Total Synthesis of Pseudotetraivprolids, Socein-Derivatives and Thiamyxins

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Dissertation

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„Nur wenige wissen, wie viel man wissen muss,
um zu wissen, wie wenig man weiß.“

Werner Heisenberg

Für Opa Herbert
von deinem „kleinen Professor“

Kurzfassung

Die vorliegende Dissertation beschreibt die jeweils erste Totalsynthese von drei Gruppen von Peptidnaturstoffen und -derivaten. Der erste Teil dieser Arbeit befasst sich mit den linearen Depsipeptiden Pseudotetraivprolid B und D. Die konvergente Totalsynthese beinhaltet die Synthese von zwei Schlüsselbausteinen über ein modifiziertes Hantzsch-Thiazol-Verfahren und eine asymmetrische Noyori-Hydrierung. Das zweite Projekt konzentrierte sich auf die Strukturaufklärung durch Totalsynthese mehrerer diastereomerer Derivate von Socein, einem Peptidnaturstoff aus der Familie der Microsclerodermine. Die Synthese der vier benötigten diastereomeren C-Furanoside wurde durch Sakurai-Allylierung mit kontrollierbarer Diastereoselektivität ermöglicht. Darüber hinaus wurde eine Synthese von (*R*)-GABOB-Derivaten durch lichtinduzierte Arndt-Eistert-Homologisierung von L-Isoserin entwickelt. Letztendlich gelang so die Synthese von drei der vier geplanten diastereomeren Socein-Derivate. Im letzten Teil dieser Arbeit wird die Totalsynthese von vier Mitgliedern der Thiamyxin-Familie (A-C und E) beschrieben. Highlights der Synthese sind eine parallele Bis-Thiazolin-Bildung mit geringer Epimerisierung und die Synthese einer ungewöhnlichen *Z*-Alkensäure. Die Ausnutzung des labilen C-2-Exomethin-Stereozentrums ermöglichte den Zugang zu den vier Naturstoffen aus einer einzigen Vorstufe über eine Sequenz aus Makrolactonisierung und Verseifung.

Abstract

This PhD thesis describes the first total synthesis of three groups of peptide natural products and natural product derivatives. The first topic addresses the linear depsipeptides pseudotetraivprolid B and D. The convergent total synthesis features the synthesis of two key building blocks via a modified Hantzsch thiazol procedure and Noyori asymmetric hydrogenation. The second project focused on the structural elucidation via total synthesis of multiple diastereomeric derivatives of socein, a peptide natural product of the family of microsclerodermins. The synthesis of the four required diastereomeric C-furanosides was accomplished via Sakurai allylation with controllable diastereoselectivity. Additionally, a novel synthesis of (*R*)-GABOB derivatives via light induced Arndt-Eistert homologation of L-isoserine was developed. This ultimately led to the synthesis of three out of four diastereomeric socein derivatives. In the last part of this thesis the total synthesis of four members of the thiamyxin family (A-C and E) is reported. A parallel bis-thiazoline formation with low epimerization and the first synthesis of an uncommon *Z*-alkenoic acid represent the key features of the synthesis. The lability of the C-2-exomethine stereocenter was used to access four natural products via a macrolactonization and saponification sequence from a single precursor.

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
ACP	acyl carrier protein
AETD	3-amino-10-(*p*-ethoxy-phenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid
Alloc	allyloxycarbonyl
AMMTD	(2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid
Anti-SMASH	antibiotics and secondary metabolites analysis shell
approx.	approximately
aq.	aqueous
Arg	arginine
Asp	aspartic acid
ax	axial
BGC	biosynthetic gene cluster
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
brine	saturated aqueous NaCl-solution
brsm	based on recovered starting material
Bz	benzoyl
CAN	ceric ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CC$_{50}$	50% cytotoxicity concentration
CDI	*N*,*N*'-carbonyldiimidazole
cf.	*confer*
CI	chemical ionization
CoA	coenzyme A
COMU	(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethyl amino-morpholino-carbenium hexafluorophosphate
conc	concentrated
config.	configuration
COSY	correlated spectroscopy
cp*	1,2,3,4,5-pentamethyl cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
CyH	cyclohexane
CYP450	cytochrome P450
Cys	cysteine
DAST	diethylaminosulfur trifluoride
dba	dibenzylidene acetone
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIC	*N*,*N*'-diisopropylcarbodiimide
DICHED	dicyclohexylethane-1,2-diol
DIPEA	*N*,*N*'-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin-periodinane
DMPU	*N*,*N*'-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
ECF	ethyl chloroformate
EDC	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide

ee	enantiomeric excess
eq	equatorial
eq.	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
et al.	*et alia*
FDA	Food and Drug Administration
Fm	9-fluorenyl methyl
Fmoc	fluorenylmethoxycarbonyl
GABOB	γ-amino-β-hydroxybutyric acid
GC-FID	gas chromatography with flame ionization detector
Gly	glycine
GNAT	GCN5-related *N*-acyltransferase-like decarboxylase
Grubbs I	benzylidene-bis(tricyclohexylphosphino)-dichlororuthenium
Grubbs II	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexyl phosphine)-ruthenium
HATU	1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HFIP	hexafluoro isopropanol
HIPS	Helmholtz Institute for Pharmaceutical Research Saarland
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMMP	2-(hydroxymethyl)-4-methylpent-3-enoic acid
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1*H*-1,2,3-benzotriazol-1-ol
HOSu	*N*-hydroxysuccinimide
Hoveyda-Grubbs	[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro(*o*-isopropoxyphenyl-methylene)-ruthenium
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQCED	heteronuclear single quantum correlation spectroscopy – DEPT edited
HTS	high-throughput screening
HZI	Helmholtz Centre for Infection Research
IBCF	isobutyl chloroformate
IC_{50}	half maximal inhibitory concentration
Ile	isoleucine
IPCF	isopropyl chloroformate
^{i}Pr	isopropyl
Ise	isoserine
KMM	potassium methyl malonate
LA	Lewis acid
LC-MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
LED	light-emitting diode
Leu	leucine
LG	leaving group
Me	methyl
Met	methionine
MHQL	2-methyl-8-quinolinole
micros.	microsclerodermin
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl
MPI	Max Planck Institute for Terrestrial Microbiology
Ms	mesyl
MT	methyl transferase
MyTSA	*N*-methyl ynetoluenesulfonamide
NBS	*N*-bromosuccinimide
*n*Bu	*n*-butyl
NHS	*N*-hydroxysuccinimide
NMI	*N*-methylimidazole
NMM	*N*-methylmorpholine

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NP	natural product
NRPS	nonribosomal peptide-synthetase
Nu	nucleophile
Orn	ornithine
oxyma	ethyl cyanohydroxyiminoacetate
Pbf	2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl
PE	petroleum ether
PFP	pentafluorophenol
PG	protecting group
Ph	phenyl
PhD	Doctor of Philosophy
Phe	phenylalanine
PhSeCys	phenyl selenocysteine
Piv	pivaloyl
PKS	polyketide-synthase
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluene sulfonate
PPY	4-pyrrolidino pyridine
prep.	preparative
Pro	proline
pTsOH	*p*-toluene sulfonic acid
Py	pyridine
PyAOP	(7-azabenzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate
QPHOS	1,2,3,4,5-pentaphenyl-1’-(di-*tert*-butylphosphanyl)ferrocene
quant.	quantitative
ref.	reference
RP	reversed-phase
rpm	rounds per minute
rt	room temperature
SAR	structure-activity relationship
Sar	sarcosine
sat.	saturated
Ser	serine
sp.	*species*
SPPS	solid phase peptide synthesis
Su	succinyl
T	temperature
t	time
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBCD	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TCBC	2,4,6-trichloro benzoyl chloride
TCEP	tris(2-carboxyethyl)phosphine
TE	thioesterase
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethane sulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropyl silane
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
TOCSY	total correlation spectroscopy
Troc	2,2,2-trichloroethyloxy
Trp	tryptophan
Trt	trityl
Ts	tosyl
TS	transition state
Tyr	tyrosine
UNCA	urethane *N*-carboxyanhydride
UV	ultra violet
Val	valine
)))	microwaving

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1. Introduction

Natural products (NPs) are evolutionarily optimized molecules fulfilling specific biological functions, which are typically described with the term privileged structures.[1] The nature of some of these functions, such as endogenous defense systems or competitive interactions, renders NPs highly interesting as potential drugs for cancer and infectious diseases. Of all new FDA-approved drugs from 1981 to 2019, 42% are natural products or natural product derived.[2] Additional 26% are either natural product mimics or had natural products as lead structures. The phenomenon of privileged structures is also reflected in the significantly higher "hit rates" in drug discovery of natural products (0.3%) versus high-throughput screenings (HTS) (<0.001%).[3] Despite these facts, the pharmaceutical industry favors HTS as the main tool because of the structural simplicity of the generated hits. Natural products are more often than not highly complex structures with various stereocenters and the isolation and structural elucidation from crude extracts is challenging. Additionally, the total synthesis becomes a "rate-limiting step" in drug discovery, making advancements in total synthesis crucial to remove this limitation.[4] Even though the total synthesis of complex NPs can not produce drugs cost-efficiently most of the time, it remains a powerful tool in the earlier stages of a project. Among other things total synthesis can enable SAR- and biosynthetic studies until the synthesis of simplified lead-structures or biotechnological efforts lead to an economically reasonable production of the desired active compound.[3–5]

However, the production of the NP or its derivatives is not the sole reason for the existence of the field of total synthesis. R. B. Woodward influenced the topic massively, admiring and celebrating it as a form of art. This led to the combined synthetic effort with Eschenmoser synthesizing highly complex structures such as vitamin B12 over the course of 12 years.[6,7] Nicolaou and Snyder describe natural product total synthesis as an unmatched "vehicle for discovery" in the realm of chemical synthesis.[8] This is greatly illustrated by several historical examples of total syntheses (Figure 1).

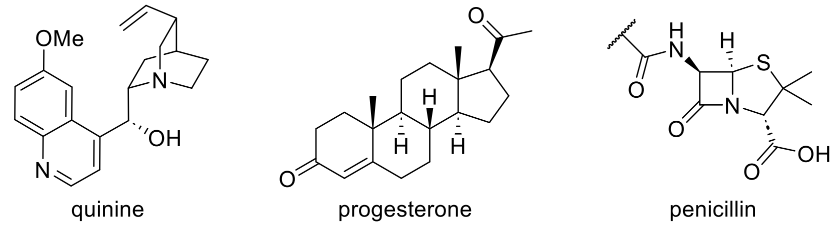


Figure 1: Historical examples for total synthesis of natural products.

Numerous attempts to synthesize quinine gave insights into the formation of heteroaromatic systems and the physical properties of quinolines and piperidines. The synthesis of the steroid progesterone led to new advances in the formation and cleavage of carbon-carbon bonds and allowed access to high quantities for the use as a drug in the form of the birth control pill. The sensitive β-lactam ring of penicillin gave the decisive impulse for the development of carbodiimides to form peptide bonds, revolutionizing the entire field of peptide synthesis.

In 2020, K. C. Nicolaou stated that "the ideal modern paradigm of total synthesis endeavours includes" four main components:[9]

1. The discovery of new methods and synthetic strategies which could ultimately lead to advancements in the field of organic synthesis.

2. A comprehensive total synthesis project should include aspects of biology or medicine within the same research group or, more desirably, through collaboration with other groups in academia or industry. These cooperative efforts enhance the project's value and create opportunities for breakthroughs and innovations, from fundamental research to applications like drug discovery. This can be applied to other fields like agrochemistry, cosmetics, material science, and more if the capability of the natural compound fits such needs.

3. The full structural elucidation of natural products or an unintended structural revision via total synthesis.

4. The challenge of total synthesis itself educates and trains young chemists in the art and science of synthesizing complex molecules, ultimately improving their problem-solving skills and their resilience in the face of failure.

These aspects and the previous examples show the value total synthesis offers to the field of organic chemistry, drug discovery and many other. The following thesis discusses the total synthesis of various peptide natural products originating from bacteria, hopefully fulfilling most of these essential components of a modern total synthesis.

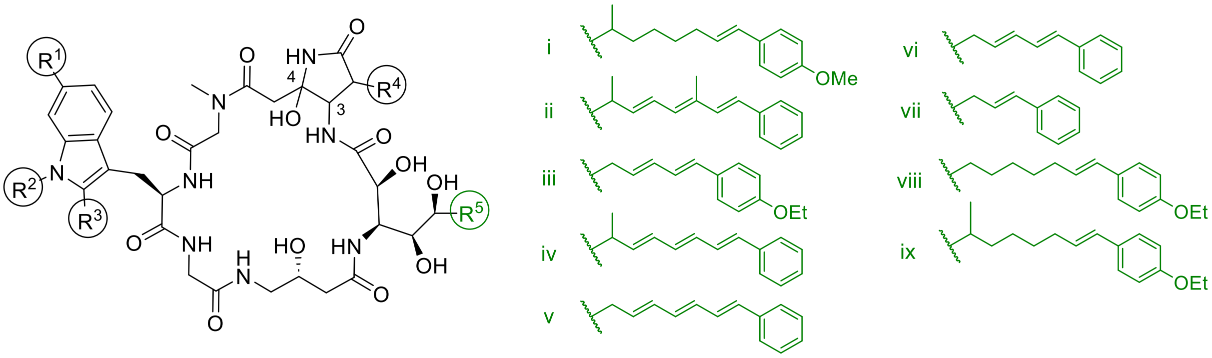
2. State of Knowledge

2.1 Microsclerodermins and Pedeins

2.1.1 Isolation and Structural Elucidation

From 1994 to 2000, the Faulkner Group isolated the microsclerodermin A-I from marine lithistid sponges of the *Microscleroderma* and *Theonella species*.[10–12] The core motif of these cyclic peptides is a 23-membered ring that features six amino acids (Table 1). While glycine, sarcosine, and (*R*)-γ-amino-β-hydroxybutyric acid (GABOB) are common to all members of the microsclerodermin family, the other three amino acids, best described as a modified tryptophan residue, an unusual 3-amino pyrrolidone-4-acetic acid, and a ω-aromatic 3-amino-2,4,5-tri-hydroxyacid, are variable units. The amino pyrrolidone unit contains a hemiaminal position that readily eliminates water when treated with mild acid or dehydrating agents, forming a dehydromicrosclerodermin. Additionally, some members of the microsclerodermin family, like microsclerodermin E,[11] were isolated as dehydromicrosclerodermins.

Table 1: Summary of the isolated microsclerodermins and the structurally and biosynthetically related pedeins.[13]



micros.	R^1	R^2	R^3	R^4	R^5	config.	isolated	total synthesis
A	H	H	COOH	OH	i	3*S*,4*S*	1994[10], 2012[14]	
B	H	H	COOH	H	i	3*R*[c],4*S*	1994[10], 2012[14]	(2016[15])[d]
C	Cl	$CONH_2$	H	H	vii	3*R*,4*R*	1998[11]	
D	Cl	H	H	H	vii	3*R*,4*R*	1998[11], 2013[13]	
E[b]	H	H	COOH	H	iii	3*R*	1998[11]	2003[16]
F + G[a]	H	H	H	H	iv	3*R*,4*R*	2000[12]	
H + I[a]	H	H	H	H	ii	3*R*,4*R*	2000[12]	
J[b]	H	H	H	H	i	3*R*[c]	2012[14]	2016[15]
K[b]	H	H	H	OH	i	3*S*	2012[14]	
L	Cl	H	H	OMe	vii	3*R*,4*R*	2013[13]	
M	H	H	H	H	v	3*R*,4*R*	2013[13]	
N	H	H	COOH	H	viii	3*R*,4*R*	2020[17]	
O	H	H	COOH	H	ix	3*R*,4*R*	2020[17]	
pedein A	Cl	H	H	OMe	vi	3*R*,4*R*	2008[18], 2013[13]	
pedein B	H	H	H	OMe	vi	3*R*,4*R*	2008[18], 2013[13]	

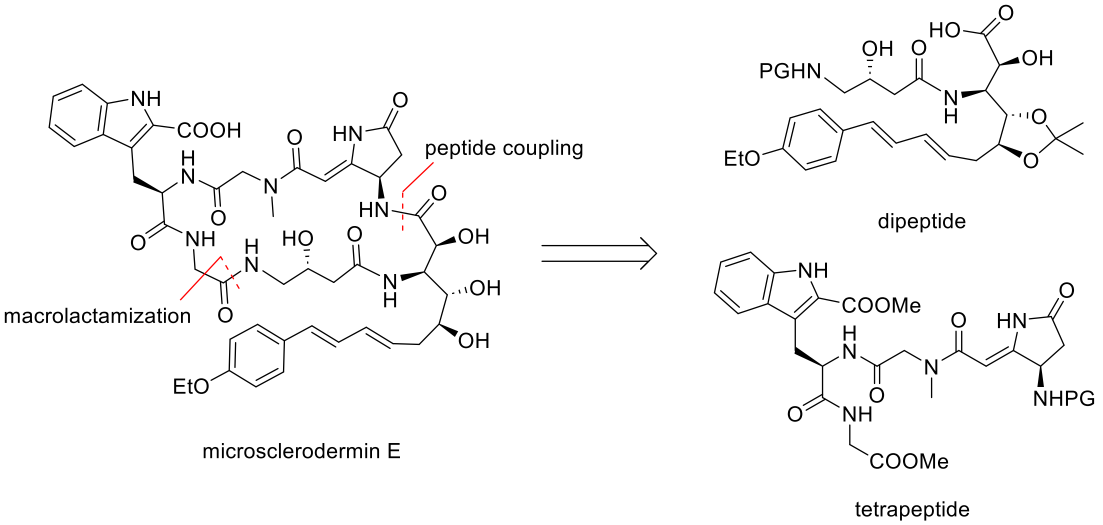
a) α,β-unsaturated tryptophane (*E*). b) are dehydromicrosclerodermins (*Z*). c) reassignment after total synthesis. d) total synthesis of dehydromicrosclerodermin B.

The key NMR signals for a dehydrated amino pyrrolidone unit of the isolated microsclerodermin E were present in the crude mixture before treatment with acid or base. Additionally, microsclerodermin D, which still contains the hemiaminal group, was isolated under the same conditions as microsclerodermin E. 2012, Li and co-workers isolated two new microsclerodermins J and K, with a dehydrated amino pyrrolidone unit from a marine sponge *Microscleroderma herdmani*.[14,19] The most recent congeners, microsclerodermin N and O, were isolated in 2020 by Matsunaga *et al.* from another marine sponge, *Pachastrella sp.* Both feature new side chains (viii, ix) at the polyhydroxylated amino acid, further increasing the already large diversity of these residues.[17] Most members of the microsclerodermin family (precisely A-M), including the dehydrated microsclerodermins E, J, and K and synthetically eliminated dehydromicrosclerodermin C, showed potent antifungal activity against *Candida albicans* in paper disk or microbial susceptibility assays.[10–14,19] For microsclerodermin A and B, the antifungal activity showed similar potency to the antifungal drug amphotericin B, suggesting that this compound class may warrant further investigation as potential antifungal leads.[19] Biological activities against cancer cell lines were reported for microsclerodermin F-I against the HCT-116 colon cancer cell line,[12] for microsclerodermins N and O against HeLa cells,[17] and microsclerodermin A against a pancreatic cancer cell line.[20]

In 2008, Kunze and co-workers isolated the pedeins A and B from the terrestrial myxobacterium *Chondromyces pediculatus* that share the above-mentioned basic structural motifs and the antifungal activity of the microsclerodermin family.[18] The Müller group added, with their isolation of microsclerodermin L and M, two more microsclerodermins to the family.[13] Additionally, they isolated microsclerodermin D (known as "marine natural product" from two lithistid sponge species) from three different *genera* of terrestrial *Myxobacteria*, which underpins the theory that these "sponge metabolites" might, in fact, originate from microbial symbionts genetically related with myxobacteria.[13,18]

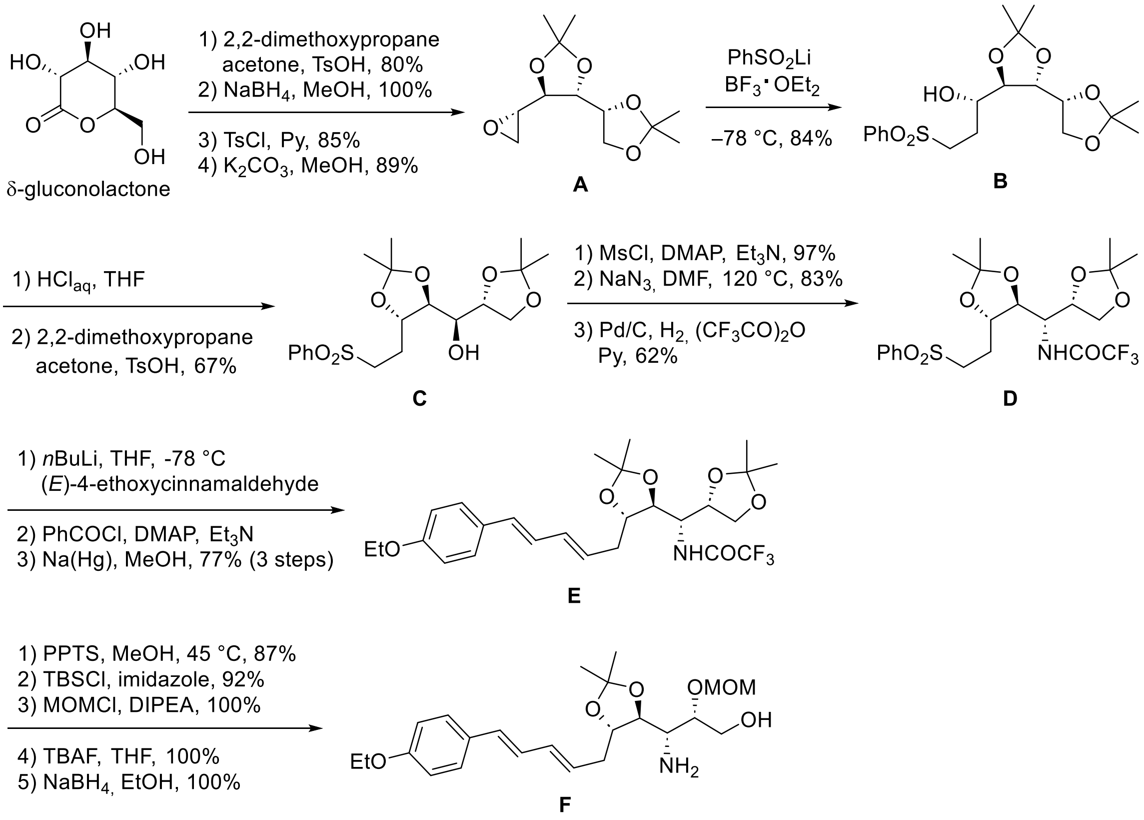
2.1.2 Total Synthesis of Microsclerodermins

The first total synthesis of a member of the microsclerodermin family, microsclerodermin E, was reported by Ma and Zhu in 2003.[16] They retrosynthetically disassembled the target molecule into a dipeptide and a tetrapeptide fragment by ring opening between glycine and (*R*)-GABOB and retro-peptide coupling between the amino pyrrolidone moiety and the 3-amino-10-(*p*-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid (AETD) moiety (Scheme 1). Further disconnections via standard peptide couplings led to four unusual amino acids as synthetic targets: AETD, (*R*)- GABOB, (*R*)-Trp-2-carboxylic acid, and the pyrrolidone building block.



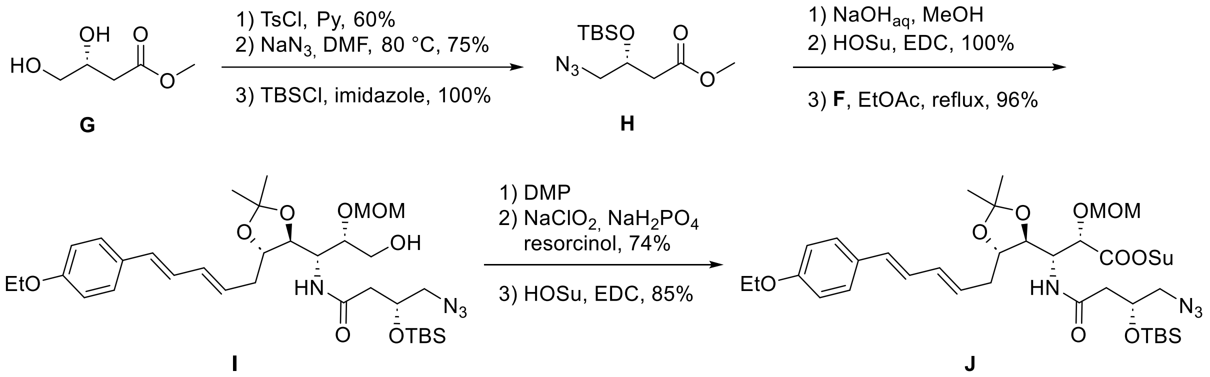
Scheme 1: Retrosynthetic analysis of microsclerodermin E by Ma and Zhu.

Acetonide formation under acidic conditions with 2,2-dimethoxypropane was accompanied by a lactone opening by *trans*-esterification to the methyl ester (Scheme 2). Reduction of the methyl ester and epoxide formation led to oxirane **A** in 61% yield over 4 steps. The epoxide was terminally opened with lithiated methyl phenyl sulfone in the presence of $BF_3{\cdot}OEt_2$. Rearrangement of the protecting groups by acidic cleavage and reprotection resulted in the sterically less obstructed alcohol **C** in 67% yield. The released hydroxy group was mesylated and subsequently substituted with sodium azide in DMF. Reduction of the azide and acylation with TFAA provided amide **D** in 50% yield over 3 steps.



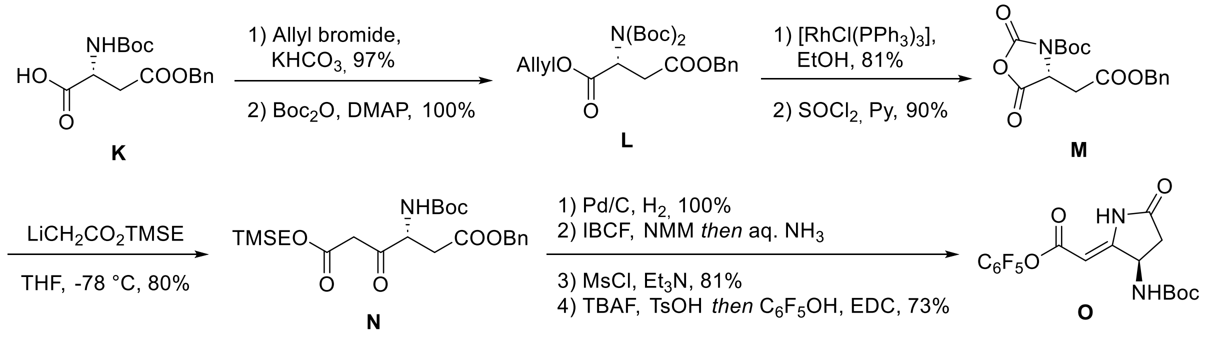
Scheme 2: Synthesis of the AETD-building block starting from δ-gluconolactone

A Julia reaction[21] with (*E*)-4-ethoxycinnamaldehyde resulted in a mixture of the desired (*E*)-configured olefination product **E** and its (*Z*)-isomer in a 5:1 ratio. Additional protecting group manipulations finalized the AETD-building block **F** in 80% yield over 5 steps. The synthesis of the (*R*)-GABOB unit started with a selective tosylation of L-malic acid derived methyl (*R*)-3,4-dihydroxybutanoate **G**[22] followed by an azide substitution (Scheme 3). The resulting hydroxy azide was TBS-protected to give the azido-GABOB derivative **H** in 45% yield over 3 steps. After saponification with sodium hydroxide, the carboxylic acid was activated as NHS-ester and coupled with AETD-building block **F**. The primary alcohol of the resulting dipeptide **I** was oxidized in a two-step protocol with a Dess-Martin oxidation followed by a Pinnick oxidation using resorcinol as a scavenger. As a preparation for the coupling with the tetrapeptide unit, the carboxylic acid was activated as the NHS-ester **J**.



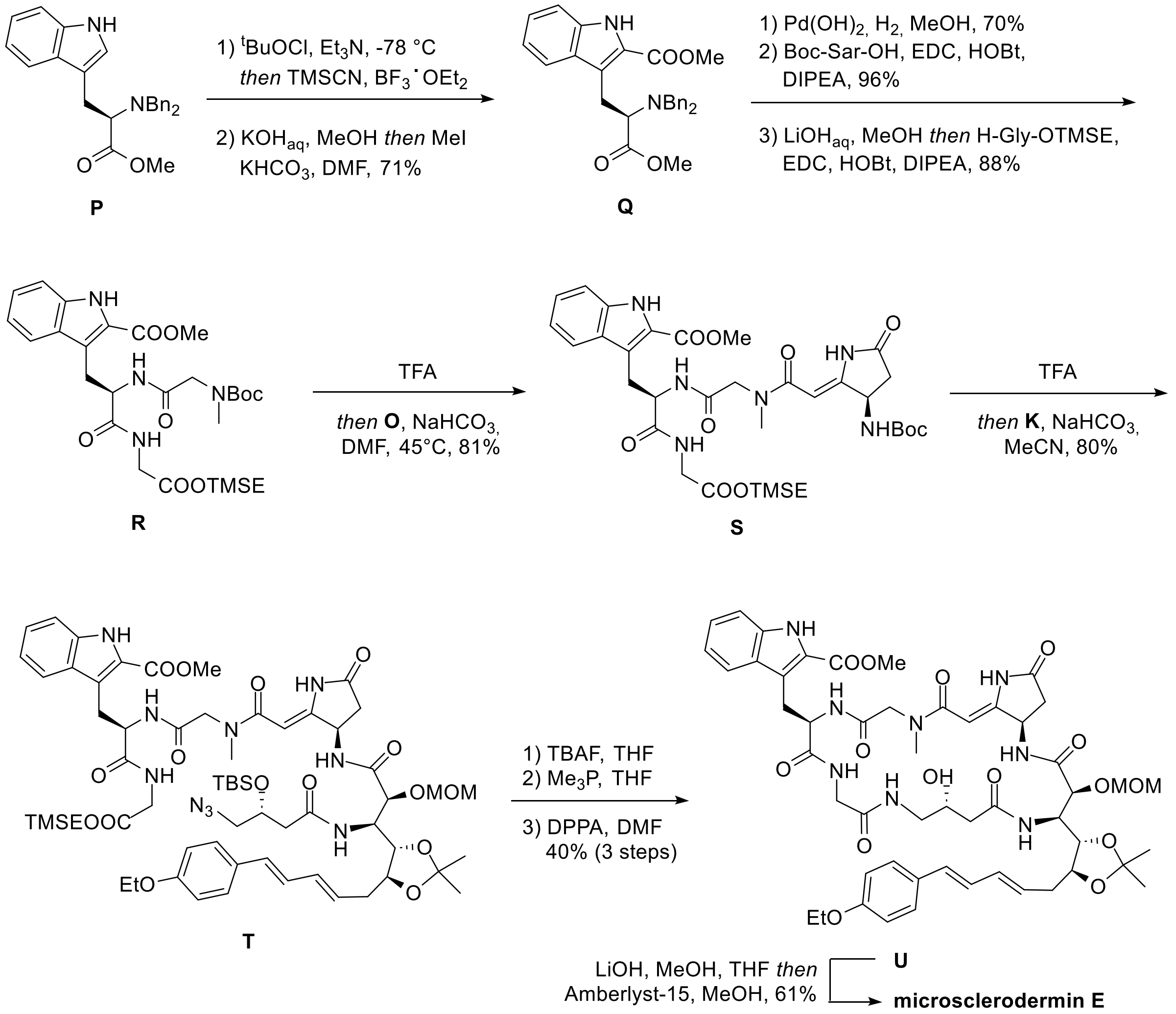
Scheme 3: Synthesis of the (*R*)-GABOB unit and coupling with AETD.

The synthesis of the amino pyrrolidone building block started with the transformation of protected D-aspartic acid **K** to the urethane *N*-carboxyanhydride (UNCA) **M** (Scheme 4) by esterification and bis-Boc protection of the amine followed by ester cleavage and acid chloride mediated cyclization. The authors reported the activation as an UNCA was essential for preserving the optical purity during the formation of β-ketoester **N** (>98% ee). Alternative active ester formations via *N,N'*-carbonyldiimidazole, *N*-hydroxysuccinimide, or pentafluorophenol resulted in partial or complete epimerization of β-ketoester **N**. Catalytic hydrogenolysis of the benzyl ester was followed by activation as a mixed anhydride and reaction with aqueous ammonia to form a hydroxy pyrrolidone. The hemiaminal was eliminated by mesylation with MsCl and Et_3N. In the last step, the TMSE-ester was cleaved with TBAF, which resulted in pronounced epimerization.



Scheme 4: Synthesis of the amino pyrrolidone unit via activation as urethane *N*-carboxyanhydride.

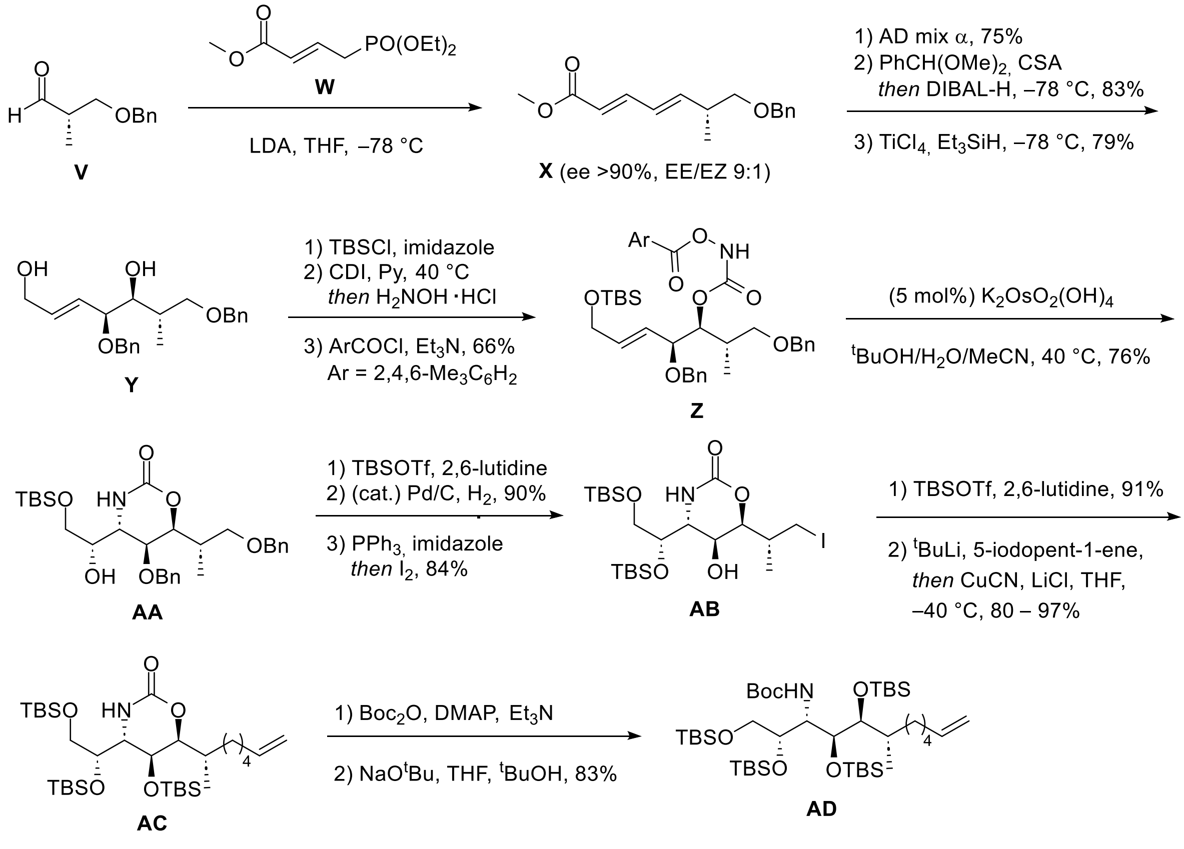
Inhibiting the base-catalyzed epimerization with *p*-toluene sulfonic acid resulted in 20% epimerization as the best result. The amino pyrrolidone building block was finished by activation of the free carboxylic acid as PFP-ester **O**. To synthesize the (*R*)-Trp-2-carboxylic acid moiety, a nitrile was introduced into tryptophan derivative **P** (Scheme 5) using a protocol of Danishefsky *et al.*[23] After saponification with potassium hydroxide and protection as methyl ester, tryptophan derivative **Q** was *N*-deprotected by hydrogenolysis. Two consecutive couplings with Boc-protected sarcosine and glycine TMSE-ester gave tripeptide **R** in 84% over 2 steps. The Boc-group was removed with trifluoroacetic acid. The resulting amine was coupled with PFP-ester **O**, affording tetrapeptide **S** in 81% yield as an inseparable mixture of diastereomers (4:1) due to the already mentioned racemization of **O**. After another acidic Boc-deprotection, the tetrapeptide was coupled with NHS-ester **J** to yield linear hexapeptide **T** in 80%. The TMSE-ester was removed with TBAF, and a Staudinger reduction with trimethyl phosphine reduced the azide to the corresponding amine. Reduction with bulkier reagents like Ph_3P, nBu_3P, and $SnCl_2$ proved to be unsuccessful. An attempted macrocyclization with EDC/HOAt was ineffective, but diphenylphosphoryl azide (DPPA) in DMF for 14 days afforded microsclerodermin E precursor **U** in 40% yield over 3 steps. The diastereomer of **U** (9% yield) was separated after the cyclization.



Scheme 5: Coupling of the building block and final deprotection.

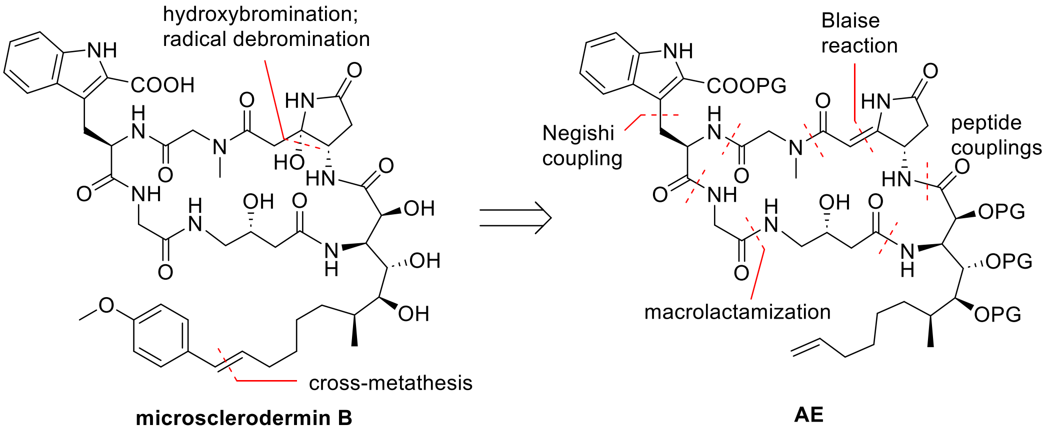
While the saponification of the methyl ester with LiOH worked without any problems, an acidic deprotection of the MOM group and the acetonide was troublesome. Optimizing this final step led to a deprotection protocol with Amberlyst-15 to give microsclerodermin E in 61% yield. Ma and Zhu reported matching analytical data of the synthetic compound with the isolated microsclerodermin E by Faulkner and co-workers, confirming their structural elucidation.

Over the years, several groups worked on the chiral synthesis of the different polyhydroxylated amino acids as the most challenging moiety in the microsclerodermins.[24–28] Contrary to the synthesis of Ma and Zhu, who used a chiral pool approach (*cf.* Scheme 2), all of these syntheses use stereoselective reactions to form most of the stereocenters. Apart from the Aitken group, which worked with a diastereoselective addition to a chiral sulfimine,[26] all use a sequence of stereoselective dihydroxylation and aminohydroxylation to introduce the four stereocenters. The synthesis of the Donohoe group, who used a tethered aminohydroxylation approach and later included it in a total synthesis of dehydromicrosclerodermin B and microsclerodermin J, is shown in Scheme 6.[15,28] Starting from the (*S*)-Roche ester derived aldehyde **V**, diene **X** was produced via Horner-Wadsworth-Emmons olefination with phosphonate **W**. A Sharpless dihydroxylation of the double bond with higher electron density followed by selective protecting group manipulations afforded compound **Y** in 60% over 3 steps. The precursor for the tethered aminohydroxylation **Z** was obtained by selective TBS-protection and introduction of the unusual functionality at the remaining hydroxy group by activation with CDI, quenching with hydroxyl amine, followed by mesitoylation.



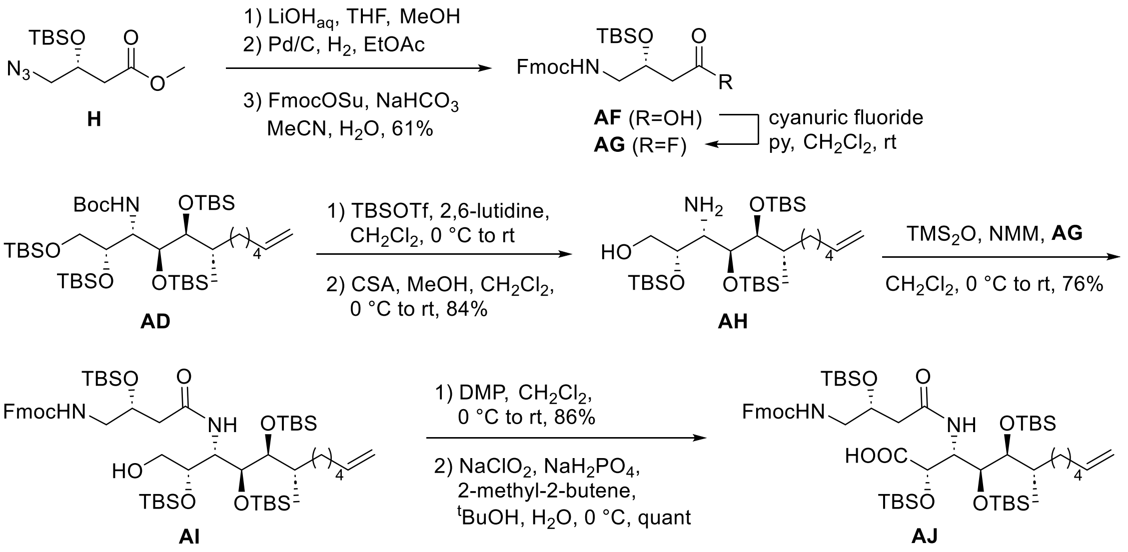
Scheme 6: Synthesis towards the AMMTD unit of Microsclerodermin B by Donohoe *et al.*

The critical step was the tethered aminohydroxylation, which gains regio- and stereoselectivity by the formation of an imido-osmium complex.[29] Application of this methodology on precursor **Z** resulted in the desired aminohydroxylated product **AA** as a single diastereomer in 76% yield. More protecting group manipulations and a sequence of iodination via Appel-type reaction and substitution with a pentenyl cuprate led to fully protected AMMTD precursor **AD**. This precursor was used in their following total synthesis of dehydromicrosclerodermin B. The retrosynthetic analysis included a late-stage olefination introducing the methoxyphenyl residue and a hydroxybromination for the hemiaminal at the amino pyrrolidone (Scheme 7). A macrolactamization, at the same position Ma and Zhu chose during their synthesis of microsclerodermin E, and the common peptide disconnections to the six amino acids further simplified **AE**. Furthermore, the authors planned a Blaise reaction for the amino pyrrolidone fragment and a Negishi coupling for the substituted tryptophan unit.



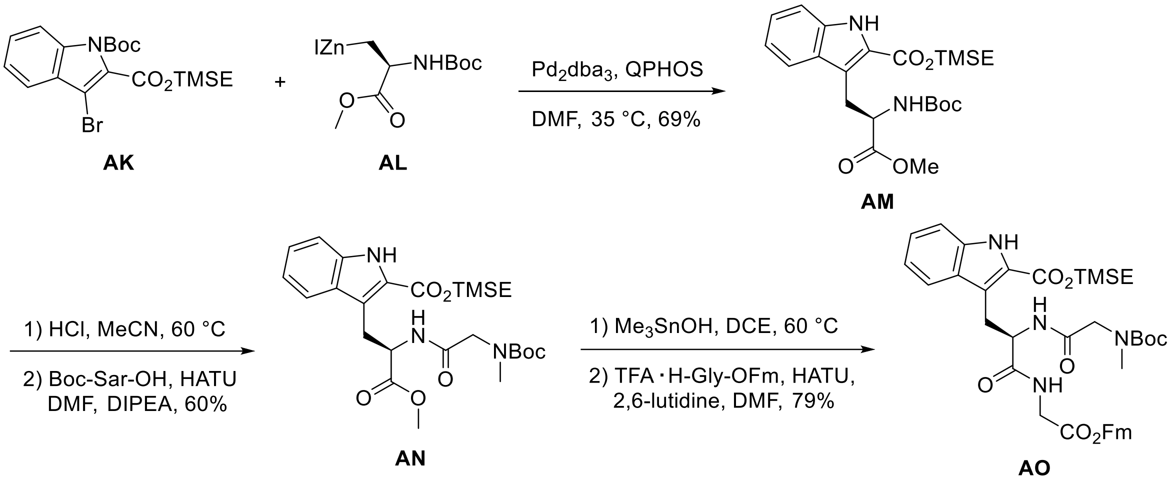
Scheme 7: Retrosynthetic analysis of microsclerodermin B by Donohoe *et al.*

The (*R*)-GABOB precursor **H** (prepared according to Ma's and Shioiri's protocol[16,30]) was transformed into **AF** by a series of saponification, catalytic hydrogenation, and Fmoc-protection (Scheme 8). Boc-deprotection and selective deprotection of the primary TBS-group in AMMTD precursor **AD** afforded **AH** in 84% yield.



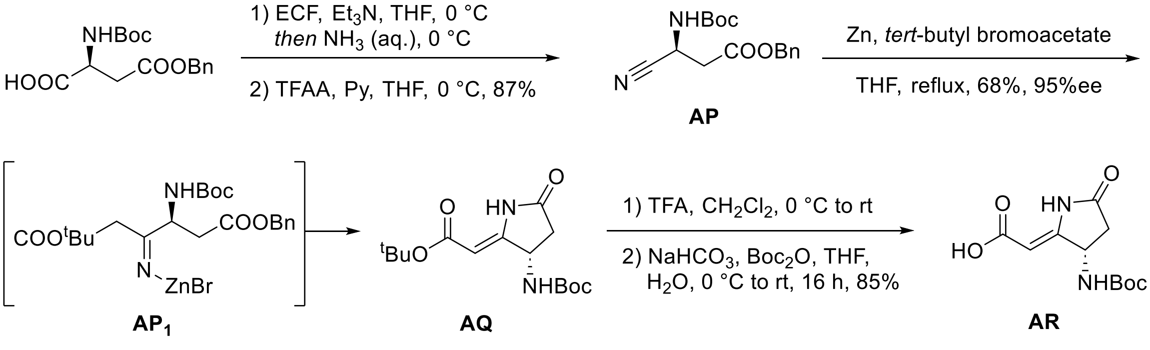
Scheme 8: Coupling of the AMMTD precursor AH and the (*R*)-GABOB acid fluoride AG.

Coupling of the amine with acid fluoride **AG** gave dipeptide **AI,** which was oxidized in a two-step procedure using a DMP- and Pinnick-oxidation to finish the AMMTD-GABOB building block **AJ**. Due to the high modularity, the Donohoe group investigated a Negishi coupling route for the formation of the substituted tryptophan unit (Scheme 9). The iodoalanine derived zinc organyl **AL** was successfully coupled with indole derivative **AK** to form protected Trp-2-CO_2TMSE **AM** in 69% yield. Two consecutive peptide couplings with Boc-protected sarcosine and the 9-fluorenyl methyl (Fm)-ester of glycine afforded tripeptide **AO**.



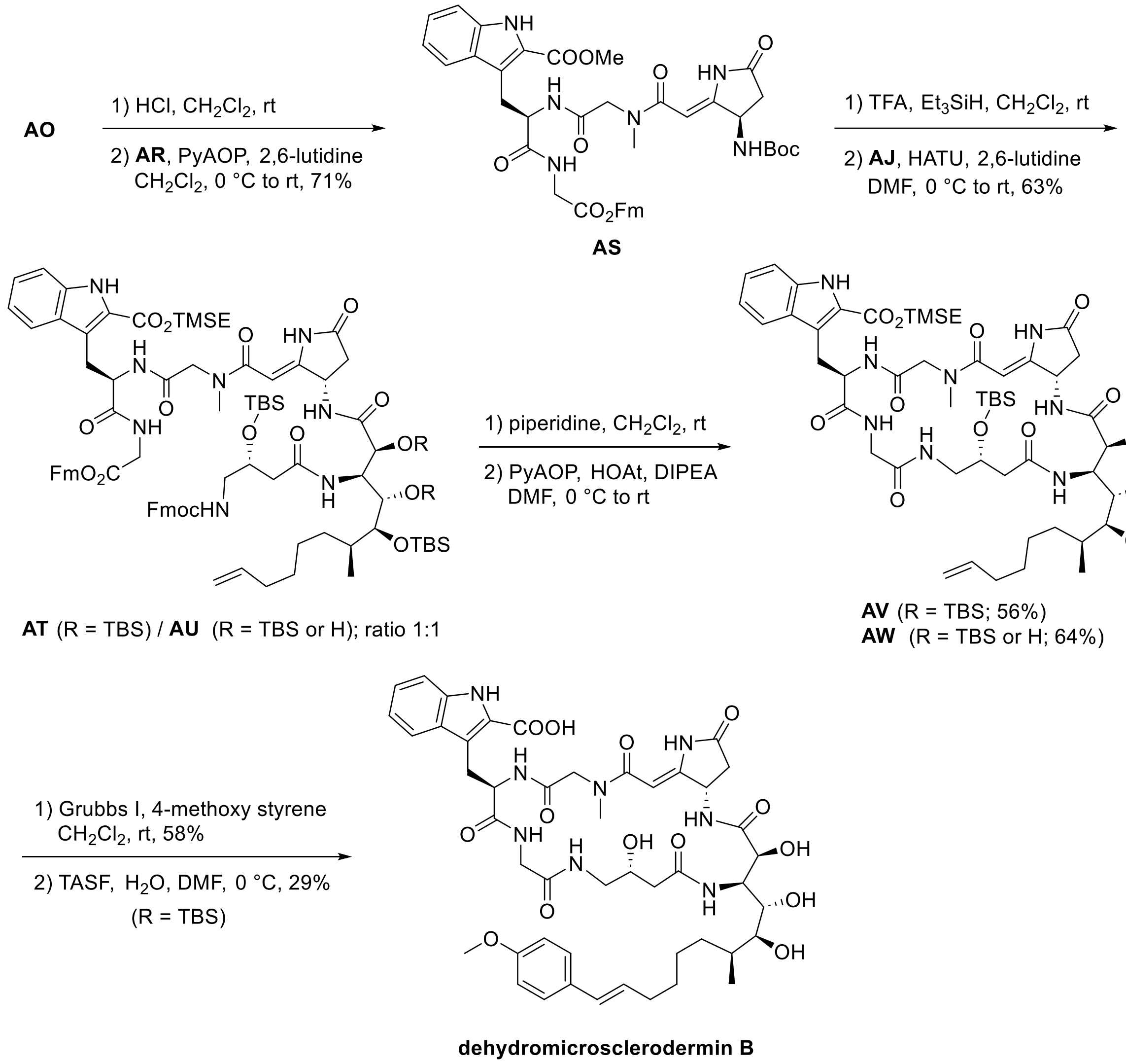
Scheme 9: Negishi coupling to form the tryptophane derivative AM and coupling to the tripeptide AO.

The amino pyrrolidone unit was prepared in analogy to an amino acid homologation protocol by Kouklovsky *et al.*, featuring a Blaise reaction as the key step (Scheme 10).[31] Introduction of a primary amide into Boc-Asp(OBn)-OH and subsequent dehydration with trifluoroacetic anhydride led to nitrile **AP**. A Blaise reaction with the zinc organyl of *tert*-butyl bromoacetate afforded the amino pyrrolidone **AQ** in 68% yield. Kouklovsky and co-workers proposed an iminozincate intermediate **AP₁** cyclizing onto the ester. In the last step of the amino pyrrolidone synthesis, TFA was used to cleave the *tert*-butyl ester. Due to the simultaneously cleaved Boc-protecting group, a reprotection with Boc-anhydride was trailed to afford carboxylic acid **AR** in 85% yield.



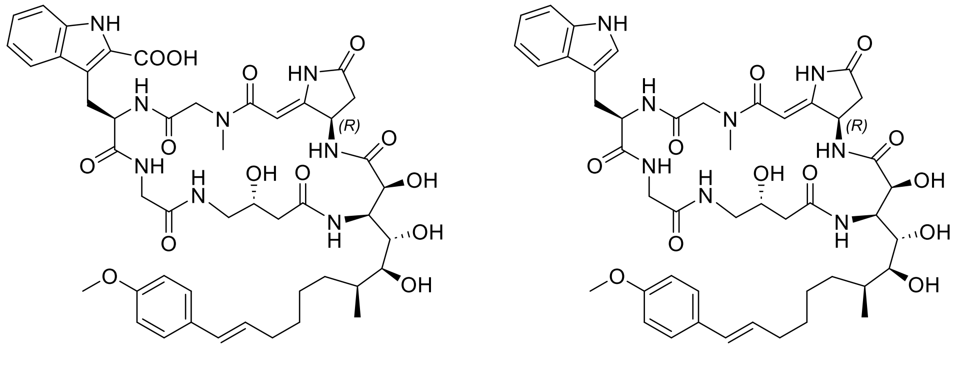
Scheme 10: Synthesis of the amino pyrrolidone unit via Blaise reaction.

After acidic Boc-cleavage of tripeptide **AO**, the resulting amine hydrochloride was coupled with **AR** using PyAOP as a coupling reagent (Scheme 11). Tetrapeptide **AS** was exposed to another acidic deprotection followed by a HATU-mediated coupling with dipeptide **AJ** to yield a 1:1 mixture of hexapeptide **AT** and its partially TBS-deprotected variant **AU** in 63%. After simultaneous deprotection of the *N*- and *C*-termini with piperidine, a macrolactamization with PyAOP/HOAt resulted in cyclic peptides **AV** and **AW** in 56% and 64% yield, respectively. According to their retrosynthetic plan, the authors attempted a hydroxybromination at the amino pyrrolidone unit with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD). Several attempts resulted in full conversion to undefined side products without observable product formation. They abandoned the hydroxybromination strategy and finished their synthesis with their advanced intermediates to the dehydromicrosclerodermin B by olefin metathesis and final deprotection in 17% yield over two steps.



Scheme 11: Coupling of the building blocks and late-stage olefin metathesis.

A comparison of the NMR-spectroscopic data of Li's isolated dehydromicrosclerodermin B and the synthesized compound showed a high deviation of the chemical shifts in the ^{13}C-NMR. The deviation is especially high for signals in the pyrrolidone and the GABOB environment with a $\Delta\delta_c$ of up to 2.3 ppm. Faulkner *et al.* reported weak NOE-correlations between the GABOB and pyrrolidone units, suggesting a conformational proximity. Due to the high prevalence of (*R*,*R*)-configurated microsclerodermins (*cf.* Table 1) and the lack of clarity in the assignment of these stereocenters by Faulkner *et al.* in 1994, the authors assumed an incorrect assignment. By using the enantiomer of amino pyrrolidone **AR**, they synthesized dehydromicrosclerodermin B again. Finally, they proved by NMR-comparison and HPLC co-injection that this compound (Figure 2) matches the isolated natural product.

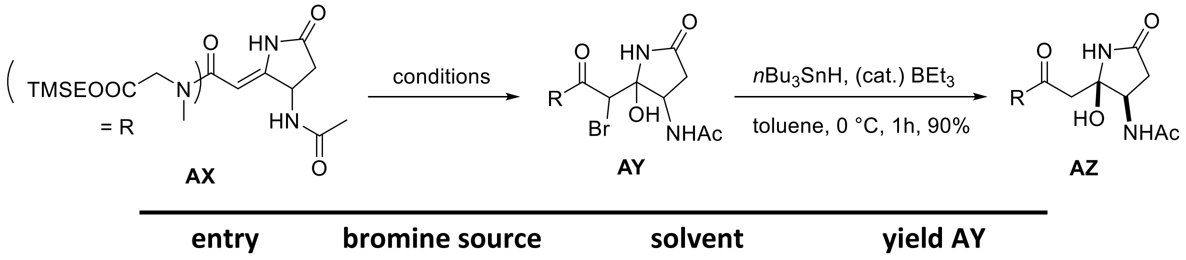


dehydromicrosclerodermin B **microsclerodermin J**

Figure 2: Reassigned structures of dehydromicrosclerodermin B and microsclerodermin J.

A similar route was used to synthesize an (*R*)-configured microsclerodermin J, which was also assigned with an (*S*)-configured stereocenter at the amino pyrrolidone unit by Li *et al.* based on the structural elucidation of microsclerodermins A and B. With this second total synthesis, the authors clarified another misassignment. The reassigned structure of microsclerodermin J is shown in Figure 2. Whether the microsclerodermins A and K really are the only microsclerodermins with an (*S*)-configured amino pyrrolidone unit has not been confirmed yet. Shortly after their total synthesis, Donohoe and co-workers published a protocol for the diastereoselective hydroxybromination of the amino pyrrolidone unit (Table 2).[32] The racemic acetylated dipeptide **AX** was used as a model substrate for testing different hydration strategies.

Table 2: Diastereoselective hydroxybromination of the amino pyrrolidone unit by Donohoe *et al.*

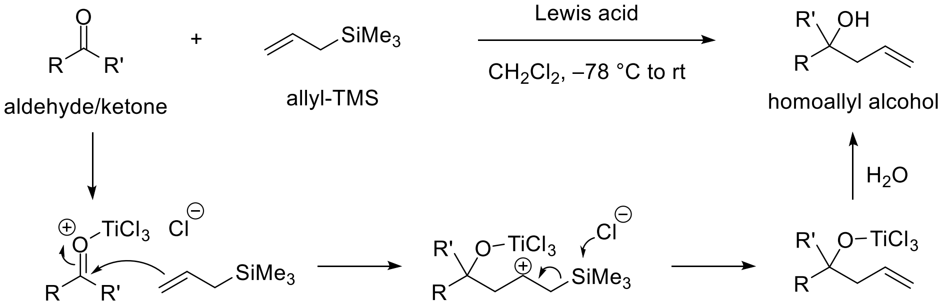


entry	bromine source	solvent	yield AY
1	2.5 eq. NBS	THF/H_2O	57%
2	2.5 eq. TBCD	THF/H_2O	81%
3	2.5 eq. Br_2	CH_2Cl_2/H_2O	76%

After several Lewis or Brønsted acid-mediated attempts failed, a hydroxybromination with NBS gave the desired product **AY** as a single (unassigned) diastereomer in 57% yield. Using TBCD or bromine improved the yield to 81% and 76%, respectively. Surprisingly, no dibromination was observed, even though 2.5 equivalents of the bromine source were used. Radical debromination afforded amino pyrrolidone **AZ** in 90% yield. NOE experiments showed a *cis*-configuration of the two stereocenters in **AZ**, which matches the configuration of the microsclerodermins. Experimenting with different acyl residues at the *N*-terminus showed that alkenes and alkynes are tolerated, while a methoxystyrene unit was preferentially hydroxybrominated at the styrene double bond. As mentioned, this strategy was not applicable in the end game of the microsclerodermin B synthesis.[15,32]

2.2 Hosomi-Sakurai Allylation of Furanoses

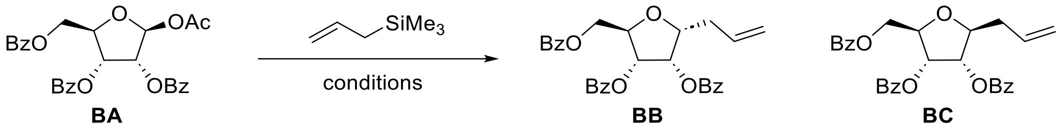
The C-allylation of furanoses is a highly important synthetic tool for the synthesis of optically pure tetrahydrofuran derivatives, which serves as an alternative to sometimes lengthy and tedious routes via acyclic precursors.[33] Among the most frequently used reagents for the allylation of various electrophiles are trimethylsilane or allylsilanes. In 1976, Hosomi and Sakurai reported a protocol for the allylation of aldehydes and ketones using allyl trimethylsilane and $TiCl_4$ or $BF_3{\cdot}OEt_2$ as Lewis acids,[34] which they expanded shortly after on the allylation of acetals (Scheme 12).[35] The Hosomi-Sakurai reaction/allylation or Sakurai allylation is generally described as a Lewis acid promoted allylation of carbonyl compounds and their derivatives using allylsilanes. The reaction mechanism starts with an activation of the carbonyl compound by the Lewis acid, which increases the electrophilicity and thus facilitates the attack of the allyl-TMS. The resulting β-silyl carbocation, which is highly stabilized by a hyperconjugation effect of the C–Si σ-orbital (β-silicon effect), eliminates TMS-Cl.[33,36] Hydrolysis of the resulting titanium alcoholate affords the homoallylic alcohol. Over time, the Sakurai allylation has shown its potential as a stereoselective transformation applied to complex molecules in the context of several total syntheses of a broad range of natural products.[36]



Scheme 12: Mechanism of the Hosomi-Sakurai allylation.[36]

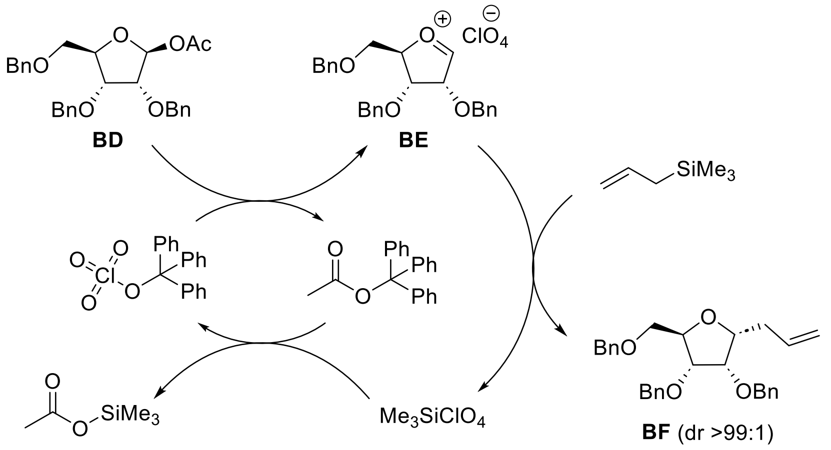
The first use of the Hosomi-Sakurai allylation on glycosyl acetals was reported by Kazikowski and Sorgi in 1982.[37] They tested several Lewis acids (LAs) such as TMSOTf, $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, and $ZnBr_2$ for their approach using an allylsilane for the allylation of an LA-generated oxonium ion derived from glycosyl acetate **BA** (Table 3). The best result, with a yield of 85% and a diastereomeric ratio of 80:20, was achieved in neat allyltrimethylsilane with $ZnBr_2$ at 110 °C (entry 1). The authors anticipated an induced stereoselectivity through neighboring group participation but were surprised by a selectivity towards the opposing stereoisomer **BB**. Shortly after, the same group reported an improved protocol for the allylation of glycosyl acetates with improved stereoselectivity using $BF_3{\cdot}OEt_2$ in acetonitrile at a much lower temperature of 0 °C (entry 3).[38] Using dichloromethane as a solvent at the same conditions nearly halved the yield and additionally decreased the stereoselectivity (entry 2). At almost the same time, Townsend and co-workers worked on the allylation of the same glycosyl acetate **BA** with TMSOTf as Lewis acid in nitromethane as a solvent.[39] With 83% yield and a dr of 89:11, their results were comparable to the improved $BF_3{\cdot}OEt_2$ protocol of the Kazikowski group.

Table 3: First reports of Sakurai allylations on glycosyl acetates.



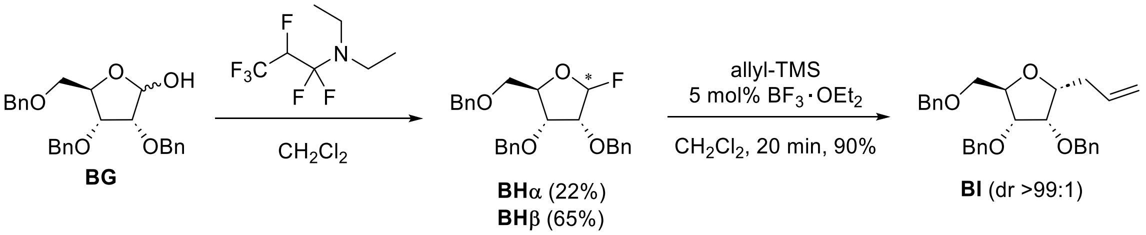
entry	conditions	yield	BB:BC	ref.
1	$ZnBr_2$, neat, 110 °C, 3 h	85%	80:20	[37]
2	$BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C to rt, 24 h	48%	71:29	[38]
3	$BF_3 \cdot OEt_2$, MeCN, 0 °C to rt, 3 h	93%	88:12	[38]
4	TMSOTf, CH_3NO_2, 0 °C, 5 h	83%	89:11	[39]

In the following years, similar procedures for the allylation of glycosyl acetals using different Lewis acids were reported.[33] An interesting catalytic approach using 5 mol% trityl perchlorate was reported by Mukaiyama and co-workers in 1984.[40] The reaction of glycosyl acetate **BD** with allyl-TMS and trityl perchlorate furnished the *C*-allylated product **BF** in 90% yield as a single diastereomer. The proposed catalytic cycle starts with the formation of the oxonium ion **BE** and the capture of the cleaved acetate by the trityl cation (Scheme 13). After the allylation with allyl-TMS, the formed TMS-perchlorate and trityl acetate recover the trityl perchlorate. Further experiments with other perchlorate-based catalysts led to the assumption that the perchlorate counter ion might block one face of oxonium ion **BE**, leading to the C-allylation products in remarkably high stereochemical purities.[33]



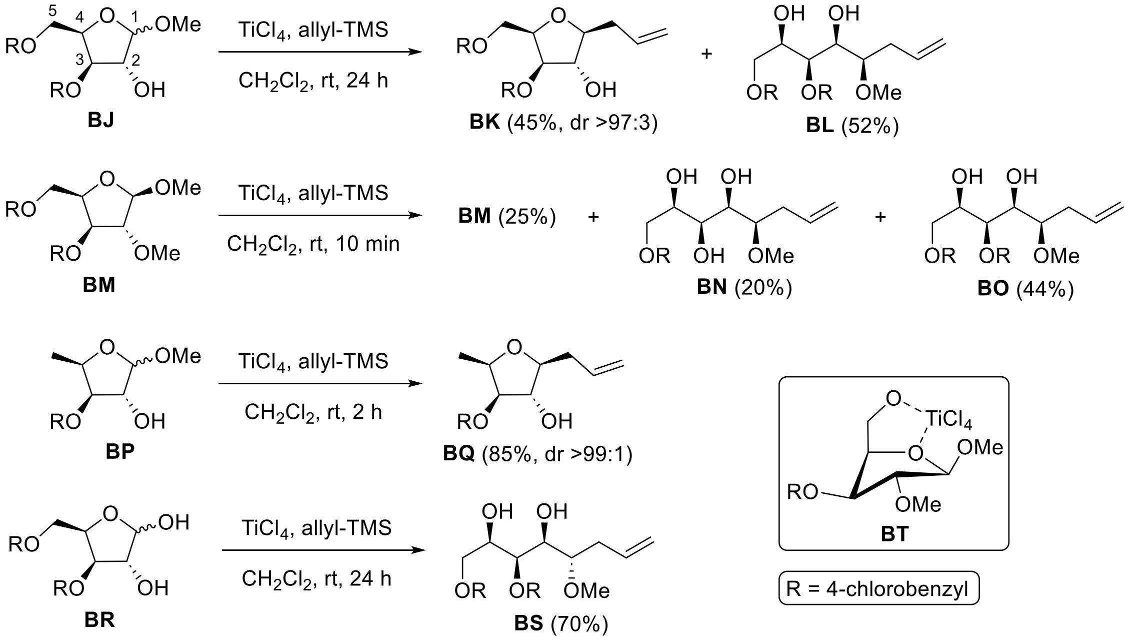
Scheme 13: Catalytic cycle of the Sakurai allylation with trityl perchlorate by Mukaiyama *et al.*[41]

Another stereoselective protocol for the Sakurai allylation was reported by Ishido *et al.* using glycosyl fluorides and catalytic amounts of $BF_3 \cdot OEt_2$ (Scheme 14).[42,43] The glycosyl fluorides were prepared using Ishikawa's reagent, the adduct of hexafluoro propene and Et_2NH. Regardless of which anomer was used in the subsequent Sakurai allylation, only the α-anomeric product **BI** was isolated in 90% yield. This observation clearly shows that the allylation does not follow an S_N2-pathway. Several ether-protected glycosyl fluorides were tested using this protocol. A solid but varying dependence of the stereoselectivity and yield on the solvent (Et_2O or CH_2Cl_2) and the amount of $BF_3 \cdot OEt_2$ was found.



Scheme 14: Hosomi-Sakurai allylation via glycosyl fluorides by Ishido *et al.*

In an attempt to use chelating agents to control the stereochemical outcome of Sakurai allylations of furanosides, Martin and co-workers used $TiCl_4$ and allyl-TMS on the 2-hydroxy furanoside **BJ** (Scheme 15).[44] In contrast to $SnCl_4$, which gave **BK** in a dr of 1:1, the reaction with $TiCl_4$ gave the 1,2-*trans* product in high selectivity (dr >97:3). However, the reaction yielded only 45% of **BK**, while the open-chain product **BL** was isolated as the main product in 52% yield. Further investigations on this subject showed that an oxygen atom at C-5 plays a crucial role in the allylation's regiochemistry. While **BJ, BM,** and **BR** all resulted in open-chain products as the main component, 4-methyl derivative **BP** exclusively formed the C-furanoside **BQ** in 85% yield as a single diastereomer. The authors proposed that chelation of 4-O and 5-O by $TiCl_4$ (**BT**), favored due to the spatial disposition of 4-O and 5-O and higher basicity of 4-O, promotes a ring-opening and the formation of an acyclic oxocarbenium ion.

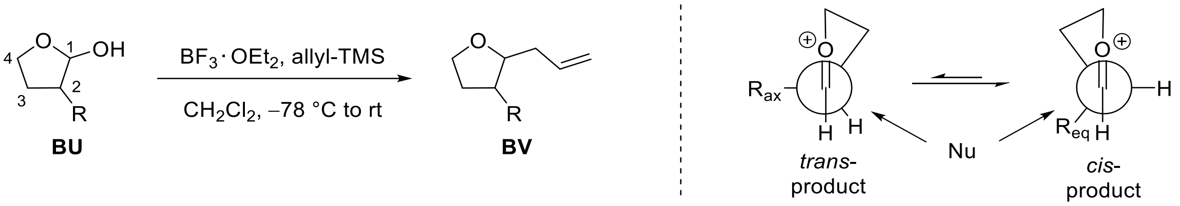


Scheme 15: Observations on ring-openings during Sakurai allylations by Martin *et al.*

Despite the significant progress made in stereoselective Sakurai allylations of furanoses, the explanation for the origin of the stereoselectivity remained both inconsistent and unconvincing.[33] In 1990, Reissig and Schmitt were among the first to explain the diastereoselectivity of Sakurai allylations of disubstituted tetrahydrofuran derivatives using a Felkin-Anh-based model.[45] The influence of the substitution pattern was investigated by permutating all positions with simple aliphatic residues with increasing sterical demand.[46] For greater consistency, the numbering of the tetrahydrofuran derivatives has been adjusted to be in line with furanosides (Table 4).

Starting with 1,2-disubstituted tetrahydrofuran **BU**, they observed a moderate selectivity towards the *trans*-product when using methyl and phenyl residues (Table 4, entries 1 and 2). Higher selectivities were achieved with the sterically demanding *tert*-butyl group (entry 3) or with sterically demanding allylsilanes. The Felkin-Anh model shows a kinetically favored *trans*-product due to the sterical hindrance of the pseudoequatorial residue (R_{eq}) in the *cis*-product. However, the conformation of the oxonium ion that delivers the *cis*-product is thermodynamically favored. These divergent effects hamper the influence of residues in the 2-position on the stereochemical outcome of the allylation.

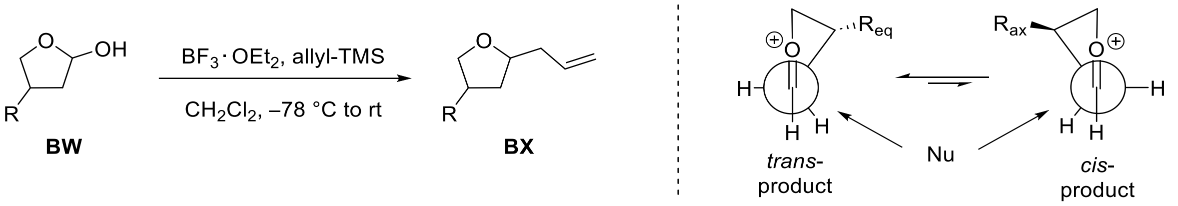
Table 4: Felkin-Anh model for Sakurai allylations of 1,2-disubstituted tetrahydrofuran derivatives by Reissig and Schmitt.



entry	lactol BU	yield BV	*trans:cis*
1	R = Me	53%	68:32
2	R = Ph	91%	63:37
3	R = ^{t}Bu	74%	98:2

Next, the 1,3-substitution pattern was investigated using the same conditions and residues (Table 5). In this case, even the less sterically demanding residues like methyl and phenyl resulted in a highly *trans*-selective formation (95:5) of **BX** (entries 1 and 2). The *tert*-butyl group increased the selectivity even more to above 98:2 (entry 3). The Felkin-Anh model shows that in the conformation that leads to the *trans*-product, the residue (R_{eq}) is in a more remote position than R_{ax} in the case of the *cis*-product transition state. Additionally to this kinetic preference, the *trans*-product also results from the thermodynamically favored conformer. These convergent effects led to significantly higher stereocontrol in the 1,3-disubstituted tetrahydrofuran derivatives.

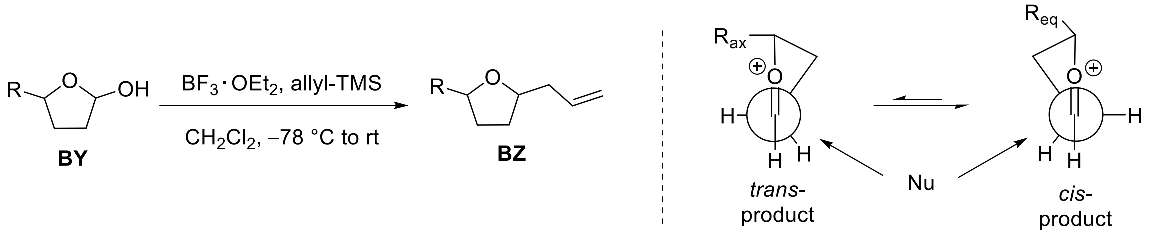
Table 5: Felkin-Anh model for 1,3-disubstituted tetrahydrofuran derivatives by Reissig and Schmitt.



entry	lactol BW	yield BX	trans:cis
1	R = Me	68%	95:5
2	R = Ph	80%	95:5
3	R = ^{t}Bu	84%	>98:2

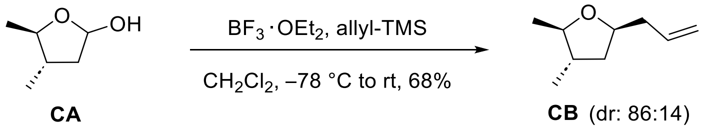
In the 1,4-disubstituted tetrahydrofuranes, the conformer leading to the *cis*-product is thermodynamically slightly favored, and the residue (R) is fairly remote from the reaction center but still shows a small shielding effect on the nucleophilic attack (Table 6). The least bulky residue (R = Me) leads to the thermodynamically preferred *cis*-product in a ratio of 40:60 (entry 1), which approximately reflects the calculated equilibrium constant of the two conformers of the oxonium ion. With growing sterical demand of the residue, the ratio slowly shifts towards the kinetically favored *trans*-product with a maximum of 88:12 in the case of the *tert*-butyl group.

Table 6: Felkin-Anh model for 1,4-disubstituted tetrahydrofuran derivatives by Reissig and Schmitt.



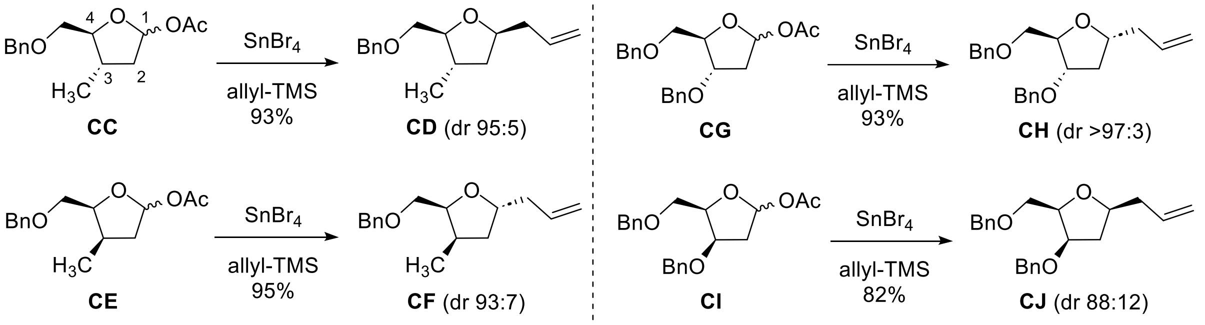
entry	lactol BY	yield BZ	*trans*:*cis*
1	R = Me	70%	40:60
2	R = Ph	80%	47:53
3	R = ^{t}Bu	72%	88:12

A Sakurai allylation of the trisubstituted THF-derivatives **CA** resulted in the desired product **CB** in 68% yield and a 1,3-*trans*:*cis* ratio of 86:14 (Scheme 16). As expected, the methyl group in the 3-position shows a higher impact on the stereoselectivity favoring the 1,3-*trans* product, comparable to Table 5 entry 1. The stereoselectivity on this trisubstituted THF-derivative is lowered due to the weak *cis*-promoting effect of the small methyl group in the 4-position. Even though Reissig's model explains the stereochemical outcome of Sakurai allylations of these aliphatic di- and trisubstituted THF-derivatives, it shows its limitations on more complex carbohydrates like **BA** or **BH** (*cf.* Table 3 and Scheme 14).[33]



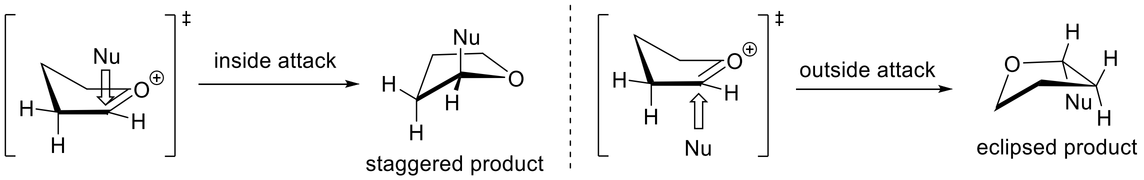
Scheme 16: Sakurai allylation of a trisubstituted tetrahydrofuran derivative by Reissig and Schmitt.

In 1999, Woerpel and co-workers introduced a stereoelectronic model in order to explain and predict stereochemical outcomes of allylations on carbohydrates where simple steric effects propose opposite selectivities (Reissig's model).[47] While the high 1,3-*trans* selectivity on the trisubstituted THF-derivatives **CC** and **CE** is in agreement with the Felkin-Anh based model by Reissig and Schmitt, the switch in selectivity toward 1,3-*cis* selectivity in the cases of **CG** and **CI** led to the hypothesis that an alkoxy group controls the approach of the nucleophile onto the same face (Scheme 17).



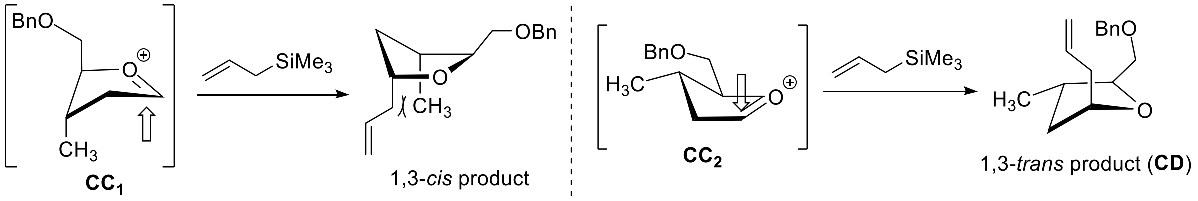
Scheme 17: Switch in selectivity from 1,3-*trans* on aliphatic residues to 1,3-*cis* for alkoxy residues.

These results, together with previous studies,[48,49] resulted in a stereoelectronic model that describes the favored "inside attack" of the nucleophile on an oxonium ion in envelope conformation as the crucial element (Scheme 18). The authors explain the selectivity toward an "inside attack" with the formation of a more stable, staggered product, while an "outside attack" results in a sterically less ideal (higher energy) eclipsed product.



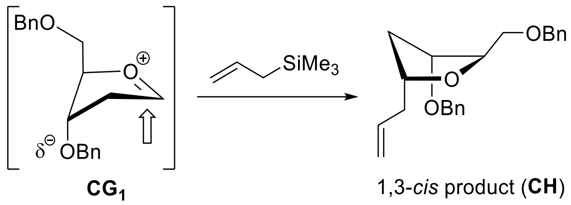
Scheme 18: Woerpel's model favoring the staggered product via an "inside attack".

Testing this model on the trisubstituted THF-derivatives in Scheme 17 gives two possible conformers for the oxonium ion derived from **CC** (Scheme 19). Both substituents in the less ideal pseudoaxial position make conformer **CC₁** the higher energy conformer. An inside attack of allyl-TMS results in a strong 1,3-diaxial steric repulsion of the methyl and allyl groups. In contrast, conformer **CC₂** has both substituents in pseudoequatorial positions and offers more room for a nucleophilic inside attack. The formation of the 1,3-*trans* product agrees with the above-mentioned experimentally obtained results for methyl substituted THF-derivatives **CD** and **CF**.



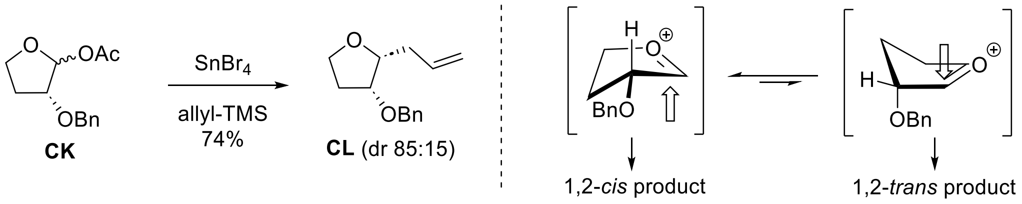
Scheme 19: "Inside attack" on two possible conformers of the oxonium ion of CC.

In contrast to the alkyl residues, an alkoxy substituent in 3-position prefers to adopt a pseudoaxial position in oxonium ions to maximize the interaction between its partial negative charge and the positively charged oxonium ion. Computational studies and experimental studies with pyran-derived oxonium ions support this theory of electrostatic interaction and, consequently, the "paradoxical conformational preference".[50] Application to the oxonium ion derived from **CG** (Scheme 17) led to the diaxial conformer **CG₁** (Scheme 20), which, via inside attack of the allyl-TMS results in the 1,3-*cis* product equaling the main product **CH**.



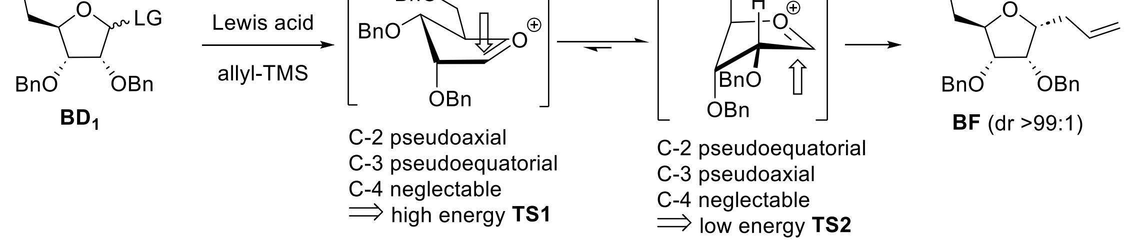
Scheme 20: Favored oxonium ion conformer of CG due to electrostatic interactions.

Expanding the model on 1,2- and 1,4-disubstituted tetrahydrofuran derivatives, Woerpel *et al.* observed a neglectable influence of a substituent in 4-position independent of the electronic nature of the substituent.[50] On the other hand, an alkoxy substituent in the 2-position showed a strong directing effect toward a 1,2-*cis* product. For example, glycosyl acetate **CK** under standard Sakurai allylation conditions gave the 1,2-*cis* allylated product **CL** in 74% yield and a dr of 85:15 (Scheme 21). Again, the opposite selectivity compared to a simple aliphatic substituent (*cf.* Table 4) indicated a stereoelectronic effect of the alkoxy group. The oxonium ion derived from **CK** prefers a conformation in which the benzyloxy group sits in a pseudoequatorial position, maximizing the overlap of the better electron-donating σ_{C-H} orbital with the vacant orbital of the oxocarbenium ion (Scheme 21). An alkyl group in the 2-position eliminates this factor due to the similar hyperconjugative donation of σ_{C-H} and σ_{C-C} orbitals. In this case, the main effect remains sterical, resulting in a slight preference for the 1,2-*trans* product (*cf.* Table 4).



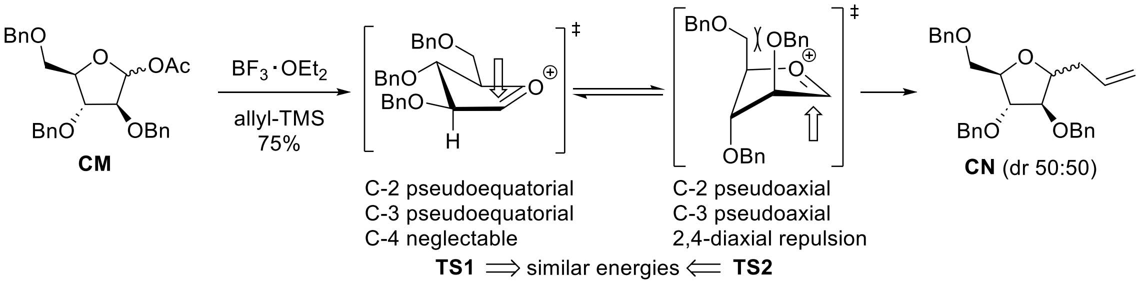
Scheme 21: Woerpel's model for the allylation of 1,2-disubstituted tetrahydrofuran derivatives.

The application of Woerpel's model to more complex tetrasubstituted furanosides clearly shows (similar to Reissig's model) the importance of convergent and divergent effects of stereocontrol by the substituents in the 2- and 3-position. For example, 2,3-*cis* alkoxy substituted glycosyl acetals such as **BD₁** show convergent stereoelectronic effects with a pseudoequatorial alkoxy substituent in C-2 maximizing the hyperconjugation and another alkoxy substituent in pseudoaxial C-3 position stabilizing the transition state (**TS2**) via electrostatic effects (Scheme 22). The highly favored transition state should selectively lead to 1,2-*cis* allylation product **BF**.[33]



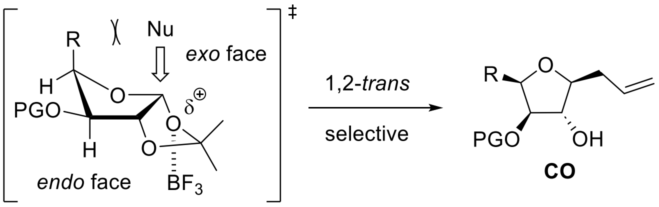
Scheme 22: Application of Woerpel's model to tetrasubstituted tetrahydrofuran derivatives (convergent effects).

Indeed, previously described experiments (*cf.* Scheme 13 and Scheme 14) showed diastereoselectivities higher than 99:1 for this Sakurai allylation using fluoride or acetate as a leaving group (LG) and $BF_3 \cdot OEt_2$ or trityl perchlorate as a Lewis acid.[41,43] Upon allylation of the 2,3-*trans* alkoxy substituted glycosyl acetate **CM**, Woerpel and co-workers obtained the allylated C-furanoside **CN** in 75% yield and a diastereomeric ratio of 1:1 (Scheme 23).[50] A closer look at the transition states revealed two possible conformers of the oxonium ion with similar energies. In the first transition state (**TS1**), the alkoxy group in C-2 is in the favored pseudoequatorial position, while the alkoxy group in C-3 is in the disfavored pseudoequatorial position. The overall sterical hindrance between the substituents is low in this transition state. Due to the higher directing effect of the C-3-position, the transition state **TS2** bearing both substituents on C-3 and C-2 pseudoaxial should be slightly favored. Still, an additional sterical interaction between the 2,4-diaxial substituents increases the energy of the transition state, making them almost equal. Another example showcasing these effects was an allylation of a glycosyl acetate without a C-4 substituent, which resulted in a slightly favored 1,3-*cis* product (dr 61:39) by removing the 2,4-diaxial sterical hindrance.[50]



Scheme 23: Application of Woerpel's model to tetrasubstituted tetrahydrofuran derivatives (divergent effects).

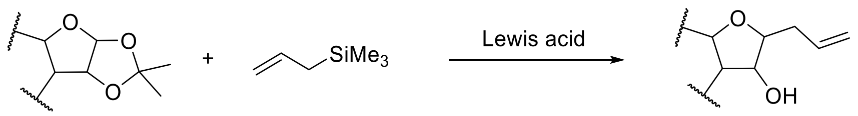
The Tellado group reported a highly 1,2-*trans* selective allylation independent of the substitution pattern on the glycosyl acetals by using a 1,2-*O*-isopropylidene protecting group with $BF_3 \cdot OEt_2$ or $TiCl_4$ as Lewis acid.[51] The authors hypothesized a transition state in which the Lewis acid (BF_3) activates the acetal without cleavage and oxonium ion formation, resulting in an S_N2-type substitution by the nucleophile, which approaches the electrophile from the *exo* face (Scheme 24).

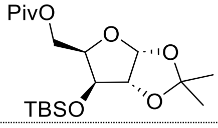
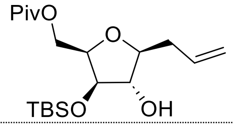
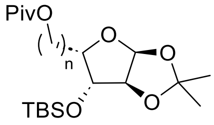
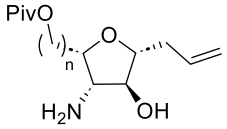
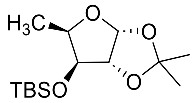
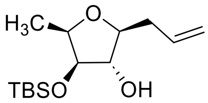
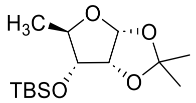
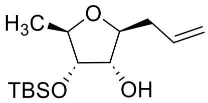
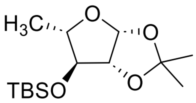
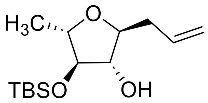
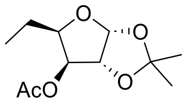
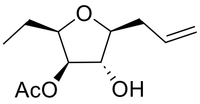


Scheme 24: S_N2-type mechanism of allylations of 1,2-isopropylidene protected furanosides by Tellado *et al.*

The authors supported their hypothesis with a series of experiments, varying the substitution pattern and stereochemistry at the 3- and 4-position of 1,2-*O*-isopropylidene protected glycosyl acetals (Table 7). In the first entry, a Sakurai allylation with $BF_3 \cdot OEt_2$ and allyl-TMS resulted in the 1,2-*trans* allylation product as a single diastereomer in 40% yield. With a mixture of $BF_3 \cdot OEt_2$ and TMSOTf, the same substrate gave the 1,2-*trans* product in an increased yield of 60% but a reduced stereoselectivity of 75:25.

Table 7: 1,2-*trans* selective allylation of 1,2-*O*-isopropylidene furanosides by Tellado *et al*.

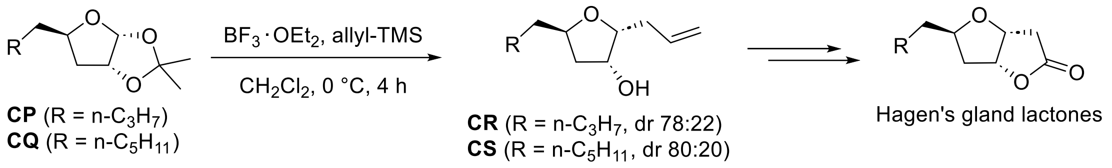


entry	substrate	Lewis acid	product	yield
1		$BF_3\cdot OEt_2$ $BF_3\cdot OEt_2$/TMSOTf (8:2)		40% 60% (dr 75:25)
2		$BF_3\cdot OEt_2$		42% (n=1)[a] 62% (n=2) 89% (n=3)
3		$BF_3\cdot OEt_2$ $TiCl_4$		74% 83%
4		$BF_3\cdot OEt_2$		47%
5		$BF_3\cdot OEt_2$		68%
6		$BF_3\cdot OEt_2$		39%[b]

a) 38% starting material recovered b) 25% starting material recovered

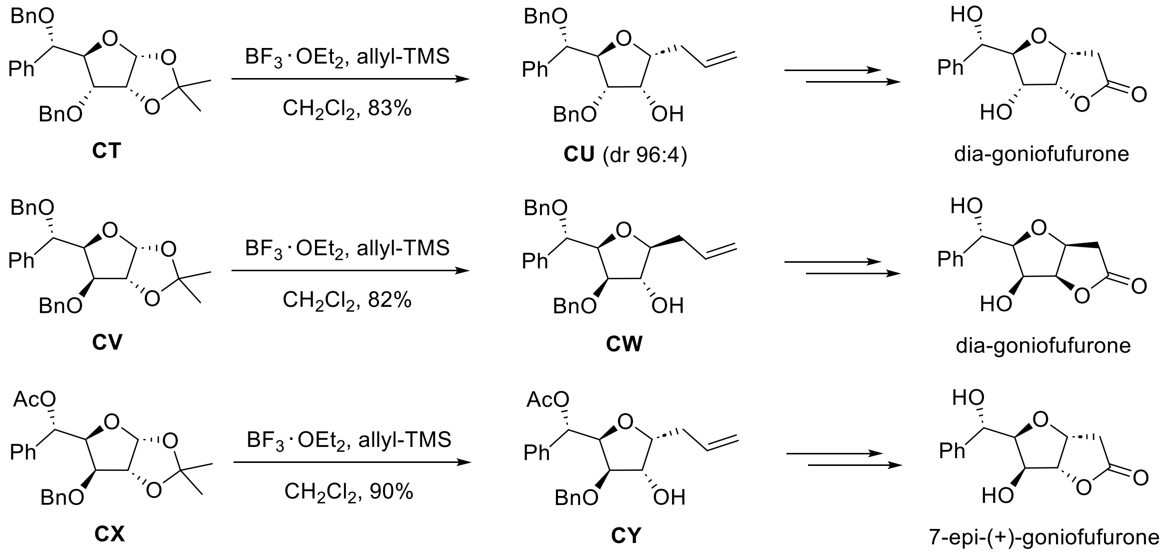
The increased Lewis acidity of the mixture resulted in a higher conversion but most likely cleaved the acetal and formed the oxonium ion, which led to a decreased stereocontrol due to the divergent effects of the 2,3-*trans* alkoxy substituents according to Woerpel's model. Reducing the sterical hindrance at C-4 by moving the pivaloyl group further away from the reaction center significantly increased the yield from 42% to 89% (entry 2). This trend supported the transition state in Scheme 24, which shows a 1,3-diaxial relation between the C-4 substituent and the approaching nucleophile. Furthermore, the authors used the substrates in entries 3 to 5 to showcase the absence of stereocontrol by the substituents at C-3 and C-4 by permutation of the stereocenters. In all cases, the products were isolated as single diastereomers with a 1,2-*trans* stereoselectivity, nullifying the usually strong influence of the alkoxy group at C-3 observed in Reissig's and Woerpel's models. Additionally, $TiCl_4$ was tolerated as a Lewis acid, resulting in an identical product with a slightly increased yield (entry 3). Over the years, several groups[33] used 1,2-*O*-isopropylidene acetals as precursors for highly 1,2-*trans* selective allylations during their syntheses of complex organic molecules such as cephalosporolide E[52], the anti-breast cancer drug eribulin (E7389)[53,54], or an intermediate of the marine natural product amphidinolide X.[55]

Nevertheless, the prediction of the stereochemical outcome of Sakurai allylations remains challenging. During the synthesis of Hagen's gland lactones by Sartillo-Piscil and co-workers, the rather simple glycosyl acetals **CP** and **CQ** formed the allylation products **CR** and **CS** in moderate diastereoselectivities of 78:22 and 80:20, respectively (Scheme 25).[56] Even though the authors used conditions very similar to Tellado's protocol, they observed "Woerpel's" 1,2-*cis* product instead of "Tellado's" 1,2-*trans* product.



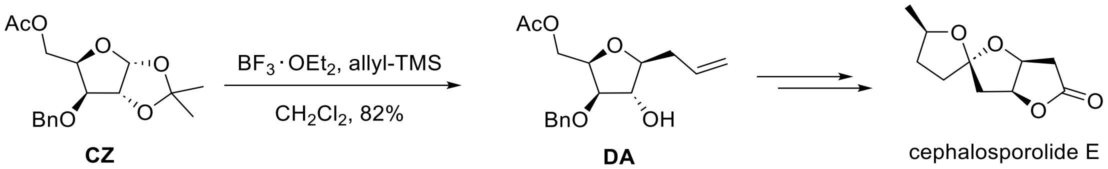
Scheme 25: 1,2-*cis* allylation of a 1,2-*O*-isopropylidene glycosyl acetal during the synthesis of Hagen's gland lactones.

Another complex example with varying 1,2-selectivities was reported during the synthesis of (+)-goniofufurone and its stereoisomers (Scheme 26).[57,58] In the first example, glycosyl acetal **CT** was transformed to the 1,2-*cis* allylation product **CU** in 83% yield and a good diastereoselectivity of 96:4. The selective formation of **CU** can be explained using Woerpel's model, in which both the C-2 and C-3 substituents show convergent *cis*-directing effects. The Sakurai allylation of its C-3 epimer **CV** afforded the 1,2-*trans* product **CW** in 82% yield as a single diastereomer. Even though **CW** would be the favored product in Woerpel's model due to the strong directing effect of the C-3 position, the high selectivity is atypical for 2,3-*trans* substituted glycosyl acetals (*cf.* Scheme 23). For the last stereoisomer of goniofufurone, Sartillo-Piscil *et al.* switched the benzyl protecting group in the 5-position to an acetate group. The resulting glycosyl acetal **CX** was again subjected to BF$_3$·OEt$_2$ and allyl-TMS, which resulted in the 1,2-*cis* allylation product **CY** as a single diastereomer. The authors explained this "anti-Woerpel" product by anchimeric assistance of the acetate protecting group that blocks the top face of the oxonium ion.



Scheme 26: Sakurai allylations during the total synthesis of goniofufurone diastereomers.

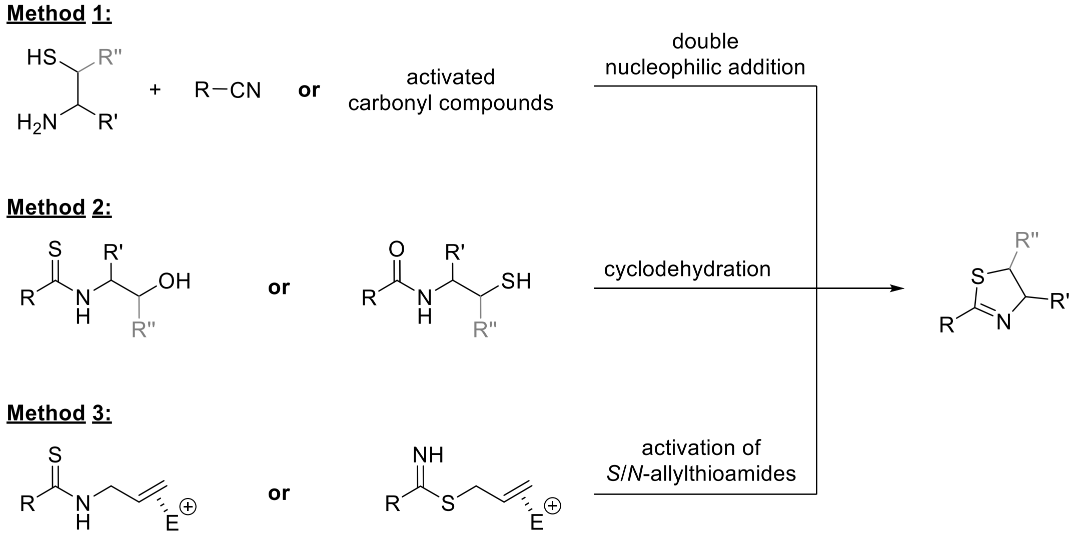
In contrast to this, during the synthesis of cephalosporolide E, the Sakurai allylation of C-5-acetylated **CZ** showed no neighboring group effect of the OAc-group which stereoselectively afforded the 1,2-*trans* product **DA** (Scheme 27).[52] This example again demonstrates the difficulty of predicting the stereochemical outcome of Sakurai allylations of furanosides.



Scheme 27: Sakurai allylation during the total synthesis of cephalosporolide E by Satillo-Piscil *et al*.

2.3 Synthesis of 2-Thiazolines and Occurrence in Natural Products

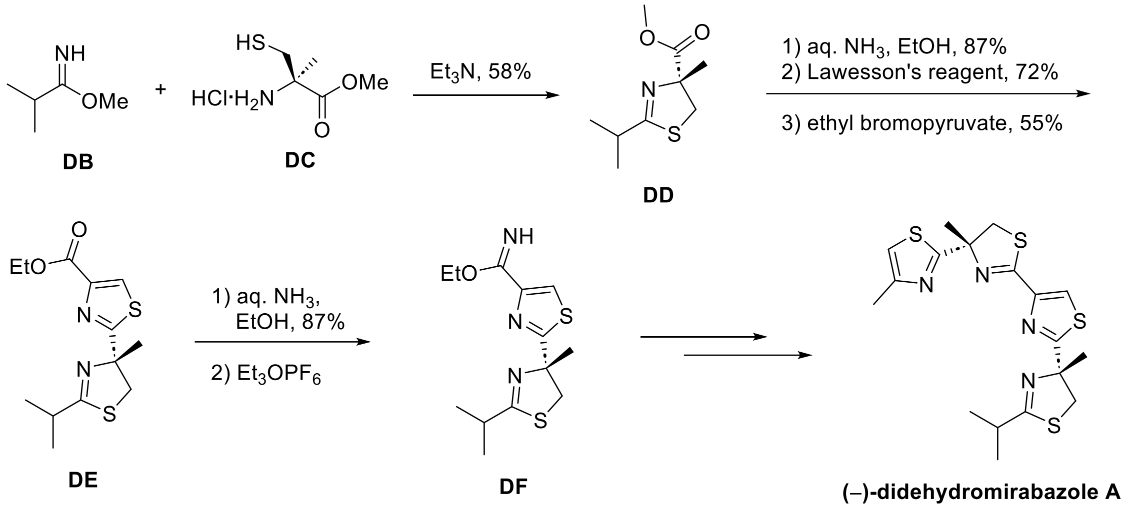
2-Thiazolines, as members of the 1,3-azole family, are five-membered heterocycles used in many areas like medicinal chemistry, the food industry, agrochemicals, and catalysis.[59,60] These applications and the high abundance in natural products make them interesting targets for the development of synthetic protocols. In general, most of these protocols can be categorized into one of the three methods shown in Scheme 28. In the first method, 1,2-aminothiols are used in a double nucleophilic addition with nitriles or activated carbonyl compounds such as iminoethers[61] or *N*-acyl benzotriazoles. Especially in the case of nitriles[60,62,63] and *N*-acyl benzotriazoles[64], the reaction conditions are quite harsh, requiring elevated temperatures or Lewis and Brønsted acid catalysts. For this reason, these protocols are mostly used for the synthesis of insensitive 2-aryl-thiazolines. Another variant belonging to the first category was described by Duñach *et al.*[65] They used 1,2-aminothiols and aldehydes to form thiazolidines, which, upon oxidation by a ruthenium catalyst and TBHP, formed the corresponding thiazolines.



Scheme 28: General methods for the synthesis of 2-thiazolines.

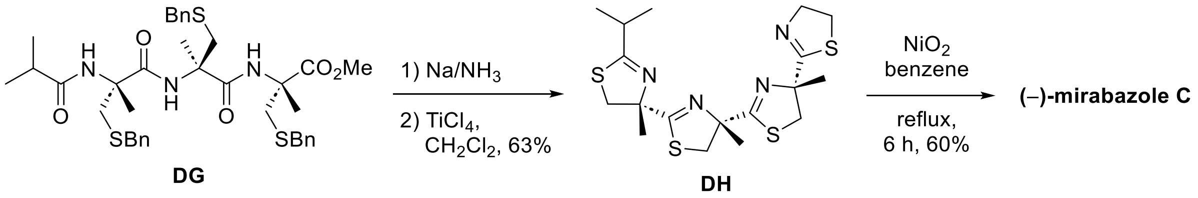
The second method is a cyclodehydration, in which an intramolecular cyclization between either a thioamide and a hydroxy group or an amide and a thiol under dehydrating conditions forms the desired thiazolines. A variety of dehydrating conditions, such as hydroxy activation via mesylation[66], dehydroxylative fluorination (DAST[67], Deoxo-fluor[68]), or dehydration via the Mitsonobu system[69] or via Burgess reagent[70] can be used.[59] A recent approach is shown as method 3, which can be described as a cyclization of *S*- or *N*-allylthioamides. Activation of the double bond was reported with electrophiles such as NBS[71] or hypervalent iodine species.[72] Alternatively, an electrochemical protocol by Wen and co-workers[73] or a photoredox catalytic approach by Nicewicz and Morse[74] facilitates the cyclization of *N*-allylthioamides.

A variation of the first method was used in Pattenden's and Thom's total synthesis of (–)-didehydromirabazole A (Scheme 29).[75,76] The activated carbonyl compound was iminoether **DB**, and α-methyl cysteine **DC** was used as the 1,2-aminothiol component . In a repetitive sequence of a 1,2-aminothiol addition and a Hantzsch thiazole synthesis, they successfully synthesized (–)-didehydromirabazole A in an overall yield of 4% over 10 steps.



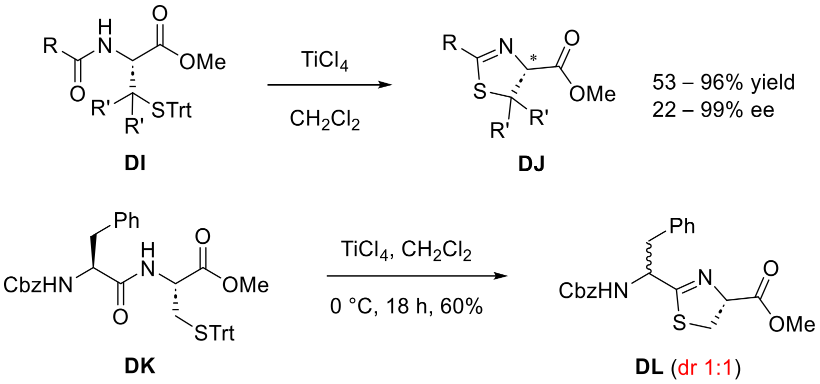
Scheme 29: Total synthesis of (–)-didehydromirabazole A via aminothiol addition to an iminoether.

In 1992, Heathcock and Walker described the total synthesis of the very similar (–)-mirabazole C using a $TiCl_4$-mediated cyclodehydration (Scheme 30).[77] After synthesis of α-methyl cysteine tripeptide **DG**, the benzyl protecting groups were removed under Birch conditions. Simultaneous ring-closure with $TiCl_4$ afforded the (–)-mirabazole C precursor **DH** in 63% yield. In the final step, the terminal unsubstituted 2-thiazoline was oxidized with nickel-(IV) oxide to yield the natural product in 60%.



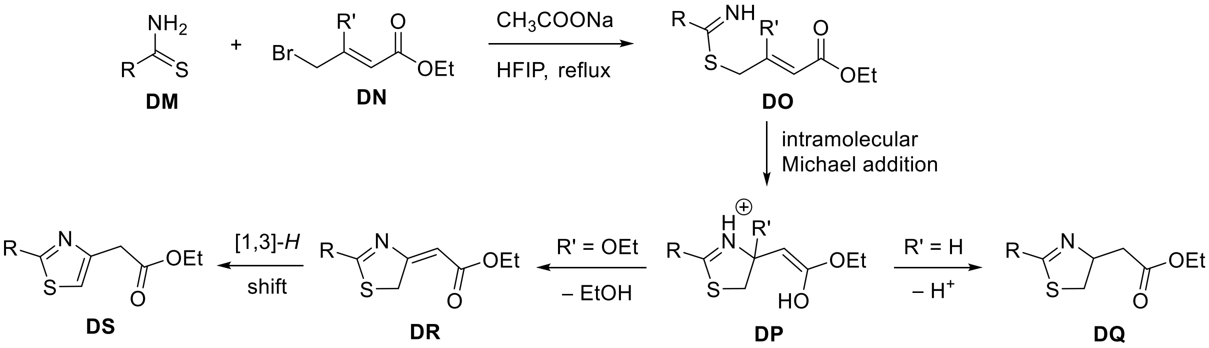
Scheme 30: $TiCl_4$-mediated cyclodehydration in the total synthesis of (-)-mirabazole C.

Kelly and co-workers investigated the scope and limitations of the $TiCl_4$-mediated approach with racemization-prone precursors.[78] Using an *S*-trityl protecting group, they achieved a higher efficiency by simultaneous deprotection and cyclodehydration with $TiCl_4$ (Scheme 31). Several Lewis acids were tested, and while most of them removed the trityl protecting group, only $TiCl_4$ successfully mediated the cyclodehydration as well. Their protocol generally showed good results for 2-aryl-thiazolines or achiral alkyl residues (R), with yields ranging from 53% to 96% and enantiomeric excesses above 90% for most substrates. An exception were electron-deficient aromatic systems such as 4-nitrophenyl, which led to a drastic drop in ee (22%). It is important to note that the epimerization of the C-2 exomethine center of thiazoline **DL** limits the applicability of $TiCl_4$-mediated thiazoline formations in peptide systems like **DK**.



Scheme 31: Tandem deprotection – cyclodehydration protocol by Kelly *et al.*

In 2017, Alam and Alsharif reported a modular synthesis of thiazolines and thiazoles using the concept of method 3 with a Michael acceptor as an internal electrophile.[79] In a one-pot procedure, they synthesized the *S*-allyl thioamides **DO**, which spontaneously cyclized via intramolecular Michael addition (Scheme 32). The thiazoline intermediate **DP** then either forms thiazole **DS** (R' = OEt) by elimination of ethanol and 1,3-*H* shift or thiazoline **DQ** (R' = H) by a simple deprotonation. This procedure allowed the synthesis of a broad range of 2-aryl thiazoles and 2-aryl thiazolines in high yields and purities without the need for column chromatography. It is necessary to note that the authors did not report substrates bearing chiral residues (R) and only synthesized racemic thiazolines, which drastically limits the application of this method to complex molecules.



Scheme 32: Modular synthesis of thiazolines and thiazoles by Alam and Alsharif.

Most protocols mentioned above lack of examples with chiral C-2 exomethine positions known for their stereochemical lability.[59,60] These epimerization processes were observed for several thiazoline-containing cyclic peptides isolated from *Lissoclinum patella* (Figure 3). Ireland *et al.* reported a significant epimerization of a leucine moiety at the C-2 exomethine position of a thiazoline during their isolation and structural elucidation of cyclopeptides tawicyclamide A and B.[80] In the case of trunkamide A, the Giralt group observed complete epimerization to the natural (*R*)-epimer (at the phenylalanine position) within days after their synthesis of the unnatural (*S*)-epimer.[81,82] Another example of this conformationally promoted full epimerization was reported by the Wipf group during their studies of lissoclinamide 7 and related cyclopeptides.[83]

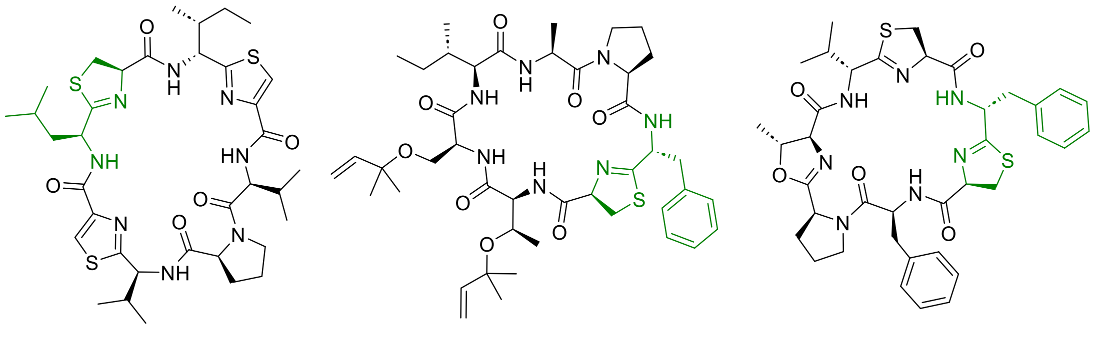

tawicyclamide B **trunkamide A** **lissoclinamide 7**

Figure 3: Thiazoline containing cyclopeptides from *Lissoclinum patella* with reported epimerization.

Most likely, the first epimerization of a C-2 exomethine position in a natural product was observed in the acid isomerization study of bacitracin A by Craig *et al*.[84,85] The bacitracins are a family of thiazoline-containing cyclic peptides produced by a strain of *Bacillus licheniformis* (Figure 4).[86] They were first isolated as a polypeptide mixture in 1945 by Johnson, Anker, and Meleney from the leg wound of a patient.[87] The potent antibiotic bacitracin A was accompanied by a low potency isomer that formed under weakly acidic conditions and equilibrated to a 1:1 mixture after two days (Figure 4). Further experiments revealed that this "low potency" isomer results from an epimerization of the isoleucine unit bound to the thiazoline moiety, proposedly via an enamine intermediate bearing an exocyclic double bond.[84,85]

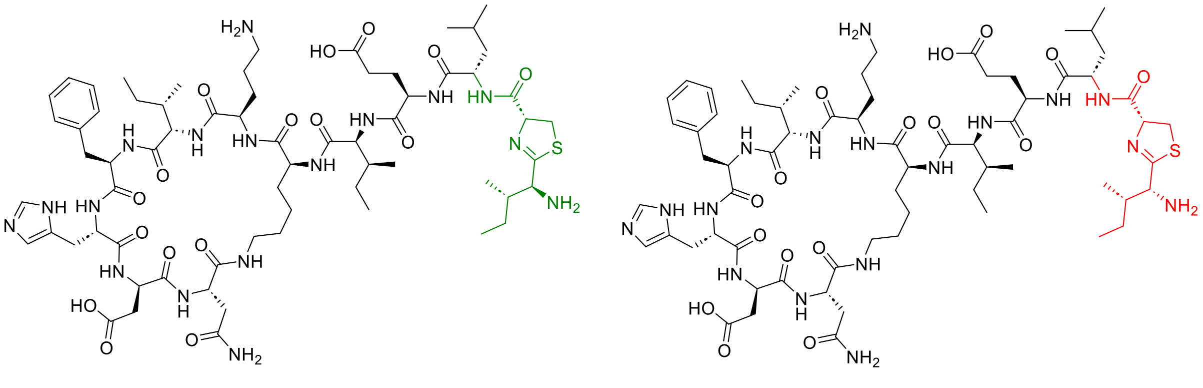
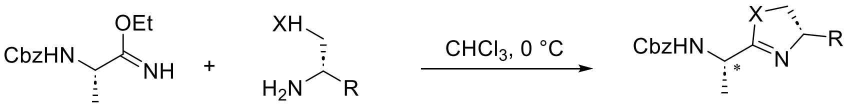

bacitracin A (high potency) **epi-bacitracin A** (low potency)

Figure 4: Bacitracin A and the low potency epimer.

After Shiba and co-workers started synthetic studies on bacitracin with a focus on the epimerization at the C-2 exomethine position, they decided to analyze the kinetics of the racemization on model peptides containing either thiazoline, oxazoline, or imidazoline units.[88,89] The model peptides **DV** were prepared from iminoether **DT**, and, with the exception of **DV$_3$**, already epimerized at the labile alanine stereocenter (Scheme 33). Measuring the racemization of **DV$_1$**, **DV$_3$**, and **DV$_4$** in a 0.5 M methanol solution and comparing it to the deuterium exchange rate in methanol-d$_4$ at 0.5 M showed similar conversion rates and first-order reaction kinetics. Due to this behavior, the deuterium exchange was used to determine the racemization rate of the model peptides under various conditions. The experiments showed a strong dependence on the temperature with a racemization half-life ($t_{1/2}$) of 1000 h at 10 °C to 5 h at 50 °C for model peptide **DV$_1$**.

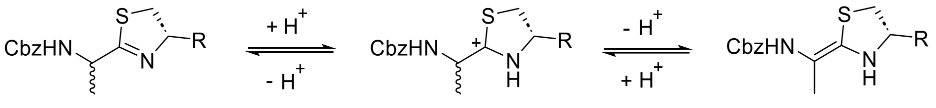


DT **DU**

DV$_1$ (X=S, R=H, 64% yield, er 84:16)
DV$_2$ (X=S, R=COOMe, 69% yield, dr 1:1)
DV$_3$ (X=O, R=COOMe, 76% yield, dr 98:2)
DV$_4$ (X=N, R=H, 41% yield, er 78:22)

Scheme 33: Synthesis of the model peptides for studying their racemization kinetics by Shiba *et al.*

In general, a high dependency on the type of heteroatom was observed: imidazoline **DV$_4$** showed the fastest racemization rate, and oxazoline **DV$_3$** the slowest ($t_{1/2}$: **DV$_4$** > **DV$_2$** > **DV$_1$** > **DV$_3$**). Furthermore, the reaction rate was 40 times faster in methanol compared to chloroform, which shows the need for a protic solvent. Triethylamine as an additive did not influence the $t_{1/2,}$ while the addition of 0.5 eq. acetic acid drastically catalyzed the racemization. With increasing amounts of acetic acid, the reaction slowed down, and no racemization was observed in strongly acidic media (MeOH:HCl_{conc} 1:1). According to these observations, the Shiba group proposed a mechanism for the racemization, with the rate-determining step being the deprotonation from cation **DX** to enamine **DY** (Scheme 34).

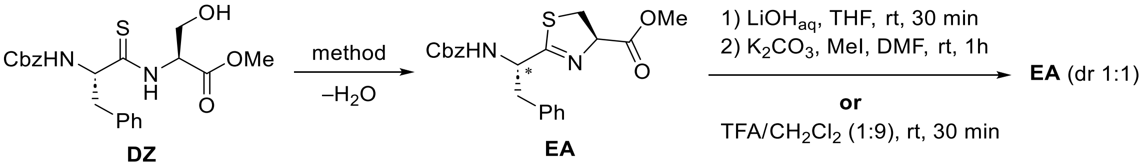


DW **DX** **DY**

Scheme 34: Proposed mechanism for the racemization of thiazolines via an enamine intermediate.

In 1994, Wipf and Fritch reported studies on the epimerization of a C-2 exomethine position during cyclodehydrations in the context of their total synthesis of lissoclinamide 7.[90] Different conditions were screened for the cyclodehydration of thionated dipeptide **DZ** (Table 8); in entries 1 and 2, the elevated temperature and harsh acidic/basic conditions led to full racemization of the labile stereocenter. The high electrophilicity of the alcohol after activation by PPh_3/DIAD allowed a short reaction time at low temperatures, resulting in a good yield of 80% and a dr of 78:22 (entry 3). The Mitsunobu conditions improved yield and dr significantly, but a diastereomeric ratio of 78:22 was still unusable for applications in total synthesis.

Table 8: Epimerization in a thioamide cyclodehydration protocol by Wipf and Fritch.

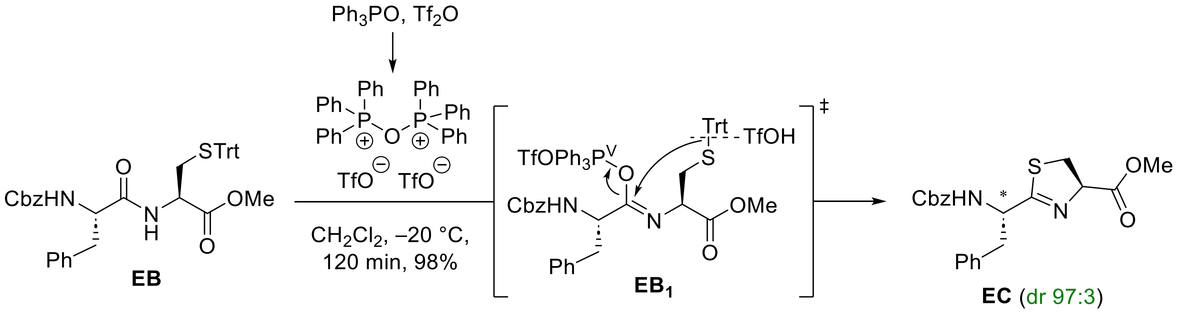


DZ **EA**

entry	method	yield EA	dr
1	TsCl, Et_3N, CH_2Cl_2, 42 °C, 1 h	40%	1:1
2	1) $SOCl_2$, 0 °C, 2 h 2) Pyridine, THF, 0 °C, 15 min	49%	1:1
3	Ph_3P, DIAD, CH_2Cl_2, -78 °C to rt, 30 min	80%	78:22
4	Burgess-reagent, THF, 65 °C, 10 min	96%	>97:3

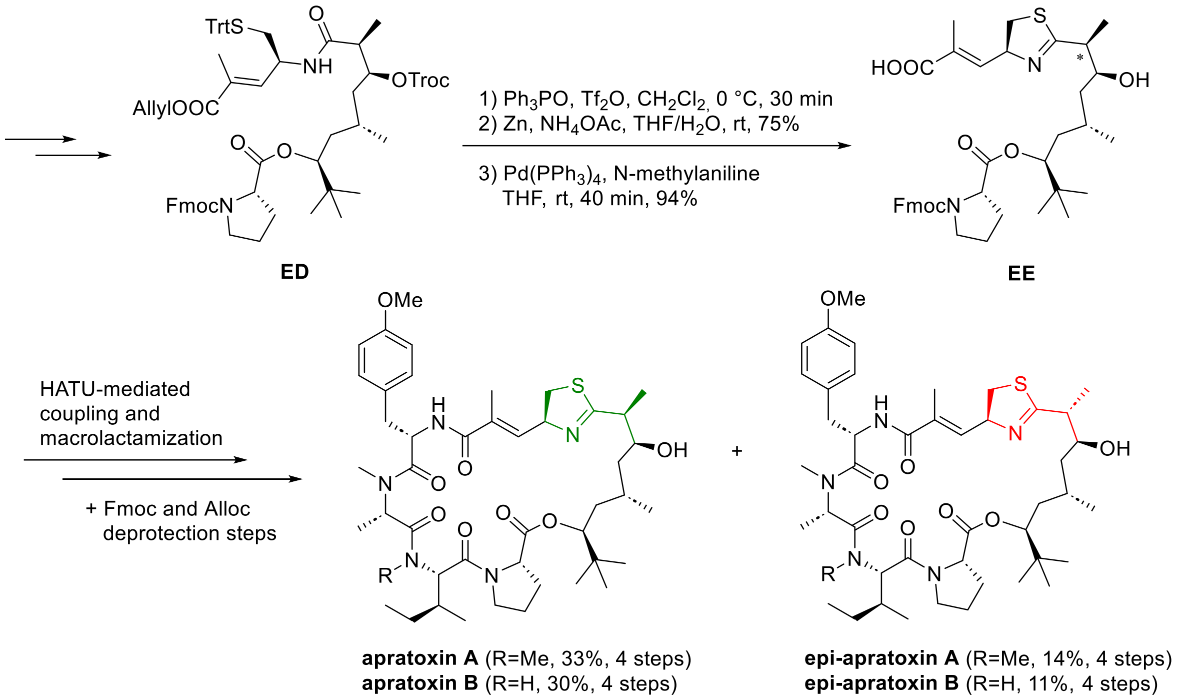
The Burgess reagent, which has successfully been used for the synthesis of enantiomerically pure oxazolines,[91] afforded the desired product **EA** in 96% yield and very high diastereomeric ratios above 97:3. Wipf and Fritch also showcased the lability of the stereocenter by reisolation of the fully racemized starting material **EA** after saponification and subsequent methylation under basic conditions or exposure to 10% TFA in CH_2Cl_2 for 30 minutes at room temperature. Due to the regular use of acid and base treatments in peptide chemistry, substantial stereochemical hazards may occur during the synthesis of thiazoline-containing products.[90]

The high abundance of thiazolines in peptide natural products led to an increasing need for low-racemization protocols for their total synthesis. Kelly *et al.* improved their above-described $TiCl_4$-mediated cyclodehydration using a phosphorous-(V)-species for the *S*-trityl deprotection and subsequent cyclodehydration.[92] Several phosphonium salts and phosphoranes were tested, but only the use of Ph_3PO/Tf_2O resulted in the formation of the desired thiazoline **EC** (Scheme 35). X-ray crystal structure analysis revealed the suspected *O*-bridged bis-phosphonium salt as the sole species formed in a solution of Ph_3PO and Tf_2O. The phosphorous(V)-species activates the amide bond, and the deprotected thiol cyclizes with concomitant cleavage of Ph_3PO via the proposed intermediate **EB₁**. The transformation showed a remarkably high yield and stereoretention at the C-2 exomethine position. The authors replaced the phenylalanine residue with other amino acids (alanine, valine, and leucine) under otherwise identical conditions, with alanine showing the lowest yield of 84% and the lowest dr of 91:9.



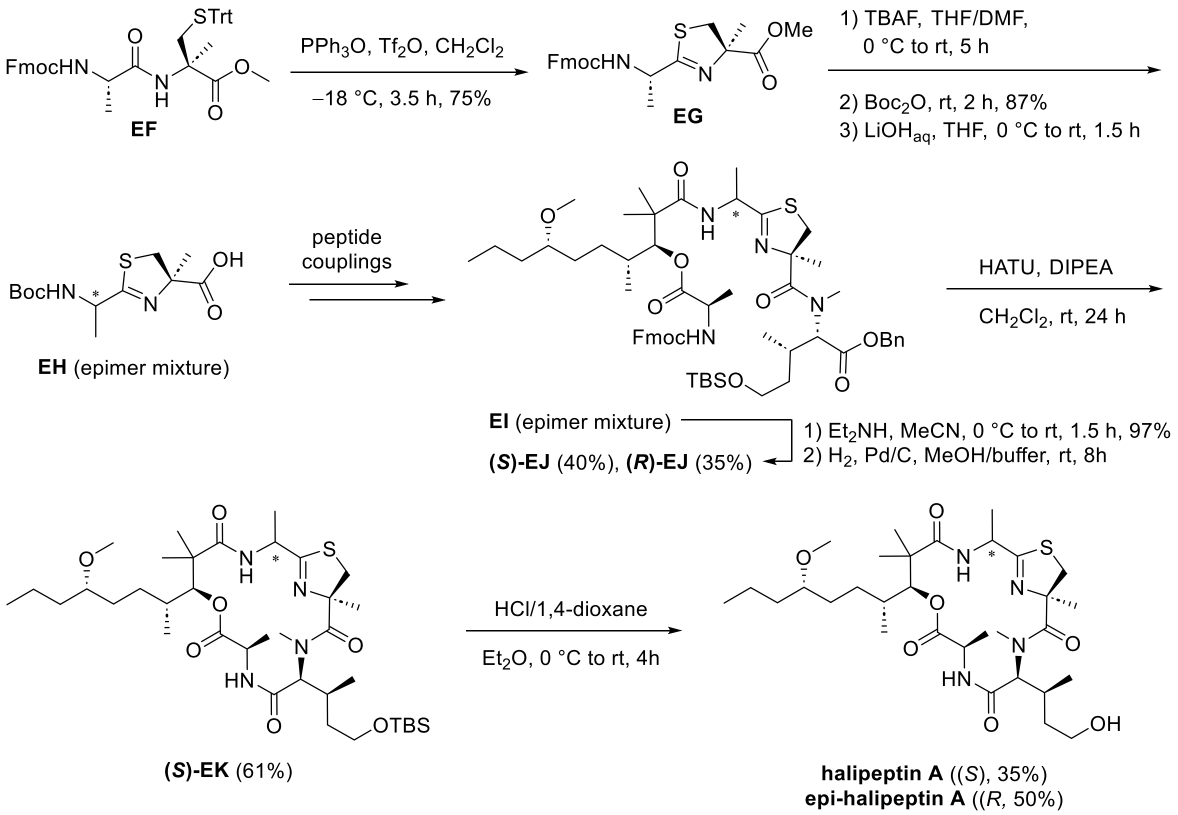
Scheme 35: Cyclodehydration protocol with an in-situ generated phosphorous-(V)-species by Kelly *et al.*[92]

Due to its stereoretentive nature and the high yields obtained with this protocol, it was used in the total syntheses of several natural products. Among these were thiazoline-containing natural products such as (+)-largazole[93], the apratoxins[94–97], and halipeptin A[98], as well as thiazole-containing compounds such as tubulysin A[99] and dendroamide A.[100] In the total synthesis of apratoxin A and B by our group, the thiazoline formation with PPh_3O/Tf_2O followed by Troc- and Alloc-deprotection of the precursor **ED** afforded thiazoline-containing building block **EE** in 71% yield over 3 steps (Scheme 36).[96] During the further transformations, including a HATU-mediated coupling and macrolactamization as well as Fmoc and Alloc deprotection steps, a decline in the diastereomeric purities was observed, which in the end led to apratoxin A and B, as well as their C-2 exomethine epimers epi-apratoxin A and B in around 30% and 12% yield, respectively.



Scheme 36: Total synthesis of apratoxin A and B by Kazmaier and Andler using Kelly's phosphorous-(V)-approach.

Similar problems were reported by Doi *et al.* during their SPPS-based total synthesis of apratoxin A, where supposedly an Fmoc-deprotection step (using a 20% piperidine solution in DMF) after the coupling step with thiazoline building block **EE** resulted in an epimerization of 15%.[97] They also reported an attempted late-stage thiazoline formation using Kelly's protocol, which resulted in a complex mixture where only 10% of the desired apratoxin A was isolated, most likely due to unwanted side reactions with the other amides.

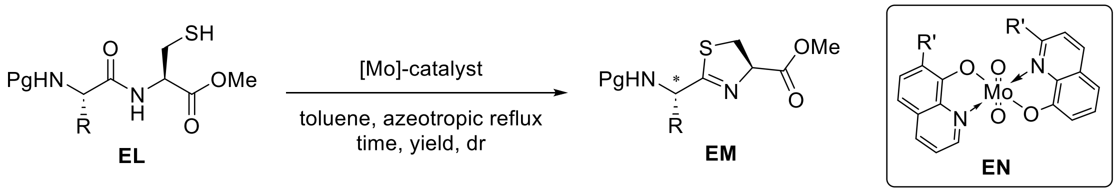


Scheme 37: Total synthesis of halipeptin A by Hamada *et al.*

In 2005, Hamada and co-workers reported a synthesis of the cyclic depsipeptide halipeptin A.[98] In an early stage, they employed cyclodehydration with PPh_3O/Tf_2O to form methylthiazoline **EG** in 75% yield without significant epimerization (Scheme 37). After the subsequent protecting group manipulations, a severe epimerization at the C-2 exomethine position was observed. The authors traced this loss in stereochemical purity back to the saponification step. A sequence of peptide couplings afforded depsipeptide **EI**, still as a mixture of epimers. After cleavage of the Fmoc group and the benzyl ester, the epimer mixture was successfully separated to give **(*S*)-EJ** and **(*R*)-EJ** in 40% and 35% yield, respectively. A HATU-mediated macrolactamization afforded protected halipeptin A **(*S*)-EK** in 61% yield. During the final deprotection with HCl in 1,4-dioxane, the Hamada group reported another extensive epimerization, which led to halipeptin A in 35% yield and its epimer epi-halipeptin A in 50% yield.

