*PrOH 80:20, 1.0 mL/min, 20 °C:

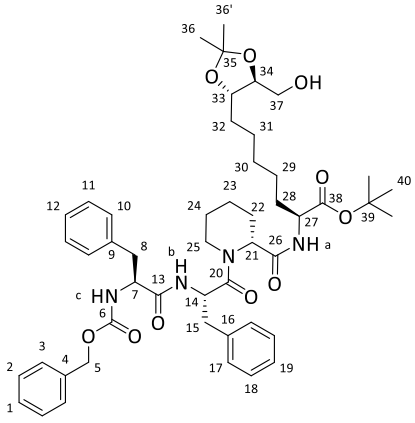
t_{R1} = 20.2 min (13 %),

t_{R2} = 26.6 min (87 %).

tert-Butyl (*S*)-2-((*R*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxamido)-7-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)heptanoate (76)

A solution of 148 mg (0.144 mmol) **75** was dissolved in 0.75 mL THF at rt. Afterwards, 0.22 mL (0.22 mmol) TBAF (1 M in THF) were added and the reaction was stirred for 3 h. For workup, the reaction was concentrated *in vacuo* at rt. The residue was redissolved in Et_2O and water was added. The layers were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the crude product was purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50). 113 mg (0.130 mmol, *dr* 81:19, 90 %) of alcohol **76** were obtained as an off-white solid.

R_f (76) = 0.13 (silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.15 – 1.67 (m, 14 H, 22-H_a, 23-H, 24-H, 28-H_a, 29-H, 30-H, 31-H, 32-H), 1.37 (s, 3 H, 36-H), 1.38 (s, 3 H, 36-H'), 1.41 (s, 9 H, 40-H), 1.77 (m, 1 H, 28-H_b), 2.31 (m, 1 H, 22-H_b), 2.87 (m, 1 H, 15-H_a), 2.95 – 3.09 (m, 3 H, 8-H, 15-H_b), 3.15 (dd, $^2J_{25ax,25eq}$ ≈ $^3J_{25ax,24ax}$ = 12.8 Hz, 1 H, 25-H_{ax}), 3.54 – 3.64 (m, 2 H, 25-H_{eq}, 37-H_a), 3.66 (ddd, $^3J_{35,37a}$ = 8.0 Hz, $^3J_{35,37b}$ = 4.2 Hz, $^3J_{35,34}$ = 3.7 Hz, 1 H, 34-H), 3.75 (d, $^2J_{37b,37a}$ = 11.4 Hz, 1 H, 37-H_b), 3.83 (m, 1 H, 33-H), 4.34 – 4.64 (m, 2 H, 7-H, 27-H), 4.81 (dt, $^3J_{14,NH}$ = 8.1 Hz, $^3J_{14,15}$ = 6.0 Hz, 1 H, 14-H), 5.07 (s, 2 H, 5-H), 5.24 (d, $^3J_{21,22a}$ = 4.5 Hz, 1 H, 21-H), 5.42 (m, 1 H, NH_c), 6.52 (br s, 1 H,

NH_b), 6.95 (d, $^3J_{NH,27}$ = 8.0 Hz, 1 H, NH_a), 7.09 (d, $^3J_{10,11}$ = 6.5 Hz, 2 H, 10-H), 7.12 – 7.37 (m, 13 H, 1-H, 2-H, 3-H, 11-H, 12-H, 17-H, 18-H, 19-H). The signal of -OH wasn't observed in the ^{1}H-NMR spectrum.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.2 (t, C-23), 24.7 (t, C-24 o. C-29 o. C-31), 25.2 (t, C-22), 25.3 (t, C-24 o. C-29 o. C-31), 25.6 (t, C-24 o. C-29 o. C-31), 27.0 (q, C-36), 27.3 (q, C-36'), 28.0 (q, C-40), 29.0 (t, C-30), 31.7 (t, C-28), 32.8 (t, C-32), 38.2 (t, C-8, C-15), 44.0 (t, C-25), 51.1 (d, C-14), 52.7 (d, C-21), 52.9 (d, C-27), 62.1 (t, C-37), 67.0 (t, C-5), 76.9 (d, C-33), 81.4 (d, C-34), 81.5 (s, C-39), 108.5 (s, C-35), 127.1 (d, C-19), 127.3 (d, C-12), 128.0 (d, C-3), 128.2 (d, C-1), 128.5 (d, C-17), 128.7 (d, C-11 o. C-18), 128.8 (d, C-11 o. C-18), 129.4 (d, C-10), 129.6 (d, C-2), 136.2 (s, C-4, C-9), 169.6 (s, C-26), 170.6 (s, C-13 o. C-20), 170.9 (s, C-13 o. C-20), 171.8 (s, C-38). The signals of C-6, C-7 and C-16 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.57 (m, 1 H, 14-H), 5.18 (m, 1 H, 21-H).

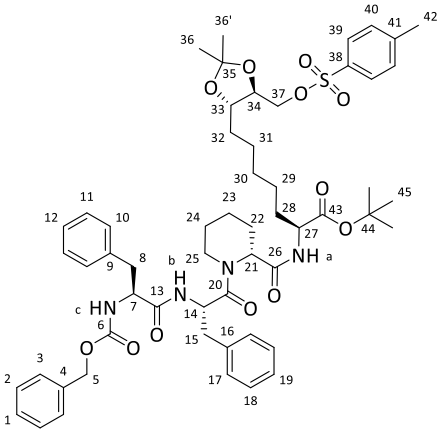
HRMS (CI):	calculated	found
$C_{49}H_{67}N_4O_{10}$ $[M+H]^+$	871.4852	871.4853
Melting point:	63-65 °C	
Optical rotation:	$[\alpha]_D^{20}$ = +18.5° (c = 1.0, $CHCl_3$)	

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 18.5 min (81 %, $[M+Na]^+$ = 894), t_{R2} = 19.4 min (19 %, $[M+Na]^+$ = 894).

tert-Butyl (*S*)-2-((*R*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-((tosyloxy)methyl)-1,3-dioxolan-4-yl)heptanoate (77)

508 mg (0.494 mmol) **75** were dissolved in 5.0 mL THF at rt. Afterwards, 742 µL (0.742 mmol) TBAF (1 M in THF) were added and the reaction was stirred for 2 h. For workup, the reaction was concentrated *in vacuo* at rt. The residue was redissolved in DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and the crude product was redissolved in 5.0 mL pyridine abs. at rt. The reaction was cooled to 0 °C before 6.9 mg (56.5 µmol) 4-DMAP and 141 mg (0.742 mmol) TosCl were added. The reaction was allowed to warm to rt overnight. For workup, the reaction was diluted with Et_2O and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. After purification by column chromatography (silica gel, PE:EA 50:50), 415 mg (0.405 mmol, 82 % over two steps) **77** were obtained as an off-white solid.

R_f (77) = 0.24 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.18 – 1.48 (m, 12 H, 22-H_a, 23-H, 24-H, 29-H, 30-H, 31-H, 32-H_a), 1.26 (s, 3 H, 36-H), 1.32 (s, 3 H, 36-H'), 1.41 (s, 9 H, 45-H), 1.50 – 1.60 (m, 2 H, 28-H_a, 32-H_b), 1.77 (m, 1 H, 28-H_b), 2.32 (d, $^{2/3}J_{22b,22a/21/23}$ = 12.4 Hz, 1 H, 22-H_b), 2.44 (s, 3 H, 42-H), 2.87 (m, 1 H, 15-H_a), 2.98 – 3.09 (m, 3 H, 8-H, 15-H_b), 3.15 (dd, $^{2}J_{25ax,25eq} \approx {}^{3}J_{25ax,24ax}$ = 13.3 Hz, 1 H, 25-H_{ax}), 3.60 (d, $^{2}J_{25eq,25ax}$ = 13.8 Hz, 1 H, 25-H_{eq}), 3.68 – 3.78 (m, 2 H, 33-H, 34-H), 4.06 (m, 2 H, 37-H), 4.33 – 4.43 (m, 2 H, 7-H, 27-H), 4.82 (dt, $^{3}J_{14,NH}$ = 7.8 Hz, $^{3}J_{14,15}$ = 5.4 Hz, 1 H, 14-H), 5.07 (s, 2 H, 5-H), 5.24 (d, $^{3}J_{21,22a}$ = 3.6 Hz, 1 H, 21-H), 5.40 (d, $^{3}J_{NH,7}$ = 6.5 Hz, 1 H, NH_c), 6.51 (br s, 1 H, NH_b), 6.95 (d, $^{3}J_{NH,27}$ = 7.3 Hz, 1 H, NH_a), 7.09 (d, $^{3}J_{10,11}$ = 6.9 Hz, 2 H, 10-H), 7.12 – 7.37 (m, 15 H, 1-H, 2-H, 3-H, 11-H, 12-H, 17-H, 18-H, 19-H, 40-H), 7.79 (d, $^{3}J_{39,40}$ = 8.2 Hz, 2 H, 39-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.3 (t, C-23), 21.6 (q, C-42), 24.7 (t, C-24 o. C-29 o. C-31), 25.2 (t, C-22), 25.4 (t, C-24 o. C-29 o. C-31), 25.7 (t, C-24 o. C-29 o. C-31), 26.6 (q, C-36), 27.3 (q, C-36'), 28.0 (q, C-45), 29.2 (t, C-30), 31.7 (t, C-28), 32.9 (t, C-32), 38.0 (t, C-8), 38.2 (t, C-15), 43.9 (t, C-25), 51.1 (d, C-14), 52.7 (d, C-21), 52.9 (d, C-27), 55.7 (d, C-7), 67.0 (t, C-5), 69.2 (t, C-37), 77.6 (d, C-33 o. C-34), 78.1 (d, C-33 o. C-34), 81.5 (s, C-44), 109.3 (s, C-35), 127.1 (d, C-12 o. C-19), 127.3 (d, C-12 o. C-19), 128.0 (d, C-39), 128.2 (d, C-3), 128.5 (d, C-1 o. C-2 o. C-11 o. C-18), 128.7 (d, C-1 o. C-2 o. C-11 o. C-18), 128.8 (d, C-1 o. C-2 o. C-11 o. C-18), 129.4 (d, C-10), 129.6 (d, C-17), 129.8 (d, C-40), 132.7 (s, C-38), 136.2 (s, C-4, C-9), 145.0 (s, C-41), 155.9 (s, C-6), 169.6 (s, C-26), 170.6 (s, C-20), 170.8 (s, C-13), 171.8 (s, C-43). The signals of C-1/C-2/C-11/C-18 and C-16 weren't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{56}H_{73}N_4O_{12}S$ $[M+H]^+$	1025.4940	1025.4942

Melting point: 56 °C

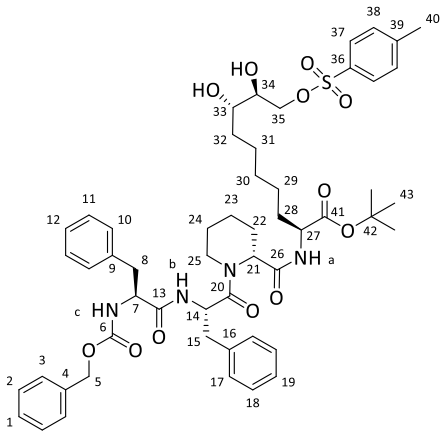
Optical rotation: $[\alpha]_D^{20}$ = +17.8° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 14.7 min ($[M+Na]^+$ = 1048).

tert-Butyl (2*S*,8*S*,9*S*)-2-((*R*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxamido)-8,9-dihydroxy-10-(tosyloxy)decanoate (78)

179 mg (0.175 mmol) **77** were dissolved in 2.0 mL THF and 2.0 mL HCl sol. (5 w% in H_2O) were added at rt. The reaction was heated to 60 °C for 24 h and concentrated *in vacuo*. The residue was diluted with brine and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. After lyophilisation, 171 mg (0.174 mmol, 99 %) of diol **78** were obtained as an off-white solid.

R_f (78) = 0.14 (silica gel, PE:EA 50:50)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.15 (m, 1 H, 22-H_a), 1.23 – 1.47 (m, 11 H, 23-H, 24-H, 29-H, 30-H, 31-H, 32-H_b), 1.41 (s, 9 H, 43-H), 1.48 – 1.69 (m, 2 H, 28-H_a, 32-H_b), 1.81 (m, 1 H, 28-H_b), 2.36 (d, $^2J_{22b,22a}$ = 13.5 Hz, 1 H, 22-H_b), 2.41 (s, 3 H, 40-H), 2.86 – 3.05 (m, 4 H, 8-H_a, 15-H, OH), 3.11 (dd, $^2J_{8b,8a}$ = 13.9 Hz, $^3J_{8b,7}$ = 5.7 Hz, 1 H, 8-H_b), 3.20 (dd, $^2J_{25ax,25eq} \approx {}^3J_{25ax,24ax}$ = 12.7 Hz, 1 H, 25-H_{ax}), 3.51 (m, 1 H, 33-H), 3.56 – 3.73 (m, 3 H, 25-H_{eq}, 34-H, OH), 4.06 (dd, $^2J_{35a,35b}$ = 10.0 Hz, $^3J_{35a,34}$ = 6.6 Hz, 1 H, 35-H_a), 4.11 (dd, $^2J_{35b,35a}$ = 10.3 Hz, $^3J_{35b,34}$ = 5.1 Hz, 1 H, 35-H_b), 4.34 – 4.52 (m, 2 H, 7-H, 27-H), 4.78 (m, 1 H, 14-H), 5.04 (m, 2 H, 5-H), 5.21 (d, $^3J_{21,22a}$ = 4.2 Hz, 1 H, 21-H), 5.41 (d, $^3J_{NH,7}$ = 8.4 Hz, 1 H, NH_c), 6.90 (br s, 1 H, NH_b), 7.00 (d, $^3J_{NH,27}$ = 7.3 Hz, 1 H, NH_a), 7.11 (d, $^3J_{17,18}$ = 6.6 Hz, 2 H, 17-H), 7.17 (d, $^3J_{10,11}$ = 7.0 Hz, 2 H, 10-H), 7.20 – 7.37 (m, 13 H, 1-H, 2-H, 3-H, 11-H, 12-H, 18-H, 19-H, 38-H), 7.78 (d, $^3J_{37,40}$ = 8.2 Hz, 2 H, 37-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.2 (t, C-23), 21.6 (q, C-40), 24.5 (t, C-24 o. C-29 o. C-31), 27.4 (t, C-24 o. C-29 o. C-31), 25.1 (t, C-22), 28.0 (q, C-43), 31.0 (t, C-28), 32.8 (t, C-32), 37.9 (t, C-8 o. C-15), 44.2 (t, C-25), 51.2 (d, C-14), 52.6 (d, C-21), 53.1 (d, C-27), 55.7 (d, C-7), 67.2 (t, C-5), 70.8 (t, C-35), 71.4 (d, C-33 o. C-34), 71.7 (d, C-33 o. C-34), 81.4 (s, C-42), 127.1 (d, C-12 o. C-19), 127.3 (d, C-12 o. C-19), 127.9 (d, C-37), 128.1 (d, C-3), 128.2 (d, C-1 o. C-2 o. C-11 o. C-18), 128.5 (d, C-1 o. C-2 o. C-11 o. C-18), 128.7 (d, C-1 o. C-2 o. C-11 o. C-18), 128.8 (d, C-1 o. C-2 o. C-11 o. C-18), 129.4 (d, C-10), 129.4 (d, C-17), 129.8 (d, C-38), 132.8 (s, C-36), 135.4 (s, C-16), 136.3 (s, C-4, C-9), 144.9 (s, C-39), 169.3 (s, C-26), 171.3 (s, C-13), 171.7 (s, C-41). The signals of C-6, C-8/C-15, C-20, C-24/C-29/C-31 and C-30 weren't observed in the ^{13}C-NMR spectrum.

