Stereoselective Modification of *N*-(α-Hydroxyacyl)-Glycine Esters via Palladium-Catalyzed Allylic Alkylation

and

Studies toward the Total Synthesis of Callipeltin A and C

Dissertation

zur Erlangung des Grades

des Doktors der Naturwissenschaften

der Naturwissenschaftlich-Technischen Fakultät

der Universität des Saarlandes

vorgelegt von

Alexander Horn

Saarbrücken

2022

Die vorliegende Arbeit wurde von Januar 2018 bis November 2021 unter Anleitung von Herrn Prof. Dr. U. Kazmaier am Institut für Organische Chemie I der Naturwissenschaftlich-Technischen Fakultät der Universität des Saarlandes angefertigt.

Tag des Kolloquiums:	24.08.2022
Dekan:	Prof. Dr. J. Walter
Berichterstatter:	Prof. Dr. U. Kazmaier
	Prof. Dr. J. Jauch
Vorsitz:	Prof. Dr. A. Speicher
Akad. Mitarbeiter:	Dr. B. Morgenstern

Success is going from failure to failure without losing your enthusiasm.

– Winston Churchill

For mini

Kurzfassung

Die vorliegende Doktorarbeit beschreibt die Entwicklung einer neuen stereoselektiven Methode der Palladium-katalysierten allylischen Alkylierung. Als Nukleophile fungieren hierbei Titan-chelatisierte Enolate von *N*-(α-Hydroxyacyl)-glycinestern welche mit einer Vielzahl an allylischen Elektrophilen umgesetzt werden konnten. Die Methode toleriert dabei eine Reihe an funktionellen Gruppen wie Halogenide oder Vinylstannane, wodurch die nachträgliche Funktionalisierung der Seitenkette ermöglicht wurde. Durch die Wahl der Reaktionsbedingungen ist der selektive Zugang zu beiden Diastereomeren möglich.

In einem weiteren Projekt wurde eine Syntheseroute für die Depsipeptide Callipeltin A und C untersucht. Im Rahmen dieses Projekts gelang die Entwicklung neuer asymmetrischer Synthesen für die Aminosäure und Hydroxysäure Bausteine der Callipeltine. Die einzelnen Bausteine wurden nachfolgend durch sukzessive Peptidknüpfungen miteinander verkuppelt. Dabei gelang die Synthese des Peptidkerns in exzellenten Ausbeuten, allerdings scheiterten jegliche Versuche der Knüpfung des cyclischen Depsipeptids mit der Seitenkette. Eine leichte Variation der Strategie ermöglichte zudem die Synthese eines vollständig geschützten Derivats von Callipeltin C. Im Rahmen der globalen Entschützung erwies sich die Spaltung der letzten Benzyl Schutzgruppe jedoch als unmöglich. Die Totalsynthese der beiden Naturstoffe gelang somit nicht, jedoch konnte eine robuste Strategie entwickelt werden, welche den Zugang zu dem geschützten Naturstoff in guten Ausbeuten erlaubt. Durch die Wahl einer alternativen Schutzgruppe sollte die vorliegende Syntheseroute somit die erste Totalsynthese von Callipeltin C ermöglichen.

Abstract

This PhD thesis describes the development of a novel method for palladium-catalyzed allylic alkylation of titanium chelated enolates of *N*-(α-Hydroxyacyl)-glycine esters. The reaction could be performed with a variety of allylic electrophiles and generally proceeds with high stereoselectivity. A multitude of functional groups is tolerated such as halogenides or vinyl stannanes, which allows for subsequent modification of the side chain. By choice of reaction conditions, both diastereomers are accessible in a selective fashion.

The second part of this thesis describes the effort toward the first total synthesis of the natural products callipeltin A and C. These complex depsipeptides contain a multitude of non-proteinogenic amino acids and a rare terminal hydroxy acid. During this project, several stereoselective approaches toward the amino acid and hydroxy acid building blocks could be developed. The research culminated in the development of a route toward the cyclic heptapeptide core of callipeltin A and the synthesis of a protected version of callipeltin C. However, the coupling of the peptide core with the side chain was unsuccessful and the final deprotection of the benzyl amide group proved impossible. While the total synthesis was ultimately unsuccessful, this thesis described an unprecedented synthetic route toward

callipeltin C precursors. This route should allow for straightforward access to the natural product by slight variations in the protection group strategy.

Table of Contents

List of abbreviations

1,2-DCE	1,2-dichloroethane
18-C-6	18-crown-6
2,2-DMP	2,2-dimethoxypropane
9-BBN	9-Borabicyclo[3.3.1.]nonane
AAR	Apparent Allyl Rotation
Ac	acetyl
acac	acetylacetone
AD	asymmetric dihydroxylation
AGDHE	(2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxy heptanoic acid
AIBN	azobisisobutyronitrile
Ala	alanine
Alloc	allyloxycarbonyl
aq.	aqueous
Ar	aryl
Arg	arginine
b	branched
BINAP	(2,2′-bis(diphenyl phosphino)-1,1′-binaphthyl)
BINOL	1,1′-Bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
BSA	Bis(trimethylsilyl)acetamide
BTCA	benzyl 2,2,2-trichloroacet-imidate
Bu	butyl
BzI	benzyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
cod	1,5-cyclooctadiene
COMU	(1-Cyano-2-ethoxy-2-oxo-ethylidenaminooxy)dimeth-ylaminomorpholino-carben-ium-hexafluorophosphate
conv.	conversion
COVID	coronavirus disease
CPA	chiral phosphoric acid
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,2-diazabicyclo[2.2.2]octane
DACH	1,2-Diaminocyclohexane
DAIB	(diacetoxyiodo)benzene
DBU	1,8-Diazabicyclo[5.4.0] undec-7-ene
DCC	dicyclohexylcarbodiimid
DCCC	droplet counter-current chromatography
DCM	dichloromethane
DFT	density functional theory
(DHQ)2 Phal	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2$ AQN	hydroquinidine (anthra-quinone-1,4-diyl) diether
(DHQD)2 Phal	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
Dibal-H	diisobutylaluminium hydride
DIC	*N*,*N*'-diisopropylcarbodiimid
DICHED	dicyclohexylethane
diMeGln	(3*S*,4*R*)-dimethylglutamine
DIPEA	*N*,*N*'-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
dmp	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino) ethane
dr	*diastereomeric ratio*
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
ECF	ethyl chloroformate
ED50	median effective dose
EDC	1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
ee	*enantiomeric excess*
EMA	European Medicines Agency

equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
FDA	Food and Drug Administration
fig.	figure
Fmoc	fluorenylmethyloxycarbonyl
Fmoc-OSu	*N*-(9-fluorenylmethoxy-carbonyloxy)succinimide
GC	gas chromatography
Gln	glutamine
Gly	glycine
glyme	dimethoxyethane
HATU	(1-[Bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBTU	(2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDAC	histone deacetylases
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HOAt	1-Hydroxy-7-azabenzo triazole
HOBt	hydroxybenzotriazole
HOSu	*N*-hydroxysuccinimide
Hpla	hydroxyphenyllactic acid
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
IBCF	*iso*-butyl chloroformate
i-Bu	*iso*-butyl
Im-H	imidazole
ipc	isopinocampheyl
i-Pr	*iso*-propyl
KHMDS	potassium hexamethyldisilazide
l	linear
LAH	lithium aluminium hydride
LED	light-emitting diode
Leu	leucine
LD50	50% lethal dose
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
Ms	methanesulfonyl
MS	mass spectrometry
MS	molecular sieves
MSNT	1-(2-Mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole
n.d.	not determined
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NCS	*N*-chlorosuccinimide
NHP	*N*-hydroxyphthalimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ns	nosyl
NSCLC	non-small-cell lung carcinoma
Nu	nucleophile
on	overnight
Ox.	oxidation
oxyma	ethyl cyanohydroxyimino acetate
Pbf	2,2,4,6,7-pentamethyl-dihydro-benzofuran-5-sulfonyl
PCC	pyridium chlorochromate
PDC	pyridium dichromate
PE	petroleum ether
PG	protecting group
Ph	phenyl

PhINNs	*N*-(*p*-nitrophenyl sulfonyl) iminophenyliodinane
PMB	*para*-methoxybenzyl
ppy	2-phenylpyridine
Pr	propyl
p-TsOH	*para*-toluenesulfonic acid
PTC	phase transfer catalysis
PyAOP	(7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
QM	quantum mechanics
rf	reflux
Rf	retention factor
RP	reversed-phase
rt	room temperature
SARS-CoV	severe acute respiratory syndrome coronavirus 2
s-Bu	*sec*-butyl
SET	single-electron transfer
SI	selectivity index
SM	starting material
SPPS	solid-phase peptide synthesis
tab.	table
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
t-Bu	*tert*-butyl
TC	thiophene-2-carboxylate
TCNHPI	tetrachloro-*N*-hydroxy phthalimide
TEMPO	(2,2,6,6-tetramethyl piperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
Thr	threonine
TIPS-	triisopropylsilyl
TIPS	triisopropylsilane
TLC	thin-layer chromatography
TMEHA	(2*R*,3*R*,4*R*) 3-Hydroxy-2,4,6-trimethylheptanoic acid
TMG	tetramethylguanidine
TMS-	trimethylsilyl-
TMS	tetramethylsilane
TPPTS	3,3’,3’’-Phosphanetriyltris (benzenesulfonic acid) trisodium salt
Trp	tryptophan
Trt	trityl
UV	ultraviolet
VFDF	Very Fast Death Factor
WHO	World Health Organization
Xyl-BINAP	2,2'-bis[di(3,5-xylyl) phosphino]-1,1'-binaphthyl
Y	yield

1. Introduction

The endless variety of intriguing chemical structures present in nature represents the primary source for drugs in the fight against human diseases. More than 50 percent of all Food and Drug Administration (FDA) approved drugs are derived from natural products or represent synthetic derivatives thereof. While tremendous progress has been made in drug development over the last century, cases of non-communicable diseases such as cardiovascular diseases, cancer, diabetes, and Parkinson's continue to increase every year. In 2019 the World Health Organization (WHO) registered 8.9 million deaths caused by ischaemic heart disease, the most common cardiovascular condition.[1] Additionally, the rise of antibiotic resistant bacteria and other infectious diseases such as COVID-19 (SARS-CoV-2) challenge health care systems around the world. Thus, the development of drugs, antibiotics, and vaccines remains among the most important human endeavors.

One of the most promising drug candidates are peptides, a class of natural products which is uniquely set between small molecules and proteins while being biochemically and therapeutically distinct from both.[2,3] The first therapeutic use dates back to the 1920s when the peptide hormone Insulin was first used to treat diabetes. Historically, the use of peptide therapeutics has been restricted to a much smaller number of approved drugs than other natural product classes. Over the last decades, however, the interest in peptide drugs has increased significantly and the market for peptide therapeutics is the fastest growing sector in the pharmaceutical industry, behind biologics. The worldwide market is expected to grow to US$ 46.6 bn until 2024.[4] Potential use of peptides as therapeutics ranges from classical hormone therapy over peptide-based vaccines[5] to peptide-based antibody-drug conjugates[6–8] and more.[2,9–11]

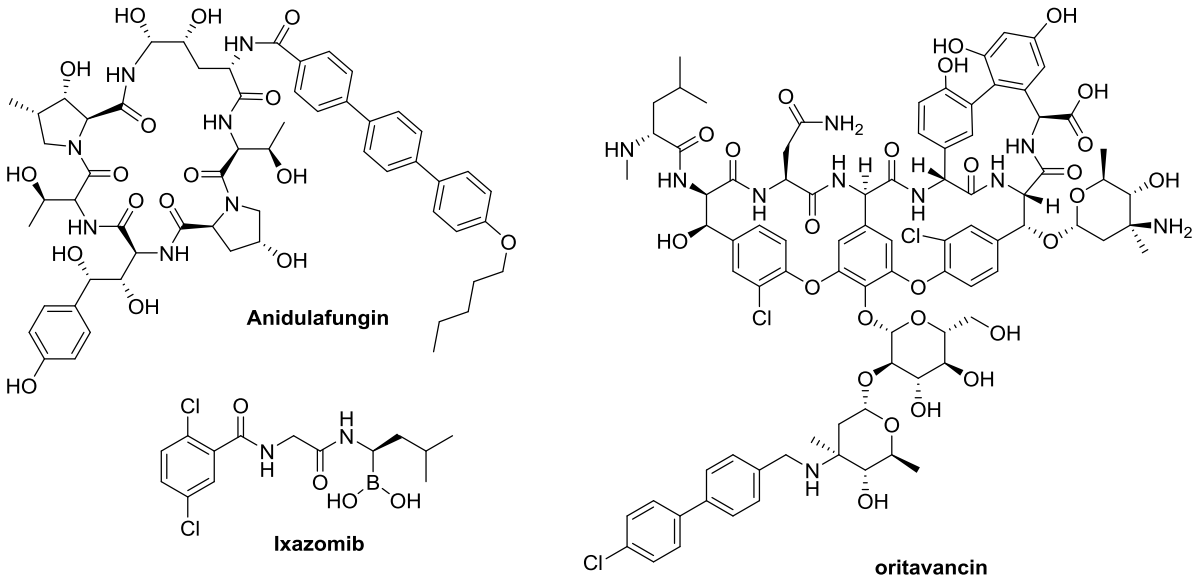


Fig. 1: Structure of FDA and EMA approved peptide therapeutics.

1. Introduction

Over the last decade, a variety of peptides has been approved by the FDA and European Medicines Agency (EMA),[12,13] such as anidulafungin,[14] an antifungal drug from Pfizer which received approval in 2006 or ixazomib,[12] a treatment for multiple myeloma, a type of white blood cell cancer, which was approved in 2015 (fig. 1). Additionally, several vancomycin-derived glycopeptides such as oritavancin (FDA 2014, EMA 2015),[14] a treatment of serious Gram-positive bacterial infections, have been approved for treatment.

The major drawbacks of peptides are poor membrane permeability,[1] low oral adsorption, and poor in vivo stability.[15] This usually requires significant synthetic modification of natural products to achieve the desired therapeutic effectiveness. A number of modifications such as cyclization and *N*-methylation have been used to improve oral bioavailability,[16] in vivo stability, and other properties.[17] Especially the use of macrocyclic peptides as drug candidates has seen significant attention over the last decade.[18] Additionally, the incorporation of non-proteinogenic amino acids is often utilized to improve metabolic stability. The structural diversity of non-proteinogenic amino acids[19] allows to tailor pharmacokinetic and -dynamic properties of peptides to a certain degree. Generally, modifications of peptides can be divided into two categories, the modification of an existing peptide by residue-specific peptide modification,[20] or the total synthesis of a peptide containing the modified amino acids.[21] While such modifications often enhance the synthetic challenge, structural simplifications also proved to be an excellent tool for generating highly active and selective drug candidates.[22]

The synthesis of such peptides might seem straightforward in the case of proteinogenic amino acids and can routinely be achieved via solid-phase peptide synthesis (SPPS),[1] but the synthesis of modified cyclic peptides proves far from trivial.[18,23] These synthetic challenges continue to drive research in method development and total synthesis. New methods are continuously required to synthesize the ever-growing diversity of synthetic building blocks, such as nonproteinogenic amino acids, in a simple and selective fashion without the extensive use of protecting groups.[24,25] Furthermore, the field of total synthesis of peptides has seen a resurgence in attention to develop new protocols to access complex peptide structures. Total synthesis also remains an important tool for structure elucidation, since misassignment of natural products and hence, potential lead structures for drug development, is still a prevalent issue.[26]

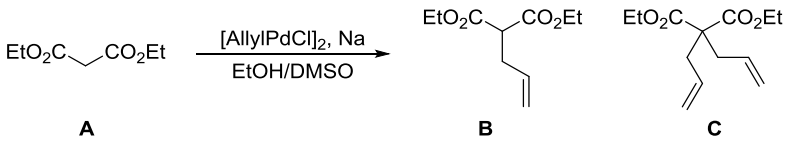
The evolution of synthetic chemistry and the associated challenges in this field have been questioned amidst the ongoing COVID-19 pandemic when Sarpong tackled the question of how organic synthesis might contribute to the effort toward such a global health crisis.[27] Sarpong emphasizes “the importance of incremental advances from proof-of-concept to successful commercialization and everything in between”. The development of new methodologies should expand the scope to include polar functional groups and heteroatoms found in biologically active molecules and the results should extend beyond only positive results but should also include reports of negative results which are often even more

valuable to the scientific community to improve our understanding of synthetic chemistry overall.

2. State of Knowledge

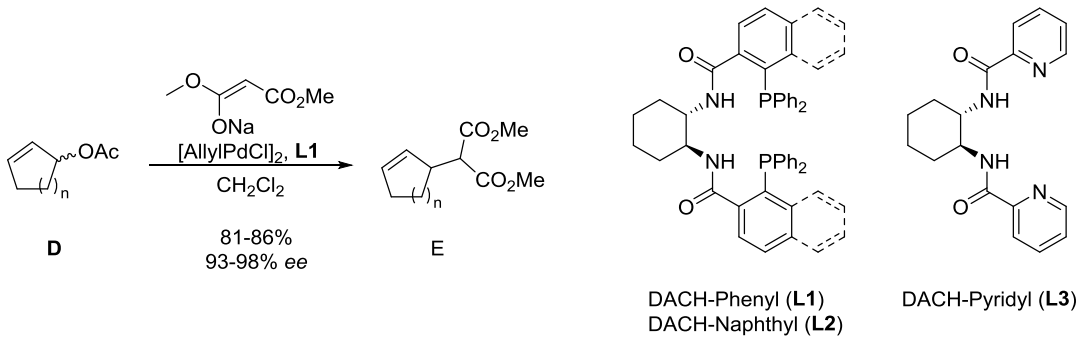
2.1 Allylic Alkylation

Throughout the last decades, a dazzling variety of transition metal-catalyzed reactions have been developed and were established as a fundamental tool in all fields of synthetic chemistry, from natural product research to multi-ton processes in the pharmaceutical industry. Transition metal-catalyzed allylic alkylations represent a prominent field of research and countless methods have been described using metals such as palladium,[28–32] ruthenium,[33–35] iridium,[36–38] rhodium,[39–43] nickel,[44–47] molybdenum,[31,48–52] iron,[53,54] and several others.[45,55–57] By far the most attention has been given to the palladium-catalyzed variant which displays a remarkable versatility in terms of scope of nucleophiles, electrophiles, and selectivity.



Scheme 1: Palladium mediated allylic alkylation described by Tsuji.[58]

The first palladium mediated allylic alkylation was described by Tsuji in 1965,[58,59] who treated different nucleophiles with stoichiometric amounts of dimeric π-allyl palladium chloride (scheme 1). Catalytic versions followed in 1970 from the groups of Atkins[60] and Hata[61] and later Trost *et al.* were able to carry out the first palladium-catalyzed asymmetric allylic alkylation.[62] The group of Trost continued to be one of the main driving forces in this field of research,[63,64] developing a multitude of allylic alkylation systems,[65–69] in particular the Trost-ligands for asymmetric allylic alkylation (scheme 2).[70,71]

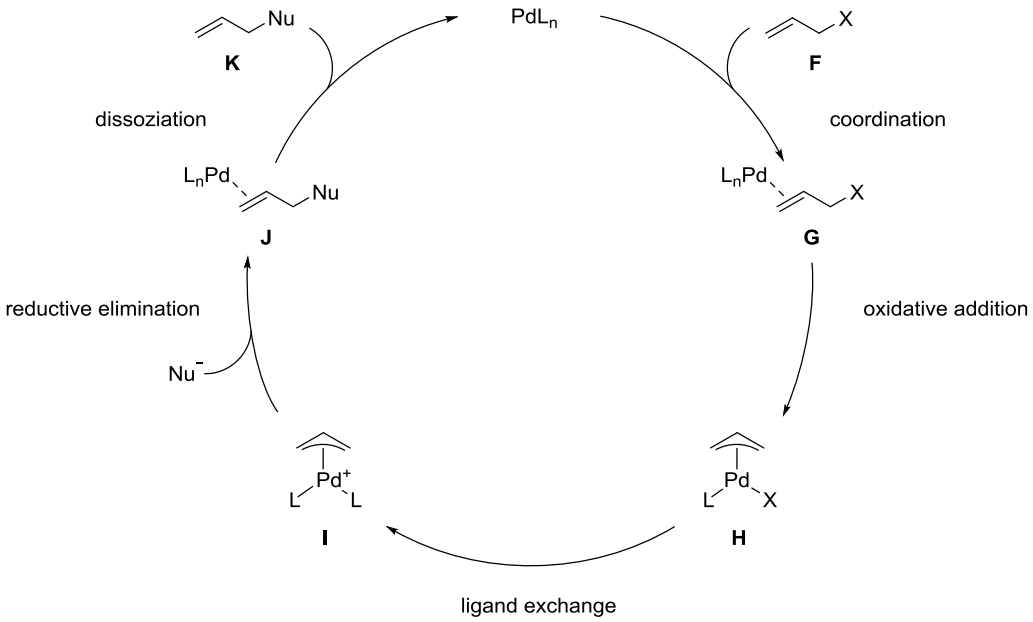


Scheme 2: Structure and use of Trost ligands in asymmetric alkylation.

Furthermore, Tsuji[72] and later Trost and Stoltz expanded the scope of palladium-catalyzed allylic alkylation by developing methods for decarboxylative allylic alkylation,[68,69,73–75] which represents a palladium-catalyzed variant of the classical Carroll rearrangement. In this case, no external allyl substrate is required, both the allyl fragment as well as the nucleophile are formed intermediary from a single starting material, either β-keto allyl esters or enol carbonate esters.[73]

2.1.1 Mechanism

The general reaction mechanism of the palladium-catalyzed allylic alkylation is depicted in scheme 3.[28,29] In the first step of the catalytic cycle, η^2-complex **G** is formed by π-coordination of the substrate **F** to the Pd(0) catalyst. Oxidative addition of palladium into the activated allylic C-X bond[76–78] then affords neutral η^3-Pd(II)-complex **H.** Subsequently, a ligand exchange from the anionic ligand X^- (typically halogenide, carbonate, carboxylate, phosphate, etc.) to a neutral ligand such as phosphines takes place. The resulting positively charged π-allyl complex **I** displays a higher electrophilicity and nucleophilic substitution takes place under reductive elimination. Finally, the product **K** is released by dissociation of the π-coordinated complex **J** and regeneration of the Pd(0) catalyst.

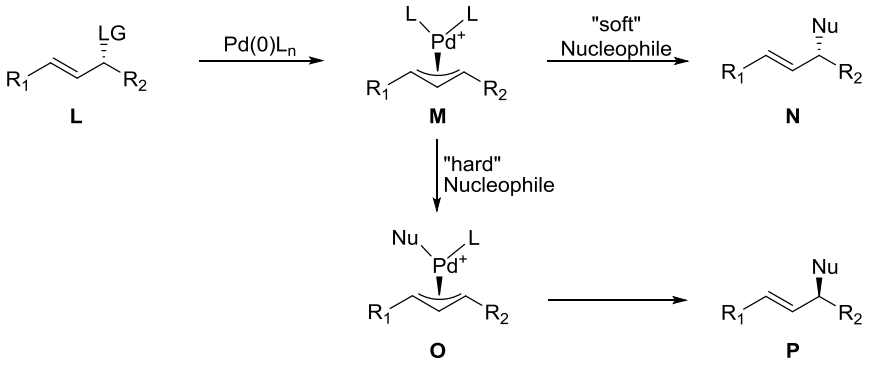


Scheme 3: General mechanism of the palladium-catalyzed allylic alkylation.[29]

2.1.2 Dynamics of Palladium π-Allyl Complexes

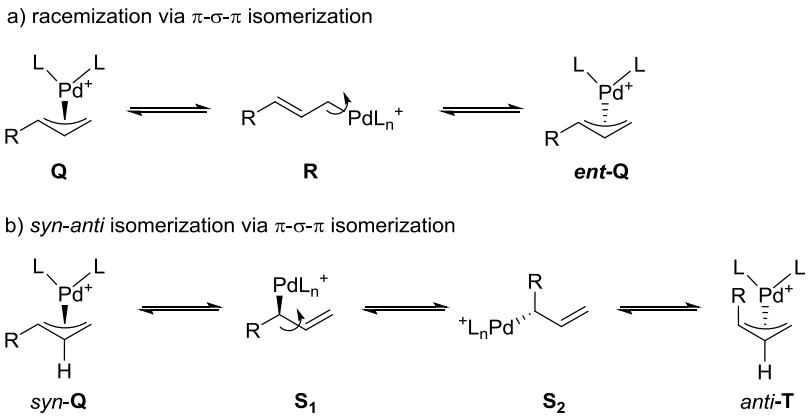
The general stereochemical course of the reaction can be divided into two mechanistic pathways,[79,80] mainly depending on the type of nucleophile which is used (scheme 4). In the first step, the formation of palladium π-allyl complex **M** occurs stereospecifically with inversion of the configuration by oxidative addition of palladium from the opposite face to the leaving group. Depending on the nucleophile, direct nucleophilic attack of the η^3-π-allyl complex or coordination to the palladium center may occur. “Soft” nucleophiles, whose conjugate acids have pK_a < 25,[81,82] such as stabilized carbanions,[28] non-stabilized enolates[83,84] as well as *N*-,[85,86] *O*-,[87,88] and *S*-nucleophiles[89,90] add directly to the allyl ligand. The nucleophilic substitution occurs from the less shielded face of the allyl complex, netting an overall retention of the configuration by two counts of inversion. In the case of “hard” nucleophiles,[91] whose conjugate acids have pK_a > 25, such as alkyl-, aryl- and alkenyl-organometallics,[92–94] addition to the electrophilic palladium center results in the formation of allyl(organyl)palladium(II) complex **O** via transmetalation. Due to this inner

sphere mechanism, reductive elimination eventually affords the alkylated product **P** with overall inverted stereochemistry.



Scheme 4: Nucleophile influence on the stereochemical course of Pd-catalyzed allylation.

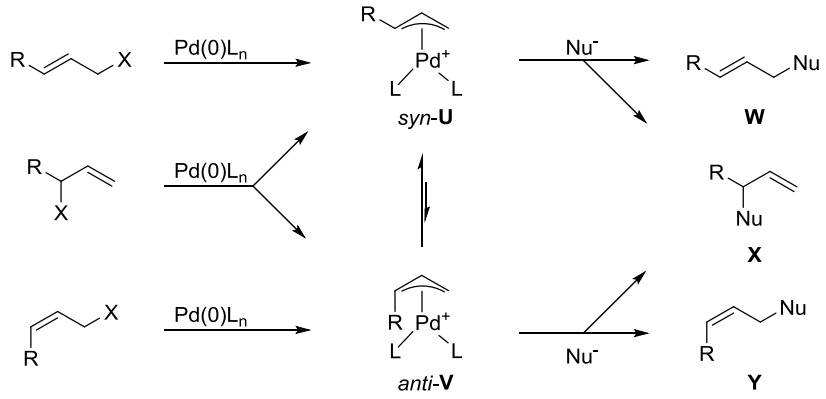
Extensive studies on these palladium π-allyl complexes have revealed the presence of various complex dynamic processes which influence allylic alkylation and other reactions involving palladium π-allyl complexes.[95,96] In the absence of a nucleophile or if the reductive elimination is slow enough, π-allyl complexes **Q** are subject to a fast equilibrium via π-σ-π-isomerization which results in the racemization of terminal allyl complexes such as **R** (scheme 5, a).[81] π-σ-π-Isomerization may also result in equilibration of *syn*-complex **Q** and *anti*-complex **T** by the formation of σ-complex $\mathbf{S_1}$ and subsequent C-C-bond rotation (scheme 5, b).[95] Typically, *syn*-complex **Q** is more stable than *anti*-complex **T**.



Scheme 5: Possible equilibria of Pd-π-allyl complexes by π-σ-π-isomerization.

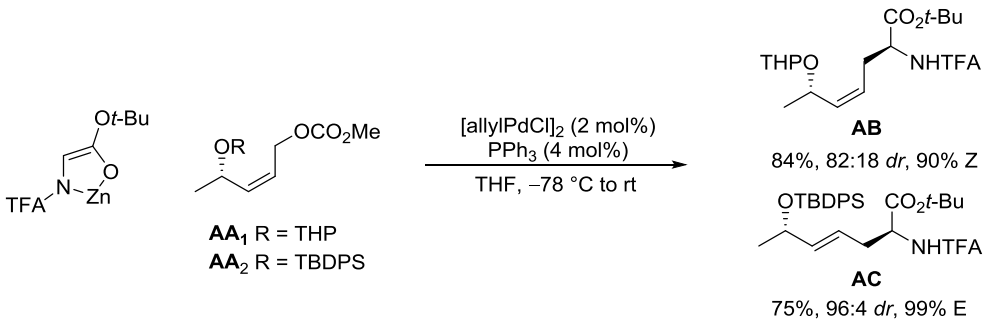
The initial formation of *syn*- or *anti*-π-allyl complexes is a direct result of the alkene structure of the allyl substrate.[81] Linear *E*-alkenes result in the formation of *syn*-complex **U** while *Z*-alkenes form *anti*-complex **V** (scheme 6). Branched substrates on the other hand result in the formation of both *syn*- and *anti*-complexes. Likewise, *syn*-complex **U** results in the formation of linear *E*-alkene **W** and/or branched product **X**. Nucleophilic attack of *anti*-complex **V** forms either branched product **X** or *Z*-alkene **Y**. This reaction pathway shows the possibility to control the product structure by choice of the allyl substrate if the nucleophilic addition to the π-allyl complex is regioselective and π-σ-π-isomerization can be

suppressed. For most substrates such a suppression of π-σ-π-isomerization is impossible, but some exceptions have been described.[97]



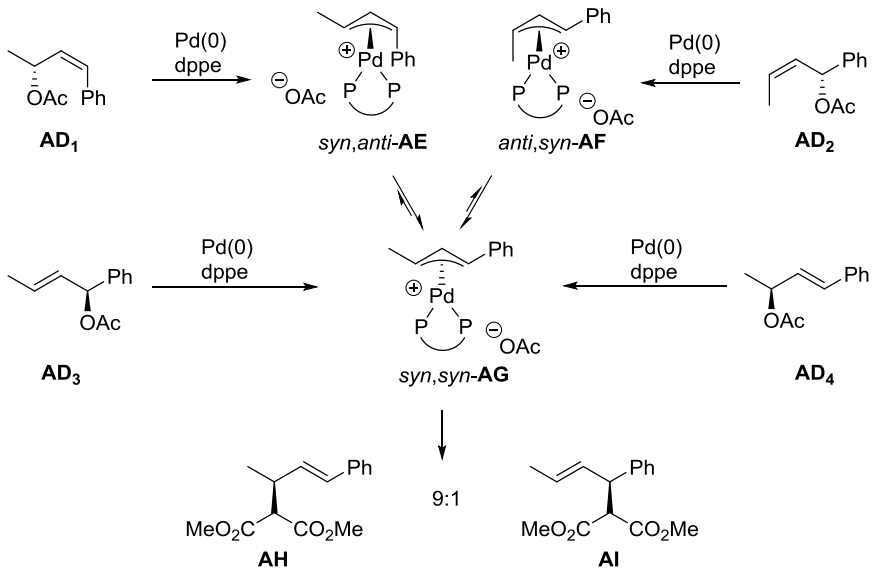
Scheme 6: Influence of allyl substrate structure on π-allyl complex and product formation.

Kazmaier *et al.* described the first suppression of π-σ-π-isomerization using highly reactive chelated ester enolates of amino acids as nucleophiles.[97–99] When *Z*-carbonate **AA$_1$** was used, transfer of the double bond geometry could be achieved in 90% selectivity (scheme 7). The group postulated reaction rates for the trapping of the *anti*-π-allyl complex by the ester enolate were significantly higher than π-σ-π-isomerization which resulted in the retention of alkene geometry. This hypothesis could be supported by the use of allyl carbonate **AA$_2$** containing the sterically demanding TBDPS group instead of the THP derivative. In this case, the reactivity of the π-allyl complex decreased due to the high sterical demand, and trapping of the complex by the ester enolate is slower than π-σ-π-isomerization which resulted in the selective formation of *E*-amino acid **AC**.



Scheme 7: Influence of allyl substrate structure on π-allyl complex and product formation.

The presence of these equilibria and the preference for *syn*-complex formation was demonstrated when four isomeric, secondary allyl carbonates **AD$_1$**-**AD$_4$** were used in allylic alkylation with dimethyl malonate (scheme 8).[100] After initial *syn*,*anti*- or *anti*,*syn*-complex formation from *Z*-allyl substrates **AD$_1$** and **AD$_2$**, π-σ-π-isomerization resulted in preferential formation of *syn*,*syn*-complex **AG.** Both *E*-alkenes **AD$_3$** and **AD$_4$** directly form the identical *syn*,*syn*-complex **AG** which resulted in the formation of alkylated malonate **AH** as the main isomer in all cases in identical product ratios.

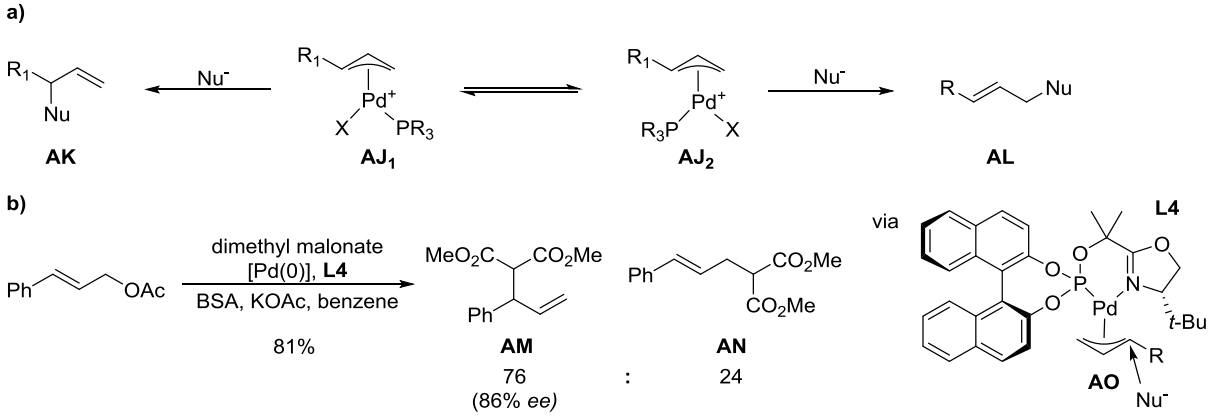


Scheme 8: Preference of *syn*,*syn*-complex formation under equilibrium conditions.[100]

Additionally, palladium π-allyl complexes may be subject to various other complex dynamic processes such as dative ligand flip,[101] palladium(0) catalyzed allyl exchange,[100,102] or apparent allyl rotation (AAR).[103–105] Isomerization via dative ligand flip results in the formation of slowly interconverting rotamers while apparent allyl rotation may result in enantiomerization, epimerization, or diastereomerization of palladium π-allyl complexes depending on the substitution pattern of the allyl fragment as well as the ligands.[81]

2.1.3 Regioselectivity

In unsymmetrically substituted η^3-allyl complexes, the issue of site-selectivity must be considered. The strategies to achieve regioselective nucleophile addition can conceptually be divided into two approaches, intramolecularly- and ligand-directed regioselectivity. While several successful reactions using the intramolecularly-directed approach have been described,[106,107] the general applicability is low due to the necessity of a specific directing group in the substrate. Hence, the second approach via ligand direction has seen more attention and a multitude of reaction systems have been developed. Pioneering work by Åkermark *et al.* displayed the preference of nucleophilic addition *trans* to π-accepting phosphor ligands compared to the *trans*-position of *N*-ligands.[108,109] Nucleophilic trapping of π-allyl complexes **AJ$_1$** and **AJ$_2$** consequently results in formation of the branched product **AK** and linear product **AL**, respectively. These results were later supported by computational studies which displayed a higher electrophilicity for the allyl terminus *trans* to the *P*-ligand.[110,111] During the last decades the "*trans*-to-P" effect has shown to be generally applicable and was exploited in asymmetric catalysis using chiral *P*,*N*-ligands.[112,113] Pfaltz and coworkers described the use of π-acidic phosphite **L4** to achieve branched selective allylic alkylation (scheme 9).[114] The phosphite ligand adds to the allyl substrate to selectively form syn-π-allyl complex **AO** which minimizes sterical repulsion of the phenyl group and the BINOL backbone and thus results in "*trans*-to-P" addition of the malonate.

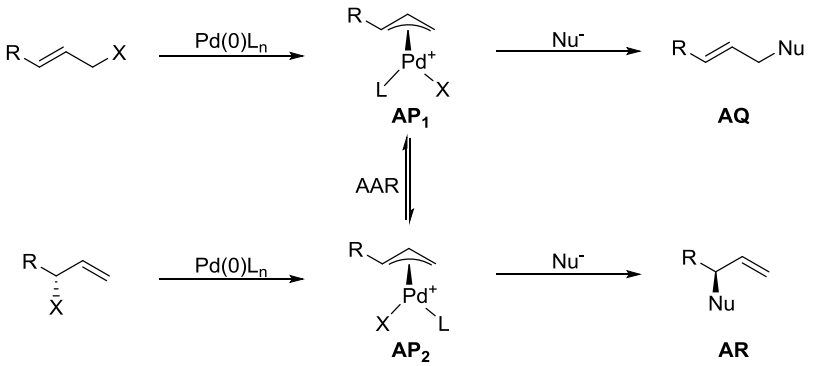


Scheme 9: Regioselective nucleophilic substitution as a result of the *trans*-effect.

While these results show the possibility to achieve branched-selective allylic alkylation using palladium π-allyl complexes, the use of other transitional metals such as ruthenium, iridium, or molybdenum in branched selective allylic alkylation is preferred in most cases.[32,36,48]

2.1.3.1. Memory Effect

The previous examples are all based upon the favored trapping of the allyl complex at the more electronically favored allylic terminus by a nucleophile or describe the tendency of addition in the more sterically accessible position, resulting in the preferential formation of the linear product. However, Malleron and Fiaud were able to show these theories were not always able to predict or explain the selective formation of a given isomer.[115] These deviations from the classical mechanism, in which the nucleophile reacts at the allylic terminus previously occupied by the leaving group are called “memory effect”.[116,117] This effect typically can be observed when bulky monophosphine ligands are used.[118] Such bulky ligands only allow for mono-coordination to palladium and thus generate unsymmetrical π-allyl complexes. Due to the preferential introduction of the *P*-ligand *trans* to the leaving group,[119] resulting from *cis*-selective oxidative addition, formation of η^3-complexes **AP_1** and **AP_2** is observed when linear or branched substrates are used, respectively (scheme 10).

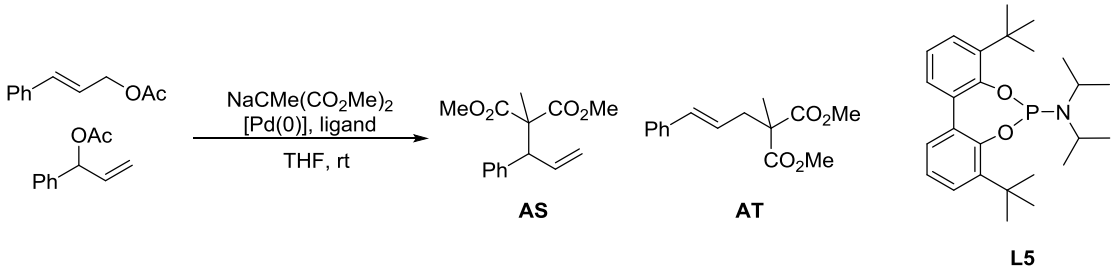


Scheme 10: Memory-effect as a result of bulky monophosphine ligands.

While **AP_1** represents the more reactive complex, it is also less stable than **AP_2** due to greater sterical repulsion of monophosphine **L** and the allyl fragment. Thus, apparent allyl rotation of **AP_2** to **AP_1** is disfavored and branched-selective allylation becomes possible.

Detailed studies have revealed a strong influence of chloride anions on the mechanism which significantly complicates the dynamics of the π-allyl complex by ligand exchange.[120] The presence of chloride anions enhances the isomerization rate between the isomeric π-allyl complexes and Curtin-Hammett conditions, the preferential reaction of the most reactive allyl complex, are reached which wipes out any type of memory effect. The examples depicted in table 1 demonstrate these considerations. Under classical conditions using triphenylphosphine (X,L = PPh_3) as ligand, the expected selectivity toward the linear product **AS** is observed in the case of both allyl substrates.[118] The bulky *P*-ligand **L5** on the other hand gave memory type linear to linear and branched to branched results.[118,121,122] When the same ligand was used in the presence of chloride anions a complete shift of the selectivity was observed. In the case of the branched substrate, preferential formation of the linear product was observed due to the increased isomerization rates between the allyl complexes.

Table 1: Influence of ligands and additives on the regioselectivity of allylic alkylation.

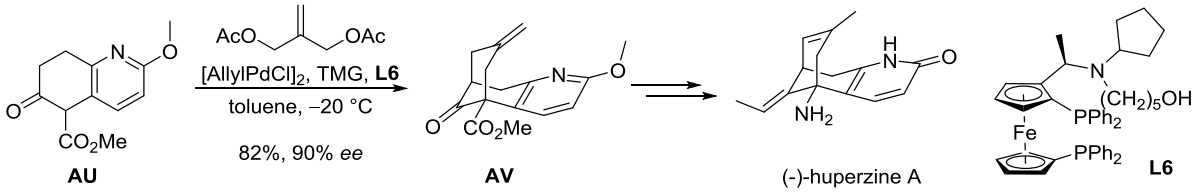


entry	ligand	substrate	linear	branched
1	PPh_3	linear	91	9
2	PPh_3	branched	92	8
3	**L5**	linear	97	3
4	**L5**	branched	33	67
5	**L5** + Cl^-	linear	99	1
6	**L5** + Cl^-	branched	84	16

2.1.4 Asymmetric Allylic Alkylation and Application in Total Synthesis

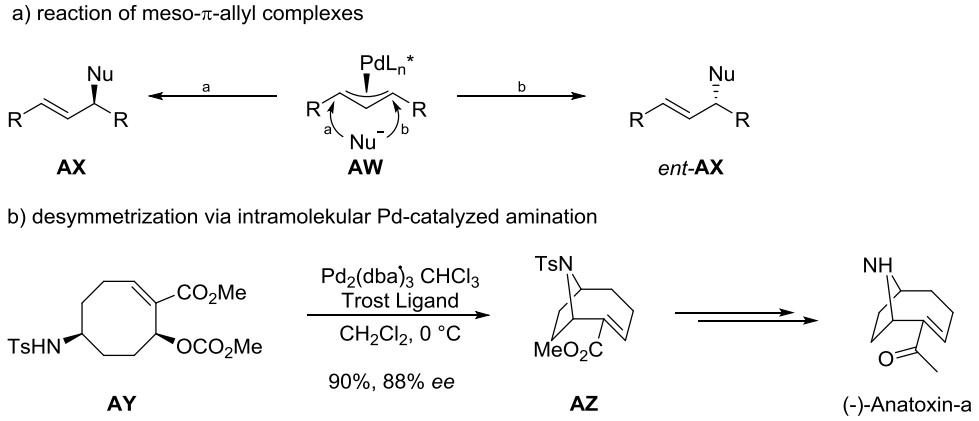
The variants for asymmetric induction during allylic alkylation can conceptually be categorized into (a) oxidative addition as the enantiodiscriminating step or (b) nucleophilic attack as the enantiodiscriminating step. In the case of slow π-σ-π-interconversion compared to nucleophilic trapping, preferential oxidative addition of enantiotopic alkene faces (variant (a)) is possible with a suitable chiral catalyst.[123,124] Due to the above-mentioned issues to suppress π-σ-π-isomerization reliably, this variant has not seen as much attention as variant (b). The second approach in turn can be divided into the use of prochiral nucleophiles, *meso*-

π-allyl complexes, or unsymmetrical substituted η^3-allyl complexes. For example, Bai *et al.* described the enantioselective bicycloannulation of a prochiral enolate generated from β-ketoester **AU** by palladium-catalyzed allylic alkylation using chiral ferrocene ligand **L6** (scheme 11).[125]



Scheme 11: Asymmetric allylic alkylation with a prochiral nucleophile.

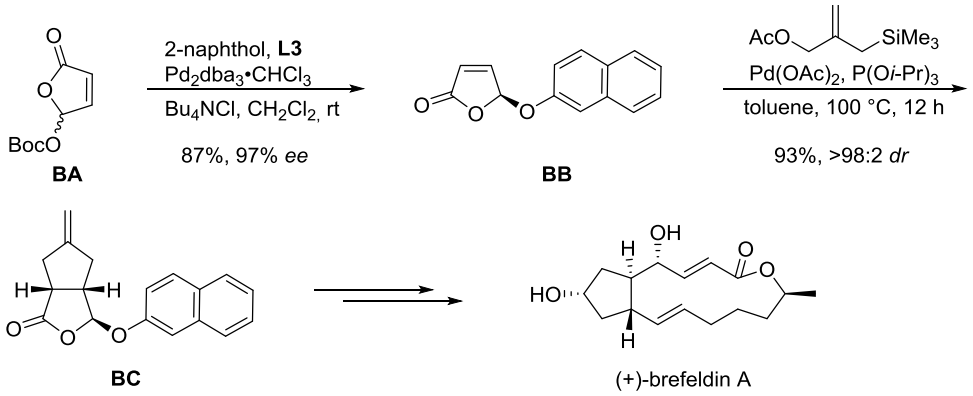
Especially the use of allyl substrates with identical substituents at C1 and C3 has seen considerable attention. In such a case both enantiomers of the allyl substrate form the identical *meso*-π-allyl complex **AW** which allows for asymmetric alkylation even with racemic allyl substrates (scheme 12, a).[81,101] In the presence of a chiral ligand the allyl termini are diastereotopic and by control of the regioselective addition, the preferential formation of one enantiomer is induced. Trost and coworkers exploited this strategy during their synthesis of alkaloid neurotoxin (-)-Anatoxin-a, also known as Very Fast Death Factor (VFDF).[126] The group generated a *meso*-π-allyl complex from cyclooctene **AY** and with the use of their signature ligand they were able to achieve desymmetrization by intramolecular enantioselective allylic amination to form bicyclic sulfonamide precursor **AZ** (scheme 12, b).



Scheme 12: *Meso*-π-allyl complexes as a tool for enantioselective allylic alkylation.

In the case of unsymmetrical enantiopure 1,3-substituted allyl substrates, regioselective addition directly results in enantioselective allylic alkylation.[81] To achieve an enantioselective reaction with racemic allyl substrates of this type, interconversion of π-allyl complexes by a different mechanism than π-σ-π-racemization, which would also induce *syn-anti*-isomerization, is required. Such allyl enantioface exchange may occur by palladium(0)-catalyzed allyl exchange,[102] thus enantioselectivity is dependent on the rates of nucleophilic trapping of the allyl complexes. Trost *et al.* were able to demonstrate the utility of this approach with the dynamic kinetic resolution of racemic *tert*-butyl carbonate **BA** with Trost ligand **L3** which gave *O*-allylation in excellent yield and selectivity (scheme 13).[127]

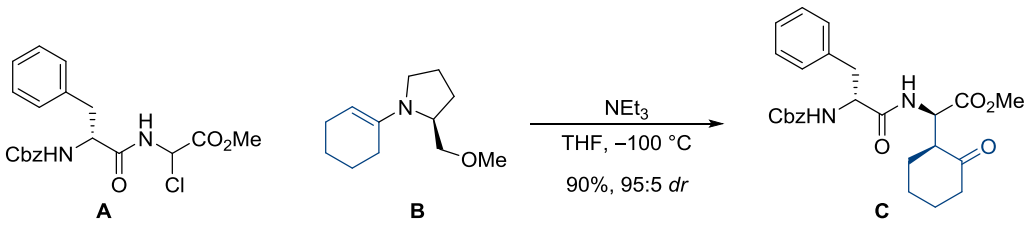
Subsequent Sakurai-type allylation followed by a second palladium-catalyzed allylic alkylation afforded bicyclic lactone **BC** as a precursor in their synthesis of (+)-brefeldin A.



Scheme 13: Dynamic kinetic asymmetric allylic alkylation by Trost *et al*.

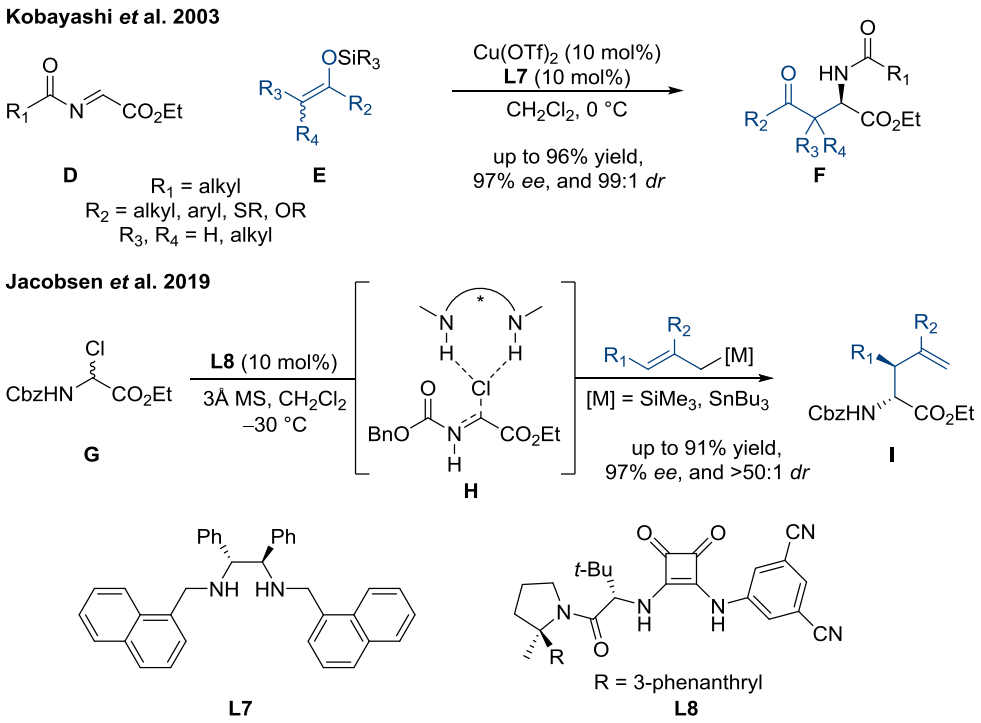
2.2 Backbone Modification of Amino acids, Peptides and Pseudo Peptides

The structural modification of amino acids and peptides is an important tool for fine-tuning the properties of bioactive peptides and proteins. Even the slightest variations in the structure may induce massive changes in conformation, folding ability, and chemical and biological properties.[128] These effects are impressively displayed in nature by the existing structural diversity of non-proteinogenic amino acids containing peptides, produced by non-ribosomal peptide-synthetases (NRPS), with distinct properties. While nature is able to selectively modify amino acids by enzyme-catalyzed reactions, synthetic modifications of complex peptides remain challenging.[128] The selective modification of a given peptide usually requires the presence of a functional handle due to the similarity of peptides in terms of functional groups.[129–133] Especially the introduction of alkyne or azide functionalities for late-stage modification by click chemistry has seen widespread application.[134] Without the installation of such a functional group in the early stages of the synthesis, usually, issues of regio-, chemo- and stereoselectivity arise during modification. Most attempts to avoid these issues and selectively modify the backbone of peptides are based on the functionalization of a glycine subunit in the peptide. The approaches can be categorized into modification via glycine cation surrogates, glycine radicals, and glycine enolates as reactive intermediates. The use of glycine cation surrogates was mainly studied by Steglich and coworkers who found α-acetoxy or α-halo glycine esters as suitable precursors to generate cation-type intermediates.[135–140]



Scheme 14: Functionalization of peptides via a glycine cation by Steglich *et al.*

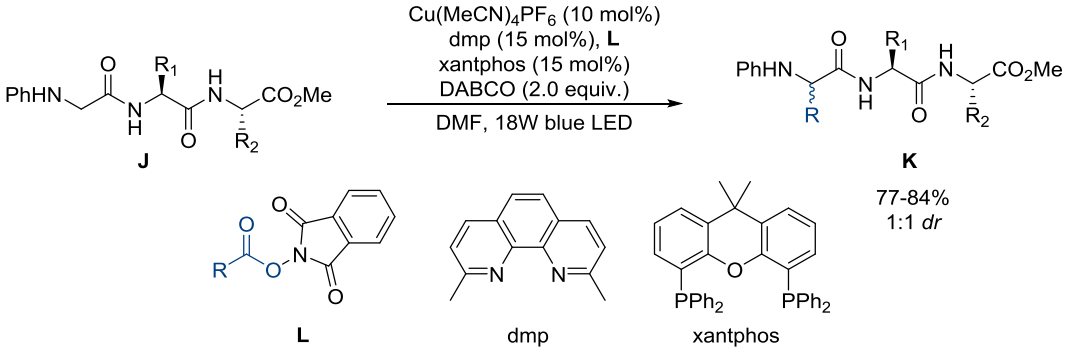
For example, treatment of α-halo glycine ester **A** with triethylamine and prolinol derived enamine **B** afforded dipeptide **C** in excellent yield and selectivity (scheme 14). The high diastereoselectivity in this example is a result of matched stereocontrol by the peptide backbone and enamine, hence, the enantiomeric enamine affords a diastereomeric ratio of 3:2 displaying the mismatched scenario. Most modern approaches, however, utilize iminoesters as glycine electrophiles.[141–146] In 2003 Kobayashi and coworkers reported the catalytic, asymmetric Mannich-type reaction of *N*-acyl iminoesters (scheme 15, upper part).[147] With the use of chiral, C_2-symmetrical diamine ligand **L7** the group was able to stereoselectively add silyl enol ethers **E** to iminoesters **D** via copper catalysis. The method allowed for the introduction of ketones, esters, and thioesters and the resulting α-amino acids **F** were obtained in high yield and selectivity. Aside from transition metal-catalyzed variants, the use of organocatalysts such as thioureas or squaramides has been applied successfully. Jacobsen, for example, described the asymmetric synthesis of α-amino esters by Mannich reaction via organocatalytic anion-binding catalysis with a bifunctional thiourea catalyst.[148] Later, Jacobsen *et al.* reported the use of squaramide **L8** as hydrogen-bond-donor catalyst in the enantioselective allylation of α-chloro glycinates (scheme 15, lower part).[149] The squaramide catalyst activates the glycinate **G** by hydrogen-bonding of the chlorine atom, thereby facilitating the addition of allyl silanes and stannanes in a highly stereoselective fashion.



Scheme 15: Modifications of glycine iminoesters.

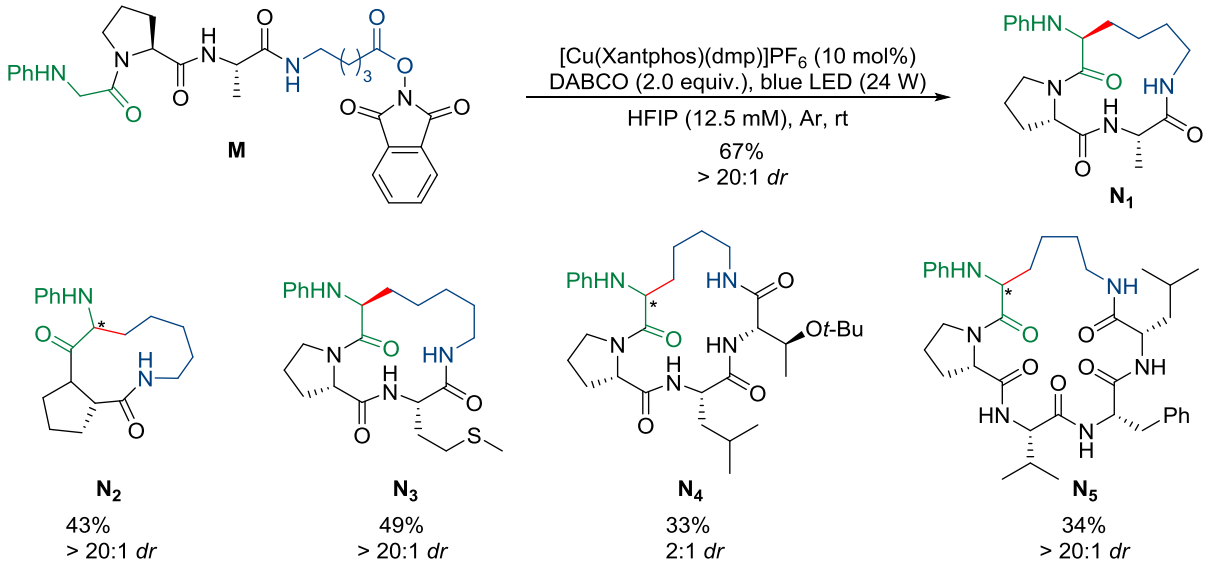
Seminal work on the modification via a radical intermediate was described by Elad *et al.*[150–152] in the late 1960s and was later continued by Easton and coworkers.[153] More recently this approach has seen a resurgence in popularity with several groups describing modern photoredox catalytic approaches of this transformation. Wang and Xu reported the visible-

light-driven, copper-catalyzed decarboxylative radical alkylation of peptides using redox-active *N*-hydroxy phthalimide (NHP) esters (scheme 16).[154] With a two-ligand system and DABCO as proton scavenger of the intermediary radical cation, sp^3-sp^3 coupling of peptides **J** and NHP esters **L** was accomplished in 77-84% yield, albeit no asymmetric induction could be achieved. Due to the intrinsic high reactivity of the odd-electron species, the enantioselective transformation remained a formidable challenge which could only be overcome very recently.



Scheme 16: Radical functionalization of glycine unit in peptides.

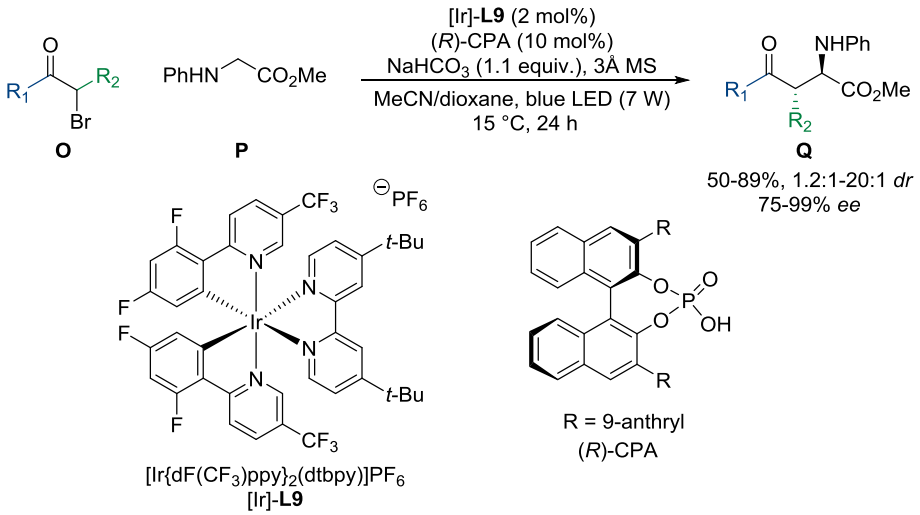
Early in 2021, the group of Chen reported the application of the method of Wang and Xu in diastereoselective fashion for the construction of macrocyclic peptides (scheme 17).[155] Chen *et al.* achieved the formation of (homo-)lysine via intramolecular C-H alkylation of an *N*-Aryl glycine unit and redox-active NHP esters in the side chain. Using high dilution conditions with HFIP as the solvent the group was able to achieve diastereoselective cyclization to afford cyclic peptides **N_1-N_5** with varying ring sizes.



Scheme 17: Macrocyclization via intramolecular radical C-H alkylation.

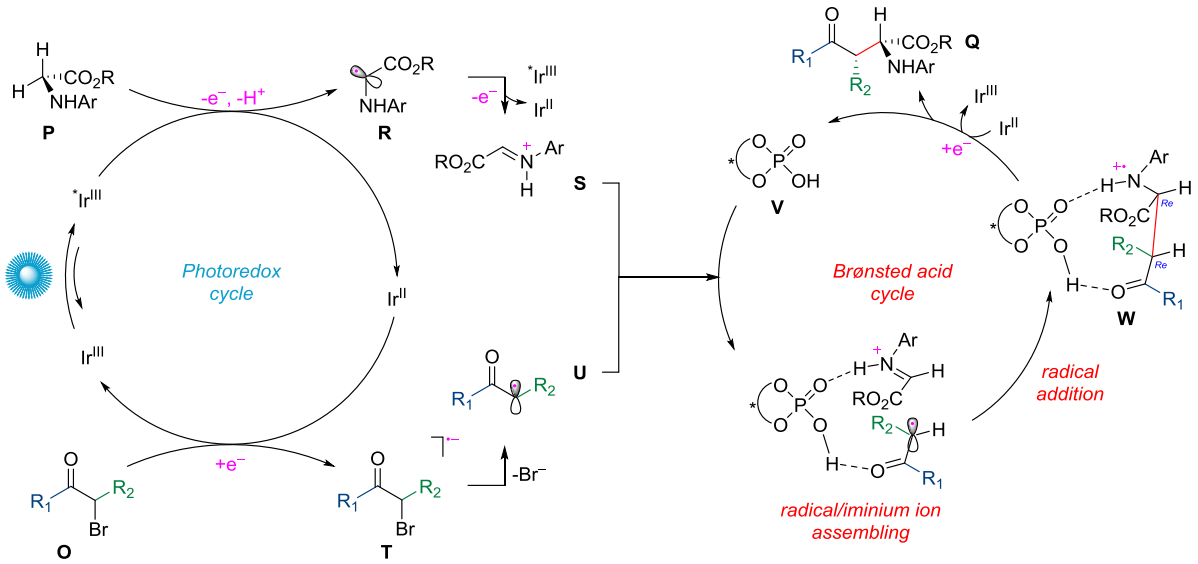
Shortly after, Wang and coworkers described the unprecedented enantioselective modification of *N*-Aryl glycines via synergistic Brønsted acid/photoredox catalysis (scheme 18).[156] This method allows for C-H functionalization with α-bromo ketones **O** as

readily available radical precursor. By substantial reaction screening, Wang *et al.* were able to combine the use of iridium bipyridyl catalyst [Ir]-**L9** and axially chiral phosphoric acid (*R*)-CPA for successful radical functionalization of glycine. The screening of the substrate spectra demonstrated a highly selective reaction with diastereomeric ratios of up to > 20:1 and enantiomeric excess of up to 99%. Exceptions were observed when R_1 represents an electron-poor aryl group such as 4-nitro or 4-cyano phenyl which gave diastereomeric mixtures of 1.2:1 to 3:1.



Scheme 18: First enantioconvergent radical C-H functionalization of *N*-Aryl glycines **P**.

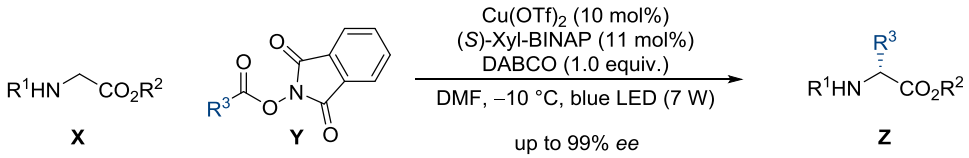
The postulated mechanism is depicted in scheme 19.[156] The reaction starts by excitation of the [Ir(III)] photocatalyst and consecutive oxidation of glycine ester **P** via SET process to an intermediary radical cation. Deprotonation of the radical cation and 1,2-H shift generates radical species **R**. After a second SET oxidation by excited state [*Ir(III)] catalyst, iminium ion **S** is obtained. The generated [Ir(II)] species then serves as a reducing agent of α-bromo ketone **O** which generates radical anion **T** and regenerates the [Ir(III)] catalyst.



Scheme 19: Postulated mechanism for C-H functionalization via dual catalysis.[156]

Mesolytic cleavage then affords the carbon-centered radical **U** which completes the photoredox cycle. The phosphoric acid **V** serves as bifunctional catalyst which binds both the iminium ion **S** as well as the carbon radical **U** via hydrogen bonding and thereby facilitates consecutive radical addition. The chiral environment of the phosphoric acid forces a stereoselective *Re-Re* face addition to generate radical cation **W**. Finally, SET reduction by a [Ir(II)] species liberates the α-amino acid **Q**.

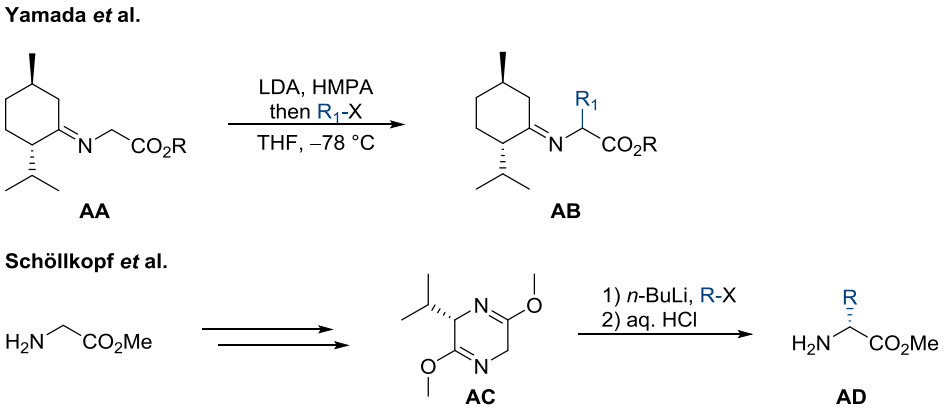
Later that year, Wang and Xu reported the asymmetric C(sp^3)-H alkylation of glycine via visible-light-induced copper catalysis using redox-active NHS-esters.[157] The groups switched from their previously described dual ligand system to the use of chiral (*S*)-Xyl-BINAP which allows for asymmetric radical addition with primary, secondary and tertiary alkyl radicals generated from their corresponding NHS esters **Y**.



Scheme 20: Enantioselective copper catalyzed C-H alkylation of glycines **X**.

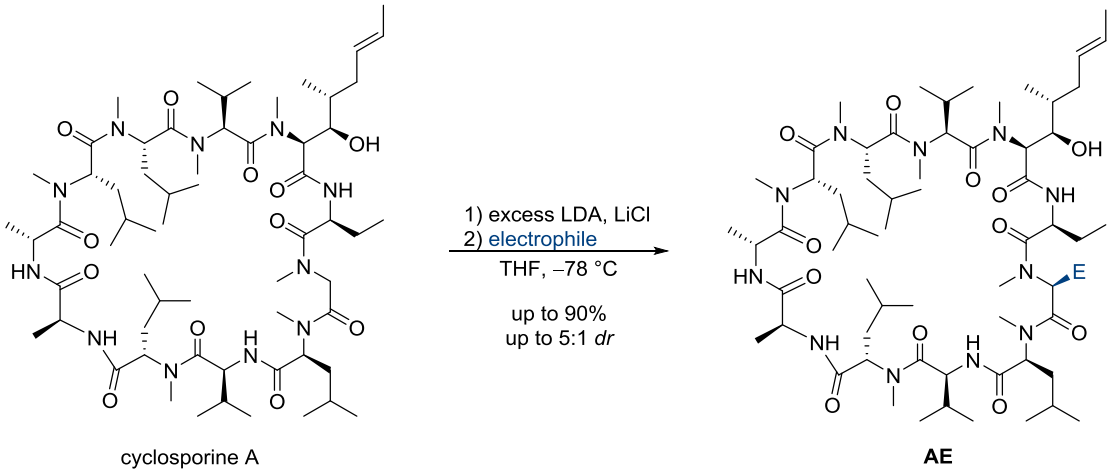
Besides these two novel enantioselective approaches, a multitude of reports for racemic and/or diastereoselective radical modifications of glycine have been described over the last couple of years, including radical C-H amination,[158] hydrazination,[159] alkoxylation,[160] multiple C-H alkylations,[161–163] alkenylations, arylations and more.[164–166] These advances allowed for the synthesis of various non proteinogenic amino acids such as β-fluoro amino acids,[167] α,β-diamino acids[168] and more and has been subject of several recent reviews.[133,169]

Prior to the rise in popularity of radical-based approaches toward amino acid and peptide functionalization, the modification via amino acid enolates, particularly glycine enolates as reactive intermediates has seen the most interest. Pioneering work was conducted by Yamada *et al.* in the late 1970's who used menthone and other chiral auxiliaries to achieve asymmetric induction (scheme 21, upper part).[170,171]



Scheme 21: Auxiliary-driven asymmetric alkylation of iminoester **AA** and bislactime **AC**.

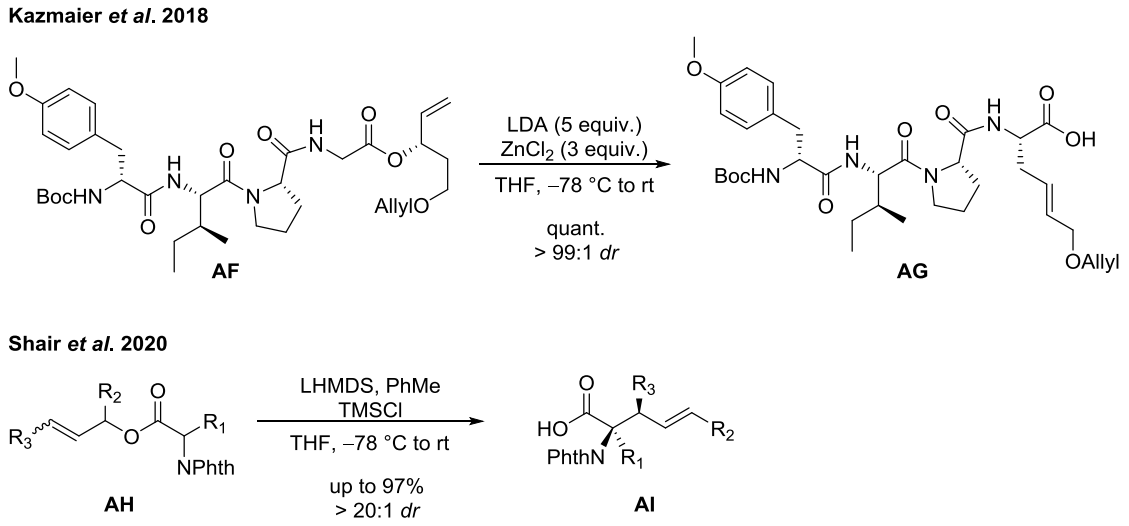
This auxiliary-based approach was extended by work from McIntosh with camphor auxiliaries,[172,173] and the Schöllkopf group which established amino acid-derived cyclic bislactimes to generate non-proteinogenic amino acids enantioselectively (scheme 21, lower part).[174–176] In the 1990s Seebach and coworkers were able to demonstrate the possibility to directly generate enolates from peptides with strong lithium bases without erosion of the configuration of amino acids (scheme 22).[177,178] Initial solubility problems of poly-lithiated peptides in nonpolar solvents due to aggregation could be surmounted by the addition of lithium chloride which facilitates deaggregation and hence increases the solubility significantly.[179,180] Eventually, this discovery led to the diastereoselective alkylation of the sarcosine unit of cyclosporine A in high yield.[181]



Scheme 22: Diastereoselective alkylation of the sarcosine unit in cyclosporine A.

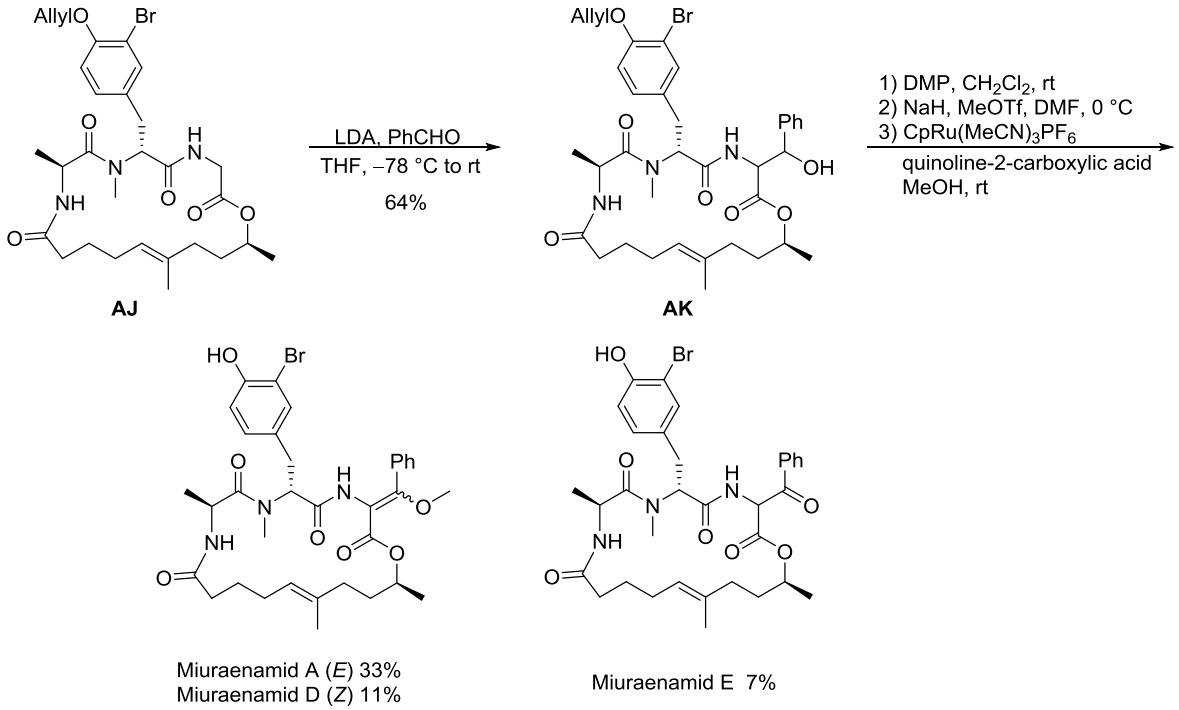
The work by Seebach sparked the interest of several other research groups which examined glycine or peptide enolates as nucleophiles for a variety of transformations.[182–184] Kazmaier *et al.* described the synthesis of α-allyl-amino acids via Claisen rearrangement using zinc chelated ester enolates of glycine allyl esters.[185,186] The use of readily available alkaloids quinine and quinidine as chiral ligands led to the asymmetric rearrangement of simple glycine allyl esters which could be applied to the synthesis of 5-epi-isofagomine.[187–189] Recently the group also described the use of chelated ester enolate Claisen rearrangement during their efforts toward the synthesis of HDAC inhibitor derivatives.[190,191] Treatment of linear tetrapeptide allyl ester **AF** with LDA and zinc chloride afforded perfect chirality transfer and Cyl-1 precursor **AG** was obtained in quantitative yield (scheme 23). Several groups described similar approaches toward γ,δ-unsaturated amino acids via Claisen rearrangement,[192–195] most notably via the Ireland modification. In 2020 the group of Stoltz reported the Ireland-Claisen rearrangement of tetrasubstituted enolates which exhibits an unusual phenomenon which they labeled as “global diastereoconvergence”.[196] This term is an attempt to describe the observed convergence of all possible olefin isomers which results in the formation of the identical diastereomer. A comprehensive study demonstrated the preservation of the diastereochemical outcome independent from the geometry of the intermediary-formed silyl enol ether and the allyl ester geometry. Studies of the mechanism

by quantum mechanical (QM) calculations via DFT coupled with local coupled-cluster theory (DLPNO-CCSD(T)) subsequently revealed a different reaction pathway for *Z*- and *E*-enol ethers. In the case of *trans* allylic olefins, *Z*- and *E*-enol ethers proceed through chair and boat transition states, respectively. For *cis* allylic olefins, the trend is reversed.



Scheme 23: Asymmetric ester enolate Claisen rearrangement.

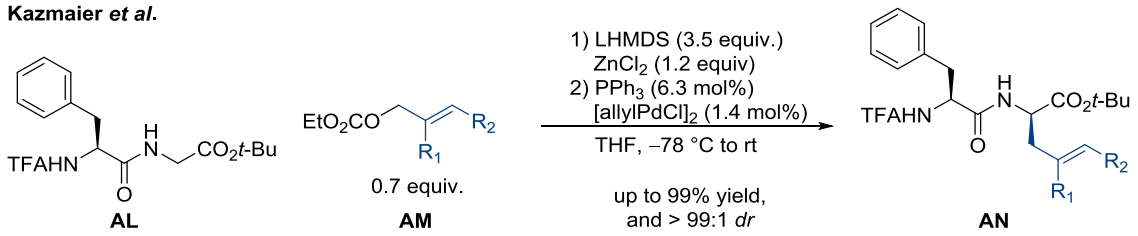
Furthermore, over the last two decades several reports of glycine or peptide modification via aldol reaction[197,198] or Michael addition[199] have been described. Kazmaier and coworkers, for example, described the late-stage modification of miuraenamide precursors via enolate chemistry.[200,201] Aldol reaction of cyclic depsipeptide **AJ** gave an inconsequential mixture of diastereomers of **AK** and subsequent modification of the β-hydroxy amino acid unit afforded the natural products miuraenamide A, D and E (scheme 24).



Scheme 24: Total synthesis of miuraenamides via late-stage aldol reaction.

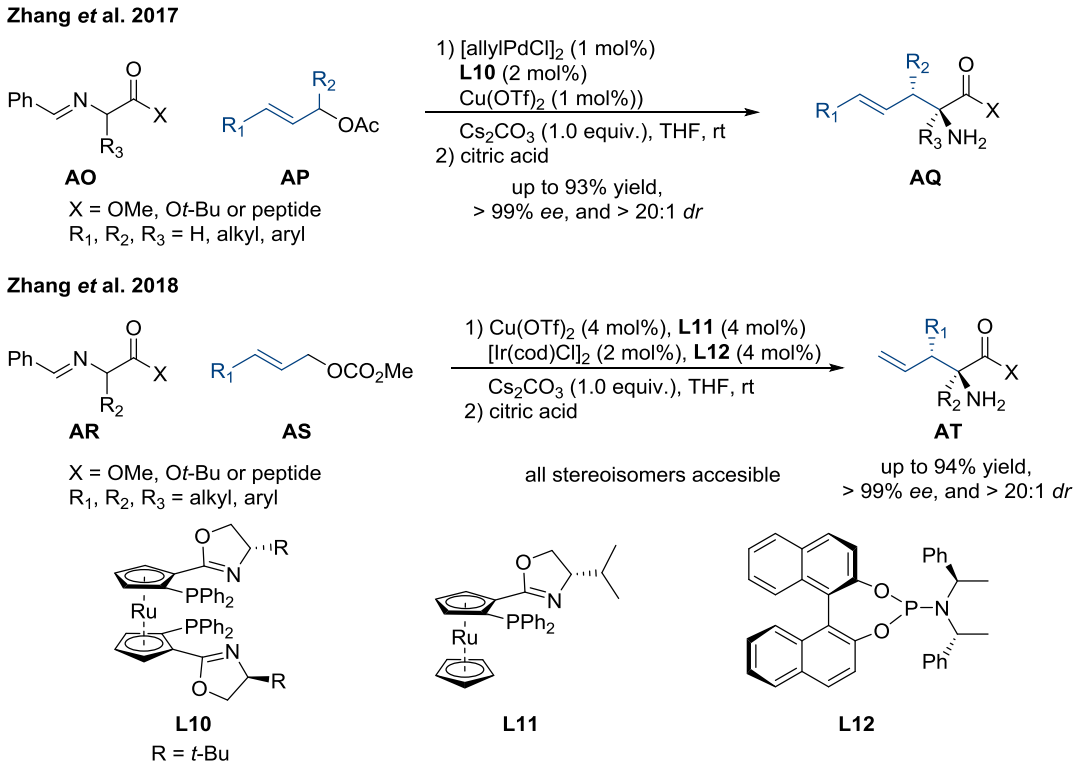
Besides these approaches which have seen reasonable interest over the last decades, the transition metal-catalyzed allylic alkylation has emerged as the most prominent tool for enolate functionalization of amino acids. In general, the variants can be separated into the use of chelated ester enolates of amino acids, which was mainly developed by the group of Kazmaier, and the use of azomethine ylides as nucleophiles. Such azomethine ylides are usually generated from aldimine or ketimine esters and therefore represent a continuation of the work of Yamada in the 1970s.

Kazmaier *et al.* described the use of zinc chelated ester enolates of TFA-glycine *tert*-butyl ester as excellent nucleophiles for transition metal-catalyzed allylic alkylation in 1999.[84] Later, they were able to apply this method to the palladium-catalyzed allylic alkylation of peptides (scheme 25),[202–204] peptide amide enolates,[205] glycolates,[206] and α-amino ketones.[207] Additionally, the group described the use of rhodium[208,209] and ruthenium[210,211] catalysts for branched selective allylic alkylations of such chelated enolates. A similar approach was followed by Trost and coworkers who described the use of azlactone enolates for palladium-[212] and molybdenum-[51] catalyzed allylic alkylation.



Scheme 25: Palladium-catalyzed allylic alkylation of chelated peptide enolates.

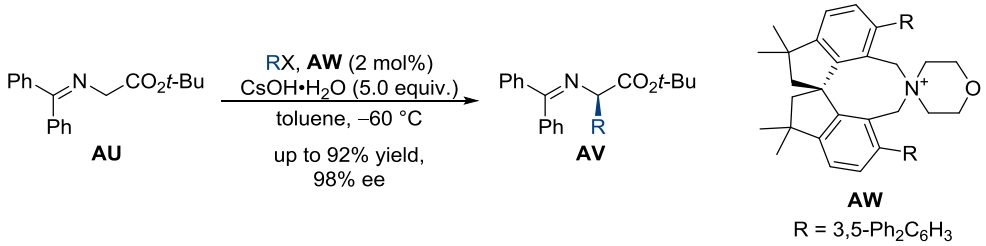
The second approach via azomethine ylides has been pursued by several different groups.[213,214] Over the last four years, this variation has seen a resurgence in popularity with reports of dual catalytic systems of copper and palladium or iridium.[215,216] Zhang and coworkers reported the allylic alkylation of aldimines **AO** via copper/palladium dual catalysis with ruthenocene ligand **L10** (scheme 26, upper part).[217] Using this protocol the group was able to achieve highly diastereo- and enantioselective alkylation with differently substituted allyl acetates. This afforded non-proteinogenic α-amino acids and α,α-disubstituted α-amino acids in high yield and selectivity. Other groups reported the use of vinyl-cyclopropanes,[218] cyclic carbonates,[219] and other electrophiles in such types of alkylations and allenes for allenylic alkylations.[220] Besides the palladium-catalyzed variant, several groups described dual catalytic systems of copper and iridium to achieve branched selective allylation of azomethine ylides. In 2018, Wang and Zhang (scheme 26, lower part) independently reported very similar copper/iridium catalysis protocols to achieve the diastereo- and enantioselective allylic alkylation of aldimines **AR**.[215,221] Both groups used a ruthenocene ligand **L11** or ferrocene ligand respectively alongside phosphoramidite ligand **L12**, which allowed the synthesis of all four stereoisomers in selective fashion.



Scheme 26: Asymmetric allylic alkylation of azomethine ylides via dual catalysis.

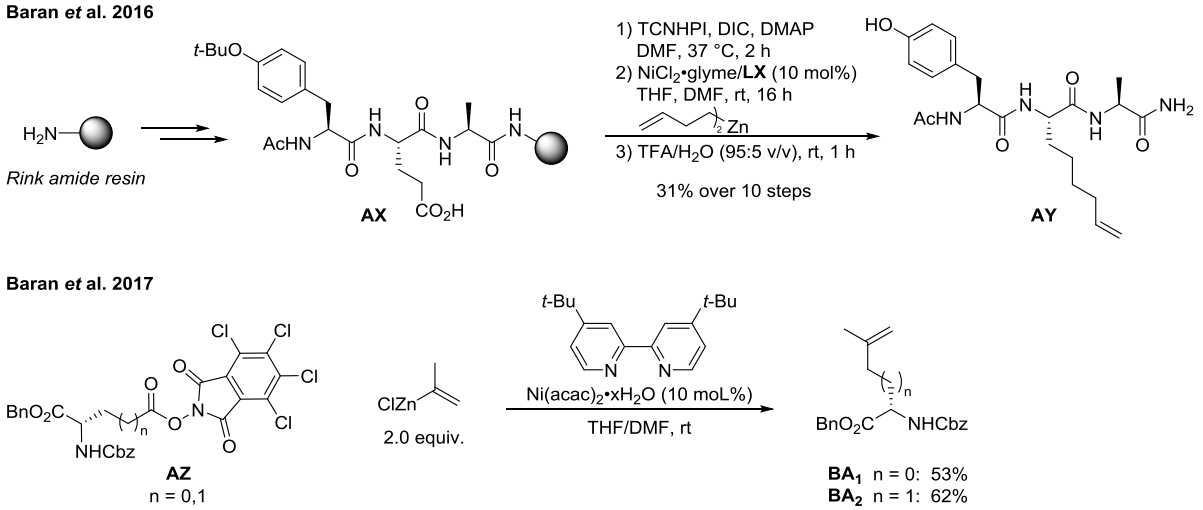
Furthermore, a combination of the approaches via allylation and rearrangement chemistry has been described by Tambar and coworkers.[222] The group developed the allylic amination of tertiary aminoesters followed by palladium-catalyzed [2,3]-Stevens rearrangement to access α-allylated glycine esters.

Alongside the transition metal-catalyzed allylic alkylation of aldimines, the allylic alkylation via phase transfer catalysis (PTC) with chiral ammonium salts has seen significant interest as well.[223–227] This method was pioneered by O'Donnell[228,229] and advanced to the current state of the art by Maruoka through the discovery of C_2-symmetric quaternary ammonium salt catalysts.[230–232] Since then, a multitude of such chiral ammonium salt catalysts have been developed for organocatalytic alkylations.[233–235] In 2021 Bai *et al.* described the synthesis of an improved quaternary ammonium salt catalyst **AW** with a rigid backbone and small dihedral angles.[236] Those modifications resulted in enhanced enantioselectivities in the alkylation of *tert*-butyl glycinate Schiff base **AU** (scheme 27).



Scheme 27: Asymmetric alkylation of glycinates via phase transfer catalysis by Bai *et al.*

While the above-mentioned approach via modifications of the glycine unit has seen the most attention, in 2009 a completely different approach was reported. Liang and Li described the first decarboxylative cross-coupling of amino acids via copper catalysis.[237] This represented the first of a series of similar reports which study the modification of amino acids via decarboxylative cross-coupling. Besides the *C*-terminal modification via decarboxylative borylation,[238] arylation,[239] Minisci-type addition[240] and other methods,[241–244] the modification of the side chain via aspartic and glutamic acid has seen significant progress. For example, in 2016 and 2017, Baran and coworkers described the nickel-catalyzed decarboxylative alkylation,[245] arylation,[246] and alkenylation[247] of amino acids with redox-active TCNHP esters (scheme 28).



Scheme 28: Modification of aspartic and glutamic acid via nickel catalyzed decarboxylative cross coupling. TCNHPI = *N-hydroxytetrachlorophthalimide*

Other popular methods such as C-H activation have frequently been used for the modification of amino acids and peptides, mainly via alanine functionalization.[248–250] Moreover, functionalization of dehydroamino acids via radical couplings[251] such as thiol-ene reaction[252–254] and transition metal catalyzed cross coupling of halo-amino acids have been described as well.

Overall, significant progress has been made in the field of peptide modification over the last decades and plenty of methods are now routinely used in the synthesis of complex non-proteinogenic amino acids and peptides, but major challenges still remain unsolved which continues to thrive further research in this area.

2.3 Callipeltins

2.3.1 Isolation and Structure Elucidation

In 1996 Zampella and coworkers collected a marine sponge *Callipelta* sp. near the east coast of New Caledonia in the Pacific Ocean.[255] The crude aqueous and ethanolic extracts exhibited several antifungal, cytotoxic and anti-HIV activities. After sequential extraction and droplet counter current chromatography (DCCC) the team was able to isolate the novel compound callipeltin A. Structure elucidation was performed by the usual means of MS, NMR and amino acid analysis which resulted in the initially proposed structure depicted in figure 2. Callipeltin A is a decapeptide containing several nonproteinogenic amino acid residues, a rare terminal β-hydroxy acid as well as a cyclic heptapeptide core. The configuration of the β-methoxy tyrosine residue could not be resolved at first.

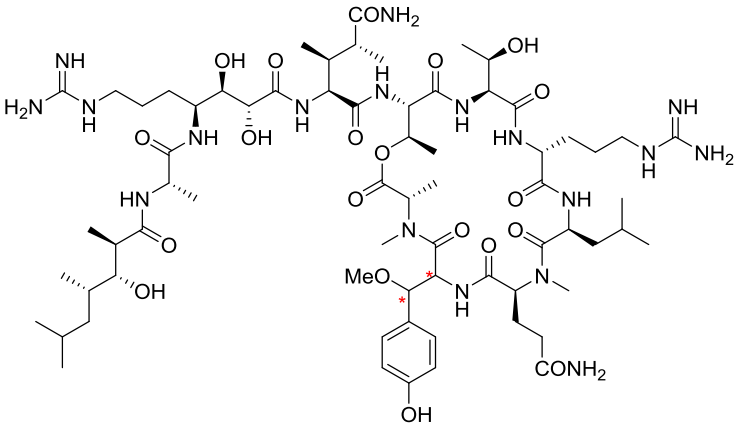


Fig. 2: Proposed structure of callipeltin A.[255]

As part of the isolation of Callipeltin D and E in 2002 the team of Zampella reevaluated their original assignment of several amino acids.[256] They reassigned the L-alanine and one L-threonine to D-alanine and D-*allo*-threonine respectively as well as the (*R*,*R*,*S*) configuration of the polyketide moiety to (*R*,*R*,*R*). Not until 8 years after the initial isolation the group was finally able to assign the β-methoxy tyrosine residue. Chemical synthesis of all stereoisomers and ozonolytic degradation to their respective aspartic acid derivatives revealed the (2*R*,3*R*) configuration of the tyrosine moiety.[257]

Following the reassignment of one threonine, the group also published a QM-NMR study of callipeltin A in which they compared calculated and experimental values of the coupling constants.[258] This led to the structural reassignment of the remaining L-threonine to a second D-*allo*-threonine. The revised structure of callipeltin A is depicted in figure 3.

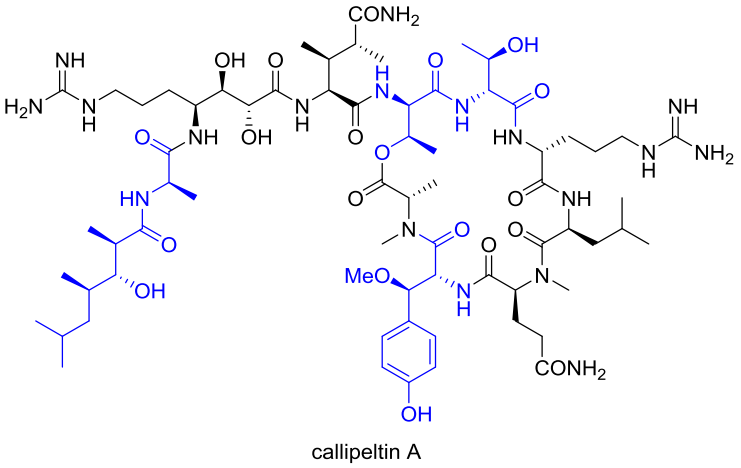


Fig. 3: Reassigned structure of callipeltin A (reassigned motifs shown in blue).

Besides the parent structure of callipeltin A, several other callipeltins have been isolated over the past two decades. Callipeltin B and C were isolated from the same sponge *Callipelta* sp. in the same year as callipeltin A.[259] Callipeltin B possesses the same cyclic depsipeptide core as callipeltin A, but varies in the *N*-terminus containing a novel pyroglutamic acid motif (fig. 4). Callipeltin C represents the acyclic form of callipeltin A.

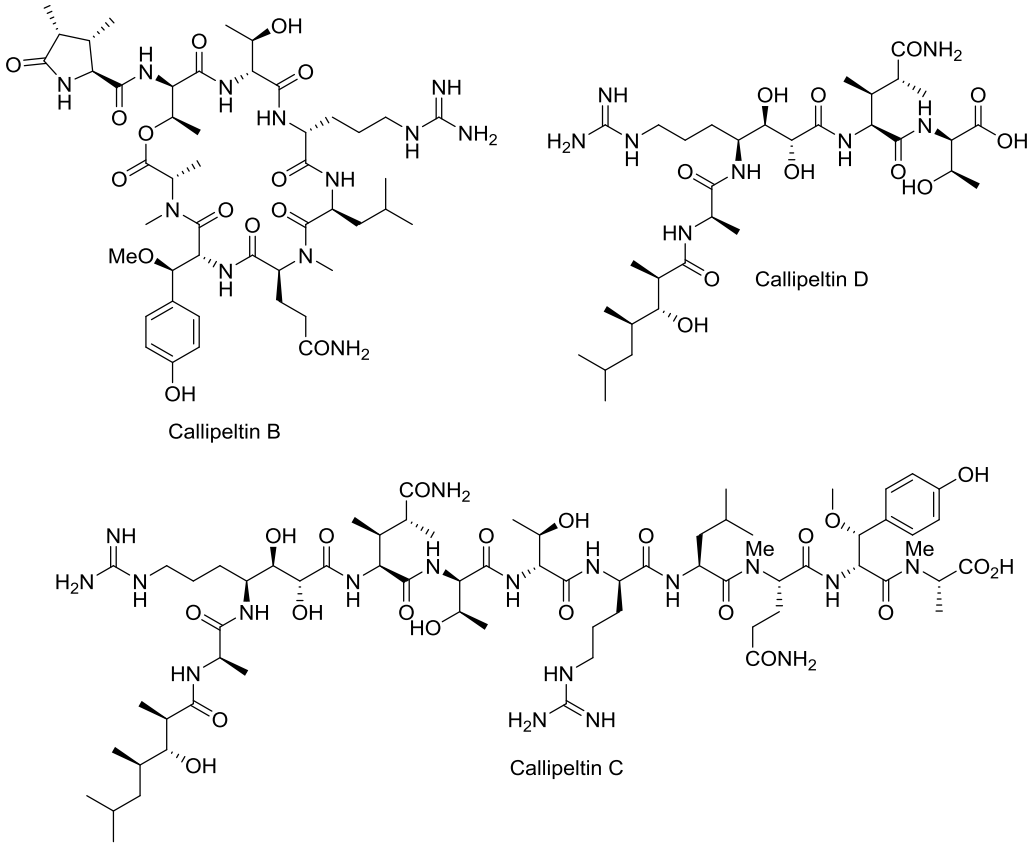


Fig. 4: Structure of callipeltins B-D.

The callipeltin family also contains some smaller structures, e.g., callipeltin D represents the sidechain of callipeltin A with an additional D-*allo*-threonine as *C*-terminus.[256] To date, the complete group of callipeltins consists of 17 representatives up to callipeltin Q.[260–262]

Additionally, several structurally related marine peptides have been isolated (fig. 5). They all share their potent antiviral activity, suggesting a similar mode of action and the importance of the novel amino acids of this group for their activity. This group of peptides includes the neamphamides,[263–265] stellatolides,[266] pipecolidepsins,[267,268] mirabamides,[269,270] homophymines,[271,272] stellettapeptins,[273] microspinosamides,[274] papuamides,[275,276] theopapuamides.[277,278]

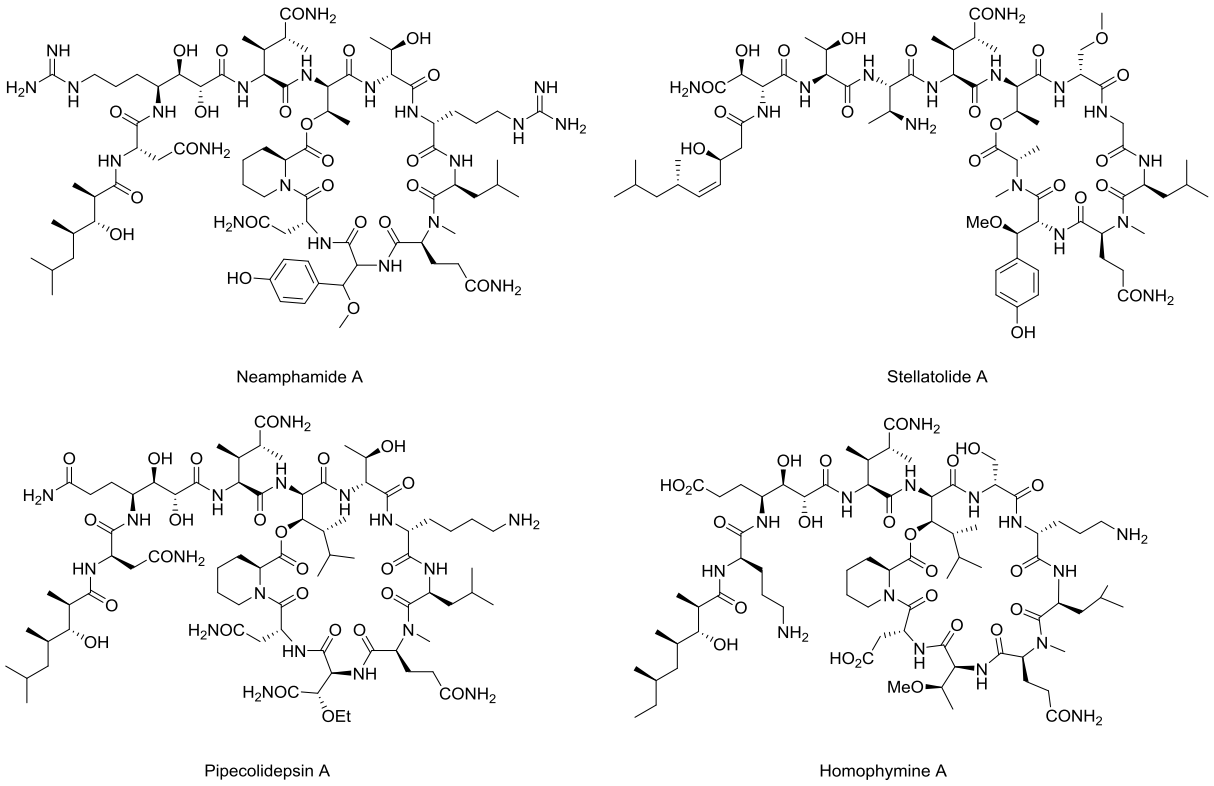


Fig. 5: Structure of related marine natural products.

2.3.2 Bioactivity

The bioactivity of callipeltin A was first described in 1996 when Zampella and coworkers described the antiviral activity against the HIV-1 strain with a CD_{50} of 0.29 µg/mL and ED_{50} of 0.01 µg/mL giving a selectivity index (SI) of 29. Additionally, they reported the antifungal activity against *Candida albicans.* The activity was measured by growth inhibition at 100 µg/disc (6 mm) with 30 mm of inhibition.[255]

Along with the isolation of callipeltin B and D, Zampella *et al.* evaluated callipeltin A-C against various human cancer cell lines (table 2).[259] Callipeltin A displayed the highest activity with IC_{50} values below 1.1 µg/mL for the human bronchopulmonary non-small-cell-lung-carcinoma cell line NSCLC-N6 and the human renal carcinoma cell line E39. While callipeltin B showed mostly similar or slightly lower activities, callipeltin C proved to be significantly less cytotoxic.

In contrast to callipeltin A both callipeltin B and C proved to be inactive as antiviral compounds.[259]

Table 2: In vitro cytotoxic activity (IC_{50} in µg/mL) of callipeltin A-C against cancer cell lines.

Tumor cells	callipeltin A	callipeltin B	callipeltin C
NSCLC-N6	< 1.1	1.3	53.5
NSCLC-N6 C15	> 30	22.5	-
NSCLC-N6 C92	< 3.3	> 30	-
NSCLC-N6 C98	< 3.3	< 3.3	-
E39	< 1.1	> 10	36.1
P388	< 3.3	< 3.3	-
M96	< 3.3	< 3.3	-

Callipeltin A was additionally reported to be a strong Inhibitor of the cardiac Na^+/Ca^{2+} exchanger (IC_{50} = 0.85 µM) inducing a positive inotropic effect accompanied by a rise in resting tension.[279,280]

Lipton *et al.* reported the synthesis and biological evaluation of a simplified derivative of callipeltin B which lacks the β-methoxy functionality at the tyrosine residue.[281] The cytotoxicity against HeLa cells decreased only slightly with IC_{50} values of 98 µM and 128 µM for callipeltin B and desmethoxycallipeltin B, respectively. This difference is smaller than expected if the methoxy group was essential for the cytotoxic activity and is more likely caused by conformational change. Lipton concluded the presence of a quinone methide motif was not necessary for the bioactivity, contrary to earlier presumptions.

The group of Konno and coworkers expanded on this study of the cytotoxic activity of callipeltin B.[282] They synthesized several simplified analogs of callipeltin B, containing mostly proteinogenic amino acids. Cytotoxicity assays against HeLa cells revealed the complete inactivity of almost all derivatives which pointed toward the necessity of a dimethyl glutamine or dimethyl pyroglutamic acid in the side chain for cytotoxic activity.

Table 3: Cytotoxic activity of callipeltins against HeLa cells.

compound	CC50 (µM)
isolated callipeltin A	0.004
synthetic callipeltin B	> 400
synthetic callipeltin M	> 400
synthetic callipeltin E	> 400
isolated callipeltin C	17
isolated callipeltin D	> 400

In 2016 Konno *et al.*, after their successful total synthesis, investigated the cytotoxicity of synthetic and isolated callipeltin B once more.[283] Surprisingly, they found no cytotoxic

activity for synthetic callipeltin B as well as callipeltin E and M. Isolated callipeltin B, provided by Zampella *et al.*, on the other hand, showed CC_{50} values of 130 µM. After analysis of the isolated callipeltin B sample, they found significant contaminations by callipeltin C and H. The group then tested the cytotoxicity of isolated and synthetic callipeltins against HeLa cells (table 3). In these assays, no cytotoxic activity was found for callipeltin B while callipeltin C showed moderate activity (CC_{50} = 17 µM). They also found no cytotoxicity for callipeltin D concluding that both linear and cyclic motifs are necessary to show cytotoxic activity.

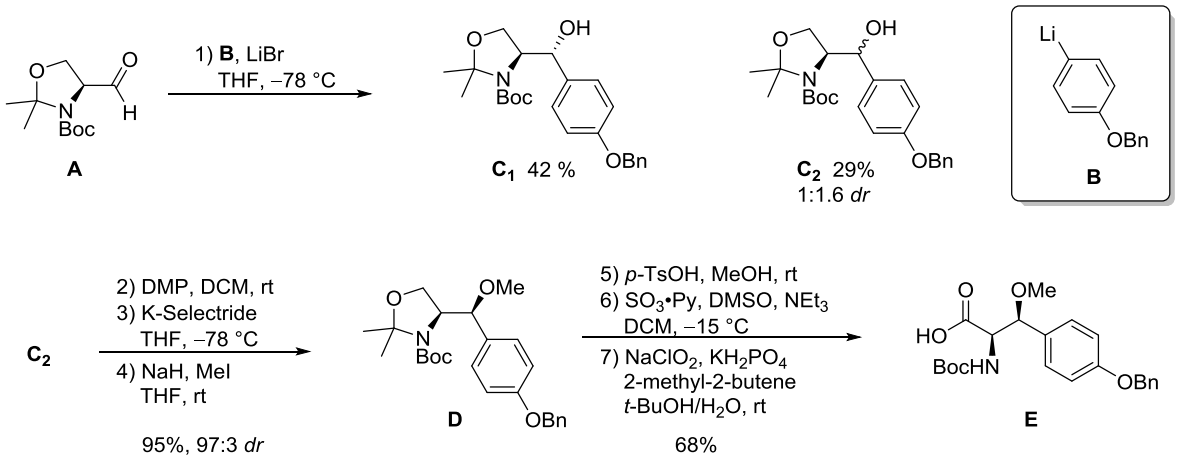
More recently isolated callipeltins N-Q were also tested against several cancer cell lines (A2058, HT-29 and MCF-7) by Tabudravu and coworkers.[262] The macrocyclic derivatives callipeltin N and O showed similar cytotoxic activities (IC_{50} 0.1-2.1 µM) as described for callipeltin A and related marine macrocyclic depsipeptides. The linear derivatives P and Q were both inactive emphasizing the necessity of both a cyclic core as well as the side chain containing the unusual amino acids for cytotoxic activity once more.

2.3.3 Synthesis Attempts and Total Synthesis of Callipeltins

Since the isolation 25 years ago numerous attempts toward the total synthesis of callipeltin A have been made. Up to date, all approaches have been unsuccessful and only the synthesis of building blocks has been achieved. While the research for a successful total synthesis of callipeltin A is still ongoing, several syntheses of less complex representatives of the callipeltin family have been described.

2.3.3.1 β-Methoxy Tyrosine

The first synthesis of this building block was reported by Hamada and coworkers in 2002.[284] In an attempt to elucidate the stereochemistry of the tyrosine residue in callipeltin A they developed a strategy to access all stereoisomers from Garner's aldehyde **A** (scheme 29).

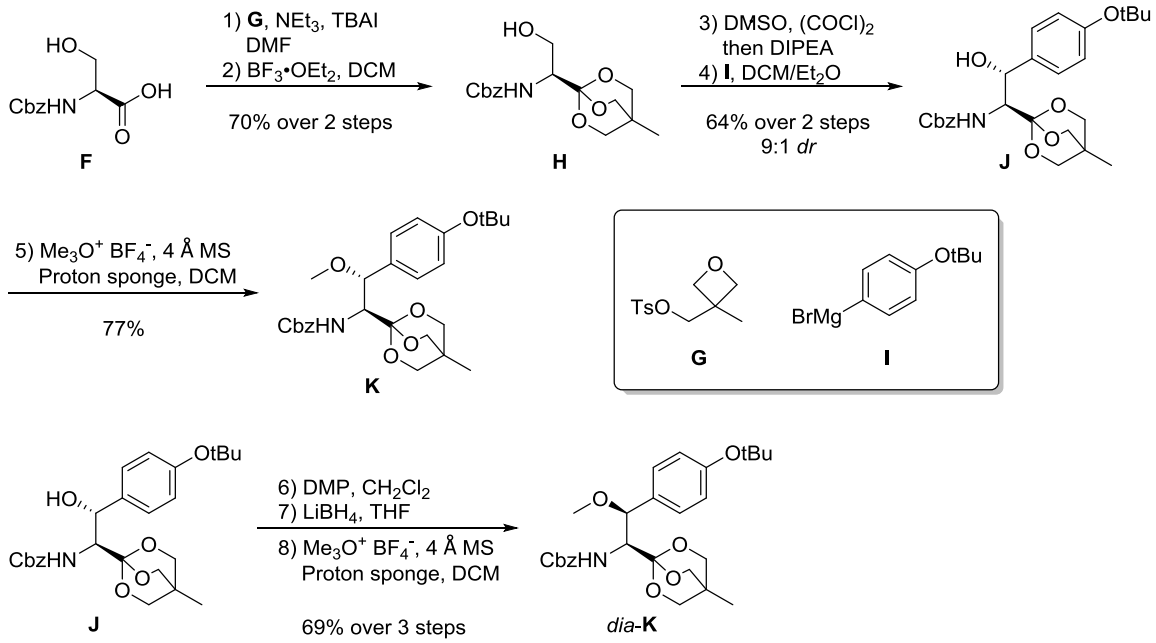


Scheme 29: Synthesis of β-methoxy tyrosine **E** from Garner aldehyde.

In the first step Garner aldehyde was treated with aryl lithium **B** which afforded alcohol **C** in moderate selectivity (3:1 *dr*). (2*S*,3*R*)-**C_1** was obtained in 42% yield after crystallization alongside 29% of a diastereomeric mixture which proved to be inseparable. To obtain

(2*S*,3*S*)-**C**, the mixture was oxidized to the corresponding ketone and subsequently reduced with *K*-Selectride. This sequence afforded a scalemic mixture, due to partial racemization in the reduction step, which required another crystallization. After methylation of the resulting alcohol with methyl iodide and sodium hydride, methyl ether **D** was obtained in 95% with 94% diastereomeric excess. Acid mediated deprotection of the acetal, follow by sequential oxidation under Parikh-Doering and Pinnick conditions afforded protected β-methoxy tyrosine **E**. The remaining isomers were synthesized via the same route from (2*S*,3*R*)-$\mathbf{C_1}$ and (*R*)-Garner's aldehyde, respectively.

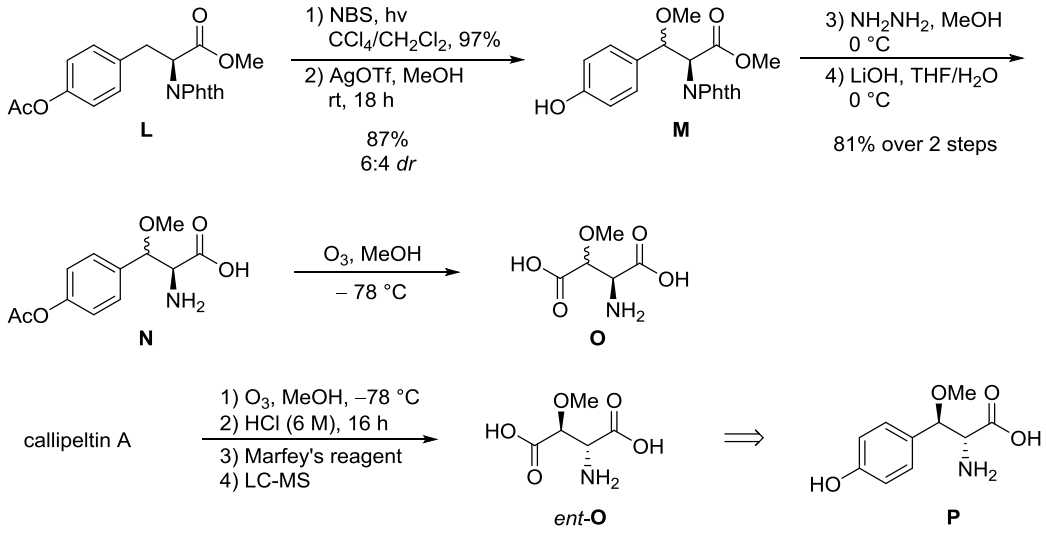
Similar to Hamada, Joullié *et al.* envisioned a strategy to access the four stereoisomers via the method of Lajoie from D- and L-serine.[285,286] Cbz-Serine **F** was transformed into the ortho-ester **H** via the oxetane ester by esterification with tosylate **G** and Lewis acid mediated cyclization (scheme 30). Oxidation to the aldehyde using Swern conditions followed by addition of Grignard reagent **I** afforded alcohol **J** in 64% yield (9:1 *dr*). *O*-methylation was achieved by treatment with Meerwein's trimethyl oxonium salt in the presence of a proton sponge and molecular sieves. Alcohol **J** was oxidized by Dess-Martin oxidation, subsequently reduced with $LiBH_4$ and methylated under the conditions described before to afford *anti*-diastereomer *dia*-**K**.