Another stereoretentive cyclodehydration protocol via molybdenum catalysis was developed by Ishihara and co-workers (Table 9).[101,102] First, the authors tested different molybdenum oxides in toluene under reflux to transform Ala-Cys dipeptide **EL** into the corresponding thiazoline **EM** (entries 1 to 3). This resulted in molybdenum diacetylacetonate (acac) dioxide as the best catalyst, with a yield of 85% and 18% epimerization of the C-2 exomethine position. Two years later, they significantly improved their protocol using molybdenum catalysts **EN** that contain quinolinols as ligands (entries 4 to 7). The simplest quinolinol (R' = H, entry 4) already led to a drastic improvement in the avoidance of epimerization (dr 96:4). The use of methyl and ethyl residues on the quinolinol ligands allowed a shorter reaction time and lower catalyst loading of 1 mol%, while also increasing the yields (entries 5 and 6).

Table 9: Molybdenum-catalyzed cyclodehydration protocol by Ishihara *et al.*



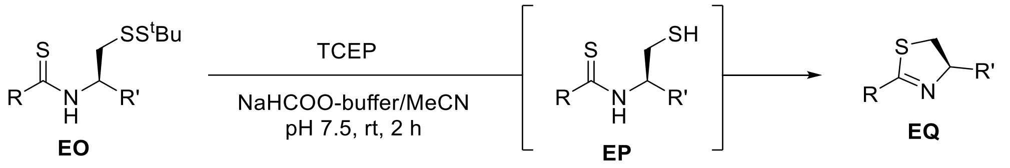
entry	[Mo]-catalyst	time	R	PG	yield	dr	ref.
1	10 mol% MoO_2	8 h	Me	Cbz	6%	---[a]	[101]
2	10 mol% $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$	8 h	Me	Cbz	16%	---[a]	[101]
3	10 mol% $MoO_2(acac)_2$	8 h	Me	Cbz	85%	82:18	[101]
4	10 mol% **EN** (R'=H)	5 h	Me	Cbz	80%	96:4	[102]
5	1 mol% **EN** (R'=Me)	5 h	Me	Cbz	93%	95:5	[102]
6	1 mol% **EN** (R'=Et)	2 h	Me	Cbz	96%	97:3	[102]
7	1 mol% **EN** (R'=Et)	1 h	Bn	Cbz	85%	98:2	[102]
8	1 mol% **EN** (R'=Et)	1 h	Me	Boc	82%	94:6	[102]
9	1 mol% **EN** (R'=Et)	1 h	Me	Fmoc	92%	96:4	[102]

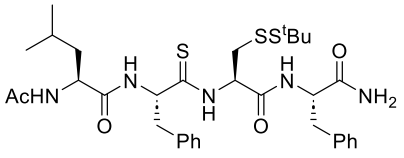
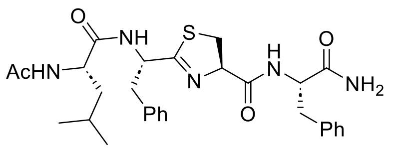
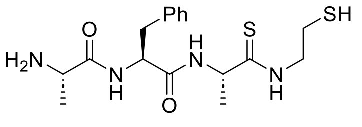
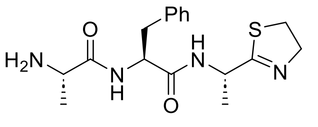
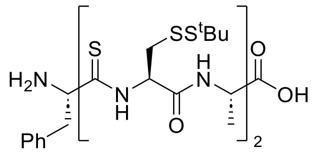
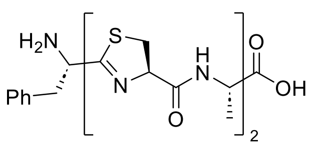
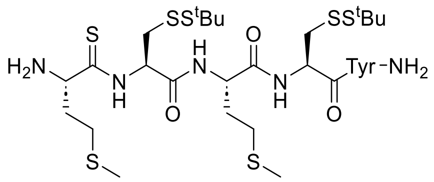
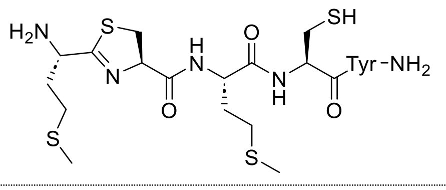
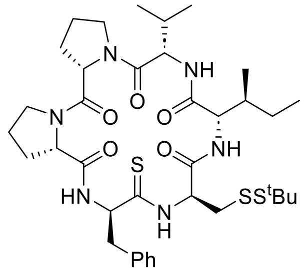
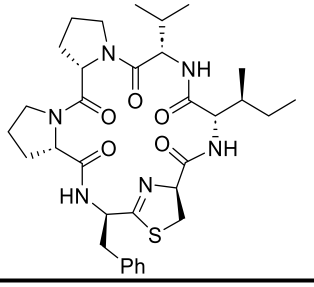
a) diastereomeric ratio not determined.

Further experiments with a Phe-Cys dipeptide (entry 7) and different common amine-protecting groups (entries 8 and 9) showed similar yields and diastereoselectivities, rendering this protocol interesting for stereoretentive thiazoline formations in peptides. Applications of Ishihara's protocol were demonstrated during the synthesis of the thiazoline containing Cbz-(*S*)-dolaphenine[103] and thiazole containing natural products: micrococcin P1[104], thiocillin I[104] and thuggacin B[105].

Earlier this year, the Schutkowski group reported a novel cyclodesulfhydration to form thiazolines in complex peptides without epimerization (Table 10).[106] In peptides **EO** containing a thioamide and a thiol protected as disulfide, the disulfide is reduced with tris(2-carboxyethyl)phosphine (TCEP) in a sodium formate or ammonium formate buffer at pH 7.5. Under these conditions, the thiol immediately cyclizes after deprotection, forming thiazoline **EQ** and releasing H_2S.

Table 10: Substrate scope for the cyclodesulfhydration by Schutkowski *et al*.



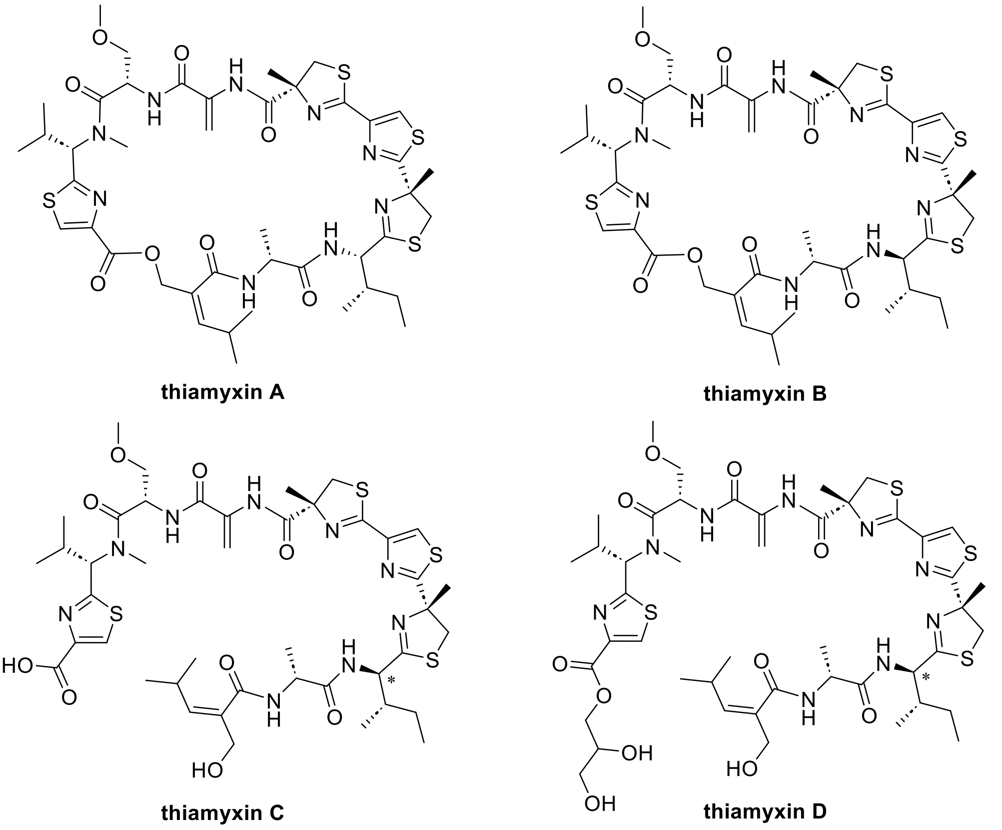
entry	starting peptide EO	product EQ	yield[a]
1			99%
2			95%
3			97%
4			97%
5[b]			94% (34%)[c]

a) Yield determined by HPLC. b) 7.5 eq. TCEP in NaHCOO-buffer/MeCN at 40 °C for 3 h. c) Isolated yield after preparative HPLC based on the resin for the full SPPS-sequence, macrolactamization, and thiazoline formation.

The procedure could also be split into two steps using TCEP without any buffer (pH 3), leading to deprotected thiol **EP** without cyclization. Exposing this thioamide-containing thiol to sodium carbonate (pH 7 – 8) then afforded thiazoline **EQ**. The authors tested a broad range of complex peptides synthesized by SPPS; a selection of those is displayed in Table 10. In the first entry, they observed a remarkably low epimerization of 0.5 % and 99% yield after a reaction time of two hours. A terminal thiazoline formation of a 1,2-aminothiol residue (entry 2) was as successful as the formation of multiple thiazolines on the starting peptide (entry 3). The Schutkowski group displayed the chemoselectivity of their protocol using a peptide bearing two protected cysteines but only one thioamide. In this case, only the cysteine unit adjacent to the thioamide formed a thiazoline (entry 4). The authors furthermore showed the applicability of their method to the total synthesis of mollamide F (entry 5). In this example, the thiazoline formation required an increased amount of TCEP and a slightly elevated temperature (40 °C) to proceed. The reported yields for this step were 94%, as determined by HPLC, and 34% after isolation via preparative HPLC for the entire sequence of SPPS, macrolactamization, and thiazoline formation.

2.4 Thiamyxins

Recently, the Müller group isolated a new group of thiazoline and thiazole containing natural products from a myxobacterial strain of the *Myxococcaceae* family found in a soil sample collected at Saarland University (Figure 5).[107] The structure of the cyclodepsipeptides thiamyxin A and B was elucidated using HRMS and MS^2 fragmentation as well as one- and two-dimensional NMR-spectroscopy. Marfey's analysis, assisted by the results of the *in silico* analysis of the biosynthetic gene cluster (BGC), was used to determine the stereochemical configuration of the amino acids. The configuration of the methylthiazolines was elucidated by comparison of the hydrolysis products of thiamyxin and thiangazole, another methylthiazoline-containing natural product whose stereochemistry has been analytically and synthetically confirmed.[62,108,109] They observed an unpreventable epimerization of the C-2 exomethine position during hydrolysis, obstructing the stereochemical assignment of the isoleucine moiety. The configurational assignment of D-*allo*-isoleucine for thiamyxin B and L-isoleucine for thiamyxin A was based on the ^{1}H-NMR chemical shifts and coupling constant differences of isoleucine and *allo*-isoleucine. This result was encouraged by the presence of an epimerization domain in the isoleucine incorporating module and the high prevalence of L-isoleucine in natural products. In addition to these cyclic depsipeptides, two open-chain variants, namely the seco acid thiamyxin C and the glycerol ester thiamyxin D, were isolated. Both were described as an inseparable diastereomeric mixture with the corresponding isoleucine-epimer in a ratio of 2:1.



thiamyxin A

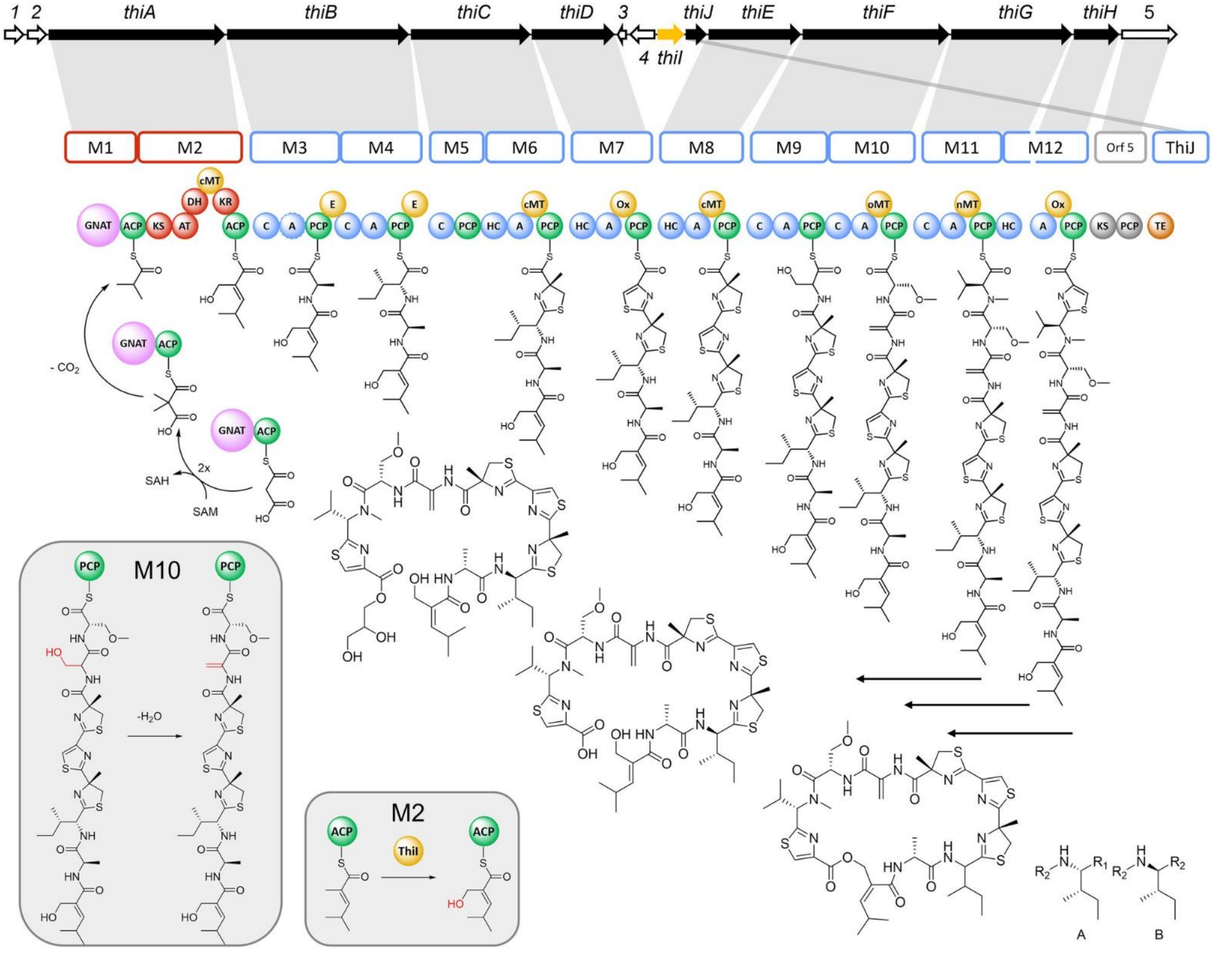
thiamyxin B

thiamyxin C

thiamyxin D

Figure 5: Thiamyxins A-D isolated from a myxobacterial strain from the *Myxococcaceae* family.

A genome mining approach using AntiSMASH[110,111] revealed a PKS-NRPS hybrid gene cluster consisting of ten NRPS and two PKS modules encoded on a total of nine genes. The authors proposed a biosynthesis model based on isotope-labeled feeding experiments and *in silico* analysis of the BGC (Scheme 38). A GNAT-domain initiates the assembly line with the uncommon formal starter unit isobutyryl-CoA generated from dimethylmalonyl-ACP in module 1. After extension with one malonyl unit by module 2 and subsequent methylation (cMT domain), a CYP450-mediated hydroxylation of the inserted methyl group finishes the PKS part. The first two NRPS modules, 3 and 4, are the alanine and isoleucine incorporating modules. Both contain epimerization domains, ultimately leading to a chain elongation with D-alanine and D-*allo*-isoleucine. Modules 6 to 8 contain heterocyclization domains responsible for the incorporation of cysteine and its subsequent cyclization to the thiazoline units. In the case of modules 6 and 8, a cMT domain methylates the thiazolines, while module 7 contains an oxidation domain to form the thiazole. After the elongation of the nascent molecule with this methylthiazoline-thiazole-methylthiazoline unit, modules 9 and 10 each incorporate a serine unit. The C-domain in module 10 dehydrates the previously introduced serine, and an oMT domain enables the *O*-methylation of the second serine.



Scheme 38: NRPS-PKS-hybrid gene cluster responsible for the biosynthesis of the thiamyxins.[107] Modules: polyketide-synthase (PKS) in red, nonribosomal peptide-synthetase (NRPS) in blue. Domains: methyl transferase (MT), epimerization (E), oxidation (Ox), heterocyclization (HC), acyl carrier protein (ACP), peptidyl carrier protein (PCP), GCN5-related *N*-acyltransferase-like decarboxylase (GNAT), ketosynthase (KS), acyltransferase (AT), dehydratase (DH), ketoreductase (KR), condensation (C), adenylation (A), thioesterase (TE).

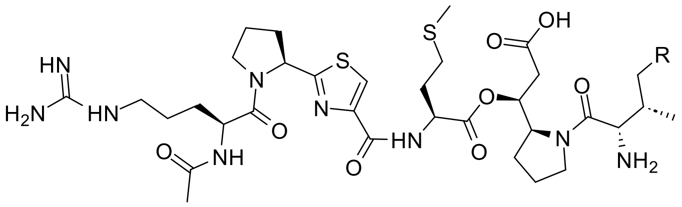
Module 11 includes a valine with a subsequent *N*-methylation by an nMT domain. After the addition of another thiazole by module 12 (analogous to module 7), a type 1 TE domain encoded on *thiJ* releases the linear precursor from the assembly line via macrolactonization affording the final thiamyxin B. Thiamyxin D is presumably a shunt product resulting from an esterification with glycerol catalyzed by the TE domain. An analogous release of the linear precursor with H_2O as a substrate or simple hydrolysis during the isolation and purification are mentioned as possible origins for the open chain product thiamyxin C.

The authors investigated the biological activity of the thiamyxins, especially thiamyxin B and C, due to their higher production rates of 0.6 mg/L and 1.4 mg/L, respectively. The cyclic thiamyxins A and B showed similar low micromolar activities against the human pathogenic corona virus hCoV-229E (IC_{50} = 2.4 – 2.5 µM). The non-cyclic thiamyxins C and D were much less active with IC_{50}-values above the highest tested concentrations of 20 µM. Assays against Dengue- and Zika-virus revealed even higher antiviral activities for thiamyxin B with IC_{50}-values of 560 nM and 1.07 µM, respectively. Due to the more than 5-fold lower cytotoxic activity (CC_{50}) compared to the IC_{50}, the Müller group reported a possible application window against the human pathogenic corona virus and a distinguished mode of action for the antiviral activity.

3. Aim of this Work

3.1 Pseudotetraivprolids

The first target structures of this PhD thesis were pseudotetraivprolid B and D, isolated from *Pseudomonas entomophila* by the Bode group at the Max Planck Institute for Terrestrial Microbiology (MPI) Marburg.[*] These linear depsipeptides differ in the *N*-terminal amino acid, being an isoleucine or a valine (Figure 6). To obtain sufficient amounts for biological testing and investigations of the biosynthetic pathway a synthetic route towards both natural products was devised.



pseudotetraivprolid D (R = H)
pseudotetraivprolid B (R = Me)

Figure 6: Pseudotetraivprolid B and D isolated from *Pseudomonas entomophila*.

3.2 Socein-Derivatives

Socein is a secondary metabolite from a myxobacterium of the *Sorangium cellulosum species* and was isolated and structurally elucidated in 1990 at the HZI Braunschweig (Figure 7).[**] The overall structure matches microsclerodermin M, which was isolated in 2014, with the only difference being the polyhydroxylated side chain (red).[13] The typical stereochemistry of the microsclerodermin family and the remarkable mutuality with microsclerodermin M led to the adaption of this stereochemistry for socein. It is the first structure proposed to contain a cyclized version of the polyhydroxylated β-amino acid (blue). Due to the unknown cyclization mechanism, the configuration of the two involved stereocenters is still unknown.

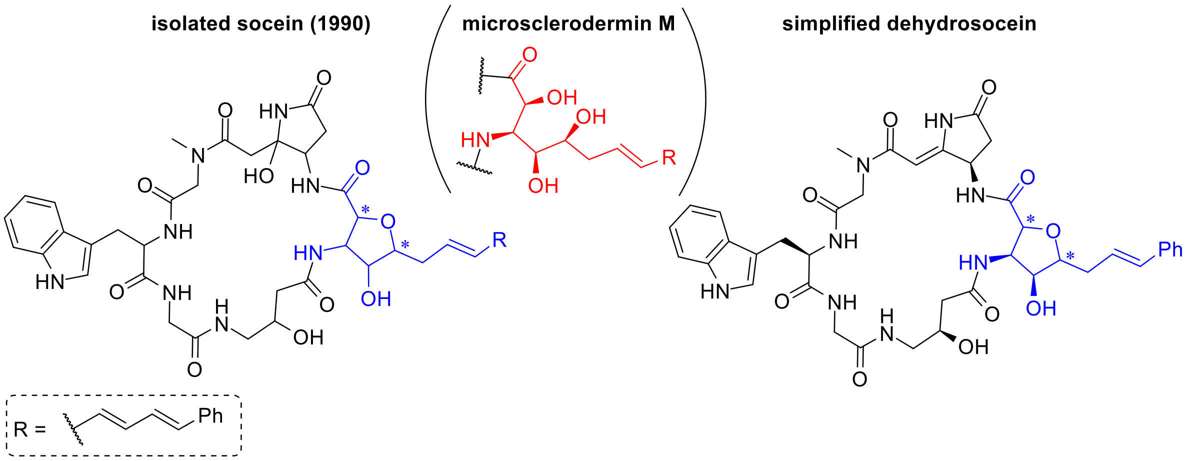


Figure 7: Isolated socein and the simplified dehydrosocein target structures.

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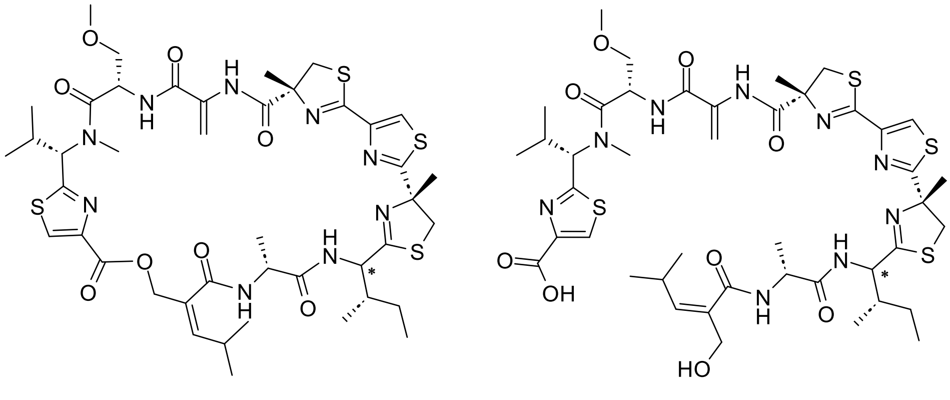
[*] Y. Shi 2023, personal communication, 01 August. [**] A. Voltz 2023, personal communication, 08 August.

The aim of this work was the synthesis of the four possible diastereomers of a simplified dehydrosocein to assist the elucidation of the stereochemistry and the biosynthetic pathway of the 5-ring formation by the Müller group at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS). Before focusing on the challenging triene phenyl residue, the introduction of a smaller side chain, like in microsclerodermin C, D, and L, was envisioned.[11,13] This hopefully preserves the observed antifungal activity while working on the elucidation of the unknown stereocenters. Due to the lack of spectral data, the Müller group is currently reisolating the natural product for comparison via NMR spectroscopy. Dehydration of the hemiaminal in the isolated compounds is standard practice[10–13] and leads to dehydrosocein, allowing an NMR comparison with the four diastereomeric target structures of this work.

3.3 Thiamyxins

A total synthesis for the thiamyxins A-C (Figure 8), recently isolated from a myxobacterial strain from the *Myxococcaceae* family (MCy9487), would allow for testing against a broader panel of human pathogenic viruses. Furthermore, this would enable studying the structure-activity relationship and pharmacokinetic properties of this class of natural products.[107] Thus, the development of a synthetic protocol to access the thiamyxin family in diastereomerically pure form was the key goal of this work. The synthesis of *epi*-thiamyxin C, now called thiamyxin E,[112] which was only observed as the minor diastereomer in the mixture of thiamyxin C,[107] in high diastereomeric purity would give additional data for the influence of the absolute stereochemistry at the α-isoleucine center on the biological activity.



(*S*)- thiamyxin A
(*R*)- thiamyxin B

(*R*)- thiamyxin C
(*S*)- thiamyxin E

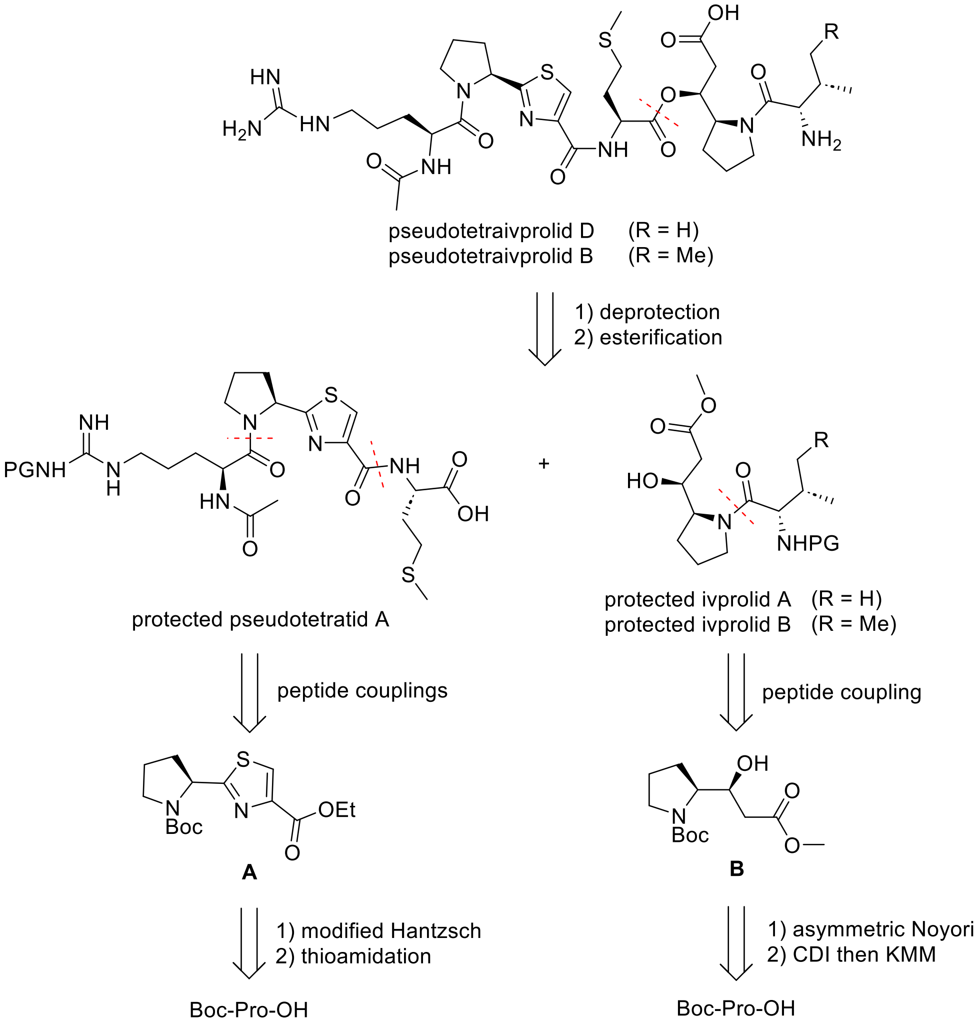
Figure 8: Thiamyxin A-C and thiamyxin E isolated from the myxobacterial strain MCy9487.

4. Results and Discussion

4.1 Pseudotetraivprolids

4.1.1 Retrosynthetic Analysis

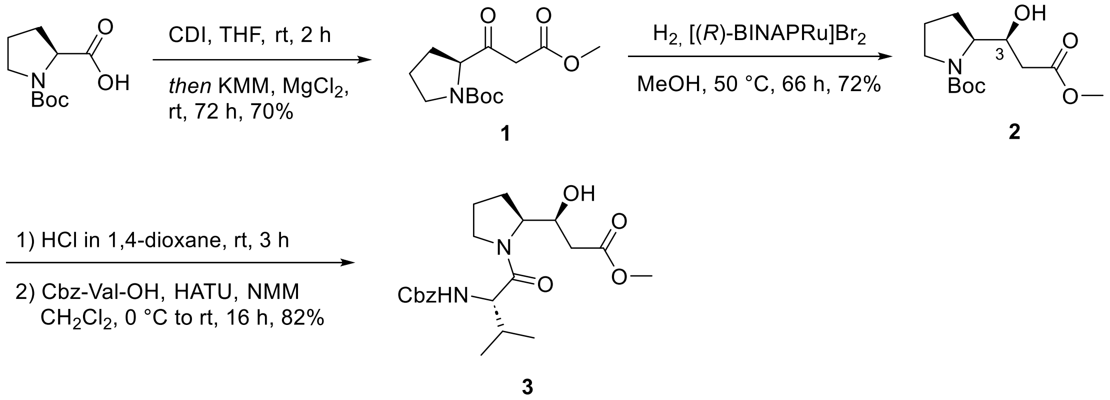
The synthesis of the pseudotetraivprolid B and D was planned via late-stage esterification of protected pseudotetratid and ivprolid (Scheme 39). This route would encompass for the synthesis of the smaller natural products by simple deprotection and, therefore, allow for the best derivatization for the three groups of natural products. The protected ivprolid can be further simplified using standard peptide couplings to the β-hydroxy ester **B**. This chiral hydroxy ester is accessible by asymmetric catalytic hydrogenation of the corresponding β-keto ester, which can be prepared from Boc-proline via a known literature procedure.[113] Disconnection of the protected pseudotetratid by another set of peptide couplings resulted in acetylated L-arginine, thiazole **A**, and L-methionine. Installation of a thioamide and a modified Hantzsch procedure affords thiazole **A** starting from Boc-L-proline.[114]



Scheme 39: Retrosynthetic analysis of pseudotetraivprolid B and D.

4.1.2 Total Synthesis of Pseudotetraivprolid B and D

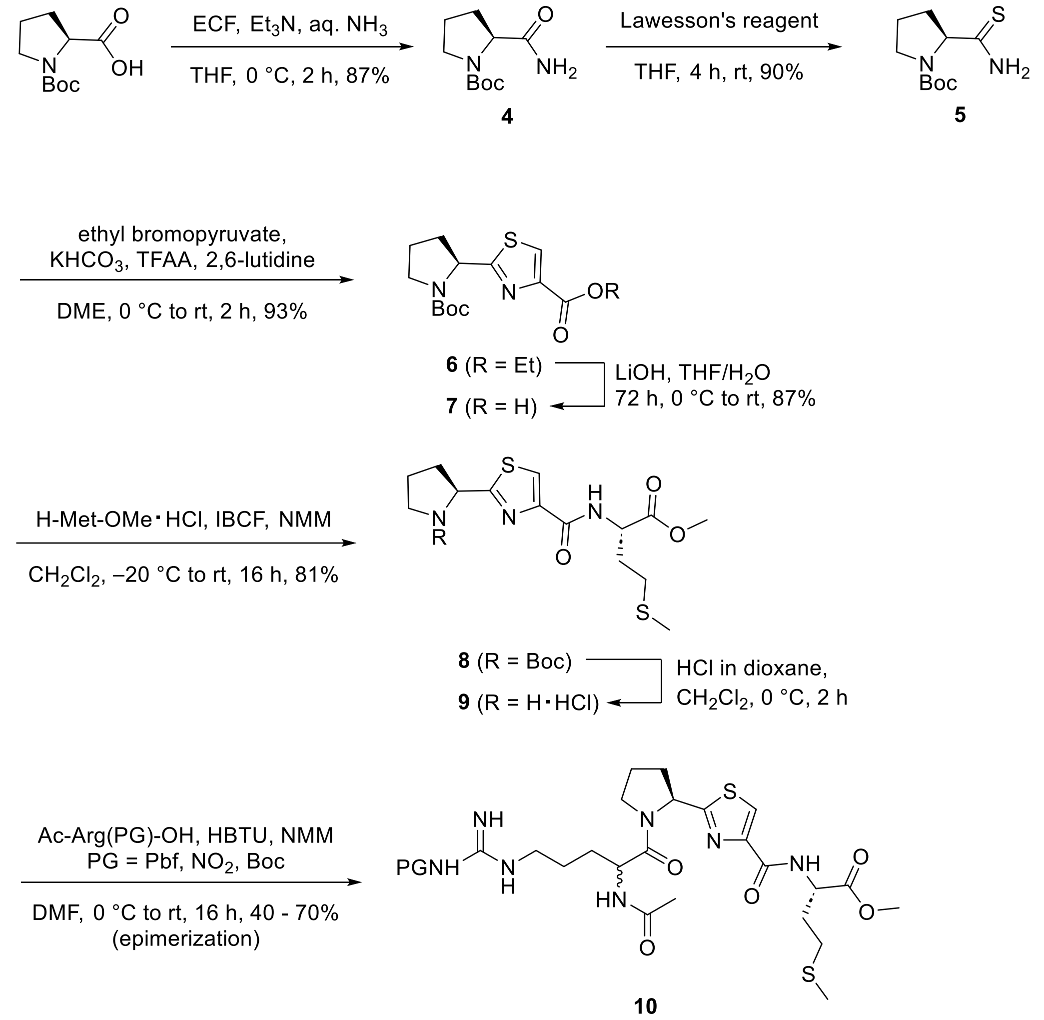
The total synthesis was started with the ivprolid A building block. Activation of Boc-L-proline with *N*,*N'*-carbonyldiimidazole (CDI) followed by reaction with potassium methyl malonate (KMM) gave β-keto ester **1** in 70% yield (Scheme 40). Noyori asymmetric hydrogenation[115] with an *in-situ* prepared BINAP-ruthenium bromide afforded the desired hydroxy ester **2** as a single diastereomer. This method was first described by Genêt *et al.*[116,117] and was used for the preparation of **2** by Greck *et al.*[113] The synthesis toward protected ivprolid **3** was finished by HATU-mediated peptide coupling with Cbz-protected L-valine.



Scheme 40: Synthesis of the protected ivprolid 3.

Prior to the above-described route, an aldol-centered approach by Hanson and co-workers[118] gave the hydroxy ester **2** as a mixture of diastereomers (dr 3:2). Since the configuration of the C-3 stereocenter was unknown at the beginning of this project, the preparation of a diastereomeric mixture was an acceptable result. The challenging chromatographic separation and the structural revision of the unassigned C-3 stereocenter by the Bode group made this route obsolete.

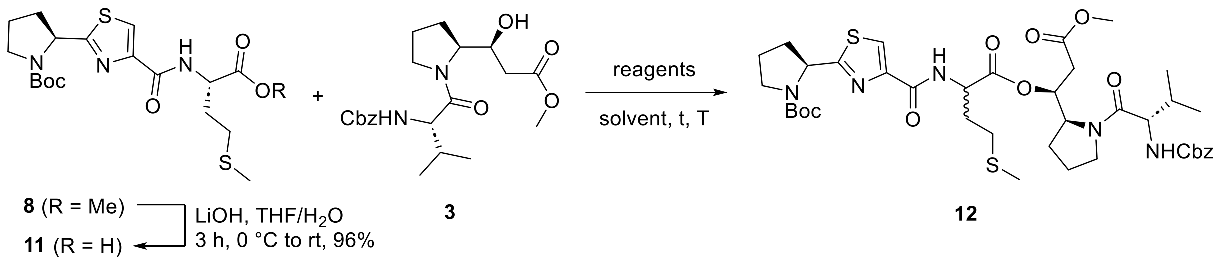
The pseudotetratid synthesis started with the introduction of a primary amide by mixed anhydride activation and quenching with aqueous ammonia (Scheme 41). Thioamidation with the well-known Lawesson's reagent[119] led to Boc-proline thioamide **5** in 90% yield. Reaction of this thioamide and ethyl bromopyruvate in a modified Hantzsch procedure by Meyers and co-workers[120] resulted in the thiazole **6** in excellent yield. After saponification of the ethyl ester with lithium hydroxide, the carboxylic acid was coupled via IBCF activation with L-methionine methyl ester. The resulting dipeptide **8** was Boc-deprotected with HCl in 1,4-dioxane and coupled with different protected acetylated arginines. In all cases, only moderate yields were obtained, but more importantly, the coupling suffered from severe epimerization, most likely due to azlactone formation, a known problem in couplings with acetylated amino acids.[121–125] Overall, the solubility and handling of these highly polar arginine-containing peptides were troublesome, and attempts of esterification with protected ivprolid **3** resulted in no conversion at all. To avoid the encountered problems, the coupling with arginine and its acetylation was planned at the end of the synthesis.



Scheme 41: Synthesis of the pseudotetratid building block 10.

The esterification of the building blocks was tested with dipeptide **11** and protected ivprolid **3** (Table 11). A comparison of entries 1 – 3 shows that Steglich conditions[126] with EDC·HCl gave the best yield with 31%. The Ghosez reagent [127] and the Yamaguchi conditions [128] gave inferior results. All three conditions resulted in significant epimerization of 20 – 30%. Increasing or decreasing the amount of DMAP did not significantly alter the yield or epimerization (entries 4 and 8). Different solvents, another carbodiimide (DCC), and microwaving the reaction did not improve yield and epimerization either (entries 5 – 7). An increased reaction time and the more reactive 4-pyrrolidino pyridine (PPY)[129] could improve the yield slightly but did not tackle the epimerization problem (entries 9 and 10). In the last entry, the use of DMAP·HCl as acylation catalyst was tested to suppress the epimerization under base-free conditions.[130] This final attempt showed no conversion, and the optimization was discontinued.

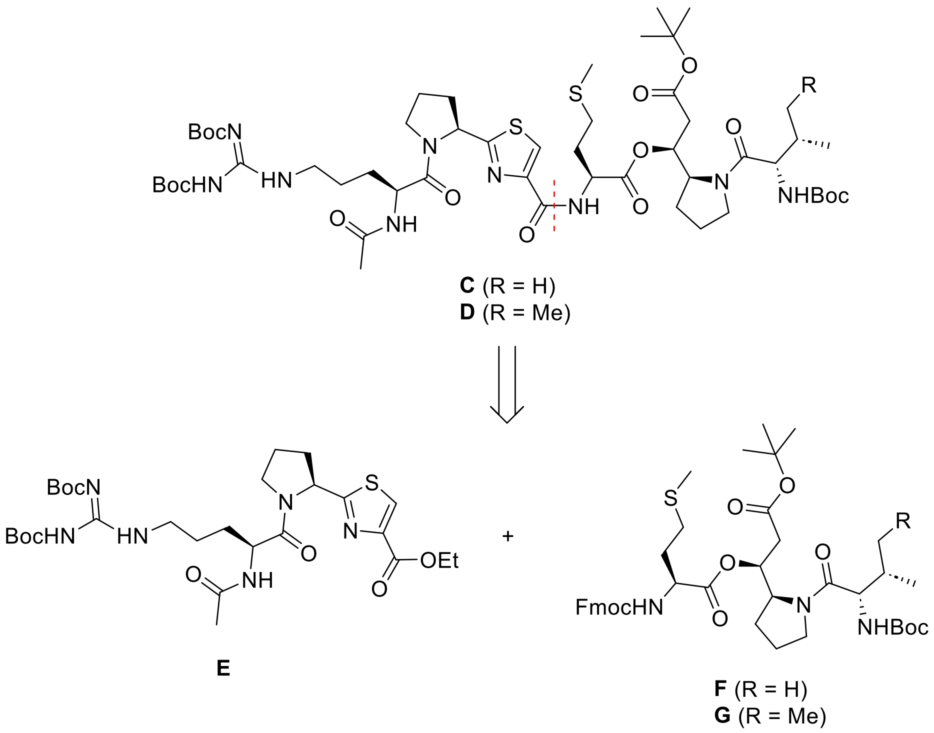
Table 11: Coupling of the building blocks via esterification.



entry	reagents	solvent	T	t	yield
1	1.1 eq. Ghosez-reagent, 2.0 eq. DMAP, 2.0 eq. DIPEA	CH_2Cl_2	0 °C to rt	18 h	12 %
2	1.0 eq. Yamaguchi reagent, 2.0 eq. DMAP, 2.0 eq. Et_3N	toluene	rt	18 h	19 %
3	1.0 eq. EDC·HCl, 2.0 eq. DMAP	CH_2Cl_2	0 °C to rt	18 h	31 %
4	1.0 eq. EDC·HCl, 4.0 eq. DMAP	CH_2Cl_2	0 °C to rt	18 h	28 %
5	1.0 eq. EDC·HCl, 2.0 eq. DMAP	MeCN	50 °C,))) 50 W	1 h	22 %
6	1.0 eq. DCC, 2.0 eq. DMAP	CH_2Cl_2	0 °C to rt	18 h	32 %
7	1.0 eq. DCC, 2.0 eq. DMAP	DMF	0 °C to rt	18 h	---
8	1.0 eq. DCC, 0.2 eq. DMAP	CH_2Cl_2	0 °C to rt	18 h	28 %
9	1.0 eq. DCC, 2.0 eq. DMAP	CH_2Cl_2	0 °C to rt	96 h	42 %
10	1.0 eq. DCC, 2.0 eq. PPY	CH_2Cl_2	0 °C to rt	18 h	37 %
11	1.0 eq. DCC, 0.1 eq. DMAP·HCl	CH_2Cl_2	0 °C to rt	18 h	---

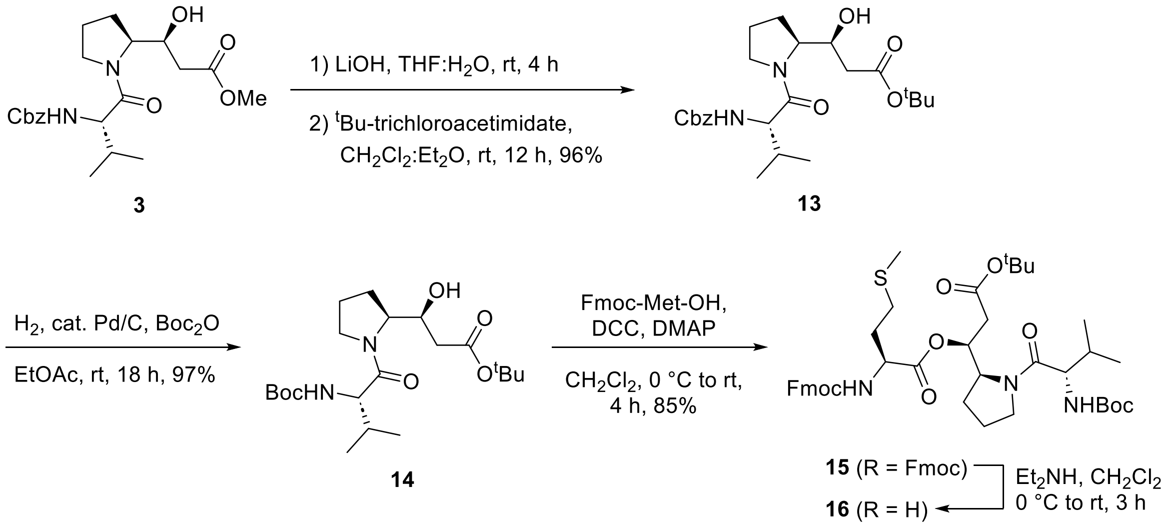
The diastereomeric mixture **12** was used to check the protecting group strategy by performing some deprotections. Boc-deprotection of **12** worked surprisingly well without any elimination at the β-oxy ester position. The saponification of the methyl ester proved impossible with lithium hydroxide due to the fast cleavage of the internal ester. Even the very mild and usually methyl ester selective Me_3SnOH in 1,2-DCE[131] cleaved mainly the internal ester prior to attacking the methyl ester. Catalytic hydrogenation of the benzyl carbamate showed no conversion under various conditions, most likely due to the thioether-induced inhibition of the catalyst.[132]

All these observations led to a new disconnection approach and an acid-labile protecting group strategy (Scheme 42). This alternative disconnection between the thiazole and the methionine moiety should avoid the issue of epimerization by coupling of a carboxylic acid containing a quaternary α-carbon while retaining the flexibility in derivatization and adjustments of a convergent synthesis. The new protecting group strategy relies on bis-Boc protection of the guanidine, a *tert*-butyl ester, and another Boc protection of the *N*-terminal amine.



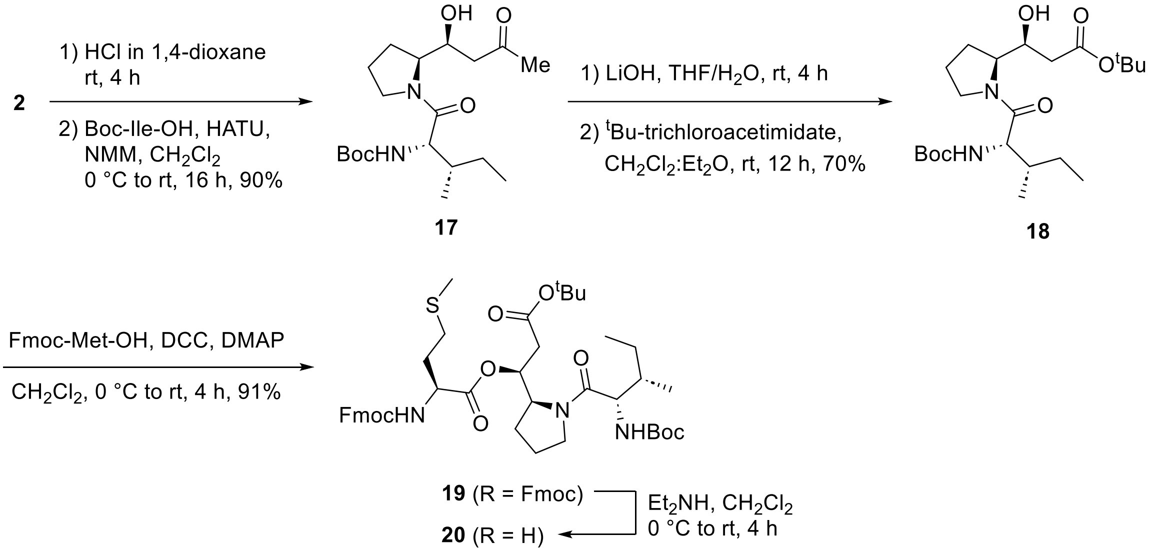
Scheme 42: New protecting group strategy and alternative disconnection approach.

Protecting group manipulations to recycle the protected ivprolid **3** are shown in Scheme 43. The methyl ester was saponified with lithium hydroxide and reprotected by treatment with *tert*-butyl trichloroacetimidate according to a protocol by Hutton and Shabani.[133] Catalytic hydrogenation in the presence of Boc-anhydride afforded protected ivprolid **14** in 93% yield over 3 steps. In the following esterification, a large excess (3.0 eq.) of Fmoc-Met-OH successfully suppressed the epimerization and improved the yield to 85%. Equimolar experiments afforded the desired product in a low yield of 40% and approx. 20% epimerization. An excess of the carboxylic acid **11** in the previously investigated esterification (*cf.* Table 11) most likely would have improved the reaction as well but was out of consideration for economic reasons.



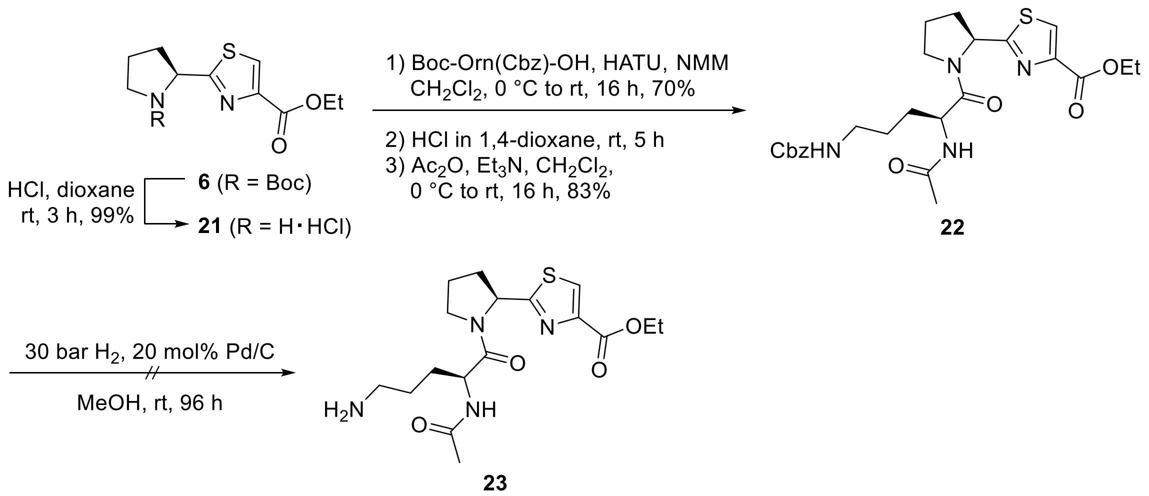
Scheme 43: Protecting group manipulations on ivprolid derivative 3 and esterification with Fmoc-Met-OH.

Similarly, the ivprolid B derived building block **19** was synthesized by coupling of hydroxy ester **2** with Boc-protected isoleucine (Scheme 44). This HATU-mediated coupling yielded protected ivprolid B **17** in 90% yield. In this case, the Boc-protection group was chosen initially to fit the new protecting group strategy. The methyl ester was saponified and reprotected as *tert*-butyl ester with the same conditions used earlier. This hydroxy ester **18** was converted via Steglich esterification with an excess of Fmoc-methionine (3.0 eq.) to obtain the tripeptide **19**.



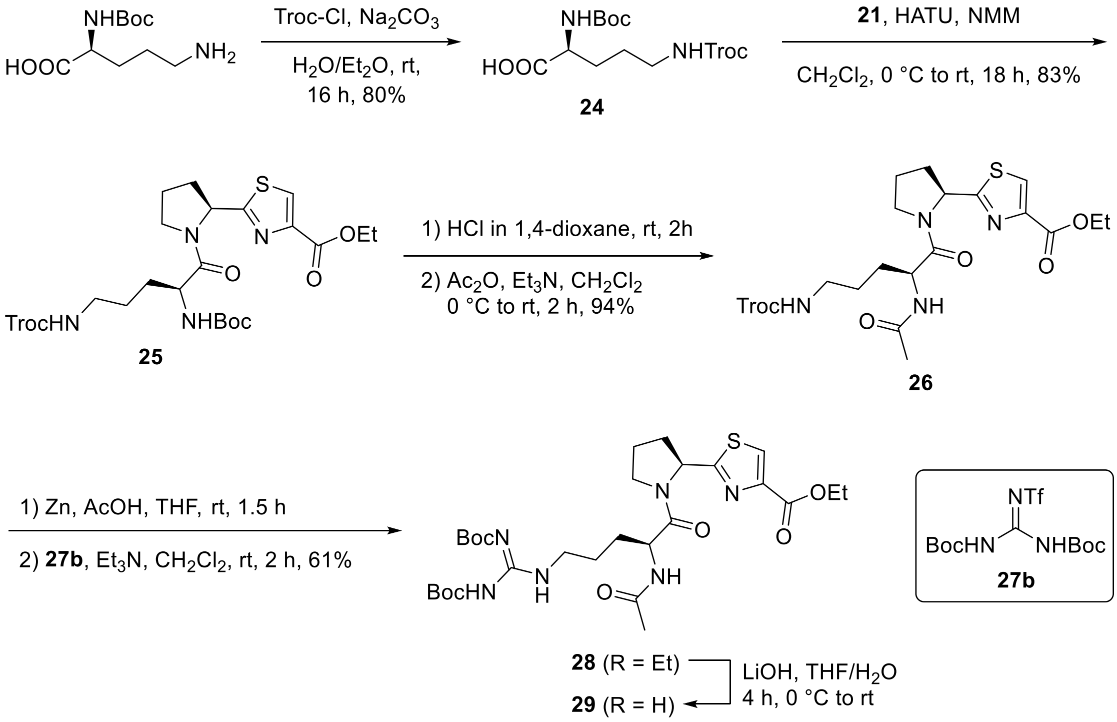
Scheme 44: Synthesis of the isoleucine building block 20.

For the synthesis of the western fragment, ornithine was chosen as an arginine precursor, planning to introduce the bis-protected Boc-guanidine at the end of the sequence. After Boc-deprotection of thiazole **6**, the resulting hydrochloride salt **21** was coupled with Boc-Orn(Cbz)-OH (Scheme 45). A second Boc-deprotection followed by acetylation with acetic anhydride gave the acetylated dipeptide **22** in 83% yield. Once again, catalytic hydrogenation in the presence of the thiazole proved impossible, emphasizing the necessity of a different protecting group in the ornithine side chain.



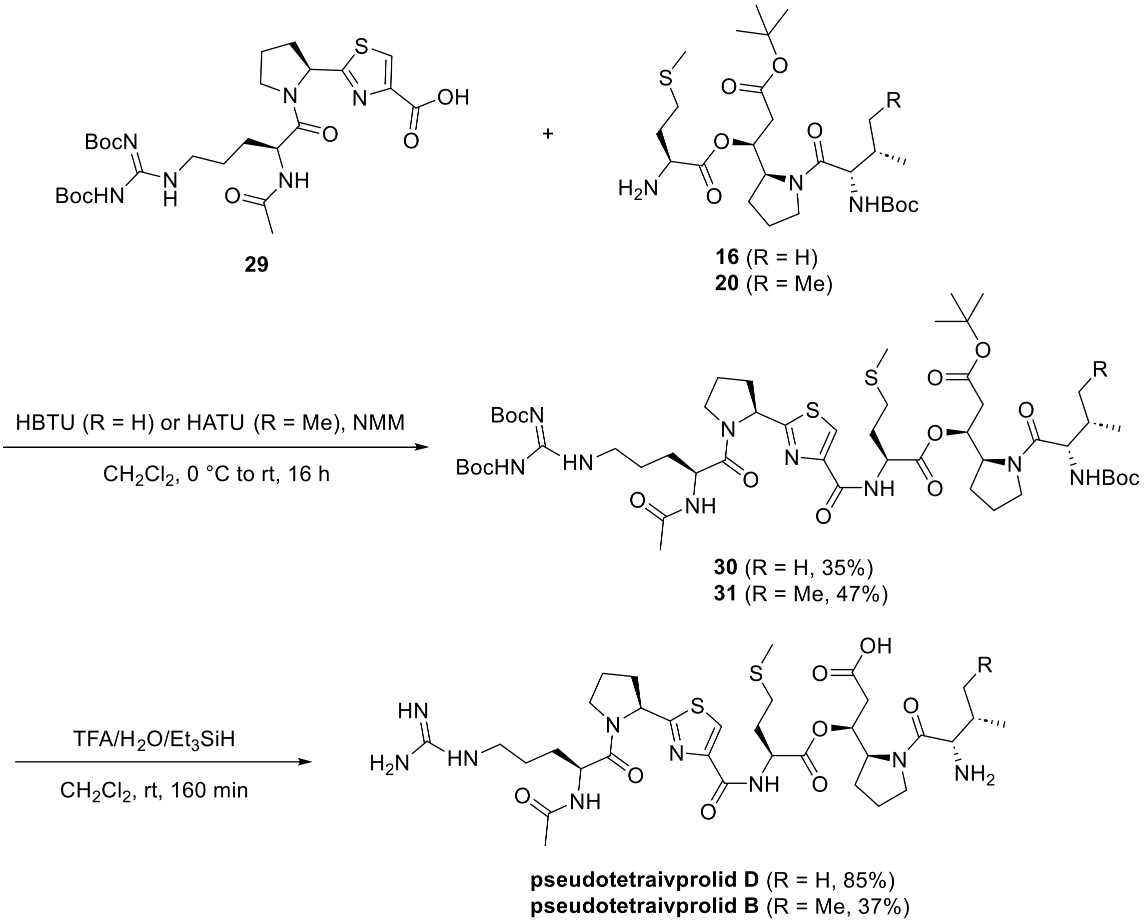
Scheme 45: Synthesis of the western fragment and attempted hydrogenation of the benzyl carbamate.

The Troc-protecting group was tested as an alternative. Therefore, the ε-amino group of ornithine was Troc-protected using standard carbamate protection conditions (Scheme 46). Boc-Orn(Troc)-OH **24** was then coupled with the hydrochloride salt **21** to give the dipeptide **25**. A sequence of deprotection and acetylation resulted in compound **26** in 94% yield. After some optimizations, cleavage of the Troc-group was achieved by treatment with zinc in acetic acid. The free amine was subsequently transformed to the bis-Boc-protected guanidine using guanidyl triflate **27b** in a protocol by Goodman et al.[134] This gave the finished western fragment and pseudotetratid precursor **28** in 61% yield over 2 steps.



Scheme 46: Synthesis of the western fragment with an adjusted protecting group strategy.

Finally, both ivprolid-derived building blocks were coupled with the saponified western fragment **29** (Scheme 47). The ivprolid A derivative **16** was coupled using HBTU, and the ivprolid B derivative **20** using HATU as a coupling agent. Both couplings gave the desired depsipeptides **30** and **31** in moderate yields of 35% and 47%, respectively. During both reactions, the methionine-oxidized depsipeptides were observed as side products. Whether the starting materials were partly oxidized or oxidation occurred during the coupling remains unclear. Further investigations on the peptide coupling to suppress the oxidation and improve the yield were not conducted due to insufficient amounts of the starting materials. In the final step, global deprotection was investigated. The first attempts were made with HCl in dioxane and TFA. With HCl, the conversion rate was low; the *tert*-butyl ester remained intact after 16 hours reaction time. TFA required a much shorter reaction time, and cleavage of the *tert*-butyl ester was observed. However, in both cases, oxidation and alkylated side products were observed by LC-MS analysis. Such oxidation and alkylation reactions are known problems during acidic deprotection, especially on peptides containing methionine or cysteine.[135]



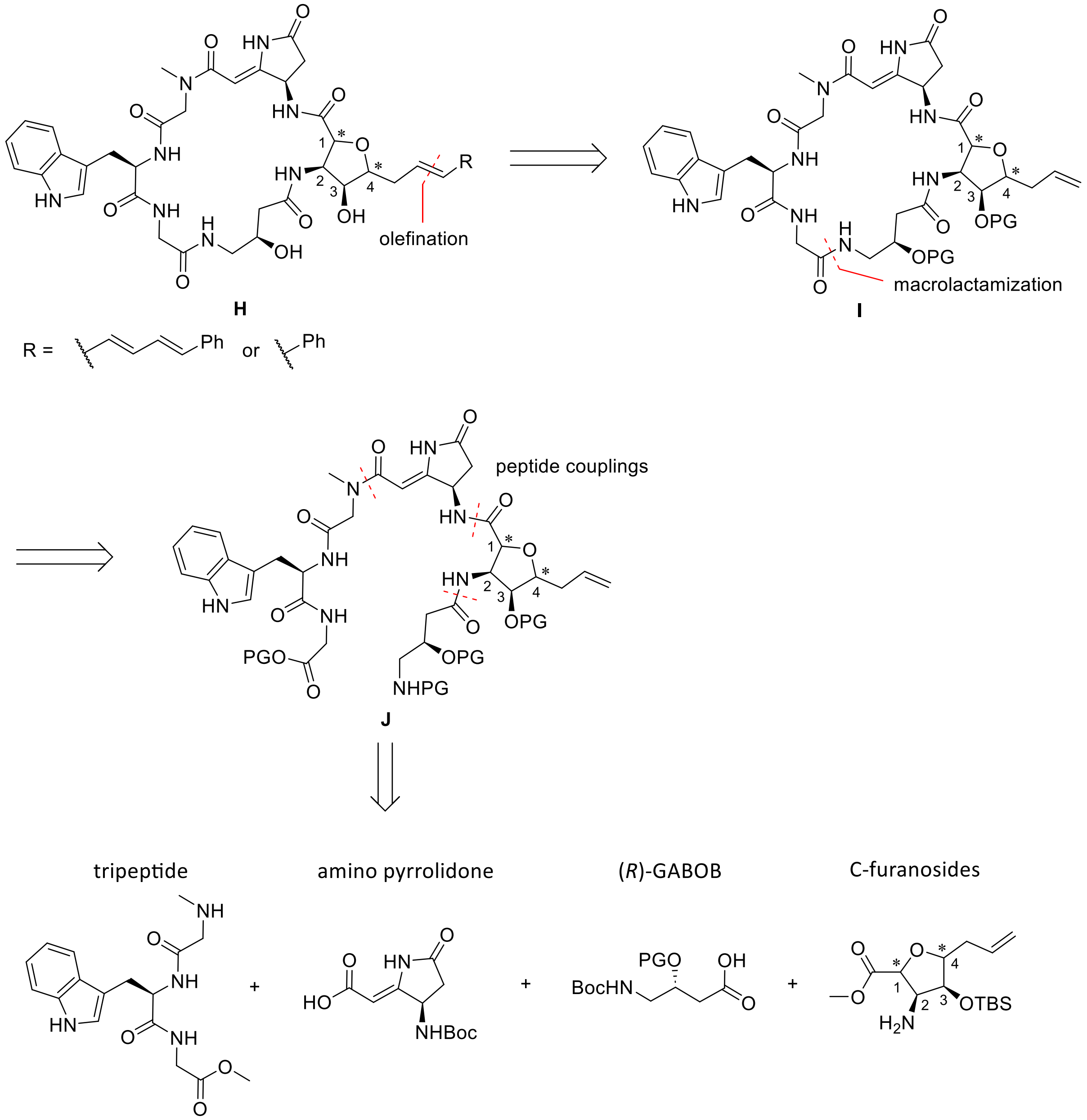
Scheme 47: Coupling of the building blocks to finish the synthesis of pseudotetraivprolid B and D

Different cleavage cocktails were tested to suppress these side reactions.[135,136] The best results were achieved with water and triethyl silane, which were entirely sufficient as scavengers. Deprotection toward pseudotetraivprolid D using the TFA/H_2O/Et_3SiH cleavage cocktail proceeded smoothly and afforded the natural product in 85% yield. The same procedure yielded pseudotetraivprolid B in 37% along with 35% yield of the corresponding *tert*-butyl ester. In this case, the reaction was stopped too early, and the *tert*-butyl ester was cleaved in an additional step. This concludes the synthetic effort toward these two novel entries of natural products and allows for the detailed study of their biological properties and biosynthetic origin. The study of the synthesized compounds is currently conducted by the Bode group and will be reported in due course. The coupling of the eastern and western fragments in this convergent approach should enable the synthesis of other derivatives of the natural products for SAR-studies.

4.2 Socein-Derivatives

4.2.1 Retrosynthetic Analysis

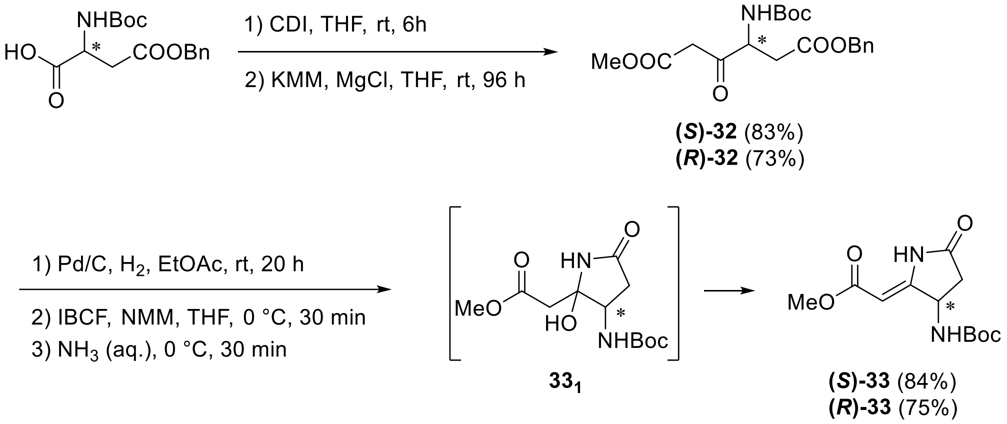
The target structures of the socein-project were the four different dehydrosocein diastereomers **H**. Installation of the olefin side chain was envisioned via late-stage olefination, which allows for the introduction of different residues. A macrolactamization was planned between the γ-amino-β-hydroxybutyric acid (GABOB) and the glycine moiety. Low sterical hindrance, no racemization potential with CH_2-groups in α-position on both ends, and the reported cyclization of microsclerodermin E[16] at this position made it the most rational option. Several disconnections at the amide functionalities led to the four main building blocks shown in Scheme 48.



Scheme 48: Retrosynthetic analysis of dehydrosocein.

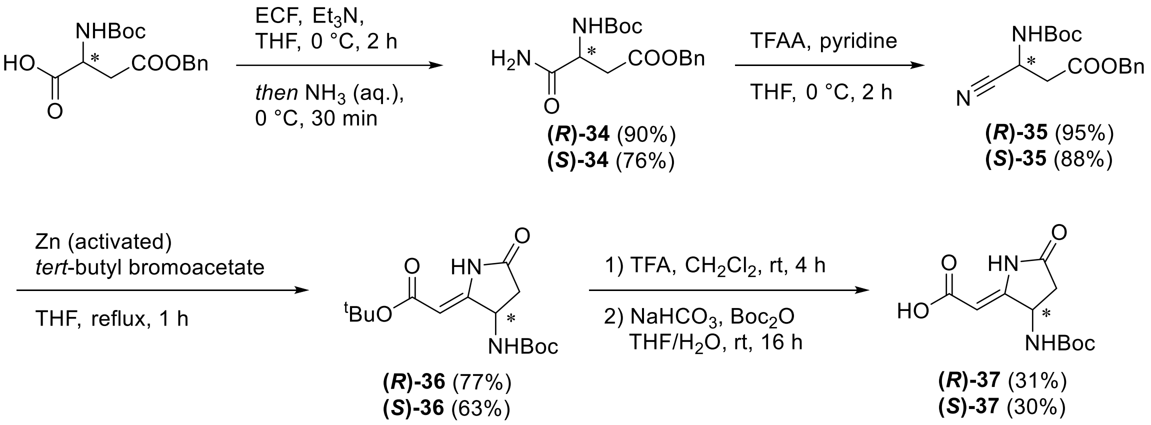
4.2.2 Synthesis of the Building Blocks

For the synthesis of the amino pyrrolidone building block, two different routes starting from protected aspartic acid were investigated. The first route by Shioiri *et al.*[30] began with the activation of the Boc-Asp(Bn)-OH with CDI and treatment with potassium methyl malonate to give β-keto ester **32** (Scheme 49). Catalytic hydrogenation of the benzyl ester, activation by IBCF, and quenching with aqueous ammonia resulted in the amino pyrrolidone **33** in a yield of 84% and 75%, respectively. The reaction is reported to give the hemiaminal **33**$_1$ as the final product, which readily undergoes elimination under acidic or basic conditions.[30] This hemiaminal **33**$_1$ could never be observed during this study, and amino pyrrolidone **33** was directly obtained instead. The synthesis was carried out with both enantiomers of aspartic acid for a valid analysis of the enantiomeric purities.



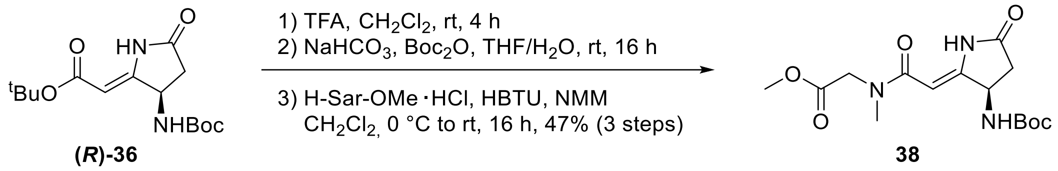
Scheme 49: Synthesis of the amino pyrrolidone according to Shioiri *et al.*

Chiral GC-FID analysis (see experimental section) of the amino pyrrolidones **33** showed no enantiomeric excess. The synthesis gave the desired amino pyrrolidone in good yields but as a racemic mixture, which made it unsuitable for this project. The second route by the group of Donohoe[15] features a Blaise reaction as a crucial step (Scheme 50). The absence of an intermediate prone to epimerization made this sequence more appealing, considering the epimerization issues encountered before. Activation of Boc-Asp(OBn)-OH as a mixed anhydride and quenching with aqueous ammonia gave the primary amides **34** in 90% and 76% yield, respectively. Once again, both enantiomers were utilized in this synthesis to generate samples for analysis of the enantiomeric purity. Nitrile **35** was prepared under dehydrating conditions with trifluoroacetic anhydride (TFAA) and pyridine. The Blaise reaction of *tert*-butyl bromoacetate and nitrile **35** and the subsequent cyclization afforded the amino pyrrolidones **36** in good yields. In the next step, any attempts to cleave the *tert*-butyl ester selectively without removal of the Boc group failed. Thus, a two-step sequence was employed in which both protecting groups were cleaved by treatment with TFA, and the amine was protected as its Boc-carbamate once more. These protecting group manipulations gave the desired amino pyrrolidone **37** in only moderate yield.



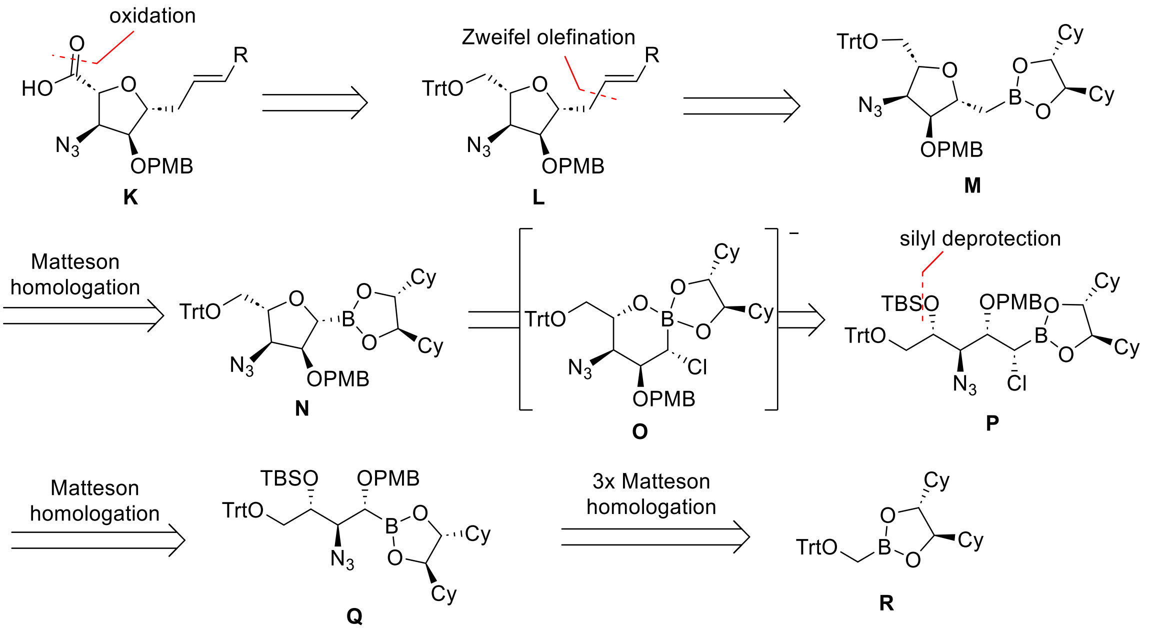
Scheme 50: Synthesis of the amino pyrrolidone according to Donohoe *et al.*

The crude yield was comparable to the reported yield of 85% for this step, but the purity was insufficient. Attempts to improve the yield by different purification methods like normal- or reversed-phase chromatography, and acid-base extractions were entirely unsuccessful. Thus, the direct coupling of the crude product with the hydrochloride salt of sarcosine methyl ester was examined (Scheme 51). Satisfactory, this improved the yield significantly, affording the dipeptide **38** in an acceptable yield of 47% yield over 3 steps. For chiral GC-FID analysis, the methyl esters of compound **37** have been prepared with TMS-diazomethane (see experimental section).[15] The chromatograms show an enantiomeric excess of 99% and >90% for the (*R*)- and (*S*)-enantiomer, respectively. The latter could not be determined precisely due to the peak tailing of the main enantiomer.



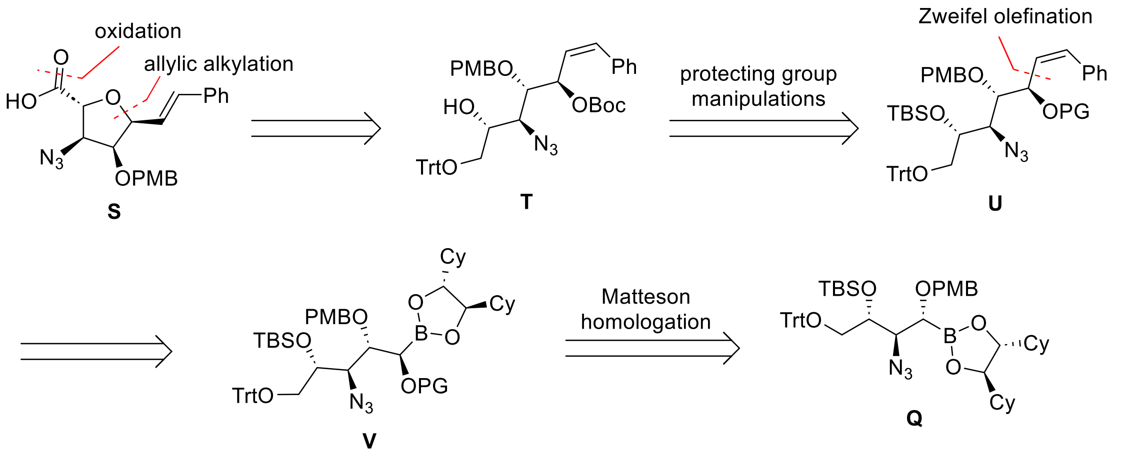
Scheme 51: Coupling of the crude amino pyrrolidone with sarcosine.

After completing the synthesis of the amino pyrrolidone, the focus was shifted toward the different diastereomeric C-furanosides. At the start, a strategy utilizing the Matteson homologation[137], a core research topic of our group, was investigated. Two routes were envisioned, leading to two differently configurated C-furanosides via a shared intermediate **Q** (Scheme 52 and Scheme 53). In the first route (Scheme 52), the introduction of the carboxylic acid functionality was planned by oxidation of the primary alcohol **L**, which was further disconnected via a Zweifel olefination[138,139]. A single Matteson homologation with a reduction of the α-chloro boronic ester would insert the CH$_2$-group into compound **N**. Installation of the tetrahydrofuran was intended by cyclization via an intramolecular 1,2-rearrangement. The required boronate **O** should be generated by silyl deprotection of the α-chloro boronic ester **P**. A sequence of Matteson homologations to insert the alkoxy groups and the azide leads back to the trityloxymethyl boronic ester **R** as known starting material.[140]



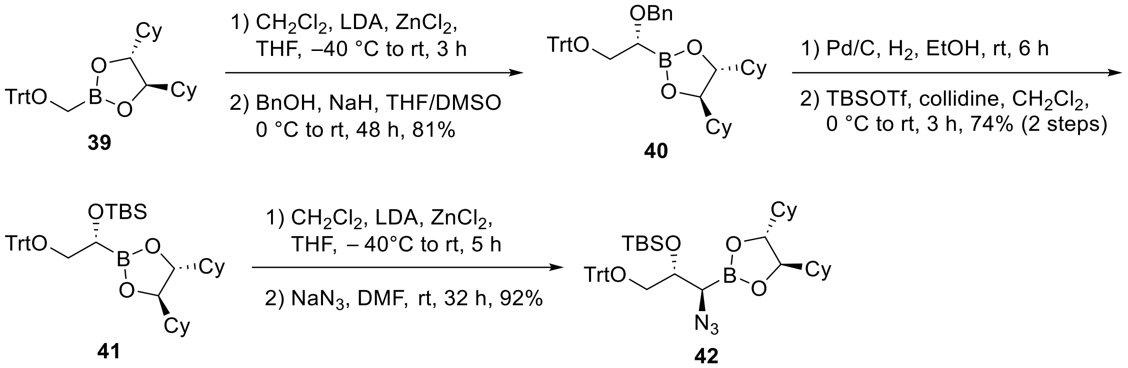
Scheme 52: Retrosynthetic analysis of C-furanoside K utilizing the Matteson homologation.

The second route in Scheme 53 revolves around the ring closing via *O*-allylation. An allylic alkylation on similar scaffolds to synthesize different chiral tetrahydrofuran and tetrahydropyran derivatives was reported by Rein and Vares in 2002.[141] To obtain the correct stereochemistry, a *Z*-configured allylic carbonate **T** was an appropriate precursor. Further disconnection via Zweifel olefination leads to boronic ester **V**, which can be traced back to the previous intermediate **Q** via protection group manipulations and a sole Matteson homologation.



Scheme 53: Retrosynthetic analysis of C-furanoside S via allylic alkylation and Matteson homologation.

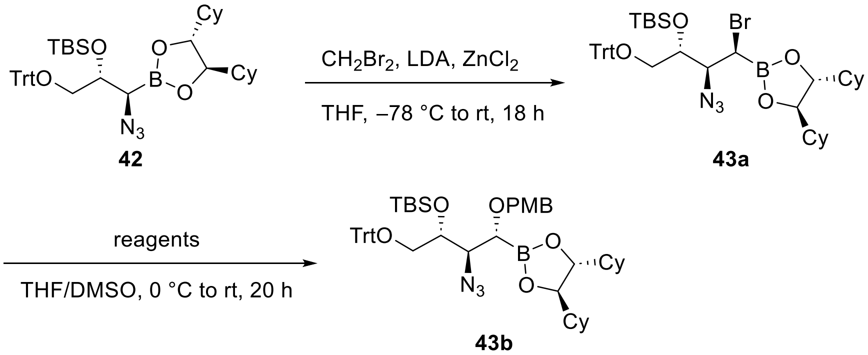
The synthesis starts with the literature known trityloxymethyl boronic ester **39**[140] containing (*R*,*R*)-DICHED[142] as a chiral auxiliary (Scheme 54). The first homologation to the α-chloro boronic ester with dichloromethyl lithium, followed by nucleophilic substitution with sodium benzylate, gave the homologated boronic ester **40** in 81% yield. The benzyl-protecting group was removed by catalytic hydrogenation, and the hydroxy group was protected with TBSOTf and 2,4,6-collidine. Subsequent homologation with sodium azide as a nucleophile afforded, after some optimization, the desired boronic ester **42** in excellent yield.



Scheme 54: Matteson homologations of tritylboronic ester 39.

The following homologation of **42** suffered from low conversion (40 – 70%) to the α-chloro boronic ester under typical conditions. Additionally, the α-chloro boronic ester showed no conversion to the desired product **43b** in a reaction with NaOPMB. Using dibromo methyl lithium in the homologation step improved the conversion to the α-bromo boronic ester **43a** to 90% (Table 12). Due to the low reactivity of the bromo boronic ester, different equivalents of the sodium alkoxide, the lithium alkoxide, and the combination with a crown ether were tested. Entries 1 – 4 show the results of a one-pot procedure where the alcoholate is just added to the reaction mixture of the homologation step. In entries 5 – 8, the same reagents were used after isolation of the α-bromo boronic ester.

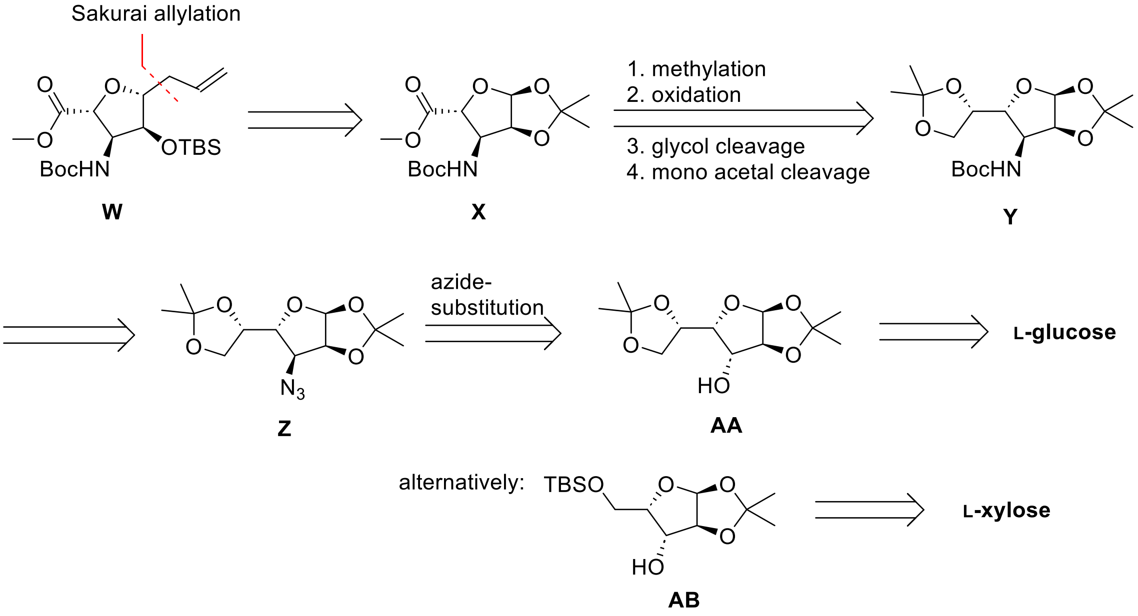
Table 12: Optimization of the substitution step of the Matteson homologation.



entry	43a	reagents	conversion
1	one-pot	1.5 eq. NaOPMB	< 10%
2	one-pot	1.5 eq. NaOPMB, 3.0 eq. 18-crown-6	25%
3	one-pot	3.0 eq. NaOPMB	< 10%
4	one-pot	1.5 eq. LiOPMB	33%
5	isolated	1.5 eq. NaOPMB	---
6	isolated	1.5 eq. NaOPMB, 3.0 eq. 18-crown-6	---
7	isolated	3.0 eq. NaOPMB	---
8	isolated	1.5 eq. LiOPMB	< 10%

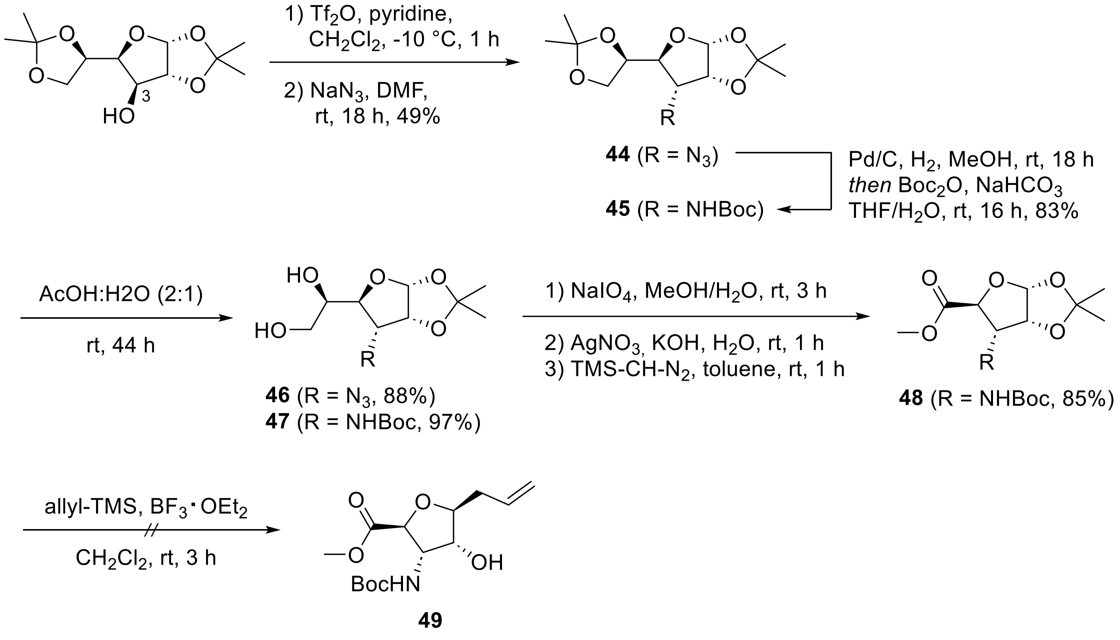
In general, the one-pot procedure afforded superior results. The best conversion of 33% was achieved with the lithium PMB-alkoxide (entry 4). Increasing the reaction time to 50 h resulted in significant decomposition of the starting material without noticeable progress toward the desired product **43b**. Matteson reported similar issues during the synthesis of L-ribose and other highly alkoxy-functionalized boronic esters.[143,144] One of the reported problems is the debenzylation of terminal benzyloxy groups when they are separated from the boronic ester by a chain of four carbons. Hence, the bulkier trityloxy group was used. The reported homologations with highly alkoxy functionalized groups were plagued with problems, and in some cases, only the introduction of a CH_2-group or oxidative elimination of the boronic ester proved feasible.[143–145] Matteson homologations with an α-azido boronic ester have been reported, but so far, only with *C*-nucleophiles in the form of lithium organyls or Grignard reagents.[146,147] These discouraging results, and the fact that our group has not successfully substituted an α-halo-β-azido boronic ester yet, led to the discontinuation of this approach.

A chiral pool synthesis utilizing the stereocenters of monosaccharides was examined next (Scheme 55). Introduction of the allyl moiety was planned via Sakurai-allylation of **X**. The synthesis of the methyl ester **X** was envisioned via selective acetal cleavage, an oxidation sequence, and methylation starting from **Y**. Transforming this Boc-protected amine back into the azide **Z** allows for the installment via standard azide substitution of the hydroxy functionality of **AA**. This bis-dimethyl acetal of L-glucose can be replaced with the protected L-xylose **AB** by simply using a different oxidation sequence during the methyl ester formation. Even though the unnatural monosaccharides are typically available at low prices, the significantly cheaper D-glucose was used first to investigate the devised route.



Scheme 55: Retrosynthetic analysis of C-furanoside W.

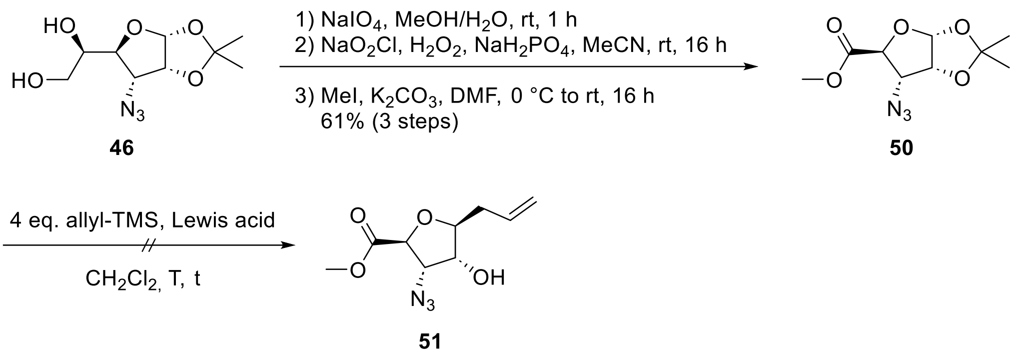
The synthesis started with the C-3 substitution sequence of bis-*O*-isopropylidene-α-D-glucofuranose (Scheme 56). Different parameters and leaving groups were investigated. The imidazole-1-sulfonate ester showed a high conversion rate. The azide **44** could, however, not be separated from several side products. The corresponding mesylate did not react at all, even at elevated temperatures of up to 120 °C. Transformation into the more reactive triflate allowed for the substitution with NaN_3 in DMF at room temperature. This afforded azide **44** in an acceptable yield. Such substitutions are bound to afford low yields due to the concave-sided attack of the azide, which was elaborated in the work of Perczel *et al.* by comparing the reactivity with the convex-sided attack of the C-3 epimer.[148] Catalytic hydrogenation in the presence of Boc-anhydride gave carbamate **45** in 83% yield. A selective acetal cleavage protocol with acetic acid[149] afforded the azide **46** and the Boc-protected amine **47** in high yields. The methyl ester **48** was prepared by an oxidation protocol by Narula *et al.*[149] Attempts of Sakurai allylation under the conditions of Tellado and co-workers to achieve 1,2-*trans*-selective allylation did not result in any conversion to the desired C-furanoside **49**.[51]



Scheme 56: Testing the proposed route with bis-*O*-isopropylidene-α-D-glucofuranose.

Due to issues with Boc-deprotection during the allylation attempts of **48**, the Sakurai allylation was tested with the corresponding azide (Table 13). This azido furanoside **50** was prepared via a three-step sequence of glycol cleavage, Pinnick-oxidation (with H_2O_2 as a scavenger),[150,151] and methylation. None of the reported procedures with $BF_3{\cdot}OEt_2$ or $TiCl_4$ resulted in product formation. In entries 1 and 2, 95% of the starting material was reisolated. With $TiCl_4$, the reaction ended in complete decomposition (entry 3). In the last entry, $Ti(O^iPr)_3Cl$ was tested as a mild alternative to $TiCl_4$, resulting in the transesterification to the isopropyl ester in quantitative fashion.

Table 13: Tested conditions for the Sakurai allylation.

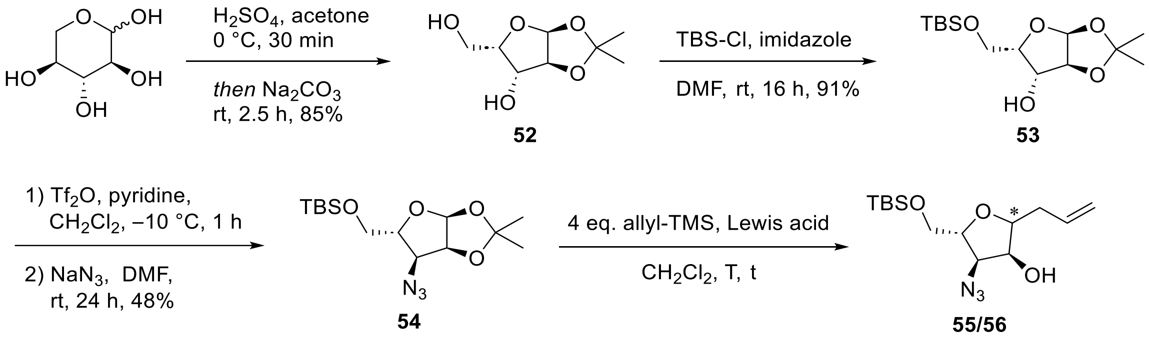


entry	Lewis acid	T	t	yield
1	2.0 eq. $BF_3 \cdot OEt_2$	0 °C to rt	3 h	---
2	5.0 eq. $BF_3 \cdot OEt_2$	0 °C to rt	6 h	---
3	2.0 eq. $TiCl_4$	−10 °C	10 min	---
4	2.0 eq. $Ti(O^iPr)_3Cl$	0 °C to rt	3 h	---[a]

a) 96% transesterification

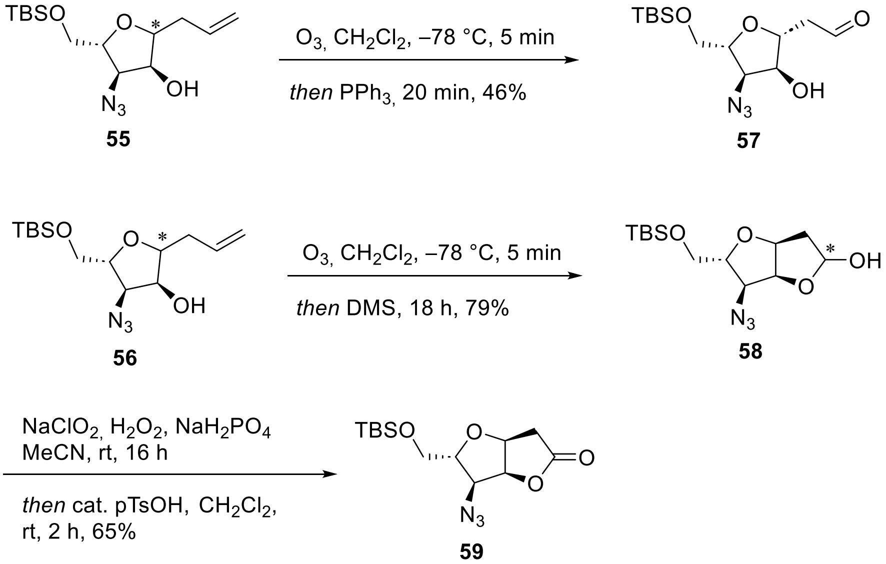
The Sakurai allylation procedure investigated by the Tellado group showed a lower yield for substrates containing an ester functionality (OAc and OPiv) as well as a yield dependency on the distance of this ester functionality to the anomeric carbon.[51]. Those observations and the above-shown results led to a more simplified substrate **54** for the Sakurai allylation (Table 14). In the first step, L-xylose was acetonide mono-protected, followed by selective TBS-protection of the primary alcohol in a protocol by Herdewijn *et al.*[152] The ensuing azide substitution gave similar yields to the substitution of the glucose derivative, which is unsurprising considering the similar sterical encumbrance. In this case, the Sakurai allylation works well with $TiCl_4$, affording the C-furanoside **55** in good yield and excellent diastereoselectivity (entry 1). Surprisingly, the allylation with $BF_3 \cdot OEt_2$ gave the desired product in an inverted dr of 2:8 and 43% yield (entry 2).

Table 14: Sakurai-allylation with L-xylose derivative 54.



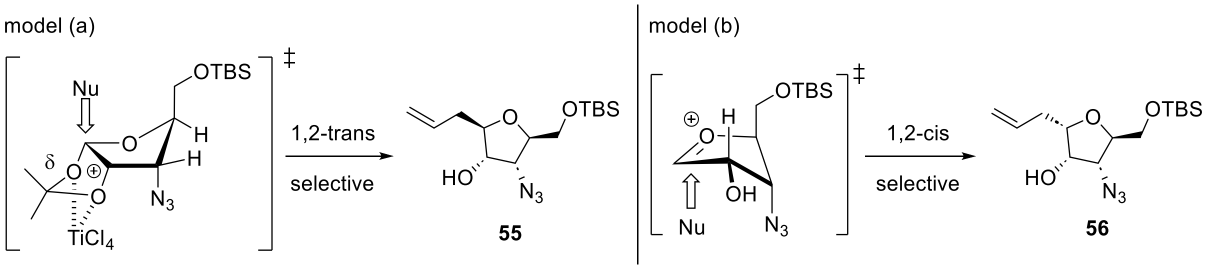
entry	Lewis acid	T	t	yield	dr
1	2.0 eq. $TiCl_4$	−20 °C	20 min	**55**, 80%	dr 97:3
2	2.0 eq. $BF_3 \cdot OEt_2$	0 °C to rt	3 h	**56**, 43%	dr 2:8

For such systems, the stereochemical inversion by changing the Lewis acid was not reported by Tellado *et al.*[51] or other groups working on this subject.[33] A strategy to elucidate the stereochemistry of both diastereomers via ozonolysis was devised. The resulting aldehyde should spontaneously form a hemiacetal, which could be further oxidized to a 5-ring lactone if the reaction was 1,2-*cis* selective. In the case of a 1,2-*trans* selective reaction, the formation of a hemiacetal should not be possible due to the high strain energy of fused *trans*-5-5-ring systems.[153,154] These highly strained structures have been difficult to synthesize and have challenged synthetic chemists for decades.[155] The ozonolysis for the $TiCl_4$ allylation product **55** gave aldehyde **57** (Scheme 57) displaying a typical aldehyde shift in the ^{1}H-NMR (δ = 9.65 ppm) as well as a high shifted carbon signal in the ^{13}C-NMR (δ = 201.5 ppm). The moderate yield likely occurred due to partial Staudinger reduction of the azide with triphenylphosphine. Thus, the following ozonolysis of the BF_3-allylation product **56** was quenched with dimethyl sulfide, resulting in a diastereomeric mixture of hemiacetal **58** in 79% yield. This hemiacetal was oxidized to the carboxylic acid under Pinnick conditions, which formed the 5-ring lactone **59** under treatment with pTsOH.



Scheme 57: Stereochemical elucidation of the Sakurai-allylation products by ozonolysis.

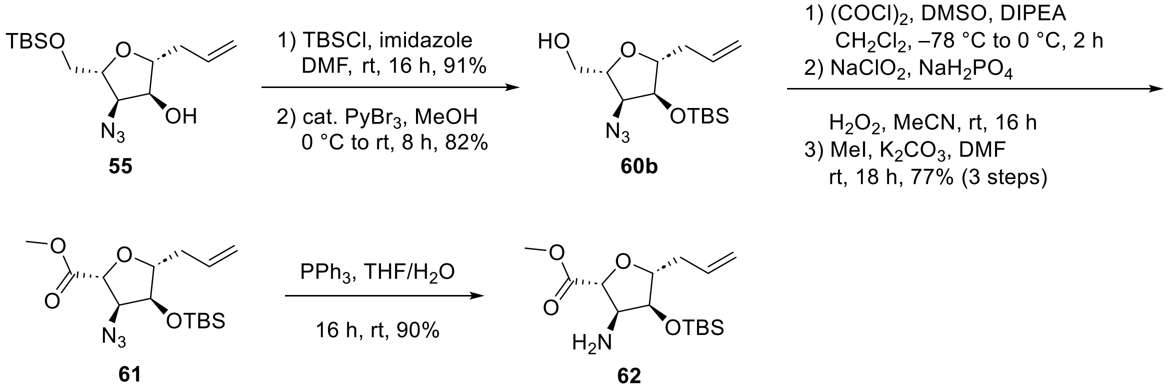
The stereochemical models for the allylation are shown in Scheme 58. The first model by Tellado *et al.* shows an S_N2-type mechanism via activation of the 1,2-*O*-isopropylidene group, which directs the nucleophilic attack to the *exo*-side of the bicyclic system.[51] If the reaction proceeds through an oxonium ion intermediate, the stereochemical outcome strongly depends on the furanoside substituents following Woerpel's model.[47,50,156] Assuming the azide does not stabilize the transition state via electrostatic interaction like an *O*-substituent and also does not exert a large steric influence, only the oxy-substituent in the 2-position should play a significant role for the stereochemical outcome of the allylation. This would result in the transition state (b) with the C-2 substituent in pseudoequatorial position, maximizing the hyperconjugative effect of the σ_{C-H} orbital and the vacant orbital of the oxonium ion.



Scheme 58: Stereochemical model for the Sakurai allylation.

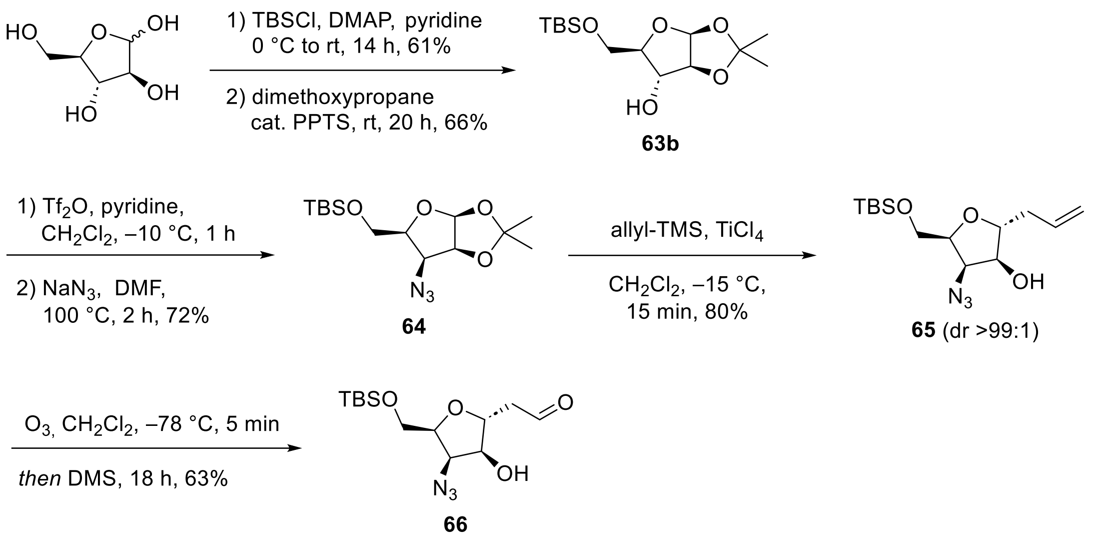
The Tellado group reported a 1,2-*trans* selectivity in all their experiments, independent of using $BF_3 \cdot OEt_2$ or $TiCl_4$, which would follow model (a). The 1,2-*cis* selectivity in the BF_3-allylation shown in this work strongly suggests an oxonium ion intermediate like model (b) because an *endo*-facial attack of a bicyclic system like model (a) is unlikely. Furthermore, the BF_3-allylation in this study showed comparable stereoselectivity to the *C*-allylation of a similar furanoside **CP**, with no substitution in C-3 position, during the synthesis of Hagen's gland lactones (*cf.* Scheme 25).[56]

Due to the high yield and diastereoselectivity, the $TiCl_4$-allylation product **55** was further transformed to finish the first diastereomer of the C-furanosides (Scheme 59). In contrast to this, the optimizations and continuation of the BF_3-allylation product **56** will be discussed later on. First, the secondary alcohol of C-furanoside **55** was TBS-protected, and the primary TBS-ether was selectively cleaved with *in-situ* generated HBr in a protocol by Jennings and Martinez-Solorio.[157] Initial attempts with an alternative orthogonal protecting group (PMB) for the secondary alcohol resulted in low yields in the protection step and were discontinued. After the direct oxidation with TEMPO gave only unsatisfactory results, a two-step sequence of Swern and Pinnick oxidation was used. After *O*-methylation with iodomethane in DMF, the methyl ester **61** was isolated in 77% yield over 3 steps. The reaction sequence was concluded with a Staudinger reduction of the azide to give the C-furanoside **62**.



Scheme 59: Final steps toward the first diastereomer of the C-furanosides.

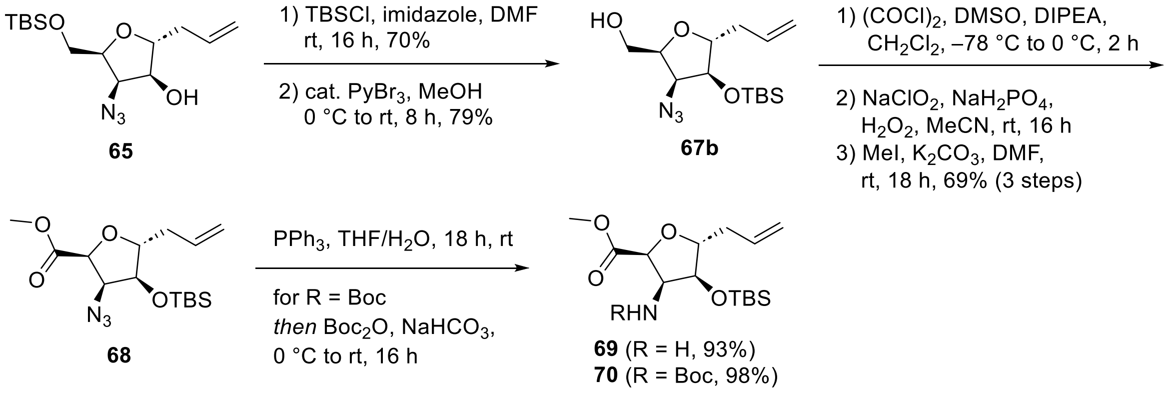
A second diastereomer should be obtainable by a similar route, using D-arabinose as the starting point. A selective TBS-protection of the primary alcohol followed by acid-catalyzed acetal formation gave the protected D-arabinose **63b** in 40% yield over 2 steps (Scheme 60).[158] Due to the inverted C-4 stereocenter and the resulting increase in sterical hindrance, the concave-sided attack is even more disfavored than in the L-xylose derivative **53**.



Scheme 60: D-arabinose route with stereochemical confirmation by ozonolysis.

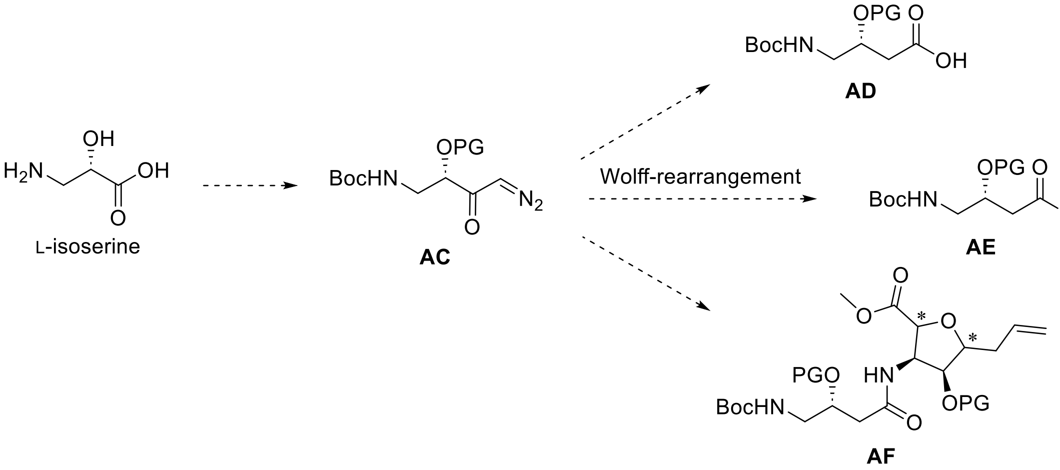
Surprisingly, the azide substitution protocol yielded the desired azide **64** in 72% by increasing the temperature to 100 °C. The absence of the anti-periplanar hydrogen atom in the triflate of **63b** allowed for the increase in temperature without competing E_2-elimination. The Sakurai allylation with $TiCl_4$ gave the C-furanoside **65** in excellent yield and diastereoselectivity (dr >99:1). The postulated 1,2-*trans* stereochemistry, identical to the previously performed Sakurai allylation, was confirmed by ozonolysis. This resulted in clean formation of the aldehyde **66** without any observable hemiacetal formation. In this case, the allylation with $BF_3{\cdot}OEt_2$ of **64** gave C-furanoside **65** in low yield as a diastereomeric mixture of 1:1. The significantly lower selectivity in comparison to the L-xylose route (*cf.* Table 14) is most likely a direct result of the high sterical demand of an all-*cis* diastereomer.

The second diastereomer was completed via the same sequence shown before, starting with TBS-protection of the secondary and selective deprotection of the primary alcohol (Scheme 61). A three-step protocol of oxidation and methylation afforded methyl ester **68** in 69% yield. In this case, the Staudinger reduction was additionally performed in the presence of Boc-anhydride to obtain a storable intermediate in Boc-protected amine **70** in almost quantitative fashion.



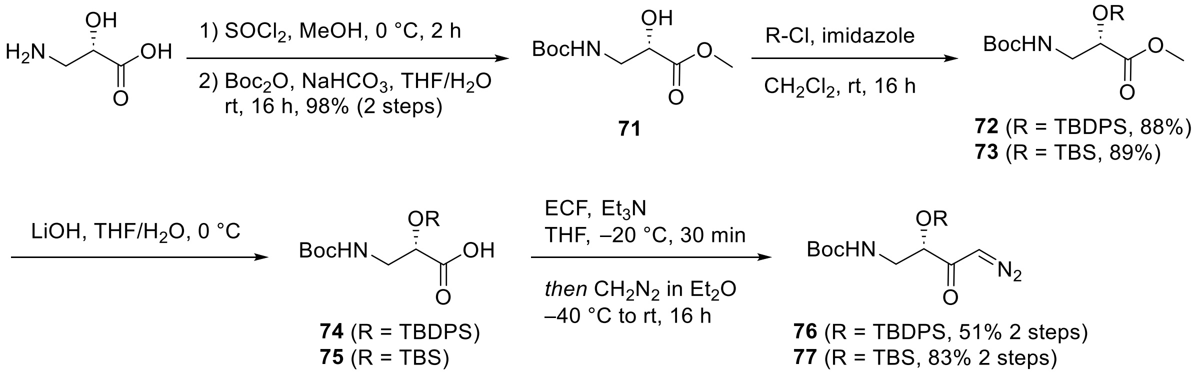
Scheme 61: Finalization of the second diastereomer of the C-furanosides.

Before continuing with the synthesis of the two remaining diastereomers, the synthesis, and coupling of the southern part ((*R*)-GABOB) of dehydrosocein with the already produced C-furanosides was investigated. Even though many syntheses for the prominent (*R*)-GABOB are known,[159] a new route starting from L-isoserine (≈1€/mmol) was investigated. An Arndt-Eistert homologation of L-isoserine should give access to (*R*)-GABOB in a straightforward fashion, with the benefit of several substitution options by using different nucleophiles in the Wolff-rearrangement (Scheme 62). Ideally, using the C-furanosides as amine nucleophiles (**AF**) would avoid potential reactivity issues of the sterically hindered amines due to the high reactivity and the low sterical demand of such ketenes.

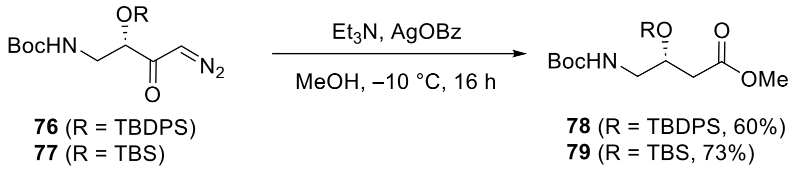


Scheme 62: Synthetic considerations of an Arndt-Eistert homologation approach.

Starting with a typical Fischer esterification and amine-protection with Boc-anhydride afforded Boc-Ise-OMe **71** in excellent yield (Scheme 63). Protection of the secondary hydroxy functionality with TBDPS-Cl and TBS-Cl gave the protected isoserines **72** and **73** in around 90% yield. The methyl ester was cleaved under standard saponification conditions with LiOH. Boc-protection and TBS-protection were tested with the free carboxylic acid, but the additional step of methyl ester protection gave much better overall yields and improved the storability of the compounds. Especially, the TBS-protected carboxylic acid **75** suffers from autocatalyzed TBS-deprotection within hours. Immediately after saponification, the carboxylic acids **74** and **75** were activated as mixed-anhydrides and, by treatment with freshly prepared diazomethane,[160] converted to the diazoketones **76** and **77** in 51% and 83% yield, respectively.

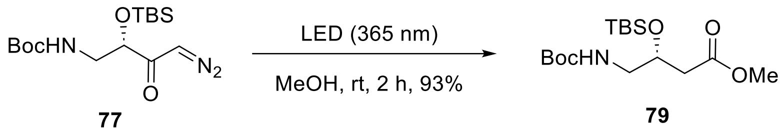


Scheme 63: Synthesis of diazoketones 76 and 77 from isoserine.



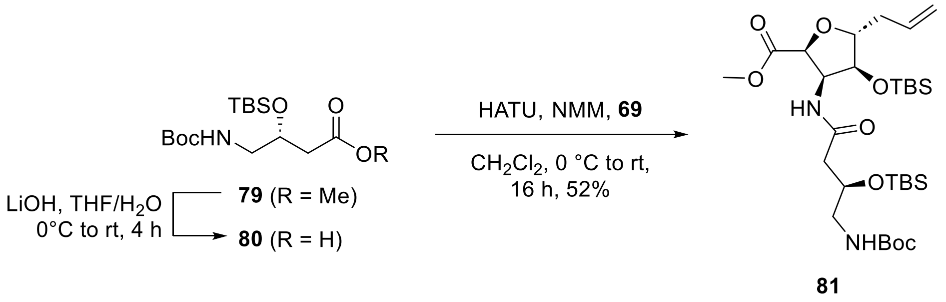
Scheme 64: Ag-catalyzed Wolff-rearrangement with MeOH as a nucleophile.

Silver catalyzed Wolff-rearrangement with methanol gave (*R*)-GABOB derivatives **78** and **79** (Scheme 64). Overall, the TBS-protecting group gave superior results compared to the TBDPS-protected derivative. Hence, the synthesis was continued with the TBS-protecting group testing a light-induced activation of the diazoketone **77** (Scheme 65). According to the literature, a variety of light sources, from UV to visible light, can be used for the activation of diazoketones.[161–163] Irradiation of the diazoketone **77** in methanol, with an 18 W blue LED (365 nm), gave the desired (*R*)-GABOB derivative **79** in an excellent yield.



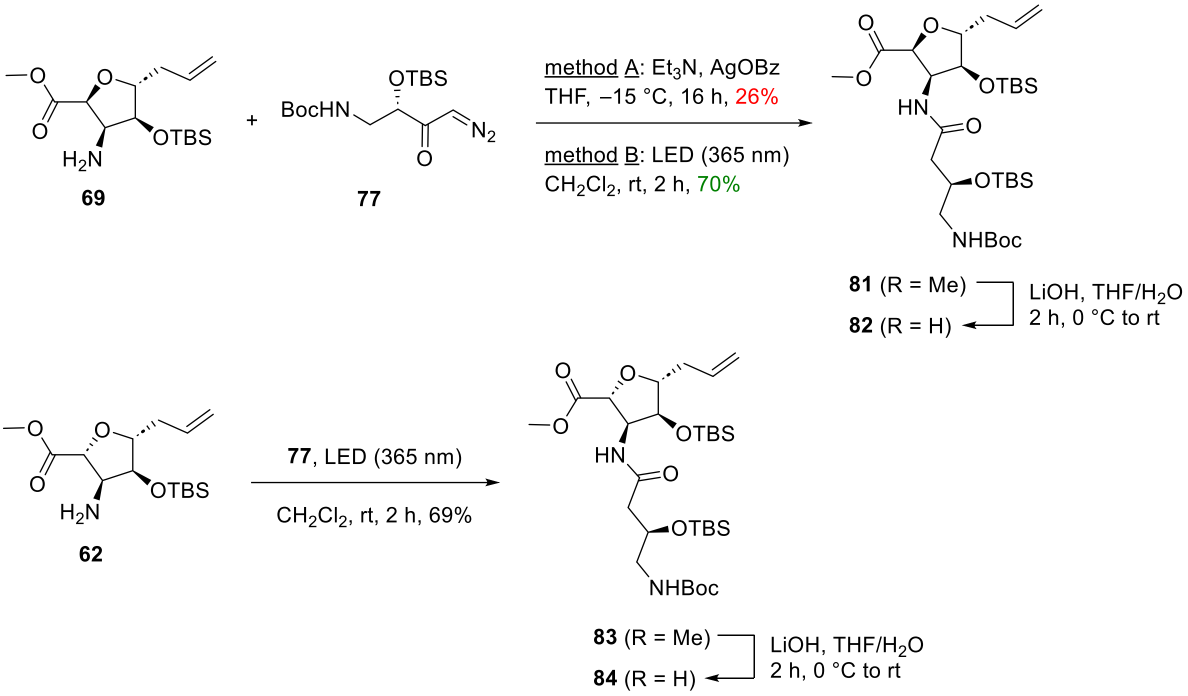
Scheme 65: Light-induced Wolff-rearrangement with MeOH as a nucleophile.

Blue LEDs with different wavelengths (365 nm, 405 nm, and 450 nm) only increased the reaction time to four hours at 450 nm but otherwise gave similar results. After the saponification of **79**, the carboxylic acid **80** was reacted with the arabinose-derived C-furanoside **69** in a standard HATU-coupling (Scheme 66). This coupling gave the dipeptide **81** in 52% yield using an excess of 1.5 equivalents of the carboxylic acid.



Scheme 66: Peptide coupling of C-furanoside 69 and (*R*)-GABOB derivative 80.

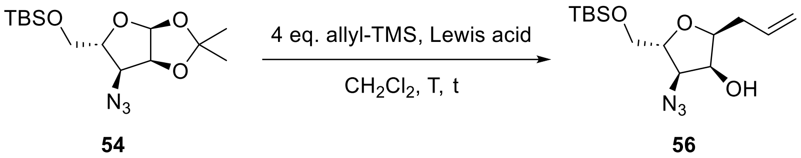
A comparison of Ag-catalyzed and light-induced Wolff-rearrangement with the C-furanoside as the nucleophile is shown in Scheme 67. The silver-catalyzed method A afforded the dipeptide **81** in 26% yield, while method B proved more successful with 70% yield. Different solvents (THF, MeCN, DMF, and CH_2Cl_2) and the addition of triethylamine as a base were tested in method B. However, all experiments gave inferior results to the initially applied conditions. Similarly, the xylose-derived C-furanoside **62** gave the diastereomeric dipeptide **83** in 69% yield. In summary, the bench-stable diazoketone **77** proved to be a highly valuable intermediate for the synthesis of GABOB derivatives. In a simple reaction setup, the light-induced Wolff-rearrangement with the C-furanosides as nucleophiles gave improved results compared to the standard amide coupling in Scheme 66.



Scheme 67: Comparison of Ag-catalyzed and light-induced Wolff-rearrangement.

The Sakurai allylation with inverse diastereoselectivity (*cf.* Table 14) provided easy access to another C-furanoside diastereomer **56**, but the low yield and nearly impossible separation of the diastereomers remained problematic. To improve yield and diastereoselectivity, different Lewis acids, which are commonly used in Sakurai-type allylations[164], were investigated (Table 15). Entries 1 and 2 show the previously described allylations with $TiCl_4$ and $BF_3{\cdot}OEt_2$. The good results with $TiCl_4$ led to the use of less reactive titan Lewis acids (entries 3 and 4). $Ti(O^iPr)_3Cl$ did not promote the reaction, while the dichloride equivalent (entry 4) resulted in deprotection side products. The most promising results were achieved with $AlCl_3$, which gave C-furanoside **56** in 51% yield and moderate selectivity (dr 7:3). Lower temperatures of –20 °C or –50 °C did not improve the yield and gave a diastereomeric ratio of 1:1. Triflate based Lewis acids showed no conversion to the desired product and with prolonged reaction time ended in decomposition (entries 8 to 10). Boron trichloride and its milder alternative BCl_2OMe[165] gave complex reaction mixtures, including the formation of traces of the desired furanoside, but isolation proved impossible (entries 11 and 12). Catalytic amounts of the Brønsted acid CSA resulted in clean TBS-deprotection without achieving any observable allylation.

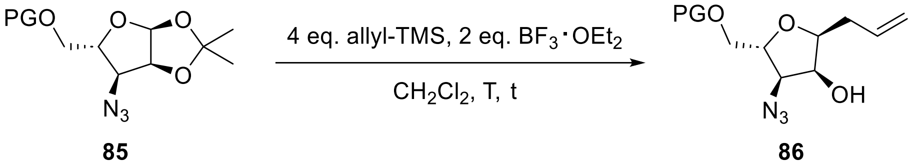
Table 15: Lewis acid screening in the Sakurai-allylation.



entry	Lewis acid	T	t	yield	dr
1	2.0 eq. $TiCl_4$	–20 °C	20 min	80%	5:95
2	2.0 eq. $BF_3{\cdot}OEt_2$	0 °C to rt	3 h	43%	80:20
3	2.0 eq. $Ti(O^iPr)_3Cl$	0 °C to rt	6 h	---	---
4	2.0 eq. $Ti(O^iPr)_2Cl_2$	–10 °C to rt	3 h	---	---
5	2.0 eq. $AlCl_3$	–20 °C to rt	2 h	51%	70:30
6	2.0 eq. $AlCl_3$	–50 °C	20 min	38%	50:50
7	2.0 eq. $AlCl_3$	–20 °C	30 min	37%	50:50
8	2.0 eq. TMSOTf	0 °C to rt	16 h	---	---
9	0.1 eq. $Bi(OTf)_3$	rt	72 h	---	---
10	2.0 eq. $Bi(OTf)_3$	rt	16 h	---	---
11	2.0 eq. BCl_3	–50 °C	30 min	---	---
12	2.0 eq. $BCl_2(OMe)$	–20 °C	2 h	---	---
13	0.05 eq. CSA	rt	24 h	---	---

In a subsequent attempt, the TBDPS- and Troc-protecting groups with higher acid stability were tested in the Sakurai allylation with $BF_3{\cdot}OEt_2$ (Table 16). Standard conditions with the Troc-protecting group showed no conversion after 24 hours (entry 1). Repeating the experiment at 80 °C, afforded the allylation product in 50% yield but low diastereoselectivity (entry 2). In the case of the TBDPS-protected derivative, the addition of another portion of $BF_3{\cdot}OEt_2$ was needed to achieve full conversion (entry 3). The allylation proceeded with similar yield but a significantly higher diastereomeric ratio. When the reaction time was increased to 44 h, the yield remained the same, but the selectivity improved slightly (entry 4). Changing the solvent to acetonitrile resulted in complete decomposition of the starting material within one hour, with neglectable conversion to the desired product. With THF as solvent, the starting material remained untouched after 18 hours of reaction time, most likely due to the coordinating effects of THF.

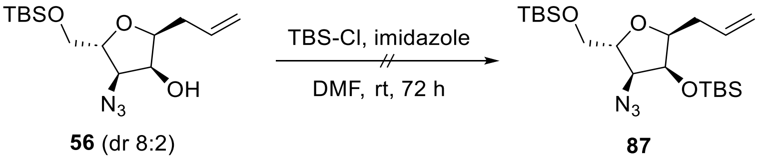
Table 16: Influence of different protecting groups and solvents in the Sakurai allylation with $BF_3{\cdot}OEt_2$.



entry	PG	solvent	T	t	yield	dr
1	Troc	CH_2Cl_2	0 °C to rt	24 h	---	---
2	Troc	CH_2Cl_2	80 °C	1 h	50%	67:33
3[a]	TBDPS	CH_2Cl_2	0 °C to rt	8 h	53%	83:17
4	TBDPS	CH_2Cl_2	0 °C to rt	44 h	51%	87:13
5	TBDPS	MeCN	0 °C to rt	1 h	---	---
6	TBDPS	THF	0 °C to rt	18 h	---	---

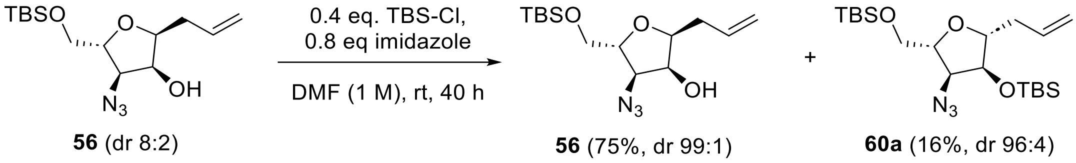
a) After 2 h, another 2.0 eq $BF_3{\cdot}OEt_2$ were added.

In a comparison of the Sakurai allylation with a TBS- and a TBDPS-protection group, the yield and diastereoselectivity could only be marginally improved. This did not justify the two additional steps for the change in protecting group. Thus, the previously described route was carried out with the diastereomeric mixture of allyl-furanoside **56**, and separation was envisioned at a later stage. If this synthesis proves fruitful, the entire route could be repeated, starting with TBDPS-protection of L-xylose as the first step. Immediate problems were encountered in the TBS-protection step displayed in Scheme 68, which showed very low conversion. Subsequent additions of more TBS-Cl and addition of the more reactive TBS-OTf proved unsuccessful to increase the conversion toward TBS-ether **87**.



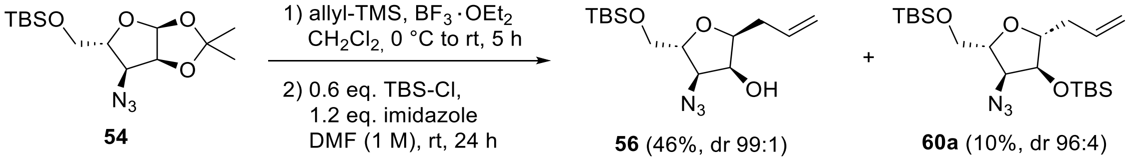
Scheme 68: Attempted TBS-protection of the C-furanoside 56.

After the realization that the low conversion might result from the selective reaction of the sterically less hindered minor diastereomer that was successfully TBS-protected before (*cf.* Scheme 59), the reaction was repeated. The first experiments clearly showed improving diastereomeric ratios of the C-furanoside **56**. After tweaking the concentration, the reaction time, and the quantities of the reactants, an optimum was found where barely any overreaction occurred, turning both products (**56** and **60a**) into useful building blocks with good diastereomeric purities (Scheme 69).



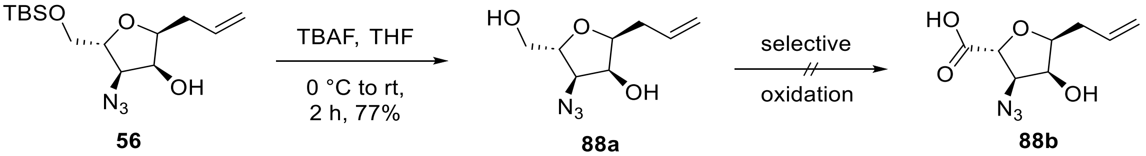
Scheme 69: Diastereomer selective TBS-protection of C-furanoside 56.

This sequence could be further improved by using a "one-pot" procedure of Sakurai allylation and subsequent TBS-protection of the crude mixture (Scheme 70). After some optimizations, this procedure improved the yield to 56% over 2 steps, affording two C-furanoside building blocks in high diastereomeric purities.



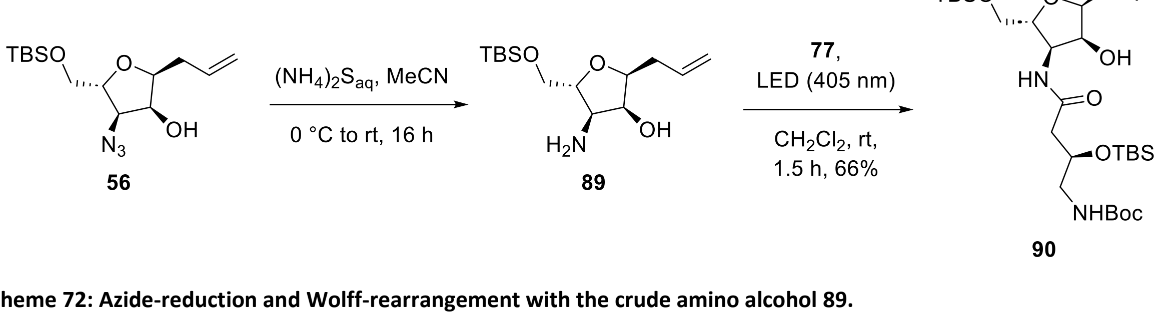
Scheme 70: "One-pot" procedure of Sakurai-allylation and TBS-protection.

After TBS-deprotection of **56**, the selective oxidation of the primary alcohol of diol **88a** was investigated. A two-step sequence of DMP-oxidation followed by Pinnick-oxidation and a one-step TEMPO-based oxidation by Li and Helm[166] were unsuccessful. The reactions did not proceed selectively, and the isolation of the highly polar product and side products was tedious.



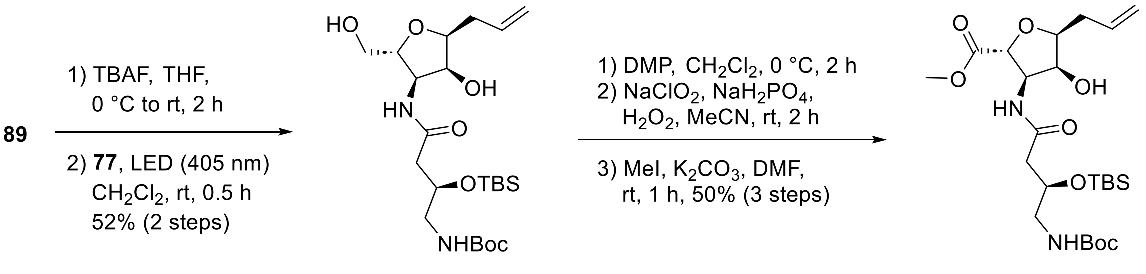
Scheme 71: Attempted preparation of carboxylic acid 89 by selective oxidation.

To avoid the issues during the isolation and to improve the selectivity of the oxidation by further increasing the sterical hindrance at the secondary alcohol, the amine reduction and reaction with diazoketone **77** in the Wolff-rearrangement was performed prior to the oxidation step (Scheme 72). In this case, the azide is reduced with ammonium sulfide by a protocol of Suna *et al.*[167,168] Overall, this biphasic procedure allowed easier isolation of the desired amino alcohol **89** in good yield and purity compared to the Staudinger reduction with PPh_3. The first tests of the Wolff-rearrangement with the amino alcohol **89** afforded the dipeptide **90** in 66% yield.



Scheme 72: Azide-reduction and Wolff-rearrangement with the crude amino alcohol 89.

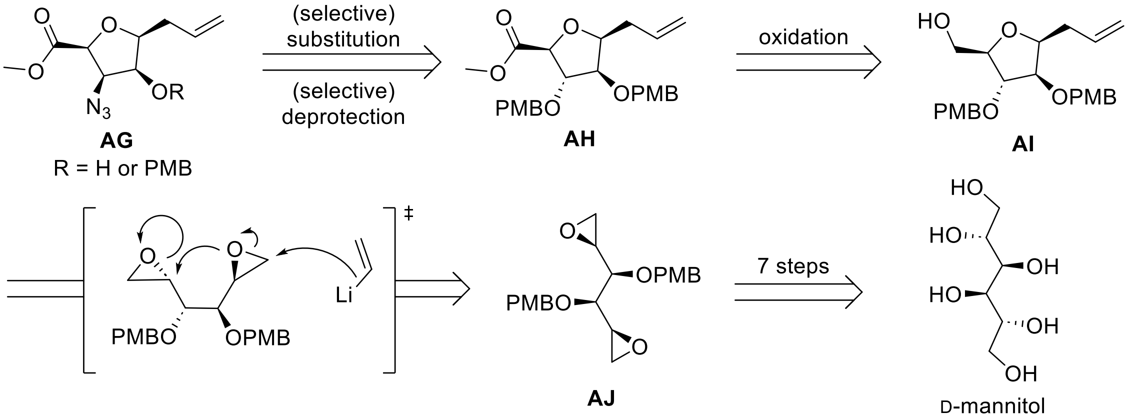
To avoid exchanging the protecting group or selective mono-TBS-deprotection, another attempt with the crude amino alcohol after TBS-deprotection was performed (Scheme 73). Wolff-rearrangement gave amide **91** in acceptable yield, considering the three competing nucleophilic centers. Selective oxidation of the primary alcohol was achieved with the sterically demanding Dess-Martin-periodinane (DMP)[169,170] along with 10% additional oxidation of the secondary alcohol. The aldehyde was further oxidized under Pinnick conditions, followed by methylation of the intermediary carboxylic acid to simplify the purification process.



91 **92**

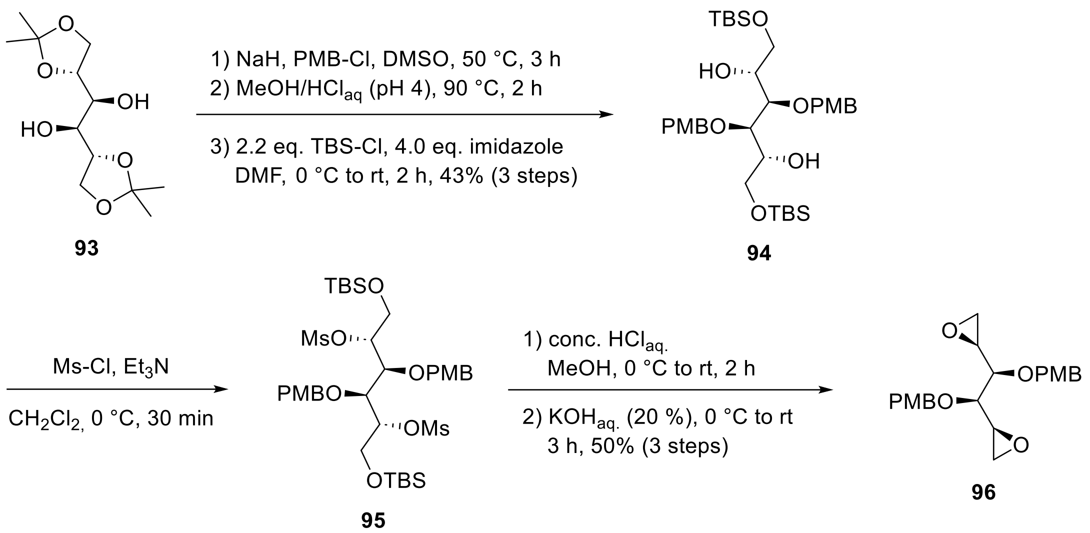
Scheme 73: Wolff-rearrangement with an amino diol followed by selective oxidation.