HRMS (CI):	calculated	found
$C_{53}H_{69}N_4O_{12}S$ $[M+H]^+$	985.4627	985.4643
Melting point:	58-60 °C	

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_R = 18.2 min ($[M+H]^+$ = 986).

(*S*)-2-((*R*)-1-(((Benzyloxy)carbonyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-((tosyloxy)methyl)-1,3-dioxolan-4-yl)heptanoic acid (80)

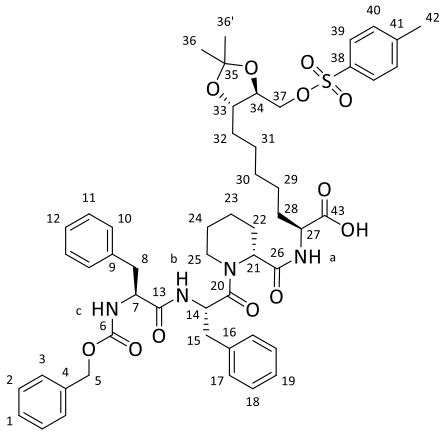
Method A:

To a solution of 25 mg (24.4 µmol) **77** in 0.25 mL DCM abs. were added 6.1 µL (4.43 mg, 43.8 µmol) triethylamine and 7.24 µL (8.89 mg, 40.0 µmol) TMSOTf at 0 °C. The cooling bath was removed and the reaction was stirred at rt for 2 h. For workup, the reaction was diluted with DCM and water was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5) gave 11.5 mg (11.9 µmol, 49 %) **80** as an off-white solid.

Method B:

500 mg (0.488 mmol) **77** were dissolved in 2.5 mL THF before 2.5 mL aq. HCl (5 w%) were added at rt. The reaction was heated to 60 °C overnight. For workup, the reaction was diluted with DCM and brine was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was redissolved in 2.5 mL DCM abs. and 2.5 mL (3.73 g, 32.7 mmol) TFA were added dropwise at rt. The reaction was stirred for 2 h at rt and concentrated *in vacuo*. The crude product was then treated with 4.8 mg (25.2 µmol) *p*TosOH·H_2O in 5.0 mL acetone at 60 °C overnight. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (silica gel, DCM:MeOH 100:0, Gradient 95:5). 373 mg (0.385 mmol, 79 % over three steps) of acid **80** were obtained as an off-white solid.

R_f (80) = 0.35 (silica gel, DCM:MeOH 95:5)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.17 – 1.37 (m, 9 H, 22-H_a, 24-H, 29-H, 30-H, 31-H), 1.27 (s, 3 H, 36-H), 1.33 (s, 3 H, 36-H'), 1.37 – 1.49 (m, 3 H, 23-H_a, 32-H), 1.54 – 1.68 (m, 2 H, 23-H_b, 28-H_a), 1.83 (m, 1 H, 28-H_b), 2.20 (m, 1 H, 22-H_b), 2.44 (s, 3 H, 42-H), 2.82 (m, 1 H, 25-H_a), 2.91 (dd, $^{2}J_{15a,15b}$ = 12.9 Hz, $^{3}J_{15a,14}$ = 5.7 Hz, 1 H, 15-H_a), 2.95 (m, 1 H, 8-H_a), 3.02 (m, 1 H, 8-H_b), 3.05 (dd, $^{2}J_{15b,15a}$ = 13.5 Hz, $^{3}J_{15b,14}$ = 4.3 Hz, 1 H, 15-H_b), 3.48 (d, $^{2}J_{25b,25a}$ = 12.4 Hz, 1 H, 25-H_b), 3.68 – 3.81 (m, 2 H, 33-H, 34-H), 4.05 (m, 2 H, 37-H), 4.38 – 4.50 (m, 2 H, 7-H, 27-H), 4.92 (m, 1 H, 14-H), 5.04 (m, 2 H, 5-H), 5.18 (br s, 1 H, 21-H), 5.39 (d, $^{3}J_{NH,7}$ = 7.5 Hz, 1 H, NH_c), 6.98 – 7.06 (m, 2 H, NH_b, NH_a), 7.11 – 7.38 (m, 17-H, 1-H, 2-H, 3-H, 10-H, 11-H, 12-H, 17-H, 18-H, 19-H, 40-H), 7.79 (d, $^{3}J_{39,40}$ = 8.3 Hz, 2 H, 39-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.9 (t, C-23), 21.6 (q, C-42), 24.7 (t, C-24 o. C-29 o. C-31), 24.7 (t, C-22), 25.4 (t, C-24 o. C-29 o. C-31), 25.6 (t, C-24 o. C-29 o. C-31), 26.6 (q, C-36), 27.3 (q, C-36'), 29.0 (t, C-30), 31.5 (t, C-28), 32.8 (t, C-32), 38.0 (t, C-8), 38.2 (t, C-15), 43.7 (t, C-25), 50.9 (d, C-14), 52.1 (d, C-21, C-27), 55.8 (d, C-7), 67.3 (t, C-5), 69.2 (t, C-37), 77.6 (d, C-33 o. C-34), 78.1 (d, C-33 o. C-34), 109.3 (s, C-35), 127.1 (d, C-12), 128.0 (d, C-39), 128.3 (d, C-3), 128.6 (d, C-1 o. C-2 o. C-11 o. C-18), 128.6 (d, C-1 o. C-2 o. C-11 o. C-18), 129.4 (d, C-10), 129.5 (d, C-17), 129.9 (d, C-40), 132.7 (s, C-38), 136.0 (s, C-9), 145.0 (s, C-41), 171.0 (s, C-20), 174.6 (s, C-43). The signals of C-1/C-2/C-11/C-18, C-4, C-6, C-12, C-13, C-19 and C-26 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.68 (m, 1 H, 27-H), 5.49 (m, 1 H, NH_c).

HRMS (CI):	calculated	found
$C_{52}H_{65}N_4O_{12}S$ $[M+H]^+$	969.4314	969.4326

Melting point: 74 °C

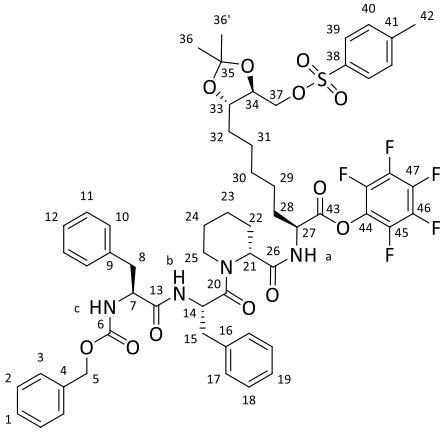
Optical rotation: $[\alpha]_D^{20}$ = +18.0° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.8 mL/min, t_R = 10.4 min ($[M+H]^+$ = 970).

Perfluorophenyl (*S*)-2-((*R*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl-L-phenylalanyl)piperidine-2-carboxamido)-7-((4*S*,5*S*)-2,2-dimethyl-5-((tosyloxy)methyl)-1,3-dioxolan-4-yl)heptanoate (81)

To a solution of 53.5 mg (55.2 µmol) **80** in 0.55 mL DCM abs. were added 12.7 mg (69.0 µmol) pentafluorophenol and 13.7 mg (71.5 µmol) EDC·HCl at 0 °C. The reaction was allowed to warm to rt overnight. Cat. amounts of EDC·HCl were then added and stirring was continued for 2 h. For workup, the reaction was diluted with DCM and 1 M HCl sol. was added. The layers were separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with sat. $NaHCO_3$ sol. and dried over Na_2SO_4. 61.4 mg (54.1 µmol, *dr* 76:24, 98 %) of Pfp ester **81** were obtained as an off-white solid.

R_f(81) = 0.32 (major) & 0.38 (minor, silica gel, PE:EA 50:50)



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.13 – 1.54 (m, 13 H, 22-H_a, 23-H, 24-H, 29-H, 30-H, 31-H, 32-H), 1.26 (s, 3 H, 36-H), 1.32 (s, 3 H, 36-H'), 1.74 (m, 1 H, 28-H_a), 1.97 (m, 1 H, 28-H_b), 2.36 (d, $^{2/3}J_{22b,22a/21/23}$ = 12.5 Hz, 1 H, 22-H_b), 2.44 (s, 3 H, 42-H), 2.88 (m, 1 H, 15-H_a), 2.94 – 3.07 (m, 3 H, 8-H, 15-H_b), 3.11 (m, 1 H, 25-H_a), 3.58 (d, $^2J_{25b,25a}$ = 13.0 Hz, 1 H, 25-H_b), 3.69 – 3.81 (m, 2 H, 33-H, 34-H), 4.02 (dd, $^2J_{37a,37b}$ = 10.9 Hz, $^3J_{37a,34}$ = 4.0 Hz, 1 H, 37-H_a), 4.07 (dd, $^2J_{37b,37a}$ = 10.6 Hz, $^3J_{37b,34}$ = 3.2 Hz, 1 H, 37-H_b), 4.38 (br s, 1 H, 7-H), 4.70 – 4.80 (m, 2 H, 14-H, 27-H), 5.06 (m, 2 H, 5-H), 5.19 (m, 1 H, NH_c), 5.33 (d, $^3J_{21,22a}$ = 4.9 Hz, 1 H, 21-H), 6.50 (br s, 1 H, NH_b), 7.09 – 7.39 (m, 18 H, 1-H, 2-H, 3-H, 10-H, 11-H, 12-H, 17-H, 18-H, 19-H, 40-H, NH_a), 7.78 (d, $^3J_{39,40}$ = 8.2 Hz, 2 H, 39-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.2 (t, C-23), 21.6 (q, C-42), 24.6 (t, C-24 o. C-29 o. C-31), 25.0 (t, C-22), 25.4 (t, C-24 o. C-29 o. C-31), 25.6 (t, C-24 o. C-29 o. C-31), 26.6 (q, C-36), 27.2 (q, C-36'), 29.0 (t, C-30), 31.0 (t, C-28), 32.8 (t, C-32), 37.9 (t, C-8, C-15), 44.1 (t, C-25), 51.1 (d, C-14), 52.5 (d, C-27), 52.5 (d, C-21), 67.1 (t, C-5), 69.1 (t, C-37), 77.6 (d, C-33 o. C-34), 78.1 (d,

C-33 o. C-34), 109.3 (s, C-35), 127.1 (d, C-3 o. C-12 o. C-19), 127.2 (d, C-3 o. C-12 o. C-19), 127.5 (d, C-3 o. C-12 o. C-19), 128.0 (d, C-39), 128.3 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 128.5 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 128.7 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 128.9 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 129.3 (d, C-10), 129.6 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 129.8 (d, C-40), 132.7 (s, C-38), 145.0 (s, C-41), 169.0 (s, C-13 o. C-20 o. C-26 o. C-43), 170.3 (s, C-13 o. C-20 o. C-26 o. C-43), 170.7 (s, C-13 o. C-20 o. C-26 o. C-43), 171.4 (s, C-13 o. C-20 o. C-26 o. C-43). The signals of C-4, C-6, C-7, C-9, C-16, C-44, C-45, C-46 and C-47 weren't observed in the ^{13}C-NMR spectrum.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, 36-H'), 4.86 (br s, 1 H, 14-H), 5.04 (s, 2 H, 5-H), 5.31 (m, 1 H, 21-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 128.2 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 128.5 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 128.8 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18), 129.9 (d, C-1 o. C-2 o. C-11 o. C-17 o. C-18).

HRMS (CI):	calculated	found
$C_{58}H_{64}F_5N_4O_{12}S$ $[M+H]^+$	1135.4156	1135.4153

Melting point: 58 °C

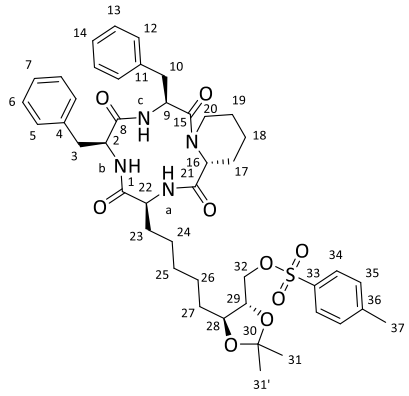
Optical rotation: $[\alpha]_D^{20}$ = +22.4° (c = 1.0, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.6 mL/min, t_{R1} = 16.3 min (24 %, $[M+Na]^+$ = 1158), t_{R2} = 16.7 min (76 %, $[M+Na]^+$ = 1158).

((4*S*,5*S*)-5-(5-((3*S*,6*S*,9*S*,15a*R*)-6,9-Dibenzyl-1,4,7,10-tetraoxotetradecahydro-2H-pyrido-[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (60)

A solution of 330 mg (0.291 mmol) **81** in 70 mL dioxane was added dropwise to a vigorously stirred suspension of 332 mg palladium on charcoal (10 w% Pd) in 450 mL dioxane and 11.0 mL EtOH at 85 °C within 6 h. During the course of the reaction, H_2 was bubbled through the reaction mixture. After complete addition, the reaction was stirred for further 1 h at 85 °C. After cooling to rt, the mixture was filtrated through a pad of Celite® and washed with chloroform. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica gel, PE:EA 100:0, 80:20, 50:50, then DCM:MeOH 95:5). 84 mg (82.3 µmol, 80 % pure, *dr* > 99:1, 28 %) of cyclic tetrapeptide **60** were obtained as an off-white solid. A small sample was further purified by reversed phase column chromatography (silica gel C-18, MeCN:H_2O 50:50, Gradient 90:10) for analytical purposes.