Scheme 30: Preparation of protected β-methoxy tyrosines **K** by Joullié *et al.*

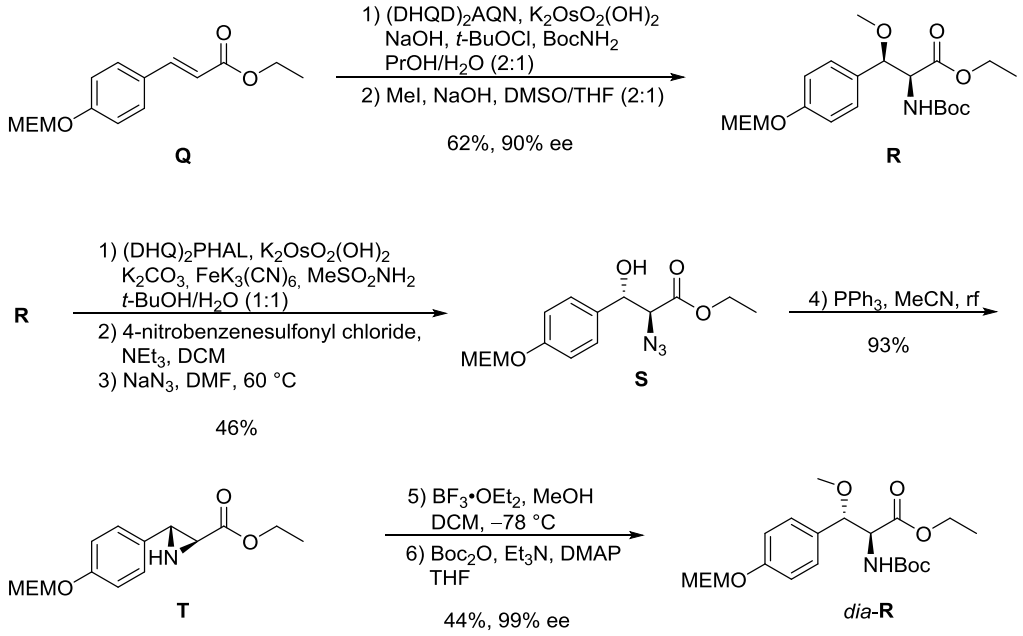
In 2005 Zampella *et al.* described the synthesis of all stereoisomers and were able to assign the relative and absolute configuration of β-methoxy tyrosine in callipeltins (scheme 31).[257] The group used Easton's method[287] of benzylic bromination followed by silver-mediated substitution to obtain a diastereomeric mixture of β-methoxy tyrosine **M**. The diastereomers were separated by HPLC, deprotected and transformed to aspartic acid derivatives by ozonolysis. For comparison, Callipeltin A was ozonolyzed and hydrolyzed and the obtained amino acid residues derivatized with Marfey's reagent.[288] After HPLC comparison with the

synthetic isomers, derivatized with Marfey's reagent, the configuration of β-methoxy tyrosine **P** in Callipeltins was assigned as (2*R*,3*R*).



Scheme 31: Identification of absolute configuration of β-methoxy tyrosine **P** in callipeltin A.

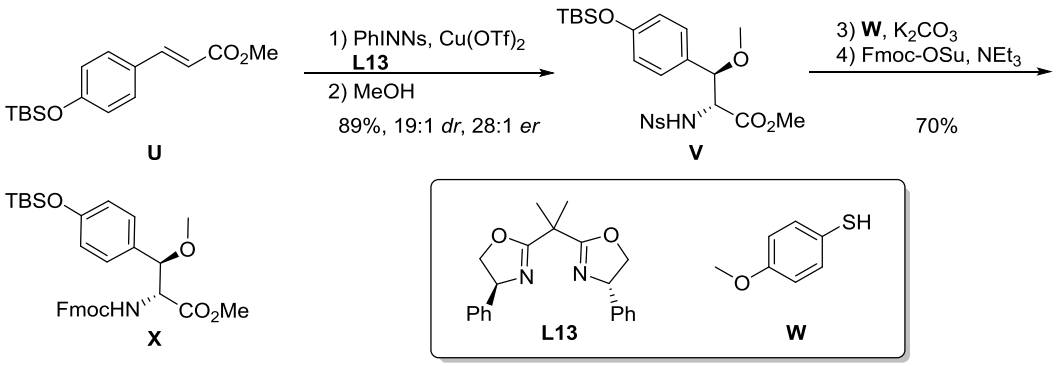
The group of Konno and coworkers reported the synthesis of β-methoxy tyrosine isomers via Sharpless amino hydroxylation and dihydroxylation.[289] *Syn*-diastereomers were accessed via amino hydroxylation of ethyl cinnamate **Q** using the chiral hydroquinidine derived ligand $(DHQD)_2AQN$ (scheme 32). After methylation with methyl iodide and sodium hydroxide β-methoxy tyrosine **R** was obtained in 62% yield and 90% enantiomeric excess. To access the *anti*-diastereomers, ethyl cinnamate **Q** was first dihydroxylated under Sharpless conditions using AD-mix α. Subsequent inversion of the C-2 stereocenter by nosylation and substitution with sodium azide afforded azide **S**.



Scheme 32: Synthesis of β-methoxy tyrosine stereoisomers **R** by Konno and coworkers.[289]

The azide was then transformed into aziridine **T** via a mixed Staudinger/Appel reaction. Lewis acid-mediated regioselective ring-opening and protection of the resulting amine as a Boc-carbamate afforded β-methoxy tyrosine *dia*-**R** in high enantiomeric excess.

Lipton *et al.* reported an approach toward β-methoxy tyrosine in 2007.[290] Starting from cinnamyl ester **U**, they developed an asymmetric aziridination with PhINNs (N-(p-nitrophenyl sulfonyl)iminophenyliodinane) as a nitrene source and bis-oxazoline ligand **L13** (scheme 33). Methanolysis of the resulting aziridine provided β-methoxy tyrosine **V** in high yield and stereoselectivity. The nosyl group was cleaved by thiolysis with thiophenol and K_2CO_3 and the amine was reprotected with Fmoc-OSu to afford tyrosine derivative **X** in 70% yield.

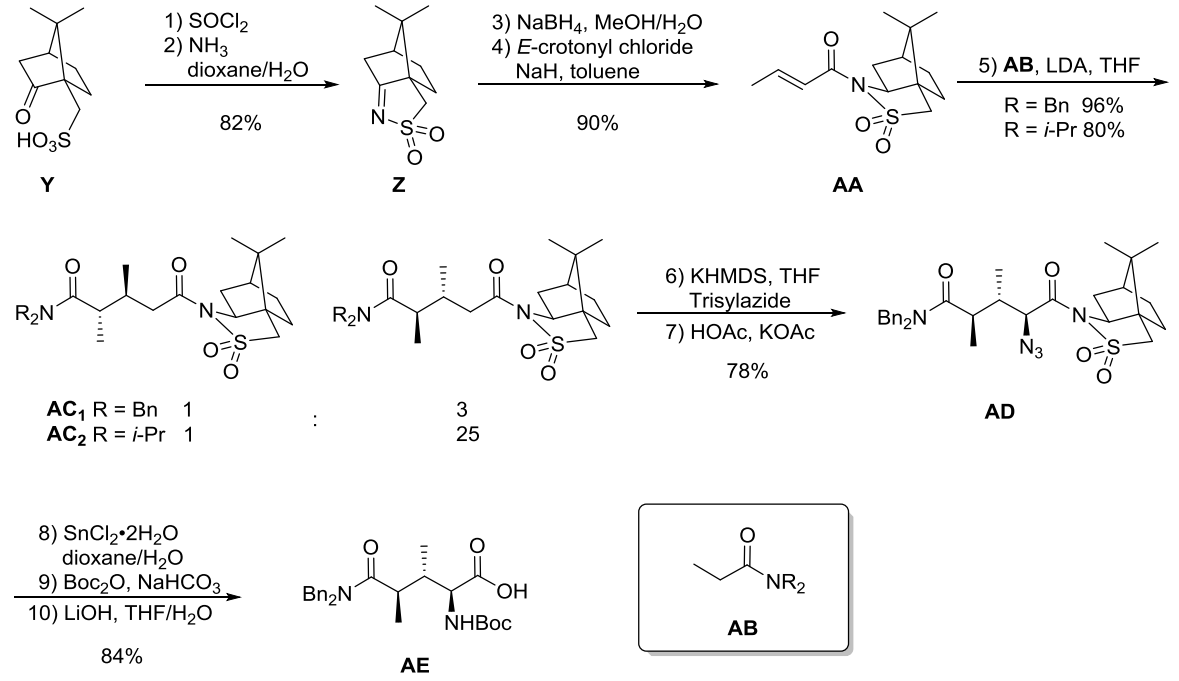


Scheme 33: Synthesis of β-methoxy tyrosine **X** by asymmetric aziridination.

Several other groups also described synthetic routes toward (2*R*,3*R*)-β-methoxy tyrosine and similar derivatives.[291–293]

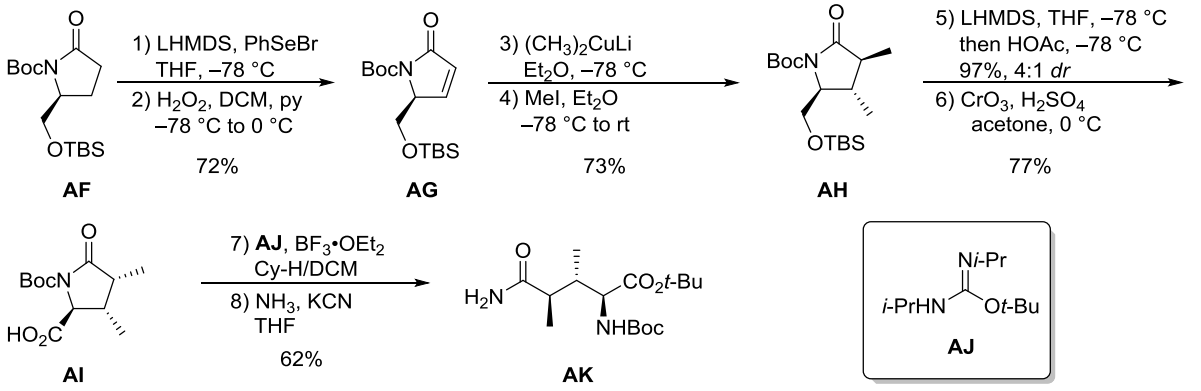
2.3.3.2 (3*S*,4*R*)-Dimethyl-L-Glutamine (diMeGln)

In 2000 Joullié and coworkers reported the first synthesis of (3*S*,4*R*)-dimethyl-L-glutamine (diMeGln) using Oppolzer's sultam as chiral auxiliary.[294,295] The camphor sultam was prepared from camphor sulfonic acid in three steps and reacted with *E*-crotonyl chloride in the presence of sodium hydride to afford sultam **AA** (scheme 34). Initial attempts of Michael addition with various enolates of type **AB** proved only moderately selective. This could be overcome by the use of di-*iso*-propylamide **AB** as sterically demanding nucleophile (25:1 *dr*). However, due to the difficulty to deprotect such diisopropylamides, the dibenzyl protected derivate was used for subsequent steps despite lower diastereoselectivity. The α-amino group was introduced by electrophilic azidation with KHMDS and trisylazide followed by equilibration of the α-stereocenter to afford **AD** as a single diastereomer in 78% yield. Reduction of the azide with tin(II) chloride, subsequent Boc protection and cleavage of the chiral sultam by saponification afforded diMeGln **AE**.



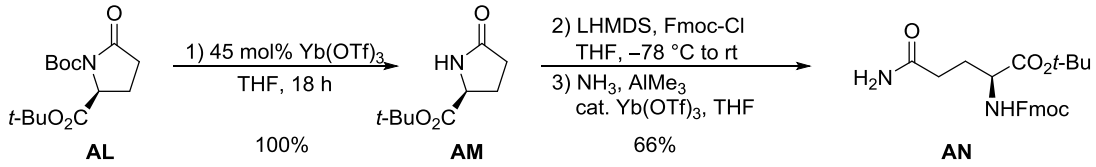
Scheme 34: Synthesis of diMeGln **AE** via auxiliary-directed Michael-addition.

The groups of Hamada and Lipton reported very similar strategies toward diMeGln employing cuprate addition approaches. Starting from lactam **AF**, prepared in 4 steps from L-pyroglutamic acid, Lipton *et al.* introduced the double bond in a two-step protocol of α-selenation and oxidative elimination (scheme 35).[296] The vicinal methyl groups were introduced by 1,4-addition of methyl cuprate to the α,β-unsaturated system followed by methylation of the resulting enolate with methyl iodide. This resulted in the exclusive formation of the *trans*,*trans*-diastereomer **AH**. To obtain the desired *cis* relationship between C-3 and C-4, **AH** was subjected to enolization with LHMDS and quenching with acetic acid at –78 °C (4:1 *dr*). The epimers were separated by column chromatography and the undesired epimer was resubmitted to the enolization conditions. After Jones oxidation, carboxylic acid **AI** was obtained in 77% as a single diastereomer. The acid was transformed to the *tert*-butyl ester using isourea **AJ** and ring-opening was achieved by treatment with ammonia in the presence of catalytic amounts of KCN to afford diMeGln **AK**.



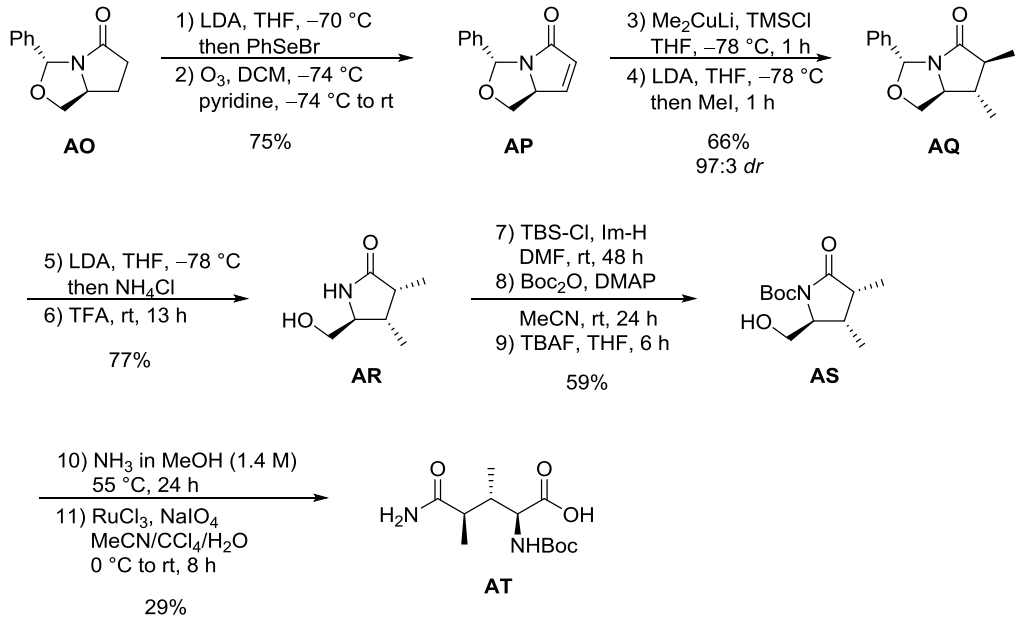
Scheme 35: Preparation of diMeGln **AK** via cuprate addition.

Since orthogonal deprotection proved difficult, Lipton and coworkers later reported the selective Boc-deprotection of lactam **AL** employing $Yb(OTf)_3$ as substoichiometric Lewis acid (scheme 36).[297] Fmoc-protection and $Yb(OTf)_3$ catalyzed ring-opening afforded protected glutamine **AN** in 66% yield.



Scheme 36: Selective Boc-deprotection by Lewis-acid catalysis.

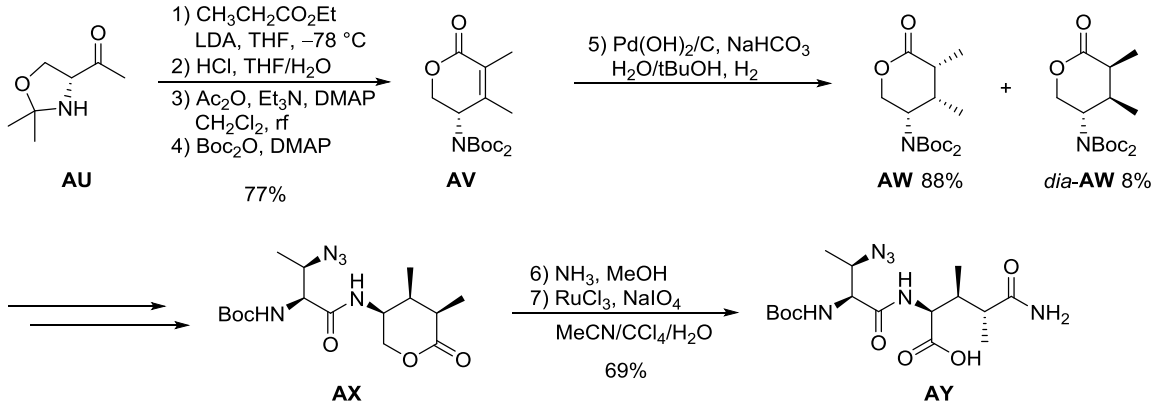
In a similar fashion, Hamada *et al.* started from pyroglutamic acid-derived lactam **AO**.[298] The α,β-unsaturation was installed by a two-step selenoxide elimination procedure matching Lipton's approach (scheme 37).[299] Cuprate addition to **AP** in the presence of TMSCl and α-methylation of the amide afforded *trans*,*trans*-lactam **AQ** in a highly diastereoselective fashion. Selective epimerization of C-4 was conducted by enolization with LDA followed by slow addition of saturated ammonium chloride solution at –78 °C. The hemiaminal was cleaved under strong acidic conditions using trifluoroacetic acid and a sequence of three protection group manipulations gave alcohol **AS**. Ring opening was achieved by exposure to ammonia at elevated temperature and the hydroxyl group was oxidized to the carboxylic acid **AT** in a one-pot procedure using $RuCl_3/NaIO_4$.



Scheme 37: Synthesis of diMeGln **AT** via cuprate addition.

As part of the total synthesis of Papuamide B, Ma and coworkers developed a strategy to access diMeGln by hydrogenation of a cyclic lactone.[300] Ketone **AU**, prepared from D-serine via a literature procedure, was subjected to aldol reaction with ethyl propionate followed by acid mediated cyclization (scheme 38). Dehydration using Ac_2O/DMAP/NEt_3 and twofold Boc-protection with Boc_2O/DMAP afforded lactone **AV** in 4 steps. The second Boc protecting

group was essential to achieve a selective hydrogenation. The hydrogenation was carried out using Pearlman's catalyst under an atmosphere of H_2 which afforded the desired *cis*-diastereomer **AW** in 88% yield along with 8% of *dia*-**AW**. After separation by flash chromatography, the amino group was deprotected and coupled to obtain dipeptide **AX**. Ring-opening by treatment with methanolic ammonia and oxidation of the hydroxyl group with $RuCl_3/NaIO_4$ gave diMeGln containing dipeptide **AY**.



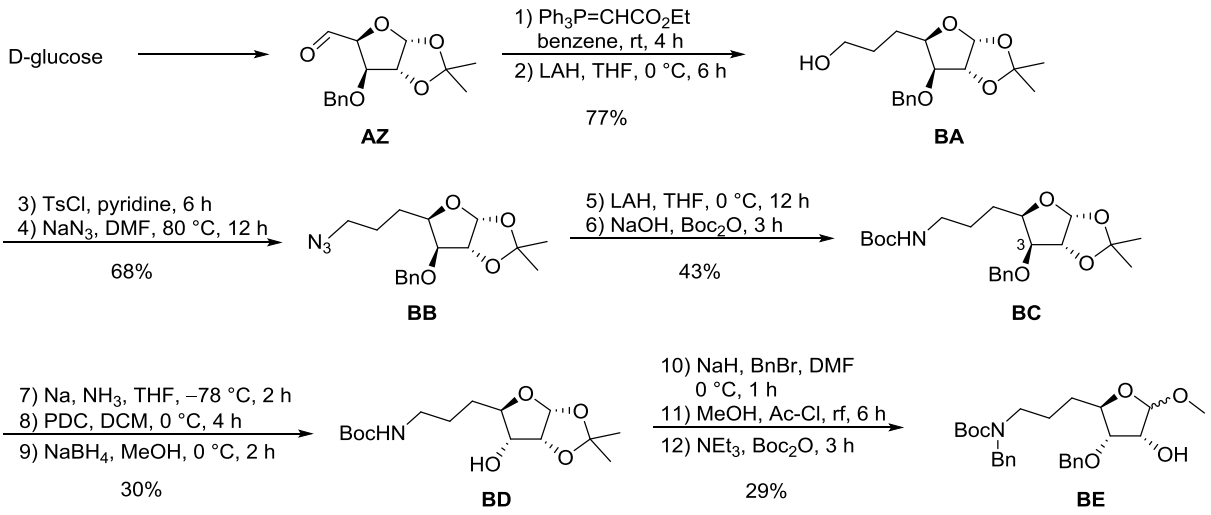
Scheme 38: Synthesis of diMeGln containing dipeptide **AY**.

In addition, the synthesis of (3*S*)-methyl glutamine[301] and (3*S*,4*R*)-dimethyl pyroglutamic acid,[296,302] constituents of other callipeltin natural products have been reported.

2.3.3.3 (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE)

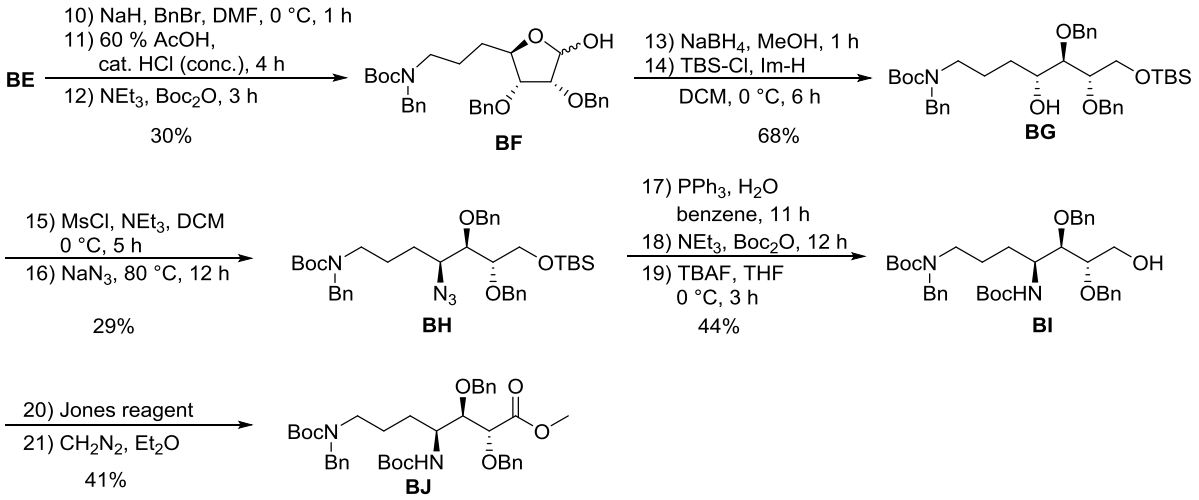
The arguably most complex amino acid residue in callipeltins, (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE) has received substantial attention with several groups reporting strategies toward this novel motif.

In 2001 Rao and coworkers reported the first synthesis of AGDHE using a chiral pool strategy.[303]



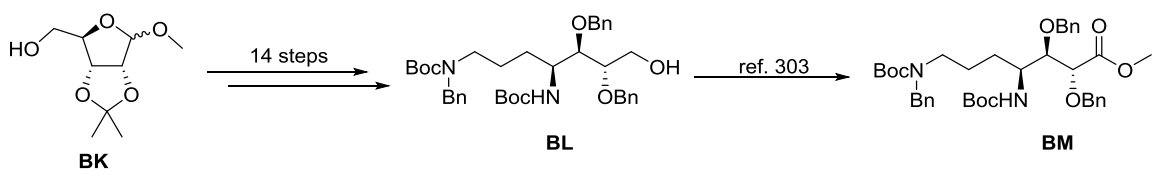
Scheme 39: Preparation of intermediate **BE** from D-glucose.

Starting from aldehyde **AZ**, derived from D-glucose through a known procedure, they installed the missing carbon framework by Wittig reaction followed by reduction of the resulting ethyl ester (scheme 39). The alcohol **BA** was transformed into the corresponding azide **BB** by tosylation and consecutive treatment with sodium azide. Reduction of the azide with LAH and protection of the amine afforded Boc-carbamate **BC** in 43% yield. Inversion of the C-3 stereocenter was accomplished through a three-step procedure. First the benzyl group was cleaved under Birch conditions, the alcohol was then oxidized with PDC and finally stereoselective reduction of the resulting ketone with sodium borohydride delivered alcohol **BD**. Through a six-step sequence of protection group manipulations, the hemiacetal **BF** was obtained (scheme 40). Ring-opening of the hemiacetal by exposure to $NaBH_4$ followed by selective TBS-protection of the primary hydroxyl group afforded silyl ether **BG** in 68% yield. The secondary alcohol was converted to azide **BH** via the mesylate ($MsCl/NEt_3$) followed by treatment with sodium azide. Staudinger reduction, Boc-protection and deprotection of the silyl ether with TBAF afforded primary alcohol **BI**. Oxidation to the carboxylic acid via Jones oxidation and esterification with diazomethane completed the synthesis of amino acid **BJ**. While the group successfully installed all stereocenters, the amino acid is still missing the guanidine motif present in callipeltin A.



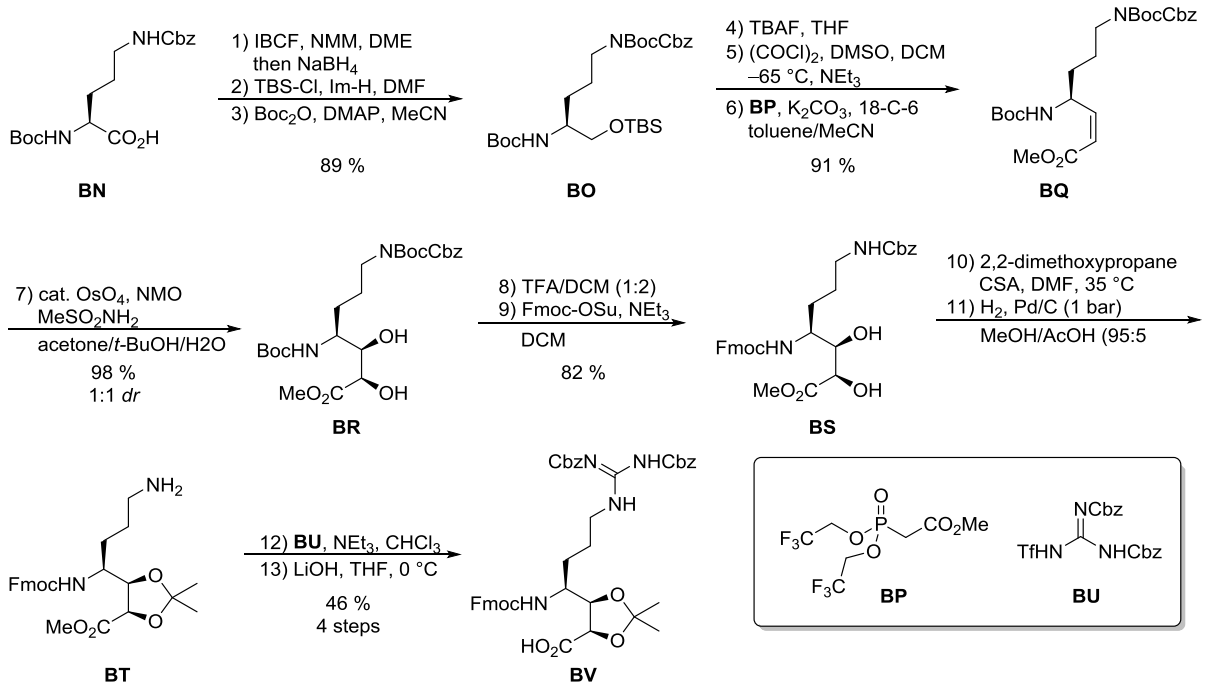
Scheme 40: Synthesis of amino acid **BJ** by Rao and coworkers.

Two years later Rao *et al.* reported a second-generation approach toward AGDHE.[304] This time they prepared alcohol **BK** from D-ribose (scheme 41). They significantly changed the early part of the protection group strategy while the synthetic transformations for the most part remained the same.



Scheme 41: Second-generation approach toward AGDHE by Rao *et al.*

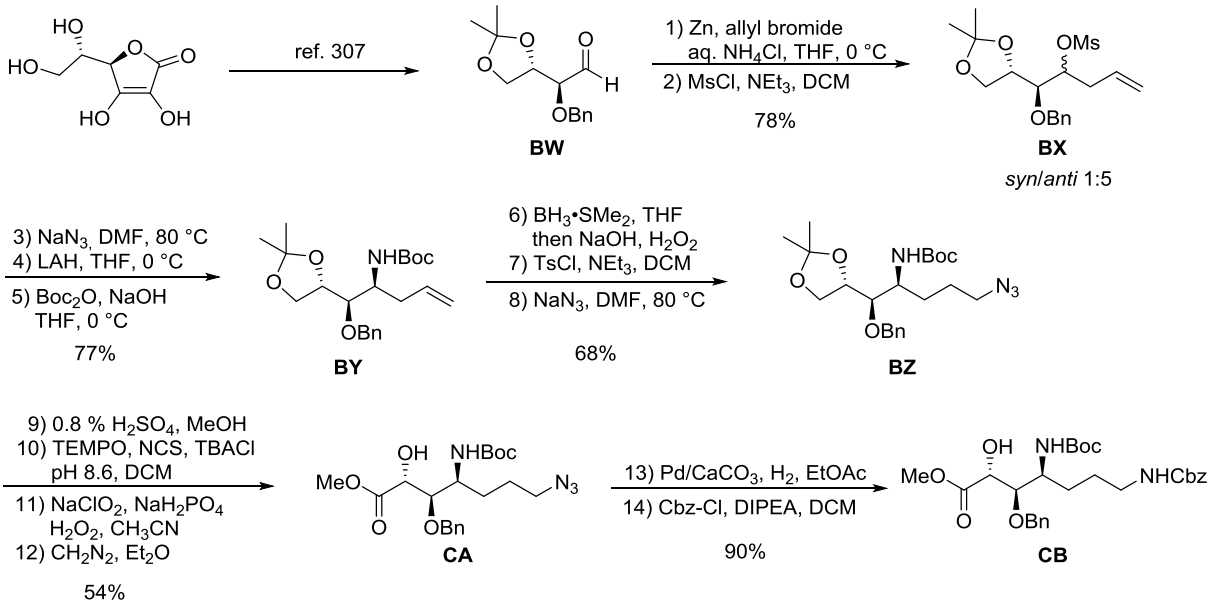
Lipton and coworkers envisioned a stereoselective dihydroxylation of an appropriate *Z*-alkene to access AGDHE.[305] Starting from protected L-ornithine **BN** they prepared silyl ether **BO** by formation of the mixed anhydride followed by reduction, TBS-protection and introduction of a secondary carbamate protecting group at the δ-amino group (scheme 42). After fluoride-induced cleavage of the silyl ether with TBAF, the alcohol was oxidized using Swern conditions ($(COCl)_2$/DMSO/NEt_3). The resulting aldehyde was subjected to Still-Gennari olefination to afford *Z*-alkene **BQ** in 91% yield. The *E*-alkene was removed by flash chromatography. Since earlier studies by Reetz *et al.* have shown that such (*S*)-configured amines undergo dihydroxylation opposing the desired selectivity, Lipton's group screened a variety of chiral ligands to reverse the selectivity. This attempt to reverse the intrinsic selectivity of addition was, however, not successful and the group performed the reaction without a chiral ligand, obtaining a 1:1 mixture of diastereomers. After separation of the diastereomeric diols **BR**, both Boc protecting groups were cleaved by treatment with TFA and the α-amino group was reprotected with Fmoc-OSu. The *trans*-diol **BS** was protected as dimethyl acetal using 2,2-dimethoxypropane in the presence of catalytic CSA in DMF. Introduction of the guanidine moiety was accomplished by removal of the Cbz group by hydrogenolysis and subsequent treatment with guanidine triflate **BU** and NEt_3. Saponification of the methyl ester afforded protected AGDHE derivative **BV** in 46% yield over 4 steps.



Scheme 42: Synthesis of AGDHE **BV** by Lipton *et al.*

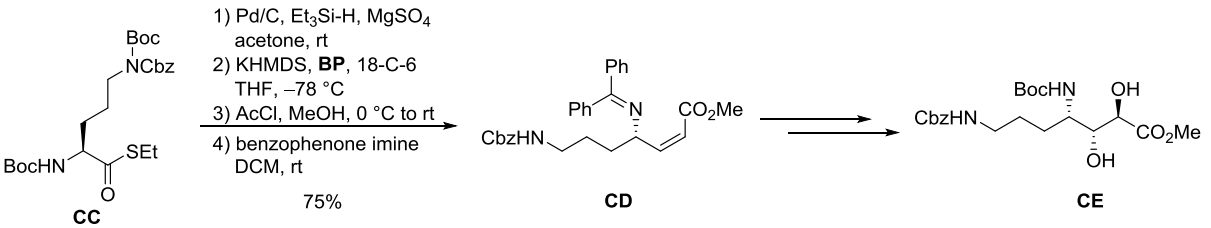
In 2006 Chandrasekhar and coworkers reported their synthesis of AGDHE starting from L-ascorbic acid.[306] Preparation of chiral aldehyde **BW** by a known procedure[307] followed by diastereoselective zinc-mediated allylation and reaction with MsCl/NEt_3 afforded mesylate **BX** as a 5:1 mixture of a*nti*/*syn* diastereomers (scheme 43). After separation via column

chromatography, the desired *anti*-mesylate was substituted with sodium azide. Reduction of the azide with $LiAlH_4$ and Boc-protection provided alkene **BY**. The alkene was subjected to hydroboration/oxidation conditions and the resulting alcohol was transformed into azide **BZ** by a similar procedure as before. Acid mediated-cleavage of the acetal was followed by two-step oxidation to the carboxylic acid and esterification with diazomethane to afford methyl ester **CA**. The terminal azide was reduced by hydrogenolysis, and the resulting amine protected as its Cbz-carbamate to obtain amino acid **CB** in 90% yield. Similar to the approach by Rao, the final installment of the guanidine moiety remained to be carried out.



Scheme 43: Chandrasekhar's approach toward AGDHE from L-ascorbic acid.

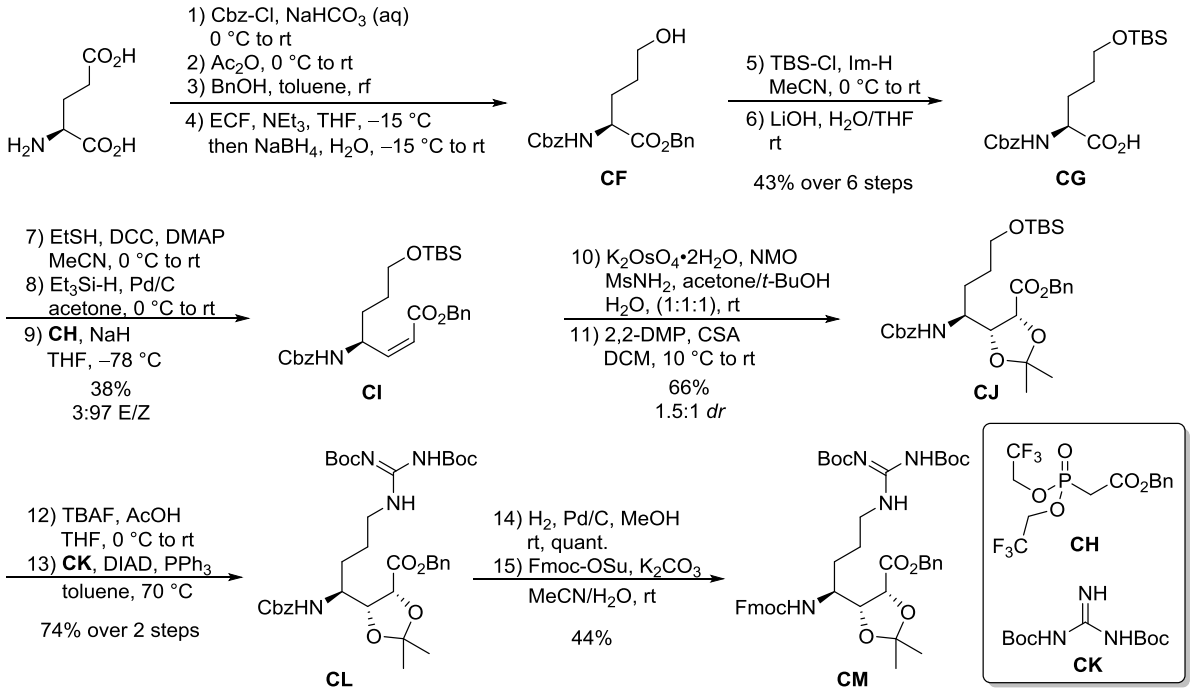
Built upon the approach of Lipton *et al.,* the group of Kim envisioned a similar approach toward AGDHE by stereoselective dihydroxylation.[308] Thioester **CC**, prepared from L-ornithine, was reduced to the corresponding aldehyde with Pd/C and Et_3Si-H and then subjected to Still-Gennari olefination (scheme 44). The Boc-protecting groups were cleaved by methanolic HCl solution and the amine was reacted with benzophenone imine to obtain *Z*-alkene **CD**. The introduction of the sterically demanding benzophenone imine was crucial to achieve a diastereoselective dihydroxylation which led to amino acid **CE** after a few additional steps.



Scheme 44: Approach toward AGDHE by benzophenone imine-controlled dihydroxylation.

Recently Konno and coworkers also reported the synthesis of the AGDHE amino acid.[309] They started their approach from L-glutamic acid which was transferred into carboxylic acid

CG through six synthetic manipulations (scheme 45). *Z*-alkene **CI** was prepared by the procedure published by Kim *et al.* consisting of thioester reduction and Still-Gennari olefination.[308] Dihydroxylation was carried out with OsO_4 in the presence of methane sulfonamide. As previously reported, the dihydroxylation proved unselective and the diastereomers had to be separated by flash chromatography. Protection of the diol as dimethyl acetal with 2,2-dimethoxypropane and camphor sulfonic acid afforded protected triol **CJ** in 66% yield. The silyl ether was cleaved, and the resulting primary alcohol was subjected to Mitsunobu conditions (DIAD/PPh_3) with guanidine **CK** to obtain γ-amino acid **CL**. Cleavage of the Cbz-carbamate and Fmoc protection yielded AGDHE derivative **CM**.



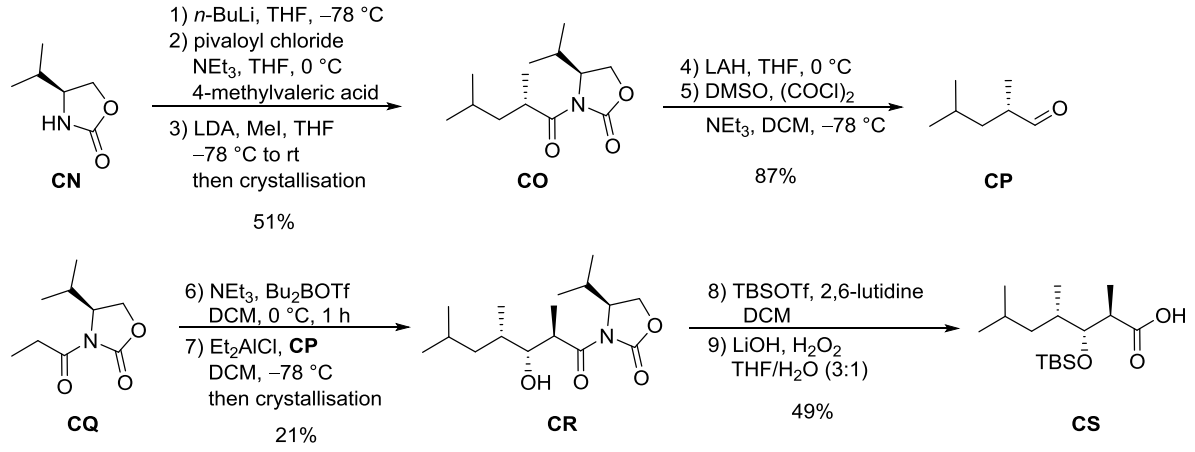
Scheme 45: Synthesis of AGDHE derivative **CM** by Konno *et al.*

Additionally, the synthesis of similar building blocks contained in callipeltins and related natural products has been reported.[268,310]

2.3.3.4 (2*R*,3*R*,4*R*) 3-Hydroxy-2,4,6-trimethylheptanoic Acid (TMEHA)

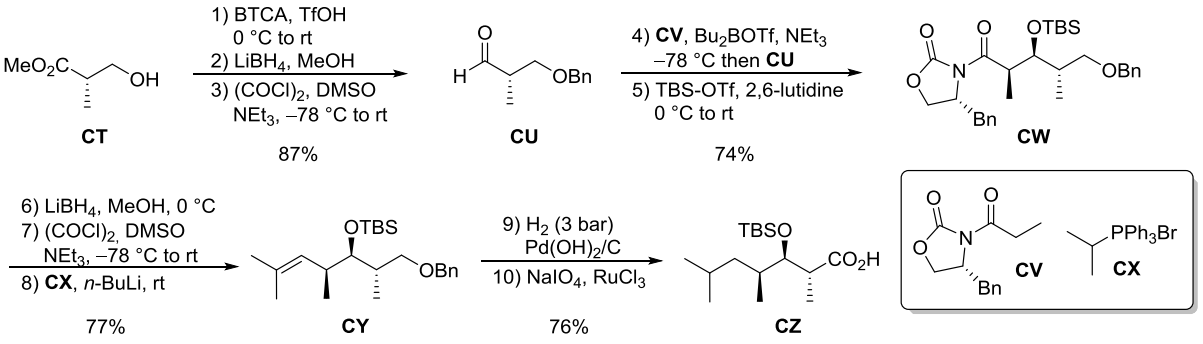
In 2002 Joullié and coworkers published the first synthesis of novel amino acid 3-hydroxy-2,4,6-trimethylheptanoic acid (TMEHA) with the initially assigned configuration of (2*R*,3*R*,4*S*).[311] The first stereogenic center was installed by Evans alkylation after coupling of L-valine derived oxazolidinone **CN** with 4-methyl valeric acid (scheme 46). Kinetic enolate formation with LDA at –78 °C followed by addition of methyl iodide afforded oxazolidinone **CO** as a single diastereomer after crystallization from hexane. Conversion of the auxiliary to the desired aldehyde **CP** was accomplished by a sequence of LAH reduction and Swern oxidation. Evans aldol reaction of crude aldehyde **CO** in the presence of Lewis acid Et_2AlCl with the boron enolate generated from propionyl imide **CQ** selectively afforded the desired *syn*,*anti*-diastereomer **CR**, albeit in low yield. The primary hydroxyl group was protected and

the auxiliary cleaved using lithium hydroxide and hydrogen peroxide to obtain β-silyloxy acid **CS**.



Scheme 46: Synthesis of (2*R*,3*R*,4*S*)-TMEHA **CS** by Joullié *et al.*

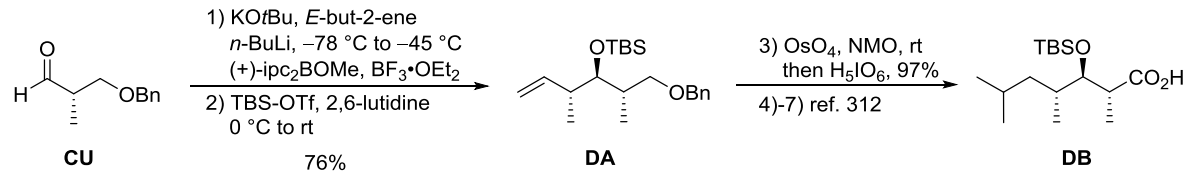
Simultaneously, D'Auria and coworkers reported a similar approach toward TMEHA.[312] After initial attempts of asymmetric crotylation using Brown's Ipc_2-boranes failed to afford a selective reaction, the group turned to well-established Evans aldol chemistry. First, methyl (2*S*)-2-methyl-3-hydroxy propionate **CT** was converted to aldehyde **CU** in a three-step sequence of benzyl protection, reduction of the methyl ester followed by Swern oxidation (scheme 47). Evans aldol reaction of aldehyde **CU** with the boron enolate derived from oxazolidinone **CV** led to the successful installment of the desired *syn*,*anti*-stereotriad. Immediate TBS protection of the resulting alcohol afforded silyl ether **CW** as a single diastereomer. The auxiliar was cleaved by reduction with $LiBH_4$ and the resulting alcohol was oxidized using Swern conditions. After Wittig olefination, alkene **CY** was obtained in 77% yield over three steps. Hydrogenation of the alkene and benzyl ether in the presence of Pearlman's catalyst followed by oxidation with $NaIO_4$ and $RuCl_3$ provided the protected β-hydroxy acid **CZ**.



Scheme 47: Preparation of (2*R*,3*R*,4*S*)-TMEHA **CZ** by D'Auria *et al.*

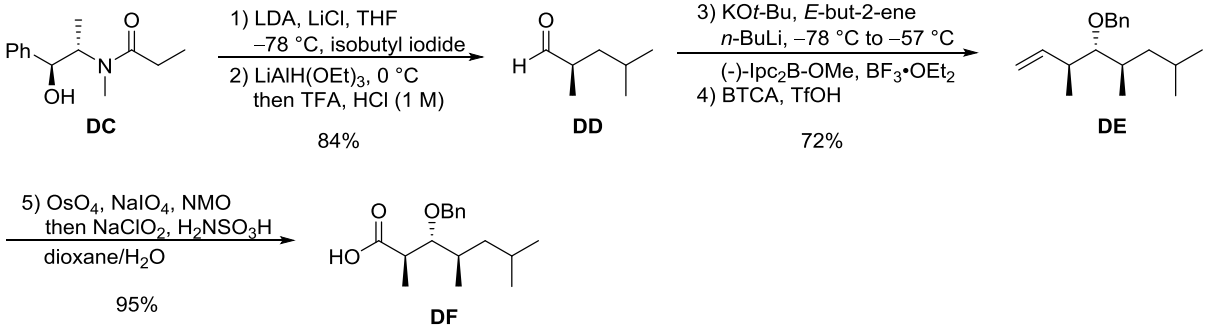
Shortly after, the same group reported the revision of the configuration of TMEHA to (2*R*,3*R*,4*R*) alongside a new synthetic approach toward the 4*R* isomer of TMEHA.[313] Starting from aldehyde **CU**, Brown's crotylboration with diisopinocampheyl borane afforded the required *trans*,*trans*-alcohol which was protected as its silyl ether **DA** (scheme 48). After

oxidative cleavage of the double bond (OsO_4/NMO/H_5IO_6), the resulting aldehyde was transformed into carboxylic acid **DB** via the previously reported procedure.



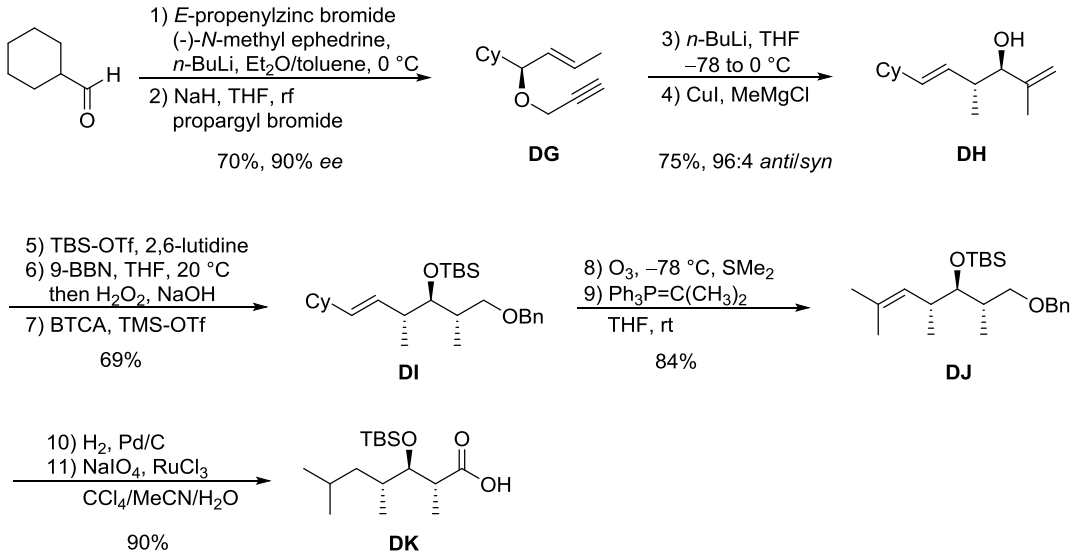
Scheme 48: Revised approach to TMEHA **DB** by D'Auria and coworkers.

Lipton *et al.* further improved the procedure developed by D'Auria by synthesizing the isopropyl containing aldehyde **DD** in 84% yield through Myers alkylation and reductive cleavage of the *N*-methyl ephedrine auxiliary (scheme 49).[314] They then used the same procedure of Brown crotylboration as D'Auria to install the two remaining stereocenters. Protection of the resulting secondary alcohol with benzyl-2,2,2-trichloracetimidate (BTCA) and triflic acid afforded alkene **DE** which was subjected to Lemieux-Jonson oxidation followed by oxidation with $NaClO_2$ to carboxylic acid **DF**.



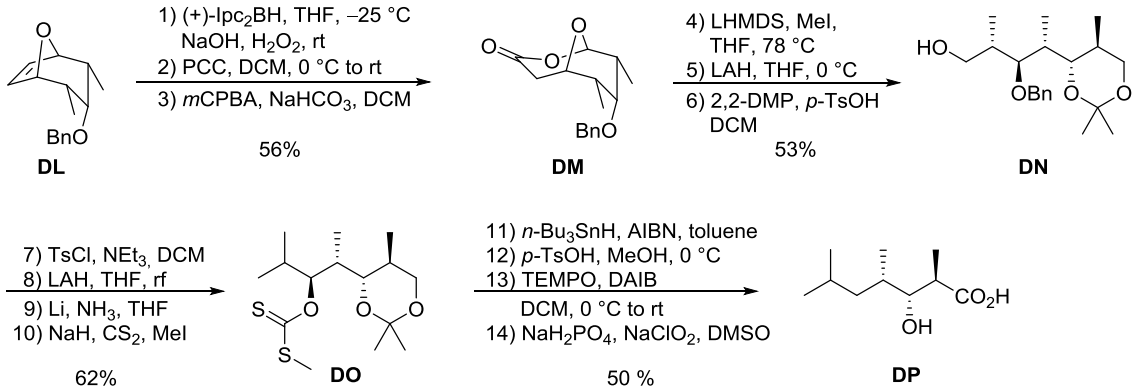
Scheme 49: Improved synthesis of carboxylic acid **DF** by Lipton.

The group of Parker and coworkers followed a completely different, albeit lengthy approach.[315] They started with the asymmetric addition of *E*-propenylzinc bromide to cyclohexyl carboxaldehyde using Oppolzer's conditions (*n*-BuLi, *N*-methyl ephedrine, scheme 50). After etherification with sodium hydride and propargyl bromide the allyl-propargyl ether **DG** was obtained in 70% yield and 90% enantiomeric excess. [2,3]-Wittig rearrangement and copper-mediated carbometallation gave allylic alcohol **DH** in selective fashion. The hydroxyl group was protected and the less sterically shielded double bond functionalized by hydroboration followed by protection of the resulting primary alcohol using benzyl-2,2,2-trichloracetimidate and triflic acid. Ozonolysis of the remaining double bond followed by reduction with dimethyl sulfide and Wittig olefination afforded olefin **DJ**. Simultaneous hydrogenation of the double bond and benzyl ether was followed by oxidation of the primary alcohol to yield β-silyloxy acid **DK**.



Scheme 50: Approach toward **DK** by [2,3]-Wittig rearrangement.

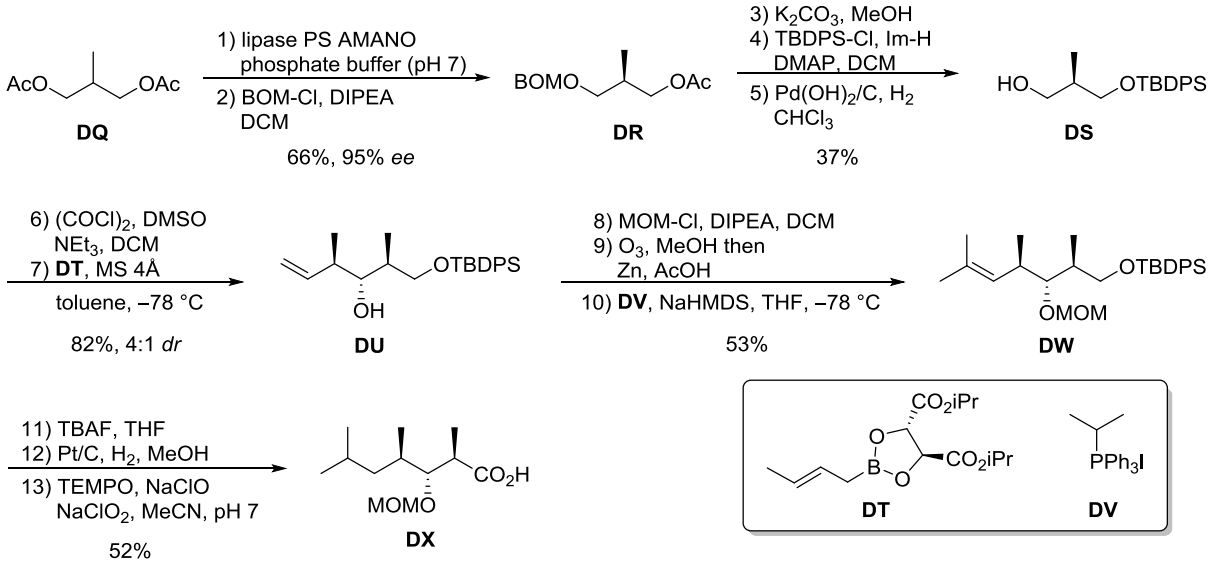
In 2010 the group of Sabitha and coworkers reported their synthesis of TMEHA starting from known bicyclic ether **DL**.[316] Functionalization of the alkene by hydroboration, oxidation of the resulting alcohol and Baeyer-Villiger oxidation afforded lactone **DM** (scheme 51). The ester was α-alkylated with LHMDS and methyl iodide, reduced to the corresponding diol and a dimethyl acetal protecting group was introduced. Tosylation of the primary hydroxyl group was followed by substitution with $LiAlH_4$ as hydride donor. Cleavage of the benzyl ether by Birch reduction and transformation into xanthogenate **DO** was achieved in 62% yield over four steps. The xanthogenate functionality was removed via radical conditions (AIBN, *n*-Bu_3SnH) followed by *para*-toluenesulfonic acid-mediated acetal cleavage. Two-step oxidation of the primary alcohol with TEMPO/DAIB and Pinnick-type oxidation completed the synthesis of hydroxy acid **DP**.



Scheme 51: Synthesis of TMEHA **DP** by Sabitha *et al.*

More recently the group of Konno reported a novel synthesis of this amino acid residue based upon a kinetic enzymatic desymmetrization.[317] Starting from diacetate **DQ**, the desymmetrization with lipase PS AMANO afforded the corresponding (*R*)-acetate **DR** in 95% enantiomeric excess after BOM-protection (scheme 52). Manipulation of the protecting groups over three steps resulted in primary alcohol **DS**. After Swern oxidation, the aldehyde

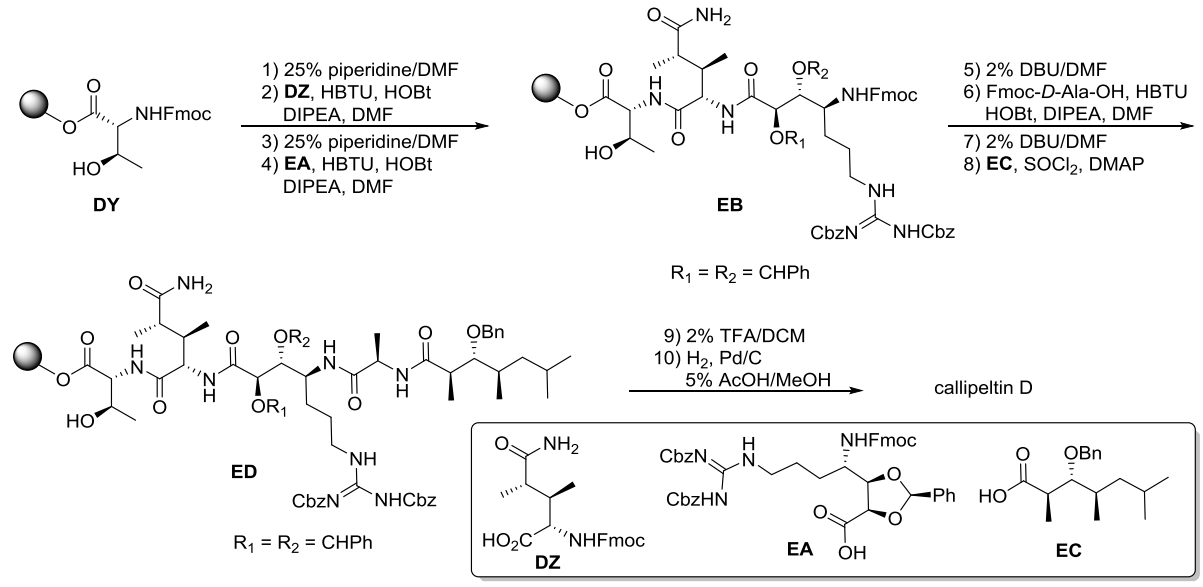
was subjected to Roush allylation to provide secondary alcohol **DU** in a moderate diastereoselectivity of 4:1. The alcohol was protected as its MOM-ether, the double bond cleaved by ozonolysis and the trisubstituted alkene was introduced by Wittig-reaction. Deprotection of silyl ether **DW** by TBAF was followed by hydrogenation of the olefin and final oxidation using TEMPO/NaClO/$NaClO_2$ to obtain TMEHA derivative **DX**.



Scheme 52: Enzymatic desymmetrization approach toward hydroxy acid **DX**.

2.3.3.5 Total Synthesis of Callipeltins

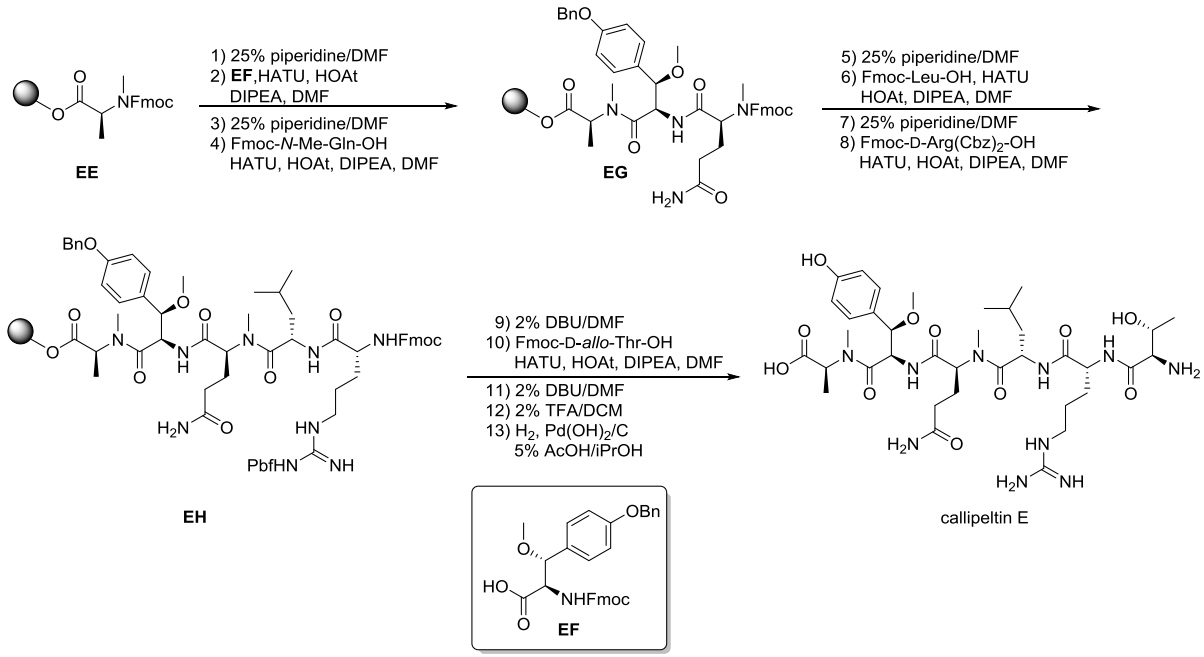
The first successful total synthesis of the callipeltins has been published by Lipton and coworkers in 2005 with the completion of callipeltin D.[318] The group employed an Fmoc-based solid-phase strategy using 2-chlorotrityl resin (scheme 53) with the synthesized building blocks in chapters 2.3.3.1 to 2.3.3.4.



Scheme 53: First total synthesis of callipeltin D by Lipton *et al.*

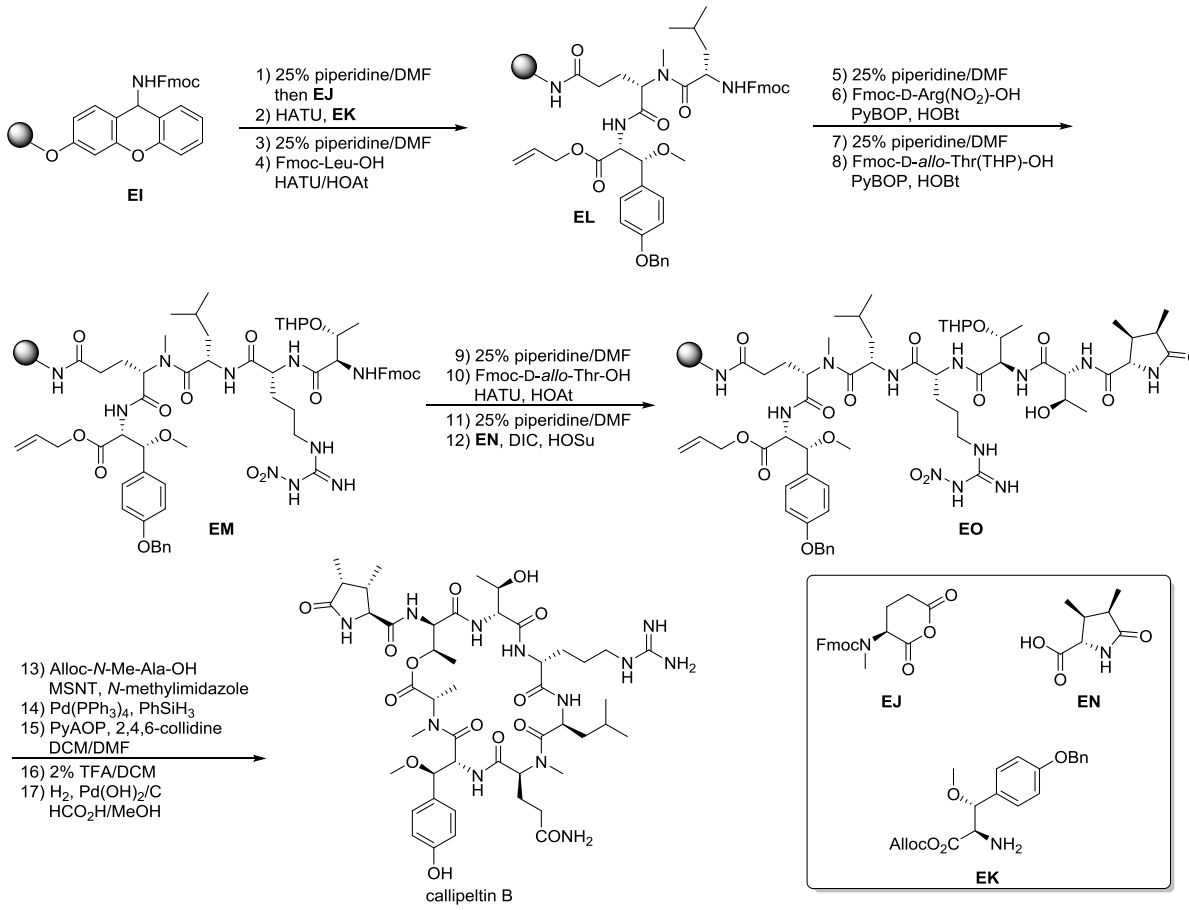
Construction of the peptide was conducted by Fmoc deprotection with piperidine (25%) or DBU (2%) in DMF and subsequent coupling with HBTU/HOBt/DIPEA. The resin-bound peptide **ED** was cleaved from the resin by treatment with trifluoroacetic acid and global deprotection by hydrogenolysis afforded callipeltin D in 35% yield.

Shortly afterward, the same group reported the synthesis of linear peptide callipeltin E.[319] Using the previously developed strategy with a 2-chloro trityl resin, they started assembly of the peptide chain from resin-bound *C*-terminal *N*-methyl-L-alanine **EE**. Callipeltin E was obtained in 20% yield over 13 steps (scheme 54). In 2011 the group of Konno reported an almost identical approach toward callipeltin E using a 2-chlorotrityl resin-based strategy,[320] only differing in the use of a MEM protecting group for the phenol instead of the benzyl ether used by Lipton.



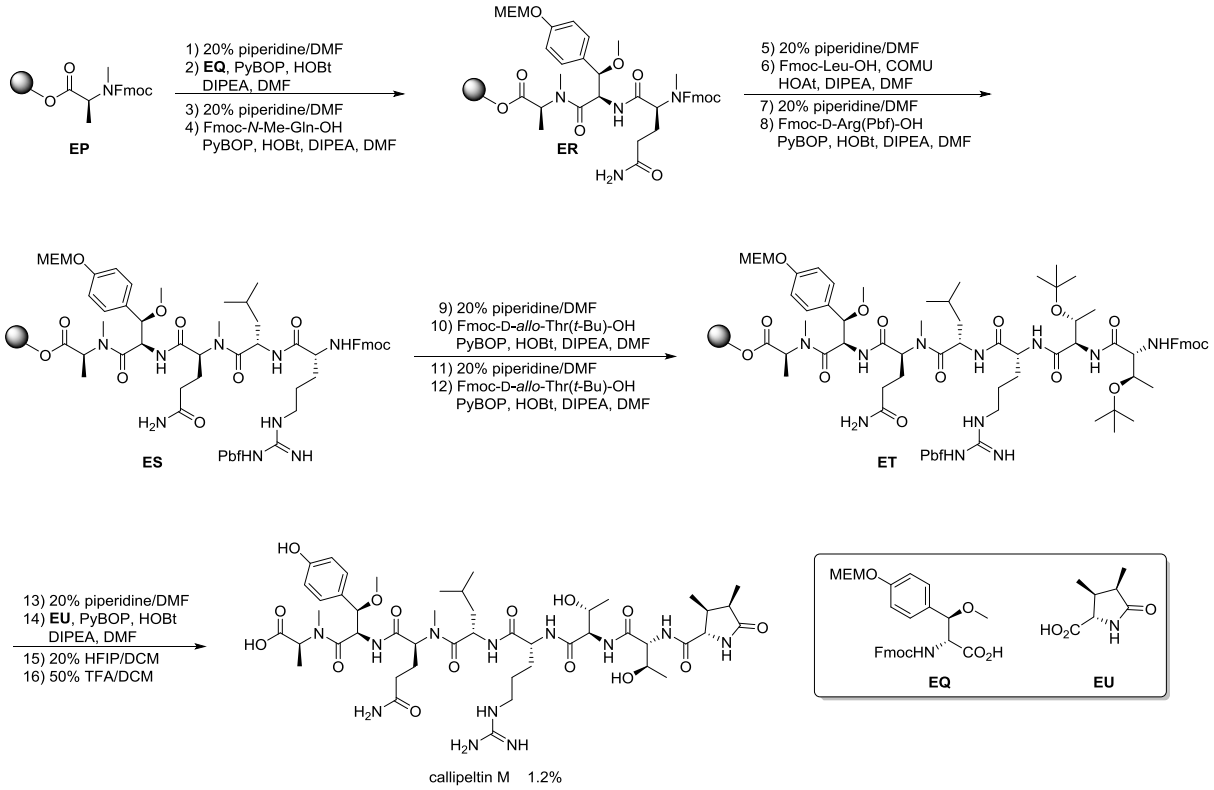
Scheme 54: Total synthesis of callipeltin E by Lipton and coworkers in 2006.

The first synthesis of callipeltin B was once again reported by the Lipton group.[321] They chose a solid-phase strategy using the tentagel-based TG Sieber amide resin anchored to the side chain of the *N*-methyl glutamine residue. After peptide chain assembly over 13 steps the *C*- and *N*-termini were deprotected using $Pd(PPh_3)_4$ and $PhSiH_3$ and cyclization was achieved on-resin with PyAOP and 2,4,6-collidine between the *N*-methyl alanine and β-methoxy tyrosine residues (scheme 55). Cleavage from the resin with trifluoroacetic acid and global deprotection by hydrogenolysis afforded callipeltin B.



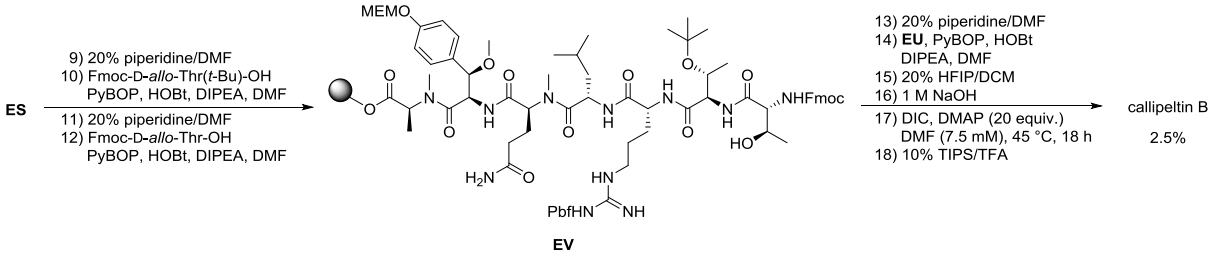
Scheme 55: Total synthesis of callipeltin B.

Almost a decade later, Konno *et al.* reported the second synthesis of callipeltin B along with callipeltin M.[322] In their unified strategy of Fmoc solid-phase synthesis to access both natural products, they chose the 2-chlorotrityl resin as solid support. The resin was attached to *C*-terminal *N*-methyl alanine. Employing typical deprotection (piperidine, DMF) and coupling (PyBOP, HOBt, DIPEA) conditions, the group was able to synthesize resin-bound linear peptide **ES** over 8 steps which served as collective intermediate for callipeltin B and M (scheme 56). The synthesis of callipeltin M was completed by three further Fmoc-SPPS steps, cleavage from the resin by HFIP/DCM and global deprotection with trifluoroacetic acid in 1% overall yield.



Scheme 56: Preparation of intermediate **ES** and total synthesis of callipeltin M.

In the case of callipeltin B, precursor **ES** was subjected to three similar coupling steps after which the linear peptide was cleaved from the resin by HFIP/DCM (scheme 57). Due to the additional introduction of **EU** at the D-*allo*-Thr residue, the saponification of this moiety with sodium hydroxide was required after which macrocyclization was achieved in 44% yield with the use of DIC/DMAP (7.5 mM, 45 °C) for activation of the *C*-terminal carboxylic acid. Callipeltin B was obtained in 2.5% overall yield after global deprotection with trifluoroacetic acid in the presence of tri-*iso*-propyl silane.



Scheme 57: Total synthesis of callipeltin B by Konno *et al.*

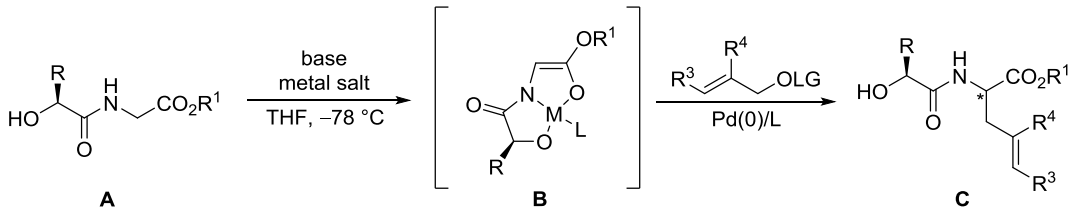
Additionally to the syntheses of callipeltin B by Lipton and Konno, both groups reported the synthesis of derivatives of callipeltin B, with Lipton synthesizing desmethoxy callipeltin B.[281] Konno *et al.* described various simplified derivatives lacking the methoxy group of the tyrosine residue and the dimethyl pyroglutamic acid.[282]

3. Aim of this Work

3.1 Palladium-Catalyzed Allylic Alkylation

The main objective of this PhD thesis was the development of a novel synthetic method which allows for the stereoselective modification of *N*-(α-Hydroxyacyl)-glycine esters and small *N*-(α-Hydroxyacyl)-peptides.

The initial hypothesis was based on previous results from transition metal-catalyzed allylic alkylation with chelated peptide enolates. We envisioned the possibility to form a stable chelate complex **B** by treatment of *N*-(α-Hydroxyacyl)-glycine esters **A** with a strong base in the presence of an appropriate metal salt (scheme 58). These chelated enolates should readily undergo alkylation with an allylic electrophile upon subjection to palladium catalysis. Moreover, the formation of such a constrained chelate complex should allow for easy discrimination of both diastereotopic faces of the enolate. This should result in the stereoselective induction of the hydroxy acid sidechain onto the newly formed stereogenic center.

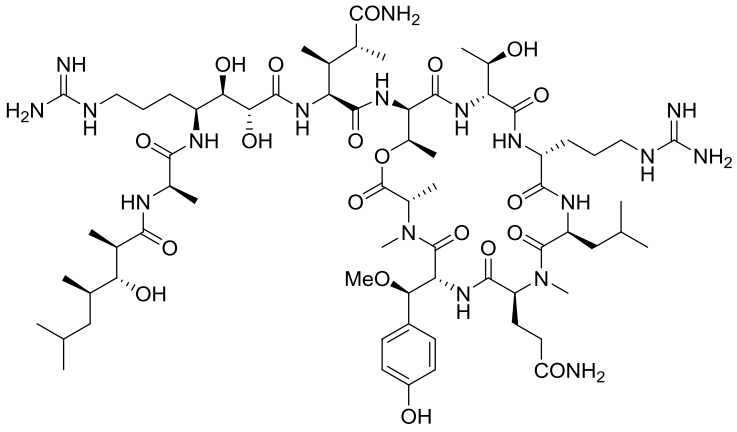


Scheme 58: Planned allylic alkylation of chelated enolate **B**.

The start of the project was aimed at the development of suitable reaction conditions which afford the allylic alkylation products in good yield and selectivity. Afterward, the substrate scope should be examined with regard to various *N*-(α-Hydroxyacyl)-glycine esters and allyl electrophiles. Subsequent modification of the newly introduced side chain should ultimately result in the preparation of various highly complex *N*-(α-Hydroxyacyl)-amino acids **C** via this new method.

3.2 Total Synthesis of Callipeltins

In a second project, a novel synthetic entry into the class of callipeltin natural products should be explored. While several representatives of this family of natural products have been successfully synthesized over the last two decades,[320–322] up to date all attempts to obtain callipeltin A by means of total synthesis have been entirely unsuccessful. The synthetic effort in this thesis was aimed toward callipeltin A and its acyclic isomer callipeltin C. Therefore, a robust synthetic route and protection group strategy should be devised, including the development of new methods for the preparation of the non-proteinogenic amino acid and hydroxy acid building blocks.



Scheme 59: Structure of callipeltin A.

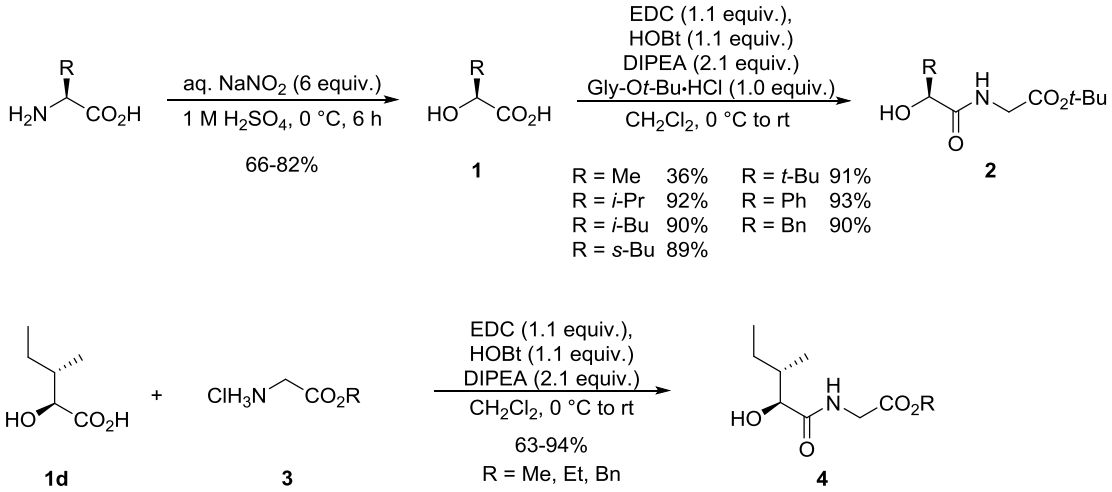
4. Results and Discussion

4.1 Allylic Alkylation of *N*-(α-Hydroxyacyl)-Glycine Esters

4.1.1 Synthesis of *N*-(α-Hydroxyacyl)-Glycine Esters

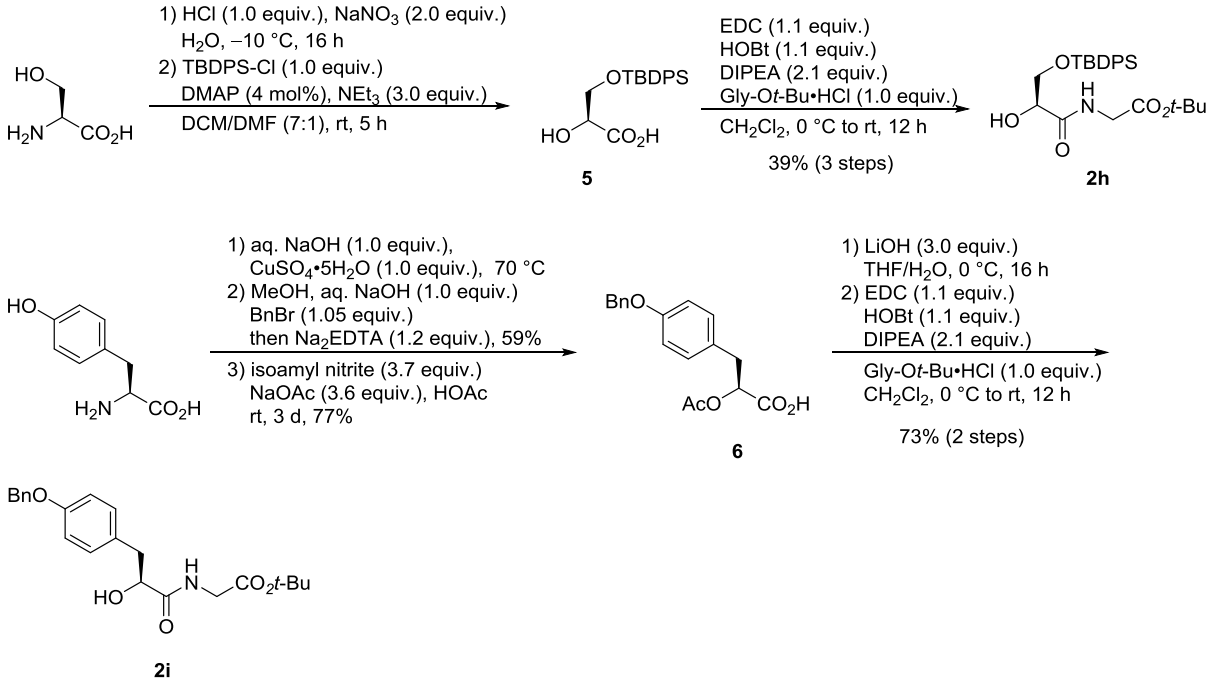
At the start of the project the synthesis of a variety of *N*-(α-Hydroxyacyl)-glycine esters was conducted. Additionally, a variety of allylic acetates, carbonates and phosphates were prepared.

The hydroxy acids **1** were synthesized from the corresponding amino acids via a protocol initially developed from Greenstein *et al.*[323–325] Direct coupling with glycine esters using EDC and HOBt afforded *N*-(α-Hydroxyacyl)-glycine esters **2** in high yield (scheme 60) except for lactic acid derivative **2a**. The low yield most likely arises from the use of the commercially available aqueous solution (40 w%) of lactic acid.



Scheme 60: Preparation of *N*-(α-Hydroxyacyl)-glycine esters **2** from amino acids.

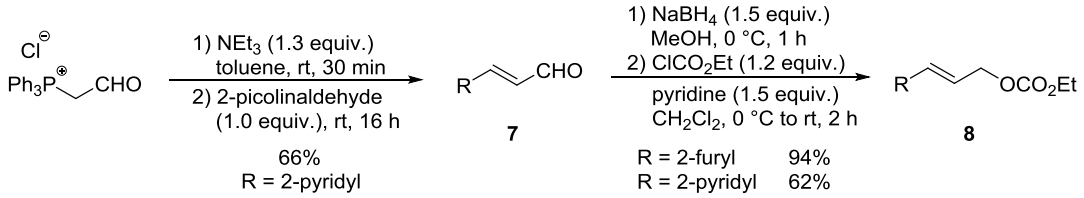
Amino acids containing any functional group in their side chain could not be converted into the hydroxy acid in the same fashion. Serine was transformed into the corresponding hydroxy acid by a slightly modified procedure using HCl instead of H_2SO_4 to avoid aqueous extraction by simple evaporation of the acidic reaction mixture (scheme 61). The crude diol was treated with TBDPS-Cl in the presence of DMAP to selectively protect the more accessible primary hydroxyl group. After coupling under the previously described conditions, *N*-(α-Hydroxyacyl)-glycine ester **2h** was obtained in 39% yield over 3 steps alongside 7% of the α-TBDPS protected product. In the case of tyrosine, the phenolic hydroxyl group was benzyl protected by complexation of the amino acid and subsequent treatment with sodium hydroxide and benzyl bromide.[326] The α-hydroxyl functionality was introduced by installment of an acetoxy group with isoamyl nitrite and sodium acetate in acetic acid in 77% yield.[327] Saponification of the acetate and coupling of the carboxylic acid with glycine *tert*-butyl ester afforded *N*-(α-Hydroxyacyl)-glycine ester **2i**.



Scheme 61: Synthesis of *N*-(α-Hydroxyacyl)-glycine ester **2h** and **2i**.

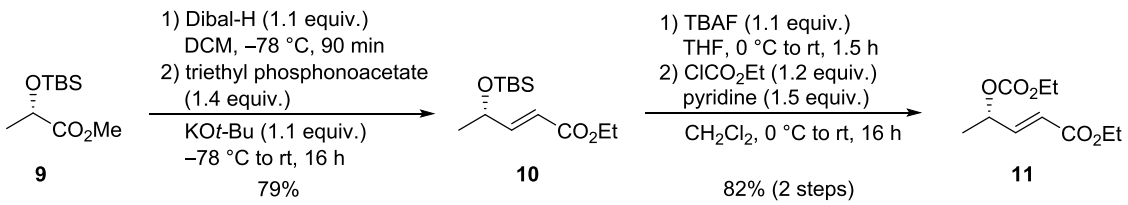
4.1.2 Preparation of Allylic Carbonates

The allylic carbonates were mostly prepared according to literature procedures.[204,328–330] For more functionalized carbonates syntheses were carried out using established synthetic protocols. The aryl substituted allyl carbonates **8** were prepared from the unsaturated aldehydes **7** by sodium borohydride reduction and treatment with ethyl chloroformate in the presence of pyridine (scheme 62).



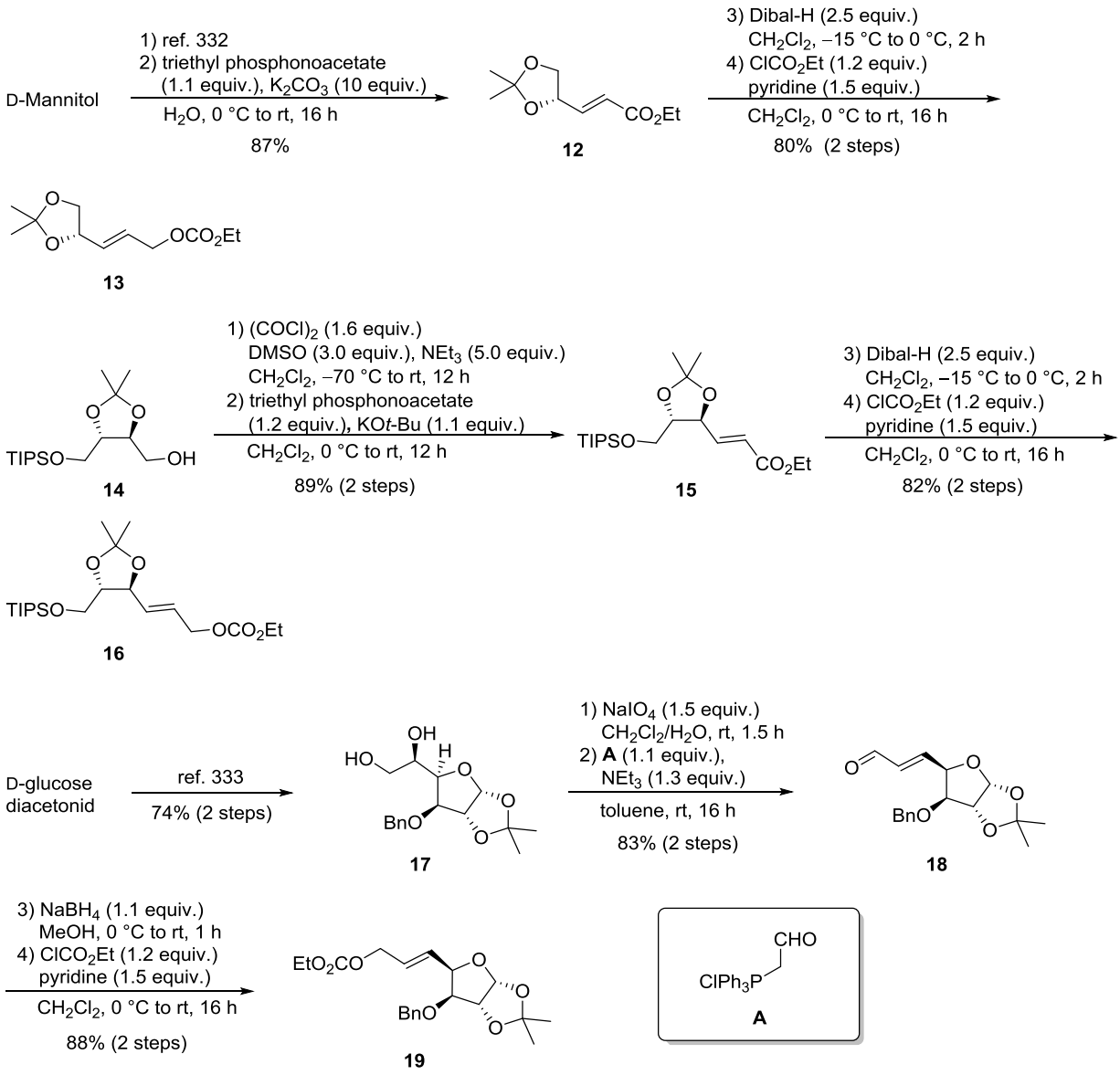
Scheme 62: Preparation of allylic carbonates **8a** and **8b**.

Lactic acid derivative **9** was transformed into unsaturated ester **10** by one-pot reduction to the aldehyde and Horner-Emmons olefination.[331] After cleavage of the silyl ether with TBAF, the alcohol was treated with ethyl chloroformate to obtain the allylic carbonate **11** in 82% yield (scheme 63).



Scheme 63: Synthesis of lactic acid derived carbonate **11**.

Some highly functionalized allylic carbonates were prepared from different sugar building blocks (scheme 64). D-Mannitol was transformed into acetal protected dihydroxy ester **12** under typical conditions,[332] reduced with Dibal-H and treated with ethyl chloroformate to afford allylic carbonate **13** in good yield. To synthesize carbonate **16**, tartaric acid derived alcohol **14** was oxidized under Swern conditions followed by Horner-Emmons olefination. Unsaturated ester **15** was then transformed into the carbonate **16** using the typical two step procedure of reduction and carbonate formation. The last carbonate was obtained from D-glucose diacetonide, which was benzyl protected followed by cleavage of the more acid labile acetal.[333] The resulting diol **17** was cleaved with sodium periodate and after Wittig olefination unsaturated aldehyde **18** was obtained in 83% yield over two steps. Finally, reduction and treatment with ethyl chloroformate gave rise to the primary carbonate **19**.

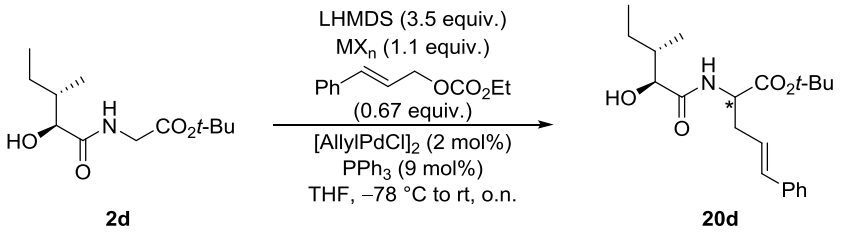


Scheme 64: Synthesis of sugar derived allylic carbonates.

4.1.3 Screening of Reaction Conditions for Allylic Alkylation of *N*-(α-Hydroxyacyl)-Glycine Esters

The screening of appropriate reaction conditions for the stereoselective modification of *N*-(α-hydroxyacyl)-glycine esters by allylic alkylation started from the conditions described for chelated amino acids and peptides.[84,202,204] When these conditions from Kazmaier *et al.* were applied, formation of the product was observed moderate yield and selectivity (tab. 4, entry 1). Several other chelating metal salts ($ZrCl_4$, $MnCl_2$, $MgBr_2{\cdot}OEt_2$, $NiBr_2$) were also tested but proved entirely unsuccessful (entry 2-5). Due to the additional oxygen functionality of *N*-(α-hydroxyacyl)-glycine esters, instead of the *N*-chelating carbamate in the case of peptides, more oxophilic Lewis acids such as Al(O*i*-Pr)$_3$ and several titanium salts were screened. In the case of Al(O*i*-Pr)$_3$ similar results to $ZnCl_2$ were obtained with slightly improved selectivity. Titanium Lewis acids also proved successful, with ClTi(O*i*-Pr)$_3$ the desired product could be obtained in high yield albeit with lower selectivity (entry 7). Ti(O*i*-Pr)$_4$ yielded the product in 64% yield with 64:36 *dr* (entry 8). More Lewis acidic salts such as $CpTiCl_3$ or Cl_2Ti(O*i*-Pr)$_2$ led to partial or complete cleavage of the *t*-butyl ester which prevented product formation (entry 9-10).

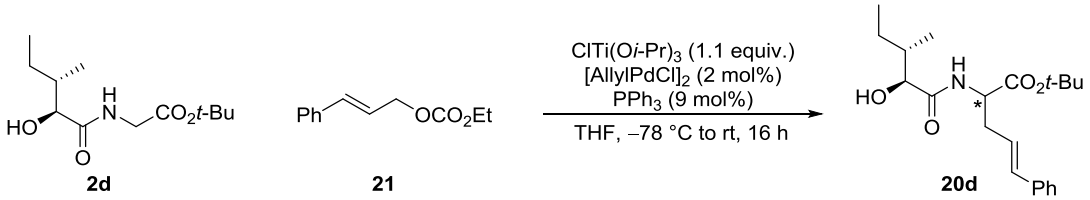
Table 4: Screening of metal salts for allylic alkylation of *N*-(α-hydroxyacyl)-glycine esters.



entry	MX_n	y [%]	*dr*	comment
1	$ZnCl_2$	53	68/32	-
2	$ZrCl_4$	/	n.d.	-
3	$MnCl_2$	/	n.d.	-
4	$MgBr_2{\cdot}OEt_2$	/	n.d.	-
5	$NiBr_2$	11	n.d.	-
6	Al(O*i*-Pr)$_3$	54	71/29	-
7	ClTi(O*i*-Pr)$_3$	86	55/45	-
8	Ti(O*i*-Pr)$_4$	64	64/46	-
9	$CpTiCl_3$	/	n.d.	*tert*-butyl ester cleavage
10	Cl_2Ti(O*i*-Pr)$_2$	/	n.d.	57% conversion

With these metal salts, several other reaction parameters were varied. At first, the influence of the base and the electrophile was examined. As depicted in table 5, using an excess of carbonate **21** resulted in a steep drop in yield (entry 1+2). Similar results have been described several times from the group of Kazmaier in the case of allylic alkylation of hydroxy acids, amino ketones and some peptides.[202,331,334] When the amount of LHMDS was reduced, near quantitative conversion was observed albeit with no diastereoselectivity (entry 3). Interestingly, in the opposite scenario when more LHMDS was used a shift in the selectivity was observed and the second diastereomer was obtained as major isomer (entry 4). Further increasing the amount of LHMDS to 5.5 equivalents resulted in a significant improvement of diastereoselectivity and the γ,δ-unsaturated ester **20d** was obtained in 77% yield and 17:83 *dr* (entry 6). Additional equivalents of LHMDS did not significantly affect the selectivity any further but resulted in slightly lower yield (entry 7). Using these new conditions, the amount of carbonate **21** was once again varied, but similar to before, the use of an excess of nucleophile gave the best results (entry 8-9).

Table 5: Variation of the base and electrophile in the allylic alkylation of **2d**.



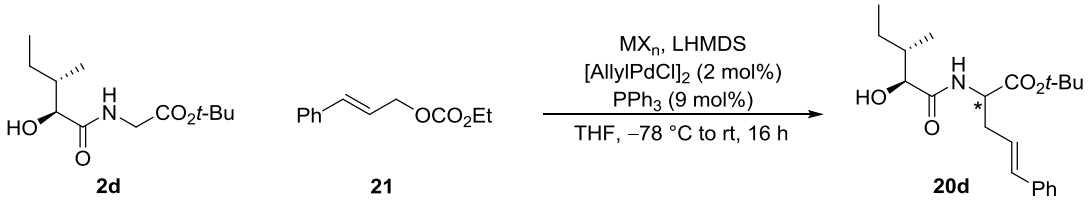
entry	equiv. LHMDS	equiv. **21**	Y [%]	*dr*
1	3.5	1.20	8	n.d.
2	3.5	2.00	36	55/45
3[a]	3.0	0.67	n.d. (95)	52/48
4	4.0	0.67	46	38/62
5	4.5	0.67	50	14/86
6	5.5	0.67	77	17/83
7	6.5	0.67	70	16/84
8	5.5	2.00	27	49/51
9[a]	5.5	0.80	n.d. (100)	34/66
10	5.5	0.50	80	15/85

[a] Conversion is depicted in parenthesis.

At the same time as those experiments were conducted, the influence of the four most promising Lewis acids was further examined. When 1.5 instead of 1.1 equivalents of

ClTi(O*i*-Pr)$_3$ were used for chelation the yield could be improved to 90% alongside a slight improvement in selectivity (tab. 6, entry 1). Further increasing the amount of Lewis acid gave similar results (entry 2) which indicates a complete chelation with 1.5 or more equivalents of Lewis acid whereas 1.1 equivalents are insufficient to achieve complete chelation. When both findings were combined and 5.5 equivalents LHMDS as well as 1.5 equivalents Lewis acid were used the best results could be obtained (entry 3). In this case the γ,δ-unsaturated ester **20d** was isolated in 82% yield and 12:88 *dr*. Using Ti(O*i*-Pr)$_4$, $ZnCl_2$ or Al(O*i*-Pr)$_3$ instead of ClTi(O*i*-Pr)$_3$ under otherwise identical conditions gave inferior results in alle three cases. While Ti(O*i*-Pr)$_4$ gave the product in similar selectivity but lower yield (entry 4), the non-titanium based metal salts did not show the same shift in selectivity toward the second diastereomer when 5.5 equivalents LHMDS were used. In fact, when $ZnCl_2$ was used under these conditions no selectivity was observed at all (entry 5). Al(O*i*-Pr)$_3$ afforded the product in low selectivity and poor yield (entry 6).

Table 6: Combined influence of Lewis acid and base on allylic alkylation.

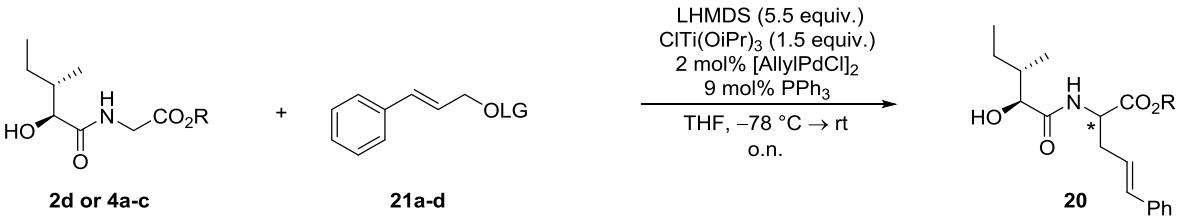


entry	equiv. LHMDS	MX_n (equiv.)	y [%]	*dr*
1	3.5	ClTi(O*i*-Pr)$_3$ (1.5)	90	65/35
2[a]	3.5	ClTi(O*i*-Pr)$_3$ (2.0)	n.d. (98)	60/40
3	5.5	ClTiO*i*-Pr$_3$ (1.5)	82	12/88
4	5.5	Ti(O*i*-Pr)$_4$ (1.5)	52	14/86
5	5.5	$ZnCl_2$ (1.5)	71	50/50
6	5.5	Al(O*i*-Pr)$_3$ (1.5)	39	66/34

[a] Conversion is depicted in parenthesis.

While the *tert*-butyl ester and the ethyl carbonate were used in all the optimizations above due to the literature precedent of these functionalities in similar reactions, other ester and leaving groups were also examined (table 7). As expected in the case of methyl and ethyl ester significantly lower yields and selectivity were obtained (entry 1+2) and the use of a benzyl ether also afforded the alkylated ester in poor yield (entry 3). Using the less reactive acetate leaving group resulted in no conversion (entry 4) while the use of the benzoate and phosphate gave the γ,δ-unsaturated ester **20d** in similar selectivity as before albeit in significantly lower yield (entry 5+6).

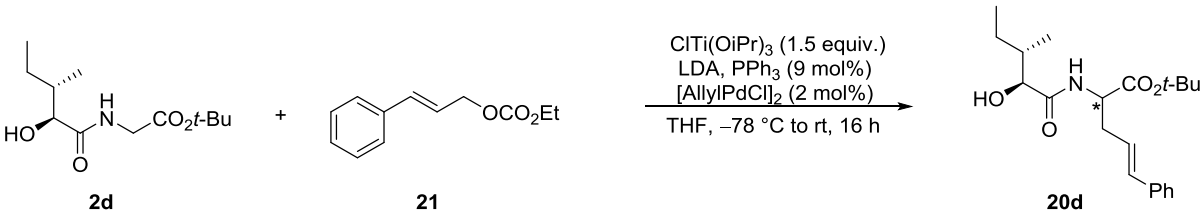
Table 7: Variation of the ester and leaving group.



entry	R	LG	Y [%]	*dr*
1	Me	CO_2Me	41	48/52
2	Et	CO_2Et	36	22/78
3	Bn	CO_2Et	29	n.d.
4	*t*-Bu	Ac	-	-
5	*t*-Bu	Bz	33	12/88
6	*t*-Bu	$PO(OEt)_2$	47	15/85

Since early optimizations have shown the formation of the other diastereomer is also possible, the reaction was further optimized to obtain both diastereomers selectively by choice of the reaction conditions. Early experiments indicated promising results when LDA was used which might be explained by the well-known behavior of titanium complexes which tend to display very fast ligand exchanges and form a multitude of hypervalent complexes. Indeed, when 3.5 equivalents LDA instead of LHMDS were used, the inversed selectivity was observed and the allylation product **20d** was obtained in a diastereomeric ratio of 97:3 (tab. 8, entry 1). In contrast to the weaker base LHMDS, when an excess of LDA was used complete decomposition of the starting material was observed (entry 2). To try to avoid even partial decomposition and therefore poor yields, the amount of LDA was reduced to 3.0 equivalents which afforded the γ,δ-unsaturated ester **20d** with perfect selectivity. However, the yields were irreproducible and fluctuated from 44 to 71% (entry 3). A reference experiment with substoichiometric amount of LDA (entry 4) confirmed the necessity of at least three equivalents of base for the successful allylic alkylation. Since yields were not reproducible with 3.0 equivalents, most likely caused by small deviations in the freshly prepared LDA stock solutions, the reaction was repeated with very slight excess of LDA (entry 6+7). In both cases the results were reproducible and afforded basically identical results as the best result with 3.0 equivalents, affording the γ,δ-unsaturated ester **20d** in 70% and 67% yield respectively while perfect selectivity was maintained. Once again, attempts to use the allylic carbonate **21** in excess resulted in inferior results (entry 8).

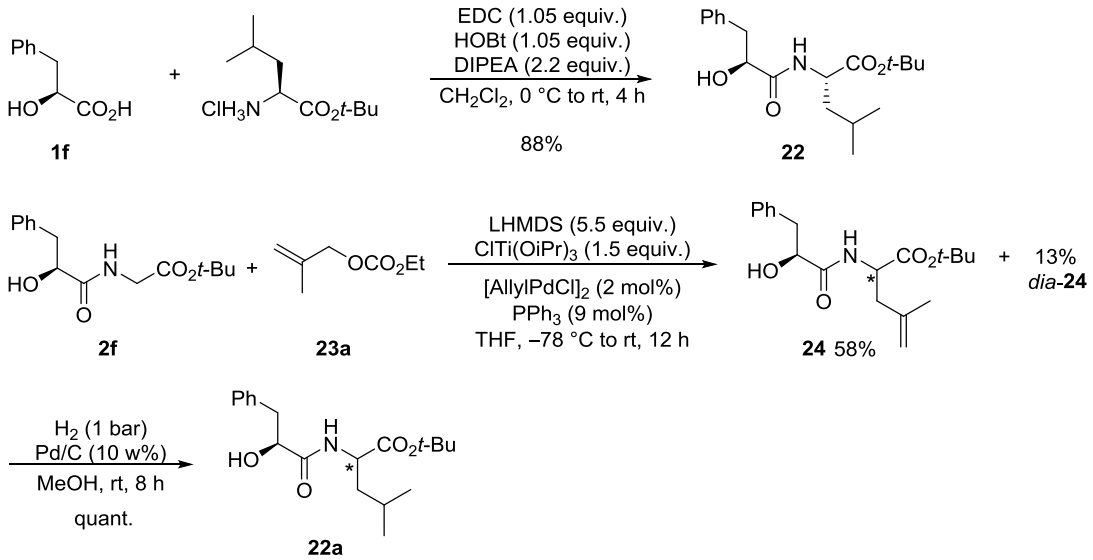
Table 8: Attempted Allylic alkylation with various amounts of LDA.



entry	equiv. LDA	Y [%]	dr	comment
1	3.5	53	97/3	-
2	5.5	-	-	decomposition
3	3.0	44-71	> 99/1	irreproducible
4	2.5	/	/	no reaction
6	3.1	70	> 99/1	-
7	3.2	67	> 99/1	-
8	3.1	/	66/34	1.2 equiv. ethyl carbonate

4.1.4 Elucidation of the Absolute Configuration

At this point both diastereomers could be accessed selectively but the configuration of the newly formed stereocenter was still unknown. Therefore, a reference sample with known configuration was prepared from L-leucine and L-phenylalanine derived hydroxy acid **1f** by simple peptide coupling (scheme 65).



Scheme 65: Preparation of reference sample **22** and synthetic sample **22a** with unknown stereochemistry.

N-(α-hydroxyacyl)-glycine ester **2f** was then reacted with allylic carbonate **23** under the previously described conditions for allylic alkylation with 5.5 equivalents of LHMDS to afford 58% and 13% of the diastereomers respectively after separation by flash chromatography. Hydrogenation of the alkene **24** gave leucine derivate **22a** which could be compared to the reference sample by HPLC analysis and NMR spectroscopy.

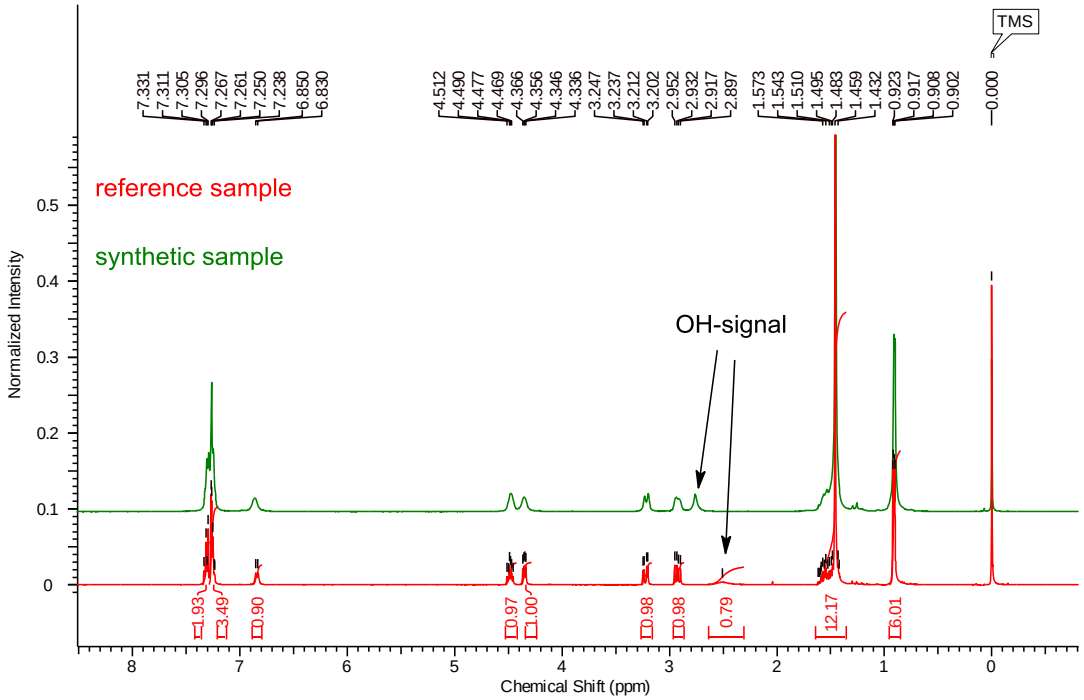
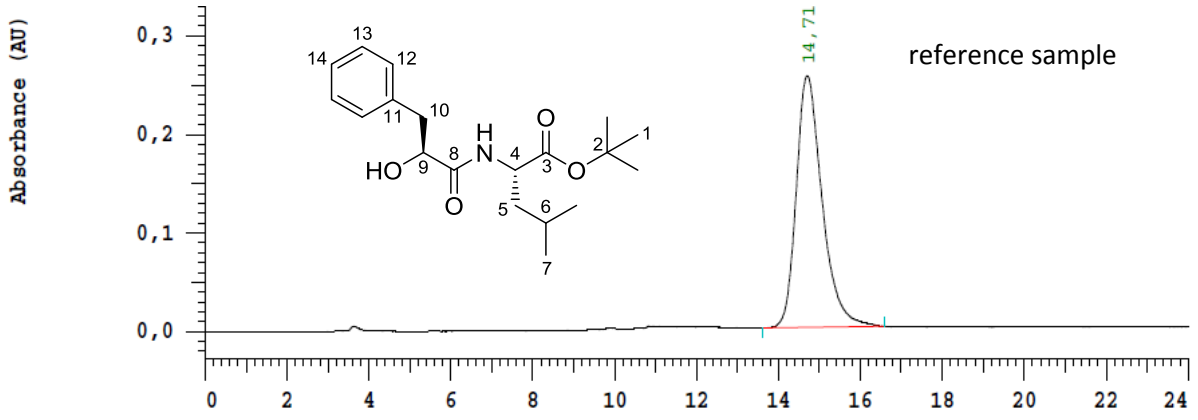


Fig. 6: ^{1}H-NMR spectrum comparison between **22a** and the reference sample **22**.

As depicted in figure 6, the NMR spectra of both samples display a perfect match except for the highly solvent and concentration dependent hydroxyl group which can be expected. Additionally, the HPLC chromatograms of both samples on a chiral ReproSil® column are identical (fig 7.). The minor diastereomer on the other hand shows a different retention time, thus confirming the identical (*S*,*S*)-configuration of the synthetic sample and the reference sample. While the retention time on a chiral Chiralcel OD-H® column are slightly different, a co-injection of both samples shows only one peak. In consequence, the LDA method generates the (*S*,*R*)-diastereomer as reported in the case of the allylic alkylation of peptides.[202]



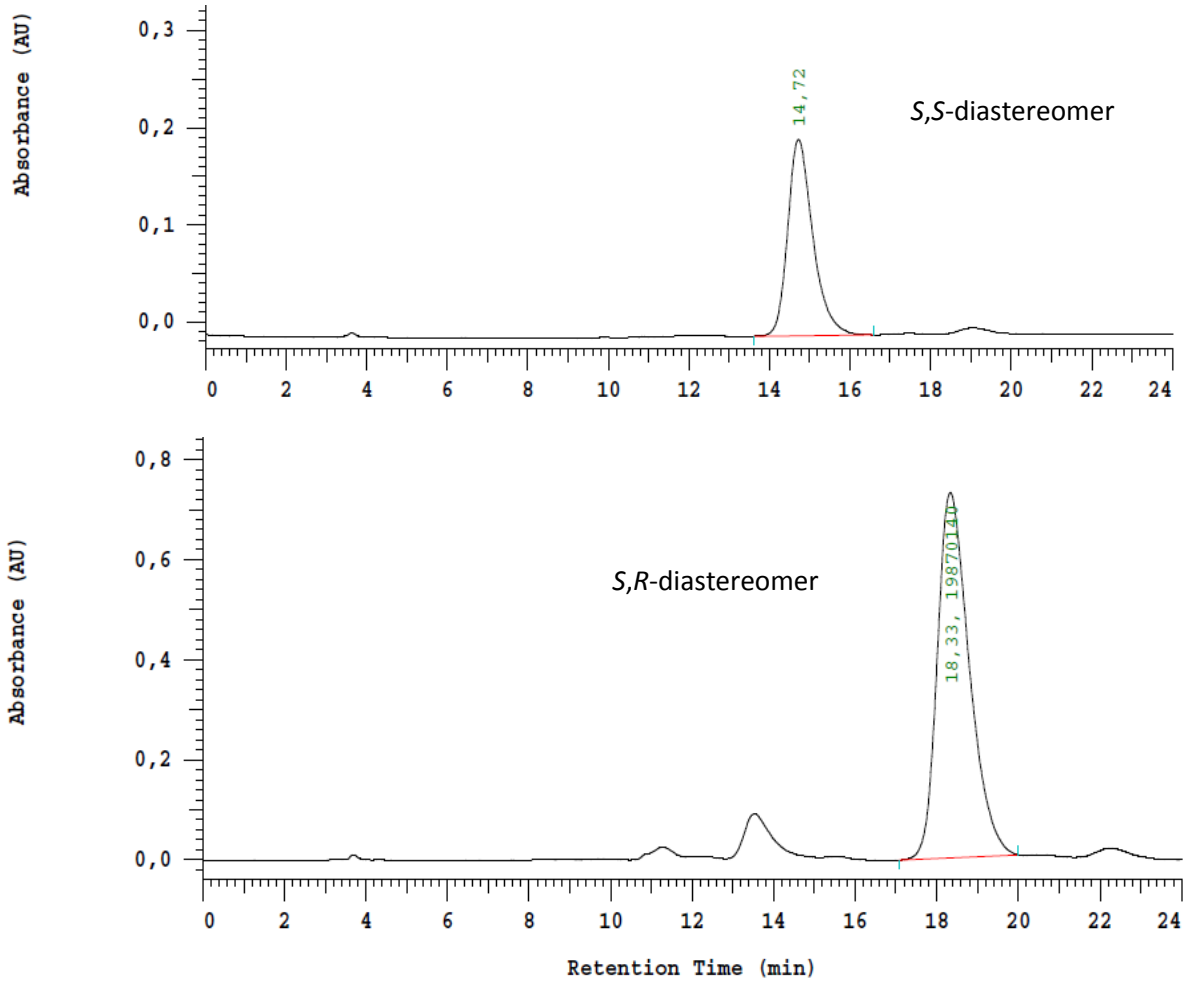


Fig. 7: Comparison of allylation diastereomers with reference sample (*S*,*S*)-**22** on a chiral Reprosil® column.