For the remaining diastereomer, a different route was planned (Scheme 74). The retrosynthetic analysis starts with either a selective PMB-deprotection or the selective transformation of the hydroxy group into a leaving group to introduce the azide. A retro-oxidation sequence would lead to primary alcohol **AI**, which might be synthesized via ring-closure by opening of bis-epoxide **AJ** with vinyl lithium. These desymmetrization reactions on bis-epoxides have been reported by Hanaoka *et al.* for alkyne lithium organyls[171] and Merrer *et al.* for aryl lithium nucleophiles[172]. In both cases, $BF_3 \cdot OEt_2$ is used to favor the 5-*exo*-tet cyclization opposed to the double substitution and 6-*endo*-ring formation.



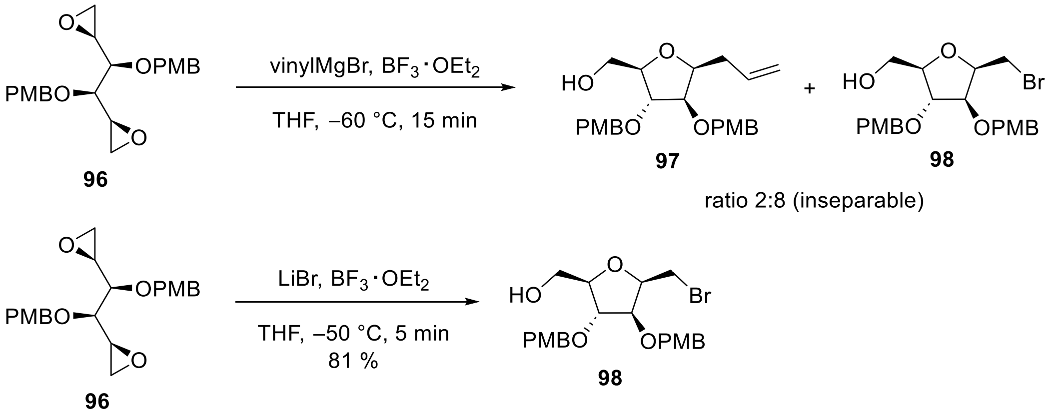
Scheme 74: Retrosynthetic analysis of C-furanoside AG.

The bis-epoxide **AJ** can be generated from D-mannitol in a 7-step procedure that has been reported previously for the corresponding bis-benzyl ether.[173] The synthesis of bis-epoxide **96** is shown in Scheme 75. Starting from literature known bis-acetonide **93**,[174] the PMB groups were installed, followed by acetonide hydrolysis and TBS-protection of the primary alcohols. Mesylation of the unprotected hydroxy groups gave mannitol derivative **95**, which was TBS-deprotected by treatment with hydrochloric acid.



Scheme 75: Synthesis of mannitol bis-epoxide 96.

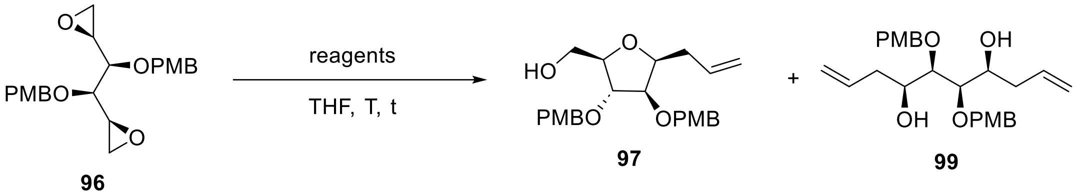
Then, epoxide formation was enabled under basic conditions to afford the desired bis-epoxide **96** in 22% over 6 steps. The overall yield was acceptable, although slightly lower than the published yields (45% over 6 steps) of the benzyl ether analogue.[173] The main difference is a significantly better yield during the last two steps of the sequence, indicating a higher sensitivity of the PMB ether toward the harsh reaction conditions. Nevertheless, the subsequent ring-closing reaction was examined. First experiments were conducted with vinyl magnesium bromide (Scheme 76) due to the more complex preparation of vinyl lithium.[175]



Scheme 76: Ring-closure induced by vinyl magnesium bromide and lithium bromide.

Surprisingly, the Grignard reagent led to the bromide as the main product in an inseparable mixture with the desired C-furanoside **97**. The formation of the bromide **98** was confirmed by the clean reaction with LiBr and NMR comparison (Scheme 76). Merrer *et al.* report similar results when using halogen-metal exchange for the preparation of their aryl lithium organyls.[172] Since halogenides must be avoided, a preparation of vinyl lithium by transmetallation from tetravinyl stannane was used.[175] The main problem of the bis-epoxide opening with vinyl lithium proved to be the selectivity between the 5-ring closure and the double addition, and the challenging separation of these two compounds (**97**, **99**). The optimization of the reaction conditions to reach a satisfying yield and selectivity is displayed in Table 17. The first two entries show the previously mentioned experiments with Grignard reagents, which afforded the corresponding halogenide adduct. With 2.0 equivalents of vinyl lithium, 43% conversion was achieved after ten minutes of reaction time at –60 °C (entry 3), while stirring for another five hours at –60 °C did not improve conversion. Increasing the amount of vinyl lithium and $BF_3{\cdot}OEt_2$ to 6.0 equivalents and lowering the temperature to –78 °C resulted in full conversion, albeit in low selectivity of 1:1 (entry 4). A comparison with entry 5 shows that a slower addition of the vinyl lithium and a higher temperature improved the selectivity with a loss in conversion. The bad solubility of the starting material at lower temperatures was assumed to be the main problem. Increasing the addition time and temperature improved the selectivity as expected, but conversion was insufficient (entry 6).

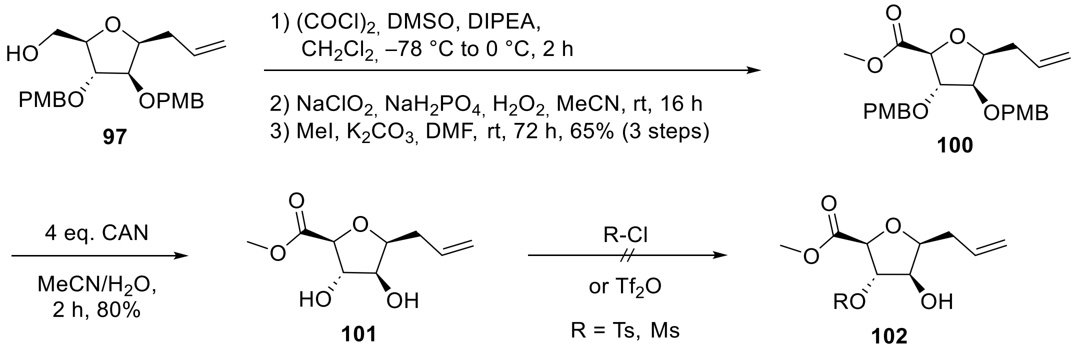
Table 17: Optimization of the ring-closing reaction with vinyl lithium.



entry	reagents	T	t (add.)[a]	conversion	ratio 97:99
1	2.0 eq. vinyl-MgBr, 2.0 eq. $BF_3{\cdot}OEt_2$	–50 °C	5 min	80%[b]	---
2	3.0 eq. vinyl-MgCl, 3.0 eq. $BF_3{\cdot}OEt_2$	–65 °C to rt	3 h	70%[b]	---
3	2.0 eq. vinyl-Li, 2.0 eq. $BF_3{\cdot}OEt_2$	–60 °C	10 min	43%	63:37
4	6.0 eq. vinyl-Li, 6.0 eq. $BF_3{\cdot}OEt_2$	–78 °C to –60 °C	60 min	100%	50:50
5	6.0 eq. vinyl-Li, 6.0 eq. $BF_3{\cdot}OEt_2$	–60 °C	1 h (10 min)	81%	78:22
6	3.0 eq. vinyl-Li, 3.0 eq. $BF_3{\cdot}OEt_2$	–50 °C	5 h (50 min)	15%	92:8
7	3.0 eq. vinyl-Li, 3.0 eq. $BF_3{\cdot}OEt_2$	–50 °C	1 h (10 min)	65%	78:22
8	6.0 eq. vinyl-Li, 6.0 eq. $BF_3{\cdot}OEt_2$	–20 °C	1 h (10 min)	40%	93:7
9	6.0 eq. vinyl-Li, 3.0 eq. $BF_3{\cdot}OEt_2$	–20 °C to rt	16 h (5 min)	100%	30:70
10	6.0 eq. vinyl-Li, 6.0 eq. $BF_3{\cdot}OEt_2$	–78 °C	5 min (4 h)	80%[c]	68:32
11[d]	6.0 eq. vinyl-Li, 6.0 eq. $BF_3{\cdot}OEt_2$	–78 °C	5 min (4 h)	73%[c]	94:6

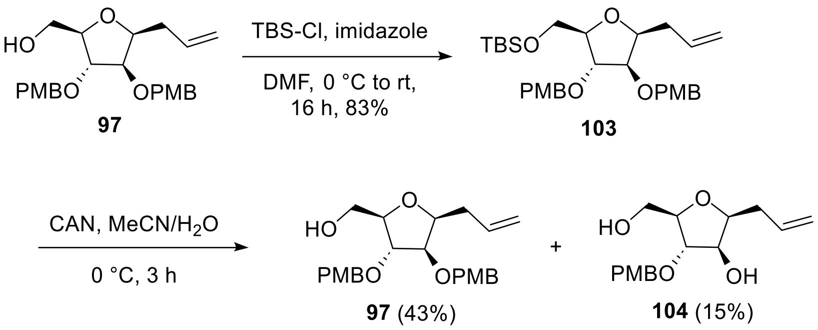
a) t = reaction time after addition, add. = time of vinyl lithium addition. b) conversion to the halogenide adduct.
c) isolated yield. d) vigorous stirring with a neodymium stirring bar.

By the assumption that the loss in conversion results from the vinyl lithium decomposing during the prolonged time at room temperature in the syringe, the addition time was reduced, and the temperature increased to −20 °C (entries 7 and 8). Addition of 6.0 equivalents of vinyl lithium in ten minutes resulted in only 40% conversion, which led to a reconsideration of the thermal stability of vinyl lithium (entry 8). It seemed more likely that the vinyl lithium reacts with BF_3 at elevated temperatures, for example, reported for the reaction of $BF(OMe)_2$ with lithium organyls.[176] Therefore, an excess of vinyl lithium compared to $BF_3{\cdot}OEt_2$ was used at −20 °C to check if the reaction behavior emphasizes this theory (entry 9). The reaction control showed a good selectivity of 95:5 and 40% conversion after 30 minutes, but in contrast to previous entries progressed to full conversion with an inverted selectivity of 30:70. This is the expected outcome if the vinyl lithium consumes the BF_3, which is responsible for the selectivity, and the excess of vinyl lithium subsequently consumes the starting material in an uncontrolled manner. The reaction temperature was lowered to –78 °C to eliminate the reaction of vinyl lithium with BF_3, and the addition time was increased to four hours to minimize the acute excess of vinyl lithium in the reaction mixture (entry 10). A good, isolated yield of 80% could be achieved, but the selectivity remained insufficient. The reaction was repeated with a strong neodymium stirring bar at 1200 rpm because the unsuccessful stirring of the thick suspension in entry 10 nullified the effect of a slow addition (four hours). Finally, the side product formation was suppressed nicely (ratio 94:6) while retaining a satisfying yield of 73%. Separating the side product from **97** proved impossible, and the mixture was used in the following oxidation procedure, starting with the Swern oxidation of the primary hydroxy group (Scheme 77). The crude aldehyde was further oxidized in a Pinnick oxidation followed by *O*-methylation with iodomethane, which gave methyl ester **100** in 65% yield over 3 steps.



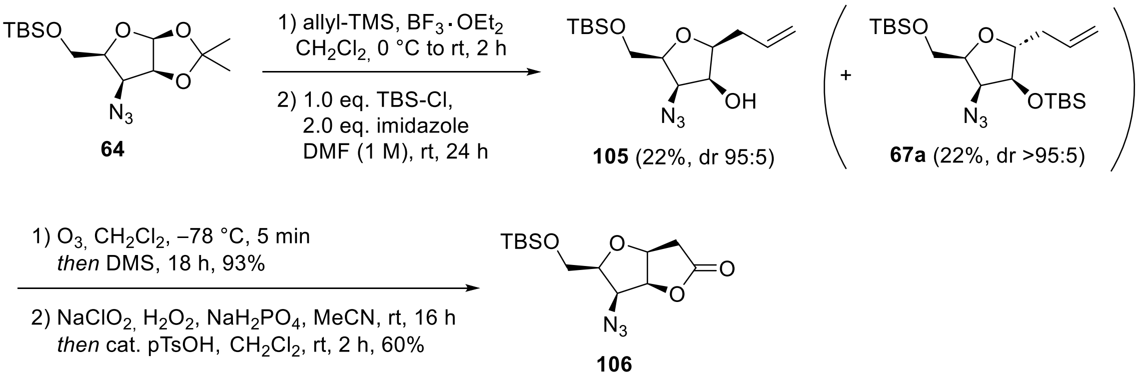
Scheme 77: Further transformation of C-furanoside 97.

Selective PMB-deprotection could not be achieved with DDQ and CAN under various conditions. The use of DDQ resulted in barely any conversion to the partially or fully deprotected product and ended in the decomposition of the starting material. In comparison, CAN showed no selectivity and produced a mixture of the mono-PMB-protected alcohols and the fully deprotected product **101**. After complete deprotection with 4.0 equivalents of CAN, selective tosylation, mesylation, and triflation were investigated. These attempts mainly ended in low conversion and in decomposition of the starting material after the addition of more reagents. Possible side reactions might be the epoxide formation or E_1-elimination (no antiperiplanar hydrogen atoms) to the α,β-unsaturated ester. As an alternative route, the primary alcohol was TBS-protected to examine if the PMB deprotection or the tosylation would be selective on this scaffold (Scheme 78). The TBS-protection under standard conditions gave compound **103** in 83% yield. Testing the selective deprotection with 2.0 equivalents of CAN surprisingly resulted in clean cleavage of the TBS-ether along with partial deprotection of the PMB-ethers. Unexpectedly, the sterically more hindered PMB group was cleaved first (confirmed by HMBC-correlations), affording the primary alcohols **97** and **104**.



Scheme 78: TBS-protection and attempted selective PMB-deprotection.

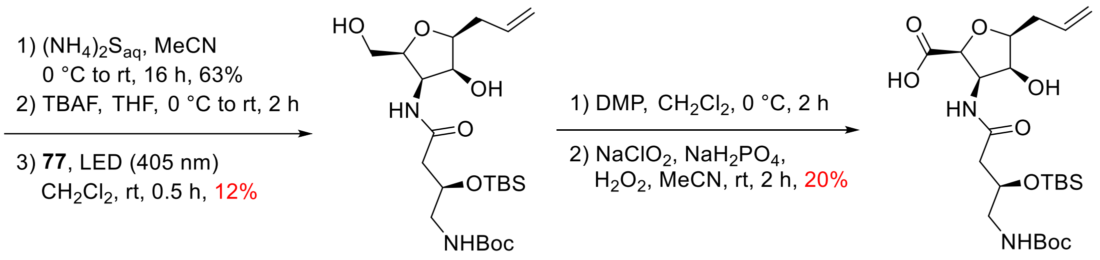
After these failed attempts, the Sakurai allylation of the D-arabinose-derived furanoside **64** was reevaluated under the previously (*cf.* Scheme 70) optimized "one-pot" conditions. The conditions for the TBS-protection were optimized once more to get both diastereomers in good diastereomeric ratios (Scheme 79). Both diastereomers were obtained in 22% yield with reasonable diastereomeric purities, confirming the earlier mentioned dr of 1:1 for the allylation step (page 59). The TBS-protection improved the yield from 26% in the allylation step to a total of 44% in 2 steps. Even though the other diastereomer **67a** could be used in the already shown route in Scheme 61, the yield of the desired product **105** was still unsatisfactory. However, no improvement could be achieved to date. The previously described sequence of ozonolysis and oxidation led to the lactone **106** confirming the 1,2-*cis* configuration.



Scheme 79: Optimized Sakurai allylation on 64 and confirmation of the stereochemistry by ozonolysis.

Nevertheless, the allylation finally gave access to all-*cis* diastereomer **105** in sufficient amounts, and the route was continued analog to diastereomer **56**. The azide was reduced with ammonium sulfide, followed by TBS-deprotection with TBAF (Scheme 80). The resulting crude amino alcohol was used in a Wolff-rearrangement with the diazoketone **77**, which yielded the amide **107** in only 12% yield. Reaction control via LC-MS showed that the conversion of the amine was rather low, but the diazoketone was completely consumed, mainly due to [2+2]-cycloaddition.[177] Indeed, the reactivity of the amino alcohol seems to be much lower compared to its diastereomer **89** due to the increased sterical hindrance in the all-*cis* configuration. The selective oxidation with DMP was tested with the small amount of isolated **107**. A low conversion rate and insufficient selectivity toward the primary alcohol of **107** further complicated the progress on the all-*cis* diastereomer. Pinnick oxidation of the crude aldehyde yielded the carboxylic acid **108** in only 20% with a low purity of around 80%.

105



107

108 (80% purity)

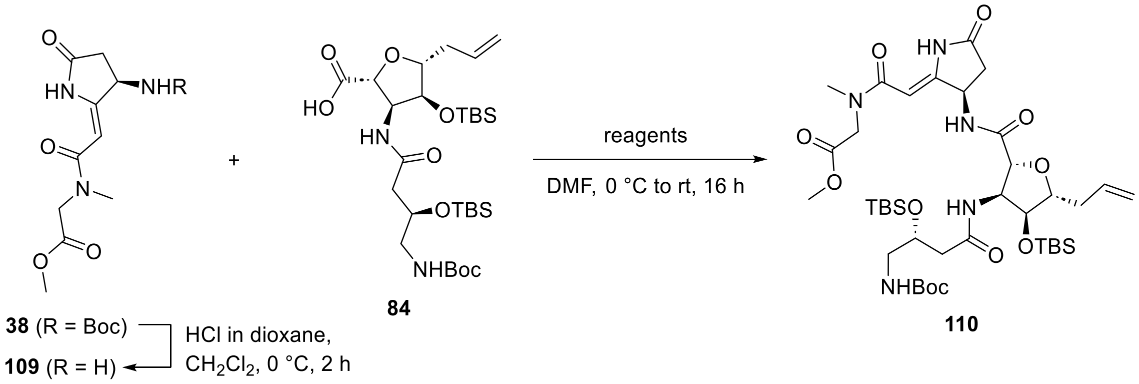
Scheme 80: Wolff-rearrangement with the all-*cis* diastereomer.

Due to several consecutive low-yielding steps, the remaining material proved insufficient to complete the synthesis of the last diastereomer. The necessity to perform extensive optimizations of several critical steps due to the high sterical demand of the all-*cis* diastereomer made this route not feasible. Therefore, the synthesis of this diastereomer was not finished, and the development of an entirely new route was planned after the completion of the socein-derivatives outside the scope of this thesis.

4.2.3 Coupling of the Building Blocks

With the different building blocks in hand, the attention was turned toward the coupling of these to afford the dehydrosocein target structures. A standard peptide coupling with EDC/HOBt between amino pyrrolidone **109** and dipeptide **84** gave tetrapeptide **110** in 70% yield, containing 25% of its epimer (Table 18, entry 1). Different conditions and peptide coupling agents were tested to reduce the epimerization. In entries 2 – 5, the coupling reagents HATU, PyAOP, and COMU were tested against the carbodiimide coupling using an excess of the hydrochloride salt **109**·HCl. The epimerization was observed via LC-MS, which showed an improvement in the EDC/HOBt coupling by using an excess of the amine component. None of the other coupling reagents decreased the epimerization rate below 13%. On the contrary, the COMU-mediated coupling increased the epimerization significantly to 33%.

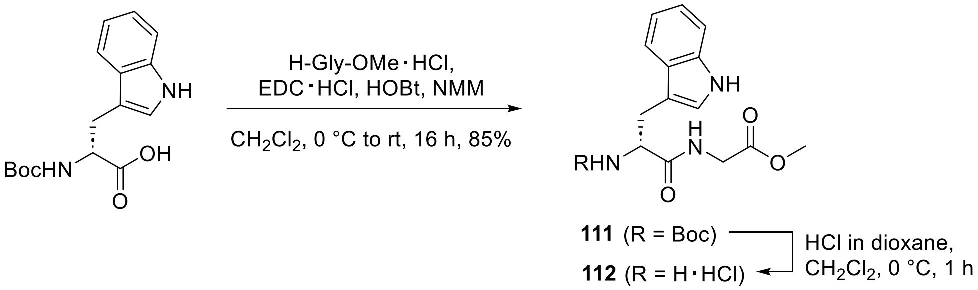
Table 18: Epimerization suppression on the coupling of 109 with 84.



entry	reagents	additives	epimer	yield
1	1.05 eq. EDC·HCl, 1.0 eq. **109**·HCl, 1.0 eq. NMM	0.2 eq. HOBt	25%	70%
2	1.05 eq. EDC·HCl, 1.5 eq. **109**·HCl 1.4 eq. NMM	0.2 eq. HOBt	13%	---[a]
3	1.05 eq. HATU, 1.5 eq. **109**·HCl 2.5 eq. lutidine	---	17%	---[a]
4	1.05 eq. PyAOP, 1.5 eq. **109**·HCl, 2.5 eq. lutidine	---	18%	---[a]
5	1.05 eq. COMU, 1.5 eq. **109**·HCl 2.5 eq. lutidine	---	33%	---[a]
6	1.05 eq. EDC·HCl, 1.5 eq. **109**·HCl 1.4 eq. NMM	1.0 eq. HOBt, 1.0 eq. $CuCl_2$	21%	89%
7	1.05 eq. EDC·HCl, 1.5 eq. **109**	0.2 eq. HOBt	7%	79%
8	1.05 eq. EDC·HCl, 1.5 eq. **109**	1.0 eq. HOBt, 1.0 eq. $CuCl_2$	8%	80%
9	1.05 eq. DIC, 1.5 eq. **109**	1.0 eq. oxyma	10%	60%
10[b]	1.05 eq. EDC·HCl, 1.5 eq. **109**	0.2 eq. HOBt	10%	96%

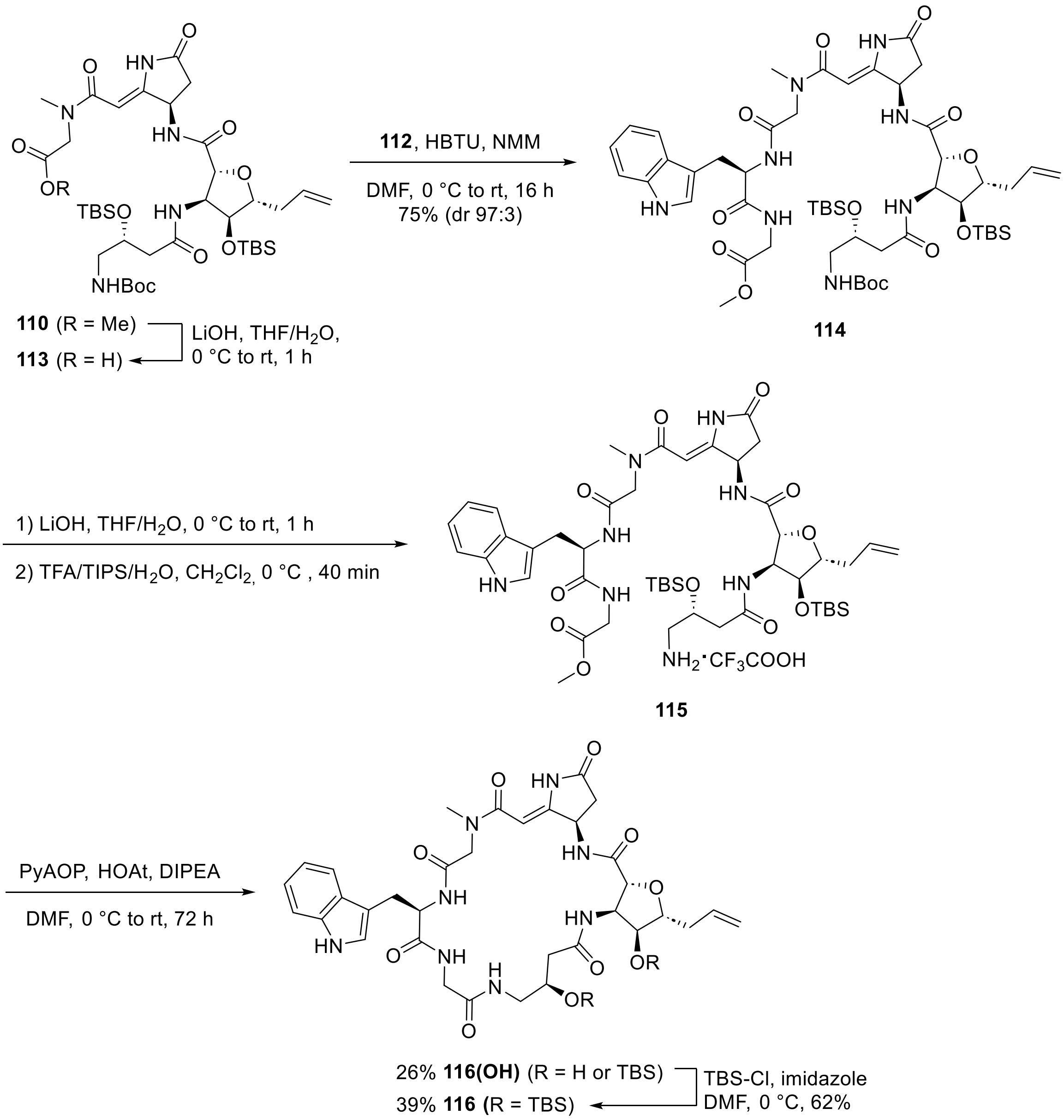
a) Epimerization determined by LC-MS – product not isolated. b) 0.15 mmol scale

Continuing with the carbodiimides, a protocol by Miyazawa and co-workers[178] using copper-(II) chloride and HOBt as additives for a remarkable epimerization suppression in the EDC-coupling was tested (entry 6). In this case, the use of $CuCl_2$ had no positive influence on the epimerization. In entries 7 – 9, the free amine **109** was used in a base-free carbodiimide coupling. Finally, the EDC/HOBt coupling in entry 7 showed acceptable results with 79% yield and an epimerization of 7%. The use of the Miyazawa protocol with $CuCl_2$ did not impact the yield or epimerization (entry 8). Another carbodiimide-based coupling reagent (DIC) in combination with oxyma could not improve the results and gave a lower yield of 60% and 10% epimerization. Repeating the conditions of entry 7 on a larger scale resulted in 96% yield, albeit with a slightly higher epimerization of 10%. For the next coupling, the dipeptide **111** was synthesized in another EDC/HOBt coupling with Boc-protected D-tryptophane and the hydrochloride salt of glycine methyl ester (Scheme 81).



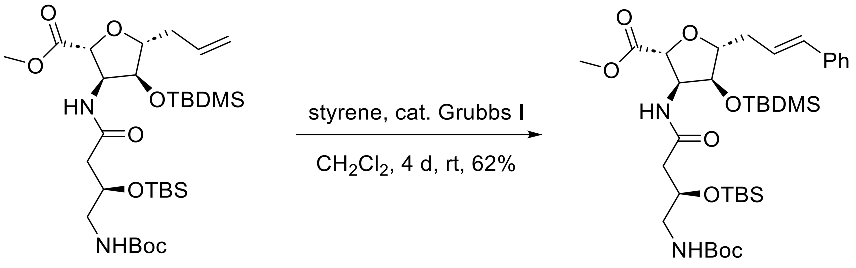
Scheme 81: Dipeptide coupling to Boc-D-Trp-Gly-OMe 111.

After Boc-cleavage of **111** under acidic conditions and saponification of tetrapeptide **110**, both building blocks were reacted in an HBTU-mediated coupling (Scheme 82). The hexapeptide **114** was isolated in 75% yield and a diastereomeric ratio of 97:3. Most of the epimer could be separated by reversed-phase column chromatography. Based upon previous experiences of acidic deprotections of larger peptides, a cleavage cocktail of TFA/TIPS was used to achieve Boc-deprotection to the TFA-salt **115**. When the Boc-deprotection was finished, one of the TBS-groups was partially cleaved. A mixture of the bis-TBS-protected peptide and the mono-TBS-protected peptide in a ratio of 6:4 was used in the subsequent macrocyclization. A high dilution protocol with PyAOP, known from the cyclization of dehydromicrosclerodermin B,[15] gave dehydrosocein precursor **116** and the mono TBS-deprotected derivative **116(OH)** in a total yield of 65% over 3 steps. Transformation of **116(OH)** to the desired bis-protected **116** was achieved by treatment with TBS-Cl and imidazole.



Scheme 82: Final coupling with dipeptide 111 and macrocyclization.

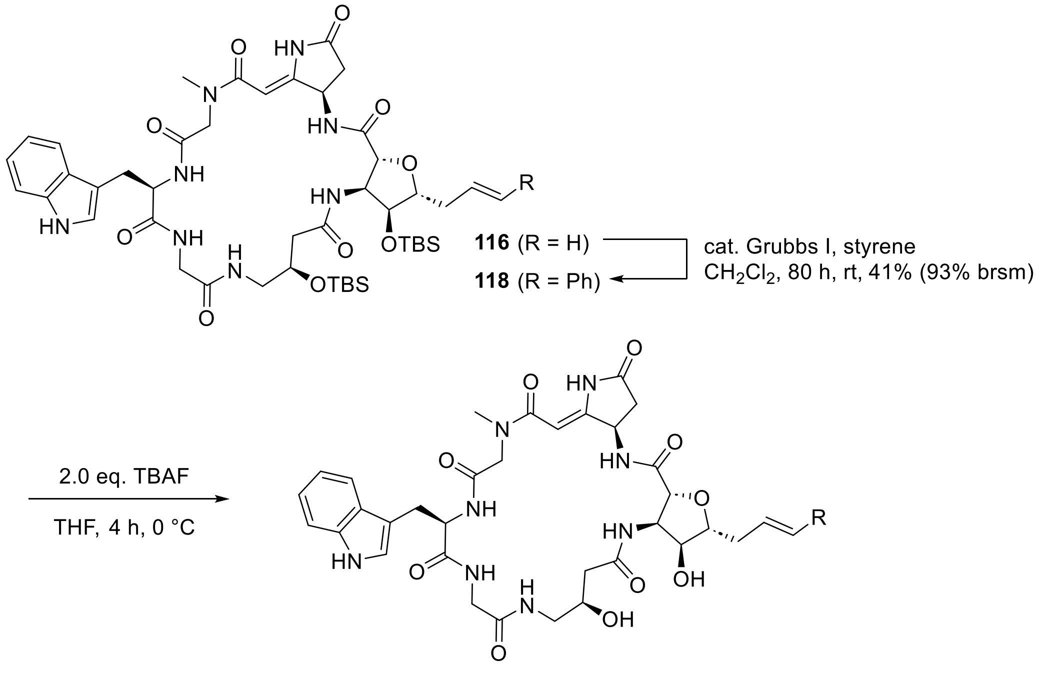
As a final step, the incorporation of an aromatic side chain was required. Hence, an olefin cross-metathesis with styrene was planned, aiming to introduce the simplified side-chain resembling that of microsclerodermin C, D, and L. Donohoe and co-workers used 4-methoxy styrene and a first-generation Grubbs catalyst for a late-stage olefination during their synthesis of dehydromicrosclerodermin B.[15] Before the Grubbs metathesis was applied to the dehydrosocein precursor **116**, a smaller test substrate was used (Scheme 83). First-generation Grubbs catalyst and a large excess of styrene resulted in the olefination product **117** in 62% yield. Although the reaction proceeded slowly and required preparative HPLC to achieve satisfactory purity, the promising yield encouraged further attempts on the more complex structure.



83 **117**

Scheme 83: Testing the Grubbs-metathesis on a smaller building block.

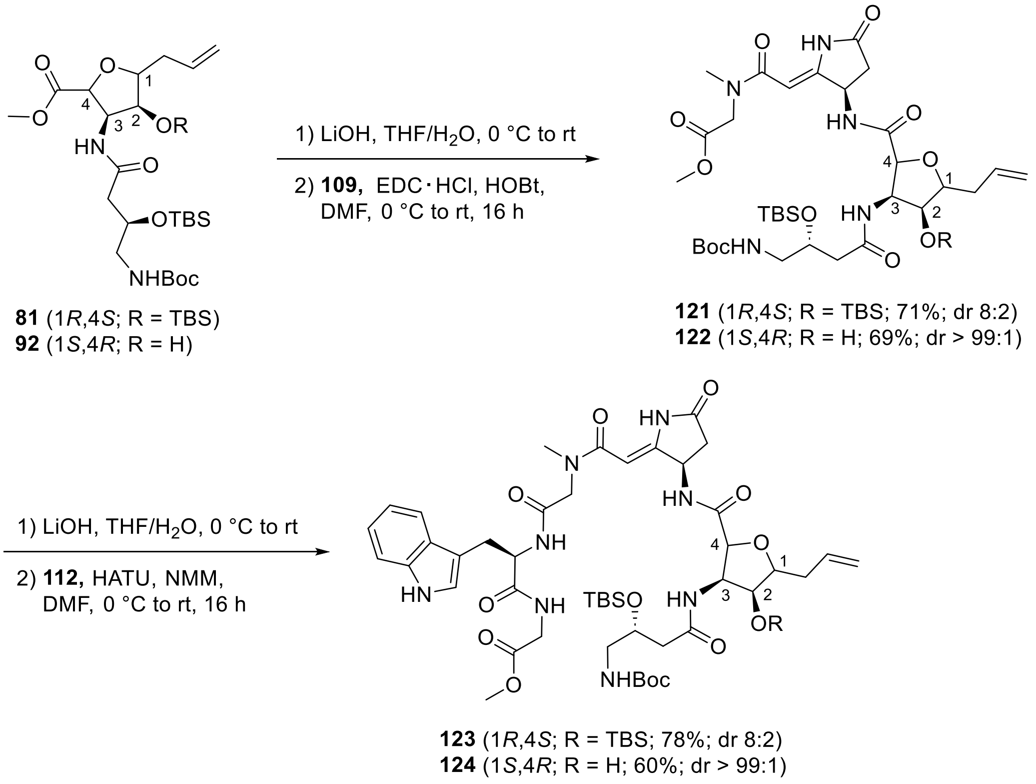
The Grubbs-metathesis conditions on the dehydrosocein precursor **116** resulted in 50% conversion. Addition of more Grubbs I-catalyst barely improved the conversion (Scheme 84). Therefore, the reaction was stopped, the desired product **118** was isolated in 41% yield, and 52% of the starting material was recovered. Deprotection by treatment with TBAF afforded two dehydrosocein derivatives, **119** and **120**, both were submitted to the HIPS for bioactivity testing. Due to the low conversion of the metathesis, µmol-scale test reactions on **116** were run with first-generation Grubbs-, second-generation Grubbs-, and Hoveyda-Grubbs-catalyst. Grubbs II showed 87% conversion compared to 50% with the first-generation Grubbs-catalyst. Hoveyda-Grubbs showed similar results to Grubbs II, but a higher amount of side product formation. Thus, the second-generation Grubbs catalyst was used in subsequent reactions.



119 (R = H, 72%)
120 (R = Ph, 96%)

Scheme 84: Introduction of the styrene side chain via Grubbs-metathesis and final deprotection.

The two remaining diastereomeric building blocks (**81**, **92**) were converted similarly (Scheme 85). Starting with **81**, saponification followed by EDC/HOBt coupling led to the tetrapeptide **121** in 71% yield. Even though the previously optimized base-free carbodiimide coupling was used, the reaction resulted in 20% epimerization. This diastereomeric mixture **121** was saponified and coupled with dipeptide **112** using HATU. In this case, the hexapeptide **123** was isolated in 79% yield, but the diastereomeric ratio remained at 8:2 due to similar retention times of the diastereomers during the reversed-phase column chromatography. The EDC/HOBt-coupling of **92** with **109** proceeded with 9% epimerization and gave the tetrapeptide **122** in 69% yield as a single diastereomer after preparative HPLC. Finally, the hexapeptide **124** was isolated in 60% yield after HATU coupling with dipeptide **112**. A comparison of the NMR-data of the different diastereomers of the tetrapeptides (**110**, **121,** and **122**) and their epimers clearly refute the α-epimerization of the activated carboxylic acid. Alternatively, an *E*,*Z*-isomerization, or an epimerization at the amino pyrrolidone via imine-enamine tautomerization would be conceivable, but none of those hypotheses could be validated.

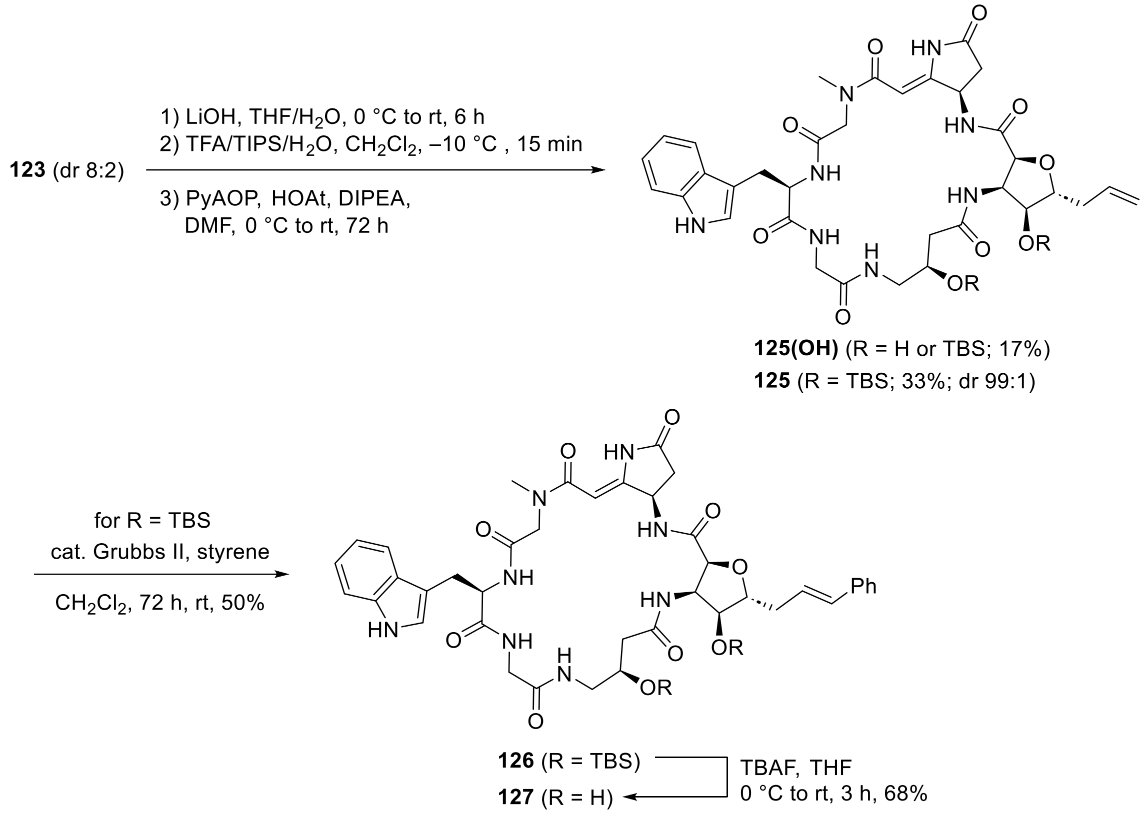


81 (1*R*,4*S*; R = TBS)
92 (1*S*,4*R*; R = H)

121 (1*R*,4*S*; R = TBS; 71%; dr 8:2)
122 (1*S*,4*R*; R = H; 69%; dr > 99:1)

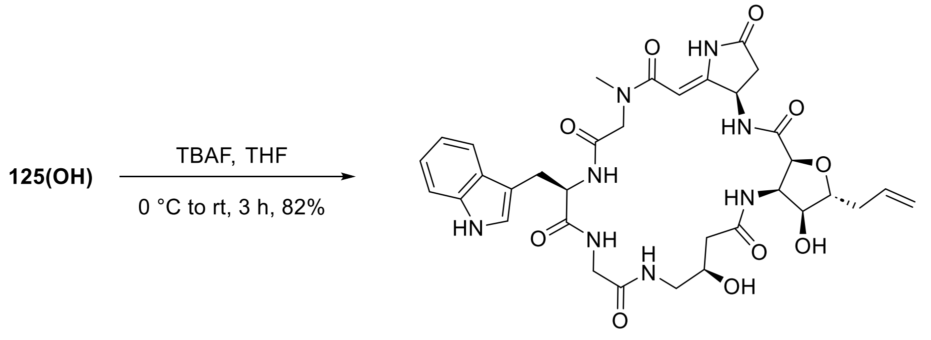
123 (1*R*,4*S*; R = TBS; 78%; dr 8:2)
124 (1*S*,4*R*; R = H; 60%; dr > 99:1)

Scheme 85: Coupling sequence of another two diastereomers.



Scheme 86: Macrocyclization, Grubbs-metathesis, and final deprotection for the D-arabinose derived diastereomer.

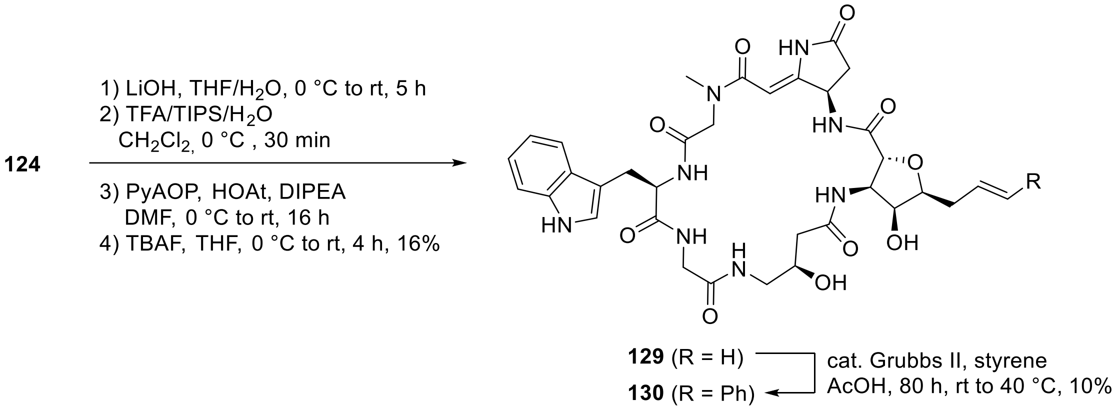
Utilizing the same sequence of saponification, acidic deprotection, and high-dilution macrocyclization on the isomeric mixture of **123** afforded the dehydrosocein precursor **125** in 33% yield along with 17% of mono-TBS-protected derivative **125(OH)** (Scheme 86). The stereoisomer was separated during the purification via preparative HPLC. Contrary to expectations, the olefin cross-metathesis with the second-generation Grubbs catalyst only marginally improved the yield to 50%. After removal of the TBS-protecting groups with TBAF, the dehydrosocein derivative **127** was isolated in good yield. Deprotection of the mono-protected cyclopeptide **125(OH)** under identical conditions gave the allyl-dehydrosocein derivative **128** in 82% yield (Scheme 87). Both derivatives were submitted to bioactivity testing at the HIPS.



128

Scheme 87: Deprotection of the mono-protected cyclopeptide 125(OH).

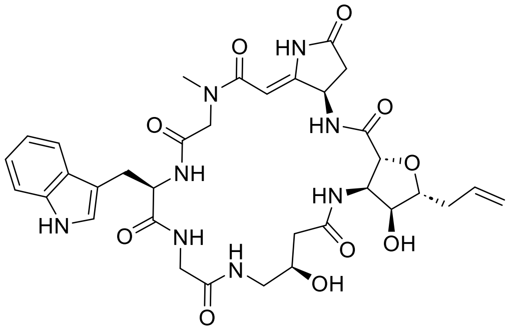
For the third diastereomer **124**, the cyclization proved more problematic (Scheme 88). Saponification and acidic deprotection proceeded cleanly, and no TBS-cleavage was observed. The cyclization with PyAOP/HOAt showed complete conversion to the desired macrolactam in the reaction control by LC-MS. However, separation of the cyclized product from the side products of the coupling reagents, like the tripyrrolidinyl phosphine oxide, turned out to be impossible. Numerous attempts using column chromatography and preparative HPLC proved unsuccessful. Consequently, a subsequent TBS-deprotection was carried out to modify the polarity and, ultimately, the retention time of the product. After another purification by preparative HPLC, the dehydrosocein derivative **129** was isolated in 16% yield over 4 steps. Due to the insolubility of the hexapeptide **129** in toluene and CH_2Cl_2, the Grubbs-metathesis was conducted in AcOH, a solvent for cross-metathesis with remarkable reaction kinetics.[179] The dehydrosocein derivative **130** could be isolated in only 10% yield even after several additions of catalyst and increasing the temperature to 40 °C.



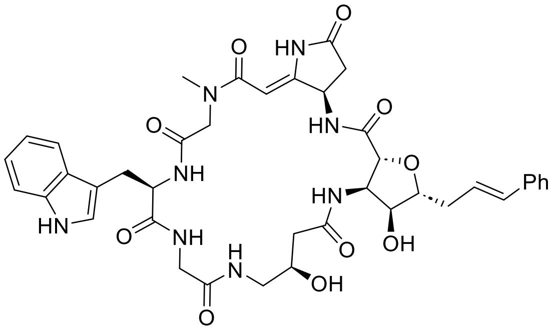
Scheme 88: Macrocyclization and Grubbs-metathesis for the second L-xylose-derived diastereomer.

These last two diastereomers (**129** and **130**) were also submitted for bioactivity testing against different bacteria and fungi. The structures and the results of the bioassays are displayed in Table 19. None of the derivatives showed any bioactivity against the tested microorganisms. The conspicuous activity of the microsclerodermin family against *Candida albicans* made it the most interesting target. However, none of the synthesized derivatives showed any antimycotic activity against this type of fungi. Currently, the reisolation of socein is pursued at the HIPS, which should deliver analytical data of socein and dehydrosocein. With this data, a conclusion about the absolute stereochemistry by comparison with the herein synthesized derivatives might be possible. This could help explain the missing bioactivity of the prepared derivatives. The analytical data should additionally indicate if the missing all-*cis* configuration represents the absolute configuration in the natural product. The hemiaminal and the more complex side chain could also prove to be more critical to the bioactivity than expected. However, all these assumptions lack substance until the data of the isolated natural product is available, as it could still be inactive per se.

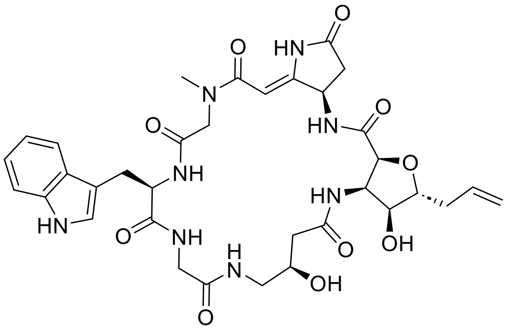
Table 19: Results of the bioactivity testing for the synthesized dehydrosocein derivatives.



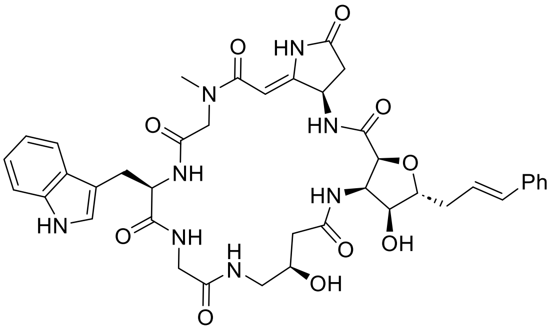
119



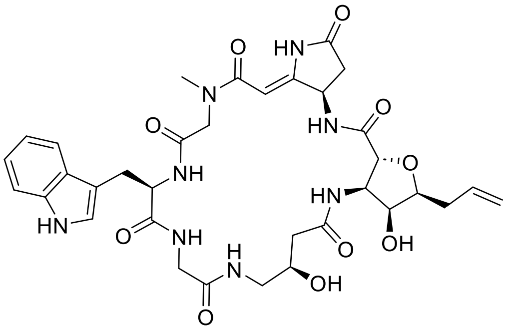
120



128



127



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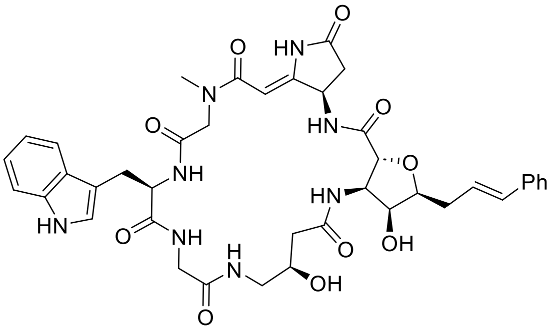


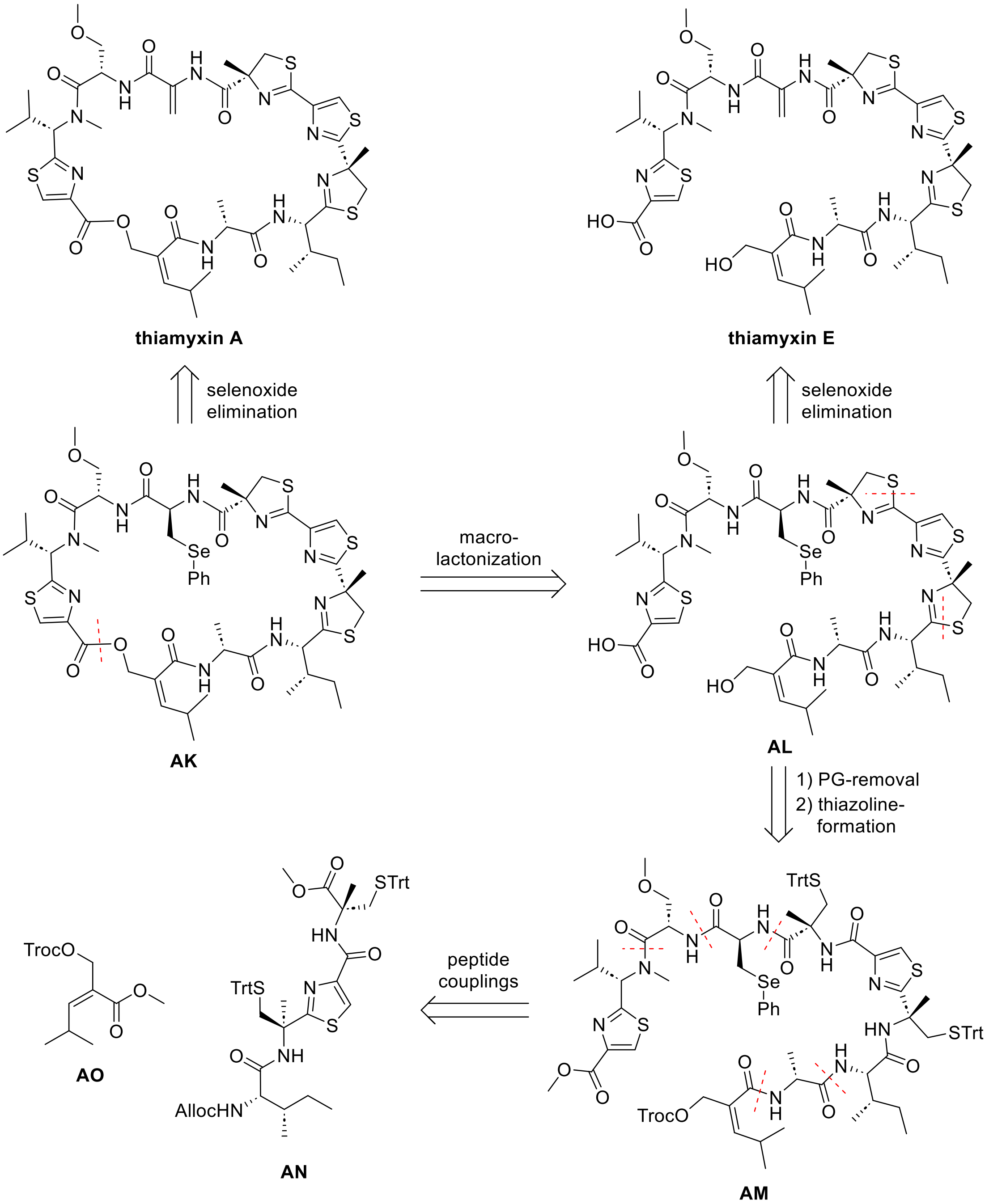
130

							IC₅₀ [µg/mL]
	C. neoformans [DSM11959]	*S. aureus* Newman	*E.coli* WT [BW2511]	*C. albicans* [DSM1665]	*P. anomala* [DSM6766]	*M. smegmatis* [MC2155]	*Hep G2*
119	>64	>64	>64	>64	>64	>64	>37
120	>64	>64	>64	>64	>64	>64	>37
128	>64	>64	>64	>64	>64	>64	>37
127	>64	>64	>64	>64	>64	>64	>37
129	>64	>64	>64	>64	>64	>64	>37
130	>64	>64	>64	>64	>64	>64	>37

4.3 Thiamyxins[112]

4.3.1 Retrosynthetic Analysis

The last part of this thesis targets the two depsipeptide natural products, the cyclic thiamyxin A and its open-chain variant thiamyxin E. This linear depsipeptide was previously only reported as a minor diastereomer in the mixture of the isolated thiamyxin C.[107] These two thiamyxins contain the natural L-isoleucine, contrary to the epimers thiamyxin B and C, containing the very expensive D-*allo*-isoleucine. The epimers should be accessible via a targeted epimerization of the acid labile C-2 exomethine position[78,84,90] of the isoleucine moiety. Due to the reported separation problems of the open-chain thiamyxins C and E[107] and more overall control, the development of an epimerization-free route was desirable.

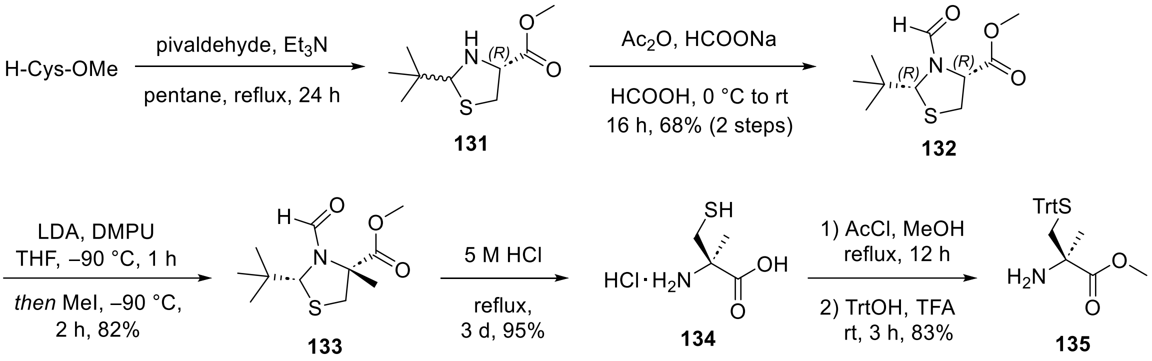


Scheme 89: Retrosynthetic analysis of thiamyxin A and E.

Both target structures, thiamyxin A and E, contain a dehydroalanine unit whose introduction was envisioned via late-stage modification due to its potential lability toward Michael addition (Scheme 89). A retro-selenoxide elimination leads to the phenyl selenocysteine containing precursors **AK** and **AL**. At this stage, a macrolactonization was planned to convert these two precursors into each other. Introduction of the methyl ester and a Troc-protecting group, both cleavable under mild-basic conditions with Me_3SnOH[131,180], followed by opening of the thiazolines, leads to octapeptide **AM**. A series of peptide couplings results in six building blocks, with the thiazoline-thiazol-thiazoline precursor **AN** and the uncommon *Z*-configurated hydroxy acid **AO** being the most interesting structures.

4.3.2 Synthesis of the Thiazoline-Thiazole-Thiazoline Building Block

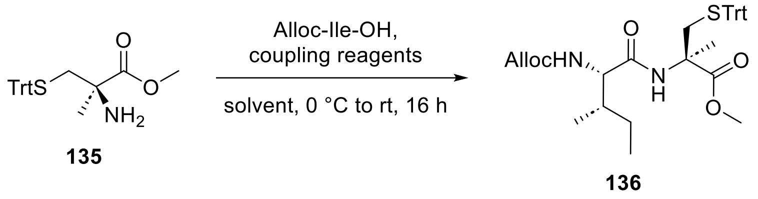
Starting with the synthesis of enantiopure α-methyl cysteine according to a protocol by Pattenden and co-workers,[181] cysteine methyl ester was condensed with pivaldehyde to the diastereomeric mixture of thiazolidine **131** (Scheme 90). Selective formylation of the *syn*-diastereomer with acetic anhydride and sodium formate in formic acid resulted in the diastereomeric pure formyl thiazolidine **132**.[182] Enolate formation and methylation at the α-position of the methyl ester gave methyl thiazolidine **133** in 82% yield as a single diastereomer, utilizing the "self-regenerating stereocenter" approach by Seebach *et al.*[183]



Scheme 90: Synthesis of α-methyl cysteine and *S*-tritylation.

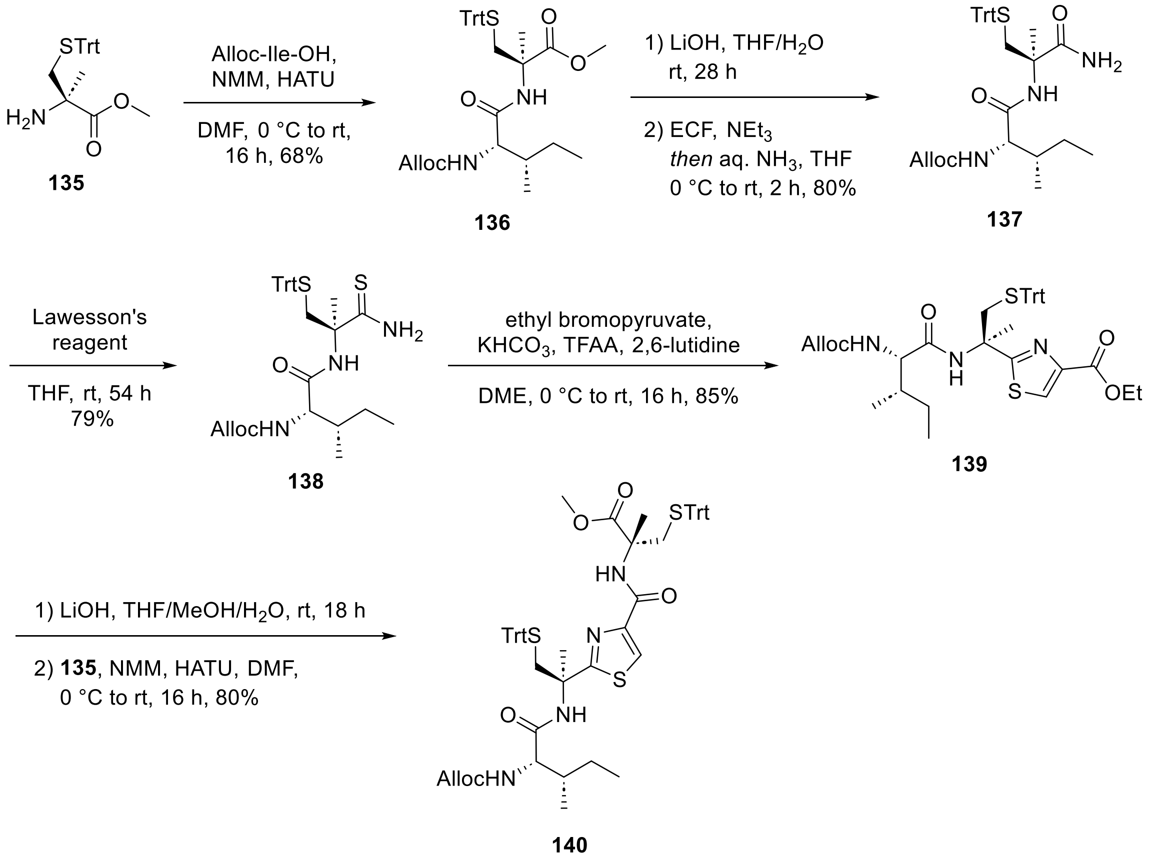
After cleavage of the auxiliary in aqueous hydrochloric acid, a Fischer esterification and *S*-tritylation with triphenylmethanol in TFA[184] afforded trityl-protected α-methyl cysteine **135** in 79% yield over 3 steps. Different conditions were screened for the following coupling with Alloc-protected L-isoleucine to optimize the initial 68% yield with HATU in dichloromethane (Table 20, entry 1). Neither DMF as a solvent nor the use of PyBOP, PyAOP or EDC/HOBt as coupling reagents positively impacted the yield (entries 2 – 5).

Table 20: Peptide coupling of α-methyl cysteine 135 and Alloc-isoleucine.



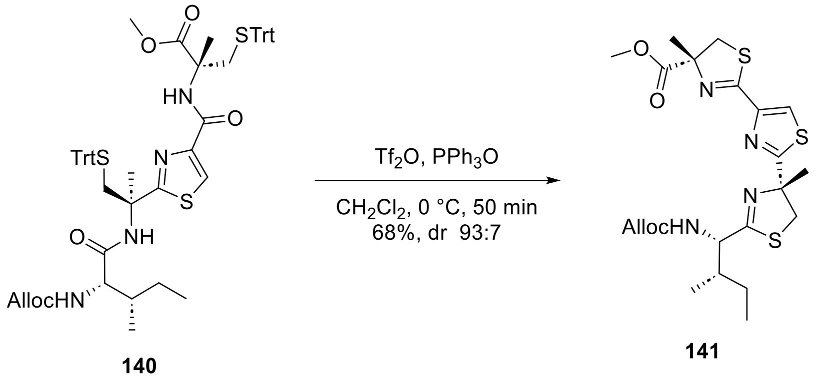
entry	coupling reagents	Alloc-Ile-OH	solvent	yield
1	1.2 eq. HATU, 2.2 eq. NMM	1.2 eq.	CH_2Cl_2	68%
2	1.2 eq. HATU, 2.2 eq. NMM	1.2 eq.	DMF	68%
3	1.2 eq. EDC·HCl, 0.2 eq. HOBt, 1.2 eq. NMM	1.2 eq.	CH_2Cl_2	52%
4	1.2 eq. PyBOP, 2.4 eq. NMM	1.2 eq.	DMF	55%
5	1.2 eq. PyAOP, 2.4 eq. NMM	1.2 eq.	DMF	63%
6	1.4 eq. IPCF, 1.3 eq. DIPEA, 0.1 eq. $BnMe_2$, 0.1 eq. NMI, 0.1 eq. HCl	1.2 eq.	dioxane/MeCN	51%

Additionally, a recently published protocol for sterically demanding amines by Fuse *et al.*[185] via an *N*-methylimidazolium active ester resulted in only 51% yield (entry 6). After these unsuccessful optimization attempts, the synthesis was continued with a modified Hantzsch thiazole synthesis (Scheme 91).[120] Saponification of the methyl ester **136** and amidation via mixed anhydride-activation gave the primary amide **137** in 80% yield. The amide group was transformed into the thioamide by treatment with Lawesson's reagent.[119] Subsequently, the thiazole was formed with ethyl bromopyruvate under dehydration conditions to yield **139** in 85% yield. After saponification of the methyl ester, a second coupling with α-methyl cysteine **135**, under identical conditions, was conducted. In this case, the final building block **140** was isolated in a good yield.



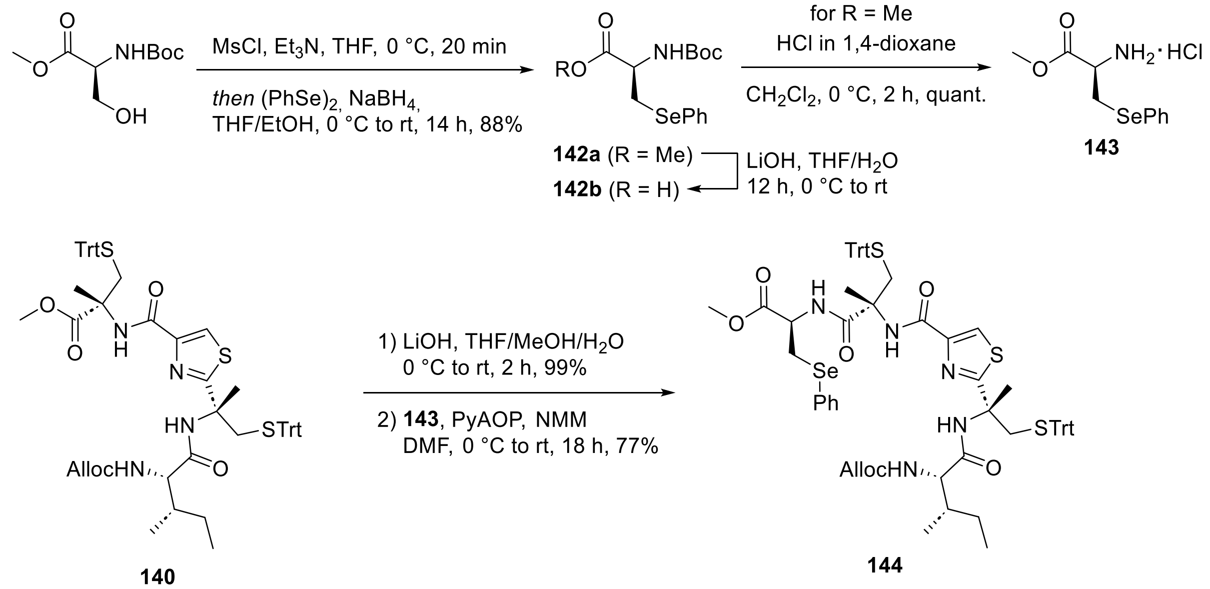
Scheme 91: Synthesis of the thiazoline precursor 140.

Before continuing with the other building blocks, the (low epimerization) thiazoline formation protocol by Kelly and co-workers[92] was tested on **140** (Scheme 92). This gave the desired bis-thiazoline **141** in 68% yield, containing 7% of its epimer. Due to the high amounts of triphenylphosphine oxide, an elaborate purification via normal- and reversed-phase chromatography was required. However, the yield and low epimerization encouraged the approach via late-stage thiazoline formation.



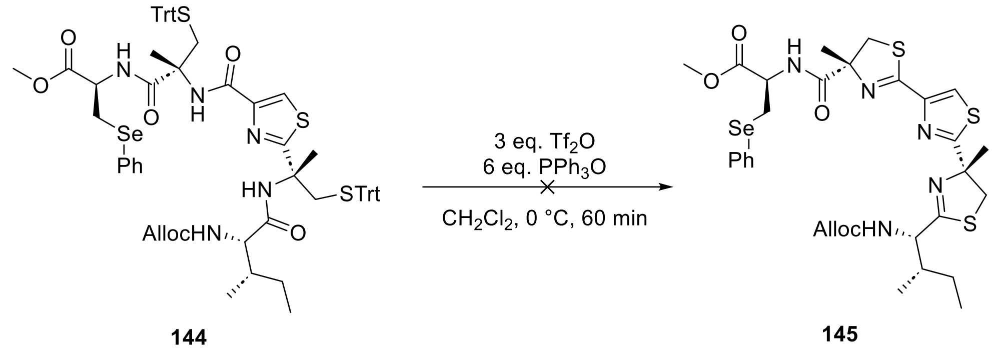
Scheme 92: Testing the low-epimerization thiazoline formation protocol.

To analyze how the selenocysteine moiety influences the thiazoline formation, the coupling of building block **140** and phenyl selenocysteine, followed by bis-thiazoline formation, was planned (Scheme 93). Therefore, phenyl selenocysteine **142a** was prepared from Boc-protected serine methyl ester in a protocol by Braga *et al.*[186] Mesylation followed by nucleophilic substitution with *in-situ* produced sodium phenyl selenide gave **142a** in 88% yield. The saponification of methyl ester **140** proved to be more problematic than expected. In THF/H_2O, the reaction progressed slowly and did not reach complete conversion after several days. Addition of methanol and reduction of the amount of water to a total ratio of THF:MeOH:H_2O (5:9:1) smoothly led to the carboxylic acid in quantitative fashion. After Boc-deprotection of **142a**, the hydrochloride salt **143** was reacted with the carboxylic acid using PyAOP as a coupling reagent. Other conditions like EDC/HOBt, EDC/DMAP, and HATU were screened, but all afforded the tetrapeptide **144** in significantly lower yields.



Scheme 93: Synthesis of phenyl selenocysteine 143 and peptide coupling with the thiazoline precursor 140.

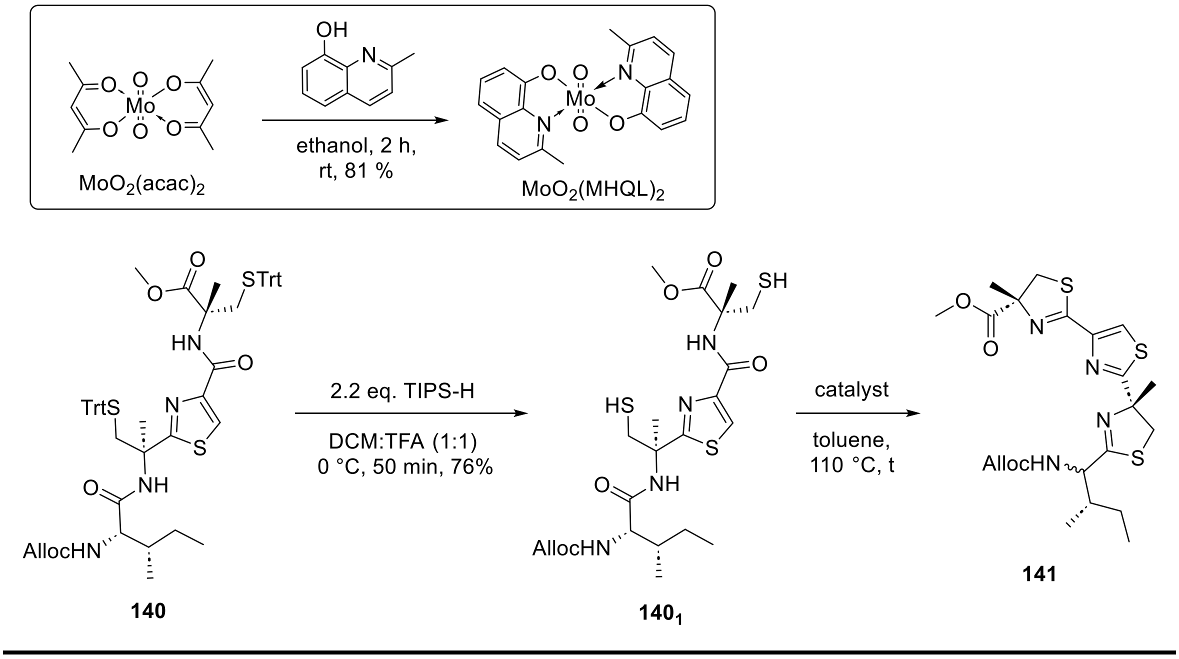
With this tetrapeptide **144** in hand, the bis-thiazoline formation was attempted again (Scheme 94). In this case, the PPh_3O/Tf_2O protocol showed a rather low conversion to a mono-cyclized product after 60 min reaction time. Continuing the reaction resulted in decomposition of the starting material without formation of the desired product **145**.



Scheme 94: Failed thiazoline formation on compound 144.

Similar problems have been reported for this protocol on highly functionalized intermediates during the synthesis of vioprolide precursors[187] and the SPPS-based total synthesis of apratoxin A.[97] Due to the high number of amide bonds, complex peptides might undergo unwanted side reactions induced via amide bond activation with the phosphorous-(V) species. Considering the number of competing amides in an octapeptide **AM** during the late-stage bis-thiazoline formation (cf. Scheme 89), another thiazoline synthesis via molybdenum catalysis was tested (Table 21). The Ishihara group reported the use of dioxo molybdenum-(VI) with acetyl acetonide (acac) or various quinolinols as ligands in thiazoline formation with low epimerization at the C-2 exomethine position.[102]

Table 21: Thiazoline formation via molybdenum-catalysis.



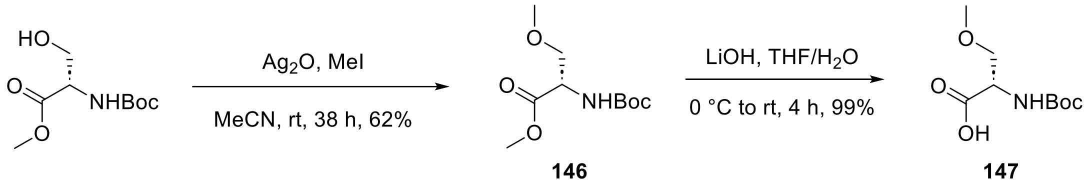
entry	catalyst	t	conversion	yield	dr
1	10mol% $MoO_2(acac)_2$	7 h	100%	40%	1:1
2	2mol% $MoO_2(MHQL)_2$	7 h	100%	48%	1:1
3	10mol% PPTS	4 h	0%	---	---
4	10mol% pTsOH	16 h	80%[a]	---[a]	1:1

a) Only mono-cyclized product was observed.

In order to evaluate this method, the trityl-protecting group of **140** was removed under acidic conditions with triisopropyl silane as a trityl-cation scavenger. Entry 1 shows the first attempt with $MoO_2(acac)_2$, which yielded the thiazoline-thiazol-thiazoline **141** in 40% yield as a mixture of diastereomers (1:1). Ishihara *et al*. achieved a significant improvement in retention of the stereocenter when using quinolinols as ligands. Thus, $MoO_2(MHQL)_2$ was synthesized by treating $MoO_2(acac)_2$ with 2-methyl-8-quinolinole in ethanol. Following the reported procedure, a lower catalyst loading of 2mol% was used, which improved the yield slightly to 48% but showed no difference in the rate of epimerization (entry 2). Additionally, Brønsted acid-catalyzed thiazoline formation was tested (entries 3 and 4). The weak acidity of pyridinium *p*-toluene sulfonate (PPTS) did not suffice to catalyze the reaction. Stronger acids such as *p*-toluene sulfonic acid (pTsOH) displayed good conversion, albeit to a mono-cyclized product with complete epimerization of the C-2 exomethine center. Due to the limited success of these "low-racemization" protocols of bis-thiazoline formations on tetrapeptide **144**, the coupling of the building blocks was continued with the cyclized thiazoline-thiazol-thiazoline building block **141**.

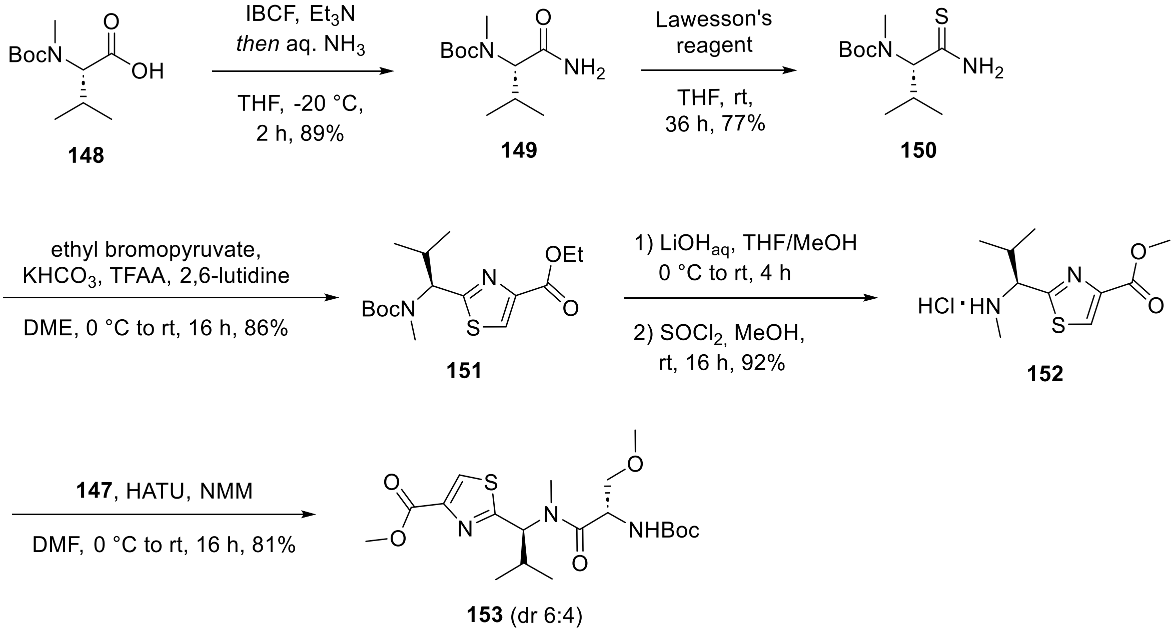
4.3.3 Synthesis of the Western Fragment

The western fragment contains the unnatural *O*-methylated serine, synthesized via a protocol by Koskinen *et al.* (Scheme 95).[188] The reaction of Boc-Ser-OMe with iodomethane in the presence of silver-(I) oxide in MeCN under exclusion of light gave methylether **146** in acceptable yield. Saponification with LiOH cleanly afforded carboxylic acid **147** as the first building block of the western fragment.



Scheme 95: *O*-Methylation of Boc-serine methyl ester according to Koskinen *et al.*

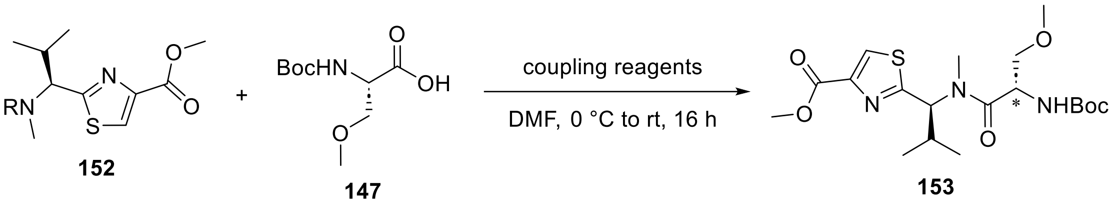
The synthesis of the thiazol fragment, starting from *N*-methylated L-valine **148,** was carried out next using the modified Hantzsch thiazol synthesis by Meyers *et al.* (Scheme 96).[120] After introduction of the primary amide, reaction with Lawesson's reagent led to the thioamide **150** in 69% yield over 2 steps. The modified Hantzsch with ethyl bromopyruvate under dehydration conditions produced thiazol **151** in high yield. Due to mild conditions (Me_3SnOH) required during the final deprotection sequence, the ethyl ester was replaced by a more sensitive methyl ester. This was achieved by saponification of the ethyl ester with LiOH followed by a simultaneous Boc-deprotection and Fischer-esterification with *in-situ* generated HCl in MeOH. The hydrochloride salt **152** was isolated in 92% yield over 2 steps and coupled with the previously synthesized *O*-methylated Boc-serine **147**. HATU as coupling reagent yielded the dipeptide **153** in good yield, but with severe epimerization resulting in a diastereomeric mixture of 6:4. High-temperature NMR and separation by preparative HPLC confirmed the diastereomers as such.



Scheme 96: Synthesis of the thiazole building block 152 and coupling with *O*-methyl serine 146.

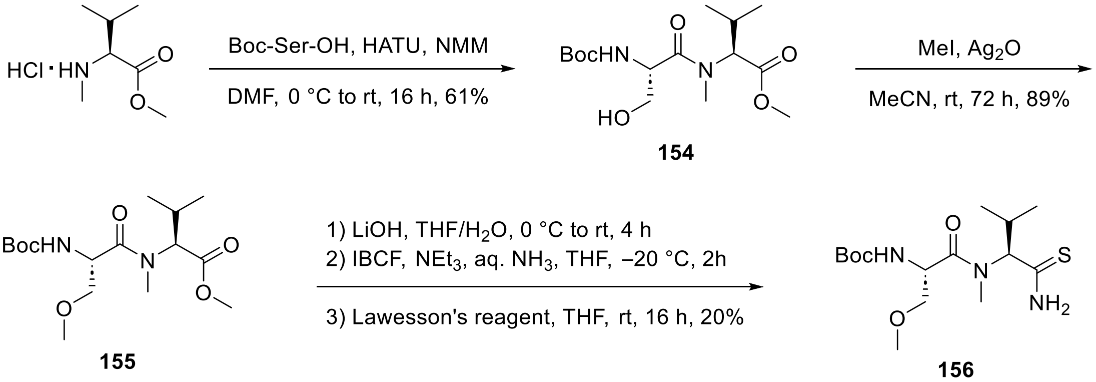
Chiral HPLC and some test couplings of **151** and **147** with phenylalanine resulted in the corresponding dipeptides in suitable diastereomeric purities, confirming the enantiomeric purities of the starting materials. Table 22 shows the use of various coupling reagents to minimize epimerization during the coupling process. In entry 2, a significant excess of the carboxylic acid **147** and addition of HOAt improved the yield slightly but did not tackle the epimerization problem. Since PyAOP did not improve upon the initial conditions (entry 3), carbodiimide-based couplings with EDC/HOBt were tested. Both attempts (entries 4 and 5) drastically reduced the yield, and the use of the free amine without additional base showed no improvement in epimerization.

Table 22: Testing different peptide coupling conditions to suppress the epimerization.



entry	R =	coupling reagents	147	dr	yield
1	H·HCl	1.1 eq. HATU, 3.3 eq. NMM	1.1 eq.	60:40	81%
2	H·HCl	2.0 eq. HATU, 4.0 eq. NMM, 1.0 eq. HOAt	2.0 eq.	60:40	91%
3	H·HCl	1.1 eq. PyAOP, 3.1 eq. NMM	1.1 eq.	63:37	89%
4	H·HCl	1.1 eq. EDC·HCl, 1.1 eq. HOBt, 1.0 eq. NMM	1.1 eq.	71:29	42%
5	H	1.1 eq. EDC·HCl, 1.1 eq. HOBt	1.1 eq.	59:41	44%

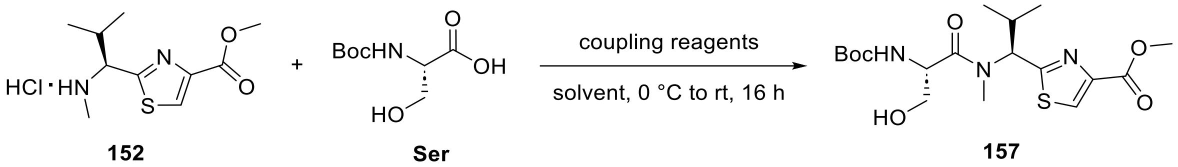
In the following attempt, the less complex *N*-methyl valine methyl ester was used in the coupling with *O*-methyl serine **147** to form the thiazol at a later stage. Because this coupling once again resulted in 35% epimerization, the reaction was repeated with Boc-Ser-OH to yield dipeptide **154** in 61% as a single diastereomer (Scheme 97). Methylation with silver-(I) oxide and iodomethane in MeCN gave the methyl ether **155** in good yield. Transformation to the thioamide **156** by treatment with Lawesson’s reagent proceeded under formation of several side products, resulting in low yield.



Scheme 97: Coupling *N*-methyl valine methyl ester with Boc-Ser-OH and attempted transformation to the thiazole.

While the thioamide formation proved problematic, the epimerization-free coupling of the unprotected serine led to a reevaluation of thiazole **152** as a coupling partner (Table 23). Indeed, the HATU-coupling with Boc-Ser-OH gave the dipeptide **157** as a single diastereomer, albeit with moderate yield (entry 1). Increasing the amount of Boc-Ser-OH led to more side reactions due to esterification of the free hydroxy group (entry 2). In entry 3, PyAOP could improve the yield slightly, but the purification was significantly more complicated. Other coupling reagents such as EDC/HOBt or BOP-Cl showed a significantly lower yield of 22% or no conversion to the desired product (entries 4 and 5). Variations of the solvent (entry 6) and reaction time (entries 7 and 8) were examined but proved ineffective. Since unreacted amine **152** was still observed in the reaction mixture, an aqueous work up was conducted, and the crude mixture was reacted with 1.0 eq. Boc-Ser-OH and coupling reagents once more. This "double coupling" led to full conversion and 47% yield with DMF as a solvent (entry 9). The use of CH_2Cl_2 resulted in incomplete conversion and slightly lower yields (entry 10). Due to the negligible improvement in yield in those double couplings, the recovery of the starting material seemed to be a more reasonable approach. Due to the similar yields but higher conversion in DMF, the coupling was performed in CH_2Cl_2 once more, affording dipeptide **157** in 41% yield along with 42% recovered starting material **152** (entry 11).

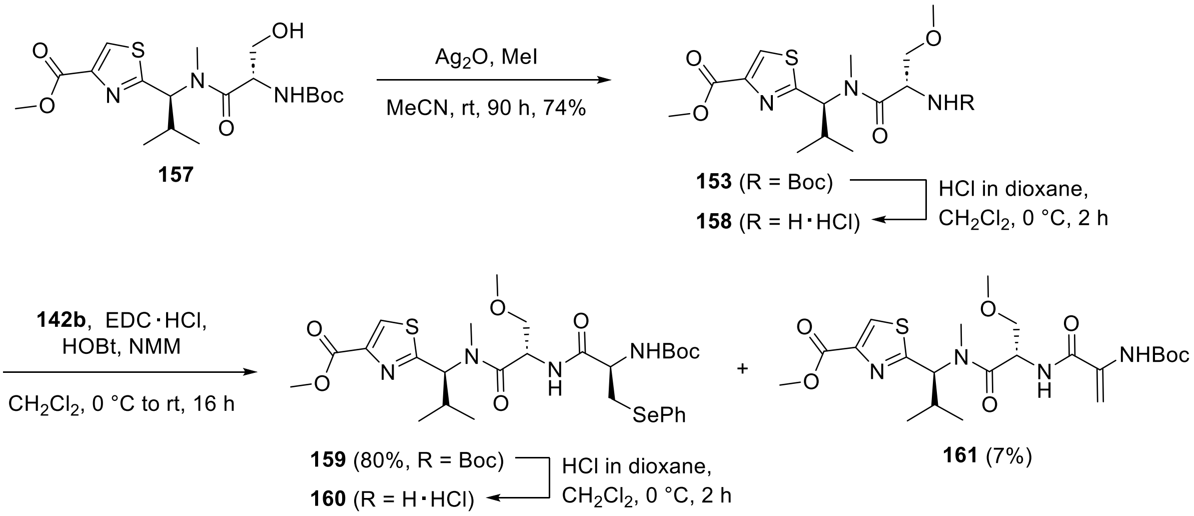
Table 23: Optimizing the coupling of thiazole building block 152 and Boc-Ser-OH.



entry	Ser	Coupling reagents	solvent	t	yield
1	1.2 eq.	1 eq. HATU, 3.1 eq. NMM	DMF	16 h	37%
2	2.0 eq.	2 eq. HATU, 4.0 eq. NMM	DMF	16 h	36%
3	1.2 eq.	1.0 eq. PyAOP 3.2 eq. NMM	DMF	16 h	43%
4	1.2 eq.	1.0 eq. EDC·HCl, 0.2 eq. HOBt, 1.4 eq. NMM	DMF	16 h	22%
5	1.0 eq.	1.0 eq. BOP-Cl, 3.1 eq. NMM	DMF	18 h	---
6	1.0 eq.	1.0 eq. HATU, 3.1 eq. NMM	CH_2Cl_2	16 h	36%
7	1.0 eq.	1.0 eq. HATU, 3.1 eq. NMM	DMF	64 h	41%
8	1.0 eq.	1.0 eq. HATU, 3.1 eq. NMM	CH_2Cl_2	64 h	38%
9[a]	1.0 eq. x2	(1.0 eq. HATU, 3.1 eq. NMM) x2	DMF	32 h	47%
10[a]	1.0 eq. x2	(1.0 eq. HATU, 3.1 eq. NMM) x2	CH_2Cl_2	32 h	40%
11	1.1 eq.	1.1 eq. HATU, 3.3 eq. NMM	CH_2Cl_2	16 h	41% (83% brsm)

a) "Double coupling" with sat. $NaHCO_3$ wash step in between.

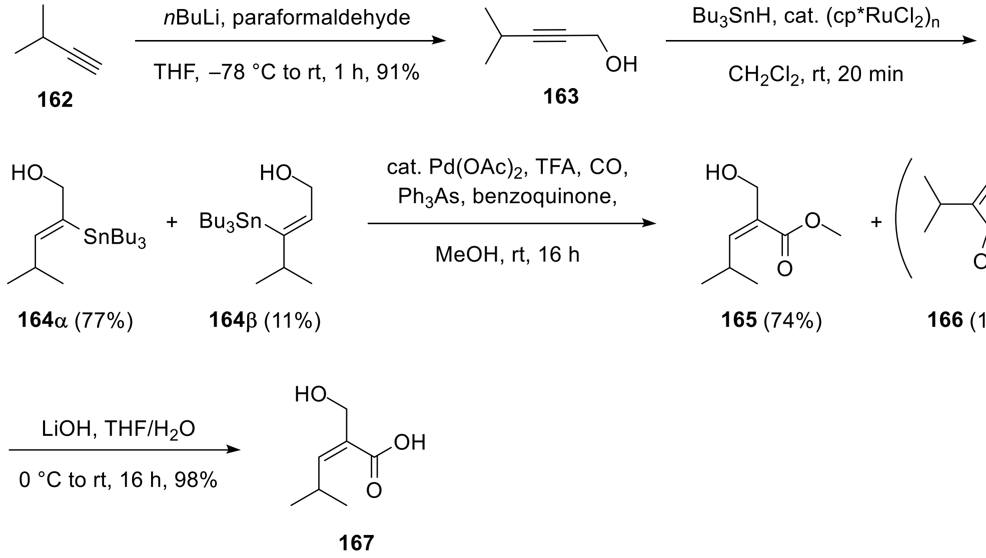
After the epimerization-free coupling to **157**, *O*-methylation under previously described conditions gave dipeptide **153** in good yield (Scheme 98). Small amounts of the *N*-methylated carbamate (10%) were observed but could easily be separated by column chromatography. The hydrochloride salt **158**, obtained by standard Boc-deprotection, was coupled with phenyl selenocysteine **142b** using EDC/HOBt. Along with the desired product **159** in 80% yield, the corresponding selenoxide elimination product **161** was isolated in small amounts. At this stage, the selenoxide elimination of **159** to **161** was tested with a protocol by Van der Donk and Levengood with $NaIO_4$ and hydrogen peroxide.[189] Both oxidants resulted in full conversion to the desired product in less than two hours, demonstrating a successful procedure for the planned late-stage oxidation on this model substrate.



Scheme 98: Completion of the western fragment by *O*-methylation and coupling with selenocysteine 142b.

4.3.4 Synthesis of HMMP

Before starting the assembly, synthesis of the last remaining building block, 2-(hydroxymethyl)-4-methylpent-3-enoic acid (HMMP), was investigated. To achieve the required double bond geometry, a *trans*-hydrostannylation by Fürstner *et al.*[190–192] was planned. The starting material for this step, propargyl alcohol **163**, was prepared by deprotonation of alkyne **162**, followed by quenching with paraformaldehyde (Scheme 99).[193] Fürstner described a protocol for *trans*-hydrostannylation of unsymmetrical alkynes using cp*-ruthenium catalysts. Combined with a protic functionality like a hydroxy- or sulfonamide group in propargyl position or close proximity to the alkyne, these catalysts result in highly selective α-stannylation products. The best-reported results were achieved with the tetrameric cluster (cp*RuCl)$_4$. Due to its high price, the cheaper oligomeric (cp*RuCl$_2$)$_n$ was used in this work.



Scheme 99: Synthesis of the *Z*-alkenoic acid 167 via *trans*-hydrostannylation and methoxy carbonylation.

In this case, the ruthenium-catalyzed addition of Bu$_3$SnH proceeded with a total yield of 88% and a selectivity of 87:13 regarding α- and β-addition. The addition occurs exclusively *trans*, which is confirmed by the typically high coupling constant in the range of 120 Hz of the β-proton with the Sn^{117}/Sn^{119}-nuclei. A *cis*-coupling constant would be significantly lower in the 60 – 70 Hz range.[190,194] Furthermore, a NOE-correlation between the CH$_2$-group and the β-proton supports this result (Figure 9). The chromatographic separation of the β-addition product was tedious but using the mixture in the following methoxy carbonylation led to the easily separable lactone **166** via cyclic hydroxy carbonylation of **164β**. This methoxy carbonylation was conducted according to a protocol by Fürstner and Sommer from their synthesis of tubelactomicin A.[191]

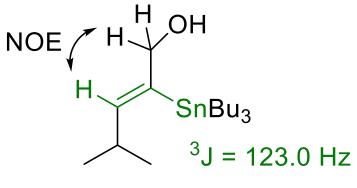
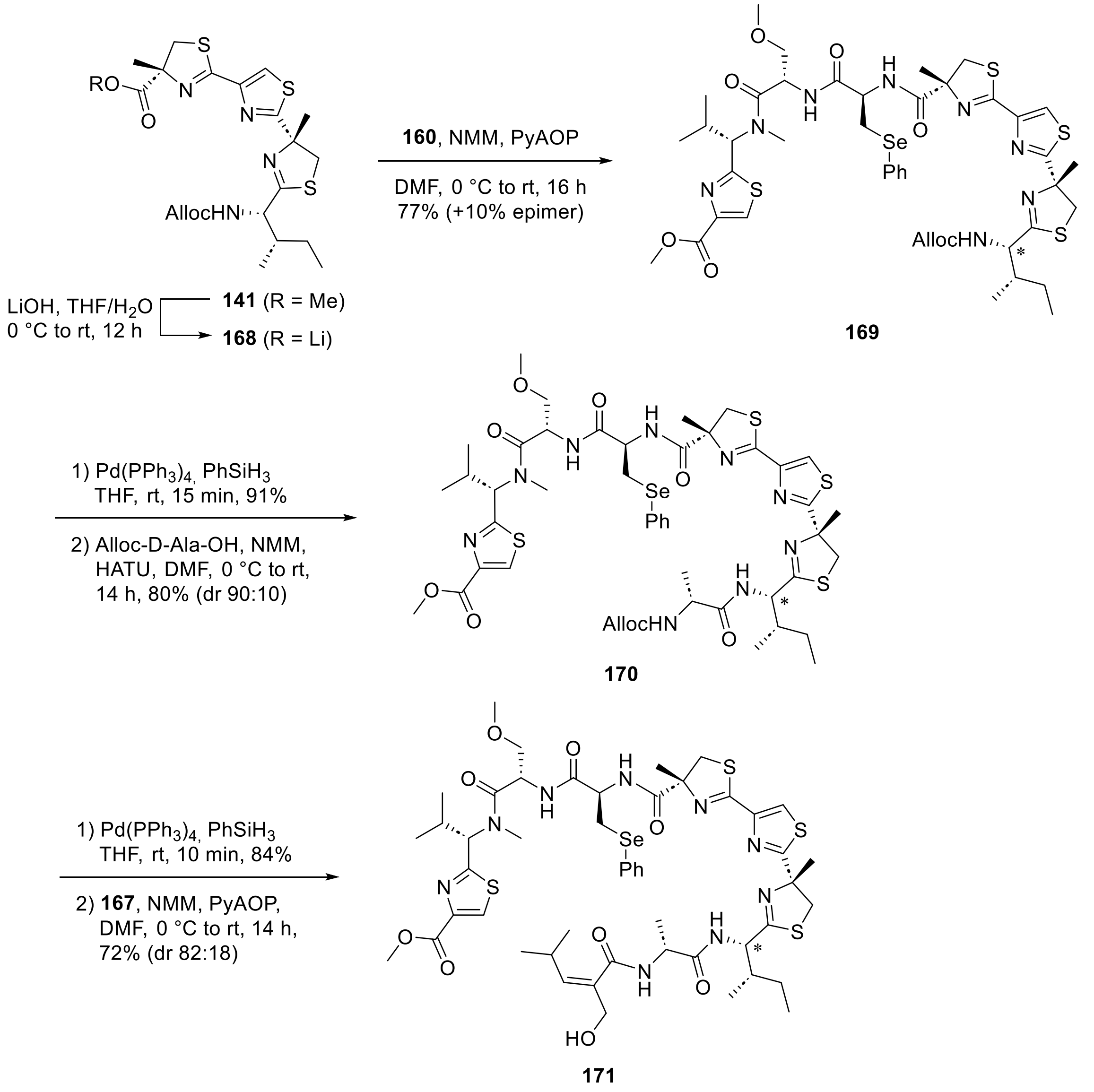


Figure 9: NOE-correlation and *trans*-coupling of 164α.

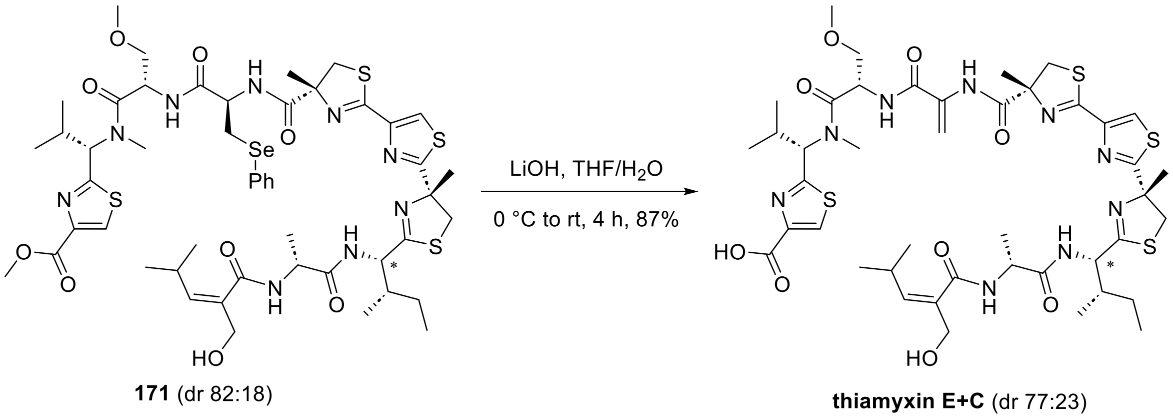
4.3.5 Coupling of the Building Blocks

The peptide assembly began with the saponification of methyl ester **141**, avoiding an acidic workup to limit the epimerization of the labile C-2 exomethine position (Scheme 100). The lithium carboxylate **168** was reacted with the tripeptide **160** via PyAOP-mediated coupling, leading to tetrapeptide **169** in 77% yield. The corresponding epimer was formed in 10% but could be separated via RP-column chromatography. In the next step, the Alloc-protecting group was removed via palladium catalysis under neutral conditions using phenyl silane as an allyl-scavenger. Isolation of the free amine, followed by HATU-coupling with Alloc-protected D-alanine afforded pentapeptide **170** in excellent yield along with 10% of its C-2 exomethine epimer. The diastereomeric mixture **170** was used in the following Alloc-deprotection and the subsequent PyAOP-coupling with HMMP **167**. This sequence led to the thiamyxin precursor **171** in 72% yield and, after another 8% epimerization during the coupling, a diastereomeric ratio of 82:18.



Scheme 100: Assembly of the building blocks.

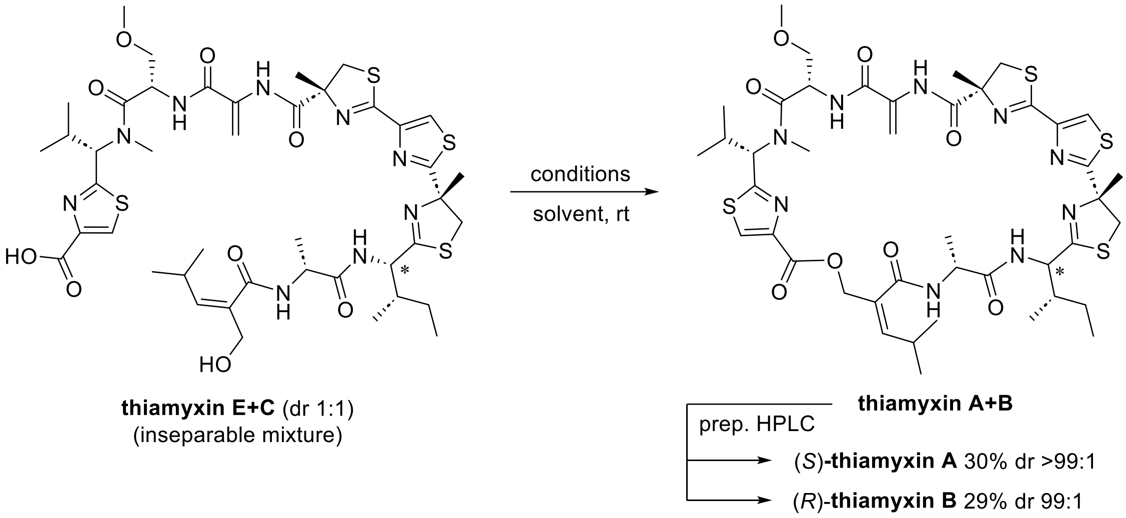
The final deprotection sequence was planned by saponification of the methyl ester, followed by a selenoxide elimination to form the dehydroalanine motif. Surprisingly, the elimination to the dehydroalanine partially occurred during the incomplete saponification using 1.0 eq. of LiOH (Scheme 101). Addition of a second equivalent of LiOH led to the mixture of (*S*)-configured thiamyxin E and the (*R*)-configured thiamyxin C in a 77:23 ratio and an excellent yield of 87%. As expected, these open-chain thiamyxins E+C proved to be inseparable by preparative HPLC.[107] Several attempts of purification under neutral conditions failed. The purification with 0.1% $HCOOH_{aq}$/MeCN as a mobile phase resulted in a 1:1 mixture of the epimers, showcasing again the lability of the C-2 exomethine position. The low epimerization of about 5% during the saponification (Scheme 101) and the reported isolation of the cyclic thiamyxins A and B in satisfactory diastereomeric purities by the Müller group[107] led to an adjustment of the synthetic strategy. A macrolactonization of the inseparable 1:1 mixture of the thiamyxins E and C should lead to the separable thiamyxins A and B, which could then be reopened via saponification to obtain the natural products thiamyxin E and C in suitable diastereomeric purities.



Scheme 101: Saponification and phenyl selenide elimination.

For the first step, the cyclization of **171,** several macrolactonization strategies were investigated (Table 24). Entry 1 shows an attempted Steglich esterification[126] with DIC/DMAP, resulting in full conversion to the unreactive *N*-acyl urea[195] without product formation. The known peptide coupling reagent PyAOP, in combination with DMAP, also used for macrolactonizations,[196] gave thiamyxin A+B in 10% yield with DMF as a solvent (entry 2). Only traces of the product were observed with CH_2Cl_2, while toluene could improve the yield to 18% (entries 3 and 4). Since the yield was rather low, and all the attempts with PyAOP showed several unknown side products, other protocols were tested. Zhao and co-workers recently reported an efficient macrolactonization via ynamide-activation using *N*-methyl ynetoluenesulfonamide (MyTSA).[197] In the first step, the formation of the α-acyloxy enamide proceeded smoothly, but the acid-catalyzed second step did not result in any product formation (entry 5). After a catalytic amount of acid was insufficient, one equivalent of *p*-toluene sulfonic acid monohydrate was added, which resulted in hydrolysis of the active ester. Yamaguchi conditions with 2,4,6-trichloro benzoyl chloride (TCBC)[128,198] in a mixture of toluene and MeCN, due to solubility issues, gave the desired macrolactone in 31% yield (entry 6).

Table 24: Macrolactonization of the mixture of thiamyxin E and C.



thiamyxin E+C (dr 1:1)
(inseparable mixture)

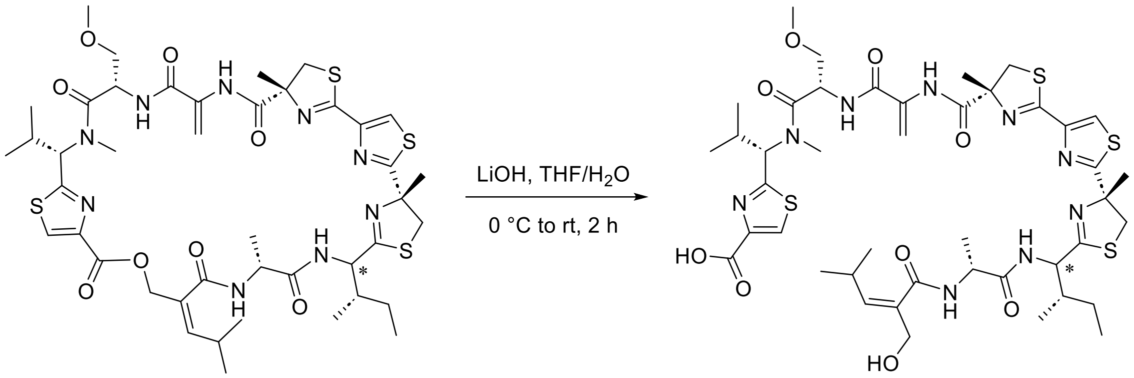
thiamyxin A+B

(*S*)-**thiamyxin A** 30% dr >99:1
(*R*)-**thiamyxin B** 29% dr 99:1

entry	conditions	solvent	t	yield
1	2 eq. DIC, 5 eq. DMAP	DMF	48 h	---
2	5 eq. PyAOP, 5 eq. Et$_3$N, 10 eq. DMAP	DMF	72 h	10%^{b}
3	5 eq. PyAOP, 5 eq. Et$_3$N, 10 eq. DMAP	CH$_2$Cl$_2$	72 h	traces
4	5 eq. PyAOP, 5 eq. Et$_3$N, 10 eq. DMAP	Tol	72 h	18%^{b}
5	1.0 eq. MyTSA *then* 5 mol% pTsOH·H$_2$O	CH$_2$Cl$_2$	24 h, 72 h	---
6	1.05 eq. TCBC, 5 eq. Et$_3$N, 10 eq. DMAP	Tol/MeCN	30 h	31%^{a,b}
7	1.05 eq. TCBC, 5 eq. Et$_3$N, 10 eq. DMAP	CH$_2$Cl$_2$	24 h	42%^{b}
8	1.05 eq. MNBA, 5 eq. Et$_3$N, 10 eq. DMAP	Tol/MeCN	24 h	48%^{b}
9	1.05 eq. MNBA, 5 eq. Et$_3$N, 10 eq. DMAP	MeCN	18 h	60%^{b}
10	1.05 eq. MNBA, 5 eq. Et$_3$N, 10 eq. PPY	MeCN	18 h	56%^{b}
11	1.05 eq. TCBC, 5 eq. Et$_3$N, 10 eq. DMAP	MeCN	1 h	63%^{a}

a) isolated yield. b) yield determined by HPLC-MS (UV-detection at 254 nm).

The use of CH$_2$Cl$_2$ with TCBC/DMAP improved the yield to 42%, which indicates Yamaguchi-type macrolactonizations as the most promising method for this cyclization. Another very efficient Yamaguchi-type reagent, 2-methyl-6-nitrobenzoic anhydride (MNBA)[199] in toluene/MeCN (entry 8) and MeCN (entry 9) further improved the yield to 48% and 60%, respectively. The typical acylation catalyst 4-pyrrolidinyl pyridine (PPY)[129] showed no improvement compared to DMAP (entry 10). In the end, the best results were achieved with TCBC in MeCN, in which case the macrolactonization proceeds in 63% yield. The cyclization reached complete conversion within just one hour of reaction time, which is remarkable since the reaction was conducted under high dilution conditions (2 mM). After purification by preparative HPLC with 0.1% HCOOH$_{aq}$/MeCN, thiamyxin A and thiamyxin B were isolated in 30% and 29% yield, respectively.



(*S*)-**thiamyxin A** (dr >99:1)
(*R*)-**thiamyxin B** (dr 99:1)

(S)-**thiamyxin E** 73% (dr 92:8)
(R)-**thiamyxin C** 61% (dr 95:5)

Scheme 102: Reopening the macrolactones to access thiamyxin E and C in good diastereomeric purities.

Formic acid was used to improve the separation and did, in contrast to the open-chain thiamyxins E and C, surprisingly, not result in epimerization of the C-2 exomethine position of thiamyxin A and B. To finalize the total synthesis of the thiamyxins, saponification of thiamyxin A and B was conducted with lithium hydroxide (Scheme 102). After purification by preparative HPLC with a neutral mobile phase (H_2O/MeCN), thiamyxin E was obtained in 73% yield and a diastereomeric ratio of 92:8. The identical procedure for thiamyxin B led to the open-chain thiamyxin C in 61% yield and a diastereomeric ratio of 95:5.

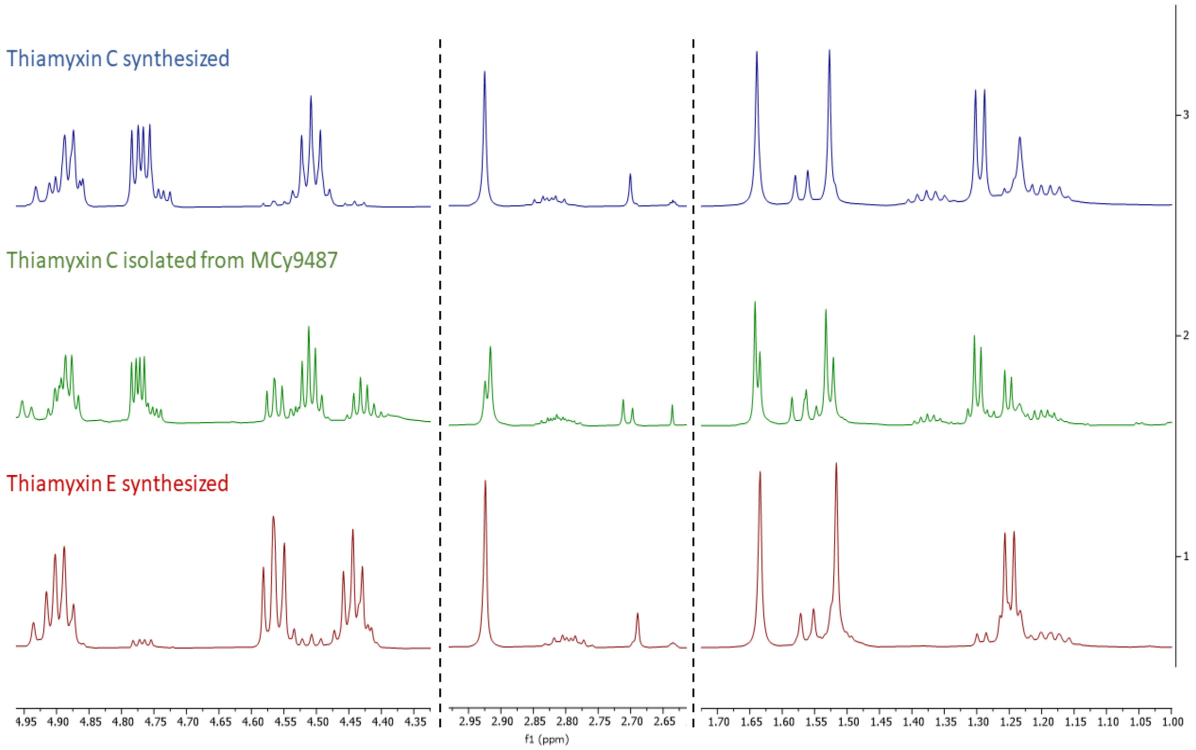


Figure 10: NMR-comparison of the synthesized thiamyxin E (dr 92:8), C (dr 95:5), and the isolated thiamyxin C (dr 2:1).[107]

The NMR-spectroscopic data of the herein synthesized thiamyxins A, B, and C, is in accordance with the published data by the Müller group, confirming their reported structures of the thiamyxin family.[107] A direct comparison of the NMR spectra of the isolated thiamyxin C with the synthesized thiamyxins E and C clearly identifies thiamyxin E as the minor diastereomer in the isolated thiamyxin C sample (Figure 10). Additional ^{1}H-NMR comparisons of cyclic thiamyxins A and B are shown in Figure 11 and Figure 12. Both synthesized compounds show near identical spectra to the genuine sample, which again confirms the elucidated structures by the Müller group.

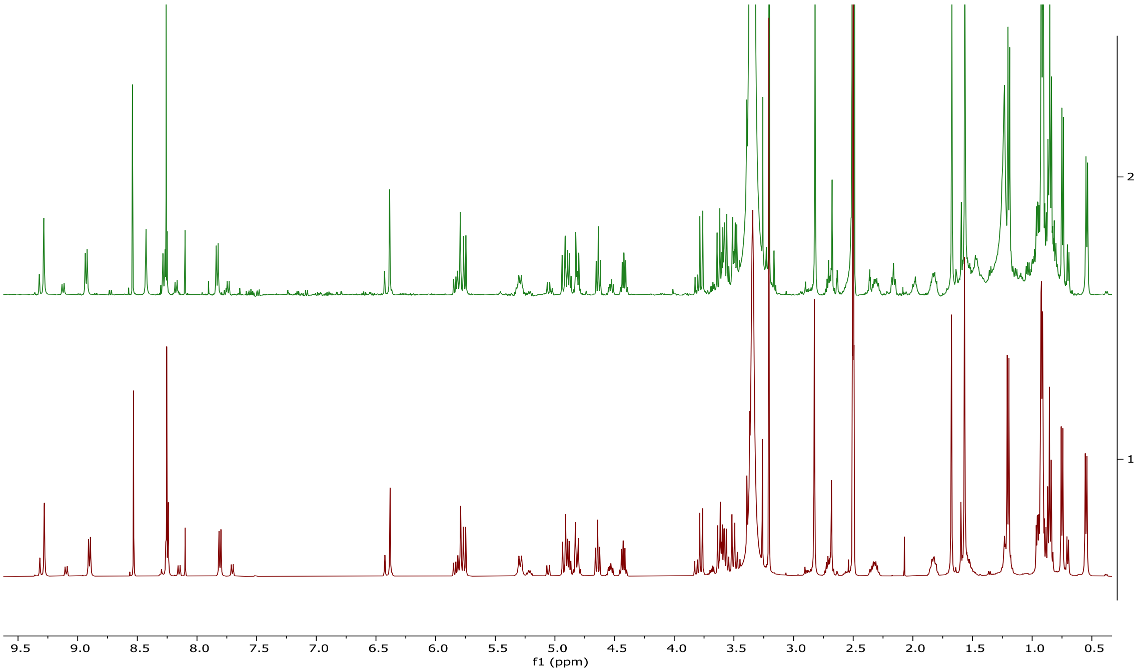


Figure 11: ^{1}H-NMR-comparison of thiamyxin A isolated (green) and synthesized (red).

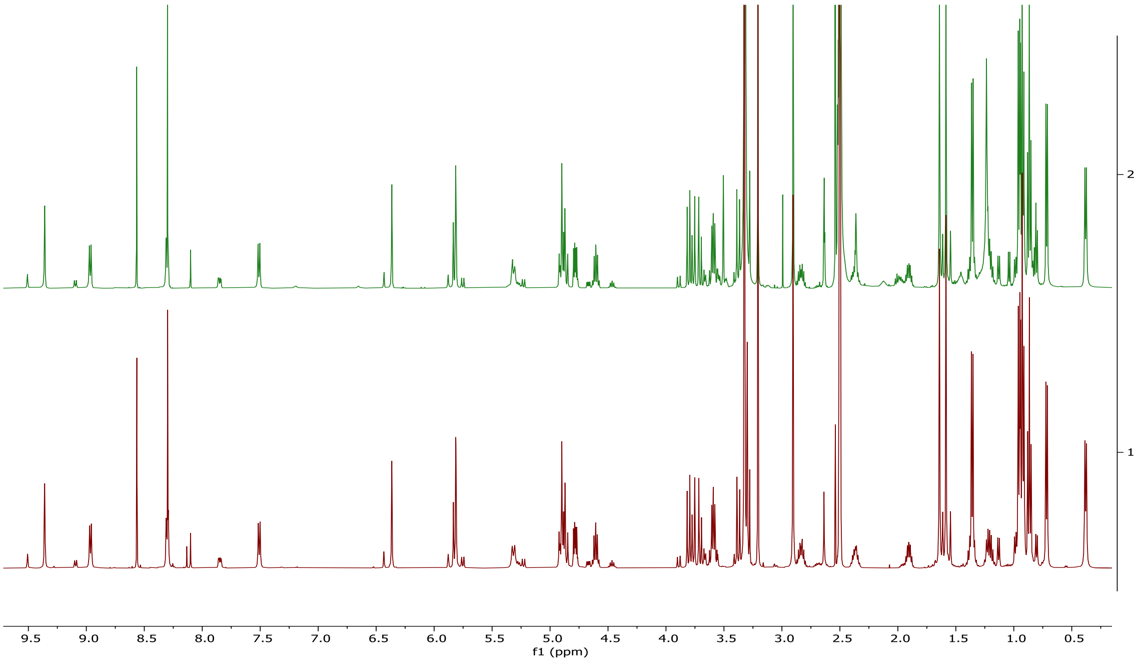


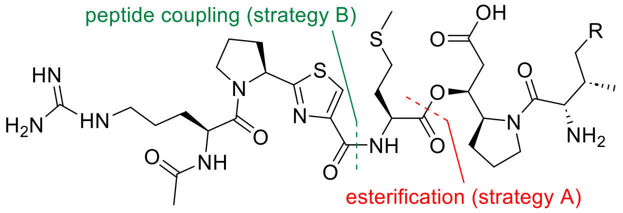
Figure 12: ^{1}H-NMR-comparison of thiamyxin B isolated (green) and synthesized (red).

In summary, the first total synthesis of the thiamyxins A-C and E was achieved. An initially envisioned late-stage thiazoline-formation could not be accomplished, but a reopening of the cyclic thiamyxins A and B via saponification solved the separation issue of the epimerization labile thiamyxins C and E. This exploitation of the labile C-2 exomethine position gave access to four natural products via the same route. The synthesized thiamyxins are currently tested for additional biological activities. Due to the high diastereomeric purities of the open-chain thiamyxins E and C, additional biological data about the influence of the stereocenter on the antiviral activity should be observable. Furthermore, the modular total synthesis could enable the synthesis of other derivatives for SAR-studies investigations on the distinguished mode of action of the antiviral activity.[107]

5. Conclusion

5.1 Pseudotetraivprolids

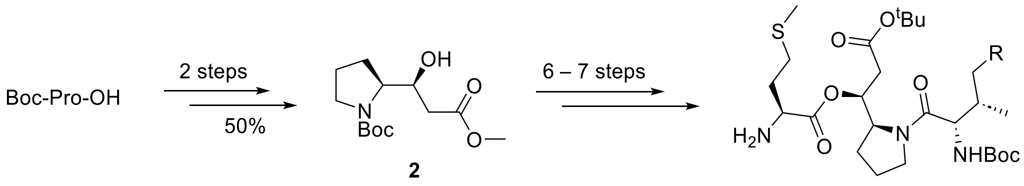
The first natural products synthesized during this thesis were the pseudotetraivprolids B and D, members of a family of linear depsipeptides isolated by the Bode group at MPI Marburg. The preferred synthetic strategy of the total synthesis of pseudotetraivprolid B and D focused on the esterification between the western and eastern fragments as key step (A, Figure 13). However, typical esterification strategies such as Yamaguchi-, Steglich- and Ghosez-conditions afforded the desired product with severe epimerization. A shift in the disconnection strategy toward the amide bond between the thiazole and the methionine unit (B) solved these issues.



pseudotetraivprolid D (R = H)
pseudotetraivprolid B (R = Me)

Figure 13: Retrosynthetic strategies for pseudotetraivprolid B and D.

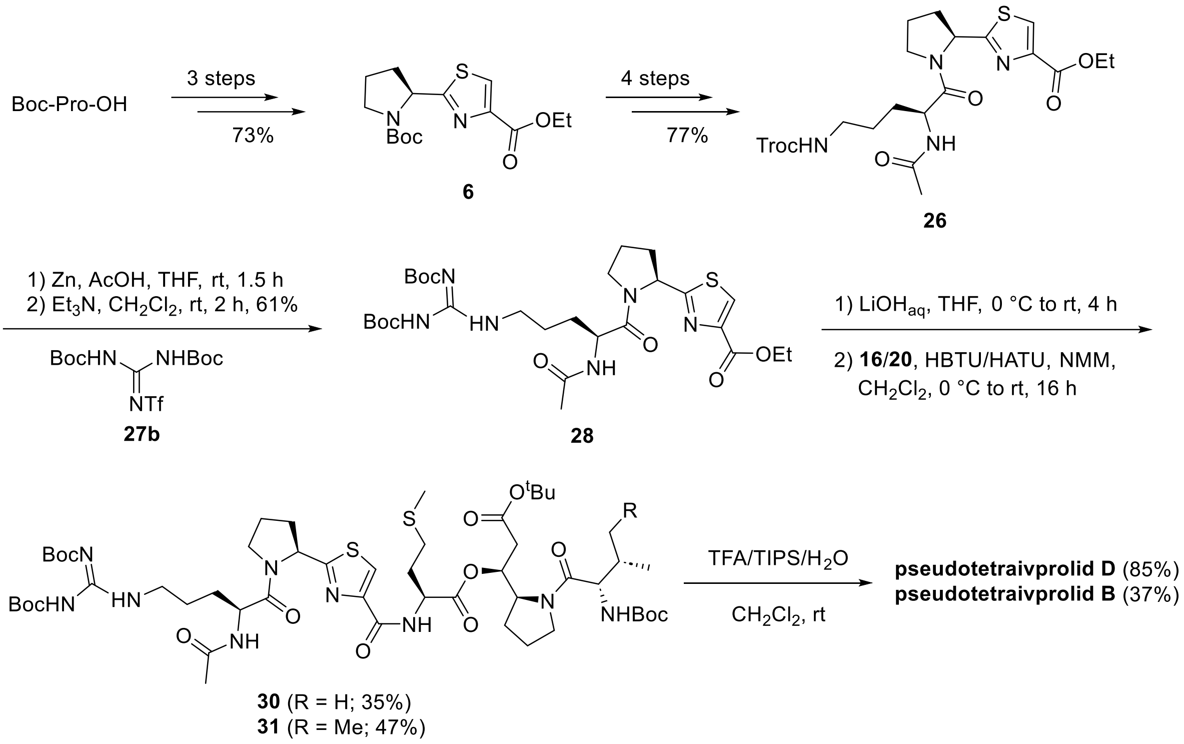
The synthesis of the eastern fragment started from proline, which was transformed into the β-hydroxyester **2** via β-ketoester formation and subsequent Noyori asymmetric hydrogenation (Scheme 103).[113] A series of protecting group manipulations, peptide coupling with valine or isoleucine, and Steglich esterification with methionine afforded the depsipeptide building blocks **16** and **20** in 65% over 7 steps and 57% over 6 steps, respectively.



16 (R = H; 65%)
20 (R = Me; 57%)

Scheme 103: Synthesis of the eastern fragments 16 and 20.

The western fragment was prepared using a modified Hantzsch thiazole procedure, starting from Boc-proline to afford thiazole **6** (Scheme 104).[114] Coupling with Troc-protected ornithine followed by acetylation of the *N*-terminus gave the acetylated dipeptide **26** in good yield. After Troc-deprotection, a late-stage introduction of the guanidyl unit was conducted by treatment with the bis-Boc-guanidyl triflate **27b**.[134] The resulting western fragment **28** was saponified and coupled with the amines **16** and **20** in 35% and 47% yield, respectively. Concurrent oxidation of the thioether moiety during the coupling or storage of the fragments limited the yield. The final deprotection with HCl or TFA suffered from low conversion and several side reactions, such as oxidation and alkylation, most likely at the thioether of the methionine unit.[135]

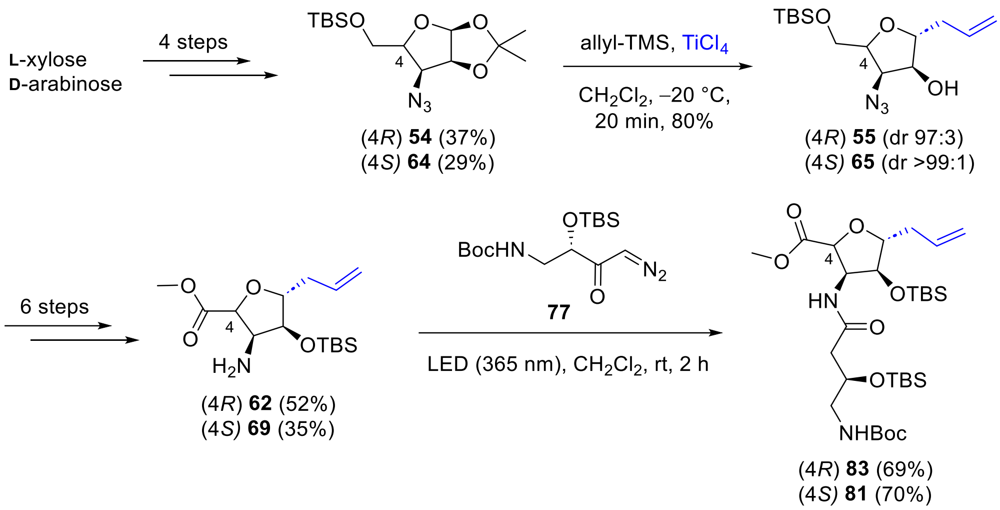


Scheme 104: Synthesis of the western fragment 28 and subsequent coupling with the eastern fragments 16 and 20.

A TFA cleavage cocktail with TIPS and water as scavengers, commonly used in solid-phase peptide synthesis, afforded pseudotetraivprolid D in 85% yield.[136] The same procedure gave the second natural product, pseudotetraivprolid B, albeit in lower yield due to incomplete hydrolysis of the *tert*-butyl ester. In summary, the first synthetic access to the natural products pseudotetraivprolid B and D was accomplished in a convergent total synthesis, allowing for derivatization of the parent compound for potential SAR-studies. The in-depth analysis of the biological activities and biosynthetic origin is currently performed by the Bode group at MPI Marburg.

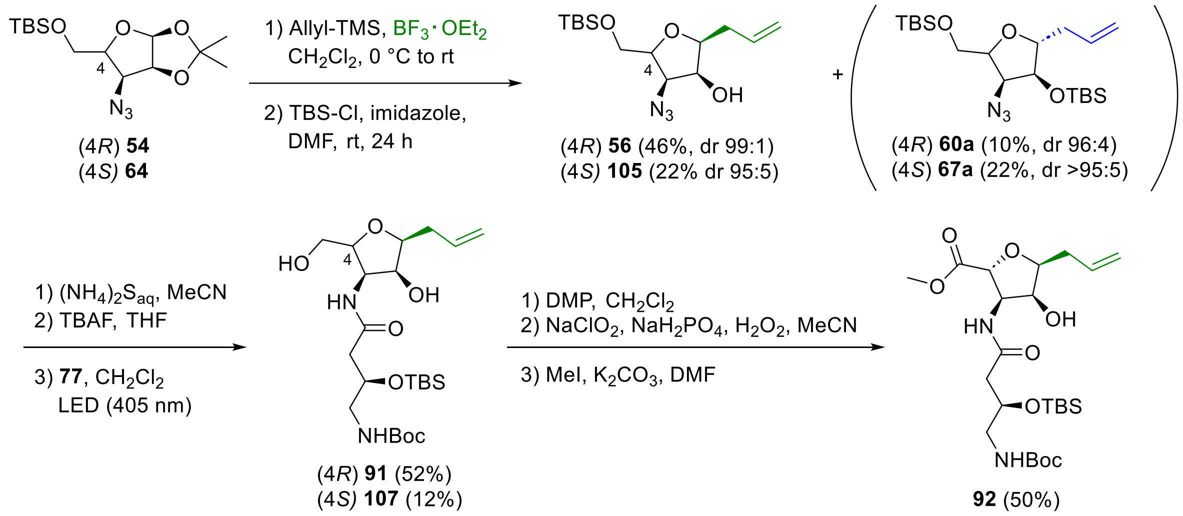
5.2 Socein-Derivatives

The objective of the second project was the full structural elucidation of socein by means of total synthesis. This natural product represents the first member of the large microsclerodermin family[10–13,17,18] with a cyclized variant of the typical polyhydroxylated side chain. The target structures were simplified dehydrosocein derivatives to assist the assignment of the two unknown stereocenters by synthesizing all conceivable diastereomers. The most challenging building blocks during the synthesis of the dehydrosocein derivatives were the various diastereomeric C-furanosides. For their synthesis, different strategies using a Matteson homologation approach or the desymmetrization of a bis-epoxide were investigated. In the end, a chiral pool approach via Sakurai allylation of L-xylose and D-arabinose derived furanosides proved successful. The 1,2-*O*-isopropylidine protected furanosides **54** and **64** were synthesized from L-xylose and D-arabinose in four steps via a selective protection sequence followed by triflation and azide substitution (Scheme 105). Sakurai allylation of these acetals in a protocol of Tellado and co-workers[51] using $TiCl_4$ and allyl-TMS afforded the expected 1,2-*trans* C-furanosides **55** and **65** in excellent yields and diastereoselectivities.



Scheme 105: Synthesis of the key building blocks 83 and 81 via Sakurai allylation and Arndt-Eistert homologation.

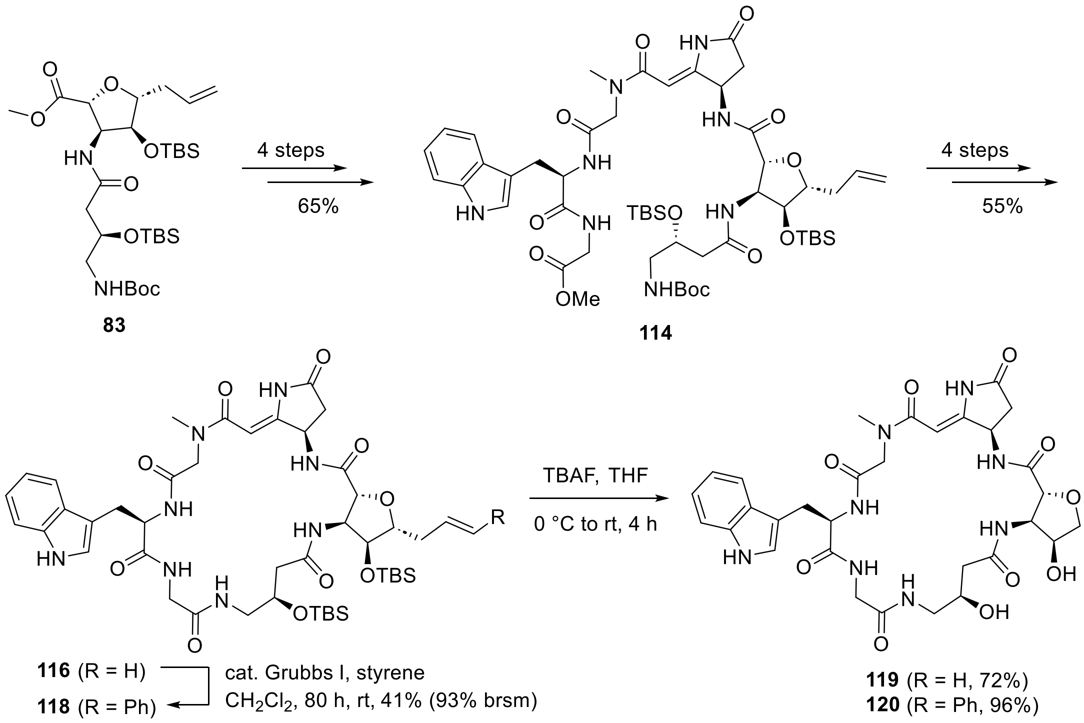
Subsequently, a sequence of protecting group manipulations, oxidation, and Staudinger reduction resulted in the 3-amino C-furanosides **62** and **69** in 52% and 35% yield over 6 steps, respectively. During this thesis, a novel route for the synthesis of (*R*)-GABOB derivatives via light-induced Arndt-Eistert homologation of L-isoserine was developed. For this purpose, the diazoketone **77** was synthesized in a short sequence and used as the substrate for Wolff-rearrangement with the amines **62** and **69** as nucleophiles. This simple reaction setup afforded the key building blocks **83** and **81** in superior yields compared to standard HATU-coupling with protected (*R*)-GABOB. Unexpectedly, the Sakurai allylation of L-xylose derived furanoside **54** with BF_3·OEt_2 as Lewis acid resulted in the 1,2-*cis* allylation product **56** in 40% yield and a dr of 80:20 (Scheme 106).



Scheme 106: Synthesis of the remaining diastereomers via Sakurai allylation with inverted diastereoselectivity.