R_f (60) = 0.38 (silica gel, DCM:MeOH 95:5)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.17 – 1.33 (m, 6 H, 19-H_a, 24-H, 25-H, 26-H_a), 1.31 (s, 3 H, 31-H), 1.37 (s, 3 H, 31-H'), 1.42 (m, 1 H, 26-H_b), 1.47 – 1.59 (m, 4 H, 17-H_a, 23-H_a, 27-H), 1.67 – 1.81 (m, 3 H, 18-H_a, 19-H_b, 23-H_b), 1.98 (m, 1 H, 17-H_b), 2.09 (m, 1 H, 18-H_b), 2.46 (s, 3 H, 37-H), 3.01 (ddd, $^{2}J_{20ax,20eq} \approx {}^{3}J_{20ax,19ax}$ = 13.2 Hz, $^{3}J_{20ax,19eq}$ = 2.7 Hz, 1 H, 20-H_{ax}), 3.07 (dd, $^{2}J_{10a,10b}$ = 14.0 Hz, $^{3}J_{10a,9}$ = 7.1 Hz, 1 H, 10-H_a), 3.21 (dd, $^{2}J_{3a,3b}$ = 13.7 Hz, $^{3}J_{3a,2}$ = 6.8 Hz, 1 H, 3-H_a), 3.24 (dd, $^{2}J_{10b,10a}$ = 13.9 Hz, $^{3}J_{10b,9}$ = 7.6 Hz, 1 H, 10-H_b), 3.62 (dd, $^{2}J_{3b,3a}$ = 13.9 Hz, $^{3}J_{3b,2}$ = 10.7 Hz, 1 H, 3-H_b), 3.74 – 3.83 (m, 3 H, 2-H, 28-H, 29-H), 3.94 (d, $^{2}J_{20eq,20ax}$ = 13.9 Hz, 1 H, 20-H_{eq}), 4.07 (dd, $^{2}J_{32a,32b}$ = 10.7 Hz, $^{3}J_{32a,29}$ = 4.4 Hz, 1 H, 32-H_a), 4.11 (dd, $^{2}J_{32b,32a}$ = 10.6 Hz, $^{3}J_{32b,29}$ = 4.3 Hz, 1 H, 32-H_b), 4.18 (dt, $^{3}J_{22,NH} \approx {}^{3}J_{22,23}$ = 8.6 Hz, 1 H, 22-H), 5.02 (d, $^{3}J_{16,17a}$ = 6.3 Hz, 1 H, 16-H), 5.35 (dt, $^{3}J_{9,NH}$ = 10.0 Hz, $^{3}J_{9,10}$ = 7.7 Hz, 1 H, 9-H), 6.39 (d, $^{3}J_{NH,2}$ = 6.0 Hz, 1 H, NH_b), 6.42 (d, $^{3}J_{NH,22}$ = 10.1 Hz, 1 H, NH_a), 7.10 (d, $^{3}J_{5,6}$ = 6.6 Hz, 2 H, 5-H), 7.19 – 7.31 (m, 8 H, 6-H, 7-H, 12-H, 13-H, 14-H), 7.36 (d, $^{3}J_{35,34}$ = 7.9 Hz, 2 H, 35-H), 7.43 (d, $^{3}J_{NH,9}$ = 10.4 Hz, 1 H, NH_c), 7.81 (d, $^{3}J_{34,35}$ = 8.5 Hz, 2 H, 34-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 19.2 (t, C-18), 21.7 (q, C-37), 24.0 (t, C-17), 25.1 (t, C-19 o. C-24 o. C-26), 25.2 (t, C-19 o. C-24 o. C-26), 25.6 (t, C-19 o. C-24 o. C-26), 26.7 (q, C-31), 27.3 (q, C-31'), 29.0 (t, C-23, C-25), 32.8 (t, C-27), 35.2 (t, C-3), 36.6 (t, C-10), 44.0 (t, C-20), 49.9 (d, C-9), 50.9 (d, C-16), 53.6 (d, C-22), 62.6 (d, C-2), 69.1 (t, C-32), 77.8 (d, C-28 o. C-29), 78.1 (d, C-28 o. C-29), 109.3 (s, C-30), 126.7 (d, C-14), 126.9 (d, C-7), 128.0 (d, C-34), 128.6 (d, C-5, C-12), 128.9 (d, C-6), 129.1 (d, C-13), 129.9 (d, C-35), 132.6 (s, C-33), 136.9 (s, C-4), 136.9 (s, C-11), 145.1 (s, C-36), 171.4 (s, C-21), 173.3 (s, C-8), 173.6 (s, C-15), 175.7 (s, C-1).

HRMS (CI):	calculated	found
$C_{44}H_{57}N_4O_9S$ $[M+H]^+$	817.3841	817.3886

Melting point: 80 °C

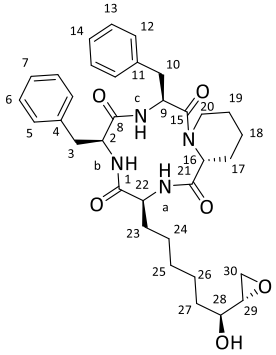
Optical rotation: $[\alpha]_D^{20}$ = –51° (c = 0.1, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 50:50, Gradient 90:10, 0.8 mL/min, t_R = 10.6 min ($[M+H]^+$ = 818).

(3*S*,6*S*,9*S*,15a*R*)-6,9-Dibenzyl-3-((*S*)-6-Hydroxy-6-((*S*)-oxiran-2-yl)hexyl)octahydro-2H-pyrido[1,2-a][1,4,7,10]tetraazacyclododecine-1,4,7,10(3H,12H)-tetraone (83)

To a solution of 12.5 mg (15.3 µmol) **60** in 1.0 mL THF was added 1.0 mL aq. HCl (5 w%) at rt and the reaction was stirred at rt overnight. The reaction was concentrated *in vacuo* and the residue was redissolved in DCM. Brine was added and the layers were separated. The aqueous phase was extracted three times with DCM and the combined organic layers were dried over Na_2SO_4. The crude product was dissolved in 3.0 mL MeOH abs. and cooled to 0 °C before 12.0 µL (12.1 mg, 79.5 µmol) DBU were added. The reaction was stirred at 0 °C for 4 h. For workup, the reaction was filtrated through a pad of Celite® and washed with EA:MeOH 90:10. The filtrate was concentrated *in vacuo* and purified by reversed phase column chromatography (silica gel C-18, H_2O:MeCN 90:10, Gradient 10:90). 5.7 mg (9.42 µmol, 62 % over two steps) of epoxyalcohol **83** were obtained as an off-white solid.

R_f (83) = 0.25 (silica gel, EA:MeOH 95:5)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.26 (m, 3 H, 19-H_a, 24-H), 1.30 – 1.38 (m, 2 H, 25-H), 1.45 – 1.59 (m, 6 H, 17-H_a, 18-H_a, 23-H_a, 26-H, 27-H_a), 1.72 (m, 1 H, 19-H_b), 1.79 (m, 1 H, 23-H_b), 1.93 – 1.99 (m, 2 H, 17-H_b, 27-H_b), 2.09 (m, 1 H, 18-H_b), 2.72 (dd, $^2J_{30a,30b}$ = 4.9 Hz, $^3J_{30a,29}$ = 2.7 Hz, 1 H, 30-H_a), 2.83 (dd, $^2J_{30b,30a}$ = 5.0 Hz, $^3J_{30b,29}$ = 4.1 Hz, 1 H, 30-H_b), 2.96 (m, 1 H, 29-H), 3.01 (ddd, $^2J_{20ax,20eq} \approx {}^3J_{20ax,19ax}$ = 13.6 Hz, $^3J_{20ax,19eq}$ = 2.6 Hz, 1 H, 20-H_{ax}), 3.08 (dd, $^2J_{10a,10b}$ = 14.0 Hz, $^3J_{10a,9}$ = 7.1 Hz, 1 H, 10-H_a), 3.20 (dd, $^2J_{3a,3b}$ = 13.6 Hz, $^3J_{3a,2}$ = 6.0 Hz, 1 H, 3-H_a), 3.25 (dd, $^2J_{10b,10a}$ = 14.0 Hz, $^3J_{10b,9}$ = 8.0 Hz, 1 H, 10-H_b), 3.44 (m, 1 H, 28-H), 3.65 (dd, $^2J_{3b,3a}$ = 13.2 Hz, $^3J_{3b,2}$ = 10.7 Hz, 1 H, 3-H_b), 3.73 (dt, $^3J_{2,NH}$ = 11.1 Hz, $^3J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 3.95 (d, $^2J_{20eq,20ax}$ = 13.6 Hz, 1 H, 20-H_{eq}), 4.17 (dt, $^3J_{22,NH} \approx {}^3J_{22,23}$ = 9.4 Hz, 1 H, 22-H), 5.01 (d, $^3J_{16,17a}$ = 5.4 Hz, 1 H, 16-H), 5.35 (dt, $^3J_{9,NH}$ = 10.0 Hz, $^3J_{9,10}$ = 7.8 Hz, 1 H, 9-H), 6.43 – 6.47 (m, 2 H, NH_a, NH_b), 7.10 (d, $^3J_{5,6}$ = 6.6 Hz, 2 H, 5-H), 7.20 – 7.31 (m, 8 H, 6-H, 7-H, 12-H, 13-H, 14-H), 7.46 (d, $^3J_{NH,9}$ = 10.4 Hz, 1 H, NH_c).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 19.2 (t, C-18), 24.0 (t, C-17), 25.0 (t, C-19 o. C-24 o. C-26), 25.1 (t, C-19 o. C-24 o. C-26), 25.2 (t, C-19 o. C-24 o. C-26), 29.0 (t, C-23, C-25), 34.1 (t, C-27), 35.2 (t, C-3), 36.5 (t, C-10), 43.9 (t, C-20), 45.1 (t, C-30), 49.9 (d, C-9), 50.9 (d, C-16), 53.6 (d, C-22), 55.3 (d, C-29), 62.8 (d, C-2), 71.4 (d, C-28), 126.7 (d, C-7 o. C-14), 126.9 (d, C-7 o. C-14),

128.5 (d, C-6 o. C-13), 128.6 (d, C-6 o. C-13), 128.9 (d, C-5), 129.1 (d, C-12), 136.9 (s, C-4 o. C-11), 137.0 (s, C-4 o. C-11), 171.4 (s, C-21), 173.3 (s, C-8), 173.6 (s, C-15), 175.8 (s, C-1).

HRMS (CI):	calculated	found
$C_{34}H_{45}N_4O_6$ $[M+H]^+$	605.3334	605.3331

Melting point: 95 °C

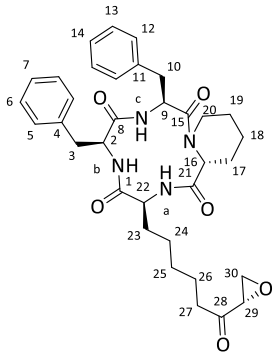
Optical rotation: $[\alpha]_D^{20}$ = –77° (c = 0.1, $CHCl_3$)

LCMS: Luna, MeCN:H_2O + 0.1 % HCOOH 10:90, Gradient 90:10, 0.8 mL/min, t_R = 9.76 min ($[M+H]^+$ = 605).

Trapoxin A[41]

To a solution of 3.9 mg (6.45 µmol) **83** in 2.0 mL DCM abs. were added 5.8 mg (13.7 µmol) DMP at rt. The reaction was stirred for 2 h, filtrated through a pad of Celite® and washed with DCM. The filtrate was concentrated *in vacuo*. Purification by reversed phase column chromatography (silica gel C-18, H_2O:MeCN 90:10, Gradient 10:90) yielded 1.7 mg (2.82 µmol, 44 %) trapoxin A as an off-white solid (after lyophilisation).

R_f (trapoxin A) = 0.36 (silica gel, EA:MeOH 95:5)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 – 1.31 (m, 5 H, 19-H_a, 24-H, 25-H), 1.48 – 1.58 (m, 4 H, 17-H_a, 23-H_a, 26-H), 1.69 – 1.81 (m, 3 H, 18-H_a, 19-H_b, 23-H_b), 1.97 (m, 1 H, 17-H_b), 2.09 (m, 1 H, 18-H_b), 2.25 (dt, $^2J_{27a,27b}$ = 17.5 Hz, $^3J_{27a,26}$ = 7.2 Hz, 1 H, 27-H_a), 2.41 (dt, $^2J_{27b,27a}$ = 17.5 Hz, $^3J_{27b,26}$ = 7.3 Hz, 1 H, 27-H_b), 2.86 (dd, $^2J_{30a,30b}$ = 5.7 Hz, $^3J_{30a,29}$ = 2.5 Hz, 1 H, 30-H_a), 3.00 (dd, $^2J_{30b,30a}$ = 6.0 Hz, $^3J_{30b,29}$ = 4.7 Hz, 1 H, 30-H_b), 3.01 (m, 1 H, 20-H_{ax}), 3.08 (dd, $^2J_{10a,10b}$ = 13.9 Hz, $^3J_{10a,9}$ = 7.3 Hz, 1 H, 10-H_a), 3.20 (dd, $^2J_{3a,3b}$ = 13.4 Hz, $^3J_{3a,2}$ = 6.2 Hz, 1 H, 3-H_a), 3.25 (dd, $^2J_{10b,10a}$ = 13.9 Hz, $^3J_{10b,9}$ = 8.2 Hz, 1 H, 10-H_b), 3.42 (dd, $^3J_{29,30b}$ = 4.7 Hz, $^3J_{29,30a}$ = 2.5 Hz, 1 H, 29-H), 3.64 (dd, $^2J_{3b,3a}$ = 13.4 Hz, $^3J_{3b,2}$ = 10.9 Hz, 1 H, 3-H_b), 3.73 (dt, $^3J_{2,NH}$ = 11.0 Hz, $^3J_{2,3}$ = 5.7 Hz, 1 H, 2-H), 3.95 (d, $^2J_{20eq,20ax}$ = 13.9 Hz, 1 H, 20-H_{eq}), 4.16 (dt, $^3J_{22,NH} \approx {}^3J_{22,23}$ = 8.4 Hz, 1 H, 22-H), 5.01 (d, $^3J_{16,17a}$ = 6.0 Hz, 1 H, 16-H), 5.35 (dt, $^3J_{9,NH}$ = 10.2 Hz, $^3J_{9,10}$ = 7.8 Hz, 1 H, 9-H), 6.38 (d, $^3J_{NH,2}$ = 5.4 Hz, 1 H, NH_b), 6.43 (d, $^3J_{NH,22}$ = 10.1 Hz, 1 H, NH_a), 7.10 (d, $^3J_{5,6}$ = 6.3 Hz, 2 H, 5-H), 7.21 – 7.31 (m, 8 H, 6-H, 7-H, 12-H, 13-H, 14-H), 7.45 (d, $^3J_{NH,9}$ = 10.1 Hz, 1 H, NH_c).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 19.2 (t, C-18), 22.7 (t, C-26), 24.0 (t, C-17), 25.1 (t, C-19), 25.2 (t, C-24), 28.6 (t, C-25), 28.9 (t, C-23), 35.2 (t, C-3), 36.2 (t, C-27), 36.5 (t, C-10), 43.9 (t, C-20), 46.1 (t, C-30), 50.0 (d, C-9), 50.9 (d, C-16), 53.4 (d, C-29), 53.5 (d, C-22), 62.8 (d, C-2), 126.7 (d, C-14), 127.0 (d, C-7), 128.5 (d, C-6 o. C-13), 128.6 (d, C-6 o. C-13), 128.9 (d, C-5), 129.1 (d, C-12), 136.9 (s, C-4, C-11), 171.4 (s, C-21), 173.3 (s, C-8), 173.6 (s, C-15), 175.7 (s, C-1), 207.6 (s, C-28).