4.1.5 Substrate Spectrum

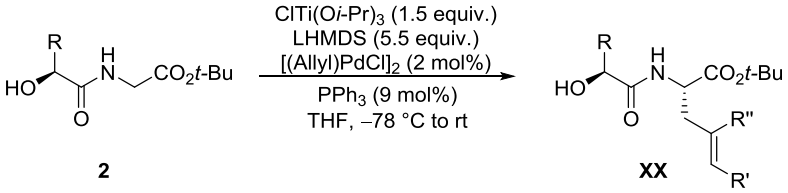
4.1.5.1 LHMDS Method

The formation of the (*S*,*S*)-diastereomer under the LHMDS conditions is somewhat surprising since all previous reports of allylic alkylation of related dipeptides were only able to access the (*S*,*R*)-diastereomers. Due to the large excess of LHMDS which was used in the presence of a fairly strong Lewis acid, a potential explanation for this shift in selectivity might be the epimerization of the ester functionality to the (*S*,*S*)-diastereomers. However, various experiments where the reaction was quenched at low temperature or the (*S*,*R*)-diastereomer was treated with an excess of LHMDS and Lewis acid could not validate this thesis. Attempts to crystallize the chelated enolate, to provide insight in the selectivity of the addition through X-ray analysis, proved unsuccessful and therefore the reason for the formation of the (*S*,*S*)-diastereomer remains unclear.

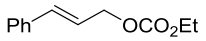
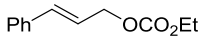
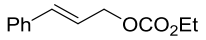
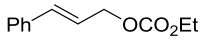
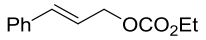
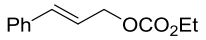
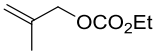
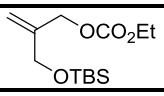
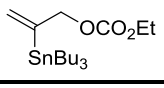
With both methods in hand the substrate spectrum was evaluated. First, *N*-(α-hydroxyacyl)-glycine esters **2** were used under LHMDS conditions which gave mixed results as depicted in table 9. The least sterically demanding ester **2a**, derived from lactic acid, did afford the alkylated ester **20aa** in 63% yield but no asymmetric induction was observed (entry 1). The

more sterically hindered derivatives, derived from the aliphatic amino acids, yielded the alkylated esters **20ab-20ae** in moderate to good selectivity depending on the sterical demand of the side chain (entry 2-5). As expected, leucine derived *N*-(α-hydroxyacyl)-glycine esters **2c** afforded the lowest diastereomeric ratio, while *tert*-leucine derivative **2e** gave the diastereomers in a ratio of 92:8. The *iso*-propyl and *sec*-butyl side chain derivatives both gave satisfactory results with yields of 79% and 82% respectively and diastereomeric ratios of around 5:1. The benzyl derivative unexpectedly gave a quite poor diastereomeric ratio (entry 6), which can not solely be explained through sterical interactions but might be the result of some type of π-π-interaction between the phenyl groups of the ester, carbonate and catalyst. When 2-substituted allylic carbonates were used in the reaction the yields were slightly lower, but the selectivity was satisfactory. Even the simple 2-methyl allyl carbonate **23a** gave the alkylated ester **24a** in good diastereoselectivity (entry 7), while the sterically demanding derivatives **23b** and **23c** afforded the (*S*,*S*)-diastereomer almost exclusively (entry 8-9). The introduction of vinyl stannane **23c** also represents the successful installment of a functional handle which should allow for further functionalization of the side chain, e.g., by transition metal catalyzed cross coupling.

Table 9: Scope of the allylic alkylation using the LHMDS method.



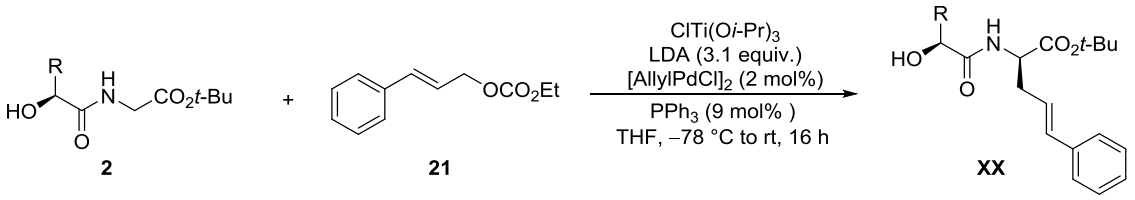
2 **XX**

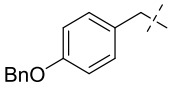
entry	allylic carbonate		R	**XX**	y [%]	*dr*
1		**21**	Me	**20aa**	63	51/49
2		**21**	*i*-Pr	**20ab**	79	83/17
3		**21**	*i*-Bu	**20ac**	78	71/29
4		**21**	*s*-Bu	**20ad**	82	88/12
5		**21**	*t*-Bu	**20ae**	68	92/8
6		**21**	Bn	**20af**	83	58/42
7		**23a**	*s*-Bu	**24a**	66	84/16
8		**23b**	*s*-Bu	**24b**	59	94/6
9		**23c**	*s*-Bu	**24ca**	59	97/3

4.1.5.2 LDA Method

Due to the promising results during optimization, a broad substrate spectrum was evaluated using the LDA method. First, the influence of the backbone of *N*-(α-hydroxyacyl)-glycine esters **2** was examined by reaction with carbonate **21** (tab 10). Diastereoselectivities proved to be exceptional under these conditions, with all products being obtained in *diastereomeric ratios* of at least 96:4. Additionally, the yields of aliphatic sidechain derivatives (entry 1-5) were satisfactory ranging from 70-82%. In the case of serine derived *N*-(α-hydroxyacyl)-glycine ester **2h** the alkylation product was obtained in poor yield when 1.5 equivalents of $ClTi(O\textit{i}\text{-}Pr)_3$ were used due to partial cleavage of the protecting group and subsequent side reactions (entry 6). When the reaction was carried out with stoichiometric amount of Lewis acid, both the serine and the tyrosine derived esters **2h** and **2i** could successfully be alkylated in good yield and almost perfect selectivity (entry 7-8).

Table 10: Variation of the backbone in allylic alkylation of *N*-(α-hydroxyacyl)-glycine esters.

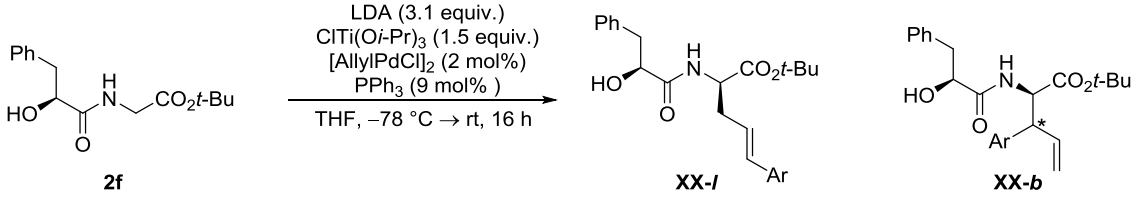


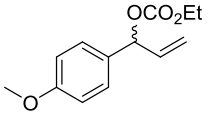
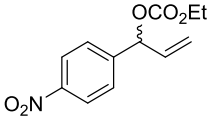
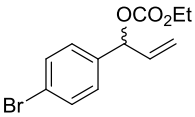
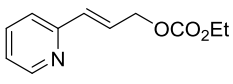
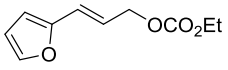
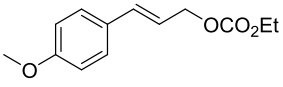
entry	R	equiv. $ClTi(O\textit{i}\text{-}Pr)_3$	**XX**	Y [%]	*dr*
1	*i*-Pr	1.50	**20bb**	73	97/3
2	*i*-Bu	1.50	**20bc**	70	96/4
3	*s*-Bu	1.50	**20bd**	78	98/2
4	*t*-Bu	1.50	**20be**	73	99/1
5	Bn	1.50	**20bf**	82	98/2
6	$CH_2OTBDPS$	1.50	**20bh**	31	98/2
7	$CH_2OTBDPS$	1.05	**20bh**	53	98/2
8		1.05	**20bi**	69	99/1

Next, several aromatic allylic carbonates were tested as depicted in tab. 11. Branched allylic carbonates like **25a**-**c** are fairly easy to prepare and usually react under terminal addition of soft nucleophiles in palladium-catalyzed allylic alkylations to form the same products as linear carbonates. When branched carbonate **25a** was used, however, a mixture of linear and branched products **26a-*l*** and **26a-*b*** was formed (entry 1). Since the formation of the branched product might result from the electron rich aromatic system which could stabilize a benzylic carbenium ion and might favor a S_N1-type addition, electron poor carbonate **25b**

was used next (entry 2). The product was formed in poor yield and a variety of side products were obtained, e.g., addition of the enolate to the nitro group, as described by Kazmaier *et al.* in the case of chelated ester enolates.[335] Bromo-substituted carbonate **25c** gave the alkylated ester in higher yield, albeit a mixture of linear and branched isomers was obtained once more (entry 3). Since the bromo substituent only generates a weak negative inductive effect and even a weak positive *meso*meric effect, the electron poor, linear pyridine derivative **8a** was used as well (entry 4). Indeed, in this case an excellent selectivity of 99:1 toward the linear product was obtained. The yield and diastereoselectivity of the reaction proved to be exceptional as well. In the case of the linear, electron rich aromatic carbonates **8b** and **8c** the formation of the branched product was observed once more. The identical product ratio in the case of linear and branched carbonate **8c** and **25a** demonstrates the independence of the carbonate structure and the resulting product. Rather, electronic effects are solely responsible for the formation of the different isomers by a distinct reaction mechanism which facilitates the formation of the branched structure in the case of electron rich substituents.

Table 11: Influence of different substituted aromatic allyl carbonates.

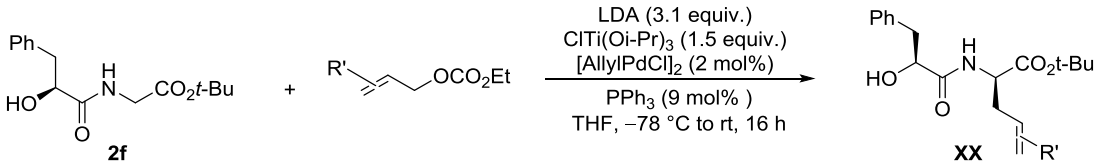


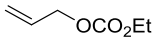
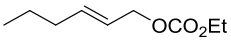
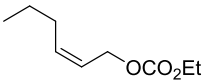
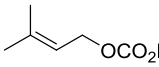
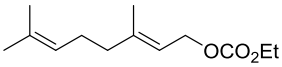
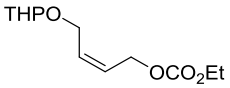
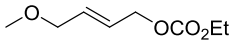
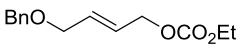
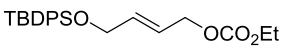
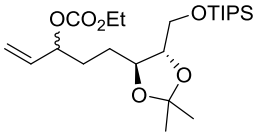
entry	allylic carbonate		XX	Y [%]	*l*/*b*	*dr* (*l*)	*dr* (*b*)
1		**25a**	**26a**	74	71/29	98/2	76/24
2		**25b**	**26b**	21	n.d.	n.d.	n.d.
3		**25c**	**26c**	64	65/35	98/2	83/17
4		**8a**	**27a**	90	99/1	99/1	-
5		**8b**	**27b**	77	77/23	98/2	81/19
6		**8c**	**26a**	57	72/28	98/2	75/25

The results of a series of aliphatic carbonates are displayed in table 12. Simple allyl ethyl carbonate **28a** gave acceptable yield and diastereoselectivity under typical conditions

(entry 1). Surprisingly, linear carbonates such as **28b** and **28c** gave a sluggish reaction with low conversion (entry 2-3). Variation of the catalyst loading, stoichiometry of enolate or electrophile and other reaction parameters gave no improvement in the case of these simple alkyl substituted allyl carbonates.

Table 12: Use of aliphatic and allyloxy carbonates in allylic alkylation.

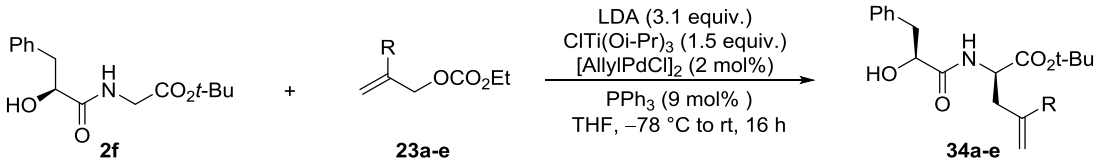


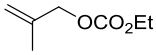
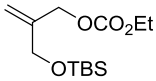
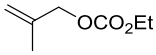
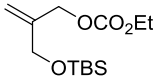
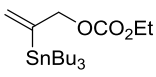
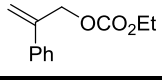
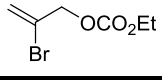
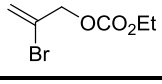
entry	allyl carbonate		conv. [%]	XX	Y [%]	*dr* (*l*)	*l*/*b*
1		**28a**	100	**29a**	76	97/3	-
2		**28b**	26	**29b**	19	n.d.	-
3		**28c**	38	**29c**	31 (*E*)	n.d.	-
4		**28d**	-	**29d**	-	-	-
5		**28e**	-	**29e**	-	-	-
6		**30a**	71	**31a**	34 (*E*)	n.d.	-
7		**30b**	100	**31b**	69	96/4	-
8		**30c**	100	**31c**	74	81/15	-
9		**30d**	100	**31d**	85	99/1	-
10		**32**	72	**33**	46	97/3	80/20

As is to be expected after these results, di-alkyl substituted allyl carbonates gave even worse results with no reaction being observed (entry 4-5). While in the case of such carbonates, the sterical demand of the resulting 1,1-disubstituted allyl complexes might serve as an explanation for the missing reaction, no improvement or explanation for the low conversion of 1-monoalkyl substituted allyl complexes could be found. Instead of using purely aliphatic

substituents, protected allyl alcohols **30a-d** were used as well. THP-protected carbonate **30a** gave similar yields to alkyl substituted carbonates, however in this case the acid labile THP group was partially cleaved by the Lewis acid which explains the poor yield (entry 6). When more stable protection groups such methyl, benzyl or TBDPS were used, satisfactory yields were observed in all cases (entry 7-9). The selectivity in the case of methyl and TBDPS protected derivatives **30b** and **30d** was also excellent, while benzyl derivative **30c** afforded a lower diastereomeric ratio. This might result from an unfavorable π-π-interaction of the phenyl groups in the nucleophile, electrophile and catalyst, but no definitive explanation for the lower selectivity could be discovered. Lastly, a branched carbonate with several protected hydroxyl groups in the side chain was tested. Unfortunately, a mixture of the linear and branched products **33-*l*** and **33-*b*** was observed once more. The linear isomer was formed in 97:3 *dr* but the reaction suffered from incomplete conversion which could not be overcome by variation of the reaction parameters. In the next step, the influence of various substituents in 2-position of the allyl complexes was examined (tab. 13).

Table 13: Substrate scope of 2-substituted allyl carbonates in allylic alkylations.



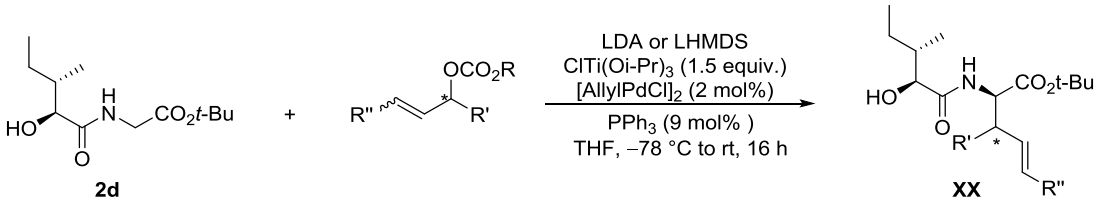
entry	allyl carbonate	conv. [%]	Y [%]	*dr*
1		64	53	99/1
2		47	33	> 99/1
3[a]		100	74	99/1
4[a]		100	77	> 99/1
5[a]		100	67	> 99/1
6[a]		100	83	> 99/1
7[a]		100	75	78/22
8[a,b]		100	96	90/10

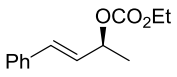
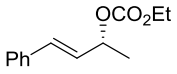
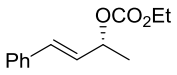
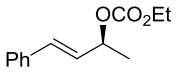
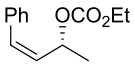
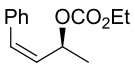
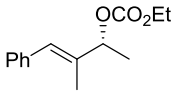
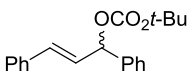
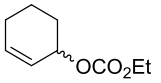
[a] 4 mol% Pd-catalyst and 18 mol% PPh_3 were used. [b] reaction was quenched at –50 °C.

Initial experiments gave the alkylated products in perfect diastereoselectivity, however the yields were rather poor (entry 1-2). In contrast to previously described results, the

conversion and yield could easily be improved by using 4 mol% instead of 2 mol% catalyst loading which resulted in the formation of **23a** and **23b** in 74% and 77% yield, respectively (entry 3-4). In addition to the alkyl and silyloxy substituents, aryl, stannyl and halogenide substituents could also be employed successfully (entry 5-8). Phenyl derivative **23d** gave the alkylated product **34d** in high yield and selectivity. Both vinylstannane **23c** and vinyl bromide **23e** allow for the introduction of a functional handle which can be used to modify the side chain further. Vinylstannane gave the functionalized ester in perfect selectivity, while vinyl bromide **23e**[336] gave a diastereomeric ratio of 78:22 under typical reaction conditions (entry 7). Periodical reaction control via TLC indicated the epimerization of the ester during thawing of the reaction mixture. Therefore, the reaction was quenched at −50 °C after complete conversion was observed to suppress any further epimerization which afforded vinyl bromide **34e** in 96% yield and 9:1 *dr*.

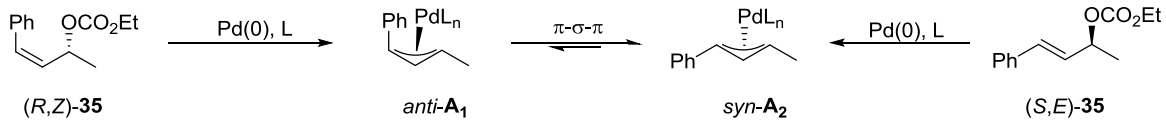
Table 14: Use of secondary carbonates in Pd-catalyzed allylic alkylation.



entry	allyl carbonate		base (equiv.)	**XX**	Y [%]	*dr*
1		(*S*,*E*)-**35**	LDA (3.1)	**36a**	80	82/18
2		(*R*,*E*)-**35**	LDA (3.1)	**36b**	76	> 99/1
3		(*R*,*E*)-**35**	LHMDS (5.5)	**36b**	81	> 99/1
4		(*S*,*E*)-**35**	LHMDS (5.5)	**36a**	77	83/17
5		(*R*,*Z*)-**35**	LHMDS (5.5)	**36a**	97 (> 98:2 E/Z)	81/19
6		(*S*,*Z*)-**35**	LHMDS (5.5)	**36b**	83 (> 98:2 E/Z)	> 99:1
7		**37**	LHMDS (5.5)	**38**	traces	n.d.
8		**39**	LDA (3.1)	**40**	77	64/36
9		**41**	LDA (3.1)	**42**	62	66/34

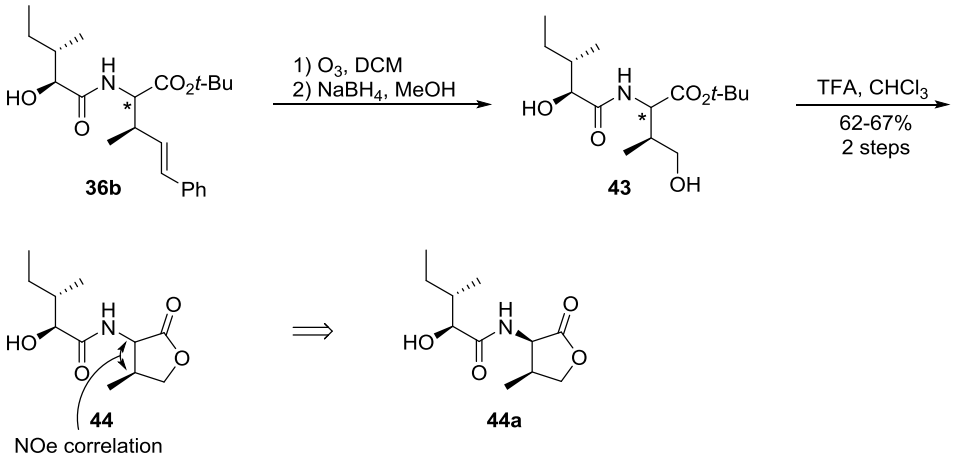
The influence of secondary carbonates and their configuration on the allylic alkylation of *N*-(α-hydroxyacyl)-glycine ester **2f** was examined next (tab. 14). First, (*S*,*E*)-**35** and (*R*,*E*)-**35**

were reacted under typical LDA conditions which gave the alkylated esters **36a** and **36b** in 80% and 76%, respectively. In the case of (*S*,*E*)-**35** a *dr* of 82:18 was observed while the use of (*R*,*E*)-**35** resulted in the formation of a single diastereomer (entry 1-2). These results perfectly demonstrate the occurrence of a matched and mismatched stereocontrol with these carbonates. Surprisingly, when the reaction was conducted under LHMDS conditions, NMR analysis indicated the formation of identical diastereomers to the LDA method (see fig. 9 chapter 6.4). The same matched case with (*R*,*E*)-**35** and mismatched case with (*S*,*E*)-**35** was observed once more. In contrast to the allylic alkylation of peptides, the reaction of *N*-(α-hydroxyacyl)-glycine ester **2f** with *Z*-carbonates (*S*,*Z*)-**35** and (*R*,*Z*)-**35** is not sufficient to suppress π-σ-π isomerization which results in the formation of the favored syn π-allyl complex $\mathbf{A_2}$ (scheme 66). As a result, (*R*,*Z*)-**35** affords (*E*)-**36a** in the mismatched case with a diastereomeric ratio of 81:19 and (*S*,*Z*)-**35** yields the matched product (*E*)-**36b** as a single diastereomer. Similar to previously, trisubstituted allyl carbonate **37** did not react under the developed conditions, probably due to the high sterical demand of the resulting π-allyl complex. Racemic carbonates **39** and **41** were then used to test the possibility to achieve desymmetrization of *meso*-π-allyl complexes using the chiral backbone of the glycine ester. However, without the presence of a chiral ligand, the allylic alkylation did not result in significant differentiation of the diastereotopic C1 and C3 termini. While the α-stereocenter of the ester was formed in perfect selectivity, the β-stereocenter in the sidechain was formed in moderate diastereoselectivity, respectively.



Scheme 66: Isomerization of π-allyl-palladium complexes.

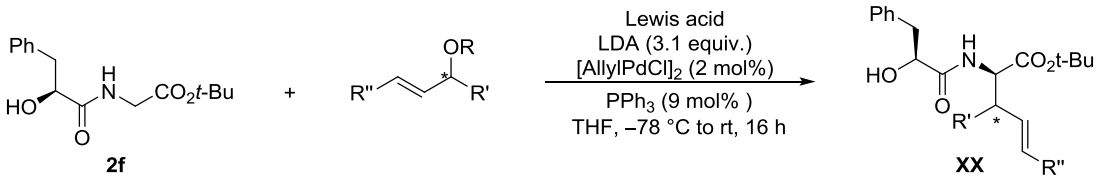
To validate the identity of the products obtained under LDA and LHMDS conditions, both alkenes **36b** were exposed to ozonolysis followed by reductive work-up with sodium borohydride (scheme 67). The resulting hydroxy ester **43** was then treated with trifluoroacetic acid in DCM to simultaneously achieve cleavage of the *tert*-butyl ester and acid catalyzed lactonization to form lactone **44** in 62% and 67% yield, respectively. Analysis via NOESY displayed a strong correlation of the protons on the tertiary lactone stereocenters in both cases. Additionally, the matching coupling constant in the ^{1}H-NMR spectra of 7.1 Hz is in agreement with reported values for similar systems,[337] confirming that in both cases the product with (*R*)-configuration of the α-stereocenter is obtained.

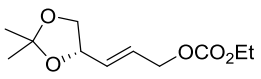
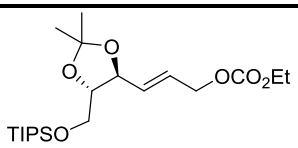
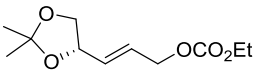
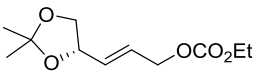
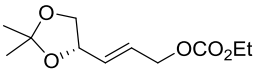
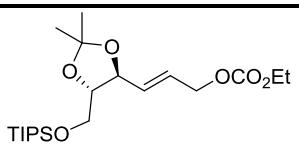
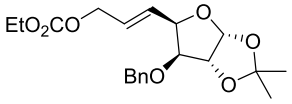
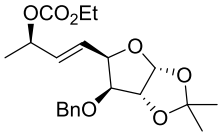
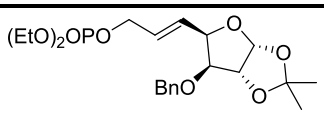


Scheme 67: Elucidation of the stereochemistry of the allylation with secondary carbonates.

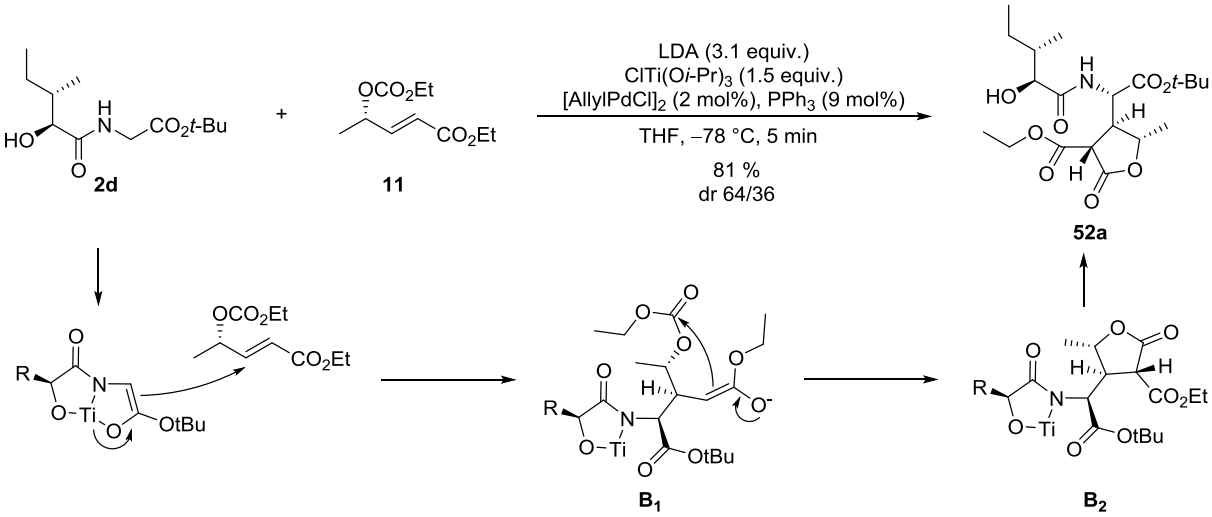
Lastly, some complex carbonates containing multiple functional groups were tested in the allylic alkylation of glycine ester **2f** using the previously developed conditions (tab. 15). When primary carbonates **13** and **16** were used however, the allylation products **45** and **46** were obtained in poor yield (entry 1-2). Due to the presence of several oxygen functionalities, the carbonate might compete for chelation with the oxophilic Lewis acid, which might explain the low yield. To verify this thesis, the reaction was conducted once more with the less oxophilic zinc chloride and in a second attempt using a larger excess of titanium Lewis acid (entry 3-4). The use of zinc chloride led to a very slight improvement in yield albeit the diastereoselectivity was insufficient. When 2.0 equivalents of $ClTi(O\textit{i}\text{-}Pr)_3$ were used, the yield remained poor, but a closer inspection of the crude reaction mixture revealed the cleavage of the acetal group in the unreacted carbonate which resulted in incomplete conversion. In an attempt to avoid cleavage of the acetal group, the reaction was conducted with stoichiometric amounts of $ClTi(O\textit{i}\text{-}Pr)_3$ analog to table 10. Indeed, this resulted in significant improvement in terms of yield and diastereoselectivity (entry 5). The alkylated ester **45** was obtained in 77% yield and a *dr* of 98:2. Tartaric acid derived carbonate **16** also displayed a clean reaction, with the allylation product being obtained in 80% yield and perfect selectivity (entry 6). In contrast, sugar derived carbonates **19** and **48** did not react under any conditions and could be reisolated in almost quantitative fashion. Attempts to use the more reactive phosphate **50** did not significantly improve the reaction and only traces of the desired product were observed by NMR spectroscopy of the crude reaction mixture.

Table 15: Use of highly functionalized allyl carbonates in the Pd-catalyzed allylic alkylation.



entry	allyl carbonate	**XX**	Lewis acid (equiv.)	**XX**	Y [%]	*dr*
1		**13**	ClTi(O*i*-Pr)$_3$ (1.50)	**45**	21	n.d.
2		**16**	ClTi(O*i*-Pr)$_3$ (1.50)	**46**	8	n.d.
3		**13**	$ZnCl_2$ (1.50)	**45**	28	72/28
4		**13**	ClTi(O*i*-Pr)$_3$ (2.00)	**45**	13	n.d.
5		**13**	ClTi(O*i*-Pr)$_3$ (1.05)	**45**	77	98/2
6		**16**	ClTi(O*i*-Pr)$_3$ (1.05)	**46**	80	99/1
7		**19**	ClTi(O*i*-Pr)$_3$ (1.05)	**47**	no reaction	-
8		**48**	ClTi(O*i*-Pr)$_3$ (1.05)	**49**	no reaction	-
9		**50**	ClTi(O*i*-Pr)$_3$ (1.05)	**51**	4	n.d.

Interestingly, when allyl carbonate **11** was used, the reaction indicated full conversion to a single, defined product after only two minutes. The expected allylic alkylation product, however, was not observed, but rather lactone **52a** as a mixture of two diastereomers (scheme 68). The structure and configuration of the main diastereomer of this lactone was unambiguously assigned via X-ray structure analysis (see fig. 8). In contrast to the allylic alkylation, the α-stereocenter is formed in *S*-configuration which is rather unexpected and a conclusive reason for the observed selectivity could not be found.



Scheme 68: Enolate addition to Michael acceptor followed by cyclization.

The lactone is presumably formed by addition of the chelated enolate to the Michael acceptor and subsequent Dieckmann-type condensation of the intermediary ester enolate $\mathbf{B_1}$ and the ethyl carbonate as depicted in scheme 68. Since a mixture of two diastereomers was obtained, the enantiomeric carbonate *ent*-**11** was used to examine the possibility of a matched/mismatched scenario in the case of the Michael addition.

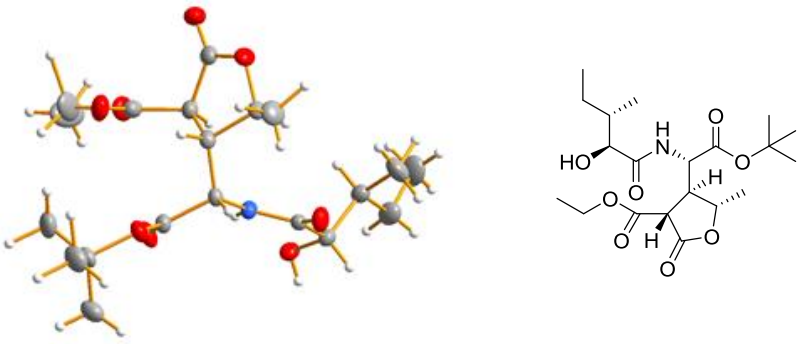
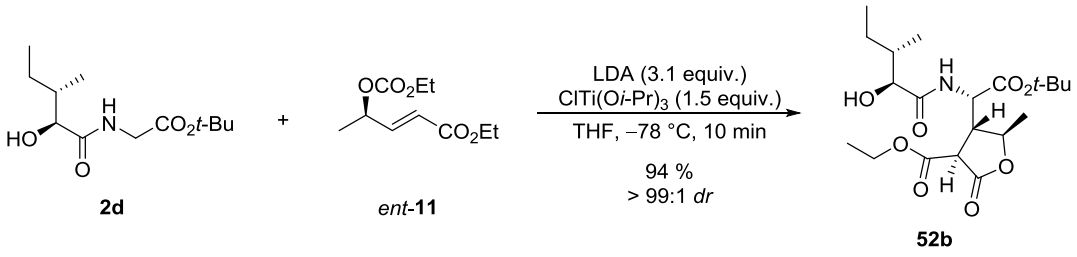


Fig. 8: X-ray structure of **52a**.

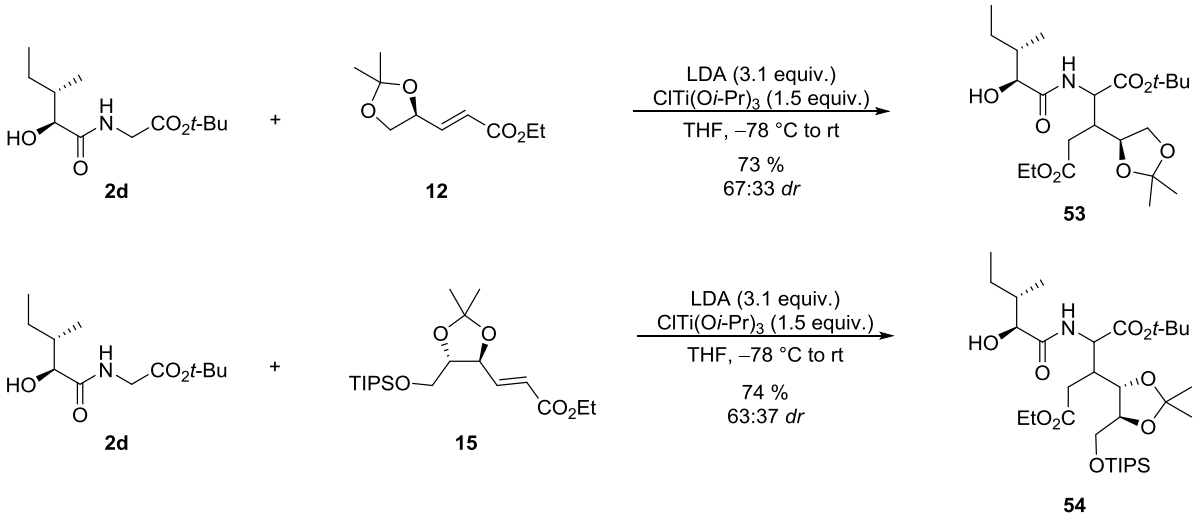
To our delight, the use of *ent*-**11** confirmed this hypothesis and lactone **52b** was formed as a single diastereomer (scheme 69).



Scheme 69: Matched case of the Michael addition and cyclization cascade reaction.

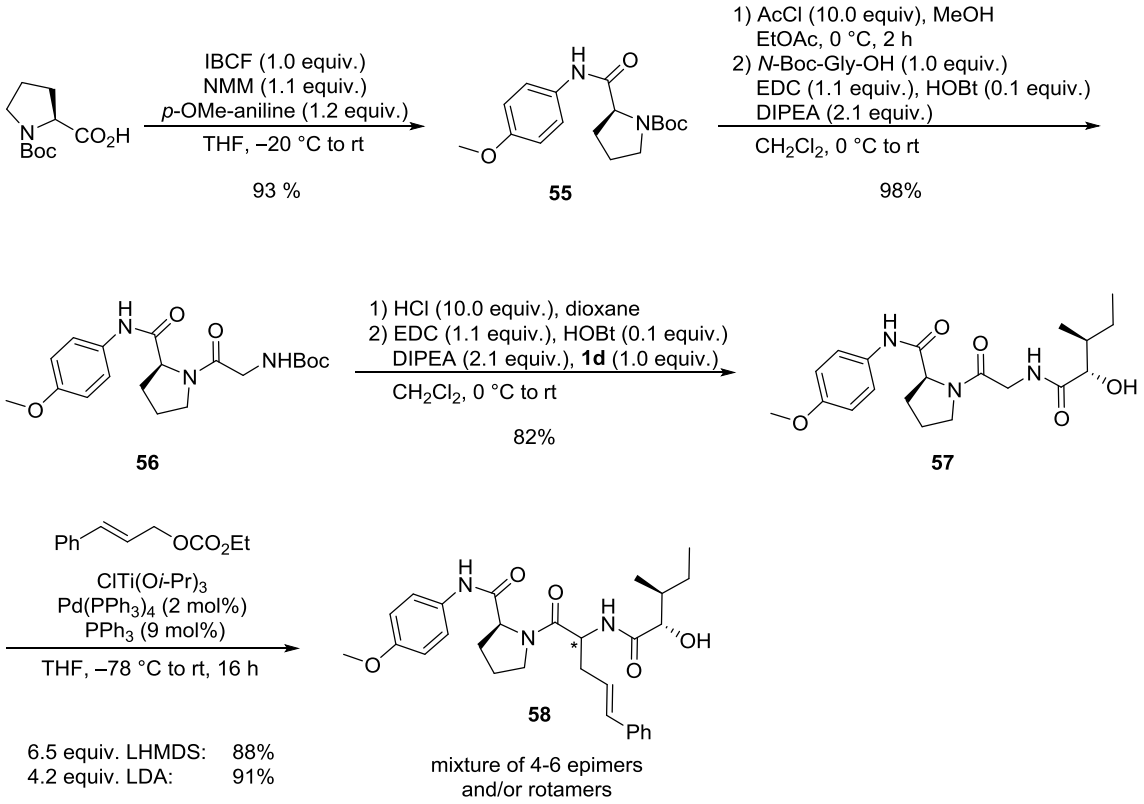
Surprisingly, when similar unsaturated esters lacking the carbonate functionality were used (scheme 70), the expected matched case Michael addition was not observed but a mixture of diastereomers was obtained. Since the diastereoselectivity was low in most attempts of

Michael addition and several other unsaturated esters gave poor conversion or product mixtures, this approach was not pursued any further during this work.



Scheme 70: Michael addition of chelated *N*-(α-hydroxyacyl)-glycine ester enolates.

Based on the positive results for the allylic alkylation of titanium chelated *N*-(α-hydroxyacyl)-glycine ester enolates, the incorporation of this structural element in a more complex peptide like fragment and the allylic alkylation thereof was analyzed.



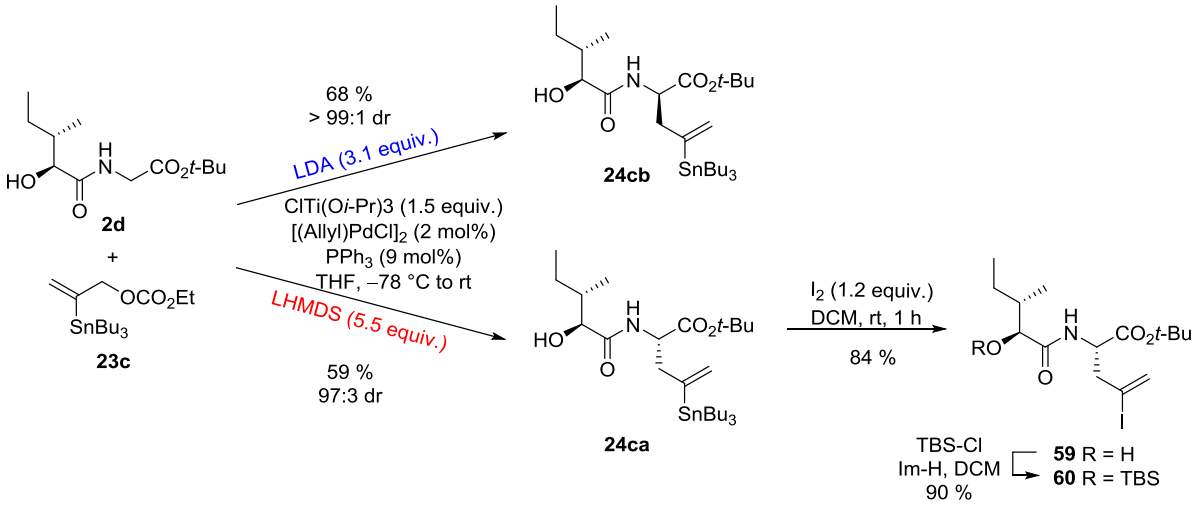
Scheme 71: Preparation and allylic alkylation of peptide**57**.

The required fragment was synthesized from Boc-proline by IBCF-mediated amidation followed by deprotection with methanolic HCl and consecutive peptide coupling with Boc-

glycine using EDC/HOBt conditions in 91% yield over three steps. Boc-deprotection and coupling with *iso*-leucine derived hydroxy acid **1d** gave rise to the pseudo tripeptide **57**. Treatment of this compound with 4.2 equivalents LDA or 6.5 equivalents LHMDS in the presence of $ClTi(O\textit{i}\text{-}Pr)_3$ according to the previously described methods resulted in the formation of the desired, dark red to black titanium chelate complex. Allylic alkylation with cinnamyl ethyl carbonate under Pd-catalysis in both cases gave the product in high yield of around 90%, albeit as a complex mixture of epimers and/or rotamers which could not be unambiguously determined by NMR and HPLC analysis. Since the secondary amide is essential for formation of the glycine enolate and simultaneously might be responsible for the epimerization, this work was not continued but the focus was shifted toward the further modification of the side chain.

4.1.6 Functionalization of the Side Chain

After the initial optimization and evaluation of the substrate spectrum, the functionalization of the side chain and possible applications in the synthesis of natural products was examined. Both developed methods proved reproducible in gram scale synthesis of vinyl stannane derivatives **24ca** and **24cb**. Subsequent treatment with iodine in dichloromethane cleanly afforded the vinyl iodide **59** in 84% yield. Since free hydroxyl groups are known to cause issues in some cross coupling systems, the alcohol was protected as its TBS-ether **60**.

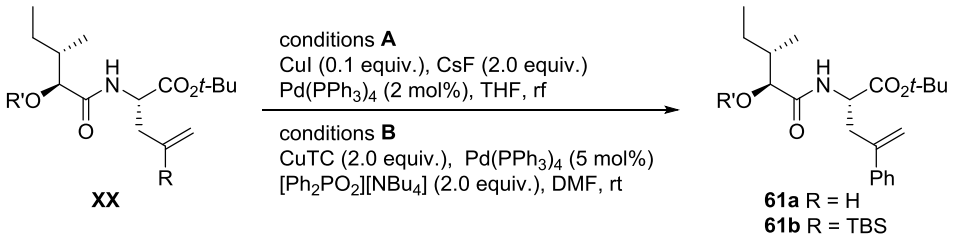


Scheme 72: Gram scale allylic alkylation.

At first, cross coupling of vinyl stannane **24ca** and vinyl iodide **59** via Stille coupling with iodobenzene or tributylphenylstannane was attempted (tab. 16). Using typical dual catalysis of copper(I) and palladium(0) (conditions A, entry 1-2) as well as other literature protocols did not result in any reaction.[338,339] Protodestannylation was the sole reaction which could be observed in these attempts. The use of TBS-protected derivative **60**, to circumvent the presence of the acidic alcohol functionality, did not improve the results in the slightest (entry 3). More promising results could be obtained when conditions developed by Fürstner and coworkers were used.[340] The group established a copper(I) thiophene-2-carboxylate

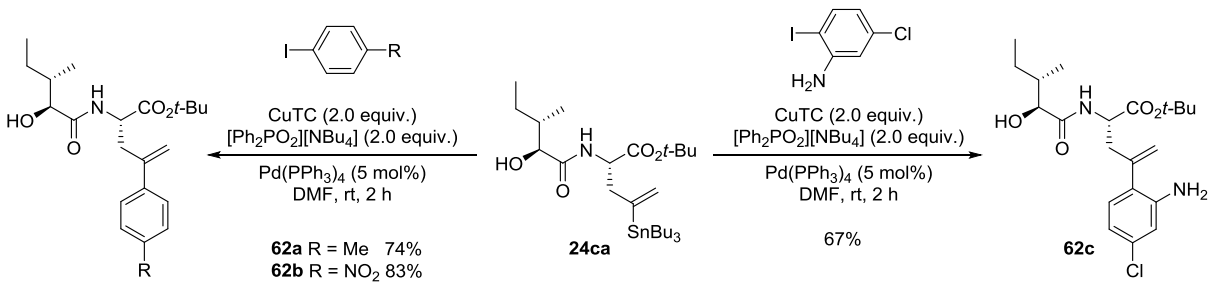
(CuTC) co-catalyst combined with a diphenylphosphinate alongside $Pd(PPh_3)_4$ as a robust catalytic system to achieve Stille coupling of challenging substrates under mild reaction conditions. Treatment of vinyl iodide **59** with tributylphenylstannane under these conditions gave rise to the desired coupling product **61a** in low yield (entry 4). The yield could be further improved using a small excess of stannane which resulted in 59% yield for the unprotected derivative **61a** and 63% in the case of TBS-protected derivative **61b** (entry 5-6). Similarly, when vinyl stannane **24ca** was reacted with iodobenzene the formation of the product was observed albeit in low yield along with 31% protodestannylation (entry 7). Increasing the amount of iodobenzene to 2.0 equivalents and the reaction time to three hours instead of one hour did improve the yield significantly (entry 8).

Table 16: Optimization of Stille cross coupling.



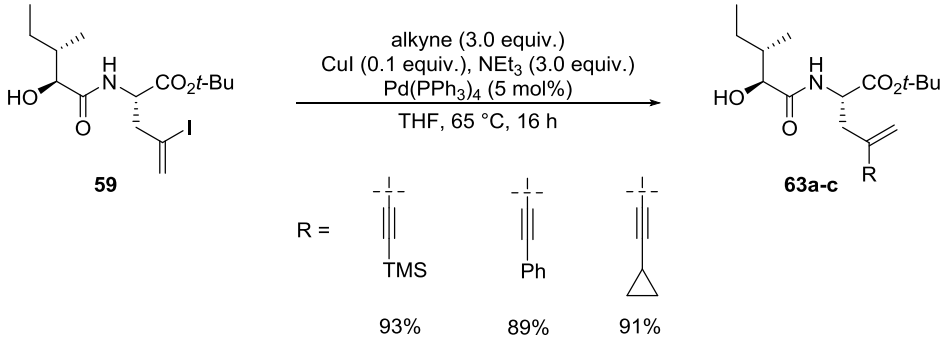
entry	**XX**	R	R'	cond.	Ph-X (equiv.)	t [h]	Y [%]
1	**24ac**	$SnBu_3$	H	A	Ph-I (1.1)	16	-
2	**59**	I	H	A	Ph-$SnBu_3$ (1.1)	16	-
3	**60**	I	TBS	A	Ph-$SnBu_3$ (1.1)	16	-
4	**59**	I	H	B	Ph-$SnBu_3$ (1.1)	1	43
5	**59**	I	H	B	Ph-$SnBu_3$ (2.0)	1	59
6	**60**	I	TBS	B	Ph-$SnBu_3$ (2.0)	1	63
7	**24ca**	$SnBu_3$	H	B	Ph-I (1.1)	1	23
8	**24ca**	$SnBu_3$	H	B	Ph-I (2.0)	3	71

The optimized conditions were then used with aryl iodides containing additional functional groups (scheme 73). Both electron withdrawing as well as electron donating substituents were tolerated, methyl as well as nitro derivatives **62a** and **62b** were obtained in 74% and 83%, respectively. Introduction of an unprotected aniline was achieved in acceptable yield and the resulting aniline **62c** can be used as a precursor to form a tryptophane derivative via nitrene insertion by a protocol developed by Kazmaier *et al.*[341,342]



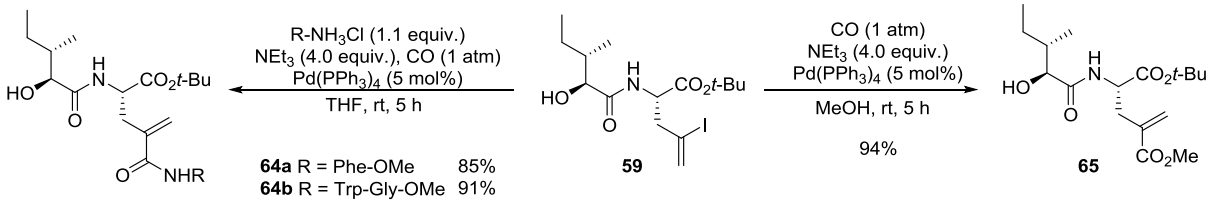
Scheme 73: Stille coupling with different aryl iodides.

Modification of the side chain via Sonogashira coupling was straightforward and proceeded in excellent yields with several terminal alkynes (scheme 74).



Scheme 74: Modification of the side chain by Sonogashira coupling.

Vinyl iodide **59** also proved to be a suitable substrate for palladium-catalyzed CO insertion and coupling with amines or alcohols. Upon treatment of vinyl iodide **59** with phenylalanine methyl ester or dipeptide H-Trp-Gly-OMe in the presence of $Pd(PPh_3)_4$ and CO, the unsaturated amides **64a** and **64b** were obtained in high yield. When the reaction was carried out in methanol, CO insertion and coupling was readily achieved to obtain α,β-unsaturated ester **65**.



Scheme 75: Modification of the side chain via CO-insertion.

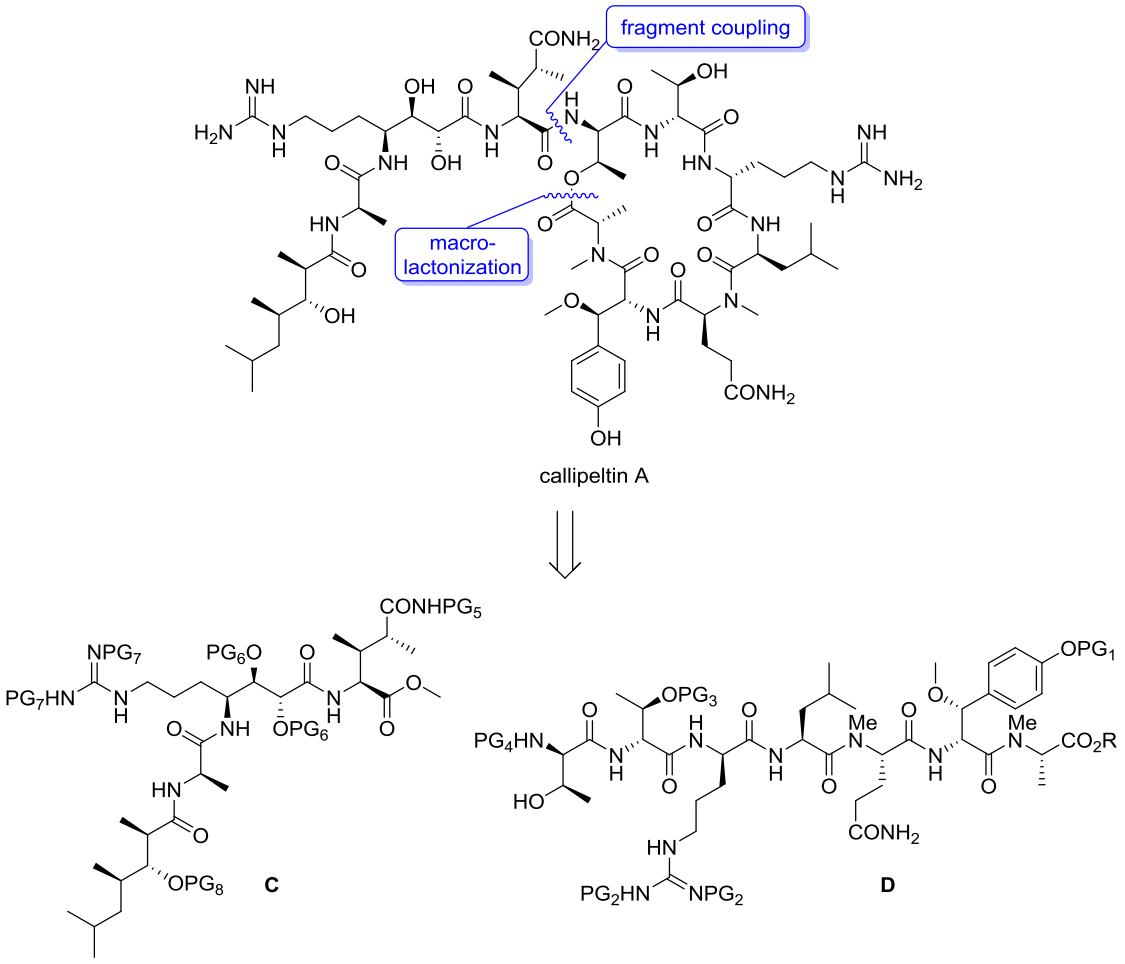
Overall, the evaluation of the allylic alkylation demonstrated the reactivity of titanium chelated *N*-(α-Hydroxyacyl)-glycine ester enolates toward a variety of allyl carbonates and displaying some limitations of both the LDA and LHMDS method. The use of such conformationally fixed titanium chelate complexes allowed for asymmetric 1,4-induction by the chiral glycine ester backbone due to shielding of one of the diastereotopic enolate faces. Thus, the reaction generally proceeds with good to excellent diastereoselectivity and yield. Several functional groups such as heteroaromatics, ethers, halogenides and stannanes are tolerated while free and protected amines are generally not tolerated due to side reactions

of the nucleophilic amino group under the extremely basic reaction conditions. While tri-substituted π-allyl complexes do not react under the described reaction conditions, the method allows for a high structural variance in the allylic carbonate. In general, 1-, 2- and 1,3-substituted π-allyl complexes undergo allylic alkylation using the herein described reaction conditions. Furthermore, the introduced functional groups allow for modification of the side chain by transition metal catalysis, e.g., Sonogashira or Stille coupling.

4.2 Studies toward the Total Synthesis of Callipeltin A and C

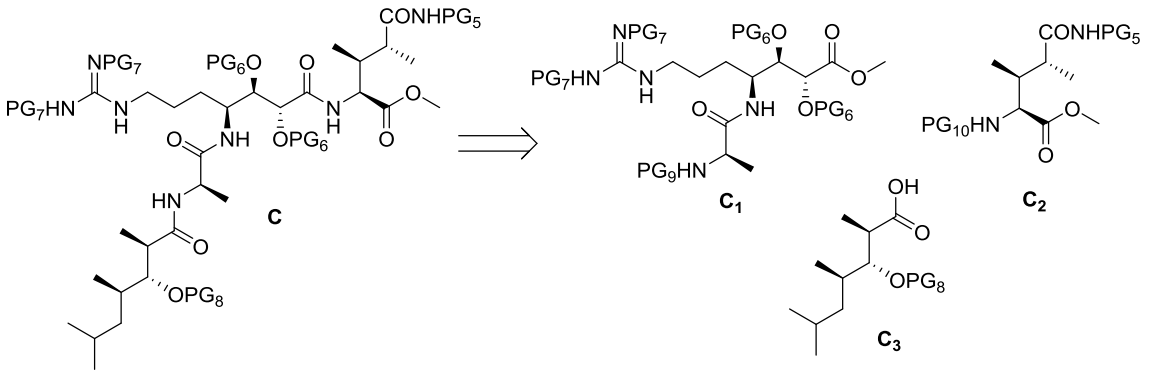
4.2.1 Retrosynthesis

Retrosynthetic analysis of callipeltin A resulted in the pursuit of two slightly different late-stage disconnections which leads to the same synthetic intermediates **C** and **D**. Both approaches, depicted in scheme 76, rely on a retro macrolactonization and disconnection of the (cyclic-) depsipeptide core from the side chain **C** which contains the majority of unusual amino acids. The key macrolactonization was planned between D-*allo*-threonine and the *N*-methyl alanine residue based on the reported macrolactonization at this position by Konno *et al.* in the total synthesis of callipeltin B.[322] Late stage coupling of retrons **C** and **D** would allow for a significant structural simplification of the synthetic intermediates up to this point. Overall, the two approaches only differ in the order in which the fragment coupling and macrocyclization is conducted. The multitude of functional groups and the resulting structural complexity of callipeltin A requires the development of a complex protection group strategy using several orthogonal protecting groups.



Scheme 76: Retrosynthetic analysis of callipeltin A.

The side chain peptide **C** was disconnected by retro-peptide coupling into the three unusual amino and hydroxy acid building blocks $\mathbf{C_1}$-$\mathbf{C_3}$ (scheme 77)

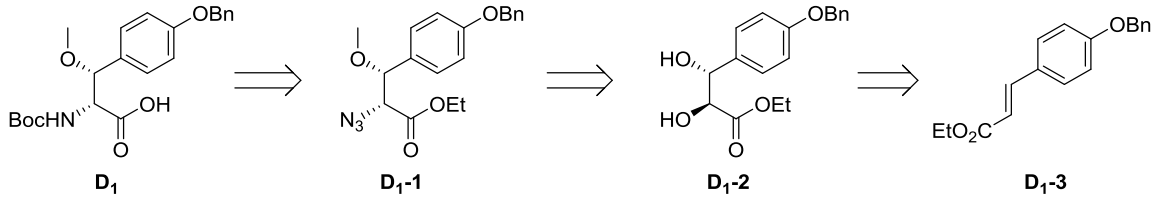


Scheme 77: Disconnection of side chain **C**.

Standard disconnection of the collective intermediate **D** results in six none proteinogenic amino acids **D_1-D_6** and Boc-L-leucine. Assembly of the linear peptide was envisioned by consecutive peptide coupling chemistry starting from *C*-terminal alanine.

4.2.2 Synthesis of Tyrosine Building Block D_1

Synthesis of β-methoxy tyrosine was envisioned via a similar route as described by Cuevas and coworkers.[266] Retrosynthetic considerations regarding protected amino acid **D_1** led to azide precursor **D_1-1** (scheme 78).

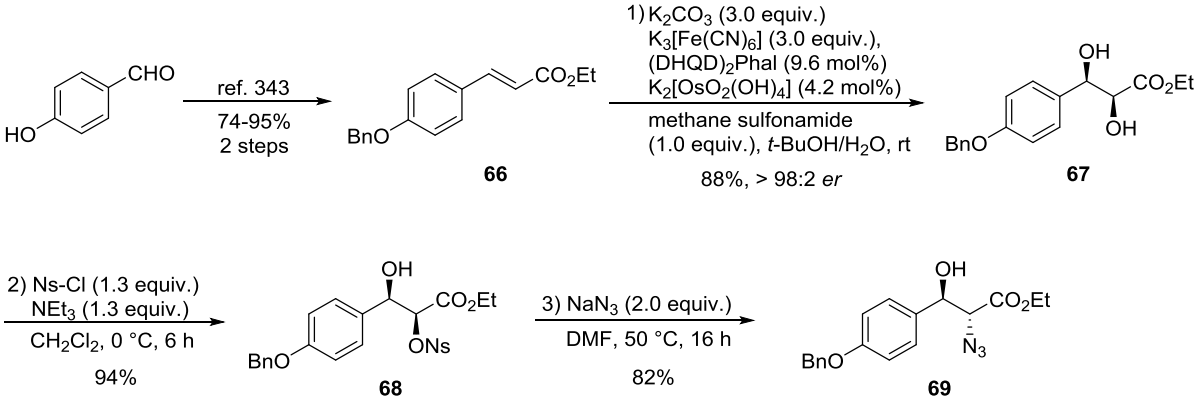


Scheme 78: Retrosynthetic analysis of β-methoxy tyrosine **D_1**.

Reduction of the azide by Staudinger reaction and saponification of the ethyl ester should afford tyrosine **D_1**. Further disconnection of the methoxy group and transformation of the azide to an α-hydroxyl functionality leads to diol **D_1-2** which can be readily obtained from cinnamic ester **D_1-3**. The alkene can be dihydroxylated via Sharpless conditions and regioselective transformation of the α-hydroxyl group by nosylation or tosylation and subsequent substitution should afford azide **D_1-1** after methylation of the second hydroxyl group.

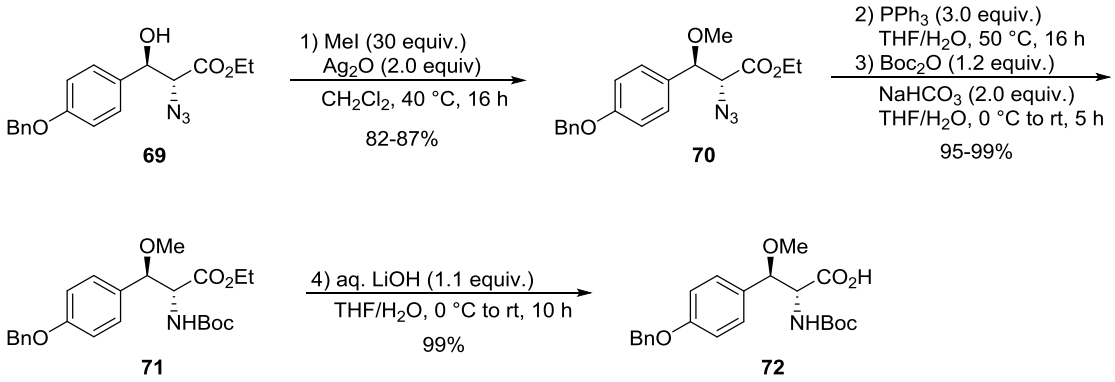
The synthesis started with the preparation of cinnamic ester **66**,[343] which was dihydroxylated by a modified procedure from Cuevas with methane sulfonamide as acid catalyst (scheme 79).[266,344] Selective nosylation of the α-hydroxyl group was readily achieved by treatment of diol **67** with nosyl chloride and triethylamine at 0 °C. However, the azide substitution suffered from the formation of several unidentified side products under various reaction conditions. The formation of these side products could be traced back to the low stability of nosylate **68** which was prone to decompose quickly by prolonged exposure to light, air, and silica at room temperature. To avoid this problem the nosylate

was purified in rapid fashion by filtration through a short column of silica and then immediately used in the substitution under exclusion of light.



Scheme 79: Synthesis of secondary alcohol **69**.

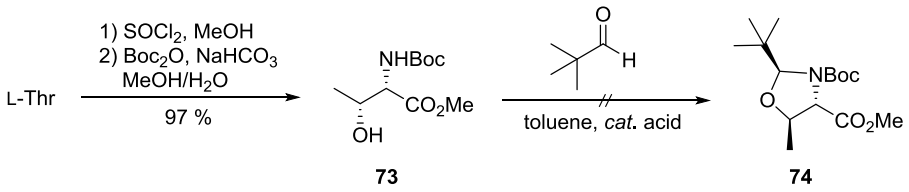
In the next step the secondary alcohol **69** was transformed into the methyl ether **70** by exposure to methyl iodide in the presence of silver oxide (scheme 80). Quantitative reduction of the azide was achieved by Staudinger reaction under conditions described by Kirschning *et al.* followed by Boc-protection under typical conditions.[345] Finally, the ethyl ester **71** was cleaved by saponification using lithium hydroxide in dioxane/water to obtain carboxylic acid **72** in 99% yield.



Scheme 80: Preparation of β-methoxy tyrosine **72**.

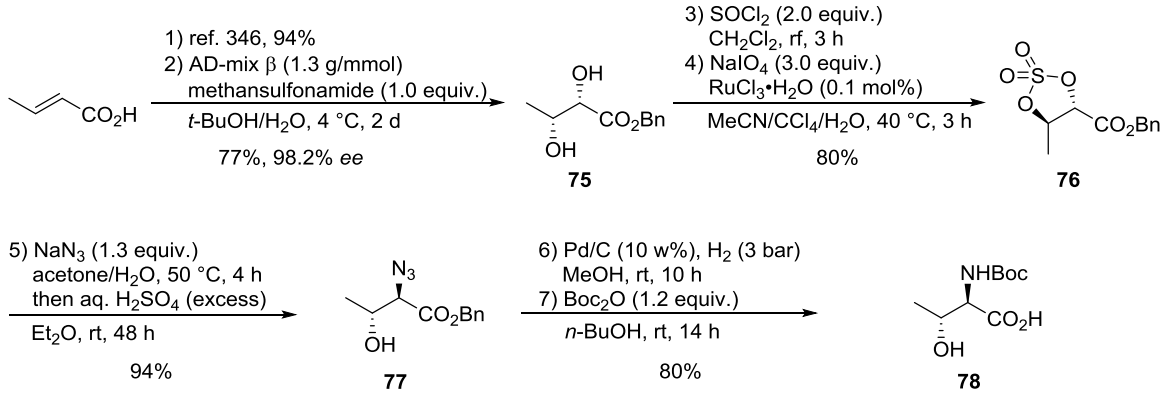
4.2.3 Synthesis of D-*allo*-Threonine

The selective hydroxyl group protection of threonine surprisingly presents a significant challenge which is usually avoided by using the commercially available *Ot*-Bu threonine derivatives. In the case of D-*allo*-threonine such derivatives are not commercially available and synthetic protocols for the preparation of such derivatives are rare. In the first attempt the epimerization of L-threonine via the oxazolidine **74** by a protocol of Shair *et al.* was planned (scheme 81). However, the cyclization of threonine **73** proved impossible and no reaction conditions have been reported by the Shair group. Even when the cyclization and Boc-protection sequence was reversed no successful preparation of oxazolidine **74** could be achieved.



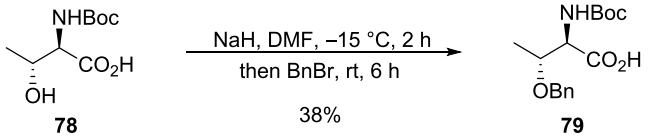
Scheme 81: Attempted synthesis of oxazolidine **74**.

The second approach followed a procedure reported by Goodman *et al.* based on the asymmetric dihydroxylation of *E*-crotonic acid.[346] After dihydroxylation, the diol **75** was transformed into cyclic sulfate **76** by treatment with thionyl chloride and oxidation with sodium periodate (scheme 82). Substitution in α-position was conducted with sodium azide in acetone/water and the resulting sulfate was cleaved with aqueous sulfuric acid to obtain azide **77** in 94% yield as a single diastereomer. Attempts to protect the secondary hydroxyl group of **77** were in its entirety unsuccessful due to epimerization of the azido ester. Thus, the azide was reduced with simultaneous cleavage of the benzyl ester by hydrogenolysis, and the resulting amine protected with Boc_2O to afford threonine **78**.



Scheme 82: Synthesis of protected D-*allo*-threonine **78**.

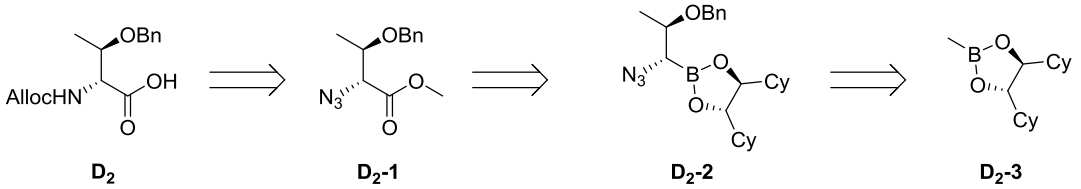
Once more protection of the hydroxy group was attempted under various conditions. However, acidic protection conditions led to Boc-deprotection and decomposition and under several basic conditions no product formation was observed. The best result could be obtained when conditions from Shin *et al.* were used.[347] Deprotonation was conducted with sodium hydride at –15 °C and subsequent treatment with benzyl bromide afforded protected threonine **79**, albeit in low yield (scheme 83).



Scheme 83: Benzyl protection of threonine **78**.

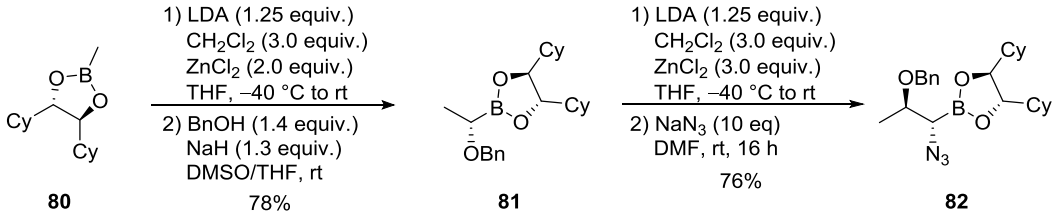
Since the yield of the protection could not be improved under any conditions, the development of a new, more flexible route was desired. The installment of the 1,2-*anti* stereocenters was envisioned via a Matteson homologation strategy, which would allow for direct introduction of a variety of alkoxy nucleophiles, hence avoiding the necessity of a

potentially challenging protection step. Standard retrosynthetic disconnections of threonine **D_2** led to azido ester **D_2-1** which should be derived from boronic ester **D_2-2** by Matteson homologation, oxidation, and esterification (scheme 84). Boronic ester **D_2-2** was traced back further to known methyl boronic ester **D_2-3** by retro Matteson homologation.



Scheme 84:Retrosynthetic analysis of threonine **D_2**.

Methyl boronic ester **80** was prepared according to a modified literature procedure starting from *trans*-stilbene in three steps.[348] Matteson homologation of **80** was attempted with in situ generated $LiCHCl_2$ (1.25 equiv.) and zinc chloride at –40 °C. After treatment of the generated chloro-boronic ester with a solution of sodium benzylate, homologated boronic ester **81** could be obtained as a single diastereomer (scheme 85). A second homologation under the same conditions, followed by treatment of the corresponding chloro-boronic ester with sodium azide in DMF afforded azide **82** in 76% yield. NMR analysis of azide **82** indicated a small loss of chirality during the substitution (96:4 *dr*) which is a typical problem during such azide substitution reactions in DMF. Since epimerization can sometimes be suppressed by the use of biphasic mixtures of ethyl acetate or nitromethane and water these conditions were also tested. However, under these conditions the reaction proceeded very slow (> 10 d reaction time) and sluggish with similar diastereoselectivity.

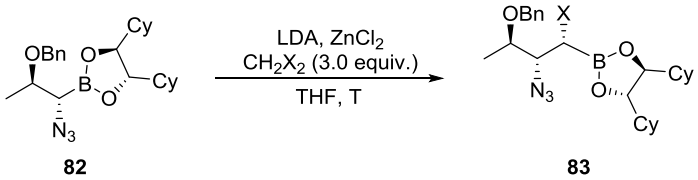


Scheme 85: Matteson homologation toward azide **82**.

Further homologation of boronic ester **82** under the same conditions as before proceeded with incomplete conversion, which required optimization of this homologation step as depicted in table 17. Additional to the incomplete conversion, homologation to the chloro-boronic ester **83a** was always accompanied with the formation of several side products (entry 1-2). To avoid these side products, homologation to the bromo-boronic ester was attempted.[349] Early attempts under the usual conditions (entry 3-4) indicated a clean reaction albeit no complete conversion occurred. Variation of several reaction conditions showed similar results in all cases as shown with the example in entry 5 when a lower amount of zinc chloride was used. Since epimerization of the bromo-boronic ester was inconsequential due to subsequent oxidation, the effect of increased amounts of LDA was analyzed. The best results were obtained when two equivalents of LDA were used which led

to a slight improvement in conversion (entry 6). Fortunately, when these conditions were used on preparative scale (10 mmol, entry 7) conversion could be improved further and bromo-boronic ester **83b** was obtained in 96% yield, containing 4% of the starting material.

Table 17: Optimization of Matteson homologation of **82**.

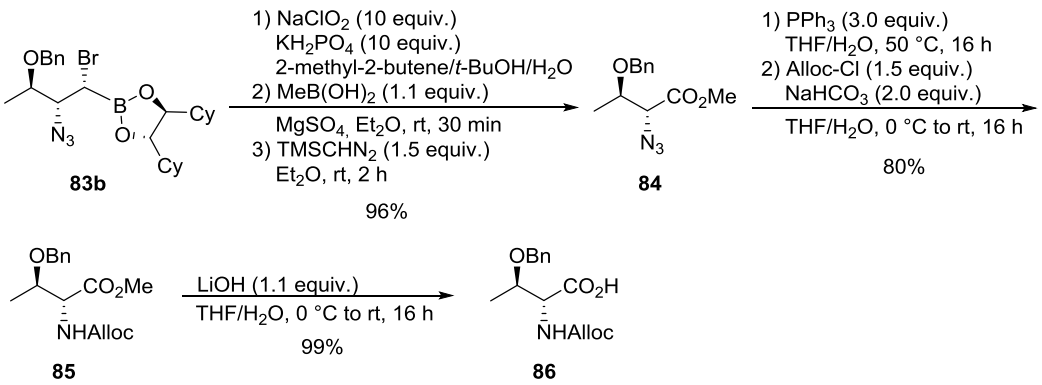


82 **83**

entry	equiv. LDA	equiv. $ZnCl_2$	T	X	conv. [%]
1	1.25	3.0	–40 °C to rt	Cl	84
2	1.15	5.0	–40 °C to rt	Cl	61
3	1.15	3.0	–78°C to rt	Br	75
4	1.25	3.0	–78°C to rt	Br	85
5	1.25	2.0	–78°C to rt	Br	87
6	2.00	3.0	–78°C to rt	Br	89
7[a]	2.00	3.0	–78°C to rt	Br	96

(reactions were performed on 0.2 mmol scale, a) reaction performed on 10 mmol scale)

Bromide **83b** was oxidized to the carboxylic acid by Pinnick type conditions with $NaClO_2$, KH_2PO_4 in the presence of 2-methyl-2-butene as scavenger (scheme 86).[350] Next, esterification of the cleaved ligand with methyl boronic acid was carried out to achieve separation by flash chromatography after treatment of the carboxylic acid with TMS-diazomethane. The α-azido ester **84** could thus be obtained in 96% yield. Reduction of the azide was achieved by Staudinger reduction and the amine was protected as its Alloc-carbamate to afford completely protected threonine **85**. Quantitative saponification with lithium hydroxide finally yielded threonine **86**.

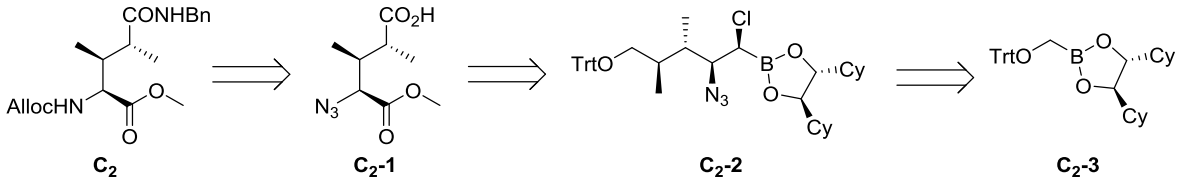


83b **84** **85** **86**

Scheme 86: Preparation of *O*-benzyl protected threonine **86**.

4.2.4 Synthesis of (3*S*,4*R*)-Dimethyl-L-Glutamine (diMeGln)

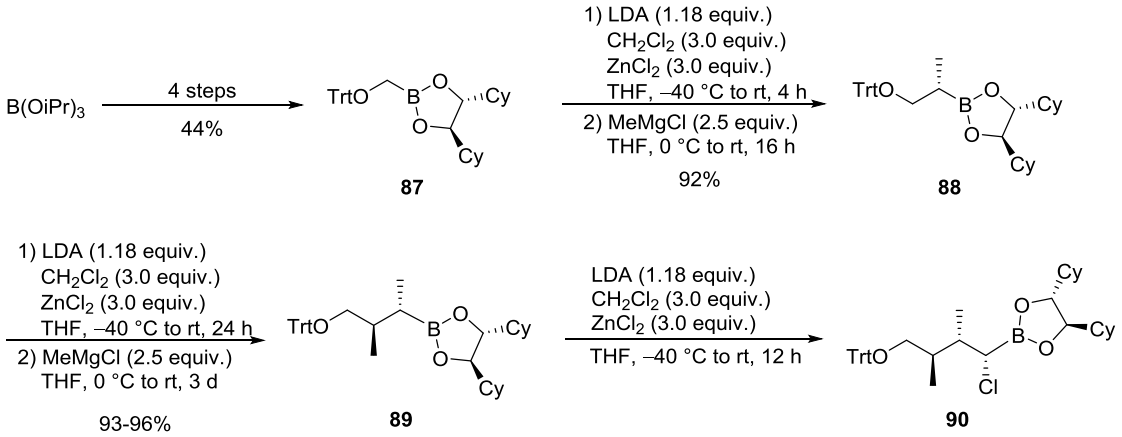
The presence of the *anti*,*anti* stereotriad in diMeGln indicated the possibility of assembling the stereocenters by asymmetric Matteson homologation. Retrosynthetic simplification of diMeGln **C_2** led to azido acid **C_2-1** which should be accessible from chloro-boronic ester **C_2-2** by a sequence of oxidation and (de-)protection steps (scheme 87). The chloro-boronic ester should be obtained by a sequence of four consecutive Matteson homologations from known boronic ester **C_2-3**.[351–353] The trityl protecting group in this route was initially chosen due to the reported advantage of the sterical demand to prevent formation of a 5 or 6-membered ate-complex by coordination of the terminal alcohol at the Lewis acidic boron center during homologation.[352,353]



C_2 **C_2-1** **C_2-2** **C_2-3**

Scheme 87: Retrosynthetic analysis of diMeGln **C_2**.

The synthetic approach started by preparation of trityl protected alcohol **87**. Since the literature procedure described by Matteson afforded only moderate yield and results were not reproducible an improved sequence was developed (see experimental section for details) to obtain **87** in 44% yield over four steps. Subsequently, the boronic ester was homologated using typical Matteson conditions to afford boronic ester **88** in high yield as a single stereoisomer (scheme 88). Using the same conditions for a second homologation step resulted in clean conversion to boronic ester **89** after three days. Shorter reaction times (10 or 24 h) or the use of methyl magnesium bromide resulted in incomplete conversion. In the next homologation the introduction of the azide group was attempted. Therefore, transformation to chloro-boronic ester **90** was conducted with typical Matteson conditions.

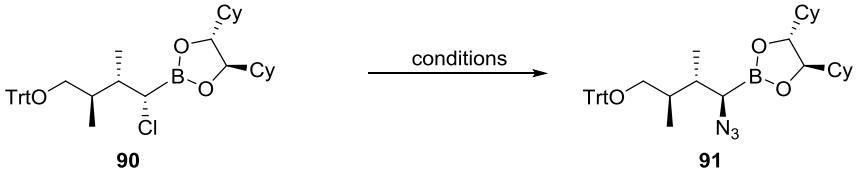


Scheme 88: Preparation of chloro-boronic ester **90** by Matteson homologation.

Initial attempts to achieve azide substitution were conducted with sodium azide in the presence of phase transfer catalyst tetrabutylammonium bromide in a solvent mixture of

nitromethane and water. However, after 12 hours only traces of the desired azide could be observed (tab. 18, entry 1). Increasing the reaction time and amount of phase transfer catalyst resulted in the formation of the desired product in 45% yield after 7 days. Since full conversion would most likely require a reaction time of several weeks and azide **91** was obtained in moderate selectivity (9:1 *dr*, entry 2) a screening of other reaction conditions was conducted. The best results were obtained when typical substitution conditions of sodium azide in DMF were employed (entry 3) which resulted in complete consumption of the starting material after 12 hours and formation of azide **91** in high diastereoselectivity.

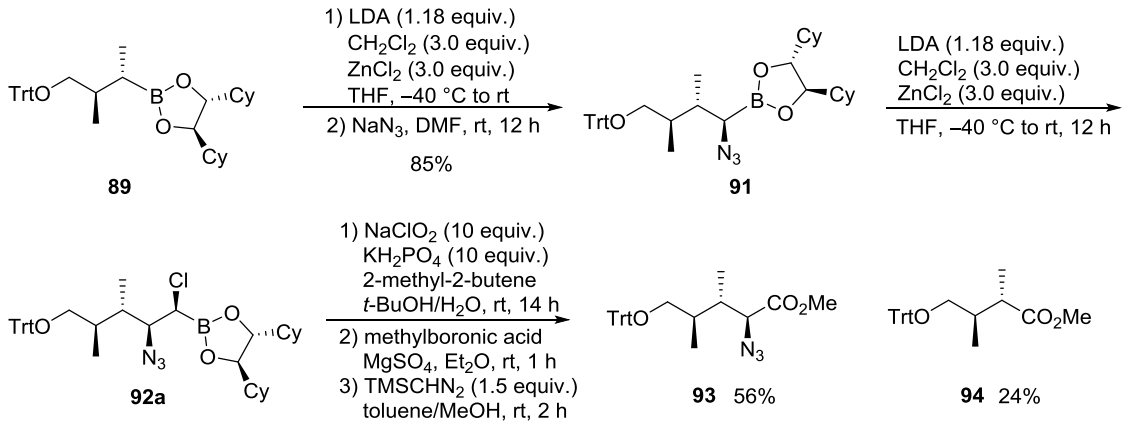
Table 18: Optimization of the azide substitution of chloro-boronic ester **90**.



90 **91**

entry	conditions	solvent	t	conv. [%]	*dr*
1	NaN_3 (10 equiv.) Bu_4NBr (0.25 equiv.)	H_2O/nitromethane	12 h	< 5	/
2	NaN_3 (10 equiv.) Bu_4NBr (0.5 equiv.)	H_2O/nitromethane	7 d	45	90:10
3	NaN_3 (10 equiv.)	DMF	12 h	100	96:4

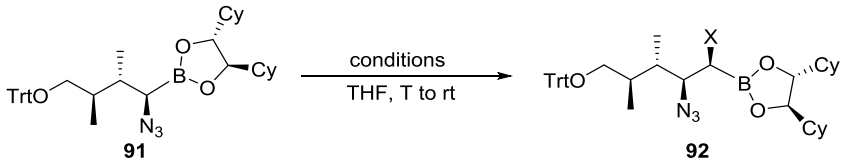
With these conditions in hand, the azide **91** could be obtained in high yield (scheme 89). Further homologation, oxidation under Pinnick-type conditions and esterification with methyl boronic acid to separate and recover the cleaved ligand was followed by diazomethane treatment. Besides the desired methyl ester **93**, ester **94** depicted in scheme 89 was isolated. This side product presumably results from incomplete homologation of azide **91** which upon expose to Pinnick-type conditions is oxidized to the corresponding carboxylic acid after α-elimination of the intermediary geminal azido alcohol.



Scheme 89: Attempted synthesis of methyl ester **93**.

Despite the use of the sterically demanding trityl protecting group, the homologation to chloro-boronic ester **92a** proved problematic and incomplete conversion was observed when standard conditions were used (tab. 19, entry 1). The problems potentially arise due to ate complex formation which inhibits homologation. In some cases, ate complex formation can be avoided by the use of additional equivalents of zinc chloride, however in this case no improvement could be achieved when four equivalents of zinc chloride were used (entry 2). Increasing the amount of base (entry 3) and using amine base free conditions (entry 4-5) did not yield any improvement as well. Similarly, the preparation of corresponding bromo boronic ester **92b** (entry 6) afforded the homologated product with 75% conversion. Since almost all reaction conditions resulted in similar conversions this might suggest the partial ate complex formation or another type of side reaction, which inhibits further reaction. With no other option, the typical conditions were employed on preparative scale (10 mmol) and the chloro-boronic ester **92a** could be obtained in 97% yield containing only traces of the starting material.

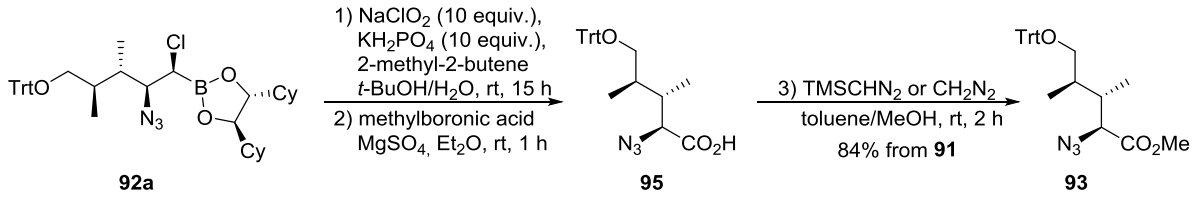
Table 19: Matteson homologation to halo-boronic esters **92**.



entry	conditions	T [°C]	X	conv [%]
1	LDA (1.25 equiv.), $ZnCl_2$ (3.0 equiv.) CH_2Cl_2 (3.0 equiv.)	–40	Cl	80
2	LDA (1.25 equiv.), $ZnCl_2$ (4.0 equiv.) CH_2Cl_2 (3.0 equiv.)	–40	Cl	79
3	LDA (1.50 equiv.), $ZnCl_2$ (4.0 equiv.) CH_2Cl_2 (3.0 equiv.)	–40	Cl	82
4	*n*-BuLi (1.05 equiv.), $ZnCl_2$ (3.0 equiv.) CH_2Cl_2 (1.6 equiv.)	–100	Cl	82
5	*n*-BuLi (2.00 equiv.), $ZnCl_2$ (3.0 equiv.) CH_2Cl_2 (3.0 equiv.)	–100	Cl	65
6	LDA (1.25 equiv.), $ZnCl_2$ (3.0 equiv.) CH_2Br_2 (3.0 equiv.)	–40	Br	75
7[a]	LDA (1.25 equiv.), $ZnCl_2$ (3.0 equiv.) CH_2Cl_2 (3.0 equiv.)	–40	Cl	97

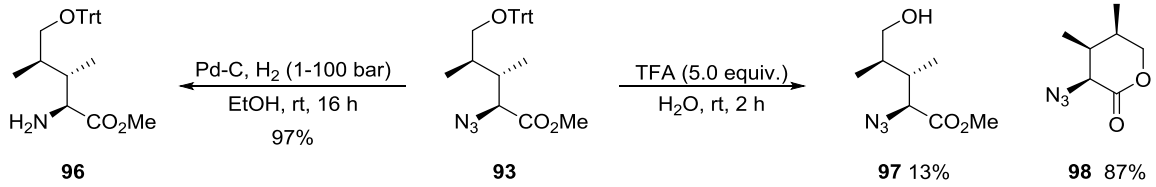
Reactions were conducted on 0.2 mmol scale; a) reaction was performed on 10 mmol scale.

Chloro-boronic ester **92a** was then transformed into methyl ester **93** in high yield by Pinnick-type oxidation,[350] esterification of the ligand and methylation of the carboxylic acid **95** (scheme 90).



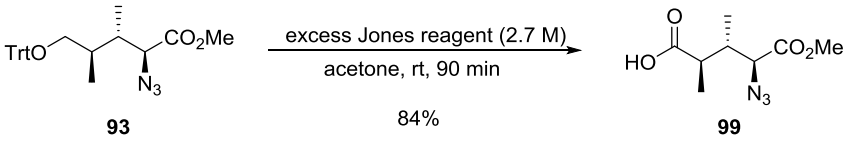
Scheme 90: Synthesis of methyl ester **93** via Pinnick-type oxidation.

In the next step the simultaneous azide reduction and trityl removal via hydrogenation was examined. As expected, the azide group was reduced readily by palladium on carbon catalyzed hydrogenation (1 bar, scheme 91). The trityl group, however, could not be cleaved by hydrogenolysis with various catalysts such as Pd-C, Pearlman's catalyst, or Raney-nickel and elevated pressure of up to 100 bar. This is a typical observation for some trityl ethers which can be overcome by removal of the trityl group under acidic conditions. Thus, trityl ether **93** was treated with aqueous trifluoroacetic acid which resulted in complete cleavage of the trityl group. The acidic conditions, however, also led to rapid lactonization of the primary alcohol **97** to form lactone **98** in 87% yield as the main product. Attempts to suppress the entropically driven lactonization using a weaker acid, Lewis acids, and/or anhydrous conditions were unsuccessful.



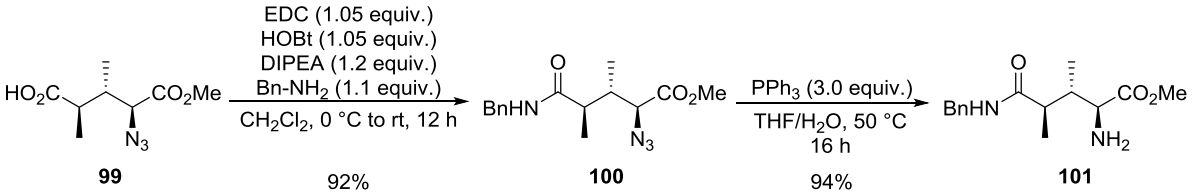
Scheme 91: Attempted removal of the trityl group by hydrogenolysis and acid hydrolysis.

Since the literature known methods for removal of the trityl group did not allow for the preparation of alcohol **97**, a different strategy was required. First, the saponification of lactone **98** was considered, which would yield the corresponding δ-hydroxy acid. Subsequent coupling of the acid, to avoid issues regarding the chemoselective transformation of one of the carboxylic acid groups after oxidation of the alcohol, would however most likely result in lactonization once more and intermediary protection of the alcohol would be required. Another approach would be the saponification and peptide coupling of methyl ester **93** prior to trityl deprotection to suppress lactonization via the less reactive amide. This would then require the deprotection and selective oxidation of the amino acid side chain incorporated into the peptide chain. To avoid these approaches which vary significantly from the initial retrosynthesis and would require multiple additional steps or the use of different protecting groups in the peptide, the direct oxidation of trityl ether **93** to the corresponding carboxylic acid was examined. Fortunately, after some optimization the direct oxidation was achieved by treatment of trityl ether **93** with excess of Jones reagent which resulted in simultaneous cleavage of the trityl group and oxidation to the acid in 84% yield (scheme 92).



Scheme 92: Novel oxidation of trityl ether **93** to carboxylic acid **99** with Jones reagent.

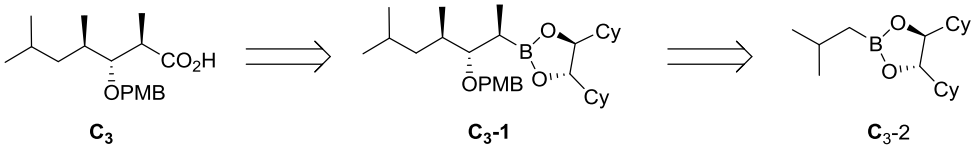
Initial attempts to transform carboxylic acid **99** into the corresponding amine by activation via mixed anhydride and treatment with ammonium chloride or ammonia in methanol resulted in no conversion and epimerization of the azido-ester. Thus, the coupling was conducted with benzyl amine as ammonia surrogate. The increased nucleophilicity of benzyl amine allows for EDC coupling in satisfactory yield and the benzyl group additionally serves as a protecting group during peptide coupling (scheme 93). This might be helpful during coupling of this amino acid since glutamine derivatives are known to form cyclic imides upon activation. At the end of the synthesis the benzyl amide can be cleaved during global deprotection via hydrogenation with, e.g., Pearlman's catalyst or by birch reduction. Due to the presence of the benzyl amide functionality the azide was reduced by Staudinger reaction with triphenylphosphine to obtain the amino ester **101** in 94% yield.



Scheme 93: Preparation of amine **101** via EDC coupling and Staudinger reduction.

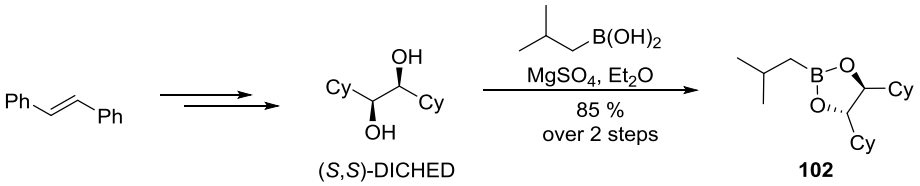
4.2.5 Synthesis of (2*R*,3*R*,4*R*) 3-Hydroxy-2,4,6-trimethylheptanoic Acid (TMEHA)

The synthesis of the only non-amino acid building block of the callipeltins, hydroxy acid TMEHA **C_3** was envisioned via a Matteson sequence, similar to the total synthesis of lagunamide A.[348] Carboxylic acid **C_3** should be accessible from chiral auxiliary containing boronic ester **C_3-1** via Pinnick-type oxidation as described for the amino acid building blocks (scheme 94). Further disconnection via Matteson reaction led to isobutyl boronic ester **C_3-2**, which should be transformed into boronic ester **C_3-1** by three consecutive Matteson homologation steps.



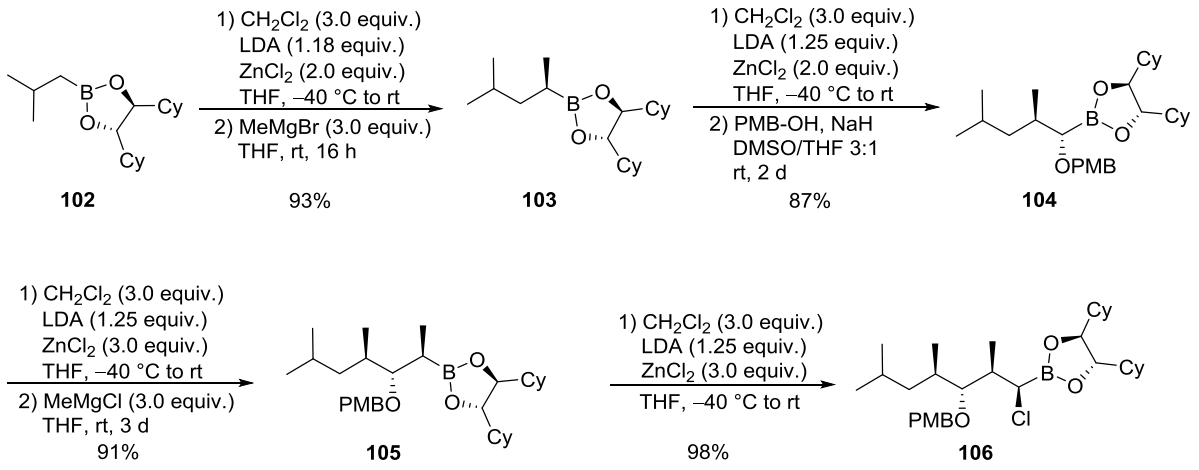
Scheme 94: Retrosynthetic analysis of 3-Hydroxy-2,4,6-trimethylheptanoic acid (TMEHA).

The required (*S*,*S*)-DICHED enantiomer was prepared according to literature procedures and esterification with isobutyl boronic acid afforded isobutyl boronic ester **102** in 85% yield over two steps (scheme 95).[348,354]



Scheme 95: Preparation of isobutyl boronic ester **102**.

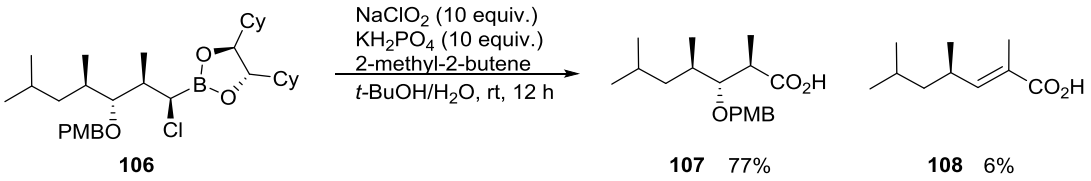
Homologation of isobutyl boronic ester **102** via Matteson reaction was conducted under the reaction conditions described previously which provided boronic ester **103** as a single diastereomer (scheme 96). Subsequent treatment with $LiCHCl_2$ at –40 °C resulted in homologation to the chloro-boronic ester which upon aqueous work up was reacted with sodium *p*-methoxy benzylate in DMSO/THF. The homologated boronic ester **104** was obtained in good yield after chromatography despite the known lability of such compounds on silica gel. Further homologation was initially thwarted by very slow reaction of the resulting chloro-boronic ester with methyl magnesium bromide, which took 14 days to complete. Use of the more reactive methyl magnesium chloride resulted in significantly enhanced reaction rates and after three days full conversion was observed, thus boronic ester **105** was obtained in 91% yield. After a fourth homologation under standard conditions and aqueous extraction the crude chloro-boronic ester **106** was obtained in almost quantitative fashion.



Scheme 96: Synthesis intermediate **106** via Matteson homologations.

Oxidation of the chloro-boronic ester **106** was first attempted via a protocol described for the synthesis of lagunamide A.[348] The treatment with hydrogen peroxide in the presence of sodium carbonate, sodium iodide, and sodium thiosulfate, however, resulted in incomplete conversion and the corresponding aldehyde was obtained in only 16% yield. Using a Pinnick-type oxidation instead,[350] the carboxylic acid was obtained in moderate yield of alongside significant amounts of elimination of the PMB ether. A closer investigation of the reaction by NMR spectroscopy indicated a clean reaction toward the carboxylic acid, hence the partial elimination of the sensitive β-PMB ether presumably occurred during acidic extraction. The formation of the elimination product **108** could mostly be suppressed by the use of a diluted

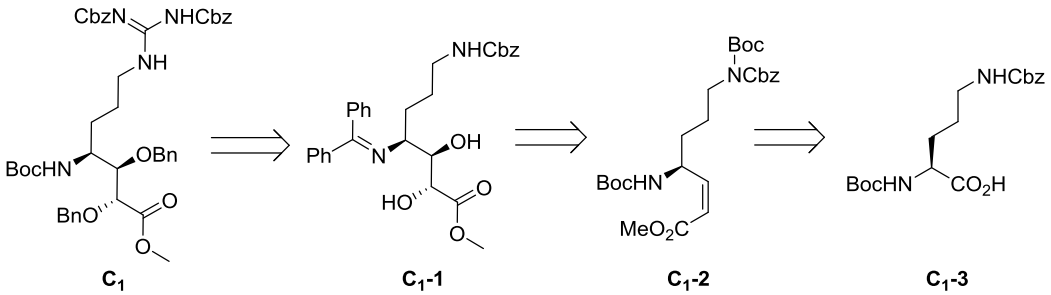
solution of citric acid for aqueous extraction and resulted in the formation of carboxylic acid **107** in 77% yield over two steps and only traces of α,β-unsaturated acid **108** (scheme 97).



Scheme 97: Oxidation of chloro-boronic ester **106**.

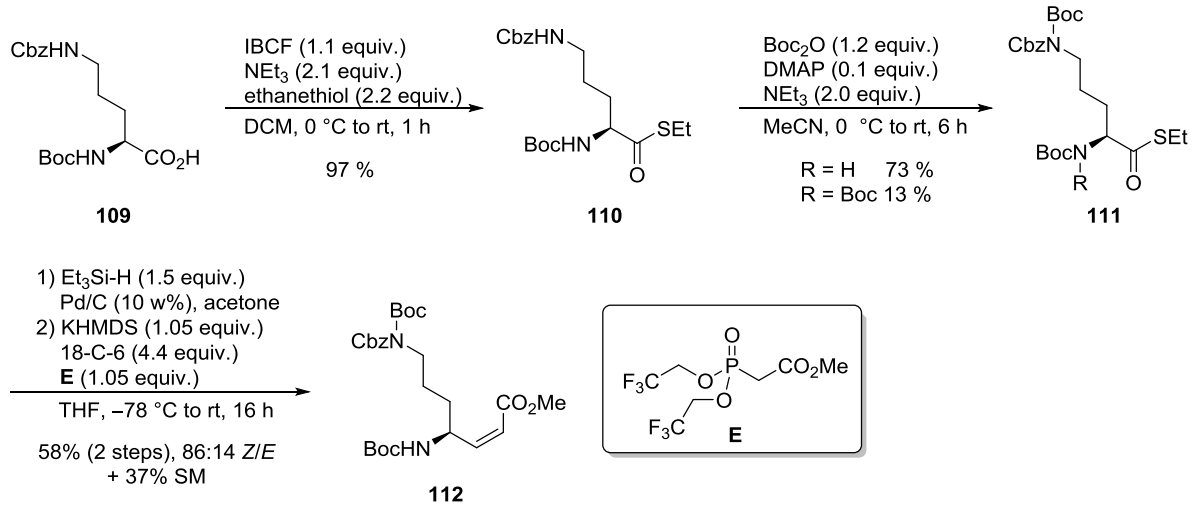
4.2.6 Synthesis of (2*R*,3*R*,4*S*)-4-Amino-7-guanidino-2,3-dihydroxyheptanoic Acid (AGDHE)

The retrosynthetic analysis of AGDHE building block $\mathbf{C_1}$ is depicted in Scheme 98. At first, AGDHE was disconnected by removal of the guanidine motif. Introduction of the guanidine moiety was planned in the last step, after complete protection, via nucleophilic substitution with guanidine triflate according to a protocol described by Goodman.[355] The diol $\mathbf{C_1}$**-1** was further simplified by retro-dihydroxylation and manipulation of the protecting groups to *Z*-alkene $\mathbf{C_1}$**-2**, which should be accessible via Still-Gennari or Ando olefination. The synthesis of the required aldehyde was planned from ornithine derivative $\mathbf{C_1}$**-3** via palladium-catalyzed Fukuyama reduction of the corresponding thioester.[308,356]



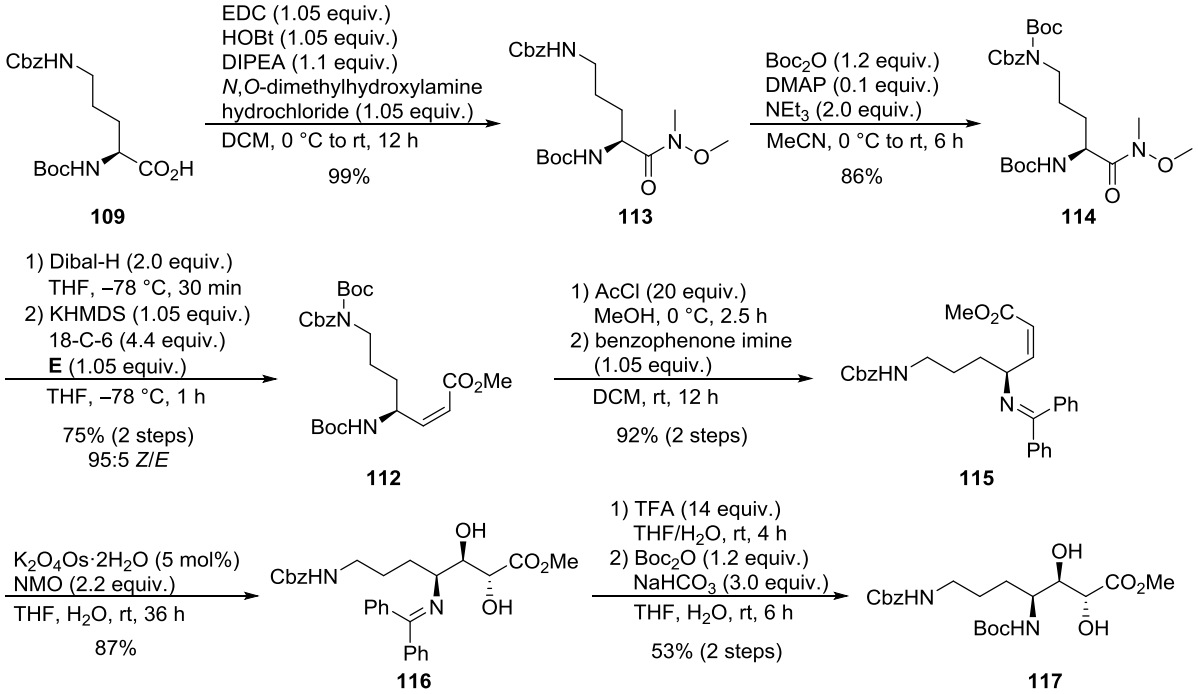
Scheme 98: Retrosynthesis of building block $\mathbf{C_1}$.

In the first step protected ornithine **109** was coupled with ethanethiol by activation via mixed anhydride to obtain thioester **110** in almost quantitative yield (scheme 99). Reduction of such thioesters is known to result in stable hemi aminal formation which prevents olefination,[308] thus a secondary carbamate protecting group was introduced on the δ-amino group. Selective protection was achieved via a protocol described by Kim and coworkers by treatment with Boc-anhydride, DMAP in the presence of NEt_3.[308] This resulted in preferential δ-protection in 73% alongside 13% of the double protected derivative. Reduction of the thioester by palladium catalysis with triethyl silane was followed by immediate treatment with Still-Gennari phosphonate **E** and KHMDS in the presence of crown ether 18-crown-6 at –78 °C.[357] Alkene **112** was obtained in 58% as 86:14 mixture of *Z* and *E* isomers alongside 37% of the starting material. After several attempts to improve the conversion of the thioester reduction were not successful, a new approach via the well-stablished reduction of the corresponding Weinreb amide was envisioned.[358–360]



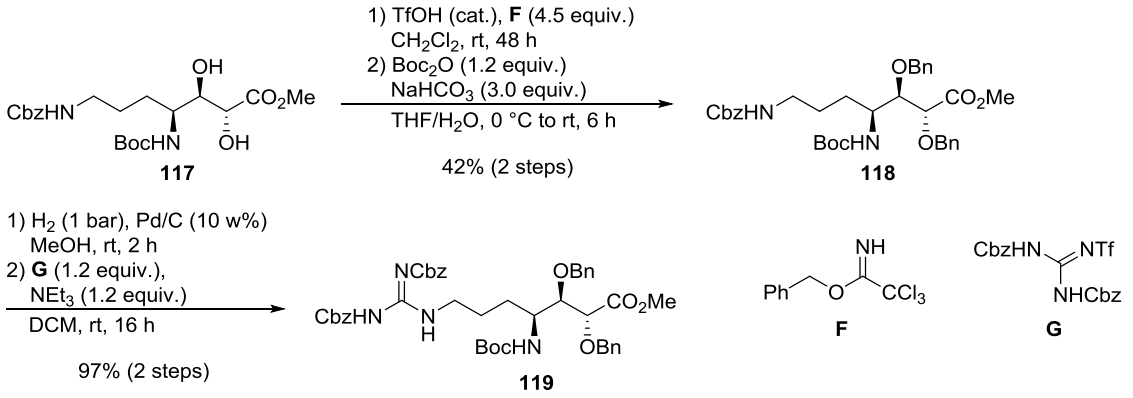
Scheme 99: Preparation of protected thioester **111** and attempted *Z*-selective olefination.

The Weinreb amide **114** was prepared by coupling of ornithine **109** with *N*,*O*-dimethyl hydroxylamine hydrochloride using EDC/HOBt in quantitative yield and introduction of the second carbamate protecting group on the δ-amine (scheme 100). Reduction of the Weinreb amide **114** under typical conditions with LAH or Dibal-H initially proved difficult. The use of LAH resulted in immediate decomposition even at −78 °C and reduction with 1.2 equivalents Dibal-H led to incomplete conversion. Treatment with additional equivalents of Dibal-H at 0 °C did not improve the reaction but rather resulted in decomposition. When the reaction was instead carried out at −78 °C with a slight excess of Dibal-H and the reaction was quenched after 30 minutes the crude aldehyde was obtained in 91% yield. Olefination under Still-Gennari conditions afforded *Z*-alkene **112** in acceptable yield and selectivity.



Scheme 100: Synthesis of diol **117** by Still-Gennari olefination and dihydroxylation.

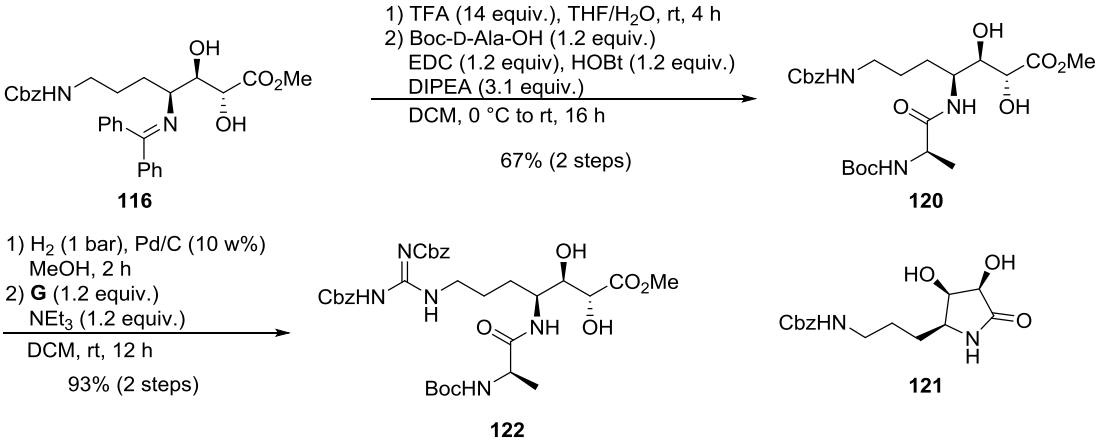
To achieve adequate diastereoselective dihydroxylation of such a non-cyclic α-amino alkene, Kim and coworkers described the necessity to introduce an aromatic imine which shields one of the alkene faces.[308] Introduction of the imine was accomplished by removal of both Boc protection groups with freshly generated HCl in methanol and condensation with benzophenone imine. Dihydroxylation of alkene **115** with potassium osmate proceeded smoothly from the unshielded alkene face and resulted in formation of diol **116** as a single diastereomer. NMR spectroscopic analysis of diol **116** revealed the existence of an equilibrium between the imine and the corresponding cyclic 5- and 6-membered hemiaminals. Thus, prior to alcohol protection, removal of the imine/hemiaminal was achieved by treatment with aqueous trifluoroacetic acid followed by reprotection as its Boc-carbamate**.** Attempts to protect diol **117** via typical literature protocols with a benzyl-, TBS-group or as a cyclic acetal were mostly unsuccessful.[361–365] While the benzyl- and TBS-protection resulted in a mixture of mono-protected diol isomers in low conversion, acidic treatment with dimethoxy propane led to partial Boc cleavage and formation of the hemiaminal. The most promising results were obtained using an excess of benzyl trichloroacetimidate **F** with catalytic amounts of triflic acid.[363] Under these conditions, bis-benzyl protection was achieved in moderate yield alongside the mono-protected diol isomers. However, due to partial cleavage of the Boc-carbamate, the crude mixture required treatment with Boc-anhydride to afford dibenzyl ether **118** (scheme 101). Since the protection of the diol proved more difficult than expected, a new strategy via alanine coupling after imine cleavage and use of the free diol functionalities during the synthesis was planned. Before, dibenzyl ether **118** was utilized as a test substrate for the planned introduction of the guanidine moiety via a protocol of Goodman.[355] Thus, the ζ-amine was deprotected by hydrogenolysis and the free amine treated with guanidine triflate **G** which afforded guanidine **119** in 97% yield. With this prove of concept in hand, a slightly modified synthetic route was explored.



Scheme 101: Attempted diol protection and guanidine introduction.