Screening various Lewis acids and protecting groups did not improve yield and diastereoselectivity, which led to the development of a Sakurai allylation protocol with subsequent diastereoselective TBS-protection. This allowed for the synthesis of two more C-furanoside diastereomers, **56** and **105**, in high diastereoselectivities. After reduction of the azide and TBS-deprotection, the resulting aminodiols were used in the Wolff-rearrangement to afford the dipeptides **91** and **107** in 52% and 12% yield, respectively. The low yield of the all-*cis* diastereomer **107** showcased the sterical hindrance of the amine in this configuration and resulted, combined with further issues during the selective oxidation, in the discontinuation of the synthetic effort toward this diastereomer. In contrast, selective oxidation of diol **91** with Dess-Martin periodinane (DMP) followed by Pinnick oxidation and *O*-methylation gave another diastereomer **92** in good yield.

With the key building blocks in hand, the assembly (exemplarily shown with **83**) of the peptide afforded the linear precursor **114** in 65% yield over 4 steps (Scheme 107). A sequence of protecting group manipulations and macrolactamization with PyAOP gave macrolactam **116** in good yield. Finally, olefin metathesis with Grubbs I catalyst and subsequent deprotection of the TBS-groups afforded the desired dehydrosocein derivatives **119** and **120**.

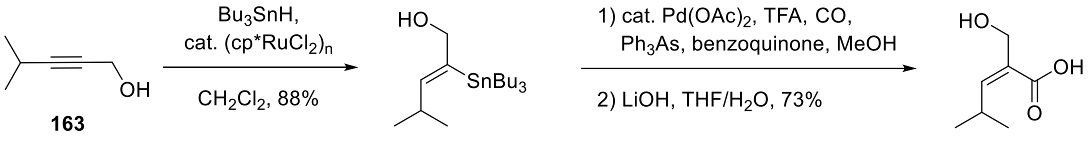


Scheme 107: Final steps of the synthesis of the dehydrosocein derivatives via a sequence of peptide couplings, macrolactamization, and Grubbs metathesis.

Two more diastereomers were synthesized in a similar route, resulting in a total of six socein-derivatives, covering three out of four possible configurations of the tetrahydrofuran unit. In conclusion, a Sakurai allylation with controllable stereoselectivity was discovered and exploited to efficiently access the four desired C-furanoside diastereomers with only two precursor furanosides. Furthermore, a light-induced Arndt-Eistert homologation of isoserine was used to develop a novel route toward (*R*)-GABOB derivatives, ultimately improving access to the desired dipeptide key building blocks. Due to insufficient analytical data of the genuine sample, the natural product is currently reisolated by the Müller group at the HIPS to identify the configuration via NMR-comparison with the herein synthesized diastereomers of simplified socein.

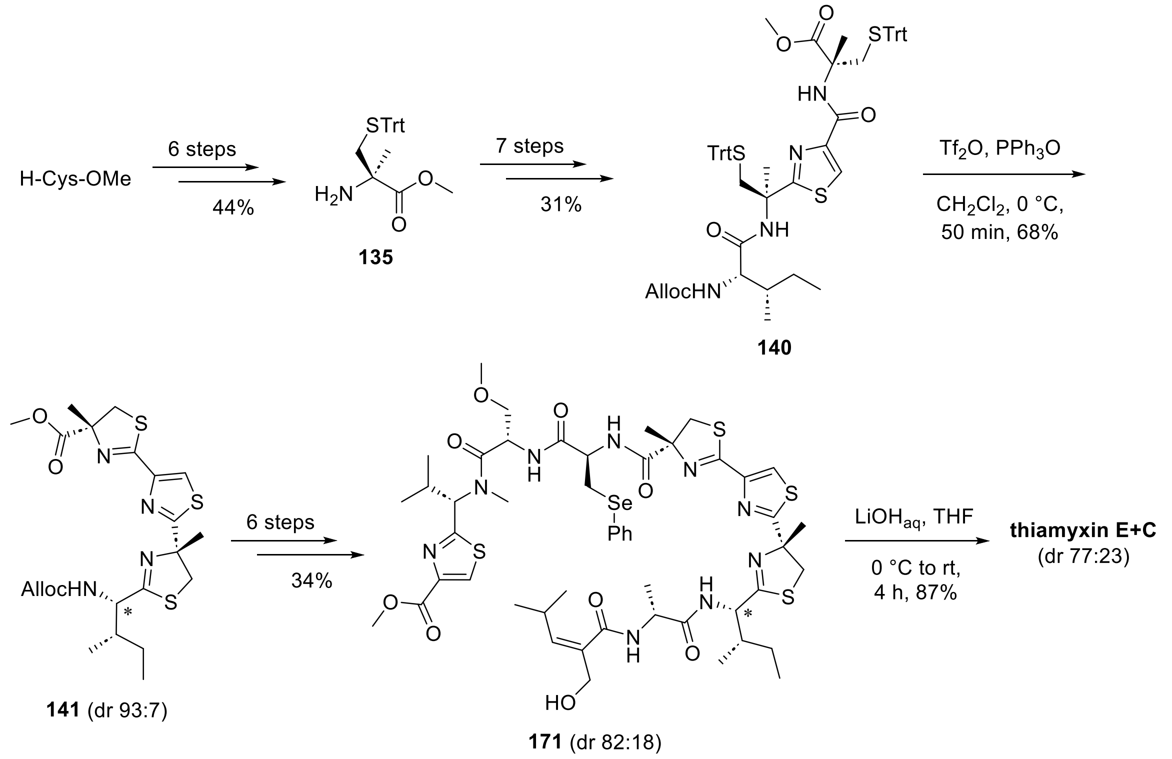
5.3 Thiamyxins[112]

The last part of this thesis describes the total synthesis of the recently highlighted thiamyxins,[200] a group of thiazoline and thiazole-rich depsipeptides with interesting antiviral activities isolated from a myxobacterial strain by the Müller group.[107] The thiamyxins feature an unusual *Z*-alkenoic acid (HMMP) and an unprecedented thiazoline-thiazole-thiazoline unit with a labile C-2 exomethine stereocenter. The synthesis of the unusual HMMP was achieved via ruthenium-catalyzed *trans*-hydrostannylation, followed by palladium-catalyzed methoxycarbonylation (Scheme 108).[190–192] This short sequence afforded the desired HMMP **167** in an overall yield of 56% over 3 steps.



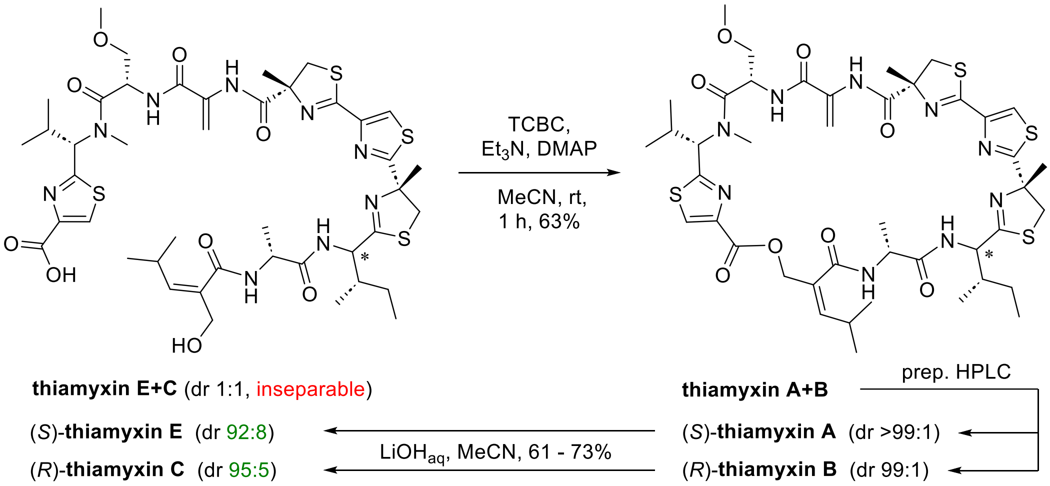
Scheme 108: Synthesis of HMMP via *trans*-hydrostannylation and methoxy carbonylation.

The complex thiazoline-thiazole-thiazoline building block **141** was synthesized via α-methyl cysteine **135**, prepared in 44% over 6 steps from L-cysteine methylester (Scheme 109). Coupling with isoleucine followed by a modified Hantzsch thiazole synthesis and a second coupling with α-methyl cysteine **135** afforded the precursor **140** in a very good yield.



Scheme 109: Synthesis of the thiazoline-thiazole-thiazoline building block 141 and consecutive peptide couplings toward thiamyxin E+C.

Due to the reported issue of inseparable thiamyxins E and C,[107] the thiazoline formation was planned at the end of the synthesis to control the epimerization of the C-2 exomethine position. After several attempts of thiazoline formation on complex thiamyxin precursors using low racemization protocols via PPh_3O/Tf_2O[92] or molybdenum catalysis[102] failed, the initially planned late-stage thiazoline formation was discarded. In contrast, the bis-thiazoline formation on the precursor **140** afforded the desired product **141** in good yield and diastereoselectivity. A sequence of subsequent peptide couplings afforded the linear thiamyxin precursor **171** with the expected epimerization of the C-2 exomethine position. Surprisingly, the saponification of the methyl ester using lithium hydroxide resulted in simultaneous elimination of the phenylselenide, affording a mixture of the natural products thiamyxin E and C in a ratio of 77:23.



Scheme 110: Macrolactonization and ring-opening strategy to afford four members of the thiamyxin family.

The anticipated separation problems of thiamyxin E and C proved accurate, and the usage of 0.1% $HCOOH_{aq}$ as mobile phase during the numerous purification attempts resulted in a 1:1 mixture (Scheme 110). After observing only 5% epimerization during the saponification of the methyl ester of **171**, a new strategy was envisioned, which is based upon the separation of cyclized thiamyxins A and B and subsequent ring-opening to access the open chain thiamyxins E and C in good diastereomeric purities. The macrolactonization was achieved using Yamaguchi conditions in acetonitrile, yielding thiamyxin A+B in 63%. Separation via preparative HPLC afforded the cyclic natural products thiamyxin A and B in excellent diastereomeric purities. Satisfactory, saponifying the cyclic thiamyxins resulted in the open chain form thiamyxin E and C in good diastereomeric purities of 92:8 and 95:5, respectively. In conclusion, the herein presented total synthesis gave access to four members of the thiamyxin family via a single precursor **171**, taking advantage of the stereochemically labile C-2 exomethine position.

6. Experimental Section

6.1 General Information

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere if an anhydrous solvent is mentioned in the procedure. Anhydrous THF was prepared by distillation over sodium/benzophenone. Other anhydrous solvents were purchased from *Acros Organics* and *Thermo Scientific*. Petroleum ether (PE), pentane, and ethyl acetate (EtOAc) were distilled before use.

NMR spectra were measured on a *Bruker* Avance II 400 (400 MHz, 5 mm BBO Probe, 298 K), a *Bruker* Avance I 500 (500 MHz, 5 mm TCI Probe, 298 K), or a *Bruker* Avance Neo 500 (500 MHz, 5 mm TCI Prodigy CryoProbe, 298 K). Spectra were calibrated on the solvent signals [$CDCl_3$ (^1H 7.27 ppm, ^{13}C 77.16 ppm) or DMSO-d6 (^1H 2.50 ppm, ^{13}C 39.52 ppm)]. The spectral data were analyzed with MestReNova 14.2 from *MestreLabReasearch S.L.* Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Multiplicities in ^1H-NMR spectra are reported as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{13}C-NMR spectra were measured boadband decoupled, theoretical multiplicity of the carbon is given as s (quaternary C-atom), d (tertiary C-Atom, t (secondary C-Atom), and q (primary C-Atom). Assignments were done using two-dimensional measurements like H,H-COSY, HSQCED, HMBC, and TOCSY.

Reaction monitoring was done by thin-layer chromatography (**TLC**) on Polygram® SIL G/UV_{254} plates by *Macherey-Nagel* ($KMnO_4$, cerium-molybdate or ninhydrin stains) and **LC-MS** analysis on a *Shimadzu* Prominence-*i* LC-2030 (*Phenomenex* Onyx® C18, 50 x 4.6 mm) coupled with *Shimadzu* LCMS-2020 (ESI ionization). All runs were performed at a 4 mL/min flow rate with a column temperature of 40 °C and 0.1% $HCOOH_{aq}$/MeCN as the mobile phase.

0.1% $HCOOH_{aq}$: MeCN	short Method (time)	long Method (time)
90:10 to 1:99	1.5 min	6.0 min
1:99	1.0 min	1.5 min
90:10	0.7 min	1.0 min

For **column chromatography,** silica gel 60M 40 – 63 µm by *Macherey Nagel* was used. Automated flash column chromatography was done on a *Büchi* Pure C815 Flash with *Teledyne Isco* RediSep R_f cartridges. Automated reversed-phase column chromatography was done on a *Büchi* Reveleris® Prep with *Büchi* FlashPure Select C18 (spherical) cartridges or *Kinesis* Telos C18 cartridges. Preparative HPLC was done with a *Büchi* Reveleris® Prep with a *Phenomenex* Luna® (C18, 5 µm, 21.2 x 250 mm).

Specific optical rotation ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$) in [deg·mL/(g·dm)]· was measured on a P-8000-T polarimeter by *A. Krüss Optronic GmbH* with a PT80 thermostat by *A. Krüss Optronic GmbH* at 20 °C (λ = 589 nm). Concentrations are given in g/100 mL.

High-resolution mass spectra (**HRMS**) were recorded at Saarland University by Rudi Thomes on a *Finnigan* MAT 95 (CI, sector field) or at HIPS Saarland on a *Bruker* maXis 4G hr-ToF (ESI, ToF).

Melting points were measured in open glass capillaries on an M3000 from *Krüss Optronic GmbH*.

GC-FID analysis was performed on a GC-2010 System from *Shimadzu* (FID-detector, AOC-20i autoinjector) with a CP-Chirasil-Dex CB (Varian, 25 m x 0.25 mm, 0.25 µm diameter).

Photochemical reactions were conducted in a EvoluChem^{TM} PhotoRedOx Box by *HepatoChem* using 18 W LED-lamps (365 nm, 405 nm and 450 nm).

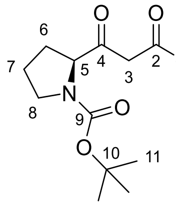
6.2 Synthesis of the Compounds

6.2.1 Pseudotetraivprolids

tert-Butyl (_S_)-2-(3-methoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate[113] 1

According to Greck *et al.*[113], *N*,*N*'-carbonyldiimidazole (2.58 g, 15.9 mmol, 1.2 eq.) was added to a solution of Boc-Pro-OH (2.85 g, 13.2 mmol) in anhydrous THF (100 mL). The reaction mixture was stirred for 2 h at room temperature before $MgCl_2$ (4.08 g, 19.9 mmol, 1.5 eq.) and potassium methyl malonate (3.13 g, 19.9 mmol, 1.5 eq.) were added. After stirring for another 72 h at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between Et_2O and 1.0 M $HCl_{aq,}$ and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, CH_2Cl_2:EtOAc 9:1) to give β-ketoester **1** (2.66 g, 9.80 mmol, 74%) as a white solid.

TLC: R_f (1) = 0.30 (silica, CH_2Cl_2:EtOAc 9:1)



1

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.25 (dd, $^3J_{5,6}$ = 8.6 Hz, $^3J_{5,6'}$ = 5.7 Hz, 1 H, 5-H), 3.72 (s, 3 H, 1-H), 3.48 (m, 2 H, 3-H), 3.42 (m, 2 H, 8-H), 2.19 (m, 1 H, 6-H'), 1.95 (m, 1 H, 6-H), 1.86 (m, 2 H, 7-H), 1.41 (s, 9 H, 11-H).

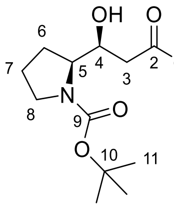
Selected rotamer signals:

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.25 (dd, $^3J_{5,6}$ = 8.4 Hz, $^3J_{5,6'}$ = 4.9 Hz, 1 H, 5-H), 3.70 (s, 3 H, 1-H), 3.57 (m, 2 H, 3-H), 2.08 (m, 1 H, 6-H'), 2.02 (m, 1 H, 6-H), 1.44 (s, 9 H, 11-H).

tert-Butyl (_S_)-2-((_S_)-1-hydroxy-3-methoxy-3-oxopropyl)pyrrolidine-1-carboxylate[113] 2

According to Greck *et al.*[113], before use, all the solvents in this reaction were degassed with argon. Bis-(2-methylallyl)-cycloocta-1,5-diene-ruthenium (II) complex (4.70 mg, 147 µmol, 2 mol%) and (*R*)-BINAP (9.20 mg, 147 µmol, 2 mol%) were dissolved in acetone (300 µL). The mixture was stirred for 1 h after adding 0.20 M HBr in MeOH (1.47 mL, 295 µmol, 4 mol%). The solvent was removed in vacuo, and a solution of the above-prepared β-ketoester (2.00 g, 7.37 mmol) in MeOH (12.5 mL) was added to the residue. After 5 min, the atmosphere was exchanged to H_2 (1 atm), and the solution was stirred for 66 h at 50 °C (sand bath). The solvent was removed in vacuo, and the crude was purified by column chromatography (silica, CH_2Cl_2:EtOAc 15% to 20% EtOAc) to give β-hydroxyester **2** (1.44 g, 5.27 mmol, 72%) as a colorless oil.

TLC: R_f (2) = 0.28 (silica, CH_2Cl_2:EtOAc 85:15)



2

^{1}**H-NMR** (500 MHz, $CDCl_3$): δ = 5.06 (s, 1 H, 4-OH), 4.01 (m, 1 H, 4-H), 3.92 (dt, $^3J_{5,4}$ = 4.4 Hz, $^3J_{5,6}$ = 7.9 Hz, 1 H, 5-H), 3.71 (s, 3 H, 1-H), 3.49 (m, 1 H, 8-H‘), 3.30 (ddd, $^2J_{8,8'}$ = 10.9 Hz, $^3J_{8,7'}$ = 7.4 Hz, $^3J_{8,7}$ = 5.4 Hz, 1 H, 8-H), 2.52 (dd, $^2J_{3',3}$ = 15.3 Hz, $^3J_{3',4}$ = 3.3 Hz, 1 H, 3-H‘), 2.43 (dd, $^2J_{3,3'}$ = 15.2 Hz, $^3J_{3,4}$ = 8.7 Hz, 1 H, 3-H), 1.99 (ddt, $^2J_{6',6}$ = 12.5 Hz, $^3J_{6',5}$ = 7.8 Hz, $^3J_{6',7}$ = 7.8 Hz, 1 H, 6-H‘), 1.89 (dtt, $^2J_{7',7}$ = 12.7 Hz, $^3J_{7',6}$ = 7.5 Hz, $^3J_{7',8}$ = 7.2 Hz, 1 H, 7-H‘), 1.78 (m, 1 H, 7-H), 1.69 (m, 1 H, 6-H), 1.46 (s, 9 H, 11-H).

^{13}**C-NMR** (125 MHz, $CDCl_3$): δ = 172.2 (s, C-2), 157.3 (s, C-9), 80.4 (s, C-10), 72.6 (d, C-4), 61.8 (d, C-5), 51.7 (q, C-1), 47.3 (t, C-8), 40.0 (t, C-3), 28.3 (t, C-6, q, C-11), 24.1 (q, C-7).

Optical rotation: $[\alpha]_D^{20}$= –83.4 (c = 1.0, $CHCl_3$)

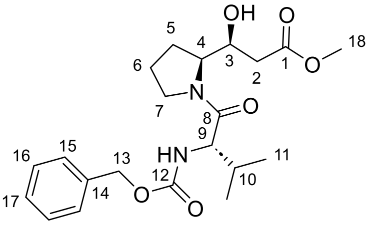
HRMS (CI):	calculated	found
$C_{13}H_{24}O_5N$ $[M+H]^+$:	274.1649	274.1646

Methyl (*S*)-3-((*S*)-1-(((benzyloxy)carbonyl)-L-valyl)pyrrolidin-2-yl)-3-hydroxypropanoate 3

β-Hydroxyester **2** (494 mg, 1.81 mmol) was dissolved in anhydrous CH_2Cl_2 (3.0 mL) and cooled to 0 °C. 4.0 M HCl in 1,4-dioxane (4.52 mL, 18.1 mmol, 10 eq.) was added, and the resulting solution was stirred for 3 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride.

A solution of the above-prepared hydrochloride salt and Cbz-Val-OH (477 mg, 1.90 mmol, 1.05 eq.) in anhydrous CH_2Cl_2 (15 mL) was cooled to 0 °C. NMM (596 µL, 5.42 mmol, 3.0 eq.) and HATU (720 mg, 1.90 mmol, 1.05 eq.) were added, and the resulting yellow solution was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, PE:EtOAc 1:1) to give dipeptide **3** (677 mg, 1.57 mmol, 87%) as a colorless resin.

TLC: R_f **(3)** = 0.51 (silica, PE:EtOAc 1:1)



3

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.38 – 7.29 (m, 5 H, 15-H, 16-H, 17-H), 5.50 (d, $^{3}J_{\mathrm{NH},9}$ = 9.4 Hz, 1 H, 12-NH), 5.08 (m, 2 H, 13-H), 4.63 (d, $^{3}J_{\mathrm{OH},3}$ = 4.4 Hz, 1 H, 3-OH), 4.39 (dd, $^{3}J_{9,\mathrm{NH}}$ = 9.2 Hz, $^{3}J_{9,10}$ = 6.1 Hz, 1 H, 9-H), 4.31 (ddd, $^{3}J_{4,3}$ = 7.7 Hz, $^{3}J_{4,5}$ = 7.5 Hz, $^{3}J_{4,5'}$ = 4.5 Hz, 1 H, 4-H), 4.01 (m, 1 H, 3-H), 3.85 (ddd, $^{2}J_{7',7}$ = 10.3 Hz, $^{3}J_{7',6}$ = 6.6 Hz, $^{3}J_{7',6'}$ = 6.6 Hz, 1 H, 7-H'), 3.72 (s, 3 H, 18-H), 3.53 (ddd, $^{2}J_{7,7'}$ = 10.3 Hz, $^{3}J_{7,6}$ = 6.5 Hz, $^{3}J_{7,6'}$ = 6.5 Hz, 1 H, 7-H), 2.52 (dd, $^{2}J_{2',2}$ = 15.3 Hz, $^{3}J_{2',3}$ = 3.4 Hz, 1 H, 2-H'), 2.46 (dd, $^{2}J_{2,2'}$ = 15.3 Hz, $^{3}J_{2,3}$ = 8.8 Hz, 1 H, 2-H), 2.07 – 1.95 (m, 3 H, 5-H', 6-H', 10-H), 1.92 (m, 1 H, 6-H), 1.70 (m, 1 H, 5-H), 1.03 (d, $^{3}J_{11',10}$ = 6.8 Hz, 3 H, 11-H'), 0.94 (d, $^{3}J_{11,10}$ = 6.8 Hz, 3 H, 11-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 174.1 (s, C-8), 172.3 (s, C-1), 156.6 (s, C-12), 136.4 (s, C-14), 128.7 (d, C-16), 128.3 (d, C-17), 128.2 (d, C-15), 72.8 (d, C-3), 67.1 (t, C-13), 62.3 (d, C-4), 57.8 (d, C-9), 52.0 (q, C-18), 48.2 (t, C-7), 40.3 (t, C-2), 31.7 (d, C-10), 27.8 (t, C-5), 24.7 (t, C-6), 19.6 (q, C-11'), 17.5 (q, C-11).

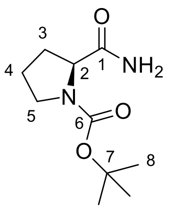
Optical rotation: $[\alpha]_D^{20}$ = –58.1 (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{21}H_{31}O_6N_2$ [M+H]$^+$:	407.2182	407.2191

***tert*-Butyl (*S*)-2-carbamoylpyrrolidine-1-carboxylate 4**

Ethyl chloroformate (578 µL, 6.02 mmol, 1.2 eq.) was dropwise added to a 0 °C cold solution of Boc-Pro-OH (1.08 g, 5.02 mmol) and triethylamine (839 µL, 6.02 mmol, 1.2 eq.) in anhydrous THF (20 mL). The resulting mixture was stirred for 1 h at 0 °C. Aqueous ammonia solution (3.33 mL, 60.2 mmol, 35 wt%, 12 eq.) was added to the reaction mixture, and stirring was continued for 1 h. The reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo to give Boc-Pro-NH$_2$ **4** (939 mg, 4.38 mmol, 87%) as a white solid.

TLC: R$_f$ (4) = 0.16 (silica, PE:EtOAc 1:1 + 1% AcOH)



4

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 7.30 (s, 1 H, 1-NH$_2$), 6.91 (s, 1 H, 1-NH$_2$), 3.97 (dd, $^{3}J_{2,3}$ = 8.4 Hz, $^{3}J_{2,3'}$ = 3.6 Hz, 1 H, 2-H), 3.36 (m, 1 H, 5-H'), 3.25 (m, 1 H, 5-H), 2.09 (m, 1 H, 3-H'), 1.84 – 1.68 (m, 3 H, 4-H, 3-H), 1.34 (s, 9 H, 8-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.6 (s, C-1), 153.3 (s, C-6), 78.3 (s, C-7), 59.6 (d, C-2), 46.4 (t, C-5), 31.0 (t, C-3), 28.1 (q, C-8), 23.2 (t, C-4).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 7.27 (s, 1 H, 1-NH$_2$), 6.86 (s, 1 H, 1-NH$_2$), 4.00 (dd, $^3J_{2,3}$ = 8.8 Hz, $^3J_{2,3'}$ = 2.9 Hz, 1 H, 2-H), 2.02 (m, 1 H, 3-H'), 1.39 (s, 9 H, 8-H).

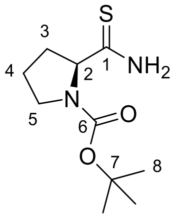
^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.3 (s, C-1), 153.6 (s, C-6), 78.4 (s, C-7), 59.4 (d, C-2), 46.4 (t, C-5), 30.0 (t, C-3), 28.2 (q, C-8), 23.9 (t, C-4).

Optical rotation:	$[\alpha]_D^{20}$= –99.4 (c = 0.5, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{10}H_{19}N_2O_3$ [M+H]$^+$:	215.1390	215.1377
Melting point:	105 – 107 °C (lit: 103.6 – 107.7 °C)[201]	

***tert*-Butyl (*S*)-2-carbamothioylpyrrolidine-1-carboxylate 5**

According to Taunton *et al.*[114], Boc-Pro-NH$_2$ **4** (1.81 g, 8.45 mmol) was dissolved in anhydrous THF (25 mL) under an atmosphere of nitrogen. Lawesson's reagent (1.71 g, 4.22 mmol, 0.5 eq.) was added, and the resulting solution was stirred for 5 h at room temperature. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography (silica, 97:3 CH$_2$Cl$_2$:MeOH) to give thioamide **5** (1.76 g, 7.64 mmol, 90%) as a white solid.

R$_f$ (5) = 0.35 (silica, CH$_2$Cl$_2$:MeOH 95:5)



5

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.52 (s, 1 H, 1-NH$_2$), 9.12 (s, 1 H, 1-NH$_2$), 4.40 (m, 1 H, 2-H), 3.45 (m, 1 H, 5-H'), 3.30 (m, 1 H, 5-H), 2.18 (m, 1 H, 3-H'), 1.89 – 1.77 (m, 2 H, 4-H', 3-H), 1.73 (m, 1 H, 4-H), 1.33 (s, 9 H, 8-H).

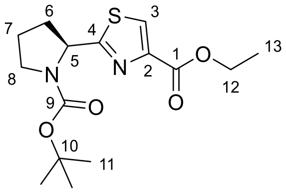
Selected rotamer signals:

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 9.07 (s, 1 H, 1-NH$_2$), 1.39 (s, 9 H, 8-H).

Ethyl (*S*)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)thiazole-4-carboxylate[114] 6

KHCO$_3$ (2.02 g, 10.1 mmol, 4.0 eq.) was added to a solution of thioamide **5** (580 mg, 2.52 mmol) in anhydrous DME (10 mL). The resulting suspension was stirred for 10 min at room temperature before ethyl bromopyruvate (1.05 mL, 7.55 mmol, 3.0 eq.) was added dropwise. The reaction mixture was stirred for 30 min at room temperature and then cooled to 0 °C. A preformed solution of TFAA (1.42 mL, 10.1 mmol, 4.0 eq.) and 2,6-lutidine (2.49 mL, 21.4 mmol, 8.5 eq.) in anhydrous DME (3.0 mL) was added dropwise to the reaction mixture over 10 min. The reaction mixture was stirred for 2 h while slowly reaching room temperature before being quenched by the addition of 1.0 M $HCl_{aq.}$ and EtOAc. After extraction of the aqueous layer with EtOAc, the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified twice by column chromatography (1. silica, PE:EtOAc 6:4; 2. silica, PE:EtOAc 75:25) to give thiazole **6** (763 mg, 2.34 mmol, 93%) as a white solid.

TLC: R_f (6) = 0.39 (silica, PE:EtOAc 1:1)



6

¹H-NMR (500 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, 3-H), 5.20 (m, 1 H, 5-H), 4.42 (q, $^3J_{12,13}$ = 7.2 Hz, 2 H, 12-H), 3.62 (m, 1 H, 8-H‘), 3.52 (ddd, $^2J_{8,8'}$ = 9.1 Hz, $^3J_{8,7}$ = 8.9 Hz, $^3J_{8,7'}$ = 8.9 Hz, 1 H, 8-H), 2.35 (m, 1 H, 6-H‘), 2.23 (m, 1 H, 6-H), 1.92 (m, 2 H, 7-H), 1.40 (t, $^3J_{13,12}$ = 7.1 Hz, 3 H, 13-H), 1.32 (s, 9 H, 11-H).

¹³C-NMR (125 MHz, DMSO-d_6, 373 K): δ = 174.7 (s, C-4), 160.2 (s, C-1), 153.1 (s, C-9), 145.6 (s, C-2), 127.4 (d, C-3), 78.8 (s, C-10), 60.0 (d, C-5), 58.3 (t, C-12), 46.1 (t, C-8), 32.4 (t, C-6), 27.5 (q, C-11), 22.6 (t, C-7), 13.6 (q, C-13).

Selected rotamer signals:

¹H-NMR (500 MHz, $CDCl_3$): δ = 5.27 (m, 1 H, 5-H), 3.44 (m, 1 H, 8-H), 1.48 (s, 9 H, 11-H).

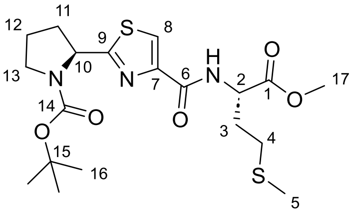
Optical rotation:	$[\alpha]_D^{20}$= –75.6 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{15}H_{22}O_4N_2S$ $[M]^+$:	326.1295	326.1299
Melting point:	98 – 101 °C	

tert-Butyl (*S*)-2-(4-(((*S*)-1-methoxy-4-(methylthio)-1-oxobutan-2-yl)carbamoyl)thiazol-2-yl)-pyrrolidine-1-carboxylate 8

1.0 M $LiOH_{aq}$ (4.60 mL, 4.60 mmol, 1.2 eq.) was added dropwise to a 0 °C cold solution of thiazole **6** (1.25 g, 3.83 mmol) in THF (20 mL). The reaction mixture was stirred for 72 h before being diluted with EtOAc and acidified with 1.0 M HCl_{aq}. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine. After drying over $MgSO_4$ and concentration in vacuo, the crude acid **7** (1.10 g, 3.32 mmol, 87%, 90wt% purity) was isolated as a yellow solid.

The crude acid **7** (1.08 g, 3.26 mmol, 90 wt%) and NMM (895 µL, 8.14 mmol, 2.5 eq.) were dissolved in anhydrous CH_2Cl_2 (25 mL) before being cooled to –20 °C. IBCF (513 µL, 3.91 mmol, 1.2 eq.) was added dropwise, and the resulting solution was stirred for 30 min at –20 °C. H-Met-OMe·HCl (781 mg, 3.91 mmol, 1.2 eq.) was added in one portion, and the reaction mixture was allowed to reach room temperature for 16 h. After dilution with EtOAc, the solution was washed with 1.0 M $HCl_{aq.}$, sat. $NaHCO_3$ solution and brine. Drying over $MgSO_4$ and concentration in vacuo led to the crude product, which was purified by column chromatography (silica, PE:EtOAc 65:35) to give dipeptide **8** (1.17 g, 2.64 mmol, 81%) as a light-yellow resin.

TLC: R_f (8) = 0.13 (silica, PE:EtOAc 7:3)



8

^{1}H-NMR (500 MHz, DMSO-d_6, 373 K): δ = 8.19 (d, $^3J_{NH,2}$ = 8.0 Hz, 1 H, 6-NH), 8.15 (s, 1 H, 8-H), 5.12 (dd, $^3J_{10,11'}$ = 8.2 Hz, $^3J_{10,11}$ = 3.1 Hz, 1 H, 10-H), 4.66 (dt, $^3J_{2,NH}$ = 7.9 Hz, $^3J_{2,3}$ = 5.7 Hz, 1 H, 2-H), 3.69 (s, 3 H, 17-H), 3.52 – 3.42 (m, 2 H, 13-H, 13-H'), 2.55 (m, 2 H, 4-H), 2.37 (ddt, $^2J_{11',11}$ = 12.8 Hz, $^3J_{11',10}$ = 8.5 Hz, $^3J_{11',12}$ = 8.5 Hz, 1 H, 11'-H), 2.18 – 2.10 (m, 3 H, 11-H, 3-H), 2.07 (s, 3 H, 5-H), 1.94 (m, 2 H, 12-H), 1.32 (s, 9 H, 16-H).

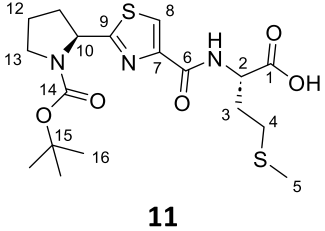
^{13}C-NMR (125 MHz, DMSO-d_6, 373 K): δ = 174.7 (s, C-9), 171.2 (s, C-1), 160.0 (s, C-6), 153.1 (s, C-14), 148.5 (s, C-7), 123.2 (d, C-8), 78.8 (s, C-15), 58.3 (d , C-10), 51.4 (q, C-17), 50.9 (d, C-2), 46.1 (t, C-13), 32.5 (t, C-11), 30.4 (t, C-3), 29.5 (t, C-4), 27.5 (q, C-16), 22.7 (t, C-12), 14.2 (q, C-5).

Optical rotation:	$[\alpha]_D^{20}$= –50.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{19}H_{30}N_3O_5S_2$ $[M+H]^+$:	444.1621	444.1625

(2-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)thiazole-4-carbonyl)-L-methionine 11

Dipeptide **8** (488 mg, 1.10 mmol) was dissolved in THF (4.0 mL). The solution was cooled to 0 °C, and 0.30 M $LiOH_{aq}$ (3.85 mL, 1.16 mmol, 1.05 eq.) was added. After stirring for 3 h, while slowly reaching room temperature, the reaction mixture was diluted with diethyl ether and acidified with 0.1 M HCl_{aq}. The aqueous layer was extracted with diethyl ether and the combined organic extracts where dried over $MgSO_4$. Concentration in vacuo led to carboxylic acid **11** (452 mg, 1.05 mmol, 96%) as a colorless resin.

TLC: R_f (11) = 0.48 (silica, PE:EtOAc 4:6)



11

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 12.47 (s, 1 H, 1-OH), 8.14 (s, 1 H, 8-H), 8.09 (d, $^3J_{NH,2}$ = 8.1 Hz, 1 H, 6-NH), 5.12 (dd, $^3J_{10,11'}$ = 8.2 Hz, $^3J_{10,11}$ = 3.2 Hz, 1 H, 10-H), 4.59 (dt, $^3J_{2,NH}$ = 8.0 Hz, $^3J_{2,3}$ = 5.2 Hz, 1 H, 2-H), 3.54 – 3.42 (m, 2 H, 13-H, 13-H'), 2.55 (m, 2 H, 4-H), 2.36 (m, 1 H, 11-H'), 2.18 – 2.08 (m, 3 H, 11-H, 3-H), 2.07 (s, 3 H, 5-H), 1.94 (dddd, $^3J_{12,11'}$ = 8.0 Hz, $^3J_{12,11}$ = 8.0 Hz, $^3J_{12,13}$ = 8.0 Hz, $^3J_{12,13'}$ = 6.3 Hz, 2 H, 12-H), 1.36 (s, 9 H, 16-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 174.6 (s, C-9), 172.0 (s, C-1), 159.9 (s, C-6), 153.1 (s, C-14), 148.5 (s, C-7), 123.0 (d, C-8), 78.8 (s, C-15), 58.3 (d, C-10), 50.9 (d, C-2), 46.0 (t, C-13), 32.5 (t, C-11), 30.7 (t, C-3), 29.5 (t, C-4), 27.5 (q, C-16), 22.6 (t, C-12), 14.2 (q, C-5).

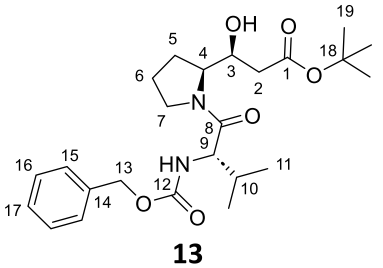
Optical rotation:	$[\alpha]_D^{20}$ = –52.1 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{18}H_{28}N_3O_5S_2$ [M+H]$^+$:	430.1465	430.1472

tert-Butyl (*S*)-3-((*S*)-1-(((benzyloxy)carbonyl)-L-valyl)pyrrolidin-2-yl)-3-hydroxypropanoate 13

0.20 M LiOH$_{aq.}$ (1.27 mL, 254 µmol, 1.1 eq.) was added to a 0 °C cold solution of dipeptide **3** (100 mg, 231 µmol) in THF (1.2 mL). The resulting solution was stirred for 3 h while slowly reaching room temperature. The reaction mixture was acidified with 1.0 M HCl$_{aq.}$ and extracted with diethyl ether. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give the crude carboxylic acid as a white foam.

A solution of *tert*-butyl 2,2,2-trichloroacetimidate (76.0 mg, 348 µmol, 1.5 eq.) in anhydrous Et$_2$O (500 µL) was added to a solution of the above-prepared carboxylic acid in anhydrous THF (1.0 mL). The reaction mixture was stirred for 16 h before the mixture was diluted with EtOAc and washed with water, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give *tert*-butyl ester **13** (100 mg, 223 µmol, 96%) as a colorless oil.

TLC: R$_f$ (13) = 0.45 (silica, PE:EtOAc 6:4)



13

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.39 – 7.29 (m, 5 H, 15-H, 16-H, 17-H), 5.51 (d, $^3J_{NH,9}$ = 9.2 Hz, 1 H, 12-NH), 5.08 (m, 2 H, 13-H), 4.42 – 4.27 (m, 3 H, 4-H, 9-H, 3-OH), 3.99 (m, 1 H, 3-H), 3.83 (ddd, $^2J_{7',7}$ = 10.1 Hz, $^3J_{7',6}$ = 6.6 Hz, $^3J_{7',6'}$ = 6.6 Hz, 1 H, 7-H'), 3.52 (ddd, $^2J_{7,7'}$ = 10.3 Hz, $^3J_{7,6}$ = 6.6 Hz, $^3J_{7,6'}$ = 6.6 Hz, 1 H, 7-H), 2.45 (dd, $^2J_{2',2}$ = 15.5 Hz, $^3J_{2',3}$ = 3.5 Hz, 1 H, 2-H'), 2.35 (dd, $^2J_{2,2'}$ = 15.5 Hz, $^3J_{2,3}$ =

8.4 Hz, 1 H, 2-H), 2.09 – 1.95 (m, 3 H, 5-H‘, 6-H‘, 10-H), 1.90 (m, 1 H, 6-H), 1.73 (m, 1 H, 5-H), 1.46 (s, 9 H, 19-H), 1.03 (d, $^{3}J_{11',10}$ = 6.7 Hz, 3 H, 11‘-H), 0.94 (d, $^{3}J_{11,10}$ = 6.7 Hz, 3 H, 11-H).

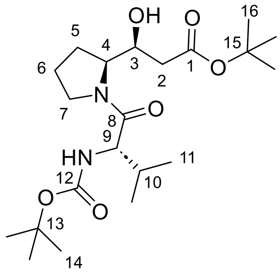
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 173.6 (s, C-8), 171.2 (s, C-1), 156.4 (s, C-12), 136.3 (s, C-14), 128.5 (d, C-16), 128.1 (d, C-17), 128.0 (d, C-15), 81.0 (s, C-18), 72.3 (d, C-3), 66.9 (t, C-13), 61.9 (d, C-4), 57.6 (d, C-9), 48.0 (t, C-7), 41.2 (t, C-2), 31.5 (d, C-10), 28.1 (q, C-19), 27.4 (t, C-5), 24.5 (t, C-6), 19.5 (q, C-11‘), 17.4 (q, C-11).

Optical rotation:	$[\alpha]_D^{20}$= –50.4 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{24}H_{37}N_2O_6$ [M+H]$^+$:	449.2646	449.2652

tert-Butyl (*S*)-3-((*S*)-1-((*tert*-butoxycarbonyl)-L-valyl)pyrrolidin-2-yl)-3-hydroxypropanoate 14

Benzyl carbamate **13** (178 mg, 397 µmol), Boc$_2$O (97 µL, 417 µmol, 1.05 eq.), and Pd/C (20.0 mg, 19.1 µmol, 10 wt% Pd, 5 mol%) were suspended in EtOAc (4.0 mL). The resulting suspension was stirred for 18 h under an atmosphere of H$_2$ (1 atm). The reaction mixture was filtered through a plug of celite® and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 1:1) to give dipeptide **14** (160 mg, 386 µmol, 97%) as a colorless oil.

TLC: R$_f$ (14) = 0.22 (silica, PE:EtOAc 6:4)



14

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 5.25 (d, $^{3}J_{NH,9}$ = 9.4 Hz, 1 H, 12-NH), 4.42 – 4.27 (m, 2 H, 4-H, 9-H), 3.99 (td, $^{3}J_{3,4}$ = 8.2 Hz, $^{3}J_{3,2}$ = 8.2 Hz, $^{3}J_{3,2'}$ = 3.5 Hz, 1 H, 3-H), 3.82 (ddd, $^{2}J_{7',7}$ = 10.1 Hz, $^{3}J_{7',6}$ = 6.7 Hz, $^{3}J_{7',6'}$ = 6.7 Hz, 1 H, 7-H‘), 3.50 (ddd, $^{2}J_{7,7'}$ = 10.2 Hz, $^{3}J_{7,6}$ = 6.4 Hz, $^{3}J_{7,6'}$ = 6.4 Hz, 1 H, 7-H), 2.44 (dd, $^{2}J_{2',2}$ = 15.5 Hz, $^{3}J_{2',3}$ = 3.6 Hz, 1 H, 2-H‘), 2.35 (dd, $^{2}J_{2,2'}$ = 15.5 Hz, $^{3}J_{2,3}$ = 8.4 Hz, 1 H, 2-H), 2.09 – 1.95 (m, 3 H, 5-H‘, 6-H‘, 10-H), 1.90 (m, 1 H, 6-H), 1.71 (m, 1 H, 5-H), 1.46 (s, 9 H, 16-H), 1.43 (s, 9 H, 14-H), 1.01 (d, $^{3}J_{11',10}$ = 6.7 Hz, 3 H, 11‘-H), 0.93 (d, $^{3}J_{11,10}$ = 6.7 Hz, 3 H, 11-H).

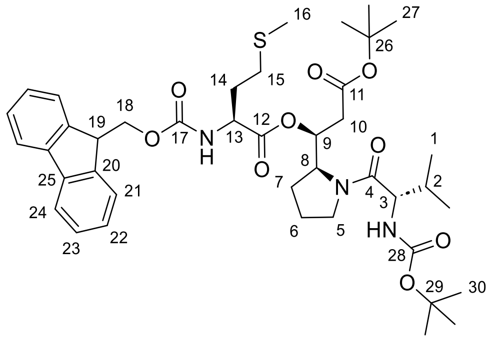
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 174.2 (s, C-8), 171.4 (s, C-1), 156.0 (s, C-12), 81.1 (s, C-15), 79.7 (s, C-13), 72.5 (d, C-3), 62.1 (d, C-4), 57.2 (d, C-9), 48.1 (t, C-7), 41.3 (t, C-2), 31.7 (d, C-10), 28.5 (q, C-14), 28.2 (q, C-16), 27.6 (t, C-5), 24.7 (t, C-6), 19.6 (q, C-11‘), 17.5 (q, C-11).

Optical rotation:	$[\alpha]_D^{20}$= –48.8 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{21}H_{39}O_6N_2$ [M+H]$^+$:	415.2803	415.2799

(*S*)-3-(*tert*-Butoxy)-1-((*S*)-1-((*tert*-butoxycarbonyl)-L-valyl)pyrrolidin-2-yl)-3-oxopropyl(((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-methioninate 15

Dipeptide **14** (139 mg, 335 µmol), Fmoc-Met-OH (374 mg, 1.01 mmol, 3.0 eq.), and DMAP (123 mg, 1.01 mmol, 3.0 eq.) were dissolved in anhydrous CH_2Cl_2 (3.0 mL). The resulting solution was cooled to 0 °C before DCC (208 mg, 1.01 mmol, 3.0 eq.) was added in one portion. The reaction mixture was stirred for 4 h while slowly reaching room temperature. After the addition of MeCN (4.0 mL), most of the urea was removed by filtration. The filtrate was diluted with EtOAc (50 mL) and washed with sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine. Drying over $MgSO_4$ and concentration in vacuo followed by column chromatography (silica, PE:EtOAc 75:25) led to depsipeptide **15** (219 mg, 285 µmol, 85%) as a white solid.

TLC: R_f (15) = 0.20 (silica, PE:EtOAc 7:3)



15

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{24,23}$ = 7.5 Hz, 2 H, 24-H), 7.62 (m, 2 H, 21-H), 7.41 (dd, $^3J_{23,24}$ = 7.5 Hz, $^3J_{23,22}$ = 7.5 Hz, 2 H, 23-H), 7.32 (dd, $^3J_{22,21}$ = 7.4 Hz, $^3J_{22,23}$ = 7.4 Hz, 2 H, 22-H), 5.61 (ddd, $^3J_{9,8}$ = 8.9 Hz, $^3J_{9,10}$ = 4.2 Hz, $^3J_{9,10'}$ = 4.2 Hz, 1 H, 9-H), 5.53 (d, $^3J_{NH,13}$ = 8.2 Hz, 1 H, 17-NH), 5.28 (d, $^3J_{NH,3}$ = 9.2 Hz, 1 H, 28-NH), 4.53 (m, 1 H, 8-H), 4.48 (m, 1 H, 13-H), 4.44 (dd, $^2J_{18',18}$ = 10.5 Hz, $^3J_{18',19}$ = 7.3 Hz, 1 H, 18-H‘), 4.37 (dd, $^2J_{18,18'}$ = 10.9 Hz, $^3J_{18,19}$ = 7.0 Hz, 1 H, 18-H), 4.31 (dd, $^3J_{3,NH}$ = 9.2 Hz, $^3J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 4.22 (dd, $^3J_{19,18}$ = 7.1 Hz, $^3J_{19,18'}$ = 7.1 Hz, 1 H, 19-H), 3.77 (dt, $^2J_{5',5}$ = 9.9 Hz, $^3J_{5',6}$ = 6.8 Hz, 1 H, 5-H‘), 3.41 (dt, $^2J_{5,5'}$ = 10.1 Hz, $^3J_{5,6}$ = 6.7 Hz, 1 H, 5-H), 2.58 – 2.48 (m, 3 H, 10-H′, 15-H), 2.43 (dd, $^2J_{10,10'}$ = 15.9 Hz, $^3J_{10,9}$ = 9.0 Hz, 1 H, 10-H), 2.17 (m, 1 H, 14-H‘), 2.10 (s, 3 H, 16-H), 2.00 – 1.84 (m, 5 H, 2-H, 6-H, 6-H′, 7-H′, 14-H), 1.79 (m, 1 H, 7-H), 1.42 (s, 9 H, 30-H), 1.41 (s, 9 H, 27-H), 0.97 (d, $^3J_{1',2}$ = 6.7 Hz, 3 H, 1′-H), 0.88 (d, $^3J_{1,2}$ = 6.8 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.5 (s, C-4), 170.6 (s, C-12), 169.4 (s, C-11), 156.0 (s, C-28), 155.9 (s, C-17), 143.9 (s, C-20′), 143.8 (s, C-20), 141.43 (s, C-25), 141.40 (s, C-25‘), 127.9 (d, C-23), 127.21 (d, C-22), 127.18 (d, C-22′), 125.2 (d, C-21), 125.1 (d, C-21‘), 120.12 (d, C-24), 120.09 (d, C-24‘), 81.4 (s, C-26), 79.6 (s, C-29), 73.3 (d, C-9), 67.1 (t, C-18), 58.1 (d, C-8), 57.1 (d, C-3), 53.5 (d, C-13), 47.9 (t, C-5), 47.3 (d, C-19), 37.5 (t, C-10), 32.3 (t, C-14), 31.6 (d, C-2), 30.0 (t, C-15), 28.5 (q, C-27), 28.1 (q, C-30), 26.4 (t, C-7), 24.7 (t, C-6), 19.8 (q, C-1‘), 17.2 (q, C-1), 15.5 (q, C-16).

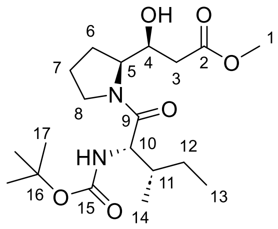
Optical rotation:	$[\alpha]_D^{20} = -20.9$ (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{41}H_{58}O_9N_3S$ $[M+H]^+$:	768.3888	768.3894

Methyl (*S*)-3-((*S*)-1-((*tert*-butoxycarbonyl)-L-isoleucyl)pyrrolidin-2-yl)-3-hydroxypropanoate 17

β-Hydroxyester **2** (479 mg, 1.75 mmol) was dissolved in anhydrous CH_2Cl_2 (4.0 mL) and cooled to 0 °C. 4.0 M HCl in 1,4-dioxane (4.38 mL, 17.5 mmol, 10 eq.) was added, and the resulting solution was stirred for 5 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride.

A solution of the above-prepared hydrochloride salt and Boc-Ile-OH (445 mg, 1.93 mmol, 1.1 eq.) in anhydrous CH_2Cl_2 (18 mL) was cooled to 0 °C. NMM (616 µL, 5.60 mmol, 3.2 eq.) and HATU (732 mg, 1.93 mmol, 1.1 eq.) were added, and the resulting yellow solution was stirred for 18 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 55:45) to give dipeptide **17** (642 mg, 1.58 mmol, 90%) as a colorless resin.

TLC: R_f (17) = 0.20 (silica, PE:EtOAc 6:4)



17

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.17 (d, $^3J_{NH,10}$ = 9.4 Hz, 1 H, 15-NH), 4.75 (d, $^3J_{OH,4}$ = 4.4 Hz, 1 H, 4-OH), 4.36 – 4.27 (m, 2 H, 5-H, 10-H), 4.02 (m, 1 H, 4-H), 3.89 (m, 1 H, 8-H‘), 3.72 (s, 3 H, 1-H), 3.51 (dt, $^2J_{8,8'}$ = 10.2 Hz, $^3J_{8,7}$ = 6.7 Hz, 1 H, 8-H), 2.54 (dd, $^2J_{3',3}$ = 15.2 Hz, $^3J_{3',4}$ = 3.6 Hz, 1 H, 3-H‘), 2.46 (dd, $^2J_{3,3'}$ = 15.2 Hz, $^3J_{3,4}$ = 8.5 Hz, 1 H, 3-H), 2.05 – 1.97 (m, 2 H, 6-H‘, 7-H‘), 1.90 (m, 1 H, 7-H), 1.77 – 1.66 (m, 2 H, 6-H, 11-H), 1.56 (m, 1 H, 12‘-H), 1.43 (s, 9 H, 17-H), 1.14 (m, 1 H, 12-H), 0.98 (d, $^3J_{14,11}$ = 6.7 Hz, 3 H, 14-H), 0.90 (t, $^3J_{13,12}$ = 7.4 Hz, 3 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.7 (s, C-9), 172.3 (s, C-2), 155.9 (s, C-15), 79.8 (s, C-16), 72.8 (d, C-4), 62.4 (d, C-5), 56.7 (d, C-10), 52.0 (q, C-1), 48.3 (t, C-8), 40.3 (t, C-3), 38.2 (d, C-11), 28.5 (q, C-17), 27.9 (t, C-6), 24.7 (t, C-7), 24.3 (t, C-12), 15.6 (q, C-14), 11.4 (q, C-13).

Optical rotation: $[\alpha]_D^{20}$= –63.6 (c = 1.0, $CHCl_3$)

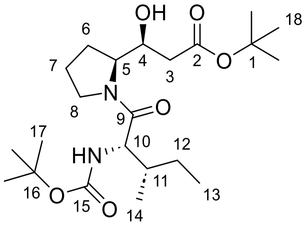
HRMS (CI):	calculated	found
$C_{19}H_{35}O_6N_2$ [M+H]$^+$:	387.2490	387.2496

***tert*-Butyl (*S*)-3-(*S*)-1-(*tert*-butoxycarbonyl)-L-isoleucyl)pyrrolidin-2-yl-3-hydroxypropanoate 18**

0.20 M $LiOH_{aq.}$ (7.97 mL, 1.59 mmol, 1.1 eq.) was added to a 0 °C cold solution of dipeptide **17** (560 mg, 1.45 mmol) in THF (7.0 mL). The resulting solution was stirred for 2 h while slowly reaching room temperature. Another portion of 0.20 M $LiOH_{aq.}$ (2.90 mL, 0.58 mmol, 0,4 eq.) was added, and the reaction mixture was stirred for two more hours. The reaction mixture was acidified with 1.0 M $HCl_{aq.}$ and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid.

A solution of *tert*-butyl 2,2,2-trichloroacetimidate (380 mg, 1.74 mmol, 1.2 eq.) in anhydrous Et_2O (3.5 mL) was added to a solution of the above-prepared carboxylic acid (540 mg, 1.45 mmol) in anhydrous THF (7.0 mL). The reaction mixture was stirred for 3 h before another portion of *tert*-butyl 2,2,2-trichloroacetimidate (95.0 mg, 0.435 mmol, 0.3 eq.) was added. After one more hour, the mixture was diluted with EtOAc, washed with water, sat. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18, H_2O:MeCN 10% to 90% MeCN) to give *tert*-butyl ester **18** (430 mg, 1.01 mmol, 70%, 80% brsm) as a colorless oil.

TLC: R_f (18) = 0.31 (silica, PE:EtOAc 6:4)



18

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.18 (d, $^3J_{NH,10}$ = 9.4 Hz, 1 H, 15-NH), 4.47 (s, 1 H, 4-OH), 4.36 – 4.28 (m, 2 H, 5-H, 10-H), 4.02 (ddd, $^3J_{4,3}$ = 8.0 Hz, $^3J_{4,5}$ = 8.0 Hz, $^3J_{4,3'}$ = 3.5 Hz, 1 H, 4-H), 3.86 (dt, $^2J_{8',8}$ = 10.0 Hz, $^3J_{8',7}$ = 6.7 Hz, 1 H, 8-H‘), 3.50 (dt, $^2J_{8,8'}$ = 10.3 Hz, $^3J_{8,7}$ = 6.4 Hz, 1 H, 8-H), 2.44 (dd, $^2J_{3',3}$ = 15.5 Hz, $^3J_{3',4}$ = 3.6 Hz, 1 H, 3-H‘), 2.35 (dd, $^2J_{3,3'}$ = 15.5 Hz, $^3J_{3,4}$ = 8.2 Hz, 1 H, 3-H), 2.07 – 1.93 (m, 2 H, 6-H‘, 7-H‘), 1.90 (m, 1 H, 7-H), 1.77 – 1.67 (m, 2 H, 6-H, 11-H), 1.57 (m, 1 H, 12-H‘), 1.43 (s, 9 H, 18-H), 1.43 (s, 9 H, 17-H), 1.14 (m, 1 H, 12-H), 0.98 (d, $^3J_{14,11}$ = 6.7 Hz, 3 H, 14-H), 0.90 (t, $^3J_{13,12}$ = 7.4 Hz, 3 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.4 (s, C-9), 171.4 (s, C-2), 155.9 (s, C-15), 81.1 (s, C-1), 79.7 (s, C-16), 72.3 (d, C-4), 62.1 (d, C-5), 56.7 (d, C-10), 48.2 (t, C-8), 41.2 (t, C-3), 38.3 (d, C-11), 28.5 (q, C-17), 28.2 (q, C-18), 27.6 (t, C-6), 24.7 (t, C-7), 24.3 (t, C-12), 15.7 (q, C-14), 11.5 (q, C-13).

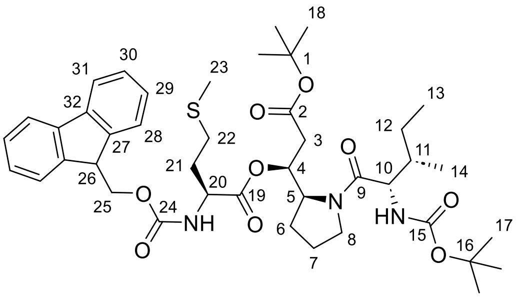
Optical rotation:	$[\alpha]_D^{20}$= –54.9 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{22}H_{41}N_2O_6$ $[M+H]^+$:	429.2959	429.2957

(*S*)-3-(*tert*-Butoxy)-1-((*S*)-1-((*tert*-butoxycarbonyl)-L-isoleucyl)pyrrolidin-2-yl)-3-oxopropyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-methioninate 19

A solution of Fmoc-Met-OH (208 mg, 560 µmol, 3.0 eq.), *tert*-butyl ester **18** (80.1 mg, 187 µmol), and DMAP (68.4 mg, 560 µmol, 3.0 eq.) in anhydrous CH_2Cl_2 (3.0 mL) was cooled to 0 °C. DCC (116 mg, 560 µmol, 3.0 eq.) was added, and the resulting solution was stirred for 4 h while slowly reaching room temperature. The reaction mixture was diluted with MeCN (2.0 mL) and filtrated.

The residue was washed with MeCN (3 x 2.0 mL), and the combined organic layers were diluted with EtOAc before being washed with sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 7:3) to give compound **19** (133 mg, 170 µmol, 91%) as a white foam.

TLC: R_f (19) = 0.51 (silica, PE:EtOAc 1:1)



19

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.78 (m, 2 H, 28-H), 7.62 (m, 2 H, 30-H), 7.33 (m, 2 H, 29-H), 7.33 (m, 2 H, 31-H), 5.64 (ddd, $^3J_{4,5}$ = 8.8 Hz, $^3J_{4,3}$ = 4.3 Hz,$^3J_{4,3'}$ = 4.3 Hz, 1 H, 4-H), 5.52 (d, $^3J_{NH,20}$ = 8.1 Hz, 1 H, 24-NH), 5.23 (d, $^3J_{NH,10}$ = 9.4 Hz, 1 H, 15-NH), 4.53 (m, 1 H, 5-H), 4.48 (m, 1 H, 20-H), 4.45 (dd, $^2J_{25',25}$ = 10.6 Hz, $^3J_{25',26}$ = 7.3 Hz, 1 H, 25-H), 4.37 (dd, $^2J_{25,25'}$ = 10.7 Hz, $^3J_{25,26}$ = 6.7 Hz, 1 H, 25-H), 4.32 (dd, $^3J_{10,NH}$ = 9.3 Hz, $^3J_{10,11}$ = 6.0 Hz, 1 H, 10-H), 4.22 (dd, $^3J_{26,25}$ = 7.2 Hz, $^3J_{26,25'}$ = 7.2 Hz, 1 H, 26-H), 3.81 (dt, $^2J_{8',8}$ = 9.8 Hz, $^3J_{8',7}$ = 7.2 Hz, 1 H, 8-H‘), 3.42 (dt, $^2J_{8,8'}$ = 10.1 Hz, $^3J_{8,7}$ = 6.8 Hz, 1 H, 8-H), 2.54 (m, 2 H, 22-H), 2.45 (m, 2 H, 3-H), 2.17 (m, 1 H, 21-H‘), 2.10 (s, 3 H, 23-H), 2.02 – 1.87 (m, 4 H, 6-H′, 7-H, 21-H), 1.82 (m, 1 H, 6-H), 1.69 (m, 1 H, 11-H), 1.51 (m, 1 H, 12-H‘), 1.44 – 1.39 (m, 18 H, 17-H, 18-H), 1.10 (m, 1 H, 12-H), 0.96 (d, $^3J_{14,11}$ = 6.6 Hz, 3 H, 14-H), 0.87 (t, $^3J_{13,12}$ = 7.4 Hz, 3 H, 13-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.5 (s, C-19), 170.4 (s, C-29), 169.2 (s, C-2), 155.8 (s, C-24), 155.7 (s, C-15), 143.8 (s, C-27‘), 143.6 (s, C-27), 141.3 (s, C-32), 141.3 (s, C-32‘), 127.7 (d, C-30), 127.1 (d, C-29‘), 127.0 (d, C-29), 125.1 (d, C-28‘), 125.0 (d, C-28), 120.0 (d, C-31), 120.0 (d, C-31‘), 81.3 (s, C-16), 79.5 (s, C-1), 72.9 (d, C-4), 66.9 (t, C-25), 57.9 (d, C-5), 56.6 (d, C-10), 53.3 (d, C-20), 47.9 (t, C-8), 47.1 (d, C-26), 38.1 (d, C-11), 37.2 (t, C-3), 32.1 (t, C-21), 29.8 (t, C-22), 28.3 (q, C-17), 27.9 (q, C-18), 26.2 (t, C-6), 24.6 (t, C-7), 23.9 (t, C-12), 15.8 (q, C-14), 15.4 (q, C-23), 11.4 (q, C-13).

Optical rotation: $[\alpha]_D^{20}$= –21.2 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{42}H_{60}N_3O_9S$ $[M+H]^+$:	782.4045	782.4065

Ethyl 2-((*S*)-1-((*S*)-2-acetamido-5-(((benzyloxy)carbonyl)amino)pentanoyl)pyrrolidin-2-yl)-thiazole-4-carboxylate 22

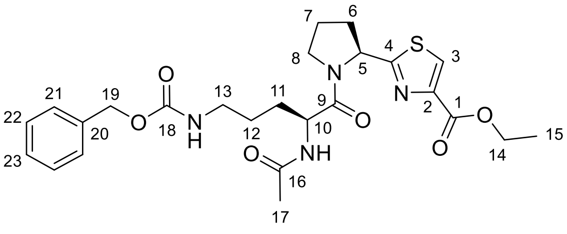
Thiazole **6** (100 mg, 306 µmol) was dissolved in anhydrous CH_2Cl_2 (1.0 mL) and cooled to 0 °C. 4.0 M HCl in 1,4-dioxane (766 µL, 3.06 mmol, 10 eq.) was added, and the resulting solution was stirred for 5 h while slowly reaching room temperature. Another portion of 4.0 M HCl in 1,4-dioxane (153 µL, 613 µmol, 2.0 eq.) was added, and the stirring continued for 1 h. The reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride salt **21** (79.5 mg, 304 µmol, 99%).

A solution of the above-prepared hydrochloride salt **21** and Boc-Orn(Cbz)-OH (112 mg, 304 µmol, 1.0 eq.) in anhydrous CH_2Cl_2 (3.0 mL) was cooled to 0 °C. NMM (100 µL, 913 µmol, 3.0 eq.) and HATU (116 mg, 304 µmol, 1.0 eq.) were added, and the resulting yellow solution was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give the Boc-dipeptide (123 mg, 214 µmol, 70%, unknown purity) as a white foam.

The above-prepared Boc-dipeptide (103 mg, 180 µmol) was dissolved in anhydrous CH_2Cl_2 (1.0 mL) and cooled to 0 °C. 4.0 M HCl in 1,4-dioxane (450 µL, 1.80 mmol, 10 eq.) was added, and the resulting solution was stirred for 5 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride salt.

A solution of the above-prepared hydrochloride salt and triethylamine (53.0 µL, 377 µmol, 2.1 eq.) in anhydrous CH_2Cl_2 (2.0 mL) was cooled to 0 °C. Acetic anhydride (34.0 µL, 359 µmol, 2.0 eq.) was added, and the reaction mixture was stirred for 2 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine before being dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, CH_2Cl_2:MeOH 95:5) to give the acetylated dipeptide **22** (77.0 mg, 149 µmol, 83%) as a white foam.

TLC: R_f (22) = 0.16 (silica, CH_2Cl_2:MeOH 95:5)



22

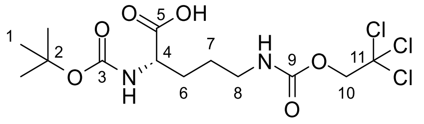
^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 8.26 (s, 1 H, 3-H), 7.72 (m, 1 H, 16-NH), 7.38 – 7.27 (m, 5 H, 21-H, 22-H, 23-H), 6.80 (m, 1 H, 18-NH), 5.34 (m, 1 H, 5-H), 5.03 (m, 2 H, 19-H), 4.57 (m, 1 H, 10-H), 4.31 (q, $^3J_{14,15}$ = 7.0 Hz, 2 H, 14-H), 3.81 (m, 1 H, 8-H), 3.70 (m, 1 H, 8-H'), 3.05 (m, 2 H, 13-H), 2.28 (m, 1 H, 6-H), 2.16 (m, 1 H, 6-H'), 2.00 (m, 2 H, 7-H), 1.85 (s, 3 H, 17-H), 1.72 (m, 1 H, 11-H), 1.61 – 1.46 (m, 3 H, 11-H', 12-H), 1.32 (t, $^3J_{15,14}$ = 7.1 Hz, 3 H, 15-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 173.1 (s, C-4), 170.7 (s, C-9), 168.5 (s, C-16), 160.2 (s, C-1), 155.6 (s, C-18), 136.9 (s, C-2), 127.7 (d, C-22), 127.6 (d, C-23), 127.6 (s, C-20), 127.1 (d, C-21), 127.0 (d, C-3), 64.7 (t, C-19), 60.0 (t, C-14), 57.9 (d, C-5), 49.8 (d, C-10), 46.3 (t, C-8), 39.5 (t, C-13), 30.9 (t, C-6), 28.2 (t, C-11), 25.2 (t, C-12), 23.6 (t, C-7), 21.7 (q, C-17), 13.6 (q, C-15).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-(((2,2,2-trichloroethoxy)carbonyl)amino)pentanoic acid 24

A solution of Troc-Cl (711 µL, 5.17 mmol, 1.2 eq.) in Et_2O (5.0 mL) was added to a solution of K_2CO_3 (1.49 g, 10.8 mmol, 2.5 eq.) and Boc-Orn-OH (1.00 g, 4.31 mmol) in H_2O (20 mL). The reaction mixture was stirred for 16 h at room temperature. The aqueous layer was washed twice with Et_2O (10 mL), and the organic layer was discarded. The aqueous layer was acidified with 1.0 M HCl_{aq} (pH 2) before being extracted thrice with Et_2O (25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, CH_2Cl_2:MeOH 95:5) to give Boc-Orn(Troc)-OH **24** (1.60 g, 3.93 mmol, 91%) as a white foam.

TLC: R_f (24) = 0.31 (silica, CH_2Cl_2:MeOH 95:5)



24

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 7.67 (t, $^3J_{NH,8}$ = 5.6 Hz, 1 H, 9-NH), 6.65 (m, 1 H, 3-NH), 4.77 (m, 2 H, 10-H), 3.78 (m, 1 H, 4-H), 3.00 (m, 2 H, 8-H), 1.66 (m, 1 H, 6-H), 1.55 – 1.40 (m, 3 H, 6-H‘, 7-H), 1.37 (s, 9 H, 1-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 155.3 (s, C-3), 154.4 (s, C-9), 96.4 (s, C-11), 77.8 (s, C-2), 73.3 (t, C-10), 53.9 (d, C-4), 40.4 (t, C-8), 29.0 (t, C-6), 28.3 (q, C-1), 25.9 (t, C-7), C-5 was not observed.

Optical rotation:	$[\alpha]_D^{20}$= +5.5 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{13}H_{22}O_6N_2Cl_3$ $[M+H]^+$:	407.0583	407.0543

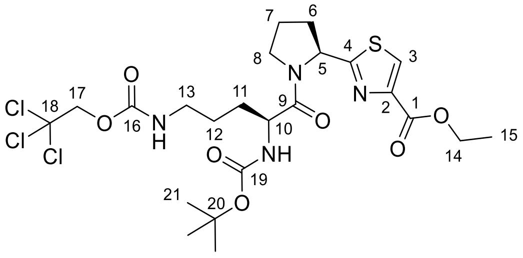
Ethyl 2-((*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-5-(((2,2,2-trichloroethoxy)carbonyl)amino) pentanoyl)pyrrolidin-2-yl)thiazole-4-carboxylate 25

Thiazole **6** (200 mg, 613 µmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and cooled to 0 °C. 4.0 M HCl in 1,4-dioxane (1.53 mL, 6.13 mmol, 10 eq.) was added, and the resulting solution was stirred for 2 h while slowly reaching room temperature. Another portion of 4.0 M HCl in 1,4-dioxane (0.31 mL, 1.23 mmol, 2.0 eq.) was added, and the stirring continued for 1 h. The reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride.

A solution of the above-prepared hydrochloride salt and Boc-Orn(Troc)-OH **24** (275 mg, 674 µmol, 1.1 eq.) in anhydrous CH_2Cl_2 (6.0 mL) was cooled to 0 °C. NMM (216 µL, 1.96 mmol, 3.2 eq.) and HATU (256 mg, 674 µmol, 1.1 eq.) were added, and the resulting yellow solution was stirred for 18 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$

and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give dipeptide **25** (315 mg, 511 µmol, 83%) as a white foam.

TLC: R$_f$ (25) = 0.35 (silica, CH_2Cl_2:MeOH 96:4)



25

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, 3-H), 5.64 (t, $^3J_{NH,13}$ = 5.7 Hz, 1 H, 16-NH), 5.49 (t, $^3J_{5,6}$ = 5.7 Hz, 1 H, 5-H), 5.35 (d, $^3J_{NH,10}$ = 8.6 Hz, 1 H, 19-NH), 4.74 (d, $^2J_{17',17}$ = 12.0 Hz, 1 H, 17'-H), 4.69 (d, $^2J_{17,17'}$ = 12.0 Hz, 1 H, 17-H), 4.55 (dt, $^3J_{10,NH}$ = 8.4 Hz, $^3J_{10,11}$ = 4.1 Hz, 1 H, 10-H), 4.40 (q, $^3J_{14,15}$ = 7.1 Hz, 2 H, 14-H), 3.79 (m, 2 H, 8-H), 3.28 (m, 2 H, 13-H), 2.32 (m, 2 H, 6-H), 2.08 (m, 2 H, 7-H), 1.84 (m, 1 H, 11-H'), 1.73 – 1.60 (m, 3 H, 11-H, 12-H), 1.43 (s, 9 H, 21-H), 1.38 (t, $^3J_{15,14}$ = 7.1 Hz, 3 H, 15-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.9 (s, C-4), 171.5 (s, C-9), 161.4 (s, C-1), 155.6 (s, C-19), 154.9 (s, C-16), 147.0 (s, C-2), 127.4 (d, C-3), 95.9 (s, C-18), 80.0 (s, C-20), 74.5 (t, C-17), 61.6 (t, C-14), 58.9 (d, C-5), 51.6 (d, C-10), 47.4 (t, C-8), 41.1 (t, C-13), 32.3 (t, C-6), 30.3 (t, C-11), 28.5 (q, C-21), 25.2 (t, C-12), 24.7 (t, C-7), 14.5 (q, C-15).

Optical rotation:	$[\alpha]_D^{20}$= –45.8 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{23}H_{34}O_7N_4Cl_3S$ $[M+H]^+$:	615.1208	615.1210

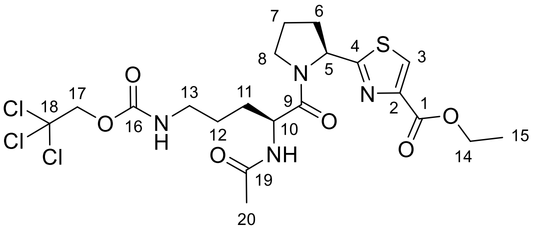
Ethyl 2-((*S*)-1-((*S*)-2-acetamido-5-(((2,2,2-trichloroethoxy)carbonyl)amino)pentanoyl) pyrrolidin-2-yl)thiazole-4-carboxylate 26

Dipeptide **25** (496 mg, 805 µmol) was dissolved in anhydrous CH_2Cl_2 (3.0 mL) and cooled to 0 °C. 4.0 M HCl in 1,4-dioxane (2.01 mL, 8.05 mmol, 10 eq.) was added, and the resulting solution was stirred for 2 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride.

A solution of the above-prepared hydrochloride salt and triethylamine (236 µL, 1.69 mmol, 2.1 eq.) in anhydrous CH_2Cl_2 (7.0 mL) was cooled to 0 °C. Acetic anhydride (152 µL, 1.61 mmol, 2.0 eq.) was added, and the reaction mixture was stirred for 2 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine before being dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical,

H_2O:MeCN 10% to 90% MeCN) to give the acetylated dipeptide **26** (421 mg, 754 µmol, 94%) as a white foam.

TLC: R_f (26) = 0.17 (silica, CH_2Cl_2:MeOH 95:5)



26

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, 3-H), 6.62 (d, $^3J_{NH,10}$ = 8.0 Hz, 1 H, 19-NH), 5.81 (t, $^3J_{NH,13}$ = 6.1 Hz, 1 H, 16-NH), 5.46 (dd, $^3J_{5,6}$ = 7.3 Hz, $^3J_{5,6'}$ = 4.3 Hz, 1 H, 5-H), 4.86 (m, 1 H, 10-H), 4.73 (d, $^2J_{17',17}$ = 12.2 Hz, 1 H, 17-H'), 4.69 (d, $^2J_{17,17'}$ = 12.1 Hz, 1 H, 17-H), 4.39 (q, $^3J_{14,15}$ = 7.1 Hz, 2 H, 14-H), 3.81 (m, 2 H, 8-H), 3.26 (m, 2 H, 13-H), 2.31 (m, 2 H, 6-H), 2.09 (m, 2 H, 7-H), 1.96 (s, 3 H, 20-H), 1.86 (m, 1 H, 11-H'), 1.75 – 1.55 (m, 3 H, 11-H, 12-H), 1.37 (t, $^3J_{15,14}$ = 7.1 Hz, 3 H, 15-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.5 (s, C-4), 171.1 (s, C-9), 169.9 (s, C-19), 161.2 (s, C-1), 154.8 (s, C-16), 146.8 (s, C-2), 127.2 (d, C-3), 95.7 (s, C-18), 74.3 (t, C-17), 61.5 (t, C-14), 58.8 (d, C-5), 50.3 (d, C-10), 47.4 (t, C-8), 40.9 (t, C-13), 32.3 (t, C-6), 29.7 (t, C-11), 25.0 (t, C-12), 24.5 (t, C-7), 23.1 (q, C-20), 14.3 (q, C-15).

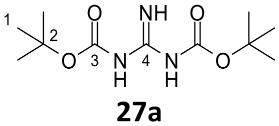
Optical rotation: $[\alpha]_D^{20}$ = –63.6 (c = 0.5, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{20}H_{28}O_6N_4Cl_3S$ [M+H]$^+$:	557.0795	557.0802

***N*-,*N*'-Bis(*tert*-butoxycarbonyl)-guanidine[134] 27a**

According to Goodman *et al.*[134], guanidine hydrochloride (1.00 g, 10.5 mmol) and sodium hydroxide (1.68 g, 41.9 mmol, 4.0 eq.) were dissolved in 1,4-dioxane/water (30 mL, 2:1). The resulting mixture was cooled to 0 °C before Boc-anhydride (5.35 mL, 23.0 mmol, 2.2 eq.) was added in one portion. The reaction mixture was stirred for 18 h while slowly reaching room temperature. After removing the 1,4-dioxane in vacuo, the suspension is diluted with water (20 mL) and extracted with EtOAc. The combined organic extracts were washed with 10 wt% citric acid$_{aq}$ and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, CH_2Cl_2:MeOH 97:3) to give bis-Boc-guanidine **27a** (1.72 g, 6.63 mmol, 63%) as a white solid.

TLC: R_f (27a) = 0.25 (silica, CH_2Cl_2:MeOH 97:3)



27a

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.39 (s, 1 H, 4-NH), 8.48 (s, 2 H, 3-NH), 1.41 (s, 18 H, 1-H).

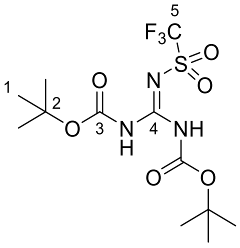
^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 158.5 (s, C-3), 158.2 (s, C-4), 79.6 (s, C-2), 27.8 (q, C-1).

Melting point: 116 – 118 °C (lit: 144 °C)[134]

N-,*N*'-Bis(*tert*-butoxycarbonyl)-*N*''-trifluoromethanesulfonyl-guanidine[134] 27b

According to Goodman *et al.*[134]*,* bis-Boc-guanidine **27a** (1.00 g, 3.86 mmol) and triethylamine (591 µL, 4.24 mmol, 1.1 eq.) were dissolved in anhydrous CH_2Cl_2 (20 mL). Triflic anhydride (717 µL, 4.24 mmol, 1.1 eq.) was added dropwise to the reaction mixture at –78 °C. The resulting solution was stirred for 5 h while slowly reaching room temperature. After dilution with CH_2Cl_2, the mixture was washed with 2.0 M sodium bisulfate solution, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (silica, CH_2Cl_2:MeOH 99:1) to give di-Boc-guanidyl triflate **27b** (1.20 g, 3.07 mmol, 80%) as a light-yellow solid.

TLC: R$_f$ (27b) = 0.48 (silica, CH_2Cl_2:MeOH 98:2)



27b

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.10 (s, 2 H, 3-NH), 1.54 (s, 18 H, 1-H).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 151.4 (s, C-3), 119.2 (q, $^1J_{C5,F}$ = 320.2 Hz), 86.0 (s, C-2), 27.8 (q, C-1), C-5 was not observed.

HRMS (CI):	calculated	found
$C_{12}H_{21}F_3N_3O_6S$ [M+H]$^+$:	392.1098	392.1090

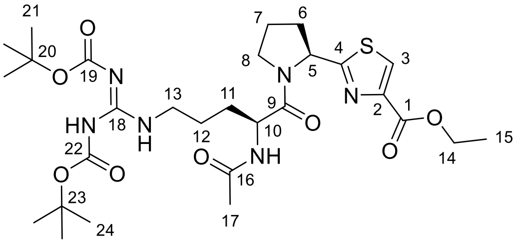
Melting point: 110 – 113 °C (lit: 115 °C)[134]

Ethyl 2-((*S*)-1-(*N*^{2}-acetyl-*N*$^\omega$,*N*$^{\omega'}$-bis(*tert*-butoxycarbonyl)-L-arginyl)pyrrolidin-2-yl)thiazole-4-carboxylate 28

Acetylated dipeptide **26** (51 mg, 91.0 µmol) was dissolved in anhydrous THF (1.0 mL). After the addition of AcOH (10.5 µL, 183 µmol, 2.0 eq.) and zinc dust (120 mg, 1.83 mmol, 20 eq.), the reaction was initiated by the addition of 1,2-dibromoethane and TMS-Cl (2 µL each) and stirred at room temperature for 90 min. Sat. $NaHCO_3$ solution was added, and the mixture was extracted with $CHCl_3$/^{i}PrOH (3:1). After concentration in vacuo, the residue was dissolved in $CHCl_3$ and dried over $MgSO_4$. Concentration in vacuo led to the crude amine.

The above-prepared crude amine and triethylamine (14.0 µL, 101 µmol, 1.1 eq.) were dissolved in anhydrous CH_2Cl_2 (1.0 mL). Di-Boc-guanidyl triflate **27b** (39.4 mg, 101 µmol, 1.1 eq.) was added, and the reaction mixture was stirred for 16 h at room temperature. After dilution with EtOAc, the mixture was washed with sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give dipeptide **28** (35.0 mg, 56.0 µmol, 61%) as a white foam.

TLC: R_f (28) = 0.44 (silica, CH_2Cl_2:MeOH 95:5)



28

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 11.49 (s, 1 H, 22-NH), 8.34 (t, $^{3}J_{NH,13}$ = 5.5 Hz, 1 H, 13-NH), 8.06 (s, 1 H, 3-H), 6.60 (d, $^{3}J_{NH,10}$ = 8.0 Hz, 1 H, 19-NH), 5.52 (dd, $^{3}J_{5,6}$ = 8.1 Hz, $^{3}J_{5,6'}$ = 2.8 Hz, 1 H, 5-H), 4.85 (ddd, $^{3}J_{10,NH}$ = 7.6 Hz, $^{3}J_{10,11}$ = 7.4 Hz, $^{3}J_{10,11'}$ = 4.6 Hz, 1 H, 10-H), 4.40 (q, $^{3}J_{14,15}$ = 7.1 Hz, 2 H, 14-H), 3.79 (m, 2 H, 8-H), 3.49 (m, 1 H, 13-H'), 3.41 (m, 1 H, 13-H), 2.40 (m, 1 H, 6-H'), 2.29 (dddd, $^{2}J_{6,6'}$ = 12.9 Hz, $^{3}J_{6,7}$ = 12.9 Hz, $^{3}J_{6,7'}$ = 8.1 Hz, $^{3}J_{6,5}$ = 8.1 Hz, 1 H, 6-H), 2.08 (m, 2 H, 7-H), 2.00 (s, 3 H, 17-H), 1.88 (m, 1 H, 11-H'), 1.76 – 1.56 (m, 3 H, 11-H, 12-H), 1.49 (s, 9 H, 21-H), 1.47 (s, 9 H, 24-H), 1.38 (t, $^{3}J_{15,14}$ = 7.2 Hz, 3 H, 15-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.2 (s, C-4), 171.4 (s, C-9), 169.9 (s, C-16), 163.5 (s, C-19), 161.2 (s, C-1), 156.2 (s, C-18), 153.2 (s, C-22), 147.1 (s, C-2), 127.1 (d, C-3), 83.1 (s, C-20), 79.3 (s, C-23), 61.4 (t, C-14), 59.0 (d, C-5), 50.2 (d, C-10), 47.3 (t, C-8), 40.1 (t, C-13), 31.9 (t, C-6), 29.4 (t, C-11), 28.2 (q, C-21), 28.0 (q, C-24), 25.1 (t, C-12), 24.4 (t, C-7), 23.1 (q, C-17), 14.3 (q, C-15).

Optical rotation: $[\alpha]_D^{20}$ = –43.8 (c = 0.5, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{28}H_{45}N_6O_8S$ $[M+H]^+$:	625.3014	625.3022

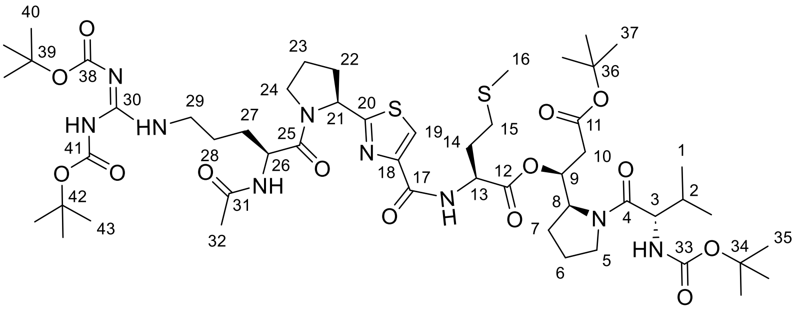
(*S*)-3-(*tert*-Butoxy)-1-((*S*)-1-((*tert*-butoxycarbonyl)-L-valyl)pyrrolidin-2-yl)-3-oxopropyl (2-((*S*)-1-(N^{2}-acetyl-N$^{\omega}$,N$^{\omega'}$-bis(*tert*-butoxycarbonyl)-L-arginyl)pyrrolidin-2-yl)thiazole-4-carbonyl)-L-methioninate 30

Dipeptide **28** (50.0 mg, 80.1 µmol) was dissolved in 420 µL THF and cooled to 0 °C. After the dropwise addition of 0.20 M $LiOH_{aq.}$ (420 µL, 84.2 µmol, 1.05 eq.) the resulting solution was stirred for 4 h while slowly reaching room temperature. The solution was neutralized by the addition of 1.0 M HCl_{aq} (84.2 µL, 84.2 µmol, 1.05 eq.) and concentrated in vacuo to give the crude carboxylic acid **29**.

Depsipeptide **15** (67.0 mg, 87.3 µmol, 1.09 eq.) was dissolved in CH_2Cl_2 (0.8 mL) and cooled to 0 °C. Diethyl amine (182 µL, 1.75 mmol, 20 eq.) was added, and the mixture was stirred for 3 h while slowly reaching room temperature. The solution was concentrated in vacuo to give the crude amine **16**.

The crude amine **16** and the crude carboxylic acid **29** were dissolved in anhydrous DMF (0.8 mL) before being cooled to 0 °C. NMM (9.69 µL, 88.0 µmol, 1.1 eq.) and HATU (30.4 mg, 80.0 µmol, 1.0 eq.) were added subsequently. The resulting solution was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5 wt% $LiCl_{aq}$, sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give protected pseudotetraivprolid D **30** (31.4 mg, 28.0 µmol, 35%) as a white foam.

LC-MS: t_R (30) = 1.59 min (short method)



30

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 11.50 (s, 1 H, 41-NH), 8.35 (t, $^3J_{NH,29}$ = 5.5 Hz, 1 H, 29-NH), 7.98 (s, 1 H, 19-H), 7.80 (d, $^3J_{NH,13}$ = 8.4 Hz, 1 H, 17-NH), 6.54 (d, $^3J_{NH,26}$ = 8.3 Hz, 1 H, 31-NH), 5.65 (ddd, $^3J_{9,10}$ = 8.5 Hz, $^3J_{9,10'}$ = 4.1 Hz, $^3J_{9,8}$ = 4.1 Hz, 1 H, 9-H), 5.46 (dd, $^3J_{21,22}$ = 7.9 Hz, $^3J_{21,22'}$ = 2.8 Hz, 1 H, 21-H), 5.29 (d, $^3J_{NH,3}$ = 9.2 Hz, 1 H, 33-NH), 4.90 – 4.81 (m, 2 H, 13-H, 26-H), 4.56 (ddd, $^3J_{8,7'}$ = 8.4 Hz, $^3J_{8,7}$ = 3.9 Hz, $^3J_{8,9}$ = 3.9 Hz, 1 H, 8-H), 4.31 (dd, $^3J_{3,NH}$ = 9.2 Hz, $^3J_{3,2}$ = 5.3 Hz, 1 H, 3-H), 3.83 (m, 1 H, 24-H'), 3.79 – 3.72 (m, 2 H, 5-H', 24-H), 3.50 (m, 1 H, 29-H), 3.47 – 3.40 (m, 2 H, 5-H, 29-H), 2.58 (m, 2 H, 15-H), 2.50 (dd, $^3J_{10',10}$ = 16.1 Hz, $^3J_{10',9}$ = 4.7 Hz, 1 H, 10-H'), 2.44 (dd, $^2J_{10,10'}$ = 16.1 Hz, $^3J_{10,9}$ = 8.7 Hz, 1 H, 10-H), 2.35 (m, 1 H, 22-H'), 2.31 – 2.24 (m, 2 H, 14-H, 22-H), 2.13 – 1.79 (m, 9 H, 2-H, 6-H, 7-H, 14-H, 23-H, 27-H'), 2.11 (s, 3 H, 16-H), 2.03 (s, 3 H, 32-H), 1.72 – 1.65 (m, 3 H, 27-H, 28-H), 1.49 (s, 9 H, 40-H), 1.48 (s, 9 H, 43-H), 1.41 (s, 9 H, 37-H), 1.40 (s, 9 H, 35-H), 0.97 (d, $^3J_{1',2}$ = 6.8 Hz, 3 H, 1'-H), 0.86 (d, $^3J_{1,2}$ = 6.8 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.9 (s, C-20), 172.4 (s, C-4), 171.7 (s, C-25), 170.7 (s, C-12), 170.1 (s, C-31), 169.3 (s, C-11), 163.6 (s, C-38), 160.7 (s, C-17), 156.4 (s, C-30), 156.0 (s, C-33), 153.4 (s, C-41), 149.3 (s, C-18), 123.6 (d, C-19), 83.4 (s, C-39), 81.3 (s, C-42), 79.6 (s, C-36), 79.4 (s, C-34), 73.5 (d, C-9), 59.0 (d, C-21), 57.9 (d, C-8), 57.0 (d, C-3), 51.6 (d, C-13), 50.5 (d, C-26), 48.0 (t, C-5), 47.5 (t, C-24), 40.3 (t, C-29), 37.3 (t, C-10), 32.2 (t, C-14), 31.8 (t, C-22), 31.6 (d, C-2), 30.1 (t, C-15), 29.5 (t, C-27), 28.4 (q, C-43), 28.4 (q, C-40), 28.2 (q, C-37), 28.1 (q, C-35), 26.4 (t, C-7), 25.5 (t, C-28), 24.8 (t, C-6), 24.6 (t, C-23), 23.4 (q, C-32), 19.8 (q, C-1), 17.1 (q, C-1'), 15.6 (q, C-16).

Optical rotation: $[\alpha]_D^{20}$ = –80.9 (c = 1.0, MeOH)

HRMS (ESI):	calculated	found
$C_{52}H_{86}N_9O_{14}S_2$ $[M+H]^+$:	1124.5730	1124.5742

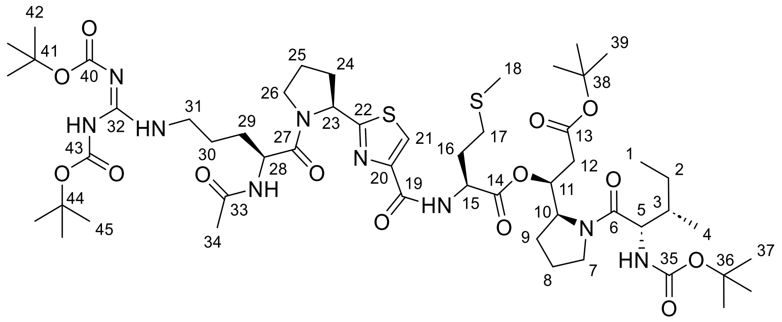
(*S*)-3-(*tert*-Butoxy)-1-((*S*)-1-((*tert*-butoxycarbonyl)-L-isoleucyl)pyrrolidin-2-yl)-3-oxopropyl (2-((*S*)-1-(N^2-acetyl-N^{ω},$N^{\omega'}$-bis(*tert*-butoxycarbonyl)-L-arginyl)pyrrolidin-2-yl)thiazole-4-carbonyl)-L-methioninate 31

Dipeptide **28** (24.0 mg, 38.4 µmol) was dissolved in THF (250 µL) and cooled to 0 °C. After the dropwise addition of 0.20 M $LiOH_{aq}$ (202 µL, 40.4 µmol, 1.05 eq.), the resulting solution was stirred for 4 h while slowly reaching room temperature. The solution was neutralized by the addition of 1.0 M HCl_{aq} (40.4 µL, 40.4 µmol, 1.05 eq.) and concentrated in vacuo to give the crude carboxylic acid **29**.

Fmoc amine **19** (30.0 mg, 38.4 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (500 µL) and cooled to 0 °C. Diethyl amine (80.0 µL, 767 µmol, 20 eq.) was added, and the mixture was stirred for 4 h while slowly reaching room temperature. Another portion of diethyl amine (80.0 µL, 767µmol, 20 eq.) was added, and stirring continued for another hour. The reaction mixture was concentrated in vacuo to give the crude amine **20**.

The above-prepared crude amine **20** and carboxylic acid **29** were dissolved in anhydrous CH_2Cl_2 (400 µL) before being cooled to 0 °C. NMM (4.54 µL, 41.0 µmol, 1.05 eq.) and HBTU (14.5 mg, 38.4 µmol) were added subsequently. The resulting solution was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with sat. NH_4Cl solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, CH_2Cl_2:MeOH 97:3) followed by preparative HPLC (H_2O:MeCN 10 % to 100% MeCN) to give protected pseudotetraivprolid B **31** (20.4 mg, 17.9 µmol, 47%) as a white foam.

TLC: R_f (31) = 0.78 (silica, CH_2Cl_2:MeOH 95:5)



31

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 11.50 (s, 1 H, 43-NH), 8.36 (t, $^3J_{NH,31}$ = 5.5 Hz, 1 H, 31-NH), 7.99 (s, 1 H, 21-H), 7.81 (d, $^3J_{NH,15}$ = 8.3 Hz, 1 H, 19-NH), 6.53 (d, $^3J_{NH,28}$ = 8.2 Hz, 1 H, 33-NH), 5.69 (ddd, $^3J_{11,12}$ = 8.7 Hz, $^3J_{11,12'}$ = 4.3 Hz, $^3J_{11,10}$ = 4.3 Hz, 1 H, 11-H), 5.47 (dd, $^3J_{23,24}$ = 7.9 Hz, $^3J_{23,24'}$ = 2.8 Hz, 1 H, 23-H), 5.24 (d, $^3J_{NH,5}$ = 9.3 Hz, 1 H, 35-NH), 4.90 – 4.82 (m, 2 H, 15-H, 28-H), 4.56 (ddd, $^3J_{10,9'}$ = 8.4 Hz, $^3J_{10,11}$ = 4.0 Hz, $^3J_{10,9}$ = 4.0 Hz, 1 H, 10-H), 4.33 (dd, $^3J_{5,NH}$ = 9.3 Hz, $^3J_{5,3}$ = 6.0 Hz, 1 H, 5-H), 3.88 – 3.72 (m, 3 H, 7-H‘, 26-H), 3.55 – 3.40 (m, 3 H, 7-H, 31-H), 2.58 (m, 2 H, 17-H), 2.47 (m, 2 H, 12-H), 2.31 (m, 2 H, 24-H), 2.15 – 1.82 (m, 9 H, 8-H, 9-H, 16-H, 25-H, 29-H'), 2.11 (s, 3 H, 18-H), 2.03 (s, 3 H, 34-H), 1.74 – 1.63 (m, 4 H, 3-H, 29-H, 30-H), 1.52 (m, 1 H, 2-H‘), 1.49 (s, 9 H, 42-H), 1.47 (s, 9 H, 45-H), 1.41 (s, 9 H, 39-H), 1.40 (s, 9 H, 37-H), 1.09 (m, 1 H, 2-H), 0.95 (d, $^3J_{4,3}$ = 6.7 Hz, 3 H, 4-H), 0.87 (t, $^3J_{1,2}$ = 7.3 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.7 (s, C-22), 172.4 (s, C-6), 171.5 (s, C-27), 170.5 (s, C-14), 170.0 (s, C-33), 169.1 (s, C-13), 163.5 (s, C-40), 160.5 (s, C-19), 156.3 (s, C-32), 155.8 (s, C-35), 153.3 (s, C-43), 149.1 (s, C-20), 123.5 (d, C-21), 83.2 (s, C-41), 81.1 (s, C-44), 79.5 (s, C-38), 79.4 (s, C-36), 73.1 (d, C-11), 58.8 (d, C-23), 57.7 (d, C-10), 56.5 (d, C-5), 51.4 (d, C-15), 50.3 (d, C-28), 47.9 (t, C-7), 47.3 (t, C-26), 40.1 (t, C-31), 38.2 (d, C-3), 36.9 (t, C-12), 32.1 (t, C-24), 31.6 (t, C-16), 30.0 (t, C-17), 29.4 (t, C-29), 28.30 (q, C-45), 28.26 (q, C-42), 28.0 (q, C-39), 27.9 (q, C-37), 26.2 (t, C-9), 25.3 (t, C-30), 24.7 (t, C-8), 24.4 (t, C-25), 23.9 (t, C-2), 23.2 (q, C-34), 15.9 (q, C-4), 15.5 (q, C-18), 11.5 (q, C-1).

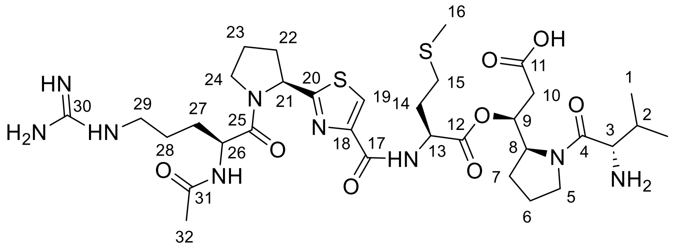
Optical rotation: $[\alpha]_D^{20} = -62.9$ (c = 1.0, MeOH)

HRMS (ESI):	calculated	found
$C_{53}H_{88}N_9O_{14}S_2$ $[M+H]^+$:	1138.5887	1138.5901

Pseudotetraivprolid D

Protected pseudotetraivprolid D **30** (31.4 mg, 28.0 µmol) was dissolved in anhydrous CH_2Cl_2 (150 µL). The deprotection mixture TFA:H_2O:TIPS (150 µL) in a ratio of 185:5:10 was added, and the solution was stirred for 160 min. The reaction was dried in high vacuum, and the residue was purified by automated reversed phase column chromatography (C18, 0.1% $HCOOH_{aq}$:MeCN 10% to 90% MeCN) followed by preparative HPLC (0.1% $HCOOH_{aq}$:MeCN 0% to 50% MeCN) to give **pseudeotetraivprolid D** (19.0 mg, 23.4 µmol, 85%) as an amorphous solid.

LC-MS: t_R (pseudotetraivprolid D) = 0.58 min (short method)



pseudotetraivprolid D

^{1}H-NMR (500 MHz, D_2O): δ = 8.16 (s, 1 H, 19-H), 5.58 (ddd, $^3J_{9,10}$ = 7.0 Hz, $^3J_{9,10'}$ = 6.7 Hz, $^3J_{9,8}$ = 3.7 Hz, 1 H, 9-H), 5.41 (dd, $^3J_{21,22}$ = 8.2 Hz, $^3J_{21,22'}$ = 3.0 Hz, 1 H, 21-H), 4.80 (m, 1 H, 13-H), 4.64 (dd, $^3J_{26,27}$ = 8.3 Hz, $^3J_{26,27'}$ = 5.1 Hz, 1 H, 26-H), 4.51 (ddd, $^3J_{8,7}$ = 8.2 Hz, $^3J_{8,9}$ = 3.8 Hz, $^3J_{8,7'}$ = 3.8 Hz, 1 H, 8-H), 4.16 (d, $^3J_{3,2}$ = 5.1 Hz, 1 H, 3-H), 3.88 (m, 2 H, 24-H), 3.68 (dt, $^2J_{5,5'}$ = 10.3 Hz, $^3J_{5,6}$ = 7.2 Hz, 1 H, 5-H), 3.43 (dt, $^2J_{5',5}$ = 10.2 Hz, $^3J_{5',6}$ = 7.0 Hz, 1 H, 5-H‘), 3.21 (m, 2 H, 29-H), 2.73 – 2.55 (m, 4 H, 10-H, 15-H), 2.41 (m, 1 H, 22-H), 2.26 (m, 1 H, 14-H), 2.21 – 2.11 (m, 5 H, 2-H, 14-H‘, 22-H‘, 23-H), 2.09 (s, 3 H, 16-H), 2.01 (s, 3 H, 32-H), 2.01 – 1.80 (m, 5 H, 6-H, 7-H, 27-H), 1.76 – 1.60 (m, 3 H, 27-H‘, 28-H), 0.99 (d, $^3J_{1',2}$ = 7.0 Hz, 3 H, 1‘-H), 0.90 (d, $^3J_{1,2}$ = 6.9 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, D_2O): δ = 175.0 (s, C-11), 174.71 (s, C-20), 174.68 (s, C-31), 173.3 (s, C-25), 172.6 (s, C-12), 169.8 (s, C-4), 163.5 (s, C-17), 157.3 (s, C-30), 148.1 (s, C-18), 125.7 (d, C-19), 74.0 (d, C-9), 59.9 (d, C-21), 59.1 (d, C-8), 57.6 (d, C-3), 52.5 (d, C-13), 51.9 (d, C-26), 49.0 (t, C-5), 48.3 (t, C-24), 41.0 (t, C-29), 36.8 (t, C-10), 32.5 (t, C-22), 30.0 (t, C-15), 29.81 (t, C-14), 29.78 (d, C-2), 28.0 (t, C-27), 26.5 (t, C-7), 24.9 (t, C-28), 24.53 (t, C-23), 24.50 (t, C-6), 22.0 (q, C-32), 18.7 (q, C-1), 16.6 (q, C-1'), 14.6 (q, C-16).

Selected rotamer signals:

^{1}H-NMR (500 MHz, D_2O): δ = 8.23 (s, 1 H, 19-H), 5.50 (m, 1 H, 21-H), 5.28 (m, 1 H, 9-H), 4.57 (dd, $^3J_{26,27}$ = 9.0 Hz, $^3J_{26,27'}$ = 4.7 Hz, 1 H, 26-H), 4.28 (d, $^3J_{3,2}$ = 5.1 Hz, 1 H, 3-H), 3.78 (m, 2 H, 24-H), 3.58 (m, 2 H, 5-H), 3.17 (m, 2 H, 29-H), 2.50 (m, 1 H, 22-H), 1.75 (s, 1 H, 32-H).

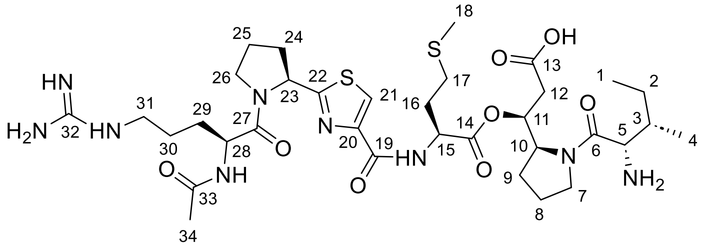
Optical rotation: $[\alpha]_D^{20} = -63.4$ (c = 0.5, DMSO)

HRMS (ESI):	calculated	found
$C_{33}H_{54}N_9O_8S_2$ $[M+H]^+$:	768.3531	768.3533

Pseudotetraivprolid B

Protected pseudotetraivprolid B **31** (17.1 mg, 15.0 µmol) was dissolved in anhydrous CH_2Cl_2 (80 µL). The deprotection mixture TFA:H_2O:TIPS (80 µL) in a ratio of 185:5:10 was added, and the solution was stirred for 160 min. The reaction was dried in high vacuum, and the residue was purified by automated reversed phase column chromatography (C18, 0.1% $HCOOH_{aq}$: MeCN 10% to 90% MeCN) followed by preparative HPLC (0.1% $HCOOH_{aq}$:MeCN 0% to 50% MeCN) to give **pseudeotetraivprolid B** (4.3 mg, 5.5 µmol, 37%) as an amorphous solid well as the corresponding *tert*-butyl ester (4.0 mg, 4.8 µmol, 32%) as an amorphous solid, due to incomplete cleavage.

LC-MS: t_R (**pseudotetraivprolid B**) = 0.58 min (short method)



pseudotetraivprolid B

^{1}H-NMR (500 MHz, D_2O): δ = 8.17 (s, 1 H, 21-H), 5.60 (m, 1 H, 11-H), 5.42 (dd, $^3J_{23,24}$ = 8.3 Hz, $^3J_{23,24'}$ = 3.0 Hz, 1 H, 23-H), 4.81 (m, 1 H, 15-H), 4.65 (dd, $^3J_{28,29}$ = 8.3 Hz, $^3J_{28,29'}$ = 5.1 Hz, 1 H, 28-H), 4.52 (ddd, $^3J_{10,9}$ = 8.3 Hz, $^3J_{10,11}$ = 4.0 Hz, $^3J_{10,9'}$ = 4.0 Hz, 1 H, 10-H), 4.20 (d, $^3J_{5,3}$ = 4.7 Hz, 1 H, 5-H), 3.89 (m, 2 H, 26-H), 3.69 (dt, $^2J_{7,7'}$ = 10.7 Hz, $^3J_{7,8}$ = 6.8 Hz, 1 H, 7-H), 3.46 (dt, $^2J_{7',7}$ = 10.6 Hz, $^3J_{7',8}$ = 7.3 Hz, 1 H, 7-H'), 3.22 (m, 2 H, 31-H), 2.70 – 2.56 (m, 4 H, 12-H, 17-H), 2.42 (m, 1 H, 24-H), 2.27 (m, 1 H, 16-H), 2.21 – 2.11 (m, 4 H, 16-H', 24-H', 25-H), 2.10 (s, 3 H, 18-H), 2.02 (s, 3 H, 34-H), 2.02 – 1.81 (m, 6 H, 3-H, 8-H, 9-H, 29-H), 1.76 – 1.60 (m, 3 H, 29-H', 30-H), 1.43 (m, 1 H, 2-H), 1.14 (m, 1 H, 2-H'), 1.00 (d, $^3J_{4,3}$ = 7.0 Hz, 3 H, 4-H), 0.85 (t, $^3J_{1,2}$ = 7.3 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, D_2O): δ = 175.0 (s, C-13), 174.84 (s, C-22), 174.81 (s, C-33), 173.4 (s, C-27), 172.7 (s, C-14), 170.0 (s, C-6), 163.6 (s, C-19), 157.4 (s, C-32), 148.2 (s, C-20), 125.8 (d, C-21), 74.0 (d, C-11), 60.1 (d, C-23), 59.2 (d, C-10), 57.4 (d, C-5), 52.6 (d, C-15), 52.0 (d, C-28), 49.1 (t, C-7), 48.4 (t, C-26), 41.2 (t, C-31), 36.7 (t, C-12), 36.5 (d, C-3), 32.6 (t, C-24), 30.1 (t, C-17), 30.0 (t, C-16), 28.2 (t, C-29), 26.5 (t, C-9), 25.0 (t, C-30), 24.7 (t, C-25), 24.6 (t, C-8), 23.9 (t, C-2), 22.1 (q, C-34), 15.4 (q, C-4), 14.8 (q, C-18), 11.4 (q, C-1).

Selected rotamer signals:

^{1}H-NMR (500 MHz, D_2O): δ = 8.24 (s, 1 H, 21-H), 5.50 (m, 1 H, 23-H), 4.57 (dd, $^3J_{28,29}$ = 8.9 Hz, $^3J_{28,29'}$ = 4.7 Hz, 1 H, 28-H), 4.31 (d, $^3J_{5,4}$ = 6.1 Hz, 1 H, 5-H), 3.79 (m, 1 H, 26-H), 3.59 (m, 2 H, 7-H), 3.18 (m, 2 H, 31-H), 1.76 (s, 3 H, 34-H), 0.91 (m, 3 H, 1-H).

Optical rotation: $[\alpha]_D^{20} = -68.5$ (c = 0.2, DMSO)

HRMS (ESI):	calculated	found
$C_{34}H_{56}N_9O_8S_2$ $[M+H]^+$:	782.3688	782.3678

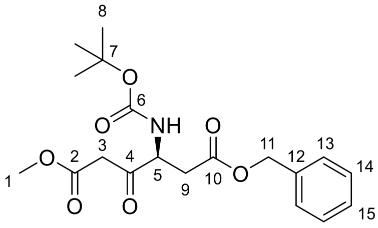
6.2.2 Socein-Derivatives

1-Benzyl 6-methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-4-oxohexanedioate[30] 32

Preparation according to Shioiri *et al.*[30]

The (*R*)-enantiomer was prepared analogously.

TLC: R$_f$ (32) = 0.62 (silica, PE:EtOAc 1:1)



32

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.32-7.41 (m, 5 H, 13-H, 14-H, 15-H), 5.64 (d, $^3J_{NH,5}$ = 8.8 Hz, 1 H, 6-NH), 5.13 (s, 2 H, 11-H), 4.60 (m, 1 H, 5-H), 3.74 (s, 3 H, 1-H), 3.66 (s, 1 H, 3-H‘), 3.65 (s, 1 H, 3-H), 3.07 (dd, $^2J_{9',9}$ = 17.3 Hz, $^3J_{9',5}$ = 4.7 Hz, 1 H, 9-H‘), 2.83 (dd, $^2J_{9,9'}$ = 17.2 Hz, $^3J_{9,5}$ = 4.4 Hz, 1 H, 9-H), 1.46 (s, 9 H, 8-H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ = 201.4 (s, C-4), 171.4 (s, C-10), 167.3 (s, C-2), 135.3 (s, C-12), 128.6 (d, C-14), 128.5 (d, C-15), 128.3 (d, C-13), 80.7 (s, C-7), 67.0 (t, C-11), 56.0 (d, C-5), 52.4 (q, C-1), 45.7 (t, C-3), 35.4 (t, C-9), 18.3 (q, C-8), C-6 was not observed.

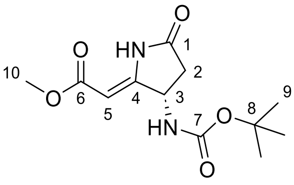
Methyl (*S,Z*)-2-(3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetate[30] 33

Preparation according to Shioiri *et al.*[30]

The (*R*)-enantiomer was prepared analogously.

Both enantiomers were isolated as racemate see GC-FID and optical rotation.

TLC: R$_f$ (33) = 0.25 (silica, PE:EtOAc 2:8)



(*S*)-33

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 9.72 (s, 1 H, 1-NH), 5.21 (m, 1 H, 5-H), 5.01 – 4.88 (m, 2 H, 3-H, 7-NH), 3.73 (s, 3 H, 10-H), 2.94 (dd, $^2J_{2',2}$ = 17.6 Hz, $^3J_{2',3}$ = 8.6 Hz, 1 H, 2-H‘), 2.43 (m, 1 H, 2-H), 1.47 (s, 9 H, 9-H).

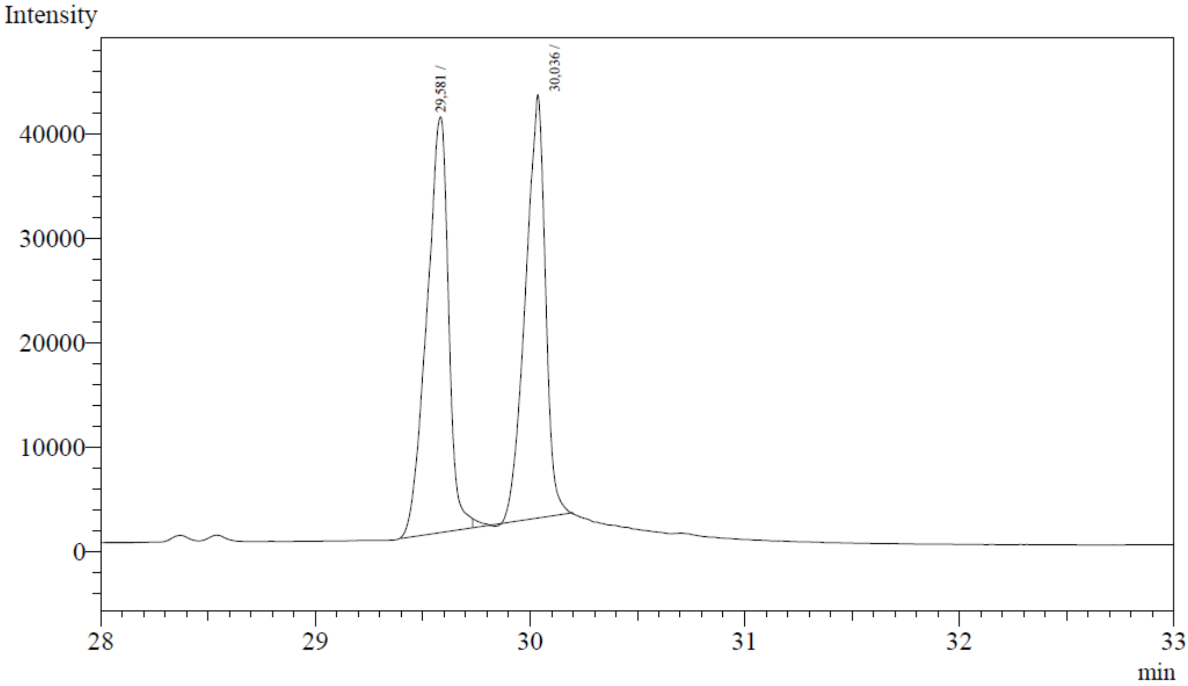
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 174.1 (s, C-1), 168.4 (s, C-6), 158.0 (s, C-4), 155.1 (s, C-7), 90.5 (d, C-5), 81.0 (s, C-8), 51.6 (q, C-10), 48.9 (d, C-3), 36.4 (t, C-2), 28.4 (q, C-9).

Optical rotation: **(*S*)-33:** $[\alpha]_D^{20}$= –0.2 (c = 2.0, CHCl$_3$)

(*R*)-33: $[\alpha]_D^{20}$= +0.1 (c = 2.0, CHCl$_3$)

HRMS (CI):	calculated	found
$C_8H_{10}O_5N_2$ [M+H-^{t}Bu]$^+$:	214.0584	214.0586

Chiral GC-FID of (*S*)-33:

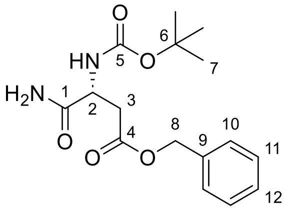


Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	29.581	280962	39188	0.000				
2	30.036	264028	39192	0.000		V		
Total		544990	78380					

Benzyl (*R*)-4-amino-3-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate[15] 34

According to Donohoe *et al.*[15], in a 250 mL Schlenk flask under an atmosphere of nitrogen, a solution of Boc-D-Asp(OBn)-OH (4.50 g, 13.9 mmol) and Triethylamine (2.33 mL, 16.7 mmol, 1.2 eq.) in anhydrous THF (90 mL) was cooled to 0 °C. Ethyl chloroformate (1.60 mL, 16.7 mmol, 1.2 eq.) was added dropwise, and the resulting suspension was stirred for 2 h at 0 °C. After the addition of aqueous ammonia solution (11.0 mL, 167 mmol, 35 wt%, 12 eq.), the reaction mixture was stirred for 30 min at 0 °C. The resulting solution was diluted with EtOAc and water. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with 0.5 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. Drying over MgSO$_4$ and concentration in vacuo gave the primary amide **34** (4.05 g, 12.6 mmol, 90%) as a white solid. The (*S*)-enantiomer was prepared via the same procedure in 76% yield.

TLC: R$_f$ (34) = 0.11 (silica, PE:EtOAc 1:1)



34

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.42 (m, 5 H, 10-H, 11-H, 12-H), 6.46 (s, 1 H, 1-NH_2), 5.71 (d, $^3J_{NH,2}$ = 12.4 Hz, 1 H, 5-NH), 5.55 (s, 1 H, 1-NH_2), 5.17 (d, $^2J_{8',8}$ = 12.4 Hz, 1 H, 8-H'), 5.14 (d, $^2J_{8,8'}$ = 12.4 Hz, 1 H, 8-H), 4.56 (m, 1 H, 2-H), 3.07 (d, $^2J_{3',3}$ = 17.2 Hz, $^3J_{3',2}$ = 4.5 Hz, 1 H, 3-H'), 2.73 (d, $^2J_{3,3'}$ = 17.2 Hz, $^3J_{3,2}$ = 6.2 Hz, 1 H, 3-H), 1.46 (s, 9 H, 7-H).

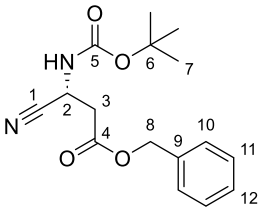
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.9 (s, C-4), 173.1 (s, C-1), 155.5 (s, C-5), 135.3 (s, C-9), 128.6 (d, C-10), 128.5 (d, C-12), 128.3 (d, C-11), 80.6 (s, C-6), 66.9 (t, C-8), 50.3 (d, C-2), 36.0 (t, C-3), 28.3 (q, C-7).

Optical rotation:	**(*R*)-34:** $[\alpha]_D^{20}$= −12.5 (c = 1.0, $CHCl_3$)	
	(*S*)-34: $[\alpha]_D^{20}$= +10.2 (c = 0.5, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{16}H_{22}O_5N_2$ $[M+H]^+$:	323.1601	323.1627
Melting point:	162 – 163 °C	

Benzyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-3-cyanopropanoate[15] 35

According to Donohoe *et al.*[15], TFAA (3.31 mL, 23.4 mmol, 2.0 eq.) was added dropwise to a solution of the primary amide **34** (3.77 g, 11.7 mmol) and pyridine (4.73 mL, 58.5 mmol, 5.0 eq.) in anhydrous THF (80 mL) at 0 °C. The reaction mixture was stirred for 2 h before being diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give the nitrile **35** (3.37 g, 11.1 mmol, 95%) as a white solid. The (*S*)-enantiomer was prepared via the same procedure in 88% yield.

TLC: R_f (35) = 0.66 (silica, PE:EtOAc 1:1)



35

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.44 (m, 5 H, 10-H, 11-H, 12-H), 5.57 (m, 1 H, 5-NH), 5.22 (s, 2 H, 8-H), 4.95 (m, 1 H, 2-H), 2.94 (d, $^2J_{3',3}$ = 17.3 Hz, $^3J_{3',2}$ = 5.0 Hz, 1 H, 3-H'), 2.86 (d, $^2J_{3,3'}$ = 17.3 Hz, $^3J_{3,2}$ = 5.3 Hz, 1 H, 3-H), 1.47 (s, 9 H, 7-H).

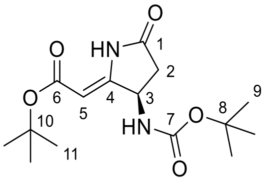
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.2 (s, C-4), 154.2 (s, C-5), 134.9 (s, C-9), 128.9 (d, C-10), 128.8 (d, C-12), 128.6 (d, C-11), 117.8 (s, C-1), 81.6 (s, C-6), 67.7 (t, C-8), 37.6 (t, C-3), 38.5 (d, C-2), 28.3 (q, C-7).

Optical rotation:	**(*R*)-35:** $[\alpha]_D^{20}$= +25.3 (c = 1.0, $CHCl_3$)	
	(*S*)-35: $[\alpha]_D^{20}$= –26.4 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{16}H_{21}O_4N_2$ $[M+H]^+$:	305.1496	305.1485
Melting point:	70 – 72 °C	

***tert*-Butyl (*R*,*Z*)-2-(3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetate[15] 36**

Preparation according to Donohoe *et al.*[15]

TLC: R_f (36) = 0.25 (silica, PE:EtOAc 7:3)



36

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1 H, 1-NH), 5.12 (m, 1 H, 5-H), 4.88 – 4.99 (m, 2 H, 3-H, 7-NH), 2.92 (dd, $^2J_{2,2'}$ = 16.6 Hz, $^3J_{2,3}$ = 7.5 Hz, 1 H, 2-H'), 2.37 (dd, $^2J_{2,2'}$ = 17.0 Hz, $^3J_{2,3}$ = 4.7 Hz, 1 H, 2-H), 1.48 (s, 9 H, 11-H), 1.46 (s, 9 H, 9-H).

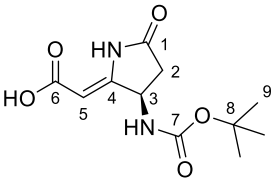
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.9 (s, C-1), 167.4 (s, C-6), 156.5 (s, C-4), 155.0 (s, C-7), 92.5 (d, C-5), 80.8 (s, s, C-8, C-10), 48.7 (d, C-3), 36.5 (t, C-2), 28.3 (q, C-9), 28.2 (q, C-11).

Optical rotation:	**(*R*)-36:** $[\alpha]_D^{20}$= +74.4 (c = 1.0, $CHCl_3$)	
	(*S*)-36: $[\alpha]_D^{20}$= –70.1 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{15}H_{25}N_2O_5$ $[M+H]^+$:	313.1758	313.1761
Melting point:	127 – 131 °C	

(*R*,*Z*)-2-(3-((*tert*-Butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetic acid[15] 37

According to Donohoe *et al.*[15], TFA (903 µL, 11.7 mmol, 20 eq.) was added to a solution of amino pyrrolidone **36** (183 mg, 586 µmol) in CH_2Cl_2 (5.0 mL) at room temperature. The reaction mixture was stirred for 4 h at room temperature before being concentrated in vacuo by redissolving in toluene twice. The residue was dissolved in THF:H_2O (1:1, 6.0 mL) and cooled to 0 °C. After addition of $NaHCO_3$ (172 mg, 2.05 mmol) and Boc_2O (136 µL, 586 µmol, 1.0 eq.), the resulting suspension was stirred for 48 h while slowly reaching room temperature. The reaction mixture was acidified with HCl_{aq} (pH = 2 – 3) and extracted thrice with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give carboxylic acid **37** (46.0 mg, 180 µmol, 31%) as a light-yellow resin. The (*S*)-enantiomer was prepared via the same procedure in 30% yield. Analytical samples (for GC-FID) of the corresponding methyl esters were prepared using TMS-Diazomethane.

TLC: R_f (37) = 0.20 (silica, PE:EtOAc 1:1)

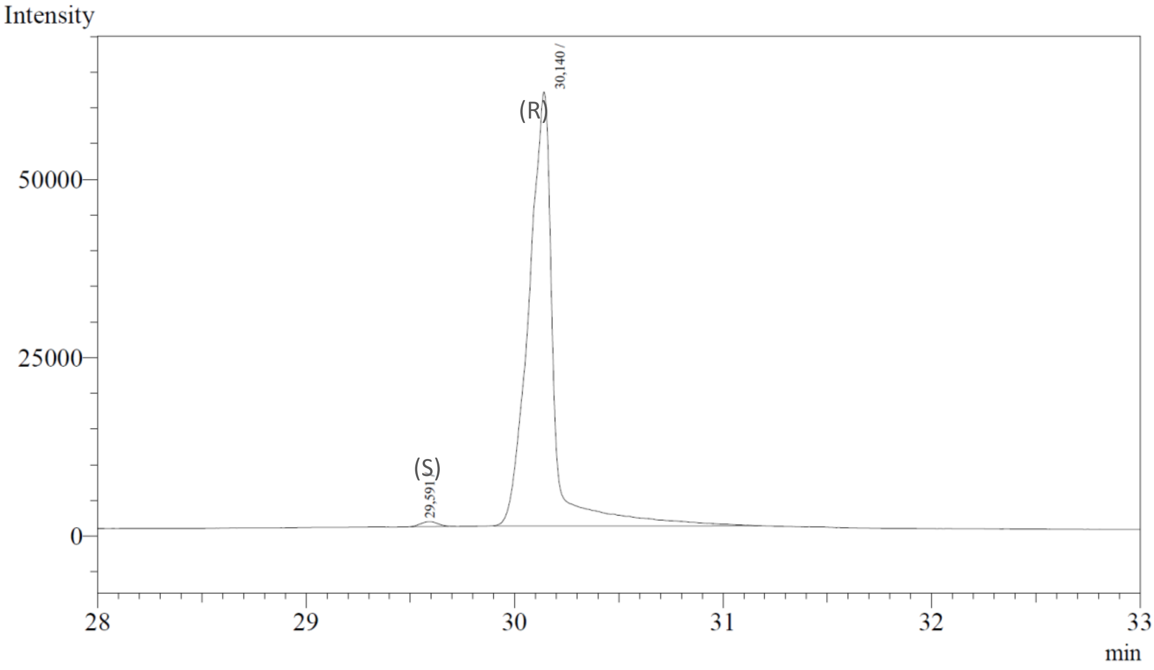


37

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.04 (s, 1 H, 6-OH), 9.98 (s, 1 H, 1-NH), 7.50 (d, $^3J_{NH,3}$ = 8.6 Hz, 1 H, 7-NH), 4.87 (s, 1 H, 5-H), 4.78 (ddd, $^3J_{3,2}$ = 9.6 Hz, $^3J_{3,NH}$ = 8.6 Hz, $^3J_{3,2'}$ = 6.0 Hz, 1 H, 3-H), 2.74 (dd, $^2J_{2,2'}$ = 17.6 Hz, $^3J_{2,3}$ = 9.6 Hz, 1 H, 2-H'), 2.32 (dd, $^2J_{2,2'}$ = 17.5 Hz, $^3J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 1.40 (s, 9 H, 9-H).

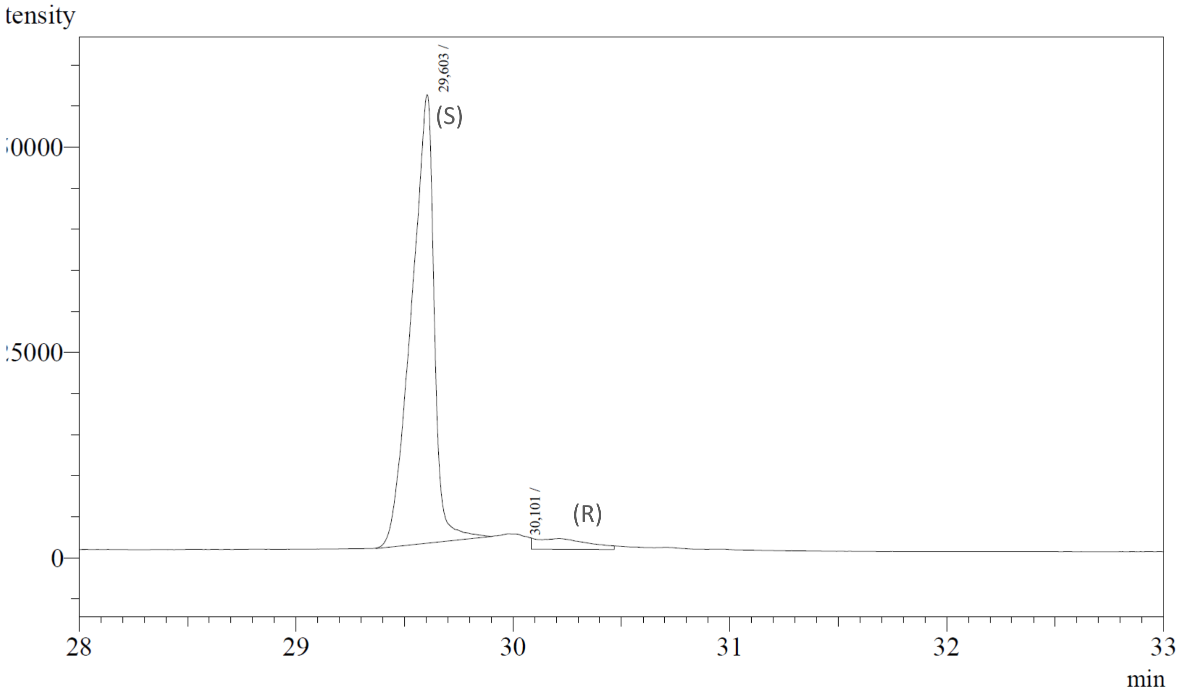
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 174.6 (s, C-1), 168.6 (s, C-6), 160.0 (s, C-4), 155.2 (s, C-7), 89.0 (d, C-5), 78.7 (s, C-8), 48.2 (d, C-3), 34.3 (t, C-2), 28.1 (q, C-9).

Chiral GC-FID of 37(OMe):



Peak#	Ret.Time	Area	Height	Conc.	Unit Mark ID#	Cmpd Name
1	29,591	3991	670	0,781		
2	30,140	506967	60258	99,219		
Total		510958	60928			

Chiral GC-FID of ent-37(OMe):



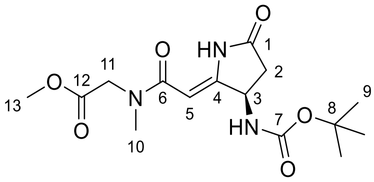
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	29,603	399659	53603	94,724				
2	30,101	22260	1205	5,276				
Total		421919	54808					

Methyl (*R*,*Z*)-*N*-(2-(3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycinate 38

TFA (6.76 mL, 88.0 mmol, 20 eq.) was added to a solution of amino pyrrolidone **36** (1.37 g, 4.39 mmol) in CH_2Cl_2 (28 mL) at room temperature. The reaction mixture was stirred for 4 h at room temperature before being concentrated in vacuo. The residue was azeotropically dried with toluene twice. The residue was dissolved in THF:H_2O (1:1, 30 mL) and cooled to 0 °C. After addition of $NaHCO_3$ (1.29 g, 15.4 mmol, 3.5 eq.) and Boc_2O (1.32 mL, 5.70 mmol, 1.3 eq.), the resulting suspension was stirred for 72 h while slowly reaching room temperature. The reaction mixture was diluted with 5 wt% $NaHCO_3$ solution (3.0 mL) and washed twice with Et_2O. The aqueous layer was acidified with HCl_{aq} (pH = 2 – 3) and extracted thrice with Et_2O. The combined organic extracts of the last extraction step were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid (873 mg).

The above-prepared carboxylic acid (873 mg) and sarcosine methyl ester hydrochloride (951 mg, 6.81 mmol, 2.0 eq.) were dissolved in anhydrous CH_2Cl_2 (28 mL). After cooling to 0 °C, NMM (1.54 mL, 14.0 mmol, 4.1 eq.) and HBTU (1.42 g, 3.75 mmol, 1.1 eq.) were added subsequentially. The reaction mixture was stirred for 16 h while slowly reaching room temperature before being diluted with EtOAc. The mixture was washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give the dipeptide **38** (700 mg, 2.05 mmol, 47% over 2 steps) as a light-yellow foam.

TLC: R$_f$ (38) = 0.10 (silica, CH_2Cl_2:MeOH 97:3)



38

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 10.25 (s, 1 H, 1-NH), 7.14 (d, $^3J_{NH,3}$ = 5.7 Hz, 1 H, 7-NH), 5.42 (s, 1 H, 5-H), 4.77 (ddd, $^3J_{3,2}$ = 9.5 Hz, $^3J_{3,NH}$ = 5.7 Hz, $^3J_{3,2'}$ = 5.6 Hz, 1 H, 3-H), 4.16 (m, 2 H, 11-H), 3.68 (s, 3 H, 13-H), 3.00 (s, 3 H, 10-H), 2.75 (dd, $^2J_{2',2}$ = 17.6 Hz, $^3J_{2',3}$ = 9.5 Hz, 1 H, 2-H'), 2.37 (dd, $^2J_{2,2'}$ = 17.6 Hz, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 1.44 (s, 9 H, 9-H).

^{13}C-NMR (125 MHz, $CDCl_3$, 298 K): δ = 174.3 (s, C-1), 168.3 (s, C-6), 170.1 (s, C-12), 155.5 (s, C-7), 157.0 (s, C-4), 88.7 (d, C-5), 80.8 (s, C-8), 52.4 (s, C-13), 49.5 (t, C-11), 49.0 (d, C-3), 36.9 (q, C-10), 36.3 (t, C-2), 28.4 (q, C-9).

Optical rotation: $[\alpha]_D^{20}$= +75.8 (c = 1.0, $CHCl_3$)

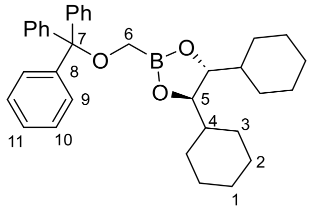
HRMS (ESI):	calculated	found
$C_{15}H_{24}N_3O_6$ [M+H]$^+$:	342.1660	342.1656

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((trityloxy)methyl)-1,3,2-dioxaborolane[202] 39

Sodium hydride (2.37 g, 59.3 mmol, 1.1 eq.) was added to a solution of triphenylmethanol (14.5 g, 53.9 mmol, 1.0 eq.) in anhydrous DMSO (108 mL). The turbid solution was stirred for 16 h at room temperature before pinacol (bromomethyl)boronate[203] (11.9 g, 53.9 mmol) was added. After stirring for another 20 h, the mixture was quenched by the addition of sat. NH_4Cl solution. Extraction with Et_2O, concentration in vacuo, and addition of pentane led to a white solid, which was filtrated and washed thoroughly with H_2O. The white solid was redissolved in Et_2O (110 mL), and pentaerythritol (18.3 g, 135 mmol, 2.5 eq.) followed by 1.0 M $NaOH_{aq}$ (162 mL, 162 mmol, 3.0 eq.) was added. The reaction mixture was stirred for 18 h at room temperature before being diluted with Et_2O (100 mL) and H_2O (400 mL). The aqueous phase was washed once with Et_2O (50 mL) and afterward acidified at 0 °C with 6 M HCl_{aq} (pH 3 – 4). After stirring for 30 min, the white solid was filtered off and dried in vacuo to give the crude ((trityloxy)methyl)boronic acid (13.0 g, 40.7 mmol, 76%).

The above-prepared crude ((trityloxy)methyl)boronic acid (12.0 g, 37.6 mmol, 1.2 eq.) and (*R*,*R*)-DICHED[142] (7.01 g, 30.9 mmol) were suspended in pentane (188 mL). After 64 h, the slightly turbid solution was filtered, and the filtrate was concentrated to around 30 mL. The residual solvent was evaporated in a nitrogen flow to give boronic ester **39** (13.8 g, 27.1 mmol, 88%) as a colorless solid.