HRMS (CI):	calculated	found
$C_{34}H_{43}N_4O_6$ $[M+H]^+$	603.3177	603.3182

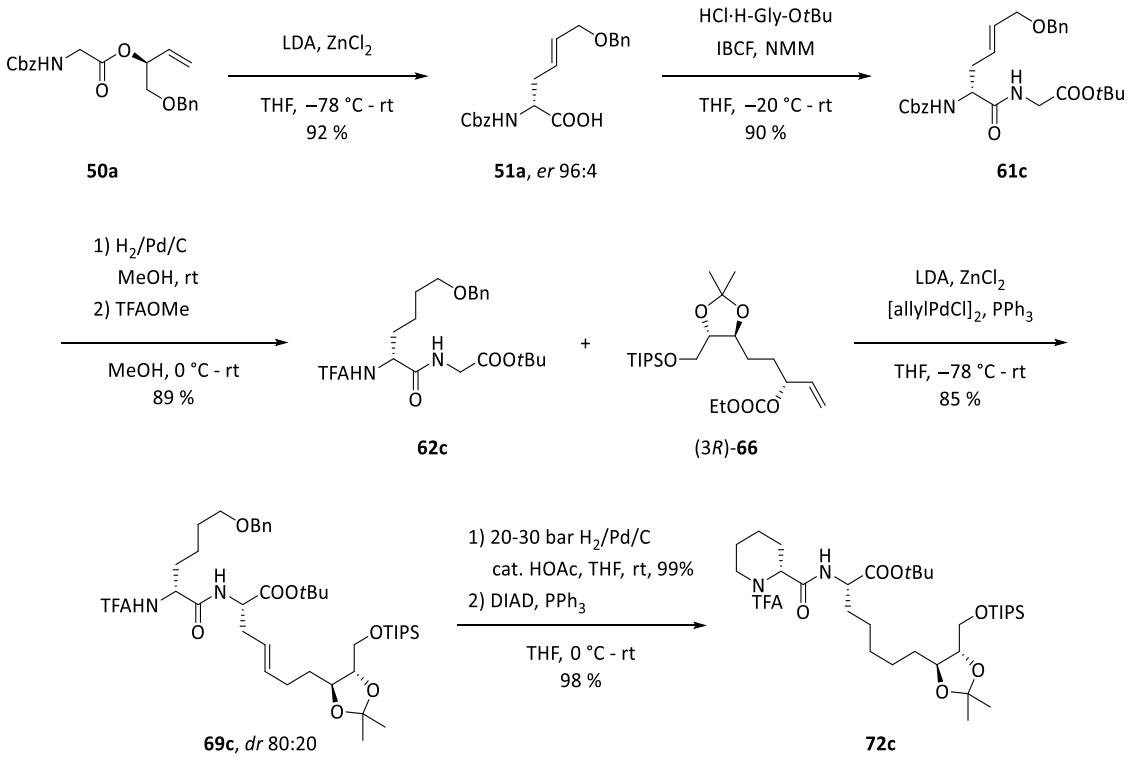
Melting point: 130-132 °C

Optical rotation: $[\alpha]_D^{22}$ = –81.7° (c = 0.425, MeOH)

6. Summary and Outlook

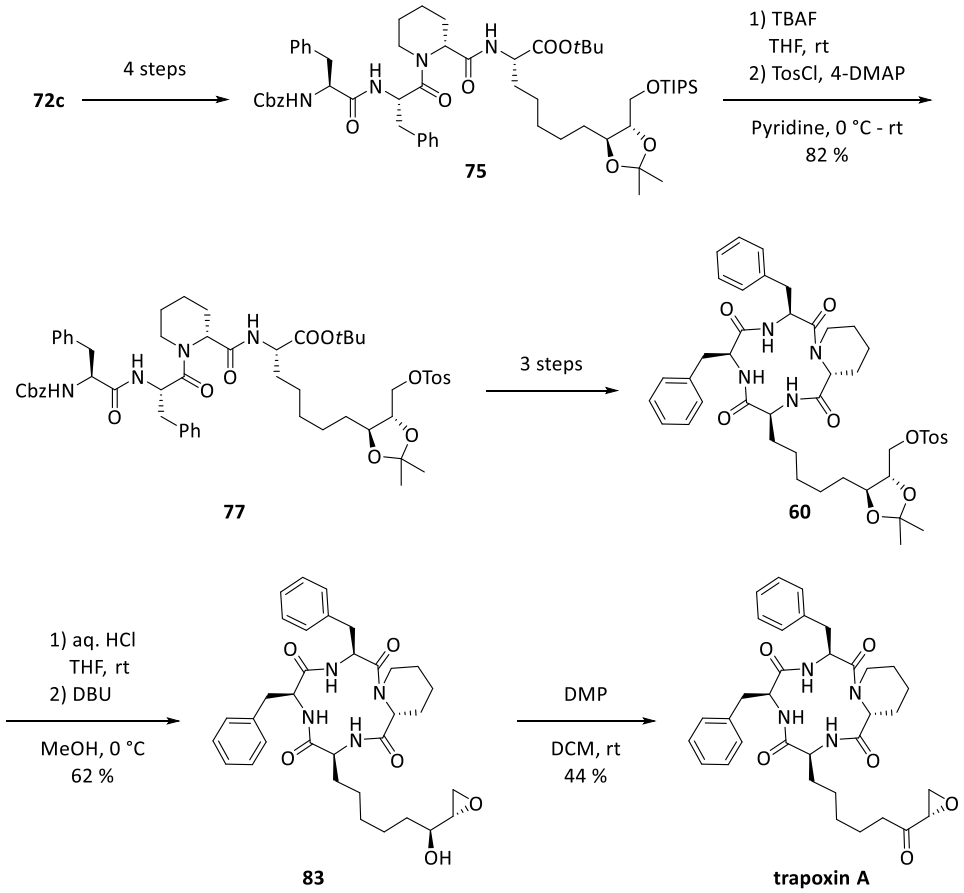
Macrocyclic histone deacetylase inhibitors (HDACi) are important natural products to study the epigenetic function of histone-modifying enzymes. The influence of these inhibitors on the development of histone research can be emphasized by the fact that the first human HDAC was isolated through affinity chromatography using a modified HDAC inhibitor.[33] These inhibitors are promising lead structures for the development of new anticancer agents, while some HDACi already have received approval by the FDA for this purpose. Additionally, synthetic inhibitors have been the focus of many recent studies. However, naturally occurring inhibitors often show higher biological activity and isoform selectivity due to their more sophisticated structural diversity.

This dissertation described the first total synthesis of the two natural HDACi trapoxin A and Cyl-1 along with derivatives thereof. The first targeted HDACi was trapoxin A, a cyclic tetrapeptide first isolated from *Helicoma ambiens* RF-1023 in 1990.[41] Trapoxin A shows detransformation activity against *sis* oncogene-transformed NIH3T3 fibroblast cells and inhibits HDAC1 activity in the nanomolar range. The configuration of its peptide backbone made several peptide modification reactions feasible. For instance, the non-proteinogenic (*R*)-pipecolinic acid was introduced *via* ester enolate Claisen rearrangement (scheme 6.1). Dipeptide **62c** was subjected to Pd-catalyzed allylic alkylation to access the second unusual amino acid, (2*S*,9*S*)-2-amino-9,10-epoxy-8-oxodecanoic acid (Aoe). With dipeptide **69c** at hand, hydrogenative debenzylation and subsequent Mitsunobu cyclization afforded the corresponding pipecolinic acid moiety in **72c**.



Scheme 6.1: Synthesis of pipecolinic acid-containing dipeptide **72c**.

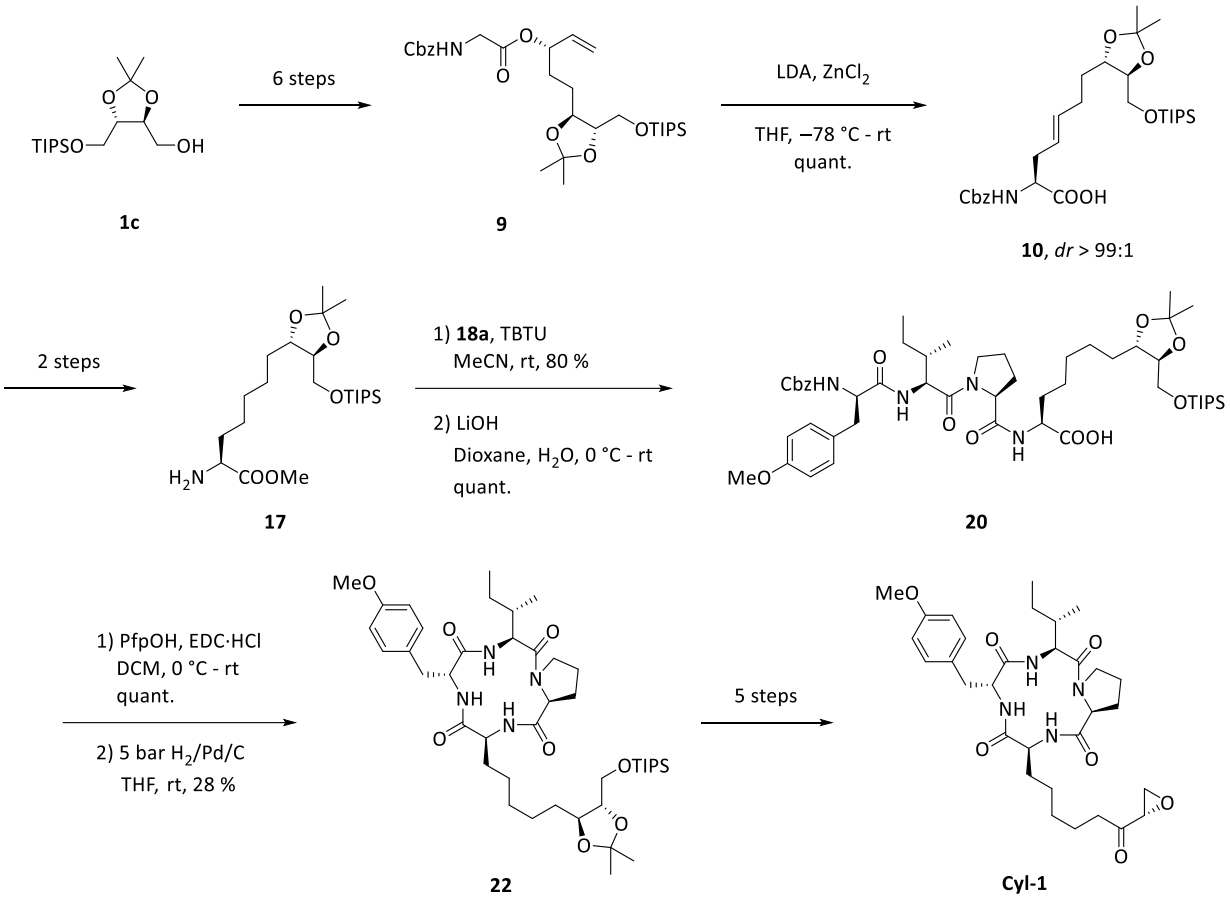
The synthesis of trapoxin A was carried on by coupling to linear tetrapeptide **75** (scheme 6.2). Replacement of the TIPS-group by a tosylate was necessary in order to selectively cleave the *tert*-butyl ester in **77**. Following activation of the carboxylic acid as Pfp ester and subsequent cyclization under hydrogenative conditions gave cyclic **60**. Installation of the α-epoxyketone moiety finally afforded the natural product trapoxin A.



Scheme 6.2: Synthesis of trapoxin A.

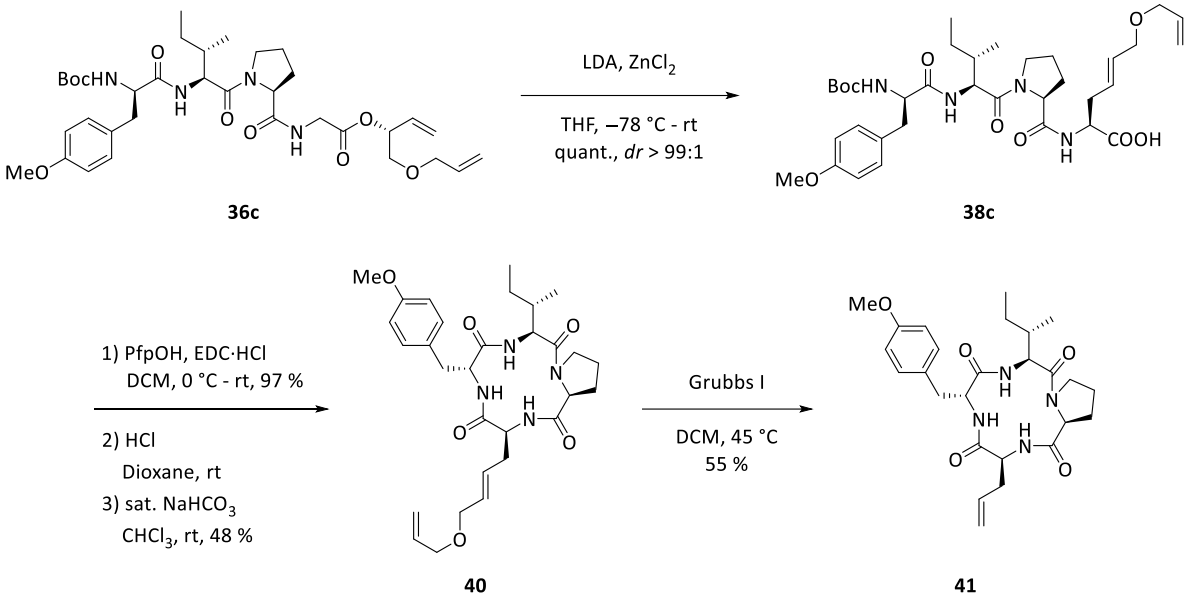
The natural HDACi Cyl-1 called for a different synthetic approach. The non-proteinogenic Aoe moiety was introduced *via* chelate enolate Claisen rearrangement of precursor **9** (scheme 6.3). Subsequent incorporation into linear tetrapeptide **20** followed by activation and macrolactamization made the cyclic precursor **22** accessible. Transformation of the Aoe side chain in accordance to the synthesis of trapoxin finally gave the natural product Cyl-1 after 17 steps (longest linear synthesis) in 2.5 % total yield.

To provide synthetic access to the presented natural products, various linear tetrapeptides bearing different protective groups, side chain functionalities and *C*-terminal amino acids were synthesized. The challenging macrocyclization towards the 12-membered ring system generally needed evaluation of the optimal ring closing position. Furthermore, synthetic strategies have been developed that allowed not only for the synthesis of the natural products but also several derivatives from a common precursor.

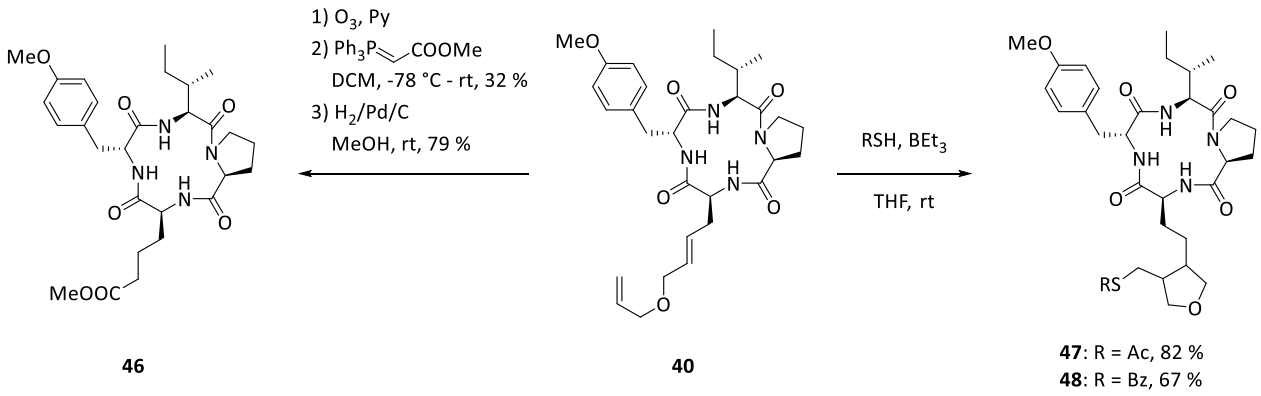


Scheme 6.3: Synthesis of Cyl-1.

Access to derivatives of Cyl-1 was gained after unprecedented peptide enolate Claisen re-arrangement of chiral allyl ester **36c** (scheme 6.4). The obtained carboxylic acid was activated as Pfp ester, Boc-deprotected and cyclized under biphasic ring closure conditions to Cyl-1 derivative **40**. Intramolecular olefin metathesis afforded allylglycine-containing macrocycle **41**, whose low solubility prevented further modifications. Macrocycle **41** was modified instead in manifold ways giving rise to derivatives of the natural product (scheme 6.5). For instance, thiol-ene click reactions with different thiols afforded tetrahydrofuran derivatives **47** and **48** in good yields.



Scheme 6.4: Peptide ester enolate Claisen rearrangement towards Cyl-1 derivatives.



Scheme 6.5: Modifications of **40** to access several derivatives of natural Cyl-1.

The presented methods could be used in succeeding studies to target the structurally similar natural product Cyl-2,[48] which contains a pipecolinic acid moiety instead of proline. Therefore, the developed synthetic route towards (*R*)-configured pipecolinic acid should easily be adaptable to synthesize the (*S*)-enantiomer accordingly. Derivatives of trapoxin A should be accessible by altering the allylic substrates utilized in Pd-catalyzed allylic alkylation.