First, the acetophenone imine group was cleaved by treatment with aqueous trifluoroacetic acid and the resulting ammonium salt was coupled with Boc-D-alanine under various conditions. In all cases partial intramolecular ring closure to lactam **121** was observed after

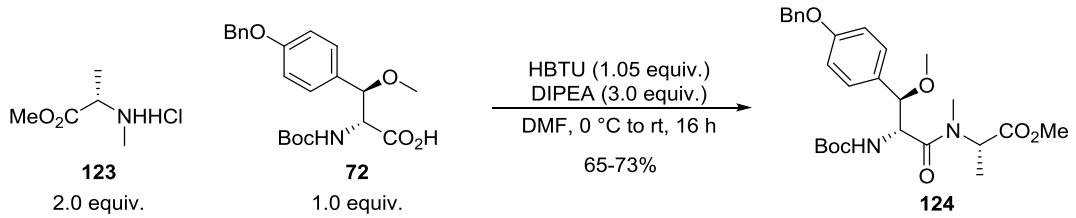
deprotonation of the ammonium salt (scheme 102). While the lactamization could not be completely suppressed under any reaction conditions, the use of EDC and HOBt as coupling reagents afforded dipeptide **120** in acceptable yield. Introduction of the guanidine moiety was achieved by the previously tested sequence of hydrogenolytic Cbz-deprotection followed by treatment with guanidine triflate **G**. The final AGDHE containing dipeptide **122** was obtained in 93% yield over two steps.



Scheme 102: Preparation of dipeptide **122**.

4.2.7 Synthesis of the Peptide Core

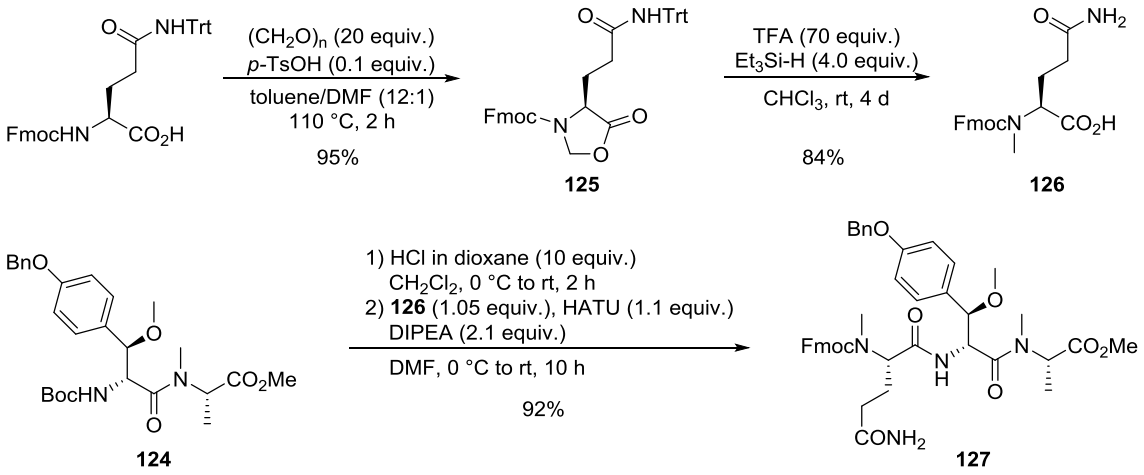
With all building blocks in hand, the synthesis of the cyclic heptapeptide core was started from *C*-terminal *N*-methyl alanine. Initial attempts to couple alanine **123** with tyrosine **72** afforded dipeptide **124** in only moderate yield (30-50%) due to the sensitive tyrosine moiety, which underwent elimination of MeOH to form the corresponding dehydroamino acid. After some optimization, activation with HBTU in the presence of an excess of readily available alanine **123** resulted in the successful formation of the desired dipeptide **124**.



Scheme 103: Synthesis of dipeptide **124**.

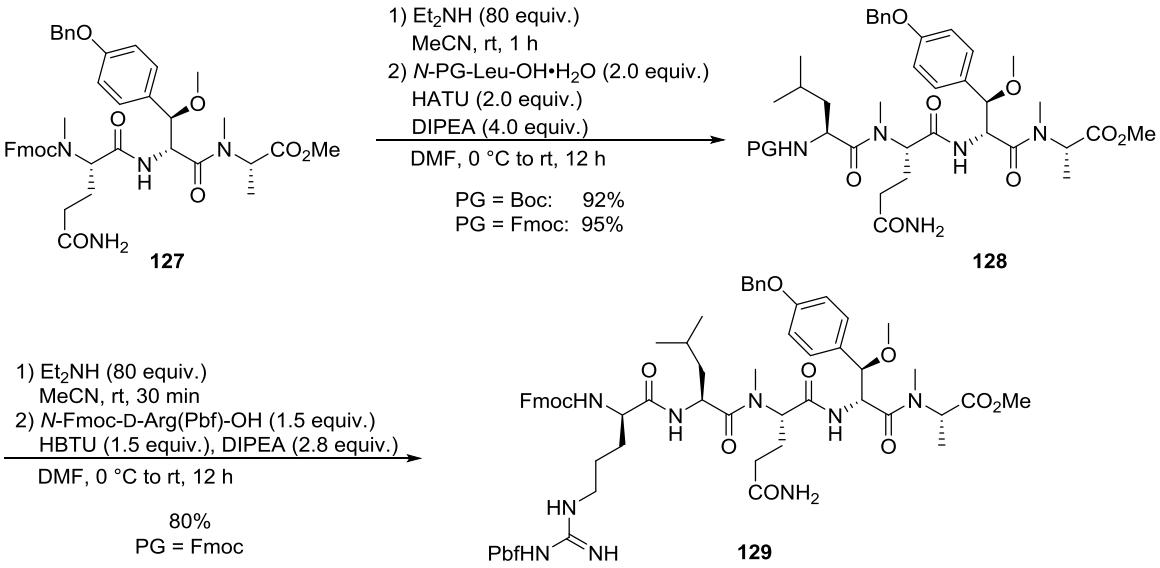
The required *N*-methyl glutamine building block for the next step was synthesized from commercially available Fmoc-Gln(Trt)-OH in a straightforward fashion.[366] First, the amino acid was transformed into the corresponding cyclic hemiaminal **125** by treatment with paraformaldehyde and catalytic amounts of *p*-toluenesulfonic acid under reflux (scheme 104). Subsequent reductive ring opening and simultaneous trityl deprotection under ionic reduction conditions afforded *N*-methyl glutamine **126** in 80% yield over two steps. HATU based coupling of dipeptide **124**, after Boc-deprotection under acidic

conditions, with *N*-methyl glutamine **126** gave tripeptide **127** without any epimerization of the activated *N*-methyl amino acid.



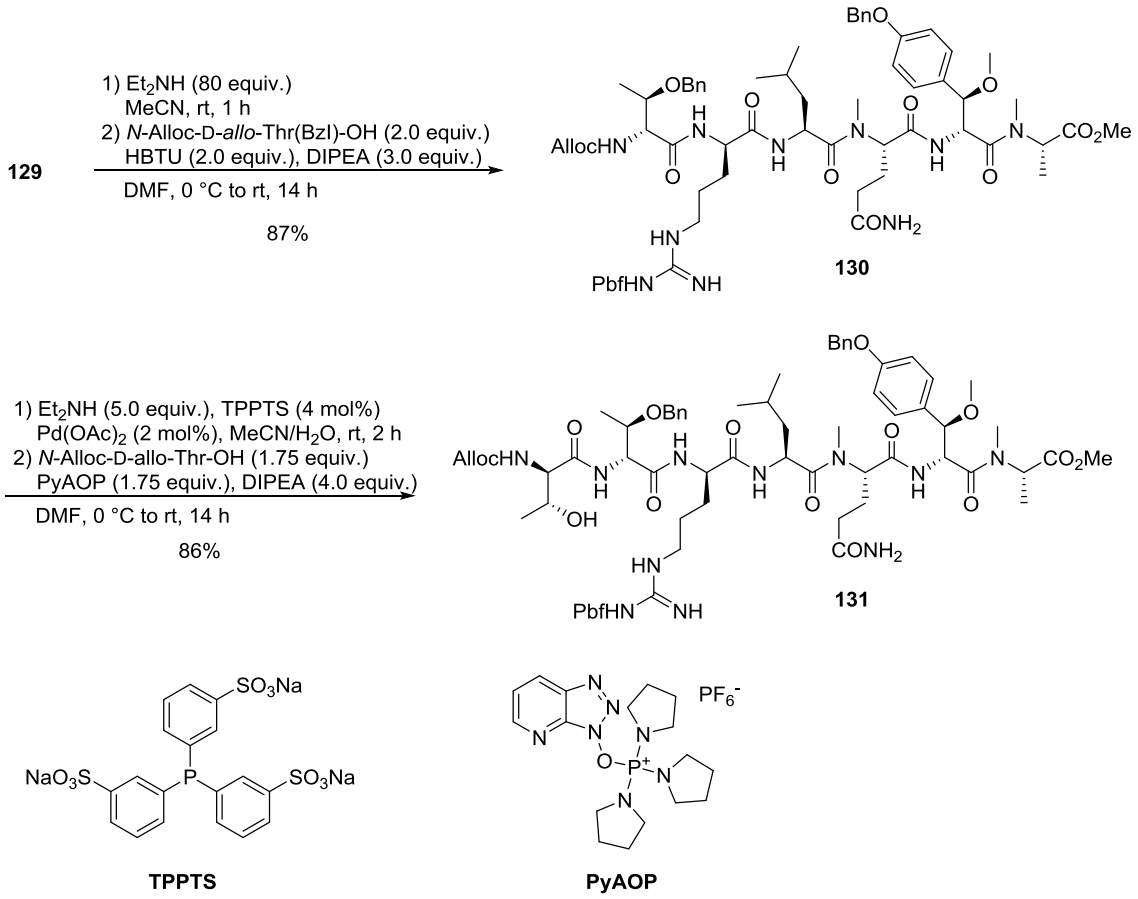
Scheme 104: Preparation of glutamine **126** and coupling to tripeptide **127**.

The *N*-terminus was cleanly deprotected with excess diethylamine in acetonitrile and coupling with *N*-Boc-Leu-OH monohydrate was accomplished using HATU as coupling reagent once more (scheme 105). Removal of the Boc-protecting group, however, proved impossible under various conditions. While treatment with hydrochloric acid or trifluoroacetic acid resulted in partial deprotection along with decomposition of the starting material, the use of Lewis acids resulted in complete decomposition of the starting material. Due to this setback, an alternative tetrapeptide **128b** containing a *N*-terminal Fmoc group was prepared in 95% yield and removal of the Fmoc-group was examined. As previously, Fmoc cleavage was achieved readily by exposure to excess diethylamine which resulted in clean conversion after 30 minutes. Subsequent coupling with commercially available *N*-Fmoc-D-Arg(Pbf)-OH using HBTU afforded pentapeptide **129**.



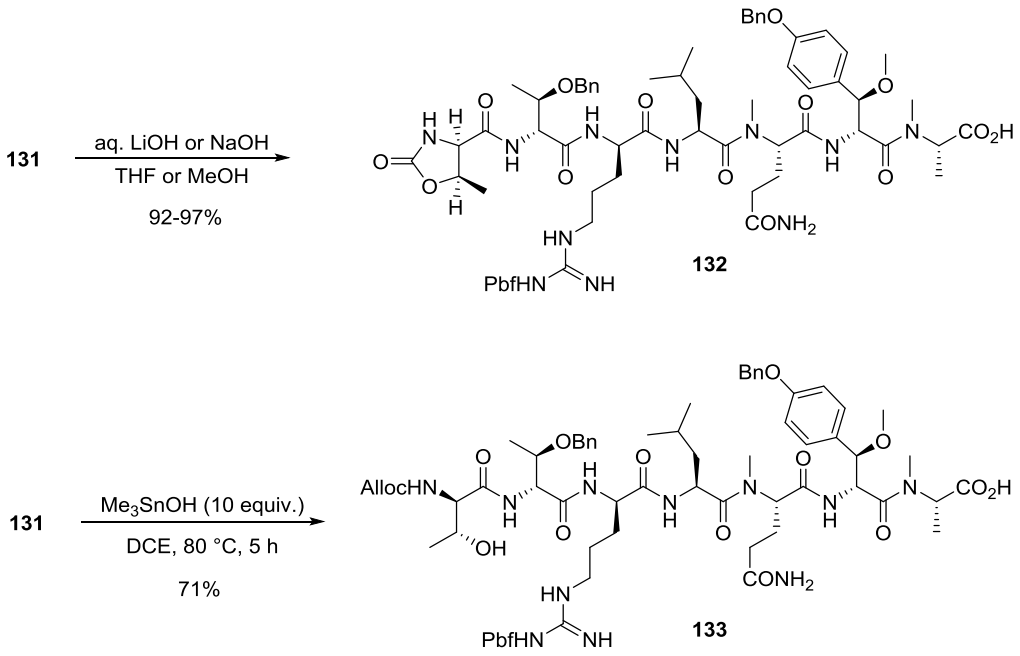
Scheme 105: Synthesis of pentapeptide **129**.

N-terminal deprotection of pentapeptide **129** was once again accomplished by treatment with excess diethylamine and the resulting free amine was reacted with *N*-Alloc-D-*allo*-Thr(BzI)-OH using HBTU as coupling reagent. Thus, hexapeptide **130** was obtained in good yield (scheme 106). Removal of the Alloc-protecting group was attempted using a protocol described by Bernard *et al.* via palladium-catalyzed allylic alkylation in aqueous media, which was successfully employed in the total synthesis of cyclomarine A and other complex peptide natural products.[367,368] Using the water soluble trisodium sulfonate phosphine ligand TPPTS allows for palladium-catalyzed allyl complex formation and trapping with diethylamine as nucleophile. This very mild method worked perfectly in the case of hexapeptide **130** which could be deprotected in quantitative fashion in 2 hours. The subsequent coupling initially proved difficult with standard coupling reagents such as HBTU, TBTU, EDC, HATU, PyBOP and COMU due to low conversion and/or sluggish reaction affording the product in only moderate yield. PyAOP,[369] the nitrogen analogue of PyBOP, which is known to be an exceptional reagent for coupling and cyclization of sensitive substrates, however, worked excellent and heptapeptide **131** could be obtained in 86% yield.



Scheme 106: Preparation of heptapeptide **131**.

In the next steps, macrolactonization followed by coupling with the side chain was planned. This required the saponification of the *C*-terminal methyl ester which was attempted by exposure to an aqueous solution of lithium hydroxide (scheme 107).



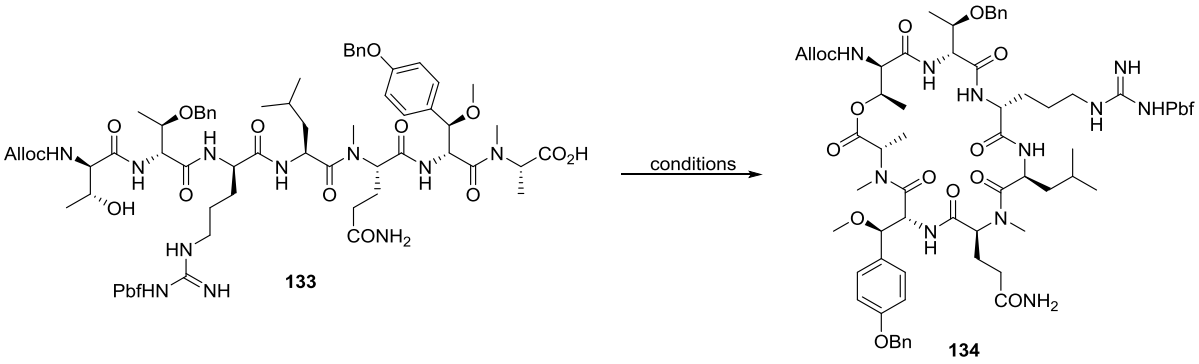
Scheme 107: Attempted saponification of methyl ester **131**.

While methyl ester **131** rapidly underwent saponification, a loss in molecular mass of 58 was detected, corresponding to the loss of an allyl alcohol fragment. NMR analysis verified the assumption of *N*-terminal oxazolidinone formation via base induced intramolecular cyclization. Attempts to suppress the oxazolidinone formation using different metal hydroxides, performing the reaction at lower temperature, or adding the hydroxide in several portions all gave similar results and afforded carboxylic acid **132** as the main product. To our delight, the use of the mild and significantly less basic saponification reagent Me_3SnOH, initially described by Nicolaou and coworkers,[370] selectively afforded the desired carboxylic acid **133** in 71% yield while formation of oxazolidinone **132** could only be observed in trace amounts.

The ensuing macrolactonization was first attempted via the protocol described by Konno *et al.* who achieved cyclization of a similar linear peptide in 44% yield during their synthesis of callipeltin B using an excess of DIC and DMAP at 45 °C.[322] In the case of linear heptapeptide **133** the macrolactone was obtained in 32% along with 64% of the *N*-acylurea resulting from acyl migration of the intermediary *O*-acylisourea (tab. 20, entry 1). While such yields are quite common for the cyclization of complex peptides and depsipeptides, additional attempts were made to increase the yield. First, the reaction was carried out under Yamaguchi conditions,[371–376] while the sequence of addition was varied and different amounts of Yamaguchi reagent, base and DMAP were evaluated (entry 2-5). Since all experiments under Yamaguchi conditions showed no product formation this attempt was discarded, and the initial reaction conditions were reexamined. The reaction was carried out with excess of DIC and DMAP at various temperatures and concentrations, but the yield could only be improved slightly when the reaction was carried out at 70 °C (entry 6). In the next attempts the use of PyAOP, which is known to be an excellent reagent for

macrolactamization and gave exceptional results in earlier peptide couplings, was studied (entry 7-8). As expected, without the addition of DMAP, the use of PyAOP at room temperature resulted in no conversion due to the lower nucleophilicity of the alcohol compared to amine couplings. When an excess of DMAP was added, however, and the reaction was conducted at elevated temperatures, the macrolactone **134** was obtained in 59% yield. Increasing the temperature to 70 °C resulted in the formation of macrolactone in exceptional yield, surprisingly, without significant erosion of the adjacent stereocenter of the activated *N*-methyl alanine. Trace amounts of the epimer (ca. 1-2%) were readily removed during purification via preparative HPLC.

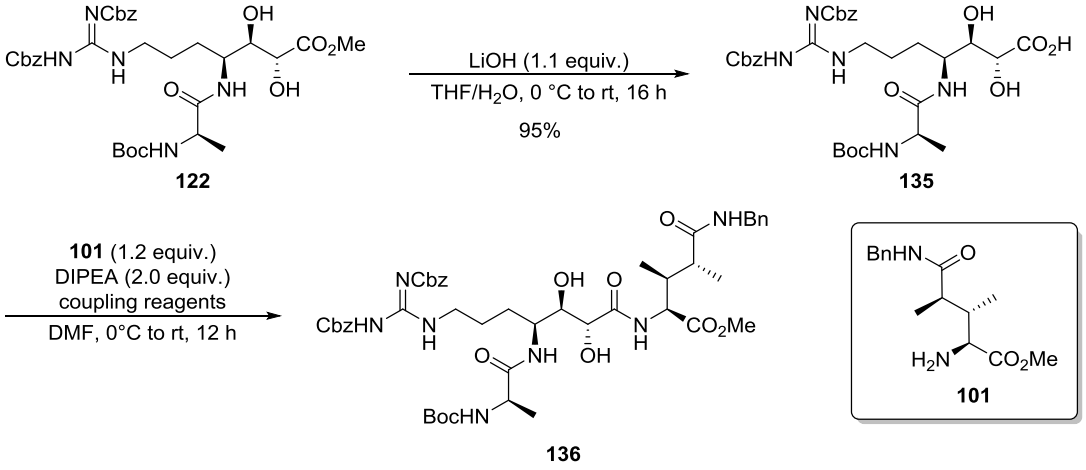
Table 20: Macrolactonization of heptapeptide **133**.



entry	conditions	solvent	c [mM]	Y [%]
1	DIC (5.0 equiv.), DMAP (20 equiv.) 45 °C, 72 h	DMF	7.5	32% + 64% *N*-acyl urea
2	Yamaguchi reagent (1.0 equiv.), DMAP (1.0 equiv.), NEt_3 (5.0 equiv.), 20 °C, 24 h	toluene	1.0	-
3	Yamaguchi reagent (1.5 equiv.), DMAP (3.0 equiv.), NEt_3 (1.5 equiv.), then dropwise peptide addition, 20 °C, 24 h	toluene	1.0	-
4	Yamaguchi reagent (1.5 equiv.) NEt_3 (2.0 equiv.), rt, 2 h then DMAP (5.0 equiv.), 20 °C, 24 h	toluene	1.0	-
5	Yamaguchi reagent (1.5 equiv.), DMAP (20 equiv.), NEt_3 (2.0 equiv.), 45 °C, 24 h	toluene	1.0	-
6	DIC (5.0 equiv.), DMAP (20 equiv.) 70 °C, 72 h	DMF	7.5	39% + 52% *N*-acyl urea
7	PyAOP (1.2 equiv.), DMAP (20 equiv.) 45 °C, 72 h	DMF	7.5	59%
8	PyAOP (1.2 equiv.), DMAP (20 equiv.) 70 °C, 16 h	DMF	7.5	83%

During the synthesis of the cyclic peptide core, the preparation of the required side chain was investigated simultaneously. First, methyl ester **122** was exposed to aqueous lithium hydroxide to achieve saponification in 95% yield. Subsequent coupling with amine **101** proved incomplete with the use of typical diimide coupling reagents such as EDC or DIC (tab. 21, entry 1-2). The use of benzotriazole based coupling reagents HBTU and HATU improved the yield significantly (entry 3-4), but the best results were once again obtained with PyAOP which afforded the tripeptide **136** in high yield (entry 5).

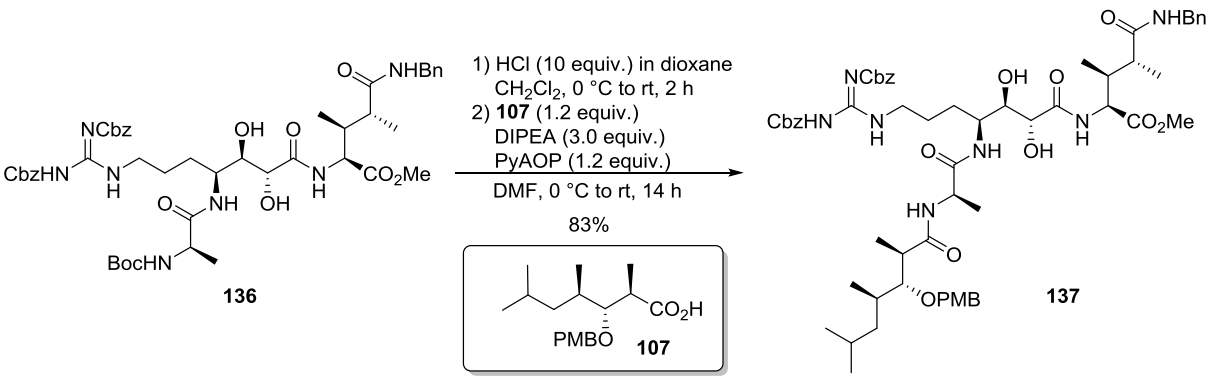
Table 21: Synthesis of tripeptide **136**.



entry	coupling reagents	Y [%]
1	EDC (1.1 equiv.), HOBt (1.1 equiv.)	38
2	DIC (1.1 equiv.), HOBt (1.1 equiv.)	32
3	HBTU (1.1 equiv.)	64
4	HATU (1.1 equiv.)	63
5	PyAOP (1.05 equiv.)	88

This left only the attachment of the hydroxy acid **107** to the side chain, which might prove difficult as suggested by results of Lipton during their synthesis of callipeltin D.[318] The group activated the hydroxy acid by transformation into its acid chloride which could be coupled in acceptable yield. Herein, the coupling via acid chloride and by standard peptide coupling was investigated. First, the *N*-terminal Boc-protecting group was cleaved with excess HCl in dioxane, and the resulting hydrochloride was subjected to several coupling conditions. In the case of hydroxy acid derivative **107**, the activation with thionyl chloride or Ghosez reagent to generate the acid chloride proved detrimental and resulted in significant decomposition of the acid and the desired peptide could not be obtained in more than 32% yield. The use of peptide coupling reagents such as HATU and PyBOP showed more promising results

affording the sidechain **137** in 45% and 51%, respectively. The best results were once again obtained with PyAOP which resulted in clean conversion and 83% yield (scheme 108).

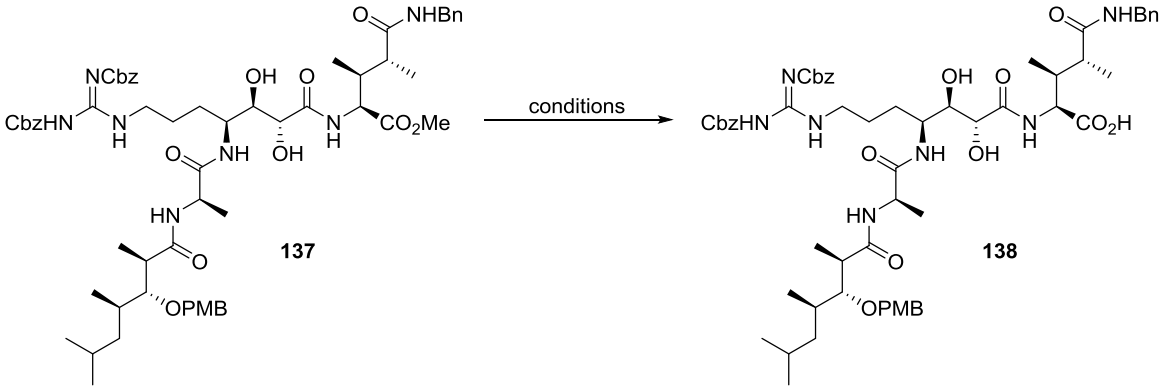


Scheme 108: Introduction of the hydroxy acid moiety.

This completes the synthesis of both major building blocks of callipeltin A and leaves the coupling of both building blocks and global deprotection as final steps of the intended synthetic route.

Prior to the crucial coupling of both building blocks, *C*-terminal saponification of the sidechain and deprotection of the amino side chain of the peptide core was conducted. While Alloc-deprotection under typical conditions proceeded smoothly and gave the corresponding amine in quantitative fashion, the saponification of ester **137** proved exceedingly difficult. Initial attempts of saponification with lithium hydroxide and several other metal hydroxides all failed due to partial cleavage of the Cbz groups and elimination of the PMB-ether to the unsaturated amide (tab 22, entry 1-2). These side reactions could not be suppressed by any variation in the reaction conditions and therefore other methods for saponification were examined. The use of Nicolaou's protocol which employs the less basic trimethyltin hydroxide resulted in acceptable yields of 54-62% (entry 3),[370] albeit significant cleavage of the Cbz-carbamates occurred as well. Attempts to circumvent the Cbz-cleavage by using less trimethyltin hydroxide (entry 4) or running the reaction at lower temperature (entry 5-7) did not generate the desired improvement in the reaction and yields were consistently low. Further attempts investigated completely different protocols for ester cleavage, e.g. a protocol described by Karlsson *et al.* (entry 8),[377] however, in all cases no significant product formation was observed. Since no methods were found to achieve selective saponification, the cleavage with trimethyltin hydroxide was examined in more detail. Substantial optimization of all reaction parameters resulted in the conditions displayed in entry 9. When the reaction was carried out in a closed vessel at a slightly lower concentration (0.05 M instead of 0.1 M) for three hours at 40 °C and three hours at 60 °C the formation of the side products could be minimized, and the carboxylic acid was obtained in 73% after two purifications via reversed-phase chromatography.

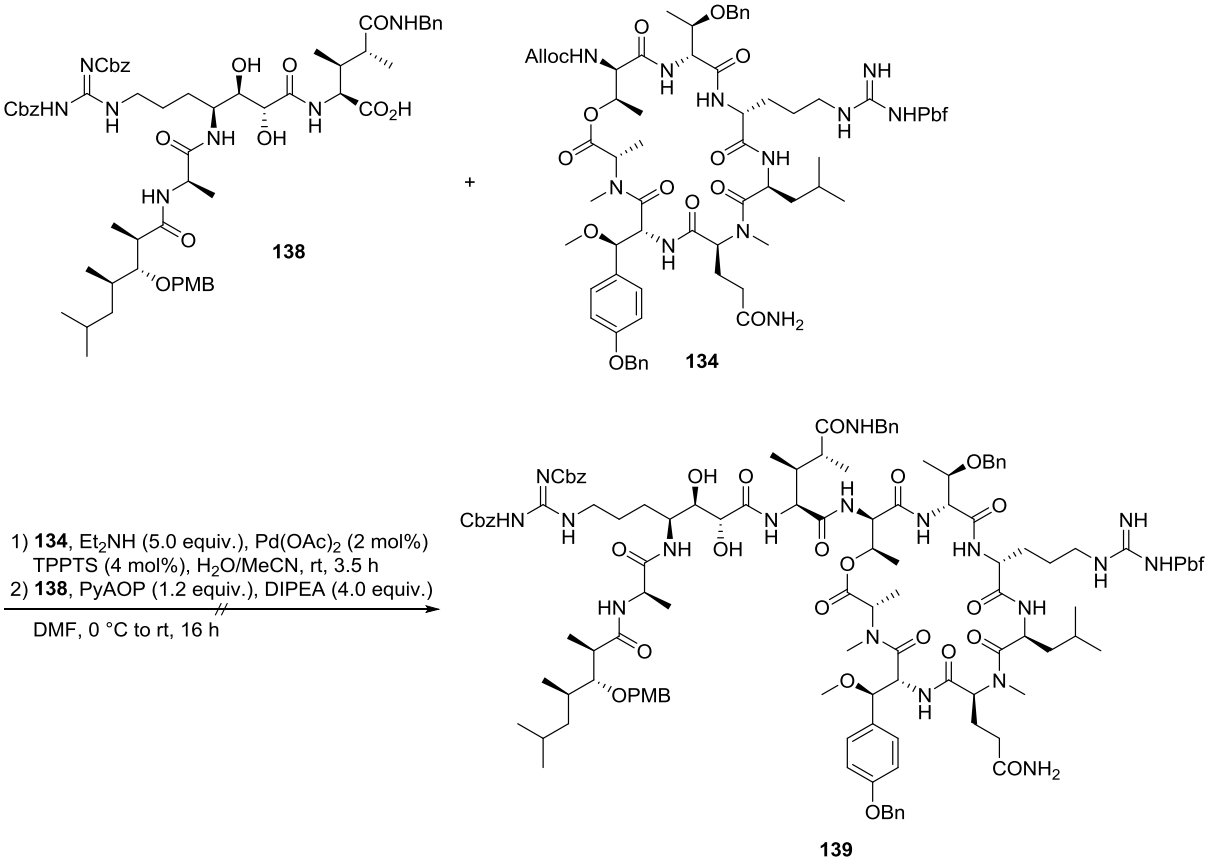
Table 22: Saponification of methyl ester **137**.



entry	conditions	solvent	T [°C]	t	conv. [%]	Y [%]
1	LiOH (1.1 equiv.)	THF/H_2O	0 to 20	16 h	68	24
2	LiOH (2.0 equiv.)	THF/H_2O	0 to 20	16 h	97	13
3	Me_3SnOH (10 equiv.)	1,2-DCE	80	4 h	100	54-62
4	Me_3SnOH (2.0 equiv.)	1,2-DCE	80	16 h	52	17
5	Me_3SnOH (10 equiv.)	1,2-DCE	60	16 h	100	29
6	Me_3SnOH (10 equiv.)	1,2-DCE	40	8 h	74	42
7	Me_3SnOH (10 equiv.)	1,2-DCE	40	16 h	100	32
8	LiBr (10 equiv.) NEt_3 (3.0 equiv.)	MeCN/H_2O	40	16 h	-	-
9	Me_3SnOH (10 equiv.)	1,2-DCE	40 + 60	3 h + 3 h	98	73

After the problems of the saponification were solved, the crucial coupling of carboxylic acid **138** with cyclic depsipeptide **134** was tackled. Therefore, the Alloc-carbamate was cleaved under previously used conditions which afforded the corresponding amine in quantitative fashion. Treatment with PyAOP in the presence of DIPEA did, however, not result in any product formation and the starting materials could be reisolated. The use of other coupling reagents, DMAP as additive, and performing the reaction at elevated temperatures was unsuccessful altogether. Since no reactions produced even traces of the protected callipeltin A **139**, some reference experiments were conducted where the cyclic peptide was coupled with glycine or reacted with acetic anhydride and acetyl chloride. Somewhat surprisingly, the primary amine did not react under any of those conditions, which could either be explained by acyl shift of the lactone to the corresponding lactam, or an unreactive peptide conformation. Since closer analysis of the 2D-NMR spectra still indicated the presence of the lactone, the peptide presumably adopts a conformation where the primary amine is completely shielded and does not react even with small, highly reactive electrophiles such as acetyl chloride. This conformational change is presumed to arise after

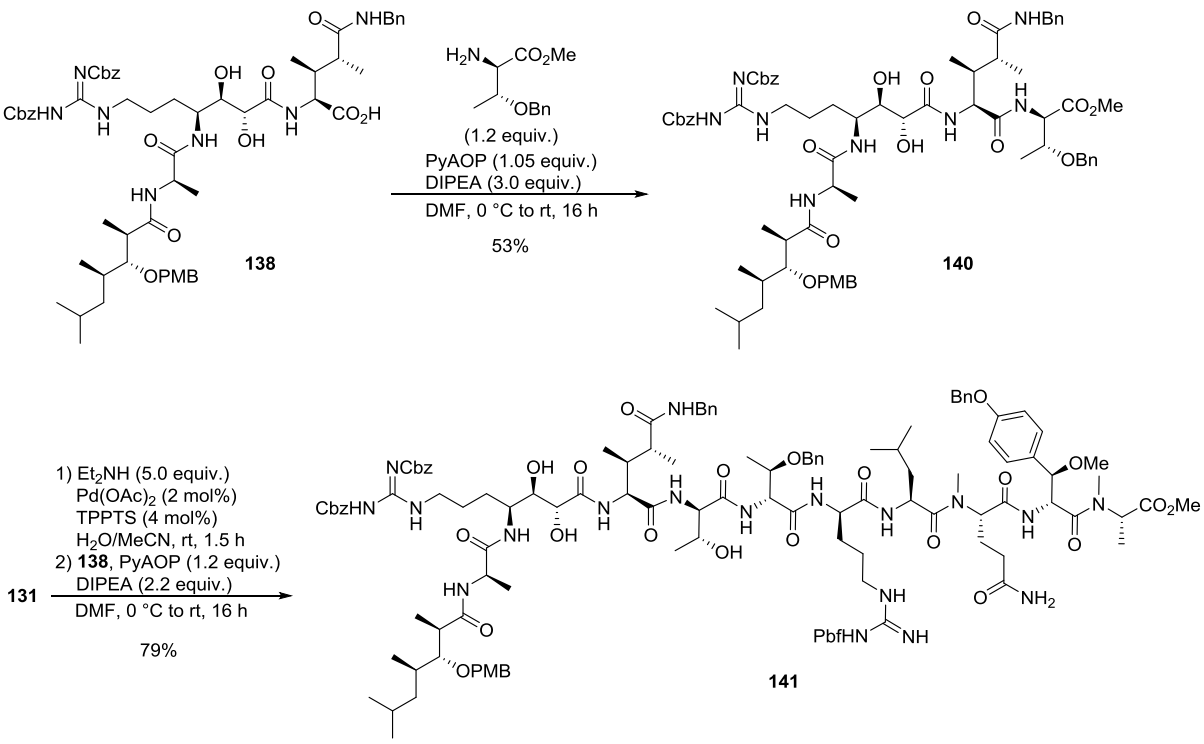
Alloc-deprotection which occurs readily even with the bulky palladium phosphine catalyst. This would be prevented by an inherent inaccessible peptide conformation, which supposedly is the result of strong hydrogen bonding of the free amine.



Scheme 109: Attempted fragment coupling toward protected callipeltin A **139**.

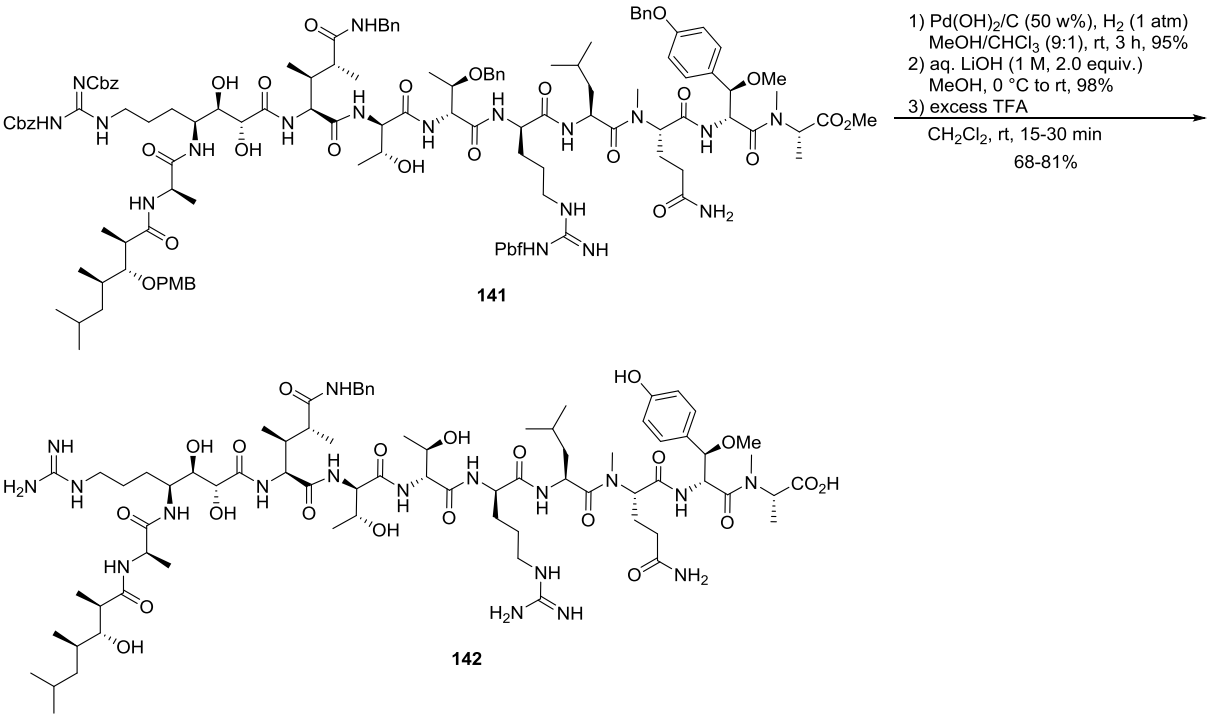
These results rendered this synthetic route as a dead end and the alternative strategy, which intended the coupling of both parts of the natural products prior to macrolactonization, was examined.

Therefore, the coupling of carboxylic acid **138** with a simple amine was tested. H-D-*allo*-Thr(BzI)-OMe was chosen since the obtained peptide is the protected version of another representative of the callipeltin family, namely callipeltin D. Under unoptimized conditions, the protected natural product **140** could be obtained in acceptable yield (scheme 110). With this result in hand, linear peptide **131** was deprotected on its *N*-terminus via standard palladium catalysis and then coupled with carboxylic acid **138** with PyAOP as reagent for activation. In this case the coupling proceeded smoothly, once again confirming the unreactive amine as primary reason for unsuccessful coupling of the cyclic peptide with acid **138**, and protected callipeltin C was obtained in 79% yield on 200 mg scale.



Scheme 110: Synthesis of protected callipeltin D **140** and C **141**.

Prior to any attempts of macrocyclization toward protected callipeltin A, the planned deprotection strategy was examined based on protected callipeltin C **141**. Therefore, the protected natural product was subjected to palladium-catalyzed hydrogenolysis to achieve global benzyl deprotection. The reaction proceeded smoothly upon treatment with Pearlman's catalyst under an atmosphere of hydrogen and both Cbz groups, the PMB ether and two benzyl groups were readily cleaved (scheme 111).

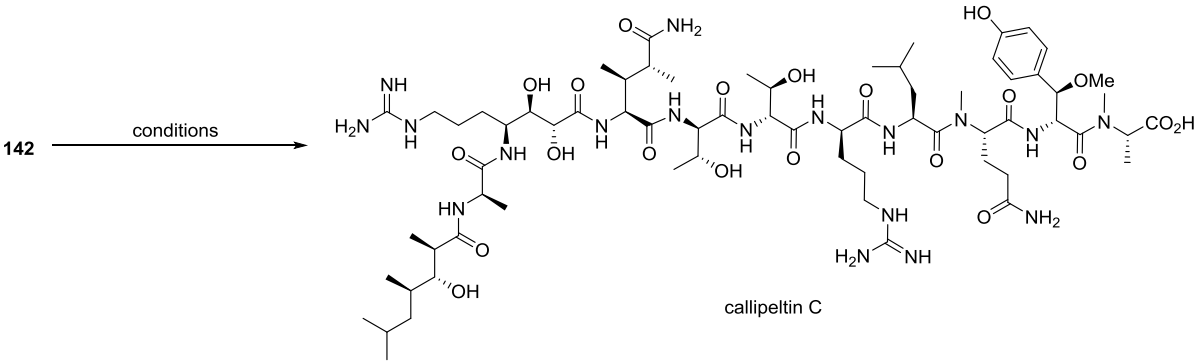


Scheme 111: Global deprotection of callipeltin C.

The benzyl amide, however, proved more stable and could not be removed at atmospheric pressure. In the next step, saponification of the *C*-terminal methyl ester was conducted by exposure to aqueous lithium hydroxide which afforded the corresponding acid in 98% yield. Subsequent attempts of acidic Pbf cleavage initially resulted in complete decomposition of the starting material, most likely due to residual H_2O since callipeltin natural products are known to be highly labile toward aqueous acidic media. This problem could be solved by quenching the saponification reaction with a small excess of 1 M hydrochloric acid at 0 °C and immediate lyophilization to remove any traces of water. Afterwards Pbf cleavage could be accomplished by treatment with excess trifluoroacetic acid for 15-30 minutes which afforded mono-benzyl protected callipeltin C **142**.

The final deprotection of the benzyl amide group was then investigated in more detail with some selected experiments depicted in table 23. At first several attempts of palladium-catalyzed hydrogenolysis at elevated hydrogen pressure were conducted. Typical conditions with palladium on carbon or Pearlman's catalyst (entry 1-3) showed no reaction at all.[378,379] Similarly, the use of acetic acid as solvent (entry 4-6), which usually shows the highest reaction rates in hydrogenolytic benzyl cleavage and has been successfully used for benzyl amide cleavage, showed no formation of callipeltin C.[380] In the case of Pearlman's catalyst at 100 bar hydrogen the partial reduction of an unidentified C-X double bond was observed by analysis via LC-MS (entry 6-7) but no reaction toward the natural product was observed. In another attempt catalytic hydrogen transfer reduction with ammonium formate and palladium on carbon was carried out at 60 °C, however, no reaction was detected (entry 8). After all attempts of hydrogenolysis failed, the deprotection by birch reduction, which is frequently used for benzyl amide cleavage, was examined.[381–386] This method was originally intended as an alternative in the case hydrogenolysis was unsuccessful since the tyrosine residue is protected from reduction due to the formation of the electron rich phenolate. Unfortunately, the use of several literature procedures as well as other conditions did not result in reduction of the benzyl amide and hence formation of the natural product (entry 9-12). In some last desperate attempts, the use of various other literature procedures for benzyl amide cleavage under more harsh conditions were conducted, e.g., the use of *para*-toluene sulfonic acid at 110 °C,[387] or NBS in $CHCl_3$.[388] But in the end, no successful deprotection toward callipeltin C could be achieved in any case.

Table 23: Attempted deprotection toward callipeltin C.



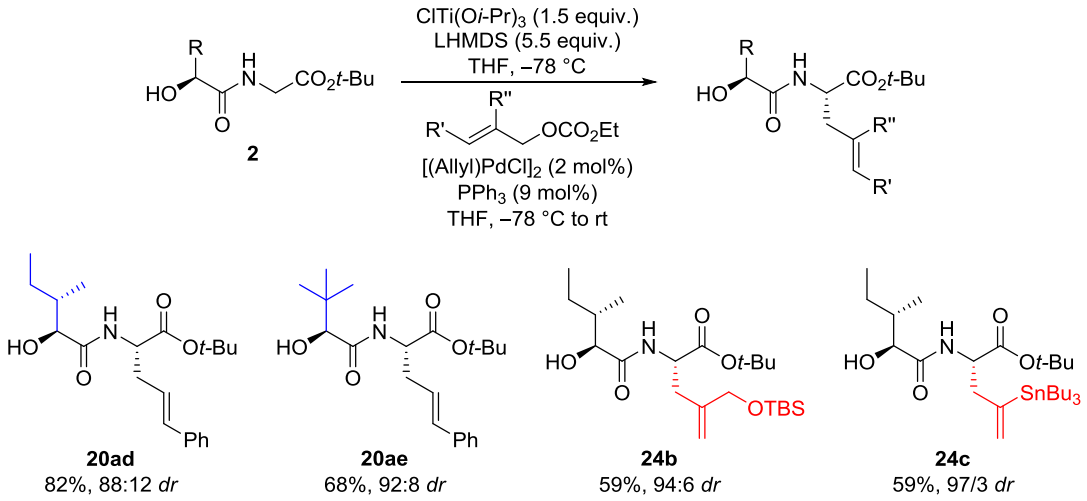
entry	conditions	T [°C]	t	conv. [%]	Y [%]
1	Pd/C, H_2 (20 bar), MeOH	20	16 h	-	-
2	Pd/C, H_2 (100 bar), MeOH	20	16 h	-	-
3	$Pd(OH)_2$/C, H_2 (100 bar), MeOH	20	16 h	-	-
4	Pd/C, H_2 (10 bar), HOAc	20	4 h	-	-
5	Pd/C, H_2 (100 bar), HOAc	20	16 h	-	-
6	$Pd(OH)_2$/C, H_2 (100 bar), HOAc	20	16 h	67 (M+2)	-
7	$Pd(OH)_2$/C, H_2 (100 bar), EtOAc/THF	20	72 h	100 (M+2)	-
8	Pd/C, NH_4HCO_2 (60 equiv.), MeOH	60	12 h	-	-
9	Na (4 equiv.), NH_3	–78	1 min	-	-
10	Na (4 equiv.), NH_3, EtOH	–78	1 min	-	-
11	Na (2-20 equiv.), NH_3	–78	30 min	-	-
12	Na (2-20 equiv.), NH_3, EtOH	–78	30 min	-	-
13	*p*-TsOH (4.0 equiv.), toluene/THF	110	1 h	decomp.	-
14	NBS (2.5 equiv.), $CHCl_3$	20	12 h	-	-

This impossible final deprotection prevented the synthesis of callipeltin C at this point and ultimately concluded the synthetic progress toward the natural product callipeltin A as well. The successful total synthesis would require a different protection group strategy of the dimethyl glutamine building block. Since the peptide core could be assembled with a protection group free glutamine sidechain, the deprotection of the dimethyl glutamine prior to incorporation into the natural product might be a promising alternative to avoid the encountered complications during this synthetic effort. The use of an unprotected glutamine or a readily cleavable protection group should allow for a straightforward access of the natural product via the herein described route.

5. Summary and Outlook

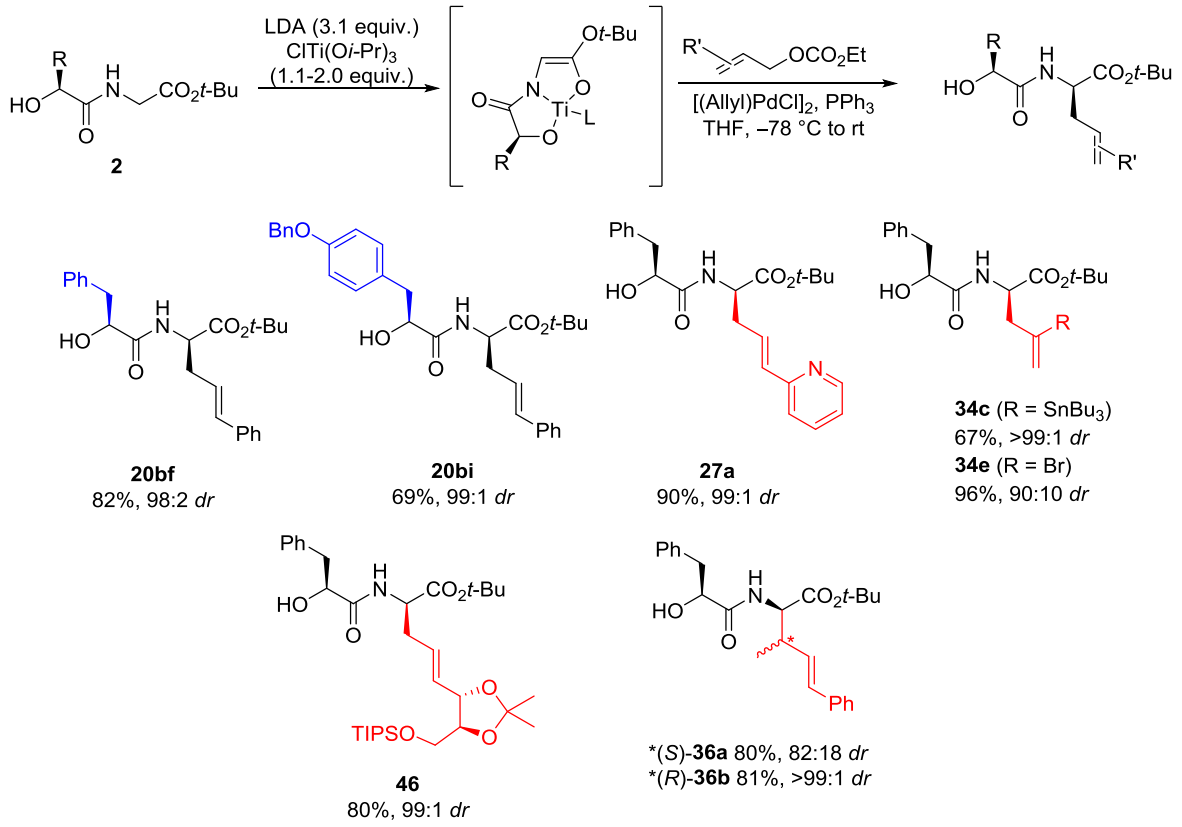
5.1 Stereoselective Modification of *N*-(α-Hydroxyacyl)-Glycine Esters via Palladium-Catalyzed Allylic Alkylation

In conclusion, two protocols for stereoselective functionalization of *N*-(α-Hydroxyacyl)-glycine esters via palladium-catalyzed allylic alkylation have been developed. Both protocols rely on the formation of a rigid titanium chelated enolate complex which induces high selectivities during allylic alkylation. Both diastereomers are accessible through variation of the reaction conditions. The first protocol uses an excess of LHMDS as base along with $ClTi(O\textit{i}\text{-}Pr)_3$ as chelating agent which results in the formation of the new stereocenter in (*S*)-configuration. Both, the variation of the *N*-(α-Hydroxyacyl)-glycine ester backbone and the use of different allyl carbonates lead to acceptable to high diastereoselectivity and yield (scheme 112). The method tolerates several functional groups as shown with TBS-ether containing derivative **24b** and vinyl stannane **24c**. The vinyl stannane motif consequently serves as functional handle which can be used to modify the side chain by typical cross coupling chemistry.



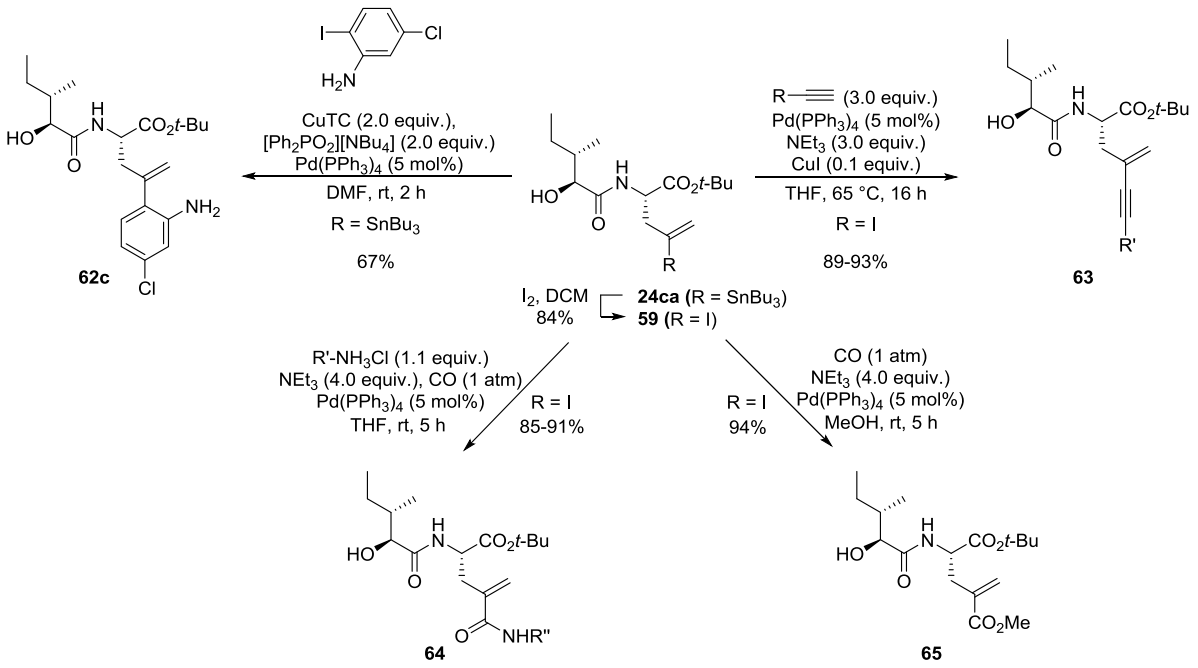
Scheme 112: Modification of *N*-(α-Hydroxyacyl)-glycine esters by allylic alkylation.

By the use of a slight excess of the stronger base LDA, an entirely reversed stereoselectivity could be achieved during allylic alkylation (scheme 113). This protocol gave exceptional results beyond the typical aliphatic side chain derivatives, but also tolerated functional groups in the *N*-(α-Hydroxyacyl)-glycine ester backbone such as TBS- and benzyl ethers. The scope of the employed allylic carbonates included a large variety of tolerated structural motifs and functional groups. This includes several types of aromatic systems, ethers, halogenides and even stannanes. Overall, this method usually affords the allylation product in high yield and diastereomeric ratio of >96:4. In the case of secondary carbonates a matched/mismatched scenario was observed which afforded **36a** in moderate selectivity while **36b** was formed as a single diastereomer.



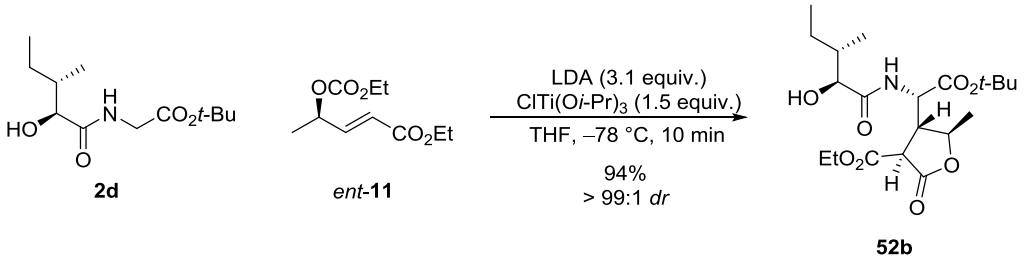
Scheme 113: Synthesis of (*S*,*R*)-diastereomers via Pd-catalyzed allylic alkylation.

The introduced vinyl stannane motif can be used to further modify the side chain, e.g., via transition metal catalyzed Stille coupling with aryl iodides (scheme 114). Tin-iodine exchange allows for various other modifications, such as Sonogashira coupling or CO-insertion reactions which affords highly functionalized derivatives.



Scheme 114: Modification of the side chain via transition metal catalysis.

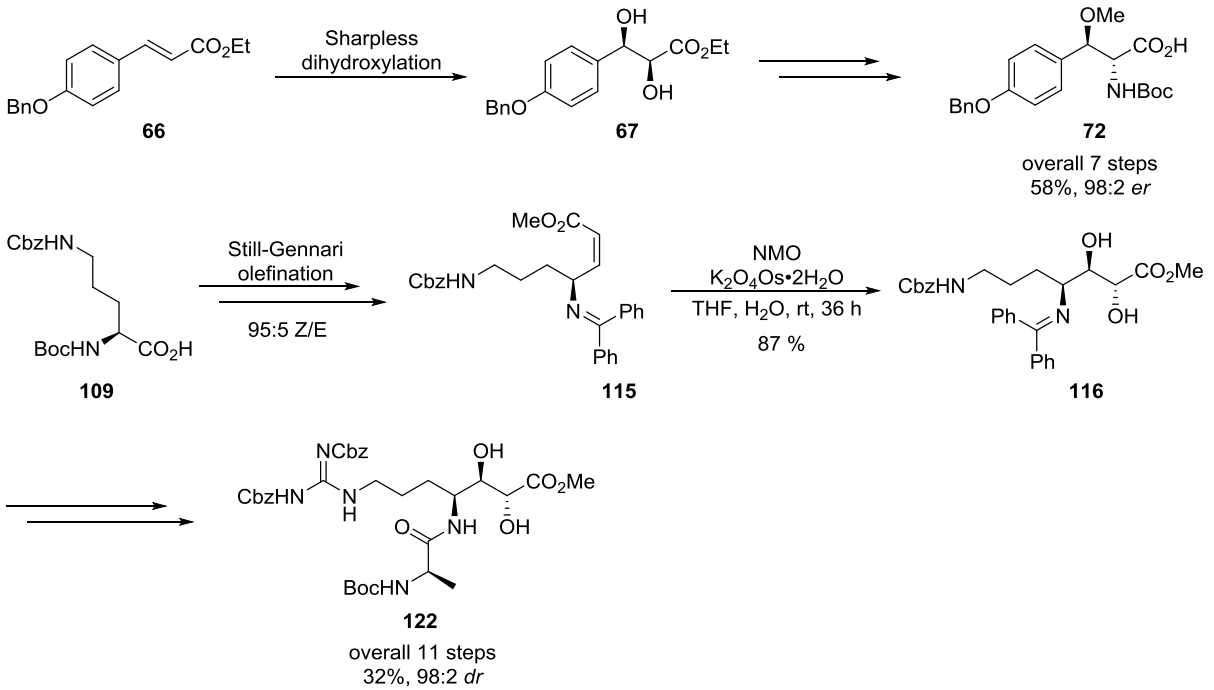
The chelated titanium enolates also proved to be promising nucleophiles in other addition reactions such as Michael addition with unsaturated ester *ent*-**11** which afforded lactone **52b** in exceptional yield and selectivity (scheme 115)



Scheme 115: Michael addition of chelated *N*-(α-Hydroxyacyl)-glycine ester enolates.

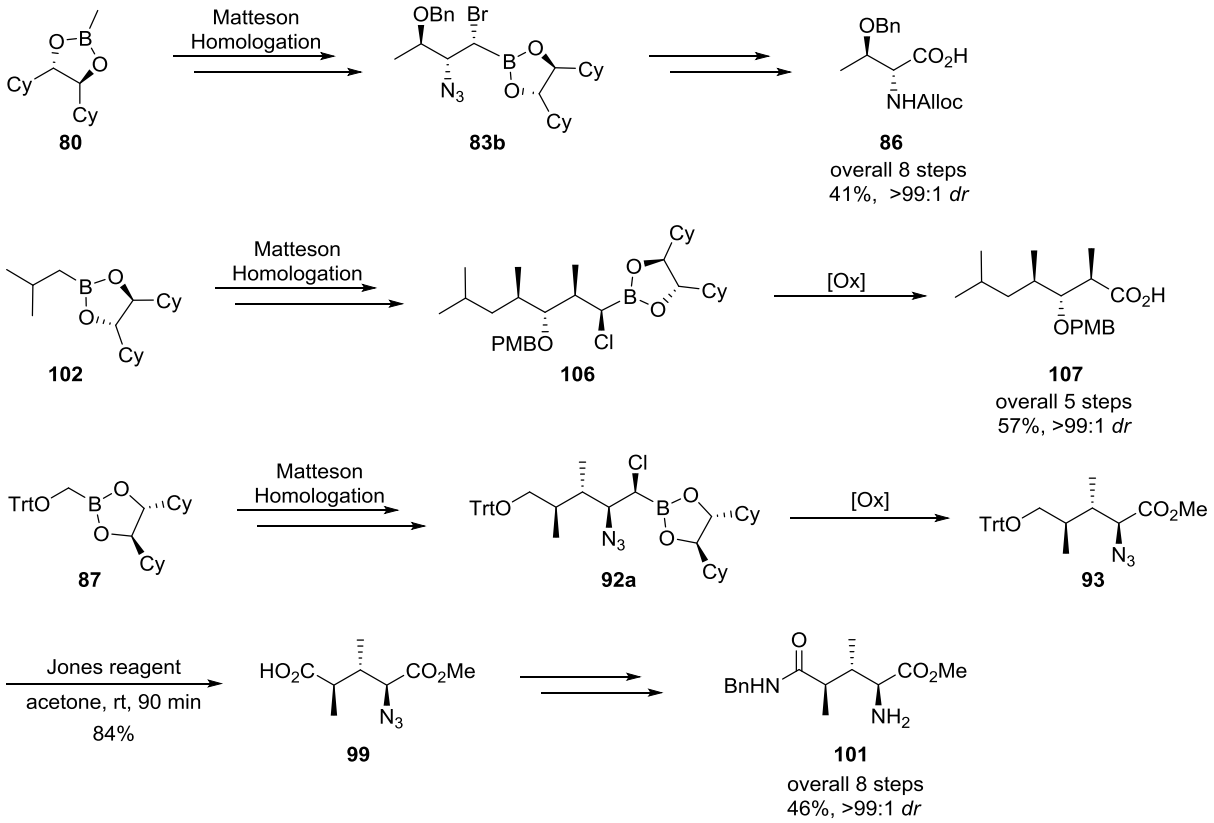
5.2 Studies toward the Total Synthesis of Callipeltin A + C

During this work, new synthetic routes toward several building blocks of callipeltin A and C have been developed. The β-methoxy tyrosine was prepared in a 7-step sequence starting with asymmetric Sharpless dihydroxylation of alkene **66** (scheme 116). Further manipulation of the functional groups, mainly transformation of the C-2 hydroxy group into the inverted amine via azide substitution afforded the amino acid **72** in 58% overall yield. The synthesis of AGDHE building block **122** was based upon previous work from Kim *et al.* which uses a Still-Gennari olefination and subsequent dihydroxylation to introduce the required *anti,syn*-stereotriade.[308] Slight modification of this route by direct coupling with Boc-D-alanine and late-stage introduction of the guanidine moiety allowed the synthesis of dipeptide **122** in 32% overall yield.



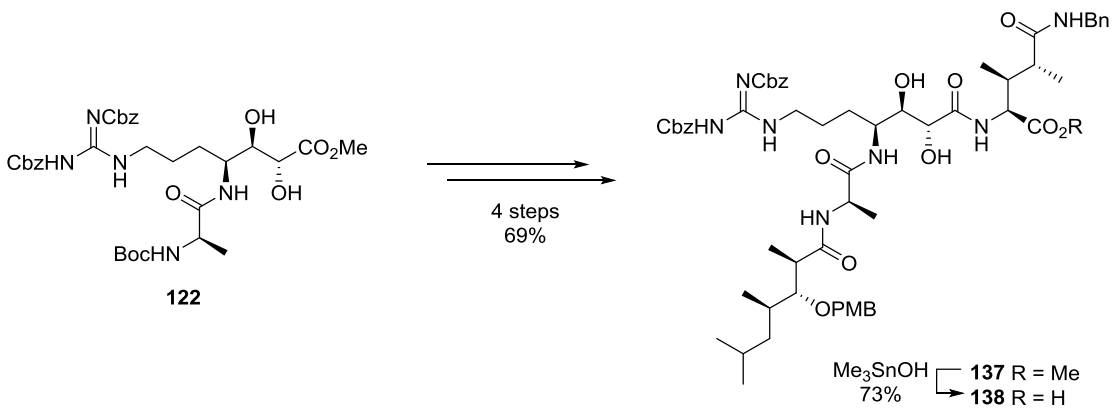
Scheme 116: Preparation of tyrosine **72** and AGDHE building block **122**.

The effort toward the three building blocks depicted in scheme 117 is based upon the homologation of boronic esters, first described by Matteson and coworkers. In the case of D-*allo*-threonine derivative **86**, the development of a sequence of Matteson reactions allowed for the direct introduction of a protected alcohol functionality. This proved crucial since *O*-protection of threonine derivatives remains quite challenging which is illustrated by the lack of any literature protocols for the introduction of most protecting groups in the threonine sidechain. A straightforward sequence of four consecutive Matteson reactions followed by oxidation successfully afforded the protected hydroxy acid **107** in 57% yield over five steps.



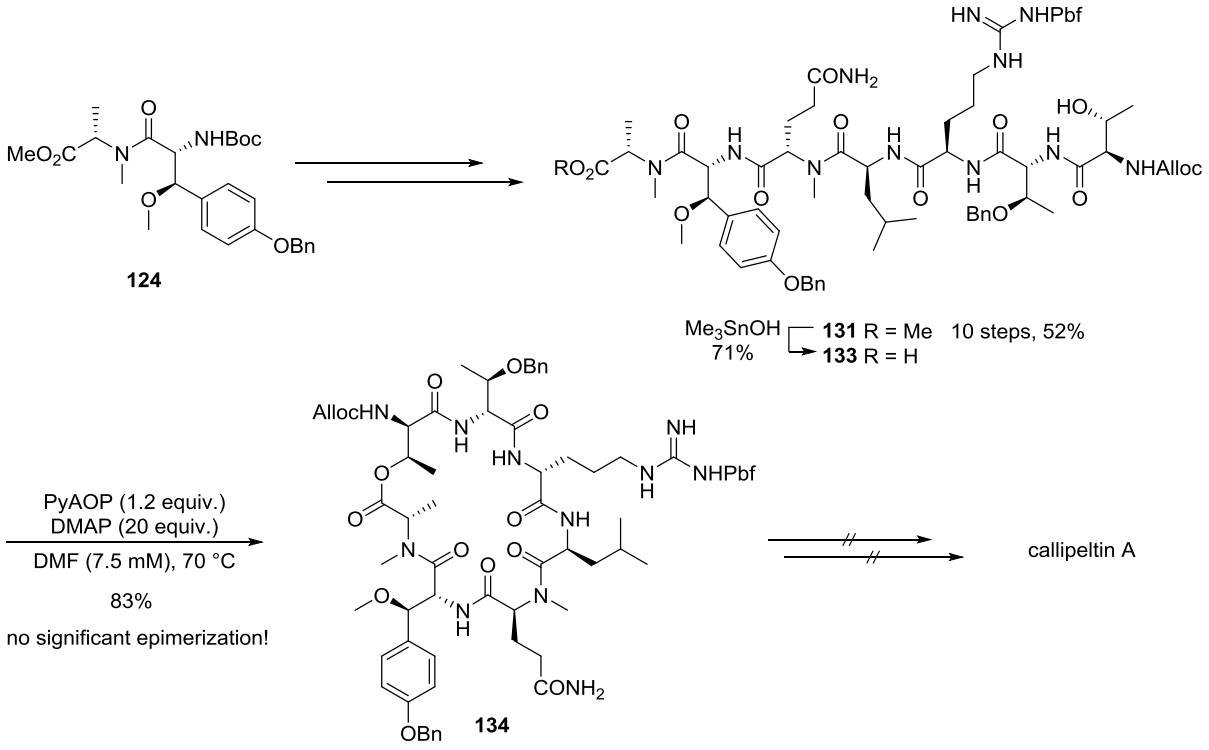
Scheme 117: Synthesis of Callipeltin building blocks via Matteson homologation.

Similarly, the stereoselective synthesis of dimethyl glutamine **101** could be achieved by introduction of all required stereocenters via Matteson homologation. Deprotection and oxidation of the terminal trityl ether proved to be the most crucial steps of the dimethyl glutamine synthesis. After all initial attempts of deprotection failed since the resulting alcohol is prone to lactonization, a novel sequence of deprotection and simultaneous oxidation via Jones reagent was found to afford carboxylic acid **99** in 84% yield. Introduction of the amide functionality and reduction of the azide finally gave rise to dimethyl glutamine **101** as a single stereoisomer in 8 steps and 46% yield. The synthesis of the sidechain was completed in straightforward fashion from AGDHE building block **122** in 4 steps (scheme 118)



Scheme 118: Synthesis of sidechain peptide **138**.

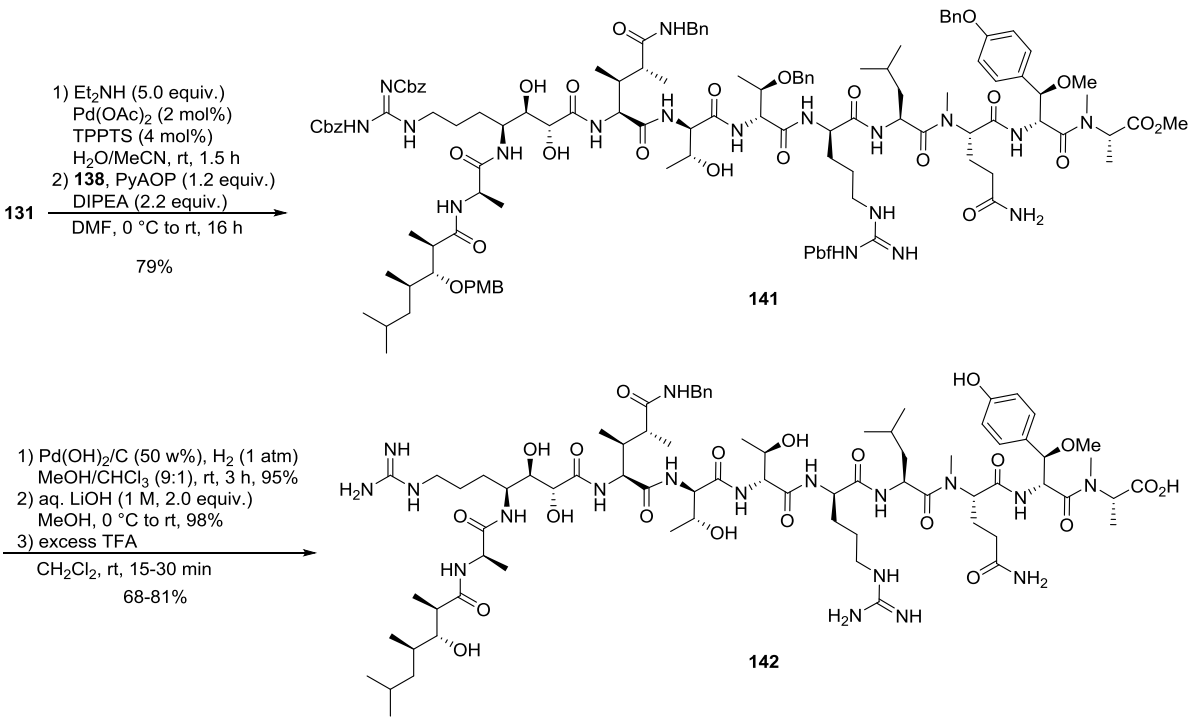
With all building blocks in hand, focus shifted toward the construction of the depsipeptide core of callipeltin A via peptide couplings starting from *C*-terminal *N*-methyl alanine. The synthesis of the linear peptide **137** could be accomplished over 10 steps in 52% yield and after *C*-terminal saponification, macrolactonization could be achieved in excellent yield with PyAOP and DMAP at elevated temperatures without significant loss of stereochemical integrity (scheme 119). However, after Alloc-deprotection the free amine proved to be completely unreactive, most likely due to an inaccessible conformation, which renders the introduction of the sidechain impossible.



Scheme 119: Synthesis of depsipeptide core **134** by macrolactonization.

In a second approach, coupling of the side chain and linear peptide **131** was conducted prior to macrocyclization, which afforded protected callipeltin C **141** in 79% yield (scheme 120). After removal of all but one protecting group, namely the benzyl amide on the glutamine residue, in a three-step sequence a dead end was reached once again. Unfortunately, the

removal of this benzyl amide proved impossible under all reaction conditions which ultimately concluded the synthetic progress toward the natural products callipeltin A and C.



Scheme 120: Attempted synthesis of callipeltin C.

In conclusion, this synthetic effort toward the total synthesis of callipeltin A and C, albeit ultimately unsuccessful, has resulted in the development of several synthetic protocols to prepare the building blocks of the callipeltins in good yield and highly stereoselective fashion. Moreover, this work describes a robust route toward a protected derivative of callipeltin C which should allow for the synthesis of the natural products A and C by only a slight variation of the protection group strategy.

6. Experimental Section

6.1 General Information

All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. THF was dried over sodium/benzophenone and was distilled before use. Dry CH_2Cl_2, diethyl ether, DMF, DMSO, toluene and pyridine were purchased from Acros Organics. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.04-0.063 mm or 0.063-0.2 mm) and with a Reveleris® flash chromatography system from Grace with RediSep®-columns from Teledyne Isco. Mixtures of ethyl acetate and petroleum ether (40–60°C fraction), dichloromethane and diethyl ether or acetonitrile and water (for reversed phase) were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Macherey-Nagel GmbH & Co. KG, Silica on TLC PET-foils, 4 x 8 cm). Visualization was accomplished with UV-light (254 nm), Cerium-molybdenum solution, $KMnO_4$ solution or with an iodine chamber. Melting points were determined with a MEL-TEMP II Melting point apparatus from Laboratory devices and are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded with a Bruker AV400 [400 MHz (^1H) and 100 MHz (^{13}C)], a Bruker AV500 [500 MHz (^1H) and 125 MHz (^{13}C)] in $CDCl_3$, or DMSO-d_6. Chemical shifts are reported in ppm relative to TMS ($CDCl_3$) or the residual solvent signal (DMSO-d_6). The multiplicity of the observed signals in the proton spectra are abbreviated with s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet) and bs (broad signal). The multiplicity in the carbon spectra describes the theoretical multiplicity of the signals without broadband decoupling. Diastereomeric ratios were determined by NMR and/or HPLC. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using chemical ionization (CI) and a Bruker MAXIS 4G UHR-TOF using electrospray ionization (ESI) at the Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS). HPLC analysis was performed on a MerckHitachi system (model LaChrom D-7000) using a Chiralcel OD-H-column (Daicel Chemical Industries) and a Reprosil® column (Dr. Maisch). LC-MS analyses were carried out on a Shimadzu system (LC-10At, autoinjector SCL-6B, mass spectrometer LC-MS-2020). A Phenomenex Luna C18(2) column (50x4.6 mm, grain size 3 µm) was used as the column. A GC-2010 System from Shimadzu (AOC-20i autoinjector, FID-detector) with a CP-Chirasil-Dex CB (Varian, 25 m x 0.25 mm, 0.25 µm internal diameter) was used for GC-FID analysis. Optical rotations were measured with a Perkin-Elmer polarimeter (model 341) in a tempered (20°C ± 1 °C) cuvette. The radiation source used was a sodium vapor lamp (λ = 589 nm).

6.2 General Procedures

General procedure 1: preparation of α-hydroxy acids

A three-necked flask was equipped with a dropping funnel and an internal thermometer, and the amino acid (1.0 equiv.) was added. The acid was dissolved in aq. sulfuric acid (1 M, 2 mL/mmol amino acid) and the solution was placed in an ice bath. A solution of $NaNO_2$ (6 equiv., 10 M in water) was slowly added over 2-6 hours at 0-4 °C. Afterwards the mixture was stirred for 4 hours at 0 °C, extracted twice with Et_2O and the combined organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the desired hydroxy acids.

General procedure 2: EDC coupling

A solution of acid (1.0 equiv.), amine hydrochloride (1.0 equiv.), HOBt (1.1 equiv.) DIPEA (2.1 equiv.) in DCM (10 mL/mmol acid) was cooled to 0 °C and EDC·HCl (1.1 equiv.) was added. The mixture was allowed to warm to room temperature, diluted with ethyl acetate and subsequently washed with HCl (1 M), sat. $NaHCO_3$ and sat. NaCl. After drying over Na_2SO_4, the solvent was removed *in vacuo* and the crude product was purified by column chromatography or recrystallization.

General procedure 3: preparation of carbonates

To a solution of alcohol (1.0 equiv.) and pyridine (1.5 equiv.) in DCM (1-2 mL/mmol alcohol) was added ethyl chloroformate (1.2 equiv.) at 0 °C. The mixture was warmed to room temperature and stirred until complete conversion was observed by TLC. After addition of Et_2O the mixture was washed with HCl (1 M) and brine and the organic layer was dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by column chromatography.

General procedure 4: Pd-catalyzed allylic alkylation

Procedure A

In a vacuum dried Schlenk flask *N*-(α-Hydroxyacyl)-glycine ester (1.0 equiv.) was dissolved in freshly distilled THF (6.5 mL/mmol) and a solution of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0-2.0 equiv., 1.0 M in hexane) was added. After stirring for 20 minutes at room temperature the mixture was cooled to −78 °C and a solution of LHMDS (5.5 equiv., 1.0 M in THF) was added.

In a second Schlenk flask PPh_3 (9 mol%) and $[AllylPdCl]_2$ (2 mol%) were dissolved in THF (3.0 mL/mmol glycine ester) and stirred for 15 minutes at −78 °C. The allyl substrate was added to the catalyst solution and after stirring for 10 minutes at −78 °C the mixture was slowly added to the enolate solution. After removal of the dry ice from the cooling bath the mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with Et_2O and hydrolyzed with water. After addition of 1 N $KHSO_4$ the layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic

layers were dried (Na_2SO_4), the solvent removed under vacuo and the residue was purified by column chromatography.

Procedure B

A solution of freshly distilled DIPA (3.2 equiv.) in dry THF (1.5 mL/mmol) was cooled to –20 °C and a solution of *n*-butyllithium (3.1 equiv., 2.5 M in hexane) was added. After 5 minutes at –20 °C the mixture was stirred for 20 minutes at room temperature before it was cooled to –78 °C.

In a second Schlenk flask the *N*-(α-Hydroxyacyl)-glycine ester (1.0 equiv.) was dissolved in freshly distilled THF (6.5 mL/mmol) and a solution of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0-2.0 equiv., 1.0 M in hexane) was added. After stirring for 20 minutes at room temperature the mixture was cooled to –78 °C and the freshly prepared LDA solution was added slowly. For complete transmetalation the mixture was stirred for further 30 minutes at the same temperature.

In a third Schlenk flask PPh_3 (9 mol%) and $[AllylPdCl]_2$ (2 mol%) were dissolved in THF (3.0 mL/mmol) and stirred for 15 minutes at –78 °C. The allyl substrate was added to the catalyst solution and after stirring for 10 minutes at –78 °C the mixture was slowly added to the enolate solution. After removal of the dry ice from the cooling bath the mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with Et_2O and hydrolyzed with water. After addition of 1 N $KHSO_4$ the layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried (Na_2SO_4), the solvent removed under vacuo and the residue was purified by column chromatography.

General procedure 5: Matteson-homologation

Preparation of the α-Halo-boronic ester: A Schlenk tube was flame dried and DIPA (1.1-2.0 equiv.) was dissolved in dry THF (0.2 mL/mmol). The tube was cooled to –20 °C and *n*-butyllithium (1.0-2.0 equiv.) was added dropwise. After complete addition the mixture was stirred for 20 minutes at room temperature.

In a second Schlenk tube zinc chloride (2.0-5.0 equiv.) was dried under high vacuum with a heat gun and after cooling to room temperature dissolved in THF (0.5 mL/mmol).

The third Schlenk tube was flame dried and the boronic ester (1.0 equiv.), CH_2Cl_2 or CH_2Br_2 (3.0 equiv.) and THF (1.4 mL/mmol) were added. After cooling to –40 °C the freshly prepared LDA solution was slowly added, and the mixture was stirred for 10-15 minutes at the same temperature. The zinc chloride solution was rapidly added, and the reaction was stirred for 4-16 hours at room temperature.

Reaction with a nucleophile: The mixture was cooled to 0 °C, a solution of the nucleophile was dropwise added, and the reaction was stirred at room temperature until complete consumption of the α-halo-boronic ester was observed (NMR). Then, the reaction was quenched by addition of sat. NH_4Cl and water and extracted thrice with pentane. After

drying (Na_2SO_4) of the combined organic layer, the solvent was removed *in vacuo* and the residue was purified by rapid filtration over a short column of silica.

General Procedure 6: Fmoc deprotection

To a solution of Fmoc-protected amino acid or peptide (1.0 equiv.) in MeCN (0.05 M) was added Et_2NH (80 equiv.) and the mixture was stirred at room temperature until complete deprotection was observed by TLC or LC-MS. The volatiles were removed *in vacuo* and the crude amine was used in the next step.

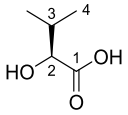
General Procedure 7: Alloc deprotection

Alloc-protected amino acid or peptide (1.0 equiv.) was dissolved in MeCN/H_2O (1:1, 0.05 M) and Et_2NH (5.0 equiv.), TPPTS (4 mol%) and $Pd(OAc)_2$ (2 mol%, 0.02 M in MeCN) were added. The mixture was stirred at room temperature until complete deprotection was observed by TLC or LC-MS. After removal of all volatiles *in vacuo*, the crude amine was directly used in the coupling step.

6.3 Synthesis of the compounds

(*S*)-2-Hydroxy-3-methylbutanoic acid (1b)

According to **GP-1**, L-valine (10.0 g, 85.0 mmol) in sulfuric acid (170 mL, 1 M) was treated with a solution of sodium nitrite (35.3 g, 512 mmol, 6.0 equiv.) in water (50 mL) at 0 °C. After aqueous work up, hydroxy acid **1b** (7.53 g, 63.7 mmol, 75%) was obtained as a colorless syrup, which solidified upon vigorous drying under high vacuum.

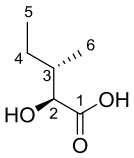


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, $^3J_{4,3}$ = 6.9 Hz, 3 H, 4-H), 1.07 (d, $^3J_{4',3}$ = 7.0 Hz, 3 H, 4-H'), 2.18 (septd, $^3J_{3,4}$ = 6.9 Hz, $^3J_{3,2}$ = 3.4 Hz, 1 H, 3-H), 4.19 (d, $^3J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 6.57 (bs, 2 H, OH, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.8 (q, C-4), 18.7 (q, C-4'), 32.0 (d, C-3), 74.9 (d, C-2), 178.6 (s, C-1).

(2*S*,3*S*)-2-Hydroxy-3-methylpentanoic acid (1d)

According to **GP-1**, L-isoleucine (7.19 g, 54.8 mmol) in sulfuric acid (110 mL, 1 M) was treated with a solution of sodium nitrite (22.7 g, 329 mmol, 6.0 equiv.) in water (35 mL) at 0 °C. After aqueous work up, hydroxy acid **1d** (5.91 g, 44.7 mmol, 82%) was obtained as a white solid.

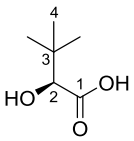


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, $^3J_{5,4}$ = 7.5 Hz, 3 H, 5-H), 1.02 (d, $^3J_{6,3}$ = 7.0 Hz, 3 H, 6-H), 1.30 (m, 1 H, 4-H_a), 1.44 (m, 1 H, 4-H_b), 1.89 (m, 1 H, 3-H), 4.19 (d, $^3J_{2,3}$ = 3.7 Hz, 1 H, 2-H), 7.47 (bs, 2 H, OH, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-5), 15.3 (q, C-6), 23.6 (t, C-4), 38.8 (d, C-3), 74.7 (d, C-2), 179.3 (s, C-1).

(*S*)-2-Hydroxy-3,3-dimethylbutanoic acid (1e)

According to **GP-1**, L-*tert*-leucine (7.50 g, 54.8 mmol) in sulfuric acid (115 mL, 1 M) was treated with a solution of sodium nitrite (23.7 g, 343 mmol, 6.0 equiv.) in water (35 mL) at 0 °C. After aqueous work up, hydroxy acid **1e** (5.01 g, 37.8 mmol, 66%) was obtained as a colorless syrup.

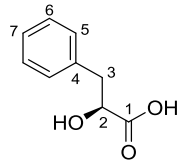


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 9 H, 4-H), 3.92 (s, 1 H, 2-H), 7.53 (bs, 2 H, OH, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.7 (q, C-4), 35.2 (s, C-3), 78.3 (d, C-2), 178.7 (s, C-1).

(*S*)-2-Hydroxy-3-phenylpropanoic acid (1f)

According to **GP-1**, L-Phenylalanine (10.0 g, 60.5 mmol) in sulfuric acid (121 mL, 1.0 M) was treated with a solution of sodium nitrite (25.1 g, 363 mmol, 6.0 equiv.) in water (35 mL) at 0 °C. After aqueous work, hydroxy acid **1f** (7.90 g, 47.5 mmol, 79%) was obtained as a white solid.



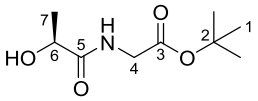
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.78 (dd, $^{2}J_{3a,3b}$ = 13.7 Hz, $^{3}J_{3a,2}$ = 8.3 Hz, 1 H, 3-H_a), 2.97 (dd, $^{2}J_{3b,3a}$ = 13.7 Hz, $^{3}J_{3b,2}$ = 4.4 Hz, 1 H, 3-H_b), 4.15 (dd, $^{3}J_{2,3a}$ = 8.3 Hz, $^{3}J_{2,3b}$ = 4.5 Hz, 1 H, 2-H), 4.87 (bs, 1 H, OH), 7.26 (m, 5 H, 5-H, 6-H, 7-H), 12.57 (bs, 1 H, COOH).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 40.1 (t, C-3), 71.1 (d, C-2), 126.2 (d, C-7), 128.0 (d, C-5), 129.4 (d, C-6), 138.2 (s, C-4), 175.2 (s, C-1).

***tert*-butyl (*S*)-(2-hydroxypropanoyl)glycinate (2a)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (1.50 g, 8.95 mmol), lactic acid **1a** (985 mg, 9.84 mmol, 30% in H_2O, 1.1 equiv.), HOBt (1.51 g, 9.84 mmol, 1.1 equiv.), DIPEA (3.44 mL, 19.7 mmol, 2.2 equiv.) and EDC (1.89 g, 9.84 mmol, 1.1 equiv.) were reacted at 0 °C. After column chromatography (silica, petroleum ether/ethyl acetate 1:2), hydroxy acid peptide **2a** (649 mg, 3.19 mmol, 36%) was obtained as a colorless oil.

R_f(2a) = 0.11 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, $^{3}J_{7,6}$ = 6.8 Hz, 3 H, 7-H), 1.48 (s, 9 H, 1-H), 3.58 (bs, 1 H, OH), 3.91 (dd, $^{2}J_{4a,4b}$ = 18.2 Hz, $^{3}J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 3.99 (dd, $^{2}J_{4b,4a}$ = 18.2 Hz, $^{3}J_{4b,NH}$ = 5.5 Hz, 1 H, 4-H_b), 4.28 (q, $^{3}J_{6,7}$ = 6.8 Hz, 1 H, 6-H), 7.14 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.9 (q, C-7), 28.0 (q, C-1), 41.5 (t, C-4), 68.4 (d, C-6), 82.4 (s, C-2), 169.1 (s, C-3), 175.0 (s, C-5).

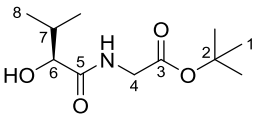
Optical rotation:	$[\alpha]_D^{20}$ = −20.8 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_9H_{18}NO_4$ $[M+H]^+$	204.1230	204.1228

***tert*-Butyl (*S*)-(2-hydroxy-3-methylbutanoyl)glycinate (2b)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (2.00 g, 11.9 mmol), hydroxy acid **1b** (1.41 g, 11.9 mmol, 1.0 equiv.), HOBt (2.01 g, 13.1 mmol, 1.1 equiv.), DIPEA (4.38 mL,

25.1 mmol, 2.1 equiv.) and EDC (2.52 g, 13.1 mmol, 1.1 equiv.) were reacted at 0 °C. After column chromatography (silica, petroleum ether/ethyl acetate 1:1), hydroxy acid peptide **1a** (2.54 g, 11.0 mmol, 92%) was obtained as a white solid.

R_f(2b) = 0.09 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, $^3J_{8,7}$ = 6.9 Hz, 3 H, 8-H), 1.04 (d, $^3J_{8',7}$ = 7.0 Hz, 3 H, 8-H'), 1.48 (s, 9 H, 1-H), 2.17 (septd, $^3J_{7,8}$ = 6.9 Hz, $^3J_{7,6}$ = 3.3 Hz, 1 H, 7-H), 3.03 (bs, 1 H, OH), 3.94 (dd, $^2J_{4a,4b}$ = 18.2 Hz, $^3J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 4.01 (dd, $^2J_{4b,4a}$ = 18.2 Hz, $^3J_{4b,NH}$ = 5.6 Hz, 1 H, 4-H_b), 4.03 (bs, 1 H, 6-H), 6.98 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.5 (q, C-8), 19.1 (q, C-8'), 28.0 (q, C-1), 31.9 (d, C-7), 41.5 (t, C-4), 76.3 (d, C-6), 82.4 (s, C-2), 169.0 (s, C-3), 173.6 (s, C-5).

Optical rotation: $[\alpha]_D^{20}$ = −46.8 (c = 1.0, $CHCl_3$)

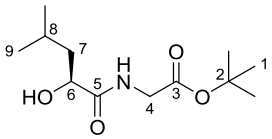
Melting point: 58−60 °C

HRMS (CI):	Calculated	Found
$C_{11}H_{22}NO_4$ $[M+H]^+$	232.1543	232.1551

***tert*-Butyl (*S*)-(2-hydroxy-4-methylpentanoyl)glycinate (2c)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (2.00 g, 11.9 mmol), (2*S*)-hydroxy-4-methylpentanoic acid (1.58 g, 11.9 mmol, 1.0 equiv.), HOBt (2.01 g, 13.1 mmol, 1.1 equiv.), DIPEA (4.38 mL, 25.1 mmol, 2.1 equiv.) and EDC·HCl (2.52 g, 13.1 mmol, 1.1 equiv.) were reacted at 0 °C. After column chromatography (silica, petroleum ether/ethyl acetate 1:1), hydroxy acid peptide **2c** (2.62 g, 10.7 mmol, 90%) was obtained as a colorless oil.

R_f(2c) = 0.22 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, $^3J_{9,8}$ = 6.6 Hz, 3 H, 9-H), 0.97 (d, $^3J_{9',8}$ = 6.6 Hz, 3 H, 9-H'), 1.48 (s, 9 H, 1-H), 1.56 (ddd,$^2J_{7a,7b}$ = 14.3 Hz, $^3J_{7a,6}$ = 9.9 Hz, $^3J_{7a,8}$ = 5.0 Hz, 1 H, 7-H_a), 1.65 (ddd,$^2J_{7b,7a}$ = 14.1 Hz, $^3J_{7b,6}$ = 9.3 Hz, $^3J_{7b,8}$ = 3.5 Hz, 1 H, 7-H_b), 1.86 (m, 1 H, 8-H), 2.69 (m, 1 H, OH), 3.91 (dd, $^2J_{4a,4b}$ = 18.2 Hz, $^3J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 4.00 (dd, $^2J_{4b,4a}$ = 18.2 Hz, $^3J_{4b,NH}$ = 5.5 Hz, 1 H, 4-H_b), 4.19 (td, $^3J_{6,7}$ = 9.8 Hz, $^3J_{6,OH}$ = 3.5 Hz, 1 H, 6-H), 6.93 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.3 (q, C-9), 23.4 (q, C-9'), 24.5 (d, C-8), 28.0 (q, C-1), 41.6 (t, C-4), 43.7 (t, C-7), 70.7 (d, C-6), 82.4 (s, C-2), 169.1 (s, C-3), 174.7 (s, C-5).

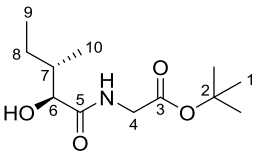
Optical rotation: $[\alpha]_D^{20}$ = −51.8 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{12}H_{23}NO_4$ [M+H]$^+$	246.1700	246.1703

***tert*-Butyl (2*S*,3*S*)-(2-hydroxy-3-methylpentanoyl)glycinate (2d)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (5.00 g, 29.8 mmol), hydroxy acid **1d** (3.94 g, 29.8 mmol, 1.0 equiv.), HOBt (5.02 g, 32.8 mmol, 1.1 equiv.), DIPEA (10.9 mL, 62.6 mmol, 2.1 equiv.) and EDC·HCl (6.29 g, 32.8 mmol, 1.1 equiv.) were reacted at 0 °C. After column chromatography (silica, petroleum ether/ethyl acetate 1:1), hydroxy acid peptide **2d** (6.51 g, 26.5 mmol, 89%) was obtained as a white solid.

R_f(2d) = 0.22 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{9,8}$ = 7.5 Hz, 3 H, 9-H), 1.01 (d, $^3J_{10,7}$ = 7.0 Hz, 3 H, 10-H), 1.22 (m, 1 H, 8-H_a), 1.44 (m, 1 H, 8-H_b), 1.48 (s, 9 H, 1-H), 1.90 (dqt, $^3J_{7,8a}$ = 10.6 Hz, $^3J_{7,10}$ = 6.8 Hz, $^3J_{7,6/8b}$ = 3.6 Hz, 1 H, 7-H), 2.95 (bs, 1 H, OH), 3.93 (dd, $^2J_{4a,4b}$ = 18.2 Hz, $^3J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 4.02 (dd, $^2J_{4b,4a}$ = 18.2 Hz, $^3J_{4b,NH}$ = 5.6 Hz, 1 H, 4-H_b), 4.06 (d, $^3J_{6,7}$ = 3.3 Hz, 1 H, 6-H), 6.97 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-9), 15.5 (q, C-10), 23.1 (t, C-8), 28.0 (q, C-1), 38.8 (d, C-7), 41.6 (t, C-4), 76.4 (d, C-6), 82.4 (s, C-2), 169.0 (s, C-3), 173.3 (s, C-5).

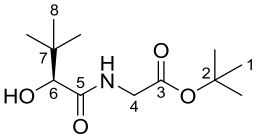
Optical rotation:	$[\alpha]_D^{20}$ = −40.7 (c = 1.0, $CHCl_3$)
Melting point:	49−51 °C

HRMS (CI):	Calculated	Found
$C_{12}H_{23}NO_4$ [M+H]$^+$	246.1700	246.1690

***tert*-Butyl (*S*)-(2-hydroxy-3,3-dimethylbutanoyl)glycinate (2e)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (3.00 g, 17.9 mmol), hydroxy acid **1e** (2.37 g, 17.9 mmol, 1.0 equiv.), HOBt (3.01 g, 19.7 mmol, 1.1 equiv.), DIPEA (6.56 mL, 37.6 mmol, 2.1 equiv.) and EDC·HCl (3.77 g, 19.7 mmol, 1.1 equiv.) were reacted at 0 °C. Column chromatography (silica, petroleum ether/ethyl acetate 1:1) gave rise to hydroxy acid peptide **2e** (4.01 g, 16.3 mmol, 91%) as a pale yellow solid.

R_f(2e) = 0.17 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 9 H, 8-H), 1.48 (s, 9 H, 1-H), 3.25 (d, $^3J_{OH,6}$ = 5.3 Hz, 1 H, OH), 3.78 (d, $^3J_{6,OH}$ = 5.0 Hz, 1 H, 6-H), 3.91 (dd, $^2J_{4a,4b}$ = 18.2 Hz, $^3J_{4a,NH}$ = 5.1 Hz, 1 H, 4-H_a), 4.02 (dd, $^2J_{4b,4a}$ = 18.2 Hz, $^3J_{4b,NH}$ = 5.6 Hz, 1 H, 4-H_b), 6.78 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9 (q, C-8), 28.0 (q, C-1), 35.0 (s, C-7), 41.6 (t, C-4), 79.6 (d, C-6), 82.4 (s, C-2), 169.0 (s, C-3), 172.8 (s, C-5).

Optical rotation: $[\alpha]_D^{20}$ = −46.9 (c = 1.0, $CHCl_3$)

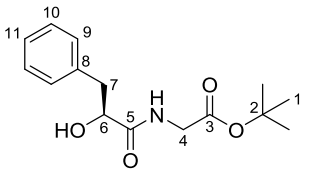
Melting point: 79−82 °C

HRMS (CI):	Calculated	Found
$C_{12}H_{23}NO_4$ $[M+H]^+$	246.1700	246.1701

***tert*-Butyl (*S*)-(2-hydroxy-3-phenylpropanoyl)glycinate (2f)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (2.00 g, 11.9 mmol), hydroxy acid **1f** (1.98 g, 11.9 mmol, 1.0 equiv.), HOBt (2.01 g, 13.1 mmol, 1.1 equiv.), DIPEA (4.38 mL, 25.1 mmol, 2.1 equiv.) and EDC·HCl (2.52 g, 13.1 mmol, 1.1 equiv.) were reacted at 0 °C. Filtration through a pad of silica (petroleum ether/ethyl acetate 1:1) and recrystallization from petroleum ether/ethyl acetate afforded hydroxy acid peptide **2f** (3.00 g, 10.7 mmol, 90%) as colorless crystals.

R_f(2f) = 0.14 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, 1-H), 2.74 (d, $^3J_{OH,6}$ = 4.7 Hz, 1 H, OH), 2.86 (dd, $^2J_{7a,7b}$ = 13.9 Hz, $^3J_{7a,6}$ = 9.0 Hz, 1 H, 7-H_a), 3.26 (dd, $^2J_{7b,7a}$ = 13.9 Hz, $^3J_{7b,6}$ = 3.5 Hz, 1 H, 7-H_b), 3.88 (dd, $^2J_{4a,4b}$ = 18.2 Hz, $^3J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 3.97 (dd, $^2J_{4b,4a}$ = 18.2 Hz, $^3J_{4b,NH}$ = 5.4 Hz, 1 H, 4-H_b), 4.33 (dt, $^3J_{6,7a}$ = 8.9 Hz, $^3J_{6,7b/OH}$ = 4.2 Hz, 1 H, 6-H), 7.02 (bs, 1 H, NH), 7.25 (m, 3 H, 9-H, 11-H), 7.32 (m, 2 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 40.8 (t, C-7), 41.5 (t, C-4), 72.9 (d, C-6), 82.4 (s, C-2), 126.9 (d, C-11), 128.7 (d, C-9), 129.5 (d, C-10), 136.9 (s, C-8), 168.8 (s, C-3), 172.8 (s, C-5).

Optical rotation: $[\alpha]_D^{20}$ = −75.3 (c = 1.0, $CHCl_3$)

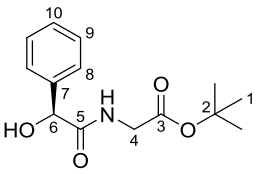
Melting point: 98−100 °C

HRMS (CI):	Calculated	Found
$C_{15}H_{22}NO_4$ $[M+H]^+$	280.1543	280.1533

***tert*-butyl (*S*)-(2-hydroxy-2-phenylacetyl)glycinate (2g)**

According to **GP-2**, *tert*-butyl glycinate hydrochloride (2.00 g, 11.9 mmol), mandelic acid (1.82 g, 11.9 mmol, 1.0 equiv.), HOBt (2.01 g, 13.1 mmol, 1.1 equiv.), DIPEA (4.38 mL, 25.1 mmol, 2.1 equiv.) and EDC·HCl (2.52 g, 13.1 mmol, 1.1 equiv.) were reacted at 0 °C. Column chromatography (silica, petroleum ether/ethyl acetate 1:1) afforded hydroxy acid peptide **2g** (2.95 g, 11.1 mmol, 93%) as colorless oil.

R_f(2g) = 0.19 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 3.72 (d, $^3J_{OH,6}$ = 3.7 Hz, 1 H, OH), 3.89 (dd, $^2J_{4a,4b}$ = 18.3 Hz, $^3J_{4a,NH}$ = 5.1 Hz, 1 H, 4-H_a), 3.96 (dd, $^2J_{4b,4a}$ = 18.3 Hz, $^3J_{4b,NH}$ = 5.4 Hz, 1 H, 4-H_b), 5.09 (d, $^3J_{6,OH}$ = 3.5 Hz, 1 H, 6-H), 6.74 (bs, 1 H, NH), 7.35 (m, 3 H, 8-H, 10-H), 7.44 (m, 2 H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 41.9 (t, C-4), 74.1 (d, C-6), 82.6 (s, C-2), 126.8 (d, C-10), 128.6 (d, C-8), 128.8 (d, C-9), 139.1 (s, C-7), 168.6 (s, C-3), 172.2 (s, C-5).

Optical rotation: $[\alpha]_D^{20}$ = −57.2 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{14}H_{20}NO_4$ $[M+H]^+$	266.1387	266.1401

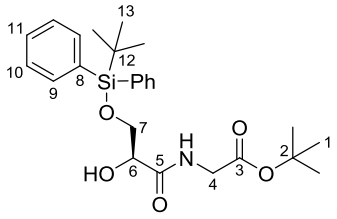
***tert*-butyl (S)-(3-((*tert*-butyldiphenylsilyl)oxy)-2-hydroxypropanoyl)glycinate (2h)**

To a solution of *L*-serine (4.20 g, 40.0 mmol) in 100 mL HCl (0.4 M) was slowly added sodium nitrite (5.52 g, 80.0 mmol, 2.0 equiv.) in 100 mL water at –10°C. After warming to room temperature, the mixture was stirred overnight, evaporated *in vacuo* and acetone was added to the white residue. After filtration the solvent was removed *in vacuo* and the residue taken up in $CHCl_3$/Aceton (20 mL) and evaporated *in vacuo* three times. The crude residue was suspended in 150 mL DCM and 20 mL DMF, cooled to 0 °C and DMAP (186 mg, 1.52 mmol), triethylamine (15.9 mL, 114 mmol) and TBDPS-Cl (9.76 mL, 38.0 mmol) were subsequently added. The mixture was stirred at rt for 3 days, extracted with HCl (1 M) twice, dried (Na_2SO_4) and evaporated *in vacuo*.

Crude hydroxy acid **5**, *tert*-butyl glycinate hydrochloride (5.03 g, 30.0 mmol, 1.0 equiv.), HOBt (4.59 g, 30.0 mmol, 1.0 equiv.) in 150 mL DCM was treated with DIPEA (10.5 ml, 60.0 mmol) and EDC-HCl (6.04 g, 31.5 mmol, 1.05 equiv.) at 0 °C. After warming to room temperature overnight the solvent was removed, EtOAc was added and the mixture was washed with HCl (1 M) twice, sat. sodium bicarbonate and brine. The organic layer was dried (Na_2SO_4), evaporated *in vacuo* and the crude product purified by column chromatography

(silica, PE/EtOAc 9:1 → 4:1 → 1:1) to afford (7.14 g, 15.6 mmol, 39% over 3 steps) of mono protected diol **2h** and diprotected diol **2h-1** (2.01 g, 2.87 mmol, 7.2%) as colorless resins.

R_f(2h) = 0.17 (PE/EtOAc 4:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, 13-H), 1.47 (s, 9 H, 1-H), 3.25 (d, $^3J_{OH,6}$ = 4.6 Hz, 1 H, OH), 3.92 (d, $^3J_{7,6}$ = 5.5 Hz, 2 H, 7-H), 3.97 (d, $^3J_{4,NH}$ = 5.3 Hz, 2 H, 4-H), 4.21 (q, $^3J_{6,7/OH}$ = 5.3 Hz, 1 H, 6-H), 7.24 (m, 1 H, NH), 7.42 (m, 6 H, 10-H, 11-H), 7.63 (dd, $^3J_{9,10}$ = 7.9 Hz, $^3J_{9,11}$ = 3.2 Hz, 2 H, 9-H), 7.64 (dd, $^3J_{9',10}$ = 7.9 Hz, $^3J_{9',11}$ = 3.2 Hz, 2 H, 9-H').

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.2 (s, C-12), 26.8 (q, C-13), 28.0 (q, C-1), 41.7 (t, C-4), 65.1 (t, C-7), 71.8 (d, C-6), 82.3 (s, C-2), 127.9 (d, C-10), 130.0 (d, C-11), 132.5 (s, C-8), 132.6 (s, C-8'), 135.5 (d, C-9), 135.5 (d, C-9'), 168.5 (s, C-3), 171.6 (s, C-5).

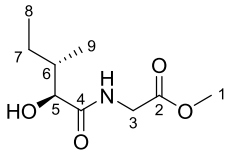
Optical rotation: $[\alpha]_D^{20}$ = −63.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{25}H_{36}NO_5Si$ $[M]^+$	458.2357	458.2361

Methyl (2*S*,3*S*)-(2-hydroxy-3-methylpentanoyl)glycinate (4a)

According to **GP-2**, methyl glycinate hydrochloride (300 mg, 2.39 mmol), hydroxy acid **1d** (316 mg, 2.39 mmol, 1.0 equiv.), HOBt (403 mg, 2.63 mmol, 1.1 equiv.), DIPEA (876 μL, 5.02 mmol, 2.1 equiv.) and EDC·HCl (504 mg, 2.63 mmol, 1.1 equiv.) were reacted at 0 °C. Column chromatography (silica, petroleum ether/ethyl acetate 2:3) afforded hydroxy acid peptide **4a** (316 mg, 1.52 mmol, 64%) as a colorless oil.

R_f(4a) = 0.07 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{8,7}$ = 7.4 Hz, 3 H, 8-H), 1.02 (d, $^3J_{9,6}$ = 7.0 Hz, 3 H, 9-H), 1.22 (m, 1 H, 7-H_a), 1.45 (m, 1 H, 7-H_b), 1.91 (m, 1 H, 6-H), 2.75 (bs, 1 H, OH), 3.77 (s, 3 H, 1-H), 4.06 (dd, $^2J_{3a,3b}$ = 18.2 Hz, $^3J_{3a,NH}$ = 5.5 Hz, 1 H, 3-H_a), 4.08 (m, 1 H, 5-H), 4.12 (dd, $^2J_{3b,3a}$ = 18.3 Hz, $^3J_{3b,NH}$ = 5.6 Hz, 1 H, 3-H_b), 7.02 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-8), 15.5 (q, C-9), 23.1 (t, C-7), 38.8 (d, C-6), 40.7 (t, C-3), 52.4 (q, C-1), 76.4 (d, C-5), 170.3 (s, C-2), 173.6 (s, C-4).

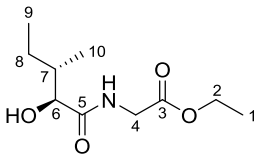
Optical rotation: $[\alpha]_D^{20}$ = −56.0 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_9H_{18}NO_4$ $[M+H]^+$	204.1230	204.1238

Ethyl (2*S*,3*S*)-(2-hydroxy-3-methylpentanoyl)glycinate (4b)

According to **GP-2**, ethyl glycinate hydrochloride (300 mg, 2.15 mmol), hydroxy acid **1d** (284 mg, 2.15 mmol, 1.0 equiv.), HOBt (362 mg, 2.36 mmol, 1.1 equiv.), DIPEA (788 μL, 4.51 mmol, 2.1 equiv.) and EDC (453 mg, 2.36 mmol, 1.1 equiv.) were reacted at 0 °C. After column chromatography (silica, petroleum ether/ethyl acetate 2:3), hydroxy acid peptide **4b** (298 mg, 1.34 mmol, 63%) was obtained as a white solid.

R_f(4b) = 0.10 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{9,8}$ = 7.4 Hz, 3 H, 9-H), 1.02 (d, $^3J_{10,7}$ = 7.0 Hz, 3 H, 10-H), 1.22 (m, 1 H, 8-H_a), 1.29 (t, $^3J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 1.45 (m, 1 H, 8-H_b), 1.91 (m, 1 H, 7-H), 2.73 (bs, 1 H, OH), 4.04 (dd, $^2J_{4a,4b}$ = 18.2 Hz, $^3J_{4a,NH}$ = 5.5 Hz, 1 H, 4-H_a), 4.09 (m, 2 H, 4-H_b, 6-H), 4.22 (q, $^3J_{2,1}$ = 7.2 Hz, 2 H, 2-H), 6.99 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-9), 14.1 (q, C-1), 15.5 (q, C-10), 23.1 (t, C-8), 38.8 (d, C-7), 40.9 (t, C-4), 61.6 (t, C-2), 76.4 (d, C-6), 169.8 (s, C-3), 173.6 (s, C-5).

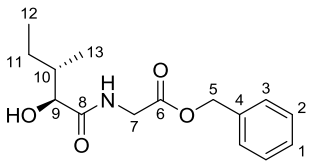
Optical rotation:	$[\alpha]_D^{20}$ = −45.0 (c = 1.0, $CHCl_3$)
Melting point:	51−53 °C

HRMS (CI):	Calculated	Found
$C_{10}H_{19}NO_4$ $[M+H]^+$	218.1387	218.1418

Benzyl (2*S*,3*S*)-(2-hydroxy-3-methylpentanoyl)glycinate (4c)

According to **GP-2**, phenyl glycinate hydrochloride (458 mg, 2.27 mmol, 1.0 equiv.), hydroxy acid **1d** (300 mg, 2.27 mmol, 1.0 equiv.), HOBt (382 mg, 2.50 mmol, 1.1 equiv.), DIPEA (833 μL, 4.77 mmol, 2.1 equiv.) and EDC (479 mg, 2.50 mmol, 1.1 equiv.) were reacted at 0 °C. Aqueous work up and column chromatography (silica, petroleum ether/ethyl acetate 3:2) afforded hydroxy acid peptide **4c** (580 mg, 2.08 mmol, 91%) as a white solid.

R_f(4c) = 0.09 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{12,11}$ = 7.5 Hz, 3 H, 12-H), 1.00 (d, $^3J_{13,10}$ = 7.0 Hz, 3 H, 13-H), 1.21 (m, 1 H, 11-H_a), 1.44 (dqd, $^2J_{11b,11a}$ = 10.9 Hz, $^3J_{11b,12}$ = 7.5 Hz, $^3J_{11b,10}$ = 4.0 Hz, 1 H,

11-H_b), 1.90 (qq, $^3J_{10,13}$ = 7.1 Hz, $^3J_{10,9/11}$ = 3.4 Hz, 1 H, 10-H), 2.59 (bs, 1 H, OH), 4.07 (d, $^3J_{9,10}$ = 3.4 Hz, 1 H, 9-H), 4.09 (d, $^3J_{7a,NH}$ = 5.0 Hz, 2 H, 7-H_a), 4.14 (d, $^3J_{7b,NH}$ = 5.0 Hz, 2 H, 7-H_b), 5.19 (s, 2 H, 5-H), 6.99 (bs, 1 H, NH), 7.36 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-12), 15.5 (q, C-13), 23.1 (t, C-11), 38.7 (d, C-10), 40.9 (t, C-7), 67.3 (t, C-5), 76.4 (d, C-9), 128.4 (d, C-3), 128.5 (d, C-1), 128.6 (d, C-2), 135.1 (s, C-4), 169.7 (s, C-6), 173.6 (s, C-8).