TLC: R$_f$ (39) = 0.55 (silica, pentane:Et_2O 9:1)



39

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.49 (m, 6 H, 9-H), 7.30 (m, 6 H, 10-H), 7.23 (m, 3 H, 11-H), 3.95 (m, 2 H, 5-H), 2.95 (d, $^2J_{6,6'}$ = 15.8 Hz, 1 H, 6-H), 2.87 (d, $^2J_{6',6}$ = 15.7 Hz, 1 H, 6-H'), 1.87 – 1.60 (m, 10 H, 1-H, 2-H, 3-H), 1.39 (m, 2 H, 4-H), 1.30 – 0.97 (m, 10 H, 2-H', 3-H').

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 144.3 (s, C-8), 129.0 (d, C-9), 127.8 (d, C-10), 126.9 (d, C-11), 87.8 (s, C-7), 83.9 (d, C-5), 43.1 (d, C-4), 28.5 (t, C-3), 27.5 (t, C-2), 26.6 (t, C-1), 26.2 (t, C-3'), 26.0 (t, C-2'), C-6 was not observed.

Optical rotation:	$[\alpha]_D^{20}$= +56.2 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{34}H_{41}BO_3$ [M]$^+$:	508.3143	508.3099
Melting point:	108 – 111 °C	

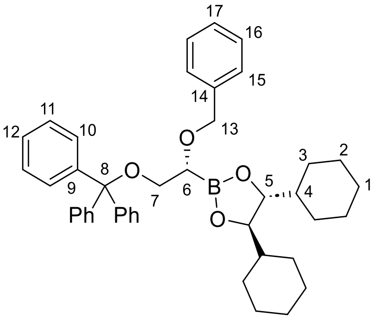
(4*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-2-(trityloxy)ethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane[144] 40

LDA solution: In a 25 mL flame-dried Schlenk tube under a nitrogen atmosphere, 2.5 M *n*-BuLi in hexane (3.93 mL, 9.83 mmol, 1.25 eq.) was added dropwise to a –40 °C cold solution of diisopropylamine (1.51 mL, 10.6 mmol, 1.35 eq.) in anhydrous THF (4.0 mL). The resulting solution was stirred for 10 min at –40 °C and for 20 min at room temperature.

Alcoholate solution: In a 50 mL flame-dried Schlenk-flask under a nitrogen atmosphere, sodium hydride (472 mg, 11.8 mmol, 60wt%, 1.5 eq.) was suspended in a mixture of anhydrous THF (4.8 mL) and anhydrous DMSO (12.8 mL). After the addition of benzyl alcohol (1.31 mL, 12.6 mmol, 1.6 eq.), the reaction mixture was stirred for 4 h at room temperature.

Homologation: In a 250 mL flame-dried Schlenk-flask under a nitrogen atmosphere, boronic ester **39** (4.00 g, 7.87 mmol) and CH_2Cl_2 (1.52 mL, 23.6 mmol, 3.0 eq.) were dissolved in anhydrous THF (11.0 mL). The above-prepared LDA solution was added dropwise at –40 °C. After stirring for 10 min, a solution of $ZnCl_2$ (3.22 g, 23.6 mmol, flame-dried in vacuo, 3.0 eq.) in anhydrous THF (14.0 mL) was added in one portion. The cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. After full conversion (NMR), the above-prepared alcoholate solution was added dropwise at 0 °C. The reaction mixture was stirred for 48 h at room temperature before being quenched by the addition of sat. NH_4Cl solution (30 mL). The aqueous layer was extracted twice with pentane (150 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 9:1) to give boronic ester **40** (4.04 g, 6.37 mmol, 81%) as a colorless resin.

TLC: R$_f$ (40) = 0.39 (silica, pentane:Et$_2$O 9:1)



40

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.54 – 7.47 (m, 8 H, 10-H, 16-H), 7.39 – 7.19 (m, 12 H, 11-H, 12-H, 15-H, 17-H), 4.67 (d, $^2J_{13,13'}$ = 12.3 Hz, 1 H, 13-H), 4.57 (d, $^2J_{13',13}$ = 12.3 Hz, 1 H, 13-H'), 3.93 (m, 2 H, 5-H), 3.55 (dd, $^3J_{6,7'}$ = 5.6 Hz, $^3J_{6,7}$ = 3.8 Hz, 1 H, 6-H), 3.40 (dd, $^2J_{7,7'}$ = 9.9 Hz, $^3J_{7,6}$ = 3.7 Hz, 1 H, 7-H), 3.35 (dd, $^2J_{7',7}$ = 10.0 Hz, $^3J_{7',6}$ = 5.6 Hz, 1 H, 7-H'), 1.86 – 1.57 (m, 10 H, 1-H, 2-H, 3-H), 1.35 (m, 2 H, 4-H), 1.25 – 0.83 (m, 10 H, 2-H', 3-H').

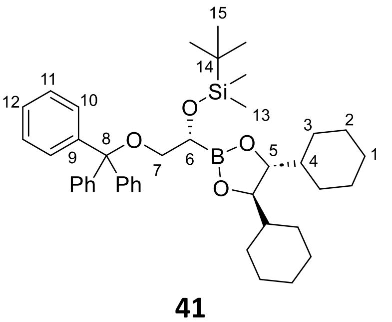
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 144.3 (s, C-9), 139.1 (s, C-14), 128.9 (d, C-10), 128.2 (d, C-15), 127.8 (d, C-16), 127.7 (d, C-11), 127.2 (d, C-17), 126.8 (d, C-12), 86.5 (s, C-8), 83.8 (d, C-5), 72.3 (t, C-13), 64.5 (t, C-7), 42.8 (d, C-4), 28.3 (t, C-3), 27.4 (t, C-2), 26.4 (t, C-1), 26.0 (t, C-3'), 25.9 (t, C-2'), C-6 was not observed.

***tert*-Butyl ((*R*)-1-((4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl)-2-(trityloxy)ethoxy)-dimethylsilane 41**

Boronic ester **40** (3.87 g, 5.97 mmol) and Pd/C (477 mg, 448 µmol, 10 wt% Pd, 7.5 mol%) were suspended in EtOH (40 mL). The resulting suspension was stirred for 18 h under an atmosphere of H$_2$ (1 atm). Another portion of Pd/C (250 mg, 237 µmol, 10 wt% Pd, 4.0 mol%) was added, and the stirring continued for 6 h under an atmosphere of H$_2$. The reaction mixture was filtered through a plug of celite® and concentrated in vacuo to give the crude secondary alcohol.

TBS-OTf (2.36 mL, 10.3 mmol, 1.7 eq.) and 2,4,6-collidine (1.82 mL, 13.7 mmol, 2.3 eq.) were added to a 0 °C cold solution of the above-prepared secondary alcohol in anhydrous CH$_2$Cl$_2$ (50 mL). The reaction mixture was stirred for 3 h while slowly reaching room temperature. Concentration in vacuo and purification by column chromatography (silica, pentane:Et$_2$O 95:5) gave boronic ester **41** (2.89 g, 4.42 mmol, 74%) as a colorless resin.

TLC: R$_f$ (41) = 0.47 (silica, pentane:Et$_2$O 96:4)



41

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.49 (m, 6 H, 10-H), 7.27 (m, 6 H, 11-H), 7.22 (m, 3 H, 12-H), 3.86 (m, 2 H, 5-H), 3.77 (dd, $^3J_{6,7}$ = 6.4 Hz, $^3J_{6,7'}$ = 5.2 Hz, 1 H, 6-H), 3.26 (dd, $^2J_{7,7'}$ = 9.1 Hz, $^3J_{7,6}$ = 6.5 Hz, 1 H, 7-H), 3.19 (dd, $^2J_{7',7}$ = 9.1 Hz, $^3J_{7',6}$ = 5.2 Hz, 1 H, 7-H‘), 1.80 – 1.56 (m, 10 H, 1-H, 2-H, 3-H), 1.30 (m, 2 H, 4-H), 1.25 – 0.86 (m, 10 H, 2-H‘, 3-H‘), 0.91 (s, 9 H, 15-H), 0.08 (s, 3 H, 13-H), 0.06 (s, 3 H, 13‘-H).

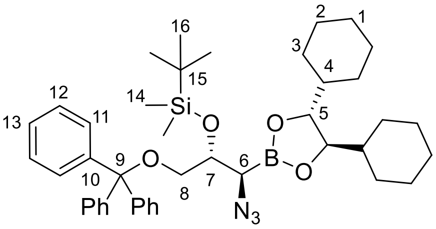
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 144.4 (s, C-9), 128.9 (d, C-10), 127.6 (d, C-11), 126.7 (d, C-12), 86.3 (s, C-8), 83.7 (d, C-5), 67.0 (t, C-7), 42.9 (d, C-4), 28.3 (t, C-3), 27.4 (t, C-2), 26.4 (t, C-1), 25.99 (t, C-3‘), 25.95 (q, C-15), 25.85 (t, C-2‘), 18.5 (s, C-14), –4.8 (q, C-13), –5.1 (q, C-13‘), C-6 was not observed.

(((1*R*,2*R*)-1-Azido-1-((4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl)-3-(trityloxy)propan-2-yl)oxy)(*tert*-butyl)dimethylsilane 42

<u>LDA solution:</u> In a 25 mL flame-dried Schlenk tube under a nitrogen atmosphere, 2.5 M *n*-BuLi in hexane (735 µL, 1.84 mmol, 1.25 eq.) was added dropwise to a –40 °C cold solution of diisopropylamine (283 µL, 1.98 mmol, 1.35 eq.) in anhydrous THF (700 µL). The resulting solution was stirred for 10 min at –40 °C and for 20 min at room temperature.

<u>Homologation:</u> In a 25 mL flame-dried Schlenk-flask under a nitrogen atmosphere, boronic ester **41** (1.01 g, 1.47 mmol) and CH_2Cl_2 (284 µL, 4.41 mmol, 3.0 eq.) were dissolved in anhydrous THF (2.0 mL). The above-prepared LDA solution was added dropwise at –40 °C. After stirring for 10 min, a solution of $ZnCl_2$ (801 mg, 5.88 mmol, flame-dried in vacuo, 4.0 eq.) in anhydrous THF (3.8 mL) was added in one portion. The cooling bath was removed, and the reaction mixture was stirred for 5 h at room temperature. After full conversion (NMR), the reaction mixture was quenched by the addition of sat. NH_4Cl solution (10 mL). The aqueous layer was extracted twice with pentane (50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in anhydrous DMF (12 mL), and sodium azide (955 mg, 14.7 mmol, 10 eq.) was added. The resulting suspension was stirred for 32 h at room temperature. After dilution with pentane and sat. NH_4Cl solution, the aqueous layer was extracted twice with pentane. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo (residual DMF was co-evaporated with heptane) to give the boronic ester **42** (954 mg, 1.35 mmol, 92%) as a light-yellow resin.

TLC: R$_f$ (42) = 0.63 (silica, pentane:Et_2O 9:1)



42

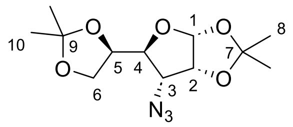
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.44 (m, 6 H, 11-H), 7.29 (m, 6 H, 12-H), 7.25 (m, 3 H, 13-H), 4.13 (ddd, $^{3}J_{7,8}$ = 8.0 Hz, $^{3}J_{7,8'}$ = 5.4 Hz, $^{3}J_{7,6}$ = 2.3 Hz, 1 H, 7-H), 3.85 (m, 2 H, 5-H), 3.50 (d, $^{3}J_{6,7}$ = 2.1 Hz, 1 H, 6-H), 3.33 (dd, $^{2}J_{8,8'}$ = 9.3 Hz, $^{3}J_{8,7}$ = 8.1 Hz, 1 H, 8-H), 3.11 (dd, $^{2}J_{8',8}$ = 9.3 Hz, $^{3}J_{8',7}$ = 5.4 Hz, 1 H, 8-H‘), 1.80 – 1.48 (m, 8 H, 1-H, 2-H, 3-H), 1.20 – 0.83 (m, 14 H, 2-H‘, 3-H‘, 4-H), 0.82 (s, 9 H, 16-H), 0.05 (s, 3 H, 14-H), –0.10 (s, 3 H, 14′-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 144.0 (s, C-10), 129.0 (d, C-11), 127.9 (d, C-12), 127.1 (d, C-13), 87.2 (s, C-9), 84.5 (d, C-5), 74.4 (d, C-7), 64.9 (t, C-8), 42.8 (d, C-4), 28.5 (t, C-3), 27.8 (t, C-2), 26.5 (t, C-1), 26.0 (t, C-3‘), 25.87 (q, C-16), 25.84 (t, C-2‘), 18.1 (s, C-15), –4.6 (q, C-14), –4.9 (q, C-14‘), C-6 was not observed.

(3a*R*,5*S*,6*R*,6a*R*)-6-Azido-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro-[2,3-d][1,3]dioxole[148] 44

Preparation, according to Perczel *et al.*[148]

TLC: R$_f$ (44) = 0.46 (silica, PE:EtOAc 7:3)



44

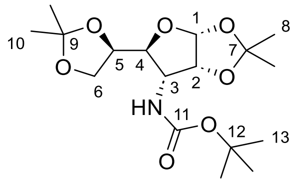
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.80 (d, $^{3}J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 4.74 (dd, $^{3}J_{2,1}$ = 3.9 Hz, $^{3}J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.23 – 4.12 (m, 2 H, 5-H, 6-H‘), 4.06 – 3.98 (m, 2 H, 4-H, 6-H), 3.50 (dd, $^{3}J_{3,4}$ = 9.0 Hz, $^{3}J_{3,2}$ = 4.8 Hz, 1 H, 3-H), 1.59 (s, 3 H, 8′-H), 1.50 (s, 3 H, 8-H), 1.39 (s, 3 H, 10′-H), 1.37 (s, 3 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 113.2 (s, C-9), 110.1 (s, C-7), 103.9 (d, C-1), 80.6 (d, C-2), 78.1 (d, C-4), 75.8 (d, C-5), 66.7 (t, C-6), 62.6 (d, C-3), 26.5 (q, C-8/C-10), 26.4 (q, C-8/C-10), 26.3 (q, C-8/C-10), 25.1 (q, C-8/C-10).

tert-Butyl ((3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro-[2,3-d][1,3]dioxol-6-yl)carbamate 45

Pd/C (31.7 mg, 29.8 µmol, 10wt% Pd, 10 mol%) was added to a solution of compound **44** (85.0 mg, 298 µmol) in MeOH (3.0 mL). The resulting suspension was stirred for 18 h under an atmosphere of H_2 (1 atm). The reaction mixture was filtered through a plug of celite® and concentrated in vacuo. The crude was dissolved in THF:H_2O (2.0 mL, 1:1). $NaHCO_3$ (88.0 mg, 1.05 mmol, 3.5 eq.) and Boc_2O (70.0 µL, 301 µmol, 1.0 eq.) were subsequently added. The reaction mixture was stirred for 16 h at room temperature before being diluted with EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 8:2) to give the Boc-amine **45** (90.0 mg, 250 µmol, 83%) as a colorless oil.

TLC: R$_f$ (45) = 0.15 (silica, PE:EtOAc 8:2)



45

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 5.81 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 4.94 (d, $^3J_{NH,3}$ = 8.7 Hz, 1 H, 11-NH), 4.59 (dd, $^3J_{2,3}$ = 4.4 Hz, $^3J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 4.26 (m, 1 H, 5-H), 4.09 (dd, $^2J_{6',6}$ = 7.8 Hz, $^3J_{6,5}$ = 6.7 Hz, 1 H, 6-H'), 3.99 (m, 1 H, 3-H), 3.94 (dd, $^2J_{6,6'}$ = 8.0 Hz, $^3J_{6,5}$ = 6.7 Hz, 1 H, 6-H), 3.85 (dd, $^3J_{4,3}$ = 9.0 Hz, $^3J_{4,5}$ = 4.0 Hz, 1 H, 4-H), 1.55 (s, 3 H, 8'-H), 1.46 (s, 9 H, 13-H), 1.45 (s, 3 H, 8-H), 1.36 (s, 3 H, 10'-H), 1.34 (s, 3 H, 10-H).

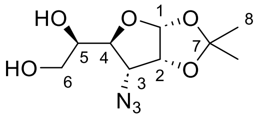
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 112.5 (s, C-7), 109.7 (s, C-9), 104.0 (d, C-1), 80.0 (s, C-12), 79.2 (d, C-2), 78.8 (d, C-4), 75.7 (d, C-5), 65.4 (t, C-6), 54.7 (d, C-3), 28.5 (q, C-13), 26.6 (q, C-8/C-10), 26.4 (q, C-8/C-10), 26.3 (q, C-8/C-10), 25.5 (q, C-8/C-10), C-11 was not observed.

Optical rotation:	$[\alpha]_D^{20}$= +52.9 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
C$_{17}$H$_{30}$NO$_7$ [M+H]$^+$:	360.2017	360.2025

(*R*)-1-((3a*R*,5*S*,6R,6a*R*)-6-azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethane-1,2-diol[148] 46

Preparation according to Perczel *et al.*[148]

TLC: R$_f$ (46) = 0.08 (silica, PE:EtOAc 1:1)



46

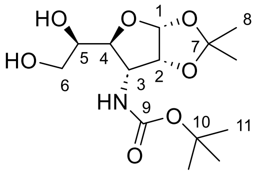
^{1}H-NMR (400 MHz, CDCl$_3$): δ = 5.82 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, 1-H), 4.78 (dd, $^3J_{2,3}$ = 4.3 Hz, $^3J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 4.12 (dd, $^3J_{4,3}$ = 9.4 Hz, $^3J_{4,5}$ = 4.1 Hz, 1 H, 4-H), 4.03 (td, $^3J_{5,6}$ = 5.0 Hz, $^3J_{5,4}$ = 4.7 Hz, 1 H, 5-H), 3.79 (d, $^3J_{6,5}$ = 5.3 Hz, 2 H, 6-H), 3.61 (dd, $^3J_{3,4}$ = 9.4 Hz, $^3J_{3,2}$ = 4.8 Hz, 1 H, 3-H), 1.60 (s, 3 H, 8'-H), 1.39 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ = 113.4 (s, C-7), 104.0 (d, C-1), 80.6 (d, C-5), 78.0 (d, C-2), 71.3 (d, C-4), 62.8 (t, C-6), 60.3 (d, C-3), 26.5 (q, C-8).

tert-Butyl ((3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]-dioxol-6-yl)carbamate 47

A solution of Boc-amine **45** (45.0 mg, 125 µmol) in H$_2$O:AcOH (750 µL, 1:2) was stirred for 44 h at room temperature. 2.0 M KOH$_{aq}$ (3.8 mL) was added dropwise to adjust the pH to ≈ 6, followed by Na$_2$CO$_3$ (≈ 200 mg) to neutralize the solution thoroughly. After concentrating in vacuo, the residue was suspended in EtOAc several times and filtrated. The filtrate was dried with Na_2SO_4 and concentrated in vacuo to give diol **47** (43.0 mg, 121 µmol, 97%) as a colorless resin.

TLC: R_f (47) = 0.08 (silica, PE:EtOAc 1:1)



47

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 5.36 (d, $^3J_{NH,3}$ = 7.8 Hz, 1 H, 9-NH), 4.63 (dd, $^3J_{2,3}$ = 5.2 Hz, $^3J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 3.99 (m, 1 H, 6-H), 3.93 (ddd, $^3J_{3,4}$ = 8.5 Hz, $^3J_{3,NH}$ = 8.5 Hz, $^3J_{3,2}$ = 5.4 Hz, 1 H, 3-H), 3.83 – 3.71 (m, 3 H, 4-H, 5-H, 6-H‘), 1.55 (s, 3 H, 8‘-H), 1.47 (s, 9 H, 11-H), 1.35 (s, 3 H, 8-H).

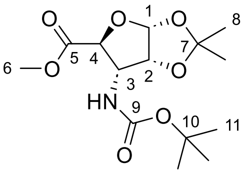
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 157.0 (s, C-9), 112.7 (s, C-7), 103.8 (d, C-1), 81.2 (s, C-10), 80.6 (d, C-5), 79.4 (d, C-2), 72.7 (d, C-4), 64.0 (t, C-6), 55.8 (d, C-3), 28.3 (q, C-11), 26.6 (q, C-8‘), 26.5 (q, C-8).

Methyl (3a*R*,5*S*,6*S*,6a*R*)-6-((*tert*-butoxycarbonyl)amino)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole-5-carboxylate 48

$NaIO_4$ (33.5 mg, 156 µmol, 1.5 eq.) was added portion-wise to a solution of diol **47** (37.0 mg, 104 µmol) in H_2O:MeOH (1.0 mL, 1:1) at room temperature. The resulting suspension was stirred for 1 h before being filtered through a pad of celite®. Concentration in vacuo gave the crude aldehyde as a light-yellow oil.

The above-prepared crude aldehyde was suspended in 0.6 M $AgNO_{3aq}$ (470 µL, 282 µmol, 2.7 eq.). 0.9 M KOH_{aq} solution (626 µL, 564 µmol, 5.4 eq.) was added, and the dark suspension was stirred for 1 h at room temperature. The reaction mixture was filtrated, and the filtrate was diluted with H_2O and CH_2Cl_2. The aqueous layer was acidified with 1.0 M HCl_{aq} (2.0 mL) and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in toluene:MeOH (1.0 mL), and TMS-diazomethane (188 µL, 376 µmol, 3.6 eq.) was added dropwise. After the addition of a few droplets of AcOH, the mixture was concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 7:3) to give methyl ester **48** (28.0 mg, 88.2 µmol, 85%) as a colorless resin.

TLC: R_f (48) = 0.54 (silica, PE:EtOAc 1:1)



48

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.98 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 5.10 (d, $^3J_{NH,3}$ = 8.3 Hz, 1 H, 9-NH), 4.64 (dd, $^3J_{2,3}$ = 3.9 Hz, $^3J_{2,1}$ = 3.9 Hz, 1 H, 2-H), 4.28 – 4.18 (m, 2 H, 4-H, 3-H), 3.77 (s, 3 H, 6-H), 1.55 (s, 3 H, 8'-H), 1.45 (s, 9 H, 11-H), 1.35 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.8 (s, C-5), 154.9 (s, C-9), 113.0 (s, C-7), 104.5 (d, C-1), 80.2 (s, C-10), 78.8 (d, C-2), 77.2 (d, C-4), 56.5 (d, C-3), 52.6 (t, C-6), 28.3 (q, C-11), 26.6 (q, C-8'), 26.5 (q, C-8).

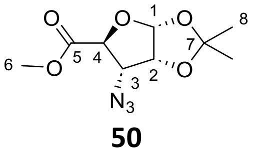
Methyl (3a*R*,5*S*,6*S*,6a*R*)-6-azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole-5-carboxylate[148] 50

$NaIO_4$ (916 mg, 4.28 mmol, 1.5 eq.) was added portion wise to a solution of compound **46** (700 mg, 2.85 mmol) in H_2O:MeOH (20 mL, 1:1) at room temperature. The resulting suspension was stirred for 1 h before being filtered through a pad of celite®. Concentration in vacuo gave the crude aldehyde as a light-yellow oil.

The above-prepared crude aldehyde was dissolved in MeCN (10 mL). A solution of NaH_2PO_4 (68.5 mg, 571 µmol, 0.2 eq.) in H_2O (1.0 mL) and H_2O_2 (291 µL, 2.86 mmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (517 mg, 4.57 mmol, 1.6 eq.) in H_2O (1.2 mL) was added dropwise. The resulting solution was stirred for 16 h while slowly reaching room temperature. After the addition of Na_2SO_4 (200 mg), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid (627 mg, 2.74 mmol, 96%) as a colorless resin.

K_2CO_3 (470 mg, 3.40 mmol, 1.5 eq.) and MeI (426 µL, 6.81 mmol, 3.0 eq.) were added to a solution of the above-prepared carboxylic acid (520 mg, 2.27 mmol) in anhydrous DMF (12 mL). The resulting suspension was stirred for 16 h at room temperature. After full conversion, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 7:3) to give methyl ester **K243** (351 mg, 1.44 mmol, 64%) as a colorless oil.

TLC: R_f (50) = 0.59 (silica, PE:EtOAc 4:6)



50

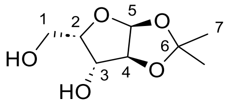
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 4.76 (dd, $^3J_{2,3}$ = 4.0 Hz, $^3J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 4.58 (d, $^3J_{4,3}$ = 9.5 Hz, 1 H, 4-H), 3.86 (s, 3 H, 6-H), 3.71 (dd, $^3J_{3,4}$ = 9.5 Hz, $^3J_{3,2}$ = 4.5 Hz, 1 H, 3-H), 1.59 (s, 3 H, 8'-H), 1.38 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5 (s, C-5), 114.0 (s, C-7), 104.8 (d, C-1), 80.0 (d, C-2), 76.1 (d, C-4), 63.5 (d, C-3), 53.1 (q, C-6), 26.7 (q, C-8'), 26.6 (q, C-8).

(3a*S*,5*S*,6*R*,6a*S*)-5-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol[152] 52

According to Herdewijn *et al.*[152], L-xylose (15.0 g, 100 mmol) was suspended in acetone (400 mL). After conc. H_2SO_4 (15.0 mL, 281 mmol, 2.82 eq.) was added dropwise, the reaction mixture was stirred for 45 min at room temperature. The resulting solution was cooled to 0 °C, and a solution of Na_2CO_3 (20.0 g, 189 mmol, 1.89 eq.) in H_2O (190 mL) was added slowly. The resulting suspension was stirred for 3 h at room temperature. Another portion of Na_2CO_3 (10.0 g, 94.5 mmol) was added to neutralize the reaction mixture fully. After stirring for 10 min, the suspension was filtered, and the filtrate was concentrated in vacuo (keeping the water bath of the rotary evaporator below 30 °C). The crude was purified by flash chromatography (silica, CH_2Cl_2:MeOH 4% to 7% MeOH) to give the monoacetonide **52** (16.1 g, 85.0 mmol, 85%) as a colorless oil.

TLC: R_f (52) = 0.15 (silica, CH_2Cl_2:MeOH 95:5)



52

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 5.80 (d, $^3J_{5,4}$ = 3.8 Hz, 1 H, 5-H), 5.12 (d, $^3J_{OH,3}$ = 4.8 Hz, 1 H, 3-OH), 4.60 (t, $^3J_{OH,1}$ = 5.6 Hz, $^3J_{OH,1'}$ = 5.6 Hz, 1 H, 1-OH), 4.37 (d, $^3J_{4,5}$ = 3.7 Hz, 1 H, 4-H), 4.00 – 3.92 (m, 2 H, 2-H, 3-H), 3.60 (ddd, $^2J_{1',1}$ = 11.4 Hz, $^3J_{1',2}$ = 5.6 Hz, $^3J_{1',OH}$ = 5.6 Hz, 1 H, 1-H'), 3.50 (ddd, $^2J_{1,1'}$ = 11.5 Hz, $^3J_{1,2}$ = 5.9 Hz, $^3J_{1,OH}$ = 5.9 Hz, 1 H, 1-H), 1.37 (s, 3 H, 7'-H), 1.22 (s, 3 H, 7-H).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 110.3 (s, C-6), 104.3 (d, C-5), 85.1 (d, C-4), 81.3 (d, C-2), 73.4 (d, C-3), 58.8 (t, C-1), 26.7 (q, C-7'), 26.1 (q, C-7).

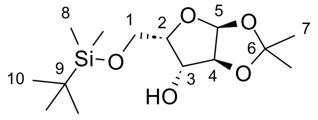
Optical rotation: $[\alpha]_D^{20}$= +15.4 (c = 2.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_8H_{15}O_5$ $[M+H]^+$:	191.0914	191.0919

(3a*S*,5*S*,6*R*,6a*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol[152] 53

According to Herdewijn *et al.*[152], monoacetonide **52** (15.6 g, 82.0 mmol) was dissolved in anhydrous DMF (90 mL). Imidazole (14.0 g, 205 mmol, 2.5 eq.) and TBS-Cl (12.4 g, 80.5 mmol, 0.98 eq.) were subsequently added, and the reaction mixture was stirred for 16 h at room temperature. After dilution with EtOAc (500 mL), the mixture was washed twice with 0.5 M HCl_{aq}, once with sat. $NaHCO_3$ solution and thrice with ice-cold H_2O (1.0 L). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give the protected L-xylose **53** (22.8 g, 74.9 mmol, 93%) as a colorless oil.

TLC: R_f (53) = 0.63 (silica, CH_2Cl_2:MeOH 97:3)



53

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 5.97 (d, $^3J_{5,4}$ = 3.6 Hz, 1 H, 5-H), 4.51 (d, $^3J_{4,5}$ = 3.7 Hz, 1 H, 4-H), 4.38 (d, $^3J_{OH,3}$ = 2.8 Hz, 1 H, 3-OH), 4.34 (d, $^3J_{3,OH}$ = 2.8 Hz, 1 H, 3-H), 4.16 – 4.10 (m, 3 H, 1-H, 2-H), 1.49 (s, 3 H, 7'-H), 1.33 (s, 3 H, 7-H), 0.90 (s, 9 H, 10-H), 0.12 (s, 3 H, 8-H), 0.12 (s, 3 H, 8'-H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ = 111.5 (s, C-6), 105.0 (d, C-5), 85.6 (d, C-4), 78.1 (d, C-2), 77.2 (d, C-3), 62.4 (t, C-1), 26.8 (q, C-7'), 26.2 (q, C-7), 25.7 (q, C-10), 18.1 (s, C-9), –5.6 (q, C-8), –5.5 (q, C-8').

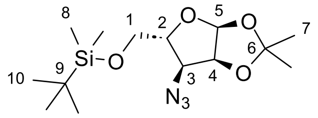
Optical rotation:	$[\alpha]_D^{20}$= +8.5 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{14}H_{29}O_5Si$ [M+H]$^+$:	305.1779	305.1784

(((3a*S*,5*R*,6*S*,6a*S*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)(*tert*-butyl)dimethylsilane 54

Triflic anhydride (4.51 mL, 26.7 mmol, 1.5 eq.) was added dropwise to a –15 °C cold solution of monoacetonide **53** (5.42 g, 17.8 mmol), and pyridine (4.32 mL, 53.4 mmol, 3.0 eq.) in anhydrous CH$_2$Cl$_2$ (60 mL). The reaction mixture was stirred for 1 h at –10 °C. After full conversion, the mixture was diluted with CH$_2$Cl$_2$ and washed with 1.0 M HCl$_{aq}$ and brine. The organic layer was dried with MgSO$_4$ and concentrated in vacuo to give the crude triflate.

The above-prepared crude triflate and tetrabutylammonium hydrogen sulfate (30.0 mg, 89.0 µmol, 0.5 mol%) were dissolved in anhydrous DMF (90 mL). After the addition of NaN$_3$ (5.79 g, 89.0 mmol, 5.0 eq.), the suspension was stirred for 24 h at room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% LiCl$_{aq}$, 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 97:3) to give the azido-sugar **54** (2.80 g, 8.50 mmol, 48%) as a colorless oil.

TLC: R$_f$ (54) = 0.53 (silica, PE:EtOAc 8:2)



54

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 5.79 (d, $^3J_{5,4}$ = 3.8 Hz, 1 H, 5-H), 4.73 (dd, $^3J_{4,3}$ = 4.2 Hz, $^3J_{4,5}$ = 4.2 Hz, 1 H, 4-H), 4.11 (ddd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{2,1}$ = 2.8 Hz, $^3J_{2,1'}$ = 2.8 Hz, 1 H, 2-H), 3.95 (dd, $^2J_{1',1}$ = 11.9 Hz, $^3J_{1',2}$ = 2.7 Hz, 1 H, 1-H'), 3.82 (dd, $^2J_{1,1'}$ = 12.0 Hz, $^3J_{1,2}$ = 2.8 Hz, 1 H, 1-H), 3.61 (dd, $^3J_{3,2}$ = 9.3 Hz, $^3J_{3,4}$ = 4.6 Hz, 1 H, 3-H), 1.58 (s, 3 H, 7'-H), 1.37 (s, 3 H, 7-H), 0.91 (s, 9 H, 10-H), 0.09 (s, 3 H, 8'-H), 0.08 (s, 3 H, 8-H).

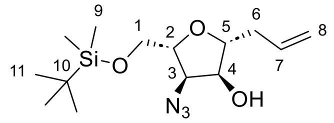
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 113.2 (s, C-6), 104.2 (d, C-5), 80.3 (d, C-4), 78.6 (d, C-2), 61.2 (d, C-3), 60.2 (t, C-1), 26.6 (q, C-7), 26.0 (q, C-10), 18.5 (s, C-9), –5.3 (q, C-8), –5.2 (q, C-8‘).

Optical rotation:	$[\alpha]_D^{20}$= –88.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{14}H_{28}NO_4Si$ $[M-N_2+H]^+$:	302.1782	302.1811

(2*R*,3*S*,4*R*,5*R*)-2-Allyl-4-azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol 55

In a 100 mL Schlenk flask under an atmosphere of nitrogen, azido-sugar **54** (1.17 g, 3.46 mmol) and allyltrimethylsilane (2.20 mL, 13.9 mmol, 4.0 eq.) were dissolved in anhydrous CH_2Cl_2 (35 mL). After cooling to –20 °C, $TiCl_4$ (759 µL, 6.92 mmol, 2.0 eq.) was added dropwise, and the stirring continued for 20 min. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ solution (3.5 mL). After pouring into more sat. $NaHCO_3$ solution, the aqueous phase was extracted once with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 9:1) to give C-furanoside **55** (866 mg, 2.76 mmol, 80%, dr 97:3) as a colorless oil.

TLC: R_f (55) = 0.23 (silica, PE:EtOAc 9:1)



55

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.80 (ddt, $^3J_{7,8'}$ = 17.1 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.65 (d, $^3J_{OH,4}$ = 5.6 Hz, 1 H, 4-OH), 5.08 (ddt, $^3J_{8',7}$ = 17.2 Hz, $^2J_{8',8}$ = 2.2 Hz, $^4J_{8',6}$ = 1.4 Hz, 1 H, 8-H′), 5.01 (ddt, $^2J_{8,8'}$ = 2.3 Hz, $^3J_{8,7}$ = 10.2 Hz, $^4J_{8,6}$ = 1.2 Hz, 1 H, 8-H), 3.93 (ddd, $^3J_{4,3}$ = 5.6 Hz, $^3J_{4,5}$ = 5.6 Hz, $^3J_{4,OH}$ = 5.6 Hz, 1 H, 4-H), 3.76 – 3.70 (m, 2 H, 2-H, 3-H), 3.66 (ddd, $^3J_{5,6}$ = 7.2 Hz, $^3J_{5,4}$ = 5.9 Hz, $^3J_{5,6'}$ = 4.9 Hz, 1 H, 5-H), 3.62 (d, $^3J_{1,2}$ = 3.4 Hz, 2 H, 1-H), 2.31 (dddt, $^2J_{6',6}$ = 14.4 Hz, $^3J_{6',7}$ = 6.5 Hz, $^3J_{6',5}$ = 4.9 Hz, $^4J_{6',8}$ = 1.4 Hz, 1 H, 6-H‘), 2.14 (dddt, $^2J_{6,6'}$ = 14.4 Hz, $^3J_{6,7}$ = 7.1 Hz, $^3J_{6,5}$ = 7.1 Hz, $^4J_{6,8}$ = 1.3 Hz, 1 H, 6-H), 0.87 (s, 9 H, 11-H), 0.09 (s, 3 H, 9‘-H), 0.08 (s, 3 H, 9-H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 134.8 (d, C-7), 116.9 (t, C-8), 81.9 (d, C-5), 80.8 (d, C-2), 74.8 (d, C-4), 63.2 (t, C-1), 62.5 (d, C-3), 37.2 (t, C-6), 25.8 (q, C-11), 18.0 (s, C-10), –5.4 (q, C-9‘), –5.5 (q, C-9).

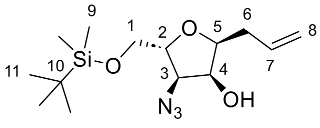
Optical rotation:	$[\alpha]_D^{20}$= –8.0 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{14}H_{28}NO_3Si$ $[M-N_2+H]^+$:	286.1833	286.1838

(2*S*,3*S*,4*R*,5*R*)-2-Allyl-4-azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol 56

In a 25 mL Schlenk tube under an atmosphere of nitrogen, allyltrimethylsilane (965 µL, 6.07 mmol, 4.0 eq.) was added to a 0 °C cold solution of compound **54** (500 mg, 1.52 mmol) in anhydrous

CH_2Cl_2 (10 mL). After stirring for 10 min, $BF_3{\cdot}OEt_2$ (801 µL, 3.04 mmol, 2.0 eq.) was added, and the stirring continued for 30 min. The cooling bath was removed, and the stirring continued for 3 h at room temperature. Another portion of allyltrimethylsilane (965 µL, 6.07 mmol, 4.0 eq.) and $BF_3{\cdot}OEt_2$ (801 µL, 3.04 mmol, 2.0 eq.) were added, and the mixture was stirred for another 2 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution (20 mL) and brine (2.0 mL) before being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was dissolved in anhydrous DMF (1.5 mL) before adding imidazole (124 mg, 1.82 mmol, 1.2 eq.) and TBS-Cl (137 mg, 911 µmol, 0.6 eq.) at room temperature. After stirring for 24 h, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 20% EtOAc) to give C-furanoside **56** (220 mg, 702 µmol, 46%, dr 99:1) and compound **60a** (70.0 mg, 164 µmol, 11%, dr 96:4) as a colorless oil.

TLC: R_f (56) = 0.35 (silica, pentane:EtOAc 8:2)



56

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 5.77 (ddt, $^3J_{7,8'}$ = 17.2 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.61 (d, $^3J_{OH,4}$ = 5.8 Hz, 1 H, 4-OH), 5.09 (ddt, $^3J_{8',7}$ = 17.2 Hz, $^2J_{8',8}$ = 2.2 Hz, $^4J_{8',6}$ = 1.5 Hz, 1 H, 8-H´), 5.00 (ddt, $^3J_{8,7}$ = 10.2 Hz, $^2J_{8,8'}$ = 2.2 Hz, $^4J_{8,6}$ = 1.1 Hz, 1 H, 8-H), 4.15 (ddd, $^3J_{4,OH}$ = 5.8 Hz, $^3J_{4,3}$ = 4.3 Hz, $^3J_{4,5}$ = 2.9 Hz, 1 H, 4-H), 4.04 (dd, $^3J_{3,4}$ = 4.6 Hz, $^3J_{3,2}$ = 3.6 Hz, 1 H, 3-H), 3.89 (ddd, $^3J_{2,1'}$ = 8.1 Hz, $^3J_{2,1}$ = 3.9 Hz, $^3J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 3.69 (dd, $^2J_{1,1'}$ = 11.2 Hz, $^3J_{1,2}$ = 3.9 H, 1 H, 1-H), 3.67 – 3.62 (m, 2 H, 5-H, 1-H‘), 2.27 (m, 2 H, 6-H), 0.86 (s, 9 H, 11-H), 0.05 (s, 3 H, 9‘-H), 0.04 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 135.2 (d, C-7), 116.7 (t, C-8), 80.8 (d, C-5), 78.2 (d, C-2), 72.6 (d, C-4), 63.3 (t, C-1), 62.5 (d, C-3), 33.9 (t, C-6), 25.8 (q, C-11), 18.0 (s, C-10), –5.35 (q, C-9‘), –5.40 (q, C-9).

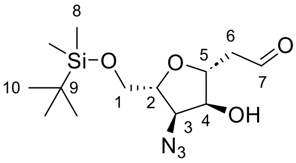
Optical rotation: $[\alpha]_D^{20}$= +18.4 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{14}H_{28}N_3O_3Si$ $[M+H]^+$:	314.1894	314.1893

2-((2*R*,3*S*,4*R*,5*R*)-4-Azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxytetrahydrofuran-2-yl)acetaldehyde 57

In a 25 mL 2-neck flask, a solution of C-furanoside **55** (90.0 mg, 287 µmol) in anhydrous CH_2Cl_2 (8.0 mL) was cooled to –78 °C. The solution was saturated with ozone until the reaction mixture turned blue (10 s). After stirring for another 30 s, the solution was degassed with N_2. Triphenylphosphine (75.0 mg, 287 µmol, 1.0 eq.) was added at –78 °C before the cooling bath was removed, and the stirring continued for 20 min. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica, PE:EtOAc 75:25) to give the aldehyde **57** (42.0 mg, 133 µmol, 46%) as a colorless resin.

TLC: R_f (57) = 0.45 (silica, pentane:EtOAc 6:4)



57

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 9.65 (dd, $^3J_{7,6}$ = 3.0 Hz, $^3J_{7,6'}$ = 1.5 Hz, 1 H, 7-H), 5.78 (d, $^3J_{OH,4}$ = 5.5 Hz, 1 H, 4-OH), 4.11 (ddd, $^3J_{5,6}$ = 8.4 Hz, $^3J_{5,4}$ = 6.5 Hz, $^3J_{5,6'}$ = 4.0 Hz, 1 H, 5-H), 4.02 (m, 1 H, 4-H), 3.83 (dd, $^3J_{3,4}$ = 5.6 Hz, $^3J_{3,2}$ = 4.3 Hz, 1 H, 3-H), 3.77 (dt, $^3J_{2,3}$ = 4.0 Hz, $^3J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 3.61 (m, 2 H, 1-H), 2.70 (ddd, $^2J_{6',6}$ = 16.2 Hz, $^3J_{6',5}$ = 4.0 Hz, $^3J_{6',7}$ = 1.5 Hz, 1 H, 6-H'), 2.44 (ddd, $^2J_{6,6'}$ = 16.0 Hz, $^3J_{6,5}$ = 8.7 Hz, $^3J_{6,7}$ = 2.4 Hz, 1 H, 6-H), 0.87 (s, 9 H, 10-H), 0.04 (s, 3 H, 8'-H), 0.03 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 201.5 (d, C-7), 81.5 (d, C-2), 77.2 (d, C-5), 75.2 (d, C-4), 63.2 (t, C-1), 62.5 (d, C-3), 46.7 (t, C-6), 25.8 (q, C-10), 17.9 (s, C-9), –5.4 (q, C-8'), –5.5 (q, C-8).

Optical rotation: $[\alpha]_D^{20}$ = –80.3 (c = 0.5, CHCl$_3$)

HRMS (CI):	calculated	found
$C_{13}H_{26}NO_4Si$ [M-N$_2$+H]$^+$:	288.1626	288.1631

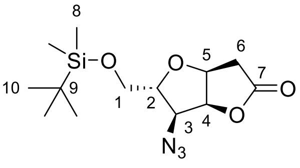
(3a*S*,5*R*,6*S*,6a*S*)-6-Azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3*H*)-one 59

In a 25 mL 2-neck flask, a solution of C-furanoside **56** (85.0 mg, 271 µmol) in anhydrous CH_2Cl_2 (6.0 mL) was cooled to –78 °C. The solution was saturated with ozone until the reaction mixture turned blue (10 s). After stirring for another 30 s, the solution was degassed with N_2. Dimethylsulfide (201 µL, 2.71 mmol, 10 eq.) was added at –70 °C and the reaction mixture was stirred for 18 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 40% EtOAc) to give the hemiacetal **58** (68.0 mg, 216 µmol, 79%) as a colorless resin.

The above-prepared hemiacetal **58** (50.0 mg, 159 µmol) was dissolved in MeCN (1.2 mL). A solution of NaH_2PO_4 (3.8 mg, 31.7 µmol, 0.2 eq.) in H_2O (100 µL) and H_2O_2 (16.0 µL, 159 µmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (28.7 mg, 254 µmol, 1.6 eq.) in H_2O (100 µL) was added dropwise. The resulting solution was stirred for 16 h at room temperature. After the addition of Na_2SO_4 (15 mg) and brine (2.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (1.0 mL) before pTsOH

(3.0 mg, 15.8 µmol, 10mol%) was added. The resulting solution was stirred for 2 h at room temperature. After concentration in vacuo, the crude was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give the lactone **59** (32.3 mg, 103 µmol, 65%) as a colorless resin.

TLC: R_f (59) = 0.17 (silica, pentane:EtOAc 8:2)



59

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.09 (dd, $^3J_{4,5}$ = 4.6 Hz, $^3J_{4,3}$ = 4.6 Hz, 1 H, 4-H), 4.86 (ddd, $^3J_{5,6}$ = 6.1 Hz, $^3J_{5,4}$ = 4.5 Hz, $^3J_{5,6'}$ = 1.4 Hz, 1 H, 5-H), 4.04 (dd, $^3J_{3,2}$ = 8.0 Hz, $^3J_{3,4}$ = 4.7 Hz, 1 H, 3-H), 4.04 (dt, $^3J_{2,3}$ = 8.0 Hz, $^3J_{2,1}$ = 2.6 Hz, 1 H, 2-H), 3.89 (dd, $^2J_{1,1'}$ = 11.8 Hz, $^3J_{1,2}$ = 2.5 Hz, 1 H, 1-H), 3.75 (dd, $^2J_{1',1}$ = 11.8 Hz, $^3J_{1',2}$ = 2.7 Hz, 1 H, 1-H‘), 2.80 (dd, $^2J_{6,6'}$ = 18.8 Hz, $^3J_{6,5}$ = 6.2 Hz, 1 H, 6-H), 2.71 (dd, $^2J_{6',6}$ = 18.6 Hz, $^3J_{6',5}$ = 1.2 Hz, 1 H, 6-H‘), 0.91 (s, 9 H, 10-H), 0.09 (s, 3 H, 8‘-H), 0.08 (s, 3 H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.7 (s, C-7), 83.3 (d, C-4), 80.8 (d, C-2), 77.2 (d, C-5), 62.0 (t, C-1), 61.6 (d, C-3), 36.8 (t, C-6), 26.0 (q, C-10), 18.5 (s, C-9), –5.2 (q, C-8‘), –5.4 (q, C-8).

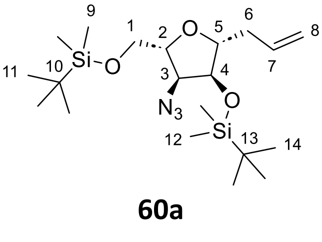
Optical rotation: $[\alpha]_D^{20}$= –156.3 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{13}H_{24}O_4N_3Si$ $[M+H]^+$:	314.1531	314.1511

(((2*R*,3*S*,4*S*,5*R*)-5-Allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methoxy)-(*tert*-butyl)dimethylsilane 60a

Imidazole (541 mg, 7.94 mmol, 3.0 eq.) and TBS-Cl (599 mg, 3.97 mmol, 1.5 eq.) were subsequently added to a 0 °C cold solution of C-furanoside **55** (830 mg, 2.65 mmol) in anhydrous DMF (12 mL). The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, pentane:EtOAc 97:3) to give compound **60a** (1.03 g, 2.40 mmol, 91%) as a colorless oil.

TLC: R_f (60a) = 0.72 (silica, PE:EtOAc 9:1)



60a

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 5.85 (ddt, $^{3}J_{7,8'}$ = 17.1 Hz, $^{3}J_{7,8}$ = 10.2 Hz, $^{3}J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.11 – 5.06 (m, 2 H, 8-H), 4.02 – 3.96 (m, 2 H, 2-H, 4-H), 3.84 (ddd, $^{3}J_{5,6}$ = 7.2 Hz, $^{3}J_{5,4}$ = 5.7 Hz, $^{3}J_{5,6'}$ = 4.7 Hz, 1 H, 5-H), 3.75 (dd, $^{3}J_{1',1}$ = 11.3 Hz, $^{3}J_{1',2}$ = 3.3 Hz, 1 H, 1-H‘), 3.70 (dd, $^{2}J_{1,1'}$ = 11.3 Hz, $^{3}J_{1,2}$ = 3.1 Hz, 1 H, 1-H), 3.66 (dd, $^{3}J_{3,4}$ = 5.3 Hz, $^{3}J_{3,2}$ = 5.3 Hz, 1 H, 3-H), 2.38 (dddt, $^{2}J_{6',6}$ = 14.2 Hz, $^{3}J_{6',7}$ = 6.3 Hz, $^{3}J_{6',5}$ = 4.7 Hz, $^{4}J_{6',8}$ = 1.5 Hz, 1 H, 6-H‘), 2.20 (dddt, $^{2}J_{6,6'}$ = 14.4 Hz, $^{3}J_{6,7}$ = 7.4 Hz, $^{3}J_{6,5}$ = 7.4 Hz, $^{4}J_{6,8}$ = 1.4 Hz, 1 H, 6-H), 0.94 (s, 9 H, 14-H), 0.92 (s, 9 H, 11-H), 0.15 (s, 3 H, 12‘-H), 0.12 (s, 3 H, 12-H), 0.09 (s, 3 H, 9‘-H), 0.08 (s, 3 H, 9-H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ = 134.4 (d, C-7), 117.5 (t, C-8), 82.7 (d, C-5), 81.6 (d, C-2), 76.6 (d, C-4), 63.3 (t, C-1), 62.9 (d, C-3), 37.6 (t, C-6), 26.1 (q, C-14), 25.9 (q, C-11), 18.5 (s, C-13), 18.2 (s, C-10), –4.4 (q, C-12‘), –4.7 (q, C-12), –5.2 (q, C-9‘), –5.4 (q, C-9).

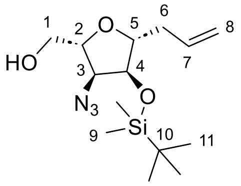
Optical rotation: $[\alpha]_D^{20}$= –7.0 (c = 1.0, CHCl$_3$)

HRMS (CI):	calculated	found
C$_{20}$H$_{42}$N$_3$O$_3$Si$_2$ [M+H]$^+$:	428.2759	428.2758

((2*R*,3*S*,4*S*,5*R*)-Allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl) methanol 60b

A solution of compound **60a** (1.02 g, 2.26 mmol) in anhydrous MeOH (16 mL) was cooled to 0 °C. After the addition of PyBr$_3$ (36.1 mg, 113 µmol, 5mol%), the reaction mixture was stirred for 8 h while slowly reaching room temperature. The solution was diluted with EtOAc and washed with 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution, and brine. The organic layer was dried with MgSO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 8:2) to give the primary alcohol **60b** (580 mg, 1.85 mmol, 82%) as a colorless oil.

TLC: R$_f$ (60b) = 0.10 (silica, PE:EtOAc 9:1)



60b

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 5.82 (ddt, $^{3}J_{7,8'}$ = 17.2 Hz, $^{3}J_{7,8}$ = 10.3 Hz, $^{3}J_{7,6}$ = 7.0 Hz, 1 H, 7-H), 5.17 – 5.11 (m, 2 H, 8-H), 4.05 – 3.99 (m, 2 H, 2-H, 4-H), 3.92 – 3.85 (m, 2 H, 1-H‘, 5-H), 3.64 (ddd, $^{2}J_{1,1'}$ = 11.9 Hz, $^{3}J_{1,OH}$ = 8.4 Hz, $^{3}J_{1,2}$ = 3.1 Hz, 1 H, 1-H), 3.58 (dd, $^{3}J_{3,2}$ = 6.8 Hz, $^{3}J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 2.39 (dddt, $^{2}J_{6',6}$ = 14.6 Hz, $^{3}J_{6',7}$ = 6.6 Hz, $^{3}J_{6',5}$ = 5.0 Hz, $^{4}J_{6',8}$ = 1.4 Hz, 1 H, 6-H‘), 2.24 (dddt, $^{2}J_{6,6'}$ = 14.3 Hz, $^{3}J_{6,7}$ = 7.0 Hz, $^{3}J_{6,5}$ = 7.0 Hz, $^{4}J_{6,8}$ = 1.3 Hz, 1 H, 6-H), 1.87 (m, 1 H, 1-OH), 0.95 (s, 9 H, 11-H), 0.16 (s, 3 H, 9‘-H), 0.13 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 133.7 (d, C-7), 118.3 (t, C-8), 83.9 (d, C-5), 80.8 (d, C-2), 76.5 (d, C-4), 62.1 (t, C-1), 61.6 (d, C-3), 37.6 (t, C-6), 25.9 (q, C-11), 18.2 (s, C-10), –4.5 (q, C-9‘), –4.7 (q, C-9).

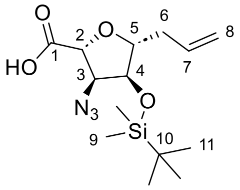
Optical rotation: $[\alpha]_D^{20}$= –3.4 (c = 1.0, CHCl$_3$)

HRMS (CI):	calculated	found
$C_{14}H_{30}NO_3Si$ $[M-N_2+3H]^+$:	288.1989	288.1995

(2*R*,3*S*,4*S*,5*R*)-5-Allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylic acid 60c

A solution of DMSO (380 µL, 5.36 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (1.2 mL) was added dropwise to a −78 °C cold solution of oxalyl dichloride (235 µL, 2.68 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (4.8 mL) keeping the temperature below −70 °C. After complete addition, the mixture was stirred at −60 to −70 °C for 30 min. A solution of primary alcohol **60** (560 mg, 1.79 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was added dropwise while keeping the temperature below −60 °C. After stirring for another 45 min, a solution of DIPEA (1.56 mL, 8.93 mmol, 5.0 eq.) in anhydrous CH_2Cl_2 (1.2 mL) was added dropwise while keeping the temperature around −60 °C. The stirring was continued for 30 min before warming to 0 °C. After the addition of 1.0 M HCl_{aq} (20 mL), the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were washed with phosphate buffer (pH 7), dried with $MgSO_4$, and concentrated in vacuo to give the crude aldehyde.

The above-prepared crude aldehyde was dissolved in MeCN (12 mL). A solution of NaH_2PO_4 (55.7 mg, 357 µmol, 0.2 eq.) in H_2O (1.2 mL) and H_2O_2 (182 µL, 1.79 mmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (323 mg, 2.86 mmol, 1.6 eq.) in H_2O (1.2 mL) was added dropwise. The resulting solution was stirred for 16 h while slowly reaching room temperature. After the addition of Na_2SO_4 (50 mg) and brine (2.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give carboxylic acid **60c** (589 mg, 1.69 mmol, 95%) as a colorless resin.



60c

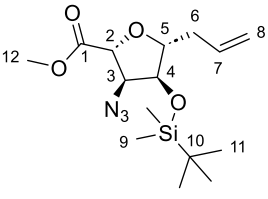
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddt, $^3J_{7,8'}$ = 16.6 Hz, $^3J_{7,8}$ = 10.5 Hz, $^3J_{7,6}$ = 7.0 Hz, 1 H, 7-H), 5.24 – 5.17 (m, 2 H, 8-H), 4.46 (d, $^3J_{2,3}$ = 4.7 Hz, 1 H, 2-H), 4.08 – 4.01 (m, 2 H, 4-H, 5-H), 3.93 (dd, $^3J_{3,2}$ = 4.7 Hz, $^3J_{3,4}$ = 4.7 Hz, 1 H, 3-H), 2.46 (m, 1 H, 6-H'), 2.32 (m, 1 H, 6-H), 0.94 (s, 9 H, 11-H), 0.16 (s, 3 H, 9'-H), 0.13 (s, 3 H, 9-H).

Methyl (2*R*,3*S*,4*S*,5*R*)-5-allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylate 61

K_2CO_3 (367 mg, 2.65 mmol, 1.6 eq.) and MeI (332 µL, 5.30 mmol, 3.2 eq.) were added to a solution of carboxylic acid **60c** (579 mg, 1.66 mmol, 94wt%) in anhydrous DMF (12 mL). The resulting suspension was stirred for 18 h at room temperature. After full conversion, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine.

The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 9:1) to give compound **61** (457 mg, 1.34 mmol, 81%) as a colorless oil.

TLC: R_f (61) = 0.50 (silica, PE:EtOAc 8:2)



61

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.86 (ddt, $^3J_{7,8'}$ = 17.2 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.18 – 5.11 (m, 2 H, 8-H), 4.45 (d, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 4.08 (dd, $^3J_{4,3}$ = 5.2 Hz, $^3J_{4,5}$ = 5.2 Hz, 1 H, 4-H), 3.97 (ddd, $^3J_{5,6}$ = 6.8 Hz, $^3J_{5,4}$ = 5.2 Hz, $^3J_{5,6'}$ = 5.2 Hz, 1 H, 5-H), 3.81 (s, 3 H, 12-H), 3.80 (dd, $^3J_{3,2}$ = 5.5 Hz, $^3J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 2.41 (dddt, $^2J_{6',6}$ = 14.8 Hz, $^3J_{6',7}$ = 6.8 Hz, $^3J_{6',5}$ = 5.3 Hz, $^4J_{6',8}$ = 1.4 Hz, 1 H, 6-H'), 2.34 (dddt, $^2J_{6,6'}$ = 14.3 Hz, $^3J_{6,7}$ = 7.0 Hz, $^3J_{6,5}$ = 7.0 Hz, $^4J_{6,8}$ = 1.3 Hz, 1 H, 6-H), 0.94 (s, 9 H, 11-H), 0.15 (s, 3 H, 9'-H), 0.12 (s, 3 H, 9-H).

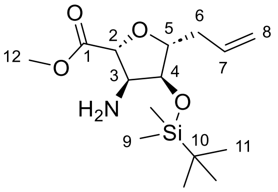
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.9 (s, C-1), 133.6 (d, C-7), 118.2 (t, C-8), 84.2 (d, C-5), 78.8 (d, C-2), 76.2 (d, C-4), 64.9 (d, C-3), 52.7 (q, C-12), 37.4 (t, C-6), 25.9 (q, C-11), 18.2 (s, C-10), –4.4 (q, C-9'), –4.7 (q, C-9).

Optical rotation:	$[\alpha]_D^{20}$= –31.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{15}H_{28}NO_4Si$ $[M-N_2+H]^+$:	314.1782	314.1802

Methyl (2*R*,3*S*,4*S*,5*R*)-5-allyl-3-amino-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylate 62

Triphenylphosphine (401 mg, 1.53 mmol, 1.2 eq.) was added to a solution of compound **61** (435 mg, 1.27 mmol) in THF:H_2O (10.4 mL, 25:1). The reaction mixture was stirred for 16 h at room temperature before another portion of triphenylphosphine (16.7 mg, 64.0 µmol, 0.05 eq.) was added. After another 2 h at room temperature, the reaction mixture was acidified with 0.1 M HCl_{aq}. The mixture was washed twice with Et_2O (discard) before sat. $NaHCO_3$ solution was added. The aqueous layer was extracted four times with Et_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give amine **62** (360 mg, 1.14 mmol, 90%) as a colorless resin.

TLC: R_f (62) = 0.22 (silica, PE:EtOAc 7:3)



62

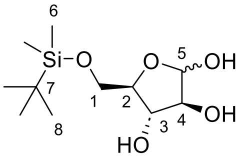
^{1}H-NMR (400 MHz, CDCl$_3$): δ = 5.85 (ddt, $^3J_{7,8'}$ = 17.2 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.1 Hz, 1 H, 7-H), 5.18 – 5.11 (m, 2 H, 8-H), 4.14 (d, $^3J_{2,3}$ = 8.3 Hz, 1 H, 2-H), 4.01 – 3.93 (m, 2 H, 4-H, 5-H), 3.80 (s, 3 H, 12-H), 3.36 (dd, $^3J_{3,2}$ = 8.2 Hz, $^3J_{3,4}$ = 4.9 Hz, 1 H, 3-H), 2.38 (m, 1 H, 6-H'), 2.30 (dddt, $^2J_{6,6'}$ = 14.1 Hz, $^3J_{6,7}$ = 6.8 Hz, $^3J_{6,5}$ = 6.8 Hz, $^4J_{6,8}$ = 1.2 Hz*,* 1 H, 6-H), 0.93 (s, 9 H, 11-H), 0.11 (s, 3 H, 9'-H), 0.10 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 172.5 (s, C-1), 134.1 (d, C-7), 118.0 (t, C-8), 85.9 (d, C-5), 82.3 (d, C-2), 76.4 (d, C-4), 58.6 (d, C-3), 52.3 (q, C-12), 38.5 (t, C-6), 26.0 (q, C-11), 18.2 (s, C-10), –4.3 (q, C-9'), –4.5 (q, C-9).

(3*S*,4*S*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2,3,4-triol[158] 63a

Preparation according to Guo *et al.*[158]

TLC: R$_f$ (63a) = 0.14 (silica, PE:EtOAc 1:1)



63a

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 6.16 (d, $^3J_{OH,5}$ = 5.5 Hz, 1 H, 5-OH), 5.20 (d, $^3J_{OH,4}$ = 4.9 Hz, 1 H, 4-OH), 5.09 (d, $^3J_{OH,3}$ = 5.5 Hz, 1 H, 3-OH), 4.89 (m, 1 H, 5-H), 3.77 (ddd, $^3J_{2,3}$ = 7.3 Hz, $^3J_{2,1}$ = 5.6 Hz, $^3J_{2,1'}$ = 2.8 Hz, 1 H, 2-H), 3.70 (dd, $^2J_{1',1}$ = 11.3 Hz, $^3J_{1',2}$ = 2.9 Hz, 1 H, 1-H'), 3.67 (m, 1 H, 4-H), 3.61 (m, 1 H, 3-H), 3.57 (dd, $^2J_{1,1'}$ = 11.3 Hz, $^3J_{1,2}$ = 5.7 Hz, 1 H, 1-H), 0.87 (s, 9 H, 8-H), 0.04 (s, 6 H, 6-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 101.9 (d, C-5), 82.7 (d, C-4), 82.5 (d, C-2), 76.2 (d, C-3), 63.5 (t, C-1), 25.9 (q, C-8), 18.1 (s, C-7), –5.2 (q, C-6).

Selected anomer signals:

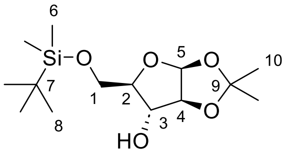
^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 6.03 (d, $^3J_{OH,5}$ = 6.5 Hz, 1 H, 5-OH), 5.12 (d, $^3J_{OH,4}$ = 5.1 Hz, 1 H, 4-OH), 5.00 (m, 1 H, 5-H), 4.72 (d, $^3J_{OH,3}$ = 6.4 Hz, 1 H, 3-OH).

Optical rotation:	$[\alpha]_D^{20}$= +10.9 (c = 1.0, MeOH)	
HRMS (CI):	calculated	found
$C_{11}H_{23}O_4Si$ [M-OH]$^+$:	247.1360	247.1366

(3aS,5R,6R,6aS)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol[158] 63b

Preparation according to Guo *et al.*[158].

TLC: R_f (63b) = 0.58 (silica, PE:EtOAc 1:1)



63b

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 5.81 (d, $^3J_{5,4}$ = 4.0 Hz, 1 H, 5-H), 5.43 (m, 1 H, 3-OH), 4.43 (d, $^3J_{4,5}$ = 4.1 Hz, 1 H, 4-H), 4.03 (m, 1 H, 3-H), 3.82 (ddd, $^3J_{2,1}$ = 7.6 Hz, $^3J_{2,1'}$ = 5.7 Hz, $^3J_{2,3}$ = 2.2 Hz, 1 H, 2-H), 3.72 (dd, $^2J_{1,1'}$ = 10.3 Hz, $^3J_{1,2}$ = 7.2 Hz, 1 H, 1-H), 3.62 (dd, $^2J_{1',1}$ = 10.3 Hz, $^3J_{1',2}$ = 5.8 Hz, 1 H, 1-H‘), 1.41 (s, 3 H, 10-H), 1.23 (s, 3 H, 10‘-H), 0.91 (s, 9 H, 8-H), 0.09 (s, 3 H, 6-H), 0.08 (s, 3 H, 6‘-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 111.1 (s, C-9), 105.3 (d, C-5), 87.8 (d, C-2), 86.7 (d, C-4), 74.3 (d, C-3), 63.0 (t, C-1), 26.7 (q, C-10), 25.8 (q, C-8), 18.1 (s, C-7), –5.2 (q, C-6), –5.3 (q, C-6‘).

Optical rotation: $[\alpha]_D^{20}$= –2.7 (c = 1.0, CHCl$_3$)

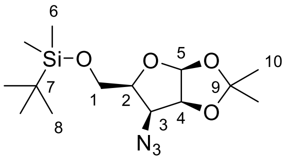
HRMS (ESI):	calculated	found
$C_{14}H_{28}O_5SiNa$ [M+Na]$^+$:	327.1598	327.1603

(((3a*S*,5*S*,6*S*,6a*S*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)(*tert*-butyl)dimethylsilane 64

Triflic anhydride (8.32 mL, 49.3 mmol, 1.5 eq.) was added dropwise to a –15 °C cold solution of monoacetonide **63b** (10.0 g, 32.8 mmol), and pyridine (7.97 mL, 99.0 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (164 mL). The reaction mixture was stirred for 1 h at –10 °C. After full conversion, the mixture was poured into ice water, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with 1.0 M HCl_{aq} and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give the crude triflate.

The above-prepared crude triflate was dissolved in anhydrous DMF (120 mL). After the addition of NaN_3 (10.7 g, 164 mmol, 5.0 eq.), the suspension was stirred for 2 h at 100 °C. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 20%) to give the azido-sugar **64** (7.79 g, 23.6 mmol, 72%) as a colorless oil.

TLC: R_f (64) = 0.36 (silica, PE:EtOAc 8:2)



64

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.76 (d, $^{3}J_{5,4}$ = 4.2 Hz, 1 H, 5-H), 4.77 (dd, $^{3}J_{4,3}$ = 5.6 Hz, $^{3}J_{4,5}$ = 4.2 Hz, 1 H, 4-H), 4.17 (ddd, $^{3}J_{2,3}$ = 6.6 Hz, $^{3}J_{2,1'}$ = 6.6 Hz, $^{3}J_{2,1}$ = 5.5 Hz, 1 H, 2-H), 4.12 (dd, $^{3}J_{3,2}$ = 6.7 Hz, $^{3}J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 4.05 (dd, $^{2}J_{1',1}$ = 10.4 Hz, $^{3}J_{1',2}$ = 6.5 Hz, 1 H, 1-H'), 3.83 (dd, $^{2}J_{1,1'}$ = 10.4 Hz, $^{3}J_{1,2}$ = 5.5 Hz, 1 H, 1-H), 1.62 (s, 3 H, 10'-H), 1.37 (s, 3 H, 10-H), 0.91 (s, 9 H, 8-H), 0.10 (s, 3 H, 6'-H), 0.10 (s, 3 H, 6-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 114.5 (s, C-9), 105.0 (d, C-5), 81.8 (d, C-2), 80.4 (d, C-4), 62.8 (t, C-1), 61.7 (d, C-3), 26.6 (q, C-10'), 26.6 (q, C-10), 26.0 (q, C-8), 18.5 (s, C-7), –5.19 (q, C-6), –5.24 (q, C-6').

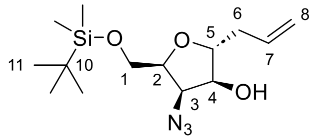
Optical rotation: $[\alpha]_D^{20}$= –53.2 (c = 1.0, $CHCl_3$)

HRMS (ESI):	calculated	found
$C_{14}H_{27}N_3O_4SiNa$ $[M+Na]^+$:	352.1663	352.1660

(2*R*,3*S*,4*R*,5*S*)-2-Allyl-4-azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol 65

In a 100 mL Schlenk flask under an atmosphere of nitrogen, azido-sugar **64** (2.81 g, 8.19 mmol) and allyltrimethylsilane (5.22 mL, 32.8 mmol, 4.0 eq.) were dissolved in anhydrous CH_2Cl_2 (55 mL). After cooling to –20 °C, $TiCl_4$ (1.81 mL, 16.4 mmol, 2.0 eq.) was added dropwise, and the stirring continued for 15 min. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ solution (10 mL). After pouring into more sat. $NaHCO_3$ solution, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 9:1) to give C-furanoside **65** (2.05 g, 6.54 mmol, 80%, dr > 99:1) as a colorless oil.

TLC: R_f (65) = 0.25 (silica, PE:EtOAc 9:1)



65

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 5.80 (ddt, $^{3}J_{7,8'}$ = 17.2 Hz, $^{3}J_{7,8}$ = 10.2 Hz, $^{3}J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.65 (d, $^{3}J_{OH,4}$ = 5.6 Hz, 1 H, 4-OH), 5.08 (ddt, $^{3}J_{8',7}$ = 17.3 Hz, $^{2}J_{8',8}$ = 2.3 Hz, $^{4}J_{8',6}$ = 1.5 Hz, 1 H, 8-H'), 5.03 (ddt, $^{3}J_{8,7}$ = 10.2 Hz, $^{2}J_{8,8'}$ = 2.3 Hz, $^{4}J_{8,6}$ = 1.1 Hz, 1 H, 8-H), 4.10 (ddd, $^{3}J_{4,5}$ = 8.2 Hz, $^{3}J_{4,3}$ = 5.2 Hz, $^{3}J_{4,OH}$ = 5.2 Hz, 1 H, 4-H), 4.04 (dd, $^{3}J_{3,4}$ = 4.7 Hz, $^{3}J_{3,2}$ = 3.6 Hz, 1 H, 3-H), 3.98 (ddd, $^{3}J_{2,1}$ = 6.4 Hz, $^{3}J_{2,1'}$ = 6.4 Hz, $^{3}J_{2,3}$ = 3.8 Hz, 1 H, 2-H), 3.68 (dd, $^{2}J_{1,1'}$ = 10.3 Hz, $^{3}J_{1,2}$ = 6.5 H, 1 H, 1-H), 3.65 (m, 1 H, 5-H), 3.59 (dd, $^{2}J_{1',1}$ = 10.3 Hz, $^{3}J_{1',2}$ = 6.2 H, 1 H, 1-H'), 2.34 (m, 1 H, 6-H'), 2.16 (dddt, $^{2}J_{6,6'}$ = 14.5 Hz,

$^3J_{6,7}$ = 7.3 Hz, $^3J_{6,5}$ = 7.3 Hz, $^4J_{6,8}$ = 1.3 Hz, 1 H, 6-H), 0.86 (s, 9 H, 11-H), 0.05 (s, 3 H, 9'-H), 0.04 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 134.9 (d, C-7), 116.9 (t, C-8), 79.5 (d, C-5), 78.1 (d, C-2), 76.0 (d, C-4), 64.9 (d, C-3), 62.2 (t, C-1), 37.1 (t, C-6), 25.7 (q, C-11), 17.9 (s, C-10), –5.3 (q, C-9'), –5.5 (q, C-9).

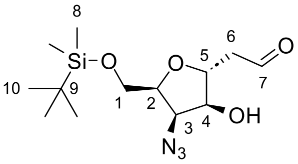
Optical rotation: $[\alpha]_D^{20}$ = –3.4 (c = 2.0, CHCl$_3$)

HRMS (CI):	calculated	found
$C_{14}H_{28}O_3N_3Si$ [M+H]$^+$:	314.1894	314.1900

2-((2*R*,3*S*,4*R*,5*S*)-4-Azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxytetrahydrofuran-2-yl)acetaldehyde 66

In a 25 mL 2-neck flask, a solution of C-furanoside **65** (90.0 mg, 287 µmol) in anhydrous CH$_2$Cl$_2$ (6.0 mL) was cooled to –78 °C. The solution was saturated with ozone until the reaction mixture turned blue (10 s). After stirring for another 30 s, the solution was degassed with N$_2$. Dimethylsulfide (212 µL, 2.87 mmol, 10 eq.) was added at –70 °C and the reaction mixture was stirred for 18 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 40% EtOAc) to give the aldehyde **66** (57.0 mg, 181 µmol, 63%) as a colorless resin.

TLC: R$_f$ (66) = 0.35 (silica, pentane:EtOAc 6:4)



66

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 9.77 (dd, $^3J_{7,6}$ = 2.0 Hz, $^3J_{7,6'}$ = 1.5 Hz, 1 H, 7-H), 4.28 – 4.23 (m, 2 H, 3-H, 5-H), 4.20 (ddd, $^3J_{2,1}$ = 6.5 Hz, $^3J_{2,3}$ = 5.4 Hz, $^3J_{2,1'}$ = 4.1 Hz, 1 H, 2-H), 4.12 (ddd, $^3J_{4,OH}$ = 9.4 Hz, $^3J_{4,5}$ = 5.7 Hz, $^3J_{4,3}$ = 5.7 Hz, 1 H, 4-H), 3.81 (dd, $^2J_{1,1'}$ = 10.5 Hz, $^3J_{1,2}$ = 6.5 Hz, 1 H, 1-H), 3.75 (dd, $^2J_{1',1}$ = 10.5 Hz, $^3J_{1',2}$ = 4.1 Hz, 1 H, 1-H'), 3.56 (d, $^3J_{OH,4}$ = 9.7 Hz, 1 H, 4-OH), 2.74 (m, 1 H, 6-H'), 2.70 (m, 1 H, 6-H), 0.92 (s, 9 H, 10-H), 0.12 (s, 3 H, 8'-H), 0.11 (s, 3 H, 8-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 200.5 (d, C-7), 79.3 (d, C-2), 78.5 (d, C-5), 76.1 (d, C-4), 64.6 (d, C-3), 62.1 (t, C-1), 47.8 (t, C-6), 26.0 (q, C-10), 18.5 (s, C-9), –5.35 (q, C-8'), –5.42 (q, C-8).

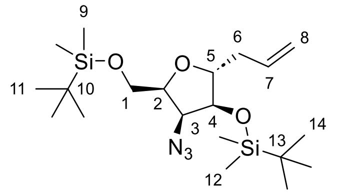
Optical rotation: $[\alpha]_D^{20}$ = –29.5 (c = 1.0, CHCl$_3$)

HRMS (CI):	calculated	found
$C_{13}H_{26}O_4NSi$ [M-N$_2$+H]$^+$:	288.1626	288.1622

(((2*S*,3*S*,4*S*,5*R*)-5-Allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane 67a

Imidazole (562 mg, 8.26 mmol, 2.8 eq.) and TBS-Cl (623 mg, 4.13 mmol, 1.4 eq.) were subsequently added to a 0 °C cold solution of C-furanoside **65** (925 mg, 2.95 mmol) in anhydrous DMF (15 mL). The reaction mixture was stirred for 16 h while slowly reaching room temperature. Another portion of TBS-Cl (311 mg, 2.06 mmol, 0.7 eq.) was added, and the stirring continued for 4 h. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, pentane:EtOAc 5% to 20% EtOAc) to give compound **67a** (887 mg, 2.07 mmol, 70%, 97%brsm) as a colorless oil.

TLC: R_f (67a) = 0.71 (silica, PE:EtOAc 8:2)



67a

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.85 (dddd, $^3J_{7,8'}$ = 17.8 Hz, $^3J_{7,8}$ = 10.3 Hz, $^3J_{7,6}$ = 7.6 Hz, $^3J_{7,6'}$ = 6.1 Hz, 1 H, 7-H), 5.14 (m, 1 H, 8-H), 5.10 (m, 1 H, 8-H‘), 4.13 (dd, $^3J_{4,5}$ = 8.1 Hz, $^3J_{4,3}$ = 4.7 Hz, 1 H, 4-H), 4.05 (ddd, $^3J_{2,1'}$ = 8.0 Hz, $^3J_{2,1}$ = 5.6 Hz, $^3J_{2,3}$ = 3.7 Hz, 1 H, 2-H), 3.90 – 3.85 (m, 2 H, 3-H, 5-H), 3.81 (dd, $^2J_{1',1}$ = 9.9 Hz, $^3J_{1',2}$ = 8.0 Hz, 1 H, 1-H‘), 3.73 (dd, $^2J_{1,1'}$ = 9.8 Hz, $^3J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 2.46 (m, 1 H, 6-H‘), 2.19 (dddt, $^2J_{6,6'}$ = 14.5 Hz, $^3J_{6,7}$ = 7.8 Hz, $^3J_{6,5}$ = 6.8 Hz, $^4J_{6,8}$ = 1.2 Hz, 1 H, 6-H), 0.95 (s, 9 H, 14-H), 0.90 (s, 9 H, 11-H), 0.16 (s, 3 H, 12‘-H), 0.13 (s, 3 H, 12-H), 0.09 (s, 3 H, 9‘-H), 0.08 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 134.2 (d, C-7), 117.8 (t, C-8), 80.3 (d, C-5), 79.0 (d, C-2), 77.2 (d, C-4), 65.5 (d, C-3), 62.1 (t, C-1), 37.1 (t, C-6), 26.0 (q, C-14), 25.8 (q, C-11), 18.5 (s, C-13), 18.1 (s, C-10), –4.3 (q, C-12‘), –4.7 (q, C-12), –5.26 (q, C-9‘), –5.32 (q, C-9).

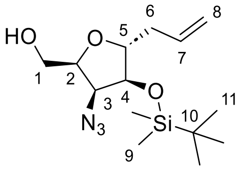
Optical rotation: $[\alpha]_D^{20}$ = –12.3 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{20}H_{42}N_3O_3Si_2$ $[M+H]^+$:	428.2759	428.2767

((2*S*,3*S*,4*S*,5*R*)-Allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)methanol 67b

A solution of compound **67a** (750 mg, 1.75 mmol) in anhydrous MeOH (12 mL) was cooled to 0 °C. After the addition of $PyBr_3$ (33.0 mg, 88.0 µmol, 5mol%), the reaction mixture was stirred for 2 h at 0 °C and 3 h at room temperature. The solution was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 7:3) to give the primary alcohol **67b** (435 mg, 1.39 mmol, 79%) as a colorless oil.

TLC: R$_f$ (67b) = 0.23 (silica, PE:EtOAc 7:3)



67b

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 5.84 (dddd, $^3J_{7,8'}$ = 17.6 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.5 Hz, $^3J_{7,6'}$ = 6.3 Hz, 1 H, 7-H), 5.15 (m, 1 H, 8-H), 5.12 (m, 1 H, 8-H'), 4.16 – 4.11 (m, 2 H, 2-H, 4-H), 3.98 – 3.94 (m, 2 H, 3-H, 5-H), 3.81 (ddd, $^2J_{1,1'}$ = 11.7 Hz, $^3J_{1,2}$ = 6.1 Hz, $^3J_{1,OH}$ = 4.2 Hz, 1 H, 1-H), 3.75 (ddd, $^2J_{1',1}$ = 11.7 Hz, $^3J_{1',OH}$ = 8.1 Hz, $^3J_{1',2}$ = 5.2 Hz, 1 H, 1-H'), 2.45 (dddt, $^2J_{6',6}$ = 14.6 Hz, $^3J_{6',7}$ = 6.1 Hz, $^3J_{6',5}$ = 4.5 Hz, $^4J_{6',8}$ = 1.6 Hz, 1 H, 6-H'), 2.21 (dddt, $^2J_{6,6'}$ = 15.0 Hz, $^3J_{6,7}$ = 7.2 Hz, $^3J_{6,5}$ = 7.2 Hz, $^4J_{6,8}$ = 1.2 Hz, 1 H, 6-H), 2.04 (dd, $^3J_{OH,1'}$ = 8.1 Hz, $^3J_{OH,1}$ = 5.2 Hz, 1 H, 1-OH), 0.95 (s, 9 H, 11-H), 0.16 (s, 3 H, 9'-H), 0.13 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 133.9 (d, C-7), 118.0 (t, C-8), 81.0 (d, C-5), 78.6 (d, C-2), 77.2 (d, C-4), 64.6 (d, C-3), 62.4 (t, C-1), 37.2 (t, C-6), 25.8 (q, C-11), 18.1 (s, C-10), –4.3 (q, C-9'), –4.7 (q, C-9).

Optical rotation: $[\alpha]_D^{20}$ = –14.2 (c = 1.0, CHCl$_3$)

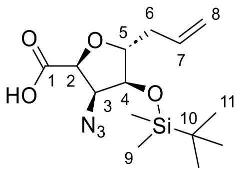
HRMS (CI):	calculated	found
$C_{14}H_{28}O_3N_3Si$ [M+H]$^+$:	314.1894	314.1900

(2*S*,3*S*,4*S*,5*R*)-5-Allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylic acid 67c

A solution of DMSO (283 µL, 3.99 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (800 µL) was added dropwise to a –78 °C cold solution of oxalyl dichloride (174 µL, 2.00 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (3.0 mL) keeping the temperature below –70 °C. After complete addition, the mixture was stirred at –60 to –70 °C for 30 min. A solution of primary alcohol **67b** (417 mg, 1.33 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added dropwise while keeping the temperature below –60 °C. After stirring for another 45 min, a solution of DIPEA (1.16 mL, 6.65 mmol, 5.0 eq.) in anhydrous CH_2Cl_2 (800 µL) was added dropwise while keeping the temperature around –60 °C. The stirring was continued for 30 min before warming to 0 °C. After the addition of 1.0 M HCl_{aq} (12 mL), the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were washed with phosphate buffer (pH 7), dried with $MgSO_4$, and concentrated in vacuo to give the crude aldehyde.

The above-prepared crude aldehyde was dissolved in MeCN (7.5 mL). A solution of NaH_2PO_4 (41.5 mg, 266 µmol, 0.2 eq.) in H_2O (750 µL) and H_2O_2 (136 µL, 1.33 mmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (240 mg, 2.13 mmol, 80wt% 1.6 eq.) in H_2O (750 µL) was added dropwise. The resulting solution was stirred for 16 h while slowly reaching room temperature. After the addition of Na_2SO_4 (176 mg) and brine (8.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give carboxylic acid **67c** (439 mg, 1.23 mmol, 93wt%, 93%) as a colorless resin.

TLC: R_f (67c) = 0.15 (silica, PE:EtOAc 8:2)



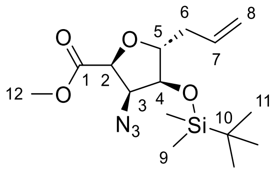
67c

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.81 (dddd, $^3J_{7,8'}$ = 16.5 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.7 Hz, $^3J_{7,6'}$ = 6.1 Hz, 1 H, 7-H), 5.18 – 5.12 (m, 2 H, 8-H), 4.56 (d, $^3J_{2,3}$ = 4.5 Hz, 1 H, 2-H), 4.21 (m, 1 H, 3-H), 4.18 – 4.11 (m, 2 H, 4-H, 5-H), 2.51 (dddd, $^2J_{6,6'}$ = 14.6 Hz, $^3J_{6,7}$ = 7.6 Hz, $^4J_{6,8}$ = 3.4 Hz, $^4J_{6,8'}$ = 1.5 Hz, 1 H, 6-H), 2.23 (m, 1 H, 6-H‘), 0.92 (s, 9 H, 11-H), 0.14 (s, 3 H, 9‘-H), 0.12 (s, 3 H, 9-H).

Methyl (2*S*,3*S*,4*S*,5*R*)-5-allyl-3-azido-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylate 68

K_2CO_3 (241 mg, 1.75 mmol, 1.5 eq.) and MeI (218 µL, 3.49 mmol, 3.0 eq.) were added to a solution of carboxylic acid **67c** (410 mg, 1.16 mmol, 93wt%) in anhydrous DMF (9.0 mL). The resulting suspension was stirred for 18 h at room temperature. After full conversion, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, PE:EtOAc 9:1) to give compound **68** (291 mg, 852 µmol, 73%) as a colorless oil.

TLC: R_f (68) = 0.25 (silica, PE:EtOAc 9:1)



68

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.86 (dddd, $^3J_{7,8'}$ = 17.7 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.7 Hz, $^3J_{7,6}$ = 5.9 Hz, 1 H, 7-H), 5.18 (ddt, $^3J_{8',7}$ = 17.2 Hz, $^2J_{8',8}$ = 1.5 Hz, $^4J_{8',6}$ = 1.5 Hz, 1 H, 8-H‘), 5.14 (m, 1 H, 8-H), 4.62 (d, $^3J_{2,3}$ = 4.6 Hz, 1 H, 2-H), 4.15 – 4.10 (m, 3 H, 3-H, 4-H, 5-H), 3.82 (s, 3 H, 12-H), 2.57 (m, 1 H, 6-H), 2.26 (m, 1 H, 6-H‘), 0.94 (s, 9 H, 11-H), 0.15 (s, 3 H, 9‘-H), 0.14 (s, 3 H, 9-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.5 (s, C-1), 133.2 (d, C-7), 118.4 (t, C-8), 81.1 (d, C-5), 77.9 (d, C-2), 76.2 (d, C-4), 65.2 (d, C-3), 52.5 (q, C-12), 36.1 (t, C-6), 25.8 (q, C-11), 18.1 (s, C-10), –4.2 (q, C-9‘), –4.8 (q, C-9).

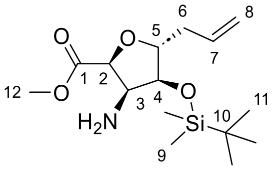
Optical rotation: $[\alpha]_D^{20}$= +17.5 (c = 0.5, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{15}H_{28}O_4N_3Si$ [M+H]$^+$:	342.1844	342.1823

Methyl (2*S*,3*S*,4*S*,5*R*)-5-allyl-3-amino-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylate 69

Triphenylphosphine (249 mg, 949 µmol, 1.2 eq.) was added to a solution of compound **68** (270 mg, 791 µmol) in THF:H_2O (6.2 mL, 25:1). The reaction mixture was stirred for 16 h at room temperature before another portion of triphenylphosphine (10.4 mg, 40.0 µmol, 0.05 eq.) was added. After another 2 h at room temperature, the reaction mixture was acidified with 0.1 M HCl_{aq}. The mixture was washed twice with Et_2O (discard) before sat. $NaHCO_3$ solution was added. The aqueous layer was extracted four times with Et_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give amine **69** (233 mg, 739 µmol, 93%) as a colorless resin.

TLC: R_f (69) = 0.16 (silica, PE:EtOAc 6:4)



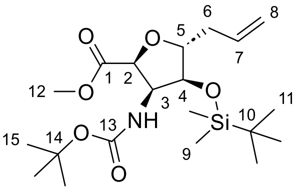
69

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddt, $^3J_{7,8'}$ = 17.2 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.0 Hz, 1 H, 7-H), 5.19 – 5.09 (m, 2 H, 8-H), 4.52 (d, $^3J_{2,3}$ = 6.1 Hz, 1 H, 2-H), 4.13 (dt, $^3J_{5,4}$ = 5.6 Hz, $^3J_{5,6}$ = 5.6 Hz, 1 H, 5-H), 3.93 (dd, $^3J_{4,5}$ = 5.3 Hz, $^3J_{4,3}$ = 5.3 Hz, 1 H, 4-H), 3.80 (s, 3 H, 12-H), 3.63 (dd, $^3J_{3,2}$ = 6.1 Hz, $^3J_{3,4}$ = 5.1 Hz, 1 H, 3-H), 2.44 (dddt, $^2J_{6',6}$ = 14.8 Hz, $^3J_{6',7}$ = 6.8 Hz, $^3J_{6',5}$ = 5.5 Hz, $^4J_{6',8}$ = 1.4 Hz, 1 H, 6-H'), 2.29 (dddt, $^2J_{6,6'}$ = 14.6 Hz, $^3J_{6,7}$ = 7.2 Hz, $^3J_{6,5}$ = 5.8 Hz, $^4J_{6,8}$ = 1.2 Hz, 1 H, 6-H), 0.91 (s, 9 H, 11-H), 0.10 (s, 6 H, 9-H).

Methyl (2*S*,3*S*,4*S*,5*R*)-5-allyl-3-((tert-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-tetrahydrofuran-2-carboxylate 70

Triphenylphosphine (77.0 mg, 293 µmol, 1.0 eq.) was added to a solution of compound **68** (100 mg, 293 µmol) in THF:H_2O (1.56 mL, 25:1). The reaction mixture was stirred for 16 h at room temperature before another portion of triphenylphosphine (7.7 mg, 29.3 µmol, 0.1 eq.) was added. After another 2 h at room temperature, H_2O (600 µL), $NaHCO_3$ (49.0 mg, 583 µmol, 2.0 eq.), and Boc_2O (81.0 µL, 350 µmol, 1.2 eq.) were added at 0 °C. The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed three times with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (silica, PE:EtOAc 9:1) to give Boc-protected amine **70** (119 mg, 286 µmol, 98%) as a colorless oil.

TLC: R_f (70) = 0.44 (silica, PE:EtOAc 8:2)



70

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddt, $^3J_{7,8'}$ = 17.7 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.1 Hz, 1 H, 7-H), 5.39 (d, $^3J_{NH,3}$ = 8.8 Hz, 1 H, 13-NH), 5.17 (ddt, $^3J_{8',7}$ = 17.2 Hz, $^2J_{8',8}$ = 1.6 Hz, $^4J_{8',6}$ = 1.6 Hz, 1 H, 8-H‘), 5.14 (m, 1 H, 8-H), 4.57 (d, $^3J_{2,3}$ = 7.5 Hz, 1 H, 2-H), 4.36 (ddd, $^3J_{3,NH}$ = 8.8 Hz, $^3J_{3,2}$ = 7.5 Hz, $^3J_{3,4}$ = 5.2 Hz, 1 H, 3-H), 4.14 (td, $^3J_{5,6}$ = 6.4 Hz, $^3J_{5,4}$ = 2.6 Hz, 1 H, 5-H), 3.99 (dd, $^3J_{4,3}$ = 5.2 Hz, $^3J_{4,5}$ = 2.6 Hz, 1 H, 4-H), 3.75 (s, 3 H, 12-H), 2.35 (m, 2 H, 6-H), 1.45 (s, 9 H, 15-H), 0.88 (s, 9 H, 11-H), 0.05 (s, 6 H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.9 (s, C-1), 155.4 (s, C-13), 133.5 (d, C-7), 118.5 (t, C-8), 85.8 (d, C-5), 79.8 (s, C-14), 76.1 (d, C-2), 73.8 (d, C-4), 55.1 (d, C-3), 52.2 (q, C-12), 38.2 (t, C-6), 28.5 (q, C-15), 25.7 (q, C-11), 18.1 (s, C-10), –4.7 (q, C-9‘), –4.9 (q, C-9).

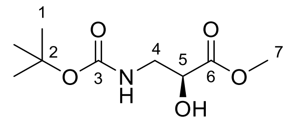
Optical rotation:	$[\alpha]_D^{20}$= +23.7 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{20}H_{38}NO_6Si$ $[M+H]^+$:	416.2463	416.2476

Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxypropanoate[204] 71

L-Isoserine (1.00 g, 9.52 mmol) was dissolved in MeOH (9.5 mL) and cooled to 0 °C. Thionyl chloride (764 µL, 10.5 mmol, 1.1 eq.) was added dropwise, and the mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo to give the crude H-Ise-OMe·HCl.

The above-prepared H-Ise-OMe·HCl and $NaHCO_3$ (1.76 g, 20.9 mmol, 2.2 eq.) were dissolved in THF:H_2O (1:1). After cooling to 0 °C, Boc_2O (2.04 g, 9.32 mmol, 0.98 eq.) was added, and the reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the organic layer was washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give Boc-Ise-OMe (2.04 g, 9.30 mmol, 98%) as a colorless resin.

TLC: R_f (71) = 0.42 (silica, CH_2Cl_2:MeOH 95:5)



71

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.95 (m, 1 H, 3-NH), 4.28 (t, $^3J_{5,4}$ = 4.5 Hz, 1 H, 5-H), 3.81 (s, 3 H, 7-H), 3.50 (m, 2 H, 4-H), 1.44 (s, 9 H, 1-H).

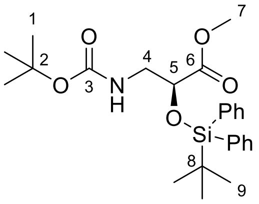
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.6 (s, C-6), 156.2 (s, C-3), 79.9 (s, C-2), 70.3 (d, C-5), 52.8 (q, C-7), 44.0 (t, C-4), 28.3 (q, C-1).

Optical rotation:	$[\alpha]_D^{20}$= +23.0 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_9H_{17}NO_5$ $[M]^+$:	219.1101	219.1107
Melting point:	40 – 42 °C	

Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldiphenylsilyl)oxy)propanoate[204] 72

Preparation according to Konopelski *et al.*[204]

TLC: R_f (72) = 0.34 (silica, PE:EtOAc 8:2)



72

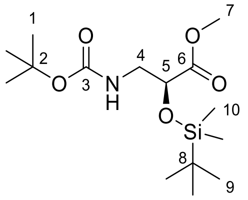
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.62 (m, 4 H, Ph-H), 7.47 – 7.35 (m, 6 H, Ph-H), 4.85 (m, 1 H, 3-NH), 4.28 (t, $^3J_{5,4}$ = 4.5 Hz, 1 H, 5-H), 3.50 (s, 3 H, 7-H), 3.46 (m, 2 H, 4-H), 1.43 (s, 9 H, 9-H), 1.12 (s, 9 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.6 (s, C-6), 155.6 (s, C-3), 135.9 (d, C-Ph), 135.7 (d, C-Ph), 132.9 (s, C-Ph), 132.7 (s, C-Ph), 130.0 (d, C-Ph), 129.9 (d, C-Ph), 127.8 (d, C-Ph), 127.6 (d, C-Ph), 71.8 (s, C-2), 60.3 (d, C-5), 51.7 (q, C-7), 44.6 (t, C-4), 28.3 (q, C-1), 26.9 (q, C-9), 19.4 (s, C-8).

Methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)propanoate 73

Imidazole (559 mg, 8.21 mmol, 1.2 eq.) and TBS-Cl (1.08 g, 7.18 mmol, 1.05 eq.) were subsequently added to a 0 °C cold solution of Boc-Ise-OMe **71** (1.50 g, 6.84 mmol) in anhydrous CH_2Cl_2 (30 mL). The resulting suspension was stirred for 16 h while slowly reaching rt. After dilution with EtOAc, the reaction mixture was washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 40% EtOAc) to give the protected isoserine **73** (2.02 g, 6.06 mmol, 89%) as a colorless resin.

TLC: R_f (73) = 0.24 (silica, PE:EtOAc 8:2)



73

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.86 (m, 1 H, 3-NH), 4.32 (dd, $^3J_{5,4}$ = 5.9 Hz, $^3J_{5,4'}$ = 5.9 Hz , 1 H, 5-H), 3.74 (s, 3 H, 7-H), 3.50 (m, 1 H, 4-H), 3.35 (ddd, $^2J_{4',4}$ = 13.4 Hz, $^3J_{4',5}$ = 6.4 Hz, $^3J_{4',NH}$ = 6.4 Hz, 1 H, 4-H'), 1.44 (s, 9 H, 1-H), 0.92 (s, 9 H, 9-H), 0.12 (s, 3 H, 10-H), 0.09 (s, 3 H, 10'-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.4 (s, C-6), 155.9 (s, C-3), 79.7 (s, C-2), 71.8 (d, C-5), 52.2 (q, C-7), 44.6 (t, C-4), 28.5 (q, C-1), 25.8 (q, C-9), 19.4 (s, C-8), –4.9 (q, C-10), –5.2 (q, C-10').

Optical rotation: $[\alpha]_D^{20}$= –18.8 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{15}H_{32}O_5NSi$ $[M+H]^+$:	334.2044	334.2035

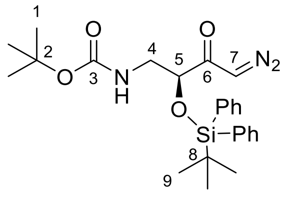
tert-Butyl (_S_)-(2-((_tert_-butyldiphenylsilyl)oxy)-4-diazo-3-oxobutyl)carbamate 76

Protected isoserine **72** (1.90 g, 4.15 mmol) was dissolved in THF:MeOH (20 mL, 3:1) and cooled to 0 °C. After the addition of 0.50 M $LiOH_{aq}$ (8.72 mL, 4.36 mmol, 1.05 eq.), the solution was stirred for 16 h while slowly reaching room temperature. After full conversion, the reaction mixture was concentrated in vacuo, and the residue was partitioned between 0.1 M HCl_{aq} and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid **74** (1.69 g, 3.81 mmol, 92%).

Diazomethane preparation: 1-Methyl-1-nitrosourea (279 mg, 2.71 mmol, 3.0 eq.) was slowly dissolved in a mixture of Et_2O (6.0 mL) and KOH_{aq} (2.0 mL, 40wt%) at –15 to –10 °C. After complete solvation, H_2O (1.0 mL) was added, and the mixture was cooled to –78 °C. The ether layer was decanted in a separation funnel and washed with H_2O.

The above-prepared carboxylic acid **74** (400 mg, 902 µmol) was dissolved in anhydrous THF (5.0 mL) and cooled to –20 °C. Triethylamine (128 µL, 920 µmol, 1.02 eq.) and ethyl chloroformate (88.0 µL, 920 µmol, 1.02 eq.) were added subsequently. The reaction mixture was stirred for 30 min before being cooled to –40 °C. The above-prepared diazomethane in Et_2O was added dropwise to the active ester suspension. The resulting mixture was stirred for 18 h while slowly reaching room temperature. The reaction mixture was diluted with H_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ solution, dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, PE:EtOAc 9:1) to give the diazoketone **76** (232 mg, 496 µmol, 55%) as a light-yellow solid.

TLC: R_f (76) = 0.30 (silica, PE:EtOAc 8:2)



76

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68 – 7.61 (m, 4 H, Ph-H), 7.49 – 7.31 (m, 6 H, Ph-H), 5.74 (m, 1 H, 7-H), 4.63 (m, 1 H, 3-NH), 4.20 (dd, $^3J_{5,4}$ = 5.1 Hz, $^3J_{5,4'}$ = 5.1 Hz, 1 H, 5-H), 3.43 (m, 1 H, 4-H'), 3.24 (m, 1 H, 4-H), 1.40 (s, 9 H, 9-H), 1.14 (s, 9 H, 1-H).

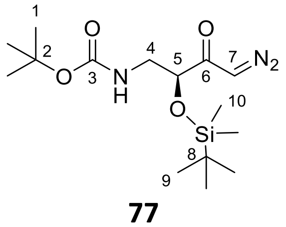
***tert*-Butyl (*S*)-(2-((*tert*-butyldimethylsilyl)oxy)-4-diazo-3-oxobutyl)carbamate 77**

Protected isoserine **73** (940 mg, 2.82 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. After the addition of 0.20 M $LiOH_{aq}$ (15.5 mL, 3.10 mmol, 1.1 eq.), the solution was stirred for 1 h while slowly reaching room temperature. After full conversion, the reaction mixture was acidified with 0.2 M $KHSO_4$ solution and extracted thrice with Et_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid **75**, which was immediately used in the following reaction.

Diazomethane preparation: 1-Methyl-1-nitrosourea (871 mg, 8.45 mmol, 3.0 eq.) was slowly dissolved in a mixture of Et_2O (18 mL) and KOH_{aq} (6.0 mL, 40wt%) at –15 to –10 °C. After complete solvation, H_2O (3.0 mL) was added, and the mixture was cooled to –78 °C. The ether layer was decanted in a separation funnel and washed with H_2O.

The above-prepared carboxylic acid **75** was dissolved in anhydrous THF (15 mL) and cooled to –20 °C. Triethylamine (412 µL, 2.96 mmol, 1.05 eq.) and ethyl chloroformate (284 µL, 2.96 mmol, 1.05 eq.) were added subsequently. The reaction mixture was stirred for 30 min before being cooled to –40 °C. The above-prepared diazomethane in Et_2O was added dropwise to the active ester suspension. The resulting mixture was stirred for 18 h while slowly reaching room temperature. The reaction mixture was diluted with H_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ solution, dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, pentane:EtOAc 9:1) to give the diazoketone **77** (845 mg, 2.34 mmol, 83%) as a light-yellow solid.

TLC: R_f (77) = 0.33 (silica, pentane:EtOAc 8:2)



77

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 1 H, 7-H), 4.82 (m, 1 H, 3-NH), 4.15 (t, $^3J_{5,4}$ = 5.7 Hz, 1 H, 5-H), 3.38 (m, 2 H, 4-H), 1.44 (s, 9 H, 1-H), 0.94 (s, 9 H, 9-H), 0.13 (s, 3 H, 10-H), 0.11 (s, 3 H, 10'-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.4 (s, C-6), 155.6 (s, C-3), 79.5 (s, C-2), 75.9 (d, C-5), 53.2 (d, C-7), 44.7 (t, C-4), 28.4 (q, C-1), 25.8 (q, C-9), 18.1 (s, C-8), –5.0 (q, C-10), –5.1 (q, C-10').

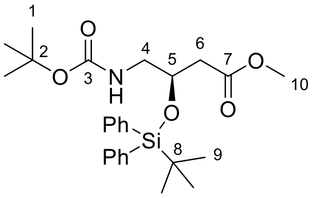
Optical rotation: $[\alpha]_D^{20}$ = –66.8 (c = 1.0, $CHCl_3$)

HRMS (ESI):	calculated	found
$C_{15}H_{30}N_3O_4Si$ $[M+H]^+$:	344.2000	344.2000

Methyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)butanoate 78

A solution of diazoketone **76** (73.0 mg, 156 µmol) in anhydrous MeOH (2.0 mL) was cooled to −10 °C. After the addition of triethylamine (65.0 µL, 468 µmol, 3.0 eq.) and AgOBz (3.9 mg, 17.0 µmol, 0.1 eq.), the black suspension was stirred for 16 h while slowly reaching room temperature. The reaction mixture was filtrated through a pad of celite®. The filtrate was washed with sat. $Na_2S_2O_3$ solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$, concentrated in vacuo, and purified by column chromatography (silica, PE:EtOAc 8:2) to give the GABOB-derivative **78** (44.0 mg, 93.0 µmol, 60%) as a colorless resin.

TLC: R_f (78) = 0.38 (silica, PE:EtOAc 8:2)



78

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 – 7.62 (m, 4 H, Ph-H), 7.48 – 7.36 (m, 6 H, Ph-H), 4.59 (m, 1 H, 3-NH), 4.25 (m, 1 H, 5-H), 3.55 (s, 3 H, 10-H), 3.20 (m, 2 H, 4-H), 2.51 (m, 2 H, 6-H), 1.40 (s, 9 H, 1-H), 1.05 (s, 9 H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.5 (s, C-7), 155.9 (s, C-3), 136.0 (d, C-Ph), 135.9 (d, C-Ph), 133.6 (s, C-Ph), 133.5 (s, C-Ph), 130.1 (d, C-Ph), 130.0 (d, C-Ph), 127.9 (d, C-Ph), 127.8 (d, C-Ph), 79.4 (s, C-2), 69.8 (d, C-5), 51.7 (q, C-10), 45.9 (t, C-4), 39.9 (t, C-6), 28.5 (q, C-1), 27.0 (q, C-9), 19.4 (s, C-8).

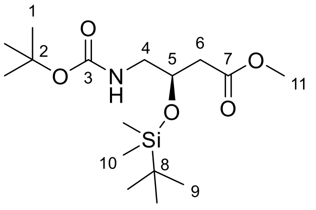
Optical rotation: $[\alpha]_D^{20}$ = +18.0 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{26}H_{38}O_5NSi$ [M+H]$^+$:	472.2514	472.2522

Methyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate 79

Diazoketone **77** (23.5 mg, 68.0 µmol) was dissolved in anhydrous MeOH (1.4 mL). The resulting yellow solution was irradiated with a blue LED (405 nm, 18 W) for 2 h at room temperature. The colorless solution was concentrated in vacuo, and the residue was purified by column chromatography (silica, pentane:EtOAc 8:2) to give GABOB-derivative **79** (22.0 mg, 63.3 µmol, 93%) as a colorless resin.

TLC: R_f (79) = 0.53 (silica, PE:EtOAc 6:4)



79

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 4.76 (m, 1 H, 3-NH), 4.23 (tt, $^3J_{5,4}$ = 5.6 Hz, $^3J_{5,6}$ = 5.6 Hz, 1 H, 5-H), 3.68 (s, 3 H, 11-H), 3.22 (m, 2 H, 4-H), 2.47 (m, 2 H, 6-H), 1.44 (s, 9 H, 1-H), 0.87 (s, 9 H, 9-H), 0.09 (s, 3 H, 10-H), 0.05 (s, 3 H, 10'-H).

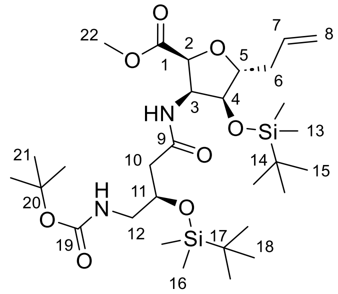
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 171.8 (s, C-7), 156.1 (s, C-3), 79.5 (s, C-2), 68.5 (d, C-5), 51.8 (q, C-11), 46.2 (t, C-4), 40.3 (t, C-6), 28.5 (q, C-1), 25.8 (q, C-9), 18.1 (s, C-8), –4.6 (q, C-10), –4.9 (q, C-10').

Optical rotation:	$[\alpha]_D^{20}$= +17.6 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{16}H_{34}NO_5Si$ [M+H]$^+$:	348.2201	348.2200

Methyl (2*S*,3*S*,4*S*,5*R*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)-oxy)butanamido)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylate 81

Diazoketone **77** (361 mg, 998 µmol, 1.5 eq.) and amine **69** (210 mg, 666 µmol) were dissolved in anhydrous CH$_2$Cl$_2$ (6.7 mL). The resulting yellow solution was irradiated with a blue LED (365 nm, 18 W) for 2 h at room temperature. The colorless solution was concentrated in vacuo, and the residue was purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give compound **81** (294 mg, 466 µmol, 70%) as a colorless resin.

TLC: R$_f$ (81) = 0.51 (silica, PE:EtOAc 7:3)



81

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 6.58 (d, $^3J_{NH,3}$ = 7.6 Hz, 1 H, 9-NH), 5.81 (ddt, $^3J_{7,8'}$ = 17.3 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.1 Hz, 1 H, 7-H), 5.20 – 5.11 (m, 2 H, 8-H), 4.90 (t, $^3J_{NH,12}$ = 5.8 Hz, 1 H, 19-NH), 4.63 – 4.56 (m, 2 H, 2-H, 3-H), 4.24 (tt, $^3J_{11,10}$ = 6.0 Hz, $^3J_{11,12}$ = 5.4 Hz, 1 H, 11-H), 4.18 (td, $^3J_{5,6}$ = 6.3 Hz, $^3J_{5,4}$ = 2.2 Hz, 1 H, 5-H), 4.02 (dd, $^3J_{4,3}$ = 4.8 Hz, $^3J_{4,5}$ = 2.3 Hz, 1 H, 4-H), 3.73 (s, 3 H, 22-H), 3.32 (m, 1 H, 12-H'), 3.17 (ddd, $^2J_{12,12'}$ = 13.7 Hz, $^3J_{12,11}$ = 5.3 Hz, $^3J_{12,NH}$ = 5.8 Hz, 1 H, 12-H), 2.41 (dd, $^2J_{10,12'}$ = 14.4 Hz, $^3J_{10,11}$ = 6.1 Hz, 1 H, 10-H), 2.37 – 2.29 (m, 3 H, 6-H, 10-H'), 1.44 (s, 9 H, 21-H), 0.89 (s, 9 H, 15-H), 0.87 (s, 9 H, 18-H), 0.11 (s, 3 H, 16'-H), 0.09 (s, 3 H, 16-H), 0.05 (s, 3 H, 13'-H), 0.04 (s, 3 H, 13-H).

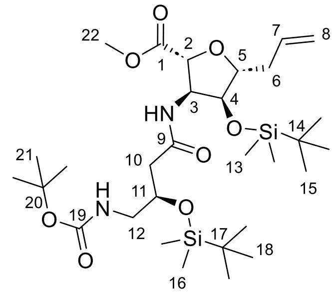
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 171.8 (s, C-1), 170.1 (s, C-9), 156.2 (s, C-19), 133.4 (d, C-7), 118.6 (t, C-8), 85.8 (d, C-5), 79.4 (s, C-20), 75.7 (d, C-2), 74.1 (d, C-4), 68.9 (d, C-11), 53.7 (d, C-3), 52.2 (q, C-22), 45.8 (t, C-12), 42.5 (t, C-10), 38.3 (t, C-6), 28.6 (q, C-21), 26.0 (q, C-18), 25.7 (q, C-15), 18.2 (s, C-17), 18.0 (s, C-14), –4.4 (q, C-16), –4.68 (q, C-16', C-13), –4.73 (q, C-13').

Optical rotation:	$[\alpha]_D^{20}$= +24.5 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{30}H_{59}N_2O_8Si_2$ [M+H]$^+$:	631.3804	631.3801

Methyl (2*R*,3*S*,4*S*,5*R*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)-oxy)butanamido)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxylate 83

Diazoketone **77** (150 mg, 415 µmol, 1.5 eq.) and amine **62** (87.0 mg, 277 µmol) were dissolved in anhydrous CH$_2$Cl$_2$ (2.8 mL). At room temperature, the resulting yellow solution was irradiated with a blue LED (365 nm, 18 W) for 1 h. The colorless solution was concentrated in vacuo, and the residue was purified by column chromatography (silica, pentane:EtOAc 8:2) to give compound **83** (120 mg, 190 µmol, 69%) as a colorless resin.

TLC: R$_f$ (83) = 0.44 (SiO$_2$, PE:EtOAc 7:3)



83

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 6.46 (d, $^3J_{NH,3}$ = 8.0 Hz, 1 H, 9-NH), 5.87 (ddt, $^3J_{7,8'}$ = 17.2 Hz, $^3J_{7,8}$ = 10.2 Hz, $^3J_{7,6}$ = 7.1 Hz, 1 H, 7-H), 5.20 – 5.11 (m, 2 H, 8-H), 4.88 (m, 1 H, 19-NH), 4.51 (ddd, $^3J_{3,2}$ = 8.0 Hz, $^3J_{3,NH}$ = 8.0 Hz, $^3J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 4.27 (d, $^3J_{2,3}$ = 7.9 Hz, 1 H, 2-H), 4.19 (tt, $^3J_{11,10}$ = 5.4 Hz, $^3J_{11,12}$ = 5.4 Hz, 1 H, 11-H), 4.06 (dd, $^3J_{4,3}$ = 5.6 Hz, $^3J_{4,5}$ = 2.8 Hz, 1 H, 4-H), 3.99 (td, $^3J_{5,6}$ = 6.3 Hz, $^3J_{5,4}$ = 2.9 Hz, 1 H, 5-H), 3.75 (s, 3 H, 22-H), 3.37 (m, 1 H, 12-H‘), 3.07 (ddd, $^2J_{12,12'}$ = 14.0 Hz, $^3J_{12,11}$ = 5.4 Hz, $^3J_{12,NH}$ = 5.4 Hz, 1 H, 12-H), 2.46 – 2.29 (m, 4 H, 6-H, 10-H), 1.45 (s, 9 H, 21-H), 0.92 (s, 9 H, 15-H), 0.90 (s, 9 H, 18-H), 0.12 (s, 3 H, 13‘-H), 0.09 (s, 6 H, 16-H), 0.09 (s, 3 H, 13-H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ = 171.5 (s, C-1), 170.0 (s, C-9), 156.4 (s, C-19), 133.8 (d, C-7), 118.2 (t, C-8), 86.0 (d, C-5), 79.9 (d, C-2), 79.5 (s, C-20), 75.0 (d, C-4), 68.8 (d, C-11), 55.0 (d, C-3), 52.5 (q, C-22), 45.3 (t, C-12), 42.5 (t, C-10), 38.1 (t, C-6), 28.6 (q, C-21), 26.0 (q, C-15), 25.9 (q, C-18), 18.2 (s, C-14), 18.1 (s, C-17), –4.4 (q, C-13‘), –4.5 (q, C-16‘), –4.6 (q, C-13), –4.7 (q, C-16).

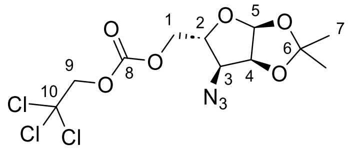
Optical rotation:	$[\alpha]_D^{20}$= –7.4 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{30}H_{59}N_2O_8Si_2$ [M+H]$^+$:	631.3804	631.3802

((3a*S*,5*R*,6*S*,6a*S*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl (2,2,2-trichloroethyl) carbonate 85a

1.0 M TBAF in THF (637 µL, 637 µmol, 1.05 eq.) was added to a 0 °C cold solution of azido-sugar **54** (200 mg, 607 µmol) in anhydrous THF (3.8 mL). The resulting solution was stirred for 2 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc, washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude primary alcohol.

Pyridine (118 µL, 1.46 mmol, 2.4 eq.), DMAP (1.5 mg, 12.0 µmol, 0.02 eq), and Troc-Cl (101 µL, 730 µmol, 1.2 eq.) were subsequently added to a 0 °C cold solution of the above-prepared primary alcohol in anhydrous CH_2Cl_2 (6.0 mL). The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 25% EtOAc) to give compound **85a** (235 mg, 602 µmol, 99%) as a colorless resin.

TLC: R_f (85a) = 0.47 (silica, pentane:EtOAc 7:3)



85a

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84 (d, $^{3}J_{5,4}$ = 3.6 Hz, 1 H, 5-H), 4.80 (m, 2 H, 9-H), 4.78 (m, 1 H, 4-H), 4.63 (dd, $^{2}J_{1',1}$ = 12.1 Hz, $^{3}J_{1',2}$ = 2.6 Hz, 1 H, 1-H'), 4.37 (dd, $^{2}J_{1,1'}$ = 12.1 Hz, $^{3}J_{1,2}$ = 4.1 Hz, 1 H, 1-H), 4.29 (ddd, $^{3}J_{2,3}$ = 9.8 Hz, $^{3}J_{2,1}$ = 4.1 Hz, $^{3}J_{2,1'}$ = 2.5 Hz, 1 H, 2-H), 3.51 (dd, $^{3}J_{3,2}$ = 9.7 Hz, $^{3}J_{3,4}$ = 4.7 Hz, 1 H, 3-H), 1.59 (s, 3 H, 7'-H), 1.39 (s, 3 H, 7-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 153.9 (s, C-8), 113.6 (s, C-6), 104.4 (d, C-5), 94.3 (s, C-10), 80.0 (d, C-4), 77.2 (t, C-9), 75.6 (d, C-2), 66.3 (t, C-1), 60.6 (d, C-3), 26.54 (q, C-7'), 26.53 (q, C-7).

Optical rotation: $[\alpha]_D^{20}$= –104.5 (c = 1.0, $CHCl_3$)

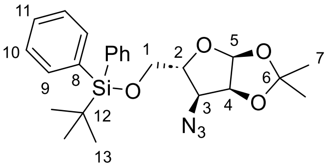
HRMS (CI):	calculated	found
$C_{11}H_{15}NO_6Cl_3$ $[M-N_2+H]^+$:	361.9959	361.9982

(((3a*S*,5*R*,6*S*,6a*S*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)(*tert*-butyl)diphenylsilane 85b

1.0 M TBAF in THF (2.56 mL, 2.56 mmol, 1.05 eq.) was added to a 0 °C cold solution of azido-sugar **54** (803 mg, 2.44 mmol) in anhydrous THF (15 mL). The resulting solution was stirred for 2 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc, washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude primary alcohol.

Imidazole (414 mg, 6.08 mmol, 2.5 eq.) and TBDPS-Cl (749 µL, 2.92 mmol, 1.2 eq.) were subsequently added to a 0 °C cold solution of the above-prepared primary alcohol in anhydrous CH_2Cl_2 (16 mL). The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 10% EtOAc) to give compound **85b** (1.03 g, 2.27 mmol, 93%) as a colorless oil.

TLC: R_f (85b) = 0.42 (silica, pentane:EtOAc 9:1)



85b

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 4 H, 10-H), 7.47 – 7.37 (m, 6 H, 9-H, 11-H), 5.84 (d, $^3J_{5,4}$ = 3.6 Hz, 1 H, 5-H), 4.77 (dd, $^3J_{4,3}$ = 4.3 Hz, $^3J_{4,5}$ = 3.8 Hz, 1 H, 4-H), 4.16 (ddd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{2,1'}$ = 2.8 Hz, $^3J_{2,1}$ = 2.8 Hz, 1 H, 2-H), 4.00 (dd, $^2J_{1',1}$ = 11.9 Hz, $^3J_{1',2}$ = 2.6 Hz, 1 H, 1-H'), 3.85 (dd, $^2J_{1,1'}$ = 11.9 Hz, $^3J_{1,2}$ = 2.9 Hz, 1 H, 1-H), 3.75 (dd, $^3J_{3,2}$ = 9.4 Hz, $^3J_{3,4}$ = 4.6 Hz, 1 H, 3-H), 1.58 (s, 3 H, 7'-H), 1.39 (s, 3 H, 7-H), 1.06 (s, 9 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.8 (d, C-10), 135.7 (d, C-10'), 133.2 (s, C-8), 133.0 (s, C-8'), 130.0 (d, C-11), 129.9 (d, C-11'), 128.0 (d, C-9), 127.9 (d, C-9'), 113.2 (s, C-6), 104.3 (d, C-5), 80.4 (d, C-4), 78.6 (d, C-2), 61.9 (t, C-1), 60.3 (d, C-3), 26.9 (q, C-13), 26.63 (q, C-7'), 26.62 (q, C-7), 19.5 (s, C-12).

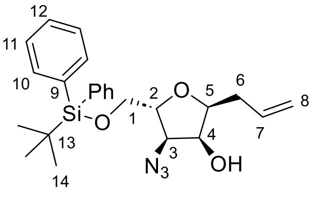
Optical rotation: $[\alpha]_D^{20} = -53.4$ (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{24}H_{31}O_4Si$ $[M-N_3]^+$:	411.1986	411.1972

(2*S*,3*S*,4*R*,5*R*)-2-Allyl-4-azido-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-3-ol 86

Allytrimethylsilane (897 µL, 5.64 mmol, 4.0 eq.) was added to a 0 °C cold solution of compound **85b** (640 mg, 1.41 mmol) in anhydrous CH_2Cl_2 (12 mL). After stirring for 10 min, $BF_3{\cdot}OEt_2$ (358 µL, 2.82 mmol, 2.0 eq.) was added, and the stirring continued for 44 h while slowly reaching room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution before being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 15% EtOAc) to give C-furanoside **86** (336 mg, 699 µmol, 50%, dr 87:13) as a colorless resin.

TLC: R_f (86) = 0.28 (silica, pentane:EtOAc 9:1)



86

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 7.66 (m, 4 H, 11-H), 7.49 – 7.40 (m, 6 H, 10-H, 12-H), 5.81 (ddt, $^{3}J_{7,8'}$ = 17.2 Hz, $^{3}J_{7,8}$ = 10.2 Hz, $^{3}J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.65 (d, $^{3}J_{OH,4}$ = 5.8 Hz, 1 H, 4-OH), 5.12 (ddt, $^{3}J_{8',7}$ = 17.4 Hz, $^{2}J_{8',8}$ = 2.1 Hz, $^{4}J_{8',6}$ = 1.5 Hz, 1 H, 8-H'), 5.04 (ddt, $^{3}J_{8,7}$ = 10.2 Hz, $^{2}J_{8,8'}$ = 2.2 Hz, $^{4}J_{8,6}$ = 1.1 Hz, 1 H, 8-H), 4.21 (ddd, $^{3}J_{4,OH}$ = 5.9 Hz, $^{3}J_{4,3}$ = 4.2 Hz, $^{3}J_{4,5}$ = 2.9 Hz, 1 H, 4-H), 4.00 (ddd, $^{3}J_{2,3}$ = 8.6 Hz, $^{3}J_{2,1}$ = 3.7 Hz, $^{3}J_{2,1'}$ = 3.7 Hz, 1 H, 2-H), 3.91 (m, 1 H, 5-H), 3.82 (dd, $^{3}J_{3,2}$ = 8.6 Hz, $^{3}J_{3,4}$ = 4.1 Hz, 1 H, 3-H), 3.77 (dd, $^{2}J_{1,1'}$ = 11.1 Hz, $^{3}J_{1,2}$ = 3.5 H, 1 H, 1-H), 3.69 (dd, $^{2}J_{1',1}$ = 11.2 Hz, $^{3}J_{1',2}$ = 3.9 H, 1 H, 1-H'), 2.31 (m, 2 H, 6-H), 0.99 (s, 9 H, 14-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 135.3 (d, C-7), 135.2 (d, C-11), 135.1 (d, C-11'), 132.83 (s, C-9), 132.76 (s, C-9'), 129.92 (d, C-12), 129.88 (d, C-12'), 127.93 (d, C-10), 127.87 (d, C-10'), 116.7 (t, C-8), 80.9 (d, C-5), 78.2 (d, C-2), 72.7 (d, C-4), 64.2 (t, C-1), 62.4 (d, C-3), 33.9 (t, C-6), 26.6 (q, C-14), 18.8 (s, C-13).

Selected C-5 epimer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 5.72 (d, $^{3}J_{OH,4}$ = 5.6 Hz, 1 H, 4-OH), 2.19 (m, 1 H, 6-H), 1.00 (s, 9 H, 14-H).

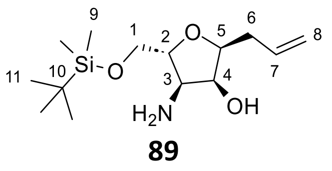
Optical rotation: $[\alpha]_D^{20}$= +26.9 (c = 1.0, CHCl$_3$)

HRMS (CI):	calculated	found
$C_{24}H_{32}N_3O_3Si$ [M+H]$^+$:	438.2207	438.2188

(2*S*,3*S*,4*R*,5*R*)-2-Allyl-4-amino-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol 89

Ammonium sulfide in H$_2$O (11.2 mL, 40wt%) was added to a 0 °C cold solution of C-furanoside **56** (700 mg, 2.23 mmol) in MeCN (11.2 mL). The biphasic mixture was stirred for 16 h while slowly reaching room temperature. After the addition of sat. NaHCO$_3$ solution (30.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo to give the crude amine **89** (642 mg, 2.21 mmol, 99%) as a colorless resin.

TLC: R$_f$ (89) = 0.10 (silica, pentane:EtOAc 2:8)



89

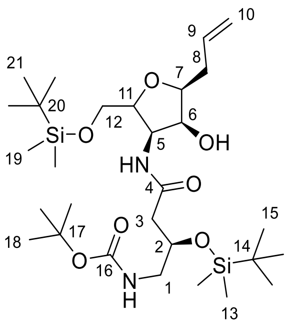
^{1}H-NMR (500 MHz, CDCl$_3$): δ = 5.85 (ddt, $^{3}J_{7,8'}$ = 17.1 Hz, $^{3}J_{7,8}$ = 10.2 Hz, $^{3}J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.15 (ddt, $^{3}J_{8',7}$ = 17.2 Hz, $^{2}J_{8',8}$ = 1.7 Hz, $^{4}J_{8',6}$ = 1.7 Hz, 1 H, 8-H'), 5.06 (ddt, $^{3}J_{8,7}$ = 10.2 Hz, $^{2}J_{8,8'}$ = 2.0 Hz, $^{4}J_{8,6}$ = 1.2 Hz, 1 H, 8-H), 3.97 (td, $^{3}J_{5,6}$ = 7.0 Hz, $^{3}J_{5,4}$ = 2.8 Hz, 1 H, 5-H), 3.94 (dd, $^{3}J_{4,3}$ = 4.4 Hz, $^{3}J_{4,5}$ =

2.9 Hz, 1 H, 4-H), 3.82 (dd, $^{2}J_{1,1'}$ = 9.8 Hz, $^{3}J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 3.69 (ddd, $^{3}J_{2,3}$ = 7.7 Hz, $^{3}J_{2,1'}$ = 6.4 Hz, $^{3}J_{2,1}$ = 3.6 Hz, 1 H, 2-H), 3.64 (dd, $^{2}J_{1',1}$ = 9.8 Hz, $^{3}J_{1',2}$ = 6.4 Hz, 1 H, 1-H'), 3.47 (dd, $^{3}J_{3,2}$ = 7.9 Hz, $^{3}J_{3,4}$ = 4.7 Hz, 1 H, 3-H), 2.46 (m, 2 H, 6-H), 0.89 (s, 9 H, 11-H), 0.06 (s, 6 H, 9-H).

***tert*-Butyl ((*R*)-4-(((2*R*,3*R*,4*S*,5*S*)-5-allyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxytetrahydrofuran-3-yl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-4-oxobutyl)carbamate 90**

Diazoketone **77** (49.3 mg, 143 µmol, 1.5 eq.) and amine **89** (27.5 mg, 96.0 µmol) were dissolved in anhydrous CH_2Cl_2 (1.0 mL). At room temperature, the resulting yellow solution was irradiated with a blue LED (405 nm, 18 W) for 1.5 h. The colorless solution was concentrated in vacuo, and the residue was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give compound **90** (38.0 mg, 63.0 µmol, 66%) as a colorless resin.

LC-MS: t_R (90) = 1.55 min (short method)



90

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.62 (d, $^{3}J_{NH,5}$ = 7.9 Hz, 1 H, 4-NH), 5.83 (ddt, $^{3}J_{9,10'}$ = 17.1 Hz, $^{3}J_{9,10}$ = 10.2 Hz, $^{3}J_{9,8}$ = 6.9 Hz, 1 H, 9-H), 5.17 (ddt, $^{3}J_{10',9}$ = 17.2 Hz, $^{2}J_{10',10}$ = 1.6 Hz, $^{4}J_{10',8}$ = 1.6 Hz, 1 H, 10-H'), 5.07 (m, 1 H, 10-H), 4.89 (t, $^{3}J_{NH,1}$ = 6.2 Hz, 1 H, 16-NH), 4.50 (ddd, $^{3}J_{5,NH}$ = 8.0 Hz, $^{3}J_{5,11}$ = 8.0 Hz, $^{3}J_{5,6}$ = 4.5 Hz, 1 H, 5-H), 4.17 – 4.10 (m, 2 H, 2-H, 6-H), 4.05 (td, $^{3}J_{7,8}$ = 7.2 Hz, $^{3}J_{7,6}$ = 2.6 Hz, 1 H, 7-H), 3.88 (dt, $^{3}J_{11,5}$ = 4.8 Hz, $^{3}J_{11,12}$ = 3.5 Hz, 1 H, 11-H), 3.82 (dd, $^{2}J_{12,12'}$ = 11.1 Hz, $^{3}J_{12,11}$ = 3.0 Hz, 1 H, 12-H), 3.74 (dd, $^{2}J_{12',12}$ = 11.0 Hz, $^{3}J_{12',11}$ = 4.0 Hz, 1 H, 12-H'), 3.17 (dd, $^{3}J_{1,2}$ = 5.8 Hz, $^{3}J_{1,NH}$ = 5.8 Hz, 2 H, 1-H), 2.81 (d, $^{3}J_{OH,6}$ = 5.8 Hz, 1 H, 6-OH), 2.45 (dd, $^{3}J_{8,7}$ = 6.7 Hz, $^{3}J_{8,9}$ = 6.7 Hz, 2 H, 8-H), 2.38 (d, $^{3}J_{3,2}$ = 6.1 Hz, 2 H, 3-H), 1.43 (s, 9 H, 18-H), 0.89 (s, 9 H, 15-H/21-H), 0.88 (s, 9 H, 21-H/15-H), 0.10 (s, 3 H, 13-H/19-H), 0.08 (s, 3 H, 13-H/19-H), 0.07 (s, 3 H, 13-H/19-H), 0.06 (s, 3 H, 13-H/19-H).

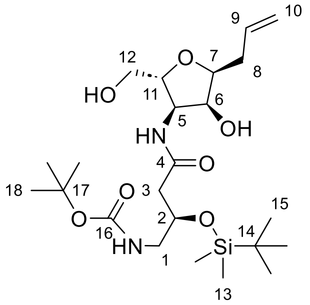
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.3 (s, C-4), 156.5 (s, C-16), 134.4 (d, C-9), 117.4 (t, C-10), 81.7 (d, C-11), 81.4 (d, C-7), 80.0 (s, C-17), 72.6 (d, C-6), 69.1 (d, C-2), 64.5 (t, C-12), 54.2 (d, C-5), 45.6 (t, C-1), 42.5 (t, C-3), 33.9 (t, C-8), 28.5 (q, C-18), 26.1 (q, C-15/C-21), 25.9 (q, C-21/C-15), 18.5 (s, C-14/C-20), 18.1 (s, C-20/C-14), –4.69 (q, C-13/C-19), –4.72 (q, C-13/C-19), –5.20 (q, C-13/C-19), –5.26 (q, C-13/C-19).

Optical rotation:	$[\alpha]_D^{20}$ = –14.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{29}H_{59}N_2O_7Si_2$ $[M+H]^+$:	603.3855	603.3856

tert-Butyl ((_R_)-4-(((2_R_,3_R_,4_S_,5_S_)-5-allyl-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl)amino)-2-((_tert_-butyldimethylsilyl)oxy)-4-oxobutyl)carbamate 91

1.0 M TBAF in THF (621 µL, 621 µmol, 1.05 eq.) was added to a 0 °C cold solution of the crude amine **89** (170 mg, 591 µmol) in anhydrous THF (5.9 mL). The resulting solution was stirred for 2 h while slowly reaching room temperature. After adding 1.0 M HCl_{aq} (621 µL, 621 µmol, 1.05 eq.), the reaction mixture was concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (5.9 mL) before diazoketone **77** (323 mg, 883 µmol, 1.5 eq.) was added. The resulting yellow solution was irradiated with a blue LED (405 nm, 18 W) at room temperature for 30 min. The reaction mixture was concentrated in vacuo, and the residue was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give compound **91** (151 mg, 309 µmol, 52%) as a colorless resin.

LC-MS: t_R (91) = 1.23 min (short method)



91

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.99 (d, $^3J_{NH,5}$ = 8.0 Hz , 1 H, 4-NH), 5.84 (ddt, $^3J_{9,10'}$ = 17.0 Hz, $^3J_{9,10}$ = 10.2 Hz, $^3J_{9,8}$ = 6.9 Hz, 1 H, 9-H), 5.18 (ddt, $^3J_{10',9}$ = 17.0 Hz, $^2J_{10',10}$ = 1.6 Hz, $^4J_{10',8}$ = 1.6 Hz, 1 H, 10-H‘), 5.10 (ddt, $^3J_{10,9}$ = 10.2 Hz, $^2J_{10,10'}$ = 2.0 Hz, $^4J_{10,8}$ = 1.1 Hz, 1 H, 10-H), 4.92 (t, $^3J_{NH,1}$ = 6.4 Hz, 1 H, 16-NH), 4.33 (ddd, $^3J_{5,NH}$ = 8.2 Hz, $^3J_{5,11}$ = 8.2 Hz, $^3J_{5,6}$ = 4.4 Hz, 1 H, 5-H), 4.19 – 4.12 (m, 2 H, 2-H, 6-H), 4.08 (td, $^3J_{7,8}$ = 7.1 Hz, $^3J_{7,6}$ = 2.8 Hz, 1 H, 7-H), 3.89 (dt, $^3J_{11,5}$ = 8.6 Hz, $^3J_{11,12}$ = 4.3 Hz, 1 H, 11-H), 3.75 (dd, $^2J_{12,12'}$ = 12.1 Hz, $^3J_{12,11}$ = 4.7 Hz, 1 H, 12-H), 3.67 (dd, $^2J_{12',12}$ = 12.2 Hz, $^3J_{12',11}$ = 4.0 Hz, 1 H, 12-H‘), 3.55 (m, 1 H, 12-OH), 3.23 (ddd, $^2J_{1,1'}$ = 14.1 Hz, $^3J_{1,2}$ = 7.2 Hz, $^3J_{1,NH}$ = 5.1 Hz, 1 H, 1-H), 3.13 (ddd, $^2J_{1',1}$ = 14.2 Hz, $^3J_{1',2}$ = 5.4 Hz, $^3J_{1',NH}$ = 5.4 Hz, 1 H, 1-H‘), 2.99 (m, 1 H, 6-OH), 2.46 (m, 2 H, 8-H), 2.42 (m, 2 H, 3-H), 1.44 (s, 9 H, 18-H), 0.89 (s, 9 H, 15-H), 0.10 (s, 3 H, 13-H), 0.08 (s, 3 H, 13-H‘).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 171.5 (s, C-4), 156.5 (s, C-16), 134.2 (d, C-9), 117.7 (t, C-10), 81.6 (d, C-11), 80.9 (d, C-7), 80.0 (s, C-17), 72.8 (d, C-6), 68.8 (d, C-2), 62.9 (t, C-12), 54.7 (d, C-5), 45.5 (t, C-1), 42.1 (t, C-3), 34.0 (t, C-8), 28.5 (q, C-18), 25.9 (q, C-15), 18.1 (s, C-14), –4.7 (q, C-13), –4.8 (q, C-13‘).

Optical rotation: $[\alpha]_D^{20}$= –20.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{17}H_{31}N_2O_7$ [M-TBS+2H]$^+$:	375.2126	375.2128

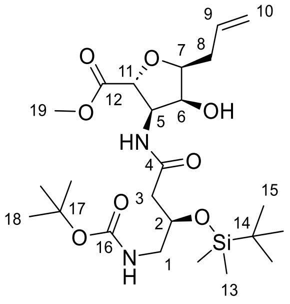
Methyl (2*R*,3*R*,4*S*,5*S*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)-oxy)butanamido)-4-hydroxytetrahydrofuran-2-carboxylate 92

In a 10 mL Schlenk tube under an atmosphere of nitrogen, DMP (138 mg, 315 µmol, 1.15 eq.) was added to a 0 °C cold solution of compound **91** (134 mg, 274 µmol) in CH_2Cl_2 (2.7 mL). The resulting solution was stirred for 100 min before another portion of DMP (18.0 mg, 41.0 µmol, 0.15 eq.) was added. After stirring for another 20 min, the reaction mixture was quenched by adding a preformed mixture of sat. $NaHCO_3$ solution and sat. NaS_2O_3 solution (4 mL, 7:3). The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude aldehyde.