The reported cytotoxicity profiles of both the natural products and their precursors/derivatives need to be complemented by HDAC inhibitory activities. Their selectivity profiles towards the different HDAC isoforms need to be evaluated and the influence of different side chains on both activity and selectivity needs assessment. Especially Cyl-1 needs to undergo intense biological testing since no inhibitory data have been reported so far.

7. Literature

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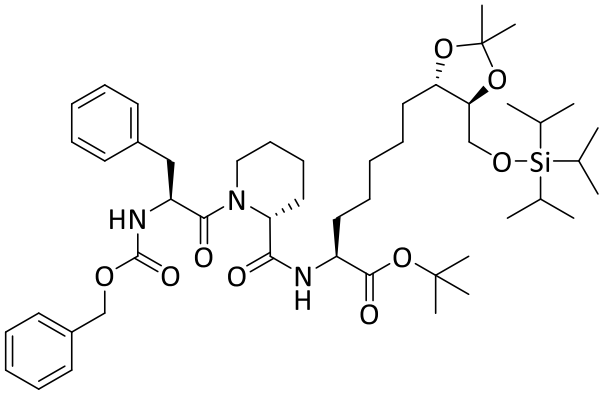
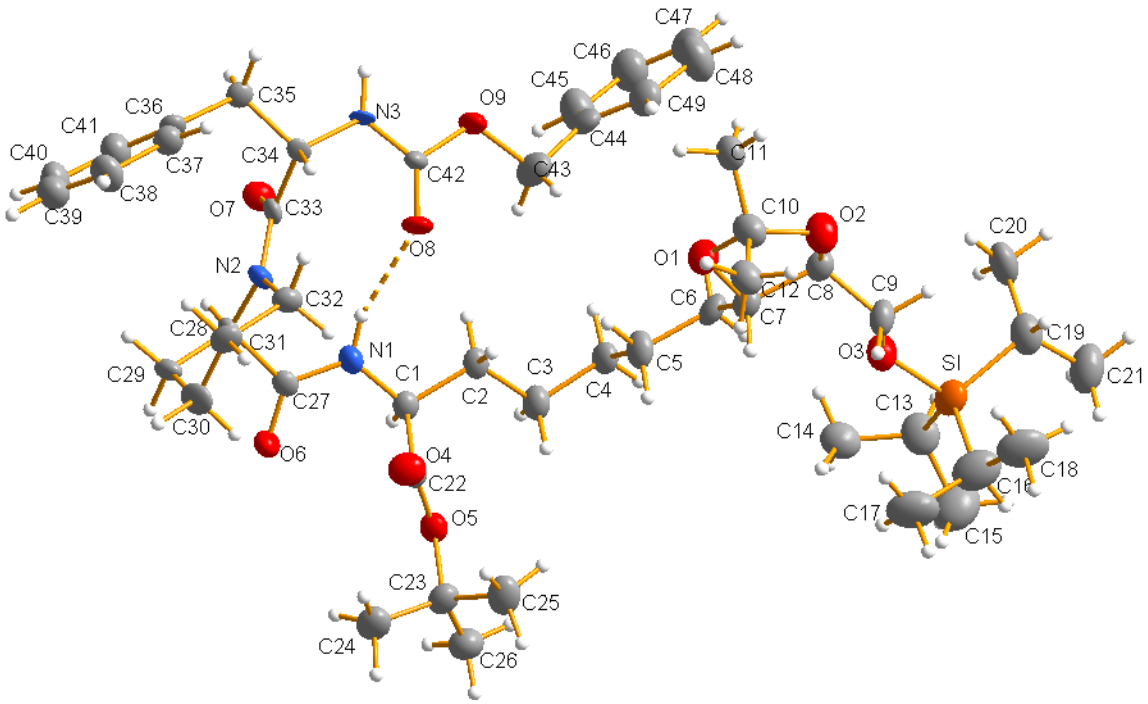
8. Appendix

8.1 Crystallographic data

Crystal structure of tripeptide **74**



chemical structure of **74** (major diastereomer)



X-ray structure of **74** (major diastereomer)

1) Crystal data and structure refinement for **74**.

Empirical formula	C49 H77 N3 O9 Si	
Formula weight	880.22	
Temperature	142(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	I2	
Unit cell dimensions	a = 12.849(3) Å	α= 90°.
	b = 8.804(3) Å	β= 90.86(2)°.
	c = 44.542(13) Å	γ = 90°.
Volume	5038(2) $Å^3$	
Z	4	
Density (calculated)	1.161 mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	1912	
Crystal size	0.14 x 0.08 x 0.025 mm^3	
Theta range for data collection	0.914 to 25.910°.	
Index ranges	-15<=h<=11, -10<=k<=10, -54<=l<=54	
Reflections collected	30742	
Independent reflections	9570 [R(int) = 0.3489]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8620 and 0.7383	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9570 / 472 / 570	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.1370, wR2 = 0.2258	
R indices (all data)	R1 = 0.4137, wR2 = 0.3414	
Absolute structure parameter	-0.1(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.446 and -0.444 $e.Å^{-3}$	

2) Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **74**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	2025(4)	5257(7)	5353(2)	43(2)
O(1)	3529(10)	1713(15)	4303(3)	44(3)
O(2)	3260(10)	687(16)	4776(3)	51(4)
O(3)	2287(9)	4278(15)	5048(3)	43(4)
O(4)	5828(9)	6497(14)	3295(3)	42(4)
O(5)	4945(8)	8660(14)	3396(3)	30(3)
O(6)	4984(9)	7513(14)	2644(3)	33(3)
O(7)	3155(8)	3173(13)	2369(3)	33(4)
N(1)	4195(10)	5690(17)	2908(3)	32(4)
N(2)	4863(10)	3498(16)	2512(3)	25(4)
N(3)	3140(9)	624(16)	2759(3)	25(3)
C(1)	4018(13)	6690(20)	3157(4)	28(4)
C(2)	3417(12)	5820(20)	3398(4)	28(4)
C(3)	3041(15)	6820(20)	3656(4)	40(5)
C(4)	2429(13)	5900(20)	3889(4)	34(5)
C(5)	3104(14)	4820(20)	4067(4)	42(5)
C(6)	2514(14)	3970(20)	4318(4)	37(5)
C(7)	3202(14)	2920(20)	4496(5)	37(4)
O(8)	3625(8)	2510(13)	3080(3)	33(3)
C(8)	2693(15)	2070(20)	4758(4)	36(4)
C(9)	2834(14)	2860(20)	5058(4)	38(5)
O(9)	2236(9)	1002(14)	3180(3)	41(4)
C(11)	3493(15)	-1000(20)	4355(5)	43(5)
C(10)	3837(14)	480(20)	4499(5)	44(4)
C(14)	1578(15)	7410(20)	4888(5)	52(6)
C(13)	1338(17)	7020(20)	5209(5)	53(5)
C(12)	4972(12)	550(20)	4573(4)	42(5)
C(15)	1540(20)	8410(30)	5412(6)	89(8)
C(16)	3247(16)	5710(30)	5570(6)	68(6)
C(17)	4111(16)	6220(30)	5367(6)	77(7)
C(18)	3649(15)	4490(30)	5773(6)	71(7)
C(19)	1141(15)	4100(30)	5588(5)	51(5)
C(20)	279(15)	3310(30)	5406(5)	59(7)
C(21)	688(17)	5040(30)	5842(5)	69(7)

C(22)	5055(14)	7280(20)	3287(4)	31(4)
C(23)	5853(14)	9490(20)	3526(5)	40(4)
C(24)	6653(15)	9730(20)	3289(5)	51(6)
C(25)	6270(14)	8630(20)	3802(4)	48(6)
C(26)	5379(15)	10960(20)	3623(5)	51(6)
C(27)	4685(13)	6190(20)	2670(4)	24(4)
C(28)	4830(12)	5040(20)	2409(4)	24(4)
C(29)	5820(12)	5420(20)	2227(4)	32(4)
C(30)	6780(12)	5030(20)	2414(5)	39(5)
C(31)	6770(13)	3380(20)	2503(4)	36(5)
C(32)	5772(12)	3020(20)	2687(4)	32(5)
C(33)	3972(13)	2660(20)	2478(4)	21(4)
C(34)	3996(11)	964(18)	2554(4)	19(3)
C(35)	3830(12)	90(20)	2263(4)	24(4)
C(36)	4657(12)	460(20)	2040(4)	31(4)
C(37)	5656(13)	-150(20)	2083(5)	36(5)
C(38)	6463(15)	240(30)	1886(5)	51(6)
C(39)	6256(16)	1240(20)	1659(5)	51(6)
C(40)	5316(17)	1870(30)	1612(5)	54(6)
C(41)	4548(16)	1500(20)	1809(5)	45(6)
C(42)	3066(13)	1450(20)	3007(4)	24(4)
C(43)	2138(17)	1890(30)	3462(5)	65(6)
C(44)	1136(15)	1380(20)	3599(5)	41(5)
C(45)	223(18)	2060(30)	3512(5)	64(7)
C(46)	-684(18)	1630(30)	3660(5)	62(7)
C(47)	-631(17)	620(30)	3892(5)	53(6)
C(48)	269(17)	10(30)	3986(6)	68(7)
C(49)	1182(15)	390(30)	3841(5)	50(6)

3) Bond lengths [Å] and angles [°] for **74**.

Si-O(3)	1.647(14)	C(5)-H(5B)	0.9900
Si-C(19)	1.86(2)	C(6)-C(7)	1.50(2)
Si-C(16)	1.87(2)	C(6)-H(6A)	0.9900
Si-C(13)	1.89(2)	C(6)-H(6B)	0.9900
O(1)-C(7)	1.43(2)	C(7)-C(8)	1.54(3)
O(1)-C(10)	1.45(2)	C(7)-H(7)	1.0000
O(2)-C(8)	1.42(2)	O(8)-C(42)	1.220(18)
O(2)-C(10)	1.46(2)	C(8)-C(9)	1.52(2)
O(3)-C(9)	1.43(2)	C(8)-H(8)	1.0000
O(4)-C(22)	1.21(2)	C(9)-H(9A)	0.9900
O(5)-C(22)	1.32(2)	C(9)-H(9B)	0.9900
O(5)-C(23)	1.49(2)	O(9)-C(42)	1.38(2)
O(6)-C(27)	1.232(19)	O(9)-C(43)	1.49(2)
O(7)-C(33)	1.236(18)	C(11)-C(10)	1.52(2)
N(1)-C(27)	1.32(2)	C(11)-H(11A)	0.9800
N(1)-C(1)	1.44(2)	C(11)-H(11B)	0.9800
N(1)-H(1)	0.8800	C(11)-H(11C)	0.9800
N(2)-C(33)	1.370(19)	C(10)-C(12)	1.49(2)
N(2)-C(28)	1.43(2)	C(14)-C(13)	1.51(3)
N(2)-C(32)	1.46(2)	C(14)-H(14A)	0.9800
N(3)-C(42)	1.33(2)	C(14)-H(14B)	0.9800
N(3)-C(34)	1.47(2)	C(14)-H(14C)	0.9800
N(3)-H(3)	0.8800	C(13)-C(15)	1.54(3)
C(1)-C(22)	1.53(2)	C(13)-H(13)	1.0000
C(1)-C(2)	1.54(2)	C(12)-H(12A)	0.9800
C(1)-H(1A)	1.0000	C(12)-H(12B)	0.9800
C(2)-C(3)	1.53(2)	C(12)-H(12C)	0.9800
C(2)-H(2A)	0.9900	C(15)-H(15A)	0.9800
C(2)-H(2B)	0.9900	C(15)-H(15B)	0.9800
C(3)-C(4)	1.54(2)	C(15)-H(15C)	0.9800
C(3)-H(3A)	0.9900	C(16)-C(18)	1.49(3)
C(3)-H(3B)	0.9900	C(16)-C(17)	1.51(3)
C(4)-C(5)	1.50(2)	C(16)-H(16)	1.0000
C(4)-H(4A)	0.9900	C(17)-H(17A)	0.9800
C(4)-H(4B)	0.9900	C(17)-H(17B)	0.9800
C(5)-C(6)	1.55(2)	C(17)-H(17C)	0.9800
C(5)-H(5A)	0.9900	C(18)-H(18A)	0.9800

C(18)-H(18B)	0.9800	C(34)-H(34)	1.0000
C(18)-H(18C)	0.9800	C(35)-C(36)	1.50(2)
C(19)-C(21)	1.53(3)	C(35)-H(35A)	0.9900
C(19)-C(20)	1.53(3)	C(35)-H(35B)	0.9900
C(19)-H(19)	1.0000	C(36)-C(41)	1.38(3)
C(20)-H(20A)	0.9800	C(36)-C(37)	1.40(2)
C(20)-H(20B)	0.9800	C(37)-C(38)	1.41(3)
C(20)-H(20C)	0.9800	C(37)-H(37)	0.9500
C(21)-H(21A)	0.9800	C(38)-C(39)	1.36(3)
C(21)-H(21B)	0.9800	C(38)-H(38)	0.9500
C(21)-H(21C)	0.9800	C(39)-C(40)	1.34(3)
C(23)-C(26)	1.49(3)	C(39)-H(39)	0.9500
C(23)-C(24)	1.50(3)	C(40)-C(41)	1.37(3)
C(23)-C(25)	1.54(3)	C(40)-H(40)	0.9500
C(24)-H(24A)	0.9800	C(41)-H(41)	0.9500
C(24)-H(24B)	0.9800	C(43)-C(44)	1.50(3)
C(24)-H(24C)	0.9800	C(43)-H(43A)	0.9900
C(25)-H(25A)	0.9800	C(43)-H(43B)	0.9900
C(25)-H(25B)	0.9800	C(44)-C(45)	1.37(3)
C(25)-H(25C)	0.9800	C(44)-C(49)	1.38(3)
C(26)-H(26A)	0.9800	C(45)-C(46)	1.40(3)
C(26)-H(26B)	0.9800	C(45)-H(45)	0.9500
C(26)-H(26C)	0.9800	C(46)-C(47)	1.36(3)
C(27)-C(28)	1.55(2)	C(46)-H(46)	0.9500
C(28)-C(29)	1.56(2)	C(47)-C(48)	1.34(3)
C(28)-H(28)	1.0000	C(47)-H(47)	0.9500
C(29)-C(30)	1.52(2)	C(48)-C(49)	1.39(3)
C(29)-H(29A)	0.9900	C(48)-H(48)	0.9500
C(29)-H(29B)	0.9900	C(49)-H(49)	0.9500
C(30)-C(31)	1.51(2)		
C(30)-H(30A)	0.9900	O(3)-Si-C(19)	108.1(9)
C(30)-H(30B)	0.9900	O(3)-Si-C(16)	110.9(9)
C(31)-C(32)	1.56(2)	C(19)-Si-C(16)	109.9(11)
C(31)-H(31A)	0.9900	O(3)-Si-C(13)	104.4(9)
C(31)-H(31B)	0.9900	C(19)-Si-C(13)	110.8(10)
C(32)-H(32A)	0.9900	C(16)-Si-C(13)	112.5(11)
C(32)-H(32B)	0.9900	C(7)-O(1)-C(10)	105.9(15)
C(33)-C(34)	1.53(2)	C(8)-O(2)-C(10)	109.0(15)
C(34)-C(35)	1.52(2)	C(9)-O(3)-Si	122.4(12)