Optical rotation: $[\alpha]_D^{20}$ = −31.1 (c = 1.0, $CHCl_3$)

Melting point: 52−55 °C

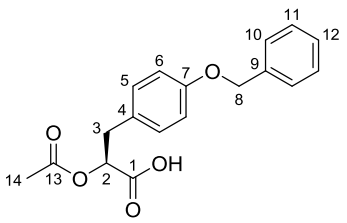
HRMS (CI):	Calculated	Found
$C_{15}H_{23}NO_4$ $[M+2H]^+$	281.1622	281.1623

(*S*)-2-Acetoxy-3-(4-(benzyloxy)phenyl)propanoic acid (6)

L-Tyrosine (7.25 g, 40.0 mmol) was dissolved in an aqueous solution of sodium hydroxide (2 M, 20 mL, 40.0 mmol, 1.0 equiv.) and warmed to 70 °C. A solution of $CuSO_4 \cdot 5H_2O$ (5.00 g, 20.4 mmol, 0.5 equiv.) in water (35 mL) was added dropwise, and the resulting solution was stirred for another hour. After successive addition of MeOH (100 mL) and NaOH (2 M, 20 mL, 40.0 mmol, 1.0 equiv.), BnBr (5.00 mL, 42.0 mmol, 1.05 equiv.) was added dropwise over a period of 30 minutes. After stirring overnight, the mixture was filtrated, the solid product washed with MeOH/H_2O (1:3, 60 mL) three times and then added to a solution of Na_2EDTA (8.74 g, 26.0 mmol) in water (100 mL). The resulting solution was stirred for 5 hours at 70 °C. After filtration and washing with water and acetone, the solid product was dried in high vacuum to afford the *O*-benzyl protected tyrosine as a beige solid (6.45 g, 23.8 mmol, 59%).

To a suspension of *O*-benzyl-L-tyrosine (4.30 g, 15.9 mmol) and NaOAc (4.68 g, 57.1 mmol, 3.6 equiv.) in glacial HOAc (50 mL) was slowly added isoamyl nitrite (7.90 mL, 58.6 mmol, 3.7 equiv.) at room temperature. The reaction mixture was stirred for 3 days at room temperature after which the mixture became clear. Hexane was added, the mixture was concentrated, and the residue redissolved in EtOAc (100 mL) and H_2O (70 mL). The solution was acidified to pH 1 by addition of HCl (6 M), and the layers were separated. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (silica, DCM + 1% HOAc) to afford AcO-L-Hpla(Bn)-OH **6** (3.83 g, 12.2 mmol, 77%) as a yellow solid.

R_f(6) = 0.14 (DCM + 1 % HOAc)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, 14-H), 3.06 (dd, $^2J_{3a,3b}$ = 14.4 Hz, $^3J_{3a,2}$ = 8.7 Hz, 1 H, 3-H_a), 3.17 (dd, $^2J_{3b,3a}$ = 14.4 Hz, $^3J_{3b,2}$ = 4.2 Hz, 1 H, 3-H_b), 5.04 (s, 2 H, 8-H), 5.21 (dd, $^3J_{2,3a}$ = 8.7 Hz, $^3J_{2,3b}$ = 4.2 Hz, 1 H, 2-H), 6.92 (d, $^3J_{6,5}$ = 8.7 Hz, 2 H, 6-H), 7.16 (d, $^3J_{5,6}$ = 8.7 Hz, 2 H, 5-H), 7.36 (m, 5 H, 10-H, 11-H, 12-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.5 (q, C-14), 36.3 (t, C-3), 70.0 (t, C-8), 72.6 (d, C-2), 114.9 (d, C-6), 127.5 (d, C-10), 127.9 (s, C-4), 128.0 (d, C-12), 128.6 (d, C-11), 130.4 (d, C-5), 137.0 (s, C-9), 158.0 (s, C-7), 170.4 (s, C-13), 174.5 (s, C-1).

Optical rotation: $[\alpha]_D^{20}$ = −1.7 (c = 1.0, $CHCl_3$)

Melting point: 104−107 °C

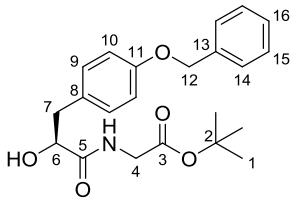
HRMS (CI):	Calculated	Found
$C_{18}H_{18}O_5$ $[M]^+$	314.1149	314.1148

***tert*-Butyl (*S*)-(3-(4-(benzyloxy)phenyl)-2-hydroxypropanoyl)glycinate (2i)**

To a solution of **6** (3.30 g, 10.5 mmol) in THF (35 mL) was added LiOH (1 M, 31.5 mL, 31.5 mmol, 3.0 equiv.) at 0 °C and the mixture was stirred overnight. The mixture was acidified by addition of HCl (1 M, aq.) and extracted two times with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was directly used without further purification.

According to **GP-2**, the hydroxy acid was dissolved in DCM (105 mL) and treated with *tert*-butyl glycinate hydrochloride (1.76 g, 10.5 mmol, 1.0 equiv.), EDC·HCl (2.21 g, 11.6 mmol, 1.1 equiv.), HOBt (1.77 g, 11.6 mmol, 1.1 equiv.) and DIPEA (3.85 mL, 22.1 mmol, 2.1 equiv.) at 0 °C. Aqueous work up and column chromatography (silica, PE/EtOAc 2:1) afforded hydroxy acid dipeptide **2i** (2.95 g, 7.67 mmol, 73% over two steps) as a white solid.

R_f(2i) = 0.09 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, 1-H), 2.60 (d, $^3J_{OH,6}$ = 4.6 Hz, 1 H, OH), 2.82 (dd, $^2J_{7a,7b}$ = 14.1 Hz, $^3J_{7a,6}$ = 8.8 Hz, 1 H, 7-H_a), 3.19 (dd, $^2J_{7b,7a}$ = 14.1 Hz, $^3J_{7b,6}$ = 3.8 Hz, 1 H, 7-H_b), 3.06 (dd, $^2J_{4a,4b}$ = 18.3 Hz, $^3J_{4a,NH}$ = 5.3 Hz, 1 H, 4-H_a), 3.17 (dd, $^2J_{4b,4a}$ = 18.3 Hz, $^3J_{4b,NH}$ = 5.5 Hz, 1 H, 4-H_b), 4.28 (dt, $^3J_{6,7a}$ = 8.8 Hz, $^3J_{6,7b/OH}$ = 4.2 Hz, 1 H, 6-H), 5.04 (s, 2 H, 12-H), 6.93 (d, $^3J_{10,9}$ = 8.7 Hz, 2 H, 10-H), 6.99 (t, $^3J_{NH,4}$ = 5.0 Hz, 1 H, NH), 7.16 (d, $^3J_{9,10}$ = 8.7 Hz, 2 H, 9-H), 7.32 (m, 1 H, 16-H), 7.40 (m, 4 H, 14-H, 15-H).

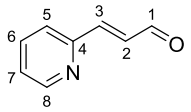
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 39.9 (t, C-7), 41.6 (t, C-4), 70.0 (t, C-12), 73.0 (d, C-6), 82.4 (s, C-2), 115.1 (d, C-10), 127.4 (d, C-14), 127.9 (s, C-8), 128.6 (d, C-16), 128.9 (d, C-15), 130.5 (d, C-9), 136.9 (s, C-13), 157.9 (s, C-11), 168.8 (s, C-3), 172.8 (s, C-5).

Optical rotation:	$[\alpha]_D^{20}$ = −53.6 (c = 1.0, $CHCl_3$)	
Melting point:	109−111 °C	
HRMS (CI):	Calculated	Found
$C_{22}H_{29}NO_5$ $[M+2H]^+$	387.2040	387.2036

(*E*)-3-(Pyridin-2-yl)acrylaldehyde (7)[330]

To a solution of (formylmethyl)triphenylphosphonium chloride (11.3 g, 33.0 mmol, 1.1 equiv.) in toluene (150 mL) was added triethylamine (5.44 ml, 39.0 mmol, 1.3 equiv.) and the mixture was stirred for 30 minutes at room temperature. To this mixture was then added a solution of picolinaldehyde (3.21 g, 30.0 mmol) in toluene (20 mL) and the reaction was stirred overnight. After filtration through a pad of celite the solvent was evaporated *in vacuo* and the crude product purified by column chromatography (silica, PE/EtOAc 2:1 → 1:1) to afford aldehyde **7** (2.63 g, 19.8 mmol, 66%, 98:2 *E*/*Z*) as black crystals.

R_f(7) = 0.13 (PE/EtOAc 2:1)



E-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.10 (dd, $^3J_{2,3}$ = 15.8 Hz, $^3J_{2,1}$ = 7.8 Hz, 1 H, 2-H), 7.33 (ddd, $^3J_{7,6}$ = 7.6 Hz, $^3J_{7,8}$ = 4.8 Hz, $^4J_{7,5}$ = 1.0 Hz, 1 H, 7-H), 7.53 (d, $^3J_{3,2}$ = 15.8 Hz, 1 H, 3-H), 7.56 (d, $^3J_{5,6}$ = 7.8 Hz, 1 H, 5-H), 7.78 (td, $^3J_{6,5/7}$ = 7.7 Hz, $^4J_{6,8}$ = 1.7 Hz, 1 H, 6-H), 8.71 (dd, $^3J_{8,7}$ = 4.8 Hz, $^4J_{8,6}$ = 0.7 Hz, 1 H, 8-H), 9.80 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 124.1 (d, C-5), 124.8 (d, C-7), 131.5 (d, C-2), 136.8 (d, C-6), 150.3 (d, C-8), 151.1 (d, C-3), 152.6 (s, C-4), 193.6 (d, C-1).

Z-isomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (ddd, $^3J_{7,6}$ = 7.5 Hz, $^3J_{7,8}$ = 4.8 Hz, $^4J_{7,5}$ = 0.9 Hz, 1 H, 7-H), 7.40 (d, $^3J_{5,6}$ = 7.8 Hz, 1 H, 5-H), 7.71 (td, $^3J_{6,5/7}$ = 7.7 Hz, $^4J_{6,8}$ = 1.7 Hz, 1 H, 6-H), 8.64 (d, $^3J_{8,7}$ = 4.5 Hz, 1 H, 8-H), 9.66 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 123.5 (d, C-7), 129.8 (d, C-5), 133.4 (d, C-2), 140.7 (d, C-6), 150.0 (d, C-8), 150.8 (d, C-3).

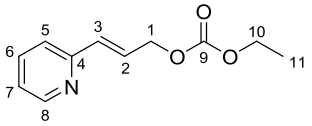
Melting point:	46−47 °C	
HRMS (CI):	Calculated	Found
C_8H_8NO $[M+H]^+$	134.0618	134.0600

(*E*)-Ethyl (3-(pyridin-2-yl)allyl) carbonate (8a)

To a solution of aldehyde **7** (1.00 g, 7.51 mmol) in MeOH (22 mL) was added $NaBH_4$ (426 mg, 11.3 mmol, 1.5 equiv.) at 0 °C. After stirring for 3 hours, the mixture was concentrated, the residue redissolved in water and extracted with diethyl ether. After drying (Na_2SO_4) the solvent was removed *in vacuo* and the crude product used without further purification.

The crude alcohol was dissolved in DCM (7.5 mL) and reacted with pyridine (911 µL, 11.3 mmol, 1.5 equiv.) and ethyl chloroformate (865 µL, 9.01 mmol, 1.2 equiv.) according to **GP-3**. Column chromatography (silica, PE/EtOAc 3:2) afforded allylic carbonate **8a** (970 mg, 4.68 mmol, 62% over two steps) as a pale yellow oil.

R_f(8a) = 0.20 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{11,10}$ = 7.2 Hz, 3 H, 11-H), 4.23 (q, $^3J_{10,11}$ = 7.1 Hz, 2 H, 10-H), 4.85 (d, $^3J_{1,2}$ = 4.6 Hz, 2 H, 1-H), 6.79 (m, 2 H, 2-H, 3-H), 7.16 (ddd, $^3J_{7,6}$ = 7.5 Hz, $^3J_{7,8}$ = 4.8 Hz, $^4J_{7,5}$ = 0.9 Hz, 1 H, 7-H), 7.29 (d, $^3J_{5,6}$ = 7.8 Hz, 1 H, 5-H), 7.64 (td, $^3J_{6,5/7}$ = 7.7 Hz, $^4J_{6,8}$ = 1.8 Hz, 1 H, 6-H), 8.57 (dd, $^3J_{8,7}$ = 4.8 Hz, $^4J_{8,6}$ = 0.7 Hz, 1 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.3 (q, C-11), 64.2 (t, C-10), 67.4 (t, C-1), 122.0 (d, C-5), 122.6 (d, C-7), 127.2 (d, C-2), 133.0 (d, C-3), 136.5 (d, C-6), 149.6 (d, C-8), 154.5 (s, C-4), 155.0 (s, C-9).

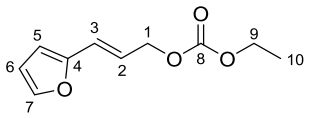
HRMS (CI):	Calculated	Found
$C_{11}H_{14}NO_3$ $[M+H]^+$	208.0968	208.0970

(*E*)-Ethyl (3-(furan-2-yl)allyl) carbonate (8b)

To a solution of (*E*)-3-(furan-2-yl)acrylaldehyde (2.00 g, 16.4 mmol) in MeOH (48 mL) was added $NaBH_4$ (929 mg, 24.6 mmol, 1.5 equiv.) at 0 °C. After stirring for 1 hour, the mixture was concentrated, the residue redissolved in water and extracted with diethyl ether. After drying (Na_2SO_4) the solvent was removed *in vacuo* and the crude product used without further purification.

The crude alcohol was dissolved in pyridine/DCM (2:1, 24 mL) and cooled to 0 °C before ethyl chloroformate (1.89 mL, 19.6 mmol, 1.2 equiv.) was added. After 4 hours, further ethyl chloroformate (2.83 mL, 29.4 mmol, 1.8 equiv.) was added, and the mixture was allowed to warm to room temperature overnight and stirred until complete consumption of the starting material was observed (TLC). The reaction was diluted with diethyl ether, washed with HCl (1 M, aq.) thrice and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the residue was purified by column chromatography (silica, PE/EtOAc 93:7) to afford the allylic carbonate **8b** (3.01 g, 15.3 mmol, 94% over two steps) as a pale yellow oil.

R_f(8b) = 0.27 (PE/EtOAc 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, $^3J_{10,9}$ = 7.2 Hz, 3 H, 10-H), 4.22 (q, $^3J_{9,10}$ = 7.2 Hz, 2 H, 9-H), 4.75 (dd, $^3J_{1,2}$ = 6.4 Hz, $^4J_{1,3}$ = 1.2 Hz, 2 H, 1-H), 6.22 (dt, $^3J_{2,3}$ = 15.8 Hz, $^3J_{2,1}$ = 6.4 Hz, 1 H, 2-H), 6.29 (d, $^3J_{5,6}$ = 3.3 Hz, 1 H, 5-H), 6.37 (dd, $^3J_{6,5}$ = 3.3 Hz, $^3J_{6,7}$ = 1.8 Hz, 1 H, 6-H), 6.50 (d, $^3J_{3,2}$ = 15.8 Hz, 1 H, 3-H), 7.36 (d, $^3J_{7,6}$ = 1.3 Hz, 1 H, 7-H).

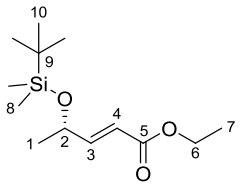
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.3 (q, C-10), 64.1 (t, C-9), 67.7 (t, C-1), 109.1 (d, C-5), 111.3 (d, C-6), 121.0 (d, C-2), 122.5 (d, C-3), 142.5 (d, C-7), 151.7 (s, C-4), 155.0 (s, C-8).

HRMS (CI):	Calculated	Found
$C_{10}H_{12}O_4$ $[M]^+$	196.0730	196.0742

ethyl (*S*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)pent-2-enoate (10)[331]

To a solution of *O*-TBS-L-lactic acid methyl ester **9** (2.18 g, 10.0 mmol) in CH_2Cl_2 (75 mL) was slowly added Dibal-H (11.0 mL, 11.0 mmol, 1.0 M in hexane, 1.1 equiv.) over 90 minutes at –78 °C. After complete addition the mixture was stirred for 2 hours at –78 °C and triethyl phosphonoacetate (3.14 g, 14.0 mmol, 1.4 equiv.) and KO*t*-Bu (1.23 g, 11.0 mmol, 1.1 equiv.) were added. The reaction was allowed to warm to room temperature overnight, citric acid (10w%) was added, and the mixture was vigorously stirred for 30 minutes and diluted with EtOAc. The layers were separated, the aqueous layer extracted twice with EtOAc and the combined organic layer was washed with brine. After drying ($MgSO_4$) the solvent was removed *in vacuo* and the crude residue purified by column chromatography (silica, PE/EtOAc 99:1 → 96:4) to afford unsaturated ester **10** (2.03 g, 7.86 mmol, 79%) as a colorless oil.

R_f(10) = 0.30 (PE/EtOAc 96:4)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, 8-H), 0.07 (s, 3 H, 8-H'), 0.91 (s, 9 H, 10-H), 1.26 (d, $^3J_{1,2}$ = 6.6 Hz, 3 H, 1-H), 1.30 (t, $^3J_{7,6}$ = 7.1 Hz, 3 H, 7-H), 4.18 (dq, $^2J_{6a,6b}$ = 10.9 Hz, $^3J_{6a,7}$ = 7.1 Hz, 1 H, 6-H_a), 4.20 (dq, $^2J_{6b,6a}$ = 10.8 Hz, $^3J_{6b,7}$ = 7.1 Hz, 1 H, 6-H_b), 4.46 (qdd, $^3J_{2,1}$ = 6.4 Hz, $^3J_{2,3}$ = 4.7 Hz, $^4J_{2,4}$ = 1.7 Hz, 1 H, 2-H), 5.98 (dd, $^3J_{4,3}$ = 15.5 Hz, $^4J_{4,2}$ = 1.8 Hz, 1 H, 4-H), 6.93 (dd, $^3J_{3,4}$ = 15.5 Hz, $^3J_{3,2}$ = 4.1 Hz, 1 H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = -4.9 (q, C-8), -4.9 (q, C-8'), 14.3 (q, C-7), 18.2 (s, C-9), 23.5 (q, C-1), 25.8 (q, C-10), 60.3 (t, C-6), 68.0 (d, C-2), 118.9 (d, C-4), 151.9 (d, C-3), 166.9 (s, C-5).

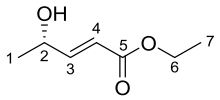
Optical rotation: $[\alpha]_D^{20}$ = +4.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{13}H_{27}O_3Si$ $[M+H]^+$	259.1724	259.1698

ethyl (*S*,*E*)-4-hydroxypent-2-enoate (10-1)[331]

To a solution of TBS-ether **10** (1.20 g, 4.64 mmol) in dry THF (15 mL) was dropwise added TBAF (5.11 mL, 5.11 mmol, 1.0 M in THF, 1.1 equiv.) at 0 °C and the mixture was stirred for 90 minutes. The reaction was diluted with diethyl ether and consecutively washed with 1 M HCl and brine. After drying ($MgSO_4$), the solvent was removed carefully under reduced pressure and the residue was purified by flash chromatography (silica, pentane/diethyl ether 1:1) to afford alcohol **10-1** (736 mg, 4.60 mmol, contains 10% diethyl ether, 99%) as colorless liquid.

R_f(10-1) = 0.28 (pentane/diethyl ether 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{7,6}$ = 7.1 Hz, 3 H, 7-H), 1.34 (d, $^3J_{1,2}$ = 6.6 Hz, 3 H, 1-H), 1.78 (bs, 1 H, OH), 4.20 (q, $^3J_{6,7}$ = 7.1 Hz, 1 H, 6-H), 4.49 (qdd, $^3J_{2,1}$ = 6.5 Hz, $^3J_{2,3}$ = 4.8 Hz, $^4J_{2,4}$ = 1.6 Hz, 1 H, 2-H), 6.02 (dd, $^3J_{4,3}$ = 15.7 Hz, $^4J_{4,2}$ = 1.7 Hz, 1 H, 4-H), 6.96 (dd, $^3J_{3,4}$ = 15.7 Hz, $^3J_{3,2}$ = 4.7 Hz, 1 H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2 (q, C-7), 22.7 (q, C-1), 60.5 (t, C-6), 67.2 (d, C-2), 119.6 (d, C-4), 150.9 (d, C-3), 166.6 (s, C-5).

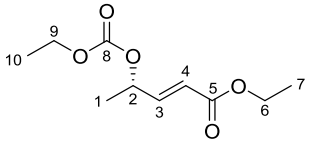
Optical rotation: $[\alpha]_D^{20}$ = +14.2 (c = 1.0, $CHCl_3$)

HRMS (CI): The compound was too volatile to obtain HRMS data.

ethyl (*S*,*E*)-4-((ethoxycarbonyl)oxy)pent-2-enoate (11)[331]

According to **GP-3** alcohol **10-1** (1.60 g, 10.0 mmol) was reacted with ethyl chloroformate (1.15 mL, 12.0 mmol, 1.2 equiv.) and pyridine (1.21 mL, 15.0 mmol, 1.5 equiv.) in dry CH_2Cl_2 (10 mL). Aqueous extraction followed by flash chromatography (silica, pentane/diethyl ether 9:1) afforded carbonate **11** (1.89 g, 8.75 mmol, 88%) as colorless liquid.

R_f(11) = 0.24 (pentane/diethyl ether 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, $^3J_{7,6}$ = 7.2 Hz, 3 H, 7-H), 1.32 (t, $^3J_{10,9}$ = 7.1 Hz, 3 H, 10-H), 1.43 (d, $^3J_{1,2}$ = 6.6 Hz, 3 H, 1-H), 4.20 (q, $^3J_{6,7}$ = 7.2 Hz, 1 H, 6-H), 4.21 (q, $^3J_{9,10}$ = 7.2 Hz, 1 H, 9-H), 5.35 (qdd, $^3J_{2,1}$ = 6.6 Hz, $^3J_{2,3}$ = 5.1 Hz, $^4J_{2,4}$ = 1.5 Hz, 1 H, 2-H), 6.01 (dd, $^3J_{4,3}$ = 15.8 Hz, $^4J_{4,2}$ = 1.6 Hz, 1 H, 4-H), 6.88 (dd, $^3J_{3,4}$ = 15.8 Hz, $^3J_{3,2}$ = 5.1 Hz, 1 H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2 (q, C-7), 14.2 (q, C-10), 19.7 (q, C-1), 60.6 (t, C-6), 64.2 (t, C-9), 72.6 (d, C-2), 121.5 (d, C-4), 145.5 (d, C-3), 154.2 (s, C-8), 166.0 (s, C-5).

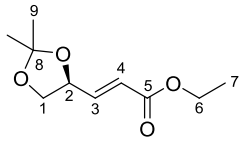
Optical rotation: $[\alpha]_D^{20}$ = −23.1 (c = 1.0, $CHCl_3$)

HRMS (CI): The compound was too volatile to obtain HRMS data.

ethyl (*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (12)[332]

Freshly prepared (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde[389] (3.97 g, 30.5 mmol) was dissolved in water followed by addition of K_2CO_3 (43.1 g, 312 mol, 10.2 equiv.) and triethyl phosphonoacetate (6.66 mL, 33.6 mmol, 1.1 equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight, extracted with CH_2Cl_2 three times and the combined organic layers were washed with brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, PE/EtOAc 9:1) to afford the unsaturated ester **12** (5.30 g, 26.5 mmol, 87%) as a colorless oil.

R_f(12) = 0.19 (PE/EtOAc 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{7,6}$ = 7.1 Hz, 3 H, 7-H), 1.41 (s, 3 H, 9-H), 1.45 (s, 3 H, 9-H'), 3.68 (dd, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1a,2}$ = 7.2 Hz, 1 H, 1-H_a), 4.19 (dd, $^2J_{1b,1a}$ = 8.3 Hz, $^3J_{1b,2}$ = 6.5 Hz, 1 H, 1-H_b), 4.21 (q, $^3J_{6,7}$ = 7.1 Hz, 2 H, 6-H), 4.67 (m, 1 H, 2-H), 6.10 (dd, $^3J_{4,3}$ = 15.6 Hz, $^4J_{4,2}$ = 1.4 Hz, 1 H, 4-H), 6.88 (dd, $^3J_{3,4}$ = 15.6 Hz, $^3J_{3,2}$ = 5.7 Hz, 1 H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2 (q, C-7), 25.7 (q, C-9), 26.4 (q, C-9'), 60.6 (t, C-6), 68.8 (t, C-1), 74.9 (d, C-2), 110.2 (s, C-8), 122.5 (d, C-4), 144.6 (d, C-3), 166.0 (s, C-5).

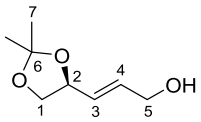
Optical rotation: $[\alpha]_D^{20}$ = +32.6 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{10}H_{17}O_4[M+H]^+$	201.1121	201.1134

(*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (12-1)[390]

To a solution of ester **12** (2.00 g, 9.99 mmol) in dry THF (30 mL) was added Dibal-H (25.0 mL, 25.0 mmol, 1.0 M in hexane, 2.5 equiv.) at –15 °C. After stirring between –15 °C to 0 °C for 2 hours, citric acid (10w%) was added and the mixture was vigorously stirred for 30 minutes. The mixture was extracted three times with CH_2Cl_2, the combined organic layer washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (silica, pentane/diethyl ether 1:1) afforded the alcohol **12-1** (1.49 g, 8.85 mmol, 89%) as a colorless liquid.

R_f(12-1) = 0.16 (pentane/diethyl ether 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, 7-H), 1.44 (s, 3 H, 7-H'), 3.61 (t, $^2J_{1a,1b} = {}^3J_{1a,2}$ = 7.9 Hz, 1 H, 1-H_a), 4.11 (dd, $^2J_{1b,1a}$ = 8.1 Hz, $^3J_{1b,2}$ = 6.2 Hz, 1 H, 1-H_b), 4.18 (dd, $^3J_{5,4}$ = 5.1 Hz, $^4J_{5,3}$ = 1.3 Hz, 2 H, 5-H), 4.54 (q, $^3J_{2,1a/1b/3}$ = 7.3 Hz, 1 H, 2-H), 5.76 (ddt, $^3J_{3,4}$ = 15.5 Hz, $^3J_{3,2}$ = 7.5 Hz, $^4J_{3,5}$ = 1.3 Hz, 1 H, 3-H), 5.91 (dt, $^3J_{4,3}$ = 15.4 Hz, $^3J_{4,5}$ = 5.1 Hz, 1 H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9 (q, C-7), 26.7 (q, C-7'), 62.7 (t, C-5), 69.4 (t, C-1), 76.4 (d, C-2), 109.4 (s, C-6), 128.5 (d, C-3), 133.4 (d, C-4).

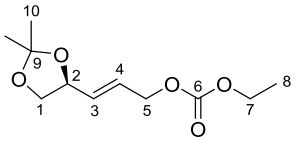
Optical rotation: $[\alpha]_D^{20}$ = +33.0 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_8H_{15}O_3$ $[M+H]^+$	159.1016	159.1013

(*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl ethyl carbonate (13)

According to **GP-3** alcohol **12-1** (720 mg, 4.55 mmol) was reacted with ethyl chloroformate (525 µL, 5.46 mmol, 1.2 equiv.) and pyridine (552 µL, 6.83 mmol, 1.5 equiv.) in dry CH_2Cl_2 (10 mL). Aqueous extraction followed by flash chromatography (silica, pentane/diethyl ether 8:2) afforded carbonate **13** (996 mg, 4.32 mmol, 95%) as colorless oil.

R_f(13) = 0.18 (pentane/diethyl ether 85:15)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, $^3J_{8,7}$ = 7.2 Hz, 3 H, 8-H), 1.39 (s, 3 H, 10-H), 1.43 (s, 3 H, 10-H'), 3.61 (t, $^2J_{1a,1b} = {}^3J_{1a,2}$ = 7.8 Hz, 1 H, 1-H_a), 4.11 (dd, $^2J_{1b,1a}$ = 8.2 Hz, $^3J_{1b,2}$ = 6.2 Hz, 1 H, 1-H_b), 4.20 (q, $^3J_{7,8}$ = 7.1 Hz, 2 H, 7-H), 4.53 (q, $^3J_{2,1a/1b}$ = 6.8 Hz, 1 H, 2-H), 4.63 (m, 2 H, 5-H), 5.80 (dd, $^3J_{3,4}$ = 15.5 Hz, $^3J_{3,2}$ = 6.9 Hz, 1 H, 3-H), 5.91 (dt, $^3J_{4,3}$ = 15.5 Hz, $^3J_{4,5}$ = 5.6 Hz, 1 H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2 (q, C-8), 25.8 (q, C-10), 26.6 (q, C-10'), 64.1 (t, C-7), 67.0 (t, C-5), 69.2 (t, C-1), 76.0 (t, C-5), 109.5 (s, C-9), 127.1 (d, C-4), 132.2 (d, C-3), 154.9 (s, C-6).

Optical rotation: $[\alpha]_D^{20}$ = +27.4 (c = 1.0, $CHCl_3$)

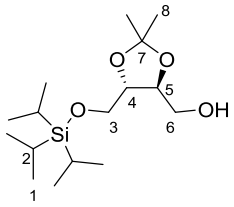
HRMS (CI):	Calculated	Found
$C_{11}H_{19}O_5$ $[M+H]^+$	231.1227	231.1250

((4*S*,5*S*)-2,2-Dimethyl-5-(((triisopropylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)methanol (14)[330]

To a suspension of Sodium hydride (60 w% in mineral oil, 2.40 g, 60.0 mmol, 1.2 equiv.) in THF (250 mL) was added dropwise a solution of 2,3-*O*-isopropylidene-L-threitol[391] (7.50 g,

55.0 mmol, 1.1 equiv.) in THF (25 mL) at 0 °C. The cooling bath was removed, and the reaction stirred at room temperature for one hour. After cooling to 0 °C, a solution of TIPS-Cl (9.84 g, 50.0 mmol) in THF (25 mL) was slowly added and the reaction was stirred for 1 h. The reaction was concentrated *in vacuo*, the residue was dissolved in diethyl ether and water was added. The layers were separated, and the aqueous phase was extracted with diethyl ether twice. The combined organic layers were dried (Na_2SO_4), and the crude product purified by column chromatography (silica, PE/EtOAc 80:20 → 50:50) to yield mono-protected alcohol **14** (15.8 g, 49.6 mmol, 89%) as a colorless oil.

R_f(14) = 0.41 (PE/EtOAc 7:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.10 (m, 21 H, 1-H, 2-H), 1.40 (s, 3 H, 8-H), 1.42 (s, 3 H, 8-H'), 2.40 (dd, $^3J_{OH,6a}$ = 8.3 Hz, $^3J_{OH,6b}$ = 4.4 Hz, 1 H, OH), 3.77 (m, 3 H, 3-H_a, 6-H), 3.91 (td, $^3J_{5,6}$ = 7.6 Hz, $^3J_{5,4}$ = 3.9 Hz, 1 H, 5-H), 3.98 (dd, $^2J_{3b,3a}$ = 9.8 Hz, $^3J_{3b,4}$ = 3.9 Hz, 1 H, 3-H_b), 4.04 (dt, $^3J_{4,3a}$ = 8.0 Hz, $^3J_{4,3b/5}$ = 4.6 Hz, 1 H, 4-H).

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

Optical rotation:	$[\alpha]_D^{20}$ = +15.6 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{16}H_{35}O_4Si$ $[M+H]^+$	319.2299	319.2307

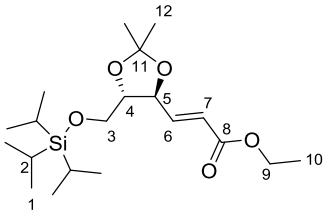
Ethyl (*E*)-3-((4*S*,5*S*)-2,2-dimethyl-5-(((triisopropylsilyl)oxy)methyl)-1,3-di-oxolan-4-yl)acrylate (15)

To a solution of oxalyl chloride (2.10 ml, 24.0 mmol, 1.6 equiv.) in dry DCM (60 mL) was added a solution of DMSO (3.19 ml, 45.0 mmol, 3.0 equiv.) in dry DCM (12 mL) at −70 °C over 30 min. After complete addition, the reaction was stirred for 10 min before a solution of **14** (4.78 g, 15.0 mmol) in dry DCM (15 mL) was added dropwise at −70 °C over 30 min. The reaction was then stirred at −70 °C for 30 min before triethylamine (10.5 ml, 75.0 mmol, 5.0 equiv.) was slowly added at −70 °C. The mixture was stirred at −70 °C for 30 minutes before being warmed to room temperature over one hour. The reaction was diluted with diethyl ether, washed twice with HCl (1 M, aq.) and brine. After drying ($MgSO_4$) the solvent was removed *in vacuo* and the crude aldehyde was used without further purification.

To a solution of the crude aldehyde (4.75 g, 15.0 mmol) in DCM (75 mL) was added triethyl phosphonoacetate (3.60 ml, 18.0 mmol, 1.2 equiv.) and KO*t*-Bu (1.85 g, 16.5 mmol, 1.1 equiv.) at 0 °C. After warming to room temperature overnight, the mixture was washed

with sat. $NaHCO_3$, HCl (1 M, sat. with NaCl) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue purified by column chromatography (silica, PE/EtOAc 96:4) to afford unsaturated ester **15** (5.16 g, 13.4 mmol, 89%) as a colorless oil.

R_f(15) = 0.11 (PE/EtOAc 98:2)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.10 (m, 21 H, 1-H, 2-H), 1.29 (t, $^3J_{10,9}$ = 7.1 Hz, 3 H, 10-H), 1.43 (s, 3 H, 12-H), 1.44 (s, 3 H, 12-H'), 3.83 (m, 2 H, 3-H), 3.95 (q, $^3J_{4,3/5}$ = 6.5 Hz, 1 H, 4-H), 4.20 (q, $^3J_{9,10}$ = 7.1 Hz, 2 H, 9-H), 4.57 (t, $^3J_{5,4/6}$ = 7.5 Hz, 1 H, 5-H), 6.13 (dd, $^3J_{7,6}$ = 15.7 Hz, $^4J_{7,5}$ = 1.5 Hz, 1 H, 7-H), 6.98 (dd, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 5.0 Hz, 1 H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 14.2 (q, C-10), 17.9 (q, C-1), 26.8 (q, C-12), 26.9 (q, C-12'), 60.4 (t, C-9), 63.4 (t, C-3), 78.1 (d, C-5), 80.8 (d, C-4), 109.8 (s, C-11), 121.8 (d, C-7), 144.8 (d, C-6), 166.1 (s, C-8).

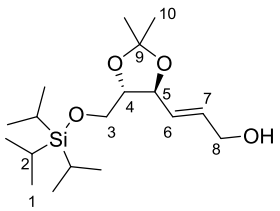
Optical rotation: $[\alpha]_D^{20}$ = −3.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{20}H_{39}O_5Si$ $[M+H]^+$	387.2561	387.2565

(*E*)-3-((4*S*,5*S*)-2,2-Dimethyl-5-(((triisopropylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)prop-2-en-1-ol (15-1)

To a solution of **15** (2.00 g, 5.17 mmol) in dry DCM (15 mL) was dropwise added a solution of Dibal-H (1.0 M in hexane, 11.9 ml, 11,90 mmol, 2.3 equiv.) at −78°C. The solution turned yellow and after 1 min. turned colorless again, which indicates full conversion. After further stirring for 15 min., a solution of sat. Na-K-tartrate was added and the mixture was warmed to room temperature. The mixture was extracted with EtOAc twice, the combined organic layer was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Column chromatography of the crude product (silica, PE/EtOAc 7:3) afforded allylic alcohol **15-1** (1.70 g, 4.93 mmol, 95%) as a colorless oil.

R_f(15-1) = 0.25 (PE/EtOAc 7:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.10 (m, 21 H, 1-H, 2-H), 1.42 (s, 3 H, 10-H), 1.43 (s, 3 H, 10-H'), 1.52 (bs, 1 H, OH), 3.78 (m, 1 H, 4-H), 3.85 (m, 2 H, 3-H), 4.17 (dd, $^3J_{8,7}$ = 5.1 Hz, $^4J_{8,6}$ =

1.4 Hz, 2 H, 8-H), 4.45 (t, $^3J_{5,4/6}$ = 7.5 Hz, 1 H, 5-H), 5.86 (ddt, $^3J_{6,7}$ = 15.5 Hz, $^3J_{6,5}$ = 7.1 Hz, $^4J_{6,8}$ = 1.6 Hz, 1 H, 6-H), 5.94 (dtd, $^3J_{7,6}$ = 15.5 Hz, $^3J_{7,8}$ = 5.1 Hz, $^4J_{7,5}$ = 0.9 Hz, 1 H, 7-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-2), 11.9 (d, C-2'), 17.9 (q, C-1), 17.9 (q, C-1'), 26.9 (q, C-10), 27.1 (q, C-10'), 62.9 (t, C-3/C-8), 62.9 (t, C-3/C-8), 78.6 (d, C-5), 81.4 (d, C-4), 109.0 (s, C-9), 128.5 (d, C-6), 133.2 (d, C-7).

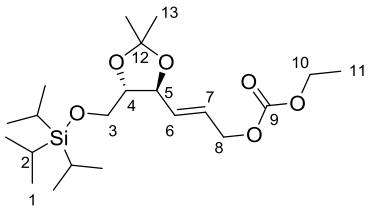
Optical rotation: $[\alpha]_D^{20}$ = −4.5 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{18}H_{37}O_4Si$ $[M+H]^+$	345.2456	345.2469

(*E*)-3-((4*S*,5*S*)-2,2-Dimethyl-5-(((triisopropylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)allyl ethyl carbonate (16)

According to **GP-3**, alcohol **15-1** (1.50 g, 4.35 mmol) in DCM (10 mL) was treated with pyridine (528 μL, 6.53 mmol, 1.5 equiv.) and ethyl chloroformate (502 μL, 5.22 mmol, 1.2 equiv.) at 0 °C. After aqueous work up, the crude residue was purified by column chromatography (silica, PE/EtOAc 92:8) to afford **16** (1.56 g, 3.74 mmol, 86%) as a colorless oil.

R_f(16) = 0.12 (PE/EtOAc 94:6)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.18 (m, 21 H, 1-H, 2-H), 1.31 (t, $^3J_{11,10}$ = 7.1 Hz, 3 H, 11-H), 1.41 (s, 3 H, 13-H), 1.42 (s, 3 H, 13-H'), 3.78 (m, 1 H, 4-H), 3.83 (dd, $^2J_{3a,3b}$ = 10.5 Hz, $^3J_{3a,4}$ = 4.3 Hz, 1 H, 3-H_a), 3.86 (dd, $^2J_{3b,3a}$ = 10.5 Hz, $^3J_{3b,4}$ = 4.2 Hz, 1 H, 3-H_b), 4.20 (q, $^3J_{10,11}$ = 7.1 Hz, 2 H, 10-H), 4.44 (dd, $^3J_{5,4}$ = 7.6 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, 5-H), 4.63 (d, $^3J_{8,7}$ = 5.3 Hz, 2 H, 8-H), 5.86 (dd, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 6.0 Hz, 1 H, 6-H), 5.94 (dt, $^3J_{7,6}$ = 15.7 Hz, $^3J_{7,8}$ = 5.3 Hz, 1 H, 7-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.9 (d, C-2), 14.3 (q, C-11), 17.9 (q, C-1), 26.9 (q, C-13), 27.0 (q, C-13'), 63.0 (t, C-3), 64.0 (t, C-10), 67.1 (t, C-8), 78.3 (d, C-5), 81.3 (d, C-4), 109.2 (s, C-12), 126.6 (d, C-7), 132.2 (d, C-6), 154.9 (s, C-9).

Optical rotation: $[\alpha]_D^{20}$ = −1.7 (c = 1.0, $CHCl_3$)

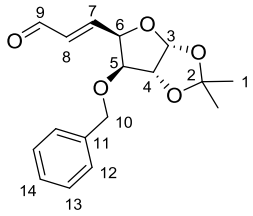
HRMS (CI):	Calculated	Found
$C_{21}H_{40}O_6Si$ $[M+H]^+$	416.2589	416.2586

(*E*)-3-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl) acrylaldehyde (18)

Diol **17**[389] (2.30 g, 7.41 mmol) was added to a biphasic mixture of CH_2Cl_2/water (30 mL, 1:1) and treated with $NaIO_4$ (2.38 g, 11.1 mmol, 1.5 equiv.) in five portions over 20 minutes. After stirring at room temperature for 90 minutes the mixture was filtrated, and the salts washed with CH_2Cl_2 and a small amount of water. The filtrate was extracted three times with CH_2Cl_2, and the combined organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude aldehyde was immediately used without further purification.

To a suspension of 2-(chlorotriphenyl-λ^5-phosphanyl)acetaldehyde (2.69 g, 7.91 mmol, 1.1 equiv.) in dry toluene (35 mL) was added NEt_3 (1.30 ml, 9.34 mmol, 1.3 equiv.) and the resulting orange solution was stirred at room temperature. After 30 minutes a solution of the crude aldehyde (2.00 g, 7.19 mmol) in toluene (10 mL) was added and the mixture was stirred overnight. The mixture was filtrated through a pad of celite, rinsed with EtOAc and the organic layer was concentrated *in vacuo*. Column chromatography (silica, PE/EtOAc 4:1 → 2:1) afforded unsaturated aldehyde **18** (1.81 g, 5.95 mmol, 83%) as a slightly yellow oil.

R_f(18) = 0.42 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, 1-H), 1.50 (s, 3 H, 1-H'), 4.04 (d, $^3J_{5,6}$ = 3.4 Hz, 1 H, 5-H), 4.47 (d, $^2J_{10a,10b}$ = 12.1 Hz, 1 H, 10-H_a), 4.67 (m, 2 H, 4-H, 10-H_b), 4.89 (ddd, $^3J_{6,7}$ = 5.0 Hz, $^3J_{6,5}$ = 3.4 Hz, $^4J_{6,8}$ = 1.5 Hz, 1 H, 6-H), 6.02 (d, $^3J_{3,4}$ = 3.7 Hz, 1 H, 3-H), 6.38 (ddd, $^3J_{8,7}$ = 15.8 Hz, $^3J_{8,9}$ = 7.8 Hz, $^4J_{8,6}$ = 1.5 Hz, 1 H, 8-H), 6.75 (dd, $^3J_{7,8}$ = 15.8 Hz, $^3J_{7,6}$ = 5.1 Hz, 1 H, 7-H), 7.31 (m, 5 H, 12-H, 13-H, 14-H), 9.58 (d, $^3J_{9,8}$ = 7.8 Hz, 1 H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.2 (q, C-1), 26.8 (q, C-1'), 72.2 (t, C-10), 79.4 (d, C-6), 82.5 (d, C-4), 83.1 (d, C-5), 105.1 (d, C-3), 112.1 (s, C-2), 127.8 (d, C-12), 128.2 (d, C-14), 128.6 (d, C-13), 133.4 (d, C-8), 136.9 (s, C-11), 150.1 (d, C-7), 193.0 (d, C-9).

Optical rotation: $[\alpha]_D^{20}$ = −37.1 (c = 1.0, $CHCl_3$)

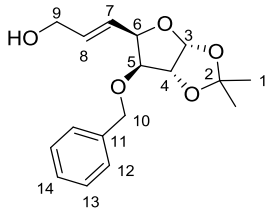
HRMS (CI):	Calculated	Found
$C_{17}H_{21}O_5$ $[M+H]^+$	305.1384	305.1402

(*E*)-3-((3aR,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl) prop-2-en-1-ol (18-1)

To a solution of aldehyde **18** (500 mg, 1.64 mmol) in MeOH (5.0 mL) was added $NaBH_4$ (93.0 mg, 2.46 mmol) at 0 °C and the mixture was stirred until complete conversion was

observed by TLC (2 hours). The reaction was diluted with EtOAc, washed with 1 M NH_4Cl, water and brine and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the crude residue was purified by flash chromatography (silica, PE/EtOAc 2:1 → 1:1) to afford allyl alcohol **18-1** (487 mg, 1.59 mmol, 97%) as a colorless oil.

R_f(18-1) = 0.28 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, 1-H), 1.50 (s, 3 H, 1-H'), 1.84 (bs, 1 H, OH), 3.86 (d, $^3J_{5,6}$ = 3.2 Hz, 1 H, 5-H), 4.15 (d, $^3J_{9,8}$ = 4.8 Hz, 2 H, 9-H), 4.52 (d, $^2J_{10a,10b}$ = 12.1 Hz, 1 H, 10-H_a), 4.64 (m, 3 H, 4-H, 6-H, 10-H_b), 5.88 (ddt, $^3J_{7,8}$ = 15.7 Hz, $^3J_{7,6}$ = 7.1 Hz, $^4J_{7,9}$ = 1.3 Hz, 1 H, 7-H), 5.95 (d, $^3J_{3,4}$ = 3.8 Hz, 1 H, 3-H), 6.00 (dtd, $^3J_{8,7}$ = 15.8 Hz, $^3J_{8,9}$ = 5.1 Hz, $^4J_{8,6}$ = 0.6 Hz, 1 H, 8-H), 7.31 (m, 5 H, 12-H, 13-H, 14-H).

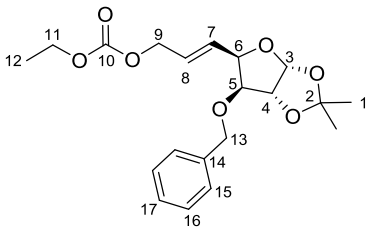
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.1 (q, C-1), 26.7 (q, C-1'), 62.8 (t, C-9), 72.1 (t, C-10), 80.5 (d, C-6), 82.8 (d, C-4), 83.3 (d, C-5), 104.7 (d, C-3), 111.5 (s, C-2), 124.9 (d, C-7), 127.6 (d, C-12), 127.8 (d, C-14), 128.4 (d, C-13), 134.2 (d, C-8), 137.4 (s, C-11).

Optical rotation:	$[\alpha]_D^{20}$ = −66.3 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{17}H_{23}O_5$ $[M+H]^+$	307.1540	307.1521

(*E*)-3-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)allyl ethyl carbonate (19)

According to **GP-3**, alcohol **18-1** (300 mg, 979 µmol) in DCM (2 mL) was treated with pyridine (119 µL, 1.47 mmol, 1.5 equiv.) and ethyl chloroformate (113 µL, 1.18 mmol, 1.2 equiv.) at 0 °C. After aqueous work up, the crude residue was purified by column chromatography (silica, PE/EtOAc 9:1) to afford carbonate **19** (338 mg, 893 µmol, 91%) as a colorless oil.

R_f(19) = 0.18 (PE/EtOAc 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{12,11}$ = 7.1 Hz, 3 H, 12-H), 1.32 (s, 3 H, 1-H), 1.49 (s, 3 H, 1-H'), 3.87 (d, $^3J_{5,6}$ = 3.1 Hz, 1 H, 5-H), 4.19 (q, $^3J_{11,12}$ = 7.1 Hz, 2 H, 11-H), 4.52 (d,

$^{2}J_{13a,13b}$ = 12.1 Hz, 1 H, 13-H_a), 4.65 (m, 5 H, 4-H, 6-H, 9-H, 13-H_b), 5.96 (m, 3 H, 3-H, 7-H, 8-H), 7.32 (m, 5 H, 15-H, 16-H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.3 (q, C-12), 26.2 (q, C-1), 26.8 (q, C-1'), 64.0 (t, C-11), 67.2 (t, C-9), 72.1 (t, C-13), 80.2 (d, C-6), 82.7 (d, C-4), 83.2 (d, C-5), 104.8 (d, C-3), 111.6 (s, C-2), 127.6 (d, C-15), 127.9 (d, C-7/C-8), 127.9 (d, C-17), 128.4 (d, C-16), 128.8 (d, C-7/C-8), 137.4 (s, C-14), 155.0 (s, C-10).

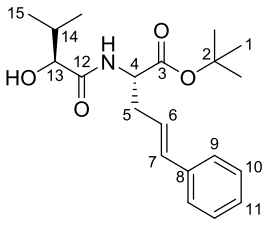
Optical rotation: $[\alpha]_D^{20}$ = −51.8 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{20}H_{27}O_7$ $[M+H]^+$	379.1751	379.1728

***tert*-Butyl (*S*,*E*)-2-((*S*)-2-hydroxy-3-methylbutanamido)-5-phenylpent-4-enoate (20ab)**

According to **GP-4A**, **2b** (67.0 mg, 289 μmol, 1.0 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.1 mg, 5.79 μmol, 2 mol%) and triphenylphosphine (6.8 mg, 26.0 μmol, 9 mol%) were reacted at –78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded (*S*,*S*)-**20ab** (46.2 mg, 133 μmol, 69 %) and (*S*,*R*)-**20bb** (6.8 mg, 20.1 μmol, 10%) separately as off-white solids.

R_f(20ab) = 0.16 (DCM/Et_2O 9:1), **R_f(20bb)** = 0.21 (DCM/Et_2O 9:1)



Main Diastereomer (*S*,*S*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, $^{3}J_{15,14}$ = 6.9 Hz, 3 H, 15-H), 1.00 (d, $^{3}J_{15',14}$ = 6.9 Hz, 3 H, 15-H'), 1.46 (s, 9 H, 1-H), 2.15 (septd, $^{3}J_{14,15}$ = 6.9 Hz, $^{3}J_{14,13}$ = 3.3 Hz, 1 H, 14-H), 2.71 (m, 2 H, 5-H), 3.14 (d, $^{3}J_{OH,13}$ = 3.9 Hz, 1 H, OH), 4.00 (bs, 1 H, 13-H), 4.67 (dt, $^{3}J_{4,NH}$ = 7.8 Hz, $^{3}J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 6.07 (dt, $^{3}J_{6,7}$ = 15.7 Hz, $^{3}J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.44 (d, $^{3}J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 7.15 (d, $^{3}J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.21 (m, 1 H, 11-H), 7.29 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.5 (q, C-15), 19.1 (q, C-15'), 28.0 (q, C-1), 31.8 (d, C-14), 36.2 (t, C-5), 52.0 (d, C-4), 76.2 (d, C-13), 82.5 (s, C-2), 123.7 (d, C-6), 126.1 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 133.9 (d, C-7), 136.8 (s, C-8), 170.9 (s, C-3), 173.1 (s, C-12).

Optical rotation: $[\alpha]_D^{20}$ = +35.5 (c = 1.0, $CHCl_3$)

Melting point: 79−82 °C

HRMS (CI):	Calculated	Found
$C_{20}H_{31}NO_4$ $[M+H]^+$	348.2169	348.2140

Minor Diastereomer (*S*,*R*):

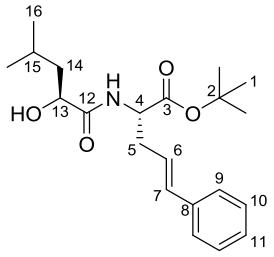
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, $^3J_{15,14}$ = 6.8 Hz, 3 H, 15-H), 1.02 (d, $^3J_{15',14}$ = 7.0 Hz, 3 H, 15-H'), 1.47 (s, 9 H, 1-H), 2.10 (septd, $^3J_{14,15}$ = 6.9 Hz, $^3J_{14,13}$ = 3.3 Hz, 1 H, 14-H), 2.54 (d, $^3J_{OH,13}$ = 5.5 Hz, 1 H, OH), 2.73 (m, 2 H, 5-H), 3.99 (dd, $^3J_{13,OH}$ = 5.4 Hz, $^3J_{13,14}$ = 3.2 Hz, 1 H, 13-H), 4.67 (dt, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.45 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.76 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH), 7.23 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.4 (q, C-15), 19.1 (q, C-15'), 28.0 (q, C-1), 32.1 (d, C-14), 36.1 (t, C-5), 52.1 (d, C-4), 76.0 (d, C-13), 82.4 (s, C-2), 123.7 (d, C-6), 126.1 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 133.8 (d, C-7), 136.8 (s, C-8), 170.6 (s, C-3), 172.9 (s, C-12).

***tert*-Butyl (*S*,*E*)-2-((*S*)-2-hydroxy-4-methylpentanamido)-5-phenylpent-4-enoate (20ac)**

According to **GP-4A**, **2c** (71.0 mg, 289 μmol, 1.0 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.1 mg, 5.79 μmol, 2 mol%) and triphenylphosphine (6.8 mg, 26.0 μmol, 9 mol%) were reacted at –78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded (*S*,*S*)-**20ac** (39.1 mg, 108 μmol, 56%) and (*S*,*R*)-**20bc** (16.0 mg, 44.3 μmol, 23%) separately as colorless resins.

R_f(20ac) = 0.26 (DCM/Et_2O 9:1), **R_f(20bc)** = 0.30 (DCM/Et_2O 9:1)



Main Diastereomer (*S*,*S*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, $^3J_{16,15}$ = 6.5 Hz, 3 H, 16-H), 0.91 (d, $^3J_{16',15}$ = 6.5 Hz, 3 H, 16-H'), 1.46 (s, 9 H, 1-H), 1.53 (m, 2 H, 14-H), 1.82 (m, 1 H, 15-H), 2.64 (m, 1 H, 5-H_a), 2.75 (m, 1 H, 5-H_b), 3.14 (d, $^3J_{OH,13}$ = 4.8 Hz, 1 H, OH), 4.15 (m, 1 H, 13-H), 4.63 (dt, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 6.07 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.4 Hz, 1 H, 6-H), 6.43 (d, $^3J_{7,6}$ = 15.8 Hz, 7-H), 7.14 (d, $^3J_{NH,4}$ = 8.0 Hz, 1 H, NH), 7.26 (m, 5 H, 9-H, 10-H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.3 (q, C-16'), 23.4 (q, C-16), 24.4 (d, C-15), 28.0 (q, C-1), 36.2 (t, C-5), 43.8 (t, C-14), 51.9 (d, C-4), 70.7 (d, C-13), 82.5 (s, C-2), 123.7 (d, C-6), 126.2 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 133.8 (d, C-7), 136.8 (s, C-8), 171.0 (s, C-3), 174.3 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = +41.1 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{21}H_{31}NO_4$ $[M+H]^+$	362.2326	362.2308

Minor Diastereomer (*S*,*R*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $^3J_{16,15}$ = 6.7 Hz, 3 H, 16-H), 0.93 (d, $^3J_{16',15}$ = 6.5 Hz, 3 H, 16-H'), 1.47 (s, 9 H, 1-H), 1.56 (m, 2 H, 14-H), 1.84 (m, 1 H, 15-H), 2.66 (d, $^3J_{OH,13}$ = 5.5 Hz, 1 H, OH), 2.72 (m, 2 H, 5-H), 4.14 (ddd, $^3J_{13,14a}$ = 9.5 Hz, $^3J_{13,OH}$ = 5.4 Hz, $^3J_{13,14b}$ = 3.8 Hz, 1 H, 13-H), 4.63 (dt, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.93 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH), 7.23 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

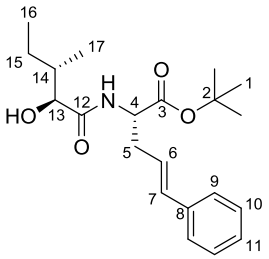
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.3 (q, C-16), 23.4 (q, C-16'), 24.5 (d, C-15), 28.0 (q, C-1), 36.1 (t, C-5), 43.9 (t, C-14), 52.1 (d, C-4), 70.5 (d, C-13), 82.5 (s, C-2), 123.7 (d, C-6), 126.2 (d, C-9), 127.5 (d, C-11), 128.5 (d, C-10), 133.9 (d, C-7), 136.8 (s, C-8), 170.7 (s, C-3), 173.9 (s, C-12).

***tert*-Butyl (*S*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-5-phenylpent-4-enoate (20ad)**

According to **GP-4A**, **1d** (71.0 mg, 289 μmol, 1.0 equiv.) LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.1 mg, 5.79 μmol, 2 mol%) and triphenylphosphine (6.8 mg, 26.0 μmol, 9 mol%) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded **2ad** (50.6 mg, 140 μmol, 72%) and **20bd** (7.0 mg, 19.0 μmol, 10%) separately as colorless oils.

R_f(20ad) = 0.20 (DCM/Et_2O 9:1), **R_f(20bd)** = 0.26 (DCM/Et_2O 9:1)

Main diastereomer (*S*,*S*):



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, $^3J_{16,15}$ = 7.4 Hz, 3 H, 16-H), 0.97 (d, $^3J_{17,14}$ = 7.4 Hz, 3 H, 17-H), 1.16 (m, 1 H, 15-H_a), 1.39 (m, 1 H, 15-H_b), 1.47 (s, 9 H, 1-H), 1.88 (sextd, $^3J_{14,15/17}$ = 6.8 Hz, $^3J_{14,13}$ = 3.9 Hz, 1 H, 14-H), 2.66 (dt, $^2J_{5a,5b}$ = 14.2 Hz, $^3J_{5a,4/6}$ = 7.1 Hz, 1 H, 5-H_a), 2.75 (m, 1 H, 5-H_b), 2.90 (d, $^3J_{OH,13}$ = 5.3 Hz, 1 H, OH), 4.03 (dd, $^3J_{13,OH}$ = 4.8 Hz, $^3J_{13,14}$ = 3.7 Hz, 1 H, 13-H), 4.60 (dt, $^3J_{4,NH}$ = 7.9 Hz, $^3J_{4,5}$ = 6.0 Hz, 1 H, 4-H), 6.07 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.5 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.7 Hz, 1 H, 7-H), 7.11 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.26 (m, 5 H, 9-H, 10-H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-16), 15.5 (q, C-17), 23.0 (t, C-15), 28.0 (q, C-1), 36.1 (t, C-5), 38.6 (d, C-14), 52.0 (d, C-4), 76.3 (d, C-13), 82.4 (s, C-2), 123.8 (d, C-6), 126.1 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 133.8 (d, C-7), 136.8 (s, C-8), 170.9 (s, C-3), 173.0 (s, C-12).

Optical rotation: $[\alpha]_D^{20}$ = +40.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{21}H_{32}NO_4$ $[M+H]^+$	362.2326	362.2341

Minor diastereomer (*S*,*R*):

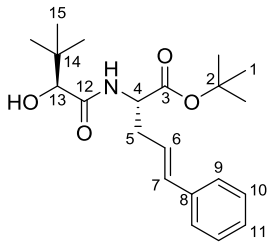
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{16,15}$ = 7.5 Hz, 3 H, 16-H), 0.99 (d, $^3J_{17,14}$ = 6.8 Hz, 3 H, 17-H), 1.20 (m, 1 H, 15-H_a), 1.41 (m, 1 H, 15-H_b), 1.47 (s, 9 H, 1-H), 1.83 (dqt, $^3J_{14,15a}$ = 10.1 Hz, $^3J_{14,17}$ = 6.8 Hz, $^3J_{14,13/15b}$ = 3.6 Hz, 1 H, 14-H), 2.69 (d, $^3J_{OH,13}$ = 5.4 Hz, 1 H, OH), 2.73 (m, 2 H, 5-H), 4.01 (dd, $^3J_{13,OH}$ = 5.3 Hz, $^3J_{13,14}$ = 3.5 Hz, 1 H, 13-H), 4.63 (dt, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.82 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH), 7.23 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-16), 15.4 (q, C-17), 23.1 (t, C-15), 28.0 (q, C-1), 36.1 (t, C-5), 39.1 (d, C-14), 52.2 (d, C-4), 76.1 (d, C-13), 82.5 (s, C-2), 123.7 (d, C-6), 126.2 (d, C-9), 127.5 (d, C-11), 128.5 (d, C-10), 133.9 (d, C-7), 136.8 (s, C-8), 170.6 (s, C-3), 172.8 (s, C-12).

***tert*-Butyl (*S*,*E*)-2-((*S*)-2-hydroxy-3,3-dimethylbutanamido)-5-phenylpent-4-enoate (20ae)**

According to **GP-4A**, **1e** (71.0 mg, 289 μmol, 1.0 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.1 mg, 5.79 μmol, 2 mol%) and triphenylphosphine (6.8 mg, 26.0 μmol, 9 mol%) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 92.5:7.5) afforded **20ae** (43.0 mg, 119 μmol, 61 %) and **20be** (4.1 mg, 11.3 μmol, 5.9%) separately as off-white solids.

R_f(20ae) = 0.16 (DCM/Et_2O 9:1), **R_f(20be)** = 0.22 (DCM/Et_2O 9:1)



Main diastereomer (*S*,*S*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 9 H, 15-H), 1.46 (s, 9 H, 1-H), 2.70 (m, 2 H, 5-H), 3.14 (d, $^3J_{OH,13}$ = 5.5 Hz, 1 H, OH), 3.74 (d, $^3J_{13,OH}$ = 5.5 Hz, 1 H, 13-H), 4.65 (dt, $^3J_{4,NH}$ = 7.6 Hz, $^3J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 6.07 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.45 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.89 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH), 7.25 (m, 5 H, 9-H, 10-H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9 (q, C-15), 28.0 (q, C-1), 35.0 (s, C-14), 36.1 (t, C-5), 52.1 (d, C-4), 79.5 (d, C-13), 82.4 (s, C-2), 123.8 (d, C-6), 126.1 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 133.9 (d, C-7), 136.8 (s, C-8), 170.8 (s, C-3), 172.2 (s, C-12).

Optical rotation: $[\alpha]_D^{20}$ = +21.0 (c = 1.0, $CHCl_3$)

Melting point: 70−72 °C

HRMS (CI):	Calculated	Found
$C_{21}H_{31}NO_4$ $[M]^+$	361.2253	361.2247

Minor diastereomer (*S*,*R*):

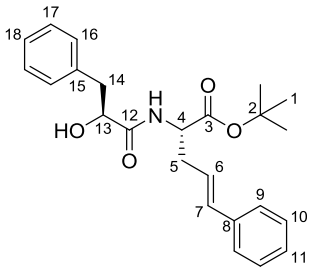
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 9 H, 15-H), 1.47 (s, 9 H, 1-H), 2.68 (m, 1 H, 5-H_a), 2.76 (m, 1 H, 5-H_b), 3.01 (d, $^3J_{OH,13}$ = 5.9 Hz, 1 H, OH), 3.71 (d, $^3J_{13,OH}$ = 6.0 Hz, 1 H, 13-H), 4.65 (dt, $^3J_{4,NH}$ = 7.5 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.45 (d, $^3J_{7,6}$ = 15.7 Hz, 1 H, 7-H), 6.65 (d, $^3J_{NH,4}$ = 7.5 Hz, 1 H, NH), 7.22 (m, 1 H, 11-H), 7.29 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.8 (q, C-15), 28.0 (q, C-1), 35.1 (s, C-14), 36.1 (t, C-5), 52.4 (d, C-4), 79.4 (d, C-13), 82.5 (s, C-2), 123.8 (d, C-6), 126.1 (d, C-9), 127.5 (d, C-11), 128.5 (d, C-10), 134.0 (d, C-7), 136.8 (s, C-8), 170.6 (s, C-3), 172.0 (s, C-12).

***tert*-butyl (*S*,*E*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-5-phenylpent-4-enoate (20af)**

According to **GP-4A**, **2f** (81.0 mg, 289 μmol, 1.0 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.1 mg, 5.79 μmol, 2 mol%) and triphenylphosphine (6.8 mg, 26.0 μmol, 9 mol%) were reacted at –78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded (*S*,*S*)-**20af** (36.9mg, 93.4 μmol, 48%) and (*S*,*R*)-**20bf** (26.8 mg, 67.7 μmol, 35%) separately as off-white solids.

R_f(20af) = 0.23 (DCM/Et_2O 9:1), **R_f(20bf)** = 0.29 (DCM/ Et_2O 9:1)



Main Diastereomer (*S*,*S*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, 1-H), 2.62 (m, 2 H, 5-H), 2.80 (d, $^3J_{OH,13}$ = 4.9 Hz, 1 H, OH), 2.89 (dd, $^2J_{14a,14b}$ = 13.9 Hz, $^3J_{14a,13}$ = 8.0 Hz, 1 H, 14-H_a), 3.17 (dd, $^2J_{14b,14a}$ = 13.9 Hz, $^3J_{14b,13}$ = 4.0 Hz, 1 H, 14-H_b), 4.33 (dt, $^3J_{13,14a}$ = 8.0 Hz, $^3J_{13,14b/OH}$ = 4.0 Hz, 1 H, 13-H), 4.60 (dt, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 5.92 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.5 Hz, 1 H, 6-H), 6.34 (d,

$^{3}J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 7.13 (d, $^{3}J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.25 (m, 10 H, 9-H, 10-H, 11-H, 16-H, 17-H, 18-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.1 (t, C-5), 40.7 (t, C-14), 52.0 (d, C-4), 72.7 (d, C-13), 82.4 (s, C-2), 123.6 (d, C-6), 126.2 (d, C-9), 126.9 (d, C-11/C-18), 127.4 (d, C-11/C-18), 128.5 (d, C-10/C-17), 128.6 (d, C-10/C-17), 129.6 (d, C-16), 133.7 (d, C-7), 136.7 (s, C-15), 136.9 (s, C-8), 170.5 (s, C-3), 172.3 (s, C-12).

Optical rotation: $[\alpha]_D^{20}$ = +47.1 (c = 1.0, $CHCl_3$)

Melting point: 83–85 °C

HRMS (CI):	Calculated	Found
$C_{24}H_{30}NO_4$ $[M+H]^+$	396.2169	396.2186

Minor Diastereomer (*S*,*R*):

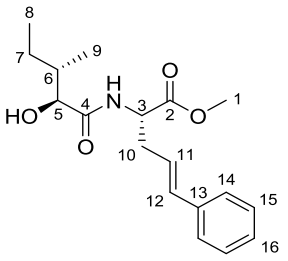
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.53 (d, $^{3}J_{OH,13}$ = 4.8 Hz, 1 H, OH), 2.69 (m, 2 H, 5-H), 2.87 (dd, $^{2}J_{14a,14b}$ = 13.9 Hz, $^{3}J_{14a,13}$ = 8.9 Hz, 1 H, 14-H_a), 3.23 (dd, $^{2}J_{14b,14a}$ = 14.0 Hz, $^{3}J_{14b,13}$ = 4.1 Hz, 1 H, 14-H_b), 4.30 (dt, $^{3}J_{13,14a}$ = 8.9 Hz, $^{3}J_{13,14b/OH}$ = 4.4 Hz, 1 H, 13-H), 4.62 (dt, $^{3}J_{4,NH}$ = 7.9 Hz, $^{3}J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 6.03 (dt, $^{3}J_{6,7}$ = 15.7 Hz, $^{3}J_{6,5}$ = 7.5 Hz, 1 H, 6-H), 6.42 (d, $^{3}J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 7.00 (d, $^{3}J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.26 (m, 10 H, 9-H, 10-H, 11-H, 16-H, 17-H, 18-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.1 (t, C-5), 41.0 (t, C-14), 52.1 (d, C-4), 72.9 (d, C-13), 82.4 (s, C-2), 123.8 (d, C-6), 126.2 (d, C-9), 127.0 (d, C-11/C-18), 127.5 (d, C-11/C-18), 128.5 (d, C-10/C-17), 128.8 (d, C-10/C-17), 129.4 (d, C-16), 133.8 (d, C-7), 136.8 (s, C-15), 136.9 (s, C-8), 170.4 (s, C-3), 172.2 (s, C-12).

methyl (*S*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-5-phenylpent-4-enoate (20ag)

According to **GP-4A**, **4a** (64.4 mg, 311 µmol, 1.0 equiv.), chlorotitanium(IV) triisopropoxide (466 µL, 466 µmol, 1.0 M in hexane, 1.5 equiv.), LHMDS (1.71 mL, 1.71 mmol, 1.0 M in THF, 5.5 equiv.), cinnamyl methyl carbonate (40.0 mg, 208 µmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.2 mg, 6.2 µmol, 2 mol%) and PPh_3 (7.3 mg, 28.0 µmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20ag** (27.0 mg, 85.1 µmol, 41%, 48:52 *dr*) was obtained as a colorless resin.

R_f(20ag) = 0.13 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, $^3J_{8,7}$ = 7.4 Hz, 3 H, 8-H), 0.97 (d, $^3J_{9,6}$ = 7.0 Hz, 3 H, 9-H), 1.16 (m, 1 H, 7-H_a), 1.38 (m, 1 H, 7-H_b), 1.87 (m, 1 H, 6-H), 2.68 (dtd, $^2J_{10a,10b}$ = 14.3 Hz, $^3J_{10a,3/11}$ = 7.2 Hz, $^4J_{10a,12}$ = 1.1 Hz, 1 H, 10-H_a), 2.76 (m, 2 H, 10-H_b, OH), 3.77 (s, 3 H, 1-H), 4.04 (dd, $^3J_{5,OH}$ = 4.4 Hz, $^3J_{5,6}$ = 3.8 Hz, 1 H, 5-H), 4.80 (ddd, $^3J_{3,NH}$ = 8.0 Hz, $^3J_{3,10a}$ = 7.0 Hz, $^3J_{3,10b}$ = 5.4 Hz, 1 H, 3-H), 6.05 (dt, $^3J_{11,12}$ = 15.8 Hz, $^3J_{11,10}$ = 7.3 Hz, 1 H, 11-H), 6.45 (d, $^3J_{12,11}$ = 15.8 Hz, 1 H, 12-H), 7.06 (d, $^3J_{NH,3}$ = 8.0 Hz, 1 H, NH), 7.27 (m, 5 H, 14-H, 15-H, 16-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-8), 15.4 (q, C-9), 23.1 (t, C-7), 35.9 (t, C-10), 38.6 (d, C-6), 51.5 (d, C-3), 52.5 (q, C-1), 76.3 (d, C-5), 123.5 (d, C-11), 126.2 (d, C-14), 127.6 (d, C-16), 128.5 (d, C-15), 134.2 (d, C-12), 136.7 (s, C-13), 170.3 (s, C-2), 173.6 (s, C-4).

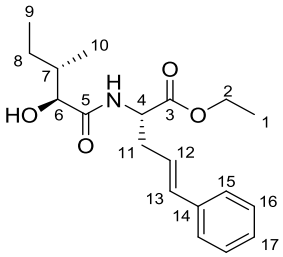
Optical rotation: $[\alpha]_D^{20}$ = +38.7 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{18}H_{26}NO_4$ $[M+H]^+$	320.1856	320.1861

ethyl (*S*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-5-phenylpent-4-enoate (20ah)

According to **GP-4A**, **4b** (64.2 mg, 289 μmol, 1.0 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20ah** (23.1 mg, 69.0 μmol, 36%, 22:78 *dr*) was obtained as a colorless resin.

R_f(20ah) = 0.15 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, $^3J_{9,8}$ = 7.4 Hz, 3 H, 9-H), 0.97 (d, $^3J_{10,7}$ = 7.0 Hz, 3 H, 10-H), 1.17 (m, 1 H, 8-H_a), 1.28 (t, $^3J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 1.38 (m, 1 H, 8-H_b), 1.87 (m, 1 H, 7-H), 2.75 (m, 3 H, 11-H, OH), 4.03 (t, $^3J_{6,7/OH}$ = 3.8 Hz, 1 H, 6-H), 4.20 (dq, $^2J_{2a,2b}$ = 10.8 Hz, $^3J_{2a,1}$ = 7.1 Hz, 1 H, 2-H_a), 4.24 (dq, $^2J_{2b,2a}$ = 10.8 Hz, $^3J_{2b,1}$ = 7.2 Hz, 1 H, 2-H_b), 4.77 (ddd, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,11a}$ = 6.7 Hz, $^3J_{4,11b}$ = 5.5 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{12,13}$ = 15.7 Hz, $^3J_{12,11}$ = 7.3 Hz, 1 H, 12-H), 6.45 (d, $^3J_{13,12}$ = 15.6 Hz, 1 H, 13-H), 7.08 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, NH), 7.27 (m, 5 H, 15-H, 16-H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-9), 14.2 (q, C-1), 15.4 (q, C-10), 23.1 (t, C-8), 36.0 (t, C-11), 38.6 (d, C-7), 51.6 (d, C-4), 61.6 (t, C-2), 76.3 (d, C-6), 123.5 (d, C-12), 126.2 (d, C-15), 127.5 (d, C-17), 128.5 (d, C-16), 134.1 (d, C-13), 136.7 (s, C-14), 171.7 (s, C-3), 173.0 (s, C-5).

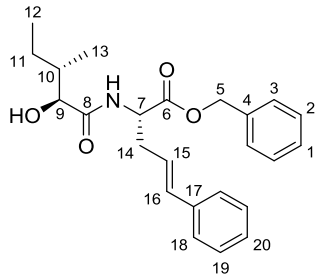
Optical rotation: $[\alpha]_D^{20}$ = +39.7 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{19}H_{28}NO_4$ $[M+H]^+$	334.2013	334.1988

benzyl (*S*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-5-phenylpent-4-enoate (20ai)

According to **GP-4A**, **4c** (81.0 mg, 289 μmol, 1.0 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 95:5), **20ai** (22.4 mg, 56.0 μmol, 29%) was obtained as a colorless resin.

R_f(20ai) = 0.19 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, $^3J_{12,11}$ = 7.5 Hz, 3 H, 12-H), 0.96 (d, $^3J_{13,10}$ = 7.0 Hz, 3 H, 13-H), 1.17 (m, 1 H, 11-H_a), 1.37 (m, 1 H, 11-H_b), 1.86 (dqt, $^3J_{10,11a}$ = 13.4 Hz, $^3J_{10,13}$ = 6.8 Hz, $^3J_{10,9/11b}$ = 3.4 Hz, 1 H, 10-H), 2.72 (m, 2 H, 14-H), 2.80 (d, $^3J_{OH,9}$ = 5.3 Hz, 1 H, OH), 4.03 (dd, $^3J_{9,OH}$ = 5.3 Hz, $^3J_{9,10}$ = 3.4 Hz, 1 H, 9-H), 4.83 (dt, $^3J_{7,NH}$ = 7.6 Hz, $^3J_{7,11}$ = 6.2 Hz, 1 H, 7-H), 5.13 (d, $^2J_{5a,5b}$ = 12.1 Hz, 1 H, 5-H_a), 5.23 (d, $^2J_{5b,5a}$ = 12.1 Hz, 1 H, 5-H_b), 5.97 (dt, $^3J_{15,16}$ = 15.7 Hz, $^3J_{15,14}$ = 7.3 Hz, 1 H, 15-H), 6.39 (d, $^3J_{16,15}$ = 15.8 Hz, 1 H, 16-H), 7.11 (d, $^3J_{NH,7}$ = 7.9 Hz, 1 H, NH), 7.23 (m, 5 H, 18-H, 19-H, 20-H), 7.33 (m, 5 H, 1-H, 2-H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-12), 15.4 (q, C-13), 23.1 (t, C-11), 36.0 (t, C-14), 38.6 (d, C-10), 51.6 (d, C-7), 67.3 (t, C-5), 76.3 (d, C-9), 123.3 (d, C-15), 126.2 (d, C-18), 127.5 (d, C-20), 128.4 (d, C-3), 128.5 (d, C-19), 128.5 (d, C-1), 128.6 (d, C-2), 134.2 (d, C-16), 135.1 (s, C-4), 136.6 (s, C-17), 169.7 (s, C-6), 173.6 (s, C-8).

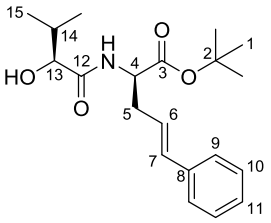
Optical rotation:	$[\alpha]_D^{20}$ = +33.2 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{24}H_{30}NO_4$ $[M+H]^+$	396.2169	396.2170

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3-methylbutanamido)-5-phenylpent-4-enoate (20bb)**

According to **GP-4B**, **2b** (67.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in

THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20bb** (49.2 mg, 142 μmol, 73%, > 99:1 dr) was obtained as a white solid.

R_f(20bb) = 0.17 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, $^3J_{15,14}$ = 6.8 Hz, 3 H, 15-H), 1.02 (d, $^3J_{15',14}$ = 7.0 Hz, 3 H, 15-H'), 1.47 (s, 9 H, 1-H), 2.10 (septd, $^3J_{14,15}$ = 6.9 Hz, $^3J_{14,13}$ = 3.3 Hz, 1 H, 14-H), 2.54 (d, $^3J_{OH,13}$ = 5.5 Hz, 1 H, OH), 2.73 (m, 2 H, 5-H), 3.99 (dd, $^3J_{13,OH}$ = 5.4 Hz, $^3J_{13,14}$ = 3.2 Hz, 1 H, 13-H), 4.67 (dt, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.45 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.76 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH), 7.23 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

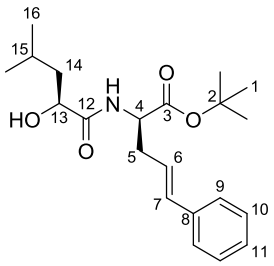
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.4 (q, C-15), 19.1 (q, C-15'), 28.0 (q, C-1), 32.1 (d, C-14), 36.1 (t, C-5), 52.1 (d, C-4), 76.0 (d, C-13), 82.4 (s, C-2), 123.7 (d, C-6), 126.1 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 133.8 (d, C-7), 136.8 (s, C-8), 170.6 (s, C-3), 172.9 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = −72.4 (c = 1.0, $CHCl_3$)	
Melting point:	108−110 °C	
HRMS (CI):	Calculated	Found
$C_{20}H_{30}NO_4$ $[M+H]^+$	348.2169	348.2178

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-4-methylpentanamido)-5-phenylpent-4-enoate (20bc)**

According to **GP-4B**, **2c** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20bc** (54.0 mg, 149 μmol, 77%, > 99:1 dr) was obtained as a colorless oil.

R_f(20bc) = 0.26 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $^3J_{16,15}$ = 6.7 Hz, 3 H, 16-H), 0.93 (d, $^3J_{16',15}$ = 6.5 Hz, 3 H, 16-H'), 1.47 (s, 9 H, 1-H), 1.56 (m, 2 H, 14-H), 1.84 (m, 1 H, 15-H), 2.66 (d, $^3J_{OH,13}$ = 5.5 Hz, 1 H, OH), 2.72 (m, 2 H, 5-H), 4.14 (ddd, $^3J_{13,14a}$ = 9.5 Hz, $^3J_{13,OH}$ = 5.4 Hz, $^3J_{13,14b}$ = 3.8 Hz, 1 H, 13-H), 4.63 (dt, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.93 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH), 7.23 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.3 (q, C-16), 23.4 (q, C-16'), 24.5 (d, C-15), 28.0 (q, C-1), 36.1 (t, C-5), 43.9 (t, C-14), 52.1 (d, C-4), 70.5 (d, C-13), 82.5 (s, C-2), 123.7 (d, C-6), 126.2 (d, C-9), 127.5 (d, C-11), 128.5 (d, C-10), 133.9 (d, C-7), 136.8 (s, C-8), 170.7 (s, C-3), 173.9 (s, C-12).

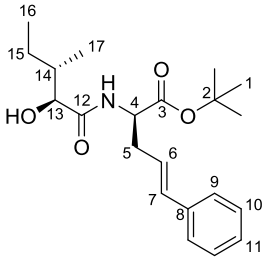
Optical rotation: $[\alpha]_D^{20}$ = −67.5 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{21}H_{31}NO_4$ $[M+H]^+$	362.2326	362.2308

***tert*-butyl (*R*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-5-phenylpent-4-enoate (20bd)**

According to **GP-4B**, **2d** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20bd** (49.8 mg, 138 μmol, 71%, > 99:1 dr) was obtained as an off-white solid.

R_f(20bd) = 0.26 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{16,15}$ = 7.5 Hz, 3 H, 16-H), 0.99 (d, $^3J_{17,14}$ = 6.8 Hz, 3 H, 17-H'), 1.20 (m, 1 H, 15-H_a), 1.41 (m, 1 H, 15-H_b), 1.47 (s, 9 H, 1-H), 1.83 (dqt, $^3J_{14,15a}$ = 10.1 Hz, $^3J_{14,17}$ = 6.8 Hz, $^3J_{14,13/15b}$ = 3.6 Hz, 1 H, 14-H), 2.69 (d, $^3J_{OH,13}$ = 5.4 Hz, 1 H, OH), 2.73 (m, 2 H, 5-H), 4.01 (dd, $^3J_{13,OH}$ = 5.3 Hz, $^3J_{13,14}$ = 3.5 Hz, 1 H, 13-H), 4.63 (dt, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.82 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH), 7.23 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-16), 15.4 (q, C-17), 23.1 (t, C-15), 28.0 (q, C-1), 36.1 (t, C-5), 39.1 (d, C-14), 52.2 (d, C-4), 76.1 (d, C-13), 82.5 (s, C-2), 123.7 (d, C-6), 126.2 (d, C-9), 127.5 (d, C-11), 128.5 (d, C-10), 133.9 (d, C-7), 136.8 (s, C-8), 170.6 (s, C-3), 172.8 (s, C-12).

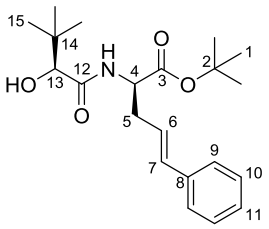
Optical rotation: $[\alpha]_D^{20}$ = −72.4 (c = 1.0, $CHCl_3$)

Melting point:	118−120 °C	
HRMS (CI):	Calculated	Found
$C_{21}H_{32}NO_4$ $[M+H]^+$	362.2326	362.2330

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3,3-dimethylbutanamido)-5-phenylpent-4-enoate (20be)**

According to **GP-4B**, **2e** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20be** (51.0 mg, 141 μmol, 73%, > 99:1 dr) was obtained as off-white solid.

R_f(20be) = 0.26 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 9 H, 15-H), 1.47 (s, 9 H, 1-H), 2.68 (m, 1 H, 5-H_a), 2.76 (m, 1 H, 5-H_b), 3.01 (d, $^3J_{OH,13}$ = 5.9 Hz, 1 H, OH), 3.71 (d, $^3J_{13,OH}$ = 6.0 Hz, 1 H, 13-H), 4.65 (dt, $^3J_{4,NH}$ = 7.5 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.06 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.45 (d, $^3J_{7,6}$ = 15.7 Hz, 1 H, 7-H), 6.65 (d, $^3J_{NH,4}$ = 7.5 Hz, 1 H, NH), 7.22 (m, 1 H, 11-H), 7.29 (m, 4 H, 9-H, 10-H).

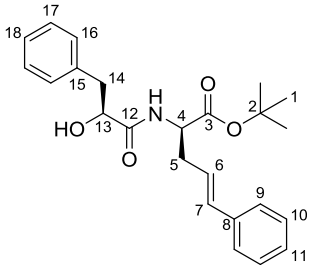
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.8 (q, C-15), 28.0 (q, C-1), 35.1 (s, C-14), 36.1 (t, C-5), 52.4 (d, C-4), 79.4 (d, C-13), 82.5 (s, C-2), 123.8 (d, C-6), 126.1 (d, C-9), 127.5 (d, C-11), 128.5 (d, C-10), 134.0 (d, C-7), 136.8 (s, C-8), 170.6 (s, C-3), 172.0 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = −48.0 (c = 1.0, $CHCl_3$)	
Melting point:	99−101 °C	
HRMS (CI):	Calculated	Found
$C_{21}H_{31}NO_4$ $[M+H]^+$	362.2326	362.2324

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-5-phenylpent-4-enoate (20bf)**

According to **GP-4B**, **2f** (81.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **20bf** (62.9 mg, 159 μmol, 82%, > 99:1 dr) was obtained as an off-white solid.

R_f(20bf) = 0.29 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.53 (d, $^3J_{OH,13}$ = 4.8 Hz, 1 H, OH), 2.69 (m, 2 H, 5-H), 2.87 (dd, $^2J_{14a,14b}$ = 13.9 Hz, $^3J_{14a,13}$ = 8.9 Hz, 1 H, 14-H_a), 3.23 (dd, $^2J_{14b,14a}$ = 14.0 Hz, $^3J_{14b,13}$ = 4.1 Hz, 1 H, 14-H_b), 4.30 (dt, $^3J_{13,14a}$ = 8.9 Hz, $^3J_{13,14b/OH}$ = 4.4 Hz, 1 H, 13-H), 4.62 (dt, $^3J_{4,NH}$ = 7.9 Hz, $^3J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 6.03 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.5 Hz, 1 H, 6-H), 6.42 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 7.00 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.26 (m, 10 H, 9-H, 10-H, 11-H, 16-H, 17-H, 18-H).

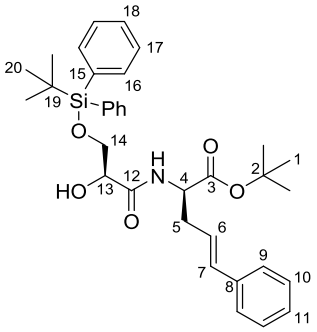
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.1 (t, C-5), 41.0 (t, C-14), 52.1 (d, C-4), 72.9 (d, C-13), 82.4 (s, C-2), 123.8 (d, C-6), 126.2 (d, C-9), 127.0 (d, C-11/C-18), 127.5 (d, C-11/C-18), 128.5 (d, C-10/C-17), 128.8 (d, C-10/C-17), 129.4 (d, C-16), 133.8 (d, C-7), 136.8 (s, C-15), 136.9 (s, C-8), 170.4 (s, C-3), 172.2 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = −85.0 (c = 1.0, $CHCl_3$)	
Melting point:	89−91 °C	
HRMS (CI):	Calculated	Found
$C_{24}H_{30}NO_4$ $[M+H]^+$	396.2169	396.2186

***tert*-butyl (*R*,*E*)-2-((*S*)-3-(4-(benzyloxy)phenyl)-2-hydroxypropanamido)-5-phenylpent-4-enoate (20bh)**

According to **GP-4B**, **2h** (132.0 mg, 289 μmol, 1.0 equiv.), chlorotitanium(IV) triisopropoxide (318 μL, 318 μmol, 1.0 M in hexane, 1.1 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 95:5), **20bh** (59.2 mg, 103 μmol, 53%, > 99:1 dr) was obtained as a colorless resin.

R_f(20bh) = 0.38 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, 20-H), 1.45 (s, 9 H, 1-H), 2.67 (m, 1 H, 5-H_a), 2.76 (m, 1 H, 5-H_b), 3.28 (d, $^3J_{OH,13}$ = 4.8 Hz, 1 H, OH), 3.86 (dd, $^2J_{14a,14b}$ = 10.2 Hz, $^3J_{14a,13}$ = 5.3Hz, 1 H, 14-H_a), 3.92 (dd, $^2J_{14b,14a}$ = 10.3 Hz, $^3J_{14b,13}$ = 5.4 Hz, 1 H, 14-H_b), 4.18 (q, $^3J_{13,14a/14b/OH}$ = 5.1 Hz, 1 H, 13-H), 4.66 (dt, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 6.09 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.43 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 7.23 (m, 5 H, 9-H, 10-H, 11-H), 7.39 (m, 7 H, 17-H,18-H, NH), 7.62 (d, $^3J_{16,17}$ = 6.8 Hz, 4 H, 16-H).

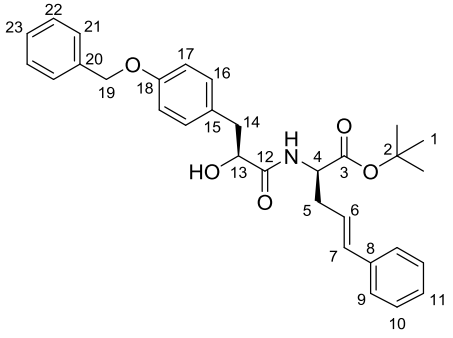
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.2 (s, C-19), 26.8 (q, C-20), 28.0 (q, C-1), 36.3 (t, C-5), 52.2 (d, C-4), 65.1 (t, C-14), 71.7 (d, C-13), 82.3 (s, C-2), 123.8 (d, C-6), 126.2 (d, C-9), 127.4 (d, C-11), 127.8 (d, C-17), 128.5 (d, C-10), 130.0 (d, C-18), 132.4 (s, C-15), 132.7 (s, C-15‘), 133.7 (d, C-7), 135.4 (s, C-16), 135.5 (s, C-16‘), 136.9 (s, C-8), 170.3 (s, C-3), 171.2 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = −74.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{31}H_{35}NO_5$ $[M+H]^+$	574.2983	574.2302

***tert*-butyl (*R*,*E*)-2-((*S*)-3-(4-(benzyloxy)phenyl)-2-hydroxypropanamido)-5-phenylpent-4-enoate (20bi)**

According to **GP-4B**, **2i** (112.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), cinnamyl ethyl carbonate (40.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 95:5), **20bi** (67.3 mg, 134 μmol, 69%, > 99:1 dr) was obtained as a pale-yellow solid.

R_f(20bi) = 0.28 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.39 (d, $^3J_{OH,13}$ = 4.6 Hz, 1 H, OH), 2.69 (m, 2 H, 5-H), 2.83 (dd, $^2J_{14a,14b}$ = 14.1 Hz, $^3J_{14a,13}$ = 8.7 Hz, 1 H, 14-H_a), 3.17 (dd, $^2J_{14b,14a}$ = 14.1 Hz, $^3J_{14b,13}$ = 4.3 Hz, 1 H, 14-H_b), 4.26 (dt, $^3J_{13,14a}$ = 8.7 Hz, $^3J_{13,14b/OH}$ = 4.4 Hz, 1 H, 13-H), 4.63 (dt, $^3J_{4,NH}$ = 7.9 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 5.02 (s, 2 H, 19-H), 6.04 (dt, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.43 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.92 (d, $^3J_{17,16}$ = 8.6 Hz, 2 H, 17-H), 6.96 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.15 (d, $^3J_{16,17}$ = 8.6 Hz, 2 H, 16-H), 7.30 (m, 10 H, 9-H, 10-H, 11-H, 21-H, 22-H, 23-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.1 (t, C-5), 40.1 (t, C-14), 52.1 (d, C-4), 70.0 (t, C-19), 72.9 (d, C-13), 82.4 (s, C-2), 115.2 (d, C-17), 123.8 (d, C-6), 126.2 (d, C-9), 127.4 (d, C-21), 127.5 (d, C-23), 127.9 (d, C-11), 128.5 (d, C-10/C-22), 128.6 (d, C-10/C-22), 128.8 (s, C-15), 130.5 (d, C-16), 133.8 (d, C-7), 136.9 (s, C-8/C-20), 136.9 (s, C-8/C-20), 157.9 (s, C-18), 170.4 (s, C-3), 172.2 (s, C-12).

Optical rotation: $[\alpha]_D^{20}$ = −68.9 (c = 1.0, $CHCl_3$)

Melting point: 109-111 °C

HRMS (CI):	Calculated	Found
$C_{31}H_{35}NO_5$ $[M+H]^+$	501.2510	501.2511

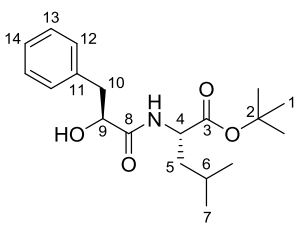
***tert*-butyl ((*S*)-2-hydroxy-3-phenylpropanoyl)-L-leucinate (22)**

Preparation of reference sample: According to **GP-2**, (*S*)-2-hydroxy-3-phenylpropanoic acid (74.3 mg, 447 μmol, 1.0 equiv.), HCl-L-Leu-O*t*-Bu (100 mg, 447 μmol, 1.0 equiv.), HOBt (75.0 mg, 492 μmol, 1.1 equiv.), DIPEA (164 µL, 939 µmol, 2.1 equiv.) and EDC·HCl (94.0 mg, 492 µmol, 1.1 equiv.) were reacted at 0 °C. Column chromatography (silica, PE/EtOAc 2:1) afforded hydroxy acid dipeptide **22** (132 mg, 394 µmol, 88 %) as a white solid.

Preparation of 22a by Allylic Alkylation and Hydrogenation: To a solution of **24** (20.0 mg, 60.0 μmol) in MeOH (1 mL) was added Pd/C (2.0 mg, 10 w%) and the mixture was stirred under an atmosphere of hydrogen (balloon) overnight. After filtration through celite, the solvent was removed *in vacuo* to afford **22a** (20.1 mg, 59.9 μmol, quant.) as a white solid.

For analytical purposes the second diastereomer was equally transformed to the saturated derivative.

R_f(22) = 0.26 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, $^3J_{7,6}$ = 6.2 Hz, 3 H, 7-H), 0.92 (d, $^3J_{7',6}$ = 6.1 Hz, 3 H, 7-H'), 1.46 (s, 9 H, 1-H), 1.52 (m, 3 H, 5-H, 6-H), 2.51 (bs, 1 H, OH), 2.92 (dd, $^2J_{10a,10b}$ = 13.9 Hz,

$^{3}J_{10a,9}$ = 8.1 Hz, 1 H, 10-H_a), 3.22 (dd, $^{2}J_{10b,10a}$ = 13.9 Hz, $^{3}J_{10b,9}$ = 3.9 Hz, 1 H, 10-H_b), 4.35 (dd, $^{3}J_{9,10a}$ = 8.1 Hz, $^{3}J_{9,10b}$ = 3.9 Hz, 1 H, 9-H), 4.48 (td, $^{3}J_{4,5a/NH}$ = 8.7 Hz, $^{3}J_{4,5b}$ = 5.2 Hz, 1 H, 4-H), 6.84 (d, $^{3}J_{NH,4}$ = 8.2 Hz, 1 H, NH), 7.26 (m, 3 H, 12-H, 14-H), 7.32 (m, 2 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.0 (q, C-7), 22.8 (q, C-7'), 24.8 (d, C-6), 28.0 (q, C-1), 40.7 (t, C-10), 41.7 (t, C-5), 50.9 (d, C-4), 72.8 (d, C-9), 81.9 (s, C-2), 126.9 (d, C-14), 128.6 (d, C-13), 129.6 (d, C-12), 136.7 (s, C-11), 172.1 (s, C-3/C-8), 172.2 (s, C-3/C-8).

Optical rotation: $[\alpha]_D^{20}$ = −71.1 (c = 1.0, $CHCl_3$)

Melting point: 99-101 °C

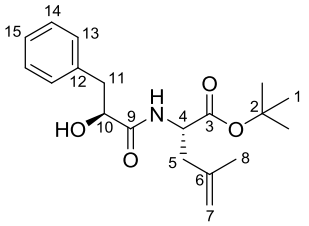
HRMS (CI):	Calculated	Found
$C_{19}H_{30}NO_4$ $[M+H]^+$	336.2169	336.2174

***tert*-butyl (*S*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-4-methylpent-4-enoate (24)**

According to **GP-4A**, **1f** (84.0 mg, 300 μmol), LHMDS (1.65 mL, 1.65 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (450 μL, 450 μmol, 1.0 M in hexane, 1.5 equiv.), carbonate **23a** (29.0 mg, 201 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.2 mg, 6.00 μmol, 2 mol%) and triphenylphosphine (7.1 mg, 27.0 μmol, 9 mol%) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded (*S*,*S*)-**24** (37.1 mg, 111 μmol, 55%) as a white solid and (*S*,*R*)-**24** (13.8 mg, 41.0 μmol, 21%) as a pale yellow solid separately.

R_f((*S*,*S*)-**24)** = 0.18 (DCM/Et_2O 9:1), **R_f(**(*S*,*R*)-**24)** = 0.28 (DCM/Et_2O 9:1)

Main diastereomer (*S*,*S*):



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 1.72 (s, 3 H, 8-H), 2.33 (dd, $^{2}J_{5a,5b}$ = 13.8 Hz, $^{3}J_{5a,4}$ = 8.0 Hz, 1 H, 5-H_a), 2.45 (dd, $^{2}J_{5b,5a}$ = 13.9 Hz, $^{3}J_{5b,4}$ = 6.0 Hz, 1 H, 5-H_b), 2.85 (dd, $^{2}J_{11a,11b}$ = 13.9 Hz, $^{3}J_{11a,10}$ = 8.3 Hz, 1 H, 11-H_a), 2.96 (d, $^{3}J_{OH,10}$ = 4.9 Hz, 1 H, OH), 3.19 (dd, $^{2}J_{11b,11a}$ = 13.9 Hz, $^{3}J_{11b,10}$ = 3.9 Hz, 1 H, 11-H_b), 4.31 (dt, $^{3}J_{10,11a}$ = 8.8 Hz, $^{3}J_{10,11b/OH}$ = 4.2 Hz, 1 H, 10-H), 4.54 (td, $^{3}J_{4,5a/NH}$ = 7.9 Hz, $^{3}J_{4,5b}$ = 6.2 Hz, 1 H, 4 H), 4.66 (s, 1 H, 7-H_a), 4.78 (s, 1 H, 7-H_b), 6.95 (d, $^{3}J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.23 (m, 3 H, 13-H, 15-H), 7.30 (m, 2 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.9 (q, C-8), 27.9 (q, C-1), 40.7 (t, C-5/C-11), 40.8 (t, C-5/C-11), 50.5 (d, C-4), 72.8 (d, C-10), 82.2 (s, C-2), 114.4 (t, C-7), 126.8 (d, C-15), 128.5 (d, C-14), 129.6 (d, C-13), 137.0 (s, C-12), 140.5 (s, C-6), 171.2 (s, C-3), 172.5 (s, C-9).

Optical rotation: $[\alpha]_D^{20}$ = −44.8 (c = 1.0, $CHCl_3$)

Melting point:	79-81 °C	
HRMS (CI):	Calculated	Found
$C_{19}H_{28}NO_4$ $[M+H]^+$	334.2013	334.2015

Minor diastereomer (*S*,*R*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 1.77 (s, 3 H, 8-H), 2.39 (dd, $^2J_{5a,5b}$ = 13.9 Hz, $^3J_{5a,4}$ = 7.9 Hz, 1 H, 5-H_a), 2.45 (d, $^3J_{OH,10}$ = 4.6 Hz, 1 H, OH), 2.52 (dd, $^2J_{5b,5a}$ = 13.9 Hz, $^3J_{5b,4}$ = 6.1 Hz, 1 H, 5-H_b), 2.86 (dd, $^2J_{11a,11b}$ = 14.0 Hz, $^3J_{11a,10}$ = 9.1 Hz, 1 H, 11-H_a), 3.25 (dd, $^2J_{11b,11a}$ = 14.1 Hz, $^3J_{11b,10}$ = 3.8 Hz, 1 H, 11-H_b), 4.29 (dt, $^3J_{10,11a}$ = 9.0 Hz, $^3J_{10,11b/OH}$ = 4.3 Hz, 1 H, 10-H), 4.59 (td, $^3J_{4,5a/NH}$ = 7.9 Hz, $^3J_{4,5b}$ = 6.3 Hz, 1 H, 4 H), 4.73 (s, 1 H, 7-H_a), 4.83 (s, 1 H, 7-H_b), 6.87 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.25 (m, 3 H, 13-H, 15-H), 7.32 (m, 2 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.9 (q, C-8), 28.0 (q, C-1), 40.9 (t, C-5/C-11), 40.9 (t, C-5/C-11), 50.7 (d, C-4), 72.9 (d, C-10), 82.2 (s, C-2), 114.4 (t, C-7), 127.0 (d, C-15), 128.8 (d, C-14), 129.4 (d, C-13), 136.8 (s, C-12), 140.7 (s, C-6), 170.9 (s, C-3), 172.1 (s, C-9).

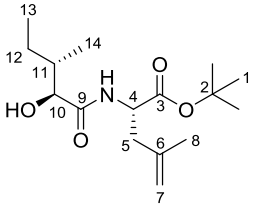
Optical rotation:	$[\alpha]_D^{20}$ = −74.0 (c = 1.0, $CHCl_3$)	
Melting point:	75-77 °C	
HRMS (CI):	Calculated	Found
$C_{19}H_{28}NO_4$ $[M+H]^+$	334.2013	334.2017

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-methylpent-4-enoate (24a)**

According to **GP-4A**, **2d** (71.0 mg, 289 μmol, 1.0 equiv.), LHMDS (1.59 mL, 1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), carbonate **23a** (28.0 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (2.1 mg, 5.79 μmol, 2 mol%) and triphenylphosphine (6.8 mg, 26.0 μmol, 9 mol%) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded (*S*,*S*,*S*)-**24a** (32.4 mg, 108 μmol, 56%) and (*S*,*S*,*R*)-**24a** (5.9 mg, 20.0 μmol, 10%) separately as white solids.

R_f((*S*,*S*,*S*)-**24a)** = 0.12 (DCM/Et_2O 9:1), **R_f(**(*S*,*S*,*R*)-**24a)** = 0.18 (DCM/Et_2O 9:1)

Main diastereomer (*S*,*S*,*S*):



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{13,12}$ = 7.5 Hz, 3 H, 13-H), 0.98 (d, $^3J_{14,11}$ = 7.0 Hz, 3 H, 14-H), 1.21 (m, 1 H, 12-H_a), 1.42 (m, 1 H, 12-H_b), 1.46 (s, 9 H, 1-H), 1.77 (s, 3 H, 8-H), 1.87 (m, 1 H, 11-H), 2.40 (dd, $^2J_{5a,5b}$ = 13.9 Hz, $^3J_{5a,4}$ = 8.3 Hz, 1 H, 5-H_a), 2.75 (dd, $^2J_{5b,5a}$ = 13.9 Hz,

$^3J_{5b,4}$ = 5.9 Hz, 1 H, 5-H_b), 3.18 (d, $^3J_{OH,10}$ = 5.1 Hz, 1 H, OH), 4.03 (t, $^3J_{10,11/OH}$ = 4.0 Hz, 1 H, 10-H), 4.60 (td, $^3J_{4,5a/NH}$ = 8.0 Hz, $^3J_{4,5b}$ = 6.2 Hz, 1 H, 4-H), 4.77 (s, 1 H, 7-H_a), 4.84 (s, 1 H, 7-H_b), 6.93 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-13), 15.4 (q, C-14), 21.7 (q, C-8), 23.1 (t, C-12), 27.9 (q, C-1), 38.6 (d, C-11), 40.8 (t, C-5), 50.5 (d, C-4), 76.2 (d, C-10), 82.3 (s, C-2), 114.4 (t, C-7), 140.6 (s, C-6), 171.6 (s, C-3), 173.1 (s, C-9).

Optical rotation: $[\alpha]_D^{20}$ = −22.1 (c = 1.0, $CHCl_3$)

Melting point: 49−52 °C

HRMS (CI):	Calculated	Found
$C_{16}H_{30}NO_4$ $[M+H]^+$	300.2169	300.2154

Minor diastereomer (*S*,*S*,*R*):

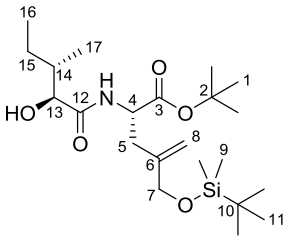
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{13,12}$ = 7.4 Hz, 3 H, 13-H), 1.01 (d, $^3J_{14,11}$ = 7.0 Hz, 3 H, 14-H), 1.21 (m, 1 H, 12-H_a), 1.43 (m, 1 H, 12-H_b), 1.46 (s, 9 H, 1-H), 1.77 (s, 3 H, 8-H), 1.84 (m, 1 H, 11-H), 2.40 (dd, $^2J_{5a,5b}$ = 13.9 Hz, $^3J_{5a,4}$ = 8.4 Hz, 1 H, 5-H_a), 2.55 (m, 2 H, 5-H_b, OH), 4.02 (dd, $^3J_{10,OH}$ = 5.0 Hz, $^3J_{10,11}$ = 3.4 Hz, 1 H, 10-H), 4.63 (td, $^3J_{4,5a/NH}$ = 8.1 Hz, $^3J_{4,5b}$ = 6.0 Hz, 1 H, 4-H), 4.76 (s, 1 H, 7-H_a), 4.84 (s, 1 H, 7-H_b), 6.62 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-13), 15.5 (q, C-14), 21.8 (q, C-8), 23.0 (t, C-12), 28.0 (q, C-1), 39.1 (d, C-11), 40.9 (t, C-5), 50.7 (d, C-4), 76.1 (d, C-10), 82.2 (s, C-2), 114.4 (t, C-7), 140.8 (s, C-6), 171.1 (s, C-3), 172.7 (s, C-9).

tert-butyl (*S*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)pent-4-enoate (24b)

According to **GP-4A**, **1d** (71.0 mg, 289 μmol), LHMDS (1.59 mmol, 1.0 M in THF, 5.5 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 1.0 M in hexane, 1.5 equiv.), carbonate **23b** (53.2 mg, 194 μmol, 0.7 equiv.), allylpalladium chloride dimer (4.2 mg, 11.6 μmol, 4 mol%) and triphenylphosphine (13.7 mg, 52.0 μmol, 18 mol%) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded **24b** (49.1 mg, 114 μmol, 59%, 94:6 *dr*) as a colorless oil.

R_f(24b) = 0.30 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, 9-H), 0.08 (s, 3 H, 9-H'), 0.88 (t, $^3J_{16,15}$ = 7.4 Hz, 3 H, 16-H), 0.92 (s, 9 H, 11-H), 0.99 (d, $^3J_{17,14}$ = 7.0 Hz, 3 H, 17-H), 1.18 (m, 1 H, 15-H_a), 1.41 (m, 1 H, 15-H_b), 1.46 (s, 9 H, 1-H), 1.85 (dqt, $^3J_{14,15a}$ = 13.4 Hz, $^3J_{14,17}$ = 6.8 Hz, $^3J_{14,13/15b}$ =

3.4 Hz, 1 H, 14-H), 2.41 (dd, $^2J_{5a,5b}$ = 14.3 Hz, $^3J_{5a,4}$ = 8.6 Hz, 1 H, 5-H_a), 2.65 (dd, $^2J_{5b,5a}$ = 14.4 Hz, $^3J_{5b,4}$ = 5.2 Hz, 1 H, 5-H_b), 2.81 (d, $^3J_{OH,13}$ = 5.4 Hz, 1 H, OH), 4.00 (dd, $^3J_{13,OH}$ = 5.4 Hz, $^3J_{13,14}$ = 3.7 Hz, 1 H, 13-H), 4.08 (d, $^2J_{7a,7b}$ = 13.8 Hz, 1 H, 7-H_a), 4.16 (d, $^2J_{7b,7a}$ = 13.7 Hz, 1 H, 7-H_b), 4.59 (td, $^3J_{4,NH/5a}$ = 8.2 Hz, $^3J_{4,5b}$ = 5.3 Hz, 1 H, 4-H), 4.90 (m, 1 H, 8-H_a), 5.11 (d, $^2J_{8b,8a}$ = 1.2 Hz, 1 H, 8-H_b), 6.94 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.4 (q, C-9), 11.8 (q, C-16), 15.4 (q, C-17), 18.3 (s, C-10), 23.1 (t, C-15), 25.9 (q, C-11), 28.0 (q, C-1), 35.8 (t, C-5), 38.8 (d, C-14), 51.0 (d, C-4), 65.2 (t, C-7), 76.2 (d, C-13), 82.2 (s, C-2), 113.0 (t, C-8), 143.6 (s, C-6), 171.2 (s, C-3), 173.0 (s, C-12).

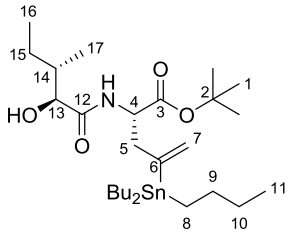
Optical rotation: $[\alpha]_D^{20}$ = −3.3 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{22}H_{44}NO_5Si$ $[M+H]^+$	430.2983	430.2992

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-(tributylstannyl)pent-4-enoate (24ca)**

According to **GP-4A**, **1d** (1.50 g, 6.11 mmol, 1.0 equiv.), chlorotitanium(IV) triisopropoxide (9.17 mL, 9.17 mmol, 1.0 M in hexane, 1.5 equiv.), LHMDS (33.6 mL, 33.6 mmol, 1.0 M in THF, 5.5 equiv.), stannyl carbonate **23c** (1.91 g, 4.10 mmol, 0.7 equiv.), allylpalladium chloride dimer (89.0 mg, 245 µmol, 4 mol%) and triphenylphosphine (289 mg, 1.10 mmol, 18 mol%) in THF (60 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 9:1 + 1 % NEt_3), vinylstannane **24ca** (1.40 g, 2.43 mmol, 59%, 97:3 *dr*) was obtained as a slightly yellow oil.

R_f(24ca) = 0.21 (DCM/Et_2O 9:1 + 1 % NEt_3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{11,10}$ = $^3J_{16,15}$ = 7.4 Hz, 12 H, 11-H, 16-H), 0.96 (m, 9 H, 8-H, 17-H), 1.17 (m, 1 H, 15-H_a), 1.32 (sext, $^3J_{10,9/11}$ = 7.3 Hz, 6 H, 10-H), 1.46 (s, 9 H, 1-H), 1.49 (m, 7 H, 9-H, 15-H_b), 1.85 (m, 1 H, 14-H), 2.48 (dd, $^2J_{5a,5b}$ = 14.1 Hz, $^3J_{5a,4}$ = 9.4 Hz, 1 H, 5-H_a), 2.78 (dd, $^2J_{5b,5a}$ = 14.1 Hz, $^3J_{5b,4}$ = 4.8 Hz, 1 H, 5-H_b), 3.21 (d, $^3J_{OH,13}$ = 5.3 Hz, 1 H, OH), 4.00 (dd, $^3J_{13,OH}$ = 5.3 Hz, $^3J_{13,14}$ = 3.7 Hz, 1 H, 13-H), 4.39 (ddd, $^3J_{4,5a}$ = 9.3 Hz, $^3J_{4,NH}$ = 7.4 Hz, $^3J_{4,5b}$ = 5.0 Hz, 1 H, 4-H), 5.24 (dd, $^3J_{7a,Sn}$ = 59.1 Hz, $^2J_{7a,7b}$ = 2.0 Hz, 1 H, 7-H_a), 5.73 (d, $^3J_{7b,Sn}$ = 128.4 Hz, 1 H, 7-H_b), 6.74 (d, $^3J_{NH,4}$ = 7.3 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 9.6 (dt, $^1J_{8,Sn}$ = 320.0 Hz, C-8), 11.8 (q, C-16), 13.7 (q, C-11), 15.5 (q, C-17), 23.2 (t, C-15), 27.3 (dt, $^3J_{10,Sn}$ = 57.2 Hz, C-10), 28.0 (q, C-1), 29.0 (dt, $^2J_{9,Sn}$ = 20.5 Hz, C-9), 38.6 (d, C-14), 43.9 (dt, $^2J_{5,Sn}$ = 40.4 Hz, C-5), 52.0 (dd, $^3J_{4,Sn}$ = 11.7 Hz, C-4), 76.2

(d, C-13), 82.0 (s, C-2), 128.3 (dt, $^{2}J_{7,Sn}$ = 24.2 Hz, C-7), 150.1 (s, C-6), 171.7 (s, C-3), 173.1 (s, C-12).

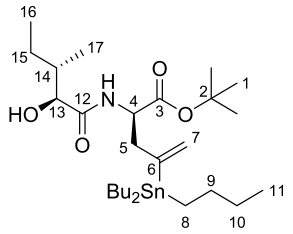
Optical rotation: $[\alpha]_D^{20}$ = −3.5 (c =0.5, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{27}H_{53}NO_4Sn$ $[M]^+$	575.2997	575.2996

***tert*-butyl (*R*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-(tributylstannyl)pent-4-enoate (24cb)**

According to **GP-4B**, **2d** (71.0 mg, 289 μmol, 1.0 equiv.), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 927 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 898 μmol, 3.1 equiv.), carbonate **23c** (81.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg, 11.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in THF (3 mL) were reacted at –78 °C. After column chromatography (silica, DCM/Et_2O 97:3 + 1% NEt_3), **24cb** (76.0 mg, 132 μmol, 68%, > 99:1 dr) was obtained as a slightly yellow oil.