The above-prepared crude aldehyde was dissolved in MeCN (2.7 mL). A solution of NaH_2PO_4 (7.5 mg, 55.0 µmol, 0.2 eq.) in H_2O (100 µL) and H_2O_2 (27.9 µL, 273 µmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (49.4 mg, 437 µmol, 1.6 eq.) in H_2O (100 µL) was added dropwise. The resulting solution was stirred for 2 h at room temperature. After the addition of Na_2SO_4 (80 mg) and brine (7.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid.

K_2CO_3 (56.5 mg, 409 µmol, 1.5 eq.) and MeI (85.0 µL, 1.36 mmol, 5.0 eq.) were added to a solution of the above-prepared carboxylic acid in anhydrous DMF (2.7 mL). The resulting suspension was stirred for 1 h at room temperature. After full conversion, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give compound **92** (70.0 mg, 135 µmol, 50%) as a colorless resin.

LC-MS: t_R (92) = 1.34 min (short method)



92

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.00 (d, $^{3}J_{NH,5}$ = 8.3 Hz, 1 H, 4-NH), 5.84 (ddt, $^{3}J_{9,10'}$ = 17.1 Hz, $^{3}J_{9,10}$ = 10.2 Hz, $^{3}J_{9,8}$ = 6.9 Hz, 1 H, 9-H), 5.21 (ddt, $^{3}J_{10',9}$ = 17.2 Hz, $^{2}J_{10',10}$ = 1.6 Hz, $^{4}J_{10',8}$ = 1.6 Hz, 1 H, 10-H‘), 5.11 (ddt, $^{3}J_{10,9}$ = 10.1 Hz, $^{2}J_{10,10'}$ = 1.2 Hz, $^{4}J_{10,8}$ = 1.2 Hz, 1 H, 10-H), 4.92 (t, $^{3}J_{NH,1}$ = 6.5 Hz, 1 H, 16-NH), 4.68 (ddd, $^{3}J_{5,NH}$ = 8.5 Hz, $^{3}J_{5,11}$ = 8.5 Hz, $^{3}J_{5,6}$ = 4.4 Hz, 1 H, 5-H), 4.33 (d, $^{3}J_{11,5}$ = 8.7 Hz, 1 H, 11-H), 4.27 (ddd, $^{3}J_{7,8}$ = 7.8 Hz, $^{3}J_{7,8'}$ = 6.5 Hz, $^{3}J_{7,6}$ = 2.7 Hz, 1 H, 7-H), 4.21 (m, 1 H, 6-H), 4.12 (tt, $^{3}J_{2,1}$ = 5.4 Hz, $^{3}J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 3.76 (s, 3 H, 19-H), 3.22 (m, 2 H, 1-H), 2.87 (m, 1 H, 6-OH), 2.53 (m, 2 H, 8-H), 2.43 (m, 2 H, 3-H), 1.45 (s, 9 H, 18-H), 0.90 (s, 9 H, 15-H), 0.12 (s, 3 H, 13-H), 0.10 (s, 3 H, 13-H‘).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.5 (s, C-12), 170.4 (s, C-4), 156.7 (s, C-16), 133.7 (d, C-9), 118.0 (t, C-10), 82.3 (d, C-7), 80.1 (s, C-17), 78.5 (d, C-11), 72.0 (d, C-6), 69.1 (d, C-2), 57.1 (d, C-5), 52.6 (q, C-19), 45.3 (t, C-1), 42.3 (t, C-3), 33.6 (t, C-8), 28.5 (q, C-18), 25.9 (q, C-15), 18.1 (s, C-14), –4.69 (q, C-13), –4.70 (q, C-13‘).

Optical rotation: $[\alpha]_D^{20}$= –14.4 (c = 1.0, $CHCl_3$)

HRMS (ESI):	calculated	found
$C_{24}H_{45}N_2O_8Si$ $[M+H]^+$:	517.2940	517.2946

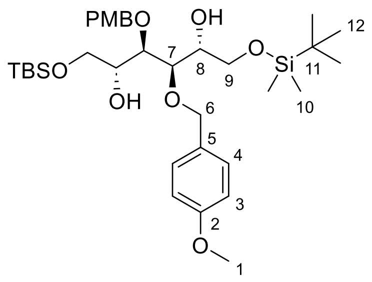
(6*R*,7*R*,8*R*,9*R*)-7,8-Bis((4-methoxybenzyl)oxy)-2,2,3,3,12,12,13,13-octamethyl-4,11-dioxa-3,12-disilatetradecane-6,9-diol 94

A solution of 1,2:5,6-Di-*O*-isopropylidene-D-mannitol[174] (7.20 g, 27.4 mmol) in DMSO (20 mL) was slowly added to a suspension of sodium hydride (2.74 g, 68.6 mmol, 2.5 eq.) in DMSO (45 mL). The resulting mixture was stirred for 30 min at room temperature before PMB-Cl (8.97 mL, 65.9 mmol, 2.4 eq.) was added, and the stirring continued for 3 h at 50 °C. The reaction mixture was diluted with 200 mL H_2O and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude fully protected mannitol.

The above-prepared fully protected mannitol was dissolved in a mixture of MeOH (120 mL) and H_2O (36 mL). After the addition of 1.0 M HCl_{aq} (0.8 mL), the mixture was refluxed for 2 h. Neutralization with sat. $NaHCO_3$ solution was followed by concentration in vacuo. The residue was redissolved in $CHCl_3$ and filtrated before the filtrate was concentrated in vacuo. Attempts to recrystallize the product from EtOH:Et_2O, PE:EtOAc, and toluene did not afford the product as a crystalline solid. The product was used as crude in the next step.

The above-prepared crude product was dissolved in DMF (27 mL). Imidazole (7.22 g, 106 mmol, 4.0 eq.) and TBS-Cl (8.59 g, 57.0 mmol, 2.1 eq.) were subsequently added at 0 °C, and the resulting solution was stirred for 2 h. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, PE:EtOAc 85:15) to give mannitol derivative **94** (7.28 g, 11.2 mmol, 41%) as a colorless solid.

TLC: R_f (94) = 0.26 (silica, PE:EtOAc 85:15)



94

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 4 H, 4-H), 6.86 (m, 4 H, 3-H), 4.66 (d, $^2J_{6,6'}$ = 11.1 Hz, 2 H, 6-H), 4.56 (d, $^2J_{6',6}$ = 11.2 Hz, 2 H, 6-H‘), 3.88 (m, 2 H, 8-H), 3.81 (m, 2 H, 7-H), 3.80 (s, 6 H, 1-H), 3.77 (dd, $^2J_{9,9'}$ = 10.2 Hz, $^3J_{9,8}$ = 3.9 Hz, 2 H, 9-H), 3.62 (dd, $^2J_{9',9}$ = 10.2 Hz, $^3J_{9',8}$ = 5.5 Hz, 2 H, 9-H‘), 2.75 (d, $^3J_{OH,8}$ = 5.2 Hz, 2 H, 8-OH), 0.92 (s, 18 H, 12-H), 0.08 (s, 6 H, 10-H), 0.08 (s, 6 H, 10‘-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.5 (s, C-2), 130.8 (s, C-5), 130.1 (d, C-3), 114.0 (d, C-4), 78.1 (d, C-7), 73.7 (t, C-6), 71.1 (d, C-8), 64.6 (t, C-9), 55.4 (q, C-1), 26.1 (q, C-12), 18.5 (s, C-11), –5.15 (q, C-10), –5.17 (q, C-10‘).

Optical rotation: $[\alpha]_D^{20}$= +26.0 (c = 0.5, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{34}H_{61}O_8Si_2$ [M+3H]$^+$:	653.3899	653.3891

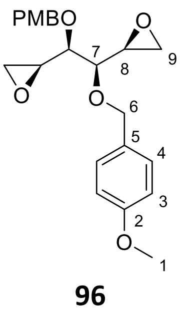
Melting point: 59 – 62 °C

(1*R*,2*R*)-1,2-Bis((4-methoxybenzyl)oxy)-1,2-di((*S*)-oxiran-2-yl)ethane 96

Triethylamine (4.16 mL, 29.9 mmol, 4.0 eq.) and Ms-Cl (1.75 mL, 22.4 mmol, 3.0 eq.) were subsequently added to a 0 °C cold solution of mannitol derivative **94** (4.86 g, 7.47 mmol) in anhydrous CH_2Cl_2 (40 mL). The reaction mixture was stirred for 30 min at 0 °C. After dilution with H_2O and CH_2Cl_2, the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were washed with 0.1 M HCl_{aq} and brine. Drying with $MgSO_4$ and concentration in vacuo gave the crude bis-mesylated product **95**.

Concentrated HCl_{aq} (1.56 mL, 18.7 mmol, 2.5 eq.) was slowly added to a 0 °C cold solution of the above-prepared bis-mesylated product **95** in MeOH (20 mL). After full addition, the cooling bath was removed, and the reaction mixture was stirred for 2 h. KOH_{aq} (12.6 g, 44.9 mmol, 20 wt%, 6.0 eq.) was slowly added at 0 °C. The cooling bath was removed, and the stirring continued for another 5 h. After concentration in vacuo, the residue was redissolved in CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with sat. $NaHCO_3$ solution and brine. After drying with $MgSO_4$ and concentration in vacuo, the crude was purified by column chromatography (silica, pentane:EtOAc 7:3) to give bis-epoxide **96** (1.57 g, 4.06 mmol, 54%) as a white foam.

TLC: R$_f$ (96) = 0.23 (silica, PE:EtOAc 6:4)



96

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 4 H, 4-H), 6.86 (m, 4 H, 3-H), 4.76 (d, $^2J_{6,6'}$ = 11.7 Hz, 2 H, 6-H), 4.54 (d, $^2J_{6',6}$ = 11.7 Hz, 2 H, 6-H‘), 3.81 (s, 6 H, 1-H), 3.26 (m, 2 H, 8-H), 3.18 (m, 2 H, 7-H), 2.77 (dd, $^2J_{9,9'}$ = 4.8 Hz, $^3J_{9,8}$ = 4.3 Hz, 2 H, 9-H), 2.50 (dd, $^2J_{9',9}$ = 4.9 Hz, $^3J_{9',8}$ = 2.7 Hz, 2 H, 9-H‘).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.4 (s, C-2), 130.1 (s, C-5), 129.8 (d, C-3), 113.8 (d, C-4), 80.2 (d, C-7), 72.0 (t, C-6), 55.4 (q, C-1), 52.6 (d, C-8), 43.2 (t, C-9).

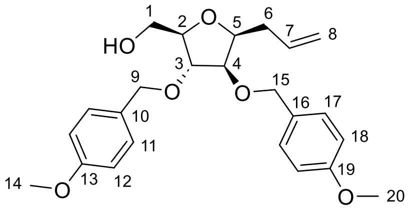
Optical rotation: $[\alpha]_D^{20}$= –74.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{22}H_{25}O_6$ $[M-H]^+$:	385.1646	385.1644

((2*R*,3*R*,4*R*,5*S*)-5-Allyl-3,4-bis((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methanol 97

2.5 M *n*-BuLi in hexane (3.11 mL, 7.76 mmol, 6.0 eq.) was added dropwise to a –78 °C cold solution of tetravinyl stannane (449 µL, 2.33 mmol, 1.8 eq.) in anhydrous THF (10 mL). The resulting solution was stirred for 20 min at –78 °C and 45 min at room temperature. This solution was added (via syringe pump for 4 h) to a vigorously stirred suspension of bis-epoxide **96** (500 mg, 1.29 mmol) and $BF_3{\cdot}OEt_2$ (984 µL, 7.76 mmol, 6.0 eq.) in anhydrous THF (16 mL) at –70 to –78 °C. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ solution and extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 50% EtOAc) to give C-furanoside **97** (391 mg, 887 µmol, 69%, 94 wt% purity: contaminated with the double substitution product **99**) as a colorless resin.

TLC: R_f (97) = 0.39 (silica, PE: EtOAc 1:1)



97

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.27 – 7.21 (m, 4 H, 11-H, 17-H), 6.92 – 6.86 (m, 4 H, 12-H, 18-H), 5.80 (ddt, $^3J_{7,8}$ = 17.1 Hz, $^3J_{7,8'}$ = 10.2 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.13 (ddt, $^3J_{8,7}$ = 17.2 Hz, $^2J_{8,8'}$ = 1.7 Hz, $^4J_{8,6}$ = 1.7 Hz, 1 H, 8-H), 5.06 (ddt, $^3J_{8',7}$ = 10.0 Hz, $^2J_{8',8}$ = 2.2 Hz, $^4J_{8',6}$ = 1.1 Hz, 1 H, 8-H‘), 4.55 (d, $^2J_{15,15'}$ = 11.4 Hz, 1 H, 15-H), 4.49 (d, $^2J_{9,9'}$ = 11.4 Hz, 1 H, 9-H), 4.45 (d, $^2J_{9',9}$ = 11.4 Hz, 1 H, 9-H‘), 4.35 (d, $^2J_{15',15}$ = 11.3 Hz, 1 H, 15-H‘), 4.06 – 3.96 (m, 3 H, 2-H, 3-H, 5-H), 3.83 – 3.81 (m, 6 H, 14-H, 20-H), 3.80 – 3.77 (m, 2 H, 1-H, 4-H), 3.63 (dd, $^2J_{1',1}$ = 11.5 Hz, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H‘), 2.48 (m, 2 H, 6-H).

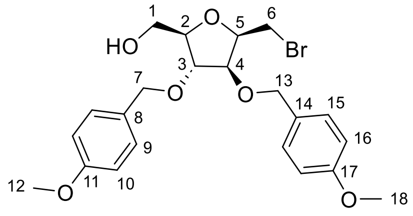
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.4 (s, C-13, C-19), 134.7 (d, C-7), 129.7 (s, C-16), 129.6 (d, C-17), 129.5 (s, C-10), 129.3 (d, C-11), 117.1 (t, C-8), 114.0 (d, C-18), 113.9 (d, C-12), 84.6 (d, C-2), 82.6 (d, C-3), 81.9 (d, C-4), 81.0 (d, C-5), 71.6 (t, C-9), 71.1 (t, C-15), 63.2 (t, C-1), 55.3 (q, C-14, C-20), 33.0 (t, C-6).

Optical rotation:	$[\alpha]_D^{20}$= –104.5 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
C$_{24}$H$_{30}$O$_6$ [M]$^+$:	414.2037	414.2018

((2*R*,3*R*,4*S*,5*R*)-5-(Bromomethyl)-3,4-bis((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methanol 98

BF$_3$·OEt$_2$ (37.0 µL, 290 µmol, 2.0 eq.) was added to a –50 °C cold solution of LiBr (25.2 mg, 290 µmol, flame-dried in vacuo, 2.0 eq.) in anhydrous THF (1.2 mL). After stirring for 5 min, a solution of bis-epoxide **96** (56.0 mg, 145 µmol) in anhydrous THF (500 µL) was added. The reaction was stirred for 5 min at –50 °C before being quenched with sat. NaHCO$_3$ solution. The aqueous layer was extracted with EtOAc. The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo. Purification by column chromatography (silica, pentane:EtOAc 6:4) afforded bromo C-furanoside **98** (55.0 mg, 118 µmol, 81%) as a colorless oil.

TLC: R$_f$ (98) = 0.15 (silica, PE:EtOAc 6:4)



98

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.26 (m, 2 H, 15-H), 7.26 (m, 2 H, 9-H), 6.91 (m, 2 H, 10-H), 6.91 (m, 2 H, 16-H), 4.56 (d, $^2J_{13,13'}$ = 11.1 Hz, 1 H, 13-H), 4.49 (d, $^2J_{7,7'}$ = 11.5 Hz, 1 H, 7-H), 4.44 (d, $^2J_{7',7}$ = 11.5 Hz, 1 H, 7-H'), 4.43 (d, $^2J_{13',13}$ = 11.1 Hz, 1 H, 13-H'), 4.29 (ddd, $^3J_{5,6}$ = 7.8 Hz, $^3J_{5,6'}$ = 6.0 Hz, $^3J_{5,4}$ = 3.4 Hz, 1 H, 5-H), 4.11 (ddd, $^3J_{2,1}$ = 4.4 Hz, $^3J_{2,3}$ = 4.4 Hz, $^3J_{2,1'}$ = 3.0 Hz, 1 H, 2-H), 4.03 – 4.00 (m, 2 H, 3-H, 4-H), 3.83 (s, 3 H, 12-H/18-H), 3.82 (s, 3 H, 18-H/12-H), 3.75 (m, 1 H, 1-H), 3.63 (m, 1 H, 1-H'), 3.57 (dd, $^2J_{6,6'}$ = 9.8 Hz, $^3J_{6,5}$ = 7.8 Hz, 1 H, 6-H), 3.50 (dd, $^2J_{6',6}$ = 9.9 Hz, $^3J_{6',5}$ = 6.0 Hz, 1 H, 6-H').

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 159.7 (s, C-17), 159.6 (s, C-11), 129.9 (d, C-15), 129.6 (s, C-14), 129.4 (d, C-9), 129.2 (s, C-8), 114.1 (d, C-16), 114.1 (d, C-10), 85.7 (d, C-2), 82.4 (d, C-3), 81.5 (d, C-4), 81.4 (d, C-5), 71.9 (t, C-13), 71.7 (t, C-7), 63.2 (t, C-1), 55.4 (q, C-12, C-18), 28.2 (t, C-6).

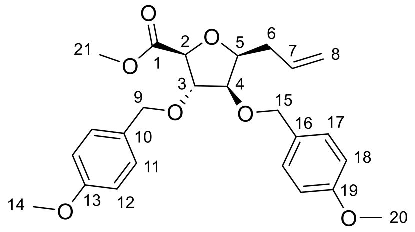
Methyl (2*S*,3*S*,4*R*,5*S*)-5-allyl-3,4-bis((4-methoxybenzyl)oxy)tetrahydrofuran-2-carboxylate 100

A solution of DMSO (183 µL, 2.57 mmol, 3.0 eq.) in anhydrous CH$_2$Cl$_2$ (500 µL) was added dropwise to a –78 °C cold solution of oxalyl dichloride (112 µL, 1.29 mmol, 1.5 eq.) in anhydrous CH$_2$Cl$_2$ (2.3 mL) keeping the temperature below –70 °C. After complete addition, the mixture was stirred at –60 to –70 °C for 30 min. A solution of C-furanoside **97** (378 mg, 857 µmol) in anhydrous CH$_2$Cl$_2$ (2.0 mL) was added dropwise while keeping the temperature below –60 °C. After stirring for another 45 min, a solution of DIPEA (747 µL, 4.29 mmol, 5.0 eq.) in anhydrous CH_2Cl_2 (500 µL) was added dropwise while keeping the temperature around –60 °C. The stirring was continued for 30 min before warming to 0 °C. After the addition of 1.0 M HCl_{aq} (10 mL), the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were washed with phosphate buffer (pH 7), dried with $MgSO_4$, and concentrated in vacuo to give the crude aldehyde.

The above-prepared crude aldehyde was dissolved in MeCN (8.5 mL). A solution of NaH_2PO_4 (23.7 mg, 172 µmol, 0.2 eq.) in H_2O (1.0 mL) and H_2O_2 (88.0 µL, 858 µmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (155 mg, 1.37 mmol, 1.6 eq.) in H_2O (1.0 mL) was added dropwise. The resulting solution was stirred for 16 h while slowly reaching room temperature. After the addition of Na_2SO_4 (200 mg) and brine (10 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid.

K_2CO_3 (178 mg, 1.29 mmol, 1.5 eq.) and MeI (161 µL, 2.58 mmol, 3.0 eq.) were added to a solution of the above-prepared carboxylic acid in anhydrous DMF (5.7 mL). The resulting suspension was stirred for 72 h at room temperature. After full conversion, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 30% EtOAc) to give compound **100** (245 mg, 554 µmol, 65%) as a colorless oil.

TLC: R_f (100) = 0.51 (silica, PE: EtOAc 6:4)



100

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 2 H, 11-H), 7.17 (m, 2 H, 17-H), 6.91 (m, 2 H, 12-H), 6.87 (m, 2 H, 18-H), 5.78 (ddt, $^3J_{7,8}$ = 17.1 Hz, $^3J_{7,8'}$ = 10.1 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.13 (ddt, $^3J_{8,7}$ = 17.2 Hz, $^2J_{8,8'}$ = 1.5 Hz, $^4J_{8,6}$ = 1.5 Hz, 1 H, 8-H), 5.05 (ddt, $^3J_{8',7}$ = 10.2 Hz, $^2J_{8',8}$ = 2.2 Hz, $^4J_{8',6}$ = 1.1 Hz, 1 H, 8-H'), 4.60 (d, $^2J_{9,9'}$ = 11.5 Hz, 1 H, 9-H), 4.49 (d, $^3J_{2,3}$ = 1.5 Hz, 1 H, 2-H), 4.49 (d, $^2J_{9',9}$ = 11.4 Hz, 1 H, 9-H'), 4.43 (d, $^2J_{15,15'}$ = 11.4 Hz, 1 H, 15-H), 4.35 (dd, $^3J_{3,4}$ = 1.4 Hz, $^3J_{3,2}$ = 1.4 Hz, 1 H, 3-H), 4.29 (d, $^2J_{15',15}$ = 11.4 Hz, 1 H, 15-H'), 4.19 (td, $^3J_{5,6}$ = 7.2 Hz, $^3J_{5,4}$ = 3.5 Hz, 1 H, 5-H), 3.82 (s, 3 H, 14-H), 3.81 (s, 3 H, 20-H), 3.77 (dd, $^3J_{4,5}$ = 3.6 Hz, $^3J_{4,3}$ = 1.1 Hz, 1 H, 4-H), 3.69 (s, 3 H, 21-H), 2.54 (m, 2 H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.5 (s, C-1), 159.6 (s, C-13), 159.4 (s, C-19), 134.7 (d, C-7), 129.8 (s, C-10), 129.6 (d, C-11), 129.5 (s, C-16), 129.5 (d, C-17), 117.3 (t, C-8), 114.0 (d, C-12), 113.9 (d, C-18), 84.8 (d, C-3), 82.3 (d, C-5), 81.5 (d, C-2), 80.8 (d, C-4), 71.5 (t, C-9), 71.3 (t, C-15), 55.4 (q, C-20/C-14), 55.4 (q, C-14/C-20), 52.4 (q, C-21), 33.3 (t, C-6).

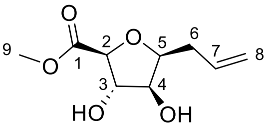
Optical rotation: $[\alpha]_D^{20}$= +33.0 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{25}H_{30}O_7$ $[M]^+$:	442.1986	442.2024

Methyl (2*S*,3*S*,4*S*,5*S*)-5-allyl-3,4-dihydroxytetrahydrofuran-2-carboxylate 101

Ceric ammonium nitrate (198 mg, 362 µmol, 4.0 eq.) was added to 0 °C cold solution of compound **100** (40.0 mg, 90.4 mmol) in MeCN:H_2O (900 µL, 10:1). The reaction mixture was stirred for 2 h at 0 °C before being concentrated in vacuo. The crude was purified by automated flash column chromatography (silica, CyH:EtOAc 10% to 60% EtOAc) to give the diol **101** (14.6 mg, 72.0 µmol, 80%) as a colorless resin.

TLC: R_f (101) = 0.10 (silica, PE: EtOAc 6:4)



101

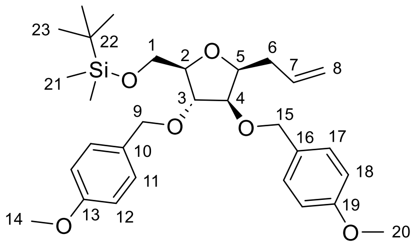
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.90 (ddt, $^3J_{7,8}$ = 17.2 Hz, $^3J_{7,8'}$ = 10.2 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.22 (ddt, $^3J_{8,7}$ = 17.2 Hz, $^2J_{8,8'}$ = 1.7 Hz, $^4J_{8,6}$ = 1.7 Hz, 1 H, 8-H), 5.13 (ddt, $^3J_{8',7}$ = 10.2 Hz, $^2J_{8',8}$ = 2.1 Hz, $^4J_{8',6}$ = 1.3 Hz, 1 H, 8-H'), 4.39 (m, 1 H, 3-H), 4.35 (d, $^3J_{2,3}$ = 1.5 Hz, 1 H, 2-H), 4.22 (td, $^3J_{5,6}$ = 7.1 Hz, $^3J_{5,4}$ = 2.9 Hz, 1 H, 5-H), 3.96 (m, 1 H, 4-H), 3.81 (s, 3 H, 9-H), 2.56 (m, 2 H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.0 (s, C-1), 134.1 (d, C-7), 117.8 (t, C-8), 83.5 (d, C-2), 82.5 (d, C-5), 81.0 (d, C-3), 77.7 (d, C-4), 52.9 (q, C-9), 33.0 (t, C-6).

(((2*R*,3*R*,4*R*,5*S*)-5-Allyl-3,4-bis((4-methoxybenzyl)oxy)tetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane 103

Imidazole (104 mg, 1.53 mmol, 2.4 eq.) and TBS-Cl (115 mg, 764 µmol, 1.2 eq.) were successively added to a 0 °C cold solution of C-furanoside **97** (264 mg, 637 µmol) in anhydrous DMF (2.1 mL). The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 15% EtOAc) to give compound **103** (278 mg, 526 µmol, 83%) as a colorless oil.

TLC: R_f (103) = 0.55 (silica, pentane: EtOAc 8:2)



103

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.27 (m, 2 H, 17-H), 7.23 (m, 2 H, 11-H), 6.90 (m, 2 H, 18-H), 6.88 (m, 2 H, 12-H), 5.79 (ddt, $^3J_{7,8}$ = 17.2 Hz, $^3J_{7,8'}$ = 10.2 Hz, $^3J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.12 (ddt, $^3J_{8,7}$ = 17.1 Hz, $^2J_{8,8'}$ = 1.6 Hz, $^4J_{8,6}$ = 1.6 Hz, 1 H, 8-H), 5.04 (m, 1 H, 8-H'), 4.52 (d, $^2J_{15,15'}$ = 11.5 Hz, 1 H, 15-H), 4.51 (d, $^2J_{9,9'}$ = 11.6 Hz, 1 H, 9-H), 4.42 (d, $^2J_{15',15}$ = 11.5 Hz, 1 H, 15-H'), 4.35 (d, $^2J_{9',9}$ = 11.4 Hz, 1 H, 9-H'), 4.03 (td, $^3J_{5,6}$ = 7.1 Hz, $^3J_{5,4}$ = 3.5 Hz, 1 H, 5-H), 3.98 (m, 1 H, 3-H), 3.94 (m, 1 H, 2-H), 3.82 (s, 6 H, 14-H, 20-H), 3.80 – 3.75 (m, 2 H, 1-H, 4-H), 3.57 (dd, $^2J_{1,1'}$ = 9.9 Hz, $^3J_{1,2}$ = 8.5 Hz, 1 H, 1-H'), 2.46 (m, 2 H, 6-H), 0.91 (s, 9 H, 23-H), 0.07 (s, 6 H, 21-H).

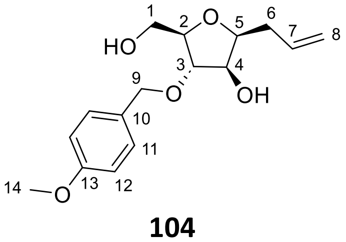
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 159.4 (s, C-13, C-19), 135.2 (d, C-7), 130.3 (s, C-16), 130.2 (s, C-10), 129.4 (d, C-11, C-17), 116.9 (t, C-8), 114.0 (d, C-18), 113.9 (d, C-12), 84.4 (d, C-2), 83.4 (d, C-3), 82.8 (d, C-4), 80.9 (d, C-5), 71.3 (t, C-9), 71.1 (t, C-15), 63.9 (t, C-1), 55.4 (q, C-14, C-20), 33.4 (t, C-6), 26.1 (q, C-23), 18.5 (s, C-22), –5.1 (q, C-21), –5.2 (q, C-21').

Optical rotation:	$[\alpha]_D^{20}$= +9.5 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{30}H_{43}O_6Si$ [M-H]$^+$:	527.2823	527.2826

(2*S*,3*R*,4*S*,5*R*)-2-Allyl-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)tetrahydrofuran-3-ol 104

A solution of CAN (547 mg, 999 µmol, 2.2 eq.) in H$_2$O (400 µL) was dropwise added to a 0 °C cold solution of compound **103** (240 mg, 454 µmol) in MeCN (4.1 mL). The resulting mixture was stirred for 3 h at 0 °C. After dilution with EtOAc and H$_2$O, the aqueous layer was extracted with EtOAc. The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 60% EtOAc) to give the diol **104** (20.0 mg, 68.2 µmol, 15%) as a colorless resin and the TBS-deprotection product **97** (81.1 mg, 195 µmol, 43%) as a colorless resin.

TLC: R$_f$ (104) = 0.10 (silica, pentane: EtOAc 1:1)



104

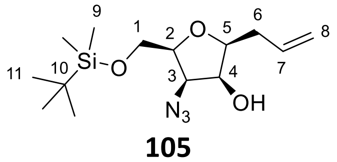
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.25 (m, 2 H, 11-H), 6.89 (m, 2 H, 12-H), 5.87 (ddt, $^{3}J_{7,8}$ = 17.2 Hz, $^{3}J_{7,8'}$ = 10.2 Hz, $^{3}J_{7,6}$ = 6.9 Hz, 1 H, 7-H), 5.18 (ddt, $^{3}J_{8,7}$ = 17.1 Hz, $^{2}J_{8,8'}$ = 1.6 Hz, $^{4}J_{8,6}$ = 1.6 Hz, 1 H, 8-H), 5.10 (ddt, $^{3}J_{8,7}$ = 10.2 Hz, $^{2}J_{8,8'}$ = 2.2 Hz, $^{4}J_{8,6}$ = 1.2 Hz, 1 H, 8-H‘), 4.57 (d, $^{2}J_{9,9'}$ = 11.4 Hz, 1 H, 9-H), 4.48 (d, $^{2}J_{9',9}$ = 11.4 Hz, 1 H, 9-H‘), 4.03 (m, 1 H, 5-H), 4.01 – 3.98 (m, 1 H, 3-H), 3.91 (m, 2 H, 2-H, 4-H), 3.85 (dd, $^{2}J_{1',1}$ = 11.7 Hz, $^{3}J_{1',2}$ = 2.7 Hz, 1 H, 1-H‘), 3.81 (s, 3 H, 14-H), 3.64 (dd, $^{2}J_{1,1'}$ = 11.7 Hz, $^{3}J_{1,2}$ = 2.1 Hz, 1 H, 1-H), 2.47 (ddt, $^{3}J_{6,5}$ = 6.9 Hz, $^{3}J_{6,7}$ = 6.9 Hz, $^{4}J_{6,8}$ = 1.4 Hz, 2 H, 6-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.5 (s, C-13), 134.6 (d, C-7), 129.8 (s, C-10), 129.5 (d, C-11), 117.3 (t, C-8), 114.0 (d, C-12), 86.6 (d, C-3), 84.1 (d, C-2), 81.9 (d, C-5), 74.5 (d, C-4), 71.7 (t, C-9), 62.7 (t, C-1), 55.4 (q, C-14), 32.9 (t, C-6).

(2*S*,3*S*,4*R*,5*S*)-2-Allyl-4-azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-ol 105

In a 250 mL Schlenk-tube under an atmosphere of nitrogen, allyltrimethylsilane (9.65 mL, 60.7 mmol, 4.0 eq.) was added to a −10 °C cold solution of compound **64** (5.00 g, 15.2 mmol) in anhydrous CH_2Cl_2 (150 mL). After stirring for 10 min, $BF_3{\cdot}OEt_2$ (8.01 mL, 30.4 mmol, 2.0 eq.) was added, and the stirring continued for 30 min. The cooling bath was removed, and the stirring continued for 2 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution (200 mL) and brine (20 mL) before being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was dissolved in anhydrous DMF (15 mL) before adding imidazole (2.07 g, 30.4 mmol, 2.0 eq.) and TBS-Cl (2.29 g, 15.2 mmol, 1.0 eq.) at room temperature. After stirring for 24 h, the reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 30% EtOAc) to give C-furanoside **105** (1.05 g, 3.35 mmol, 22%, dr 95:5) and compound **67a** (1.43 g, 3.34 mmol, 22%, dr 95:5) as a colorless oil.

TLC: R_f (105) = 0.37 (silica, pentane:EtOAc 85:15)



105

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.85 (ddt, $^{3}J_{7,8'}$ = 17.1 Hz, $^{3}J_{7,8}$ = 10.1 Hz, $^{3}J_{7,6}$ = 7.0 Hz, 1 H, 7-H), 5.16 (ddt, $^{3}J_{8',7}$ = 17.1 Hz, $^{2}J_{8',8}$ = 1.7 Hz, $^{4}J_{8',6}$ = 1.6 Hz, 1 H, 8-H′), 5.09 (ddt, $^{3}J_{8,7}$ = 10.2 Hz, $^{2}J_{8,8'}$ = 2.1 Hz, $^{4}J_{8,6}$ = 1.1 Hz, 1 H, 8-H), 4.52 (d, $^{3}J_{OH,4}$ = 11.7 Hz, 1 H, 4-OH), 4.30 (dd, $^{3}J_{3,2}$ = 9.0 Hz, $^{3}J_{3,4}$ = 4.7 Hz, 1 H, 3-H), 4.14 (ddd, $^{3}J_{2,3}$ = 9.0 Hz, $^{3}J_{2,1}$ = 3.1 Hz, $^{3}J_{2,1'}$ = 1.4 Hz, 1 H, 2-H), 4.11 (ddd, $^{3}J_{4,OH}$ = 11.6 Hz, $^{3}J_{4,3}$ = 4.7 Hz, $^{3}J_{4,5}$ = 2.8 Hz, 1 H, 4-H), 3.82 (ddd, $^{3}J_{5,6'}$ = 7.4 Hz, $^{3}J_{5,6}$ = 6.5 Hz, $^{3}J_{5,4}$ = 2.8 Hz, 1 H, 5-H), 3.74 (dd, $^{2}J_{1,1'}$ = 11.2 Hz, $^{3}J_{1,2}$ = 3.1 H, 1 H, 1-H), 3.69 (dd, $^{2}J_{1',1}$ = 11.2 Hz, $^{3}J_{1',2}$ = 1.4 H, 1 H, 1-H‘), 2.47 (dddt, $^{2}J_{6,6'}$ = 14.5 Hz, $^{3}J_{6,7}$ = 6.6 Hz, $^{3}J_{6,5}$ = 6.6 Hz, $^{4}J_{6,8}$ = 1.4 Hz, 1 H, 6-H), 2.39 (dddt, $^{2}J_{6',6}$ = 14.7 Hz, $^{3}J_{6',7}$ = 7.4 Hz, $^{3}J_{6',5}$ = 7.4 Hz, $^{4}J_{6',8}$ = 1.3 Hz, 1 H, 6-H‘), 0.95 (s, 9 H, 11-H), 0.15 (s, 6 H, 9-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 134.4 (d, C-7), 117.5 (t, C-8), 81.2 (d, C-5), 78.1 (d, C-2), 71.4 (d, C-4), 64.2 (d, C-3), 61.9 (t, C-1), 34.0 (t, C-6), 25.9 (q, C-11), 18.6 (s, C-10), –5.5 (q, C-9‘), –5.6 (q, C-9).

Optical rotation: $[\alpha]_D^{20}$= +56.6 (c = 1.0, $CHCl_3$)

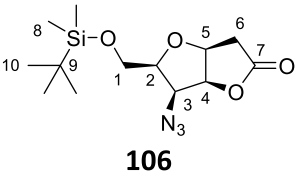
HRMS (ESI):	calculated	found
$C_{14}H_{28}N_3O_3Si$ $[M+H]^+$:	314.1894	314.1895

(3a*S*,5*S*,6*S*,6a*S*)-6-Azido-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuro[3,2-b]furan-2(3*H*)-one 106

In a 25 mL 2-neck flask, a solution of C-furanoside **105** (100 mg, 319 µmol) in anhydrous CH_2Cl_2 (6.0 mL) was cooled to –78 °C. The solution was saturated with ozone until the reaction mixture turned blue (10 s). After stirring for another 30 s, the solution was degassed with N_2. Dimethylsulfide (236 µL, 3.19 mmol, 10 eq.) was added at –70 °C and the reaction mixture was stirred for 18 h while slowly reaching room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 40% EtOAc) to give the hemiacetal (94.0 mg, 298 µmol, 93%) as a colorless resin.

The above-prepared hemiacetal (50.0 mg, 159 µmol) was dissolved in MeCN (1.2 mL). A solution of NaH_2PO_4 (3.8 mg, 31.7 µmol, 0.2 eq.) in H_2O (100 µL) and H_2O_2 (16.0 µL, 159 µmol, 30wt%, 1.0 eq.) were subsequently added. After cooling to 0 °C, a solution of $NaClO_2$ (28.7 mg, 254 µmol, 1.6 eq.) in H_2O (100 µL) was added dropwise. The resulting solution was stirred for 16 h at room temperature. After the addition of Na_2SO_4 (15 mg) and brine (2.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (1.0 mL) before pTsOH (3.0 mg, 15.8 µmol, 10mol%) was added. The resulting solution was stirred for 2 h at room temperature. After concentration in vacuo, the crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 50% EtOAc) to give the lactone **106** (30.0 mg, 96.1 µmol, 60%) as a colorless resin.

TLC: R_f (106) = 0.31 (silica, pentane:EtOAc 6:4)



106

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.17 (dd, $^3J_{4,5}$ = 6.8 Hz, $^3J_{4,3}$ = 5.8 Hz, 1 H, 4-H), 4.70 (ddd, $^3J_{5,6}$ = 7.8 Hz, $^3J_{5,4}$ = 6.8 Hz, $^3J_{5,6'}$ = 3.4 Hz, 1 H, 5-H), 4.29 (dd, $^3J_{3,4}$ = 5.8 Hz, $^3J_{3,2}$ = 3.9 Hz, 1 H, 3-H), 3.95 (ddd, $^3J_{2,1}$ = 6.8 Hz, $^3J_{2,1'}$ = 5.8 Hz, $^3J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 3.88 (dd, $^2J_{1,1'}$ = 10.3 Hz, $^3J_{1,2}$ = 6.8 Hz, 1 H, 1-H), 3.80 (dd, $^2J_{1',1}$ = 10.3 Hz, $^3J_{1',2}$ = 5.9 Hz, 1 H, 1-H‘), 2.79 (dd, $^2J_{6,6'}$ = 18.8 Hz, $^3J_{6,5}$ = 7.8 Hz, 1 H, 6-H), 2.69 (dd, $^2J_{6',6}$ = 18.8 Hz, $^3J_{6',5}$ = 3.5 Hz, 1 H, 6-H‘), 0.91 (s, 9 H, 10-H), 0.10 (s, 3 H, 8′-H), 0.09 (s, 3 H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.6 (s, C-7), 82.3 (d, C-4), 81.8 (d, C-2), 76.1 (d, C-5), 63.3 (t, C-1), 61.3 (d, C-3), 35.7 (t, C-6), 26.0 (q, C-10), 18.4 (s, C-9), –5.3 (q, C-8'), –5.4 (q, C-8).

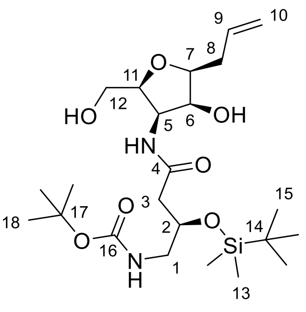
Optical rotation:	$[\alpha]_D^{20}$= –160.9 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{13}H_{24}N_3O_4Si$ $[M+H]^+$:	314.1531	314.1532

***tert*-Butyl ((*R*)-4-(((2*S*,3*R*,4*S*,5*S*)-5-allyl-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-4-oxobutyl)carbamate 107**

Ammonium sulfide in H_2O (7.5 mL, 40wt%) was added to a 0 °C cold solution of C-furanoside **105** (470 mg, 1.50 mmol) in MeCN (7.5 mL). The biphasic mixture was stirred for 16 h while slowly reaching room temperature. After the addition of sat. $NaHCO_3$ solution (20.0 mL), the mixture was extracted thrice with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude amine (300 mg, 939 µmol, 63%, 90wt% purity) as a colorless resin.

1.0 M TBAF in THF (1.07 mL, 1.07 mmol, 1.15 eq.) was added to a 0 °C cold solution of the above-prepared crude amine (298 mg, 933 µmol) in anhydrous THF (4.7 mL). The resulting solution was stirred for 2 h while slowly reaching room temperature. After adding 1.0 M HCl_{aq} (1.07 mL, 1.07 mmol, 1.15 eq.), the reaction mixture was concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (9.4 mL) before diazoketone **77** (444 mg, 1.22 mmol, 1.3 eq.) was added. The resulting yellow solution was irradiated with a blue LED (405 nm, 18 W) at room temperature for 3 h. After dilution with EtOAc, the mixture was washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution, and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give compound **107** (55 mg, 113 µmol, 12%) as a colorless resin.

LC-MS: t_R (107) = 1.29 min (short method)



107

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.71 (d, $^3J_{NH,5}$ = 7.3 Hz , 1 H, 4-NH), 5.85 (ddt, $^3J_{9,10'}$ = 17.2 Hz, $^3J_{9,10}$ = 10.2 Hz, $^3J_{9,8}$ = 7.0 Hz, 1 H, 9-H), 5.17 (ddt, $^3J_{10',9}$ = 17.1 Hz, $^2J_{10',10}$ = 1.7 Hz, $^4J_{10',8}$ = 1.5 Hz, 1 H, 10-H'), 5.08 (ddt, $^3J_{10,9}$ = 10.2 Hz, $^2J_{10,10'}$ = 2.1 Hz, $^4J_{10,8}$ = 1.1 Hz, 1 H, 10-H), 4.93 (dd, $^3J_{NH,1}$ = 9.4 Hz, $^3J_{NH,1'}$ = 3.4 Hz, 1 H, 16-NH), 4.63 (ddd, $^3J_{5,11}$ = 8.9 Hz, $^3J_{5,NH}$ = 7.3 Hz, $^3J_{5,6}$ = 4.6 Hz, 1 H, 5-H), 4.38 (d, $^3J_{11,5}$ = 8.8 Hz, 1 H, 11-H), 4.23 (m, 1 H, 2-H), 3.85 (dd, $^3J_{6,5}$ = 4.7 Hz, $^3J_{6,7}$ = 2.5 Hz, 1 H, 12-H), 3.81

(td, $^3J_{7,8}$ = 6.9 Hz, $^3J_{7,6}$ = 2.4 Hz, 1 H, 7-H), 3.75 (dd, $^2J_{12,12'}$ = 12.2 Hz, $^3J_{12,11}$ = 2.0 Hz, 1 H, 12-H), 3.55 (d, $^2J_{12',12}$ = 12.2 Hz, 1 H, 12-H‘), 3.40 (ddd, $^2J_{1,1'}$ = 13.8 Hz, $^3J_{1,\mathrm{NH}}$ = 9.4 Hz, $^3J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 3.03 (ddd, $^2J_{1',1}$ = 14.3 Hz, $^3J_{1',2}$ = 3.6 Hz, $^3J_{1',\mathrm{NH}}$ = 3.6 Hz, 1 H, 1-H‘), 2.52 – 2.39 (m, 3 H, 3-H, 8-H), 2.35 (dd, $^2J_{3',3}$ = 14.3 Hz, $^3J_{3',2}$ = 3.6 Hz, 1 H, 3-H‘), 1.44 (s, 9 H, 18-H), 0.90 (s, 9 H, 15-H), 0.11 (s, 3 H, 13-H), 0.10 (s, 3 H, 13-H‘).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 170.1 (s, C-4), 157.1 (s, C-16), 134.5 (d, C-9), 117.4 (t, C-10), 80.7 (s, C-17), 80.5 (d, C-7), 78.5 (d, C-11), 71.5 (d, C-6), 69.1 (d, C-2), 60.4 (t, C-12), 54.9 (d, C-5), 44.8 (t, C-1), 41.4 (t, C-3), 33.6 (t, C-8), 28.5 (q, C-18), 25.9 (q, C-15), 18.2 (s, C-14), –4.7 (q, C-13), –4.8 (q, C-13‘).

Optical rotation: $[\alpha]_D^{20}$= +48.5 (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{23}H_{45}N_2O_7Si$ [M+H]$^+$:	489.2991	489.2997

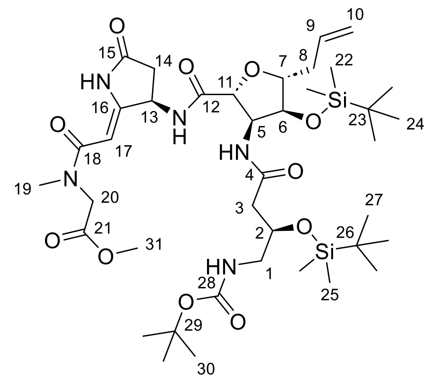
Methyl *N*-((*Z*)-2-((*R*)-3-((2*R*,3*S*,4*S*,5*R*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxamido)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycinate 110

0.20 M LiOH$_{aq}$ (741 µL, 148 µmol, 1.1 eq.) was slowly added to a 0 °C cold solution of **83** (85.0 mg, 135 µmol) in THF (700 µL). The resulting mixture was stirred for 2 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl$_{aq}$ and extracted with CH$_2$Cl$_2$. The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo to give the crude carboxylic acid **84** as a colorless resin.

4.0 M HCl in dioxane (806 µL, 3.22 mmol, 10 eq.) was added to a solution of dipeptide **38** (110 mg, 322 µmol) in CH$_2$Cl$_2$ (800 µL) at 0 °C. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between 1.0 M K$_2$CO$_3$ solution and CH$_2$Cl$_2$. The aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo to give the crude amine **109** (52.0 mg, 216 µmol, 67%) as a colorless resin.

The above-prepared crude carboxylic acid **84** and amine **109** (48.7 mg, 202 µmol, 1.5 eq.) were dissolved in anhydrous DMF (1.3 mL). After cooling to 0 °C, EDC·HCl (28.4 mg, 148 µmol, 1.1 eq.) and HOBt (4.1 mg, 27.0 µmol, 0.2 eq.) were added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% LiCl$_{aq}$, 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give tetrapeptide **110** (108 mg, 129 µmol, 96%, dr 90:10) as a white foam.

LC-MS: t_R (110) = 5.00 min (long method)



110

^{1}**H-NMR** (500 MHz, DMSO-d$_6$, 373 K): δ = 10.29 (s, 1 H, 15-NH), 8.11 (d, $^3J_{NH,13}$ = 8.2 Hz, 1 H, 12-NH), 7.30 (d, $^3J_{NH,5}$ = 8.2 Hz, 1 H, 4-NH), 6.09 (m, 1 H, 28-NH), 5.89 (ddt, $^3J_{9,10}$ = 17.1 Hz, $^3J_{9,10'}$ = 10.2 Hz, $^3J_{9,8}$ = 6.9 Hz, 1 H, 9-H), 5.37 (m, 1 H, 17-H), 5.17 – 5.06 (m, 3 H, 10-H, 13-H), 4.38 (m, 1 H, 5-H), 4.17 – 4.08 (m, 4 H, 2-H, 11-H, 20-H), 4.02 (m, 1 H, 6-H), 3.91 (td, $^3J_{7,8}$ = 6.4 Hz, $^3J_{7,6}$ = 4.2 Hz, 1 H, 7-H), 3.67 (s, 3 H, 31-H), 3.10 – 2.96 (m, 2 H, 1-H), 3.02 (s, 3 H, 19-H), 2.75 (dd, $^2J_{14,14'}$ = 17.5 Hz, $^3J_{14,13}$ = 9.5 Hz, 1 H, 14-H'), 2.42 – 2.33 (m, 4 H, 3-H', 8-H, 14-H), 2.24 (dd, $^2J_{3,3'}$ = 14.6 Hz, $^3J_{3,2}$ = 5.9 Hz, 1 H, 3-H), 1.45 (s, 9 H, 30-H), 0.91 (s, 9 H, 24-H), 0.87 (s, 9 H, 27-H), 0.08 (s, 6 H, 25-H), 0.07 (s, 3 H, 22'-H), 0.06 (s, 3 H, 22-H).

^{13}**C-NMR** (125 MHz, DMSO-d$_6$, 298 K): δ = 174.7 (s, C-15), 169.9 (s, C-21), 169.9 (s, C-12), 169.3 (s, C-4), 167.8 (s, C-18), 157.6 (s, C-16), 155.6 (s, C-28), 134.5 (d, C-9), 117.5 (t, C-10), 87.1 (d, C-17), 84.3 (d, C-7), 80.0 (s, C-29), 77.5 (d, C-11), 74.2 (d, C-6), 68.5 (d, C-2), 54.2 (d, C-5), 51.7 (q, C-31), 48.9 (t, C-20), 46.7 (d, C-13), 45.4 (t, C-1), 41.8 (t, C-3), 37.4 (t, C-8), 36.3 (q, C-19), 34.4 (t, C-14), 28.3 (q, C-30), 25.8 (q, C-27), 25.7 (q, C-24), 17.8 (s, C-26), 17.7 (s, C-23), –4.75 (q, C-25'), –4.83 (q, C-22'), –4.90 (q, C-25), –4.92 (q, C-22).

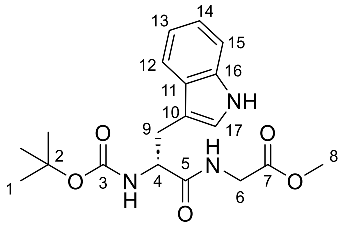
Optical rotation: $[\alpha]_D^{20} = -2.9$ (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{39}H_{70}N_5O_{11}Si_2$ [M+H]$^+$:	840.4605	840.4603

Methyl (*tert*-butoxycarbonyl)-D-tryptophylglycinate 111

Boc-D-Trp-OH (1.00 g, 3.29 mmol) and H-Gly-OMe·HCl (454 mg, 3.61 mmol, 1.1 eq.) were dissolved in anhydrous CH$_2$Cl$_2$ (33 ml) and cooled to 0 °C. EDC·HCl (630 mg, 3.29 mmol, 1.0 eq.), HOBt (503 mg, 3.29 mmol, 1.0 eq.), and NMM (369 µl, 3.29 mmol, 1.0 eq.) were added subsequentially, and the reaction mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried with MgSO$_4$ and concentrated in vacuo. The crude product was purified by automated column chromatography (silica, pentane:EtOAc 0% to 60% EtOAc) to give the dipeptide **111** (1.10 g, 2.78 mmol, 85%) as a white foam.

TLC: R$_f$ (111) = 0.15 (silica, pentane:EtOAc 1:1)



111

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.43 (m, 1 H, 17-NH), 7.62 (d, $^3J_{15,14}$ = 7.9 Hz, 1 H, 15-H), 7.34 (d, $^3J_{12,13}$ = 8.2 Hz, 1 H, 12-H), 7.18 (ddd, $^3J_{13,12}$ = 8.0 Hz, $^3J_{13,14}$ = 6.9 Hz, $^4J_{13,15}$ = 1.2 Hz, 1 H, 13-H), 7.11 (ddd, $^3J_{14,15}$ = 8.0 Hz, $^3J_{14,13}$ = 7.0 Hz, $^4J_{14,12}$ = 1.0 Hz, 1 H, 14-H), 7.07 (m, 1 H, 17-H), 6.47 (t, $^3J_{NH,6}$ = 5.4 Hz, 1 H, 5-NH), 5.23 (d, $^3J_{NH,4}$ = 8.6 Hz, 1 H, 3-NH), 4.51 (m, 1 H, 4-H), 3.90 (m, 2 H, 6-H), 3.67 (s, 3 H, 8-H), 3.31 (m, 1 H, 9-H‘), 3.21 (m, 1 H, 9-H), 1.42 (s, 9 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.2 (s, C-5), 170.0 (s, C-7), 155.7 (s, C-3), 136.3 (s, C-16), 127.6 (s, C-11), 123.5 (d, C-17), 122.3 (d, C-13), 119.7 (d, C-14), 118.8 (d, C-15), 111.4 (d, C-12), 110.4 (s, C-10), 80.3 (s, C-2), 55.2 (d, C-4), 52.4 (q, C-8), 41.3 (t, C-6), 28.4 (q, C-1), 28.3 (t, C-9).

Optical rotation:	$[\alpha]_D^{20}$= +7,6 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{19}H_{27}N_3O_5$ $[M+2H]^+$:	377.1945	377.1934

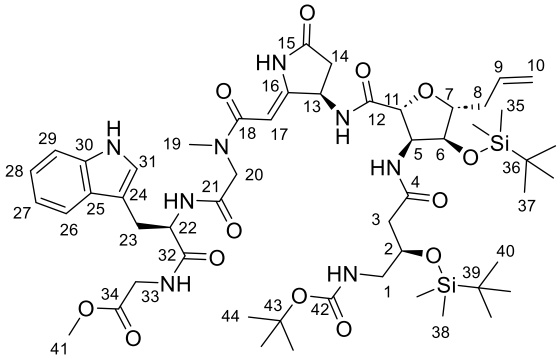
Methyl *N*-((*Z*)-2-((*R*)-3-((2*R*,3*S*,4*S*,5*R*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxamido)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycyl-D-tryptophylglycinate 114

0.20 M $LiOH_{aq}$ (570 µL, 114 µmol, 1.1 eq.) was slowly added to a 0 °C cold solution of tetrapeptide **110** (87.0 mg, 104 µmol) in THF (500 µL). The resulting mixture was stirred for 2 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl_{aq} and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid **113** as a white foam.

4.0 M HCl in dioxane (531 µL, 2.13 mmol, 10 eq.) was added to a solution of dipeptide **111** (83.2 mg, 208 µmol) in CH_2Cl_2 (50 µL) at 0 °C. After stirring for 1 h, the reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride salt **112**.

The above-prepared crude carboxylic acid **113** and amine hydrochloride **112** (2.0 eq.) were dissolved in anhydrous DMF (1.0 mL). After cooling to 0 °C, NMM (47.0 µL, 427 µmol, 4.1 eq.) and HBTU (43.4 mg, 115 µmol, 1.1 eq.) were subsequently added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give hexapeptide **114** (85.0 mg, 78.0 µmol, 75%, dr 97:3) as a white foam. The epimer from the previous coupling was mainly separated during the column chromatography (hence the improved diastereomeric ratio).

LC-MS: t_R (114) = 1.73 min (short method)



114

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.79 (m, 1 H, 31-NH), 10.39 (s, 1 H, 15-NH), 8.45 – 8.36 (m, 2 H, 12-NH, 32-NH), 8.09 (d, $^3J_{NH,22}$ = 8.5 Hz, 1 H, 21-NH), 7.76 (d, $^3J_{NH,5}$ = 8.3 Hz, 1 H, 4-NH), 7.57 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.31 (d, $^3J_{26,27}$ = 8.1 Hz, 1 H, 26-H), 7.13 (s, 1 H, 31-H), 7.04 (ddd, $^3J_{27,26}$ = 8.1 Hz, $^3J_{27,28}$ = 6.9 Hz, $^4J_{27,29}$ = 1.2 Hz, 1 H, 27-H), 6.97 (ddd, $^3J_{28,29}$ = 8.0 Hz, $^3J_{28,27}$ = 6.9 Hz, $^4J_{28,26}$ = 1.1 Hz, 1 H, 28-H), 6.66 (m, 1 H, 42-NH), 5.85 (m, 1 H, 9-H), 5.29 (s, 1 H, 17-H), 5.15 – 5.02 (m, 3 H, 10-H, 13-H), 4.57 (m, 1 H, 22-H), 4.33 (ddd, $^3J_{5,11}$ = 7.2 Hz, $^3J_{5,NH}$ = 7.2 Hz, $^3J_{5,6}$ = 7.2 Hz, 1 H, 5-H), 4.10 (d, $^3J_{11,5}$ = 6.9 Hz, 1 H, 11-H), 4.03 (m, 1 H, 2-H), 3.98 – 3.76 (m, 6 H, 6-H, 7-H, 20-H, 33-H), 3.64 (s, 3 H, 41-H), 3.17 (dd, $^2J_{23',23}$ = 14.7 Hz, $^3J_{23',22}$ = 4.8 Hz, 1 H, 23-H'), 3.03 – 2.88 (m, 3 H, 1-H, 23-H), 2.84 (s, 3 H, 19-H), 2.73 (m, 1 H, 14-H'), 2.38 – 2.24 (m, 4 H, 3-H', 8-H, 14-H), 2.16 (dd, $^2J_{3,3'}$ = 14.7 Hz, $^3J_{3,2}$ = 6.1 Hz, 1 H, 3-H), 1.36 (s, 9 H, 44-H), 0.86 (s, 9 H, 37-H), 0.82 (s, 9 H, 40-H), 0.03 (s, 6 H, 38-H), 0.02 (s, 3 H, 35'-H), 0.01 (s, 3 H, 35-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.7 (s, C-15), 171.9 (s, C-32), 170.2 (s, C-34), 169.9 (s, C-12), 169.3 (s, C-4), 168.1 (s, C-21), 167.6 (s, C-18), 157.0 (s, C-16), 155.6 (s, C-42), 136.0 (s, C-30), 134.5 (d, C-9), 127.3 (s, C-25), 123.6 (d, C-31), 120.8 (d, C-27), 118.3 (d, C-28), 118.2 (d, C-29), 117.6 (t, C-10), 111.2 (d, C-26), 109.9 (s, C-24), 87.6 (d, C-17), 84.3 (d, C-7), 79.9 (d, C-11), 77.5 (s, C-43), 74.1 (d, C-6), 68.5 (d, C-2), 54.2 (d, C-5), 53.2 (d, C-22), 51.7 (q, C-41), 50.0 (t, C-20), 46.6 (d, C-13), 45.3 (t, C-1), 41.8 (t, C-3), 40.7 (t, C-33), 37.4 (t, C-8), 36.2 (q, C-19), 34.5 (t, C-14), 28.3 (q, C-44), 27.7 (t, C-23), 25.8 (q, C-40), 25.7 (q, C-37), 17.8 (s, C-39), 17.7 (s, C-36), –4.75 (q, C-38'), –4.82 (q, C-35'), –4.90 (q, C-38), –4.92 (q, C-35).

Optical rotation: $[\alpha]_D^{20}$= +45.0 (c = 0.5, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{52}H_{83}N_8O_{13}Si_2$ [M+H]$^+$:	1083.5613	1083.5622

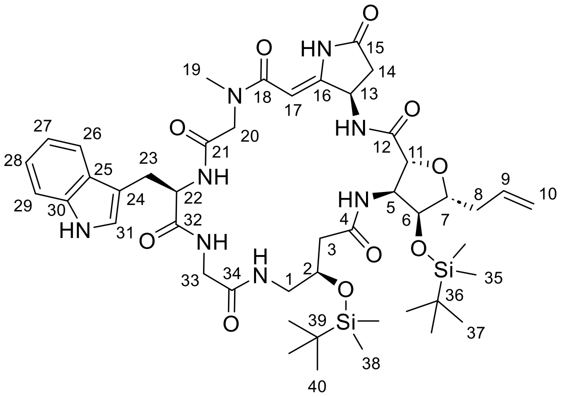
(2*R*,3*S*,3a*S*,7*R*,14*R*,23a*R*,25a*R*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-allyl-3,7-bis((*tert*-butyldimethylsilyl)oxy)-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 116

0.20 M $LiOH_{aq}$ (359 µL, 72.0 µmol, 1.05 eq.) was slowly added to a 0 °C cold solution of hexapeptide **114** (74.0 mg, 68.3 µmol) in THF (350 µL). The resulting mixture was stirred for 4 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl_{aq} and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid as a white foam.

A preformed cleavage cocktail TFA:TIPS:H_2O (260 µL, 185:10:5) was added to a solution of the crude carboxylic acid in anhydrous CH_2Cl_2 (300 µL) at 0 °C. After 110 min, reaction control via LC-MS showed full conversion (60% Boc-deprotection and 40% Boc- and monoTBS-deprotection). The reaction mixture was concentrated in vacuo. The residue was dissolved in anhydrous DMF (70 mL). After cooling to 0 °C, DIPEA (119 µL, 683 µmol, 10 eq.), HOAt (105 mg, 683 µmol, 10 eq.), and PyAOP (356 mg, 683 µmol, 10 eq.) were added. The reaction mixture was stirred for 72 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give the protected dehydrosocein precursor **116** (25.0 mg, 26.5 µmol, 39%) as a white foam and its mono-TBS-deprotected variant **116(OH)** (15.0 mg, 17.9 mmol, 26%) as a white foam.

Imidazole (2.6 mg, 38.0 mmol, 2.1 eq.) and TBS-Cl (3.0 mg, 19.8 mmol, 1.1 eq.) were subsequently added to a 0 °C cold solution of the mono-TBS-deprotected variant **116(OH)** (15.0 mg, 17.9 mmol) in anhydrous DMF (180 µL). The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give another portion of the protected dehydrosocein precursor **116** (10.5 mg, 11.1 µmol, 62%) as a white foam.

LC-MS: t_R (116) = 1.57 min (short method)



116

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.86 (m, 1 H, 31-NH), 10.36 (s, 1 H, 15-NH), 8.67 (d, $^3J_{NH,22}$ = 8.2 Hz, 1 H, 21-NH), 8.26 (d, $^3J_{NH,13}$ = 8.3 Hz, 1 H, 12-NH), 8.17 (dd, $^3J_{NH,33'}$ = 7.5 Hz, $^3J_{NH,33}$ = 5.0 Hz, 1 H, 32-NH), 7.52 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.35 (d, $^3J_{26,27}$ = 8.1 Hz, 1 H, 26-H), 7.26 – 7.20 (m, 2 H, 31-H, 34-NH), 7.07 (dd, $^3J_{28,29}$ = 7.6 Hz, $^3J_{28,27}$ = 7.6 Hz, 1 H, 28-H), 7.03 – 6.95 (m, 2 H, 27-H, 4-NH), 5.86 (ddt, $^3J_{9,10}$ = 17.2 Hz, $^3J_{9,10'}$ = 10.2 Hz, $^3J_{9,8}$ = 7.0 Hz, 1 H, 9-H), 5.24 (s, 1 H, 17-H), 5.19 (m, 1 H, 13-H), 5.13 (dd, $^2J_{10',10}$ = 2.0 Hz, $^3J_{10',9}$ = 17.3 Hz, 1 H, 10-H‘), 5.07 (dd, $^2J_{10,10'}$ = 2.1 Hz, $^3J_{10,9}$ = 10.2 Hz, 1 H, 10-H), 4.50 (d, $^2J_{20',20}$ = 15.6 Hz, 1 H, 20-H‘), 4.37 (ddd, $^3J_{5,11}$ = 9.2 Hz, $^3J_{5,NH}$ = 9.2 Hz, $^3J_{5,6}$ = 5.2 Hz, 1 H, 5-H), 4.25 (ddd, $^3J_{22,23}$ = 9.9 Hz, $^3J_{22,NH}$ = 5.0 Hz, $^3J_{22,23'}$ = 5.0 Hz, 1 H, 22-H), 4.18 (m, 1 H, 2-H), 3.99 (d, $^3J_{11,5}$ = 9.2 Hz, 1 H, 11-H), 3.90 (dd, $^3J_{6,5}$ = 5.3 Hz, $^3J_{6,7}$ = 1.9 Hz, 1 H, 6-H), 3.85 (td, $^3J_{7,8}$ = 6.6 Hz, $^3J_{7,6}$ = 1.9 Hz, 1 H, 7-H), 3.77 (dd, $^2J_{33',33}$ = 16.9 Hz, $^3J_{33',NH}$ = 7.6 Hz, 1 H, 33-H‘), 3.46 (d, $^2J_{20,20'}$ = 16.0 Hz, 1 H, 20-H), 3.42 (m, 1 H, 33-H), 3.21 (dd, $^2J_{23',23}$ = 14.7 Hz, $^3J_{23',22}$ = 4.3 Hz, 1 H, 23-H‘), 3.16 (s, 3 H, 19-H), 3.14 (m, 1 H, 1-H‘), 3.00 (dd, $^2J_{23,23'}$ = 14.8 Hz, $^3J_{23,22}$ = 9.8 Hz, 1 H, 23-H), 2.82 – 2.73 (m, 2 H, 1-H, 14-H‘), 2.37 – 2.23 (m, 3 H, 8-H, 14-H), 2.13 (m, 2 H, 3-H), 0.89 (s, 9 H, 40-H), 0.78 (s, 9 H, 37-H), 0.04 (s, 6 H, 35-H), 0.02 (s, 3 H, 38-H), 0.02 (s, 3 H, 38‘-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.2 (s, C-15), 171.8 (s, C-21), 171.5 (s, C-32), 169.5 (s, C-12), 169.1 (s, C-4), 168.5 (s, C-34), 168.4 (s, C-18), 156.4 (s, C-16), 136.2 (s, C-30), 134.4 (d, C-9), 126.9 (s, C-25), 123.9 (d, C-31), 121.0 (d, C-28), 118.3 (d, C-27), 118.1 (d, C-29), 117.6 (t, C-10), 111.4 (d, C-26), 109.8 (s, C-24), 87.9 (d, C-17), 85.9 (d, C-7), 79.0 (d, C-11), 74.6 (d, C-6), 67.6 (d, C-2), 55.6 (d, C-22), 54.1 (d, C-5), 51.5 (t, C-20), 46.6 (d, C-13), 44.5 (t, C-1), 42.8 (t, C-3), 42.5 (t, C-33), 37.7 (t, C-8), 37.5 (q, C-19), 34.2 (t, C-14), 26.4 (t, C-23), 25.7 (q, C-40), 25.7 (q, C-37), 17.8 (s, C-39), 17.6 (s, C-36), –4.7 (q, C-35‘), –4.8 (q, C-38‘), –4.85 (q, C-35), –4.93 (q, C-38).

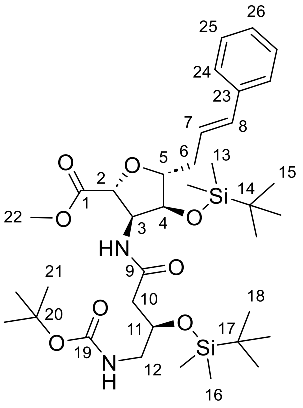
Optical rotation: $[\alpha]_D^{20}$= –21.4 (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{46}H_{71}N_8O_{10}Si_2$ [M+H]$^+$:	951.4826	951.4836

Methyl (2*R*,3*S*,4*S*,5*R*)-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-butanamido)-4-((*tert*-butyldimethylsilyl)oxy)-5-cinnamyltetrahydrofuran-2-carboxylate 117

In a 4 mL brown glass-vial under an argon atmosphere, compound **83** (7.5 mg, 12 µmol) was dissolved in argon-degassed, anhydrous CH$_2$Cl$_2$ (240 µL). After the addition of styrene (13.8 µL, 119 µmol, 10 eq.) and Grubbs I catalyst (1.0 mg, 1.2 µmol, 10 mol%), the reaction mixture was stirred for 2 days. Another portion of Grubbs I catalyst (1.0 mg, 1.2 µmol, 10mol%) was added, and the stirring was continued for 2 days. After adsorption on isolute®, the mixture was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 40% to 100% MeCN) to give the olefination product **117** (5.2 mg, 7.4 µmol, 62%) as a colorless resin.

LC-MS: t_R (117) = 1.93 min (short method)



117

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 (m, 2 H, 24-H), 7.30 (m, 2 H, 25-H), 7.22 (m, 1 H, 26-H), 6.49 (m, 1 H, 9-NH), 6.48 (d, $^3J_{8,7}$ = 16.2 Hz, 1 H, 8-H), 5.87 (dt, $^3J_{7,8}$ = 16.0 Hz, $^3J_{7,6}$ = 7.2 Hz, 1 H, 7-H), 4.87 (m, 1 H, 19-NH), 4.55 (ddd, $^3J_{3,2}$ = 7.9 Hz, $^3J_{3,NH}$ = 7.9 Hz, $^3J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 4.30 (d, $^3J_{2,3}$ = 7.7 Hz, 1 H, 2-H), 4.19 (tt, $^3J_{11,10}$ = 5.5 Hz, $^3J_{11,12}$ = 5.5 Hz, 1 H, 11-H), 4.12 (dd, $^3J_{4,3}$ = 5.6 Hz, $^3J_{4,5}$ = 3.0 Hz, 1 H, 4-H), 4.06 (td, $^3J_{5,6}$ = 6.4 Hz, $^3J_{5,4}$ = 2.9 Hz, 1 H, 5-H), 3.77 (s, 3 H, 22-H), 3.38 (m, 1 H, 12-H‘), 3.07 (ddd, $^2J_{12,12'}$ = 14.0 Hz, $^3J_{12,11}$ = 5.4 Hz, $^3J_{12,NH}$ = 5.4 Hz, 1 H, 12-H), 2.60 (dddd, $^2J_{6,6'}$ = 14.5 Hz, $^3J_{6,5}$ = 6.6 Hz, $^3J_{6,7}$ = 6.9 Hz, $^4J_{6,8}$ = 1.6 Hz, 1 H, 6-H), 2.51 (dddd, $^2J_{6',6}$ = 14.3 Hz, $^3J_{6',7}$ = 7.6 Hz, $^3J_{6',5}$ = 6.5 Hz, $^4J_{6',8}$ = 1.6 Hz, 1 H, 6-H‘), 2.39 (dd, $^2J_{10,10'}$ = 13.9 Hz, $^3J_{10,11}$ = 6.0 Hz, 1 H, 10-H), 2.32 (dd, $^2J_{10',10}$ = 13.9 Hz, $^3J_{10',11}$ = 5.2 Hz, 1 H, 10-H), 1.45 (s, 9 H, 21-H), 0.91 (s, 9 H, 15-H/18-H), 0.89 (s, 9 H, 18-H/15-H), 0.11 (s, 3 H, 13-H/16-H), 0.08 (s, 3 H, 13-H/16-H), 0.07 (s, 3 H, 13-H/16-H), 0.07 (s, 3 H, 13-H/16-H).

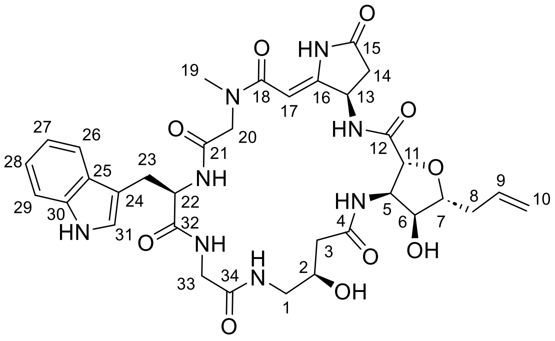
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 171.6 (s, C-1), 170.0 (s, C-9), 156.4 (s, C-19), 137.3 (s, C-23), 133.3 (d, C-8), 128.7 (d, C-25), 127.4 (d, C-26), 126.3 (d, C-24), 125.2 (d, C-7), 86.2 (d, C-5), 79.9 (d, C-2), 79.5 (s, C-20), 74.9 (d, C-4), 68.8 (d, C-11), 55.0 (d, C-3), 52.6 (q, C-22), 45.2 (t, C-12), 42.4 (t, C-10), 37.3 (t, C-6), 28.6 (q, C-21), 26.0 (q, C-15/C-18), 25.9 (q, C-18/C-15), 18.2 (s, C-14/C-17), 18.1 (s, C-17/C-14), –4.4 (q, C-13/C-16), –4.5 (q, C-13/C-16), –4.6 (q, C-13/C-16), –4.7 (q, C-13/C-16).

Optical rotation:	$[\alpha]_D^{20}$ = –14.4 (c = 0.5, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{36}H_{63}N_2O_8Si_2$ $[M+H]^+$:	707.4117	707.4133

(2*R*,3*S*,3a*R*,7*R*,14*R*,23a*R*,25a*R*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-allyl-3,7-dihydroxy-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 119

1.0 M TBAF in THF (9.05 µL, 9.05 µmol, 2.05 eq.) was added to a 0 °C cold solution of protected dehydrosocein precursor **116** (4.2 mg, 4.4 µmol) in anhydrous THF (100 µL). The resulting solution was stirred for 4 h while slowly reaching room temperature. After the addition of a droplet of H_2O, the reaction mixture was adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 10% to 85% MeCN) to give dehydrosocein precursor **119** (2.3 mg, 3.2 µmol, 72%) as an amorphous solid after lyophilization.

LC-MS: t_R (119) = 0.71 min (short method)



119

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.86 (d, $^{3}J_{NH,31}$ = 2.4 Hz, 1 H, 31-NH), 10.39 (s, 1 H, 15-NH), 8.57 (d, $^{3}J_{NH,22}$ = 5.7 Hz, 1 H, 21-NH), 8.46 (d, $^{3}J_{NH,13}$ = 8.3 Hz, 1 H, 12-NH), 8.29 (t, $^{3}J_{NH,33}$ = 6.2 Hz, 1 H, 32-NH), 7.60 (d, $^{3}J_{NH,5}$ = 8.4 Hz, 1 H, 4-NH), 7.52 (d, $^{3}J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.34 (d, $^{3}J_{26,27}$ = 8.0 Hz, 1 H, 26-H), 7.26 (t, $^{3}J_{NH,1}$ = 5.2 Hz, 1 H, 34-NH), 7.21 (d, $^{3}J_{31,NH}$ = 2.3 Hz, 1 H, 31-H), 7.07 (ddd, $^{3}J_{28,29}$ = 8.1 Hz, $^{3}J_{28,27}$ = 7.0 Hz, $^{4}J_{28,26}$ = 1.2 Hz, 1 H, 28-H), 6.99 (ddd, $^{3}J_{27,26}$ = 7.9 Hz, $^{3}J_{27,28}$ = 6.9 Hz, $^{4}J_{27,29}$ = 1.0 Hz, 1 H, 27-H), 5.85 (ddt, $^{3}J_{9,10}$ = 17.1 Hz, $^{3}J_{9,10'}$ = 10.3 Hz, $^{3}J_{9,8}$ = 6.8 Hz, 1 H, 9-H), 5.48 (d, $^{3}J_{OH,6}$ = 4.2 Hz, 1 H, 6-OH), 5.38 (d, $^{4}J_{17,13}$ = 1.5 Hz, 1 H, 17-H), 5.18 (m, 1 H, 13-H), 5.12 (ddt, $^{3}J_{10',9}$ = 17.3 Hz, $^{2}J_{10',10}$ = 1.7 Hz, $^{4}J_{10',8}$ = 1.7 Hz, 1 H, 10-H‘), 5.04 (ddt, $^{3}J_{10,9}$ = 10.2 Hz, $^{2}J_{10,10'}$ = 2.2 Hz, $^{4}J_{10,8}$ = 1.2 Hz, 1 H, 10-H), 4.67 (d, $^{3}J_{OH,2}$ = 4.9 Hz, 1 H, 2-OH), 4.56 (d, $^{3}J_{20',20}$ = 15.8 Hz, 1 H, 20-H‘), 4.39 (ddd, $^{3}J_{5,11}$ = 8.6 Hz, $^{3}J_{5,NH}$ = 8.6 Hz, $^{3}J_{5,6}$ = 5.5 Hz, 1 H, 5-H), 4.18 (ddd, $^{3}J_{22,23}$ = 10.1 Hz, $^{3}J_{22,NH}$ = 5.2 Hz, $^{3}J_{22,23'}$ = 5.2 Hz, 1 H, 22-H), 3.97 (m, 1 H, 2-H), 3.89 (d, $^{3}J_{11,5}$ = 8.8 Hz, 1 H, 11-H), 3.86 – 3.77 (m, 2 H, 6-H, 7-H), 3.61 (m, 2 H, 33-H), 3.44 (d, $^{2}J_{20,20'}$ = 15.8 Hz, 1 H, 20-H), 3.19 (dd, $^{2}J_{23',23}$ = 14.7 Hz, $^{3}J_{23',22}$ = 4.6 Hz, 1 H, 23-H‘), 3.16 – 3.09 (m, 4 H, 1-H, 19-H), 3.01 (dd, $^{2}J_{23,23'}$ = 14.7 Hz, $^{3}J_{23,22}$ = 9.4 Hz, 1 H, 23-H), 2.80 (m, 1 H, 1-H‘), 2.75 (dd, $^{2}J_{14,14'}$ = 17.5 Hz, $^{3}J_{14,13}$ = 9.6 Hz, 1 H, 14-H), 2.35 – 2.20 (m, 5 H, 3-H, 8-H, 14-H‘).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.4 (s, C-15), 171.5 (s, C-32), 171.0 (s, C-21), 170.3 (s, C-4), 169.9 (s, C-12), 168.8 (s, C-34), 168.2 (s, C-18), 156.4 (s, C-16), 136.1 (s, C-30), 134.9 (d, C-9), 127.0 (s, C-25), 124.0 (d, C-31), 121.0 (d, C-28), 118.4 (d, C-27), 118.1 (d, C-29), 117.1 (t, C-10), 111.4 (d, C-26), 109.8 (s, C-24), 88.2 (d, C-17), 85.8 (d, C-7), 80.3 (d, C-11), 72.9 (d, C-6), 66.0 (d, C-2), 55.5 (d, C-22), 54.3 (d, C-5), 50.7 (t, C-20), 46.4 (d, C-13), 45.0 (t, C-1), 42.5 (t, C-33), 41.5 (t, C-3), 37.8 (t, C-8), 37.1 (q, C-19), 34.2 (t, C-14), 26.2 (t, C-23).

Optical rotation: $[\alpha]_D^{20} = -39.3$ (c = 0.3, MeOH)

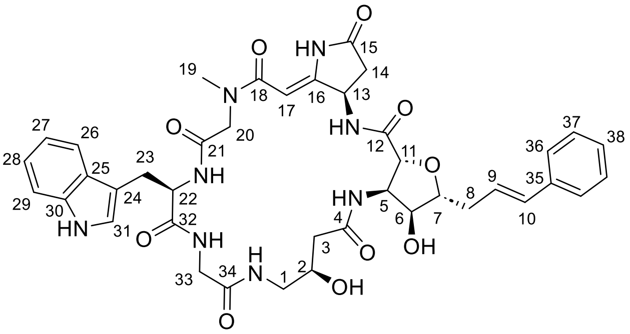
HRMS (ESI):	calculated	found
$C_{34}H_{43}N_8O_{10}$ $[M+H]^+$:	723.3097	723.3097

(2*R*,3*S*,3a*R*,7*R*,14*R*,23a*R*,25a*R*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-cinnamyl-3,7-dihydroxy-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 120

In a 4 mL brown glass-vial under an atmosphere of argon, protected dehydrosocein precursor **116** (8.0 mg, 8.4 µmol) was dissolved in argon-degassed, anhydrous CH_2Cl_2 (200 µL). After the addition of styrene (9.73 µL, 84.1 µmol, 10 eq.) and Grubbs I catalyst in CH_2Cl_2 (42.0 µL, 0.841 µmol, 0.02 M, 10mol%), the reaction mixture was stirred for 24 h. Another portion of Grubbs I catalyst (42.0 µL, 0.841 µmol, 0.02 M, 10mol%) was added, and the stirring was continued for 56 h. After adsorption on isolute®, the mixture was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give the olefination product **118** (3.5 mg, 3.41 µmol, 41%, 93%brsm) as a white foam.

1.0 M TBAF in THF (6.98 µL, 6.98 µmol, 2.05 eq.) was added to a 0 °C cold solution of the above-prepared olefination product **118** (3.5 mg, 3.41 µmol) in anhydrous THF (70 µL). The resulting solution was stirred for 4 h while slowly reaching room temperature. After the addition of a droplet of H_2O, the reaction mixture was adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 10% to 100% MeCN) to give dehydrosocein derivative **120** (2.6 mg, 3.25 µmol, 96%) as an amorphous solid after lyophilization.

LC-MS: t_R (120) = 0.89 min (short method)



120

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.86 (d, $^3J_{NH,31}$ = 2.4 Hz, 1 H, 31-NH), 10.39 (s, 1 H, 15-NH), 8.57 (d, $^3J_{NH,22}$ = 5.7 Hz, 1 H, 21-NH), 8.48 (d, $^3J_{NH,13}$ = 8.3 Hz, 1 H, 12-NH), 8.29 (t, $^3J_{NH,33}$ = 6.0 Hz, 1 H, 32-NH), 7.60 (d, $^3J_{NH,5}$ = 8.6 Hz, 1 H, 4-NH), 7.52 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.39 (m, 2 H, 36-H), 7.34 (d, $^{3}J_{26,27}$ = 8.0 Hz, 1 H, 26-H), 7.30 (m, 2 H, 37-H), 7.24 (m, 1 H, 34-NH), 7.23 – 7.18 (m, 2 H, 31-H, 38-H), 7.07 (ddd, $^{3}J_{28,29}$ = 8.2 Hz, $^{3}J_{28,27}$ = 7.0 Hz, $^{4}J_{28,26}$ = 1.2 Hz, 1 H, 28-H), 6.99 (ddd, $^{3}J_{27,26}$ = 7.9 Hz, $^{3}J_{27,28}$ = 7.0 Hz, $^{4}J_{27,29}$ = 1.1 Hz, 1 H, 27-H), 6.49 (d, $^{3}J_{10,9}$ = 16.0 Hz, 1 H, 10-H), 6.37 (dt, $^{3}J_{9,10}$ = 15.9 Hz, $^{3}J_{9,8}$ = 7.0 Hz, 1 H, 9-H), 5.52 (d, $^{3}J_{OH,6}$ = 4.3 Hz, 1 H, 6-OH), 5.39 (d, $^{4}J_{17,13}$ = 1.6 Hz, 1 H, 17-H), 5.20 (m, 1 H, 13-H), 4.66 (d, $^{3}J_{OH,2}$ = 4.9 Hz, 1 H, 2-OH), 4.55 (d, $^{3}J_{20',20}$ = 15.8 Hz, 1 H, 20-H‘), 4.45 (ddd, $^{3}J_{5,11}$ = 8.7 Hz, $^{3}J_{5,NH}$ = 8.7 Hz, $^{3}J_{5,6}$ = 5.6 Hz, 1 H, 5-H), 4.18 (ddd, $^{3}J_{22,23}$ = 10.0 Hz, $^{3}J_{22,NH}$ = 5.2 Hz, $^{3}J_{22,23'}$ = 5.2 Hz, 1 H, 22-H), 3.98 (m, 1 H, 2-H), 3.95 – 3.91 (m, 2 H, 11-H, 7-H), 3.88 (m, 1 H, 6-H), 3.62 (m, 2 H, 33-H), 3.44 (d, $^{2}J_{20,20'}$ = 15.8 Hz, 1 H, 20-H), 3.19 (dd, $^{2}J_{23',23}$ = 14.6 Hz, $^{3}J_{23',22}$ = 4.6 Hz, 1 H, 23-H‘), 3.16 – 3.08 (m, 4 H, 1-H, 19-H), 3.01 (dd, $^{2}J_{23,23'}$ = 14.7 Hz, $^{3}J_{23,22}$ = 9.5 Hz, 1 H, 23-H), 2.79 (m, 1 H, 1-H‘), 2.75 (dd, $^{2}J_{14,14'}$ = 17.7 Hz, $^{3}J_{14,13}$ = 9.8 Hz, 1 H, 14-H), 2.46 (m, 2 H, 8-H), 2.33 (dd, $^{2}J_{14',14}$ = 17.8 Hz, $^{3}J_{14',13}$ = 6.3 Hz 1 H, 14-H‘), 2.22 (m, 2 H, 3-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.4 (s, C-15), 171.5 (s, C-32), 171.0 (s, C-21), 170.2 (s, C-4), 170.0 (s, C-12), 168.8 (s, C-34), 168.3 (s, C-18), 156.4 (s, C-16), 137.2 (s, C-35), 136.1 (s, C-30), 131.6 (d, C-10), 128.5 (d, C-37), 127.1 (d, C-38), 127.0 (s, C-25), 126.6 (d, C-9), 125.9 (d, C-36), 124.0 (d, C-31), 121.0 (d, C-28), 118.4 (d, C-27), 118.1 (d, C-29), 111.4 (d, C-26), 109.8 (s, C-24), 88.2 (d, C-17), 86.1 (d, C-7), 80.3 (d, C-11), 73.0 (d, C-6), 66.0 (d, C-2), 55.5 (d, C-22), 54.4 (d, C-5), 50.7 (t, C-20), 46.4 (d, C-13), 45.0 (t, C-1), 42.5 (t, C-33), 41.5 (t, C-3), 37.2 (q, C-19), 37.0 (t, C-8), 34.2 (t, C-14), 26.2 (t, C-23).

Optical rotation: $[\alpha]_D^{20} = -28.6$ (c = 0.3, MeOH)

HRMS (ESI):	calculated	found
$C_{40}H_{47}N_8O_{10}$ [M+H]$^+$:	799.3410	799.3420

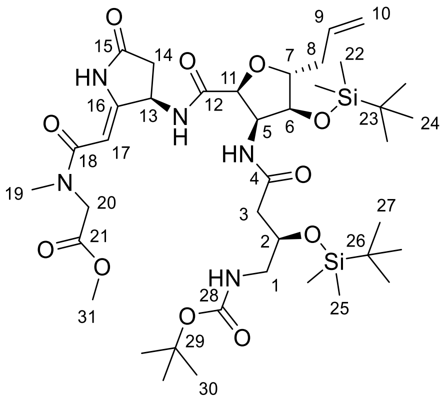
Methyl *N*-((*Z*)-2-((*R*)-3-((2*S*,3*S*,4*S*,5*R*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxamido)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycinate 121

0.30 M LiOH$_{aq}$ (277 µL, 83.0 µmol, 1.05 eq.) was slowly added to a 0 °C cold solution of compound **81** (49.7 mg, 78.8 µmol) in THF (500 µL). The resulting mixture was stirred for 2 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl$_{aq}$ and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid **82** as a colorless resin.

4.0 M HCl in dioxane (732 µL, 2.93 mmol, 10 eq.) was added to a solution of dipeptide **38** (100 mg, 293 µmol) in CH_2Cl_2 (500 µL) at 0 °C. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between sat. $NaHCO_3$ solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude amine **109** (44.0 mg, 182 µmol, 62%) as a colorless resin.

The above-prepared crude carboxylic acid **82** and amine **109** (37.5 mg, 156 µmol, 2.0 eq.) were dissolved in anhydrous DMF (800 µL). After cooling to 0 °C, EDC·HCl (16.4 mg, 86.0 µmol, 1.1 eq.) and HOBt (2.4 mg, 16.0 µmol, 0.2 eq.) were added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give tetrapeptide **121** (47.0 mg, 56.0 µmol, 71%, dr 80:20) as a white foam.

LC-MS: t_R (121) = 1.73 min (short method)



121

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 10.30 (s, 1 H, 15-NH), 8.16 (d, $^3J_{NH,13}$ = 7.5 Hz, 1 H, 12-NH), 7.15 (d, $^3J_{NH,5}$ = 8.7 Hz, 1 H, 4-NH), 6.12 (m, 1 H, 28-NH), 5.87 (m, 1 H, 9-H), 5.38 (m, 1 H, 17-H), 5.16 (ddt, $^3J_{10,9}$ = 17.1 Hz, $^2J_{10,10'}$ = 1.8 Hz, $^4J_{10,8}$ = 1.8 Hz, 1 H, 10-H), 5.11 (ddt, $^3J_{10',9}$ = 10.2 Hz, $^2J_{10',10}$ = 2.0 Hz, $^4J_{10',8}$ = 1.1 Hz, 1 H, 10-H'), 4.88 (m, 1 H, 13-H), 4.59 (m, 1 H, 5-H), 4.37 (d, $^3J_{11,5}$ = 6.8 Hz, 1 H, 11-H), 4.14 (m, 2 H, 20-H), 4.12 – 4.06 (m, 3 H, 2-H, 6-H, 7-H), 3.67 (s, 3 H, 31-H), 3.09 – 2.99 (m, 2 H, 1-H), 3.02 (s, 3 H, 19-H), 2.69 (dd, $^2J_{14,14'}$ = 17.5 Hz, $^3J_{14,13}$ = 9.4 Hz, 1 H, 14-H), 2.45 (dd, $^2J_{14',14}$ = 17.5 Hz, $^3J_{14',13}$ = 5.2 Hz, 1 H, 14-H'), 2.41 – 2.20 (m, 4 H, 3-H, 8-H), 1.39 (s, 9 H, 30-H), 0.88 (s, 9 H, 24-H), 0.87 (s, 9 H, 27-H), 0.08 (s, 3 H, 25-H/22-H), 0.07 (s, 3 H, 25-H/22-H), 0.06 (s, 3 H, 25-H/22-H), 0.05 (s, 3 H, 25-H/22-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 173.7 (s, C-15), 169.8 (s, C-12), 169.1 (s, C-21), 168.4 (s, C-4), 167.5 (s, C-18), 156.3 (s, C-16), 155.0 (s, C-28), 133.6 (d, C-9), 116.9 (t, C-10), 87.1 (d, C-17), 83.3 (d, C-7), 77.2 (s, C-29), 76.1 (d, C-11), 73.9 (d, C-6), 67.9 (d, C-2), 52.8 (d, C-5), 51.0 (q, C-31), 47.3 (d, C-13), 45.6 (t, C-1), 41.7 (t, C-3), 36.7 (t, C-8), 34.0 (t, C-14), 27.8 (q, C-30), 25.3 (q, C-27), 25.1 (q, C-24), 17.2 (s, C-26), 17.1 (s, C-23), –5.28 (q, C-25/C-22), –5.33 (q, C-25/C-22), –5.40 (q, C-25/C-22), –5.47 (q, C-25/C-22), C-20 and C-19 were not observed.

Selected epimer/isomer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 8.21 (d, $^3J_{NH,13}$ = 8.6 Hz, 1 H, 12-NH), 7.21 (d, $^3J_{NH,5}$ = 8.6 Hz, 1 H, 4-NH), 5.19 (m, 1 H, 13-H), 4.44 (d, $^3J_{11,5}$ = 7.1 Hz, 1 H, 11-H), 1.40 (s, 9 H, 30-H), 0.88 (s, 9 H, 24-H/27-H), 0.86 (s, 9 H, 24-H/27-H), 0.09 (s, 3 H, 25-H/22-H), 0.07 (s, 3 H, 25-H/22-H), 0.06 (s, 3 H, 25-H/22-H), 0.03 (s, 3 H, 25-H/22-H).

Optical rotation: $[\alpha]_D^{20}$= +21.2 (c = 1.0, DMSO)

HRMS (ESI):	calculated	found
$C_{39}H_{70}N_5O_{11}Si_2$ $[M+H]^+$:	840.4605	840.4604

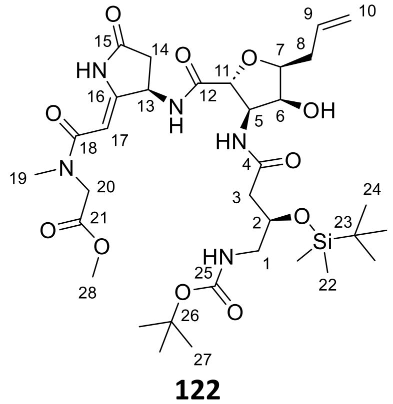
Methyl *N*-((*Z*)-2-((*R*)-3-((2*R*,3*R*,4*S*,5*S*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-4-hydroxytetrahydrofuran-2-carboxamido)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycinate 122

0.40 M $LiOH_{aq}$ (351 µL, 141 µmol, 1.1 eq.) was slowly added to a 0 °C cold solution of compound **92** (66.0 mg, 128 µmol) in MeCN (640 µL). The resulting mixture was stirred for 16 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl_{aq} and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid as a colorless resin.

4.0 M HCl in dioxane (586 µL, 2.34 mmol, 10 eq.) was added to a solution of dipeptide **38** (80 mg, 234 µmol) in CH_2Cl_2 (400 µL) at 0 °C. After stirring for 3 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between 1.0 M K_2CO_3 solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude amine (37.0 mg, 153 µmol, 65%) as a colorless resin.

The above-prepared crude carboxylic acid and amine (37.0 mg, 153 µmol, 1.2 eq.) were dissolved in anhydrous DMF (1.1 mL). After cooling to 0 °C, EDC·HCl (26.8 mg, 140 µmol, 1.1 eq.) and HOBt (3.9 mg, 25.0 µmol, 0.2 eq.) were added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 10% to 100% MeCN) to give tetrapeptide **122** (64.0 mg, 88.0 µmol, 69%, dr >99:1) as a colorless resin. An epimer/isomer (6.1 mg, 8.4 µmol, 7%) was separated during the preparative HPLC step.

LC-MS: t_R (122) = 3.09 min (long method)



122

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 10.30 (s, 1 H, 15-NH), 8.21 (d, $^3J_{NH,13}$ = 8.6 Hz, 1 H, 12-NH), 7.42 (d, $^3J_{NH,5}$ = 8.1 Hz, 1 H, 4-NH), 6.16 (m, 1 H, 25-NH), 5.86 (ddt, $^3J_{9,10}$ = 17.1 Hz, $^3J_{9,10'}$ = 10.3 Hz,

$^3J_{9,8}$ = 6.9 Hz, 1 H, 9-H), 5.40 (s, 1 H, 17-H), 5.13 (ddt, $^3J_{10,9}$ = 17.5 Hz, $^2J_{10,10'}$ = 1.8 Hz, $^4J_{10,8}$ = 1.8 Hz, 1 H, 10-H), 5.09 (m, 1 H, 13-H), 5.03 (ddt, $^3J_{10',9}$ = 10.3 Hz, $^2J_{10',10}$ = 2.3 Hz, $^4J_{10',8}$ = 1.3 Hz, 1 H, 10-H‘), 4.89 (d, $^3J_{OH,6}$ = 5.3 Hz, 1 H, 6-OH), 4.47 (m, 1 H, 5-H), 4.15 (m, 2 H, 20-H), 4.13 – 4.08 (m, 2 H, 2-H, 7-H), 4.06 (d, $^3J_{11,5}$ = 8.3 Hz, 1 H, 11-H), 4.00 (ddd, $^3J_{6,OH}$ = 5.2 Hz, $^3J_{6,7}$ = 5.2 Hz, $^3J_{6,5}$ = 2.9 Hz, 1 H, 6-H), 3.67 (s, 3 H, 28-H), 3.07 – 3.00 (m, 5 H, 1-H, 19-H), 2.73 (dd, $^2J_{14,14'}$ = 17.5 Hz, $^3J_{14,13}$ = 9.6 Hz, 1 H, 14-H), 2.46 – 2.37 (m, 2 H, 8-H, 14-H‘), 2.37 – 2.25 (m, 3 H, 3-H, 8-H‘), 1.40 (s, 9 H, 27-H), 0.88 (s, 9 H, 24-H), 0.06 (s, 3 H, 22-H), 0.05 (s, 3 H, 22‘-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 173.8 (s, C-15), 170.9 (s, C-12), 169.3 (s, C-4), 169.1 (s, C-21), 167.6 (s, C-18), 156.6 (s, C-16), 155.1 (s, C-25), 134.5 (d, C-9), 115.9 (t, C-10), 87.2 (d, C-17), 81.6 (d, C-7), 78.9 (d, C-11), 77.3 (s, C-26), 70.5 (d, C-6), 68.4 (d, C-2), 56.2 (d, C-5), 51.0 (q, C-28), 46.5 (d, C-13), 45.5 (t, C-1), 41.5 (t, C-3), 34.2 (t, C-14), 32.7 (t, C-8), 27.8 (q, C-27), 25.3 (q, C-24), 17.2 (s, C-23), –5.3 (q, C-22), –5.4 (q, C-22‘), C-20 and C-19 were not observed.

Optical rotation:	$[\alpha]_D^{20}$= +2.4 (c = 1.0, CHCl$_3$)	
HRMS (ESI):	calculated	found
$C_{33}H_{56}N_5O_{11}Si$ [M+H]$^+$:	726.3740	726.3750

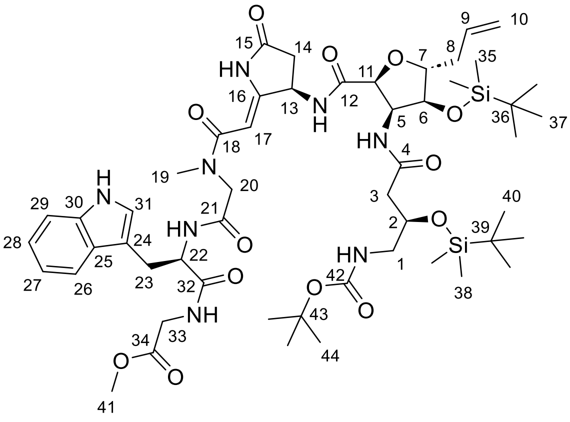
Methyl *N*-((*Z*)-2-((*R*)-3-((2*S*,3*S*,4*S*,5*R*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-2-carboxamido)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycyl-D-tryptophylglycinate 123

0.30 M LiOH$_{aq}$ (137 µL, 40.8 µmol, 1.05 eq.) was slowly added to a 0 °C cold solution of tetrapeptide **121** (33.0 mg, 39.3 µmol) in THF (200 µL). The resulting mixture was stirred for 2 h while slowly reaching room temperature. Another portion of 0.30 M LiOH$_{aq}$ (13.0 µL, 3.93 µmol, 0.1 eq.) was added, and the stirring continued for 1 h. After full conversion, the mixture was acidified with 0.1 M HCl$_{aq}$ and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid as a white foam.

4.0 M HCl in dioxane (196 µL, 784 µmol, 10 eq.) was added to a solution of dipeptide **111** (31.0 mg, 78.4 µmol) in CH_2Cl_2 (100 µL) at 0 °C. After stirring for 1 h, the reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride salt **112**.

The above-prepared crude carboxylic acid and amine hydrochloride **112** (2.0 eq.) were dissolved in anhydrous DMF (500 µL). After cooling to 0 °C, NMM (17.0 µL, 159 µmol, 4.1 eq.) and HATU (15.5 mg, 40.8 µmol, 1.05 eq.) were subsequently added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% LiCl$_{aq}$, 1.0 M HCl$_{aq}$, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give hexapeptide **123** (33.0 mg, 30.5 µmol, 78%, dr 80:20) as a white foam. The analytical characterizations were done with a diastereomerically pure fraction.

LC-MS: t_{R} (123) = 4.68 min (long method)



123

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.80 (s, 1 H, 31-NH), 10.40 (s, 1 H, 15-NH), 8.44 (t, $^{3}J_{\mathrm{NH},33}$ = 5.8 Hz, 1 H, 32-NH), 8.40 (d, $^{3}J_{\mathrm{NH},13}$ = 7.8 Hz, 1 H, 12-NH), 8.13 (d, $^{3}J_{\mathrm{NH},22}$ = 8.5 Hz, 1 H, 21-NH), 7.58 (d, $^{3}J_{29,28}$ = 8.0 Hz, 1 H, 29-H), 7.50 (d, $^{3}J_{\mathrm{NH},5}$ = 8.5 Hz, 1 H, 4-NH), 7.31 (d, $^{3}J_{26,27}$ = 8.0 Hz , 1 H, 26-H), 7.13 (s, 1 H, 31-H), 7.05 (ddd, $^{3}J_{27,26}$ = 8.1 Hz, $^{3}J_{27,28}$ = 6.9 Hz, $^{4}J_{27,29}$ = 1.2 Hz, 1 H, 27-H), 6.97 (ddd, $^{3}J_{28,29}$ = 7.9 Hz, $^{3}J_{28,27}$ = 7.0 Hz, $^{4}J_{28,26}$ = 1.1 Hz, 1 H, 28-H), 6.67 (t, $^{3}J_{\mathrm{NH},1}$ = 6.1 Hz, 1 H, 42-NH), 5.84 (m, 1 H, 9-H), 5.32 (s, 1 H, 17-H), 5.18 – 5.06 (m, 2 H, 10-H), 4.87 (m, 1 H, 13-H), 4.64 – 4.49 (m, 2 H, 5-H, 22-H), 4.39 (d, $^{3}J_{11,5}$ = 6.1 Hz, 1 H, 11-H), 4.09 – 3.87 (m, 5 H, 2-H, 6-H, 7-H, 20-H), 3.86 (m, 2 H, 33-H), 3.64 (s, 3 H, 41-H), 3.17 (dd, $^{2}J_{23',23}$ = 14.6 Hz, $^{3}J_{23',22}$ = 4.7 Hz, 1 H, 23-H‘), 3.02 – 2.86 (m, 3 H, 1-H, 23-H), 2.83 (s, 3 H, 19-H), 2.64 (m, 1 H, 14-H‘), 2.40 – 2.21 (m, 4 H, 3-H‘, 8-H, 14-H), 2.16 (m, 1 H, 3-H), 1.36 (s, 9 H, 44-H), 0.83 (s, 9 H, 37-H/40-H), 0.82 (s, 9 H, 40-H/37-H), 0.03 (s, 6 H, 35-H/38-H), 0.02 (s, 3 H, 38-H/35-H), 0.01 (s, 3 H, 38-H/35-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.7 (s, C-15), 171.9 (s, C-32), 170.2 (s, C-34), 169.8 (s, C-12), 169.2 (s, C-4), 168.2 (s, C-21), 167.7 (s, C-18), 156.8 (s, C-16), 155.6 (s, C-42), 136.0 (s, C-30), 134.3 (d, C-9), 127.3 (s, C-25), 123.7 (d, C-31), 120.8 (d, C-27), 118.4 (d, C-29), 118.2 (d, C-28), 117.7 (t, C-10), 111.3 (d, C-26), 110.0 (s, C-24), 87.7 (d, C-17), 82.7 (d, C-7), 77.5 (s, C-43), 77.1 (d, C-11), 74.1 (d, C-6), 68.3 (d, C-2), 53.2 (d, C-22), 53.1 (d, C-5), 51.7 (q, C-41), 49.9 (t, C-20), 47.3 (d, C-13), 45.5 (t, C-1), 41.9 (t, C-3), 40.7 (t, C-33), 37.2 (t, C-8), 36.3 (q, C-19), 34.4 (t, C-14), 28.3 (q, C-44), 27.8 (t, C-23), 25.8 (q, C-40/C-37), 25.7 (q, C-37/C-40), 17.8 (s, C-39/C-36), 17.7 (s, C-39/C-36), –4.77 (q, C-38/C-35), –4.90 (q, C-35, C-38), –5.05 (q, C-35/C-38).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.44 (s, 1 H, 15-NH), 8.53 (m, 1 H, 32-NH), 8.23 (m, 1 H, 21-NH), 7.42 (m, 1 H, 4-NH), 5.22 (s, 17-H), 4.70 (m, 1 H, 13-H), 4.33 (d, $^{3}J_{11,5}$ = 6.1 Hz, 1 H, 11-H), 2.61 (s, 3 H, 19-H).

Optical rotation: $[\alpha]_{D}^{20}$ = +37.5 (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
C$_{52}$H$_{83}$N$_8$O$_{13}$Si$_2$ [M+H]$^+$:	1083.5613	1083.5616

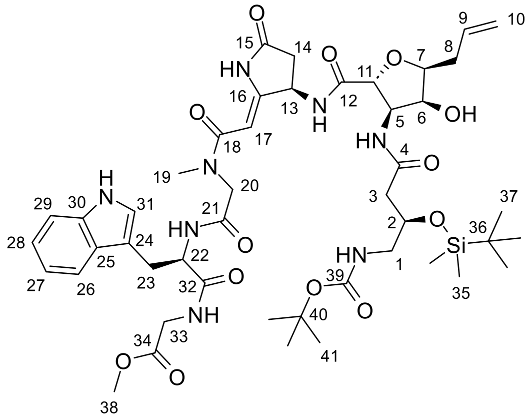
Methyl *N*-((*Z*)-2-((*R*)-3-((2*R*,3*R*,4*S*,5*S*)-5-allyl-3-((*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-4-hydroxytetrahydrofuran-2-carboxamido)-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycyl-D-tryptophylglycinate 124

0.40 M $LiOH_{aq}$ (201 µL, 80.0 µmol, 1.1 eq.) was slowly added to a 0 °C cold solution of tetrapeptide **122** (53.0 mg, 73.0 µmol) in THF (700 µL). The resulting mixture was stirred for 2 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl_{aq} and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid as a white foam.

4.0 M HCl in dioxane (367 µL, 1.47 mmol, 10 eq.) was added to a solution of dipeptide **111** (58.0 mg, 147 µmol) in CH_2Cl_2 (50 µL) at 0 °C. After stirring for 3 h, the reaction mixture was concentrated in vacuo to give the crude amine as hydrochloride salt **112**.

The above-prepared crude carboxylic acid and amine hydrochloride **112** (2.0 eq.) were dissolved in anhydrous DMF (1.0 mL). After cooling to 0 °C, NMM (33.0 µL, 299 µmol, 4.1 eq.) and HATU (30.6 mg, 80.0 µmol, 1.1 eq.) were subsequently added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give hexapeptide **124** (42.2 mg, 43.5 µmol, 60%, dr > 99:1) as a white foam.

LC-MS: t_R (124) = 1.25 min (short method)



124

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.80 (s, 1 H, 31-NH), 10.40 (s, 1 H, 15-NH), 8.48 (d, $^3J_{NH,13}$ = 8.6 Hz, 1 H, 12-NH), 8.42 (t, $^3J_{NH,33}$ = 5.5 Hz, 1 H, 32-NH), 8.09 (d, $^3J_{NH,22}$ = 8.2 Hz, 1 H, 21-NH), 7.87 (d, $^3J_{NH,5}$ = 8.4 Hz, 1 H, 4-NH), 7.57 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.31 (d, $^3J_{26,27}$ = 8.0 Hz , 1 H, 26-H), 7.13 (s, 1 H, 31-H), 7.05 (ddd, $^3J_{27,26}$ = 8.2 Hz, $^3J_{27,28}$ = 7.0 Hz, $^4J_{27,29}$ = 1.2 Hz, 1 H, 27-H), 6.97 (ddd, $^3J_{28,29}$ = 7.9 Hz, $^3J_{28,27}$ = 7.0 Hz, $^4J_{28,26}$ = 1.1 Hz, 1 H, 28-H), 6.70 (m, 1 H, 39-NH), 5.81 (m, 1 H, 9-H), 5.34 (s, 1 H, 17-H), 5.30 (d, $^3J_{OH,6}$ = 5.1 Hz, 1 H, 6-OH), 5.16 – 5.06 (m, 2 H, 10-H, 13-H), 5.02 (m, 1 H, 10-H‘), 4.57 (m, 1 H, 22-H), 4.44 (ddd, $^3J_{5,11}$ = 8.7 Hz, $^3J_{5,NH}$ = 8.7 Hz, $^3J_{5,6}$ = 4.2 Hz, 1 H, 5-H), 4.07 (td, $^3J_{7,8}$ = 7.1 Hz, $^3J_{7,6}$ = 2.5 Hz, 1 H, 7-H), 4.39 (d, $^3J_{11,5}$ = 6.1 Hz, 1 H, 11-H), 4.04 – 3.88 (m, 5 H, 2-H, 6-H, 11-H, 20-H), 3.86 (d, $^3J_{33,NH}$ = 6.2 Hz, 1 H, 33-H), 3.64 (s, 3 H, 38-H), 3.17 (dd, $^2J_{23',23}$ = 14.7 Hz, $^3J_{23',22}$ = 4.9 Hz, 1 H, 23-H‘), 2.98 – 2.90 (m, 3 H, 1-H, 23-H), 2.87 (s, 3 H, 19-H), 2.73 (m, 1 H, 14-H), 2.40 – 2.19 (m, 5 H, 3-H, 8-H, 14-H‘), 1.37 (s, 9 H, 41-H), 0.82 (s, 9 H, 37-H), 0.03 (s, 3 H, 35-H), 0.00 (s, 3 H, 35‘-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.8 (s, C-15), 171.9 (s, C-32), 171.4 (s, C-12), 170.2 (s, C-34), 169.8 (s, C-4), 168.2 (s, C-21), 167.7 (s, C-18), 157.0 (s, C-16), 155.6 (s, C-39), 136.0 (s, C-30), 135.0 (d, C-9), 127.3 (s, C-25), 123.6 (d, C-31), 120.8 (d, C-27), 118.3 (d, C-29), 118.2 (d, C-28), 116.9 (t, C-10), 111.2 (d, C-26), 109.9 (s, C-24), 87.9 (d, C-17), 82.2 (d, C-7), 78.9 (d, C-11), 77.5 (s, C-40), 70.8 (d, C-6), 68.9 (d, C-2), 56.5 (d, C-5), 53.2 (d, C-22), 51.7 (q, C-38), 50.2 (t, C-20), 46.4 (d, C-13), 45.4 (t, C-1), 41.8 (t, C-3), 40.7 (t, C-33), 36.3 (q, C-19), 34.7 (t, C-14), 33.5 (t, C-8), 28.3 (q, C-41), 27.7 (t, C-23), 25.8 (q, C-37), 17.8 (s, C-36), –4.9 (q, C-35’), –5.0 (q, C-35).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.76 (s, 1 H, 31-NH), 10.43 (s, 1 H, 15-NH), 8.17 (m, 1 H, 32-NH/21-NH), 7.92 (m, 1 H, 32-NH/21-NH), 5.21 (s, 1 H, 17-H), 4.97 (m, 1 H, 13-H), 4.62 (m, 1 H, 22-H), 1.38 (s, 9 H, 41-H), 0.83 (s, 9 H, 37-H), 0.04 (s, 3 H, 35-H), 0.01 (s, 3 H, 35‘-H).

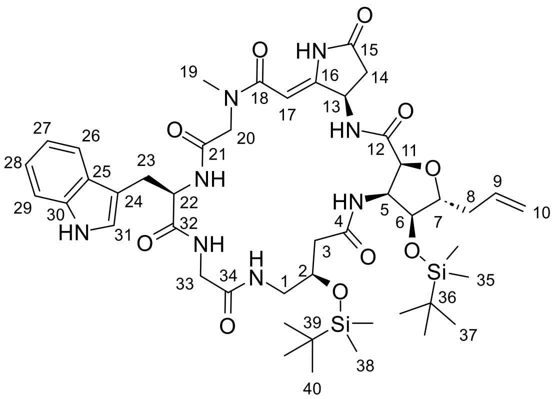
Optical rotation:	$[\alpha]_D^{20}$= +27.6 (c = 1.0, CHCl$_3$)	
HRMS (ESI):	calculated	found
$C_{46}H_{69}N_8O_{13}Si$ [M+H]$^+$:	969.4748	969.4733

(2*R*,3*S*,3a*S*,7*R*,14*R*,23a*R*,25a*S*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-allyl-3,7-bis((*tert*-butyldimethylsilyl)oxy)-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 125

0.30 M LiOH$_{aq}$ (92.0 µL, 28.0 µmol, 1.0 eq.) was slowly added to a 0 °C cold solution of hexapeptide **123** (30.0 mg, 27.7 µmol) in THF (200 µL). The resulting mixture was stirred for 6 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl$_{aq}$ and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid as a white foam.

A preformed cleavage cocktail TFA:TIPS:H_2O (107 µL, 185:10:5) was added to a solution of the crude carboxylic acid in anhydrous CH_2Cl_2 (30 µL) at –10 °C. After 15 min, reaction control via LC-MS showed full conversion (70% Boc-deprotection and 30% Boc- and monoTBS-deprotection). The reaction mixture was concentrated in vacuo. The residue was dissolved in anhydrous DMF (25 mL). After cooling to 0 °C, DIPEA (48.0 µL, 277 µmol, 10 eq.), HOAt (42.7 mg, 277 µmol, 10 eq.), and PyAOP (144 mg, 277 µmol, 10 eq.) were added. The reaction mixture was stirred for 72 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% LiCl$_{aq}$, 1.0 M HCl$_{aq}$, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 10% to 100% MeCN) to give the protected dehydrosocein precursor **125** (8.7 mg, 9.15 µmol, 33%, dr > 99:1) as a white foam and its mono-TBS-deprotected variant **125(OH)** (3.9 mg, 4.66 µmol, 17%) as a white foam. The epimer from the tetrapeptide coupling was separated during the preparative HPLC (hence the improved diastereomeric ratio).

LC-MS: t_R (125) = 1.52 min (short method)



125

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.95 (s, 1 H, 15-NH), 8.61 (m, 1 H, 31-NH), 7.73 (dd, $^3J_{NH,33}$ = 8.2 Hz, $^3J_{NH,33'}$ = 3.5 Hz , 1 H, 32-NH), 7.64 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.41 (d, $^3J_{26,27}$ = 8.1 Hz, 1 H, 26-H), 7.24 (ddd, $^3J_{27,26}$ = 8.1 Hz, $^3J_{27,28}$ = 7.0 Hz, $^4J_{27,29}$ = 1.2 Hz, 1 H, 27-H), 7.19 – 7.13 (m, 2 H, 28-H, 34-NH), 7.12 (d, $^3J_{31,NH}$ = 2.4 Hz, 1 H, 31-H), 7.01 (m, 1 H, 12-NH), 6.71 (m, 1 H, 21-NH), 6.36 (m, 1 H, 4-NH), 5.83 (m, 1 H, 9-H), 5.70 (d, $^4J_{17,13}$ = 1.5 Hz, 1 H, 17-H), 5.22 – 5.15 (m, 2 H, 10-H), 5.04 (m, 1 H, 13-H), 4.65 (m, 1 H, 22-H), 4.60 (ddd, $^3J_{5,6}$ = 5.9 Hz, $^3J_{5,NH}$ = 5.9 Hz, $^3J_{5,11}$ = 3.5 Hz, 1 H, 5-H), 4.45 (dd, $^2J_{33,33'}$ = 17.1 Hz, $^3J_{33,NH}$ = 8.4 Hz, 1 H, 33-H), 4.37 (d, $^3J_{11,5}$ = 3.4 Hz, 1 H, 11-H), 4.23 (dd, $^3J_{6,7}$ = 6.9 Hz, $^3J_{6,5}$ = 5.5 Hz, 1 H, 6-H), 4.08 (m, 1 H, 2-H), 4.05 – 3.98 (m, 2 H, 7-H, 20-H), 3.45 – 3.33 (m, 3 H, 1-H, 23-H), 3.35 (s, 3 H, 19-H), 3.27 (d, $^2J_{20',20}$ = 14.2 Hz, 1 H, 20-H'), 3.23 (dd, $^2J_{33',33}$ = 17.2 Hz, $^3J_{33',NH}$ = 3.6 Hz, 1 H, 33-H'), 3.05 (ddd, $^2J_{1',1}$ = 13.4 Hz, $^3J_{1',NH}$ = 4.5 Hz, $^3J_{1',2}$ = 4.5 Hz, 1 H, 1-H'), 2.63 (dd, $^2J_{14,14'}$ = 17.6 Hz, $^3J_{14,13}$ = 9.9 Hz, 1 H, 14-H'), 2.53 (m, 1 H, 8-H), 2.35 – 2.23 (m, 3 H, 3-H, 8-H', 14-H'), 2.19 (dd, $^2J_{3',3}$ = 15.2 Hz, $^3J_{3,2}$ = 4.3 Hz, 2 H, 3-H'), 0.91 (s, 9 H, 40-H), 0.85 (s, 9 H, 37-H), 0.13 (s, 3 H, 38-H/35-H), 0.10 (s, 3 H, 38-H/35-H), 0.08 (s, 3 H, 35-H/38-H), 0.04 (s, 3 H, 35-H/38-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.9 (s, C-15), 172.3 (s, C-21), 171.7 (s, C-32), 171.1 (s, C-4), 170.1 (s, s, C-12, C-34), 170.0 (s, C-18), 155.6 (s, C-16), 136.4 (s, C-30), 133.1 (d, C-9), 127.7 (s, C-25), 123.4 (d, C-31), 122.6 (d, C-27), 120.1 (d, C-28), 118.9 (t, C-10), 118.6 (d, C-29), 111.7 (d, C-26), 109.6 (s, C-24), 90.9 (d, C-17), 82.6 (d, C-7), 81.1 (d, C-11), 74.9 (d, C-6), 68.3 (d, C-2), 55.7 (d, C-22), 54.8 (t, C-20), 54.7 (d, C-5), 47.6 (d, C-13), 45.0 (t, C-1), 42.9 (t, C-33), 41.1 (t, C-3), 39.4 (q, C-19), 37.2 (t, C-8), 34.3 (t, C-14), 26.1 (q, t, C-40, C-23), 26.0 (q, C-37), 18.1 (s, s, C-36, C-39), –4.1 (q, C-38), –4.2 (q, C-38'), –4.9 (q, C-35), –5.0 (q, C-35').

Optical rotation: $[\alpha]_D^{20}$= +7.4 (c = 1.0, $CHCl_3$)

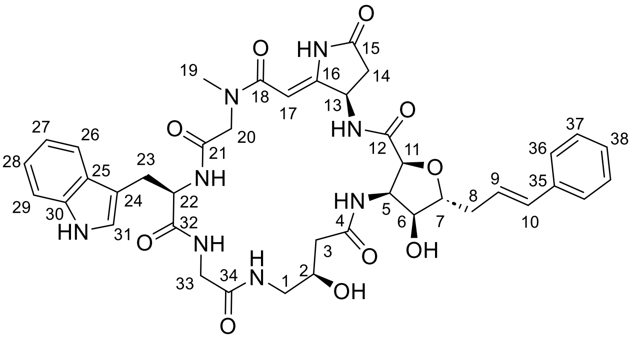
HRMS (ESI):	calculated	found
$C_{46}H_{71}N_8O_{10}Si_2$ [M+H]$^+$:	951.4826	951.4832

(2*R*,3*S*,3a*R*,7*R*,14*R*,23a*R*,25a*S*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-cinnamyl-3,7-dihydroxy-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 127

In a 4 mL brown-glass vial under an atmosphere of argon, protected dehydrosocein precursor **125** (8.4 mg, 8.8 µmol) was dissolved in argon-degassed, anhydrous CH_2Cl_2 (150 µL). After the addition of styrene (15.3 µL, 132 µmol, 15 eq.) and Grubbs II catalyst in CH_2Cl_2 (73.6 µL, 0.883 µmol, 0.012 M, 10mol%), the reaction mixture was stirred for 48 h. Another portion of Grubbs II catalyst (73.6 µL, 0.883 µmol, 0.012 M, 10mol%) was added, and the stirring was continued for 24 h. After adsorption on isolute®, the mixture was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give the olefination product **126** (4.5 mg, 4.4 µmol, 50%) as a white foam.

1.0 M TBAF in THF (5.84 µL, 5.84 µmol, 1.5 eq.) was added to a 0 °C cold solution of the above-prepared olefination product **126** (4.0 mg, 3.9 µmol) in anhydrous THF (70 µL). The resulting solution was stirred for 4 h while slowly reaching room temperature. After the addition of a droplet of H_2O, the reaction mixture was adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 10% to 100% MeCN) to give dehydrosocein derivative **127** (2.1 mg, 2.6 µmol, 68%) as an amorphous solid after lyophilization.

LC-MS: t_R (127) = 0.90 min (short method)



127

^{1}H-NMR (500 MHz, MeOD-d$_4$): δ = 7.68 (d, $^{3}J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.36 (m, 2 H, 36-H), 7.30 – 7.23 (m, 3 H, 26-H, 37-H), 7.18 (m, 1 H, 38-H), 7.16 (s, 1 H, 31-H), 7.11 (m, 1 H, 28-H), 7.04 (m, 1 H, 27-H), 6.49 (d, $^{3}J_{10,9}$ = 16.2 Hz , 1 H, 10-H), 6.22 (dt, $^{3}J_{9,10}$ = 15.8 Hz, $^{3}J_{9,8}$ = 7.1 Hz, 1 H, 9-H), 4.80 (s, 1 H, 17-H), 4.67 (dd, $^{3}J_{5,11}$ = 8.5 Hz, $^{3}J_{5,6}$ = 4.5 Hz, 1 H, 5-H), 4.49 (dd, $^{3}J_{22,23}$ = 10.9 Hz, $^{3}J_{22,23'}$ = 4.4 Hz, 1 H, 22-H), 4.34 (d, $^{3}J_{11,5}$ = 8.5 Hz, 1 H, 11-H), 4.27 (m, 1 H, 13-H), 4.24 (d, $^{2}J_{20',20}$ = 17.8 Hz, 1 H, 20-H‘), 4.21 – 4.13 (m, 2 H, 2-H, 7-H), 4.05 (d, $^{3}J_{6,5}$ = 4.5 Hz, 1 H, 6-H), 4.02 (d, $^{2}J_{33',33}$ = 16.6 Hz, 1 H, 33-H‘), 3.76 (d, $^{2}J_{33,33'}$ = 16.5 Hz, 1 H, 33-H), 3.72 (d, $^{2}J_{20,20'}$ = 17.9 Hz, 1 H, 20-H), 3.46 (m, 1 H, 1-H‘), 3.37 (dd, $^{2}J_{23',23}$ = 14.4 Hz, $^{3}J_{23',22}$ = 4.5 Hz, 1 H, 23-H‘), 3.17 (m, 1 H, 1-H), 3.03 (dd, $^{2}J_{23,23'}$ =

14.5 Hz, $^3J_{23,22}$ = 10.9 Hz, 1 H, 23-H), 2.93 (s, 3 H, 19-H), 2.70 (dd, $^2J_{3,3'}$ = 14.3 Hz, $^3J_{3,2}$ = 9.9 Hz, 1 H, 3-H), 2.63 – 2.33 (m, 5 H, 3-H‘, 8-H, 14-H).

^{13}C-NMR (125 MHz, MeOD-d$_4$): δ = 177.3 (s, C-15), 174.8 (s, C-32), 174.0 (s, C-12), 173.5 (s, C-4), 173.1 (s, C-21), 172.4 (s, C-34), 170.1 (s, C-18), 157.3 (s, C-16), 138.8 (s, C-35), 138.5 (s, C-30), 134.2 (d, C-10), 129.5 (d, C-37), 128.3 (d, C-38), 128.1 (s, C-25), 127.1 (d, C-36), 126.2 (d, C-9), 125.2 (d, C-31), 122.6 (d, C-28), 120.1 (d, C-27), 119.6 (d, C-29), 112.6 (d, C-26), 110.0 (s, C-24), 90.2 (d, C-17), 87.9 (d, C-7), 75.7 (d, C-11), 73.6 (d, C-6), 68.7 (d, C-2), 56.3 (d, C-22), 55.1 (d, C-5), 54.4 (t, C-20), 46.8 (d, C-13), 46.4 (t, C-1), 44.2 (t, C-33), 41.1 (t, C-3), 38.8 (t, C-8), 35.6 (q, C-19), 35.2 (t, C-14), 28.3 (t, C-23).

Selected rotamer signals:

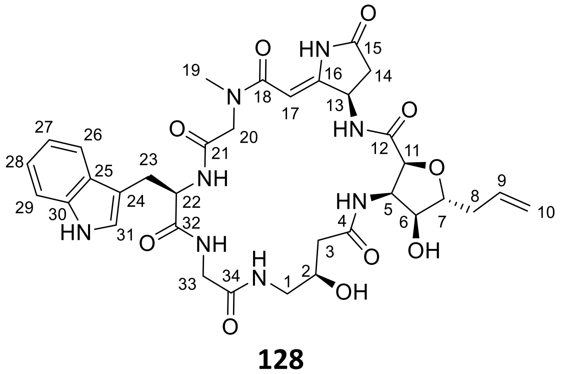
^{1}H-NMR (500 MHz, MeOD-d$_4$): δ = 7.57 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.02 (m, 1 H, 27-H), 6.53 (d, $^3J_{10,9}$ = 15.6 Hz, 1 H, 10-H), 6.30 (dt, $^3J_{9,10}$ = 15.2 Hz, $^3J_{9,8}$ = 7.1 Hz, 1 H, 9-H), 5.67 (s, 1 H, 17-H), 5.27 (m, 1 H, 13-H), 4.73 (dd, $^3J_{5,11}$ = 4.9 Hz, $^3J_{5,6}$ = 4.9 Hz, 1 H, 5-H), 4.53 (d, $^3J_{11,5}$ = 4.6 Hz, 1 H, 11-H), 4.41 (d, $^2J_{20',20}$ = 15.7 Hz, 1 H, 20-H‘), 4.09 (m, 1 H, 6-H), 3.11 (s, 3 H, 19-H), 2.84 (m, 1 H, 14-H).

Optical rotation:	$[\alpha]_D^{20}$= –39.3 (c = 0.3, MeOH)	
HRMS (ESI):	calculated	found
$C_{40}H_{47}N_8O_{10}$ [M+H]$^+$:	799.3410	799.3406

(2*R*,3*S*,3a*R*,7*R*,14*R*,23a*R*,25a*S*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-allyl-3,7-dihydroxy-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 128

1.0 M TBAF in THF (4.47 µL, 4.47 µmol, 1.1 eq.) was added to a 0 °C cold solution of mono-TBS-deprotected variant **125(OH)** (3.4 mg, 4.06 µmol) in anhydrous THF (300 µL). The resulting solution was stirred for 3 h while slowly reaching room temperature. After the addition of a droplet of H$_2$O, the reaction mixture was adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give dehydrosocein precursor **128** (2.4 mg, 3.32 µmol, 82%) as an amorphous solid after lyophilization.

LC-MS: t$_R$ (128) = 0.70 min (short method)



128

^{1}H-NMR (500 MHz, MeOD-d$_4$): δ = 7.69 (d, $^{3}J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.27 (d, $^{3}J_{26,27}$ = 8.0 Hz, 1 H, 26-H), 7.16 (s, 1 H, 31-H), 7.11 (ddd, $^{3}J_{28,29}$ = 8.0 Hz, $^{3}J_{28,27}$ = 7.0 Hz, $^{4}J_{28,26}$ = 1.2 Hz, 1 H, 28-H), 7.05 (ddd, $^{3}J_{27,26}$ = 8.0 Hz, $^{3}J_{27,28}$ = 7.0 Hz, $^{4}J_{27,29}$ = 1.1 Hz, 1 H, 27-H), 5.81 (ddt, $^{3}J_{9,10}$ = 17.2 Hz, $^{3}J_{9,10'}$ = 10.3 Hz, $^{3}J_{9,8}$ = 6.9 Hz, 1 H, 9-H), 5.12 (m, 1 H, 10-H'), 5.07 (m, 1 H, 10-H), 4.79 (d, $^{4}J_{17,13}$ = 1.6 Hz, 1 H, 17-H), 4.62 (dd, $^{3}J_{5,11}$ = 8.5 Hz, $^{3}J_{5,6}$ = 4.5 Hz, 1 H, 5-H), 4.49 (dd, $^{3}J_{22,23}$ = 10.7 Hz, $^{3}J_{22,23'}$ = 4.7 Hz, 1 H, 22-H), 4.30 (d, $^{3}J_{11,5}$ = 8.5 Hz, 1 H, 11-H), 4.25 (d, $^{2}J_{20',20}$ = 17.9 Hz, 1 H, 20-H'), 4.24 (m, 1 H, 13-H), 4.17 (m, 1 H, 2-H), 4.11 (t, $^{3}J_{7,8}$ = 6.8 Hz, 1 H, 7-H), 4.02 (d, $^{2}J_{33',33}$ = 16.6 Hz, 1 H, 33-H'), 3.98 (d, $^{3}J_{6,5}$ = 4.5 Hz, 1 H, 6-H), 3.77 (d, $^{2}J_{33,33'}$ = 16.3 Hz, 1 H, 33-H), 3.73 (d, $^{2}J_{20,20'}$ = 17.6 Hz, 1 H, 20-H), 3.47 (m, 1 H, 1-H'), 3.38 (dd, $^{2}J_{23',23}$ = 14.5 Hz, $^{3}J_{23',22}$ = 4.6 Hz, 1 H, 23-H'), 3.19 (m, 1 H, 1-H), 3.03 (dd, $^{2}J_{23,23'}$ = 14.5 Hz, $^{3}J_{23,22}$ = 10.9 Hz, 1 H, 23-H), 2.95 (s, 3 H, 19-H), 2.70 (dd, $^{2}J_{3,3'}$ = 14.5 Hz, $^{3}J_{3,2}$ = 10.1 Hz, 1 H, 3-H), 2.53 – 2.18 (m, 5 H, 3-H', 8-H, 14-H).

^{13}C-NMR (125 MHz, MeOD-d$_4$): δ = 177.2 (s, C-15), 174.8 (s, C-32), 174.0 (s, C-12), 173.5 (s, C-4), 173.1 (s, C-21), 172.4 (s, C-34), 170.1 (s, C-18), 157.3 (s, C-16), 138.5 (s, C-30), 135.0 (d, C-9), 128.1 (s, C-25), 125.2 (d, C-31), 122.6 (d, C-28), 120.1 (d, C-27), 119.6 (d, C-29), 118.2 (t, C-10), 112.6 (d, C-26), 110.0 (s, C-24), 90.1 (d, C-17), 87.6 (d, C-7), 75.6 (d, C-11), 73.5 (d, C-6), 68.7 (d, C-2), 56.3 (d, C-22), 55.0 (d, C-5), 54.4 (t, C-20), 46.8 (d, C-13), 46.4 (t, C-1), 44.2 (t, C-33), 41.1 (t, C-3), 39.6 (t, C-8), 35.6 (q, C-19), 35.2 (t, C-14), 28.3 (t, C-23).

Selected rotamer signals:

^{1}H-NMR (500 MHz, MeOD-d$_4$): δ = 7.58 (d, $^{3}J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.34 (d, $^{3}J_{26,27}$ = 8.2 Hz , 1 H, 26-H), 7.18 (s, 1 H, 31-H), 7.09 (m, 1 H, 28-H), 7.03 (m, 1 H, 27-H), 5.89 (ddt, $^{3}J_{9,10}$ = 17.2 Hz, $^{3}J_{9,10'}$ = 10.1 Hz, $^{3}J_{9,8}$ = 7.0 Hz, 1 H, 9-H), 5.67 (d, $^{4}J_{17,13}$ = 1.5 Hz, 1 H, 17-H), 5.27 (ddd, $^{3}J_{13,14}$ = 9.7 Hz, $^{3}J_{13,14'}$ = 5.4 Hz, $^{4}J_{13,17}$ = 1.5 Hz, 1 H, 13-H), 5.16 (m, 1 H, 10-H'), 4.70 (m, 1 H, 5-H), 4.41 (d, $^{2}J_{20',20}$ = 15.7 Hz, 1 H, 20-H'), 4.34 (dd, $^{3}J_{22,23}$ = 8.7 Hz, $^{3}J_{22,23'}$ = 5.7 Hz, 1 H, 22-H), 3.68 (d, $^{2}J_{20,20'}$ = 16.0 Hz, 1 H, 20-H), 3.12 (s, 3 H, 19-H), 2.86 (dd, $^{2}J_{14,14'}$ = 17.9 Hz, $^{3}J_{14,13}$ = 9.9 Hz, 1 H, 14-H), 2.58 – 2.14 (m, 5 H, 3-H, 8-H, 14-H').

Optical rotation:	$[\alpha]_D^{20}$= +38.0 (c = 0.3, MeOH)	
HRMS (ESI):	calculated	found
$C_{34}H_{43}N_8O_{10}$ [M+H]$^+$:	723.3097	723.3103

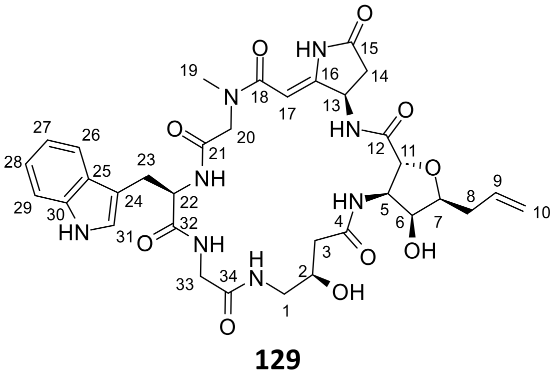
(2*S*,3*S*,3a*R*,7*R*,14*R*,23a*R*,25a*R*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-allyl-3,7-dihydroxy-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 129

0.40 M LiOH$_{aq}$ (95.0 µL, 38.0 µmol, 1.05 eq.) was slowly added to a 0 °C cold solution of hexapeptide **124** (35.0 mg, 36.0 µmol) in THF (250 µL). The resulting mixture was stirred for 5 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 0.1 M HCl$_{aq}$ and extracted with CH_2Cl_2 and $CHCl_3$. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid as a white foam.