C(22)-O(5)-C(23)	120.6(14)	H(5A)-C(5)-H(5B)	107.7
C(27)-N(1)-C(1)	120.1(16)	C(7)-C(6)-C(5)	112.8(15)
C(27)-N(1)-H(1)	119.9	C(7)-C(6)-H(6A)	109.0
C(1)-N(1)-H(1)	119.9	C(5)-C(6)-H(6A)	109.0
C(33)-N(2)-C(28)	117.2(13)	C(7)-C(6)-H(6B)	109.0
C(33)-N(2)-C(32)	124.5(14)	C(5)-C(6)-H(6B)	109.0
C(28)-N(2)-C(32)	117.6(13)	H(6A)-C(6)-H(6B)	107.8
C(42)-N(3)-C(34)	118.1(14)	O(1)-C(7)-C(6)	108.5(16)
C(42)-N(3)-H(3)	121.0	O(1)-C(7)-C(8)	103.0(16)
C(34)-N(3)-H(3)	121.0	C(6)-C(7)-C(8)	116.6(16)
N(1)-C(1)-C(22)	110.5(15)	O(1)-C(7)-H(7)	109.5
N(1)-C(1)-C(2)	108.7(15)	C(6)-C(7)-H(7)	109.5
C(22)-C(1)-C(2)	110.6(15)	C(8)-C(7)-H(7)	109.5
N(1)-C(1)-H(1A)	109.0	O(2)-C(8)-C(9)	107.0(15)
C(22)-C(1)-H(1A)	109.0	O(2)-C(8)-C(7)	103.7(16)
C(2)-C(1)-H(1A)	109.0	C(9)-C(8)-C(7)	113.3(17)
C(3)-C(2)-C(1)	113.8(16)	O(2)-C(8)-H(8)	110.9
C(3)-C(2)-H(2A)	108.8	C(9)-C(8)-H(8)	110.9
C(1)-C(2)-H(2A)	108.8	C(7)-C(8)-H(8)	110.9
C(3)-C(2)-H(2B)	108.8	O(3)-C(9)-C(8)	108.8(15)
C(1)-C(2)-H(2B)	108.8	O(3)-C(9)-H(9A)	109.9
H(2A)-C(2)-H(2B)	107.7	C(8)-C(9)-H(9A)	109.9
C(2)-C(3)-C(4)	111.9(16)	O(3)-C(9)-H(9B)	109.9
C(2)-C(3)-H(3A)	109.2	C(8)-C(9)-H(9B)	109.9
C(4)-C(3)-H(3A)	109.2	H(9A)-C(9)-H(9B)	108.3
C(2)-C(3)-H(3B)	109.2	C(42)-O(9)-C(43)	113.4(14)
C(4)-C(3)-H(3B)	109.2	C(10)-C(11)-H(11A)	109.5
H(3A)-C(3)-H(3B)	107.9	C(10)-C(11)-H(11B)	109.5
C(5)-C(4)-C(3)	113.0(15)	H(11A)-C(11)-H(11B)	109.5
C(5)-C(4)-H(4A)	109.0	C(10)-C(11)-H(11C)	109.5
C(3)-C(4)-H(4A)	109.0	H(11A)-C(11)-H(11C)	109.5
C(5)-C(4)-H(4B)	109.0	H(11B)-C(11)-H(11C)	109.5
C(3)-C(4)-H(4B)	109.0	O(1)-C(10)-O(2)	106.2(15)
H(4A)-C(4)-H(4B)	107.8	O(1)-C(10)-C(12)	110.9(16)
C(4)-C(5)-C(6)	113.5(15)	O(2)-C(10)-C(12)	108.4(16)
C(4)-C(5)-H(5A)	108.9	O(1)-C(10)-C(11)	108.3(16)
C(6)-C(5)-H(5A)	108.9	O(2)-C(10)-C(11)	108.6(16)
C(4)-C(5)-H(5B)	108.9	C(12)-C(10)-C(11)	114.1(17)
C(6)-C(5)-H(5B)	108.9	C(13)-C(14)-H(14A)	109.5

C(13)-C(14)-H(14B)	109.5	H(18A)-C(18)-H(18C)	109.5
H(14A)-C(14)-H(14B)	109.5	H(18B)-C(18)-H(18C)	109.5
C(13)-C(14)-H(14C)	109.5	C(21)-C(19)-C(20)	111.0(18)
H(14A)-C(14)-H(14C)	109.5	C(21)-C(19)-Si	111.0(16)
H(14B)-C(14)-H(14C)	109.5	C(20)-C(19)-Si	113.0(16)
C(14)-C(13)-C(15)	110(2)	C(21)-C(19)-H(19)	107.1
C(14)-C(13)-Si	114.1(16)	C(20)-C(19)-H(19)	107.1
C(15)-C(13)-Si	112.1(15)	Si-C(19)-H(19)	107.1
C(14)-C(13)-H(13)	106.8	C(19)-C(20)-H(20A)	109.5
C(15)-C(13)-H(13)	106.8	C(19)-C(20)-H(20B)	109.5
Si-C(13)-H(13)	106.8	H(20A)-C(20)-H(20B)	109.5
C(10)-C(12)-H(12A)	109.5	C(19)-C(20)-H(20C)	109.5
C(10)-C(12)-H(12B)	109.5	H(20A)-C(20)-H(20C)	109.5
H(12A)-C(12)-H(12B)	109.5	H(20B)-C(20)-H(20C)	109.5
C(10)-C(12)-H(12C)	109.5	C(19)-C(21)-H(21A)	109.5
H(12A)-C(12)-H(12C)	109.5	C(19)-C(21)-H(21B)	109.5
H(12B)-C(12)-H(12C)	109.5	H(21A)-C(21)-H(21B)	109.5
C(13)-C(15)-H(15A)	109.5	C(19)-C(21)-H(21C)	109.5
C(13)-C(15)-H(15B)	109.5	H(21A)-C(21)-H(21C)	109.5
H(15A)-C(15)-H(15B)	109.5	H(21B)-C(21)-H(21C)	109.5
C(13)-C(15)-H(15C)	109.5	O(4)-C(22)-O(5)	127.3(17)
H(15A)-C(15)-H(15C)	109.5	O(4)-C(22)-C(1)	121.9(18)
H(15B)-C(15)-H(15C)	109.5	O(5)-C(22)-C(1)	110.7(15)
C(18)-C(16)-C(17)	108.9(19)	O(5)-C(23)-C(26)	102.5(14)
C(18)-C(16)-Si	116.0(17)	O(5)-C(23)-C(24)	109.6(17)
C(17)-C(16)-Si	111.9(18)	C(26)-C(23)-C(24)	111.9(19)
C(18)-C(16)-H(16)	106.5	O(5)-C(23)-C(25)	109.4(16)
C(17)-C(16)-H(16)	106.5	C(26)-C(23)-C(25)	109.4(17)
Si-C(16)-H(16)	106.5	C(24)-C(23)-C(25)	113.5(17)
C(16)-C(17)-H(17A)	109.5	C(23)-C(24)-H(24A)	109.5
C(16)-C(17)-H(17B)	109.5	C(23)-C(24)-H(24B)	109.5
H(17A)-C(17)-H(17B)	109.5	H(24A)-C(24)-H(24B)	109.5
C(16)-C(17)-H(17C)	109.5	C(23)-C(24)-H(24C)	109.5
H(17A)-C(17)-H(17C)	109.5	H(24A)-C(24)-H(24C)	109.5
H(17B)-C(17)-H(17C)	109.5	H(24B)-C(24)-H(24C)	109.5
C(16)-C(18)-H(18A)	109.5	C(23)-C(25)-H(25A)	109.5
C(16)-C(18)-H(18B)	109.5	C(23)-C(25)-H(25B)	109.5
H(18A)-C(18)-H(18B)	109.5	H(25A)-C(25)-H(25B)	109.5
C(16)-C(18)-H(18C)	109.5	C(23)-C(25)-H(25C)	109.5

H(25A)-C(25)-H(25C)	109.5	C(31)-C(32)-H(32B)	109.9
H(25B)-C(25)-H(25C)	109.5	H(32A)-C(32)-H(32B)	108.3
C(23)-C(26)-H(26A)	109.5	O(7)-C(33)-N(2)	123.2(16)
C(23)-C(26)-H(26B)	109.5	O(7)-C(33)-C(34)	117.4(14)
H(26A)-C(26)-H(26B)	109.5	N(2)-C(33)-C(34)	119.2(14)
C(23)-C(26)-H(26C)	109.5	N(3)-C(34)-C(35)	109.3(13)
H(26A)-C(26)-H(26C)	109.5	N(3)-C(34)-C(33)	108.8(14)
H(26B)-C(26)-H(26C)	109.5	C(35)-C(34)-C(33)	107.7(15)
O(6)-C(27)-N(1)	123.0(19)	N(3)-C(34)-H(34)	110.3
O(6)-C(27)-C(28)	120.3(18)	C(35)-C(34)-H(34)	110.3
N(1)-C(27)-C(28)	116.6(17)	C(33)-C(34)-H(34)	110.3
N(2)-C(28)-C(27)	112.6(16)	C(36)-C(35)-C(34)	111.2(14)
N(2)-C(28)-C(29)	110.5(15)	C(36)-C(35)-H(35A)	109.4
C(27)-C(28)-C(29)	111.0(14)	C(34)-C(35)-H(35A)	109.4
N(2)-C(28)-H(28)	107.5	C(36)-C(35)-H(35B)	109.4
C(27)-C(28)-H(28)	107.5	C(34)-C(35)-H(35B)	109.4
C(29)-C(28)-H(28)	107.5	H(35A)-C(35)-H(35B)	108.0
C(30)-C(29)-C(28)	109.1(16)	C(41)-C(36)-C(37)	116.0(18)
C(30)-C(29)-H(29A)	109.9	C(41)-C(36)-C(35)	125.0(17)
C(28)-C(29)-H(29A)	109.9	C(37)-C(36)-C(35)	118.7(17)
C(30)-C(29)-H(29B)	109.9	C(36)-C(37)-C(38)	120(2)
C(28)-C(29)-H(29B)	109.9	C(36)-C(37)-H(37)	119.9
H(29A)-C(29)-H(29B)	108.3	C(38)-C(37)-H(37)	119.9
C(31)-C(30)-C(29)	110.5(15)	C(39)-C(38)-C(37)	119(2)
C(31)-C(30)-H(30A)	109.5	C(39)-C(38)-H(38)	120.7
C(29)-C(30)-H(30A)	109.5	C(37)-C(38)-H(38)	120.7
C(31)-C(30)-H(30B)	109.5	C(40)-C(39)-C(38)	123(2)
C(29)-C(30)-H(30B)	109.5	C(40)-C(39)-H(39)	118.4
H(30A)-C(30)-H(30B)	108.1	C(38)-C(39)-H(39)	118.4
C(30)-C(31)-C(32)	109.8(15)	C(39)-C(40)-C(41)	117(2)
C(30)-C(31)-H(31A)	109.7	C(39)-C(40)-H(40)	121.4
C(32)-C(31)-H(31A)	109.7	C(41)-C(40)-H(40)	121.4
C(30)-C(31)-H(31B)	109.7	C(40)-C(41)-C(36)	125(2)
C(32)-C(31)-H(31B)	109.7	C(40)-C(41)-H(41)	117.7
H(31A)-C(31)-H(31B)	108.2	C(36)-C(41)-H(41)	117.7
N(2)-C(32)-C(31)	108.7(15)	O(8)-C(42)-N(3)	126.2(18)
N(2)-C(32)-H(32A)	109.9	O(8)-C(42)-O(9)	121.7(18)
C(31)-C(32)-H(32A)	109.9	N(3)-C(42)-O(9)	112.1(15)
N(2)-C(32)-H(32B)	109.9	O(9)-C(43)-C(44)	105.5(15)

O(9)-C(43)-H(43A)	110.6
C(44)-C(43)-H(43A)	110.6
O(9)-C(43)-H(43B)	110.6
C(44)-C(43)-H(43B)	110.6
H(43A)-C(43)-H(43B)	108.8
C(45)-C(44)-C(49)	122(2)
C(45)-C(44)-C(43)	119(2)
C(49)-C(44)-C(43)	119(2)
C(44)-C(45)-C(46)	118(2)
C(44)-C(45)-H(45)	121.2
C(46)-C(45)-H(45)	121.2
C(47)-C(46)-C(45)	120(2)
C(47)-C(46)-H(46)	120.0
C(45)-C(46)-H(46)	120.0
C(48)-C(47)-C(46)	122(2)
C(48)-C(47)-H(47)	118.9
C(46)-C(47)-H(47)	118.9
C(47)-C(48)-C(49)	119(2)
C(47)-C(48)-H(48)	120.4
C(49)-C(48)-H(48)	120.4
C(44)-C(49)-C(48)	119(2)
C(44)-C(49)-H(49)	120.4
C(48)-C(49)-H(49)	120.4

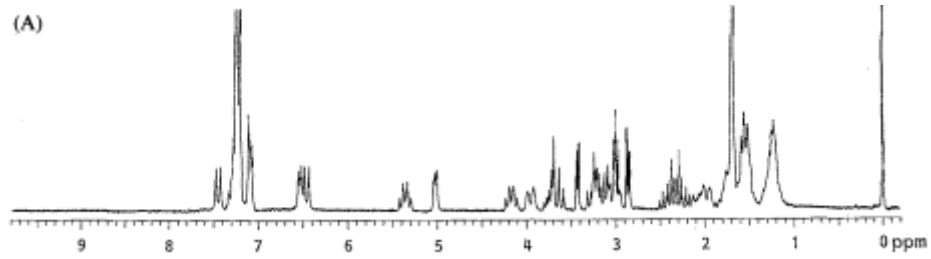
4) Anisotropic displacement parameters ($Å^2 x\ 10^3$) **74**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si	33(3)	55(4)	43(4)	-12(3)	9(3)	3(3)
O(1)	49(8)	42(7)	40(7)	-7(6)	13(6)	5(6)
O(2)	53(7)	54(8)	47(8)	0(6)	13(6)	11(6)
O(3)	45(8)	44(7)	40(8)	0(6)	12(6)	6(6)
O(4)	27(6)	43(8)	55(10)	-5(7)	2(6)	6(5)
O(5)	20(6)	36(6)	33(8)	0(6)	5(5)	2(5)
O(6)	43(8)	27(6)	29(8)	2(6)	5(6)	-6(6)
O(7)	21(6)	35(8)	43(9)	3(6)	-1(6)	2(5)
N(1)	31(8)	38(9)	28(7)	0(6)	9(5)	-8(7)
N(2)	18(5)	27(6)	29(9)	6(6)	4(5)	-7(5)
N(3)	20(6)	29(8)	28(7)	-5(6)	2(5)	-20(6)
C(1)	22(7)	35(9)	27(7)	1(6)	0(5)	0(6)
C(2)	18(8)	40(11)	26(8)	3(7)	0(6)	3(7)
C(3)	36(10)	51(11)	32(9)	-2(7)	8(7)	-1(8)
C(4)	29(9)	45(11)	30(9)	-4(8)	9(7)	-1(8)
C(5)	40(10)	53(12)	32(10)	0(8)	11(8)	7(8)
C(6)	38(10)	47(10)	26(9)	-15(7)	4(7)	0(7)
C(7)	34(9)	44(8)	31(8)	-7(6)	7(6)	1(7)
O(8)	28(7)	31(7)	41(9)	-10(6)	6(6)	-18(5)
C(8)	32(9)	46(8)	31(8)	-5(6)	4(6)	-3(6)
C(9)	44(11)	45(9)	26(9)	0(7)	7(8)	7(8)
O(9)	41(7)	45(9)	38(7)	-15(6)	17(6)	-27(6)
C(11)	41(11)	49(9)	39(13)	-1(8)	15(9)	-2(8)
C(10)	38(8)	46(8)	50(9)	-1(7)	13(7)	-2(7)
C(14)	44(13)	46(14)	65(12)	4(9)	2(9)	4(11)
C(13)	43(11)	56(9)	61(11)	5(8)	7(9)	14(8)
C(12)	40(7)	39(13)	46(13)	4(10)	10(7)	2(7)
C(15)	100(20)	78(13)	86(17)	-11(11)	0(14)	15(12)
C(16)	46(9)	72(14)	85(13)	-19(10)	-6(8)	8(8)
C(17)	46(11)	80(17)	106(17)	-18(13)	-6(10)	-15(11)
C(18)	37(12)	78(15)	96(16)	-14(12)	-19(11)	-2(10)
C(19)	42(9)	67(12)	45(10)	4(8)	10(7)	5(8)
C(20)	48(11)	88(15)	41(13)	11(11)	13(9)	-13(11)
C(21)	69(13)	91(17)	47(12)	-3(11)	10(9)	13(12)