R_f(24cb) = 0.25 (DCM/Et_2O 94:6 + 1% NEt_3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, $^{3}J_{16,15}$ = 7.4 Hz, 3 H, 16-H), 0.89 (t, $^{3}J_{11,10}$ = 7.3 Hz, 9 H, 11-H), 0.96 (m, 9 H, 8-H, 17-H), 1.18 (m, 1 H, 15-H_a), 1.32 (sext, $^{3}J_{10,9/11}$ = 7.3 Hz, 6 H, 10-H), 1.46 (s, 9 H, 1-H), 1.48 (m, 7 H, 9-H, 15-H_b), 1.85 (dqt, $^{3}J_{14,15a}$ = 10.1 Hz, $^{3}J_{14,17}$ = 6.8 Hz, $^{3}J_{14,13/15b}$ = 3.6 Hz, 1 H, 14-H), 2.48 (dd, $^{2}J_{5a,5b}$ = 14.2 Hz, $^{3}J_{5a,4}$ = 9.3 Hz, 1 H, 5-H_a), 2.71 (d, $^{3}J_{OH,13}$ = 5.3 Hz, 1 H, OH), 2.80 (dd, $^{2}J_{5b,5a}$ = 14.1 Hz, $^{3}J_{5b,4}$ = 5.1 Hz, 1 H, 5-H_b), 3.99 (dd, $^{3}J_{13,OH}$ = 5.2 Hz, $^{3}J_{13,14}$ = 3.4 Hz, 1 H, 13-H), 4.39 (ddd, $^{3}J_{4,5a}$ = 9.1 Hz, $^{3}J_{4,NH}$ = 7.9 Hz, $^{3}J_{4,5b}$ = 5.2 Hz, 1 H, 4-H), 5.24 (dd, $^{3}J_{7a,Sn}$ = 58.9Hz, $^{2}J_{7a,7b}$ = 2.2 Hz, 1 H, 7-H_a), 5.73 (dd, $^{3}J_{7b,Sn}$ = 128.3 Hz, $^{2}J_{7b,7a}$ = 0.9 Hz, 1 H, 7-H_b), 6.58 (d, $^{3}J_{NH,4}$ = 7.6 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 9.6 (dt, $^{1}J_{8,Sn}$ = 319.9 Hz, C-8), 11.8 (q, C-16), 13.6 (q, C-11), 15.5 (q, C-17), 22.9 (t, C-15), 27.3 (dt, $^{3}J_{10,Sn}$ = 58.7 Hz, C-10), 28.0 (q, C-1), 29.0 (dt, $^{2}J_{9,Sn}$ = 19.8 Hz, C-9), 39.0 (d, C-14), 43.9 (dt, $^{2}J_{5,Sn}$ = 41.1 Hz, C-5), 52.0 (dd, $^{3}J_{4,Sn}$ = 11.7 Hz, C-4), 76.2 (d, C-13), 81.9 (s, C-2), 128.2 (dt, $^{2}J_{7,Sn}$ = 24.2 Hz, C-7), 150.2 (s, C-6), 171.2 (s, C-3), 172.6 (s, C-12).

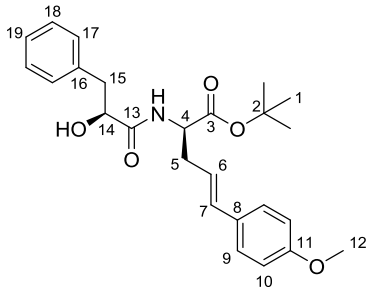
Optical rotation: $[\alpha]_D^{20}$ = −16.5 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{23}H_{44}NO_4Sn$ $[M\text{-}C_4H_9]^+$	518.2287	518.2269

tert-butyl (_R_,_E_)-2-((_S_)-2-hydroxy-3-phenylpropanamido)-5-(4-methoxyphenyl)pent-4-enoate (26a)

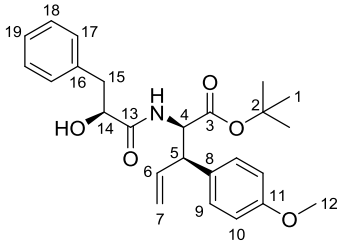
According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), allyl carbonate **25a** (45.9 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded an inseparable mixture of **26a-*l*/*b*** (60.7 mg, 143 μmol, 74%, 71:29 *l*/*b*, 76:24 *dr* branched isomer) as a pale-yellow oil.

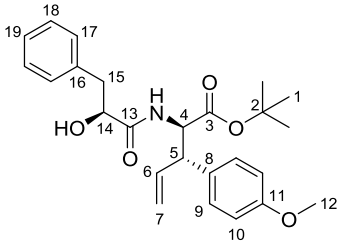
R_f(26a) = 0.25 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 2.57 (d, $^3J_{OH,13}$ = 4.9 Hz, 1 H, OH), 2.63 (m, 1 H, 5-H_a), 2.69 (m, 1 H, 5-H_b), 2.86 (dd, $^2J_{15a,15b}$ = 13.9 Hz, $^3J_{15a,14}$ = 9.0 Hz, 1 H, 15-H_a), 3.23 (dd, $^2J_{15b,15a}$ = 13.9 Hz, $^3J_{15,14}$ = 4.0 Hz, 1 H, 15-H_b), 3.79 (s, 3 H, 12-H), 4.29 (dt, $^3J_{14,15a}$ = 8.9 Hz, $^3J_{14,15b/OH}$ = 4.4 Hz, 1 H, 14-H), 4.60 (dt, $^3J_{4,NH}$ = 7.9 Hz, $^3J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 5.88 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.36 (d, $^3J_{7,6}$ = 15.6 Hz, 1 H, 7-H), 6.83 (d, $^3J_{10,9}$ = 8.7 Hz, 1 H, 10-H), 7.00 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, NH), 7.26 (m, 7 H, 9-H, 17-H, 18-H, 19-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.1 (t, C-5), 41.0 (t, C-15), 52.2 (d, C-4), 55.2 (q, C-12), 72.8 (d, C-14), 82.3 (s, C-2), 113.9 (d, C-10), 121.4 (d, C-6), 127.0 (d, C-19), 127.3 (s, C-8), 128.7 (d, C-9, C-18), 129.4 (d, C-17), 133.2 (d, C-7), 136.8 (s, C-16), 159.0 (s, C-11), 170.5 (s, C-3), 172.2 (s, C-13).





branched diastereomer 1 (selected signals)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 9 H, 1-H), 2.52 (d, $^3J_{OH,13}$ = 4.8 Hz, 1 H, OH), 2.86 (m, 1 H, 15-H_a), 3.22 (m, 1 H, 15-H_b), 3.60 (t, $^3J_{5,4/6}$ = 8.4 Hz, 1 H, 5-H), 3.78 (s, 3 H, 12-H), 4.29 (m, 1 H, 14-H), 4.78 (t, $^3J_{4,5/NH}$ = 8.6 Hz, 1 H, 4-H), 5.11 (m, 2 H, 7-H), 5.99 (m, 1 H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.7 (q, C-1), 40.7 (t, C-15), 52.6 (d, C-4), 56.2 (q, C-12), 72.8 (d, C-14), 82.0 (s, C-2), 113.8 (d, C-10), 117.5 (t, C-7), 129.3 (d, C-9/C-17), 129.7 (d, C-9/C-17), 136.8 (s, C-16), 137.0 (d, C-6), 158.7 (s, C-11), 170.0 (s, C-3), 172.2 (s, C-13).

branched diastereomer 2 (selected signals)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.45 (d, $^{3}J_{OH,13}$ = 4.9 Hz, 1 H, OH), 2.79 (dd, $^{2}J_{15a,15b}$ = 13.9 Hz, $^{3}J_{15a,14}$ = 9.0 Hz, 1 H, 15-H_a), 3.17 (m, 1 H, 15-H_b), 4.21 (dt, $^{3}J_{14,15a}$ = 9.0 Hz, $^{3}J_{14,15b/OH}$ = 4.3 Hz, 1 H, 14-H), 4.86 (dd, $^{3}J_{4,NH}$ = 9.0 Hz, $^{3}J_{4,5}$ = 6.5 Hz, 1 H, 4-H), 5.11 (m, 2 H, 7-H), 5.99 (m, 1 H, 6-H).

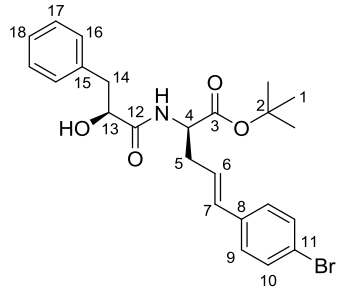
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.9 (q, C-1), 72.8 (d, C-14), 82.3 (s, C-2).

HRMS (CI):	Calculated	Found
$C_{25}H_{32}NO_5$ $[M+H]^+$	426.2275	426.2283

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-5-(4-methoxyphenyl)pent-4-enoate (26c)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), allyl carbonate **25b** (55.4 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in dry THF (3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded an inseparable mixture of **26c-*l*/*b*** (59.4 mg, 124 μmol, 64%, 65:35 *l*/*b*, 83:17 *dr* branched isomer) as a pale-yellow oil.

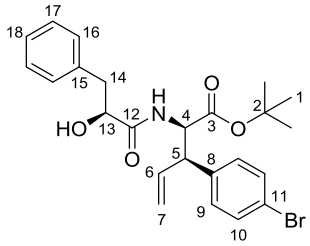
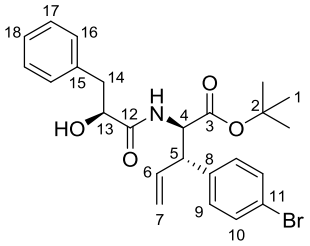
R_f(26c) = 0.27 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 2.54 (d, $^{3}J_{OH,13}$ = 4.9 Hz, 1 H, OH), 2.64 (m, 1 H, 5-H_a), 2.71 (m, 1 H, 5-H_b), 2.87 (dd, $^{2}J_{14a,14b}$ = 13.9 Hz, $^{3}J_{14a,13}$ = 8.9 Hz, 1 H, 14-H_a), 3.23 (dd, $^{2}J_{14b,14a}$ = 13.9 Hz, $^{3}J_{14,13}$ = 4.0 Hz, 1 H, 14-H_b), 4.30 (dt, $^{3}J_{13,14a}$ = 9.0 Hz, $^{3}J_{13,14b/OH}$ = 4.4 Hz, 1 H, 13-H), 4.62 (dt, $^{3}J_{4,NH}$ = 7.9 Hz, $^{3}J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 6.03 (dt, $^{3}J_{6,7}$ = 15.7 Hz, $^{3}J_{6,5}$ = 7.3 Hz, 1 H, 6-H), 6.36 (d, $^{3}J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 7.02 (d, $^{3}J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.16 (d, $^{3}J_{9,10}$ = 8.4 Hz, 2 H, 9-H), 7.25 (m, 3 H, 16-H, 18-H), 7.30 (m, 2 H, 17-H), 7.41 (d, $^{3}J_{10,9}$ = 8.4 Hz, 2 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.2 (t, C-5), 40.9 (t, C-14), 52.0 (d, C-4), 72.9 (d, C-13), 82.5 (s, C-2), 121.2 (d, C-6), 124.8 (s, C-11), 127.1 (d, C-18), 127.7 (d, C-9), 128.8 (d,

C-17), 129.4 (d, C-16), 131.5 (d, C-10), 132.5 (d, C-7), 135.8 (s, C-8), 136.7 (s, C-15), 170.4 (s, C-3), 172.2 (s, C-12).

branched diastereomer 1 (selected signals)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 9 H, 1-H), 2.49 (d, $^3J_{OH,13}$ = 4.8 Hz, 1 H, OH), 2.87 (m, 1 H, 14-H_a), 3.22 (m, 1 H, 14-H_b), 3.63 (t, $^3J_{5,4/6}$ = 8.3 Hz, 1 H, 5-H), 4.29 (m, 1 H, 13-H), 4.80 (t, $^3J_{4,5/NH}$ = 8.4 Hz, 1 H, 4-H), 5.13 (m, 2 H, 7-H), 5.96 (m, 1 H, 6-H), 7.12 (d, $^3J_{10,9}$ = 8.4 Hz, 1 H,).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.7 (q, C-1), 52.7 (d, C-4), 82.4 (s, C-2), 130.0 (d, C-9), 131.6 (d, C-10).

branched diastereomer 2 (selected signals)

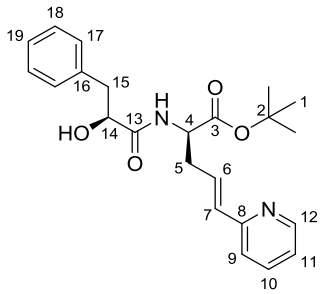
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 1-H), 2.79 (dd, $^2J_{14a,14b}$ = 13.9 Hz, $^3J_{14a,13}$ = 9.0 Hz, 1 H, 14-H_a), 4.21 (dt, $^3J_{13,14a}$ = 8.9 Hz, $^3J_{13,14b/OH}$ = 4.3 Hz, 1 H, 13-H), 4.88 (dd, $^3J_{4,NH}$ = 9.1 Hz, $^3J_{4,5}$ = 6.4 Hz, 1 H, 4-H), 5.13 (m, 2 H, 7-H), 5.96 (m, 1 H, 6-H).

HRMS (CI):	Calculated	Found
$C_{24}H_{29}BrNO_4$ $[M+H]^+$	474.1274	474.1270

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-5-(pyridin-2-yl)pent-4-enoate (27a)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), carbonate **8a** (40.3 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After reversed phase chromatography (C18-silica, H_2O/MeCN 100:0 → 40:60 → 0:100), **27a** (69.0 mg, 174 μmol, 90%, > 99:1 *dr*) was obtained as an off-white solid.

R_f(27a) = 0.10 (DCM/diethyl ether 7:3)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 2.67 (m, 1 H, 5-H_a), 2.76 (m, 1 H, 5-H_b), 2.84 (dd, $^2J_{15a,15b}$ = 13.9 Hz, $^3J_{15a,14}$ = 9.1 Hz, 1 H, 15-H_a), 3.22 (dd, $^2J_{15b,15a}$ = 14.0 Hz, $^3J_{15b,14}$ = 3.6 Hz, 1 H, 15-H_b), 3.84 (bs, 1 H, OH), 4.30 (dd, $^3J_{14,15a}$ = 9.1 Hz, $^3J_{14,15b}$ = 3.8 Hz, 1 H, 14-H), 4.64 (dt, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,5}$ = 6.0 Hz, 1 H, 4-H), 6.48 (m, 2 H, 6-H, 7-H), 7.07 (ddd, $^3J_{11,10}$ = 7.5 Hz, $^3J_{11,12}$ = 5.0 Hz, $^4J_{11,9}$ = 1.1 Hz, 1 H, 11-H), 7.25 (m, 7 H, 9-H, 17-H, 18-H, 19-H, NH), 7.59 (td, $^3J_{10,9/11}$ = 7.7 Hz, $^4J_{10,12}$ = 1.1 Hz, 1 H, 10-H), 8.37 (ddd, $^3J_{12,11}$ = 5.0 Hz, $^4J_{12,10}$ = 1.7 Hz, $^5J_{12,9}$ = 1.0 Hz, 1 H, 12-H).

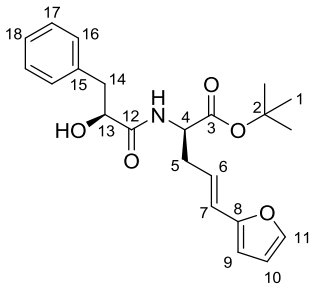
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 35.9 (t, C-5), 40.8 (t, C-15), 51.9 (d, C-4), 72.9 (d, C-14), 82.4 (s, C-2), 121.0 (d, C-9), 122.1 (d, C-11), 126.8 (d, C-19), 128.6 (d, C-18), 129.0 (d, C-6), 129.5 (d, C-17), 133.5 (d, C-7), 136.6 (d, C-10), 137.3 (s, C-16), 149.2 (d, C-12), 155.1 (s, C-8), 170.2 (s, C-3), 172.8 (s, C-13).

Optical rotation:	$[\alpha]_D^{20}$ = −91.2 (c = 1.0, $CHCl_3$)	
Melting point:	124-126 °C	
HRMS (CI):	Calculated	Found
$C_{23}H_{29}N_2O_4$ $[M+H]^+$	397.2122	397.2128

***tert*-butyl (*R*,*E*)-5-(furan-2-yl)-2-((*S*)-2-hydroxy-3-phenylpropanamido)pent-4-enoate (27b)**

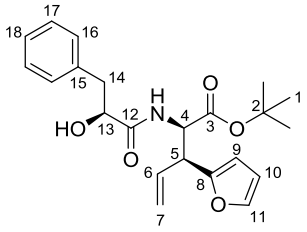
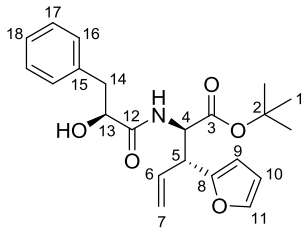
According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **8b** (40.3 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 90:10) afforded an inseparable mixture of **27b-*l*/*b*** (58.0 mg, 150 μmol, 77%, 77/23 *l*/*b*, *ca*. 4/1 *dr* branched product) as a yellow oil.

R_f(27b) = 0.27 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 2.65 (m, 2 H, 5-H), 2.74 (d, $^3J_{OH,13}$ = 6.5 Hz, 1 H, OH), 2.85 (dd, $^2J_{14a,14b}$ = 13.9 Hz, $^3J_{14a,13}$ = 8.9 Hz, 1 H, 14-H_a), 3.22 (dd, $^2J_{14b,14a}$ = 13.9 Hz, $^3J_{14b,13}$ = 3.9 Hz, 1 H, 14-H_b), 4.29 (dt, $^3J_{13,14a}$ = 9.0 Hz, $^3J_{13,14b/OH}$ = 4.4 Hz, 1 H, 13-H), 4.59 (dt, $^3J_{4,NH}$ = 7.9 Hz, $^3J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 5.97 (dt, $^3J_{6,7}$ = 15.7 Hz, $^3J_{6,5}$ = 7.6 Hz, 1 H, 6-H), 6.15 (d, $^3J_{9,10}$ = 3.2 Hz, 1 H, 9-H), 6.22 (d, $^3J_{7,6}$ = 15.7 Hz, 1 H, 7-H), 6.33 (dd, $^3J_{10,9}$ = 3.3 Hz, $^3J_{10,11}$ = 1.8 Hz, 1 H, 10-H), 7.04 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.28 (m, 6 H, 11-H, 16-H, 17-H, 18-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 35.8 (t, C-5), 40.9 (t, C-14), 52.1 (d, C-4), 72.8 (d, C-13), 82.4 (s, C-2), 107.3 (d, C-9), 111.1 (d, C-10), 122.1 (d, C-6/C-7), 122.4 (d, C-6/C-7), 126.9 (d, C-18), 128.7 (d, C-17), 129.4 (d, C-16), 136.9 (s, C-15), 141.8 (d, C-11), 152.3 (s, C-8), 170.3 (s, C-3), 172.3 (s, C-12).

branched diastereomer 1 (selected signals)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, 1-H), 2.70 (m, 1 H, OH), 3.93 (dd, $^{3}J_{5,6}$ = 8.6 Hz, $^{3}J_{5,4}$ = 5.4 Hz, 1 H, 5-H), 4.89 (dd, $^{3}J_{13,14a}$ = 9.0 Hz, $^{3}J_{13,14b}$ = 5.4 Hz, 1 H, 13-H), 5.20 (m, 2 H, 7-H), 5.89 (m, 1 H, 6-H), 6.10 (m, 1-H, 9-H), 6.29 (m, 1 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.9 (q, C-1), 40.8 (t, C-14), 46.4 (d, C-5), 82.5 (s, C-2), 107.0 (d, C-9), 110.2 (d, C-10), 141.9 (d, C-11), 152.3 (s, C-8), 169.2 (s, C-3).

branched diastereomer 2 (selected signals)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 1-H), 2.70 (m, 1 H, OH), 4.03 (dd, $^{3}J_{5,6}$ = 7.5 Hz, $^{3}J_{5,4}$ = 4.5 Hz, 1 H, 5-H), 4.93 (dd, $^{3}J_{13,14a}$ = 9.3 Hz, $^{3}J_{13,14b}$ = 4.8 Hz, 1 H, 13-H), 5.20 (m, 2 H, 7-H)

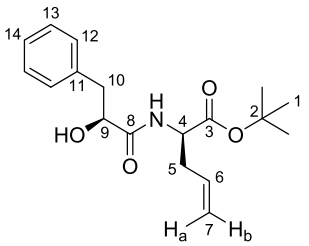
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.8 (q, C-1), 82.3 (s, C-2), 107.5 (d, C-9), 142.0 (d, C-11).

HRMS (CI):	Calculated	Found
$C_{22}H_{28}NO_5$ $[M+H]^+$	386.1962	386.1962

***tert*-butyl (*R*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)pent-4-enoate (29a)**

According to **GP-4B**, **2f** (81.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), allyl ethyl carbonate (25.3 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 95:5), **29a** (47.0 mg, 147 μmol, 76%, > 99:1 dr) was obtained as a colorless oil.

R_f(29a) = 0.35 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.52 (m, 2 H, 5-H), 2.81 (m, 1 H, OH), 2.85 (dd, $^2J_{10a,10b}$ = 13.9 Hz, $^3J_{10a,9}$ = 9.1 Hz, 1 H, 10-H_a), 3.23 (dd, $^2J_{10b,10a}$ = 13.9 Hz, $^3J_{10b,9}$ = 3.9 Hz, 1 H, 10-H_b), 4.29 (dt, $^3J_{9,10a}$ = 9.1 Hz, $^3J_{9,10b/OH}$ = 4.3 Hz, 1 H, 9-H), 4.54 (dt, $^3J_{4,NH}$ = 8.1 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 5.10 (m, 2 H, 7-H), 5.66 (ddt, $^3J_{6,7a}$ = 8.1 Hz, $^3J_{6,7b}$ = 5.8 Hz, $^3J_{6,5}$ = 8.1 Hz, 1 H, 6-H), 7.02 (d, $^3J_{NH,4}$ = 8.0 Hz, 1 H, NH), 7.25 (m, 3 H, 12-H, 14-H), 7.31 (m, 2 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 36.6 (t, C-5), 40.9 (t, C-10), 51.7 (d, C-4), 72.9 (d, C-9), 82.3 (s, C-2), 118.9 (t, C-7), 126.9 (d, C-14), 128.7 (d, C-13), 129.4 (d, C-12), 132.2 (d, C-6), 136.9 (s, C-11), 170.4 (s, C-3), 172.3 (s, C-8).

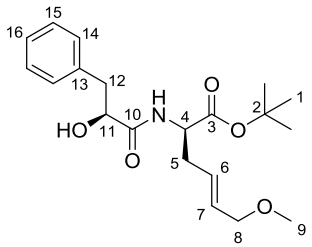
Optical rotation: $[\alpha]_D^{20}$ = −86.1 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{18}H_{26}NO_4$ $[M+H]^+$	320.1856	320.1874

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-6-methoxyhex-4-enoate (31b)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (304 μL, 304 μmol, 1.0 M in hexane, 1.05 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), carbonate **30b** (33.8 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 8:2), **31b** (49.0 mg, 135 μmol, 69%, > 99:1 *dr*) was obtained as a colorless oil.

R_f(3bj) = 0.15 (DCM/diethyl ether 8:2)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 2.48 (dt, $^2J_{5a,5b}$ = 14.1 Hz, $^3J_{5a,4/6}$ = 6.6 Hz, 1 H, 5-H_a), 2.58 (m, 1 H, 5-H_b), 2.82 (d, $^3J_{OH,11}$ = 4.8 Hz, 1 H, OH), 2.85 (dd, $^2J_{12a,12b}$ = 14.0 Hz, $^3J_{12a,11}$ = 9.1 Hz, 1 H, 12-H_a), 3.22 (dd, $^2J_{12b,12a}$ = 14.0 Hz, $^3J_{12b,11}$ = 3.9 Hz, 1 H, 12-H_b), 3.28 (s, 3 H, 9-H), 3.83 (d, $^3J_{8,7}$ = 5.4 Hz, 2 H, 8-H), 4.29 (dt, $^3J_{11,12a}$ = 8.9 Hz, $^3J_{11,12b/OH}$ = 4.3 Hz, 1 H, 11-H), 4.54 (dt, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 5.57 (m, 2 H, 6-H, 7-H), 6.98 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.25 (m, 3 H, 14-H, 16-H), 7.32 (m, 2 H, 15-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 35.2 (t, C-5), 40.9 (t, C-12), 51.8 (d, C-4), 57.8 (q, C-9), 72.6 (t, C-8), 72.9 (d, C-11), 82.3 (s, C-2), 126.9 (d, C-16), 127.6 (d, C-6), 128.7 (d, C-15), 129.4 (d, C-14), 130.8 (d, C-7), 137.0 (s, C-13), 170.3 (s, C-3), 172.4 (s, C-10).

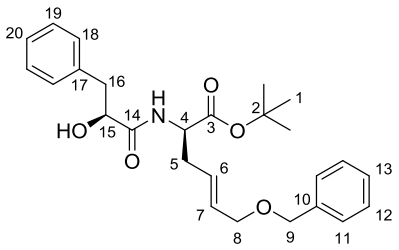
Optical rotation: $[\alpha]_D^{20}$ = −82.4 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{20}H_{30}NO_5$ $[M+H]^+$	364.2118	364.2126

***tert*-butyl (*R*,*E*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-6-methoxyhex-4-enoate (31c)**

According to **GP-4B**, **2f** (162.0 mg, 580 μmol), chlorotitanium(IV) triisopropoxide (870 μL, 870 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (265 μL, 1.86 mmol, 3.2 equiv.), *n*-BuLi (719 μL, 1.80 mmol, 2.5 M in hexane, 3.1 equiv.), carbonate **30c** (97.0 mg, 389 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (8.5 mg, 23.1 μmol, 4 mol%) and PPh_3 (27.4 mg, 104 μmol, 18 mol%) in THF (6 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 8:2), **31c** (127 mg, 289 μmol, 74%, 85:15 *dr*) was obtained as a colorless oil.

R_f(31c) = 0.31 (DCM/diethyl ether 8:2)



Main diastereomer (*S*,*R*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 1-H), 2.48 (m, 1 H, 5-H_a), 2.58 (m, 1 H, 5-H_b), 2.82 (m, 1 H, OH), 2.83 (dd, $^2J_{16a,16b}$ = 13.9 Hz, $^3J_{16a,15}$ = 9.1 Hz, 1 H, 16-H_a), 3.20 (dd, $^2J_{16b,16a}$ = 13.9 Hz, $^3J_{16b,15}$ = 3.9 Hz, 1 H, 16-H_b), 3.93 (d, $^2J_{8,7}$ = 5.6 Hz, 2 H, 8-H), 4.25 (dt, $^3J_{15,16a}$ = 9.0 Hz, $^3J_{15,16b/OH}$ = 4.3 Hz, 1 H, 15-H), 4.46 (s, 2 H, 9-H), 4.53 (dt, $^3J_{4,NH}$ = 8.0 Hz, $^3J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 5.55 (dt, $^3J_{6,7}$ = 15.4 Hz, $^3J_{6,5}$ = 7.0 Hz, 1 H, 6-H), 5.65 (dt, $^3J_{7,6}$ = 15.4 Hz, $^3J_{7,8}$ = 5.7 Hz, 1 H, 7-H), 7.00 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.27 (m, 10 H, 11-H, 12-H, 13-H, 18-H, 19-H, 20-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 35.2 (t, C-5), 40.8 (t, C-16), 51.8 (d, C-4), 70.2 (t, C-8), 72.0 (t, C-9), 72.9 (d, C-15), 82.3 (s, C-2), 126.9 (d, C-20), 127.6 (d, C-6), 127.6 (d, C-11), 127.7 (d, C-13), 128.3 (d, C-12), 128.6 (d, C-19), 129.4 (d, C-18), 130.8 (d, C-7), 137.0 (s, C-17), 138.1 (s, C-10), 170.3 (s, C-3), 172.4 (s, C-14).

Minor diastereomer (*S*,*S*) (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, 1-H), 2.48 (m, 2 H, 5-H), 2.83 (m, 2 H, OH, 16-H_a), 2.87 (m, 2 H, OH, 16-H_a), 3.18 (dd, $^2J_{16b,16a}$ = 13.8 Hz, $^3J_{16b,15}$ = 3.8 Hz, 1 H, 16-H_b), 3.91 (m, 2 H, 8-H), 4.29 (m, 1 H, 15-H), 4.46 (s, 2 H, 9-H), 4.49 (m, 1 H, 4-H), 5.44 (dt, $^3J_{16a,16n}$ = 15.4 Hz, $^3J_{16a,15}$ = 7.0 Hz, 1 H, ..), 5.55 (m, 1 H, ..), 7.09 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.27 (m, 10 H, 11-H, 12-H, 13-H, 18-H, 19-H, 20-H).

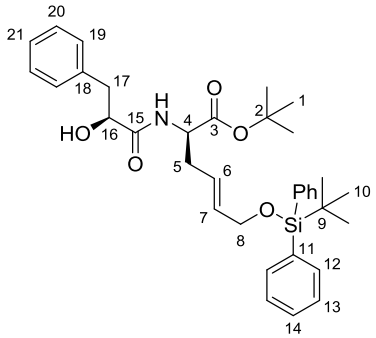
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.9 (q, C-1), 35.2 (t, C-5), 40.7 (t, C-16), 51.7 (d, C-4), 70.1 (t, C-8), 71.9 (t, C-9), 72.7 (d, C-15), 82.3 (s, C-2), 127.5 (d, C-6), 128.3 (d, C-12), C, 128.5 (d, C-19), 129.6 (d, C-18), 130.8 (d, C-7), 136.8 (s, C-17), 138.1 (s, C-10), 170.4 (s, C-3/C-14), 170.5 (s, C-3/C-14).

HRMS (CI):	Calculated	Found
$C_{26}H_{34}NO_5$ $[M+H]^+$	440.2431	440.2437

***tert*-butyl (*R*,*E*)-6-((*tert*-butyldiphenylsilyl)oxy)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-hex-4-enoate (31d)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **30d** (77.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.9 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 98:2 → 93:7), **31d** (97.1 mg, 165 μmol, 85%, > 99:1 *dr*) was obtained as a colorless oil.

R_f(31d) = 0.53 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, 10-H), 1.45 (s, 9 H, 1-H), 2.54 (m, 3 H, 5-H, OH), 2.84 (dd, $^2J_{17a,17b}$ = 13.9 Hz, $^3J_{17a,16}$ = 9.1 Hz, 1 H, 17-H_a), 3.22 (dd, $^2J_{17b,17a}$ = 13.9 Hz, $^3J_{17b,16}$ = 3.8 Hz, 1 H, 17-H_b), 4.12 (m, 2 H, 8-H), 4.26 (dt, $^3J_{16,17a}$ = 9.1Hz, $^3J_{16,17b/OH}$ = 4.3 Hz, 1 H, 16-H), 4.54 (dt, $^3J_{4,5a}$ = 7.9Hz, $^3J_{4,5b/NH}$ = 5.5 Hz, 1 H, 4-H), 5.60 (m, 2 H, 6-H, 7-H), 6.97 (d, $^3J_{NH,4}$ = 5.5 Hz, 1 H, NH), 7.23 (m, 3 H, 19-H, 21-H), 7.30 (m, 2 H, 20-H), 7.39 (m, 6 H, 12-H/13-H, 14-H), 7.65 (m, 4 H, 12-H/13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.2 (s, C-9), 26.7 (q, C-10), 28.0 (q, C-1), 35.0 (t, C-5), 40.9 (t, C-17), 51.9 (d, C-4), 64.0 (t, C-8), 72.9 (d, C-16), 82.2 (s, C-2), 123.7 (d, C-6), 126.9 (d, C-21), 127.6 (d, C-12/C-13), 128.7 (d, C-20), 129.4 (d, C-19), 129.6 (d, C-12/C-13), 133.4 (d, C-7), 133.5 (d, C-14), 135.5 (s, C-11), 136.9 (s, C-18), 170.4 (s, C-3), 172.2 (s, C-15).

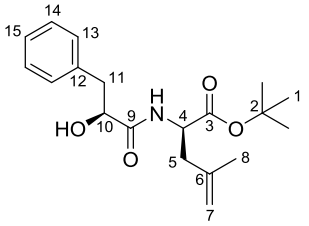
Optical rotation:	$[\alpha]_D^{20}$ = −57.5 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{35}H_{46}NO_5Si$ $[M+H]^+$	588.3140	588.3131

***tert*-butyl (*R*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-4-methylpent-4-enoate (34a)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **23a** (28.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg,11.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in THF

(3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 470:30) afforded **34a** (48.1 mg, 144 μmol, 74%, > 99:1 dr) as a colorless oil.

R_f(34a) = 0.21 (DCM/diethyl ether 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 1-H), 1.77 (s, 3 H, 8-H), 2.39 (dd, $^2J_{5a,5b}$ = 13.9 Hz, $^3J_{5a,4}$ = 7.9 Hz, 1 H, 5-H_a), 2.45 (d, $^3J_{OH,10}$ = 4.6 Hz, 1 H, OH), 2.52 (dd, $^2J_{5b,5a}$ = 13.9 Hz, $^3J_{5b,4}$ = 6.1 Hz, 1 H, 5-H_b), 2.86 (dd, $^2J_{11a,11b}$ = 14.0 Hz, $^3J_{11a,10}$ = 9.1 Hz, 1 H, 11-H_a), 3.25 (dd, $^2J_{11b,11a}$ = 14.1 Hz, $^3J_{11b,10}$ = 3.8 Hz, 1 H, 11-H_b), 4.29 (dt, $^3J_{10,11a}$ = 9.0 Hz, $^3J_{10,11b/OH}$ = 4.3 Hz, 1 H, 10-H), 4.59 (td, $^3J_{4,5a/NH}$ = 7.9 Hz, $^3J_{4,5b}$ = 6.3 Hz, 1 H, 4 H), 4.73 (s, 1 H, 7-H_a), 4.83 (s, 1 H, 7-H_b), 6.87 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.25 (m, 3 H, 13-H, 15-H), 7.32 (m, 2 H, 14-H).

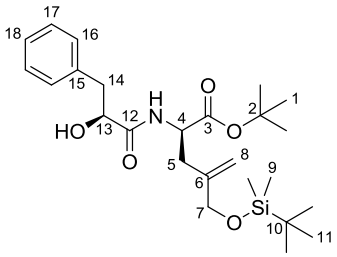
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.9 (q, C-8), 28.0 (q, C-1), 40.9 (t, C-5/C-11), 40.9 (t, C-5/C-11), 50.7 (d, C-4), 72.9 (d, C-10), 82.2 (s, C-2), 114.4 (t, C-7), 127.0 (d, C-15), 128.8 (d, C-14), 129.4 (d, C-13), 136.8 (s, C-12), 140.7 (s, C-6), 170.9 (s, C-3), 172.1 (s, C-9).

Optical rotation:	$[\alpha]_D^{20}$ = −74.0 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{19}H_{28}NO_4$ $[M+H]^+$	334.2013	334.2017

***tert*-butyl (*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-((*S*)-2-hydroxy-3-phenylpropanamido)pent-4-enoate (34b)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **23b** (53.3 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg,11.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 95:5), **34b** (69.0 mg, 149 μmol, 77%, > 99:1 dr) was obtained as a colorless oil.

R_f(34b) = 0.34 (DCM/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, 9-H), 0.08 (s, 3 H, 9-H'), 0.91 (s, 9 H, 11-H), 1.46 (s, 9 H, 1-H), 2.37 (dd, $^2J_{5a,5b}$ = 14.3 Hz, $^3J_{5a,4}$ = 8.4 Hz, 1 H, 5-H_a), 2.63 (dd, $^2J_{5b,5a}$ = 14.3 Hz, $^3J_{5b,4}$ = 5.5 Hz, 1 H, 5-H_b), 2.77 (d, $^3J_{OH,13}$ = 4.8 Hz, 1 H, OH), 2.84 (dd, $^2J_{14a,14b}$ = 14.0 Hz, $^3J_{14a,13}$ = 9.1 Hz, 1 H, 14-H_a), 3.23 (dd, $^3J_{14b,14a}$ = 13.9 Hz, $^3J_{14b,13}$ = 3.7 Hz, 1 H, 14-H_b), 4.06 (d, $^2J_{7a,7b}$ = 13.7 Hz, 1 H, 7-H_a), 4.14 (d, $^2J_{7b,7a}$ = 13.8 Hz, 1 H, 7-H_b), 4.26 (dt, $^3J_{13,14a}$ = 9.0 Hz, $^3J_{13,14b/OH}$ = 4.3 Hz, 1 H, 13-H), 4.57 (td, $^3J_{4,NH/5a}$ = 8.3 Hz, $^3J_{4,5b}$ = 5.5 Hz, 1 H, 4-H), 4.88 (m, 1 H, 8-H_a), 5.10 (d, $^2J_{8a,8b}$ = 1.5 Hz, 1 H, 8-H_b), 7.02 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, NH), 7.24 (m, 3 H, 16-H, 18-H), 7.30 (m, 2 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.4 (q, C-9), 18.3 (s, C-10), 25.9 (q, C-11), 28.0 (q, C-1), 35.8 (t, C-5), 40.9 (t, C-14), 50.9 (d, C-4), 65.3 (t, C-7), 72.8 (d, C-13), 82.1 (s, C-2), 113.0 (t, C-8), 127.0 (d, C-18), 128.7 (d, C-17), 129.4 (d, C-16), 136.9 (s, C-15), 143.6 (s, C-6), 170.9 (s, C-3), 172.3 (s, C-12).

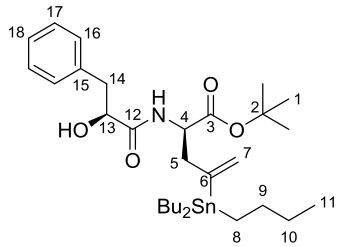
Optical rotation: $[\alpha]_D^{20}$ = −36.5 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{25}H_{42}NO_5Si$ $[M+H]^+$	463.2731	463.2749

***tert*-butyl (*R*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-4-(tributylstannyl)pent-4-enoate (34c)**

According to **GP-4B**, **2f** (1.00 g, 3.58 mmol), chlorotitanium(IV) triisopropoxide (5.37 mL, 5.37 mmol, 1.0 M in hexane, 1.5 equiv.), DIPA (1.63 mL, 11.5 mmol, 3.2 equiv.), *n*-BuLi (4.44 mL, 11.1 mmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **23c** (1.12 g, 2.40 mmol, 0.7 equiv.), $[AllylPdCl]_2$ (52.0 mg, 143 µmol, 4 mol%) and PPh_3 (169 mg, 644 µmol, 18 mol%) in THF (36 mL) were reacted at −78 °C. Column chromatography (silica, PE/DCM/Et_2O 5/5/1 + 1% NEt_3) afforded **34c** (979 mg, 1.61 mmol, 67%, > 99:1 *dr*) as a colorless oil.

R_f(34c) = 0.47 (PE/DCM/Et_2O 5/5/2 + 1% NEt_3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{11,10}$ = 7.3 Hz, 9 H, 11-H), 0.98 (m, 6 H, 8-H), 1.32 (sext, $^3J_{10,9/11}$ = 7.3 Hz, 6 H, 10-H), 1.46 (s, 9 H, 1-H), 1.50 (m, 6 H, 9-H), 2.46 (m, 1 H, OH), 2.48 (dd, $^2J_{5a,5b}$ = 14.0 Hz, $^3J_{5a,4}$ = 9.1 Hz, 1 H, 5-H_a), 2.78 (dd, $^2J_{5b,5a}$ = 14.1 Hz, $^3J_{5b,4}$ = 5.3 Hz, 1 H, 5-H_b), 2.86 (dd, $^2J_{14a,14b}$ = 14.0 Hz, $^3J_{14a,13}$ = 9.2 Hz, 1 H, 14-H_a), 3.26 (dd, $^2J_{14b,14a}$ = 14.0 Hz, $^3J_{14b,13}$ = 3.7 Hz, 1 H, 14-H_b), 4.26 (dd, $^3J_{13,14a}$ = 9.2 Hz, $^3J_{13,14b}$ = 3.7 Hz, 1 H, 13-H), 4.41 (ddd, $^3J_{4,5a}$ = 8.8 Hz, $^3J_{4,NH}$ = 7.8 Hz, $^3J_{4,5b}$ = 5.4 Hz, 1 H, 4-H), 5.24 (dd, $^3J_{7a,Sn}$ = 58.2 Hz, $^2J_{7a,7b}$ = 2.1 Hz, 1 H, 7-H_a), 5.73 (d, $^3J_{7b,Sn}$ = 128.1 Hz, 1 H, 7-H_b), 6.74 (d, $^3J_{NH,4}$ = 7.5 Hz, 1 H, NH), 7.25 (m, 3 H, 16-H, 18-H), 7.32 (m, 2 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 9.6 (dt, $^1J_{8,Sn}$ = 320.0 Hz, C-8), 13.7 (q, C-11), 27.3 (dt, $^3J_{10,Sn}$ = 58.0 Hz, C-10), 28.0 (q, C-1), 29.0 (dt, $^2J_{9,Sn}$ = 19.8 Hz, C-9), 40.9 (t, C-14), 43.9 (dt, $^2J_{5,Sn}$ = 40.4 Hz, C-5), 52.1 (dd, $^3J_{4,Sn}$ = 11.0 Hz, C-4), 72.9 (d, C-13), 81.9 (s, C-2), 127.0 (d, C-18), 128.4 (dt, $^2J_{7,Sn}$ = 24.2 Hz, C-7), 128.8 (d, C-17), 129.5 (d, C-16), 136.9 (s, C-15), 150.0 (s, C-6), 171.0 (s, C-3), 172.1 (s, C-12).

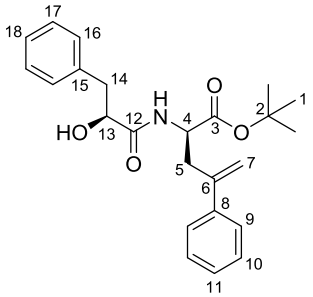
Optical rotation: $[\alpha]_D^{20}$ = −49.2 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{30}H_{52}NO_4Sn$ $[M+H]^+$	610.2913	610.2912

***tert*-butyl (*R*)-2-((*S*)-2-hydroxy-3-phenylpropanamido)-4-phenylpent-4-enoate (34d)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **23d** (40.1 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg,11.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in THF (3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 92:8) afforded **34d** (63.9 mg, 162 μmol, 83%, > 99:1 dr) as a colorless oil.

R_f(34d) = 0.14 (DCM/diethyl ether 94:6)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, 1-H), 1.98 (d, $^3J_{OH,13}$ = 5.9 Hz, 1 H, OH), 2.74 (dd, $^2J_{14a,14b}$ = 14.0 Hz, $^3J_{14a,13}$ = 9.2 Hz, 1 H, 14-H_a), 2.93 (dd, $^2J_{5a,5b}$ = 14.2 Hz, $^3J_{5a,4}$ = 6.2 Hz, 1 H, 5-H_a), 3.09 (m, 1 H, 5-H_b), 3.12 (dd, $^2J_{14b,14a}$ = 13.8 Hz, $^3J_{14b,13}$ = 3.6 Hz, 1 H, 14-H_b), 4.07 (dt, $^3J_{13,14a}$ = 9.3 Hz, $^3J_{13,14b/OH}$ = 4.7 Hz, 1 H, 13-H), 4.65 (dt, $^3J_{4,NH}$ = 7.7 Hz, $^3J_{4,5}$ = 6.3 Hz, 1 H, 4-H), 5.11 (m, 1 H, 7-H_a), 5.32 (d, $^2J_{7b,7a}$ = 1.3 Hz, 1 H, 7-H_b), 6.82 (d, $^3J_{NH,4}$ = 7.7 Hz, 1 H, NH), 7.20 (m, 2 H, 9-H), 7.29 (m, 6 H, 10-H, 11-H, 17-H, 18-H), 7.39 (m, 2 H, 16-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 37.9 (t, C-5), 40.6 (t, C-14), 51.9 (d, C-4), 73.0 (d, C-13), 82.3 (s, C-2), 116.4 (t, C-7), 126.4 (d, C-9), 126.9 (d, C-18), 127.7 (d, C-11), 128.4 (d, C-10), 128.6 (d, C-17), 129.4 (d, C-16), 137.0 (s, C-15), 140.7 (s, C-8), 144.1 (s, C-6), 170.3 (s, C-3), 171.9 (s, C-12).

Optical rotation: $[\alpha]_D^{20}$ = −82.7 (c = 1.0, $CHCl_3$)

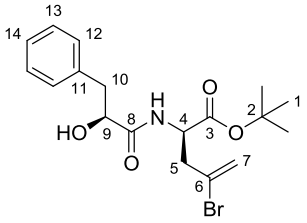
HRMS (CI):	Calculated	Found
$C_{24}H_{29}NO_4$ $[M]^+$	395.2091	395.2095

***tert*-butyl (*R*)-4-bromo-2-((*S*)-2-hydroxy-3-phenylpropanamido)pent-4-enoate (34e)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (435 μL, 435 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), 2-bromoallyl ethyl carbonate (40.6 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg, 10.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in THF (3 mL) were reacted at –78 °C. The reaction was hydrolyzed at −50 °C and after work up and column chromatography (silica, DCM/Et_2O 9:1) (*S*,*R*)-**34e** (66.5 g, 167 μmol, 86%) and (*S*,*S*)-**34e** (7.5 mg, 19.0 μmol, 9.7 %) were obtained as pale-yellow solids.

R_f((*S*,*R*)-34e) = 0.33 (DCM/Et_2O 9:1), **R_f((*S*,*S*)-34e)** = 0.25 (DCM/Et_2O 9:1)

Main diastereomer (*S*,*R*):



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, 1-H), 2.70 (d, $^3J_{OH,9}$ = 4.8 Hz, 1 H, OH), 2.86 (m, 2 H, 5-H_a, 10-H_a), 2.97 (dd, $^2J_{5b,5a}$ = 14.8 Hz, $^3J_{5b,4}$ = 5.8 Hz, 1 H, 5-H_b), 3.25 (dd, $^2J_{10b,10a}$ = 13.9 Hz, $^3J_{10b,9}$ = 3.7 Hz, 1 H, 10-H_b), 4.30 (dt, $^3J_{9,10a}$ = 9.0 Hz, $^3J_{9,10b/OH}$ = 4.3 Hz, 1 H, 9-H), 4.67 (td, $^3J_{4,5a/NH}$ = 7.0 Hz, $^3J_{4,5b}$ = 6.0 Hz, 1 H, 4-H), 5.51 (d, $^2J_{7a,7b}$ = 1.7 Hz, 1 H, 7-H_a), 5.63 (m, 1 H, 7-H_b), 7.01 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.26 (m, 3 H, 12-H, 14-H), 7.33 (m, 2 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 40.8 (t, C-10), 43.3 (t, C-5), 51.1 (d, C-4), 72.8 (d, C-9), 82.8 (s, C-2), 120.4 (s, C-6), 127.0 (d, C-14), 128.0 (t, C-7), 128.7 (d, C-13), 129.4 (d, C-12), 136.9 (s, C-11), 169.6 (s, C-3), 172.4 (s, C-8).

Optical rotation:	$[\alpha]_D^{20}$ = −59.0 (c = 1.0, $CHCl_3$)	
Melting point:	83−85 °C	
HRMS (CI):	Calculated	Found
$C_{18}H_{26}NO_4Br$ $[M+2H]^+$	399.1040	399.1036

Minor Diastereomer (*S*,*S*):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, 1-H), 2.59 (d, $^3J_{OH,9}$ = 4.8 Hz, 1 H, OH), 2.84 (ddd, $^2J_{5a,5b}$ = 14.8 Hz, $^3J_{5a,4}$ = 6.9 Hz, $^4J_{5a,7}$ = 0.7 Hz, 1 H, 5-H_a), 2.88 (dd, $^2J_{10a,10b}$ = 13.9 Hz, $^3J_{10a,9}$ = 8.4 Hz, 1 H, 10-H_a), 2.93 (ddd, $^2J_{5b,5a}$ = 14.8 Hz, $^3J_{5b,4}$ = 5.8 Hz, $^4J_{5b,7a/7b}$ = 0.6 H, 1 H, 5-H_b), 3.23 (dd, $^2J_{10b,10a}$ = 13.9 Hz, $^3J_{10b,9}$ = 3.9 Hz, 1 H, 10-H_b), 4.34 (dt, $^3J_{9,10a}$ = 8.5 Hz, $^3J_{9,10b/OH}$ = 4.2 Hz, 1 H, 9-H), 4.69 (ddd, $^3J_{4,NH}$ = 7.9 Hz, $^3J_{4,5a}$ = 6.7 Hz, $^3J_{4,5b}$ = 5.9 H, 1 H, 4-H), 5.48 (d, $^2J_{7a,7b}$ = 1.7 Hz, 1 H, 7-H_a), 5.56 (m, 1 H, 7-H_b), 7.01 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.26 (m, 3 H, 12-H, 14-H), 7.32 (m, 2 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-1), 40.8 (t, C-10), 43.3 (t, C-5), 50.9 (d, C-4), 72.9 (d, C-9), 82.9 (s, C-2), 120.4 (s, C-6), 127.0 (d, C-14), 127.8 (t, C-7), 128.7 (d, C-13), 129.6 (d, C-12), 136.7 (s, C-11), 169.8 (s, C-3), 172.3 (s, C-8).

Optical rotation: $[\alpha]_D^{20}$ = −28.8 (c = 1.0, $CHCl_3$)

Melting point: 82−84 °C

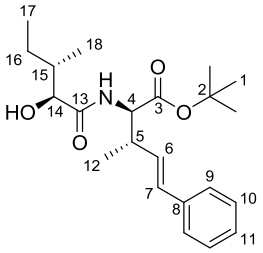
HRMS (CI):	Calculated	Found
$C_{18}H_{26}NO_4Br$ $[M+2H]^+$	399.1040	399.1019

***tert*-butyl (2*R*,3*S*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-3-methyl-5-phenylpent-4-enoate (36a)**

According to **GP-4B**, **2d** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), carbonate (*S*,*E*)-**35** (42.7 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 9:1), the diastereomers (*R*,*S*,*S*,*S*)-**36a** (46.0 mg, 123 μmol, 63%) and (*S*,*S*,*S*,*S*)-**36a** (10.1 mg, 27.0 mmol, 14%) were separately obtained as white solids (56.1 mg, 149 μmol, 77%, 82:18 *dr* overall).

R_f((*R*,*S*,*S*,*S*)-**36a)** = 0.20 (DCM/Et_2O 9:1), **R_f(**(*S*,*S*,*S*,*S*)-**36a)** = 0.14 (DCM/Et_2O 9:1)

Main diastereomer (*R*,*S*,*S*,*S*)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{17,16}$ = 7.4 Hz, 3 H, 17-H), 0.99 (d, $^3J_{18,15}$ = 7.0 Hz, 3 H, 18-H), 1.17 (d, $^3J_{12,5}$ = 6.9 Hz, 3 H, 12-H), 1.20 (m, 1 H, 16-H_a), 1.39 (m, 1 H, 16-H_b), 1.44 (s, 9 H, 1-H), 1.83 (dqt, $^3J_{15,16a}$ = 10.0 Hz, $^3J_{15,18}$ = 6.8 Hz, $^3J_{15,14/16b}$ = 3.2 Hz, 1 H, 15-H), 2.82 (sext, $^3J_{5,4/6/12}$ = 6.9 Hz, 1 H, 5-H), 2.96 (d, $^3J_{OH,14}$ = 5.4 Hz, 1 H, OH), 4.02 (dd, $^3J_{14,OH}$ = 5.2 Hz, $^3J_{14,15}$ = 3.4 Hz, 1 H, 14-H), 4.60 (dd, $^3J_{4,NH}$ = 8.9 Hz, $^3J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 6.10 (dd, $^3J_{6,7}$ = 15.9 Hz, $^3J_{6,5}$ = 7.9 Hz, 1 H, 6-H), 6.39 (d, $^3J_{7,6}$ = 15.9 Hz, 1 H, 7-H), 6.86 (d, $^3J_{NH,4}$ = 8.9 Hz, 1 H, NH), 7.21 (m, 1 H, 11-H), 7.29 (m, 4 H, 9-H, 10-H).

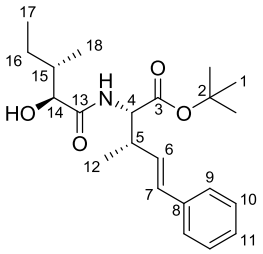
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-17), 15.5 (q, C-18), 16.2 (q, C-12), 23.0 (t, C-16), 28.0 (q, C-1), 39.1 (d, C-15), 40.6 (d, C-5), 56.4 (d, C-4), 76.1 (d, C-14), 82.4 (s, C-2), 126.2 (d, C-9), 127.3 (d, C-11), 128.5 (d, C-10), 130.4 (d, C-6), 131.0 (d, C-7), 136.9 (s, C-8), 170.2 (s, C-3), 173.0 (s, C-13).

Optical rotation: $[\alpha]_D^{20}$ = −81.3 (c = 1.0, $CHCl_3$)

Melting point: 119−121 °C

HRMS (CI):	Calculated	Found
$C_{22}H_{34}NO_4$ $[M+H]^+$	376.2482	376.2485

Minor diastereomer (*S*,*S*,*S*,*S*)



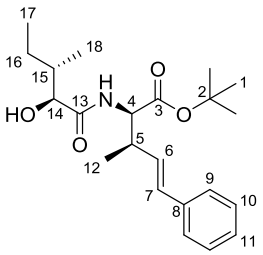
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, $^3J_{17,16}$ = 7.4 Hz, 3 H, 17-H), 0.98 (d, $^3J_{18,15}$ = 7.0 Hz, 3 H, 18-H), 1.17 (d, $^3J_{12,5}$ = 6.9 Hz, 3 H, 12-H), 1.21 (m, 1 H, 16-H_a), 1.42 (m, 1 H, 16-H_b), 1.47 (s, 9 H, 1-H), 1.88 (sextd, $^3J_{15,16/18}$ = 6.8 Hz, $^3J_{15,14}$ = 4.0 Hz, 1 H, 15-H), 2.72 (d, $^3J_{OH,14}$ = 5.3 Hz, 1 H, OH), 2.95 (m, 1 H, 5-H), 4.04 (dd, $^3J_{14,OH}$ = 5.0 Hz, $^3J_{14,15}$ = 3.7 Hz, 1 H, 14-H), 4.60 (dd, $^3J_{4,NH}$ = 8.8 Hz, $^3J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 6.08 (dd, $^3J_{6,7}$ = 15.9 Hz, $^3J_{6,5}$ = 7.8 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.9 Hz, 1 H, 7-H), 6.96 (d, $^3J_{NH,4}$ = 8.8 Hz, 1 H, NH), 7.22 (m, 1 H, 11-H), 7.30 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-17), 15.4 (q, C-18), 16.6 (q, C-12), 23.2 (t, C-16), 28.1 (q, C-1), 38.7 (d, C-15), 40.0 (d, C-5), 56.6 (d, C-4), 76.4 (d, C-14), 82.4 (s, C-2), 126.2 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 129.8 (d, C-6), 131.5 (d, C-7), 136.9 (s, C-8), 170.5 (s, C-3), 173.1 (s, C-13).

tert-butyl (2*R*,3*R*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-3-methyl-5-phenylpent-4-enoate (36b)

According to **GP-4B**, **2d** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (359 μL, 897 μmol, 2.5 M in hexane, 3.1 equiv.), carbonate (*R*,*E*)-**35** (42.7 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **36b** (59.3 mg, 158 μmol, 81%, > 99:1 dr) was obtained as a white solid.

R_f(36b) = 0.24 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{17,16}$ = 7.5 Hz, 3 H, 17-H), 0.99 (d, $^3J_{18,15}$ = 7.0 Hz, 3 H, 18-H), 1.16 (d, $^3J_{12,5}$ = 6.8 Hz, 3 H, 12-H), 1.22 (m, 1 H, 16-H_a), 1.40 (m, 1 H, 16-H_b), 1.46 (s, 9 H, 1-H), 1.88 (m, 1 H, 15-H), 2.95 (m, 1 H, 5-H), 3.01 (d, $^3J_{OH,14}$ = 5.3 Hz, 1 H, OH), 4.02 (dd,

$^3J_{14,OH}$ = 5.0 Hz, $^3J_{14,15}$ = 3.4 Hz, 1 H, 14-H), 4.60 (dd, $^3J_{4,NH}$ = 8.7 Hz, $^3J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 6.08 (dd, $^3J_{6,7}$ = 15.9 Hz, $^3J_{6,5}$ = 7.8 Hz, 1 H, 6-H), 6.44 (d, $^3J_{7,6}$ = 15.9 Hz, 1 H, 7-H), 6.86 (d, $^3J_{NH,4}$ = 8.7 Hz, 1 H, NH), 7.21 (m, 1 H, 11-H), 7.27 (m, 4 H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-17), 15.5 (q, C-18), 16.5 (q, C-12), 23.1 (t, C-16), 28.0 (q, C-1), 39.0 (d, C-15), 40.0 (d, C-5), 56.7 (d, C-4), 76.1 (d, C-14), 82.3 (s, C-2), 126.1 (d, C-9), 127.4 (d, C-11), 128.5 (d, C-10), 129.7 (d, C-6), 131.4 (d, C-7), 136.8 (s, C-8), 170.2 (s, C-3), 173.2 (s, C-13).

Optical rotation: $[\alpha]_D^{20}$ = −24.0 (c = 1.0, $CHCl_3$)

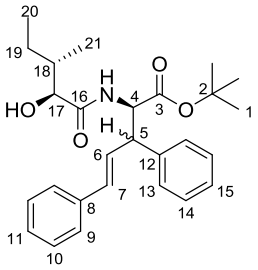
Melting point: 128−129 °C

HRMS (CI):	Calculated	Found
$C_{22}H_{34}NO_4$ $[M+H]^+$	376.2482	376.2493

***tert*-butyl (2*R*,*E*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-3,5-diphenylpent-4-enoate (40)**

According to **GP-4B**, **2f** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (353 μL, 883 μmol, 2.5 M in hexane, 3.05 equiv.), carbonate **39** (60.2 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in dry THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 91:9), **40** (65.1 mg, 149 μmol, 77%, 64:36 dr) was obtained as a colorless resin.

R_f(40) = 0.29 (DCM/Et_2O 9:1)



Main diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, $^3J_{20,19}$ = 7.5 Hz, 3 H, 20-H), 0.89 (d, $^3J_{21,18}$ = 7.0 Hz, 3 H, 21-H), 1.08 (m, 1 H, 19-H_a), 1.19 (m, 1 H, 19-H_b), 1.35 (s, 9 H, 1-H), 1.79 (m, 1 H, 18-H), 2.65 (m, 1 H, OH), 3.89 (m, 2 H, 4-H, 17-H), 5.00 (dd, $^3J_{5,6}$ = 8.7 Hz, $^3J_{5,4}$ = 7.8 Hz, 1 H, 5-H), 6.40 (dd, $^3J_{6,7}$ = 15.8 Hz, $^3J_{6,5}$ = 8.5 Hz, 1 H, 6-H), 6.47 (d, $^3J_{7,6}$ = 15.8 Hz, 1 H, 7-H), 6.59 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, NH), 7.27 (m, 10 H, 9-H, 10-H, 11-H, 13-H, 14-H, 15-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-20), 15.4 (q, C-21), 22.9 (t, C-19), 27.6 (q, C-1), 38.9 (d, C-18), 52.9 (d, C-5), 56.5 (d, C-4), 76.2 (d, C-17), 82.2 (s, C-2), 126.3 (d, C-6), 127.3 (d, C-15), 128.1 (d, C-9), 128.4 (d, C-13), 128.5 (d, C-10/C-14), 132.7 (d, C-7), 136.7 (s, C-8), 139.3 (s, C-12), 170.1 (s, C-3), 172.9 (s, C-16).

Minor diastereomer

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, $^3J_{21,18}$ = 7.0 Hz, 3 H, 21-H), 1.08 (m, 1 H, 19-H_a), 1.22 (s, 9 H, 1-H), 1.79 (sextd, $^3J_{18,17/19a/21}$ = 6.8 Hz, $^3J_{18,19b}$ = 3.1 Hz, 1 H, 18-H), 3.89 (m, 2 H, 4-H, 17-H), 4.95 (t, $^3J_{5,4/6}$ = 8.7 Hz, 1 H, 5-H), 6.42 (m, 2 H, 6-H, 7-H), 6.84 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH), 7.27 (m, 10 H, 9-H, 10-H, 11-H, 13-H, 14-H, 15-H).

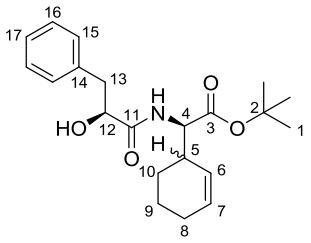
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-20), 15.4 (q, C-21), 22.9 (t, C-19), 27.6 (q, C-1), 38.9 (d, C-18), 52.9 (d, C-5), 56.5 (d, C-4), 76.2 (d, C-17), 82.2 (s, C-2), 126.3 (d, C-6), 127.3 (d, C-15), 128.1 (d, C-9), 128.4 (d, C-13), 128.5 (d, C-10, C-14), 132.7 (d, C-7), 136.7 (s, C-8), 139.3 (s, C-12), 170.1 (s, C-3), 172.9 (s, C-16).

HRMS (CI):	Calculated	Found
$C_{27}H_{36}NO_4$ $[M+H]^+$	438.2639	438.2644

***tert*-butyl (2*R*)-2-(cyclohex-2-en-1-yl)-2-((*S*)-2-hydroxy-3-phenylpropanamido)acetate (42)**

According to **GP-4B**, **2f** (71.0 mg, 289 μmol), chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.), DIPA (132 μL, 926 μmol, 3.2 equiv.), *n*-BuLi (353 μL, 883 μmol, 2.5 M in hexane, 3.05 equiv.), carbonate **41** (33.1 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (2.1 mg, 5.8 μmol, 2 mol%) and PPh_3 (6.8 mg, 26.0 μmol, 9 mol%) in dry THF (3 mL) were reacted at −78 °C. After column chromatography (silica, DCM/Et_2O 9:1), **42** (43.0 mg, 120 μmol, 62%, 66:34 dr) was obtained as a colorless resin.

R_f(42) = 0.36 (DCM/Et_2O 9:1)



Main diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32 (m, 1 H, 10-H_a), 1.46 (s, 9 H, 1-H), 1.52 (m, 1 H, 9-H_a), 1.77 (m, 2 H, 9-H_b, 10-H_b), 1.97 (m, 2 H, 8 H), 2.58 (d, $^3J_{OH,12}$ = 4.9 Hz, 1 H, OH), 2.70 (m, 1 H, 5-H), 2.87 (dd, $^2J_{13a,13b}$ = 13.9 Hz, $^3J_{13a,12}$ = 2.9 Hz, 1 H, 13-H_a), 3.24 (dd, $^2J_{13b,13a}$ = 13.9 Hz, $^3J_{13b,12}$ = 4.3 Hz, 1 H, 13-H_b), 4.31 (m, 1 H, 12-H), 4.49 (dd, $^3J_{4,NH}$ = 8.9 Hz, $^3J_{4,5}$ = 4.2 Hz, 1 H, 4-H), 5.45 (m, 1 H, 7-H), 5.84 (m, 1 H, 6-H), 6.83 (d, $^3J_{NH,4}$ = 8.8 Hz, 1 H, NH), 7.25 (m, 3 H, 15-H, 17-H), 7.32 (m, 2 H, 16-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.5 (d, C-9), 24.8 (t, C-8), 25.9 (t, C-10), 28.0 (q, C-1), 39.1 (d, C-5), 40.9 (t, C-13), 55.7 (d, C-4), 72.9 (d, C-12), 82.1 (s, C-2), 125.4 (d, C-7), 127.0 (d, C-16), 128.8 (d, C-17), 129.4 (d, C-15), 131.1 (d, C-6), 136.9 (s, C-14), 170.4 (s, C-3), 172.6 (s, C-11).

Minor diastereomer

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32 (m, 1 H, 10-H_a), 1.46 (s, 9 H, 1-H), 1.52 (m, 1 H, 9-H_a), 1.64 (m, 1 H, 10-H_b), 1.77 (m, 1 H, 9-H_b), 1.97 (m, 2 H, 8-H), 2.60 (d, $^3J_{OH,12}$ = 5.0 Hz, 1 H, OH), 2.70 (m, 1 H, 5-H), 2.90 (dd, $^2J_{13a,13b}$ = 13.9 Hz, $^3J_{13a,12}$ = 3.1 Hz, 1 H, 13-H_a), 3.22 (dd, $^2J_{13b,13a}$ = 13.9 Hz, $^3J_{13b,12}$ = 4.5 Hz, 1 H, 13-H_b), 4.31 (m, 1 H, 12-H), 4.55 (dd, $^3J_{4,NH}$ = 8.7 Hz, $^3J_{4,5}$ = 4.8 Hz, 1 H, 4-H), 5.52 (m, 1 H, 7 H), 5.78 (dd, $^3J_{6,7}$ = 10.2 Hz, $^3J_{6,5}$ = 2.8 Hz, 1 H, 6-H), 6.91 (d, $^3J_{NH,4}$ = 8.4 Hz, 1 H, NH), 7.25 (m, 3 H, 15-H, 17-H), 7.32 (m, 2 H, 16-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.5 (t, C-9), 24.2 (t, C-10), 24.8 (t, C-8), 28.0 (q, C-1), 40.9 (t, C-13), 55.5 (d, C-4), 72.8 (d, C-12), 82.2 (s, C-2), 126.9 (d, C-7), 129.4 (d, C-15), 131.1 (d, C-6), 170.2 (s, C-3), 172.4 (s, C-11).

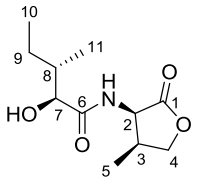
HRMS (CI):	Calculated	Found
$C_{21}H_{30}NO_4$ $[M+H]^+$	360.2169	360.2178

(2*S*,3*S*)-2-hydroxy-3-methyl-N-((3*R*,4*S*)-4-methyl-2-oxotetrahydrofuran-3-yl)pentanamide (44a)

Ozone was passed through solution of **35b** (50.0 mg, 133 μmol) in DCM/MeOH (1:1, 2 mL) at −78 °C for 2 minutes before the excess ozone was removed by passing N_2 through the solution. $NaBH_4$ (10.1 mg, 266 μmol, 2.0 equiv.) was added and after 2 minutes the cooling bath was removed, and the mixture stirred for 45 minutes. After TLC showed full conversion, the mixture was diluted with EtOAc and HCl (1 M, aq.) and the layers were separated. The aqueous layer was extracted twice with EtOAc, the combined organic layers were dried (Na_2SO_4), evaporated *in vacuo* and the crude product was immediately used in the next step.

The crude alcohol **43** was dissolved in $CHCl_3$ (1 mL) and TFA (100 μL, 1.30 mmol, 9.8 equiv.) was added. After stirring at room temperature for 22 hours, the mixture was concentrated *in vacuo* and the residue purified by column chromatography (silica, DCM/diethyl ether 7:3) to afford lactone **44a** (18.9 mg, 82.4 mmol, 62% over 2 steps) as colorless crystals.

R_f(44a) = 0.19 (DCM/Et_2O 7:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{10,9}$ = 7.5 Hz, 3 H, 10-H), 0.99 (d, $^3J_{5,3}$ = 7.2 Hz, 3 H, 5-H), 1.04 (d, $^3J_{11,8}$ = 7.0 Hz, 3 H, 11-H), 1.24 (m, 1 H, 9-H_a), 1.45 (m, 1 H, 9-H_b), 1.92 (dqt, $^3J_{8,9a}$ = 10.1 Hz, $^3J_{8,11}$ = 6.9 Hz, $^3J_{8,7/9b}$ = 3.7 Hz, 1 H, 8-H), 2.69 (d, $^3J_{OH,7}$ = 4.8 Hz, 1 H, OH), 3.03 (m, 1 H, 3-H), 4.13 (m, 2 H, 4-H_a, 7-H), 4.45 (dd, $^2J_{4b,4a}$ = 9.2 Hz, $^3J_{4b,3}$ = 5.2 Hz, 1 H, 4-H_b), 4.71 (dd, $^3J_{2,3}$ = 7.1 Hz, $^3J_{2,NH}$ = 6.4 Hz, 1 H, 2-H), 6.95 (d, $^3J_{NH,2}$ = 4.9 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-10), 12.8 (q, C-5), 15.5 (q, C-11), 23.2 (t, C-9), 33.9 (d, C-3), 38.9 (d, C-8), 52.9 (d, C-2), 72.7 (t, C-4), 76.3 (d, C-7), 174.1 (s, C-1), 174.9 (s, C-6).

Optical rotation: $[\alpha]_D^{20}$ = −107.0 (c = 1.0, $CHCl_3$)

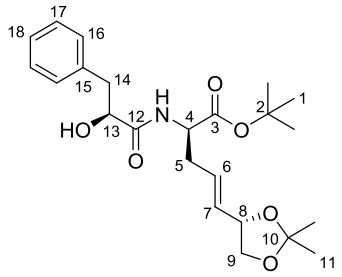
Melting point: 129−131 °C

HRMS (CI):	Calculated	Found
$C_{11}H_{20}NO_4$ $[M+H]^+$	230.1387	230.1383

***tert*-butyl (*R*,*E*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-((*S*)-2-hydroxy-3-phenylpropanamido)pent-4-enoate (45)**

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (304 μL, 304 μmol, 1.0 M in hexane, 1.05 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **13** (44.7 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg, 11.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in dry THF (3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 9:1) afforded **45** (63.0 mg, 150 μmol, 77%, > 99:1 *dr*) as a colorless oil.

R_f(45) = 0.30 (DCM/Et_2O 8:2)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, 11-H), 1.38 (s, 3 H, 11-H'), 1.47 (s, 9 H, 1-H), 2.48 (m, 1 H, 5-H_a), 2.58 (m, 1 H, 5-H_b), 2.75 (d, $^3J_{OH,13}$ = 4.6 Hz, 1 H, OH), 2.85 (dd, $^2J_{14a,14b}$ = 13.9 Hz, $^3J_{14a,13}$ = 9.2 Hz, 1 H, 14-H_a), 3.23 (dd, $^2J_{14b,14a}$ = 13.9 Hz, $^3J_{14b,13}$ = 3.8 Hz, 1 H, 14-H_b), 3.53 (t, $^2J_{9a,9b}$ = $^3J_{9a,8}$ = 7.9 Hz, 1 H, 9-H_a), 4.04 (dd, $^2J_{9b,9a}$ = 8.2 Hz, $^3J_{9b,8}$ = 6.2 Hz, 1 H, 9-H_b), 4.29 (dt, $^3J_{13,14a}$ = 9.1 Hz, $^3J_{13,14b/OH}$ = 4.3 Hz, 1 H, 13-H), 4.43 (q, $^3J_{8,7/9}$ = 7.2 Hz, 1 H, 8-H), 4.54 (dt, $^3J_{4,NH}$ = 8.1 Hz, $^3J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 5.51 (dd, $^3J_{7,6}$ = 15.3 Hz, $^3J_{7,8}$ = 7.3 Hz, 1 H, 7-H), 5.62 (dt, $^3J_{6,7}$ = 15.3 Hz, $^3J_{6,5}$ = 7.0 Hz, 1 H, 6-H), 6.97 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, NH), 7.25 (m, 3 H, 16-H, 18-H), 7.32 (m, 2 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.7 (q, C-11), 26.6 (q, C-11'), 28.0 (q, C-1), 35.2 (t, C-5), 40.9 (t, C-14), 51.6 (d, C-4), 69.2 (t, C-9), 72.9 (d, C-13), 76.5 (d, C-8), 82.4 (s, C-2), 109.3 (s, C-10), 126.9 (d, C-18), 128.4 (d, C-6), 128.7 (d, C-17), 129.4 (d, C-16), 132.2 (d, C-7), 136.9 (s, C-15), 170.2 (s, C-3), 172.3 (s, C-12).

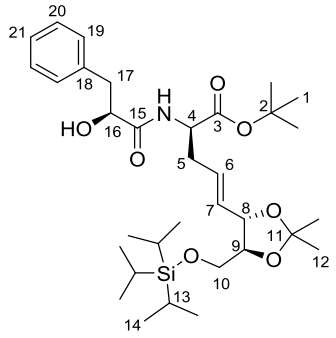
Optical rotation: $[\alpha]_D^{20}$ = −48.8 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{23}H_{34}NO_6$ $[M+H]^+$	420.2381	420.2377

tert-butyl (_R_,_E_)-5-((4_S_,5_S_)-2,2-dimethyl-5-(((triisopropylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)-2-((_S_)-2-hydroxy-3-phenylpropanamido)pent-4-enoate (46)

According to **GP-4B**, **2f** (81.0 mg, 290 μmol), chlorotitanium(IV) triisopropoxide (304 μL, 304 μmol, 1.0 M in hexane, 1.05 equiv.), DIPA (132 μL, 928 μmol, 3.2 equiv.), *n*-BuLi (360 μL, 899 μmol, 2.5 M in hexane, 3.1 equiv.), ethyl carbonate **16** (81.0 mg, 194 μmol, 0.7 equiv.), $[AllylPdCl]_2$ (4.2 mg, 11.6 μmol, 4 mol%) and PPh_3 (13.7 mg, 52.0 μmol, 18 mol%) in dry THF (3 mL) were reacted at −78 °C. Column chromatography (silica, DCM/Et_2O 8:2) afforded **46** (63.0 mg, 150 μmol, 80%, > 99:1 *dr*) as a colorless oil.

R_f(46) = 0.22 (DCM/Et_2O 8:2)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.06 (m, 21 H, 13-H, 14-H), 1.37 (s, 6 H, 12-H), 1.47 (s, 9 H, 1-H), 2.47 (dt, $^2J_{5a,5b}$ = 14.2 Hz, $^3J_{5a,4/6}$ = 6.6 Hz, 1 H, 5-H_a), 2.61 (dt, $^2J_{5b,5a}$ = 14.2 Hz, $^3J_{5b,4/6}$ = 5.8 Hz, 1 H, 5-H_b), 2.81 (m, 1 H, OH), 2.84 (dd, $^2J_{17a,17b}$ = 14.1 Hz, $^3J_{17a,16}$ = 9.2 Hz, 1 H, 17-H_a), 3.23 (dd, $^2J_{17b,17a}$ = 13.9 Hz, $^3J_{17b,16}$ = 3.6 Hz, 1 H, 17-H_b), 3.71 (dt, $^3J_{9,8}$ = 8.1 Hz, $^3J_{9,10}$ = 4.0 Hz, 1 H, 9-H), 3.78 (dd, $^2J_{10a,10b}$ = 10.9 Hz, $^3J_{10a,9}$ = 3.9 Hz, 1 H, 10-H_a), 3.82 (dd, $^2J_{10b,10a}$ = 10.9 Hz, $^3J_{10b,9}$ = 4.8 Hz, 1 H, 10-H_b), 4.28 (dt, $^3J_{16,17a}$ = 9.3 Hz, $^3J_{16,17b/OH}$ = 3.9 Hz, 1 H, 16-H), 4.33 (dd, $^3J_{8,9}$ = 7.8 Hz, $^3J_{8,7}$ = 6.9 Hz, 1 H, 8-H), 4.54 (dt, $^3J_{4,NH}$ = 7.7 Hz, $^3J_{4,5}$ = 6.0 Hz, 1 H, 4-H), 5.59 (m, 2 H, 6-H, 7-H), 6.98 (d, $^3J_{NH,4}$ = 8.1 Hz, 1 H, NH), 7.25 (m, 3 H, 19-H, 21-H), 7.32 (m, 2 H, 20-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (d, C-13), 17.9 (q, C-14), 26.9 (q, C-12), 27.0 (q, C-12'), 28.0 (q, C-1), 35.2 (t, C-5), 40.8 (t, C-17), 51.6 (d, C-4), 62.7 (t, C-10), 73.0 (d, C-16), 78.3 (d, C-8), 81.6 (d, C-9), 82.3 (s, C-2), 109.0 (s, C-11), 126.9 (d, C-21), 128.1 (d, C-6), 128.6 (d, C-20), 129.4 (d, C-19), 132.3 (d, C-7), 137.0 (s, C-18), 170.2 (s, C-3), 172.3 (s, C-15).

Optical rotation: $[\alpha]_D^{20}$ = −51.7 (c = 1.0, $CHCl_3$)

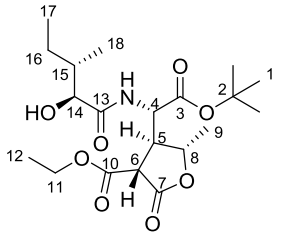
HRMS (CI):	Calculated	Found
$C_{29}H_{46}NO_7Si$ $[M-C_4H_9]^+$	548.3038	548.3032

ethyl (3_S_,4_S_,5_S_)-4-((_S_)-2-(_tert_-butoxy)-1-((2_S_,3_S_)-2-hydroxy-3-methylpentanamido)-2-oxoethyl)-5-methyl-2-oxotetrahydrofuran-3-carboxylate (52a)

To a solution of glycine ester **2d** (71.0 mg, 289 μmol) in dry THF (2 mL) was added chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.) and the mixture was cooled to −78 °C. After 10 minutes a freshly prepared solution of LDA (897 μL, 897 μmol, 1.0 M in THF/hexane, 3.1 equiv.) was added dropwise and the mixture was stirred

for 30 minutes to achieve complete chelate complex formation which results in a dark red to black solution. Then, a solution of carbonate **11** (41.9 mg, 194 μmol, 0.7 equiv.) in dry THF (1 mL) was slowly added and the reaction mixture was allowed to warm to room temperature. After 10 minutes discoloration of the solution indicates complete conversion, and the reaction mixture was diluted with diethyl ether and 1 M $KHSO_4$-solution. The layers were separated, the aqueous layer extracted twice with diethyl ether and the combined organic layer was dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography (silica, DCM/Et_2O 9:1) to afford lactone **52a** (61.0 mg, 164 μmol, 85%, 64:36 *dr*) as an off-white solid. The diastereomeric mixture was recrystallized from pentane/diethyl ether to afford the main diastereomer as colorless prisms, which was subjected to X-ray crystallographic analysis.

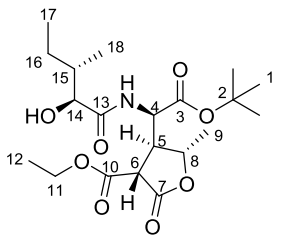
R_f(52a) = 0.14 (DCM/Et_2O 8:2)



Main diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{17,16}$ = 7.5 Hz, 3 H, 17-H), 0.99 (d, $^3J_{18,15}$ = 7.0 Hz, 3 H, 18-H), 1.23 (m, 1 H, 16-H_a), 1.33 (t, $^3J_{12,11}$ = 7.1 Hz, 3 H, 12-H), 1.38 (m, 1 H, 16-H_b), 1.47 (s, 9 H, 1-H), 1.56 (d, $^3J_{9,8}$ = 6.1 Hz, 3 H, 9-H), 1.89 (m, 1 H, 15-H), 2.77 (d, $^3J_{OH,14}$ = 5.4 Hz, 1 H, OH), 3.11 (ddd, $^3J_{5,6}$ = 9.4 Hz, $^3J_{5,8}$ = 7.9 Hz, $^3J_{5,4}$ = 3.5 Hz, 1 H, 5-H), 3.55 (d, $^3J_{6,5}$ = 9.4 Hz, 1 H, 6-H), 4.07 (dd, $^3J_{14,OH}$ = 5.2 Hz, $^3J_{14,15}$ = 3.7 Hz, 1 H, 14-H), 4.22 (dq, $^2J_{11a,11b}$ = 10.8 Hz, $^3J_{11a,12}$ = 7.2 Hz, 1 H, 11-H_a), 4.27 (dq, $^2J_{11b,11a}$ = 10.8 Hz, $^3J_{11b,12}$ = 7.2 Hz, 1 H, 11-H_b), 4.42 (dq, $^3J_{8,5}$ = 7.7 Hz, $^3J_{8,9}$ = 6.2 Hz, 1 H, 8-H), 4.67 (dd, $^3J_{4,NH}$ = 8.1 Hz, $^3J_{4,5}$ = 3.4 Hz, 1 H, 4-H), 7.34 (d, $^3J_{NH,4}$ = 7.9 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-17), 14.0 (q, C-12), 15.4 (q, C-18), 19.7 (q, C-9), 23.4 (t, C-16), 27.8 (q, C-1), 38.8 (d, C-15), 48.9 (d, C-6), 49.3 (d, C-5), 51.1 (d, C-4), 62.5 (t, C-11), 76.4 (d, C-14), 77.6 (d, C-8), 84.3 (s, C-2), 167.1 (s, C-10), 168.9 (s, C-3), 170.3 (s, C-7), 174.1 (s, C-13).



Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{17,16}$ = 7.5 Hz, 3 H, 17-H), 1.01 (d, $^3J_{18,15}$ = 7.0 Hz, 3 H, 18-H), 1.20 (m, 1 H, 16-H_a), 1.31 (t, $^3J_{12,11}$ = 7.2 Hz, 3 H, 12-H), 1.38 (m, 1 H, 16-H_b), 1.48 (s, 9 H, 1-H), 1.48 (d, $^3J_{9,8}$ = 7.0 Hz, 3 H, 9-H), 1.92 (m, 1 H, 15-H), 2.12 (d, $^3J_{OH,14}$ = 4.4 Hz, 1 H, OH), 3.45 (td, $^3J_{5,4/6}$ = 10.4 Hz, $^3J_{5,8}$ = 7.7 Hz, 1 H, 5-H), 3.55 (d, $^3J_{6,5}$ = 11.3 Hz, 1 H, 6-H), 4.06 (dd, $^3J_{14,OH}$ = 4.2 Hz, $^3J_{14,15}$ = 3.6 Hz, 1 H, 14-H), 4.22 (dq, $^2J_{11a,11b}$ = 10.8 Hz, $^3J_{11a,12}$ = 7.2 Hz, 1 H, 11-H_a), 4.27 (dq, $^2J_{11b,11a}$ = 10.8 Hz, $^3J_{11b,12}$ = 7.2 Hz, 1 H, 11-H_b), 4.89 (t, $^3J_{4,5/NH}$ = 10.0 Hz, 1 H, 4-H), 4.93 (quint., $^3J_{8,9/5}$ = 7.0 Hz, 1 H, 8-H), 7.34 (d, $^3J_{NH,4}$ = 9.7 Hz, 1 H, NH).

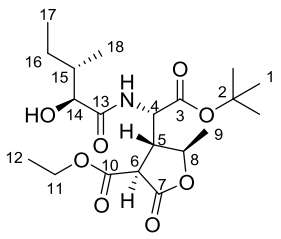
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-17), 14.0 (q, C-12), 15.4 (q, C-18), 16.3 (q, C-9), 23.1 (t, C-16), 27.9 (q, C-1), 38.6 (d, C-15), 45.9 (d, C-5), 48.9 (d, C-6), 50.5 (d, C-4), 62.5 (t, C-11), 76.6 (d, C-14), 77.2 (d, C-8), 83.8 (s, C-2), 168.0 (s, C-10), 168.8 (s, C-3), 170.1 (s, C-7), 172.9 (s, C-13).

HRMS (CI):	Calculated	Found
$C_{20}H_{34}NO_8$ $[M+H]^+$	416.2279	416.2283

ethyl (3*R*,4*R*,5*R*)-4-((*R*)-2-(*tert*-butoxy)-1-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-2-oxoethyl)-5-methyl-2-oxotetrahydrofuran-3-carboxylate (52b)

To a solution of glycine ester **2d** (71.0 mg, 289 μmol) in dry THF (2 mL) was added chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.) and the mixture was cooled to –78 °C. After 10 minutes a freshly prepared solution of LDA (897 μL, 897 μmol, 1.0 M in THF/hexane, 3.1 equiv.) was added dropwise and the mixture was stirred for 30 minutes to achieve complete chelate complex formation which results in a dark red to black solution. Then, a solution of carbonate *ent*-**11** (41.9 mg, 194 μmol, 0.7 equiv.) in dry THF (1 mL) was slowly added and the reaction mixture was allowed to warm to room temperature. After 10 minutes discoloration of the solution indicates complete conversion, and the reaction mixture was diluted with diethyl ether and 1 M $KHSO_4$-solution. The layers were separated, the aqueous layer extracted twice with diethyl ether and the combined organic layer was dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography (silica, DCM/Et_2O 9:1) to afford lactone **52b** (76.1 mg, 183 μmol, 94%, >99:1 *dr*) as a white solid.

R_f(52b) = 0.16 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{17,16}$ = 7.4 Hz, 3 H, 17-H), 0.99 (d, $^3J_{18,15}$ = 6.8 Hz, 3 H, 18-H), 1.20 (m, 1 H, 16-H_a), 1.33 (t, $^3J_{12,11}$ = 7.1 Hz, 3 H, 12-H), 1.40 (m, 1 H, 16-H_b), 1.48 (d,

$^3J_{9,8}$ = 6.2 Hz, 3 H, 9-H), 1.49 (s, 9 H, 1-H), 1.81 (m, 1 H, 15-H), 2.59 (d, $^3J_{OH,14}$ = 5.7 Hz, 1 H, OH), 3.50 (ddd, $^3J_{5,6}$ = 10.7 Hz, $^3J_{5,4}$ = 9.7 Hz, $^3J_{5,8}$ = 7.3 Hz, 1 H, 5-H), 3.60 (d, $^3J_{6,5}$ = 10.8 Hz, 1 H, 6-H), 3.93 (dd, $^3J_{14,OH}$ = 5.6 Hz, $^3J_{14,15}$ = 4.2 Hz, 1 H, 14-H), 4.19 (dq, $^2J_{11a,11b}$ = 10.8 Hz, $^3J_{11a,12}$ = 7.1 Hz, 1 H, 11-H_a), 4.31 (dq, $^2J_{11b,11a}$ = 10.8 Hz, $^3J_{11b,12}$ = 7.1 Hz, 1 H, 11-H_b), 4.73 (t, $^3J_{4,5/NH}$ = 9.4 Hz, 1 H, 4-H), 4.92 (quint, $^3J_{8,5/10}$ = 6.7 Hz, 1 H, 8-H), 7.34 (d, $^3J_{NH,4}$ = 9.2 Hz, 1 H, NH).

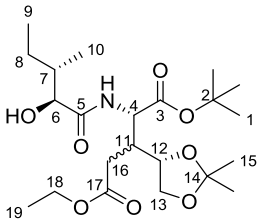
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-17), 13.9 (q, C-12), 15.3 (q, C-18), 16.3 (q, C-9), 23.4 (t, C-16), 27.9 (q, C-1), 38.9 (d, C-15), 44.7 (d, C-5), 48.9 (d, C-6), 51.4 (d, C-4), 62.7 (t, C-11), 76.1 (d, C-14), 77.2 (d, C-8), 84.0 (s, C-2), 167.8 (s, C-10), 168.8 (s, C-3), 169.9 (s, C-7), 173.7 (s, C-13).

Optical rotation:	$[\alpha]_D^{20}$ = −42.9 (c = 1.0, $CHCl_3$)	
Melting point:	125−127 °C	
HRMS (CI):	Calculated	Found
$C_{20}H_{34}NO_8$ $[M+H]^+$	416.2279	416.2288

1-(*tert*-butyl) 5-ethyl (2*R*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)pentanedioate (53)

To a solution of glycine ester **2d** (71.0 mg, 289 μmol) in dry THF (2 mL) was added chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.) and the mixture was cooled to −78 °C. After 10 minutes a freshly prepared solution of LDA (897 μL, 897 μmol, 1.0 M in THF/hexane, 3.1 equiv.) was added dropwise and the mixture was stirred for 30 minutes to achieve complete chelate complex formation which results in a dark red to black solution. Then, a solution of ester **12** (41.9 mg, 209 μmol, 0.7 equiv.) in dry THF (1 mL) was slowly added and the reaction mixture was allowed to warm to room temperature. After 10 minutes discoloration of the solution indicates complete conversion, and the reaction mixture was diluted with diethyl ether and 1 M $KHSO_4$-solution. The layers were separated, the aqueous layer extracted twice with diethyl ether and the combined organic layer was dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography (silica, DCM/Et_2O 85:15) to afford ester **53** (63.2 mg, 141 μmol, 73%, 67:33 *dr*) as a pale-yellow oil.

R_f(53) = 0.17 (DCM/Et_2O 85:15)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{9,8}$ = 7.5 Hz, 3 H, 9-H), 1.01 (d, $^3J_{10,7}$ = 7.0 Hz, 3 H, 10-H), 1.24 (m, 1 H, 8-H_a), 1.27 (t, $^3J_{19,18}$ = 7.1 Hz, 3 H, 19-H), 1.34 (s, 3 H, 15-H), 1.43 (s, 3 H,

15-H'), 1.47 (m, 1 H, 8-H_b), 1.48 (s, 9 H, 1-H), 1.85 (sextd, $^3J_{7,8/10}$ = 6.8 Hz, $^3J_{7,6}$ = 3.9 Hz, 1 H, 7-H), 2.30 (dd, $^2J_{16a,16b}$ = 16.3 Hz, $^3J_{16a,11}$ = 5.6 Hz, 1 H, 16-H_a), 2.48 (dd, $^2J_{16b,16a}$ = 16.3 Hz, $^3J_{16b,11}$ = 7.6 Hz, 1 H, 16-H_b), 2.62 (dtd, $^3J_{11,16b}$ = 7.7 Hz, $^3J_{11,12/16a}$ = 5.8 Hz, $^3J_{11,4}$ = 3.8 Hz, 1 H, 11-H), 3.62 (t, $^3J_{13a,12}$ = 7.6 Hz, 1 H, 13-H_a), 4.03 (m, 3 H, 6-H, 12-H, 13-H_b), 4.15 (q, $^3J_{18,19}$ = 7.2 Hz, 2 H, 18-H), 4.73 (dd, $^3J_{4,NH}$ = 8.7 Hz, $^3J_{4,11}$ = 3.6 Hz, 1 H, 4-H), 7.46 (d, $^3J_{NH,4}$ = 8.7 Hz, 1 H, NH).

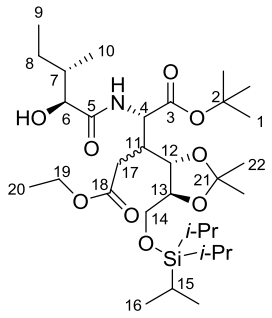
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-9), 14.1 (q, C-19), 15.3 (q, C-10), 23.4 (t, C-8), 25.4 (q, C-15), 26.5 (q, C-15'), 28.0 (q, C-1), 32.9 (t, C-16), 38.9 (d, C-7), 40.9 (d, C-11), 53.7 (d, C-4), 61.1 (t, C-18), 67.6 (t, C-13), 76.0 (d, C-6), 76.3 (d, C-12), 82.6 (s, C-2), 109.3 (s, C-14), 169.9 (s, C-3), 171.7 (s, C-17), 173.2 (s, C-5).

HRMS (CI):	Calculated	Found
$C_{22}H_{40}NO_8$ $[M+H]^+$	446.2748	446.2742

1-(*tert*-butyl) 5-ethyl (2*R*)-3-((4*S*,5*S*)-2,2-dimethyl-5-(((triisopropylsilyl)oxy)methyl)-1,3-dioxolan-4-yl)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)pentanedioate (54)

To a solution of glycine ester **2d** (71.0 mg, 289 μmol) in dry THF (2 mL) was added chlorotitanium(IV) triisopropoxide (434 μL, 434 μmol, 1.0 M in hexane, 1.5 equiv.) and the mixture was cooled to –78 °C. After 10 minutes a freshly prepared solution of LDA (897 μL, 897 μmol, 1.0 M in THF/hexane, 3.1 equiv.) was added dropwise and the mixture was stirred for 30 minutes to achieve complete chelate complex formation which results in a dark red to black solution. Then, a solution of ester **15** (75.0 mg, 194 μmol, 0.7 equiv.) in dry THF (1 mL) was slowly added and the reaction mixture was allowed to warm to room temperature. After 10 minutes discoloration of the solution indicates complete conversion, and the reaction mixture was diluted with diethyl ether and 1 M $KHSO_4$-solution. The layers were separated, the aqueous layer extracted twice with diethyl ether and the combined organic layer was dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography (silica, DCM/Et_2O 85:15) to afford ester **54** (89.7 mg, 144 μmol, 74%, 63:37 *dr*) as a colorless resin.

R_f(54) = 0.25 (DCM/Et_2O 85:15)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{9,8}$ = 7.4 Hz, 3 H, 9-H), 1.00 (d, $^3J_{10,7}$ = 6.8 Hz, 3 H, 10-H), 1.07 (m, 21 H, 15-H, 16-H), 1.22 (m, 1 H, 8-H_a), 1.26 (t, $^3J_{20,19}$ = 7.2 Hz, 3 H, 20-H), 1.37 (s, 3 H, 22-H), 1.45 (s, 3 H, 22-H'), 1.46 (m, 1 H, 8-H_b), 1.47 (s, 9 H, 1-H), 1.84 (sextd, $^3J_{7,8/10}$ =

6.7 Hz, $^{3}J_{7,6}$ = 4.0 Hz, 1 H, 7-H), 2.56 (m, 2 H, 17-H), 2.66 (m, 2 H, 11-H, OH), 3.76 (dd, $^{2}J_{14a,14b}$ = 10.7 Hz, $^{3}J_{14a,13}$ = 5.9 Hz, 1 H, 14-H_a), 3.81 (dd, $^{2}J_{14b,14a}$ = 10.6 Hz, $^{3}J_{14b,13}$ = 3.7 Hz, 1 H, 14-H_b), 3.91 (td, $^{3}J_{13,12/14a}$ = 6.0 Hz, $^{3}J_{13,14b}$ = 3.7 Hz, 1 H, 13-H), 4.01 (d, $^{3}J_{6,7}$ = 3.5 Hz, 1 H, 6-H), 4.03 (dd, $^{3}J_{12,11}$ = 9.2 Hz, $^{3}J_{12,13}$ = 6.4 Hz, 1 H, 12-H), 4.14 (qd, $^{3}J_{19a,20}$ = 7.1 Hz, $^{2}J_{19a,19b}$ = 2.0 Hz, 1 H, 19-H_a), 4.15 (qd, $^{3}J_{19b,20}$ = 7.1 Hz, $^{2}J_{19b,19a}$ = 2.0 Hz, 1 H, 19-H_b), 4.83 (dd, $^{3}J_{4,NH}$ = 8.5 Hz, $^{3}J_{4,11}$ = 2.8 Hz, 1 H, 4-H), 7.48 (d, $^{3}J_{NH,4}$ = 8.6 Hz, 1 H, NH).

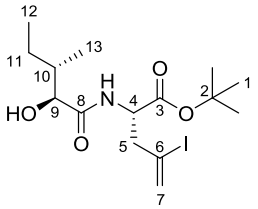
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C15), 11.9 (d, C-9), 14.1 (q, C-20), 15.3 (q, C-10), 17.9 (q, C-16), 23.4 (d, C-8), 27.2 (q, C-22), 27.4 (q, C-22‘), 28.0 (q, C-1), 32.9 (t, C-17), 39.0 (d, C-11), 41.3 (d, C-7), 53.6 (d, C-4), 60.9 (t, C-19), 64.3 (t, C-14), 76.0 (d, C-6), 79.3 (d, C-12), 80.8 (d, C-13), 82.3 (s, C-2), 109.1 (s, C-21), 170.0 (s, C-3), 171.9 (s, C-18), 172.9 (s, C-5).

HRMS (CI):	Calculated	Found
$C_{32}H_{62}NO_9Si$ $[M+H]^+$	632.4188	632.4201

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-iodopent-4-enoate (59)**

To a solution of **24ca** (300 mg, 522 µmol) in DCM (5 mL) was added a solution of iodine (159 mg, 627 µmol, 1.2 equiv.) in DCM (5 mL) at room temperature. After 1 hour, the mixture was diluted with DCM, washed with sat. $Na_2S_2O_3$ solution and the aqueous layer was extracted with DCM. The combined organic layers were dried (Na_2SO_4), evaporated *in vacuo* and the residue purified by column chromatography (silica, DCM/Et_2O 9:1) to afford vinyl iodide **59** (180 mg, 438 µmol, 84%) as a white solid.

R_f(59) = 0.16 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^{3}J_{12,11}$ = 7.5 Hz, 3 H, 12-H), 1.00 (d, $^{3}J_{13,10}$ = 7.0 Hz, 3 H, 13-H), 1.22 (m, 1 H, 11-H_a), 1.44 (m, 1 H, 11-H_b), 1.48 (s, 9 H, 1-H), 1.89 (m, 1 H, 10-H), 2.83 (dd, $^{2}J_{5a,5b}$ = 14.9 Hz, $^{3}J_{5a,4}$ = 8.1 Hz, 1 H, 5-H_a), 2.87 (d, $^{3}J_{OH,9}$ = 5.4 Hz, 1 H, OH), 2.95 (dd, $^{2}J_{5b,5a}$ = 14.8 Hz, $^{3}J_{5b,4}$ = 5.5 Hz, 1 H, 5-H_b), 4.05 (dd, $^{3}J_{9,OH}$ = 5.0 Hz, $^{3}J_{9,10}$ = 3.7 Hz, 1 H, 9-H), 4.70 (td, $^{3}J_{4,NH/5a}$ = 8.0 Hz, $^{3}J_{4,5b}$ = 5.8 Hz, 1 H, 4-H), 5.84 (s, 1 H, 7-H_a), 6.15 (s, 1 H, 7-H_b), 6.97 (d, $^{3}J_{NH,4}$ = 7.7 Hz, 1 H, NH).

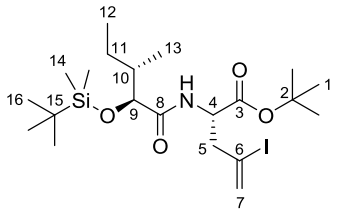
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-12), 15.5 (q, C-13), 23.2 (t, C-11), 28.0 (q, C-1), 38.7 (d, C-10), 47.2 (t, C-5), 51.9 (d, C-4), 76.3 (d, C-9), 82.9 (s, C-2), 103.8 (s, C-6), 129.2 (t, C-7), 170.1 (s, C-8), 173.0 (s, C-3).

Optical rotation:	$[\alpha]_D^{20}$ = −9.1 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{15}H_{26}INO_4$ $[M+H]^+$	412.0979	412.0976

tert-butyl (_S_)-2-((2_S_,3_S_)-2-((_tert_-butyldimethylsilyl)oxy)-3-methylpentanamido)-4-iodo-pent-4-enoate (60)

To a solution of alcohol **59** (200 mg, 486 µmol) in DCM (5 mL) were added imidazole (49.7 mg, 729 µmol, 1.5 equiv.) and TBS-Cl (81.0 mg, 535 µmol, 1.1 equiv.) at 0 °C and the mixture was stirred at room temperature for 8 hours. The reaction was diluted with EtOAc and subsequently washed with water, 1 M HCl and brine. After drying (Na_2SO_4) of the organic layer, the solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, PE/DCM/Et_2O 100:50:10) to afford TBS-ether **60** (231 mg, 440 µmol, 90%) as a colorless oil.

R_f(60) = 0.54 (DCM/Et_2O 96:4)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6 H, 14-H), 0.88 (t, $^3J_{12,11}$ = 7.4 Hz, 3 H, 12-H), 0.93 (d, $^3J_{13,10}$ = 7.0 Hz, 3 H, 13-H), 0.96 (s, 9 H, 16-H), 1.21 (m, 1 H, 11-H_a), 1.47 (s, 9 H, 1-H), 1.51 (m, 1 H, 11-H_b), 1.79 (m, 1 H, 10-H), 2.80 (ddd, $^2J_{5a,5b}$ = 14.7 Hz, $^3J_{5a,4}$ = 8.1 Hz, $^4J_{5a,7}$ = 0.7 Hz, 1 H, 5-H_a), 2.95 (dd, $^2J_{5b,5a}$ = 14.8 Hz, $^3J_{5b,4}$ = 6.1 Hz, 1 H, 5-H_b), 4.03 (d, $^3J_{9,10}$ = 3.3 Hz, 1 H, 9-H), 4.63 (td, $^3J_{4,NH/5a}$ = 7.8 Hz, $^3J_{4,5b}$ = 6.2 Hz, 1 H, 4-H), 5.82 (d, $^2J_{7a,7b}$ = 1.3 Hz, 1 H, 7-H_a), 6.14 (d, $^2J_{7b,7a}$ = 1.3 Hz, 1 H, 7-H_b), 6.99 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = -5.0 (q, C-14), 11.9 (q, C-12), 15.4 (q, C-13), 18.0 (s, C-15), 23.8 (t, C-11), 25.8 (q, C-16), 28.0 (q, C-1), 39.8 (d, C-10), 47.5 (t, C-5), 51.9 (d, C-4), 77.2 (d, C-9), 82.4 (s, C-2), 104.2 (s, C-6), 129.0 (t, C-7), 169.7 (s, C-8), 172.8 (s, C-3).

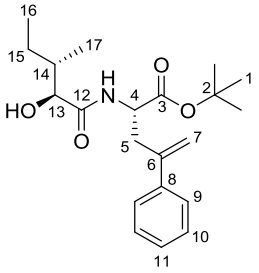
Optical rotation:	$[\alpha]_D^{20}$ = −14.5 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{21}H_{41}INO_4Si$ $[M+H]^+$	526.1844	526.1850

tert-butyl (_S_)-2-((2_S_,3_S_)-2-hydroxy-3-methylpentanamido)-4-phenylpent-4-enoate (61a)

A schlenk tube was charged with $[Ph_2PO_2][NBu]_4$ (48.0 mg, 104 µmol, 2.0 equiv.) and the phosphinate was carefully melted *in vacuo* with a heat gun. Before solidification, dry DMF (0.3 mL, degassed with Argon) was added and iodobenzene (21.3 mg, 104 µmol, 2.0 equiv.), CuTC (19.9 mg, 104 µmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (3.0 mg, 2.6 µmol, 5 mol%) were subsequently added. After addition of a solution of stannane **24ca** (30.0 mg, 52.0 µmol, 1.0 equiv.) in dry DMF (0.7 mL, degassed with Argon), the tube was sealed and stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and water and filtrated through a pad of celite. The layers were separated, and the organic layer washed twice with water. After drying (Na_2SO_4), the solvent was removed under reduced pressure

and the residue purified by column chromatography (silica/K_2CO_3 9:1, DCM/Et_2O 9:1) to afford **61a** (13.4 mg, 37.0 μmol, 74%) as a colorless resin.

R_f(61a) = 0.14 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{16,15}$ = 7.3 Hz, 3 H, 16-H), 0.94 (d, $^3J_{17,14}$ = 7.0 Hz, 3 H, 17-H), 1.11 (m, 1 H, 15-H_a), 1.33 (m, 1 H, 15-H_b), 1.41 (s, 9 H, 1-H), 1.76 (m, 1 H, 14-H), 2.60 (d, $^3J_{OH,13}$ = 5.4 Hz, 1 H, OH), 2.94 (dd, $^2J_{5a,5b}$ = 14.4 Hz, $^3J_{5a,4}$ = 7.2Hz, 1 H, 5-H_a), 3.03 (ddd, $^2J_{5b,5a}$ = 14.4 Hz, $^3J_{5b,4}$ = 6.1 Hz, $^3J_{5b,7}$ = 0.6 Hz, 1 H, 5-H_b), 3.86 (dd, $^3J_{13,OH}$ = 5.3 Hz, $^3J_{13,14}$ = 3.7 H, 1 H, 13-H), 4.53 (td, $^3J_{4,5a/NH}$ = 7.2 Hz, $^3J_{4,5b}$ = 6.4 Hz, 1 H, 4-H), 5.14 (d, $^2J_{7a,7b}$ = 1.0 Hz, 1 H, 7-H_a), 5.35 (d, $^2J_{7b,7a}$ = 1.1 Hz, 1 H, 7-H_b), 6.67 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH), 7.28 (m, 1 H, 11-H), 7.34 (m, 2 H, 10-H/11-H), 7.39 (m, 2 H, 10-H/11-H).

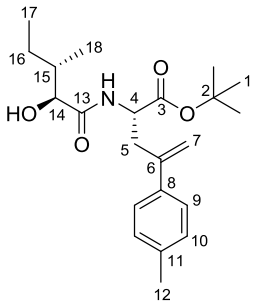
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-16), 15.4 (q, C-17), 23.2 (t, C-15), 28.0 (q, C-1), 38.4 (t, C-5), 38.9 (d, C-14), 51.7 (d, C-4), 76.0 (d, C-13), 82.3 (s, C-2), 115.2 (t, C-7), 126.2 (d, C-9), 127.8 (d, C-11), 128.5 (d, C-10), 141.0 (s, C-8), 146.7 (s, C-6), 170.9 (s, C-3), 172.8 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = +3.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{21}H_{32}NO_4$ $[M+H]^+$	362.2326	362.2297

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-(*p*-tolyl)pent-4-enoate (62a)**

A Schlenk tube was charged with $[Ph_2PO_2][NBu]_4$ (64.0 mg, 139 μmol, 2.0 equiv.) and the phosphinate was carefully melted *in vacuo* with a heat gun. Before solidification, dry DMF (0.3 mL, degassed with Argon) was added followed by addition of 4-iodotoluene (30.4 mg, 139 μmol, 2.0 equiv.), CuTC (26.6 mg, 139 μmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (4.0 mg, 3.5 μmol, 5 mol%). After addition of a solution of stannane **24ca** (40.0 mg, 70.0 μmol, 1.0 equiv.) in dry DMF (0.7 mL, degassed with Argon), the tube was sealed and stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and water and filtrated through a pad of celite. The layers were separated, and the organic layer washed twice with water. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue purified by column chromatography (silica/K_2CO_3 9:1, DCM/Et_2O 92:8) to afford **62a** (19.3 mg, 51.5 μmol, 74%) as a white solid.

R_f(62a) = 0.15 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, $^{3}J_{17,16}$ = 7.5 Hz, 3 H, 17-H), 0.94 (d, $^{3}J_{18,15}$ = 7.0 Hz, 3 H, 18-H), 1.13 (m, 1 H, 16-H_a), 1.33 (m, 1 H, 16-H_b), 1.41 (s, 9 H, 1-H), 1.76 (dqt, $^{3}J_{15,16a}$ = 13.5 Hz, $^{3}J_{15,18}$ = 6.9 Hz, $^{3}J_{15,14/16b}$ = 4.0 Hz, 1 H, 15-H), 2.34 (s, 3 H, 12-H), 2.73 (bs, 1 H, OH), 2.91 (dd, $^{2}J_{5a,5b}$ = 14.3 Hz, $^{3}J_{5a,4}$ = 7.5 Hz, 1 H, 5-H_a), 3.01 (dd, $^{2}J_{5b,5a}$ = 14.3 Hz, $^{3}J_{5b,4}$ = 6.1 Hz, 1 H, 5-H_b), 3.87 (d, $^{3}J_{14,15}$ = 3.7 Hz, 1 H, 14-H), 4.52 (td, $^{3}J_{4,5a/NH}$ = 7.5 Hz, $^{3}J_{4,5b}$ = 6.2 Hz, 1 H, 4-H), 5.09 (d, $^{2}J_{7a,7b}$ = 0.9 Hz, 1 H, 7-H_a), 5.31 (d, $^{2}J_{7b,7a}$ = 1.1 Hz, 1 H, 7-H_b), 6.69 (d, $^{3}J_{NH,4}$ = 7.6 Hz, 1 H, NH), 7.14 (d, $^{3}J_{10,9}$ = 8.0 Hz, 2 H, 10-H), 7.30 (d, $^{3}J_{9,10}$ = 8.1 Hz, 2 H, 9-H).

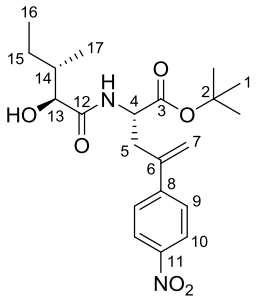
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-17), 15.4 (q, C-18), 21.1 (q, C-12), 23.2 (t, C-16), 27.9 (q, C-1), 38.2 (t, C-5), 38.7 (d, C-15), 51.6 (d, C-4), 76.1 (d, C-14), 82.3 (s, C-2), 115.3 (t, C-7), 126.2 (d, C-9), 129.2 (d, C-10), 137.1 (s, C-8), 137.7 (s, C-11), 143.7 (s, C-6), 171.0 (s, C-3), 172.8 (s, C-13).

Optical rotation:	$[\alpha]_{\mathrm{D}}^{20}$ = +1.4 (c = 1.0, $CHCl_3$)	
Melting point:	119-121 °C	
HRMS (CI):	Calculated	Found
$C_{18}H_{26}NO_4$ $[M\text{-}C_4H_7]^+$	320.1862	320.1885

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-(4-nitrophenyl)pent-4-enoate (62b)**

A Schlenk tube was charged with $[Ph_2PO_2][NBu]_4$ (64.0 mg, 139 μmol, 2.0 equiv.) and the phosphinate was carefully melted *in vacuo* with a heat gun. Before solidification, dry DMF (0.3 mL, degassed with Argon) was added and 1-iodo-4-nitrobenzene (34.7 mg, 139 μmol, 2.0 equiv.), CuTC (26.6 mg, 139 μmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (4.0 mg, 3.5 μmol, 5 mol%) were subsequently added. After addition of a solution of stannane **24ca** (40.0 mg, 70.0 μmol, 1.0 equiv.) in dry DMF (0.7 mL, degassed with Argon), the tube was sealed and stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and water and filtrated through a pad of celite. The layers were separated, and the organic layer washed twice with water. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue purified by column chromatography (silica/K_2CO_3 9:1, DCM/Et_2O 90:10) to afford **62b** (19.3 mg, 51.5 μmol, 74%) as a white solid.

R_f(62b) = 0.23 (DCM/Et_2O 85:15)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, $^{3}J_{16,15}$ = 7.5 Hz, 3 H, 16-H), 0.96 (d, $^{3}J_{17,14}$ = 7.0 Hz, 3 H, 17-H), 1.16 (m, 1 H, 15-H_a), 1.32 (m, 1 H, 15-H_b), 1.42 (s, 9 H, 1-H), 1.82 (m, 1 H, 14-H), 2.69 (d, $^{3}J_{OH,13}$ = 5.1 Hz, 1 H, OH), 3.01 (m, 2 H, 5-H), 3.95 (t, $^{3}J_{13,14/OH}$ = 4.0 Hz, 1 H, 13-H), 4.52 (q, $^{3}J_{4,5/NH}$ = 7.1 Hz, 1 H, 4-H), 5.32 (s, 1 H, 7-H_a), 5.50 (s, 1 H, 7-H_b), 6.95 (d, $^{3}J_{NH,4}$ = 7.6 Hz, 1 H, NH), 7.60 (d, $^{3}J_{9,10}$ = 8.7 Hz, 2 H, 9-H), 8.22 (d, $^{3}J_{10,9}$ = 8.7 Hz, 2 H, 10-H).

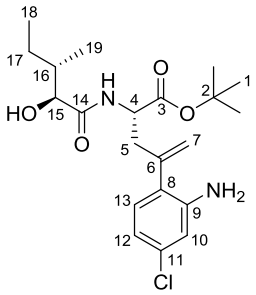
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-16), 15.4 (q, C-17), 23.2 (t, C-15), 28.0 (q, C-1), 38.4 (t, C-5), 38.6 (d, C-14), 51.2 (d, C-4), 76.3 (d, C-13), 82.9 (s, C-2), 119.2 (t, C-7), 123.8 (d, C-10), 127.2 (d, C-9), 142.4 (s, C-6), 146.4 (s, C-8), 147.3 (s, C-11), 170.6 (s, C-3), 172.8 (s, C-12).