A preformed cleavage cocktail TFA:TIPS:H_2O (1.0 mL, 185:10:5) was added to a solution of the crude carboxylic acid in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C. After 30 min, reaction control via LC-MS showed full conversion. The reaction mixture was concentrated in vacuo. The residue was dissolved in anhydrous DMF (18 mL). After cooling to 0 °C, DIPEA (63.0 µL, 361 µmol, 10 eq.), HOAt (55.7 mg, 361 µmol, 10 eq.), and PyAOP (188 mg, 361 µmol, 10 eq.) were added. The reaction mixture was stirred for 16 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) followed by preparative HPLC (H_2O:MeCN 20% to 90% MeCN) and preparative HPLC (0.1% $HCOOH_{aq}$:MeCN 20% to 90% MeCN) to give the cyclized dehydrosocein precursor (7.0 mg, unknown purity).

1.0 M TBAF in THF (10.0 µL, 10.0 µmol) was added to a 0 °C cold solution of cyclized dehydrosocein precursor (7.0 mg, unknown purity) in anhydrous THF (80 µL). The resulting solution was stirred for 4 h while slowly reaching room temperature. After the addition of a droplet of H_2O, the reaction mixture was adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, 0.1% $HCOOH_{aq}$:MeCN 0% to 50% MeCN) followed by preparative HPLC (0.1% $HCOOH_{aq}$:MeCN 0% to 70% MeCN) to give dehydrosocein precursor **129** (4.1 mg, 5.7 µmol, 16% from **124**) as an amorphous solid after lyophilization.

LC-MS: t_R (129) = 1.16 min (long method)



129

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.87 (d, $^3J_{NH,31}$ = 2.4 Hz, 1 H, 31-NH), 10.39 (s, 1 H, 15-NH), 8.54 – 8.46 (m, 2 H, 21-NH, 12-H), 8.31 (t, $^3J_{NH,33}$ = 6.2 Hz, 1 H, 32-NH), 7.73 (d, $^3J_{NH,5}$ = 8.4 Hz, 1 H, 4-NH), 7.52 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.34 (d, $^3J_{26,27}$ = 8.0 Hz, 1 H, 26-H), 7.28 (t, $^3J_{NH,1}$ = 5.5 Hz, 1 H, 34-NH), 7.21 (d, $^3J_{31,NH}$ = 2.3 Hz, 1 H, 31-H), 7.07 (ddd, $^3J_{28,29}$ = 8.1 Hz, $^3J_{28,27}$ = 6.8 Hz, $^4J_{28,26}$ = 1.2 Hz, 1 H, 28-H), 6.99 (ddd, $^3J_{27,26}$ = 7.9 Hz, $^3J_{27,28}$ = 7.0 Hz, $^4J_{27,29}$ = 1.1 Hz, 1 H, 27-H), 5.80 (ddt, $^3J_{9,10}$ = 17.0 Hz, $^3J_{9,10'}$ = 10.1 Hz, $^3J_{9,8}$ = 6.8 Hz, 1 H, 9-H), 5.41 (m, 1 H, 6-OH), 5.38 (d, $^4J_{17,13}$ = 1.6 Hz, 1 H, 17-H), 5.16 (m, 1 H, 13-H), 5.11 (m, 1 H, 10-H'), 5.01 (m, 1 H, 10-H), 4.67 (d, $^3J_{OH,2}$ = 4.9 Hz, 1 H, 2-OH), 4.57 (d, $^3J_{20',20}$ = 15.9 Hz, 1 H, 20-H'), 4.53 (ddd, $^3J_{5,11}$ = 8.6 Hz, $^3J_{5,NH}$ = 8.6 Hz, $^3J_{5,6}$ = 4.4 Hz, 1 H, 5-H), 4.19 (ddd, $^3J_{22,23}$ = 10.0 Hz, $^3J_{22,NH}$ = 5.2 Hz, $^3J_{22,23'}$ = 5.2 Hz, 1 H, 22-H), 4.08 (td, $^3J_{7,8}$ = 6.9 Hz, $^3J_{7,6}$ = 2.6 Hz, 1 H, 7-H), 4.01 – 3.93 (m, 2 H, 2-H, 6-H), 3.91 (d, $^3J_{11,5}$ = 8.6 Hz, 1 H, 11-H), 3.65

(dd, $^{2}J_{33,33'}$ = 16.9 Hz, $^{3}J_{33,NH}$ = 5.9 Hz, 1 H, 33-H), 3.58 (dd, $^{2}J_{33',33}$ = 16.9 Hz, $^{3}J_{33',NH}$ = 6.2 Hz, 1 H, 33-H‘), 3.43 (d, $^{2}J_{20,20'}$ = 15.9 Hz, 1 H, 20-H), 3.18 (dd, $^{2}J_{23',23}$ = 14.7 Hz, $^{3}J_{23',22}$ = 4.8 Hz, 1 H, 23-H‘), 3.15 – 3.09 (m, 4 H, 1-H, 19-H), 3.01 (dd, $^{2}J_{23,23'}$ = 14.8 Hz, $^{3}J_{23,22}$ = 9.5 Hz, 1 H, 23-H), 2.79 (m, 1 H, 1-H‘), 2.74 (dd, $^{2}J_{14,14'}$ = 17.6 Hz, $^{3}J_{14,13}$ = 9.7 Hz, 1 H, 14-H), 2.38 – 2.17 (m, 5 H, 3-H, 8-H, 14-H‘).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 174.4 (s, C-15), 171.5 (s, C-32), 171.4 (s, C-12), 170.9 (s, C-21), 170.3 (s, C-4), 168.8 (s, C-34), 168.2 (s, C-18), 156.5 (s, C-16), 136.1 (s, C-30), 135.2 (d, C-9), 127.0 (s, C-25), 124.0 (d, C-31), 121.0 (d, C-28), 118.4 (d, C-27), 118.1 (d, C-29), 116.8 (t, C-10), 111.4 (d, C-26), 109.8 (s, C-24), 88.1 (d, C-17), 82.6 (d, C-7), 79.3 (d, C-11), 71.0 (d, C-6), 66.0 (d, C-2), 56.5 (d, C-5), 55.4 (d, C-22), 50.6 (t, C-20), 46.3 (d, C-13), 45.0 (t, C-1), 42.5 (t, C-33), 41.4 (t, C-3), 37.1 (q, C-19), 34.3 (t, C-14), 33.6 (t, C-8), 26.3 (t, C-23).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.84 (m, 1 H, 31-NH), 10.43 (s, 1 H, 15-NH), 7.56 (m, 1 H, 29-H), 7.14 (m, 1 H, 31-H), 4.89 (m, 1 H, 13-H), 4.42 (m, 1 H, 5-H), 2.63 (s, 3 H, 19-H).

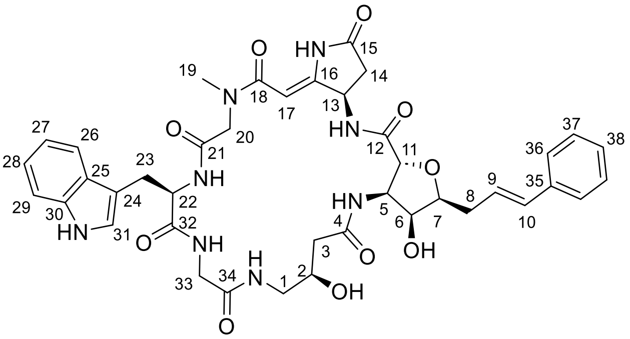
Optical rotation: $[\alpha]_D^{20}$= -15.4 (c = 0.5, DMSO)

HRMS (ESI):	calculated	found
$C_{34}H_{43}N_8O_{10}$ [M+H]$^+$:	723.3097	723.3100

(2*S*,3*S*,3a*R*,7*R*,14*R*,23a*R*,25a*R*,*Z*)-14-((1*H*-Indol-3-yl)methyl)-2-cinnamyl-3,7-dihydroxy-18-methyl-2,3,3a,6,7,8,9,11,12,14,15,17,18,23a,24,25a-hexadecahydrofuro[2,3-q]pyrrolo[2,3-m][1,4,7,10,15,19]hexaazacyclotricosine-5,10,13,16,19,22,25(4*H*,21*H*,23*H*)-heptaone 130

In a 4 mL brown-glass vial under an atmosphere of argon, dehydrosocein precursor **129** (3.5 mg, 4.84 µmol) was dissolved in argon-degassed AcOH (150 µL). After the addition of styrene (8.41 µL, 73.0 µmol, 15 eq.) and Grubbs II catalyst in AcOH (40.5 µL, 0.485 µmol, 0.012 M, 10mol%), the reaction mixture was stirred for 24 h. Another portion of Grubbs II catalyst (40.5 µL, 0.485 µmol, 0.012 M, 10mol%) was added, and the stirring was continued for 28 h at 40 °C. After adsorption on isolute®, the mixture was purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) followed by preparative HPLC (0.1% HCOOH$_{aq}$:MeCN 0% to 90% MeCN) to give the dehydrosocein derivative **130** (0.4 mg, 0.5 µmol, 10%) as an amorphous solid after lyophilization.

LC-MS: t$_R$ (130) = 0.87 min (short method)



130

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 10.87 (d, $^3J_{NH,31}$ = 2.4 Hz, 1 H, 31-NH), 10.39 (s, 1 H, 15-NH), 8.58 – 8.48 (m, 2 H, 21-NH, 12-NH), 8.31 (t, $^3J_{NH,33}$ = 5.6 Hz, 1 H, 32-NH), 7.81 (d, $^3J_{NH,5}$ = 8.4 Hz, 1 H, 4-NH), 7.52 (d, $^3J_{29,28}$ = 7.9 Hz, 1 H, 29-H), 7.38 (m, 2 H, 36-H), 7.33 (d, $^3J_{26,27}$ = 8.1 Hz, 1 H, 26-H), 7.32 – 7.27 (m, 3 H, 34-NH, 37-H), 7.22 – 7.17 (m, 2 H, 31-H, 38-H), 7.07 (m, 1 H, 28-H), 6.99 (m, 1 H, 27-H), 6.48 (d, $^3J_{10,9}$ = 15.9 Hz, 1 H, 10-H), 6.28 (dt, $^3J_{9,10}$ = 15.9 Hz, $^3J_{9,8}$ = 7.1 Hz, 1 H, 9-H), 5.51 (m, 1 H, 6-OH), 5.39 (s, 1 H, 17-H), 5.16 (m, 1 H, 13-H), 4.71 (m, 1 H, 2-OH), 4.57 (d, $^2J_{20',20}$ = 15.8 Hz, 1 H, 20-H‘), 4.54 (m, 1 H, 5-H), 4.22 – 4.13 (m, 2 H, 7-H, 22-H), 4.05 – 3.94 (m, 2 H, 2-H, 6-H), 3.96 (d, $^3J_{11,5}$ = 8.8 Hz, 1 H, 11-H), 3.65 (dd, $^2J_{33,33'}$ = 16.9 Hz, $^3J_{33,NH}$ = 5.6 Hz, 1 H, 33-H), 3.57 (m, 1 H, 33-H‘), 3.42 (d, $^2J_{20,20'}$ = 15.8 Hz, 1 H, 20-H), 3.18 (dd, $^2J_{23',23}$ = 14.9 Hz, $^3J_{23',22}$ = 4.7 Hz, 1 H, 23-H‘), 3.15 – 3.06 (m, 4 H, 1-H, 19-H), 3.01 (dd, $^2J_{23,23'}$ = 14.7 Hz, $^3J_{23,22}$ = 9.4 Hz, 1 H, 23-H), 2.79 (m, 1 H, 1-H‘), 2.74 (dd, $^2J_{14,14'}$ = 17.6 Hz, $^3J_{14,13}$ = 9.6 Hz, 1 H, 14-H), 2.32 (dd, $^2J_{14',14}$ = 17.6 Hz, $^3J_{14,13}$ = 6.1 Hz, 1 H, 14-H‘), 2.44 (m, 2 H, 8-H, covered by the DMSO-d_5 signal), 2.24 (m, 2 H, 3-H).

^{13}C-NMR-shifts extracted from 2D-NMR data (HMBC, HSQCED) due to insufficient material for a 1D ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 174.3 (s, C-15), 170.8 (s, C-12), 170.2 (s, C-4), 168.2 (s, C-18), 156.3 (s, C-16), 136.2 (s, C-30), 131.1 (d, C-10), 128.3 (d, C-37), 127.0 (s, C-25), 126.7 (d, d, C-9, C-38), 125.9 (s, C-35), 125.6 (d, C-36), 123.7 (d, C-31), 120.8 (d, C-28), 118.0 (d, C-27), 117.9 (d, C-29), 111.1 (d, C-26), 109.8 (s, C-24), 87.7 (d, C-17), 82.6 (d, C-7), 79.0 (d, C-11), 70.8 (d, C-6), 65.8 (d, C-2), 56.2 (d, C-5), 55.0 (d, C-22), 50.3 (t, C-20), 46.0 (d, C-13), 44.7 (t, C-1), 42.1 (t, C-33), 41.4 (t, C-3), 36.8 (q, C-19), 35.0 (t, C-8), 34.3 (t, C-14), 26.0 (t, C-23), C-21, C-32 and C-34 were not observed.

Optical rotation:	insufficient amount of material	
HRMS (ESI):	calculated	found
$C_{40}H_{47}N_8O_{10}$ [M+H]$^+$:	799.3410	799.3417

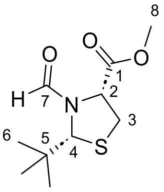
6.2.3 Thiamyxins[112]

Methyl (2*R*,4*R*)-2-(*tert*-butyl)-3-formylthiazolidine-4-carboxylate[181] 132

According to Seebach *et al.*[183], a suspension of (*R*)-methyl cysteinate hydrochloride (14.0 g, 78.0 mmol), pivaldehyde (17.1 mL, 157 mmol, 2.0 eq.), and triethylamine (12.0 mL, 86.0 mmol, 1.1 eq.) in pentane (90 mL) was refluxed (oil bath) in a 250 mL round bottom flask with Dean-Stark apparatus. After 18 h, the triethylamine hydrochloride was filtered off through a pad of celite®. The filter cake was washed with Et_2O (100 mL), and the filtrate was concentrated in vacuo to give the crude thiazolidine **131** (16.2 g).

According to Pattenden *et al.*[181], in a 250 mL round bottom flask, the crude thiazolidine **131** (12.2 g, 60.3 mmol) and sodium formate (4.59 g, 67.5 mmol, 1.1 eq.) were dissolved in formic acid (90 mL). The solution was cooled to 0 °C before acetic anhydride (17.6 mL, 187 mmol, 3.1 eq.) was added dropwise over 40 min. The reaction mixture was stirred for 16 h while slowly reaching room temperature. The mixture was concentrated in vacuo, and the residue was neutralized with sat. $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (silica, pentane:EtOAc 7:3) to give formyl thiazolidine **132** (9.48 g, 41.0 mmol, 68%) as a white solid. Recrystallisation from petroleum ether gave formyl thiazolidine **132** (6.42 g, 27.8 mmol, 46%) as colorless crystals.

TLC: R_f (132) = 0.46 (silica, pentane:EtOAc 1:1)



132

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, 7-H), 4.90 (dd, $^3J_{2,3}$ = 8.7 Hz, $^3J_{2,3'}$ = 8.7 Hz, 1 H, 2-H), 4.75 (s, 1 H, 4-H), 3.78 (s, 3 H, 8-H), 3.33 (dd, $^2J_{3',3}$ = 11.0 Hz, $^3J_{3',2}$ = 8.5 Hz, 1 H, 3-H'), 3.28 (dd, $^2J_{3,3'}$ = 10.5 Hz, $^3J_{3,2}$ = 9.2 Hz, 1 H, 3-H), 1.04 (s, 9 H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.2 (s, C-1), 162.8 (s, C-7), 75.3 (d, C-4), 61.6 (d, C-2), 52.8 (q, C-8), 38.7 (s, C-5), 33.0 (t, C-3), 26.5 (q, C-6).

Selected rotamer signals:
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, 7-H), 5.28 (s, 1 H, 4-H), 4.79 (dd, $^3J_{2,3}$ = 8.8 Hz, $^3J_{2,3'}$ = 7.2 Hz, 1 H, 2-H), 3.82 (s, 3 H, 8-H), 3.45 (dd, $^2J_{3,3'}$ = 12.0 Hz, $^3J_{3,2}$ = 7.2 Hz, 1 H, 3-H), 0.98 (s, 9 H, 6-H).

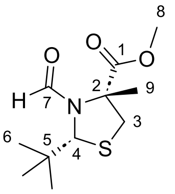
Optical rotation: $[\alpha]_D^{20}$= –101.3 (c = 1.0, $CHCl_3$); Lit: $[\alpha]_D^{20}$= –130.4 (c = 1.03, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{10}H_{18}NO_3S$ $[M+H]^+$:	232.1002	232.1012

Methyl (2*R*,4*R*)-2-(*tert*-butyl)-3-formyl-4-methylthiazolidine-4-carboxylate[181] 133

In a 500 mL Schlenk flask under an atmosphere of nitrogen, diisopropylamine (5.92 mL, 41.5 mmol, 1.5 eq.) was dissolved in anhydrous THF (130 mL) and cooled to –78 °C. A solution of 2.5 M *n*BuLi in hexane (11.6 mL, 29.1 mmol, 1.05 eq.) was added dropwise over 5 min, followed by anhydrous DMPU (19.0 mL, 157 mmol, 5.7 eq.). The resulting mixture was stirred for 1 h at –78 °C. After cooling to –90 °C, a solution of formyl thiazolidine **132** (6.40 g, 27.7 mmol) in anhydrous THF (8.0 mL) was added dropwise over 10 min. The resulting solution was stirred for 1 h at –90 °C. After the addition of iodomethane (2.08 mL, 33.2 mmol, 1.2 eq.) over 5 min, stirring was continued for 2 h at –90 °C. The cooling bath was removed, and the reaction mixture was warmed to room temperature before the solvents were removed in vacuo. The residue was partitioned between Et_2O (100 mL) and brine (100 mL). The aqueous layer was extracted with Et_2O. The combined ether extracts were washed with sat. $Na_2S_2O_3$ solution, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, pentane:EtOAc 83:17) to give methyl thiazolidine **133** (5.57 g, 22.7 mmol, 82%) as colorless crystals.

TLC: R_f (133) = 0.22 (silica, pentane:EtOAc 8:2)



133

¹H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, 7-H), 4.66 (s, 1 H, 4-H), 3.76 (s, 3 H, 8-H), 3.32 (d, $^2J_{3',3}$ = 11.6 Hz, 1 H, 3-H'), 2.72 (d, $^2J_{3,3'}$ = 11.6 Hz, 1 H, 3-H), 1.75 (s, 3 H, 9-H), 1.06 (s, 9 H, 6-H).

¹³C-NMR (100 MHz, $CDCl_3$): δ = 172.1 (s, C-1), 161.2 (s, C-7), 74.4 (d, C-4), 70.1 (s, C-2), 52.8 (q, C-8), 41.5 (t, C-3), 39.5 (s, C-5), 26.7 (q, C-6), 20.7 (q, C-9).

Rotamer signals:

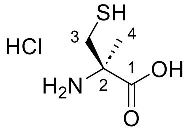
¹H-NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H, 7-H), 5.29 (s, 1 H, 4-H), 3.81 (s, 3 H, 8-H), 3.63 (d, $^2J_{3',3}$ = 11.6 Hz, 1 H, 3-H'), 2.86 (d, $^2J_{3,3'}$ = 12.3 Hz, 1 H, 3-H), 1.78 (s, 3 H, 9-H), 0.95 (s, 9 H, 6-H).

¹³C-NMR (100 MHz, $CDCl_3$): δ = 173.1 (s, C-1), 162.9 (s, C-7), 71.8 (d, C-4), 69.9 (s, C-2), 53.3 (q, C-8), 42.2 (t, C-3), 40.3 (s, C-5), 28.2 (q, C-9), 27.1 (q, C-6).

Optical rotation:	$[\alpha]_D^{20}$ = –91.3 (c = 1.0, $CHCl_3$); Lit: $[\alpha]_D^{20}$ = –100.2 (c = 1.4, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{11}H_{20}NO_3S$ $[M+H]^+$:	246.1158	246.1165

(*R*)-2-Amino-3-mercapto-2-methylpropanoic acid hydrochloride[181] 134

In a 100 mL round bottom flask, methyl thiazolidine **133** (2.20 g, 8.97 mmol) in 5.0 molar HCl_{aq} (34 mL) was refluxed (oil bath) for 72 h. The reaction mixture was cooled to room temperature before being concentrated in vacuo. The crude α-methyl cysteine hydrochloride **134** (1.53 g, 8.91 mmol, 99%) was obtained as a yellow solid.



134

^{1}H-NMR (400 MHz, D_2O): δ = 3.16 (d, $^2J_{3',3}$ = 15.0 Hz, 1 H, 3-H'), 2.88 (d, $^2J_{3,3'}$ = 15.1 Hz, 1 H, 3-H), 1.58 (s, 3 H, 4-H).

^{13}C-NMR (100 MHz, D_2O): δ = 172.7 (s, C-1), 61.3 (s, C-2), 30.1 (t, C-3), 21.0 (q, C-4).

Optical rotation:	$[\alpha]_D^{20}$= +8.5 (c = 1.0, H_2O);	Lit: $[\alpha]_D^{20}$= +8.13 (c = 1.58, H_2O)
HRMS (CI):	calculated	found
$C_4H_{10}NO_2S$ $[M+H]^+$:	136.0427	136.0439

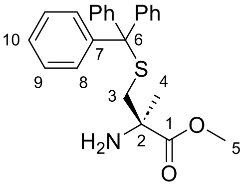
Methyl (*R*)-2-amino-2-methyl-3-(tritylthio)propanoate 135

In a 250 mL Schlenk flask under an atmosphere of nitrogen, acetyl chloride (8.04 mL, 113 mmol, 5.0 eq.) was slowly added to 0 °C cold anhydrous MeOH (75 mL). After stirring for 30 min at 0 °C, the solution was added to α-methyl cysteine hydrochloride **134** (3.88 g, 22.6 mmol). The reaction mixture was refluxed (oil bath) for 6 h and then concentrated in vacuo. The conversion was only around 50%. The procedure was repeated to achieve 90% conversion to the crude methyl ester (4.31 g, 19.7 mmol, 87%, (85 wt% purity)).

In a 100 mL round bottom flask, the crude methyl ester (2.00 g, 9.16 mmol, 85 wt%) was added to a solution of triphenylmethanol (2.74 g, 10.5 mmol, 1.15 eq.) in TFA (21.5 mL) at room temperature. The resulting orange solution was stirred at room temperature for 3 h. After concentrating in vacuo, the residue was partitioned between $CHCl_3$ (10 mL) and water (10 mL) and basified with K_2CO_3. The organic layer was washed with sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by reversed-phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give *S*-trityl cysteine derivative **135** (3.52 g, 8.99 mmol, 98%) as a light-yellow resin.

Alternative purification method: Normal phase chromatography (silica, CH_2Cl_2:MeOH 0% to 7% MeOH)

TLC: R_f (135) = 0.66 (silica, CH_2Cl_2:MeOH 9:1)



135

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 6 H, 9-H), 7.27 (m, 6 H, 8-H), 7.19 (m, 3 H, 10-H), 3.68 (s, 3 H, 5-H), 2.59 (d, $^2J_{3',3}$ = 11.4 Hz, 1 H, 3-H'), 2.36 (d, $^2J_{3,3'}$ = 11.5 Hz, 1 H, 3-H), 1.80 (s, 2 H, 2-NH_2), 1.22 (s, 3 H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.3 (s, C-1), 144.6 (s, C-7), 129.7 (d, C-9), 128.0 (d, C-8), 126.8 (d, C-10), 66.7 (s, C-6), 57.9 (s, C-2), 52.5 (q, C-5), 42.3 (t, C-3), 26.4 (q, C-4).

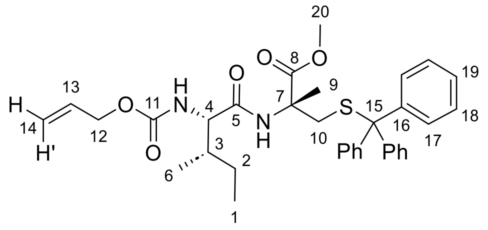
Optical rotation: $[\alpha]_D^{20}$= +20.7 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{24}H_{26}NO_2S$ $[M+H]^+$:	392.1679	392.1676

Methyl (*R*)-2-((2*S*,3*S*)-2-((allyloxy)carbonyl)amino)-3-methylpentanamido)-2-methyl-3-(tritylthio)propanoate 136

In a 50 mL round bottom flask, a solution of Alloc-Ile-OH (312 mg, 1.45 mmol, 1.1 eq.) and *S*-trityl cysteine derivative **135** (526 mg, 1.32 mmol) in anhydrous CH_2Cl_2 (13.2 mL) was cooled to 0 °C. After the addition of NMM (325 µL, 2.90 mmol, 2.2 eq.) and HATU (551 mg, 1.45 mmol, 1.1 eq.), the reaction mixture was stirred for 16 h while slowly reaching room temperature. The mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by reversed-phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give dipeptide **136** (526 mg, 893 µmol, 68%) as a white foam.

LC-MS: t_R (136) = 1.58 min (short method)



136

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 6 H, 17-H), 7.29 (m, 6 H, 18-H), 7.23 (m, 3 H, 19-H), 6.49 (s, 1 H, 5-NH), 5.90 (ddt, $^3J_{13,14'}$ = 17.5 Hz, $^3J_{13,14}$ = 10.7 Hz, $^3J_{13,12}$ = 5.6 Hz, 1 H, 13-H), 5.30 (d, $^3J_{14',13}$ = 17.7 Hz, 1 H, 14-H'), 5.29 (m, 1 H, 11-NH), 5.19 (d, $^3J_{14,13}$ = 10.4 Hz, 1 H, 14-H), 4.56 (m, 2 H, 12-H), 4.02 (dd, $^3J_{4,3}$ = 8.1 Hz, $^3J_{4,NH}$ = 5.7 Hz, 1 H, 4-H), 3.67 (s, 3 H, 20-H), 3.01 (d, $^2J_{10',10}$ = 11.7 Hz, 1 H, 10-H'), 2.65 (d, $^2J_{10,10'}$ = 11.7 Hz, 1 H, 10-H), 1.89 (m, 1 H, 3-H), 1.59 (m, 1 H, 2-H'), 1.43 (s, 3 H, 9-H), 1.14 (m, 1 H, 2-H), 0.96 (d, $^3J_{6,3}$ = 6.8 Hz, 3 H, 6-H), 0.93 (t, $^3J_{1,2}$ = 7.4 Hz, 3 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.5 (s, C-5), 173.2 (s, C-8), 156.2 (s, C-11), 144.5 (s, C-16), 132.8 (d, C-13), 129.6 (d, C-17), 128.1 (d, C-18), 126.9 (d, C-19), 117.9 (t, C-14), 66.6 (s, C-15), 66.0 (t, C-12), 59.8 (d, C-4), 59.4 (s, C-7), 53.0 (q, C-20), 38.0 (t, C-10), 37.7 (d, C-3), 24.7 (t, C-2), 23.0 (q, C-9), 15.6 (q, C-6), 11.8 (q, C-1).

Optical rotation: $[\alpha]_D^{20}$= –14.4 (c = 1.0, $CHCl_3$)

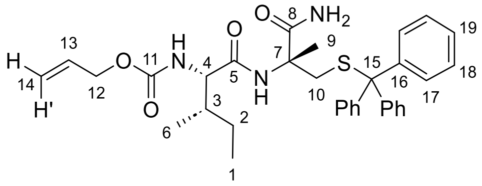
HRMS (ESI):	calculated	found
$C_{34}H_{41}N_2O_5S$ $[M+H]^+$:	589.2731	589.2733

Allyl ((2*S*,3*S*)-1-(((*R*)-1-amino-2-methyl-1-oxo-3-(tritylthio)propan-2-yl)amino)-3-methyl-1-oxopentan-2-yl)carbamate 137

In a 100 mL round bottom flask, dipeptide **136** (2.55 g, 4.33 mmol) was dissolved in THF (28 mL) and MeOH (2.0 mL) and cooled to 0 °C. 0.30 M $LiOH_{aq}$ (15.9 mL, 4.76 mmol, 1.1 eq.) was added, and the reaction mixture was stirred for 20 h while slowly reaching room temperature. Another portion of 0.30 M $LiOH_{aq}$ (4.33 mL, 1.30 mmol, 0.3 eq.) was added, and stirring continued for 5 h before more 0.30 M $LiOH_{aq}$ (4.33 mL, 1.30 mmol, 0.3 eq.) was added. After 34 h, the reaction mixture was acidified with 1.0 M HCl_{aq} and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid.

In a 100 mL Schlenk flask under an atmosphere of nitrogen, the above-prepared crude carboxylic acid and triethylamine (688 µL, 4.94 mmol, 1.15 eq.) were dissolved in anhydrous THF (27.4 mL). After cooling to 0 °C, ECF (474 µL, 4.94 mmol, 1.15 eq.) was added dropwise. The resulting suspension was stirred for 1 h at 0 °C before an aqueous ammonia solution (2.73 mL, 49.4 mmol, 35 wt%, 11.5 eq.) was added, and stirring was continued for another hour. The reaction mixture was diluted with EtOAc and water, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with 0.5 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and concentrating in vacuo, the crude product was purified by column chromatography (silica, pentane:EtOAc 4:6) to give the primary amide **137** (2.00 g, 3.48 mmol, 80%) as a white solid.

TLC: R_f (137) = 0.16 (silica, pentane:EtOAc 1:1)



137

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.46 (m, 6 H, 17-H), 7.30 (m, 6 H, 18-H), 7.23 (m, 3 H, 19-H), 6.53 (s, 1 H, 8-NH‘), 6.42 (s, 1 H, 5-NH), 5.75 (ddt, $^3J_{13,14'}$ = 17.5 Hz, $^3J_{13,14}$ = 10.7 Hz, $^3J_{13,12}$ = 5.6 Hz, 1 H, 13-H), 5.29 (s, 1 H, 8-NH), 5.22 (ddt, $^3J_{14',13}$ = 17.2 Hz, $^2J_{14',14}$ = 1.4 Hz, $^4J_{14',12}$ = 1.4 Hz, 1 H, 14-H‘), 5.13 – 5.18 (m, 2 H, 14-H, 11-NH), 4.53 (ddt, $^2J_{12',12}$ = 13.1 Hz, $^3J_{12',13}$ = 5.8 Hz $^4J_{12',14}$ = 1.4 Hz, 1 H, 12-H‘), 4.31 (dd, $^2J_{12,12'}$ = 13.1 Hz, $^3J_{12,13}$ = 5.8 Hz, 1 H, 12-H), 3.85 (dd, $^3J_{4,3}$ = 6.5 Hz, $^3J_{4,NH}$ = 5.4 Hz, 1 H, 4-H), 3.08 (d, $^2J_{10',10}$ = 12.3 Hz, 1 H, 10-H‘), 2.47 (d, $^2J_{10,10'}$ = 12.3 Hz, 1 H, 10-H), 1.84 (m, 1 H, 3-H), 1.48 (m, 1 H, 2-H‘), 1.43 (s, 3 H, 9-H), 1.14 (ddq, $^2J_{2,2'}$ = 14.2 Hz, $^3J_{2,3}$ = 9.3 Hz, $^3J_{2,1}$ = 7.3 Hz, 1 H, 2-H), 0.96 (d, $^3J_{6,3}$ = 6.9 Hz, 3 H, 6-H), 0.91 (t, $^3J_{1,2}$ = 7.4 Hz, 3 H, 1-H).

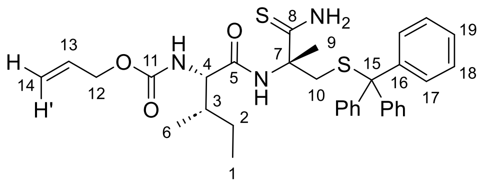
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.7 (s, C-8), 170.8 (s, C-5), 156.8 (s, C-11), 144.5 (s, C-16), 132.3 (d, C-13), 129.6 (d, C-17), 128.2 (d, C-18), 127.0 (d, C-19), 118.5 (t, C-14), 67.1 (s, C-15), 66.4 (t, C-12), 60.7 (d, C-4), 59.2 (s, C-7), 39.2 (t, C-10), 36.9 (d, C-3), 23.7 (q, C-9), 25.0 (t, C-2), 15.9 (q, C-6), 11.7 (q, C-1).

Optical rotation:	$[\alpha]_D^{20}$= +29.1 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{33}H_{40}N_3O_4S$ $[M+H]^+$:	574.2734	574.2742
Melting point:	97 – 102 °C	

Allyl ((2*S*,3*S*)-1-(((*S*)-1-amino-2-methyl-1-thioxo-3-(tritylthio)propan-2-yl)amino)-3-methyl-1-oxopentan-2-yl)carbamate 138

In a 100 mL Schlenk flask under an atmosphere of nitrogen, primary amide **137** (1.69 g, 2.95 mmol) and Lawesson's reagent (1.19 g, 2.95 mmol, 1.0 eq.) were dissolved in anhydrous THF (20 mL). The reaction mixture was stirred for 54 h before being concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 70% EtOAc) to give thioamide **138** (1.37 g, 2.32 mmol, 79%) as a white solid.

TLC: R_f (138) = 0.33 (silica, pentane:EtOAc 6:4)



138

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, 8-NH‘), 7.44 – 7.48 (m, 7 H, 17-H, 8-NH), 7.31 (m, 6 H, 18-H), 7.23 (m, 3 H, 19-H), 6.63 (s, 1 H, 5-NH), 5.70 (ddt, $^3J_{13,14'}$ = 16.5 Hz, $^3J_{13,14}$ = 10.4 Hz, $^4J_{13,12}$ = 5.8 Hz, 1 H, 13-H), 5.19 (ddt, $^3J_{14',13}$ = 17.2 Hz, $^2J_{14',14}$ = 1.5 Hz, $^4J_{14',12}$ = 1.5 Hz, 1 H, 14-H‘), 5.09 – 5.14 (m, 2 H, 14-H, 11-NH), 4.51 (ddt, $^2J_{12',12}$ = 13.1 Hz, $^3J_{12',13}$ = 6.0 Hz $^4J_{12',14}$ = 1.4 Hz, 1 H, 12-H‘), 4.26 (dd, $^2J_{12,12'}$ = 13.0 Hz, $^3J_{12,13}$ = 5.8 Hz, 1 H, 12-H), 3.85 (m, 1 H, 4-H), 3.35 (d, $^2J_{10',10}$ = 12.1 Hz, 1 H, 10-H‘), 2.48 (d, $^2J_{10,10'}$ = 12.1 Hz, 1 H, 10-H), 1.85 (m, 1 H, 3-H), 1.61 (s, 3 H, 9-H), 1.45 (m, 1 H, 2-H‘), 1.14 (ddq, $^2J_{2,2'}$ = 14.2 Hz, $^3J_{2,3}$ = 9.3 Hz, $^3J_{2,1}$ = 7.3 Hz, 1 H, 2-H), 0.96 (d, $^3J_{6,3}$ = 6.9 Hz, 3 H, 6-H), 0.91 (t, $^3J_{1,2}$ = 7.4 Hz, 3 H, 1-H).

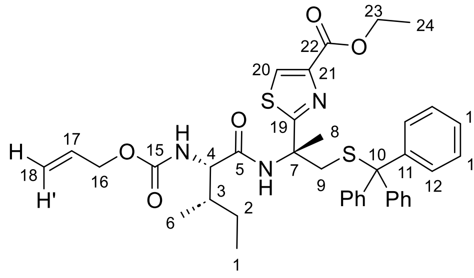
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.7 (s, C-8), 170.3 (s, C-5), 157.2 (s, C-11), 144.5 (s, C-16), 132.1 (d, C-13), 129.6 (d, C-17), 128.2 (d, C-18), 127.0 (d, C-19), 118.8 (t, C-14), 67.2 (s, C-15), 66.7 (t, C-12), 64.0 (s, C-7), 61.1 (d, C-4), 42.0 (t, C-10), 36.7 (d, C-3), 27.1 (q, C-9), 25.1 (t, C-2), 16.0 (q, C-6), 11.7 (q, C-1).

Optical rotation:	$[\alpha]_D^{20}$= +51.6 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{33}H_{40}N_3O_3S_2$ $[M+H]^+$:	590.2506	590.2499
Melting point:	160 – 163 °C	

Ethyl 2-((4*S*,7*S*)-7-((*S*)-*sec*-butyl)-4-methyl-6,9-dioxo-1,1,1-triphenyl-10-oxa-2-thia-5,8-diazatridec-12-en-4-yl)thiazole-4-carboxylate 139

In a 100 mL Schlenk tube under N_2 atmosphere, thioamide **138** (1.34 g, 2.27 mmol) was dissolved in anhydrous DME (17.5 mL). After addition of $KHCO_3$ (1.82 g, 18.2 mmol, 8.0 eq.), the suspension was stirred for 10 min at room temperature. Ethyl bromopyruvate (0.950 mL, 6.82 mmol, 3.0 eq.) was added, and the reaction mixture was stirred for another 3 h at room temperature. A preformed solution of TFAA (1.28 mL, 9.09 mmol, 4.0 eq.) and 2,6-lutidine (2.25 mL, 19.3 mmol, 8.5 eq.) in anhydrous DME (2.0 mL) was added dropwise to the reaction mixture at 0 °C. The resulting mixture was stirred for 5 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 60% EtOAc) to give thiazole **139** (1.32 g, 1.92 mmol, 85%) as a light-yellow foam.

TLC: R_f (139) = 0.38 (silica, pentane:EtOAc 7:3)



139

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, 20-H), 7.41 (m, 6 H, 12-H), 7.30 (m, 6 H, 13-H), 7.23 (m, 3 H, 14-H), 6.69 (s, 1 H, 5-NH), 5.70 (ddt, $^3J_{17,18'}$ = 16.5 Hz, $^3J_{17,18}$ = 10.8 Hz, $^3J_{17,16}$ = 5.6 Hz, 1 H, 17-H), 5.29 (dq, $^3J_{NH,4}$ = 8.3 Hz, 1 H, 15-NH), 5.28 (d, $^3J_{18',17}$ = 17.0 Hz, 1 H, 18-H'), 5.18 (d, $^3J_{18,17}$ = 10.5 Hz, 1 H, 18-H), 4.58 (dd, $^2J_{16',16}$ = 13.2 Hz, $^3J_{16',17}$ = 5.6 Hz, 1 H, 16-H'), 4.52 (dd, $^2J_{16,16'}$ = 13.4 Hz, $^3J_{16,17}$ = 5.5 Hz, 1 H, 16-H), 4.39 (q, $^3J_{23,22}$ = 7.1 Hz, 2 H, 23-H), 4.04 (dd, $^3J_{4,NH}$ = 8.9 Hz, $^3J_{4,3}$ = 5.8 Hz, 1 H, 4-H), 2.99 (d, $^2J_{9',9}$ = 12.2 Hz, 1 H, 9-H'), 2.84 (d, $^2J_{9,9'}$ = 12.1 Hz, 1 H, 9-H), 1.86 (m, 1 H, 3-H), 1.78 (s, 3 H, 8-H), 1.51 (m, 1 H, 2-H'), 1.39 (t, $^3J_{24,23}$ = 7.1 Hz, 3 H, 24-H), 1.12 (m, 1 H, 2-H), 0.98 (d, $^3J_{6,3}$ = 6.8 Hz, 3 H, 6-H), 0.91 (t, $^3J_{1,2}$ = 7.4 Hz, 3 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2 (s, C-19), 170.7 (s, C-5), 161.3 (s, C-22), 156.2 (s, C-15), 146.4 (s, C-21), 144.4 (s, C-11), 132.8 (d, C-17), 129.6 (d, C-12), 128.2 (d, C-13), 127.9 (d, C-20), 127.1 (d, C-14), 118.0 (t, C-18), 67.3 (s, C-10), 66.0 (t, C-16), 61.4 (t, C-23), 59.8 (d, C-4), 59.2 (s, C-7), 43.0 (t, C-9), 37.8 (d, C-3), 26.2 (q, C-8), 24.5 (t, C-2), 15.9 (q, C-6), 14.5 (q, C-24), 11.7 (q, C-1).

Optical rotation: $[\alpha]_D^{20}$ = −26.1 (c = 1.0, $CHCl_3$)

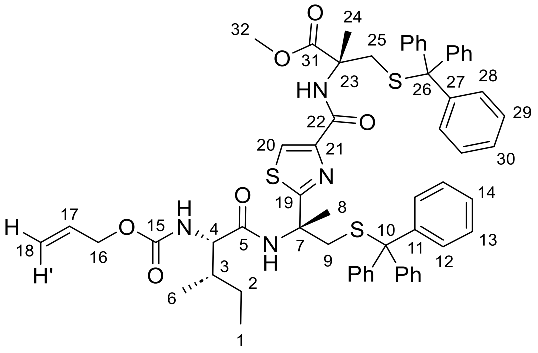
HRMS (ESI):	calculated	found
$C_{38}H_{44}N_3O_5S_2$ $[M+H]^+$:	686.2717	686.2714

Methyl (*R*)-2-(2-((4*S*,7*S*)-7-((*S*)-*sec*-butyl)-4-methyl-6,9-dioxo-1,1,1-triphenyl-10-oxa-2-thia-5,8-diazatridec-12-en-4-yl)thiazole-4-carboxamido)-2-methyl-3-(tritylthio)propanoate 140

In a 50 mL round bottom flask, a solution of thiazole **139** (1.30 g, 1.90 mmol) in THF (8.0 mL) and MeOH (2.0 mL) was cooled to 0 °C. 0.30 M $LiOH_{aq}$ (6.44 mL, 1.93 mmol, 1.0 eq.) was slowly added, and the resulting solution was stirred for 18 h while slowly reaching room temperature. Another portion of LiOH monohydrate (24.0 mg, 569 µmol, 0.3 eq.) was added, and stirring continued for another 6 h at room temperature. The reaction mixture was acidified with 0.1 M HCl_{aq} and extracted three times with Et_2O. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid.

The above-prepared carboxylic acid and *S*-trityl cysteine derivative **135** (779 mg, 1.99 mmol, 1.05 eq.) were dissolved in anhydrous DMF (18.0 mL). The solution was cooled to 0 °C before NMM (438 µL, 3.98 mmol, 2.1 eq.) and HATU (721 mg, 1.90 mmol, 1.0 eq.) were added. The reaction mixture was stirred for 18 h while slowly reaching room temperature. After dilution with EtOAc, the mixture was washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 60% EtOAc) to give tripeptide **140** (1.56 g, 1.51 mmol, 80%) as a white foam.

TLC: R_f (140) = 0.33 (silica, pentane:EtOAc 6:4)



140

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.98 (s, 1 H, 20-H), 7.90 (s, 1 H, 22-NH), 7.40 – 7.46 (m, 12 H, 12-H, 28-H), 7.16 – 7.34 (m, 18 H, 13-H, 14-H, 29-H, 30-H), 6.55 (s, 1 H, 5-NH), 5.85 (ddt, $^3J_{17,18'}$ = 16.2 Hz, $^3J_{17,18}$ = 10.7 Hz, $^3J_{17,16}$ = 5.6 Hz, 1 H, 17-H), 5.21 – 5.31 (m, 2 H, 18-H', 15-NH), 5.16 (m, 1 H, 18-H), 4.55 (dd, $^2J_{16',16}$ = 13.1 Hz, $^3J_{16',17}$ = 5.6 Hz, 1 H, 16-H'), 4.50 (dd, $^2J_{16,16'}$ = 13.7 Hz, $^3J_{16,17}$ = 5.4 Hz, 1 H, 16-H), 4.04 (dd, $^3J_{4,NH}$ = 8.2 Hz, $^3J_{4,3}$ = 5.6 Hz, 1 H, 4-H), 3.70 (s, 3 H, 32-H), 3.07 (d, $^2J_{9',9}$ = 11.8 Hz, 1 H, 9-H'), 2.82 – 2.97 (m, 3 H, 9-H, 25-H), 1.82 (m, 1 H, 3-H), 1.74 (s, 3 H, 8-H), 1.50 (m, 1 H, 2-H'), 1.48 (s, 3 H, 24-H), 1.12 (m, 1 H, 2-H), 0.97 (d, $^3J_{6,3}$ = 6.8 Hz, 3 H, 6-H), 0.90 (t, $^3J_{1,2}$ = 7.4 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.6 (s, C-19), 173.2 (s, C-31), 170.7 (s, C-5), 160.0 (s, C-22), 156.2 (s, C-15), 148.8 (s, C-21), 144.6 (s, C-27), 144.4 (s, C-11), 132.7 (d, C-17), 129.7 (d, C-29), 129.6 (d, C-13), 128.2 (d, C-12), 128.0 (d, C-28), 127.0 (d, C-14), 126.8 (d, C-30), 124.0 (d, C-20), 117.9 (t, C-18), 67.4 (s, C-10), 66.7 (s, C-26), 66.0 (t, C-16), 59.7 (d, C-4), 59.3 (s, C-23), 58.8 (s, C-7), 52.9 (q, C-32), 42.9 (t, C-9), 38.0 (t, C-25), 37.4 (d, C-3), 26.0 (q, C-8), 24.6 (t, C-2), 23.2 (q, C-24), 15.8 (q, C-6), 11.6 (q, C-1).

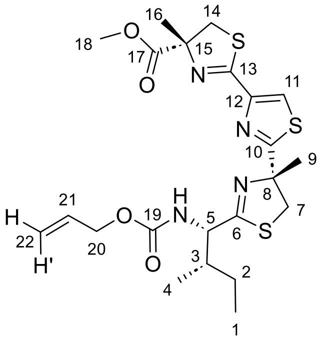
Optical rotation: $[\alpha]_D^{20} = -21.0$ (c = 0.5, $CHCl_3$)

HRMS (ESI):	calculated	found
$C_{60}H_{63}N_4O_6S_3$ $[M+H]^+$:	1031.3904	1031.3912

Methyl (4*R*,4''*S*)-2''-((1*S*,2*S*)-1-(((allyloxy)carbonyl)amino)-2-methylbutyl)-4,4''-dimethyl-4,4'',5,5''-tetrahydro-[2,4':2',4''-terthiazole]-4-carboxylate 141

In a 50 mL Schlenk tube under an atmosphere of nitrogen, triflic anhydride (323 µL, 1.91 mmol, 2.2 eq.) was slowly added to a solution of triphenylphosphine oxide (1.06 g, 3.82 mmol, 4.4 eq.) in anhydrous CH_2Cl_2 (6.2 mL) at 0 °C. After stirring for 10 min, a solution of tripeptide **140** (895 mg, 868 µmol) in anhydrous CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C. The bright-yellow solution was stirred for 40 min at 0 °C while slowly turning orange. The reaction mixture was quenched with 10% $NaHCO_3$ solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 60% EtOAc) followed by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give bis-thiazoline **141** (302 mg, 591 µmol, 68%) as a white foam.

TLC: R_f (141) = 0.29 (silica, pentane:EtOAc 6:4)



141

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1 H, 11-H), 5.94 (ddt, $^3J_{21,22'}$ = 16.3 Hz, $^3J_{21,22}$ = 10.7 Hz, $^3J_{21,20}$ = 5.6 Hz, 1 H, 21-H), 5.42 (d, $^3J_{NH,5}$ = 8.9 Hz, 1 H, 19-NH), 5.33 (ddt, $^3J_{22',21}$ = 16.5 Hz, $^2J_{22',22}$ = 1.7 Hz, $^4J_{22',20}$ = 1.7 Hz, 2 H, 22-H'), 5.23 (d, $^3J_{22,21}$ = 10.5 Hz, 1 H, 22-H), 4.60 (dt, $^3J_{20,21}$ = 5.7 Hz, $^4J_{20,22}$ = 1.5 Hz, 2 H, 20-H), 4.55 (dd, $^3J_{5,NH}$ = 8.8 Hz, $^3J_{5,3}$ = 5.1 Hz, 1 H, 5-H), 3.86 (d, $^2J_{7,7'}$ = 11.3 Hz, 1 H, 7-H), 3.85 (d, $^2J_{14,14'}$ = 11.4 Hz, 1 H, 14-H), 3.81 (s, 3 H, 18-H), 3.55 (d, $^2J_{14',14}$ = 11.4 Hz, 1 H, 14-H'), 3.26 (d, $^2J_{7',7}$ = 11.4 Hz, 1 H, 7-H'), 1.94 (m, 1 H, 3-H), 1.74 (s, 3 H, 16-H), 1.66 (s, 3 H, 9-H), 1.53 (m, 1 H, 2-H), 1.18 (m, 1 H, 2-H'), 1.00 (d, $^3J_{4,3}$ = 6.8 Hz, 3 H, 4-H), 0.92 (t, $^3J_{1,2}$ = 7.4 Hz, 3 H, 1-H).

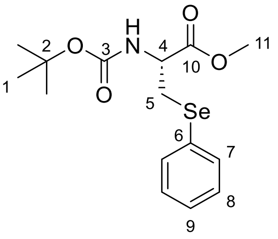
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 176.2 (s, C-13), 173.9 (s, C-17), 173.7 (s, C-6), 163.5 (s, C-10), 155.9 (s, C-19), 148.8 (s, C-12), 132.8 (d, C-21), 121.4 (d, C-11), 118.0 (t, C-22), 84.7 (s, C-8), 83.8 (s, C-15), 66.0 (t, C-20), 58.2 (d, C-5), 53.1 (q, C-18), 44.6 (t, C-14), 41.5 (t, C-7), 39.3 (d, C-3), 28.0 (q, C-16), 24.6 (t, C-2), 24.2 (q, C-9), 15.8 (q, C-4), 11.8 (q, C-1).

Optical rotation:	$[\alpha]_D^{20}$= –178.0 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{22}H_{31}N_4O_4S_3$ $[M+H]^+$:	511.1502	511.1502

Methyl (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(phenylselanyl)propanoate 142a

Preparation according to Braga *et al.*[186]

TLC: R_f (142a) = 0.52 (silica, pentane:EtOAc 8:2)



142a

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.55 (m, 2 H, 8-H), 7.33 – 7.22 (m, 3 H, 7-H, 9-H), 5.35 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, 3-NH), 4.67 (m, 1 H, 4-H), 3.51 (s, 3 H, 11-H), 3.34 (d, $^3J_{5,4}$ = 5.0 Hz, 2 H, 5-H), 1.42 (s, 9 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.2 (s, C-10), 155.1 (s, C-3), 133.8 (d, s, C-8, C-6), 129.3 (d, C-7), 127.7 (d, C-9), 80.2 (s, C-2), 53.4 (d, C-4), 52.4 (q, C-11), 30.8 (t, C-5), 28.4 (q, C-1).

Optical rotation:	$[\alpha]_D^{20}$= +49.9 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{15}H_{21}NO_4Se$ $[M]^+$:	359.0630	359.0623

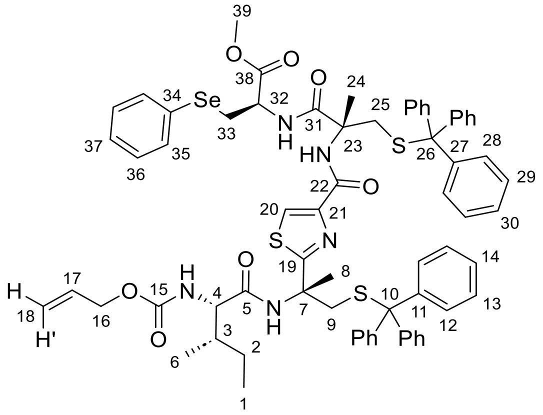
Methyl (*R*)-2-((*R*)-2-(2-((4*S*,7*S*)-7-((*S*)-*sec*-butyl)-4-methyl-6,9-dioxo-1,1,1-triphenyl-10-oxa-2-thia-5,8-diazatridec-12-en-4-yl)thiazole-4-carboxamido)-2-methyl-3-(tritylthio)propanamido)-3-(phenylselanyl)propanoate 144

In a 5 mL round bottom flask, 1.5 M $LiOH_{aq}$ (100 µL, 150 µmol, 1.5 eq.) was slowly added to a 0 °C cold solution of tripeptide **140** (103 mg, 100 µmol) in THF (500 µL) and MeOH (900 µL). The resulting mixture was stirred for 2 h while slowly reaching room temperature. After full conversion, the mixture was acidified with 1.0 M HCl_{aq} and extracted thrice with Et_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid (101 mg, 99.2 mmol, 99%) as a white foam.

In a 5 mL round bottom flask, 4.0 M HCl in dioxane (349 µL, 1.40 mmol, 10 eq.) was added to a solution of selenocysteine **142a** (50.0 mg, 140 µmol) in CH_2Cl_2 (300 µL) at 0 °C. After stirring for 2 h, the reaction mixture was concentrated in vacuo to give the crude hydrochloride salt **143** (41.0 mg, 139 µmol, 100%).

In a 25 mL round bottom flask, the above-prepared crude carboxylic acid (42.0 mg, 41.3 µmol), the crude hydrochloride salt **143** (18.2 mg, 62.0 µmol, 1.5 eq.), and NMM (18.2 µL, 165 µmol, 4.0 eq.) were dissolved in DMF (420 µL). After cooling to 0 °C, PyAOP (22.6 mg, 43.0 µmol, 1.05 eq.) was added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 10% to 50% EtOAc) to give compound **144** (40.0 mg, 31.8 µmol, 77%) as a white foam.

TLC: R_f (144) = 0.29 (silica, pentane:EtOAc 6:4)



144

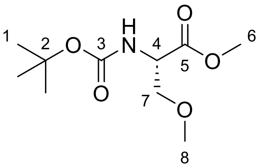
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.99 (s, 1 H, 20-H), 7.89 (s, 1 H, 22-NH), 7.47 – 7.41 (m, 14 H, 12-H, 28-H, 36-H), 7.33 – 7.15 (m, 22 H, 13-H, 14-H, 29-H, 30-H, 31-NH, 35-H, 37-H), 6.46 (s, 1 H, 5-NH), 5.86 (ddt, $^3J_{17,18'}$ = 16.5 Hz, $^3J_{17,18}$ = 10.8 Hz, $^3J_{17,16}$ = 5.9 Hz, 1 H, 17-H), 5.30 – 5.21 (m, 2 H, 18-H‘, 15-NH), 5.17 (m, 1 H, 18-H), 4.83 (m, 1 H, 32-H), 4.60 – 4.47 (m, 2 H, 16-H), 3.94 (m, 1 H, 4-H), 3.39 (s, 3 H, 39-H), 3.32 (m, 2 H, 33-H), 3.13 (d, $^2J_{9',9}$ = 12.1 Hz, 1 H, 9-H‘), 2.88 (d, $^2J_{25',25}$ = 12.2 Hz, 1 H, 25-H‘), 2.82 (d, $^2J_{25,25'}$ = 12.1 Hz, 1 H, 25-H), 2.71 (d, $^2J_{9,9'}$ = 12.1 Hz, 1 H, 9-H), 1.80 (m, 1 H, 3-H), 1.72 (s, 3 H, 8-H), 1.51 (m, 1 H, 2-H‘), 1.46 (s, 3 H, 24-H), 1.12 (m, 1 H, 2-H), 0.97 (d, $^3J_{6,3}$ = 6.7 Hz, 3 H, 6-H), 0.91 (t, $^3J_{1,2}$ = 7.3 Hz, 3 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.9 (s, C-19), 172.4 (s, C-5), 170.8 (s, C-38), 170.6 (s, C-31), 160.7 (s, C-22), 156.3 (s, C-15), 148.8 (s, C-21), 144.7 (s, C-27), 144.4 (s, C-11), 133.8 (d, C-36), 132.7 (d, C-17), 129.8 (d, C-29), 129.6 (d, C-13), 129.2 (d, C-35), 129.0 (s, C-34), 128.3 (d, C-12), 128.1 (d, C-28), 127.6 (d, C-37), 127.1 (d, C-14), 126.9 (d, C-30), 124.5 (d, C-20), 117.9 (t, C-18), 67.5 (s, C-10), 67.2 (s, C-26), 66.0 (t, C-16), 59.3 (s, C-23), 59.8 (d, C-4), 58.8 (s, C-7), 52.3 (d, q, C-32, C-39), 43.3 (t, C-25), 38.7 (t, C-9), 37.4 (d, C-3), 30.0 (t, C-33), 25.7 (q, C-8), 24.5 (t, C-2), 23.2 (q, C-24), 16.0 (q, C-6), 11.6 (q, C-1).

Methyl *N*-(*tert*-butoxycarbonyl)-*O*-methyl-L-serinate[188] 146

Preparation according to Koskinen *et al.*[188]

TLC: R_f (146) = 0.21 (silica, pentane:EtOAc 8:2)



146

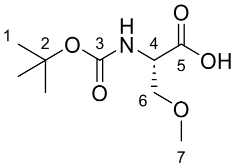
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.37 (d, $^3J_{NH,4}$ = 8.6 Hz, 1 H, 3-NH), 4.41 (m, 1 H, 4-H), 3.80 (dd, $^2J_{7',7}$ = 9.5 Hz, $^3J_{7',4}$ = 3.2 Hz, 1 H, 7-H'), 3.76 (s, 3 H, 6-H), 3.58 (dd, $^2J_{7,7'}$ = 9.5 Hz, $^3J_{7,4}$ = 3.3 Hz, 1 H, 7-H), 3.33 (s, 3 H, 8-H), 1.44 (s, 9 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.3 (s, C-5), 155.6 (s, C-3), 80.1 (s, C-2), 72.6 (t, C-7), 59.4 (q, C-8), 54.0 (d, C-4), 52.6 (q, C-6), 28.4 (q, C-1).

Optical rotation:	$[\alpha]_D^{20}$= +14.4 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{10}H_{20}NO_5$ $[M+H]^+$:	234.1336	234.1343

N-(*tert*-butoxycarbonyl)-*O*-methyl-L-serine 147

In a 25 mL round bottom flask, Boc-Ser(Me)-OMe **146** (1.00 g, 4.29 mmol) was dissolved in THF (21 mL). 0.30 M $LiOH_{aq}$ (15.0 mL, 4.50 mmol, 1.05 eq.) was added dropwise at 0 °C, and the resulting mixture was stirred for 2 h while slowly reaching room temperature. The reaction mixture was acidified with 1.0 M HCl_{aq} and extracted thrice with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give the carboxylic acid **147** (1.04 g, 4.29 mmol, quant., 90wt% purity) as a colorless resin.



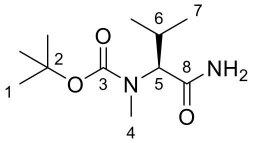
147

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.65 (s, 1 H, 5-OH), 6.91 (d, $^3J_{NH,4}$ = 8.2 Hz, 1 H, 3-NH), 4.12 (ddd, $^3J_{4,NH}$ = 8.2 Hz, $^3J_{4,5}$ = 6.4 Hz, $^3J_{4,5'}$ = 4.5 Hz, 1 H, 4-H), 3.54 (m, 2 H, 6-H), 3.23 (s, 3 H, 7-H), 1.38 (s, 9 H, 1-H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 172.0 (s, C-5), 155.3 (s, C-3), 78.2 (s, C-2), 71.4 (t, C-6), 58.2 (q, C-7), 53.6 (d, C-4), 28.2 (q, C-1).

***tert*-Butyl (*S*)-(1-amino-3-methyl-1-oxobutan-2-yl)(methyl)carbamate[205] 149**

In a 500 mL Schlenk flask under an atmosphere of nitrogen, a solution of Boc-*N*-Me-Val-OH **148** (7.94 g, 34.3 mmol) and triethylamine (6.22 mL, 44.7 mmol, 1.3 eq.) in anhydrous THF (172 mL) was cooled to –20 °C. Isobutyl chloroformate (5.79 mL, 44.7 mmol, 1.3 eq.) was added dropwise, and the resulting suspension was stirred for 1 h at –20 °C. After the addition of aqueous ammonia solution (22.8 mL, 412 mmol, 35 wt%, 12 eq.), the reaction mixture was stirred for 1 h at 0 °C. The resulting solution was diluted with EtOAc and water, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with 0.5 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. Drying over $MgSO_4$ and concentration in vacuo gave the crude amide, which was purified by recrystallisation from cyclohexane to give Boc-*N*-Me-Val-NH_2 **149** (7.05 g, 30.6 mmol, 89%) as a white solid.



149

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 6.73 (s, 2 H, 8-NH_2), 4.05 (d, $^3J_{5,6}$ = 10.4 Hz, 1 H, 5-H), 2.78 (s, 3 H, 4-H), 2.13 (dhept, $^3J_{6,5}$ = 10.3 Hz, $^3J_{6,7}$ = 6.6 Hz, 1 H, 6-H), 1.44 (s, 9 H, 1-H), 0.92 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, 7-H), 0.82 (d, $^3J_{7',6}$ = 6.7 Hz, 3 H, 7'-H).

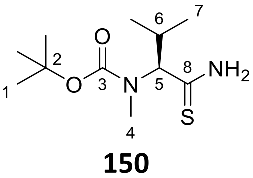
^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 171.3 (s, C-8), 154.9 (s, C-3), 78.5 (s, C-2), 63.3 (d, C-5), 29.4 (q, C-4), 27.6 (q, C-1), 26.0 (d, C-6), 19.0 (q, C-7), 18.1 (q, C-7').

Optical rotation:	$[\alpha]_D^{20}$= –129.1 (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{11}H_{23}N_2O_3$ $[M+H]^+$:	231.1703	231.1699

***tert*-Butyl (*S*)-(1-amino-3-methyl-1-thioxobutan-2-yl)(methyl)carbamate 150**

In a 250 mL Schlenk flask under an atmosphere of nitrogen, Lawesson's reagent (4.83 g, 11.9 mmol, 0.5 eq.) was added to a solution of Boc-*N*-Me-Val-NH_2 **149** (5.50 g, 23.9 mmol) in anhydrous THF (65 mL). The reaction mixture was stirred for 36 h at room temperature. Concentration in vacuo followed by automated flash chromatography (silica, CyH:EtOAc 0% to 20% EtOAc) led to a light-green solid. This solid was suspended in CH_2Cl_2 at 40 °C for 5 min. After cooling to 0 °C, the solid was filtered off, washed with 0 °C cold CH_2Cl_2, and dried in vacuo to give thioamide **150** (4.53 g, 18.4 mmol, 77%) as a white solid.

TLC: R$_f$ (150) = 0.51 (silica, pentane:EtOAc 6:4)



150

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.28 (s, 1 H, 8-NH$_2$), 7.58 (s, 1 H, 8-NH$_2$), 4.15 (m, 1 H, 5-H), 2.91 (s, 3 H, 4-H), 2.48 (m, 1 H, 6-H), 1.45 (s, 9 H, 1-H), 0.99 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, 7-H), 0.91 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H). **^{13}C-NMR** (125 MHz, CDCl$_3$): δ = 206.8 (s, C-8), 157.4 (s, C-3), 80.8 (s, C-2), 28.5 (q, C-1), 28.2 (d, C-6), 20.1 (q, C-7), 19.0 (q, C-7'), C-4 and C-5 were not observed.

Optical rotation: $[\alpha]_D^{20}$ = –231.8 (c = 1.0, CHCl$_3$)

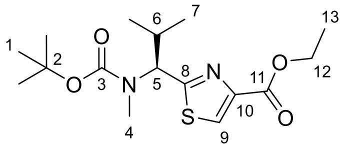
HRMS (ESI):	calculated	found
$C_{11}H_{23}N_2O_2S$ [M+H]$^+$:	247.1475	247.1480

Melting point: 164 – 165 °C

Ethyl (*S*)-2-(1-((*tert*-butoxycarbonyl)(methyl)amino)-2-methylpropyl)thiazole-4-carboxylate 151

In a 250 mL Schlenk flask under an atmosphere of nitrogen, thioamide **150** (4.14 g, 16.8 mmol) was dissolved in anhydrous DME (100 mL). After addition of KHCO$_3$ (13.5 g, 134 mmol, 8.0 eq.), the suspension was stirred for 10 min at room temperature. The reaction mixture was cooled to 0 °C, and ethyl bromopyruvate (7.03 mL, 50.4 mmol, 3.0 eq.) was added. After stirring for 3 h at room temperature, a preformed mixture of TFAA (9.49 mL, 67.2 mmol, 4.0 eq.) and 2,6-lutidine (16.6 mL, 143 mmol, 8.5 eq.) was added dropwise at 0 °C. The resulting mixture was stirred for 16 h while slowly reaching room temperature. After full conversion, the reaction mixture was diluted with EtOAc and washed with 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 20% EtOAc) to give thiazole **151** (4.97 g, 14.5 mmol, 86%) as a light-yellow oil.

TLC: R$_f$ (151) = 0.35 (silica, pentane:EtOAc 8:2)



151

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 8.39 (s, 1 H, 9-H), 4.95 (d, $^3J_{5,6}$ = 10.5 Hz, 1 H, 5-H), 4.33 (q, $^3J_{12,13}$ = 7.1 Hz, 2 H, 12-H), 2.75 (s, 3 H, 4-H), 2.53 (dhept, $^3J_{6,5}$ = 10.6 Hz, $^3J_{6,7}$ = 6.6 Hz, $^3J_{6,7'}$ = 6.6 Hz, 1 H, 6-H), 1.44 (s, 9 H, 1-H), 1.33 (t, $^3J_{13,12}$ = 7.1 Hz, 3 H), 0.98 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.94 (d, $^3J_{7',6}$ = 6.5 Hz, 3 H, 7'-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 168.9 (s, C-8), 160.1 (s, C-11), 154.4 (s, C-3), 145.4 (s, C-10), 128.2 (d, C-9), 79.1 (s, C-2), 62.6 (d, C-5), 60.1 (t, C-12), 29.5 (q, C-4), 28.5 (d, C-6), 27.6 (q, C-1), 19.6 (q, C-7), 18.5 (q, C-7'), 13.5 (q, C-13).

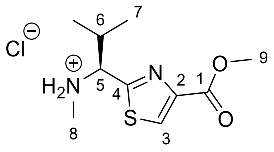
Optical rotation: $[\alpha]_D^{20}$ = –119.6 (c = 1.0, CHCl$_3$); Lit $[\alpha]_D^{22}$ = –129.9 (c = 1.2, CHCl$_3$)[206]

HRMS (CI):	calculated	found
$C_{16}H_{27}N_2O_4S$ [M+H]$^+$:	343.1686	343.1694

(*S*)-1-(4-(Methoxycarbonyl)thiazol-2-yl)-*N*,2-dimethylpropan-1-aminium chloride 152

In a 50 mL round bottom flask, a solution of thiazole **151** (800 mg, 2.34 mmol) in a mixture of THF (10 mL) and MeOH (5.0 mL) was cooled to 0 °C. 0.30 M $LiOH_{aq}$ (11.7 mL, 3.50 mmol, 1.5 eq.) was added dropwise, and the reaction mixture was stirred for 4 h while slowly reaching room temperature. After full conversion, the reaction mixture was acidified with 1.0 M HCl_{aq} and extracted thrice with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the crude carboxylic acid, which was used without further purification.

The above-prepared carboxylic acid was dissolved in MeOH (12 mL) before thionyl chloride (204 µL, 2.80 mmol, 1.2 eq.) was added dropwise at room temperature. After stirring for 16 h at room temperature, the reaction mixture was concentrated in vacuo to give H-Me-Val-thiazole-OMe·HCl **152** (550 mg, 2.08 mmol, 89%) as a white foam.



152

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.34 (m, 1 H, 8-NH), 9.97 (m, 1 H, 8-NH'), 8.33 (s, 1 H, 3-H), 4.45 (m, 1 H, 5-H), 3.95 (s, 3 H, 9-H), 2.74 (m, 1 H, 6-H), 2.63 (t, $^3J_{8,NH}$ = 5.4 Hz, 3 H, 8-H), 1.27 (d, $^3J_{7,6}$ = 6.7 Hz, 3 H, 7-H), 1.00 (d, $^3J_{7',6}$ = 6.7 Hz, 3 H, 7'-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.6 (s, C-4), 161.4 (s, C-1), 146.7 (s, C-2), 130.6 (d, C-3), 67.4 (d, C-5), 52.8 (q, C-9), 32.0 (q, d, C-8, C-6), 20.2 (q, C-7), 18.8 (q, C-7').

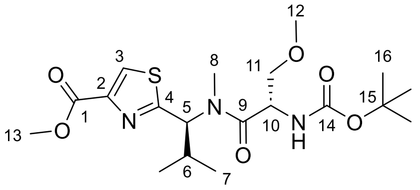
Optical rotation: $[\alpha]_D^{20}$= –15.8 (c = 1.0, $CHCl_3$)

HRMS (CI):	calculated	found
$C_{10}H_{17}N_2O_2S$ [M+H]$^+$:	229.1005	229.1008

Methyl 2-((*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-*N*-methylpropanamido)-2-methylpropyl)thiazole-4-carboxylate 153

In a 100 mL round bottom flask, Ag_2O (3.93 g, 16.9 mmol, 5.1 eq.) was suspended in a solution of hydroxy peptide **157** (1.38 g, 3.32 mmol) in MeCN (28 mL). After the addition of iodomethane (2.08 mL, 33.2 mmol, 10 eq.), the reaction mixture was stirred for 90 h at room temperature under light exclusion. LCMS showed full conversion and around 10% *O*- and *N*-methylation. The suspension was filtered through a pad of celite®, and the filtrate was concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 50% EtOAc) to give *O*-methyl serine dipeptide **153** (1.05 g, 2.45 mmol, 74%) as a colorless resin.

TLC: R$_f$ (153) = 0.22 (silica, pentane:EtOAc 6:4)



153

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 8.43 (s, 1 H, 3-H), 6.52 (m, 1 H, 14-NH), 5.42 (m, 1 H, 5-H), 4.62 (m, 1 H, 10-H), 3.86 (s, 3 H, 13-H), 3.49 (m, 2 H, 11-H), 3.21 (s, 3 H, 12-H), 2.98 (s, 3 H, 8-H), 2.59 (dhept, $^3J_{6,5}$ = 10.5 Hz, $^3J_{6,7}$ = 6.6 Hz, 1 H, 6-H), 1.39 (s, 9 H, 16-H), 0.94 (m, 6 H, 7-H).

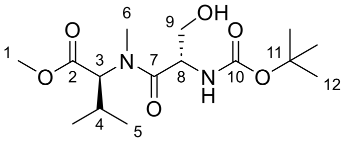
^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 170.7 (s, C-9), 168.2 (s, C-4), 160.6 (s, C-1), 154.5 (s, C-14), 144.9 (s, C-2), 128.7 (d, C-3), 78.0 (s, C-15), 71.5 (t, C-11), 60.6 (d, C-5), 57.8 (q, C-12), 51.2 (q, C-13), 50.2 (d, C-10), 30.1 (q, C-8), 27.8 (d, C-6), 27.6 (q, C-16), 19.5 (q, C-7), 18.3 (q, C-7ʹ).

Optical rotation:	$[\alpha]_D^{20}$= –131.7 (c = 1.0, CHCl$_3$)	
HRMS (CI):	calculated	found
$C_{19}H_{32}N_3O_6S$ [M+H]$^+$:	430.2006	430.2007

Methyl *N*-((*tert*-butoxycarbonyl)-L-seryl)-*N*-methyl-L-valinate 154

In a 100 mL round bottom flask, a solution of Boc-Ser-OH (236 mg, 1.15 mmol, 1.10 eq.), H-Me-Val-OMe·HCl (190 mg, 1.05 mmol), and NMM (356 µL, 3.24 mmol, 3.1 eq.) in DMF (10.5 mL) was cooled to 0 °C. After addition of HATU (437 mg, 1.15 mmol, 1.10 eq.), the reaction mixture was stirred for 16 h while slowly reaching room temperature. The mixture was diluted with EtOAc and washed with 5wt% LiCl$_{aq}$, 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica, pentane:EtOAc 7:3) to give hydroxy peptide **154** (212 mg, 638 µmol, 61%) as a colorless resin.

TLC: R$_f$ (154) = 0.15 (silica, pentane:EtOAc 6:4)



154

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 6.27 (m, 1 H, 10-NH), 4.63 (m, 1 H, 3-H), 4.53 (ddd, $^3J_{8,NH}$ = 8.4 Hz, $^3J_{8,9}$ = 6.2 Hz, $^3J_{8,9'}$ = 6.2 Hz, 1 H, 8-H), 3.65 (s, 3 H, 1-H), 3.60 (dd, $^2J_{9,9'}$ = 10.8 Hz, $^3J_{9,8}$ = 6.2 Hz, 1 H, 9-H), 3.50 (dd, $^2J_{9',9}$ = 10.9 Hz, $^3J_{9,8}$ = 6.2 Hz, 1 H, 9-Hʹ), 3.02 (s, 3 H, 6-H), 2.21 (dhept, $^3J_{4,3}$ = 10.2 Hz, $^3J_{4,5}$ = 6.6 Hz, 1 H, 4-H), 1.39 (s, 9 H, 12-H), 0.97 (d, $^3J_{5,4}$ = 6.6 Hz, 3 H, 5-H), 0.97 (d, $^3J_{5',4}$ = 6.5 Hz, 3 H, 5ʹ-H).

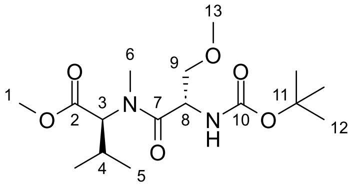
^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 171.2 (s, C-7), 170.2 (s, C-2), 154.5 (s, C-10), 77.8 (s, C-11), 61.4 (d, C-3), 61.3 (t, C-9), 52.5 (d, C-8), 50.9 (q, C-1), 27.7 (q, C-12), 27.6 (d, C-4), 19.0 (q, C-5), 18.1 (q, C-5ʹ), C-6 was not observed.

Optical rotation:	$[\alpha]_D^{20} = -119.5$ (c = 1.0, $CHCl_3$)	
HRMS (CI):	calculated	found
$C_{15}H_{29}N_2O_6$ $[M+H]^+$:	333.2020	333.2017

Methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*O*-methyl-L-seryl)-*N*-methyl-L-valinate 155

In a 25 mL round bottom flask, Ag_2O (676 mg, 2.92 mmol, 5.1 eq.) was suspended in a solution of hydroxy peptide **154** (190 mg, 572 µmol) in MeCN (4.8 mL). After the addition of iodomethane (357 µL, 5.72 mmol, 10 eq.), the reaction mixture was stirred for 24 h at room temperature under light exclusion. Another portion of iodomethane (357 µL, 5.72 mmol, 10 eq.) was added, and the stirring continued for another 48 h. The suspension was filtered through a pad of celite®, and the filtrate was concentrated in vacuo. The crude product was purified by automated flash chromatography (silica, CyH:EtOAc 0% to 50% EtOAc) to give *O*-methyl serine dipeptide **155** (174 mg, 502 µmol, 88%) as a colorless oil.

TLC: R_f (155) = 0.35 (silica, pentane:EtOAc 6:4)



155

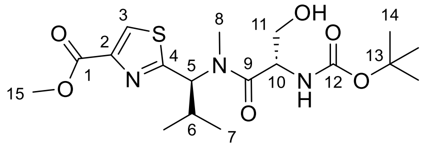
^{1}H-NMR (500 MHz, DMSO-d_6, 373 K): δ = 6.44 (m, 1 H, 10-NH), 4.73 – 4.51 (m, 2 H, 3-H, 8-H), 3.65 (s, 3 H, 1-H), 3.51 (dd, $^2J_{9,9'}$ = 10.0 Hz, $^3J_{9,8}$ = 6.3 Hz, 1 H, 9-H), 3.47 (dd, $^2J_{9',9}$ = 10.0 Hz, $^3J_{9,8}$ = 6.5 Hz, 1 H, 9-H'), 3.26 (s, 3 H, 13-H), 3.00 (s, 3 H, 6-H), 2.22 (dhept, $^3J_{4,3}$ = 10.1 Hz, $^3J_{4,5}$ = 6.6 Hz, 1 H, 4-H), 1.40 (s, 9 H, 12-H), 0.97 (d, $^3J_{5,4}$ = 6.7 Hz, 3 H, 5-H), 0.84 (d, $^3J_{5',4}$ = 6.6 Hz, 3 H, 5'-H).

^{13}C-NMR (125 MHz, DMSO-d_6, 373 K): δ = 170.7 (s, C-7), 170.1 (s, C-2), 154.4 (s, C-10), 78.0 (s, C-11), 71.6 (t, C-9), 61.8 (d, C-3), 57.8 (q, C-13), 50.8 (q, C-1), 50.1 (d, C-8), 31.0 (q, C-6), 27.6 (q, C-12), 26.5 (d, C-4), 19.0 (q, C-5), 18.0 (q, C-5').

Methyl 2-((*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-*N*-methylpropanamido)-2-methylpropyl)thiazole-4-carboxylate 157

In a 250 mL round bottom flask, a solution of Boc-Ser-OH (2.04 g, 9.91 mmol, 1.05 eq.), H-Me-Val-thiazole-OMe·HCl **152** (2.50 g, 9.44 mmol) and NMM (3.43 mL, 31.2 mmol, 3.3 eq.) in CH_2Cl_2 (94 mL) was cooled to 0 °C. After the addition of HATU (3.77 g, 9.91 mmol, 1.05 eq.), the reaction mixture was stirred for 22 h while slowly reaching room temperature. The mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ solution and brine before being dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give hydroxy peptide **157** (1.60 g, 3.85 mmol, 41%, 83% brsm) as a white foam. The starting material was reisolated as the free amine base.

LC-MS: t$_R$ (157) = 0.99 min (short method)



157

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373 K): δ = 8.42 (s, 1 H, 3-H), 6.35 (m, 1 H, 12-NH), 5.42 (m, 1 H, 5-H), 4.52 (m, 1 H, 10-H), 3.86 (s, 3 H, 15-H), 3.58 (m, 1 H, 11-H‘), 3.51 (dd, $^2J_{11,11'}$ = 10.7 Hz, $^3J_{11,10}$ = 6.2 Hz, 1 H, 11-H), 3.00 (s, 3 H, 8-H), 2.59 (dhept, $^3J_{6,5}$ = 10.6 Hz, $^3J_{6,7}$ = 6.6 Hz, 1 H, 6-H), 1.39 (s, 9 H, 14-H), 0.94 (m, 6 H, 7-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$, 373 K): δ = 171.2 (s, C-9), 168.4 (s, C-4), 160.7 (s, C-1), 154.6 (s, C-12), 144.9 (s, C-2), 128.7 (d, C-3), 77.9 (s, C-13), 61.2 (t, C-11), 60.6 (d, C-5), 52.6 (d, C-10), 51.2 (q, C-15), 30.1 (q, C-8), 27.9 (d, C-6), 27.7 (q, C-14), 19.5 (q, C-7), 18.4 (q, C-7‘).

Optical rotation: $[\alpha]_D^{20} = -153.3$ (c = 1.0, CHCl$_3$)

HRMS (CI):	calculated	found
$C_{18}H_{30}N_3O_6S$ [M+H]$^+$:	416.1850	416.1850

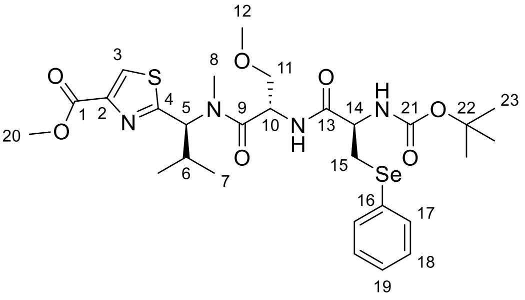
Methyl 2-((6*R*,9*S*,12*S*)-9-(methoxymethyl)-2,2,11,13-tetramethyl-4,7,10-trioxo-6-((phenylselanyl)methyl)-3-oxa-5,8,11-triazatetradecan-12-yl)thiazole-4-carboxylate 159

In a 25 mL round bottom flask, Boc-PhSeCys-OMe **142a** (520 mg, 1.45 mmol) was dissolved in THF (9.7 mL). 0.40 M LiOH$_{aq}$ (3.63 mL, 1.45 mmol, 1.0 eq.) was added dropwise at 0 °C, and the resulting mixture was stirred for 12 h while slowly reaching room temperature. The reaction mixture was acidified with 0.1 M HCl$_{aq}$ and extracted thrice with Et$_2$O. The combined organic extracts were dried over $_{MgSO4}$ and concentrated in vacuo to give the crude Boc-PhSeCys-OH **142b** as a colorless oil with 10% of the elimination product (Boc-dehydroalanine methyl ester) as an impurity.

In a 10 mL round bottom flask, HCl in dioxane (2.91 mL, 11.6 mmol, 4.0 M, 10 eq.) was added to a solution of *O*-methyl serine dipeptide **153** (500 mg, 1.16 mmol) in CH$_2$Cl$_2$ (1.0 mL) at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo to give the crude hydrochloride **158**.

In a 25 mL round bottom flask, the crude hydrochloride **158**, the crude Boc-PhSeCys-OH **142b** (1.2 eq.), and NMM (179 µL, 1.63 mmol, 1.4 eq.) were dissolved in anhydrous CH$_2$Cl$_2$ (11.6 mL). After cooling to 0 °C, EDC·HCl (268 mg, 1.40 mmol, 1.2 eq.) and HOBt (35.7 mg, 233 µmol, 0.2 eq.) were added subsequentially. The reaction mixture was stirred for 16 h while slowly reaching room temperature. After full conversion, the mixture was diluted with EtOAc and washed with 1.0 M HCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude tripeptide was purified by automated flash chromatography (silica, CyH:EtOAc 10% to 70% EtOAc) followed by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give tripeptide **159** (607 mg, 0.926 mmol, 80%) as a colorless resin and the elimination product **161** (40.0 mg, 80.2 µmol, 7%) as a colorless resin.

TLC: R$_f$ (159) = 0.18 (silica, pentane:EtOAc 1:1)



159

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 8.52 (s, 1 H, 3-H), 8.30 (d, $^3J_{NH,10}$ = 8.0 Hz, 1 H, 13-NH), 7.48 (m, 2 H, 18-H), 7.33 – 7.24 (m, 3 H, 17-H, 19-H), 7.08 (d, $^3J_{NH,14}$ = 8.5 Hz, 1 H, 21-NH), 5.41 (d, $^3J_{5,6}$ = 10.9 Hz, 1 H, 5-H), 4.85 (m, 1 H, 10-H), 4.19 (ddd, $^3J_{14,NH}$ = 8.9 Hz, $^3J_{14,15}$ = 8.9 Hz, $^3J_{14,15'}$ = 4.7 Hz, 1 H, 14-H), 3.83 (s, 3 H, 20-H), 3.49 (dd, $^2J_{11,11'}$ = 9.6 Hz, $^3J_{11,10}$ = 6.7 Hz, 1 H, 11-H), 3.42 (dd, $^2J_{11',11}$ = 9.6 Hz, $^3J_{11',10}$ = 6.2 Hz, 1 H, 11-H'), 3.19 (m, 1 H, 15-H), 3.16 (s, 3 H, 12-H), 3.04 (dd, $^2J_{15',15}$ = 9.6 Hz, $^3J_{15',14}$ = 6.2 Hz, 1 H, 15-H'), 2.92 (s, 3 H, 8-H), 2.53 (m, 1 H, 6-H), 1.38 (s, 9 H, 23-H), 0.87 (d, $^3J_{7,6}$ = 6.4 Hz, 3 H, 7-H), 0.84 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 170.2 (s, C-9, C-13), 168.3 (s, C-4), 161.1 (s, C-1), 155.1 (s, C-21), 145.1 (s, C-2), 131.7 (d, C-18), 130.2 (s, C-16), 130.1 (d, C-3), 129.2 (d, C-17), 126.8 (d, C-19), 78.4 (s, C-22), 71.4 (t, C-11), 60.3 (d, C-5), 58.4 (q, C-12), 54.3 (d, C-14), 52.1 (q, C-20), 48.8 (d, C-10), 30.3 (q, C-8), 29.4 (t, C-15), 28.1 (q, C-23), 28.0 (d, C-6), 19.5 (q, C-7), 18.3 (q, C-7').

Selected rotamer signals:

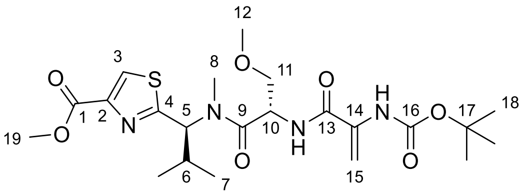
^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 8.47 (s, 1 H, 3-H), 7.45 (m, 2 H, 18-H), 5.15 – 5.09 (m, 2 H, 5-H, 10-H), 4.12 (m, 1 H, 14-H), 3.82 (s, 3 H, 20-H), 3.59 (m, 1 H, 11-H), 3.14 (s, 3 H, 12-H), 2.72 (s, 3 H, 8-H), 0.96 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.94 (d, $^3J_{7',6}$ = 6.5 Hz, 3 H, 7'-H).

Optical rotation: $[\alpha]_D^{20}$ = –91.1 (c = 1.0, $CHCl_3$)

HRMS (ESI):	calculated	found
$C_{28}H_{41}N_4O_7SSe$ $[M+H]^+$:	657.1856	657.1860

Methyl 2-((9*S*,12*S*)-9-(methoxymethyl)-2,2,11,13-tetramethyl-6-methylene-4,7,10-trioxo-3-oxa-5,8,11-triazatetradecan-12-yl)thiazole-4-carboxylate 161

TLC: R$_f$ (161) = 0.14 (silica, pentane:EtOAc 1:1)



161

^{1}H-NMR (500 MHz, DMSO-d_6, 373 K): δ = 8.42 (s, 1 H, 3-H), 8.14 (m, 1 H, 13-NH), 7.69 (m, 1 H, 16-NH), 5.67 (s, 1 H, 15-H), 5.45 (s, 1 H, 15-H'), 5.43 (m, 1 H, 5-H), 4.97 (m, 1 H, 10-H), 3.86 (s, 3 H, 19-H), 3.59 (m, 2 H, 11-H), 3.22 (s, 3 H, 12-H), 2.97 (s, 3 H, 8-H), 2.59 (m, 1 H, 6-H), 1.44 (s, 9 H, 18-H), 0.94 (m, 6 H, 7-H).

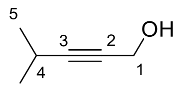
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (s, C-9), 168.0 (s, C-4), 163.1 (s, C-13), 160.6 (s, C-1), 151.9 (s, C-16), 145.0 (s, C-2), 134.9 (s, C-14), 128.7 (d, C-3), 101.5 (t, C-15), 79.2 (s, C-17), 71.1 (t, C-11), 60.5 (d, C-5), 57.9 (q, C-12), 51.3 (q, C-19), 49.4 (d, C-10), 30.0 (q, C-8), 27.8 (d, C-6), 27.5 (q, C-18), 19.5 (q, C-7), 18.4 (q, C-7').

Optical rotation:	$[\alpha]_D^{20}$= –99.1 (c = 1.0, $CHCl_3$)	
HRMS (ESI):	calculated	found
$C_{22}H_{35}N_4O_7S$ $[M+H]^+$:	499.2221	499.2232

4-Methylpent-2-yn-1-ol[207] 163

Preparation according to Corey and Larionov.[193]

TLC: R_f (163) = 0.25 (silica, pentane:Et_2O 8:2)



163

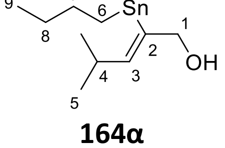
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.26 (d, $^5J_{1,4}$ = 2.0 Hz, 2 H, 1-H), 2.46 (heptt, $^3J_{4,5}$ = 6.9 Hz, $^5J_{4,1}$ = 2.0 Hz, 1 H, 4-H), 1.58 (m, 1 H, 1-OH), 1.17 (d, $^3J_{5,4}$ = 6.9 Hz, 6 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 92.1 (s, C-3), 77.6 (s, C-2), 51.6 (t, C-1), 23.0 (q, C-5), 20.6 (d, C-4).

(*Z*)-4-Methyl-2-(tributylstannyl)pent-2-en-1-ol 164α

In a 100 mL Schlenk tube under an atmosphere of argon, 4-methylpent-2-yn-1-ol (1.25 g, 11.5 mmol) and $[cp^*RuCl_2]_n$ (88.0 mg, 287 µmol, 2.5 mol%) were dissolved in anhydrous CH_2Cl_2 (55 mL). Tributylstannane (3.70 mL, 13.8 mmol, 1.2 eq.) was added dropwise over 5 min at room temperature. The reaction mixture was stirred for 20 min before the solvent was removed under reduced pressure. The crude mixture was purified by automated flash chromatography (silica, pentane:EtOAc 0% to 15% EtOAc) to give (*Z*)-4-methyl-2-(tributylstannyl)pent-2-en-1-ol **164α** (3.44 g, 8.85 mmol, 77%) and (*Z*)-4-methyl-3-(tributylstannyl)-pent-2-en-1-ol **164β** (497 mg, 1.28 mmol, 11%) as colorless oils.

TLC: R_f (164α) = 0.65 (silica, pentane:EtOAc 8:2)



164α

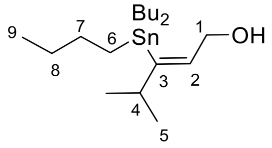
^{1}H-NMR (400 MHz, CDCl$_3$): δ = 6.02 (dt, $^3J_{3,4}$ = 9.8 Hz, $^4J_{3,1}$ = 1.4 Hz, $^3J_{3,Sn}$ = 123.0 Hz, 1 H, 3-H), 4.16 (m, 2 H, 1-H), 2.16 (dhept, $^3J_{4,3}$ = 9.7 Hz, $^3J_{4,5}$ = 6.7 Hz, 1 H, 4-H), 1.50 (m, 6 H, 7-H), 1.33 (tq, $^3J_{8,6}$ = 7.3 Hz, $^3J_{8,7}$ = 7.3 Hz, 6 H, 8-H), 0.99 (d, $^3J_{5,4}$ = 6.8 Hz, 6 H, 5-H), 0.93 – 1.04 (m, 6 H, 6-H), 0.90 (t, $^3J_{9,8}$ = 7.3 Hz, 9 H, 9-H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ = 149.1 (d, C-3), 140.1 (s, C-2), 70.6 (t, C-1), 34.3 (d, C-4), 29.4 (t, C-7), 27.6 (t, C-8), 23.4 (q, C-5), 13.8 (q, C-9), 10.4 (t, C-6).

HRMS (ESI):	calculated	found
$C_{14}H_{29}OSn$ [M-nBu]$^+$:	333.1235	333.1250

(*Z*)-4-Methyl-3-(tributylstannyl)pent-2-en-1-ol 164β

TLC: R$_f$ (164β) = 0.52 (silica, pentane:EtOAc 8:2)



164β

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 6.03 (td, $^3J_{2,1}$ = 6.8 Hz, $^4J_{2,4}$ = 1.3 Hz, $^3J_{2,Sn}$ = 130.3 Hz, 1 H, 2-H), 4.07 (m, 2 H, 1-H), 2.46 (heptd, $^3J_{4,5}$ = 6.8 Hz, $^4J_{4,2}$ = 1.4 Hz, 1 H, 4-H), 1.48 (m, 6 H, 7-H), 1.33 (m, 6 H, 8-H), 1.01 (d, $^3J_{5,4}$ = 6.8 Hz, 6 H, 5-H), 0.92 – 0.97 (m, 6 H, 6-H), 0.90 (t, $^3J_{9,8}$ = 7.3 Hz, 9 H, 9-H).

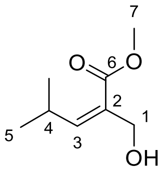
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 156.7 (s, C-3), 134.7 (d, C-2), 65.4 (t, C-1), 37.4 (d, C-4), 29.3 (t, C-7), 27.5 (t, C-8), 23.0 (q, C-5), 13.8 (q, C-9), 11.2 (t, C-6).

HRMS (CI):	calculated	found
$C_{14}H_{29}OSn$ [M-*n*Bu]$^+$:	333.1235	333.1245

Methyl (*Z*)-2-(hydroxymethyl)-4-methylpent-2-enoate 165

In a 250 mL round bottom flask, (*Z*)-4-methyl-2-(tributylstannyl)pent-2-en-1-ol **164α** (2.58 g, 6.63 mmol) and TFA (204 µL, 2.65 mmol, 0.4 eq.) were dissolved in MeOH (66 mL). Benzoquinone (1.08 g, 9.94 mmol, 1.5 eq.), triphenyl arsine (203 mg, 663 µmol, 10 mol%), and Pd(OAc)$_2$ (104 mg, 464 µmol, 7 mol%) were added, and the reaction mixture was stirred under an atmosphere of CO (1 atm) at room temperature for 16 h. After dilution with TBME, the suspension was filtered through a plug of celite®, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (silica, pentane:EtOAc 7:3) to give *Z*-alkenoate **165** (777 mg, 4.91 mmol, 74%) as a colorless oil and lactone **166** (84.0 mg, 666 µmol, 10%) as a colorless oil.

TLC: R$_f$ (165) = 0.36 (silica, pentane:EtOAc 7:3)



165

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.01 (d, $^3J_{3,4}$ = 9.9 Hz, 1 H, 3-H), 4.21 (s, 2 H, 1-H), 3.78 (s, 3 H, 7-H), 3.29 (dhept, $^3J_{4,3}$ = 10.0 Hz, $^3J_{4,5}$ = 6.6 Hz, 1 H, 4-H), 2.37 (s, 1 H, 1-OH), 1.01 (d, $^3J_{5,4}$ = 6.7 Hz, 6 H, 5-H).

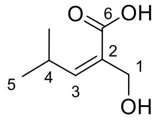
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.7 (s, C-6), 152.9 (d, C-3), 128.4 (s, C-2), 65.4 (t, C-1), 51.6 (q, C-7), 28.3 (q, C-5), 22.5 (d, C-4).

HRMS (CI):	calculated	found
$C_8H_{15}O_3$ $[M+H]^+$:	159.1016	159.1023

(*Z*)-2-(Hydroxymethyl)-4-methylpent-2-enoic acid 167

In a 10 mL round bottom flask, a solution of *Z*-alkenoate **165** (266 mg, 1.68 mmol) in THF (8.4 mL) was cooled to 0 °C. 0.40 M $LiOH_{aq}$ (5.89 mL, 2.35 mmol, 1.4 eq.) was added at 0 °C, and the reaction mixture was stirred for 16 h while slowly reaching room temperature. After acidifying with 1.0 M HCl_{aq}, the mixture was extracted thrice with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give *Z*-alkenoic acid **167** (240 mg, 1.65 mmol, 98%) as a colorless oil.

TLC: R_f (167) = 0.28 (silica, pentane:EtOAc 1:1)



167

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.17 (d, $^3J_{3,4}$ = 10.0 Hz, 1 H, 3-H), 4.27 (s, 2 H, 1-H), 3.44 (dhept, $^3J_{4,3}$ = 10.0 Hz, $^3J_{4,5}$ = 6.7 Hz, 1 H, 4-H), 1.05 (d, $^3J_{5,4}$ = 6.6 Hz, 6 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.5 (s, C-6), 156.1 (d, C-3), 127.5 (s, C-2), 65.5 (t, C-1), 28.5 (q, C-5), 22.5 (d, C-4).

HRMS (CI):	calculated	found
$C_7H_{13}O_3$ $[M+H]^+$:	145.0859	145.0865

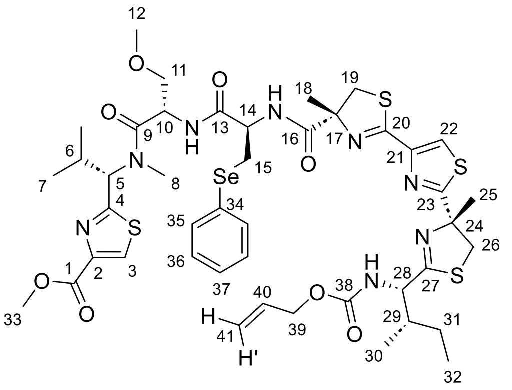
Methyl 2-((*S*)-1-((*S*)-2-((*R*)-2-((4*R*,4''*S*)-2''-((1*S*,2*S*)-1-(((allyloxy)carbonyl)amino)-2-methylbutyl)-4,4''-dimethyl-4,4'',5,5''-tetrahydro-[2,4':2',4''-terthiazole]-4-carboxamido)-3-(phenylselanyl)-propanamido)-3-methoxy-*N*-methylpropanamido)-2-methylpropyl)thiazole-4-carboxylate 169

In a 25 mL round bottom flask, 0.40 M $LiOH_{aq}$ (1.45 mL, 581 µmol, 1.0 eq.) was slowly added to a 0 °C cold solution of bis-thiazoline **141** (294 mg, 576 µmol) in THF (3.8 mL). The resulting mixture was stirred for 12 h while slowly reaching room temperature. After full conversion, the mixture was concentrated in vacuo to give the crude lithium carboxylate **168** as a white solid.

In a 4 mL brown glass vial, 4.0 M HCl in dioxane (1.72 mL, 6.86 mmol, 10 eq.) was added to a solution of tripeptide **159** (450 mg, 686 µmol) in CH_2Cl_2 (1.0 mL) at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo to give the crude hydrochloride salt **160**.

In a 25 mL round bottom flask, the crude lithium carboxylate **168**, the crude hydrochloride salt **160** (1.2 eq.), and NMM (158 µL, 1.44 mmol, 2.5 eq.) were dissolved in DMF (5.8 mL). After cooling to 0 °C, PyAOP (315 mg, 604 µmol, 1.05 eq.) was added, and the resulting mixture was stirred for 16 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 5wt% $LiCl_{aq}$, 1.0 M HCl_{aq}, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give compound **169** (458 mg, 443 µmol, 77%) as a white foam and C-28 epimer **169epi** (58.0 mg, 56.0 µmol, 10%) as a white foam.

LC-MS: t_R (169) = 1.53 min (short method)



169

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.14 (s, 1 H, 3-H), 7.90 (s, 1 H, 22-H), 7.72 (m, 1 H, 13-NH), 7.41 (m, 2 H, 36-H), 7.16 (d, $^3J_{NH,14}$ = 7.7 Hz, 1 H, 16-NH), 7.13 – 7.07 (m, 3 H, 35-H, 37-H), 5.92 (ddt, $^3J_{40,41'}$ = 17.1 Hz, $^3J_{40,41}$ = 10.3 Hz, $^3J_{40,39}$ = 5.4 Hz, 1 H, 40-H), 5.44 (d, $^3J_{NH,28}$ = 8.8 Hz, 1 H, 38-NH), 5.38 (m, 1 H, 5-H), 5.32 (ddt, $^3J_{41',40}$ = 17.2 Hz, $^2J_{41',41}$ = 1.6 Hz, $^4J_{41',39}$ = 1.6 Hz, 1 H, 41-H‘), 5.22 (ddt, $^3J_{41,40}$ = 10.3 Hz, $^2J_{41,41'}$ = 1.3 Hz, $^4J_{41,39}$ = 1.3 Hz, 1 H, 41-H), 5.00 (ddd, $^3J_{10,NH}$ = 7.0 Hz, $^3J_{10,11}$ = 7.0 Hz, $^3J_{10,11'}$ = 5.3 Hz, 1 H, 10-H), 4.65 (ddd, $^3J_{14,NH}$ = 8.0 Hz, $^3J_{14,15}$ = 6.1 Hz, $^3J_{14,15'}$ = 6.1 Hz, 1 H, 14-H), 4.58 (m, 2 H, 39-H), 4.56 (dd, $^3J_{28,NH}$ = 8.7 Hz, $^3J_{28,29}$ = 5.1 Hz, 1 H, 28-H), 3.93 (s, 3 H, 33-H), 3.85 (d, $^2J_{19,19'}$ = 11.4 Hz, 1 H, 19-H), 3.66 (d, $^2J_{26,26'}$ = 11.5 Hz, 1 H, 26-H), 3.56 (d, $^2J_{19',19}$ = 11.3 Hz, 1 H, 19-H‘), 3.51 (dd, $^2J_{11',11}$ = 9.2 Hz, $^3J_{11',10}$ = 5.3 Hz, 1 H, 11-H‘), 3.43 (dd, $^2J_{11,11'}$ = 9.3 Hz, $^3J_{11,10}$ = 6.9 Hz, 1 H, 11-H), 3.37 (dd, $^2J_{15,15'}$ = 13.0 Hz, $^3J_{15,14}$ = 6.0 Hz, 1 H, 15-H), 3.32 (d, $^2J_{26',26}$ = 11.6 Hz, 1 H, 26-H‘), 3.19 (s, 3 H, 12-H), 3.14 (dd, $^2J_{15',15}$ = 12.9 Hz, $^3J_{15',14}$ = 6.2 Hz, 1 H, 15-H‘), 3.05 (s, 3 H, 8-H), 2.78 (m, 1 H, 6-H), 1.94 (m, 1 H, 29-H), 1.72 (s, 3 H, 18-H), 1.60 (s, 3 H, 25-H), 1.54 (m, 1 H, 31-H), 1.18 (m, 1 H, 31-H‘), 1.00 (d, $^3J_{30,29}$ = 6.8 Hz, 3 H, 30-H), 0.95 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.92 (d, $^3J_{7',6}$ = 7.0 Hz, 3 H, 7′-H), 0.91 (t, $^3J_{32,31}$ = 6.4 Hz, 3 H, 32-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 176.2 (s, C-20), 174.9 (s, C-27), 173.8 (s, C-16), 170.3 (s, C-9), 169.5 (s, C-13), 168.2 (s, C-4), 161.9 (s, C-1), 155.9 (s, C-38), 148.6 (s, C-21), 146.2 (s, C-2), 132.80 (d, C-36), 132.75 (d, C-40), 129.2 (d, C-35), 129.1 (s, C-34), 128.8 (d, C-3), 127.4 (d, C-37), 118.0 (t, C-41), 84.8 (s, C-24), 83.7 (s, C-17), 72.5 (t, C-11), 65.9 (t, C-39), 59.2 (q, C-12), 58.1 (d, C-28), 52.7 (d, C-14), 52.5 (q, C-33), 49.6 (d, C-10), 44.5 (t, C-19), 41.0 (t, C-26), 39.2 (d, C-29), 32.0 (q, C-8), 29.4 (t, C-15), 28.6 (d, C-6), 28.0 (q, C-18), 24.9 (q, C-25), 24.6 (t, C-31), 20.3 (q, C-7), 19.2 (q, C-7‘), 15.7 (q, C-30), 11.8 (q, C-32), C-5, C-22 and C-23 were not observed.

Selected rotamer signals:

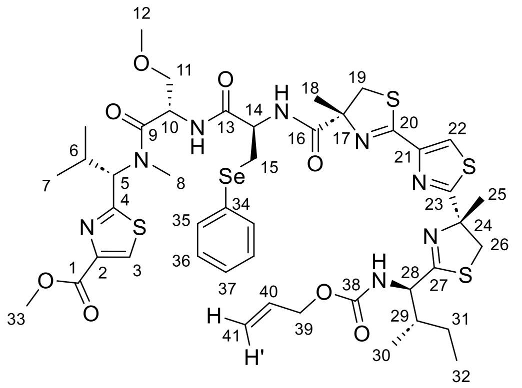
^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.08 (s, 1 H, 3-H), 7.38 (m, 2 H, 36-H), 3.90 (s, 3 H, 33-H), 2.93 (s, 3 H, 8-H), 1.03 (d, $^{3}J_{7,6}$ = 6.7 Hz, 3 H, 7-H).

Optical rotation: $[\alpha]_D^{20}$= –192.1 (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{44}H_{59}N_8O_8S_4Se$ [M+H]$^+$:	1035.2498	1035.2505

C-28 epimer 169epi

LC-MS: t$_R$ (169epi) = 1.57 min (short method)



169epi

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.11 (s, 1 H, 3-H), 7.95 (s, 1 H, 22-H), 7.75 (m, 1 H, 13-NH), 7.60 (m, 2 H, 36-H), 7.32 – 7.25 (m, 3 H, 35-H, 37-H), 7.08 (d, $^{3}J_{NH,14}$ = 8.0 Hz, 1 H, 16-NH), 5.94 (ddt, $^{3}J_{40,41'}$ = 16.9 Hz, $^{3}J_{40,41}$ = 10.8 Hz, $^{3}J_{40,39}$ = 5.7 Hz, 1 H, 40-H), 5.43 (d, $^{3}J_{NH,28}$ = 8.8 Hz, 1 H, 38-NH), 5.33 (d, $^{3}J_{41',40}$ = 17.2 Hz, 1 H, 41-H‘), 5.28 (m, 1 H, 5-H), 5.23 (d, $^{3}J_{41,40}$ = 10.5 Hz, 1 H, 41-H), 4.97 (ddd, $^{3}J_{10,NH}$ = 7.3 Hz, $^{3}J_{10,11}$ = 7.3 Hz, $^{3}J_{10,11'}$ = 5.2 Hz, 1 H, 10-H), 4.66 (m, 1 H, 14-H), 4.60 (m, 2 H, 39-H), 4.56 (dd, $^{3}J_{28,NH}$ = 8.9 Hz, $^{3}J_{28,29}$ = 5.0 Hz, 1 H, 28-H), 3.93 (s, 3 H, 33-H), 3.84 – 3.78 (m, 2 H, 19-H, 26-H), 3.56 (d, $^{2}J_{19',19}$ = 11.4 Hz, 1 H, 19-H‘), 3.50 (dd, $^{2}J_{11',11}$ = 9.2 Hz, $^{3}J_{11',10}$ = 5.3 Hz, 1 H, 11-H‘), 3.43 – 3.31 (m, 3 H, 11-H, 15-H, 26-H‘), 3.23 (dd, $^{2}J_{15',15}$ = 12.9 Hz, $^{3}J_{15',14}$ = 6.8 Hz, 1 H, 15-H‘), 3.18 (s, 3 H, 12-H), 3.01 (s, 3 H, 8-H), 2.75 (m, 1 H, 6-H), 1.95 (m, 1 H, 29-H), 1.73 (s, 3 H, 18-H), 1.57 (s, 3 H, 25-H), 1.54 (m, 1 H, 31-H), 1.19 (m, 1 H, 31-H‘), 1.00 (d, $^{3}J_{30,29}$ = 6.8 Hz, 3 H, 30-H), 0.93 (t, $^{3}J_{32,31}$ = 7.5 Hz, 3 H, 32-H), 0.87 (d, $^{3}J_{7,6}$ = 6.2 Hz, 3 H, 7-H), 0.86 (d, $^{3}J_{7',6}$ = 6.5 Hz, 3 H, 7‘-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 176.4 (s, C-20), 174.9 (s, C-27), 173.8 (s, C-16), 170.4 (s, C-9), 169.5 (s, C-13), 168.3 (s, C-4), 164.4 (s, C-23), 161.9 (s, C-1), 155.9 (s, C-38), 148.7 (s, C-21), 146.2 (s, C-2), 133.2 (d, C-36), 132.9 (d, C-40), 129.53 (s, C-34), 129.48 (d, C-35), 128.9 (d, C-3), 127.6 (d, C-37), 121.7 (d, C-22), 118.0 (t, C-41), 84.8 (s, C-24), 83.7 (s, C-17), 72.6 (t, C-11), 66.0 (t, C-39), 59.2 (q, C-12), 58.2 (d, C-28), 52.7 (d, C-14), 52.5 (q, C-33), 49.7 (d, C-10), 44.6 (t, C-19), 41.2 (t, C-26), 39.3 (d, C-29), 32.3 (q, C-8), 29.1 (t, C-15), 28.6 (d, C-6), 27.9 (q, C-18), 24.68 (q, C-25), 24.65 (t, C-31), 20.3 (q, C-7), 19.2 (q, C-7‘), 15.8 (q, C-30), 11.8 (q, C-32), C-5 was not observed.

Selected rotamer signals:

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.55 (m, 2 H, 36-H), 6.91 (d, $^3J_{NH,14}$ = 8.4 Hz, 1 H, 16-NH), 3.89 (s, 3 H, 33-H), 2.85 (s, 3 H, 8-H).

Optical rotation: $[\alpha]_D^{20}$ = −119.1 (c = 1.0, CHCl$_3$)

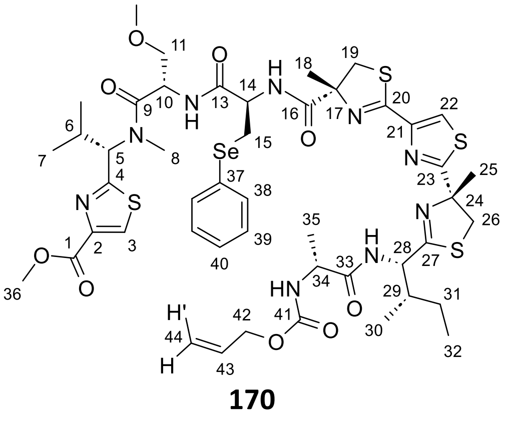
HRMS (ESI):	calculated	found
$C_{44}H_{59}N_8O_8S_4Se$ [M+H]$^+$:	1035.2498	1035.2511

Methyl 2-((*S*)-1-((S)-2-((*R*)-2-((4*R*,4''*S*)-2''-((1*S*,2*S*)-1-((*R*)-2-(((allyloxy)carbonyl)amino)propanamido)-2-methylbutyl)-4,4''-dimethyl-4,4'',5,5''-tetrahydro-[2,4':2',4''-terthiazole]-4-carboxamido)-3-(phenylselanyl)propanamido)-3-methoxy-*N*-methylpropanamido)-2-methylpropyl)-thiazole-4-carboxylate 170

In a 25 mL Schlenk tube under an atmosphere of nitrogen, Pd(PPh$_3$)$_4$ (43.8 mg, 38.0 µmol, 8 mol%) was added to a solution of compound **169** (490 mg, 474 µmol) and phenylsilane (236 µL, 1.90 mmol, 4.0 eq.) in anhydrous THF (4.8 mL). After 15 min, the solvent was partly removed, the mixture adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give the corresponding free amine (410 mg, 432 µmol, 91%) as a white foam, which was immediately used in the following coupling reaction.

In a 25 mL round bottom flask, a solution of the above-prepared free amine (407 mg, 428 µmol), Alloc-D-Ala-OH (119 mg, 685 µmol, 1.6 eq.), and NMM (135 µL, 1.20 mmol, 2.8 eq.) in anhydrous DMF (4.3 mL) was cooled to 0 °C. After the addition of HATU (252 mg, 664 µmol, 1.5 eq.), the mixture was stirred for 14 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl$_{aq}$, 5wt% LiCl$_{aq}$, sat. NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give compound **170** (381 mg, 344 µmol, 80%, dr 90:10 (C-28 epimer)) as a white foam. The analytical characterizations were done with a diastereomerically pure (dr >99:1) fraction.

LC-MS: t$_R$ (170) = 1.44 min (short method)



170

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.10 (s, 1 H, 3-H), 7.85 (s, 1 H, 22-H), 7.68 (d, $^3J_{NH,14}$ = 8.0 Hz, 1 H, 16-NH), 7.38 – 7.30 (m, 3 H, 39-H, 13-NH), 7.08 – 7.00 (m, 3 H, 38-H, 40-H), 6.98 (d, $^3J_{NH,28}$ = 8.9 Hz, 1 H, 33-NH), 5.83 (ddt, $^3J_{43,44'}$ = 16.8 Hz, $^3J_{43,44}$ = 10.8 Hz, $^3J_{43,42}$ = 5.7 Hz, 1 H, 43-H), 5.60 (d, $^3J_{NH,34}$ = 7.5 Hz, 1 H, 41-NH), 5.36 (m, 1 H, 5-H), 5.23 (d, $^3J_{44',43}$ = 17.1 Hz , 1 H, 44-H‘), 5.13 (d, $^3J_{44,43}$ = 10.5 Hz, 1 H, 44-H), 4.98 (ddd, $^3J_{10,NH}$ = 6.9 Hz, $^3J_{10,11}$ = 6.9 Hz, $^3J_{10,11'}$ = 6.9 Hz, 1 H, 10-H), 4.77 (dd, $^3J_{28,NH}$ = 8.8 Hz, $^3J_{28,29}$ = 5.4 Hz, 1 H, 28-H), 4.69 (ddd, $^3J_{14,NH}$ = 7.9 Hz, $^3J_{14,15}$ = 4.2 Hz, $^3J_{14,15'}$ = 4.2 Hz, 1 H, 14-H), 4.51 (m, 2 H, 42-H), 4.30 (m, 1 H, 34-H), 3.88 (s, 3 H, 36-H), 3.78 (d, $^2J_{19,19'}$ = 11.4 Hz, 1 H, 19-H), 3.57 (d, $^2J_{26,26'}$ = 11.5 Hz, 1 H, 26-H), 3.51 – 3.45 (m, 2 H, 11-H, 19-H‘), 3.41 (dd, $^2J_{11',11}$ = 9.3 Hz, $^3J_{11',10}$ = 6.9 Hz, 1 H, 11-H‘), 3.32 – 3.23 (m, 2 H, 15-H, 26-H‘), 3.14 (s, 3 H, 12-H), 3.12 (m, 1 H, 15-H‘), 3.01 (s, 3 H, 8-H), 2.73 (m, 1 H, 6-H), 1.94 (m, 1 H, 29-H), 1.66 (s, 3 H, 18-H), 1.53 (s, 3 H, 25-H), 1.50 (m, 1 H, 31-H), 1.36 (d, $^3J_{35,34}$ = 7.0 Hz, 3 H, 35-H), 1.14 (m, 1 H, 31-H‘), 0.93 (d, $^3J_{30,29}$ = 6.9 Hz, 3 H, 30-H), 0.90 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.89 – 0.83 (m, 6 H, 7‘-H, 32-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 176.0 (s, C-20), 174.7 (s, C-27), 173.4 (s, C-16), 172.0 (s, C-33), 170.3 (s, C-9), 169.4 (s, C-13), 168.1 (s, C-4), 163.8 (s, C-23), 161.7 (s, C-1), 155.9 (s, C-41), 148.5 (s, C-21), 146.0 (s, C-2), 132.6 (d, C-39), 132.5 (d, C-43), 129.0 (s, C-37, d, C-38), 128.7 (d, C-3), 127.2 (d, C-40), 121.3 (d, C-22), 117.8 (t, C-44), 84.7 (s, C-24), 83.5 (s, C-17), 72.3 (t, C-11), 65.8 (t, C-42), 59.0 (q, C-12), 55.9 (d, C-28), 52.43 (d, C-14), 52.36 (q, C-36), 50.3 (d, C-34), 49.4 (d, C-10), 44.3 (t, C-19), 40.9 (t, C-26), 38.6 (d, C-29), 31.8 (q, C-8), 29.5 (t, C-15), 28.4 (d, C-6), 27.8 (q, C-18), 24.6 (q, C-25), 24.5 (t, C-31), 20.1 (q, C-7), 19.1 (q, C-7‘), 18.6 (q, C-35), 15.6 (q, C-30), 11.5 (q, C-32), C-5 was not observed.

Selected rotamer signals:
^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.04 (s, 1 H, 3-H), 3.85 (s, 3 H, 36-H), 2.88 (s, 3 H, 8-H), 0.98 (d, $^3J_{7,6}$ = 6.9 Hz, 3 H, 7-H).

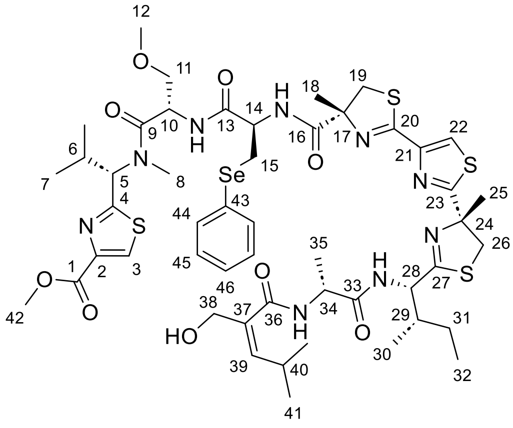
Optical rotation:	$[\alpha]_D^{20}$= –129.7 (c = 1.0, CHCl$_3$)	
HRMS (ESI):	calculated	found
$C_{47}H_{64}N_9O_9S_4Se$ [M+H]$^+$:	1106.2870	1106.2869

Methyl 2-((*S*)-1-((*S*)-2-((*R*)-2-((4*R*,4''*S*)-2''-((1*S*,2*S*)-1-((*R*)-2-((*Z*)-2-(hydroxymethyl)-4-methyl-pent-2-enamido)propanamido)-2-methylbutyl)-4,4''-dimethyl-4,4'',5,5''-tetrahydro-[2,4':2',4''-terthiazole]-4-carboxamido)-3-(phenylselanyl)propanamido)-3-methoxy-*N*-methylpropan-amido)-2-methylpropyl)thiazole-4-carboxylate 171

In a 25 mL Schlenk tube under an atmosphere of nitrogen, Pd(PPh$_3$)$_4$ (24.7 mg, 21.0 µmol, 7 mol%) was added to a solution of compound **170** (337 mg, 305 µmol, dr 90:10) and phenylsilane (114 µL, 915 µmol, 3.0 eq.) in anhydrous THF (3.1 mL). After 10 min, the solvent was partly removed, the residue adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, H$_2$O:MeCN 10% to 90% MeCN) to give the corresponding free amine (262 mg, 257 µmol, 84%) as a white foam, which was immediately used in the following coupling reaction.

In a 25 mL round bottom flask, a solution of the above-prepared free amine (262 mg, 257 µmol), *Z*-alkenoic acid **167** (48.2 mg, 308 µmol, 1.2 eq.), and NMM (74.8 µL, 667 µmol, 2.6 eq.) in anhydrous DMF (3.4 mL) was cooled to 0 °C. After addition of PyAOP (147 mg, 282 µmol, 1.1 eq.), the resulting mixture was stirred for 12 h while slowly reaching room temperature. The reaction mixture was diluted with EtOAc and washed with 1.0 M HCl_{aq}, 5wt% $LiCl_{aq}$, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by automated reversed phase column chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give compound **171** (211 mg, 184 µmol, 72%, dr 82:18 (C-28 epimer)) as a white foam.

LC-MS: t_R (171) = 1.40 min (short method)



171

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.14 (s, 1 H, 3-H), 7.95 (s, 1 H, 22-H), 7.72 (d, $^3J_{NH,14}$ = 7.9 Hz, 1 H, 16-NH), 7.43 (m, 2 H, 45-H), 7.17 (m, 1 H, 33-NH), 7.16 – 7.10 (m, 4 H, 44-H, 46-H, 13-NH), 7.00 (m, 1 H, 36-NH), 5.64 (d, $^3J_{39,40}$ = 10.1 Hz, 1 H, 39-H), 5.40 (d, $^3J_{5,6}$ = 10.8 Hz, 1 H, 5-H), 5.01 (ddd, $^3J_{10,NH}$ = 7.3 Hz, $^3J_{10,11}$ = 7.3 Hz, $^3J_{10,11'}$ = 5.2 Hz, 1 H, 10-H), 4.83 (dd, $^3J_{28,NH}$ = 8.6 Hz, $^3J_{28,29}$ = 5.3 Hz, 1 H, 28-H), 4.69 – 4.61 (m, 2 H, 14-H, 34-H), 4.22 (d, $^2J_{38,38'}$ = 12.2 Hz, 1 H, 38-H), 4.16 (d, $^2J_{38',38}$ = 12.0 Hz, 1 H, 38-H‘), 3.94 (s, 3 H, 42-H), 3.87 (m, 1 H, 19-H), 3.68 (d, $^2J_{26,26'}$ = 11.5 Hz, 1 H, 26-H), 3.57 – 3.50 (m, 2 H, 11-H, 19-H‘), 3.45 (dd, $^2J_{11',11}$ = 9.2 Hz, $^3J_{11',10}$ = 7.0 Hz, 1 H, 11-H‘), 3.36 (m, 1 H, 15-H), 3.32 (d, $^2J_{26',26}$ = 11.6 Hz, 1 H, 26-H‘), 3.20 (s, 3 H, 12-H), 3.17 (dd, $^2J_{15',15}$ = 13.0 Hz, $^3J_{15',14}$ = 6.3 Hz, 1 H, 15-H‘), 3.06 (s, 3 H, 8-H), 3.01 (m, 1 H, 40-H), 2.80 (m, 1 H, 6-H), 2.00 (m, 1 H, 29-H), 1.76 (s, 3 H, 18-H), 1.61 (s, 3 H, 25-H), 1.55 (m, 1 H, 31-H), 1.45 (d, $^3J_{35,34}$ = 7.1 Hz, 3 H, 35-H), 1.23 (m, 1 H, 31-H‘), 1.05 – 0.98 (m, 9 H, 30-H, 41-H), 0.96 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.95 – 0.90 (m, 6 H, 7‘-H, 32-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 176.2 (s, C-20), 174.8 (s, s, C-27, C-16), 172.0 (s, C-33), 170.4 (s, C-9), 169.6 (s, C-13), 168.9 (s, C-36), 168.3 (s, C-4), 163.8 (s, C-23), 162.0 (s, C-1), 148.6 (s, C-21), 146.6 (d, C-39), 146.3 (s, C-2), 132.94 (s, C-43), 132.93 (d, C-45), 131.7 (s, C-37), 129.3 (d, C-44), 128.7 (d, C-3), 127.5 (d, C-46), 121.9 (d, C-22), 84.8 (s, C-24), 83.8 (s, C-17), 72.6 (t, C-11), 66.2 (t, C-38), 62.6 (d, C-5), 59.2 (q, C-12), 56.3 (d, C-28), 52.8 (d, C-14), 52.5 (q, C-42), 49.7 (d, C-10), 48.7 (d, C-34), 44.5 (t, C-19), 41.1 (t, C-26), 39.0 (d, C-29), 32.0 (q, C-8), 29.4 (t, C-15), 28.6 (d, C-6), 28.4

(d, C-40), 27.88 (q, C-18), 24.9 (t, C-31), 24.8 (q, C-25), 22.85 (q, C-41), 22.83 (q, C-41‘), 20.3 (q, C-7), 19.3 (q, C-7‘), 17.8 (q, C-35), 15.9 (q, C-30), 11.8 (q, C-32).

Selected rotamer signals:

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.09 (s, 1 H, 3-H), 5.34 (d, $^3J_{5,6}$ = 7.5 Hz, 1 H, 5-H), 7.40 (m, 2 H, 45-H), 3.92 (s, 3 H, 42-H), 2.94 (s, 3 H, 8-H).

Selected C-28 epimer signals:

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.04 (d, $^3J_{NH,28}$ = 9.1 Hz, 1 H, 33-NH), 6.84 (d, $^3J_{NH,34}$ = 7.5 Hz, 1 H, 36-NH), 4.25 (d, $^2J_{38,38'}$ = 11.8 Hz, 1 H, 38-H), 4.17 (d, $^2J_{38',38}$ = 11.9 Hz, 1 H, 38-H‘), 3.61 – 3.57 (m, 2 H, 11-H, 19-H), 1.49 (d, $^3J_{35,34}$ = 7.1 Hz, 3 H, 35-H).

^{13}C-NMR (125 MHz, CDCl$_3$): δ = 172.1 (s, C-33), 168.8 (s, C-36), 145.7 (d, C-39), 132.2 (s, C-37), 129.1 (d, C-44), 66.1 (t, C-38), 54.9 (d, C-28), 49.0 (d, C-34), 44.6 (t, C-19), 39.1 (d, C-29), 28.5 (d, C-40), 27.90 (q, C-18), 26.7 (t, C-31), 22.88 (q, C-41), 18.2 (q, C-35), 13.8 (q, C-30), 12.0 (q, C-32).

HRMS (ESI):	calculated	found
$C_{50}H_{70}N_9O_9S_4Se$ [M+H]$^+$:	1148.3339	1148.3346

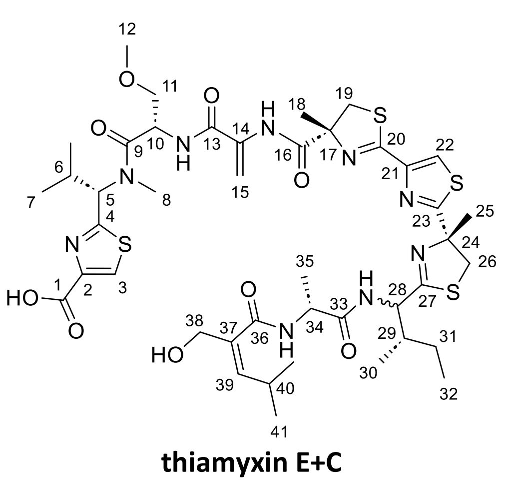
Mixture of thiamyxin E+C

In a 4 mL brown glass vial, 0.40 M LiOH$_{aq}$ (458 µL, 183 µmol, 2.1 eq.) was added to a 0 °C cold solution of compound **171** (100 mg, 87.0 µmol) in THF (580 µL). The reaction mixture was stirred for 2 h while slowly reaching room temperature. After the addition of another portion of 0.40 M LiOH$_{aq}$ (218 µL, 87.1 µmol, 1.0 eq.), the mixture was stirred for another 2 h at room temperature. After full conversion, the reaction mixture was adsorbed on isolute® and purified by automated reversed phase column chromatography (C18 spherical, 0.10% HCOOH$_{aq}$:MeCN 10% to 90% MeCN) to give **thiamyxin E+C** (74 mg, 87.0 µmol, 87%, dr 77:23) as a white foam.

If purified again by preparative HPLC with 0.10% HCOOH$_{aq}$:MeCN, the diastereomeric ratio changed to 1:1. The diastereomers remain inseparable by preparative HPLC.

Full analytical characterization is provided in the thiamyxin E and thiamyxin C sections.

LC-MS: t$_R$ (thiamyxin E+C) = 1.21 min (short method)



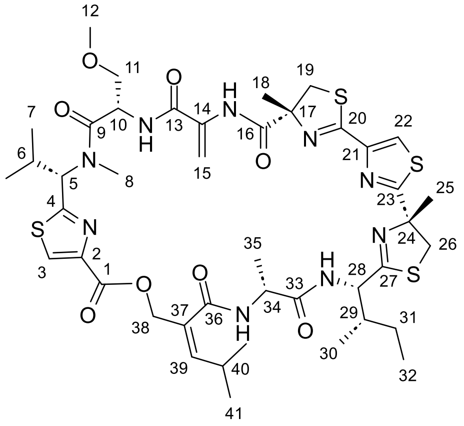
thiamyxin E+C

HRMS (ESI):	calculated	found
$C_{43}H_{62}N_9O_9S_4$ [M+H]$^+$:	976.3548	976.3545

Thiamyxin A and B

In a 100 mL Schlenk tube under an atmosphere of nitrogen, 2,4,6-trichlorobenzoyl chloride (12.0 µL, 74.1 µmol, 1.1 eq.) was added at room temperature to a solution of **thiamyxin E+C** (66.0 mg, 67.8 µmol, dr 1:1), Triethylamine (47.1 µmol, 338 µmol, 5.0 eq.) and DMAP (83.0 mg, 676 µmol, 10 eq.). The reaction mixture was stirred for 1 h before being concentrated in vacuo. The residue was adsorbed on isolute® and purified by automated reversed phase chromatography (C18 spherical, H_2O:MeCN 10% to 90% MeCN) to give a mixture of **thiamyxin A+B** (41.0 mg, 42.8 µmol, 63%) as a white foam. The mixture was separated by preparative HPLC (0.10% $HCOOH_{aq}$:MeCN 40% to 90% MeCN, 2 runs) followed by lyophilization to give **thiamyxin A** (19.4 mg, 20.2 µmol, 30%, dr > 99:1) and **thiamyxin B** (19.0 mg, 19.8 µmol, 29%, dr 99:1) as amorphous solids.

LC-MS: t_R (thiamyxin A) = 3.78 min (long method)



thiamyxin A

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.28 (s, 1 H, 16-NH), 8.90 (d, $^3J_{\mathrm{NH},10}$ = 7.9 Hz, 1 H, 13-NH), 8.53 (s, 1 H, 3-H), 8.25 (s, 1 H, 22-H), 8.25 (d, $^3J_{\mathrm{NH},28}$ = 8.5 Hz, 1 H, 33-NH), 7.81 (d, $^3J_{\mathrm{NH},34}$ = 8.1 Hz, 1 H, 36-NH), 6.38 (m, 1 H, 15-H), 5.79 (m, 1 H, 15-H'), 5.76 (d, $^3J_{39,40}$ = 10.1 Hz, 1 H, 39-H), 5.29 (d, $^3J_{5,6}$ = 10.8 Hz, 1 H, 5-H), 4.92 (d, $^2J_{38,38'}$ = 13.2 Hz, 1 H, 38-H), 4.88 (ddd, $^3J_{10,\mathrm{NH}}$ = 7.6 Hz, $^3J_{10,11}$ = 7.2 Hz, $^3J_{10,11'}$ = 7.2 Hz, 1 H, 10-H), 4.82 (m, 1 H, 38-H'), 4.64 (dd, $^3J_{28,\mathrm{NH}}$ = 8.8 Hz, $^3J_{28,29}$ = 8.8 Hz, 1 H, 28-H), 4.43 (dq, $^3J_{34,\mathrm{NH}}$ = 7.1 Hz, $^3J_{34,35}$ = 7.1 Hz, 1 H, 34-H), 3.77 (d, $^2J_{19,19'}$ = 11.6 Hz, 1 H, 19-H), 3.63 (d, $^2J_{26,26'}$ = 11.4 Hz, 1 H, 26-H), 3.62 – 3.54 (m, 2 H, 11-H, 11-H'), 3.50 (d, $^2J_{26',26}$ = 11.6 Hz, 1 H, 26-H'), 3.38 (d, $^2J_{19',19}$ = 11.7 Hz, 1 H, 19-H'), 3.21 (s, 3 H, 12-H), 2.83 (s, 3 H, 8-H), 2.72 (m, 1 H, 40-H), 2.33 (m, 1 H, 6-H), 1.83 (m, 1 H, 29-H), 1.68 (s, 3 H, 25-H), 1.57 (s, 3 H, 18-H), 1.55 (m, 1 H, 31-H), 1.21 (m, 1 H, 31-H'), 1.20 (d, $^3J_{35,34}$ = 7.0 Hz, 3 H, 35-H), 0.94 – 0.89 (m, 9 H, 41-H, 41'-H 30-H), 0.86 (t, $^3J_{32,31}$ = 7.3 Hz, 3 H, 32-H), 0.75 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, 7-H), 0.55 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 176.3 (s, C-23), 174.9 (s, C-27), 172.9 (s, C-16), 171.8 (s, C-33), 170.2 (s, C-9), 168.4 (s, C-4), 165.9 (s, C-36), 163.9 (s, C-20), 163.0 (s, C-13), 160.6 (s, C-1), 147.9 (s, C-21), 145.1 (s, C-2), 142.9 (d, C-39), 133.0 (s, C-14), 130.5 (d, C-3), 130.0 (s, C-37), 122.1 (d, C-22), 102.8 (t, C-15), 85.0 (s, C-17), 83.0 (s, C-24), 71.0 (t, C-11), 66.1 (t, C-38), 60.1 (d, C-5), 58.4 (q, C-12), 56.0 (d, C-28), 49.6 (d, C-10), 48.6 (d, C-34), 43.7 (t, C-26), 40.8 (t, C-19), 37.2 (d, C-29), 30.3 (q, C-8), 28.1 (d, C-6), 27.8 (d, C-40), 27.4 (q, C-25), 25.5 (q, C-18), 24.6 (t, C-31), 22.6 (q, C-41), 22.4 (q, C-41'), 19.9 (q, C-7), 19.2 (q, C-35), 18.6 (q, C-7'), 15.4 (q, C-30), 10.6 (q, C-32).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.32 (s, 1 H, 16-NH), 9.10 (d, $^{3}J_{\mathrm{NH},10}$ = 7.9 Hz, 1 H, 13-NH), 8.24 (s, 1 H, 3-H), 8.15 (d, $^{3}J_{\mathrm{NH},28}$ = 8.9 Hz, 1 H, 33-NH), 8.10 (s, 1 H, 22-H), 7.70 (d, $^{3}J_{\mathrm{NH},34}$ = 8.1 Hz, 1 H, 36-NH), 6.43 (m, 1 H, 15-H'), 5.84 (d, $^{3}J_{39,40}$ = 9.8 Hz, 1 H, 39-H), 5.81 (m, 1 H, 15-H'), 5.21 (ddd, $^{3}J_{10,\mathrm{NH}}$ = 8.1 Hz, $^{3}J_{10,11}$ = 8.1 Hz, $^{3}J_{10,11'}$ = 5.6 Hz, 1 H, 10-H), 5.06 (d, $^{3}J_{5,6}$ = 10.4 Hz, 1 H, 5-H), 4.57 – 4.50 (m, 2 H, 28-H, 34-H), 3.82 (d, $^{2}J_{19,19'}$ = 11.6 Hz, 1 H, 19-H), 3.68 (dd, $^{2}J_{11',11}$ = 10.1 Hz, $^{3}J_{11',10}$ = 5.6 Hz, 1 H, 11-H'), 3.46 (d, $^{2}J_{26',26}$ = 11.4 Hz, 1 H, 26-H'), 3.26 (s, 3 H, 12-H), 2.88 (m, 1 H, 40-H), 2.68 (s, 3 H, 8-H), 2.54 (m, 1 H, 6-H), 1.60 (s, 3 H, 18-H), 0.96 (d, $^{3}J_{41,40}$ = 6.5 Hz, 3 H, 41-H), 0.95 (d, $^{3}J_{41',40}$ = 6.5 Hz, 3 H, 41'-H), 0.70 (d, $^{3}J_{7,6}$ = 6.5 Hz, 3 H, 7-H).