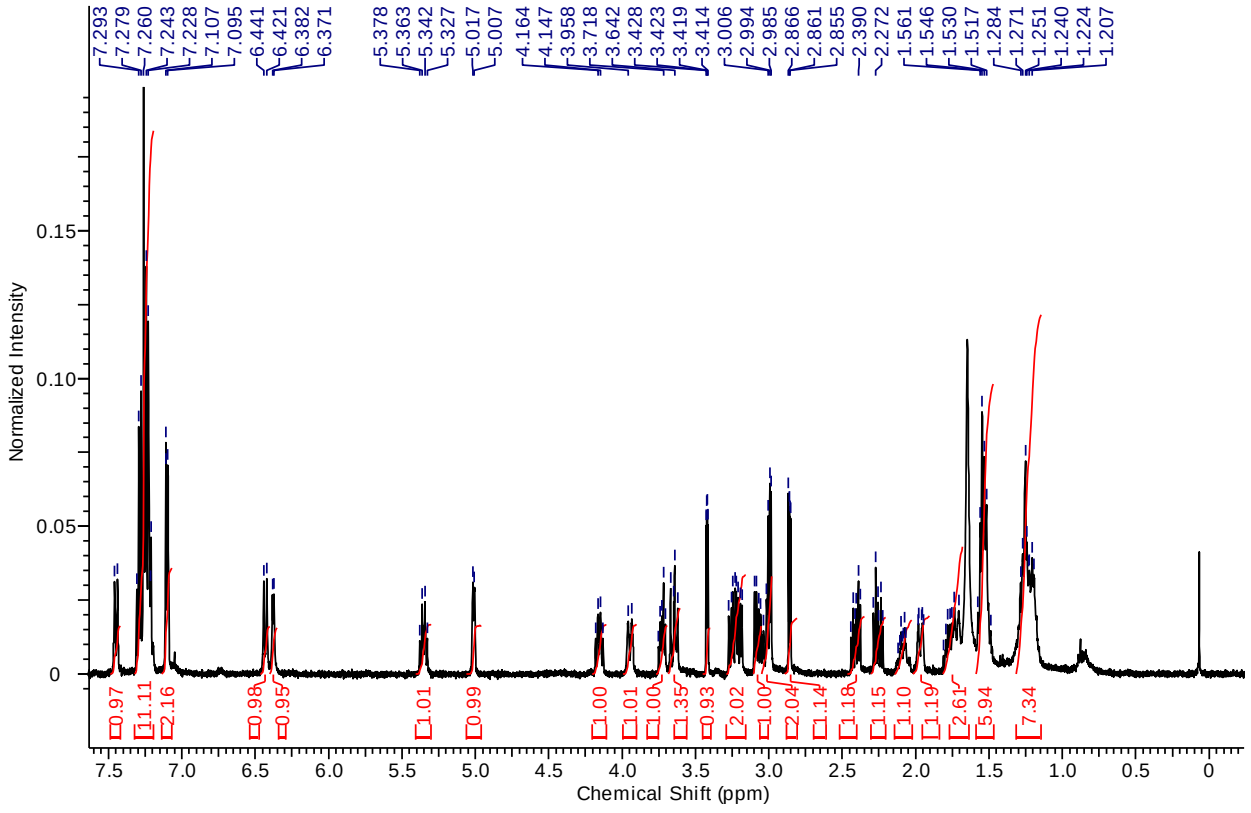
C(22)	26(7)	41(8)	28(11)	-1(7)	6(7)	1(6)
C(23)	33(9)	51(9)	35(10)	-8(7)	0(7)	-8(7)
C(24)	38(9)	70(15)	46(11)	-10(9)	3(8)	-18(9)
C(25)	28(10)	74(13)	43(11)	-1(9)	1(8)	-1(9)
C(26)	53(12)	50(10)	48(14)	-8(9)	4(10)	-11(8)
C(27)	14(8)	31(7)	27(8)	3(6)	0(6)	-1(6)
C(28)	19(7)	29(7)	24(8)	3(5)	6(6)	-7(5)
C(29)	30(7)	30(10)	36(9)	-9(8)	13(6)	-15(7)
C(30)	19(7)	51(10)	47(12)	-7(9)	18(7)	-6(7)
C(31)	19(7)	50(10)	38(12)	-11(8)	-1(7)	-8(7)
C(32)	25(7)	34(10)	36(10)	-2(8)	-2(6)	-6(6)
C(33)	17(6)	28(7)	17(10)	3(6)	7(6)	-3(5)
C(34)	7(7)	28(7)	23(7)	5(5)	-5(5)	-2(5)
C(35)	15(7)	32(9)	26(7)	-1(6)	-3(5)	0(7)
C(36)	22(7)	44(11)	27(8)	-7(7)	0(6)	-15(7)
C(37)	28(7)	47(12)	35(11)	-3(9)	2(6)	-7(7)
C(38)	32(8)	72(14)	49(12)	3(10)	11(7)	-11(8)
C(39)	49(10)	61(14)	44(13)	-3(9)	7(8)	-17(9)
C(40)	53(9)	71(14)	38(11)	8(10)	7(8)	-12(9)
C(41)	45(9)	52(12)	38(10)	4(9)	4(7)	-7(8)
C(42)	26(8)	23(9)	22(7)	1(6)	-1(6)	-12(6)
C(43)	60(10)	82(14)	52(10)	-31(9)	24(8)	-27(9)
C(44)	43(8)	45(12)	36(10)	-22(8)	13(7)	-15(7)
C(45)	55(9)	80(15)	57(13)	8(12)	16(8)	-1(9)
C(46)	50(10)	81(16)	57(14)	-3(12)	12(9)	-3(9)
C(47)	52(9)	65(15)	42(13)	-20(10)	18(8)	-9(9)
C(48)	56(9)	86(16)	61(13)	14(12)	19(9)	-4(10)
C(49)	44(9)	62(13)	44(11)	-10(10)	13(8)	-2(9)

8.2 NMR-spectra of natural products

NMR-spectra of trapoxin A and data comparison[41]



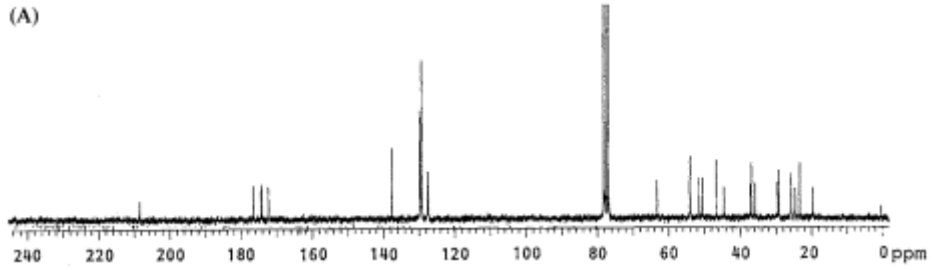
^{1}H-NMR spectrum (200 MHz, $CDCl_3$) of isolated trapoxin A



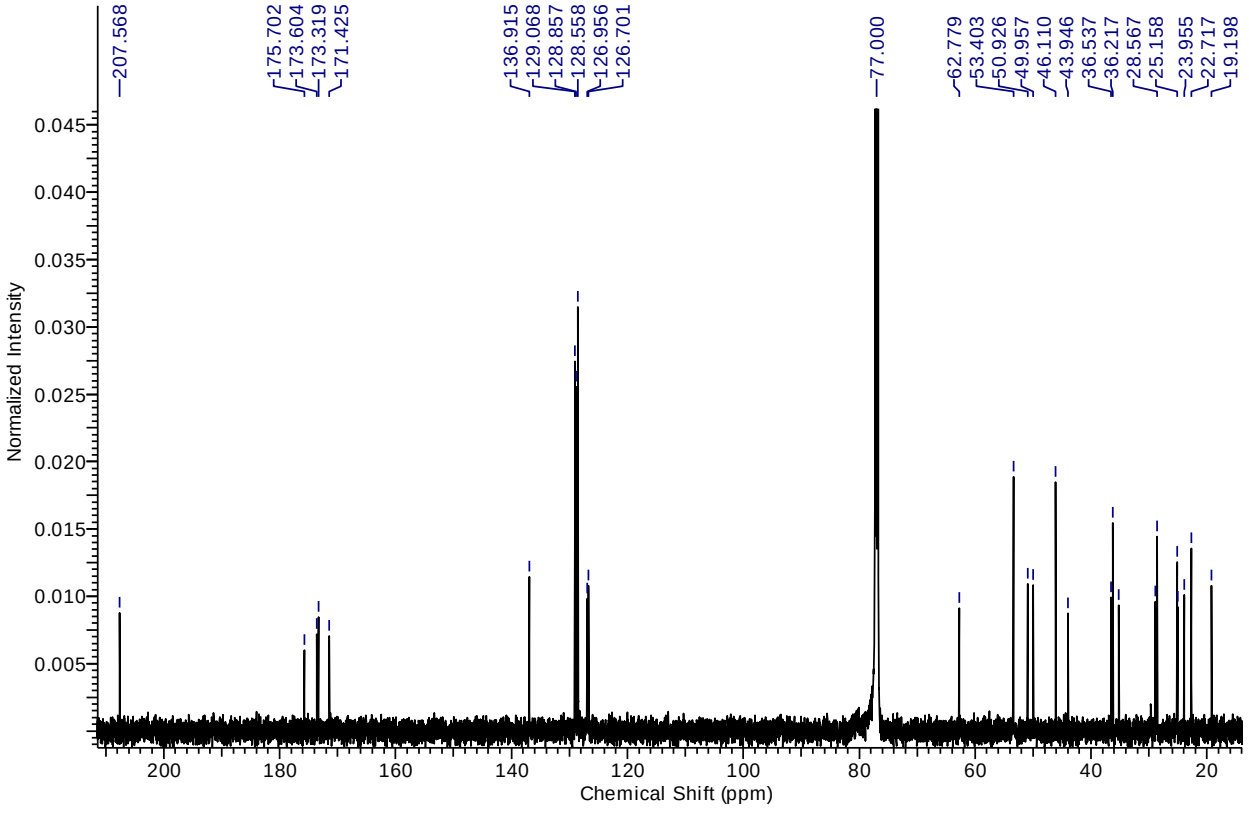
^{1}H-NMR spectrum (500 MHz, $CDCl_3$) of synthesized trapoxin A

Data comparison of ^{1}H-NMR for trapoxin A:

	isolated		synthesized	
No.	δ [ppm]	*J* [Hz]	δ [ppm]	*J* [Hz]
1	7.46	d, 10	7.45	d, 10
2	7.27	s	7.21 – 7.37	m
3	7.11	m	7.10	d, 6.3
4	6.46	m	6.43 + 6.38	d, 10.1 + d, 5.4
5	5.36	q, 9	5.35	q, 8.6
6	5.02	d, 5	5.01	d, 4.8
7	4.17	q, 9	4.16	q, 7.9
8	3.96	d, 9	3.95	d, 12
9	3.43	dd, 2.4, 4.6	3.42	dd, 2.5, 4.7
10	2.98	dd, 4.6, 5.8	2.99	dd, 4.7, 6.0
11	2.86	dd, 2.4, 5.8	2.86	dd, 2.5, 5.7



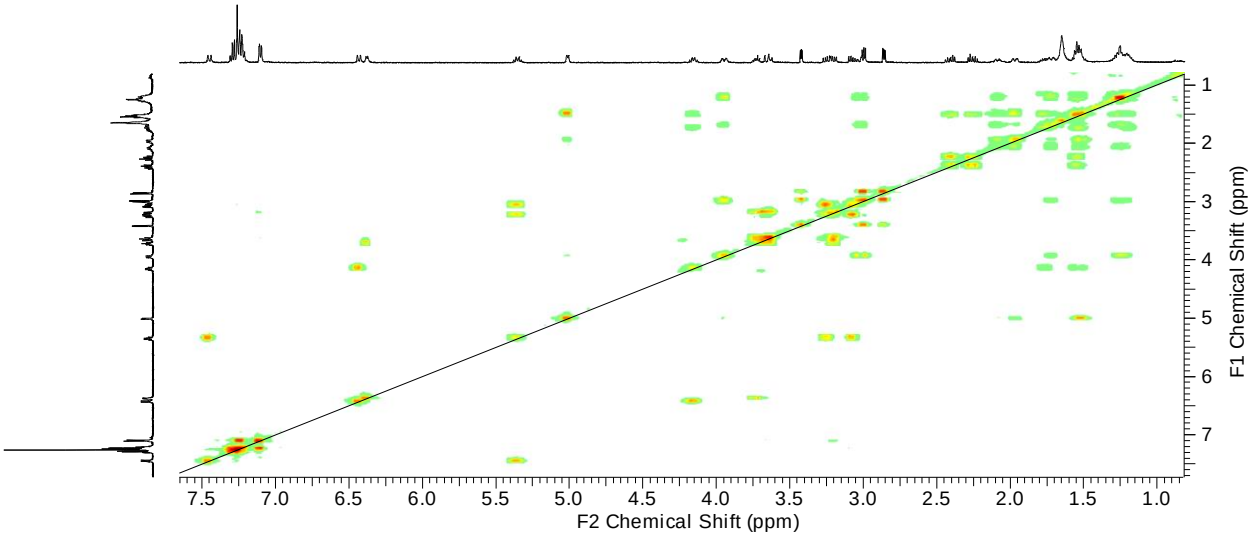
^{13}C-NMR spectrum (50 MHz, $CDCl_3$) of isolated trapoxin A



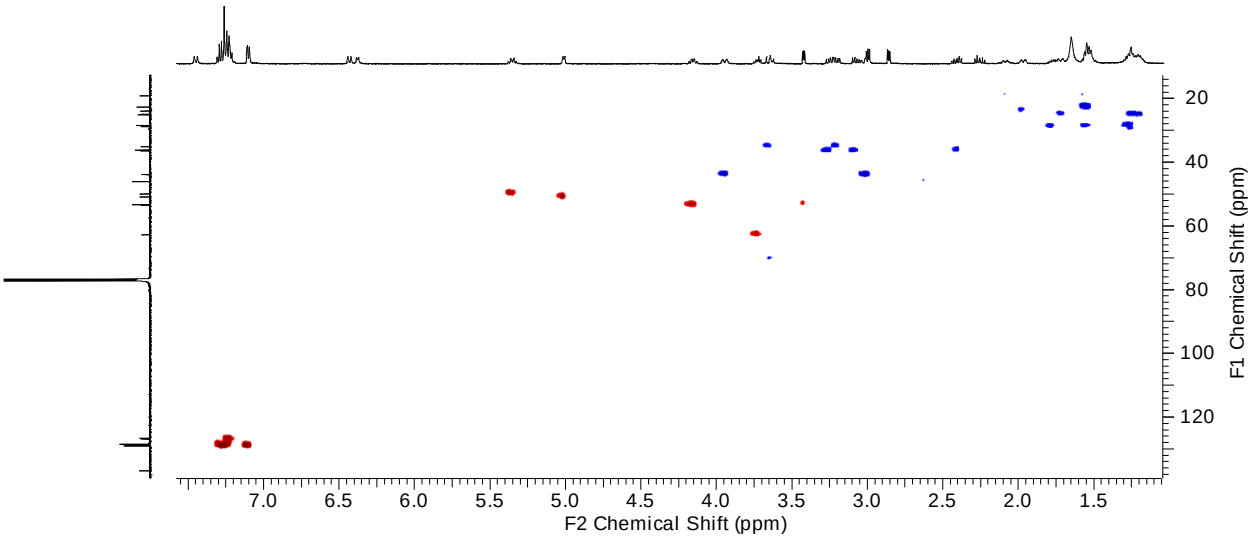
^{13}C-NMR spectrum (125 MHz, $CDCl_3$) of synthesized trapoxin A