Optical rotation:	$[\alpha]_D^{20}$ = −14.6 (c = 1.0, $CHCl_3$)	
Melting point:	74-76 °C	
HRMS (CI):	Calculated	Found
$C_{21}H_{31}N_2O_6$ $[M+H]^+$	407.2177	407.2170

***tert*-butyl (*S*)-4-(2-amino-4-chlorophenyl)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-pent-4-enoate (62c)**

A schlenk tube was charged with $[Ph_2PO_2][NBu]_4$ (64.0 mg, 139 μmol, 2.0 equiv.) and the phosphinate was carefully melted *in vacuo* with a heat gun. Before solidification, dry DMF (0.3 mL, degassed with Argon) was added and 5-chloro-2-iodo-aniline (34.7 mg, 139 μmol, 2.0 equiv.), CuTC (26.6 mg, 139 μmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (4.0 mg, 3.5 μmol, 5 mol%) were added. After addition of a solution of stannane **24ca** (40.0 mg, 70.0 μmol, 1.0 equiv.) in dry DMF (0.7 mL, degassed with Argon), the tube was sealed and stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and water and filtrated through a pad of celite. The layers were separated and the organic layer washed twice with water. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue purified by column chromatography (silica/K_2CO_3 9:1, DCM/Et_2O 85:15) to afford **62c** (19.3 mg, 51.5 μmol, 74%) as a colorless resin

R_f(62c) = 0.12 (DCM/Et_2O 85:15)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{18,17}$ = 7.4 Hz, 3 H, 18-H), 0.94 (d, $^3J_{19,16}$ = 6.8 Hz, 3 H, 19-H), 1.09 (m, 1 H, 17-H_a), 1.29 (m, 1 H, 17-H_b), 1.43 (s, 9 H, 1-H), 1.75 (dqt, $^3J_{16,17a}$ = 13.4 Hz, $^3J_{16,19}$ = 6.8 Hz, $^3J_{16,15/17b}$ = 3.5 Hz, 1 H, 16-H), 2.81 (dd, $^2J_{5a,5b}$ = 14.1 Hz, $^3J_{5a,4}$ = 6.4 Hz, 1 H, 5-H_a), 2.95 (dd, $^2J_{5b,5a}$ = 14.1 Hz, $^3J_{5b,4}$ = 5.0 Hz, 1 H, 5-H_b), 3.86 (d, $^3J_{15,16}$ = 3.8 Hz, 1 H, 15-H), 4.57 (dt, $^3J_{4,NH}$ = 7.7 Hz, $^3J_{4,5}$ = 6.1 Hz, 1 H, 4-H), 5.20 (d, $^2J_{7a,7b}$ = 1.3 Hz, 1 H, 7-H_a), 5.36 (s, 1 H, 7-H_b), 6.70 (m, 2 H, 10-H, 12-H), 6.92 (m, 2 H, 13-H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.7 (q, C-18), 15.4 (q, C-19), 23.1 (t, C-17), 28.0 (q, C-1), 38.6 (d, C-16), 39.6 (t, C-5), 51.8 (d, C-4), 76.2 (d, C-15), 82.6 (s, C-2), 115.5 (d, C-10), 118.4 (d, C-12), 119.5 (t, C-7), 125.7 (s, C-8), 129.8 (d, C-13), 133.8 (s, C-11), 141.7 (s, C-6), 144.5 (s, C-9), 170.7 (s, C-3), 173.0 (s, C-14).

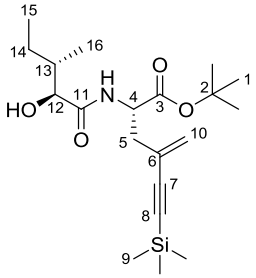
Optical rotation: $[\alpha]_D^{20}$ = +44.4 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{21}H_{32}ClN_2O_4$ $[M+H]^+$	411.2045	411.2049

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-methylene-6-(trimethylsilyl)-hex-5-ynoate (63a)**

A 4 mL vial was charged with **59** (30.0 mg, 72.9 µmol), TMS-acetylene (31.0 µL, 219 µmol, 3.0 equiv.) and triethylamine (31.0 µL, 219 µmol, 3.0 equiv.). Dry THF (1.0 mL) was added, the mixture was purged with Argon and CuI (1.4 mg, 7.3 µmol, 0.1 equiv.) and $Pd(PPh_3)_4$ (2.5 mg, 2.2 µmol, 5 mol%) were added. The vial was sealed, and the mixture was stirred at 65 °C for 16 hours. The mixture was concentrated *in vacuo* and purified by column chromatography (silica, DCM/Et_2O 9:1) to afford alkyne **63a** (25.9 mg, 67.9 µmol, 93%) as an off-white solid.

R_f(63a) = 0.21 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 9 H, 9-H), 0.90 (t, $^3J_{15,14}$ = 7.5 Hz, 3 H, 15-H), 1.00 (d, $^3J_{16,13}$ = 6.9 Hz, 3 H, 16-H), 1.23 (m, 1 H, 14-H_a), 1.44 (m, 1 H, 14-H_b), 1.47 (s, 9 H, 1-H), 1.85

(m, 1 H, 13-H), 2.59 (dd, $^2J_{5a,5b}$ = 14.2 Hz, $^3J_{5a,4}$ = 7.5 Hz, 1 H, 5-H_a), 2.67 (dd, $^2J_{5b,5a}$ = 14.2 Hz, $^3J_{5b,4}$ = 5.3 Hz, 1 H, 5-H_b), 2.85 (bs, 1 H, OH), 4.02 (dd, $^3J_{12,OH}$ = 4.7 Hz, $^3J_{12,13}$ = 3.9 Hz, 1 H, 12-H), 4.69 (td, $^3J_{4,NH/5a}$ = 7.7 Hz, $^3J_{4,5b}$ = 5.6 Hz, 1 H, 4-H), 5.34 (d, $^2J_{10a,10b}$ = 1.0 Hz, 1 H, 10-H_a), 5.50 (d, $^2J_{10b,10a}$ = 1.2 Hz, 1 H, 10-H_b), 6.96 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −0.2 (q, C-9), 11.8 (q, C-15), 15.5 (q, C-16), 23.2 (t, C-14), 28.0 (q, C-1), 38.9 (d, C-13), 39.0 (t, C-5), 51.5 (d, C-4), 76.2 (d, C-12), 82.3 (s, C-2), 95.6 (s, C-8), 104.4 (s, C-7), 125.6 (t, C-10), 126.5 (s, C-6), 170.5 (s, C-3), 173.0 (s, C-11).

Optical rotation: $[\alpha]_D^{20}$ = −11.6 (c = 0.5, $CHCl_3$)

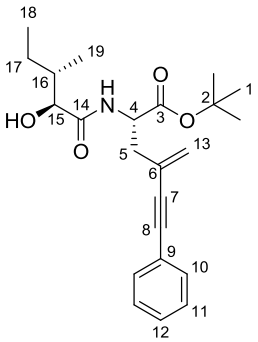
Melting point: 90−92 °C

HRMS (CI):	Calculated	Found
$C_{20}H_{35}NO_4Si$ $[M]^+$	381.2330	381.2305

***tert*-butyl (*R*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-methylene-6-phenylhex-5-ynoate (63b)**

A 4 mL vial was charged with **59** (20.0 mg, 48.6 µmol), phenylacetylene (16.0 µL, 146 µmol, 3.0 equiv.) and triethylamine (20.0 µL, 146 µmol, 3.0 equiv.). Dry THF (1.0 mL) was added, the mixture was purged with Argon and Cu(I)I (0.9 mg, 4.9 µmol, 0.1 equiv.) and $Pd(PPh_3)_4$ (1.7 mg, 1.5 µmol, 5 mol%) were added. The vial was sealed, and the mixture was stirred at 65 °C for 16 hours. The mixture was concentrated *in vacuo* and purified by column chromatography (silica, DCM/Et_2O 9:1) to afford alkyne **63b** (16.7 mg, 43.3 µmol, 89%) as a colorless oil.

R_f(63b) = 0.15 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, $^3J_{18,17}$ = 7.5 Hz, 3 H, 18-H), 1.00 (d, $^3J_{19,16}$ = 7.0 Hz, 3 H, 19-H), 1.17 (m, 1 H, 17-H_a), 1.42 (m, 1 H, 17-H_b), 1.46 (s, 9 H, 1-H), 1.84 (m, 1 H, 16-H), 2.70 (dd, $^2J_{5a,5b}$ = 14.1 Hz, $^3J_{5a,4}$ = 7.2 Hz, 1 H, 5-H_a), 2.64 (dd, $^2J_{5b,5a}$ = 14.3 Hz, $^3J_{5b,4}$ = 5.5 Hz, 1 H, 5-H_b), 2.82 (bs, 1 H, OH), 4.02 (m, 1 H, 15-H), 4.79 (td, $^3J_{4,NH/5a}$ = 7.6 Hz, $^3J_{4,5b}$ = 5.5 Hz, 1 H, 4-H), 5.20 (d, $^2J_{13a,13b}$ = 1.0 Hz, 1 H, 13-H_a), 5.32 (d, $^2J_{13b,13a}$ = 1.2 Hz, 1 H, 13-H_b), 7.01 (d, $^3J_{NH,4}$ = 7.8 Hz, 1 H, NH), 7.31 (m, 3 H, 11-H, 12-H), 7.46 (m, 2 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-18), 15.4 (q, C-19), 23.2 (t, C-17), 28.0 (q, C-1), 38.8 (d, C-16), 39.3 (t, C-5), 51.5 (d, C-4), 76.3 (d, C-15), 82.4 (s, C-2), 88.6 (s, C-7), 90.6 (s, C-8),

122.7 (s, C-9), 124.8 (t, C-13), 126.5 (s, C-6), 128.3 (d, C-11), 128.4 (d, C-12), 131.6 (d, C-10), 170.6 (s, C-3), 173.0 (s, C-14).

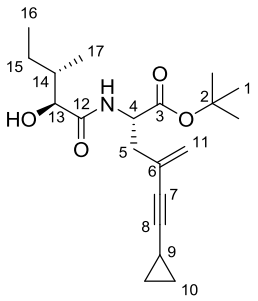
Optical rotation: $[\alpha]_D^{20}$ = −5.7 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{23}H_{32}NO_4$ $[M+H]^+$	386.2326	386.2322

***tert*-butyl (*R*)-6-cyclopropyl-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-methylenehex-5-ynoate (63c)**

A 4 mL vial was charged with **59** (20.0 mg, 48.6 µmol), ethynyl cyclopropane (12.0 µL, 146 µmol, 3.0 equiv.) and triethylamine (20.0 µL, 146 µmol, 3.0 equiv.). Dry THF (1.0 mL) was added, the mixture was purged with Argon and CuI (0.9 mg, 4.9 µmol, 0.1 equiv.) as well as $Pd(PPh_3)_4$ (1.7 mg, 1.5 µmol, 5 mol%) were added. The vial was sealed, and the mixture was stirred at 65 °C for 16 hours after which TLC showed full consumption of the starting material. The mixture was concentrated *in vacuo* and purified by column chromatography (silica, DCM/Et_2O 9:1) to afford alkyne **63c** (15.5 mg, 44.4 µmol, 91%) as a colorless oil.

R_f(63c) = 0.17 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.74 (m, 2 H, 10-H_a), 0.81 (m, 2 H, 10-H_b), 0.90 (t, $^3J_{16,15}$ = 7.5 Hz, 3 H, 16-H), 1.00 (d, $^3J_{17,14}$ = 7.0 Hz, 3 H, 17-H), 1.22 (m, 1 H, 15-H_a), 1.34 (tt, $^3J_{9,10a}$ = 8.1 Hz, $^3J_{9,10b}$ = 5.1 Hz, 1 H, 9-H), 1.45 (m, 1 H, 15-H_b), 1.47 (s, 9 H, 1-H), 1.86 (m, 1 H, 14-H), 2.56 (dd, $^2J_{5a,5b}$ = 14.1 Hz, $^3J_{5a,4}$ = 7.2 Hz, 1 H, 5-H_a), 2.64 (dd, $^2J_{5b,5a}$ = 14.1 Hz, $^3J_{5b,4}$ = 5.3 Hz, 1 H, 5-H_b), 2.93 (m, 1 H, OH), 4.03 (dd, $^3J_{13,OH}$ = 4.4 Hz, $^3J_{13,14}$ = 4.0 Hz, 1 H, 13-H), 4.68 (td, $^3J_{4,NH/5a}$ = 7.6 Hz, $^3J_{4,5b}$ = 5.5 Hz, 1 H, 4-H), 5.20 (d, $^2J_{11a,11b}$ = 1.0 Hz, 1 H, 11-H_a), 5.32 (d, $^2J_{11b,11a}$ = 1.6 Hz, 1 H, 11-H_b), 7.01 (d, $^3J_{NH,4}$ = 7.6 Hz, 1 H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 0.0 (d, C-9), 8.5 (t, C-10), 11.8 (q, C-16), 15.5 (q, C-17), 23.2 (t, C-15), 28.0 (q, C-1), 38.8 (d, C-14), 39.4 (t, C-5), 51.4 (d, C-4), 75.2 (s, C-7), 76.3 (d, C-13), 82.3 (s, C-2), 95.0 (s, C-8), 123.4 (t, C-11), 126.7 (s, C-6), 170.6 (s, C-3), 173.0 (s, C-12).

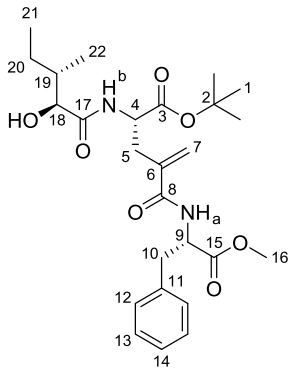
Optical rotation: $[\alpha]_D^{20}$ = −3.5 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{20}H_{32}NO_4$ $[M+H]^+$	350.2326	350.2295

***tert*-butyl (*S*)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-(((*S*)-1-methoxy-1-oxo-3-phenyl propan-2-yl)carbamoyl)pent-4-enoate (64a)**

To a solution of **59** (20.0 mg, 48.6 µmol), HCl-L-Phe-OMe (12.6 mg, 58.4 µmol, 1.2 equiv.) in THF (1 mL) was added triethylamine (27.0 µL, 195 µmol, 4.0 equiv.) and $Pd(PPh_3)_4$ (2.8 mg, 2.43 µmol, 5 mol%) and CO was passed through the solution. The reaction was stirred at room temperature for 5 hours under an atmosphere of CO after which a dark red color occurred. The mixture was diluted with EtOAc, washed with HCl (1 M, aq.) and dried (Na_2SO_4). After removal of the solvent *in vacuo* the residue was purified by column chromatography (silica, DCM/MeOH 95:5) to afford **64a** (20.3 mg, 41.4 µmol, 85%) as an off-white solid.

R_f(64a) = 0.29 (DCM/MeOH 95:5)



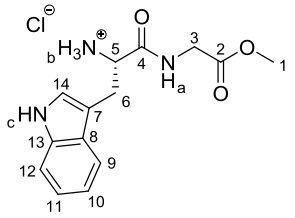
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{21,20}$ = 7.4 Hz, 3 H, 21-H), 0.99 (d, $^3J_{22,19}$ = 6.9 Hz, 3 H, 22-H), 1.22 (m, 1 H, 20-H_a), 1.42 (m, 1 H, 20-H_b), 1.44 (s, 9 H, 1-H), 1.83 (m, 1 H, 19-H), 2.73 (d, $^3J_{5,4}$ = 6.5 Hz, 2 H, 5-H), 3.00 (bs, 1 H, OH), 3.15 (dd, $^2J_{10a,10b}$ = 13.9 Hz, $^3J_{10a,9}$ = 6.2 Hz, 1 H, 10-H_a), 3.22 (dd, $^2J_{10b,10a}$ = 13.9 Hz, $^3J_{10b,9}$ = 5.8 Hz, 1 H, 10-H_b), 3.75 (s, 3 H, 16-H), 3.98 (t, $^3J_{18,19/OH}$ = 4.3 Hz, 1 H, 18-H), 4.41 (q, $^3J_{4,5/NHb}$ = 6.7 Hz, 1 H, 4-H), 4.91 (dt, $^3J_{9,NHa}$ = 7.6 Hz, $^3J_{9,10}$ = 6.0 Hz, 1 H, 9-H), 5.43 (s, 1 H, 7-H_a), 5.64 (s, 1 H, 7-H_b), 6.67 (d, $^3J_{NHa,9}$ = 7.5 Hz, 1 H, NH_a), 7.12 (m, 2 H, 12-H), 7.25 (m, 3 H, 13-H, 14-H), 7.56 (d, $^3J_{NHb,4}$ = 7.1 Hz, 1 H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-21), 15.3 (q, C-22), 23.2 (t, C-20), 28.0 (q, C-1), 34.7 (t, C-5), 37.6 (t, C-10), 38.9 (d, C-19), 52.4 (q, C-16), 52.7 (d, C-4), 53.4 (d, C-9), 75.9 (d, C-18), 82.3 (s, C-2), 122.3 (t, C-7), 127.1 (d, C-14), 128.6 (d, C-13), 129.2 (d, C-12), 135.8 (s, C-11), 140.1 (s, C-6), 167.9 (s, C-8), 170.1 (s, C-3), 171.9 (s, C-15), 173.5 (s, C-17).

Optical rotation:	$[\alpha]_D^{20}$ = +18.0 (c = 1.0, $CHCl_3$)	
Melting point:	77–79 °C	
HRMS (CI):	Calculated	Found
$C_{26}H_{39}N_2O_7$ $[M+H]^+$	491.2752	491.2723

tert-butyl (*S*)-4-(((*S*)-3-(1*H*-indol-3-yl)-1-((2-methoxy-2-oxoethyl)amino)-1-oxopropan-2-yl)car-bamoyl)-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)pent-4-enoate (64b)

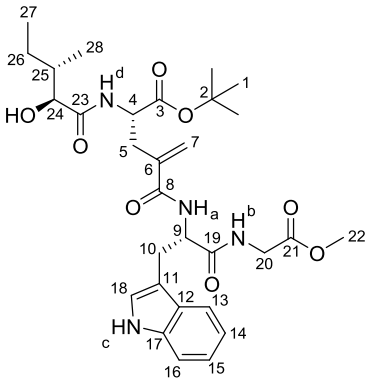
At 0 °C *N*-Boc-L-Trp-Gly-OMe (300 mg, 799 μmol) was treated with HCl (4.0 M in dioxane, 2.0 mL, 8.00 mmol, 10 equiv.) for 2 hours until complete Boc-deprotection was observed by TLC. The solvent was removed *in vacuo* to afford HCl-L-Trp-Gly-OMe (249 mg, 799 μmol, quant.) as a white hygroscopic solid.



^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.13 (dd, $^2J_{6a,6b}$ = 14.8 Hz, $^3J_{6a,5}$ = 8.0 Hz, 1 H, 6-H_a), 3.28 (dd, $^2J_{6b,6a}$ = 14.8 Hz, $^3J_{6b,5}$ = 5.5 Hz, 1 H, 6-H_b), 3.65 (s, 3 H, 1-H), 3.92 (dd, $^2J_{3a,3b}$ = 17.5 Hz, $^3J_{3a,NHa}$ = 5.8 Hz, 1 H, 3-H_a), 3.97 (dd, $^2J_{3b,3a}$ = 17.5 Hz, $^3J_{3b,NHa}$ = 5.8 Hz, 1 H, 3-H_b), 4.05 (m, 1 H, 5-H), 7.01 (td, $^3J_{10,9/11}$ = 7.4 Hz, $^4J_{10,12}$ = 0.9 Hz, 1 H, 10-H), 7.09 (td, $^3J_{11,10/12}$ = 7.4 Hz, $^4J_{11,9}$ = 1.0 Hz, 1 H, 11-H), 7.25 (d, $^3J_{14,NHc}$ = 2.3 Hz, 1 H, 14-H), 7.37 (d, $^3J_{12,11}$ = 8.1 Hz, 1 H, 12-H), 7.71 (d, $^3J_{9,10}$ = 7.8 Hz, 1 H, 9-H), 8.19 (bs, 3 H, NH_3^+), 9.13 (t, $^3J_{NHa,3}$ = 5.7 Hz, 1 H, NH_a), 11.1 (d, $^3J_{NHc,14}$ = 1.2 Hz, 1 H, NH_c).

To a solution of **59** (20.0 mg, 48.6 μmol), HCl-L-Trp-Gly-OMe (16.7 mg, 53.6 μmol, 1.1 equiv.) in THF (1 mL) was added triethylamine (27.0 μL, 195 μmol, 4.0 equiv.) and $Pd(PPh_3)_4$ (2.8 mg, 2.43 μmol, 5 mol%) and CO was passed through the solution. The reaction was stirred at room temperature for 5 hours under an atmosphere of CO after which a dark red color occurred. The mixture was diluted with EtOAc, washed with HCl (1 M) and dried (Na_2SO_4). After removal of the solvent *in vacuo* the residue was purified by column chromatography (silica, DCM/MeOH 95:5) to afford **64b** (26.0 mg, 44.3 μmol, 91%) as a colorless resin.

R_f(64b) = 0.14 (DCM/MeOH 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, $^3J_{27,26}$ = 7.5 Hz, 3 H, 27-H), 0.85 (d, $^3J_{28,25}$ = 6.9 Hz, 3 H, 28-H), 1.06 (m, 1 H, 26-H_a), 1.27 (m, 1 H, 26-H_b), 1.41 (s, 9 H, 1-H), 1.66 (m, 1 H, 25-H), 2.31 (dd, $^2J_{5a,5b}$ = 13.8 Hz, $^3J_{5a,4}$ = 9.8 Hz, 1 H, 5-H_a), 3.10 (dd, $^2J_{5b,5a}$ = 13.6 Hz, $^3J_{5b,4}$ = 3.1 Hz, 1 H, 5-H_b), 3.24 (bs, 1 H, OH), 3.22 (dd, $^2J_{10a,10b}$ = 14.8 Hz, $^3J_{10a,9}$ = 6.0 Hz, 1 H, 10-H_a), 3.48 (dd,

$^{2}J_{10b,10a}$ = 14.9 Hz, $^{3}J_{10b,9}$ = 5.5 Hz, 1 H, 10-H_b), 3.68 (s, 3 H, 22-H), 3.85 (m, 2 H, 20-H_a, 24-H), 4.05 (dd, $^{2}J_{20b,20a}$ = 17.6 Hz, $^{3}J_{20b,NH}$ = 6.0 Hz, 1 H, 20-H_b), 4.55 (ddd, $^{3}J_{4,5a}$ = 9.8 Hz, $^{3}J_{4,NHd}$ = 7.9 Hz, $^{3}J_{4,5b}$ = 3.5 Hz, 1 H, 4-H), 4.92 (dt, $^{3}J_{9,NHa}$ = 7.6 Hz, $^{3}J_{9,10}$ = 5.9 Hz, 1 H, 9-H), 5.20 (m, 2 H, 7-H), 6.38 (d, $^{3}J_{NHa,9}$ = 8.4 Hz, 1 H, NH_a), 7.11 (m, 1 H, 14-H), 7.17 (m, 2 H, 15-H, 18-H), 7.35 (d, $^{3}J_{16,15}$ = 8.1 Hz, 1 H, 16-H), 7.44 (d, $^{3}J_{NHd,4}$ = 7.8 Hz, 1 H, NH_d), 7.61 (d, $^{3}J_{13,14}$ = 7.8 Hz, 1 H, 13-H), 7.67 (t, $^{3}J_{NHb,20}$ = 5.6 Hz, 1 H, NH_b), 8.46 (bs, 1 H, NH_c).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.6 (q, C-27), 15.3 (q, C-28), 23.5 (t, C-26), 26.9 (t, C-10), 27.9 (q, C-1), 36.7 (t, C-5), 38.6 (d, C-25), 41.2 (t, C-20), 51.5 (d, C-4), 52.1 (q, C-22), 53.8 (d, C-9), 75.9 (d, C-24), 82.7 (s, C-2), 109.8 (s, C-11), 111.4 (d, C-16), 118.3 (d, C-13), 119.6 (d, C-14), 121.4 (t, C-7), 122.1 (d, C-15), 123.5 (d, C-18), 127.7 (s, C-12), 136.1 (s, C-17), 140.8 (s, C-6), 167.9 (s, C-8), 170.5 (s, C-21), 170.8 (s, C-3), 171.9 (s, C-19), 173.7 (s, C-23).

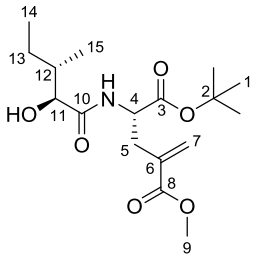
Optical rotation: $[\alpha]_D^{20}$ = +18.0 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{29}H_{37}N_4O_4$ $[M\text{-}CH_2CO_2Me]^+$	513.2713	513.2678

1-(*tert*-butyl) 5-methyl *(S)*-2-((2*S*,3*S*)-2-hydroxy-3-methylpentanamido)-4-methylenepentanedioate (65)

To a solution of **59** (30.0 mg, 72.9 µmol) in dry MeOH (1 mL) was added triethylamine (41.0 µL, 292 µmol, 4.0 equiv.) and $Pd(PPh_3)_4$ (4.2 mg, 3.7 µmol, 5 mol%) and CO was passed through the solution. The reaction was stirred at room temperature for 5 hours under an atmosphere of CO after which a dark red color occurred. The mixture was concentrated *in vacuo*, and the residue purified by column chromatography (silica, DCM/diethyl ether 9:1) to afford **65** (23.4 mg, 68.1 µmol, 93%) as a colorless oil.

R_f(65) = 0.11 (DCM/Et_2O 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, $^{3}J_{14,13}$ = 7.5 Hz, 3 H, 14-H), 0.99 (d, $^{3}J_{15,12}$ = 7.0 Hz, 3 H, 15-H), 1.19 (m, 1 H, 13-H_a), 1.40 (m, 1 H, 13-H_b), 1.44 (s, 9 H, 1-H), 1.83 (m, 1 H, 12-H), 2.72 (dd, $^{2}J_{5a,5b}$ = 14.2 Hz, $^{3}J_{5a,4}$ = 8.6 Hz, 1 H, 5-H_a), 2.82 (dd, $^{2}J_{5b,5a}$ = 14.2 Hz, $^{3}J_{5b,4}$ = 5.4 Hz, 1 H, 5-H_b), 2.90 (d, $^{3}J_{OH,11}$ = 5.5 Hz, 1 H, OH), 3.78 (s, 3 H, 9-H), 4.00 (dd, $^{3}J_{11,OH}$ = 5.3 Hz, $^{3}J_{11,12}$ = 3.7 Hz, 1 H, 11-H), 4.66 (td, $^{3}J_{4,5a/NH}$ = 8.3 Hz, $^{3}J_{4,5b}$ = 5.6 Hz, 1 H, 4-H), 5.69 (s, 1 H, 7-H_a), 6.27 (s, 1 H, 7-H_b), 7.12 (d, $^{3}J_{NH,4}$ = 7.8 Hz, 1 H, NH).

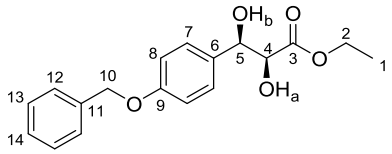
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.8 (q, C-14), 15.4 (q, C-15), 23.2 (t, C-13), 28.0 (q, C-1), 34.7 (t, C-5), 38.7 (d, C-12), 52.1 (d, C-4), 52.2 (q, C-9), 76.1 (d, C-11), 82.4 (s, C-2), 128.6 (t, C-7), 135.8 (s, C-6), 167.3 (s, C-8), 170.6 (s, C-3), 173.1 (s, C-10).

Optical rotation:	$[\alpha]_D^{20}$ = −12.1 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{17}H_{30}NO_6$ $[M+H]^+$	344.2068	344.2065

ethyl (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-2,3-dihydroxypropanoate (67)[389]

To a well stirred mixture of *t*-BuOH (420 mL) and H_2O (420 mL) were successively added K_2CO_3 (35.1 g, 254 mmol, 3.0 equiv.), $K_3[Fe(CN)_6]$ (84.0 g, 254 mmol, 3.0 equiv.), $(DHQD)_2Phal$ (633 mg, 813 µmol, 9.6 mol%) and $K_2[OsO_2(OH)_4]$ (131 mg, 356 µmol, 4.2 mol%). After addition of methanesulfonamide (8.05 g, 85.0 mmol, 1.0 equiv.) the solution was cooled to 0 °C, stirred for 5 minutes and cinnamyl ester **66** (23.9 g, 85.0 mmol, 1.0 equiv.) was added. The resulting solution was stirred at 0 °C for 2 hours and then at room temperature until complete consumption of the starting material was observed by TLC. The reaction was quenched by addition of sat. $Na_2S_2O_3$ solution and the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Recrystallization (PE/EtOAc) and flash chromatography (silica, PE/EtOAc 1:1) afforded diol **67** (23.6 g, 74.5 mmol, 88%, >98% *ee*) as white solid.

R_f(67) = 0.27 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 2.65 (d, $^3J_{OHb,5}$ = 6.8 Hz, 1 H, OH_b), 3.09 (d, $^3J_{OHa,4}$ = 5.9 Hz, 1 H, OH_a), 4.25 (q, $^3J_{2,1}$ = 7.1 Hz, 2 H, 2-H), 4.32 (dd, $^3J_{4,OHa}$ = 5.9 Hz, $^3J_{4,5}$ = 3.2 Hz, 1 H, 4-H), 4.94 (dd, $^3J_{5,OHb}$ = 6.6 Hz, $^3J_{5,4}$ = 3.2 Hz, 1 H, 5-H), 5.07 (s, 2 H, 10-H), 6.97 (m, 2 H, 8-H), 7.37 (m, 7 H, 7-H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.1 (q, C-1), 62.1 (t, C-2), 70.0 (t, C-10), 74.2 (d, C-5), 74.7 (d, C-4), 114.7 (d, C-8), 127.4 (d, C-12), 127.6 (d, C-7), 127.9 (d, C-14), 128.5 (d, C-13), 132.3 (s, C-6), 136.9 (s, C-11), 158.6 (s, C-9), 172.7 (s, C-3).

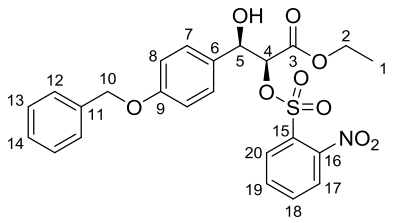
Optical rotation:	$[\alpha]_D^{20}$ = –7.3 (c = 1.0, $CHCl_3$)	
Melting point:	123-125 °C	
HRMS (CI):	Calculated	Found
$C_{18}H_{18}O_4$ $[M\text{-}H_2O]^+$	298.1200	298.1179

ethyl (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-3-hydroxy-2-(((2-nitrophenyl)sulfonyl)oxy)propanoate (68)[389]

Diol **67** (6.00 g, 19.0 mmol, 1.0 equiv.) was dissolved in anhydrous DCM (150 mL), the solution cooled to 0 °C and 2-nitrobenzenesulfonyl chloride (5.46 g, 24.7 mmol, 1.3 equiv.) was added. After dropwise addition of triethylamine (3.44 mL, 24.7 mmol, 1.3 equiv.) over 5 min. the mixture was stirred for 5.5 hours at 0-3 °C. The reaction was acidified to pH = 2 by addition of aqueous HCl (1 M), the layers were separated, and the aqueous layer extracted twice with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated at room temperature under reduced pressure. Rapid flash chromatography

(silica, DCM/EtOAc 9:1) afforded nosylate **68** (9.31 g, 17.8 mmol, 94%, contains 4% EtOAc) as yellow resin which was immediately used in the consecutive step.

R_f(68) = 0.40 (DCM/EtOAc 9:1)



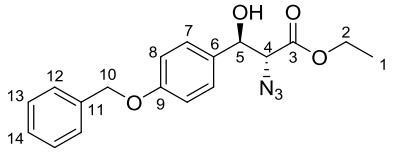
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, $^3J_{1,2}$ = 7.1 Hz, 3 H, 1-H), 2.49 (bs, 1 H, OH), 4.09 (dq, $^2J_{2a,2b}$ = 10.8 Hz, $^3J_{2a,1}$ = 7.3 Hz, 1 H, 2-H_a), 4.12 (dq, $^2J_{2b,2a}$ = 10.8 Hz, $^3J_{2b,1}$ = 7.1 Hz, 1 H, 2-H_b), 5.02 (s, 2 H, 10-H), 5.08 (d, $^3J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 5.14 (d, $^3J_{5,4}$ = 5.0 Hz, 1 H, 5-H), 6.84 (d, $^3J_{8,7}$ = 8.7 Hz, 2 H, 8-H), 7.22 (d, $^3J_{7,8}$ = 8.7 Hz, 2 H, 7-H), 7.36 (m, 5 H, 12-H, 13-H, 14-H), 7.66 (m, 1 H, 18-H), 7.73 (m, 2 H, 17-H, 19-H), 8.00 (d, $^3J_{20,19}$ = 7.8 Hz, 1 H, 20-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.8 (q, C-1), 62.2 (t, C-2), 69.9 (t, C-10), 73.4 (d, C-5), 83.5 (d, C-4), 114.8 (d, C-8), 124.8 (d, C-17), 127.4 (d, C-12), 127.8 (d, C-7), 128.1 (d, C-14), 128.6 (d, C-13), 129.3 (s, C-6), 129.6 (s, C-15), 131.3 (d, C-20), 132.3 (d, C-18), 134.8 (d, C-19), 136.7 (s, C-11), 148.0 (s, C-16), 159.0 (s, C-9), 166.2 (s, C-3).

ethyl (2*R*,3*R*)-2-azido-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate (69)[389]

Under an atmosphere of N_2, freshly prepared nosylate **68** (9.51 g, 19.0 mmol, 1.0 equiv.) was dissolved in anhydrous DMF and sodium azide (2.47 g, 37.9 mmol, 2.0 equiv.) was added. After heating to 50 °C overnight the mixture was diluted with EtOAc, washed three times with water and once with brine. The solvent was evaporated, and the crude product purified by column chromatography (silica, PE/EtOAc 8:2) to obtain azide **69** (5.40 g, 15.8 mmol, 83%) as a yellow solid.

R_f(69) = 0.33 (PE/EtOAc 4:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 2.79 (d, $^3J_{OH,5}$ = 4.3 Hz, 1 H, OH), 4.08 (d, $^3J_{4,5}$ = 7.1 Hz, 1 H, 4-H), 4.25 (q, $^3J_{2,1}$ = 7.1 Hz, 2 H, 1-H), 4.96 (dd, $^3J_{5,4}$ = 7.0 Hz, $^3J_{5,OH}$ = 4.5 Hz, 1 H, 5-H), 5.07 (s, 2 H, 10-H), 6.98 (d, $^3J_{8,7}$ = 8.7 Hz, 2 H, 8-H), 7.31 (d, $^3J_{7,8}$ = 8.7 Hz, 2 H, 7-H), 7.38 (m, 5 H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, C-1), 62.1 (t, C-2), 66.8 (d, C-4), 70.0 (t, C-10), 73.7 (d, C-5), 114.9 (d, C-8), 127.4 (d, C-12), 127.9 (d, C-7), 128.0 (d, C-14), 128.6 (d, C-13), 131.3 (s, C-6), 136.8 (s, C-11), 159.1 (s, C-9), 168.9 (s, C-3).

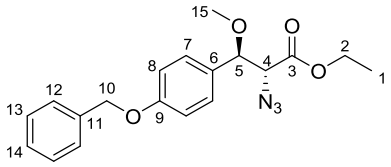
Optical rotation: $[\alpha]_D^{20}$ = +8.4 (c = 1.0, $CHCl_3$)

Melting point:	95-98 °C (decomposition)	
HRMS (CI):	Calculated	Found
$C_{16}H_{23}N_3O_3$ $[M\text{-}C_2H_5O]^+$	305.1739	305.1692

ethyl (2*R*,3*R*)-2-azido-3-(4-(benzyloxy)phenyl)-3-methoxypropanoate (70)

To a solution of azide **69** (7.50 g, 22.0 mmol) in CH_2Cl_2 (440 mL) were added silver oxide (10.2 g, 43.9 mmol, 2.0 equiv.) and methyl iodide (41.2 mL, 659 mmol, 30.0 equiv.). The mixture was stirred at reflux overnight, additional silver oxide (5.09 g, 22.0, 1.0 equiv.) was added, and the reaction stirred for another 8 hours before being filtrated through a pad of celite. The solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, PE/EtOAc 95:5 → 9:1) to afford methyl ether **70** (6.79 g, 19.1 mmol, 87%) as a colorless oil.

R_f(70) = 0.31 (PE/EtOAc 8:2)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 3.24 (s, 3 H, 15-H), 4.00 (d, $^3J_{4,5}$ = 7.3 Hz, 1 H, 4-H), 4.23 (dq, $^2J_{2a,2b}$ = 10.8 Hz, $^3J_{2a,1}$ = 7.2 Hz, 1 H, 2-H_a), 4.26 (dq, $^2J_{2b,2a}$ = 10.8 Hz, $^3J_{2b,1}$ = 7.2 Hz, 1 H, 2-H_b), 4.49 (d, $^3J_{5,4}$ = 7.3 Hz, 1 H, 5-H), 5.07 (s, 2 H, 10-H), 6.99 (d, $^3J_{8,7}$ = 8.7 Hz, 2 H, 8-H), 7.28 (d, $^3J_{7,8}$ = 8.6 Hz, 2 H, 7-H), 7.37 (m, 5 H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.1 (q, C-1), 56.9 (q, C-15), 61.8 (t, C-2), 66.4 (d, C-4), 70.0 (t, C-10), 82.7 (d, C-5), 114.9 (d, C-8), 127.5 (d, C-12), 128.0 (d, C-14), 128.6 (d, C-13), 128.8 (s, C-6), 128.8 (d, C-7), 136.8 (s, C-11), 159.3 (s, C-9), 168.5 (s, C-3).

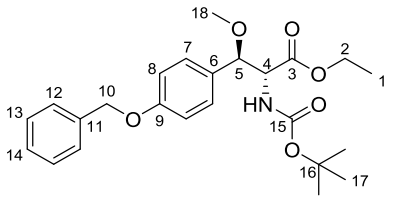
Optical rotation:	$[\alpha]_D^{20}$ = +14.7 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{19}H_{21}NO_4$ $[M\text{-}N_2]^+$	327.1465	327.1482

ethyl (2*R*,3*R*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy propanoate (71)

Methyl ether **70** (9.06 g, 25.5 mmol) was dissolved in THF/H_2O (255 mL, 25:1), triphenylphosphine (20.1 g, 76.0 mmol, 3.0 equiv.) was added and the mixture was heated to 50 °C for 16 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in THF/H_2O (350 mL, 2.5:1). Boc_2O (7.10 mL, 30.6 mmol, 1.2 equiv.) and $NaHCO_3$ (4.28 g, 51.0 mmol, 2.0 equiv.) were added and the reaction was stirred for 6 hours at 0 °C. The mixture was acidified with 1 M HCl (pH = 2) and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried

(Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica, PE/EtOAc 85:15) afforded Boc-protected amine **71** (10.8 g, 25.2 mmol, 99%) as a colorless resin.

R_f(71) = 0.24 (PE/EtOAc 85:15)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, $^3J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 1.40 (s, 9 H, 17-H), 3.30 (s, 3 H, 15-H), 4.10 (q, $^3J_{2,1}$ = 7.0 Hz, 1 H, 2-H), 4.48 (d, $^3J_{5,4}$ = 4.5 Hz, 1 H, 5-H), 4.56 (dd, $^3J_{4,NH}$ = 8.7 Hz, $^3J_{4,5}$ = 5.5 Hz, 1 H, 4-H), 5.06 (s, 2 H, 10-H), 5.12 (d, $^3J_{NH,4}$ = 8.8 Hz, 1 H, NH), 6.96 (d, $^3J_{8,7}$ = 8.7 Hz, 2 H, 8-H), 7.21 (d, $^3J_{7,8}$ = 8.6 Hz, 2 H, 7-H), 7.37 (m, 5 H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, C-1), 28.2 (q, C-17), 57.4 (q, C-18), 58.4 (d, C-4), 61.1 (t, C-2), 70.0 (t, C-10), 79.8 (d, C-16), 83.3 (d, C-5), 114.7 (d, C-8), 127.4 (d, C-12), 128.0 (d, C-7), 128.2 (d, C-14), 128.6 (d, C-13), 129.2 (s, C-6), 136.9 (s, C-11), 155.1 (s, C-15), 158.8 (s, C-9), 170.3 (s, C-3).

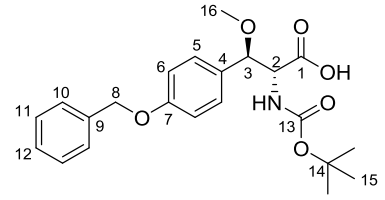
Optical rotation: $[\alpha]_D^{20}$ = +21.3 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{24}H_{32}NO_6$ $[M+H]^+$	430.2224	430.2248

(2*R*,3*R*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxypropanoic acid (72)

To a solution of ethyl ester **71** (1.66 g, 3.86 mmol) in THF (39 mL) was slowly added a freshly prepared solution of lithium hydroxide (4.25 mL, 4.25 mmol, 1.0 M in H_2O, 1.1 equiv.) at 0 °C. After complete conversion (TLC), the mixture was concentrated, the residue redissolved in water and acidified with 1 M HCl (pH = 2). The aqueous layer was extracted twice with EtOAc, and the combined organic layer washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **72** (1.53 g, 3.81 mmol, 99%) as a white solid.

R_f(72) = 0.09 (PE/EtOAc 7:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, 15-H), 3.23 (s, 3 H, 16-H), 4.41 (d, $^3J_{3,2}$ = 4.8 Hz, 1 H, 3-H), 4.49 (dd, $^3J_{2,NH}$ = 8.9 Hz, $^3J_{2,3}$ = 5.1 Hz, 1 H, 2-H), 4.99 (s, 2 H, 8-H), 5.06 (d,

$^{3}J_{NH,2}$ = 8.9 Hz, 1 H, NH), 6.89 (d, $^{3}J_{6,5}$ = 8.7 Hz, 2 H, 6-H), 7.14 (d, $^{3}J_{5,6}$ = 8.6 Hz, 2 H, 5-H), 7.25 (m, 1 H, 12-H), 7.33 (m, 4 H, 10-H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.2 (q, C-15), 57.3 (q, C-16), 58.2 (d, C-2), 70.0 (t, C-8), 80.3 (s, C-14), 83.0 (d, C-3), 114.8 (d, C-6), 127.5 (d, C-6, C-10), 128.0 (d, C-5), 128.2 (d, C-12), 128.6 (d, C-11), 136.8 (s, C-4/C-9), 126.9 (s, C-4/C-9), 158.9 (s, C-7/C-13), 159.0 (s, C-7/C-13), 174.0 (s, C-1).

Optical rotation: $[\alpha]_D^{20}$ = -35.9 (c = 1.0, $CHCl_3$)

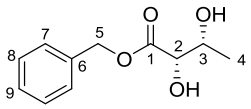
Melting point: 105-107 °C

HRMS (CI):	Calculated	Found
$C_{22}H_{28}NO_6$ $[M+H]^+$	402.1911	401.1887

benzyl (2*S*,3*R*)-2,3-dihydroxybutanoate (75)[346]

To a well stirred solution of AD-mix β (40.0 g) in *t*-BuOH/H_2O (300 mL, 1:1) was added benzyl crotonate (5.29 g, 30.0 mmol) and the mixture was stirred at 0-4 °C for 48 hours. The reaction was quenched by addition of sat. $Na_2S_2O_3$ solution and diluted with diethyl ether. After separation of the layers, the organic layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica, PE/EtOAc 6:4) afforded diol **75** (4.83 g, 23.0 mmol, 77%) as a colorless oil.

R_f(75) = 0.19 (PE/EtOAc 6:4)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, $^{3}J_{4,3}$ = 6.5 Hz, 3 H, 4-H), 2.07 (d, $^{3}J_{OH,3}$ = 8.2 Hz, 1 H, OH), 3.09 (d, $^{3}J_{OH,2}$ = 5.7 Hz, 1 H, OH), 4.06 (dd, $^{3}J_{2,OH}$ = 5.6 Hz, $^{3}J_{2,3}$ = 2.6 Hz, 1 H, 2-H), 4.12 (m, 1 H, 3-H), 5.26 (s, 2 H, 5-H), 7.37 (m, 5 H, 7-H, 8-H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.7 (q, C-4), 67.7 (t, C-5), 68.7 (d, C-3), 74.4 (d, C-2), 128.3 (d, C-7), 128.6 (d, C-9), 128.7 (d, C-8), 134.9 (s, C-6), 173.2 (s, C-1).

Optical rotation: $[\alpha]_D^{20}$ = +14.2 (c = 1.0, $CHCl_3$)

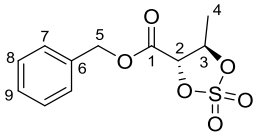
HRMS (CI):	Calculated	Found
$C_{11}H_{15}NO_4$ $[M+H]^+$	211.0965	211.0979

benzyl (4*S*,5*R*)-5-methyl-1,3,2-dioxathiolane-4-carboxylate 2,2-dioxide (76)[346]

To a solution of diol **75** (4.20 g, 20.0 mmol) in CH_2Cl_2 (33 mL) was dropwise added thionyl chloride (2.92 mL, 40.0 mmol, 2.0 equiv.) and the solution was heated to reflux for 3 hours. After removal of the solvent the crude sulfite was dried on high vacuo for one hour and subsequently dissolved in a mixture of MeCN/CCl_4/H_2O (90 mL, 1:1:1.5). $NaIO_4$ (12.8 g, 60.0 mmol, 3.0 equiv.) and $RuCl_3 \cdot H_2O$ (5.00 mg, 24.1 µmmol, 0.1 mol%) were added and the

mixture was stirred for 3 hours at 40 °C. The reaction was diluted with diethyl ether, the layers separated, and the organic layer was dried ($MgSO_4$). After removal of the solvent *in vacuo* the residue was purified by column chromatography (silica, PE/EtOAc 3:1) to yield sulfate **76** (4.35 g, 16.0 mmol, 80%) as a colorless oil.

R_f(76) = 0.22 (PE/EtOAc 3:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.71 (d, $^3J_{4,3}$ = 6.2 Hz, 3 H, 4-H), 4.86 (d, $^3J_{2,3}$ = 7.6 Hz, 1 H, 2-H), 5.04 (dq, $^3J_{3,2}$ = 7.6 Hz, $^3J_{3,4}$ = 6.2 Hz, 1 H, 3-H), 5.28 (d, $^2J_{5a,5b}$ = 12.1 Hz, 1 H, 5-H_a), 5.32 (d, $^2J_{5b,5a}$ = 12.1 Hz, 1 H, 5-H_b), 7.38 (m, 5 H, 7-H, 8-H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.6 (q, C-4), 68.7 (t, C-5), 80.4 (d, C-3), 81.1 (d, C-2), 128.6 (d, C-7), 128.8 (d, C-8), 129.1 (d, C-9), 133.9 (s, C-6), 164.4 (s, C-1).

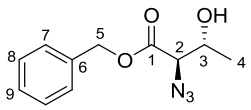
Optical rotation: $[\alpha]_D^{20}$ = +9.6 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{11}H_{13}O_6S$ $[M+H]^+$	273.0427	273.0398

benzyl (2*R*,3*R*)-2-azido-3-hydroxybutanoate (77)[346]

Cyclic sulfate **76** (4.20 g, 15.4 mmol) was dissolved in acetone/H_2O (93.5 mL, 10:1) and sodium azide (1.30 g, 20.1 mmol, 1.3 equiv.) was added. The mixture was heated to 50 °C until complete consumption of the starting material was observed (TLC) and the solvents removed *in vacuo*. The residue was redissolved in diethyl ether/H_2O (310 mL, 30:1), cooled to 0 °C and 2 M H_2SO_4 solution (25 mL) was added dropwise. The resulting mixture was vigorously stirred for 48 hours, the layers separated, and the organic layer concentrated *in vacuo*. Flash chromatography (silica, PE/EtOAc 9:1 → 3:1) afforded azide **77** (3.41 g, 14.5 mmol, 94%) as a colorless oil.

R_f(77) = 0.57 (PE/EtOAc 3:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, $^3J_{4,3}$ = 6.4 Hz, 3 H, 4-H), 2.27 (d, $^3J_{OH,3}$ = 6.6 Hz, 1 H, OH), 3.99 (d, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 4.14 (m, 1 H, 3-H), 5.24 (d, $^2J_{5a,5b}$ = 12.2 Hz, 1 H, 5-H_a), 5.28 (d, $^2J_{5b,5a}$ = 12.2 Hz, 1 H, 5-H_b), 7.38 (m, 5 H, 7-H, 8-H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.0 (q, C-4), 67.1 (d, C-2), 67.7 (t, C-5), 68.1 (d, C-3), 128.4 (d, C-7), 128.7 (d, C-8, C-9), 134.8 (s, C-6), 168.7 (s, C-1).

Optical rotation: $[\alpha]_D^{20}$ = +58.7 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found

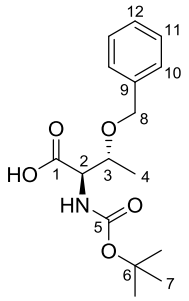
$C_{11}H_{14}N_3O_3$ $[M+H]^+$	236.1030	236.1038

_O_-benzyl-_N_-(_tert_-butoxycarbonyl)-D-_allo_-threonine (79)

To a solution of azide **77** (3.30 g, 14.0 mmol) in MeOH (20 mL) was added palladium on carbon (330 mg, 10 w%) and the mixture was stirred under H_2 (3 bar) for 12 hours. After filtration over celite, the filtrate was concentrated *in vacuo* and redissolved in *n*-BuOH (60 mL). Boc_2O (3.58 mL, 15.4 mmol, 1.1 equiv.), $NaHCO_3$ (1.82 g, 21.6 mmol, 1.5 equiv.) and water (20 mL) were added, and the solution was stirred for 10 hours at room temperature. The reaction mixture was concentrated, redissolved in EtOAc and threonine **78** (2.46 g, 11.2 mmol, 80%) was precipitated by addition of hexane.

Threonine **78** was dissolved in DMF (40 mL), cooled to –15 °C and NaH (987 mg, 24.7 mmol, 2.2 equiv., 60% dispersion in mineral oil) was added. After stirring for 2 hours at –15 °C, benzyl bromide (1.47 mL, 12.3 mmol, 1.1 equiv.) was added and the mixture stirred at room temperature for 5 hours. The reaction was quenched by careful addition of water and washed twice with diethyl ether. Acidification to pH 3-4 by aq. citric acid (10 w%) was followed by extraction with EtOAc (3x) and washing of the combined organic layer with brine. After drying (Na_2SO_4) and removal of the solvent under reduced pressure, flash chromatography (silica, PE/EtOAc 4:1 → 3:1) afforded *O*-Bn-threonine **79** (1.31 g, 4.23 mmol, 38%) as an off-white solid.

R_f(79) = 0.13 (PE/EtOAc 3:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, $^3J_{4,3}$ = 6.5 Hz, 3 H, 4-H), 1.44 (s, 9 H, 7-H), 3.90 (m, 1 H, 3-H), 4.57 (m, 3 H, 2-H, 8-H), 5.27 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, NH), 7.30 (m, 5 H, 10-H, 11-H, 12-H), 10.37 (bs, 1 H, COOH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.1 (q, C-4), 28.3 (q, C-7), 56.7 (d, C-2), 71.0 (t, C-8), 74.9 (d, C-3), 80.2 (s, C-6), 127.8 (d, C-10, C-12), 128.4 (d, C-11), 137.7 (s, C-9), 155.6 (s, C-5), 175.0 (s, C-1).

Optical rotation: $[\alpha]_D^{20}$ = –8.2 (c = 1.0, $CHCl_3$)

Melting point: 170-172 °C

HRMS (CI):	Calculated	Found
$C_{16}H_{24}NO_5$ $[M+H]^+$	310.1649	310.1653

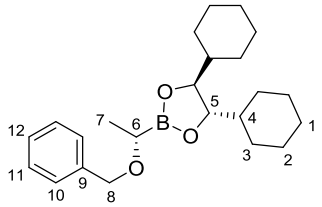
(4*S*,5*S*)-2-((*S*)-1-(benzyloxy)ethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (81)

According to **GP-5**, boronic ester **80**[348] (4.00 g, 16.0 mmol) was reacted with CH_2Cl_2 (3.09 mL, 48.0 mmol, 3.0 equiv.), DIPA (3.08 mL, 21.6 mmol, 1.35 equiv.), *n*-BuLi (7.99 mL, 20.0 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (4.36 g, 32.0 mmol, 2.0 equiv.) overnight.

The nucleophile solution was prepared by suspending sodium hydride (831 mg, 20.8 mmol, 1.3 equiv.) in dry DMSO/THF (42 mL, 3:1) and stirring at room temperature for 6 hours after addition of benzyl alcohol (2.33 mL, 22.4 mmol, 1.4 equiv.).

To the solution of the chloro-boronic ester mixture was added the nucleophile solution at 0 °C and the mixture was stirred at room temperature until complete consumption of the starting material was observed (NMR). After aqueous work-up and flash chromatography (silica, pentane/diethyl ether 9:1), benzyl ether **81** (4.01 g, 10.8 mmol, 68%) was obtained as a colorless oil.

R_f(81) = 0.30 (pentane/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.11 (m, 10 H, 1-H, 2-H, 3-H), 1.32 (d, $^3J_{7,6}$ = 7.5 Hz, 3 H, 7-H), 1.36 (m, 2 H, 4-H), 1.60 (m, 2 H, 3-H‘), 1.68 (m, 2 H, 2-H‘), 1.77 (m, 6 H, 1-H‘, 2-H‘‘, 3-H‘‘), 3.45 (q, $^3J_{6,7}$ = 7.5 Hz, 1 H, 6-H), 3.91 (d, $^3J_{5,4}$ = 3.7 Hz, 1 H, 5-H), 3.93 (d, $^3J_{5',4}$ = 3.6 Hz, 1 H, 5-H‘), 4.54 (d, $^2J_{8a,8b}$ = 12.0 Hz, 1 H, 8-H_a), 4.59 (d, $^2J_{8b,8a}$ = 12.0 Hz, 1 H, 8-H_b), 7.25 (m, 1 H, 12-H), 7.33 (m, 4 H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.8 (q, C-7), 25.9 (t, C-2), 26.0 (t, C-2‘), 26.4 (t, C-1), 27.3 (t, C-3), 28.1 (t, C-3‘), 42.9 (d, C-4), 62.8 (d, C-6), 71.6 (t, C-8), 83.6 (d, C-5), 127.3 (d, C-12), 127.8 (d, C-10), 128.2 (d, C-11), 139.1 (s, C-9).

Optical rotation: $[\alpha]_D^{20}$ = –57.3 (c = 1.0, $CHCl_3$)

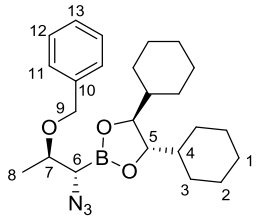
HRMS (CI):	Calculated	Found
$C_{23}H_{36}BO_3$ $[M+H]^+$	371.2752	371.2784

(4*S*,5*S*)-2-((1*S*,2*R*)-1-azido-2-(benzyloxy)propyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (82)

According to **GP-5**, benzyl ether **81** (3.80 g, 10.3 mmol) was treated with CH_2Cl_2 (1.98 mL, 30.8 mmol, 3.0 equiv.), DIPA (1.97 mL, 13.9 mmol, 1.35 equiv.), *n*-BuLi (5.13 mL, 12.8 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (4.20 g, 30.8 mmol, 3.0 equiv.) overnight. After aqueous work up and removal of the solvent, the chloro-boronic ester was dissolved in DMF (103 mL). Sodium azide (6.67 g, 103 mmol, 10.0 equiv.) was added and the mixture was stirred at room temperature for 12 hours. Aqueous work up and flash chromatography

(silica, pentane/diethyl ether 95:5) afforded azide **82** (3.43 g, 8.02 mmol, 79%, 96:4 *dr*) as a colorless oil.

R_f(82) = 0.49 (pentane/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.06 (m, 10 H, 1-H, 2-H, 3-H), 1.31 (d, $^3J_{8,7}$ = 6.4 Hz, 3 H, 8-H), 1.33 (m, 2 H, 4-H), 1.59 (m, 2 H, 3-H‘), 1.66 (m, 2 H, 2-H‘), 1.74 (m, 6 H, 1-H‘, 2-H‘‘, 3-H‘‘), 3.30 (d, $^3J_{6,7}$ = 3.1 Hz, 1 H, 6-H), 3.91 (qd, $^3J_{7,8}$ = 6.4 Hz, $^3J_{7,6}$ = 3.2 Hz, 1 H, 7-H), 3.94 (m, 2 H, 5-H), 4.58 (s, 2 H, 9-H), 7.25 (m, 1 H, 11-H), 7.33 (m, 4 H, 12-H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.2 (q, C-8), 25.8 (t, C-2), 25.9 (t, C-2‘), 26.3 (t, C-1), 27.3 (t, C-3), 28.3 (t, C-3‘), 42.8 (d, C-4), 53.2 (d, C-6), 70.7 (t, C-9), 77.0 (d, C-7), 84.2 (d, C-5), 127.4 (d, C-12), 127.4 (d, C-13), 128.3 (d, C-11), 138.4 (s, C-10).

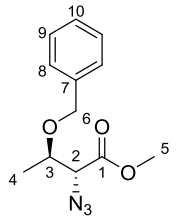
Optical rotation: $[\alpha]_D^{20}$ = –41.6.0 (c = 1.0, $CHCl_3$)

HRMS (CI): The compound decomposes during the measurements.

methyl (2*R*,3*R*)-2-azido-3-(benzyloxy)butanoate (84)

According to **GP-5**, azide **82** (2.00 g, 4.70 mmol) was treated with dibromomethane (985 µL, 14.1 mmol, 3.0 equiv.), DIPA (905 µL, 6.35 mmol, 1.35 equiv.), *n*-BuLi (2.35 mL, 5.88 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (1.92 g, 14.1 mmol, 3.0 equiv.) at –78 °C and stirred at room temperature for 12 hours. After aqueous work up, the bromo-boronic ester was suspended in *t*-BuOH/H_2O (135 mL, 2:1) and 2-methyl-2-butene (19.9 mL, 188 mmol, 40.0 equiv.), sodium chlorite (5.31 g, 47.0 mmol, 10.0 equiv.) and KH_2PO_4 (6.40 g, 47.0 mmol, 10.0 equiv.) were added. The mixture was stirred at room temperature overnight, acidified with 10% citric acid (pH 4) and extracted three times with diethyl ether. Washing of the combined organic layer with sat. $Na_2S_2O_3$ and drying over Na_2SO_4 was followed by esterification of the cleaved diol with methylboronic acid (338 mg, 5.64 mmol, 1.2 equiv.) in diethyl ether (40 mL) in the presence of $MgSO_4$ (1.13 g, 9.40 mmol, 2.0 equiv.). After filtration of the mixture and evaporation of the solvent, the residue was dissolved in toluene/MeOH (94 mL, 5:1) and TMS-diazomethane (3.53 mL, 7.05 mmol, 1.5 equiv.) was added. After complete consumption of the starting material (TLC), the reaction was diluted with diethyl ether and quenched by addition of 10% acetic acid. The layers were separated, the aqueous layer extracted once with diethyl ether and the combined organic layer was washed with sat. $NaHCO_3$ solution and brine. Drying over Na_2SO_4 and purification via flash chromatography (silica, pentane/diethyl ether 92:8) afforded methyl ester **84** (1.13 g, 4.53 mmol, 96%) as a colorless oil.

R_f(84) = 0.41 (pentane/diethyl ether 4:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, $^3J_{4,3}$ = 6.2 Hz, 3 H, 4-H), 3.78 (s, 3 H, 5-H), 3.98 (qd, $^3J_{3,4}$ = 6.2 Hz, $^3J_{3,2}$ = 5.3 Hz, 1 H, 3-H), 4.06 (d, $^3J_{2,3}$ = 5.0 Hz, 1 H, 2-H), 4.55 (d, $^2J_{6a,6b}$ = 11.7 Hz, 1 H, 6-H_a), 4.62 (d, $^2J_{6b,6a}$ = 11.7 Hz, 1 H, 6-H_b), 7.32 (m, 5 H, 8-H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.9 (q, C-4), 52.6 (q, C-5), 65.5 (d, C-2), 71.3 (t, C-6), 75.3 (d, C-3), 127.6 (d, C-8), 127.8 (d, C-10), 128.4 (d, C-9), 137.6 (s, C-7), 169.0 (s, C-1).

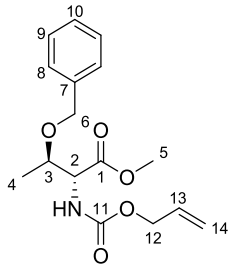
Optical rotation: $[\alpha]_D^{20}$ = –23.9 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{12}H_{15}NO_3$ $[M\text{-}N_2]^+$	221.1046	221.1057

methyl *N*-((allyloxy)carbonyl)-*O*-benzyl-D-*allo*-threoninate (85)

To a solution of azide **84** (900 mg, 3.61 mmol) in THF/H_2O (36 mL, 25:1) was added PPh_3 (2.84 g, 10.8 mmol, 3.0 equiv.) and the mixture was heated to 50 °C for 15 hours. After cooling to room temperature, H_2O (10 mL) and $NaHCO_3$ (607 mg, 7.22 mmol, 2.0 equiv.) were added. The mixture was cooled to 0 °C, allyl chloroformate (578 µL, 5.42 mmol, 1.5 equiv.) was added dropwise and the reaction was stirred overnight. The reaction was quenched with 1 M HCl, the mixture extracted three times with CH_2Cl_2, and the combined organic layer was washed with brine. After drying (Na_2SO_4), evaporation of the solvent under reduced pressure and flash chromatography (silica, pentane/diethyl ether 3:1 → 2:1) the Alloc-protected amine **85** (891 mg, 2.90 mmol, 80%) was obtained as a colorless oil.

R_f(85) = 0.15 (pentane/diethyl ether 3:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, $^3J_{4,3}$ = 6.5 Hz, 3 H, 4-H), 3.75 (s, 3 H, 5-H), 3.87 (m, 1 H, 3-H), 4.56 (m, 5 H, 2-H, 6-H, 12-H), 5.21 (d, $^3J_{14a,13}$ = 10.4 Hz, 1 H, 14-H_a), 5.30 (d, $^3J_{14b,13}$ = 17.1 Hz, 1 H, 14-H_b), 5.39 (d, $^3J_{NH,2}$ = 8.3 Hz, 1 H, NH), 5.91 (ddt, $^3J_{13,14b}$ = 16.8 Hz, $^3J_{13,14a}$ = 10.9 Hz, $^3J_{13,12}$ = 5.5 Hz, 1 H, 13-H), 7.30 (m, 5 H, 8-H, 9-H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.1 (q, C-4), 52.3 (q, C-5), 57.2 (d, C-2), 65.8 (t, C-12), 70.9 (t, C-6), 74.9 (d, C-3), 117.8 (t, C-14), 127.6 (d, C-8), 127.7 (d, C-10), 128.3 (d, C-9), 132.5 (d, C-13), 137.8 (s, C-7), 155.8 (s, C-11), 170.7 (s, C-1).

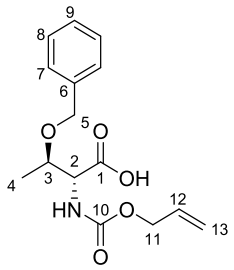
Optical rotation: $[\alpha]_D^{20}$ = −12.7 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{16}H_{22}NO_5$ $[M+H]^+$	308.1492	308.1486

***N*-((allyloxy)carbonyl)-*O*-benzyl-D-*allo*-threonine (86)**

Methyl ester **85** (400 mg, 1.30 mmol) was dissolved in THF (13 mL) and LiOH (1.43 mL, 1.43 mmol, 1.0 M, 1.0 equiv.) was added at 0 °C. After stirring at room temperature until complete conversion was observed by (TLC), the reaction was acidified (pH 2) with 1 M HCl and extracted three times with diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **86** (377 mg, 1.28 mmol, 99%) as a colorless oil.

R_f(86) = 0.06 (pentane/diethyl ether 7:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, $^3J_{4,3}$ = 6.4 Hz, 3 H, 4-H), 3.93 (m, 1 H, 3-H), 4.58 (m, 5 H, 2-H, 5 H, 11-H), 5.21 (d, $^3J_{13a,12}$ = 10.6 Hz, 1 H, 13-H_a), 5.31 (d, $^3J_{13b,12}$ = 17.2 Hz, 1 H, 13-H_b), 5.49 (d, $^3J_{NH,2}$ = 8.1 Hz, 1 H, NH), 5.91 (ddt, $^3J_{12,13b}$ = 16.8 Hz, $^3J_{12,13a}$ = 10.9 Hz, $^3J_{12,11}$ = 5.4 Hz, 1 H, 12-H), 7.31 (m, 5 H, 7-H, 8-H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.1 (q, C-4), 56.9 (d, C-2), 65.9 (t, C-11), 71.0 (t, C-5), 74.9 (d, C-3), 117.8 (t, C-13), 127.8 (d, C-7), 127.8 (d, C-9), 128.4 (d, C-8), 132.6 (d, C-12), 137.8 (s, C-6), 156.0 (s, C-10), 172.8 (s, C-1).

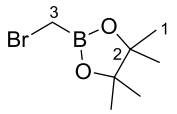
Optical rotation: $[\alpha]_D^{20}$ = −17.4 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{15}H_{20}NO_5$ $[M+H]^+$	294.1336	294.1355

2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[392]

A solution of triisopropylborate (16.4 mL, 70.4 mmol, 1.1 equiv.) and dibromomethane (5.36 mL, 77.0 mmol, 1.2 equiv.) in dry THF (100 mL) was cooled to −78 °C and *n*-butyllithium (25.6 mL, 64.0 mmol, 2.5 M in hexane) was carefully added over 90 minutes, maintaining a reaction temperature below −75 °C. After complete addition the mixture was stirred for 90 minutes at −78 °C, warmed to room temperature and further stirred for two hours. The

mixture was cooled to 0 °C, methanesulfonic acid (4.16 mL, 64.0 mmol, 1.0 equiv.) was added dropwise and the reaction stirred for 1 hour at room temperature. Transesterification of the resulting boronic ester was performed by addition of pinacol (7.56 g, 64.0 mmol, 1.0 equiv.) at 0 °C and stirring at room temperature for one hour. The volatiles were removed *in vacuo*, the residue suspended in CH_2Cl_2, filtrated and washed with CH_2Cl_2. After removal of the solvent under reduced pressure from the filtrate, the residue was distilled (50-53 °C, 0.43 mbar) to afford the bromo-boronic ester (10.4 g, 47.1 mmol, 74%) as a colorless liquid.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 12 H, 1-H), 2.59 (s, 2 H, 3-H).

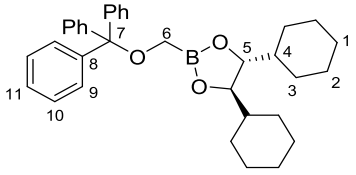
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.6 (q, C-1), 84.5 (s, C-2). C-3 not observed

(4*R*,5*R*)-4,5-dicyclohexyl-2-((trityloxy)methyl)-1,3,2-dioxaborolane (87)

To a solution of trityl alcohol (14.1 g, 54.3 mmol) in DMSO was added sodium hydride (2.39 g, 59.8 mmol, 60% in mineral oil, 1.1 equiv.) in two portions and the mixture was stirred overnight. 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.0 g, 54.3 mmol, 1.0 equiv.) was added and the mixture was stirred until complete consumption of the starting material was observed (NMR). The reaction was quenched by addition of sat. NH_4Cl solution and extracted twice with diethyl ether. The solvent was removed *in vacuo*, pentane was added, and the mixture concentrated to obtain an off-white solid. After filtration and washing with water the solid was redissolved in diethyl ether and aqueous sodium hydroxide solution (163 mL, 163 mmol, 1.0 M, 3.0 equiv.) as well as pentaerythritol (18.5 g, 136 mmol, 2.5 equiv.) were added. The suspension was stirred overnight at room temperature and was diluted with water and diethyl ether until two clear layers formed. The layers were separated, the aqueous layer neutralized (pH 6) by addition of 6 M HCl solution and the precipitate filtrated and dried *in vacuo*.

After suspending of the crude boronic acid (80% purity) in pentane (166 mL), (*R*,*R*)-DICHED[348] (6.01 g, 26.6 mmol, 0.8 equiv.) was added and the reaction was stirred at room temperature for 2 hours. The mixture was filtrated, washed with diethyl ether, the solvent removed under reduced pressure and the residue purified by flash chromatography (silica, pentane/diethyl ether 9:1) to yield chiral boronic ester **87** (14.6 g, 28.7 mmol, 53% over two steps) as a white solid.

R_f(87) = 0.51 (pentane/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.13 (m, 10 H, 1-H, 2-H, 3-H), 1.37 (m, 2 H, 4-H), 1.66 (m, 4 H, 2-H‘, 3-H‘), 1.80 (m, 6 H, 1-H‘, 2-H‘‘, 3-H‘‘), 2.85 (d, $^2J_{6a,6b}$ = 15.7 Hz, 1 H, 6-H_a), 2.94 (d, $^2J_{6b,6a}$ = 15.8 Hz, 1 H, 6-H_b), 3.93 (d, $^3J_{5,4}$ = 4.5 Hz, 2 H, 5-H), 7.20 (m, 3 H, 11-H), 7.28 (m, 6 H, 10-H), 7.48 (m, 6 H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9 (t, C-2), 26.0 (t, C-2‘), 26.5 (t, C-1), 27.4 (t, C-3), 28.4 (t, C-3‘), 42.9 (d, C-4), 50.5 (t, C-6), 83.8 (d, C-5), 87.7 (s, C-7), 126.7 (d, C-11), 127.7 (d, C-10), 128.9 (d, C-9), 144.2 (s, C-8).

Optical rotation: $[\alpha]_D^{20}$ = −12.7 (c = 1.0, $CHCl_3$)

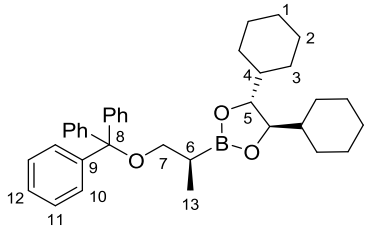
Melting point: 95−97 °C

HRMS (CI): The compound decomposes during the measurements.

(4*R*,5*R*)-4,5-dicyclohexyl-2-((*S*)-1-(trityloxy)propan-2-yl)-1,3,2-dioxaborolane (88)

According to **GP-5** boronic ester **87** (3.50 g, 6.88 mmol) was reacted with CH_2Cl_2 (1.33 mL, 20.7 mmol, 3.0 equiv.), DIPA (1.32 mL, 9.29 mmol, 1.35 equiv.), *n*-BuLi (3.44 mL, 8.60 mmol, 2.5 M in hexane, 1.25 equiv.), zinc chloride (2.81 g, 20.7 mmol, 3.0 equiv.) in THF (27.5 mL) and stirred at room temperature for 3.5 hours. After treatment with methylmagnesium chloride (5.74 mL, 17.2 mmol, 3.0 M, 2.5 equiv.) for 20 hours and aqueous work up, the crude product was purified by flash chromatography (silica, pentane/diethyl ether 9:1) to afford boronic ester **88** (3.38 g, 6.30 mmol, 92%) as a white solid.

R_f(88) = 0.55 (pentane/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, $^3J_{13,6}$ = 7.3 Hz, 3 H, 13-H), 1.02 (m, 4 H, 3-H), 1.16 (m, 6 H, 1-H, 2-H), 1.30 (m, 2 H, 4-H), 1.46 (m, 1 H, 6-H), 1.62 (m, 4 H, 2-H‘, 3-H‘), 1.73 (m, 6 H, 1-H‘, 2-H‘‘, 3-H‘‘), 3.03 (dd, $^2J_{7a,7b}$ = 8.0 Hz, $^3J_{7a,6}$ = 7.2 Hz, 1 H, 7-H_a), 3.18 (dd, $^2J_{7b,7a}$ = 8.1 Hz, $^3J_{7b,6}$ = 7.6 Hz, 1 H, 7-H_b), 3.84 (d, $^3J_{5,4}$ = 4.7 Hz, 2 H, 5-H), 7.20 (m, 3 H, 12-H), 7.27 (m, 6 H, 11-H), 7.46 (m, 6 H, 10-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.0 (q, C-13), 18.3 (d, C-6), 25.9 (t, C-2), 26.0 (t, C-2‘), 26.4 (t, C-1), 27.3 (t, C-3), 28.3 (t, C-3‘), 43.0 (d, C-4), 66.6 (t, C-7), 83.3 (d, C-5), 86.1 (s, C-8), 126.6 (d, C-12), 127.5 (d, C-11), 128.8 (d, C-10), 144.6 (s, C-9).

Optical rotation: $[\alpha]_D^{20}$ = −36.4 (c = 1.0, $CHCl_3$)

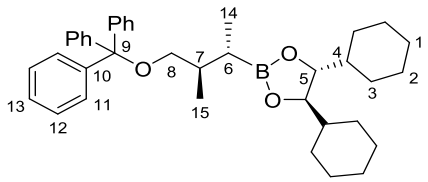
Melting point: 91−93 °C

HRMS (CI): The compound decomposes during the measurements.

(4*R*,5*R*)-4,5-dicyclohexyl-2-((2*S*,3*R*)-3-methyl-4-(trityloxy)butan-2-yl)-1,3,2-dioxaborolane (89)

According to **GP-5** boronic ester **88** (2.74 g, 5.11 mmol) was treated with CH_2Cl_2 (986 µL, 15.3 mmol, 3.0 equiv.), DIPA (983 µL, 6.89 mmol, 1.35 equiv.), *n*-BuLi (2.55 mL, 6.38 mmol, 2.5 M in hexane, 1.25 equiv.), zinc chloride (2.09 g, 15.3 mmol, 3.0 equiv.) in THF (20 mL) and was stirred at room temperature for 16 hours. After reaction with methylmagnesium chloride (4.26 mL, 12.8 mmol, 3.0 M, 2.5 equiv.) and aqueous work up, the crude product was purified by flash chromatography (silica, pentane/diethyl ether 9:1) to afford boronic ester **89** (2.78 g, 4.92 mmol, 96%) as a colorless resin.

R_f(89) = 0.57 (pentane/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, $^3J_{14,6}$ = 7.6 Hz, 3 H, 14-H), 0.94 (m, 4 H, 3-H), 1.01 (d, $^3J_{15,7}$ = 6.8 Hz, 3 H, 15-H), 1.16 (m, 8 H, 1-H, 2-H, 4-H), 1.30 (m, 1 H, 6-H), 1.54 (m, 2 H, 3-H‘), 1.71 (m, 8 H, 1-H‘, 2-H‘, 3-H‘‘), 1.88 (m, 1 H, 7-H), 2.89 (dd, $^2J_{8a,8b}$ = 8.5 Hz, $^3J_{8a,7}$ = 7.3 Hz, 1 H, 8-H_a), 3.06 (dd, $^2J_{8b,8a}$ = 8.7 Hz, $^3J_{8b,7}$ = 5.3 Hz, 1 H, 8-H_b), 3.73 (d, $^3J_{5,4}$ = 4.8 Hz, 2 H, 5-H), 7.20 (m, 3 H, 13-H), 7.27 (m, 6 H, 12-H), 7.46 (m, 6 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.3 (q, C-14), 16.7 (q, C-15), 19.9 (d, C-6), 25.9 (t, C-2), 26.0 (t, C-2‘), 26.4 (t, C-1), 27.5 (t, C-3), 28.4 (t, C-3‘), 36.6 (d, C-7), 43.0 (d, C-4), 67.4 (t, C-8), 83.2 (d, C-5), 86.1 (s, C-9), 126.7 (d, C-13), 127.6 (d, C-12), 128.8 (d, C-11), 144.6 (s, C-10).

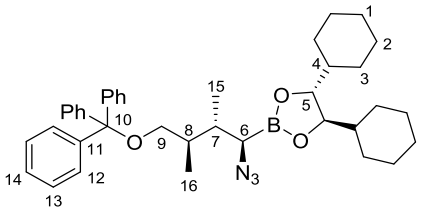
Optical rotation: $[\alpha]_D^{20}$ = –26.1 (c = 1.0, $CHCl_3$)

HRMS (CI): The compound decomposes during the measurements.

(4*R*,5*R*)-2-((1*R*,2*S*,3*R*)-1-azido-2,3-dimethyl-4-(trityloxy)butyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (91)

According to **GP-5** boronic ester **89** (5.80 g, 10.3 mmol) was reacted with CH_2Cl_2 (1.98 mL, 30.8 mmol, 3.0 equiv.), DIPA (1.97 mL, 13.9 mmol, 1.35 equiv.), *n*-BuLi (5.14 mL, 12.8 mmol, 2.5 M in hexane, 1.25 equiv.), zinc chloride (4.20 g, 30.8 mmol, 3.0 equiv.) in THF (60 mL). After stirring overnight at room temperature and aqueous work up the crude chloro-boronic ester was dissolved in DMF (103 mL). Sodium azide (6.68 g, 103 mmol, 10.0 equiv.) was added and the mixture was stirred at room temperature until complete consumption of the starting material was observed (NMR). Aqueous work up and flash chromatography, (silica, pentane/diethyl ether 9:1) yielded azide **91** (5.43 g, 8.76 mmol, 85%) as a colorless resin.

R_f(91) = 0.59 (pentane/diethyl ether 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, $^3J_{15,7}$ = 7.0 Hz, 3 H, 15-H), 0.96 (m, 2 H, 3-H), 1.05 (d, $^3J_{16,8}$ = 6.8 Hz, 3 H, 16-H), 1.09 (m, 2 H, 3-H‘), 1.25 (m, 8 H, 1-H, 2-H, 4-H), 1.59 (m, 2 H, 3-H‘‘), 1.67 (m, 2 H, 1-H‘), 1.77 (m, 6 H, 2-H‘, 3-H‘‘‘), 1.87 (m, 1 H, 7-H), 1.97 (m, 1 H, 8-H), 2.91 (dd, $^2J_{9a,9b}$ = 8.9 Hz, $^3J_{9a,8}$ = 6.5 Hz, 1 H, 9-H_a), 3.14 (m, 2 H, 6-H, 9-H_b), 3.73 (m, 2 H, 5-H), 7.20 (m, 3 H, 14-H), 7.27 (m, 6 H, 13-H), 7.46 (m, 6 H, 12-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.8 (q, C-15), 16.5 (q, C-16), 25.8 (t, C-2), 25.9 (t, C-2‘), 26.4 (t, C-1), 27.4 (t, C-3), 28.5 (t, C-3‘), 35.8 (d, C-8), 38.0 (d, C-7), 42.9 (d, C-4), 52.2 (d, C-6), 65.6 (t, C-9), 84.1 (d, C-5), 86.3 (s, C-10), 126.8 (d, C-14), 127.7 (d, C-13), 128.8 (d, C-12), 144.4 (s, C-11).

Optical rotation: $[\alpha]_D^{20}$ = –63.8 (c = 1.0, $CHCl_3$)

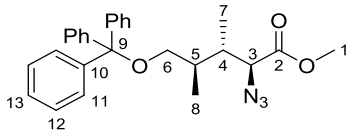
HRMS (CI): The compound decomposes during the measurements.

methyl (2*S*,3*S*,4*R*)-2-azido-3,4-dimethyl-5-(trityloxy)pentanoate (93)

According to **GP-5** azide **91** (2.00 g, 3.23 mmol) was treated with CH_2Cl_2 (623 µL, 9.68 mmol, 3.0 equiv.), DIPA (621 µL, 4.36 mmol, 1.35 equiv.), *n*-BuLi (1.61 mL, 4.03 mmol, 2.5 M in hexane, 1.25 equiv.), zinc chloride (1.32 g, 9.68 mmol, 3.0 equiv.) in THF (19 mL). After stirring overnight at room temperature and aqueous work up, the crude chloro-boronic ester was immediately used in the next step.

The residue was suspended in a mixture of *t*-BuOH/H_2O (93 mL, 2:1) and 2-methyl-2-butene (13.7 mL, 129 mmol, 40.0 equiv.), sodium chlorite (3.65 g, 32.3 mmol, 10.0 equiv.) and KH_2PO_4 (4.40 g, 32.3 mmol, 10.0 equiv.) were added in quick succession. After stirring overnight, the reaction was quenched by careful acidification (pH 3-4) with aqueous citric acid solution (10w%). The mixture was extracted three times with diethyl ether and the combined organic layer was washed with sat. $Na_2S_2O_3$ solution. Drying over Na_2SO_4 was followed by esterification of the cleaved diol with methylboronic acid (232 mg, 3.88 mmol, 1.2 equiv.) in diethyl ether (30 mL) in the presence of $MgSO_4$ (778 mg, 6.46 mmol, 2.0 equiv.). After filtration of the mixture and evaporation of the solvent the residue was dissolved in toluene/MeOH (66 mL, 5:1) and TMS-diazomethane (2.42 mL, 4.85 mmol, 1.5 equiv.) was added. After complete consumption of the starting material (TLC), the reaction was diluted with diethyl ether and quenched by addition of 10% acetic acid. The layers were separated, the aqueous layer extracted once with diethyl ether and the combined organic layer was washed with sat. $NaHCO_3$ solution and brine. Drying over Na_2SO_4 and purification via flash chromatography (silica, pentane/DCM/diethyl ether 90:10:0.3) afforded methyl ester **93** (1.19 g, 2.68 mmol, 83%) as a colorless oil.

R_f(93) = 0.29 (pentane/DCM/diethyl ether 85:15:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.67 (d, $^3J_{7,4}$ = 7.0 Hz, 3 H, 7-H), 0.98 (d, $^3J_{8,5}$ = 7.0 Hz, 3 H, 8-H), 1.99 (m, 1 H, 4-H), 2.17 (m, 1 H, 5-H), 2.99 (dd, $^2J_{6a,6b}$ = 9.4 Hz, $^3J_{6a,5}$ = 5.9 Hz, 1 H, 6-H_a), 3.03 (dd, $^2J_{6b,6a}$ = 9.3 Hz, $^3J_{6b,5}$ = 6.5 Hz, 1 H, 6-H_b), 3.75 (s, 3 H, 1-H), 3.93 (d, $^3J_{3,4}$ = 8.6 Hz, 1 H, 3-H), 7.23 (m, 3 H, 13-H), 7.30 (m, 6 H, 12-H), 7.45 (m, 6 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.0 (q, C-7), 16.4 (q, C-8), 34.0 (d, C-5), 38.6 (d, C-4), 52.2 (q, C-1), 65.2 (t, C-6), 65.6 (d, C-3), 86.7 (s, C-9), 126.9 (d, C-13), 127.8 (d, C-12), 128.7 (d, C-11), 144.1 (s, C-10), 171.0 (s, C-2).

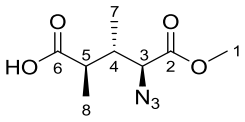
Optical rotation: $[\alpha]_D^{20}$ = –11.9 (c = 1.0, $CHCl_3$)

HRMS (CI): The compound decomposes during the measurements.

(2*R*,3*S*,4*S*)-4-azido-5-methoxy-2,3-dimethyl-5-oxopentanoic acid (99)

To a solution of azide **93** (1.21 g, 2.73 mmol) in acetone (35 mL) was added an excess of Jones reagent (10 mL, 2.7 M) and the mixture was stirred at room temperature until complete consumption of the starting material was observed by TLC (1.5-2 hours). The reaction was quenched by addition of *i*-PrOH until a green solution persisted, the precipitate was filtrated off through a pad of celite and washed with diethyl ether. After extraction of the filtrate with sat. $NaHCO_3$ solution (2x) and acidification (pH 1-2) of the combined aqueous layer with 6 M HCl solution, the aqueous layer was extracted twice with diethyl ether. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. Flash chromatography (silica, pentane/diethyl ether 7:3) afforded carboxylic acid **99** (493 mg, 2.29 mmol, 84%) as a colorless liquid which was immediately used in the next step or stored in the freezer at –20 °C.

R_f(99) = 0.15 (pentane/diethyl ether 7:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, $^3J_{7,4}$ = 6.8 Hz, 3 H, 7-H), 1.22 (d, $^3J_{8,5}$ = 7.1 Hz, 3 H, 8-H), 2.24 (dqd, $^3J_{4,3}$ = 8.8 Hz, $^3J_{4,7}$ = 6.9 Hz, $^3J_{4,5}$ = 5.0 H, 1 H, 4-H), 2.85 (qd, $^3J_{5,8}$ = 7.1 Hz, $^3J_{5,4}$ = 4.8 Hz, 1 H, 5-H), 3.82 (s, 3 H, 1-H), 4.00 (d, $^3J_{3,4}$ = 8.8 Hz, 1 H, 3-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.4 (q, C-7), 14.4 (q, C-8), 38.4 (d, C-4), 40.2 (d, C-5), 52.5 (q, C-1), 65.2 (d, C-3), 170.3 (s, C-2), 179.4 (s, C-6).

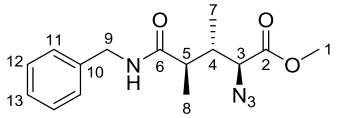
Optical rotation: $[\alpha]_D^{20}$ = –6.5 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_8H_{14}N_3O_4$ $[M+H]^+$	216.0979	216.1005

methyl (2*S*,3*S*,4*R*)-2-azido-5-(benzylamino)-3,4-dimethyl-5-oxopentanoate (100)

Carboxylic acid **99** (250 mg, 1.16 mmol) was dissolved in dry DMF (12 mL) and benzylamine (140 µL, 1.28 mmol, 1.1 equiv.), DIPEA (243 µL, 1.39 mmol, 1.2 equiv.), HOBt (187 mg, 1.22 mmol, 1.05 equiv.) and EDC (234 mg, 1.22 mmol, 1.05 equiv.) were successively added at 0 °C. After warming to room temperature overnight the reaction was diluted with diethyl ether and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue purified via flash chromatography (silica, DCM/diethyl ether 95:5) to afford amide **100** (325 mg, 1.07 mmol, 92%) as a white solid.

R_f(100) = 0.27 (DCM/diethyl ether 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, $^3J_{7,4}$ = 6.8 Hz, 3 H, 7-H), 1.20 (d, $^3J_{8,5}$ = 7.0 Hz, 3 H, 8-H), 2.27 (sext, $^3J_{4,3/5/7}$ = 6.8 Hz, 1 H, 4-H), 2.85 (quint, $^3J_{5,4/8}$ = 6.8 Hz, 1 H, 5-H), 3.80 (s, 3 H, 1-H), 3.94 (d, $^3J_{3,4}$ = 6.8 Hz, 1 H, 3-H), 4.44 (d, $^3J_{9,NH}$ = 6.8 Hz, 2 H, 9-H), 5.88 (bs, 1 H, NH), 7.30 (m, 5 H, 11-H, 12-H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.9 (q, C-7), 15.8 (q, C-8), 38.9 (d, C-4), 42.1 (d, C-5), 43.5 (t, C-9), 52.5 (q, C-1), 65.4 (d, C-3), 127.6 (d, C-13), 127.8 (d, C-11), 128.7 (d, C-12), 138.2 (s, C-10), 170.4 (s, C-2), 173.7 (s, C-6).

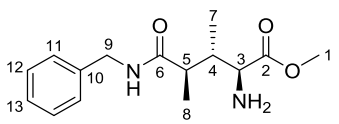
Optical rotation:	$[\alpha]_D^{20}$ = –26.0 (c = 1.0, $CHCl_3$)
Melting point:	85-87 °C

HRMS (CI):	Calculated	Found
$C_{15}H_{21}N_4O_3$ $[M+H]^+$	305.1608	305.1606

methyl (2*S*,3*S*,4*R*)-2-amino-5-(benzylamino)-3,4-dimethyl-5-oxopentanoate (101)

To a solution of azide **100** (406 mg, 1.33 mmol) in THF/H_2O (13mL, 25:1) was added PPh_3 (1.05 g, 4.00 mmol, 3.0 equiv.) and the reaction was heated to 50 °C for 16 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography (silica, DCM/MeOH 92:8) to afford amine **101** (362 mg, 1.30 mmol, 97%) as a colorless oil.

R_f(101) = 0.12 (DCM/MeOH 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $^3J_{7,4}$ = 7.0 Hz, 3 H, 7-H), 1.18 (d, $^3J_{8,5}$ = 7.0 Hz, 3 H, 8-H), 1.60 (bs, 2 H, NH_2), 1.97 (quintd, $^3J_{4,3/7}$ = 7.1 Hz, $^3J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 2.68 (qd, $^3J_{5,8}$ = 7.0 Hz, $^3J_{5,4}$ = 5.5 Hz, 1 H, 5-H), 3.30 (d, $^3J_{3,4}$ = 7.6 Hz, 1 H, 3 H), 3.72 (s, 3 H, 1-H), 4.43 (d, $^3J_{9,NH}$ = 5.7 Hz, 2 H, 9-H), 6.84 (bs, 1 H, NH), 7.29 (m, 5 H, 11-H, 12-H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.3 (q, C-7), 15.5 (q, C-8), 40.6 (d, C-4/C-5), 40.7 (d, C-4/C-5), 43.4 (t, C-9), 51.9 (q, C-1), 57.7 (d, C-3), 127.4 (d, C-13), 127.8 (d, C-11), 128.7 (d, C-12), 138.7 (s, C-10), 174.1 (s, C-6), 176.0 (s, C-2).

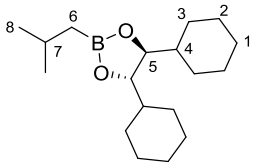
Optical rotation: $[\alpha]_D^{20}$ = –22.4 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{15}H_{23}N_2O_3$ $[M+H]^+$	279.1703	279.1707

(4*S*,5*S*)-4,5-dicyclohexyl-2-isobutyl-1,3,2-dioxaborolane (102)

To a solution of isobutylboronic acid (3.67 g, 36.0 mmol, 1.1 equiv.) in diethyl ether (163 mL) was added (*S*,*S*)-DICHED[348] (7.40 g, 32.7 mmol) and $MgSO_4$ (11.8 g, 98.0 mmol, 3.0 equiv.). The mixture was stirred overnight, filtrated and concentrated *in vacuo*. Flash chromatography (silica, pentane/diethyl ether 95:5) afforded boronic ester **102** (8.10 g, 27.7 mmol, 85%) as colorless liquid.

R_f(102) = 0.58 (pentane/diethyl ether 98:2)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, $^3J_{6,7}$ = 7.1 Hz, 2 H, 6-H), 0.94 (d, $^3J_{8,7}$ = 6.6 Hz, 3 H, 8-H), 0.94 (d, $^3J_{8',7}$ = 6.6 Hz, 3 H, 8-H'), 0.99 (m, 2 H, 2-H), 1.06 (m, 2 H, 3-H), 1.19 (m, 6 H, 1-H, 2-H', 3-H'), 1.31 (m, 2 H, 4-H), 1.59 (m, 2 H, 3-H'), 1.68 (m, 2 H, 1-H'), 1.77 (m, 6 H, 1-H'', 2-H'', 3-H'''), 1.86 (sept., $^3J_{7,8/6}$ = 6.6 Hz, 1 H, 7-H), 3.83 (m, 2 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.8 (d, C-7), 25.2 (q, C-8), 25.3 (q, C-8'), 25.9 (t, C-2), 26.0 (t, C-3), 26.5 (t, C-1), 27.4 (t, C-2'), 28.4 (t, C-3'), 33.5 (t, C-6), 43.1 (d, C-4), 83.2 (d, C-5).

Optical rotation: $[\alpha]_D^{20}$ = +16.7 (c = 1.0, $CHCl_3$)

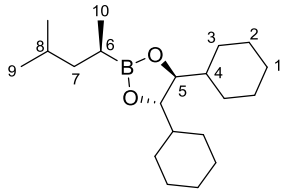
HRMS (CI):	Calculated	Found
$C_{18}H_{34}BO_2$ $[M+H]^+$	293.2646	293.2621

(4*S*,5*S*)-4,5-dicyclohexyl-2-((*R*)-4-methylpentan-2-yl)-1,3,2-dioxaborolane (103)

According to **GP-5** boronic ester **102** (4.00 g, 13.7 mmol) was treated with CH_2Cl_2 (2.64 mL, 41.1 mmol, 3.0 equiv.), DIPA (2.44 mL, 17.1 mmol, 1.25 equiv.), *n*-BuLi (6.46 mL, 16.2 mmol, 2.5 M in hexane, 1.18 equiv.) and zinc chloride (3.73 g, 27.4 mmol, 2.0 equiv.) in dry THF (34 mL). After stirring overnight, a solution of methylmagnesium bromide (11.4 mL,

34.2 mmol, 3.0 M in THF, 2.5 equiv.) was added dropwise at 0 °C and the reaction was stirred at room temperature for 16 hours. Aqueous work-up and flash chromatography (silica, pentane/diethyl ether 95:5) afforded boronic ester **103** (4.09 g, 12.8 mmol, 93%) as colorless liquid.

R_f(103) = 0.55 (pentane/diethyl ether 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, $^3J_{9,8}$ = 6.7 Hz, 3 H, 9-H), 0.87 (d, $^3J_{9',8}$ = 6.7 Hz, 3 H, 9-H'), 0.97 (m, 5 H, 2-H, 10-H), 1.06 (m, 2 H, 3-H), 1.17 (m, 8 H, 1-H, 2-H', 3-H', 6-H, 7-H), 1.31 (m, 3 H, 4-H, 7-H'), 1.59 (m, 2 H, 3-H'), 1.68 (m, 3 H, 1-H', 8-H), 1.77 (m, 6 H, 1-H'', 2-H'', 3-H'''), 3.82 (m, 2 H, 5-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.0 (q, C-10), 22.3 (q, C-9), 22.9 (q, C-9'), 25.9 (t, C-2), 26.0 (t, C-3), 26.5 (t, C-1), 26.5 (t, C-2'), 26.7 (d, C-6), 27.4 (d, C-8), 28.3 (t, C-3'), 33.5 (t, C-7), 42.7 (d, C-4), 43.1 (d, C-4'), 83.1 (d, C-5).

Optical rotation: $[\alpha]_D^{20}$ = +47.1 (c = 1.0, $CHCl_3$)

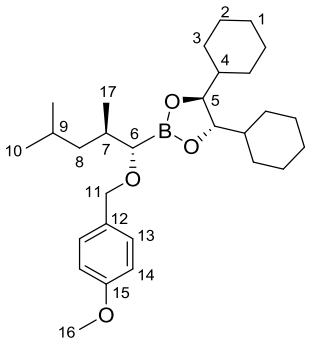
HRMS (CI):	Calculated	Found
$C_{20}H_{38}BO_2$ $[M+H]^+$	321.2959	321.2959

(4*S*,5*S*)-4,5-dicyclohexyl-2-((1*S*,2*R*)-1-((4-methoxybenzyl)oxy)-2,4-dimethylpentyl)-1,3,2-dioxaborolane (104)

According to **GP-5** boronic ester **103** (3.50 g, 10.9 mmol) was treated with CH_2Cl_2 (2.11 mL, 32.8 mmol, 3.0 equiv.), DIPA (2.10 mL, 14.8 mmol, 1.35 equiv.), *n*-BuLi (5.46 mL, 13.7 mmol, 2.5 M, 1.25 equiv.) and zinc chloride (2.98 g, 21.9 mmol, 2.0 equiv.) in dry THF (40 mL) and stirred overnight.

To prepare the nucleophile solution sodium hydride (568 mg, 14.2 mmol, 60% in mineral oil, 1.3 equiv.) was suspended in a mixture of dry THF/DMSO (26 mL, 1:2.8) and *p*-methoxybenzyl alcohol (1.90 mL, 15.3 mmol, 1.4 equiv.) was added. The mixture was stirred at room temperature for 4 hours and then added to the chloro-boronic ester solution. After 15 hours the reaction was quenched, extracted and purified by flash chromatography (silica, pentane/diethyl ether 95:5) to afford PMB-ether **104** (4.46 g, 9.48 mmol, 87%) as a colorless liquid.

R_f(104) = 0.29 (pentane/diethyl ether 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, $^{3}J_{10,9}$ = 6.6 Hz, 3 H, 10-H), 0.87 (d, $^{3}J_{10',9}$ = 6.6 Hz, 3 H, 10-H'), 0.93 (d, $^{3}J_{17,7}$ = 6.7 Hz, 3 H, 17-H), 0.99 (m, 2 H, 2-H), 1.09 (m, 2 H, 3-H), 1.19 (m, 7 H, 1-H, 2-H', 3-H', 8-H), 1.30 (m, 3 H, 4-H, 8-H'), 1.60 (m, 2 H, 3-H'), 1.68 (m, 3 H, 1-H', 9-H), 1.78 (m, 6 H, 1-H'', 2-H'', 3-H'''), 1.94 (m, 1 H, 7-H), 3.14 (d, $^{3}J_{6,7}$ = 5.8 Hz, 1 H, 6-H), 3.80 (s, 3 H, 16-H), 3.88 (m, 2 H, 5-H), 4.41 (d, $^{2}J_{11a,11b}$ = 11.7 Hz, 1 H, 11-H_a), 4.51 (d, $^{2}J_{11b,11a}$ = 11.7 Hz, 1 H, 11-H_b), 6.85 (d, $^{3}J_{13,14}$ = 8.6 Hz, 2 H, 13-H), 7.27 (d, $^{3}J_{14,13}$ = 8.3 Hz, 2 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.0 (q, C-17), 22.0 (q, C-10), 23.7 (q, C-10'), 25.3 (d, C-7), 25.9 (t, C-2), 26.0 (t, C-3), 26.5 (t, C-1), 27.6 (d, C-9), 28.4 (t, C-2'/C-3'), 32.7 (t, C-2'/C-3'), 33.5 (t, C-8), 43.0 (d, C-4), 43.0 (d, C-4'), 55.2 (d, C-6), 72.1 (t, C-11), 83.6 (d, C-5), 113.5 (d, C-14), 129.3 (d, C-13), 131.5 (s, C-12), 158.9 (s, C-15).

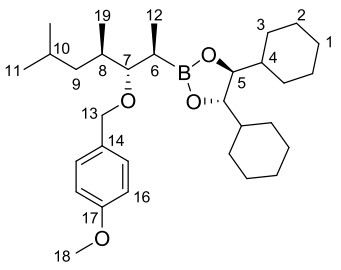
Optical rotation: $[\alpha]_{D}^{20}$ = +67.7 (c = 1.0, $CHCl_3$)

HRMS (CI): The compound decomposes during the measurements.

(4*S*,5*S*)-4,5-dicyclohexyl-2-((2*R*,3*S*,4*R*)-3-((4-methoxybenzyl)oxy)-4,6-dimethylheptan-2-yl)-1,3,2-dioxaborolane (105)

According to **GP-5** boronic ester **104** (3.50 g, 7.44 mmol) was reacted with CH_2Cl_2 (1.44 mL, 22.3 mmol, 3.0 equiv.), DIPA (1.43 mL, 10.0 mmol, 1.35 equiv.), *n*-BuLi (3.72 mL, 9.30 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (3.04 g, 22.3 mmol, 3.0 equiv.) in dry THF (32 mL). After stirring for 4 hours, a solution of methylmagnesium chloride (7.44 mL, 22.3 mmol, 3.0 M in THF, 3.0 equiv.) was added dropwise at 0 °C and the reaction was stirred at room temperature for 48 hours. Aqueous work-up and flash chromatography (silica, pentane/diethyl ether 98:2) afforded boronic ester **105** (3.39 g, 6.80 mmol, 91%) as a colorless liquid.

R_f(105) = 0.60 (pentane/diethyl ether 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, $^3J_{11,10}$ = 6.6 Hz, 3 H, 11-H), 0.86 (d, $^3J_{11',10}$ = 6.7 Hz, 3 H, 11-H'), 0.88 (d, $^3J_{19,8}$ = 6.6 Hz, 3 H, 19-H), 0.96 (m, 2 H, 2-H), 1.01 (d, $^3J_{12,6}$ = 7.5 Hz, 3 H, 12-H), 1.07 (m, 3 H, 3-H, 9-H_a), 1.15 (m, 9 H, 1-H, 2-H', 3-H', 8-H), 1.26 (m, 2 H, 4-H), 1.39 (ddd, $^2J_{9b,9a}$ = 13.5 Hz, $^3J_{9b,10}$ = 10.0 Hz, $^3J_{9b,8}$ = 3.6 Hz, 1 H, 9-H_b), 1.55 (m, 2 H, 3-H''), 1.61 (m, 2 H, 1-H', 10-H), 1.75 (m, 6 H, 1-H'', 2-H'', 3-H''', 6-H), 3.27 (t, $^3J_{7,6/8}$ = 5.6 Hz, 1 H, 7-H), 3.78 (m, 2 H, 5-H), 3.79 (s, 3 H, 18-H), 4.45 (d, $^2J_{13a,13b}$ = 11.4 Hz, 1 H, 13-H_a), 4.54 (d, $^2J_{13b,13a}$ = 11.4 Hz, 1 H, 13-H_b), 6.85 (d, $^3J_{15,16}$ = 8.6 Hz, 2 H, 15-H), 7.27 (d, $^3J_{16,15}$ = 8.3 Hz, 2 H, 16-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.1 (q, C-12), 16.4 (q, C-19), 21.5 (q, C-11), 24.2 (q, C-11'), 25.5 (d, C-8), 25.9 (t, C-2), 26.0 (t, C-3), 26.5 (t, C-1), 27.8 (d, C-10), 28.5 (t, C-9), 33.5 (d, C-6), 43.0 (d, C-4), 55.3 (q, C-18), 71.9 (t, C-13), 83.4 (d, C-5), 87.2 (d, C-7), 113.5 (d, C-16), 128.6 (d, C-15), 131.9 (s, C-14), 158.7 (s, C-17).

Optical rotation: $[\alpha]_D^{20}$ = +37.4 (c = 1.0, $CHCl_3$)

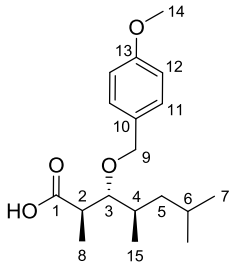
HRMS (CI): The compound decomposes during the measurements.

(2*R*,3*R*,4*R*)-3-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoic acid (107)

According to **GP-5** boronic ester **105** (1.45 g, 2.91 mmol) was treated with CH_2Cl_2 (561 µL, 8.73 mmol, 3.0 equiv.), DIPA (560 µL, 3.93 mmol, 1.35 equiv.), *n*-BuLi (1.45 mL, 3.64 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (1.19 g, 8.73 mmol, 3.0 equiv.) in dry THF (18 mL). After stirring for 16 hours the reaction was quenched by addition of sat. NH_4Cl solution and after 5 minutes the mixture was diluted with water. The mixture was extracted three times with pentane, the combined organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure.

The residue was suspended in a mixture of *t*-BuOH/H_2O (84 mL, 2:1) and 2-methyl-2-butene (6.00 mL, 56.6 mmol, 19.5 equiv.), sodium chlorite (3.29 g, 29.1 mmol, 10.0 equiv.) and KH_2PO_4 (3.96 g, 29.1 mmol, 10.0 equiv.) were added in quick succession. After stirring overnight, the reaction was quenched by careful acidification (pH 3) with aqueous HCl (1 M) solution. The mixture was extracted three times with diethyl ether and the combined organic layer was washed with sat. $Na_2S_2O_3$ solution and dried (Na_2SO_4). Esterification of the cleaved diol with isobutylboronic acid (356 mg, 3.49 mmol, 1.2 equiv.) in diethyl ether (25 mL) in the presence of $MgSO_4$ (701 mg, 5.82 mmol, 2.0 equiv.) was followed by filtration and evaporation of the solvent. Flash chromatography (silica, PE/EtOAc 9:1) afforded hydroxy acid **XX** (690 mg, 2.24 mmol, 77%) as a colorless oil and boronic ester **107** (782 mg, 2.68 mmol, 92%) as a colorless liquid.

R_f(107) = 0.18 (PE/EtOAc 4:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.90 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7-H'), 0.96 (d, $^3J_{15,4}$ = 7.0 Hz, 3 H, 15-H), 1.18 (m, 1 H, 5-H_a), 1.23 (d, $^3J_{8,2}$ = 7.2 Hz, 3 H, 8-H), 1.60 (m, 2 H, 5-H_b, 6-H), 1.86 (m, 1 H, 4-H), 2.77 (qd, $^3J_{2,8}$ = 7.1 Hz, $^3J_{2,3}$ = 5.8 Hz, 1 H, 2-H), 3.45 (dd, $^3J_{3,2}$ = 5.4 Hz, $^3J_{3,4}$ = 4.8 Hz, 1 H, 3-H), 3.79 (s, 3 H, 14-H), 4.52 (d, $^2J_{9a,9b}$ = 10.8 Hz, 1 H, 9-H_a), 4.60 (d, $^2J_{9b,9a}$ = 10.8 Hz, 1 H, 9-H_b), 6.86 (d, $^3J_{11,12}$= 8.7 Hz, 2 H, 11-H), 7.24 (d, $^3J_{12,11}$ = 8.7 Hz, 2 H, 12-H).

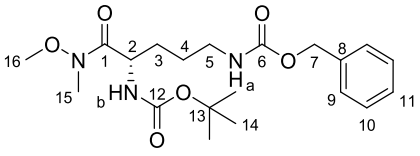
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.4 (q, C-8), 16.0 (q, C-15), 21.4 (q, C-7), 23.9 (q, C-7‘), 25.2 (d, C-6), 33.0 (d, C-4), 40.9 (t, C-5), 41.9 (d, C-2), 55.3 (q, C-14), 74.1 (t, C-9), 85.7 (d, C-3), 113.9 (d, C-12), 129.5 (d, C-11), 129.8 (s, C-10), 159.4 (s, C-13), 178.5 (s, C-1).

Optical rotation:	$[\alpha]_D^{20}$ = +23.9(c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{18}H_{28}O_4$ $[M]^+$	308.1982	308.1981

benzyl *tert*-butyl (5-(methoxy(methyl)amino)-5-oxopentane-1,4-diyl)(*S*)-dicarbamate (113)

To a solution of acid **109** (35.0 g, 81.0 mmol, 85%) in dry CH_2Cl_2 (400 mL) were subsequently added *N*,*O*-dimethylhydroxylamine hydrochloride (8.32 g, 85.0 mmol, 1.05 equiv.), DIPEA (15.6 mL, 89.0 mmol, 1.1 equiv.), HOBt (13.1 g, 85.0 mmol, 1.05 equiv.) and EDC (16.3 g, 85.0 mmol, 1.05 equiv.) at 0 °C. After stirring overnight, the reaction mixture was diluted with EtOAc and washed with HCl solution (1 M), sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the Weinreb amide **113** (34.1 g, 81.0 mmol, 97%) as a yellow resin.

R_f(113) = 0.15 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, 14-H), 1.58 (m, 3 H, 3-H_a, 4-H), 1.72 (m, 1 H, 3-H_b), 3.17 (s, 3 H, 15-H), 3.19 (m, 2 H, 5-H), 3.73 (s, 3 H, 16-H), 4.66 (bs, 1 H, 2-H), 5.08 (s, 2 H, 7-H), 5.20 (bs, 1 H, NH_a), 5.38 (d, $^3J_{NHb,2}$ = 9.1 Hz, 1 H, NH_b), 7.31 (m, 5 H, 9H, 10-H,11-H).

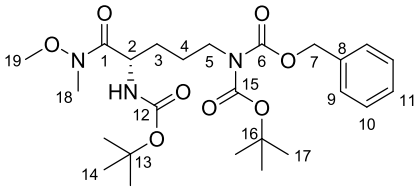
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.6 (t, C-4), 28.2 (q, C-14), 30.0 (t, C-3), 31.9 (q, C-15), 40.4 (t, C-5), 49.8 (d, C-2), 61.4 (q, C-16), 66.3 (t, C-7), 79.4 (s, C-13), 127.8 (d, C-9), 127.9 (d, C-11), 128.3 (d, C-10), 136.5 (s, C-8), 155.4 (s, C-6), 156.2 (s, C-12), 172.7 (s, C-1).

Optical rotation:	$[\alpha]_D^{20}$ = +7.3 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{20}H_{32}N_3O_6$ $[M+H]^+$	410.2286	410.2284

benzyl (S)-(*tert*-butoxycarbonyl)(4-((*tert*-butoxycarbonyl)amino)-5-(methoxy(methyl) amino)-5-oxopentyl)carbamate (114)

To a solution of Weinreb amide **113** (33.2 g, 81.0 mmol) in MeCN (580 mL) at 0 °C were added Boc_2O (19.8 mL, 85.0 mmol, 1.05 equiv.), NEt_3 (22.6 mL, 162 mmol, 2.0 equiv.) and DMAP (990 mg, 8.10 mmol, 0.1 equiv.). After stirring overnight further Boc_2O (1.88 mL, 8.10 mmol, 0.1 equiv.) was added and the mixture was stirred until complete conversion was observed (TLC). Then, the reaction mixture was quenched by addition of sat. aq. NH_4Cl solution and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. After column chromatography (silica, PE/EtOAc 1:1) the Weinreb amide **114** (35.7 g, 70.1 mmol, 86%) was obtained as a colorless resin.

R_f(114) = 0.29 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, 14-H/17-H), 1.46 (s, 9 H, 14-H/17-H), 1.52 (m, 1 H, 3-H_a), 1.68 (m, 3 H, 3-H_b, 4-H), 3.18 (s, 3 H, 18-H), 3.65 (dd, $^3J_{5,4a}$ = 7.2 Hz, $^3J_{5,4b}$ = 5.3 Hz, 2 H, 5-H), 3.74 (s, 3 H, 19-H), 4.65 (bs, 1 H, 2-H), 5.16 (d, $^3J_{NH,2}$ = 9.1 Hz, 1 H, NH), 5.21 (s, 2 H, 7-H), 7.35 (m, 5 H, 9-H, 10-H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.0 (t, C-4), 27.9 (q, C-14/C-17), 28.3 (q, C-14/C-17), 30.1 (t, C-3), 32.0 (q, C-18), 46.2 (t, C-5), 50.2 (d, C-2), 61.5 (q, C-19), 68.3 (t, C-7), 79.5 (s, C-13/C-16), 82.7 (s, C-13/C-16), 128.2 (d, C-9), 128.2 (d, C-11), 128.5 (d, C-10), 135.5 (s, C-8), 151.9 (s, C-15), 153.8 (s, C-6), 155.5 (s, C-12), 172.8 (s, C-1).

Optical rotation:	$[\alpha]_D^{20}$ = +12.1(c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{25}H_{40}N_3O_8$ $[M+H]^+$	510.2810	510.2814

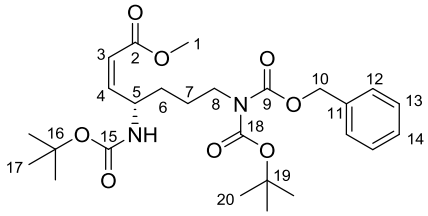
methyl (*S*,*Z*)-7-(((benzyloxy)carbonyl)(*tert*-butoxycarbonyl)amino)-4-((*tert*-butoxycarbonyl)amino)hept-2-enoate (112)[308]

To a solution of Weinreb amide **114** (7.08 g, 13.9 mmol) in dry THF (139 mL) was added Dibal-H (27.8 mL, 27.8 mmol, 1.0 M in hexane, 2.0 equiv.) over 10 minutes at −78 °C. After 20 minutes the reaction mixture was diluted with Et_2O, quenched with an aqueous solution of citric acid (10 w%) and the dry ice bath was removed. Stirring was continued until two

clear layers were obtained (45 min) and the layers were separated. The aqueous layer was extracted twice with diethyl ether and the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. After additional drying in high vacuo for 30 minutes the crude aldehyde was used immediately in the next step.