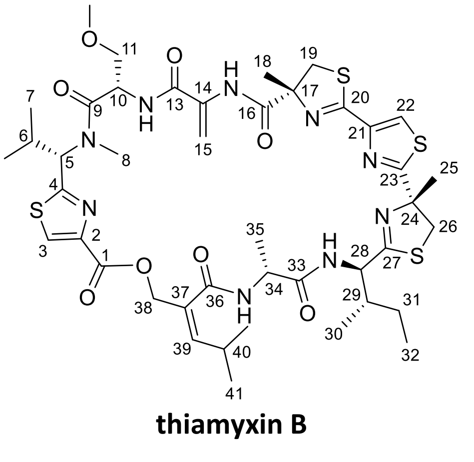
^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 176.2 (s, C-23), 173.9 (s, C-27), 171.4 (s, C-33), 169.0 (s, C-9), 167.4 (s, C-4), 166.4 (s, C-36), 164.1 (s, C-20), 163.1 (s, C-13), 160.1 (s, C-1), 147.6 (d, C-39), 147.3 (s, C-21), 145.4 (s, C-2), 129.7 (d, C-3), 128.8 (s, C-37), 122.0 (d, C-22), 103.0 (t, C-15), 84.8 (s, C-17), 83.4 (s, C-24), 71.7 (t, C-11), 67.2 (t, C-38), 61.8 (d, C-5), 55.6 (d, C-28), 48.6 (d, C-10), 47.7 (d, C-34), 42.3 (t, C-26), 37.3 (d, C-29), 29.5 (q, C-8), 28.4 (d, C-6), 28.2 (d, C-40), 24.5 (t, C-31), 22.4 (q, C-41), 22.3 (q, C-41'), 20.1 (q, C-7), 18.9 (q, C-35), 17.8 (q, C-7'), 15.5 (q, C-30), 10.9 (q, C-32).

Optical rotation: $[\alpha]_{D}^{20} = -94.5$ (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{43}H_{60}N_9O_8S_4$ [M+H]$^+$:	958.3442	958.3441

Thiamyxin B

LC-MS: t$_R$ (thiamyxin B) = 3.88 min (long method)



thiamyxin B

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.36 (s, 1 H, 16-NH), 8.96 (d, $^{3}J_{\mathrm{NH},10}$ = 7.5 Hz, 1 H, 13-NH), 8.56 (s, 1 H, 3-H), 8.30 (s, 1 H, 22-H), 8.30 (d, $^{3}J_{\mathrm{NH},28}$ = 9.5 Hz, 1 H, 33-NH), 7.51 (d, $^{3}J_{\mathrm{NH},34}$ = 7.8 Hz, 1 H, 36-NH), 6.37 (m, 1 H, 15-H), 5.82 (d, $^{3}J_{39,40}$ = 9.6 Hz, 1 H, 39-H), 5.81 (m, 1 H, 15-H‘), 5.32 (d, $^{3}J_{5,6}$ = 10.6 Hz, 1 H, 5-H), 4.91 (d, $^{2}J_{38,38'}$ = 12.4 Hz, 1 H, 38-H), 4.89 (m, 1 H, 10-H), 4.86 (d, $^{2}J_{38',38}$ = 11.8 Hz, 1 H, 38-H‘), 4.78 (dd, $^{3}J_{28,\mathrm{NH}}$ = 9.4 Hz, $^{3}J_{28,29}$ = 4.8 Hz, 1 H, 28-H), 4.61 (dq, $^{3}J_{34,\mathrm{NH}}$ = 7.1 Hz, $^{3}J_{34,35}$ = 7.1 Hz, 1 H, 34-H), 3.81 (d, $^{2}J_{19,19'}$ = 11.7 Hz, 1 H, 19-H), 3.76 (d, $^{2}J_{26,26'}$ = 11.5 Hz, 1 H, 26-H), 3.71 (d, $^{2}J_{26',26}$ = 11.4 Hz, 1 H, 26-H‘), 3.63 – 3.55 (m, 2 H, 11-H, 11-H‘), 3.38 (d, $^{2}J_{19',19}$ = 11.7 Hz, 1 H, 19-H‘), 3.21 (s, 3 H, 12-H), 2.90 (s, 3 H, 8-H), 2.83 (m, 1 H, 40-H), 2.36 (m, 1 H, 6-H), 1.91 (m, 1 H, 29-H), 1.64 (s, 3 H, 25-H), 1.58 (s, 3 H, 18-H), 1.37 (m, 1 H, 31-H), 1.36 (d, $^{3}J_{35,34}$ = 6.9 Hz, 3 H, 35-H), 1.21 (m, 1 H, 31-H‘), 0.98 – 0.90 (m, 9 H, 41-H, 41‘-H 30-H), 0.87 (t, $^{3}J_{32,31}$ = 7.4 Hz, 3 H, 32-H), 0.72 (d, $^{3}J_{7,6}$ = 6.4 Hz, 3 H, 7-H), 0.38 (d, $^{3}J_{7',6}$ = 6.6 Hz, 3 H, 7‘-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 176.5 (s, C-23), 173.1 (s, C-27), 172.9 (s, C-16), 171.6 (s, C-33), 170.6 (s, C-9), 168.3 (s, C-4), 165.8 (s, C-36), 163.8 (s, C-20), 163.1 (s, C-13), 160.5 (s, C-1), 147.5 (s, C-21), 146.6 (d, C-39), 145.2 (s, C-2), 132.7 (s, C-14), 130.5 (d, C-3), 129.2 (s, C-37), 122.5 (d, C-22), 102.5 (t, C-15), 84.9 (s, C-17), 83.3 (s, C-24), 71.0 (t, C-11), 67.0 (t, C-38), 59.8 (d, C-5), 58.5 (q, C-12), 53.6 (d, C-28), 49.5 (d, C-10), 47.6 (d, C-34), 43.3 (t, C-26), 40.8 (t, C-19), 37.5 (d, C-29), 30.2 (q, C-8), 28.3 (q, C-25), 28.0 (d, C-6), 27.8 (d, C-40), 25.9 (t, C-31), 25.5 (q, C-18), 22.4 (q, C-41), 22.2 (q, C-41‘), 20.1 (q, C-7), 19.5 (q, C-35), 18.3 (q, C-7‘), 14.2 (q, C-30), 11.5 (q, C-32).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.51 (s, 1 H, 16-NH), 9.09 (d, $^{3}J_{\mathrm{NH},10}$ = 8.5 Hz, 1 H, 13-NH), 8.31 (s, 1 H, 3-H), 8.10 (s, 1 H, 22-H), 7.87 – 7.83 (m, 2 H, 33-NH, 36-NH), 6.43 (m, 1 H, 15-H), 5.88 (m, 1 H, 15-H‘), 5.75 (d, $^{3}J_{39,40}$ = 9.9 Hz, 1 H, 39-H), 5.23 (d, $^{3}J_{5,6}$ = 10.3 Hz, 1 H, 5-H), 4.90 (d, $^{2}J_{38,38'}$ = 14.1 Hz, 1 H, 38-H), 4.67 (dd, $^{3}J_{28,\mathrm{NH}}$ = 9.0 Hz, $^{3}J_{28,29}$ = 4.6 Hz, 1 H, 28-H), 4.47 (dq, $^{3}J_{34,\mathrm{NH}}$ = 7.2 Hz, $^{3}J_{34,35}$ = 7.2 Hz, 1 H, 34-H), 3.89 (d, $^{2}J_{19,19'}$ = 11.5 Hz, 1 H, 19-H), 3.67 (d, $^{2}J_{26',26}$ = 11.4 Hz, 1 H, 26-H‘), 3.28 (s, 3 H, 12-H), 2.69 (m, 1 H, 40-H), 2.64 (s, 3 H, 8-H), 2.51 (m, 1 H, 6-H), 1.96 (m, 1 H, 29-H), 1.61 (s, 3 H, 25-H), 1.55 (s, 3 H, 18-H), 1.13 (d, $^{3}J_{35,34}$ = 7.0 Hz, 3 H, 35-H), 0.99 (d, $^{3}J_{41,40}$ = 6.9 Hz, 3 H, 41-H), 0.80 (d, $^{3}J_{30,29}$ = 6.8 Hz, 3 H, 30-H).

Optical rotation: $[\alpha]_D^{20}$ = −105.9 (c = 1.0, CHCl$_3$)

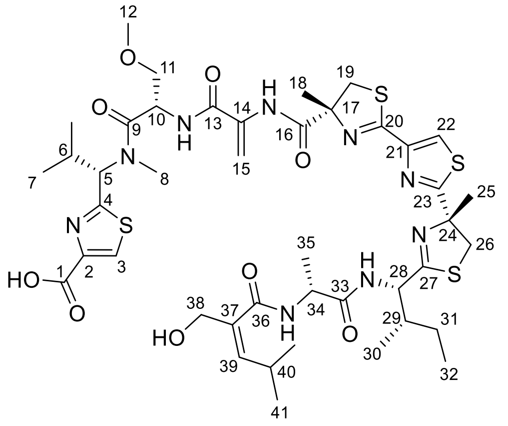
HRMS (ESI):	calculated	found
$C_{43}H_{60}N_9O_8S_4$ [M+H]$^+$:	958.3442	958.3438

Thiamyxin E

In a 1 mL glass vial, 0.40 M LiOH$_{aq}$ (24.8 µL, 9.91 µmol, 1.0 eq.) was added to a 0 °C cold solution of **thiamyxin A** (9.5 mg, 9.91 µmol) in THF (100 µL). The reaction mixture was stirred for 2 h while slowly reaching room temperature. After the addition of 0.10 M HCl$_{aq}$ (99.1 µL, 9.91 µmol, 1.0 eq.), the mixture was concentrated in vacuo and purified by preparative HPLC (H$_2$O:MeCN 40% to 90% MeCN) followed by lyophilization to give **thiamyxin E** (7.2 mg, 7.32 µmol, 73%, dr 92:8) as an amorphous solid.

(Preparative HPLC with 0.10% HCOOH$_{aq}$ led to a lower diastereomeric ratio of around 80:20.)

LC-MS: t$_R$ (thiamyxin E) = 2.84 min (long method)



thiamyxin E

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.30 (s, 1 H, 16-NH), 8.84 (d, $^3J_{NH,10}$ = 7.4 Hz, 1 H, 13-NH), 8.39 (s, 1 H, 3-H), 8.21 (m, 1 H, 33-NH), 8.19 (s, 1 H, 22-H), 7.87 (d, $^3J_{NH,34}$ = 7.6 Hz, 1 H, 36-NH), 6.38 (m, 1 H, 15-H), 5.78 (m, 1 H, 15-H‘), 5.44 (d, $^3J_{39,40}$ = 9.8 Hz, 1 H, 39-H), 5.39 (d, $^3J_{5,6}$ = 10.9 Hz, 1 H, 5-H), 4.90 (m, 1 H, 10-H), 4.57 (dd, $^3J_{28,NH}$ = 8.8 Hz, $^3J_{28,29}$ = 7.3 Hz, 1 H, 28-H), 4.44 (m, 1 H, 34-H), 4.02 (d, $^2J_{38,38'}$ = 12.8 Hz, 1 H, 38-H), 3.98 (d, $^2J_{38',38}$ = 12.8 Hz, 1 H, 38-H‘), 3.74 (d, $^2J_{19,19'}$ = 11.6 Hz, 1 H, 19-H), 3.64 – 3.59 (m, 2 H, 26-H, 26-H‘), 3.58 – 3.51 (m, 2 H, 11-H, 11-H‘), 3.39 (d, $^2J_{19',19}$ = 11.6 Hz, 1 H, 19-H‘), 3.19 (s, 3 H, 12-H), 2.92 (s, 3 H, 8-H), 2.80 (m, 1 H, 40-H), 2.46 (m, 1 H, 6-H), 1.92 (m, 1 H, 29-H), 1.63 (s, 3 H, 25-H), 1.52 (s, 3 H, 18-H), 1.51 (m, 1 H, 31-H), 1.25 (d, $^3J_{35,34}$ = 7.1 Hz, 3 H, 35-H), 1.19 (m, 1 H, 31-H‘), 0.94 – 0.87 (m, 9 H, 41-H, 41‘-H, 30-H), 0.86 – 0.80 (m, 6 H, 32-H, 7-H), 0.74 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7‘-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 176.3 (s, C-23), 173.8 (s, C-27), 172.7 (s, C-16), 172.2 (s, C-33), 170.1 (s, C-9), 167.8 (s, C-4), 167.5 (s, C-36), 163.3 (s, C-20), 163.1 (s, C-13), 162.1 (s, C-1), 147.7 (s, C-21), 147.0 (s, C-2), 139.8 (d, C-39), 134.4 (s, C-37), 133.3 (s, C-14), 129.1 (d, C-3), 122.3 (d, C-22), 103.1 (t, C-15), 85.0 (s, C-17), 83.3 (s, C-24), 70.8 (t, C-11), 63.2 (t, C-38), 59.8 (d, C-5), 58.3 (q, C-12), 55.2 (d, C-28), 50.0 (d, C-10), 48.2 (d, C-34), 43.3 (t, C-26), 40.4 (t, C-19), 37.3 (d, C-29), 29.9 (q, C-8), 27.9 (d, C-6), 27.4 (d, C-40), 27.0 (q, C-25), 24.9 (q, C-18), 24.3 (t, C-31), 22.8 (q, C-41), 22.7 (q, C-41‘), 20.0 (q, C-7), 18.9 (q, C-7‘), 18.7 (q, C-35), 15.6 (q, C-30), 10.9 (q, C-32).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.11 (d, $^3J_{NH,10}$ = 8.9 Hz, 1 H, 13-NH), 8.14 (s, 1 H, 22-H), 5.17 (ddd, $^3J_{10,NH}$ = 7.4 Hz, $^3J_{10,11}$ = 7.4 Hz, $^3J_{10,11'}$ = 7.4 Hz, 1 H, 10-H), 4.05 (d, $^2J_{38,38'}$ = 12.8 Hz, 1 H, 38-H), 3.26 (s, 3 H, 12-H), 2.69 (s, 3 H, 8-H), 1.57 (s, 3 H, 18-H), 1.55 (s, 3 H, 25-H), 0.70 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, 7-H).

Selected C-28 epimer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 4.77 (dd, $^3J_{28,NH}$ = 8.8 Hz, $^3J_{28,29}$ = 5.0 Hz, 1 H, 28-H), 4.51 (m, 1 H, 34-H), 1.29 (d, $^3J_{35,34}$ = 7.0 Hz, 3 H, 35-H).

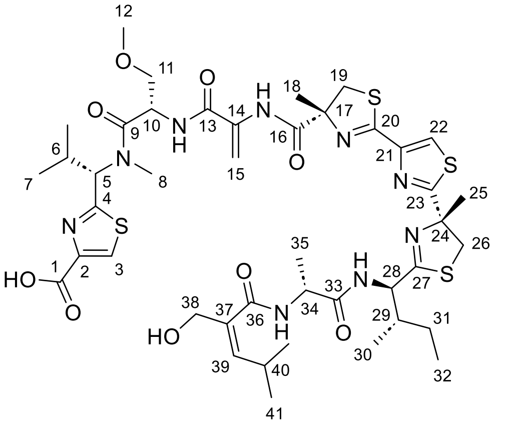
Optical rotation: $[\alpha]_D^{20}$ = −140.2 (c = 1.0, CHCl$_3$)

HRMS (ESI):	calculated	found
$C_{43}H_{62}N_9O_9S_4$ [M+H]$^+$:	976.3548	976.3580

Thiamyxin C

In a 1 mL glass vial, 0.40 M $LiOH_{aq}$ (21.1 µL, 8.44 µmol, 1.05 eq.) was added to a 0 °C cold solution of **thiamyxin B** (7.7 mg, 8.04 µmol) in THF (80 µL). The reaction mixture was stirred for 2 h while slowly reaching room temperature. After addition of 0.10 M HCl_{aq} (84 µL, 8.44 µmol, 1.05 eq.), the mixture was concentrated in vacuo and purified by preparative HPLC (H_2O:MeCN 40% to 90% MeCN) followed by lyophilization to give **thiamyxin C** (4.8 mg, 4.92 µmol, 61%, dr 95:5) as an amorphous solid.

LC-MS: t_R (thiamyxin C) = 2.86 min (long method)



Thiamyxin C

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.30 (s, 1 H, 16-NH), 8.85 (d, $^3J_{NH,10}$ = 7.4 Hz, 1 H, 13-NH), 8.34 (s, 1 H, 3-H), 8.22 (d, $^3J_{NH,28}$ = 8.9 Hz, 1 H, 33-NH), 8.20 (s, 1 H, 22-H), 7.90 (d, $^3J_{NH,34}$ = 7.5 Hz, 1 H, 36-NH), 6.38 (m, 1 H, 15-H), 5.78 (m, 1 H, 15-H'), 5.44 (dt, $^3J_{39,40}$ = 9.9 Hz, $^4J_{39,38}$ = 1.3 Hz, 1 H, 39-H), 5.39 (d, $^3J_{5,6}$ = 10.9 Hz, 1 H, 5-H), 4.89 (m, 1 H, 10-H), 4.77 (dd, $^3J_{28,NH}$ = 8.9 Hz, $^3J_{28,29}$ = 4.9 Hz, 1 H, 28-H), 4.51 (dq, $^3J_{34,NH}$ = 7.5 Hz, $^3J_{34,35}$ = 7.0 Hz, 1 H, 34-H), 3.99 (m, 2 H, 38-H), 3.75 (d, $^2J_{19,19'}$ = 11.6 Hz, 1 H, 19-H), 3.64 (d, $^2J_{26,26'}$ = 11.6 Hz, 1 H, 26-H), 3.60 (d, $^2J_{26',26}$ = 11.6 Hz, 1 H, 26-H'), 3.58 – 3.51 (m, 2 H, 11-H, 11-H'), 3.39 (d, $^2J_{19',19}$ = 11.6 Hz, 1 H, 19-H'), 3.19 (s, 3 H, 12-H), 2.93 (s, 3 H, 8-H), 2.83 (m, 1 H, 40-H), 2.46 (m, 1 H, 6-H), 2.00 (m, 1 H, 29-H), 1.64 (s, 3 H, 25-H), 1.53 (s, 3 H, 18-H), 1.37 (m, 1 H, 31-H), 1.29 (d, $^3J_{35,34}$ = 7.0 Hz, 3 H, 35-H), 1.19 (m, 1 H, 31-H'), 0.95 – 0.89 (m, 9 H, 30-H, 41-H, 41'-H), 0.86 (t, $^3J_{32,31}$ = 7.4 Hz, 3 H, 32-H), 0.83 (d, $^3J_{7,6}$ = 6.3 Hz, 3 H, 7-H), 0.74 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H).

^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 176.7 (s, C-23), 175.4 (s, C-27), 172.8 (s, C-16), 172.6 (s, C-33), 170.1 (s, C-9), 168.9 (s, C-4), 167.6 (s, C-36), 163.4 (s, C-20), 163.1 (s, C-13), 162.2 (s, C-1), 147.7 (s, s, C-2, C-21), 139.6 (d, C-39), 134.5 (s, C-37), 133.2 (s, C-14), 128.7 (d, C-3), 122.2 (d, C-22), 103.0 (t, C-15), 85.0 (s, C-17), 83.7 (s, C-24), 70.8 (t, C-11), 63.1 (t, C-38), 59.7 (d, C-5), 58.3 (q, C-12), 54.2 (d, C-28), 50.0 (d, C-10), 47.8 (d, C-34), 43.1 (t, C-26), 40.4 (t, C-19), 37.6 (d, C-29), 29.9 (q, C-8), 27.9 (d, C-6), 27.5 (q, C-25), 27.3 (d, C-40), 25.7 (t, C-31), 25.0 (q, C-18), 22.80 (q, C-41), 22.76 (q, C-41‘), 20.0 (q, C-7), 18.9 (q, C-7‘), 18.4 (q, C-35), 14.4 (q, C-30), 11.3 (q, C-32).

Selected rotamer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.12 (d, $^3J_{\mathrm{NH},10}$ = 8.9 Hz, 1 H, 13-NH), 8.17 (s, 1 H, 22-H), 5.18 (ddd, $^3J_{10,\mathrm{NH}}$ = 7.3 Hz, $^3J_{10,11}$ = 7.3 Hz, $^3J_{10,11'}$ = 7.3 Hz, 1 H, 10-H), 4.73 (dd, $^3J_{28,\mathrm{NH}}$ = 8.9 Hz, $^3J_{28,29}$ = 5.2 Hz, 1 H, 28-H), 3.44 (d, $^2J_{19',19}$ = 11.6 Hz, 1 H, 19-H‘), 3.26 (s, 3 H, 12-H), 2.70 (s, 3 H, 8-H), 1.58 (s, 3 H, 18-H), 1.56 (s, 3 H, 25-H), 0.69 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, 7-H).

Selected C-28 epimer signals:

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 4.57 (dd, $^3J_{28,\mathrm{NH}}$ = 8.5 Hz, $^3J_{28,29}$ = 7.8 Hz, 1 H, 28-H), 4.44 (m, 1 H, 34-H), 3.76 (d, $^2J_{19,19'}$ = 11.6 Hz, 1 H, 19-H).

Optical rotation:	$[\alpha]_D^{20}$ = –130.2 (c = 0.5, CHCl$_3$)	
HRMS (ESI):	calculated	found
$C_{43}H_{62}N_9O_9S_4$ [M+H]$^+$:	976.3548	976.3572

7. Literature

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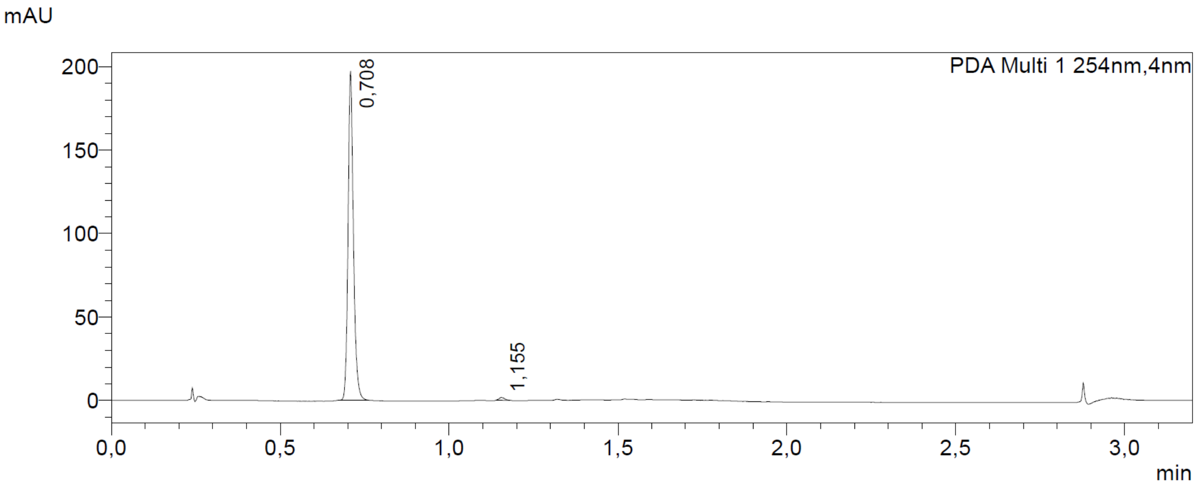
8. Appendix

8.1 HPLC-Chromatograms of the Target Compounds

Simplified dehydrosocein 119

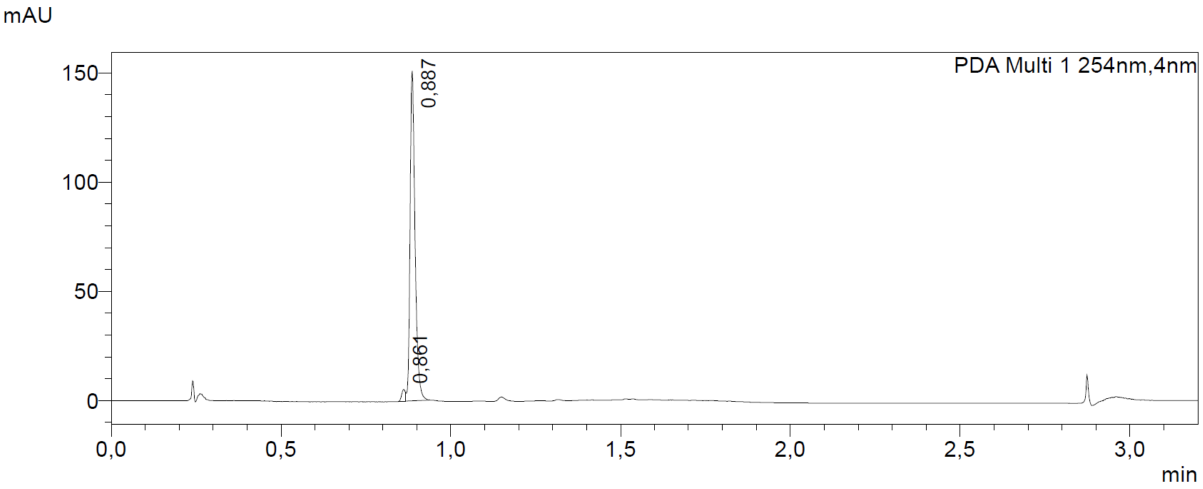


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	0,708	99,105
2	1,155	0,895
Total		100,000

Simplified dehydrosocein 120

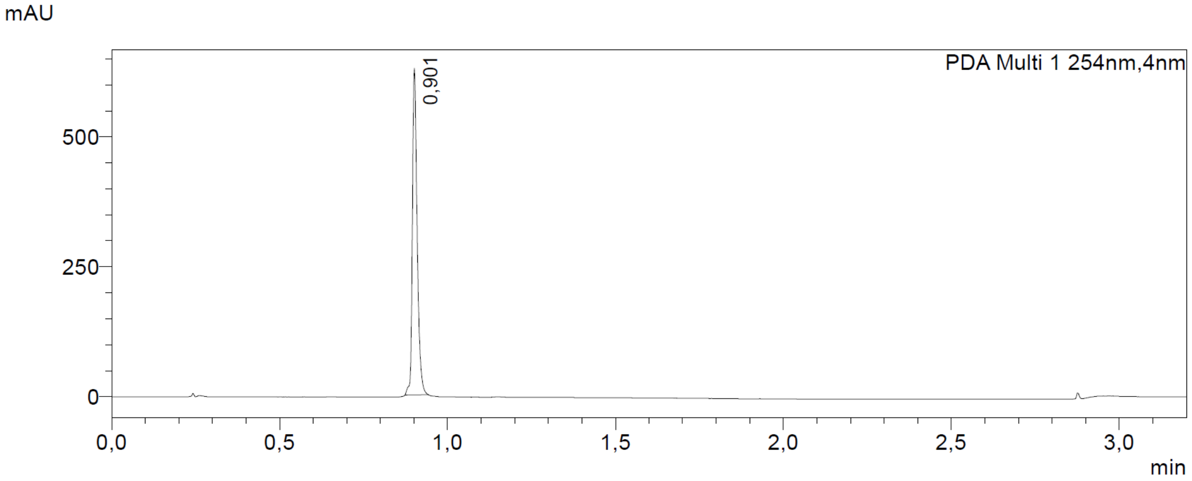


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	0,861	2,454
2	0,887	97,546
Total		100,000

Simplified dehydrosocein 127

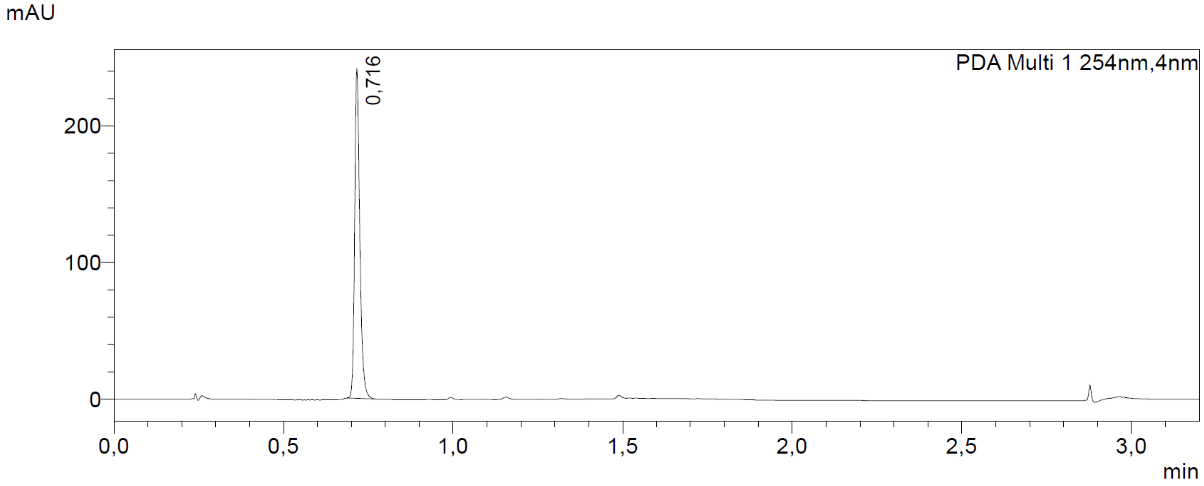


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	0,901	100,000
Total		100,000

Simplified dehydrosocein 128

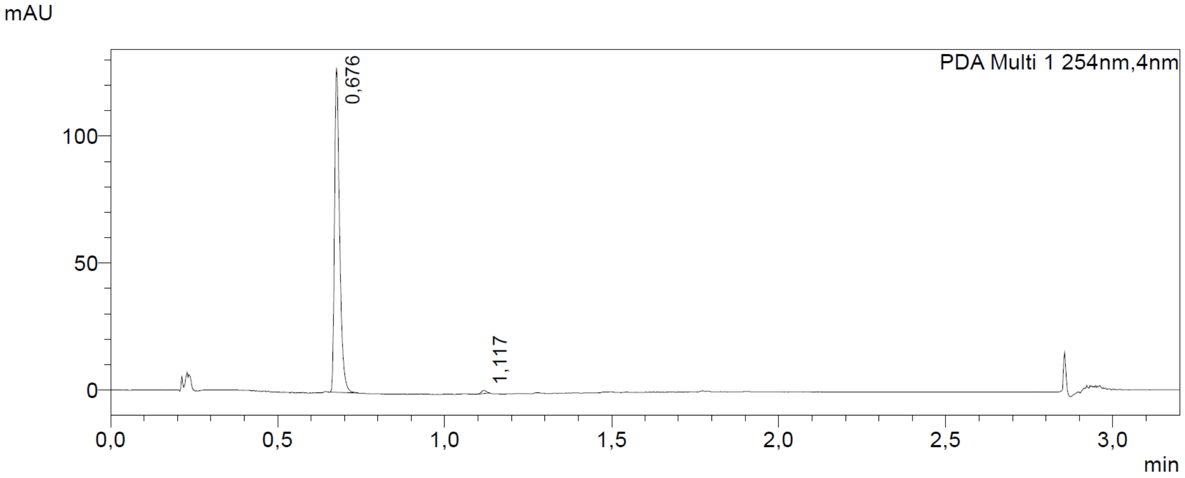


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	0,716	100,000
Total		100,000

Simplified dehydrosocein 129

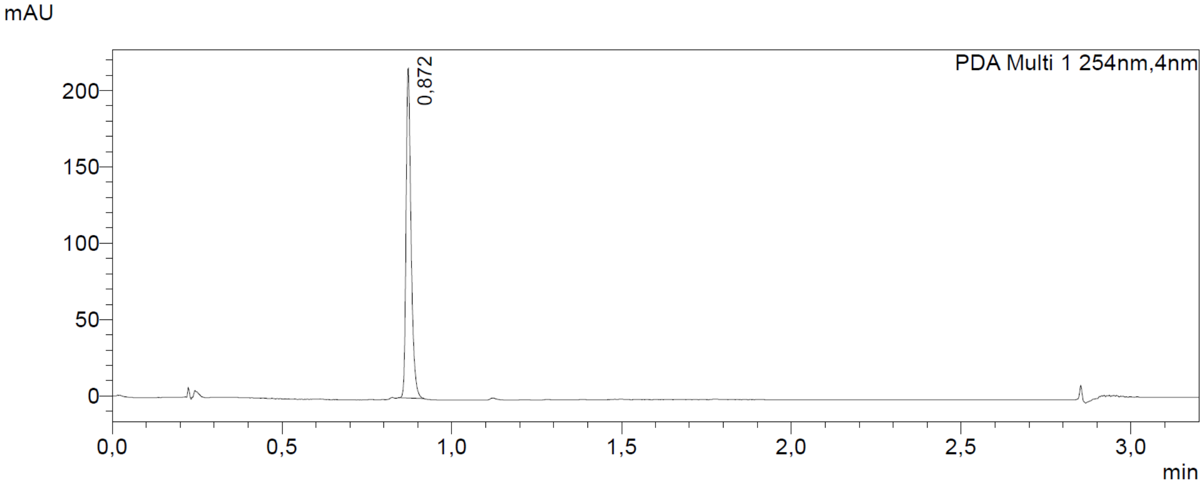


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	0,676	99,041
2	1,117	0,959
Total		100,000

Simplified dehydrosocein 130

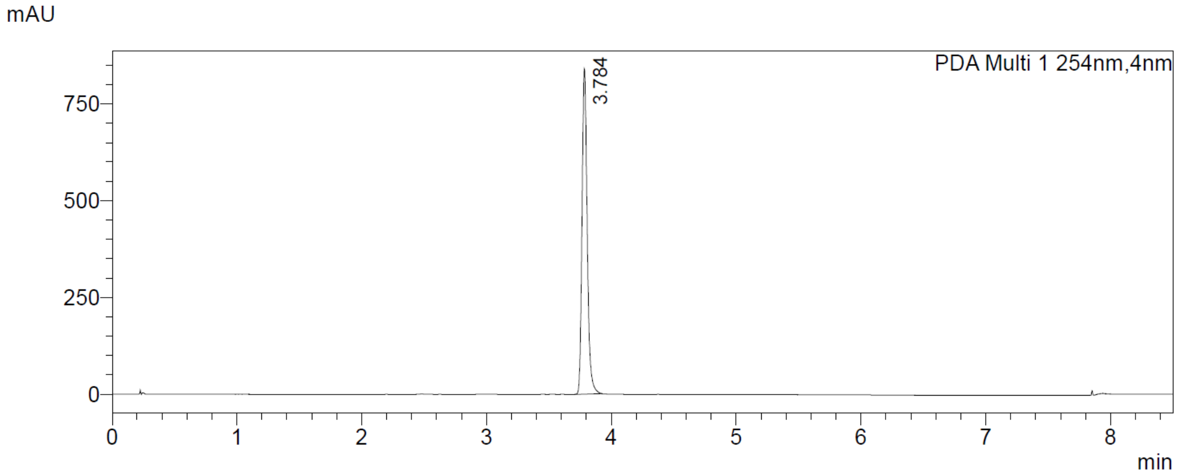


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	0,872	100,000
Total		100,000

Thiamyxin A

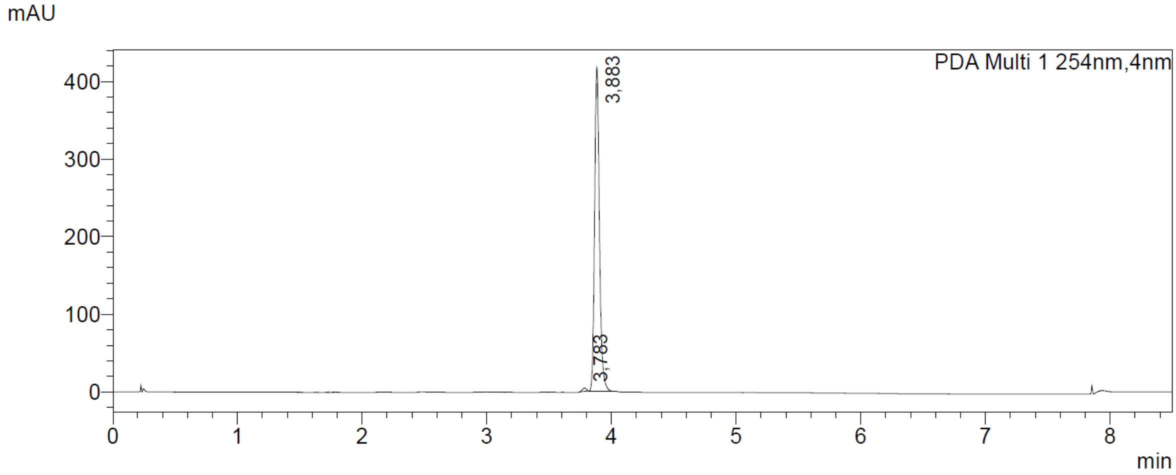


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	3.784	100.000
Total		100.000

Thiamyxin B

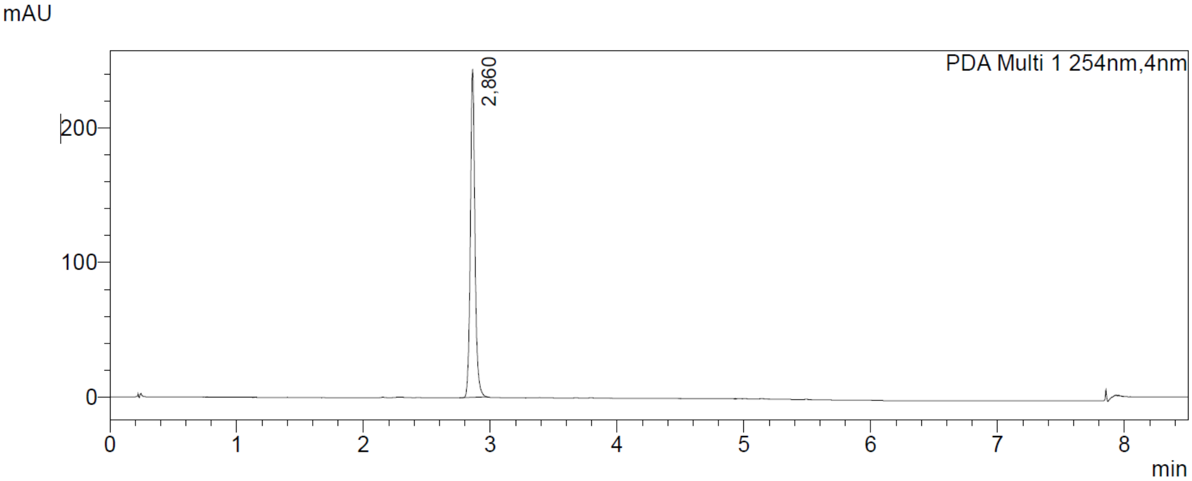


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	3,783	0,887
2	3,883	99,113
Total		100,000

Thiamyxin C

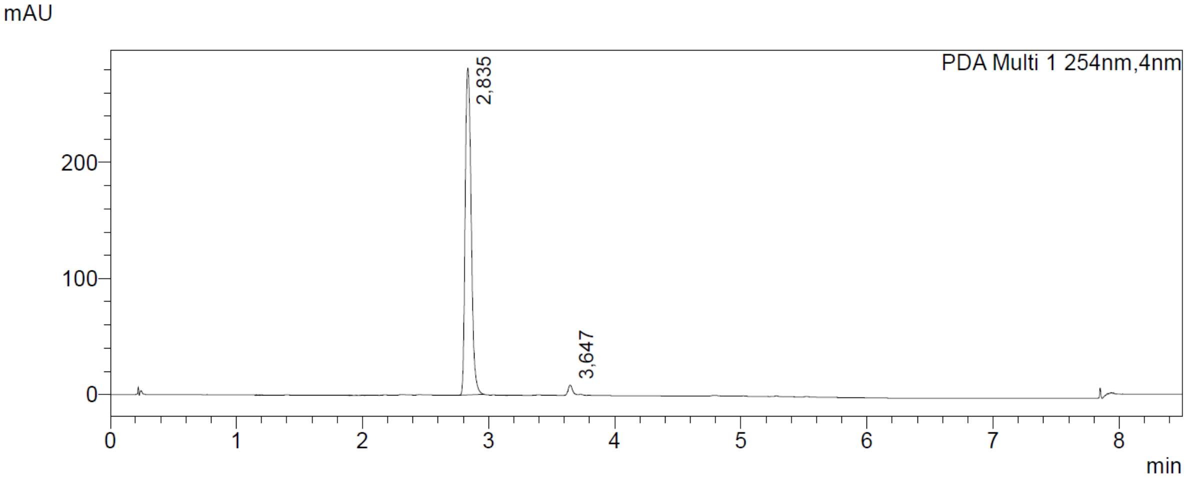


Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	2,860	100,000
Total		100,000

Thiamyxin E



Peak Table

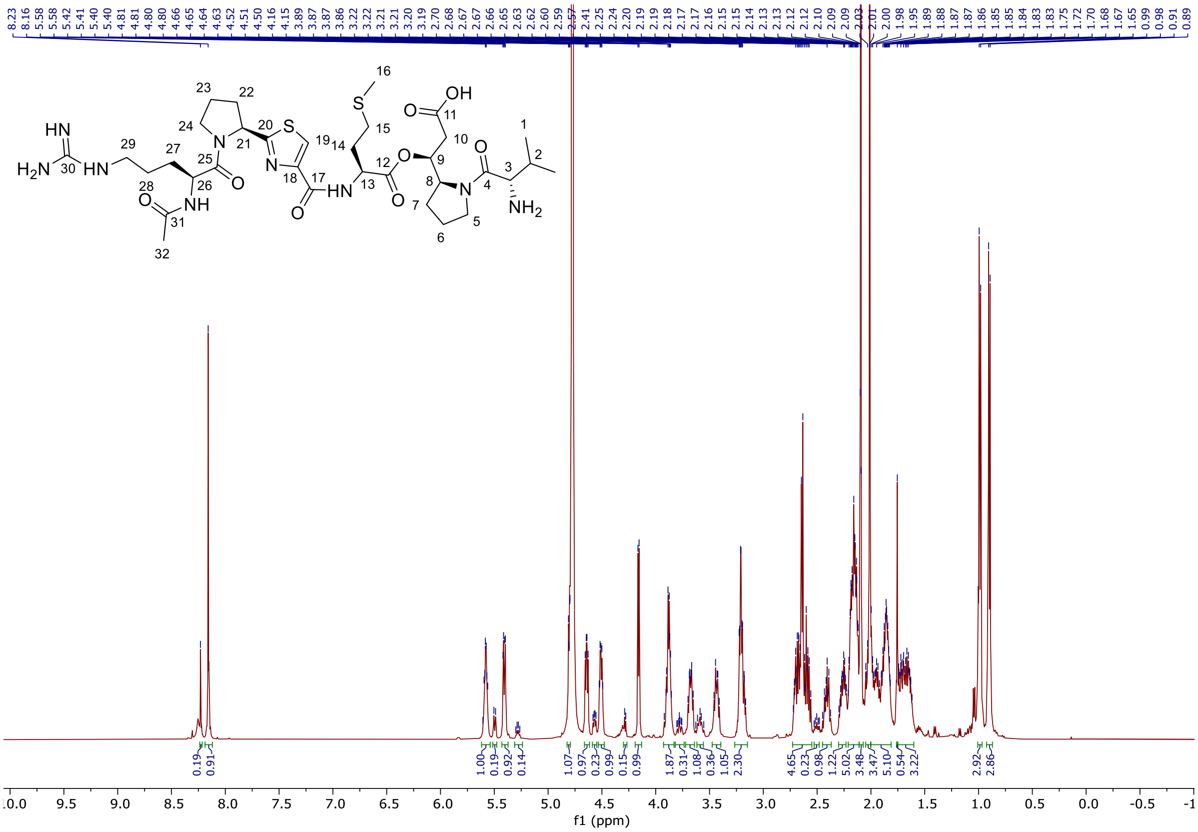
PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	2,835	99,133
2	3,647	0,867
Total		100,000

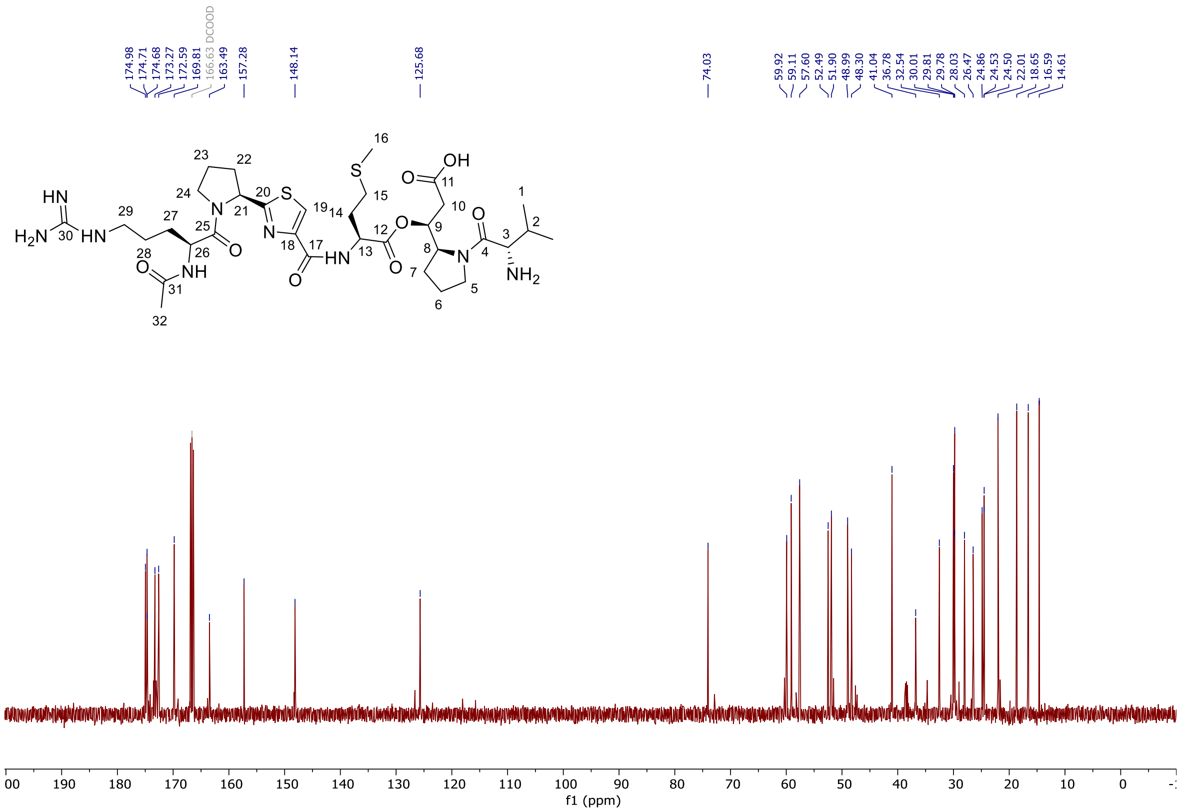
8.2 NMR-Spectra of the Target Compounds

Pseudotetraivprolid D

^{1}H-NMR (500 MHz, D_2O):

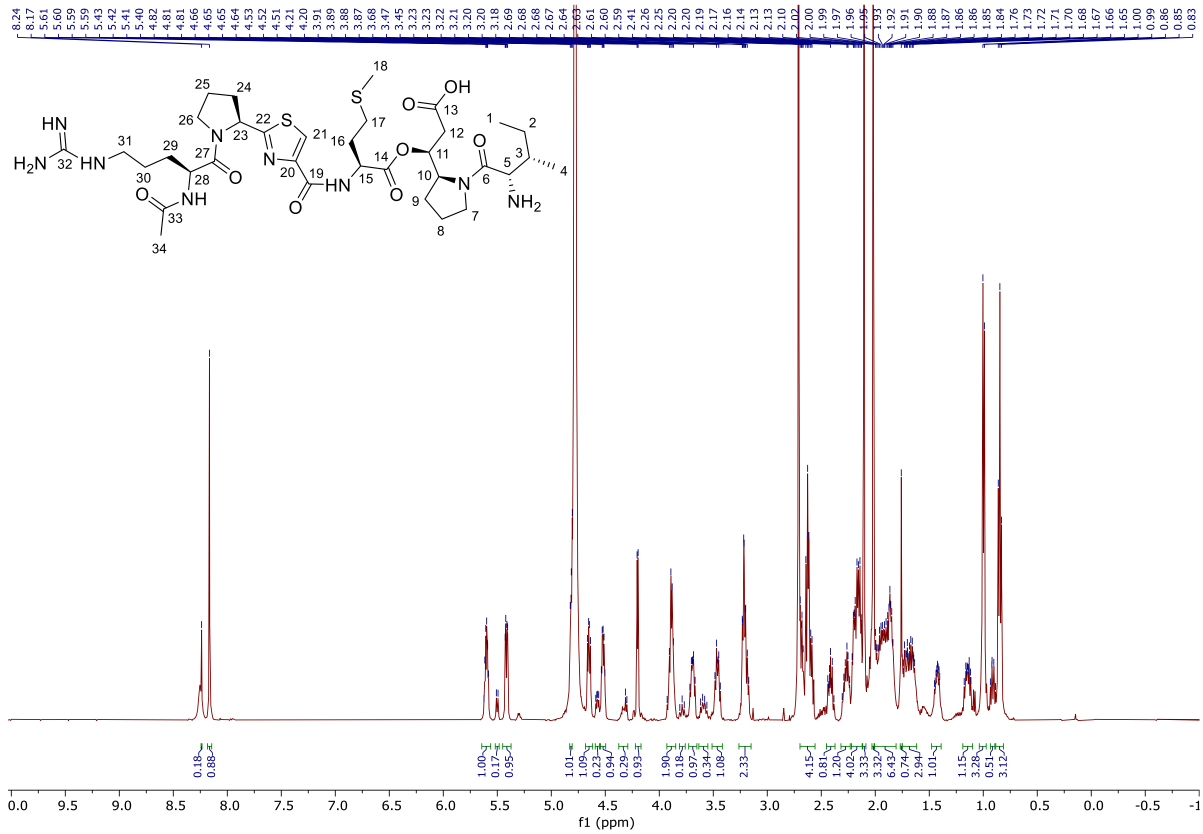


^{13}C-NMR (125 MHz, D_2O):

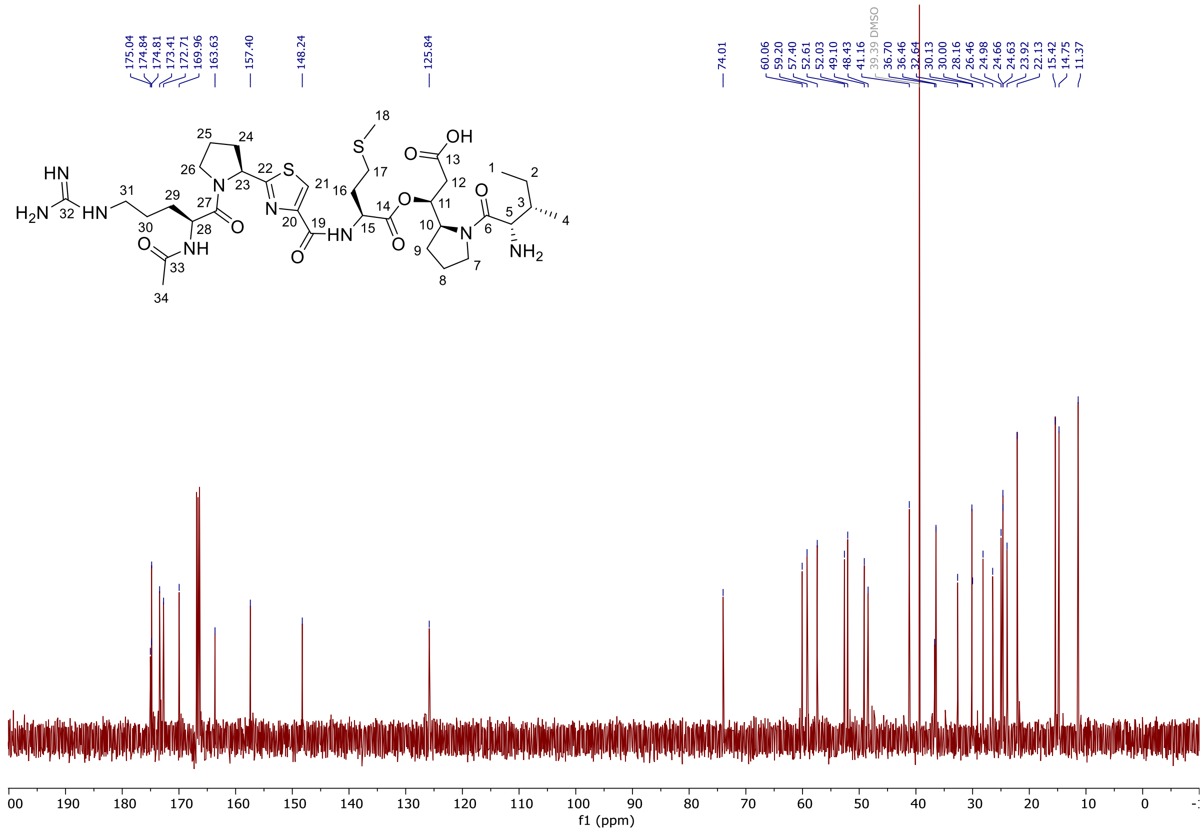


Pseudotetraivprolid B

^{1}H-NMR (500 MHz, D_2O):

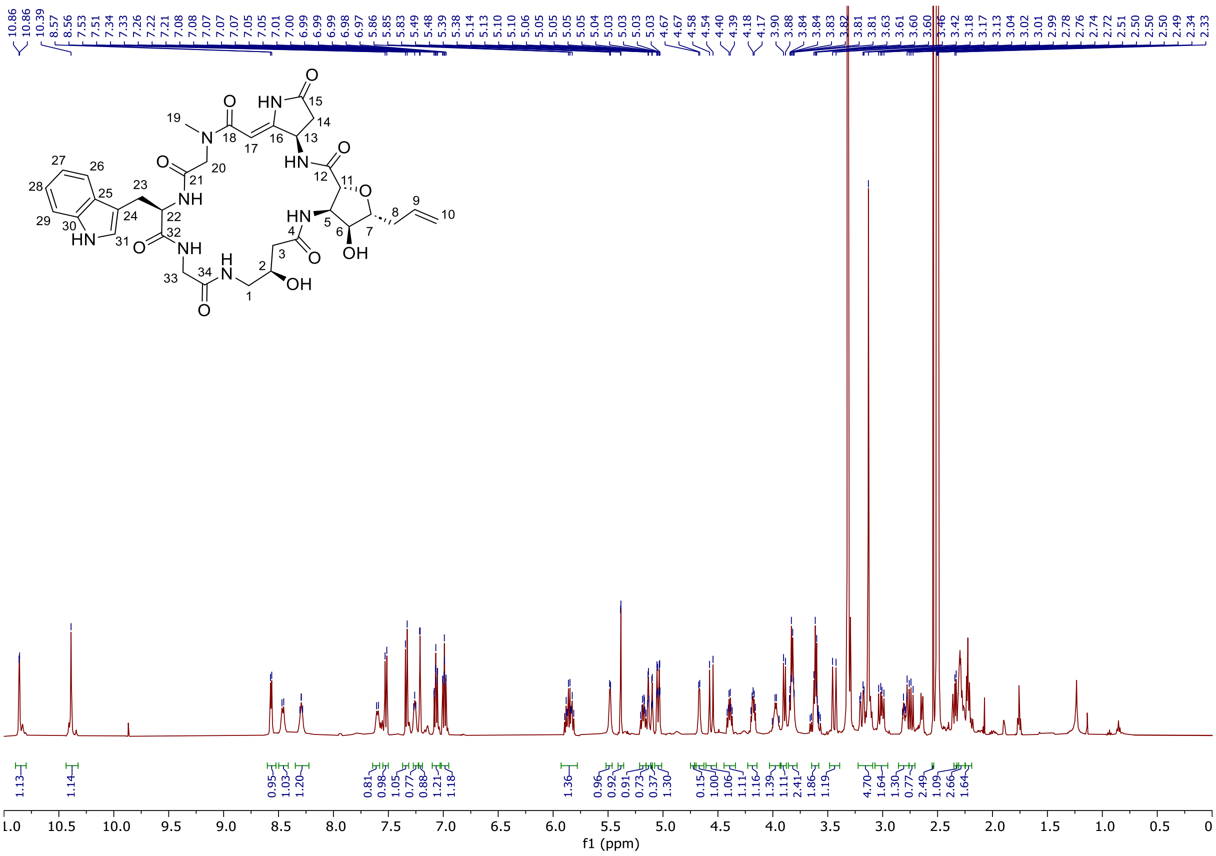


^{13}C-NMR (125 MHz, D_2O):

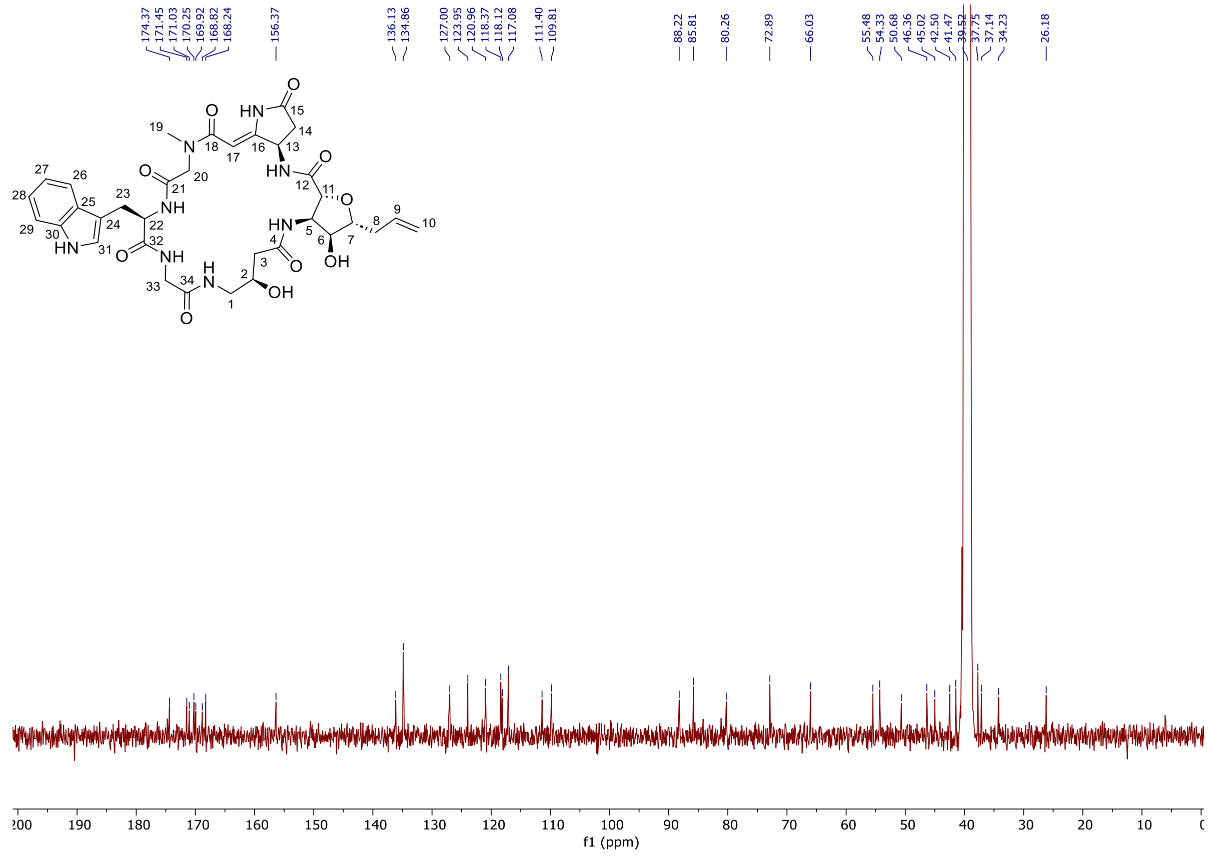


Simplified dehydrosocein 119

^{1}H-NMR (500 MHz, DMSO-d$_6$):

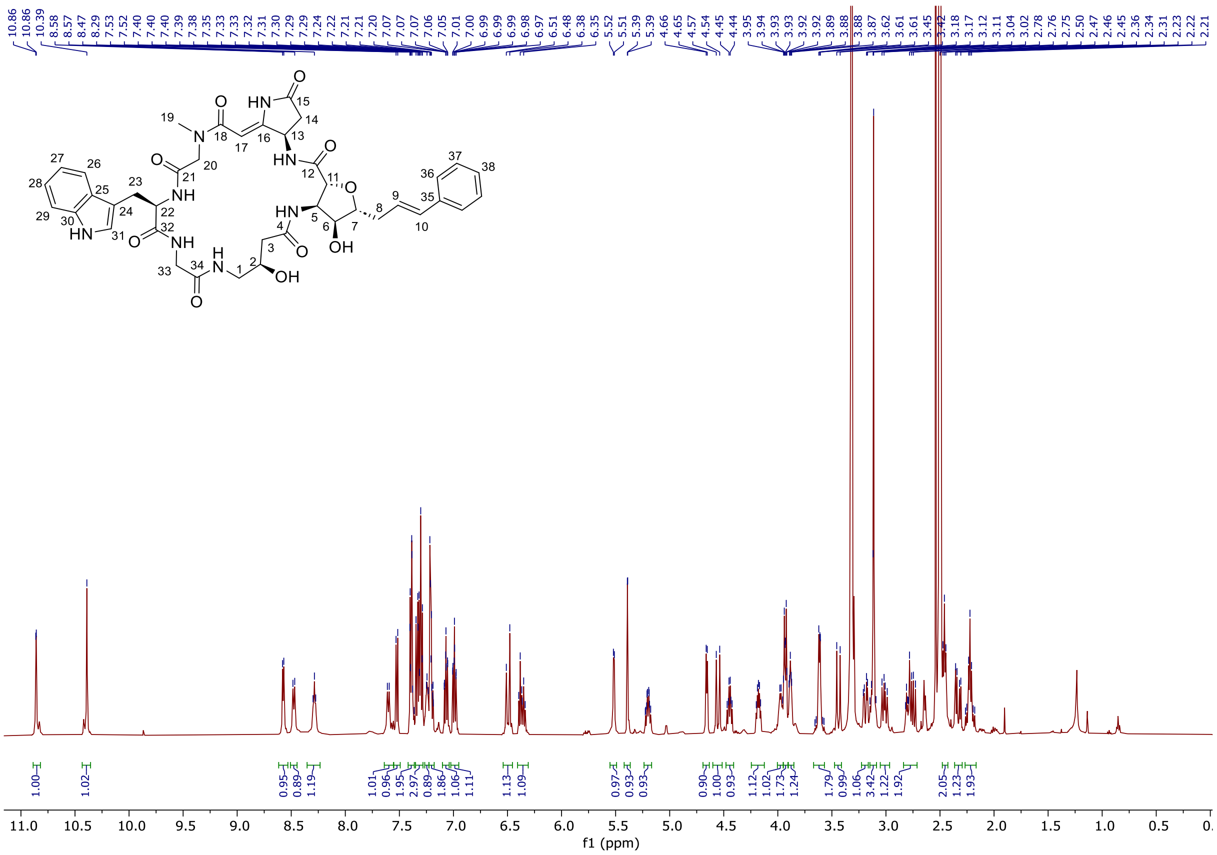


^{13}C-NMR (125 MHz, DMSO-d$_6$):

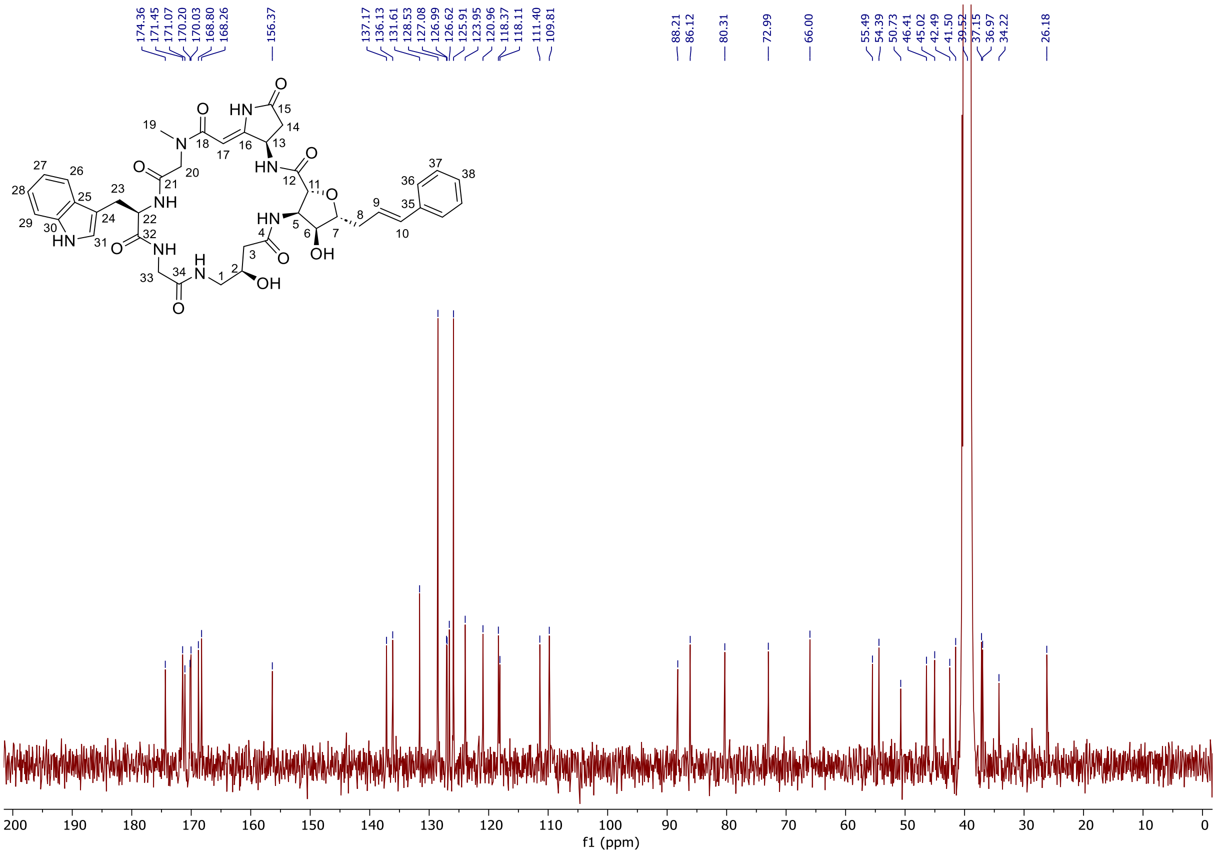


Simplified dehydrosocein 120

¹H-NMR (500 MHz, DMSO-d$_6$):

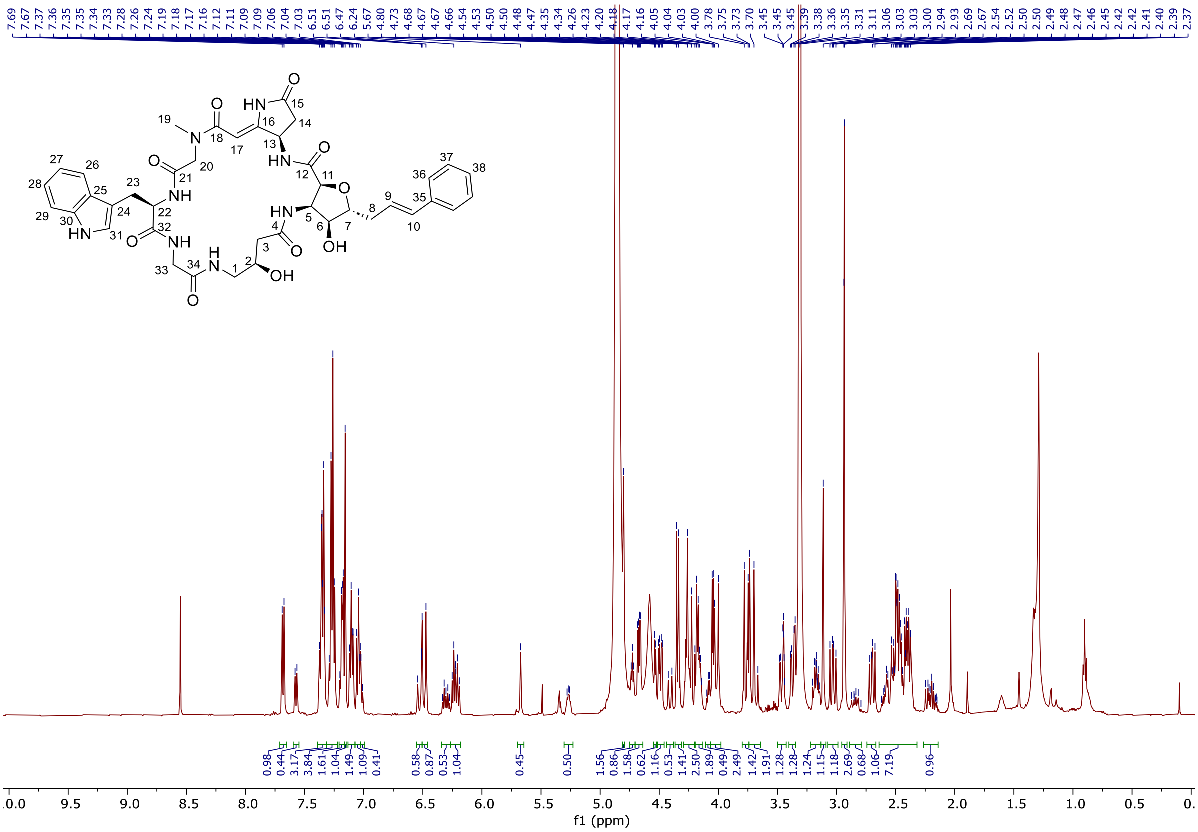


¹³C-NMR (125 MHz, DMSO-d$_6$):

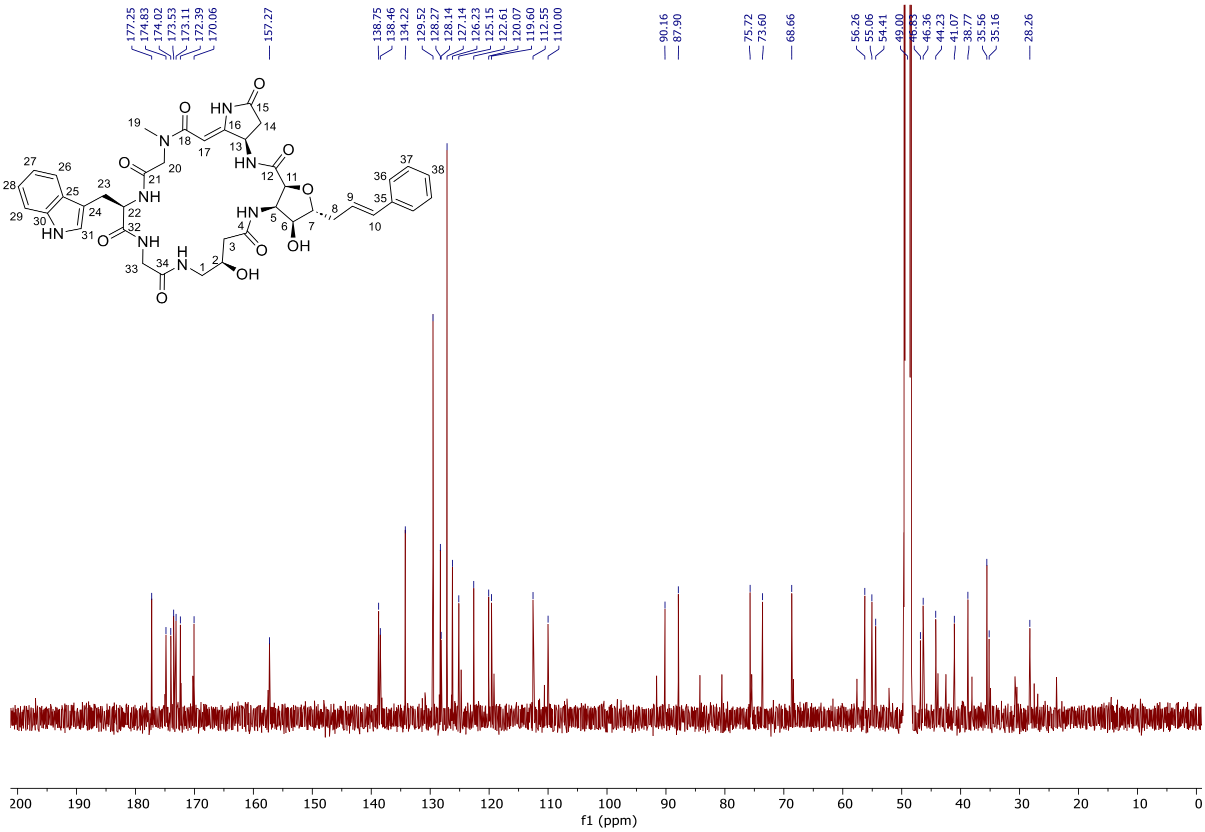


Simplified dehydrosocein 127

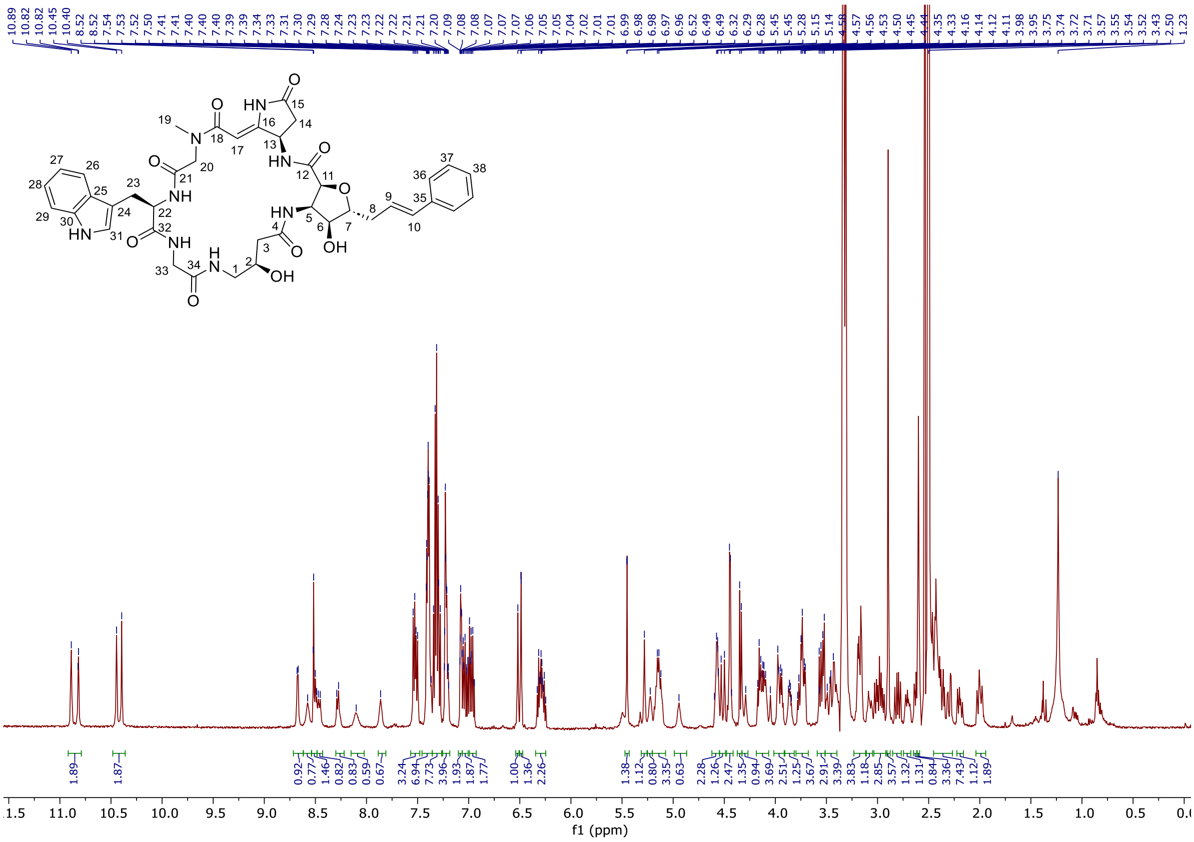
^{1}H-NMR (500 MHz, MeOD-d$_4$): (2:1 rotamers)



^{13}C-NMR (125 MHz, MeOD-d$_4$): (2:1 rotamers)

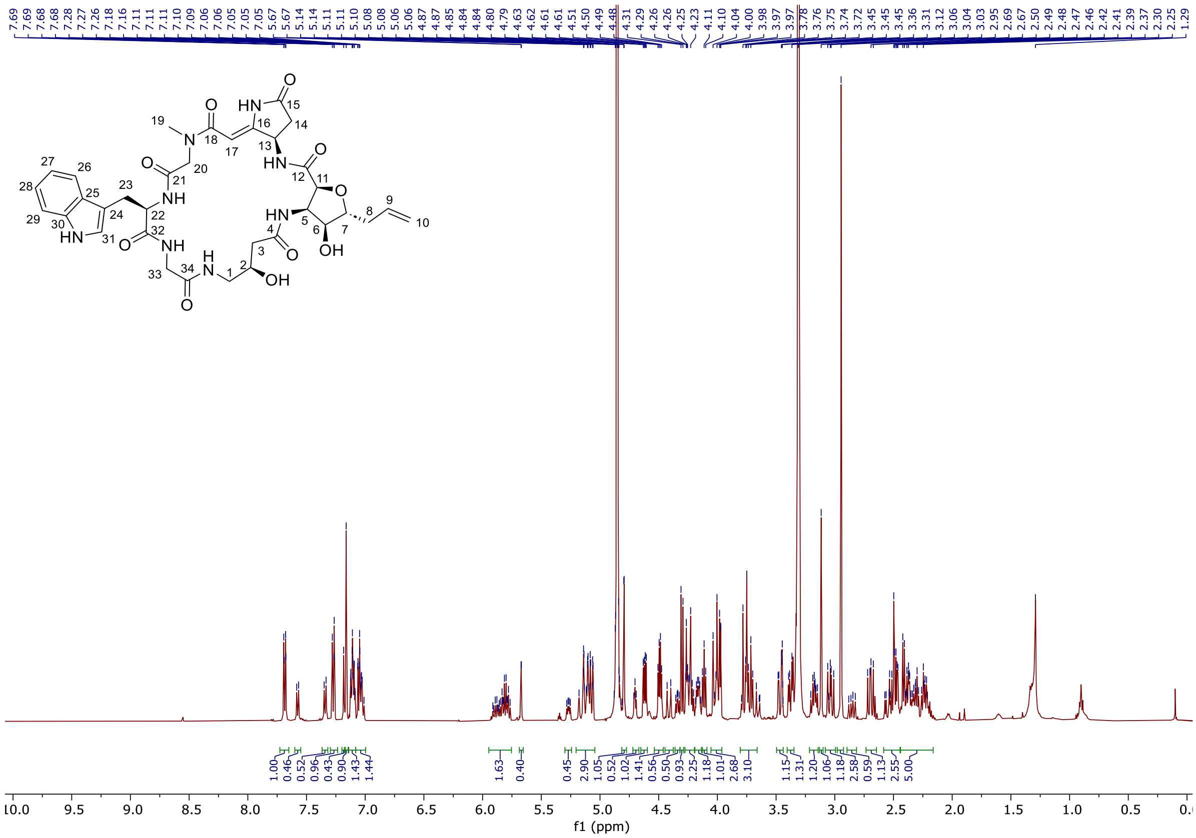


^{1}H-NMR (500 MHz, DMSO-d$_6$): (1:1 rotamers)

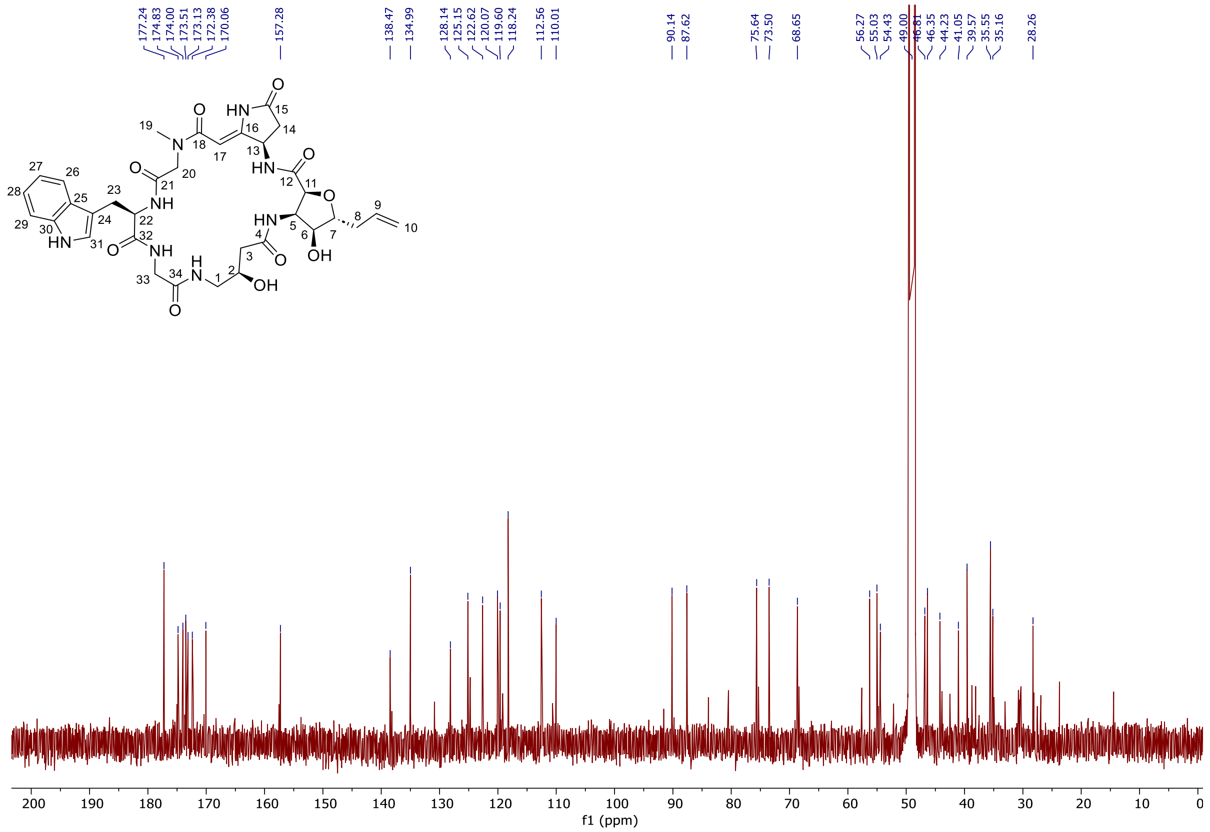


Simplified dehydrosocein 128

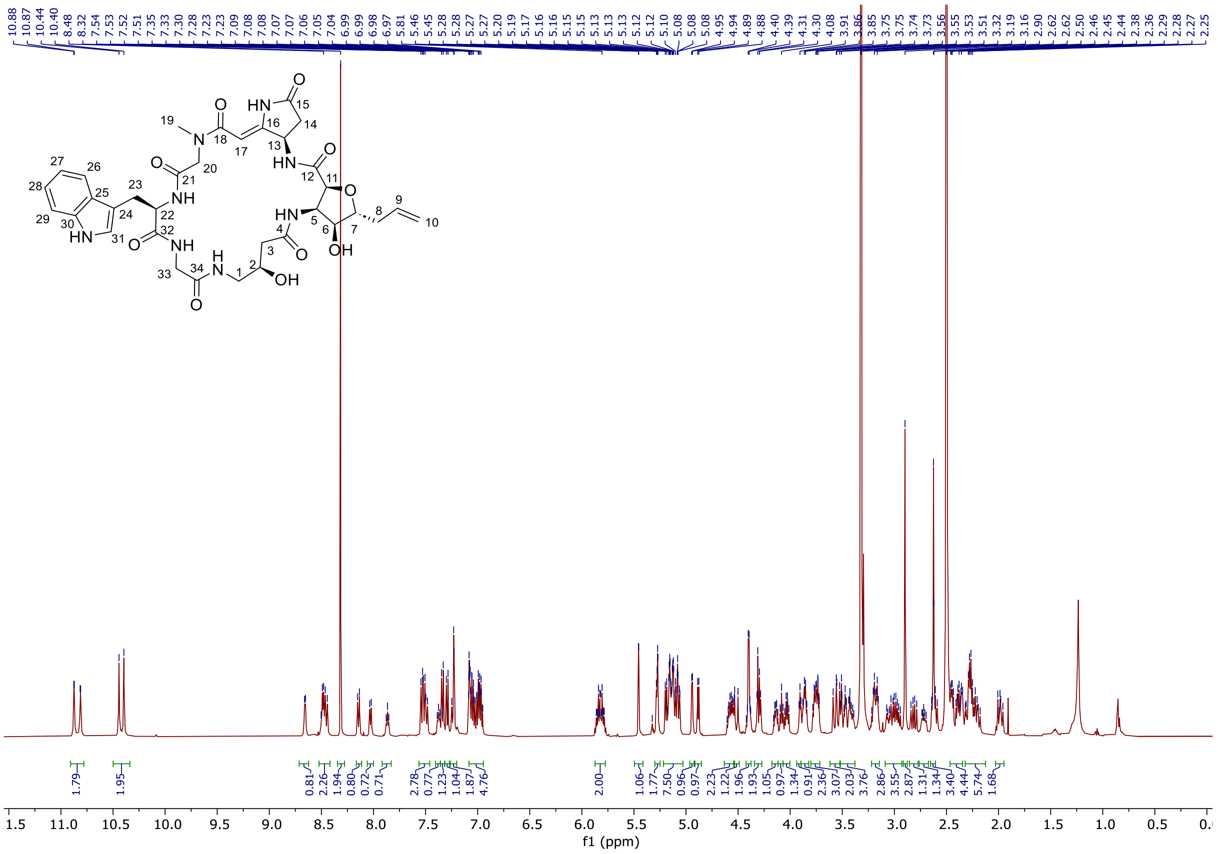
^{1}H-NMR (500 MHz, MeOD-d$_4$): (2:1 rotamers)



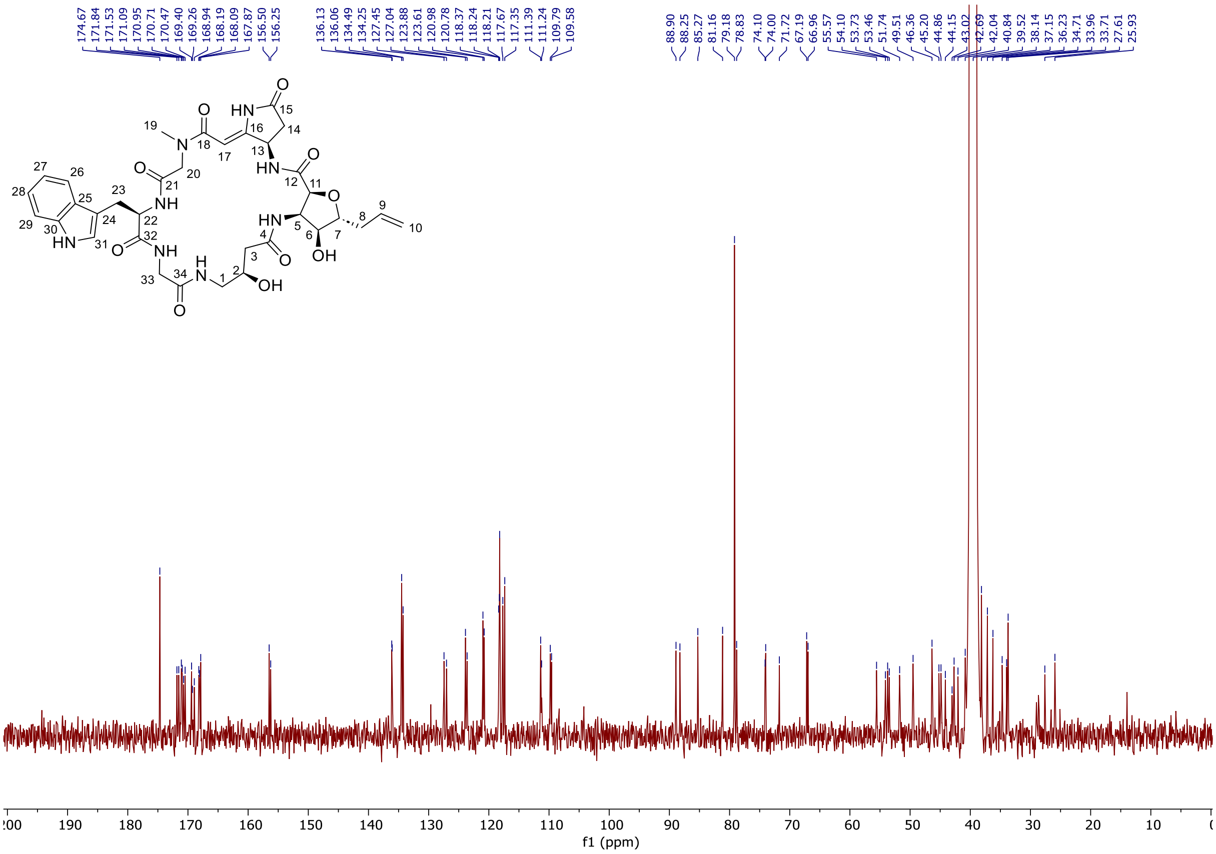
^{13}C-NMR (125 MHz, MeOD-d$_4$): (2:1 rotamers)



^{1}H-NMR (500 MHz, DMSO-d$_6$): (1:1 rotamers)

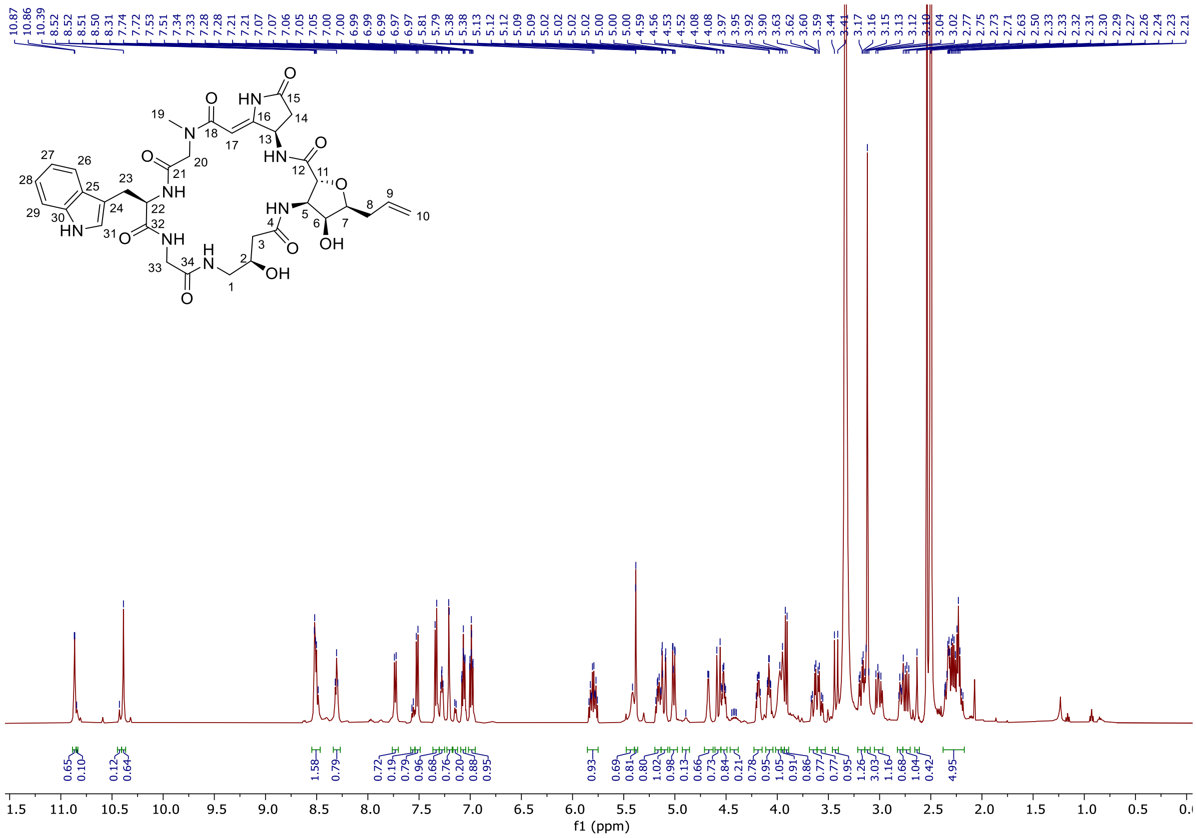


^{13}C-NMR (125 MHz, DMSO-d$_6$): (1:1 rotamers)

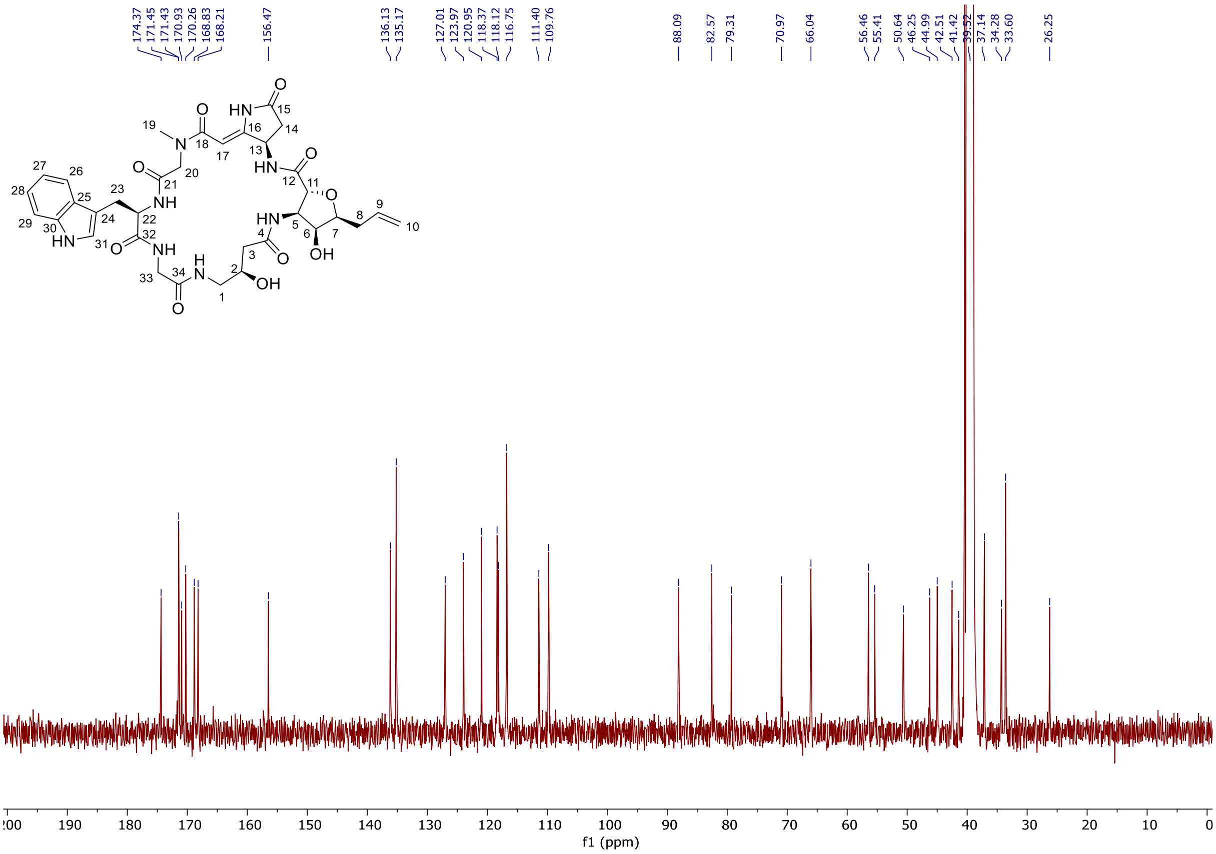


Simplified dehydrosocein 129

^{1}H-NMR (500 MHz, DMSO-d$_6$): (rotamers 8:2)

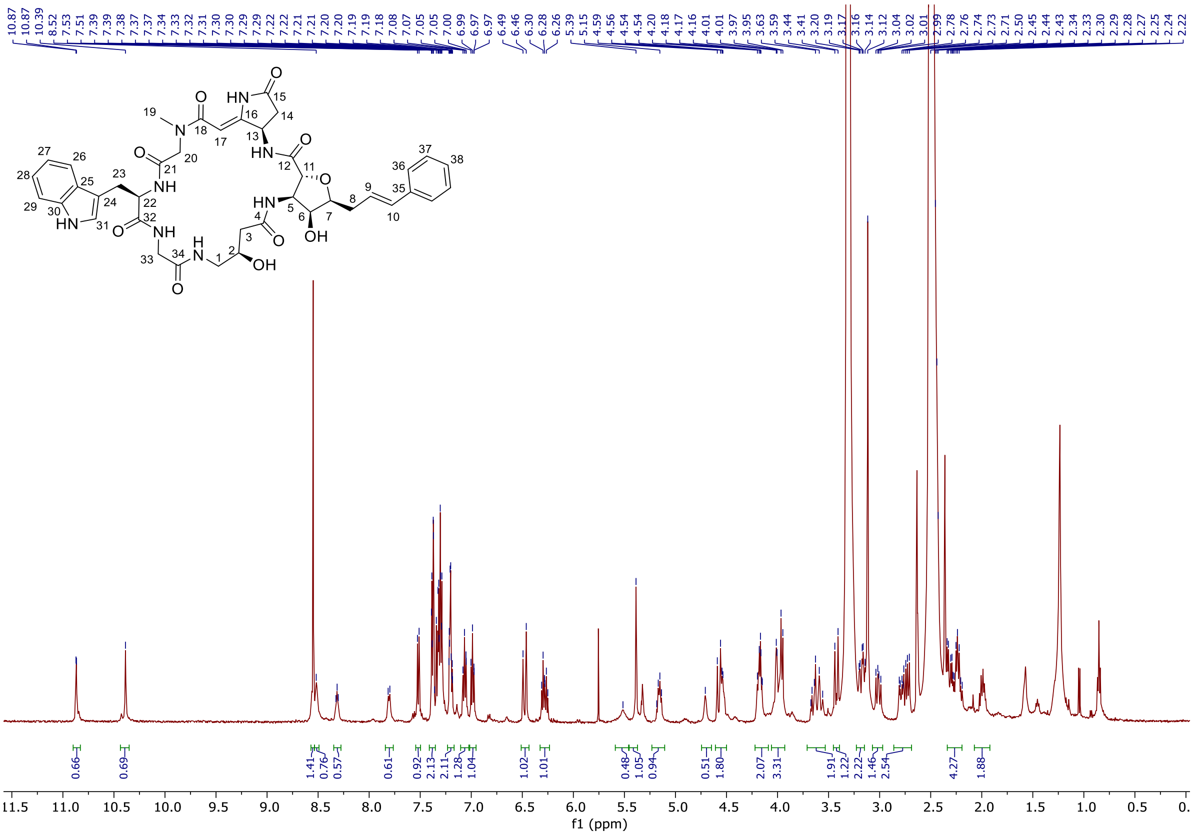


^{13}C-NMR (125 MHz, DMSO-d$_6$):

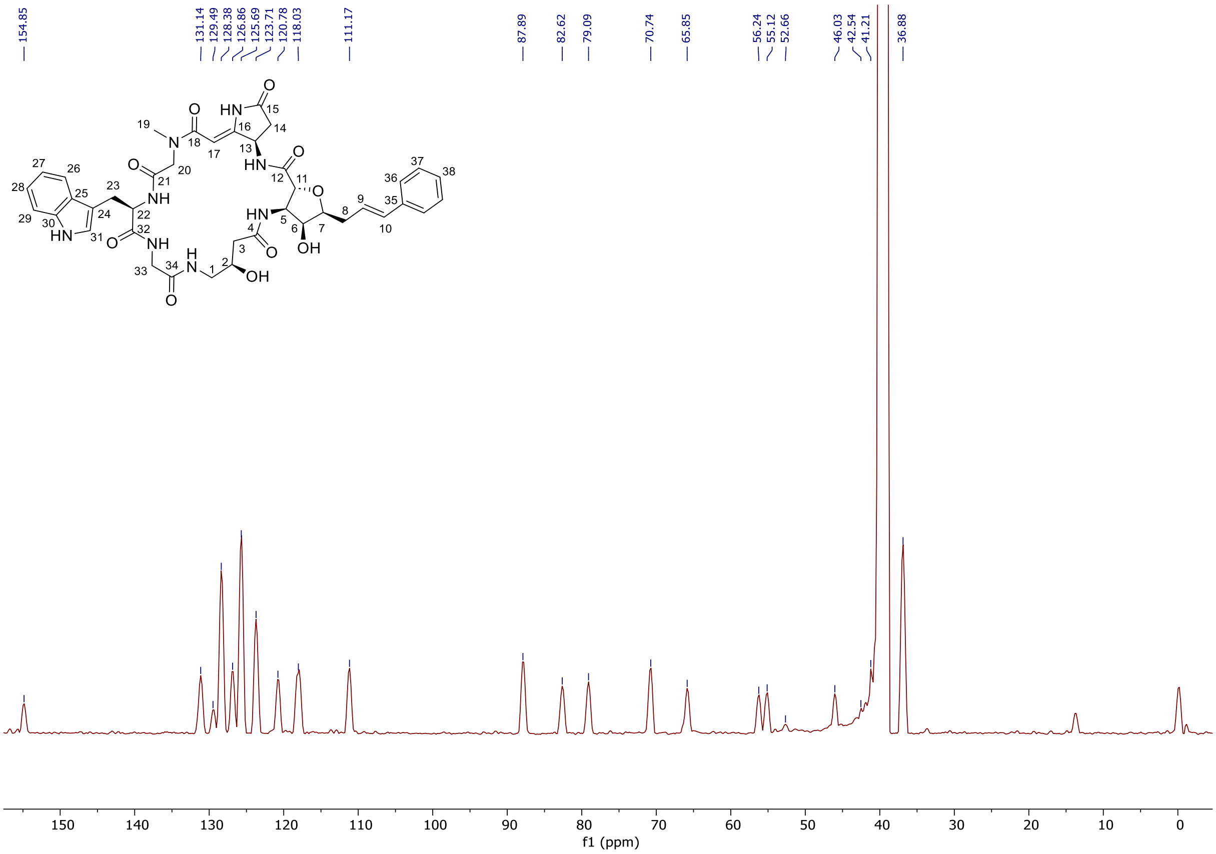


Simplified dehydrosocein 130

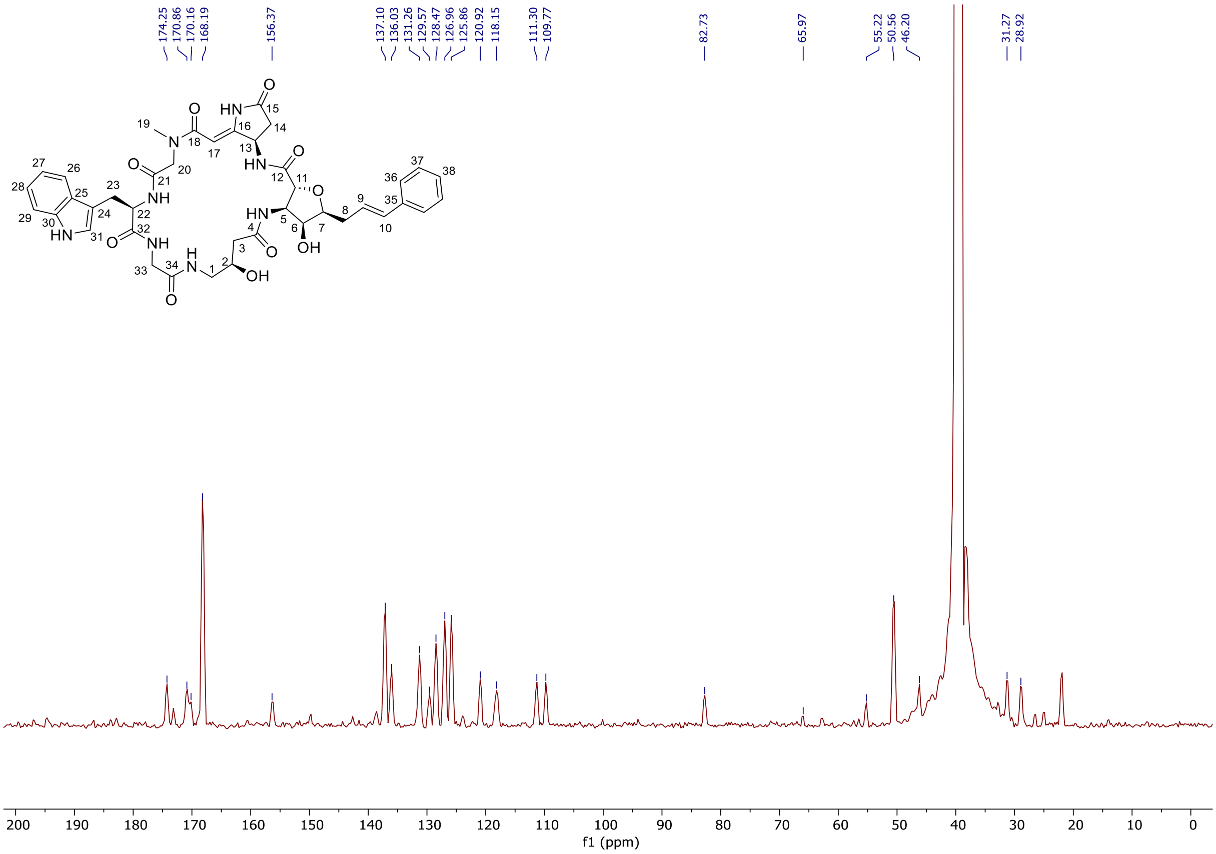
^{1}H-NMR (500 MHz, DMSO-d$_6$):



HSQCED-1D-projektion (125 MHz, DMSO-d$_6$):

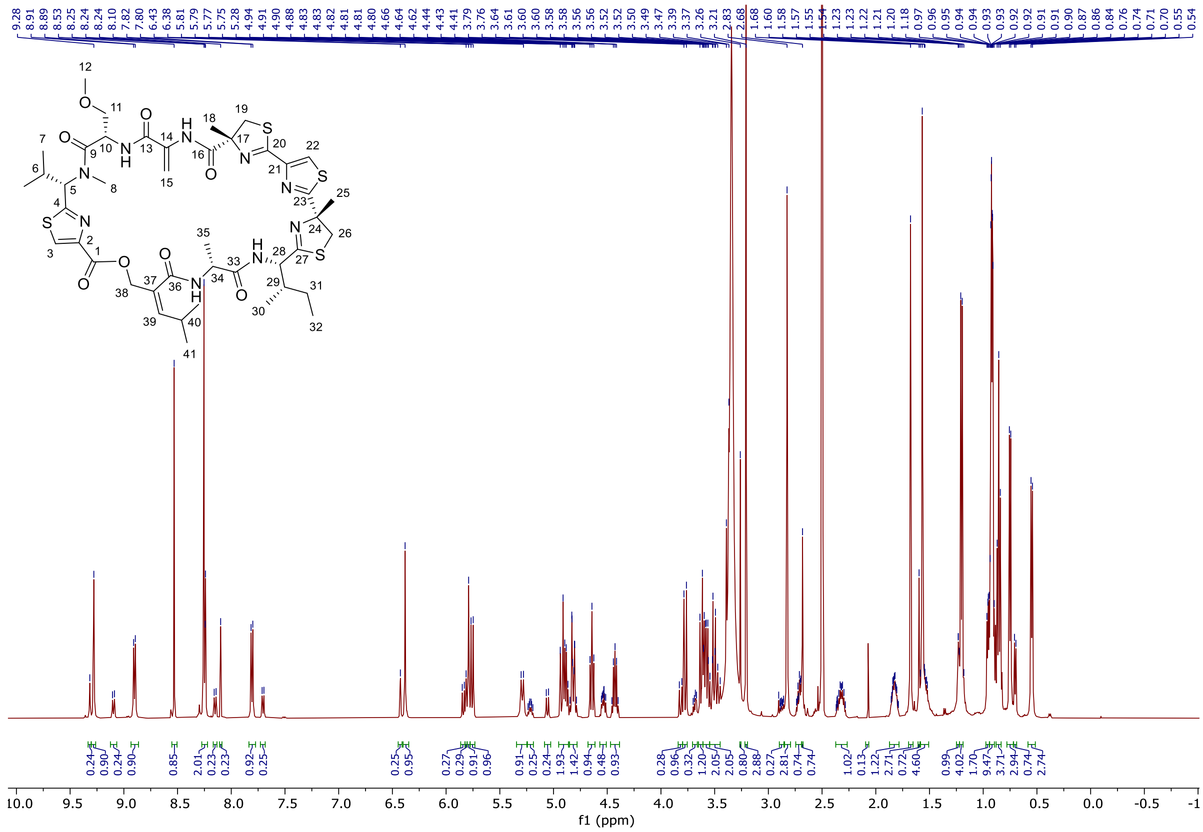


HMBC-1D-projektion (125 MHz, DMSO-d$_6$):

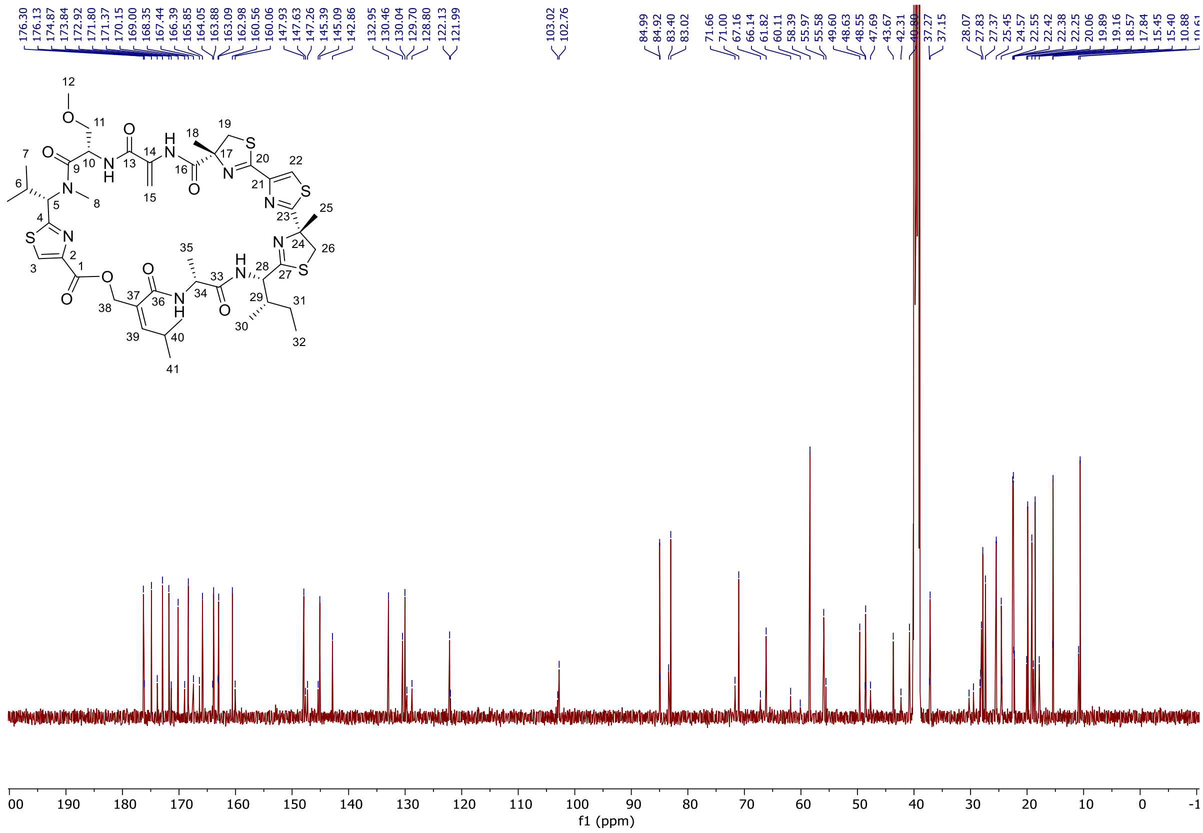


Thiamyxin A

^{1}H-NMR (500 MHz, DMSO-d$_6$):

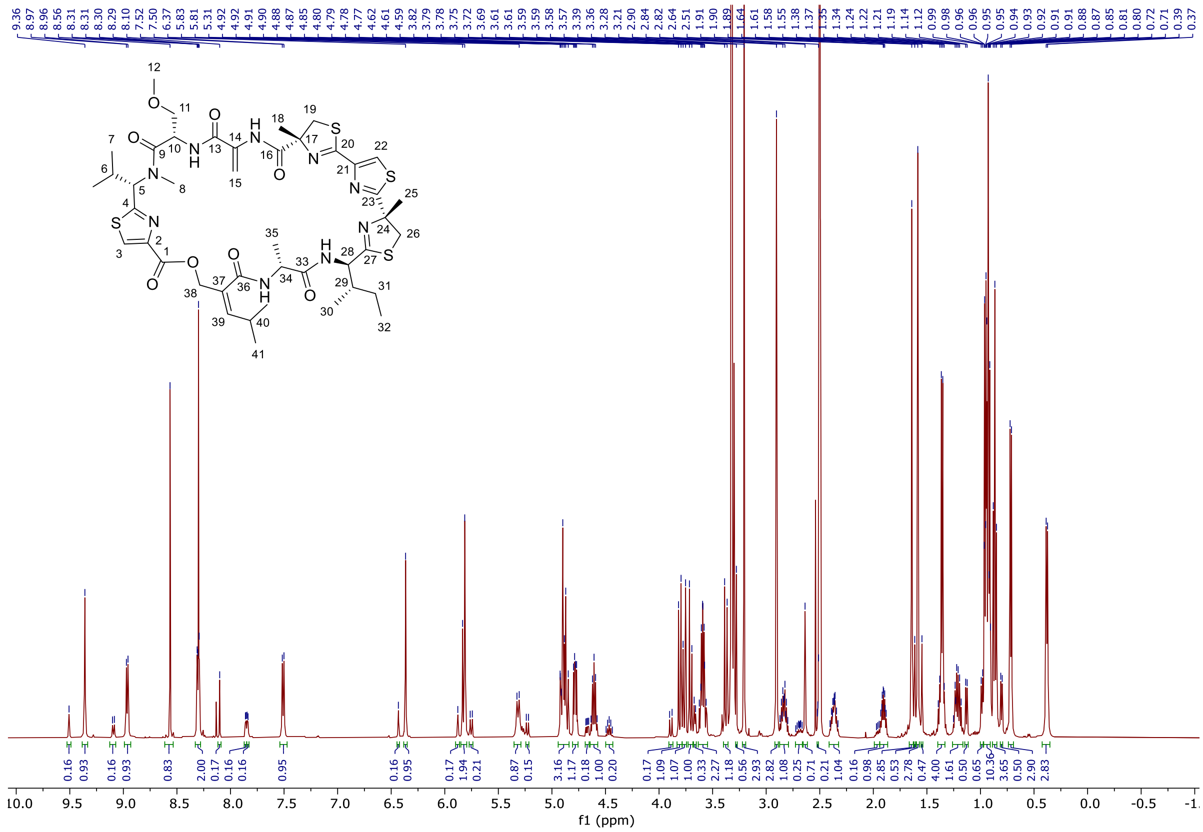


^{13}C-NMR (125 MHz, DMSO-d$_6$):

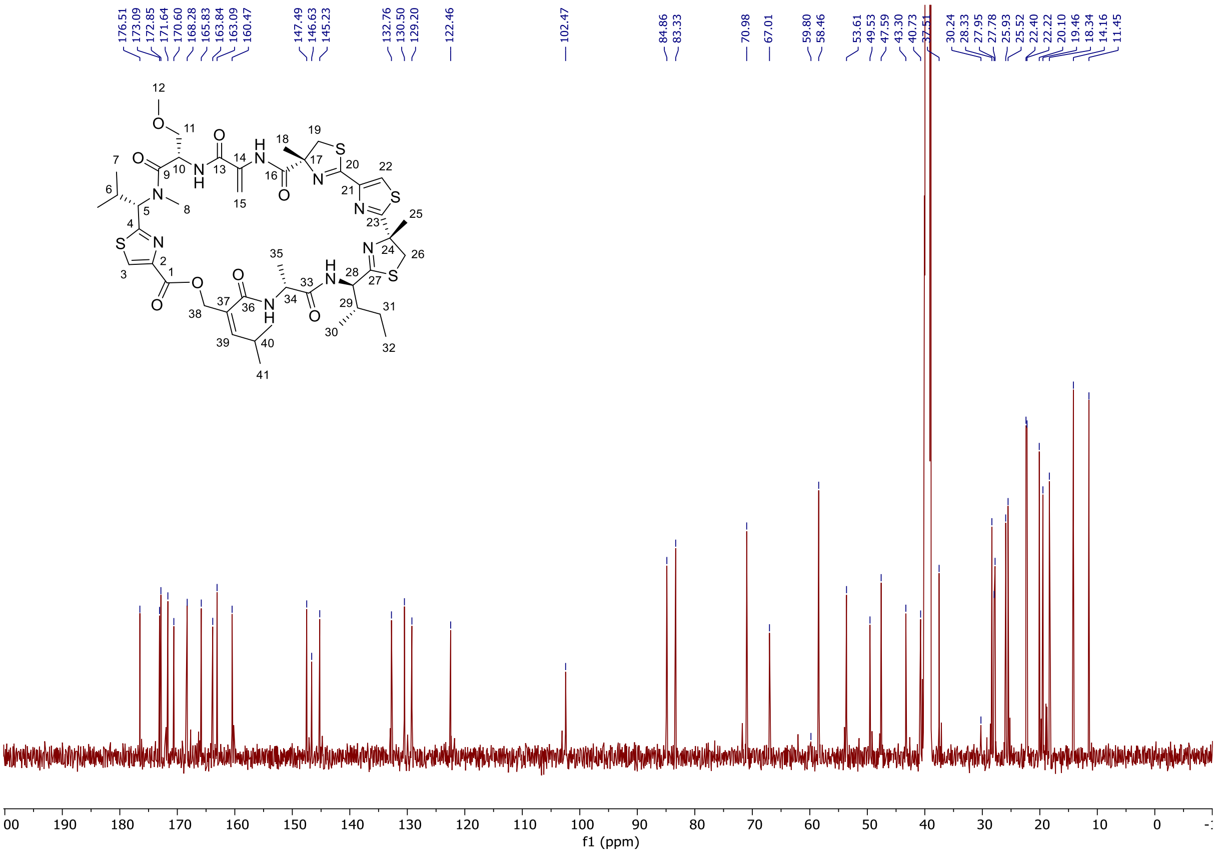


Thiamyxin B

^{1}**H-NMR** (500 MHz, DMSO-d$_6$):

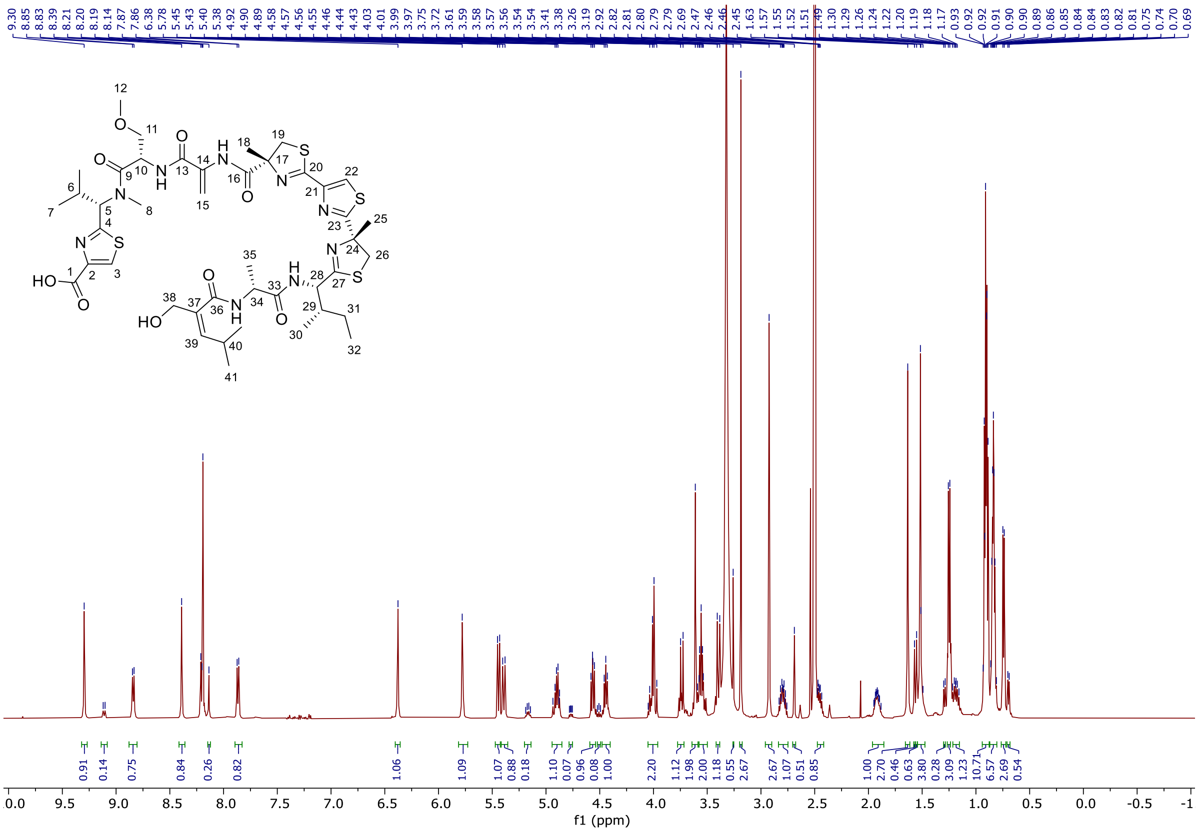


^{13}**C-NMR** (125 MHz, DMSO-d$_6$):

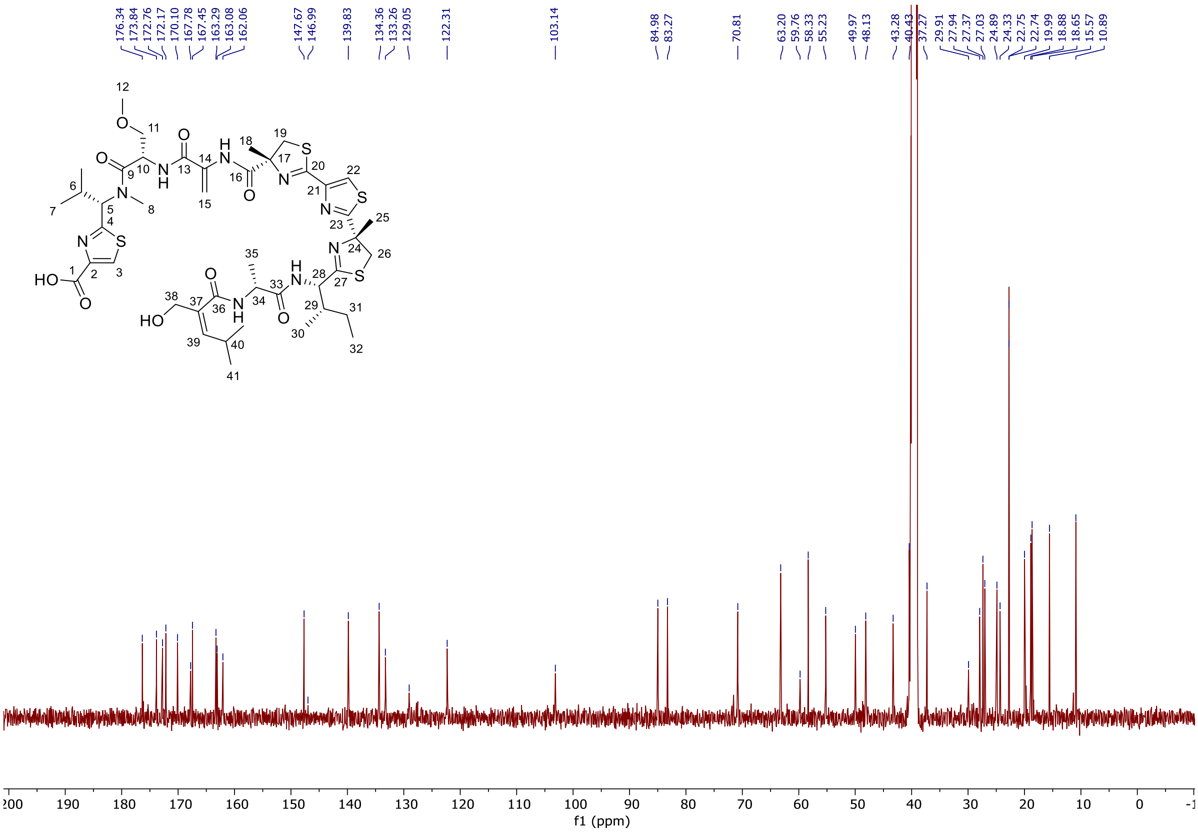


Thiamyxin E

^{1}H-NMR (500 MHz, DMSO-d$_6$):

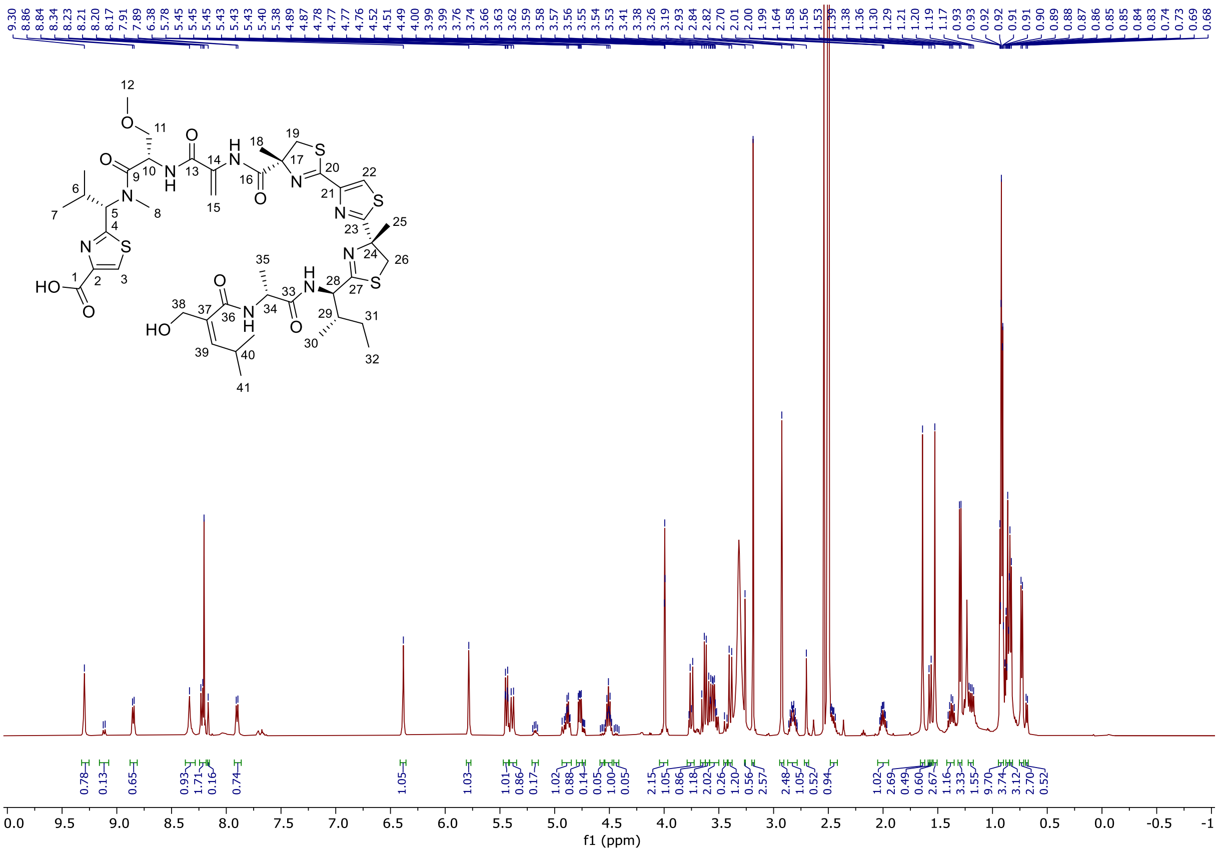


^{13}C-NMR (125 MHz, DMSO-d$_6$):

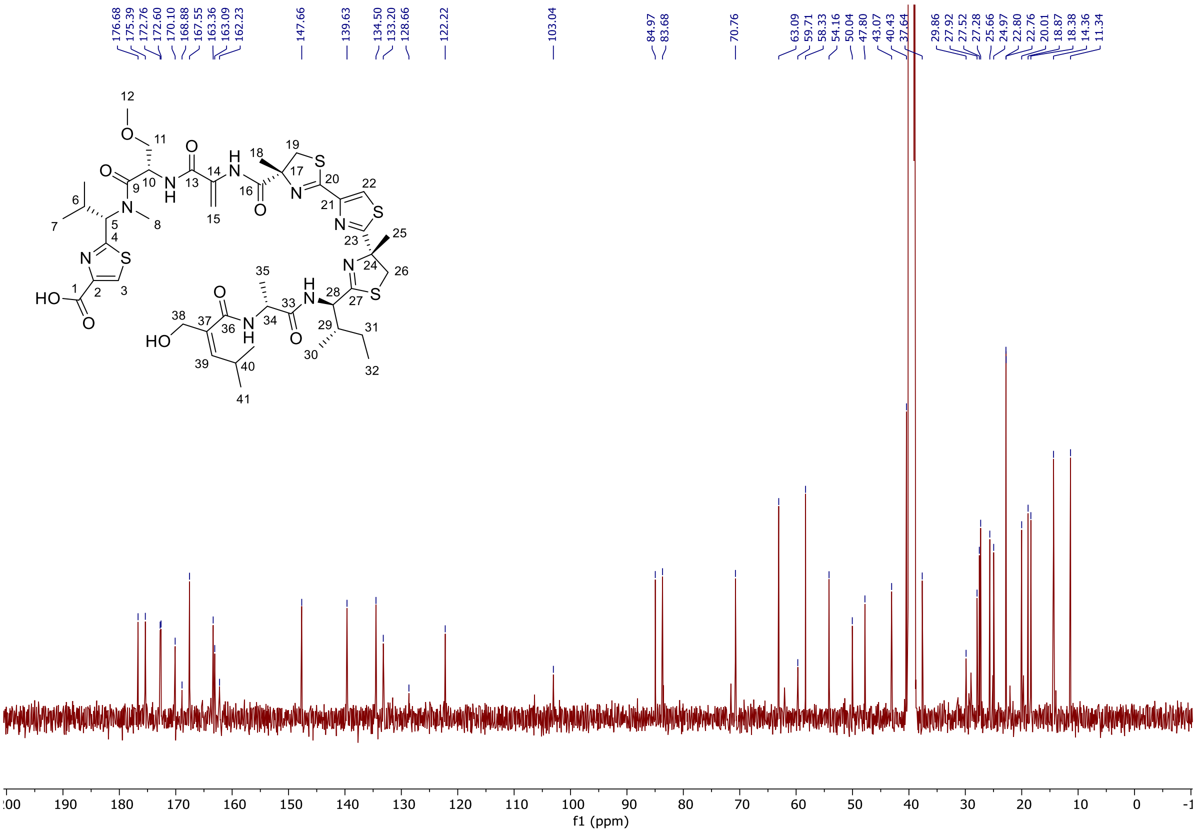


Thiamyxin C

^{1}H-NMR (500 MHz, DMSO-d$_6$):



^{13}C-NMR (125 MHz, DMSO-d$_6$):



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Bei Lukas Junk, Alexander Horn und Oliver Andler möchte ich mich für das gewissenhafte Korrekturlesen dieser Arbeit bedanken. Besonders möchte ich mich bei Alex bedanken, der während der schriftlichen Ausarbeitung dieser Arbeit ein hervorragender Büronachbar war, dem es nie zu viel wurde, wenn ich mal wieder Tür hineingeplatzt bin, um mich abzulenken oder um seine Meinung zu bitten.

Meinem Kollegen/Freund/Arbeitsehepartner Andreas Siebert möchte ich für die großartige Zeit, die vielen Diskussionen und die Kreativpausen im Labor und natürlich auch außerhalb des Labors danken.

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