Data comparison of ^{13}C-NMR for trapoxin A:

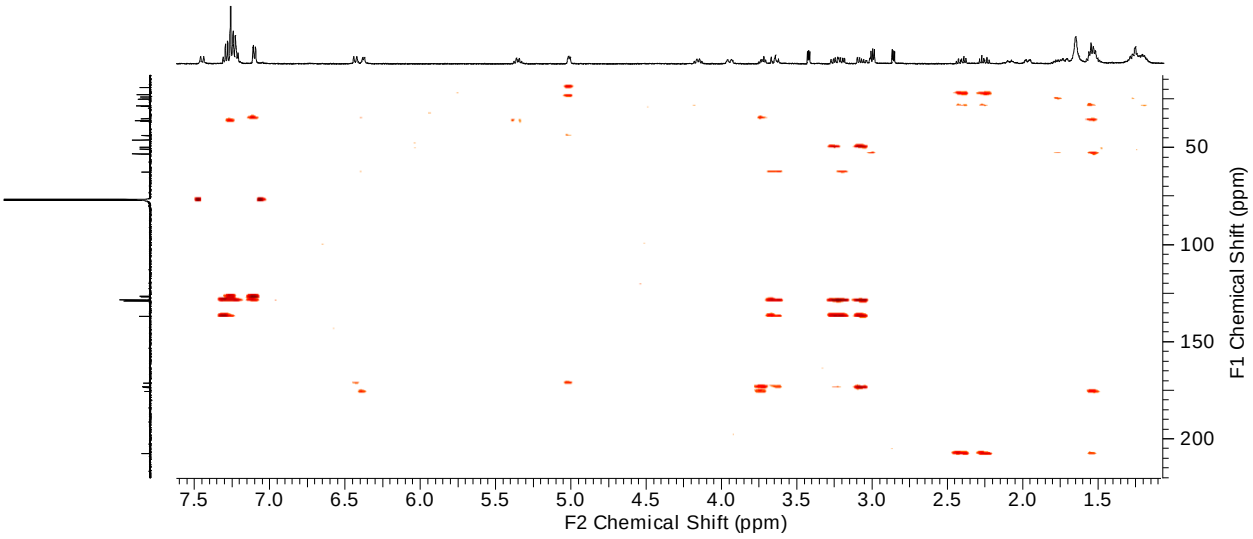
No.	δ (isolated) [ppm]	δ (synthesized) [ppm]
1	208.24	207.57
2	176.35	175.70
3	174.22	173.60
4	173.95	173.32
5	172.05	171.43
6	137.44	136.92
7	129.56	129.07
8	129.35	128.86
9	129.04	128.56 + 128.54
10	127.43	126.96
11	127.18	126.70
12	63.07	62.78
13	53.82	53.48
14	53.69	53.40
15	51.20	50.93
16	50.23	49.96
17	46.38	46.11
18	44.20	43.95
19	36.80	36.54
20	36.49	36.22
21	35.45	35.19
22	29.18	28.89
23	28.82	28.57
24	25.40	25.16
25	25.39	25.06
26	24.17	23.96
27	22.94	22.72
28	19.43	19.20



HH-COSY spectrum of synthesized trapoxin A

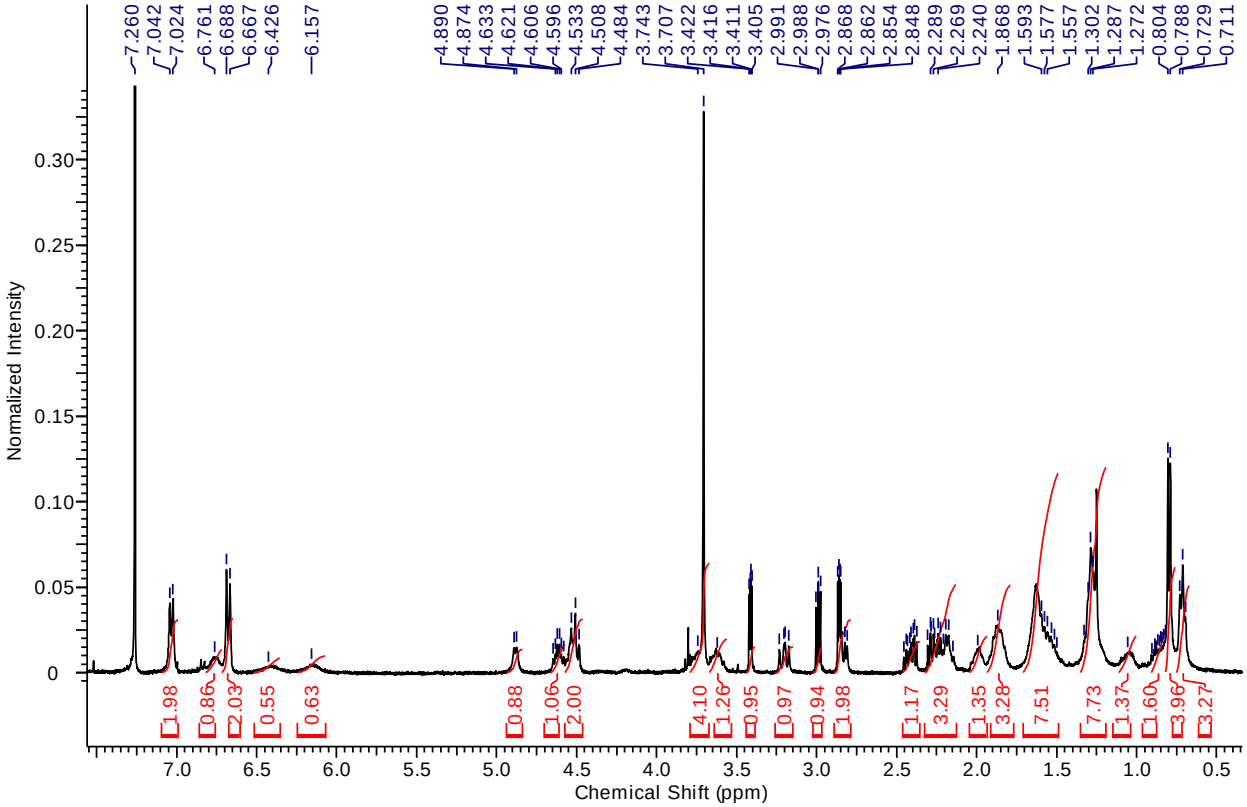


HSQCed spectrum of synthesized trapoxin A



HMBC spectra of synthesized trapoxin A

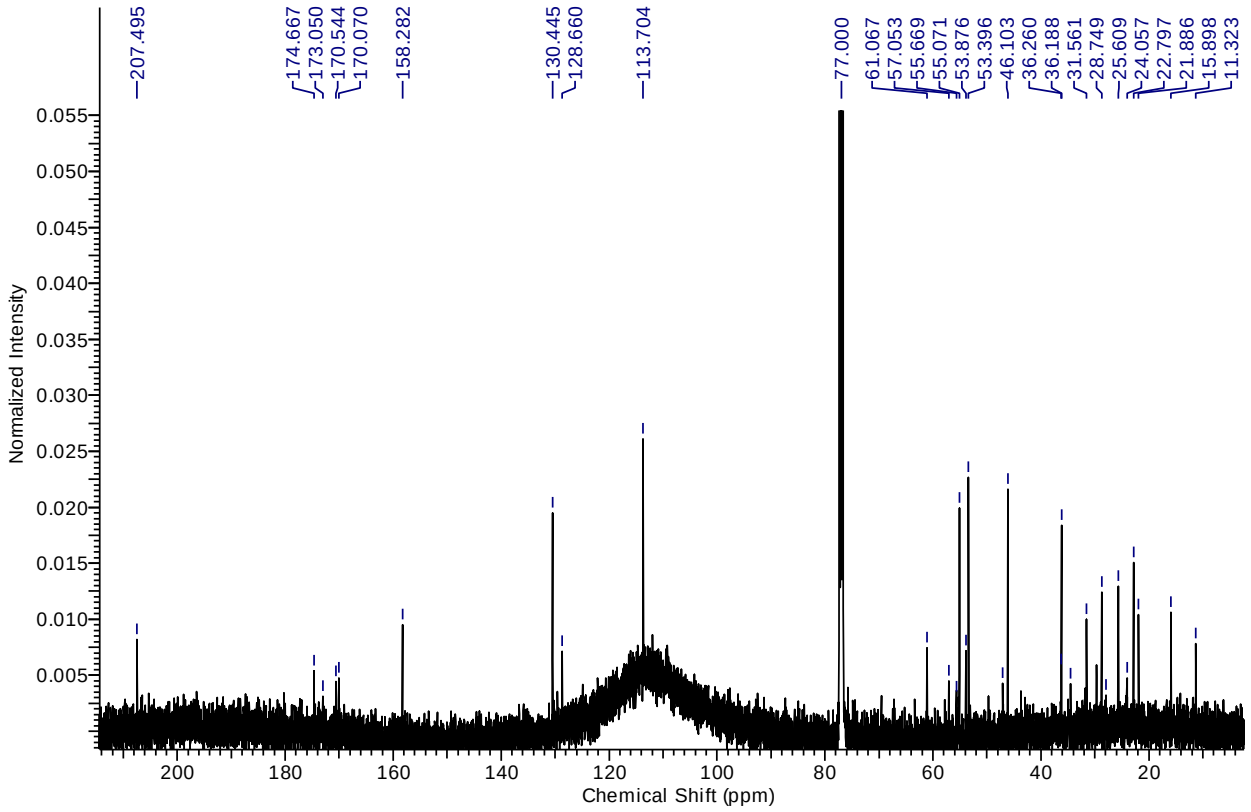
NMR-spectra of Cyl-1 and data comparison[47]



^{1}H-NMR spectrum (500 MHz, $CDCl_3$) of synthesized Cyl-1

Data comparison of ^{1}H-NMR for Cyl-1:

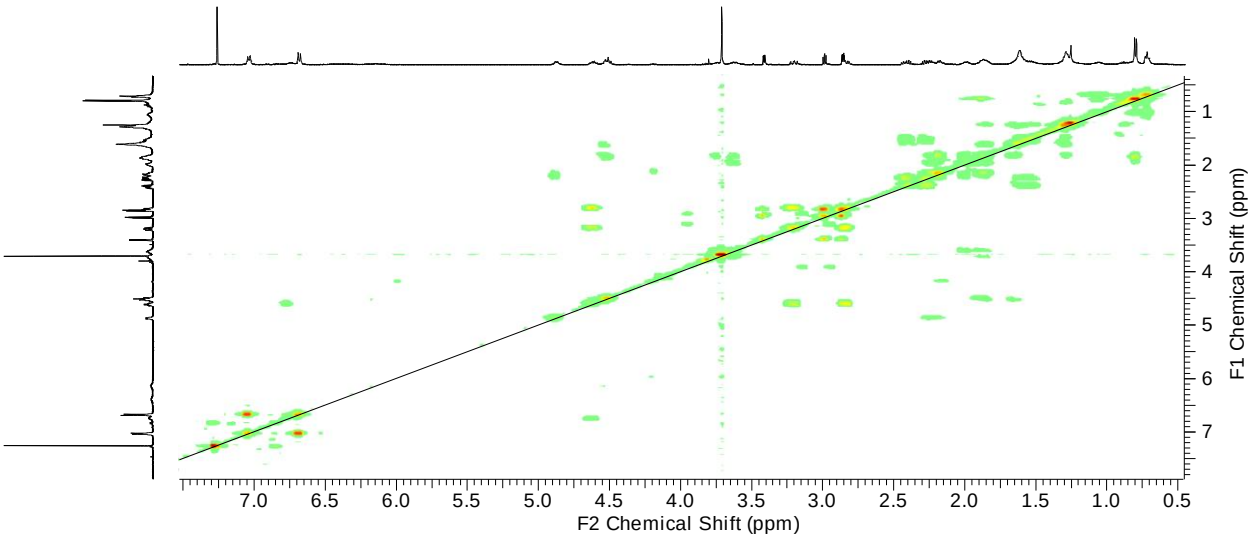
	isolated		synthesized	
No.	δ [ppm]	*J* [Hz]	δ [ppm]	*J* [Hz]
1	3.41	2.5, 4.5	3.41	2.5, 4.5
2	2.99	4.5, 6.0	2.99	4.5, 5.8
3	2.86	2.5, 6.0	2.86	2.5, 5.8



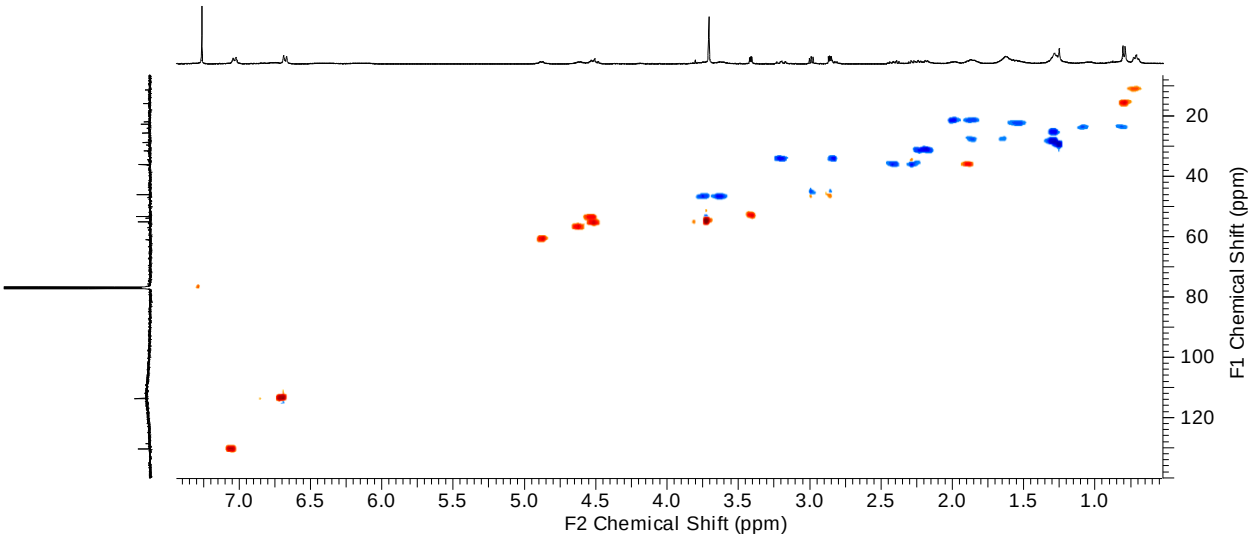
^{13}C-NMR spectrum (125 MHz, $CDCl_3$) of synthesized Cyl-1

Data comparison of ^{13}C-NMR for Cyl-1:

No.	δ (isolated) [ppm]	δ (synthesized) [ppm]
1	207.4	207.5
2	53.5	53.4
3	46.2	46.1



HH-COSY spectrum of synthesized Cyl-1



HSQCed spectrum of synthesized Cyl-1