A Schlenk flask containing 18-C-6 (16.2 g, 61.1 mmol, 4.4 equiv.) was dried in high vacuo for 30 minutes and Still-Gennari phosphonate **E** (4.64 g, 14.6 mmol, 1.05 equiv.) in dry THF (75 mL) was added. The mixture was cooled to −78 °C and a solution of KHMDS (29.2 mL, 14.6 mmol, 0.5 M in toluene, 1.05 equiv.) was added dropwise. After stirring for 30 minutes at −78 °C cold solution of the crude aldehyde in dry THF (50 mL) was added over 20 minutes via transfer cannula. The reaction was kept at −78 °C for 2 hours, warmed to room temperature overnight and diluted with EtOAc. After quenching by addition of sat. NH_4Cl solution the aqueous layer was extracted twice with EtOAc, and the combined organic layer washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (silica, PE/EtOAc 4:1) afforded *Z*-olefin **112** (5.01 g, 9.89 mmol, 96:4 Z/E, 71%) as colorless resin.

R_f(112) = 0.54 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, 17-H/20-H), 1.47 (s, 9 H, 17-H/20-H), 1.54 (m, 2 H, 6-H), 1.68 (m, 2 H, 7-H), 3.66 (m, 2 H, 8-H), 3.70 (s, 3 H, 1-H), 4.79 (bs, 1 H, NH), 5.06 (quint, $^3J_{5,4/6/NH}$ = 7.4 Hz, 1 H, 5-H), 5.22 (s, 2 H, 10-H), 5.78 (dd, $^3J_{3,4}$ = 11.6 Hz, $^4J_{3,5}$ = 0.9 Hz, 1 H, 3-H), 6.06 (bs, 1 H, 4-H), 7.36 (m, 5 H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.2 (t, C-7), 27.9 (q, C-17/C-20), 28.3 (q, C-17/C-20), 31.6 (t, C-6), 46.2 (t, C-8), 49.0 (d, C-5), 51.3 (q, C-1), 68.3 (t, C-10), 79.4 (s, C-16/C-19), 82.8 (s, C-16/C-19), 119.6 (d, C-3), 128.3 (d, C-12), 128.3 (d, C-14), 128.5 (d, C-13), 135.6 (s, C-11), 150.2 (d, C-4), 152.0 (s, C-18), 153.8 (s, C-9), 155.2 (s, C-15), 166.0 (s, C-2).

Optical rotation: $[\alpha]_D^{20}$ = +18.8 (c = 1.0, $CHCl_3$)

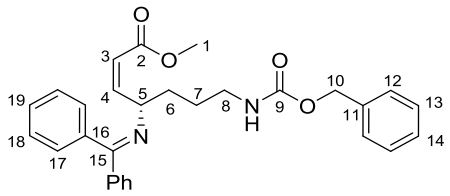
HRMS (CI):	Calculated	Found
$C_{26}H_{39}N_2O_8$ $[M+H]^+$	507.2701	507.2716

methyl (*S*,*Z*)-7-(((benzyloxy)carbonyl)amino)-4-((diphenylmethylene)amino)hept-2-enoate (115)

To a mixture of EtOAc (20 mL) and MeOH (7.67 mL, 190 mmol, 40.0 equiv.) was added AcCl (6.74 mL, 95.0 mmol, 20.0 equiv.) at 0 °C and the resulting mixture was stirred for 30 min. Alkene **112** (2.40 g, 4.74 mmol) in EtOAc (10 mL) was added to the HCl solution, the mixture stirred for 4 hours at 0 °C and then concentrated under reduced pressure.

The crude hydrochloride was suspended in DCM (50 mL), benzophenone imine (902 mg, 4.98 mmol, 1.05 equiv.) was added and the mixture stirred until complete consumption of the starting material was detected (TLC). After addition of sat. $NaHCO_3$ solution, the layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (silica, PE/EtOAc 4:1) afforded imine **115** (1.97 g, 4.19 mmol, 88%) as a pale-yellow oil.

R_f(115) = 0.12 (PE/EtOAc 4:1)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.43 (m, 1 H, 7-H_a), 1.54 (m, 1 H, 7-H_b), 1.64 (m, 1 H, 6-H_a), 1.79 (m, 1 H, 6-H_b), 3.03 (dq, $^2J_{8a,8b}$ = 13.4 Hz, $^3J_{8a,7/NH}$ = 6.5 Hz, 1 H, 8-H_a), 3.17 (m, 1 H, 8-H_b), 3.50 (s, 3 H, 1-H), 4.95 (bs, 1 H, NH), 5.01 (td, $^3J_{5,4/6a}$ = 8.3 Hz, $^3J_{5,6b}$ = 5.2 Hz, 1 H, 5-H), 5.07 (s, 2 H, 10-H), 5.71 (dd, $^3J_{3,4}$ = 11.7 Hz, $^4J_{3,5}$ = 0.9 Hz, 1 H, 3-H), 6.36 (dd, $^3J_{4,3}$ = 11.7 Hz, $^3J_{4,5}$ = 8.8 Hz, 1 H, 4-H), 7.07 (m, 2 H, 17-H'), 7.34 (m, 11 H, 12-H, 13-H, 14-H, 18-H, 19-H), 7.60 (m, 4 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, C-7), 33.2 (t, C-6), 40.3 (t, C-8), 51.1 (q, C-1), 59.9 (d, C-5), 66.4 (t, C-10), 117.9 (d, C-3), 127.6 (d, C-12), 128.0 (d, C-14), 128.0 (d, C-19), 128.1 (d, C-17/C-18), 128.4 (d, C-17/C-18), 128.4 (d, C-17'/C-18'), 128.5 (d, C-13), 130.2 (d, C-19'), 136.7 (s, C-11), 136.9 (s, C-16), 139.7 (s, C-16'), 150.1 (d, C-4), 156.3 (s, C-9), 166.1 (s, C-2), 169.5 (s, C-15).

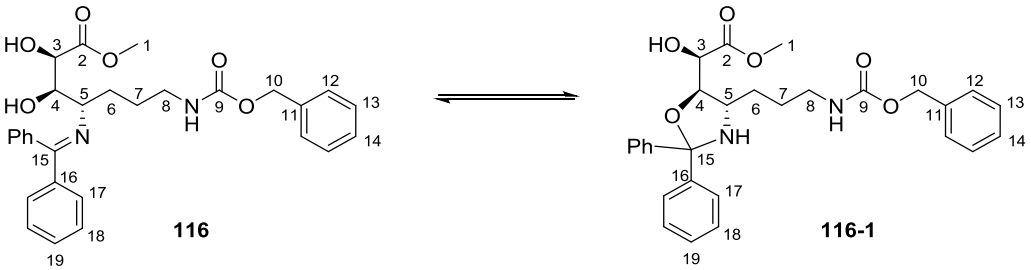
Optical rotation: $[\alpha]_D^{20}$ = +63.9 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{29}H_{31}N_2O_4$ $[M+H]^+$	471.2278	471.2276

methyl (2*R*,3*R*,4*S*)-7-(((benzyloxy)carbonyl)amino)-4-((diphenylmethylene)amino)-2,3-dihydroxyheptanoate (116)

Alkene **115** (1.90 g, 4.04 mmol) was dissolved in THF/H_2O (50 mL, 1:1) and NMO (1.84 mL, 8.88 mmol, 2.2 equiv.), $K_2OsO_4{\cdot}2H_2O$ (74.0 mg, 202 µmol, 5 mol%) were successively added. The mixture was stirred at room temperature for 48 hours, quenched by addition of sat. $Na_2S_2O_3$ solution and stirred vigorously for one hour until a clear, brown solution emerges. After three extractions with diethyl ether, the combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (silica, DCM/diethyl ether 9:1) afforded the diol **116** (1.82 g, 3.61 mmol, 89%) as a colorless foam. NMR spectra showed diol **116** exists in equilibrium with its hemiaminal **116-1**.

R_f(3bl) = 0.45 (DCM/acetone 4:1)



116 **116-1**

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.26 (m, 1 H, 6-H_a), 1.45 (m, 1 H, 6-H_b), 1.63 (m, 1 H, 7-H_a), 1.77 (m, 1 H, 7-H_b), 2.44 (bs, 1 H, OH), 3.01 (m, 1 H, OH), 3.18 (m, 2 H, 8-H), 3.41 (m, 1 H, 5-H), 3.54 (s, 3 H, 1-H), 3.83 (dd, $^{3}J_{3,4}$= 6.8 Hz, $^{3}J_{3,OH}$ = 3.7 Hz, 1 H, 3-H), 4.28 (bs, 1 H, 4-H), 5.00 (bs, 1 H, 5-H), 5.08 (s, 2 H, 10-H), 7.19 (m, 2 H, 18-H), 7.29 (m, 9 H, 12-H, 13-H, 14-H, 17-H, 19-H), 7.54 (m, 4 H, 17-H‘, 18-H‘).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.6 (t, C-7), 30.6 (t, C-6), 40.6 (t, C-8), 52.3 (q, C-1), 60.0 (d, C-5), 66.6 (t, C-10), 71.8 (d, C-4), 84.5 (d, C-3), 100.5 (s, C-15), 125.8 (d, C-18), 125.9 (d, C-18‘), 127.5 (d, C-12), 127.7 (d, C-14), 128.1 (d, C-13), 128.1 (d, C-19), 128.3 (d, C-19‘), 128.5 (d, C-17), 128.5 (d, C-17‘), 136.6 (s, C-11), 144.5 (s, C-16), 144.7 (s, C-16‘), 156.4 (s, C-9), 172.5 (s, C-2).

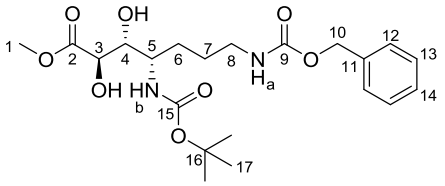
HRMS (CI):	Calculated	Found
$C_{29}H_{33}N_2O_6$ $[M+H]^+$	505.2333	505.2331

methyl (2*R*,3*R*,4*S*)-7-(((benzyloxy)carbonyl)amino)-4-((*tert*-butoxycarbonyl)amino)-2,3-dihydroxyheptanoate (117)

To a solution of imine **116** (1.00 g, 1.98 mmol) in THF/H_2O (20 mL, 18:1) was dropwise added TFA (2.14 mL,27.7 mmol, 14.0 equiv.) and the mixture was stirred at room temperature for four hours. The solvent was removed *in vacuo* and azeotropic co-evaporation with toluene, to remove traces of TFA, afforded the deprotected amine as its TFA salt.

The crude TFA salt was dissolved in THF/H_2O (20 mL, 1:1), $NaHCO_3$ (499 mg, 5.95 mmol, 3.0 equiv.) and Boc-anhydride (552 µL, 2.38 mmol, 1.2 equiv.) were added and the mixture was stirred at room temperature for 14 hours. The reaction was quenched by addition of sat. NH_4Cl and extracted three times with EtOAc. After drying (Na_2SO_4), the solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, PE/EtOAc 1:1) to afford amino acid **117** (560 mg, 1.06 mmol, 53%) as a colorless oil.

R_f(117) = 0.07 (PE/EtOAc 1:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, 17-H), 1.61 (m, 4 H, 6-H, 7-H), 3.22 (m, 2 H, 8-H), 3.46 (d, $^{3}J_{OH,4}$ = 2.2 Hz, 1 H, OH), 3.71 (m, 1 H, 3-H), 3.83 (s, 3 H, 1-H), 3.86 (m, 1 H, 5-H), 3.96

(dd, $^3J_{4,3}$ = 8.7 Hz, $^3J_{4,5}$ = 5.4 Hz, 1 H, 4-H), 4.83 (d, $^3J_{OH,3}$ = 6.6 Hz, 1 H, OH), 4.88 (m, 2 H, NH_a, NH_b), 5.09 (s, 2 H, 10-H), 7.33 (m, 5 H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.9 (t, C-7), 28.3 (q, C-17), 28.8 (t, C-6), 40.7 (t, C-8), 50.4 (d, C-5), 52.7 (q, C-1), 66.7 (t, C-10), 71.2 (d, C-4), 73.7 (d, C-3), 80.6 (s, C-16), 128.1 (d, C-12, C-14), 128.5 (d, C-13), 136.5 (s, C-11), 156.5 (s, C-9), 157.6 (s, C-15), 174.1 (s, C-2).

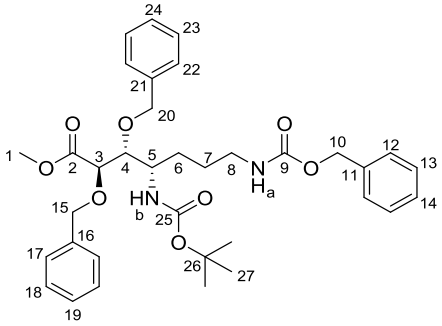
Optical rotation: $[\alpha]_D^{20}$ = –27.8 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{21}H_{33}N_2O_8$ $[M+H]^+$	441.2231	441.2241

methyl (2*R*,3*R*,4*S*)-2,3-bis(benzyloxy)-7-(((benzyloxy)carbonyl)amino)-4-((*tert*-butoxy-carbonyl)amino)heptanoate (118)

To a solution of diol **117** (410 mg, 931 µmol) in diethyl ether (9.3 mL) was added benzyl 2,2,2-trichloroacetimidate (520 µL, 2.79 mmol, 3.0 equiv.) and triflic acid (465 µL, 46.5 µmol, 0.1 M in Et_2O, 5mol%) at 0 °C. After stirring for 10 hours at room temperature additional benzyl 2,2,2-trichloroacetimidate (260 µL, 1.40 mmol, 1.5 equiv.) was added and the reaction was stirred for 4 hours. The mixture was diluted with THF/H_2O (9 mL, 1:1) and neutralized by addition of $NaHCO_3$ (235 mg, 2.79 mmol, 3.0 equiv.). Boc_2O (259 µL, 1.12 mmol, 1.2 equiv.) was added, the reaction stirred at room temperature for 5 hours and then quenched by addition of sat. NH_4Cl solution. The aqueous layer was extracted three times with EtOAc, the combined organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. Two purifications via flash chromatography (silica, PE/EtOAc, 95:5 → 4:1 and 85:15 → 1:1) afforded dibenzyl ether **118** (243 mg, 391 µmol, 42%) as a colorless resin.

R_f(118) = 0.18 (PE/EtOAc 2:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, 27-H), 1.50 (m, 4 H, 6-H, 7-H), 3.15 (m, 2 H, 8-H), 3.65 (s, 3 H, 1-H), 3.71 (m, 1 H, 4-H), 3.94 (d, $^3J_{3,4}$ = 8.6 Hz, 1 H, 3-H), 4.01 (m, 1 H, 5-H), 4.50 (m, 4 H, 15-H, 20-H), 4.87 (m, 2 H, NH_a, NH_b), 5.08 (s, 2 H, 10-H), 7.29 (m, 15 H, 12-H, 13-H, 14-H, 17-H, 18-H, 19-H, 22-H, 23-H, 24-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.6 (t, C-7), 28.3 (q, C-27), 30.0 (t, C-6), 40.7 (t, C-8), 50.4 (d, C-5), 51.9 (q, C-1), 66.5 (t, C-10), 73.3 (t, C-15/C-20), 74.7 (t, C-15/C-20), 78.3 (d, C-3), 79.2 (d, C-4), 80.6 (s, C-26), 128.0 (d, C-12, C-17/C-22), 128.1 (d, C-14, C-17/C-22), 128.4 (d, C-18,

C-23), 128.4 (d, C-19, C-24), 128.6 (d, C-13), 136.6 (s, C-11), 136.6 (s, C-16/C-21), 137.3 (s, C-16/C-21), 155.7 (s, C-9), 156.3 (s, C-25), 172.0 (s, C-2).

Optical rotation: $[\alpha]_D^{20}$ = –14.1 (c = 1.0, $CHCl_3$)

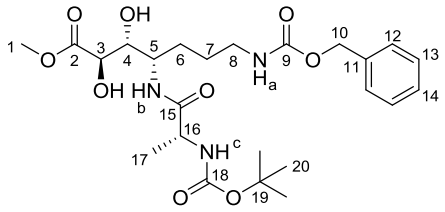
HRMS (CI):	Calculated	Found
$C_{35}H_{45}N_2O_8$ $[M+H]^+$	621.3170	621.3179

methyl (2*R*,3*R*,4*S*)-7-(((benzyloxy)carbonyl)amino)-4-((*R*)-2-((*tert*-butoxycarbonyl)amino) propanamido)-2,3-dihydroxyheptanoate (120)

To a solution of imine **116** (3.15 g, 6.24 mmol) in THF/H_2O (70 mL, 18:1) was dropwise added TFA (6.73 mL, 87.0 mmol, 14.0 equiv.) and the mixture was stirred at room temperature for four hours. The solvent was removed *in vacuo* and azeotropic co-evaporation with toluene, to remove traces of TFA, afforded the deprotected amine as its TFA salt.

The crude TFA salt was dissolved in DCM and Boc-D-alanine (1.42 g, 7.49 mmol, 1.2 equiv.), DIPEA (3.38 mL, 19.3 mmol, 3.1 equiv.), HOBt (1.15 g, 7.49 mmol, 1.2 equiv.) and EDC (1.44 g, 7.49 mmol, 1.2 equiv.) were successively added at 0 °C. After warming to room temperature overnight the mixture was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The solvent was removed *in vacuo* and the crude mixture purified by flash chromatography (silica, DCM/MeOH 96:4) to afford dipeptide **120** (2.13 g, 4.16 mmol, 67%) as a colorless foam.

R_f(120) = 0.29 (DCM/MeOH 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, $^3J_{17,16}$ = 6.9 Hz, 3 H, 17-H), 1.41 (s, 9 H, 20-H), 1.48 (m, 4 H, 6-H, 7-H), 3.03 (q, $^3J_{8,7/NH}$ = 6.4 Hz, 2 H, 8-H), 3.61 (ddd, $^3J_{4,3}$ = 8.5 Hz, $^3J_{4,5}$ = 6.6 Hz, $^3J_{4,OH}$= 2.0 Hz, 1 H, 4-H), 3.64 (s, 3 H, 1-H), 3.81 (dd, $^3J_{3,4}$ = 8.4 Hz, $^3J_{3,OH}$ = 4.9 Hz, 1 H, 3-H), 3.99 (m, 2 H, 5-H, 16-H), 4.81 (d, $^3J_{NHb,5}$ = 6.6 Hz, 1 H, NH_b), 5.03 (s, 2 H, 10-H), 5.16 (d, $^3J_{OH,3}$ = 5.0 Hz, 1 H, OH), 6.47 (bs, 1 H, OH/NH_a), 6.73 (bs, 1 H, OH/NH_a), 7.09 (d, $^3J_{NHc,16}$ = 8.8 Hz, 1 H, NH_c), 7.32 (m, 5 H, 12-H, 13-H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.1 (q, C-17), 26.7 (t, C-7), 28.2 (q, C-20), 28.4 (t, C-6), 40.6 (t, C-8), 49.6 (d, C-5), 50.6 (d, C-16), 52.6 (q, C-1), 66.6 (t, C-10), 71.3 (d, C-4), 73.8 (d, C-3), 80.5 (s, C-19), 128.1 (d, C-12), 128.1 (d, C-14), 128.5 (d, C-13), 136.5 (s, C-11), 155.7 (s, C-18), 156.5 (s, C-9), 173.9 (s, C-2), 175.2 (s, C-15).

Optical rotation: $[\alpha]_D^{20}$ = +37.2 (c = 1.0, $CHCl_3$)

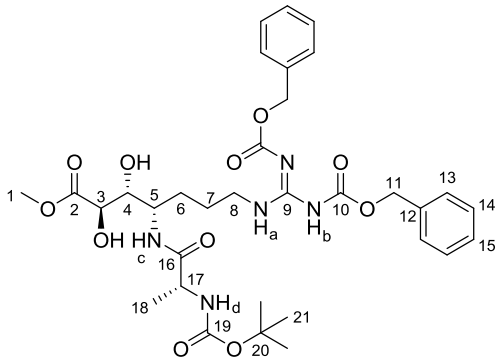
HRMS (CI):	Calculated	Found
$C_{24}H_{38}N_3O_9$ $[M+H]^+$	512.2603	512.2612

methyl (2*R*,3*R*,4*S*)-7-((*E*)-2,3-bis((benzyloxy)carbonyl)guanidino)-4-((*R*)-2-((*tert*-butoxy-carbonyl)amino)propanamido)-2,3-dihydroxyheptanoate (122)

Cbz-carbamate **120** (1.29 g, 2.52 mmol) was dissolved in MeOH (25 mL) and Pd/C (129 mg, 10 w%) was added. After stirring under an atmosphere of hydrogen for four hours, the mixture was filtrated, and the solvent was removed under reduced pressure.

Under an atmosphere of nitrogen, the crude amine was dissolved in DCM (20 mL) and NEt_3 (421 µL, 3.02 mmol, 1.2 equiv.) and triflate **G**[355] (1.39 g, 3.02 mmol, 1.2 equiv.) were added. After stirring at room temperature overnight, the mixture was diluted with EtOAc and successively washed with 1 M $KHSO_4$ solution and brine. The organic layer was dried ($MgSO_4$), the solvent evaporated, and the crude product purified by flash chromatography (silica, DCM/MeOH 97:3) to afford guanidine **122** (1.34 g, 1.95 mmol, 77%) as a white foam.

R_f(122) = 0.26 (DCM/MeOH 97:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, $^3J_{18,17}$ = 7.3 Hz, 3 H, 18-H), 1.40 (s, 9 H, 21-H), 1.64 (m, 3 H, 6-H_a, 7-H), 1.82 (m, 1 H, 6-H_b), 3.32 (dq, $^3J_{8a,8b}$ = 12.4 Hz, $^3J_{8a,7/NH}$ = 5.7 Hz, 1 H, 8-H_a), 3.54 (m, 1 H, 8-H_b), 3.73 (dd, $^3J_{4,3}$ = 9.0 Hz, $^3J_{4,5}$ = 1.4 Hz, 1 H, 4-H), 3.80 (s, 3 H, 1-H), 3.84 (d, $^3J_{3,4}$ = 8.8 Hz, 1 H, 3-H), 4.15 (m, 2 H, 5-H, 17-H), 5.10 (m, 1 H, NH_c/NH_d), 5.11 (s, 2 H, 11-H), 5.18 (s, 2 H, 11-H‘), 7.34 (m, 10 H, 13-H, 14-H, 15-H), 8.40 (t, $^3J_{NHa,8}$ = 5.8 Hz, 1 H, NH_a), 11.73 (bs, 1 H, NH_b).

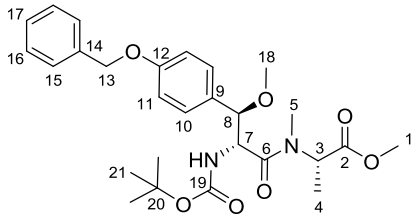
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.2 (q, C-18), 26.6 (t, C-7), 27.2 (t, C-6), 28.2 (q, C-21), 40.5 (t, C-8), 50.2 (d, C-5), 50.4 (d, C-17), 52.5 (q, C-1), 67.3 (t, C-11), 68.3 (t, C-11‘), 71.3 (d, C-4), 74.1 (d, C-3), 80.2 (s, C-20), 128.1 (d, C-15), 128.3 (d, C-13), 128.4 (d, C-13‘), 128.5 (d, C-14), 128.7 (d, C-14‘), 128.8 (d, C-15‘), 134.5 (s, C-12), 136.4 (s, C-12‘), 154.8 (s, C-10), 155.5 (s, C-19), 156.4 (s, C-9), 163.3 (s, C-10‘), 173.7 (s, C-2), 175.4 (s, C-16).

Optical rotation:	$[\alpha]_D^{20}$ = +31.0 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{33}H_{46}N_5O_{11}$ $[M+H]^+$	688.3188	688.3207

methyl *N*-((2*R*,3*R*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-propan-oyl)-*N*-methyl-L-alaninate (124)

To a solution of tyrosine **72** (7.93 g, 19.8 mmol) in dry DMF (198 mL) were added N-methyl-*L*-alanine methyl ester hydrochloride (6.07 g, 39.5 mmol, 2.0 equiv.), DIPEA (10.4 mL, 59.3 mmol, 3.0 equiv.) and HBTU (7.87 g, 20.7 mmol, 1.05 equiv.) at 0 °C. The mixture was allowed to warm to room temperature overnight, was diluted with EtOAc and successively washed with sat. solution of $NaHCO_3$, 1 M HCl and brine. After drying over Na_2SO_4, the solvent was removed *in vacuo* and the residue purified twice via column chromatography (silica, PE/EtOAc 8:2 → 7:3 → 1:1) to obtain dipeptide **124** (9.29 g, 18.6 mmol, 94%) as a colorless resin.

R_f(124) = 0.15 (PE/EtOAc 7:3)



Main Rotamer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H, 21-H), 1.37 (d, $^3J_{4,3}$ = 7.2 Hz, 3 H, 4-H), 2.91 (s, 3 H, 5-H), 3.17 (s, 3 H, 18-H), 3.71 (s, 3 H, 1-H), 4.23 (d, $^3J_{8,7}$ = 8.1Hz, 1 H, 8-H), 4.84 (t, $^3J_{7,8/NH}$ = 9.0 Hz, 1 H, 7-H), 5.06 (s, 2 H, 13-H), 5.25 (m, 1 H, 3-H), 6.96 (d, $^3J_{11,10}$ = 8.6 Hz, 2 H, 11-H), 7.34 (m, 7 H, 10-H, 15-H, 16-H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.3 (q, C-4), 28.1 (q, C-21), 31.7 (q, C-5), 52.2 (q, C-1), 52.5 (d, C-3), 54.2 (d, C-7), 57.0 (q, C-18), 70.0 (t, C-13), 79.4 (s, C-20), 85.4 (d, C-8), 114.6 (d, C-11), 127.4 (d, C-15), 127.9 (d, C-17), 128.6 (d, C-10/C-16), 129.0 (d, C-10/C-16), 129.9 (s, C-9), 136.9 (s, C-14), 154.5 (s, C-19), 158.9 (s, C-12), 171.5 (s, C-6), 172.0 (s, C-2).

Minor Rotamer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 9 H, 21-H), 1.50 (d, $^3J_{4,3}$ = 7.1 Hz, 3 H, 4-H), 2.97 (s, 3 H, 5-H), 3.08 (s, 3 H, 18-H), 3.76 (s, 3 H, 1-H), 4.17 (d, $^3J_{8,7}$ = 8.9Hz, 1 H, 8-H), 5.25 (m, 1 H, 3-H).

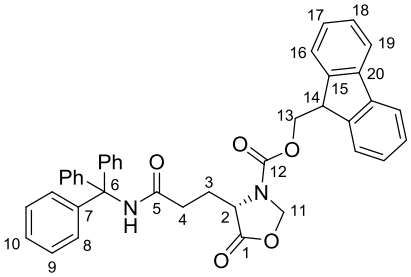
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.2 (q, C-4), 28.1 (q, C-21), 29.8 (q, C-5), 54.0 (d, C-7), 56.8 (q, C-18), 85.0 (d, C-8), 114.5 (d, C-11), 127.4 (d, C-15), 128.1 (d, C-17), 128.6 (d, C-10/C-16), 129.1 (d, C-10/C-16), 129.8 (s, C-9), 172.0 (s, C-2).

Optical rotation:	$[\alpha]_D^{20}$ = +43.2 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{27}H_{37}N_2O_7$ $[M+H]^+$	501.2595	501.2602

(9H-fluoren-9-yl)methyl (*S*)-5-oxo-4(3-oxo-3-(tritylamino)propyl)oxazolidine-3-carboxylate (125)[319]

In a 500 mL three-neck round-bottom flask fitted with a Dean-Stark apparatus, *p*-formaldehyde (9.83 g, 327 mmol, 20 equiv.) and *p*-TsOH (311 mg, 1.64 mmol, 0.1 equiv.) were suspended in dry toluene (250 mL). After addition of a solution of N_δ-Trityl-N_α-Fmoc-glutamine (10.0 g, 16.4 mmol) in DMF (20 mL) the mixture was heated to reflux for two hours. The resulting clear solution was cooled to room temperature, diluted with EtOAc and successively washed with sat. $NaHCO_3$ (3x), water and brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by flash chromatography (silica, PE/EtOAc 6:4) to afford oxazolidinone **125** (9.66 g, 15.5 mmol, 95%) as a white solid.

R_f(125) = 0.30 (PE/EtOAc 6:4)



^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.85 (m, 2 H, 3-H), 2.18 (m, 1 H, 4-H_a), 2.36 (m, 1 H, 4-H_b), 4.00 (m, 1 H, 14-H), 4.30 (t, $^3J_{2,3}$ = 6.3 Hz, 1 H, 2-H), 4.41 (dd, $^2J_{13a,13b}$ = 10.3 Hz, $^3J_{13a,14}$ = 6.3 Hz, 1 H, 11-H_a), 4.47 (dd, $^2J_{13b,13a}$ = 10.3 Hz, $^3J_{13b,14}$ = 6.6 Hz, 1 H, 13-H_b), 5.12 (bs, 1 H, 11-H_a), 5.32 (m, 1 H, 11-H_b), 7.15 (m, 6 H, 8-H), 7.19 (m, 3 H, 10-H), 7.25 (m, 6 H, 9-H), 7.31 (m, 2 H, 17-H), 7.40 (m, 2 H, 18-H), 7.64 (dd, $^3J_{16,17}$ = 7.3 Hz, $^4J_{16,18}$= 3.2 Hz, 2 H, 16-H), 7.87 (d, $^3J_{19,18}$ = 7.3 Hz, 2 H, 19-H), 8.59 (bs, 1 H, NH).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 26.0 (t, C-3), 30.8 (t, C-4), 46.6 (d, C-14), 54.9 (d, C-2), 67.2 (t, C-13), 77.8 (t, C-11), 120.2 (d, C-16), 125.2 (d, C-17), 126.4 (d, C-10), 127.3 (d, C-18/C-19), 127.5 (d, C-8), 127.8 (d, C-18/C-19), 128.6 (d, C-9), 140.8 (s, C-20), 143.6 (s, C-15), 144.9 (s, C-7), 170.8 (s, C-1), 172.4 (s, C-5).

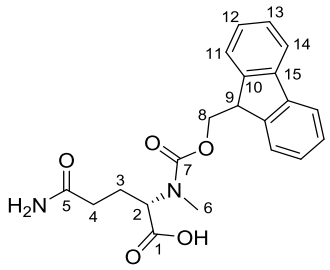
Optical rotation:	$[\alpha]_D^{20}$ = –17.3 (c = 1.0, $CHCl_3$)	
Melting point:	100-102 °C	
HRMS (CI):	Calculated	Found
$C_{40}H_{35}N_2O_5$ $[M+H]^+$	623.2540	623.2562

***N*^{2}-(((9H-fluoren-9-yl)methoxy)carbonyl)-*N*^{2}-methyl-L-glutamine (126)**[319]

Oxazolidinone **125** (9.00 g, 14.5 mmol) was dissolved in $CHCl_3$ (115 mL) and trifluoroacetic acid (78.0 mL, 1.01 mol, 70 equiv.) was added which resulted in a dark orange solution. After addition of Et_3Si-H (9.23 mL, 57.8 mmol, 4.0 equiv.) the reaction was sealed and over 4 days the mixture gradually turned colorless again. The solvent was removed *in vacuo* and the

residue co-evaporated with toluene twice. Flash chromatography (silica, DCM/MeOH 95:5 → 9:1) yielded glutamine **126** (4.86 g, 12.7 mmol, 88%) as a white solid.

R_f(126) = 0.21 (DCM/MeOH 9:1)



Major Rotamer:

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.86 (m, 1 H, 3-H_a), 2.09 (m, 3 H, 4-H, 3-H_b), 2.78 (s, 3 H, 6-H), 4.28 (m, 3 H, 8-H, 9-H), 4.51 (m, 1 H, 2-H), 6.76 (s, 2 H, NH), 7.31 (m, 2 H, 13-H), 7.42 (t, $^3J_{12,11/13}$ = 7.0 Hz, 2 H, 12-H), 7.66 (d, $^3J_{11,12}$ = 7.5 Hz, 2 H, 11-H), 7.89 (m, 2 H, 14-H), 12.85 (bs, 1 H, COOH).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.0 (t, C-4), 30.6 (t, C-3), 31.5 (q, C-6), 46.6 (d, C-9), 58.2 (d, C-2), 66.9 (t, C-8), 120.1 (d, C-11), 125.1 (d, C-12), 127.2 (d, C-13/C-14), 127.7 (d, C-13/C-14), 140.7 (s, C-15), 143.8 (s, C-10), 143.8 (s, C-10‘), 156.1 (s, C-7), 172.4 (s, C-1), 173.3 (s, C-5).

Minor Rotamer (selected signals):

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.77 (s, 3 H, 6-H), 6.80 (s, 1 H, NH), 7.63 (d, $^3J_{11,12}$ = 7.6 Hz, 2 H, 11-H).

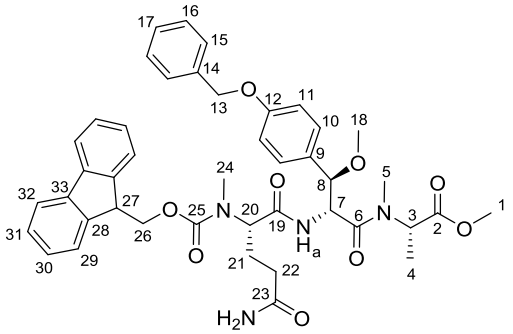
Optical rotation:	$[\alpha]_D^{20}$ = –9.3 (c = 1.0, $CHCl_3$)	
Melting point:	150-151 °C (decomposition)	
HRMS (CI):	Calculated	Found
$C_{21}H_{24}N_2O_5$ $[M+2H]^+$	384.1680	384.1668

methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (127)

Dipeptide **124** (3.10 g, 6.19 mmol) was dissolved in DCM (15 mL) and treated with HCl (15.5 mL, 61.9 mmol, 4.0 M in dioxane, 10.0 equiv.) at 0 °C until complete Boc-deprotection was observed by TLC. The mixture was concentrated, dried in high vacuum and redissolved in dry DMF (62 mL). To the hydrochloride solution were added, glutamine **126** (2.49 g, 6.50 mmol, 1.05 equiv.), DIPEA (2.27 mL, 13.0 mmol, 2.1 equiv.) and HATU (2.59 g, 6.81 mmol, 1.1 equiv.) at 0 °C and the reaction was stirred overnight. The mixture was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue purified by flash

chromatography (silica, DCM/MeOH 98:2 → 97:3) to yield tripeptide **127** (4.37 g, 5.71 mmol, 92%) as a white amorphous solid.

R_f(127) = 0.27 (DCM/MeOH 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, $^3J_{4,3}$ = 7.2 Hz, 3 H, 4-H), 1.84 (m, 3 H, 21-H, 22-H_a), 2.04 (m, 1 H, 22-H_b), 2.66 (s, 3 H, 5-H/24-H), 2.95 (s, 3 H, 5-H/24-H), 3.15 (s, 3 H, 18-H), 3.63 (s, 3 H, 1-H), 4.25 (m, 1 H, 27-H), 4.29 (d, $^3J_{8,7}$ = 7.8 Hz, 1 H, 8-H), 4.45 (m, 2 H, 7-H, 20-H), 5.03 (m, 2 H, 26-H), 5.19 (m, 2 H, 13-H), 5.26 (bs, 1 H, 3-H), 6.74 (m, 1 H, NH_a), 6.95 (d, $^3J_{11,12}$ = 8.1 Hz, 2 H, 11-H), 7.25 (m, 1 H, NH_2), 7.35 (m, 11 H, 10-H, 15-H, 16-H, 17-H, 30-H, 31-H), 7.58 (d, $^3J_{29,30}$ = 7.5 Hz, 2 H, 29-H), 7.76 (d, $^3J_{32,31}$ = 7.5 Hz, 2 H, 32-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.3 (q, C-4), 23.7 (t, C-21), 29.9 (q, C-24), 31.8 (q/t, C-5, C-22), 47.2 (d, C-27), 47.2 (d, C-20), 52.2 (q, C-1), 52.7 (q, C-18), 57.0 (d, C-3), 58.3 (d, C-7), 70.0 (t, C-13), 77.2? (t, C-26), 84.5 (d, C-8), 114.7 (d, C-11), 120.0 (d, C-29), 125.0 (d, C-30), 127.1 (d, C-17), 127.5 (d, C-15), 127.7 (d, C-10), 127.7 (d, C-31/C-32), 128.1 (d, C-31/C-32), 128.6 (d, C-16), 129.7 (s, C-9), 136.7 (s, C-14), 141.3 (s, C-28/C-33), 141.3 (s, C-28/C-33), 158.9 (s, C-12, C-25), 168.7 (s, C-2/C-6/C-19/C-23), 170.8 (s, C-2/C-6/C-19/C-23), 171.8 (s, C-2/C-6/C-19/C-23).

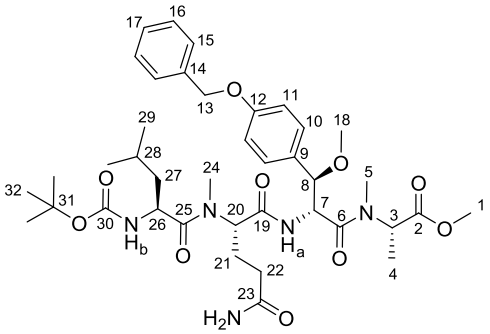
Optical rotation:	$[\alpha]_D^{20}$ = –29.3 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{43}H_{49}N_4O_9$ $[M+H]^+$	765.3494	765.3477

methyl *N*-((2*R*,3*R*)-2-((*S*)-5-amino-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-*N*,4-dimethyl-pentan-amido)-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (128a)

To a solution of tripeptide **127** (723 mg, 945 µmol) in MeCN (20 mL) was added diethylamine (7.90 mL, 76.0 mmol, 80.0 equiv.) and the mixture was stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the crude product was dried in high vacuum for 4 hours. The amine and Boc-L-leucine hydrate (471 mg, 1.89 mmol, 2.0 equiv.) were dissolved in dry DMF (18 mL) and treated with DIPEA (660 µL, 3.78 mmol, 4.0 equiv.) and HATU (719 mg, 1.89 mmol, 2.0 equiv.) at 0 °C. After warming to room temperature overnight, the reaction was diluted with EtOAc and successively washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed *in*

vacuo and the residue purified by flash chromatography (silica, DCM/MeOH 97:3 → 95:5) to afford tetrapeptide **128a** (660 mg, 873 µmol, 92%) as a white solid.

R_f(128a) = 0.29 (DCM/MeOH 95:5)



^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ = 0.89 (d, $^3J_{29,28}$ = 6.6 Hz, 6 H, 29-H), 1.33 (d, $^3J_{4,3}$ = 6.9 Hz, 3 H, 4-H), 1.36 (m, 1 H, 27-H_a), 1.40 (s, 9 H, 32-H), 1.43 (m, 1 H, 27-H_b), 1.53 (m, 2 H, 21-H), 1.67 (m, 1 H, 28-H), 1.80 (m, 2 H, 22-H), 2.74 (s, 3 H, 24-H), 2.99 (s, 3 H, 5-H), 3.10 (s, 3 H, 18-H), 3.63 (s, 3 H, 1-H), 4.36 (m, 2 H, 8-H, 20-H/26-H), 4.77 (m, 1 H, 7-H), 4.92 (m, 1 H, 3-H), 5.03 (m, 1 H, 20-H/26-H), 5.10 (s, 2 H, 13-H), 6.37 (bs, 1 H, NH_a/NH_b), 6.53 (bs, 2 H, NH_2), 6.97 (d, $^3J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.27 (d, $^3J_{10,11}$ = 7.8 Hz, 2 H, 10-H), 7.32 (m, 1 H, 17-H), 7.39 (m, 2 H, 16-H), 7.44 (m, 2 H, 15-H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 13.4 (q, C-4), 21.0 (q, C-29), 22.1 (q, C-29‘), 23.4 (t, C-21), 23.8 (d, C-28), 27.7 (q, C-32), 29.6 (q, C-24), 31.1 (t, C-22), 31.4 (q, C-5), 40.1 (t, C-27), 48.9 (d, C-20/C-26), 51.1 (q, C-1), 52.0 (d, C-3), 52.6 (d, C-7), 55.4 (d, C-20/C-26), 56.0 (q, C-18), 69.2 (t, C-13), 77.8 (s, C-31), 82.7 (d, C-8), 114.1 (d, C-11), 127.0 (d, C-15), 127.1 (d, C-17), 127.8 (d, C-16), 128.5 (d, C-10), 129.8 (s, C-9), 136.8 (s, C-14), 154.7 (s, C-30), 158.0 (s, C-12), 168.5 (s, C-6/C-19/C-23/C-25), 169.7 (s, C-6/C-19/C-23/C-25), 170.9 (s, C-2), 172.8 (s, C-6/C-19/ C-23/C-25).

Optical rotation: $[\alpha]_D^{20}$ = −31.6 (c = 1.0, $CHCl_3$)

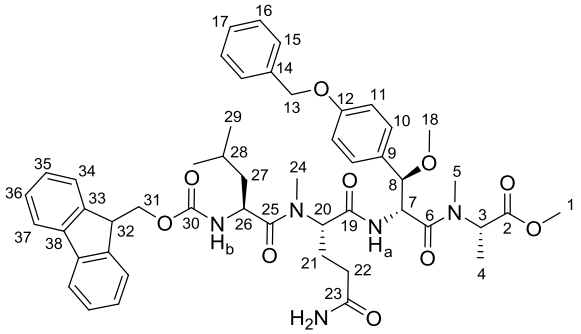
HRMS (CI):	Calculated	Found
$C_{39}H_{58}N_5O_{10}$ $[M+H]^+$	756.4178	756.4201

methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-*N*,4-dimethyl-pentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (128b)

A solution of tripeptide **127** (2.11 mg, 2.76 mmol) in MeCN (55 mL) was treated with diethylamine (23.1 mL, 221 mmol, 80.0 equiv.) at room temperature for 60 minutes. The solvent was removed *in vacuo* and the crude product was dried in high vacuum for 4 hours. The residue was dissolved in dry DMF (55 mL) and Fmoc-L-leucine (1.95 g, 5.52 mmol, 2.0 equiv.), DIPEA (1.93 mL, 11.0 mmol, 4.0 equiv.) as well as HATU (2.10 g, 5.52 mmol, 2.0 equiv.) were added at 0 °C. After 15 hours, the mixture was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4),

the solvent removed *in vacuo* and the crude product purified by flash chromatography (silica, DCM/MeOH 97:3 → 95:5) to afford tetrapeptide **128b** (2.30 g, 2.62 mmol, 95%) as a colorless foam.

R_f(128b) = 0.36 (DCM/MeOH 95:5)



^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ = 0.87 (d, $^3J_{29,28}$ = 6.6 Hz, 3 H, 29-H), 0.89 (d, $^3J_{29',28}$ = 6.9 Hz, 3 H, 29-H'), 1.27 (m, 2 H, 27-H), 1.32 (d, $^3J_{4,3}$ = 6.0 Hz, 3 H, 4-H), 1.59 (m, 2 H, 21-H_a, 28-H), 1.80 (m, 3 H, 21-H_b, 22-H), 2.97 (s, 6 H, 5-H, 24-H), 3.10 (s, 3 H, 18-H), 3.58 (dd, $^3J_{20,21a}$ = 8.2 Hz, $^3J_{20,21b}$ = 5.0 Hz, 1 H, 20-H), 3.63 (s, 3 H, 1-H), 4.36 (d, $^3J_{8,7}$ = 7.8 Hz, 1 H, 8-H), 4.37 (m, 1 H, 32-H), 4.73 (bs, 1 H, 7-H), 4.90 (m, 1 H, 3-H), 5.03 (m, 1 H, 26-H), 5.10 (s, 2 H, 13-H), 6.22 (s, 2 H, 31-H), 6.55 (bs, 2 H, NH), 6.97 (d, $^3J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.27 (m, 2 H, 10-H), 7.32 (m, 3 H, 17-H, 35-H), 7.39 (m, 4 H, 15-H, 36-H), 7.44 (m, 2 H, 16-H), 7.81 (d, $^3J_{34,35}$ = 7.5 Hz, 2 H, 34-H), 7.86 (d, $^3J_{37,36}$ = 7.2 Hz, 2 H, 37-H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 13.4 (q, C-4), 21.3 (q, C-29), 22.3 (q, C-29'), 23.4 (t, C-21), 23.7 (d, C-28), 28.4 (t, C-27), 31.5 (t, C-22), 31.5 (q, C-5, C-24), 44.9 (d, C-32), 48.7 (d, C-20), 51.1 (q, C-1), 52.0 (d, C-3), 52.6 (d, C-7), 55.0 (d, C-26), 56.0 (q, C-18), 69.2 (t, C-13), 83.0 (d, C-8), 108.4 (t, C-31), 114.1 (d, C-11), 119.3 (d, C-34), 120.7 (d, C-34'), 126.6 (d, C-35), 126.8 (d, C-37), 126.9 (d, C-36), 127.1 (d, C-15), 127.8 (d, C-17), 128.3 (d, C-10), 128.5 (d, C-16), 128.8 (s, C-9), 136.8 (s, C-14), 139.1 (s, C-38), 142.3 (s, C-33), 158.0 (s, C-30), 161.3 (s, C-12), 166.1 (s, C-6/C-19/C-23/C-25), 169.8 (s, C-6/C-19/C-23/C-25), 170.9 (s, C-2), 172.8 (s, C-6/ C-19/C-23/C-25).

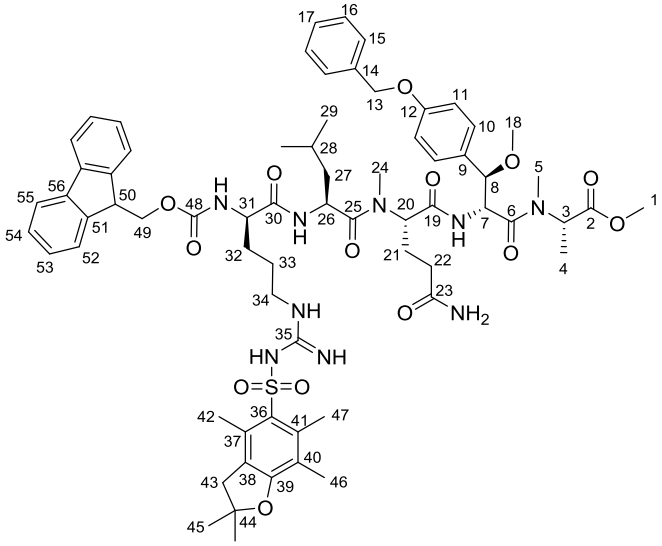
Optical rotation:	$[\alpha]_D^{20}$ = –61.2 (c = 1.0, $CHCl_3$)	
HRMS (CI):	Calculated	Found
$C_{39}H_{58}N_5O_{10}$ $[M+H]^+$	756.4178	756.4201

methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dime-thylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropan-oyl)-*N*-methyl-L-alaninate (129)

After Fmoc-deprotection of tetrapeptide **128b** (74.0 mg, 84.3 µmol) with diethylamine (704 µL, 6.74 mmol, 80 equiv.) in MeCN (1.7 mL) according to **GP-6**, the amine was dissolved in dry DMF (840 µL) and N_α-Fmoc-N_ω-Pbf-D-arginine (82.0 mg, 126 µmol, 1.5 equiv.) was

added. Addition of DIPEA (41.1 µL, 235 µmol, 2.8 equiv.) and HBTU (47.8 mg, 126 µmol, 1.5 equiv.) at 0 °C was followed by stirring for 15 hours and dilution with EtOAc. The mixture was washed with 1 M HCl, sat. $NaHCO_3$ solution and brine, the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica, DCM/MeOH 95:5 → 9:1) afforded pentapeptide **129** (86.2 mg, 67.0 µmol, 80%) as a colorless foam.

R_f(129) = 0.08 (DCM/MeOH 95:5)



^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ = 0.85 (d, $^3J_{29,28}$ = 6.6 Hz, 6 H, 29-H), 1.32 (m, 3 H, 4-H), 1.42 (s, 6 H, 45-H), 1.45 (m, 4 H, 21-H, 27-H), 1.58 (m, 2 H, 28-H, 33-H_a), 1.68 (m, 1 H, 33-H_b), 1.79 (m, 2 H, 32-H), 2.02 (s, 3 H, 46-H), 2.47 (s, 3 H, 42-H), 2.53 (s, 3 H, 47-H), 2.74 (bs, 3 H, 5-H/24-H), 2.95 (s, 2-H, 43-H), 3.00 (m, 3 H, 5-H/24-H), 3.09 (m, 5 H, 18-H, 34-H), 3.62 (bs, 3 H, 1-H), 4.06 (m, 1 H, 20-H), 4.21 (t, $^3J_{50,49}$ = 6.9 Hz, 1 H, 50-H), 4.30 (d, $^3J_{49,50}$ = 6.9 Hz, 2 H, 49-H), 4.37 (m, 1 H, 26-H/31-H), 4.69 (m, 2 H, 3-H, 26-H/31-H), 4.94 (m, 1 H, 7-H), 5.04 (m, 1 H, 8-H), 5.09 (s, 2 H, 13-H), 6.41 (s, 2 H, NH_2), 6.55 (m, 2 H, NH), 6.96 (d, $^3J_{11,10}$ = 8.8 Hz, 2 H, 11-H), 6.98 (m, 1 H, NH), 7.27 (m, 2 H, 54-H), 7.31 (m, 3 H, 17-H, 53-H), 7.38 (m, 4 H, 10-H, 55-H), 7.43 (t, $^3J_{16,15/17}$ = 7.1 Hz, 2 H, 16-H), 7.68 (dd, $^3J_{15,16}$ = 7.2 Hz, $^4J_{15,17}$ = 4.7 Hz, 2 H, 15-H), 7.71 (m, 1 H, NH), 7.85 (d, $^3J_{52,53}$ = 7.5 Hz, 2 H, 52-H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 11.4 (q, C-46), 13.4 (q, C-4), 16.8 (q, C-47), 18.1 (q, C-42), 21.1 (q, C-29), 22.4 (q, C-29‘), 23.8 (d, C-28), 25.0 (t, C-21), 27.7 (q, C-45), 29.1 (t, C-33), 29.8 (q, C-5/C-24), 31.1 (t, C-32), 31.4 (q, C-5/C-24), 39.5 (t, C-34), 39.9 (t, C-27), 42.2 (t, C-43), 46.4 (d, C-50), 47.1 (d, C-3), 51.1 (q, C-1), 51.9 (q, C-18), 52.5 (d, C-7), 54.1 (d, C-20), 55.5 (d, C-26/C-31), 56.0 (d, C-26/C-31), 65.5 (t, C-49), 69.2 (t, C-13), 82.7 (d, C-8), 85.6 (s, C-44), 114.1 (d, C-11), 115.7 (s, C-37), 119.4 (d, C-52), 123.7 (s, C-41), 124.6 (d, C-15), 126.5 (d, C-53), 126.5 (d, C-53‘), 126.9 (d, C-16), 127.0 (d, C-17), 127.1 (d, C-55), 127.8 (d, C-10), 128.5 (d, C-54), 129.8 (s, C-9), 131.0 (s, C-40), 134.2 (s, C-38), 136.6 (s, C-36), 136.8 (s, C-14), 140.3 (s, C-56), 143.3 (s, C-51), 143.4 (s, C-51‘), 155.2 (s, C-35), 155.7 (s, C-48), 157.1 (s, C-39), 158.0 (s, C-12), 168.5 (s, C-6), 169.8 (s, C-2/C-19/C-30), 170.8 (s, C-2/C-19/C-30), 172.1 (s, C-2/C-19/C-30), 172.1 (s, C-23), 172.8 (s, C-25).

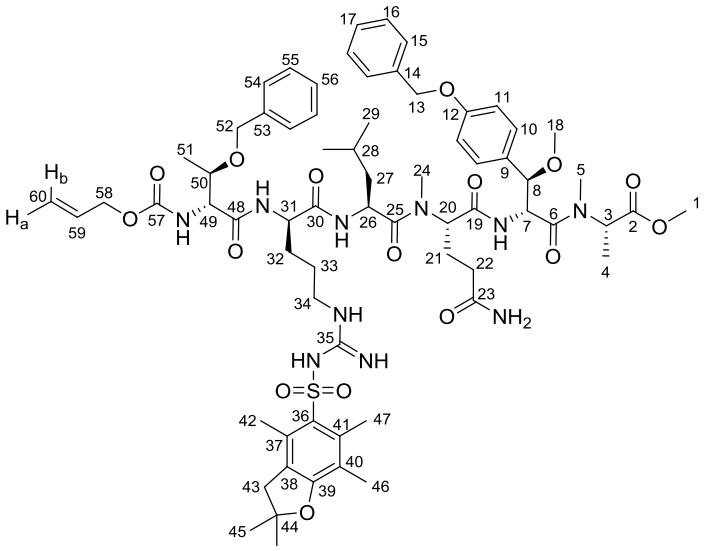
Optical rotation: $[\alpha]_D^{20}$ = –49.0 (c = 1.0, $CHCl_3$)

HRMS (ESI):	Calculated	Found
$C_{68}H_{88}N_9O_{14}S$ $[M+H]^+$	1286.6166	1286.6201

methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-(benzyloxy)-butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)-pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)-phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (130)

According to **GP-6** pentapeptide **129** (1.80 g, 1.40 mmol) was treated with diethylamine (11.7 mL, 112 mmol, 80.0 equiv.) in MeCN (28 mL) for 30 minutes. To a solution of the deprotected amine in dry DMF (14 mL) were added *N*-Alloc-(*O*Bn)-D-*allo*-threonine (605 mg, 1.96 mmol, 1.4 equiv.), DIPEA (611 µL, 3.50 mmol, 2.5 equiv.) and HBTU (743 mg, 1.96 mmol, 1.4 equiv.) at 0 °C. After stirring at room temperature overnight, the reaction was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure and the residue purified by flash chromatography (silica, DCM/MeOH 95:5 → 9:1) to afford hexapeptide **130** (1.59 g, 1.19 mmol, 85%) as a white foam.

R_f(130) = 0.13 (DCM/MeOH 95:5)



^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ = 0.85 (d, $^3J_{29,28}$ = 6.2 Hz, 3 H, 29-H), 0.87 (d, $^3J_{29',28}$ = 6.2 Hz, 3 H, 29-H'), 1.10 (d, $^3J_{51,50}$ = 6.3 Hz, 3 H, 51-H), 1.32 (d, $^3J_{4,3}$ = 6.9 Hz, 3 H, 4-H), 1.43 (s, 6 H, 45-H), 1.45 (m, 3 H, 21-H_b, 27-H), 1.58 (m, 3 H, 21-H_a, 28-H, 33-H_a), 1.71 (m, 1 H, 33-H_b), 1.78 (m, 2 H, 32-H), 2.03 (s, 3 H, 46-H), 2.46 (s, 3 H, 42-H), 2.50 (s, 3 H, 5-H/24-H), 2.52 (s, 3 H, 47-H), 2.73 (bs, 3 H, 5-H/24-H), 2.96 (bs, 2 H, 43-H), 3.00 (m, 1 H, 49-H), 3.05 (m, 2 H, 34-H), 3.10 (bs, 3 H, 18-H), 3.63 (bs, 3 H, 1-H), 3.88 (m, 1 H, 50-H), 4.06 (m, 1 H, NH), 4.38 (m, 3 H, 8-H, 26-H, 31-H), 4.51 (m, 4 H, 52-H, 58-H), 4.68 (m, 1 H, 3-H), 4.75 (m, 1 H, NH), 4.92 (m, 1 H, 7-H), 5.03 (m, 1 H, 20-H), 5.09 (s, 2 H, 13-H), 5.16 (dq, $^3J_{60a,59}$ = 10.7 Hz, $^4J_{60a,58}$ = $^2J_{60a,60b}$ = 1.3 Hz, 1 H, 60-H_a), 5.29 (dq, $^3J_{60b,59}$ = 17.3 Hz, $^4J_{60b,58}$ = $^2J_{60b,60a}$ = 1.6 Hz, 1 H, 60-H_b),

5.90 (ddt, $^3J_{59,60b}$ = 17.2 Hz, $^3J_{59,60a}$ = 10.6 Hz, $^3J_{59,58}$ = 5.4 Hz, 1 H, 59-H), 6.40 (s, 2 H, NH_2), 6.52 (m, 2 H, NH), 6.81 (d, $^3J_{NH,49}$ = 5.3 Hz, 1 H, NH), 6.97 (d, $^3J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.25 (m, 2 H, 54-H), 7.31 (m, 4 H, 10-H, 17-H, 56-H), 7.38 (m, 2 H, 55-H), 7.44 (m, 2 H, 16-H), 7.72 (d, $^3J_{15,16}$ = 7.2 Hz, 2 H, 15-H), 7.80 (m, 1 H, NH).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 11.5 (q, C-46), 13.4 (q, C-4), 15.0 (q, C-51), 16.8 (q, C-47), 18.1 (q, C-42), 21.0 (q, C-29), 22.4 (q, C-29‘), 23.7 (d, C-28), 24.8 (t, C-21, C-22), 27.7 (q, C-45), 29.2 (t, C-33), 29.7 (q, C-5/C-24), 31.1 (t, C-32), 31.5 (q, C-5/C-24), 39.4 (t, C-34), 39.9 (t, C-27), 42.2 (t, C-43), 47.0 (d, C-3), 51.1 (q, C-1), 52.0 (d, C-20, C-26/C-31), 52.6 (d, C-7), 55.3 (q, C-18), 56.0 (d, C-49), 57.6 (d, C-26/C-31), 64.2 (t, C-52/C-58), 69.2 (t, C-13), 69.6 (t, C-52/C-58), 74.1 (d, C-50), 82.7 (d, C-8), 85.6 (s, C-44), 114.1 (d, C-11), 115.7 (s, C-37), 116.5 (t, C-60), 123.8 (s, C-41), 126.6 (d, C-15), 126.8 (d, C-16), 126.9 (d, C-17), 127.1 (d, C-54), 127.5 (d, C-10), 127.8 (d, C-55), 128.5 (d, C-56), 129.8 (s, C-9), 131.0 (s, C-40), 132.9 (d, C-59), 134.2 (s, C-38), 136.7 (s, C-36), 136.8 (s, C-14), 138.3 (s, C-53), 155.3 (s, C-35), 155.7 (s, C-57), 157.1 (s, C-39), 158.0 (s, C-12), 168.9 (s, C-30), 169.8 (s, C-6), 170.8 (s, C-2), 172.0 (s, C-19, C-23), 172.8 (s, C-25, C-48).

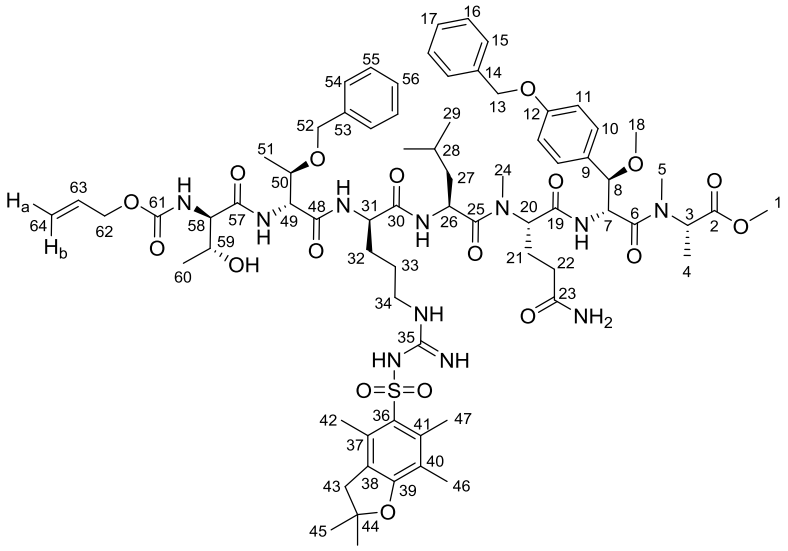
Optical rotation: $[\alpha]_D^{20}$ = –47.2 (c = 1.0, $CHCl_3$)

HRMS (ESI):	Calculated	Found
$C_{68}H_{93}N_{10}O_{16}S$ $[M+H]^+$	1337.6486	1337.6451

methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-hydroxybutanamido)-3-(benzyloxy)butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (131)

To a solution of Alloc-protected peptide **130** (1.27 g, 948 µmol) in MeCN/H_2O (19 mL, 1:1) were added diethylamine (495 µL, 4.74 mmol, 5.0 equiv.), TPPTS (22.0 mg, 38.0 µmol, 4mol%) and $Pd(OAc)_2$ (948 µL, 19.0 µmol, 0.02 M in MeCN, 2mol%) and the mixture was stirred for 3 hours at room temperature. After removal of the solvent *in vacuo* and drying in high vacuum, the residue was dissolved in dry DMF (9.5 mL) and cooled to 0 °C. Alloc-*D*-*allo*-threonine (359 mg, 1.66 mmol, 1.75 equiv.), DIPEA (662 µL, 3.79 mmol, 4.0 equiv.) and PyAOP (865 mg, 1.66 mmol,1.75 equiv.) were added and the reaction was stirred overnight. The mixture was diluted with EtOAc, successively washed with 1 M HCl, sat. $NaHCO_3$ solution and brine and the organic layer dried over Na_2SO_4. After removal of the solvent *in vacuo*, flash chromatography (silica, DCM/MeOH 96:4 → 95:5) and lyophilization, heptapeptide **131** (1.17 g, 812 µmol, 86%) was obtained as a white amorphous solid.

R_f(131) = 0.29 (DCM/MeOH 93:7)



^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ = 0.85 (d, $^{3}J_{29,28}$ = 7.2 Hz, 3 H, 29-H), 0.87 (d, $^{3}J_{29',28}$ = 6.9 Hz, 3 H, 29-H'), 1.10 (d, $^{3}J_{51,50}$ = 6.3 Hz = $^{3}J_{60,59}$ = 6.3 Hz, 6 H, 51-H, 60-H), 1.32 (d, $^{3}J_{4,3}$ = 6.9 Hz, 3 H, 4-H), 1.43 (s, 6 H, 45-H), 1.45 (m, 4 H, 27-H, 32-H), 1.58 (m, 2 H, 28-H, 33-H_a), 1.71 (m, 1 H, 33-H_b), 1.78 (m, 4 H, 21-H, 22-H), 2.03 (s, 3 H, 46-H), 2.46 (s, 3 H, 42-H), 2.52 (s, 3 H, 47-H), 2.73 (bs, 3 H, 5-H/24-H), 2.99 (m, 5 H, 5-H/24-H, 43-H), 3.05 (m, 2 H, 34-H), 3.09 (bs, 3 H, 18-H), 3.63 (bs, 3 H, 1-H), 3.91 (m, 2 H, 50-H, 59-H), 4.09 (dd, $^{3}J_{49,NH}$ = 8.5 Hz, $^{3}J_{49,50}$ = 7.2 Hz, 1 H, 49-H), 4.31 (m, 1 H, 31-H), 4.37 (m, 1 H, 8-H), 4.50 (m, 3 H, 52-H, 62-H_a), 4.56 (m, 1 H, 62-H_b), 4.63 (dd, $^{3}J_{58,59}$ = 7.5 Hz, $^{3}J_{58,NH}$ = 5.3 Hz, 1 H, 58-H), 4.69 (m, 1 H, 3-H), 4.76 (m, 1 H, 20-H), 4.93 (m, 1 H, 7-H), 5.04 (m, 1 H, 26-H), 5.09 (s, 2 H, 13-H), 5.16 (dq, $^{3}J_{64a,63}$ = 10.5 Hz, $^{4}J_{64a,62}$ = $^{2}J_{64a,64b}$ = 1.4 Hz, 1 H, 64-H_a), 5.29 (dq, $^{3}J_{64b,63}$ = 17.3 Hz, $^{4}J_{64b,63}$ = $^{2}J_{64b,64a}$ = 1.6 Hz, 1 H, 64-H_b), 5.90 (ddt, $^{3}J_{63,64b}$ = 17.3 Hz, $^{3}J_{63,64a}$ = 10.7 Hz, $^{3}J_{63,62}$ = 5.3 Hz, 1 H, 63-H), 6.40 (s, 2 H, NH_2), 6.49 (m, 2 H, NH), 6.76 (d, ^{3}J = 6.0 Hz, 1 H, NH), 6.97 (d, $^{3}J_{11,10}$ = 8.5 Hz, 2 H, 11-H), 7.24 (m, 2 H, 54-H), 7.30 (m, 6 H, 10-H, 15-H, 17-H, 56-H), 7.38 (m, 2 H, 55-H), 7.44 (m, 2 H, 16-H), 7.69 (m, 2 H, NH), 7.74 (m, ^{3}J = 7.8 Hz, 1 H, NH).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 11.4 (q, C-46), 13.4 (q, C-4), 15.2 (q, C-51), 16.8 (q, C-47), 18.1 (q, C-42), 19.3 (q, C-60), 21.0 (q, C-29), 22.4 (q, C-29'), 23.7 (d, C-28), 24.8 (t, C-32), 27.7 (s, C-45), 28.0 (t, C-21), 28.9 (t, C-22), 29.6 (q, C-5/C-24), 31.4 (q, C-5/C-24), 39.4 (t, C-34), 39.9 (t, C-27), 42.2 (t, C-43), 47.1 (d, C-3), 51.1 (q, C-1), 51.9 (d, C-26), 52.0 (d, C-31), 52.6 (d, C-7), 55.3 (d, C-58), 55.6 (q, C-18), 57.6 (d, C-20), 60.1 (d, C-49), 64.1 (t, C-52/C-62), 66.8 (d, C-59), 69.2 (t, C-13), 69.6 (t, C-52/C-62), 73.9 (d, C-50), 82.7 (d, C-8), 85.6 (s, C-44), 114.1 (d, C-11), 115.7 (s, C-37), 116.3 (t, C-64), 123.7 (s, C-41), 126.6 (d, C-15), 126.9 (d, C-16), 126.9 (d, C-17), 127.1 (d, C-54), 127.4 (d, C-10), 127.8 (d, C-55), 128.5 (d, C-56), 129.8 (s, C-9), 131.0 (s, C-40), 133.0 (d, C-63), 134.2 (s, C-38), 136.6 (s, C-36), 136.8 (s, C-14), 138.2 (s, C-53), 155.2 (s, C-35), 155.7 (s, C-61), 157.1 (s, C-39), 158.0 (s, C-12), 168.7 (s, C-30), 169.8 (s, C-6), 170.3 (s, C-57), 170.8 (s, C-2), 172.1 (s, C-19, C-23), 172.9 (s, C-25, C-48).

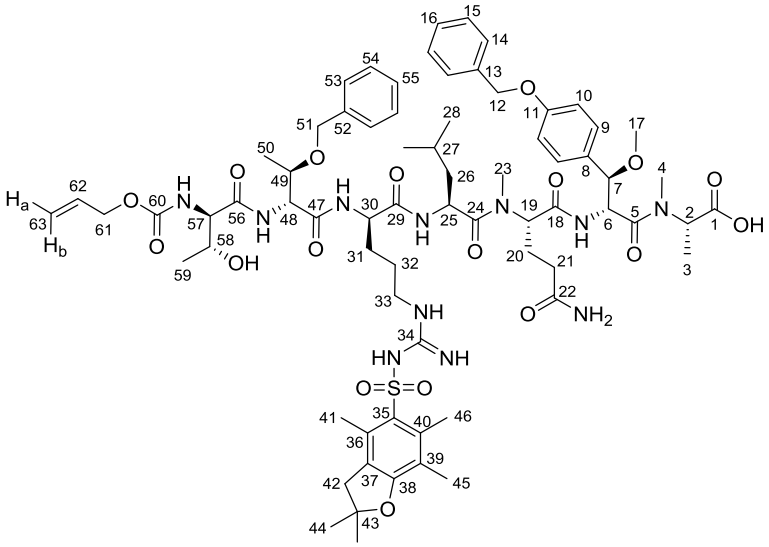
Optical rotation: $[\alpha]_D^{20}$ = −15.1 (c = 1.0, $CHCl_3$)

HRMS (ESI):	Calculated	Found
$C_{72}H_{100}N_{11}O_{18}S$ $[M+H]^+$	1438.6963	1438.6937

***N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-hydroxy-butanamido)-3-(benzyloxy)butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentan-amido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alanine (133)**

To a solution of methyl ester **131** (300 mg, 208 µmol) in 1,2-dichlorethane (2 mL) was added trimethyltin hydroxide (377 mg, 2.08 mmol, 10.0 equiv.) and the reaction was heated to 80 °C for 5 hours. After cooling to room temperature, the mixture was diluted with EtOAc and washed with 1 M $KHSO_4$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue purified by reversed-phase chromatography (C18, H_2O/MeCN 95:5 → 0:100) to afford carboxylic acid **133** (203 mg, 142 µmol, 68%) as an off-white solid.

R_f(133) = 0.18 (DCM/MeOH 9:1)



^{1}H-NMR (500 MHz, DMSO-d_6): δ = 0.85 (m, 6 H, 28-H), 1.10 (d, $^3J_{50,49}$ = 6.3 Hz = $^3J_{59,58}$ = 6.3 Hz, 6 H, 50-H, 59-H), 1.32 (d, $^3J_{3,2}$ = 7.0 Hz, 3 H, 3-H), 1.43 (s, 6 H, 44-H), 1.45 (m, 4 H, 26-H, 31-H), 1.59 (m, 2 H, 27-H, 32-H_a), 1.70 (m, 1 H, 32-H_b), 1.80 (m, 4 H, 20-H, 21-H), 2.03 (s, 3 H, 45-H), 2.46 (s, 3 H, 41-H), 2.52 (s, 3 H, 46-H), 2.73 (bs, 3 H, 4-H/23-H), 2.99 (bs, 5-H, 4-H/23-H, 42-H), 3.04 (m, 2 H, 33-H), 3.09 (bs, 3 H, 17-H), 3.91 (m, 2 H, 49-H, 58-H), 4.09 (dd, $^3J_{48,NH}$ = 8.5 Hz, $^3J_{48,49}$ = 7.1 Hz, 1 H, 48-H), 4.31 (m, 2 H, 7-H, 30-H), 4.49 (m, 3 H, 51-H, 61-H_a), 4.56 (m, 1 H, 61-H_b), 4.63 (dd, $^3J_{57,58}$ = 7.6 Hz, $^3J_{57,NH}$ = 5.0 Hz, 1 H, 57-H), 4.67 (m, 1 H, 2-H), 4.77 (m, 1 H, 19-H), 4.94 (m, 1 H, 6-H), 5.05 (m, 1 H, 25-H), 5.09 (s, 2 H, 12-H), 5.16 (dq, $^3J_{63a,62}$ = 10.5 Hz, $^4J_{63a,61}$ = $^2J_{63a,63b}$ = 1.4 Hz, 1 H, 63-H_a), 5.29 (dq, $^3J_{63b,62}$ = 17.3 Hz, $^4J_{63b,62}$ = $^2J_{63b,63a}$ = 1.6 Hz, 1 H, 63-H_b), 5.90 (ddt, $^3J_{62,63b}$ = 17.2 Hz, $^3J_{62,63a}$ = 10.6 Hz, $^3J_{62,61}$ = 5.4 Hz, 1 H, 62-H), 6.41 (s, 2 H, NH_2), 6.51 (m, 2 H, NH), 6.76 (d, ^3J = 7.5 Hz, 1 H, NH), 6.96 (d, $^3J_{10,9}$ =

7.8 Hz, 2 H, 10-H), 7.24 (m, 3 H, 16-H, 53-H), 7.30 (m, 5 H, 9-H, 14-H, 55-H), 7.38 (m, 2 H, 54-H), 7.44 (m, 2 H, 15-H), 7.66 (d, ^3J = 7.8 Hz, 1 H, NH), 7.74 (m, 2 H, NH).

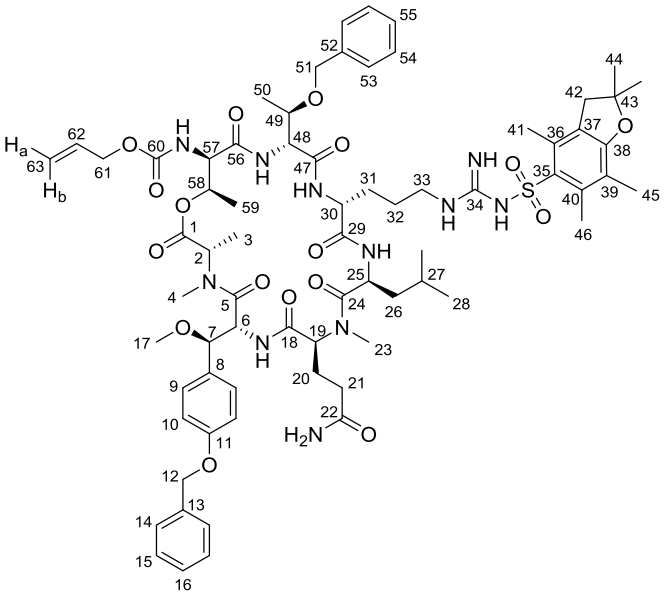
^{13}C-NMR (125 MHz, DMSO-d_6): δ = 11.5 (q, C-45), 13.9 (q, C-3), 15.2 (q, C-50), 16.8 (q, C-46), 18.1 (q, C-41), 19.3 (q, C-59), 21.0 (q, C-28), 22.4 (q, C-28‘), 23.8 (d, C-27), 24.8 (t, C-31), 27.7 (q, C-44), 28.3 (t, C-20), 28.9 (t, C-21), 29.7 (q, C-4/C-23), 30.8 (q, C-4/C-23), 39.4 (t, C-33), 39.9 (t, C-26), 42.2 (t, C-42), 47.1 (d, C-2), 51.7 (d, C-25), 52.0 (d, C-30), 52.1 (d, C-6), 55.3 (d, C-57), 55.6 (q, C-17), 56.0 (d, C-19), 60.1 (d, C-48), 64.1 (t, C-51/C-61), 66.8 (d, C-58), 69.2 (t, C-12), 69.6 (t, C-51/C-61), 73.9 (d, C-49), 83.0 (d, C-7), 85.6 (s, C-43), 114.1 (d, C-10), 115.7 (s, C-36), 116.4 (t, C-63), 123.8 (s, C-40), 126.6 (d, C-14), 126.9 (d, C-15, C-16), 127.1 (d, C-53), 127.5 (d, C-9), 127.8 (d, C-54), 128.5 (d, C-55), 129.9 (s, C-8), 131.0 (s, C-39), 133.0 (d, C-62), 134.2 (s, C-37), 136.7 (s, C-35), 136.8 (s, C-13), 138.2 (s, C-52), 155.2 (s, C-34), 155.7 (s, C-60), 157.1 (s, C-38), 158.0 (s, C-11), 168.7 (s, C-1, C-29), 169.8 (s, C-5), 170.3 (s, C-56), 172.2 (s, C-18, C-22), 172.9 (s, C-24, C-47).

Optical rotation:	$[\alpha]_D^{20}$ = –33.1 (c = 1.0, $CHCl_3$)	
Melting point:	93-95 °C	
HRMS (ESI):	Calculated	Found
$C_{71}H_{98}N_{11}O_{18}S$ $[M+H]^+$	1424.6807	1424.6851

allyl ((3*S*,6*R*,9*S*,12*S*,15*R*,18*R*,21*R*,22*R*)-9-(3-amino-3-oxopropyl)-18-((*R*)-1-(benzyloxy)ethyl)-6-((*R*)-(4-(benzyloxy)phenyl)(methoxy)methyl)-12-isobutyl-3,4,10,22-tetramethyl-2,5,8,11,14,17,20-heptaoxo-15-(3-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)propyl)-1-oxa-4,7,10,13,16,19-hexaazacyclodocosan-21-yl)carbamate (134)

To a solution of linear peptide **133** (180 mg, 126 µmol) in DMF (17 mL) was added DMAP (308 mg, 2.52 mmol, 20.0 equiv.) and PyAOP (79.0 mg, 151 µmol, 1.2 equiv.) and the reaction was heated to 70 °C for 15 hours. After dilution with EtOAc, the mixture was washed with 1 M $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and the residue purified by column chromatography (silica, DCM/MeOH 97:3 → 95:5) to afford macro lactone **134** (148 mg, 105 µmol, 83%) as a white solid.

R_f(134) = 0.14 (DCM/MeOH 95:5)



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, $^{3}J_{28,27}$ = 6.5 Hz, 3 H, 28-H), 0.94 (d, $^{3}J_{28',27}$ = 6.5 Hz, 3 H, 28-H'), 1.15 (m, 1 H, 26-H_a), 1.18 (d, $^{3}J_{59,58}$ = 6.5 Hz, 3 H, 59-H), 1.26 (m, 5 H, 31-H, 50-H), 1.35 (d, $^{3}J_{3,2}$ = 7.3 Hz, 3 H, 3-H), 1.44 (s, 6 H, 44-H), 1.54 (m, 5 H, 20-H, 21-H_a, 32-H), 1.67 (m, 3 H, 21-H_b, 26-H_b, 27-H), 2.08 (s, 3 H, 41-H), 2.52 (s, 3 H, 46-H), 2.58 (s, 3 H, 45-H), 2.80 (bs, 3 H, 4-H), 2.93 (bs, 5-H, 23-H, 42-H), 3.06 (m, 2 H, 33-H), 3.16 (bs, 3 H, 17-H), 4.03 (qd, $^{3}J_{49,50}$ = 8.5 Hz, $^{3}J_{49,48}$ = 7.1 Hz, 1 H, 49-H), 4.32 (t, $^{3}J_{30,31}$ = 4.6 Hz, 1 H, 30-H), 4.43 (d, $^{4}J_{51a,51b}$ = 11.9 Hz, 1 H, 51-H_a), 4.52 (m, 3 H, 7-H, 25-H, 48-H), 4.59 (d, $^{4}J_{51b,51a}$ = 11.9 Hz, 1 H, 51-H_b), 4.63 (dd, $^{2}J_{61a,61b}$ = 13.3 Hz, $^{3}J_{61a,62}$ = 5.8 Hz, 1 H, 61-H_a), 4.65 (m, 1 H, 19-H), 4.69 (dd, $^{2}J_{61b,61a}$ = 13.3 Hz, $^{3}J_{61b,62}$ = 5.3 Hz, 1 H, 61-H_b), 4.81 (dd, $^{3}J_{57,NH}$ = 8.6 Hz, $^{3}J_{57,58}$ = 1.9 Hz, 1 H, 57-H), 5.07 (s, 2 H, 12-H), 5.09 (t, $^{3}J_{6,7/NH}$ = 9.5 Hz, 1 H, 6-H), 5.25 (m, 1 H, 2-H), 5.26 (d, $^{3}J_{63a,62}$ = 10.5 Hz, 1 H, 63-H_a), 5.33 (m, 1 H, 58-H), 5.37 (d, $^{3}J_{63b,62}$ = 17.5 Hz, 1 H, 63-H_b), 5.55 (d, ^{3}J = 6.6 Hz, 1 H, NH), 5.67 (bs, 1 H, NH), 6.01 (m, 2 H, 62-H, NH), 6.14 (m, 1 H, NH), 6.24 (bs, 2 H, NH), 6.81 (d, $^{3}J_{NH,57}$ = 7.1 Hz, 1 H, NH), 7.00 (d, $^{3}J_{10,9}$ = 8.6 Hz, 2 H, 10-H), 7.24 (m, 3 H, 16-H, 53-H), 7.33 (m, 7 H, 9-H, 15-H, 54-H, 55-H), 7.42 (m, 2 H, 14-H), 7.54 (m, 2 H, NH), 7.62 (m, 1 H, NH).

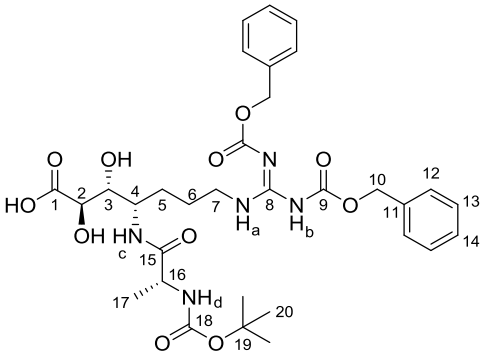
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 12.4 (q, C-41), 13.5 (q, C-3), 13.8 (q, C-59), 15.9 (q, C-50), 17.9 (q, C-45), 19.1 (q, C-46), 21.0 (q, C-28), 23.1 (q, C-28'), 23.9 (t, C-20/C-32), 24.7 (t, C-20/C-32), 25.0 (d, C-27), 28.6 (q, C-44), 29.7 (t, C-31), 30.0 (q, C-4), 30.2 (q, C-23), 31.2 (t, C-21), 38.8 (t, C-26), 40.7 (t, C-33), 43.2 (t, C-42), 49.5 (d, C-25/C-48), 51.4 (d, C-25/C-48), 51.7 (d, C-2), 52.6 (d, C-6), 55.3 (d, C-19), 56.8 (q, C-17), 57.6 (d, C-57), 59.3 (d, C-30), 66.6 (t, C-61), 70.0 (t, C-12), 70.7 (t, C-51), 70.9 (d, C-58), 72.6 (d, C-49), 83.3 (d, C-7), 86.3 (s, C-43), 114.5 (d, C-10), 117.3 (s, C-36), 118.4 (t, C-63), 124.5 (s, C-40), 127.5 (d, C-9), 127.7 (d, C-14), 128.0 (d, C-16/C-53), 128.0 (d, C-16/C-53), 128.6 (d, C-54/C-55), 128.6 (d, C-54/C-55), 129.7 (d, C-15), 130.1 (s, C-8), 132.2 (s/d, C-39/C-62), 132.4 (s/d, C-39/C-62), 133.1 (s, C-37), 136.8 (s, C-13), 137.4 (s, C-52), 138.2 (s, C-35), 156.2 (s, C-34/C-60), 156.5 (s, C-34/C-60), 158.6 (s, C-38), 158.8 (s, C-11), 168.8 (s, C-18/C-22/C-29), 169.1 (s, C-18/C-22/C-29), 170.1 (s, C-56), 170.2 (s, C-5), 170.5 (s, C-1), 172.5 (s, C-18/C-22/C-29), 173.9 (s, C-24), 174.4 (s, C-47).

Optical rotation:	$[\alpha]_D^{20}$ = –51.8 (c = 1.0, $CHCl_3$)	
Melting point:	112-114 °C	
HRMS (ESI):	Calculated	Found
$C_{71}H_{95}N_{11}O_{17}S$ $[M+H]^+$	1406.6701	1406.6682

(2*R*,3*R*,4*S*)-7-((*E*)-2,3-bis((benzyloxy)carbonyl)guanidino)-4-((*R*)-2-((*tert*-butoxycarbonyl) amino)propanamido)-2,3-dihydroxyheptanoic acid (135)

At 0 °C, a solution of methyl ester **122** (720 mg, 1.05 mmol) in THF (10.5 mL) was treated with lithium hydroxide (1.15 mL, 1.15 mmol, 1.0 M, 1.1 equiv.) and slowly warmed to room temperature overnight. Additional LiOH (105 µL, 105 µmol, 1.0 M, 0.1 equiv.) was added and the mixture was stirred until complete conversion was observed (LC-MS). The reaction was acidified by addition of 1 M HCl (pH 2) and extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Lyophilization afforded the carboxylic acid **135** (687 mg, 1.02 mmol, 97%) as a white sticky resin.

R_f(135) = 0.44 (DCM/MeOH 9:1)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, $^3J_{17,16}$ = 7.0 Hz, 3 H, 17-H), 1.40 (s, 9 H, 20-H), 1.64 (m, 3 H, 5-H_a, 6-H), 1.82 (m, 1 H, 5-H_b), 3.32 (m, 1 H, 7-H_a), 3.56 (m, 1 H, 7-H_b), 3.69 (m, 1 H, 2-H), 3.77 (m, 1 H, 3-H), 4.08 (m, 1 H, 4-H/16-H), 4.16 (m, 1 H, 4-H/16-H), 5.09 (d, $^2J_{10a,10b}$ = 12.2Hz, 1 H, 10-H_a), 5.14 (d, $^2J_{10b,10a}$ = 12.2 Hz, 1 H, 10-H_b), 5.19 (s, 2 H, 10-H'), 7.34 (m, 10 H, 12-H, 13-H, 14-H, NH_c/NH_d), 7.52 (bs, 1 H, NH_c/NH_d), 8.43 (t, $^3J_{NHa,7}$ = 5.3 Hz, 1 H, NH_a), 11.76 (bs, 1 H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.1 (q, C-17), 26.5 (t, C-6), 26.8 (t, C-5), 28.2 (q, C-20), 40.4 (t, C-7), 50.5 (d, C-4/C-16), 50.8 (d, C-4/C-16), 67.3 (t, C-10), 68.3 (t, C-10‘), 69.5 (d, C-3), 73.6 (d, C-2), 80.3 (s, C-19), 128.2 (d, C-14), 128.4 (d, C-12), 128.5 (d, C-12‘), 128.5 (d, C-13), 128.7 (d, C-13‘), 128.8 (d, C-14‘), 134.5 (s, C-11), 136.3 (s, C-11‘), 153.8 (s, C-9), 155.5 (s, C-18), 156.5 (s, C-8), 163.3 (s, C-9‘), 175.0 (s, C-1), 176.3 (s, C-15).

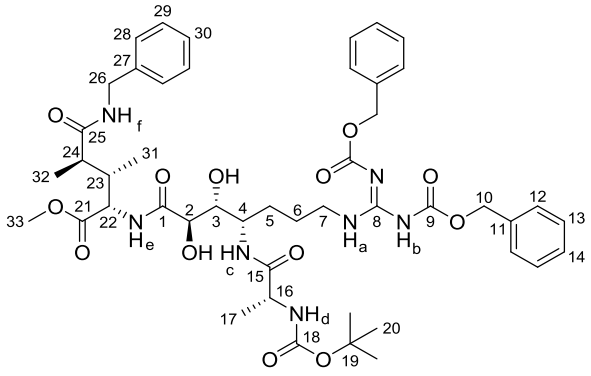
Optical rotation: $[\alpha]_D^{20}$ = –36.9 (c = 1.0, $CHCl_3$)

HRMS (CI):	Calculated	Found
$C_{32}H_{44}N_5O_{11}$ $[M+H]^+$	674.3032	674.3015

methyl (10*S*,11*R*,12*R*,15*S*,*E*)-15-((2*S*,3*R*)-4-(benzylamino)-3-methyl-4-oxobutan-2-yl)-5-(((benzyloxy)carbonyl)amino)-10-((*R*)-2-((*tert*-butoxycarbonyl)amino)propanamido)-11,12-dihydroxy-3,13-dioxo-1-phenyl-2-oxa-4,6,14-triazahexadec-4-en-16-oate (136)

To a solution of carboxylic acid **135** (662 mg, 983 µmol) and amine **101** (328 mg, 1.18 mmol, 1.2 equiv.) in dry DMF (9.8 mL) were added DIPEA (343 µL, 1.97 mmol, 2.0 equiv.) and PyAOP (538 mg, 1.03 mmol, 1.05 equiv.) at 0 °C. The mixture was stirred for 14 hours, diluted with EtOAc and successively washed with 1 M HCl, sat. $NaHCO_3$ and brine. After drying of the organic layer over Na_2SO_4, the solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, DCM/MeOH 95:5) to afford tripeptide **136** (810 mg, 867 µmol, 88%) as a white solid.

R_f(136) = 0.15 (DCM/MeOH 95:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, $^3J_{31,23}$ = 7.1 Hz, 3 H, 31-H), 1.22 (d, $^3J_{32,24}$ = 6.8 Hz, 3 H, 32-H), 1.25 (d, $^3J_{17,16}$ = 7.0 Hz, 3 H, 17-H), 1.39 (s, 9 H, 20-H), 1.63 (m, 3 H, 5-H_a, 6-H), 1.89 (m, 2 H, 5-H_b, 23-H), 2.34 (qd, $^3J_{24,32}$ = 6.7 Hz, $^3J_{24,23}$ = 4.5 Hz, 1 H, 24-H), 3.31 (m, 1 H, 7-H_a), 3.60 (m, 2 H, 2-H, 7-H_b), 3.75 (s, 3 H, 33-H), 3.77 (m, 1 H, 3-H), 4.09 (m, 1 H, 4-H/16-H), 4.17 (m, 1 H, 4-H/16-H), 4.43 (dd, $^2J_{26a,26b}$ = 14.7 Hz, $^3J_{26a,NH}$ = 5.6 Hz, 1 H, 26-H_a), 4.48 (dd, $^2J_{26b,26a}$ = 14.7 Hz, $^3J_{26b,NH}$ = 5.6 Hz, 1 H, 26-H_b), 4.56 (m, 2 H, 22-H, NH_c/NH_d), 5.02 (m, 1 H, NH_f), 5.09 (d, $^2J_{10a,10b}$ = 12.2Hz, 1 H, 10-H_a), 5.13 (d, $^2J_{10b,10a}$ = 12.2 Hz, 1 H, 10-H_b), 5.18 (s, 2 H, 10-H'), 5.77 (d, $^3J_{NH,22}$ = 4.2 Hz, 1 H, NH_e), 7.30 (m, 15 H, 12-H, 13-H, 14-H, 28-H, 29-H, 30-H), 7.84 (d, $^3J_{NH,4/16}$ = 9.0 Hz, 1 H, NH_c/NH_d), 8.38 (t, $^3J_{NH,7}$ = 5.8 Hz, 1 H, NH_a), 11.76 (s, 1 H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.6 (q, C-31), 16.4 (q, C-32), 18.3 (q, C-17), 26.8 (t, C-6), 26.9 (t, C-5), 28.2 (q, C-20), 40.4 (t, C-7), 40.9 (d, C-24), 41.5 (d, C-23), 43.5 (t, C-26), 50.4 (d, C-4/C-16), 50.5 (d, C-4/C-16), 52.4 (q, C-33), 55.1 (d, C-22), 67.2 (t, C-10), 68.2 (t, C-10‘), 69.2 (d, C-3), 74.5 (d, C-2), 80.1 (s, C-19), 127.3 (d, C-29/C-30), 127.9 (d, C-28), 128.0 (d, C-29/C-30), 128.3 (d, C-14), 128.4 (d, C-12), 128.4 (d, C-12‘), 128.6 (d, C-13), 128.7 (d, C-13‘), 128.8 (d, C-14‘), 134.5 (s, C-11), 136.5 (s, C-11‘), 138.6 (s, C-27), 153.8 (s, C-9), 155.2 (s, C-18), 156.4 (s, C-8), 163.4 (s, C-9‘), 171.2 (s, C-21), 172.8 (s, C-25), 175.3 (s, C-1), 176.0 (s, C-15).

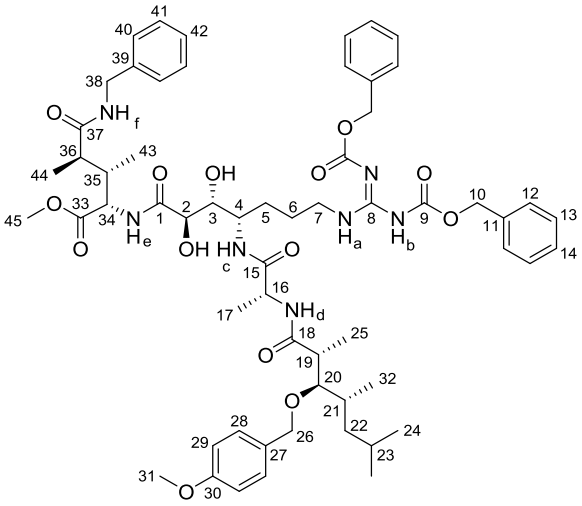
Optical rotation:	$[\alpha]_D^{20}$ = –22.7 (c = 1.0, $CHCl_3$)	
Melting point:	87-89 °C	
HRMS (ESI):	Calculated	Found
$C_{47}H_{64}N_7O_{13}$ $[M+H]^+$	934.4557	934.4581

methyl (10*S*,11*R*,12*R*,15*S*,*E*)-15-((2*S*,3*R*)-4-(benzylamino)-3-methyl-4-oxobutan-2-yl)-5-(((benz-yloxy)carbonyl)amino)-11,12-dihydroxy-10-((*R*)-2-((2*R*,3*R*,4*R*)-3-((4-methoxy-benzyl)oxy)-2,4,6-trimethylheptanamido)propanamido)-3,13-dioxo-1-phenyl-2-oxa-4,6,14-triazahexadec-4-en-16-oate (137)

To a solution of Boc-protected amine **136** (526 mg, 563 µmol) in DCM (5.6 mL) was added a solution of HCl (1.41 mL, 5.63 mmol, 4.0 M in dioxane, 10.0 equiv.) at 0 °C. After complete deprotection was observed by TLC, the solvent was removed *in vacuo* and the residue dried in high vacuum.

The crude hydrochloride was diluted in dry DMF (5.6 mL) and carboxylic acid **107** (208 mg, 676 µmol, 1.2 equiv.) was added. After cooling to 0 °C, DIPEA (295 µL, 1.69 mmol, 3.0 equiv.) and PyAOP (352 mg, 676 µmol, 1.2 equiv.) were added and the mixture warmed to room temperature overnight. The reaction was diluted with EtOAc, successively washed with 1.0 M HCl, sat. $NaHCO_3$ and brine and the organic layer dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (silica, DCM/MeOH 98.5:1.5 → 97.5:2.5) to afford methyl ester **137** (527 mg, 469 µL, 83%) as a white solid.

R_f(137) = 0.22 (DCM/MeOH 97:3)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, $^3J_{24,23}$ = 6.5 Hz, 3 H, 24-H), 0.88 (d, $^3J_{43,35}$ = 6.5 Hz, 3 H, 43-H), 0.89 (d, $^3J_{24',23}$ = $^3J_{32,21}$ = 6.9 Hz, 6 H, 24-H', 32-H), 1.16 (m, 2 H, 22-H), 1.17 (d, $^3J_{25,19}$ = 7.3 Hz, 3 H, 25-H), 1.19 (d, $^3J_{44,36}$ = 7.0 Hz, 3 H, 44-H), 1.23 (d, $^3J_{17,16}$ = 7.1 Hz, 3 H, 17-H), 1.62 (m, 4-H, 5-H_a, 6-H, 21-H), 1.75 (m, 1 H, 5-H_b), 1.85 (m, 1 H, 23-H), 1.91 (m, 1 H, 35-H), 2.31 (qd, $^3J_{36,44}$ = 6.7 Hz, $^3J_{36,35}$ = 4.4 Hz, 1 H, 36-H), 2.56 (qd, $^3J_{19,25}$ = 7.2 Hz, $^3J_{19,20}$ =

3.9 Hz, 1 H, 19-H), 3.26 (dd, $^3J_{20,21}$ = 5.2 Hz, $^3J_{20,19}$ = 4.2 Hz, 1 H, 20-H), 3.29 (m, 1 H, 7-H_a), 3.47 (dq, $^2J_{7b,7a}$ = 13.1 Hz, $^3J_{7b,6/NH}$ = 6.6 Hz, 1 H, 7-H_b), 3.57 (d, $^3J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 3.60 (dd, $^3J_{3,2}$ = 9.6 Hz, $^3J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 3.74 (s, 3 H, 45-H), 3.79 (s, 3 H, 31-H), 4.04 (m, 1 H, 4-H), 4.38 (m, 1 H, 16-H), 4.43 (m, 2 H, 26-H), 4.47 (d, $^2J_{38a,38b}$ = 10.8 Hz, 1 H, 38-H_a), 4.56 (m, 2 H, 34-H, 38-H_b), 5.10 (d, $^2J_{10a,10b}$ = 12.5Hz, 1 H, 10-H_a), 5.14 (d, $^2J_{10b,10a}$ = 12.6 Hz, 1 H, 10-H_b), 5.17 (s, 2 H, 10-H'), 5.65 (d, $^3J_{NH,4}$ = 3.8 Hz, 1 H, NH_c), 6.88 (d, $^3J_{29,28}$ = 8.7 Hz, 2 H, 29-H), 6.97 (d, $^3J_{NH,16}$ = 9.2 Hz, 1 H, NH_d), 7.28 (m, 18 H, 12-H, 13-H, 14-H, 28-H, 40-H, 41-H, 42-H, NH_f), 7.80 (d, $^3J_{NH,34}$ = 9.2 Hz, 1 H, NH_e), 8.33 (t, $^3J_{NH,7}$ = 5.5 Hz, 1 H, NH_a), 11.74 (s, 1 H, NH_b).

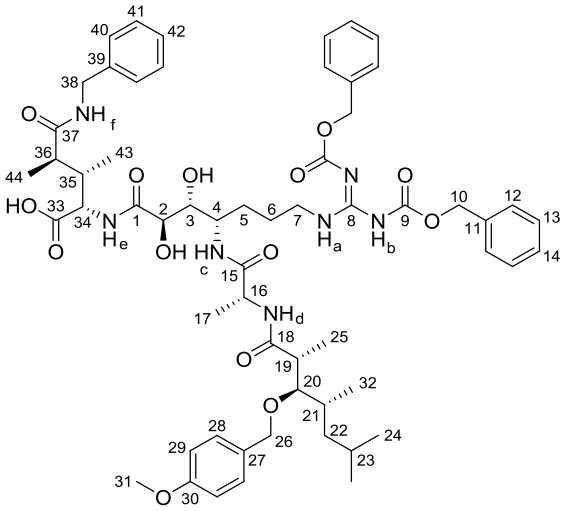
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.6 (q, C-24'/C-32), 15.7 (q, C-24'/C-32), 16.3 (q, C-44), 17.3 (q, C-25), 17.3 (q, C-17), 21.5 (q, C-24), 23.8 (q, C-43), 25.1 (d, C-21), 26.3 (t, C-6), 27.6 (t, C-5), 33.4 (d, C-23), 40.6 (t, C-7), 40.9 (d, C-36), 41.3 (d, C-35), 41.6 (t, C-22), 43.2 (d, C-19), 43.5 (t, C-26), 48.9 (d, C-16), 50.0 (d, C-4), 52.3 (q, C-45), 55.0 (d, C-34), 55.3 (q, C-31), 67.1 (t, C-10), 68.2 (t, C-10'), 69.4 (d, C-3), 74.2 (d, C-2), 74.2 (t, C-38), 85.5 (d, C-20), 113.8 (d, C-29), 127.2 (d, C-14/C-42), 127.9 (d, C-28), 128.1 (d, C-12), 128.4 (d, C-12'), 128.4 (d, C-13/C-41), 128.5 (d, C-13/C-41), 128.7 (d, C-13'/C-41), 128.8 (d, C-14/C-42), 129.2 (d, C-40), 130.1 (s, C-27), 134.5 (s, C-11), 136.7 (s, C-11'), 138.6 (s, C-39), 153.8 (s, C-9), 156.2 (s, C-8), 159.3 (s, C-30), 163.5 (s, C-9'), 171.2 (s, C-33), 172.9 (s, C-37), 175.1 (s, C-1/C-15), 175.2 (s, C-1/C-15), 176.1 (s, C-18).

Optical rotation:	$[\alpha]_D^{20}$ = –64.5 (c = 1.0, $CHCl_3$)	
Melting point:	131-133 °C	
HRMS (ESI):	Calculated	Found
$C_{60}H_{82}N_7O_{14}$ $[M+H]^+$	1124.5914	1124.5897

(10*S*,11*R*,12*R*,15*S*,*E*)-15-((2*S*,3*R*)-4-(benzylamino)-3-methyl-4-oxobutan-2-yl)-5-(((benzyloxy)carbonyl)amino)-11,12-dihydroxy-10-((*R*)-2-((2*R*,3*R*,4*R*)-3-((4-methoxybenzyl)oxy)-2,4,6-tri-methylheptanamido)propanamido)-3,13-dioxo-1-phenyl-2-oxa-4,6,14-triazahexadec-4-en-16-oic acid (138)

Methyl ester **137** (160 mg, 142 µmol) was dissolved in 1,2-dichlorethane (2.8 mL) and Me_3SnOH (257 mg, 1.42 mmol, 10.0 equiv.) was added. The suspension was heated to 40 °C for 3 hours and further 3 hours at 60 °C. After dilution with EtOAc, the mixture was washed with three times with citric acid (10w%) and once with brine. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue purified by flash chromatography (silica, DCM/MeOH 95:5 → 9:1) to afford carboxylic acid **138** (115 mg, 104 µmol, 73%) as an off-white solid.

R_f(138) = 0.13 (DCM/MeOH 93:7)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, $^{3}J_{24,23}$ = 6.5 Hz, 3 H, 24-H), 0.87 (d, $^{3}J_{24',23}$ = $^{3}J_{32,21}$ = 6.6 Hz, 6 H, 24-H', 32-H), 0.92 (d, $^{3}J_{43,35}$ = 7.0 Hz, 3 H, 43-H), 1.16 (m, 2 H, 22-H), 1.17 (d, $^{3}J_{25,19}$ = 7.3 Hz, 3 H, 25-H), 1.19 (d, $^{3}J_{44,36}$ = 7.0 Hz, 3 H, 44-H), 1.23 (d, $^{3}J_{17,16}$ = 7.1 Hz, 3 H, 17-H), 1.62 (m, 4-H, 5-H_a, 6-H, 21-H), 1.75 (m, 1 H, 5-H_b), 1.85 (m, 1 H, 23-H), 2.05 (m, 1 H, 35-H), 2.45 (quint, $^{3}J_{36,35/44}$ = 6.4 Hz, 1 H, 36-H), 2.56 (qd, $^{3}J_{19,25}$ = 7.2 Hz, $^{3}J_{19,20}$ = 4.2 Hz, 1 H, 19-H), 3.26 (m, 2 H, 7-H_a, 20-H), 3.42 (m, 1 H, 7-H_b), 3.55 (d, $^{3}J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 3.63 (m, 1 H, 3-H), 3.77 (s, 3 H, 31-H), 4.02 (m, 1 H, 4-H), 4.39 (m, 3 H, 16-H, 26-H), 4.48 (d, $^{2}J_{38a,38b}$ = 10.8 Hz, 1 H, 38-H_a), 4.54 (m, 1 H, 34-H), 4.55 (d, $^{2}J_{38b,38a}$ = 10.8 Hz, 1 H, 38-H_b), 5.10 (s, 2 H, 10-H), 5.15 (s, 2 H, 10-H'), 6.86 (d, $^{3}J_{29,28}$ = 8.7 Hz, 2 H, 29-H), 7.06 (m, 2 H, NH_c, NH_d), 7.28 (m, 18 H, 12-H, 13-H, 14-H, 28-H, 40-H, 41-H, 42-H, NH_f), 7.90 (d, $^{3}J_{NH,34}$ = 7.5 Hz, 1 H, NH_e), 8.36 (t, $^{3}J_{NH,7}$ = 5.3 Hz, 1 H, NH_a), 11.73 (s, 1 H, NH_b).

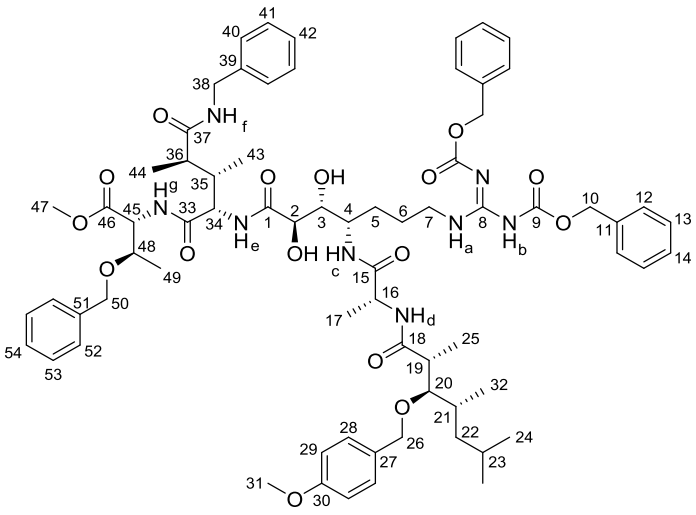
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.9 (q, C-43), 15.7 (q, C-32), 16.3 (q, C-44), 17.2 (q, C-25), 17.5 (q, C-17), 21.5 (q, C-24), 23.9 (q, C-24'), 25.1 (d, C-21), 26.2 (t, C-6), 27.7 (t, C-5), 33.4 (d, C-23), 40.1 (d, C-36), 40.7 (t, C-7), 41.5 (d, C-35), 42.1 (t, C-22), 43.2 (d, C-19), 43.5 (t, C-26), 49.0 (d, C-16), 50.0 (d, C-4), 54.9 (d, C-34), 55.3 (q, C-31), 67.1 (t, C-10), 68.2 (t, C-10'), 69.7 (d, C-3), 74.3 (d/t, C-2, C-38), 85.5 (d, C-20), 113.9 (d, C-29), 127.3 (d, C-14/C-42), 127.8 (d, C-14/C-42), 127.9 (d, C-28), 128.0 (d, C-12), 128.4 (d, C-12'), 128.5 (d, C-13/C-41), 128.6 (d, C-13/C-41), 128.7 (d, C-13'), 128.8 (d, C-14'), 129.2 (d, C-40), 130.1 (s, C-27), 134.5 (s, C-11), 136.6 (s, C-11'), 138.3 (s, C-39), 153.8 (s, C-9), 156.2 (s, C-8), 159.3 (s, C-30), 163.4 (s, C-9'), 174.5 (s, C-37), 174.7 (s, C-1, C-33), 175.0 (s, C-15), 176.3 (s, C-18).

Optical rotation:	$[\alpha]_D^{20}$ = –28.3 (c = 1.0, $CHCl_3$)	
Melting point:	105-107 °C	
HRMS (ESI):	Calculated	Found
$C_{59}H_{80}N_7O_{14}$ $[M+H]^+$	1110.5758	1110.5761

methyl *O*-benzyl-*N*-((2*S*,3*S*,4*R*)-5-(benzylamino)-2-((2*R*,3*R*,4*S*)-7-((*E*)-2,3-bis((benzyloxy)-carbonyl)guanidino)-2,3-dihydroxy-4-((*R*)-2-((2*R*,3*R*,4*R*)-3-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanamido)propanamido)heptanamido)-3,4-dimethyl-5-oxopentanoyl)-D-allo-threoninate (140)

A solution of carboxylic acid **138** (40.0 mg, 36.0 µmol) and H-D-*allo*-Thr(OBzl)-OMe·HCl (11.2 mg, 43.1 µmol, 1.2 equiv.) in dry DMF (360 µL) was cooled to 0 °C and DIPEA (18.9 µL, 108 µmol, 3.0 equiv.) and PyAOP (19.7 mg, 38.0 µmol, 1.05 equiv.) were added. After warming to room temperature overnight, the mixture was diluted with EtOAc and subsequently washed with 1 M HCl, sat. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by preparative HPLC (C-18, H_2O/MeCN 100:0 → 0:100) to afford protected callipeltin D **140** (25.0 mg, 18.9 µmol, 53%) as a colorless foam.

R_f(140) = 0.39 (DCM/MeOH 92.5:7:5)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, $^3J_{24,23}$ = 6.5 Hz, 3 H, 24-H), 0.87 (d, $^3J_{43,35}$ = 7.0 Hz, 3 H, 43-H), 0.88 (d, $^3J_{24',23}$ = 6.5 Hz, 3 H, 24-H'), 0.89 (d, $^3J_{32,21}$ = 6.6 Hz, 3 H, 32-H), 1.13 (d, $^3J_{44,36}$ = 7.0 Hz, 3 H, 44-H), 1.16 (m, 2 H, 22-H), 1.16 (d, $^3J_{49,48}$ = 6.5 Hz, 3 H, 49-H), 1.17 (d, $^3J_{25,19}$ = 7.2 Hz, 3 H, 25-H), 1.23 (d, $^3J_{17,16}$ = 7.1 Hz, 3 H, 17-H), 1.27 (m, 1 H, 5-H_a), 1.57 (m, 3-H, 6-H, 21-H), 1.73 (m, 1 H, 5-H_b), 1.85 (m, 1 H, 23-H), 1.97 (m, 1 H, 35-H), 2.40 (qd, $^3J_{36,44}$ = 6.8 Hz, $^3J_{36,35}$ = 3.2 Hz, 1 H, 36-H), 2.56 (qd, $^3J_{19,25}$ = 7.0 Hz, $^3J_{19,20}$ = 4.0 Hz, 1 H, 19-H), 3.25 (m, 2 H, 7-H_a, 20-H), 3.43 (dt, $^2J_{7b,7a}$ = 13.1 Hz, $^3J_{7b,6}$ = 6.6 Hz, 1 H, 7-H_b), 3.56 (d, $^3J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 3.65 (dd, $^3J_{3,2}$ = 9.5 Hz, $^3J_{3,4}$ = 4.2 Hz, 1 H, 3-H), 3.74 (s, 3 H, 47-H), 3.79 (s, 3 H, 31-H), 3.84 (qd, $^3J_{48,49}$ = 6.5 Hz, $^3J_{48,45}$ = 3.7 Hz, 1 H, 48-H), 4.02 (m, 1 H, 4-H), 4.27 (t, $^3J_{34,35/NH}$ = 8.7 Hz, 1 H, 34-H), 4.37 (quint., $^3J_{16,17/NH}$ = 6.9 Hz, 1 H, 16-H), 4.39 (d, $^3J_{38,NH}$ = 5.8 Hz, 1 H, 38-H), 4.48 (d, $^2J_{26a,26b}$ = $^2J_{50a,50b}$ = 11.3 Hz, 2 H, 26-H_a, 50-H_a), 4.53 (d, $^2J_{50b,50a}$ = 11.7 Hz, 1 H, 50-H_b), 4.57 (d, $^2J_{26b,26a}$ = 10.6 Hz, 1 H, 26-H_b), 4.64 (bs, 1 H, OH), 4.85 (dd, $^3J_{45,NH}$ = 8.3 Hz, $^3J_{45,48}$ = 3.7 Hz, 1 H, 45-H), 5.10 (d, $^2J_{10a,10b}$ = 12.6 Hz, 1 H, 10-H_a), 5.14 (s, $^2J_{10b,10a}$ = 12.7 Hz, 1 H, 10-H_b), 5.16 (s, 2 H, 10-H'), 5.58 (d, $^3J_{OH,3}$ = 4.3 Hz, 1 H, OH), 6.38 (d, $^3J_{NH,45}$ = 8.3 Hz, 1 H, NH_g), 6.88 (d, $^3J_{29,28}$ = 8.7 Hz, 2 H, 29-H), 6.96 (d, $^3J_{NH,4}$ = 9.3 Hz, 1 H, NH_c), 7.15 (d, $^3J_{NH,16}$ =

6.4 Hz, 1 H, NH_d), 7.28 (m, 22 H, 12-H, 13-H, 14-H, 28-H, 40-H, 41-H, 42-H, 52-H, 53-H, 54-H), 7.54 (t, $^3J_{NH,38}$ = 5.7 Hz, 1 H, NH_f), 7.97 (d, $^3J_{NH,34}$ = 9.0 Hz, 1 H, NH_e), 8.31 (t, $^3J_{NH,7}$ = 5.4 Hz, 1 H, NH_a), 11.74 (s, 1 H, NH_b).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.2 (q, C-43), 15.6 (q, C-32), 16.2 (q, C-44), 16.4 (q, C-25), 17.2 (q, C-49), 17.3 (q, C-17), 21.5 (q, C-24), 23.8 (q, C-24‘), 25.1 (d, C-21), 26.3 (t, C-6), 29.7 (t, C-5), 33.4 (d, C-23), 39.7 (d, C-36), 40.6 (d, C-35), 40.8 (t, C-7), 41.6 (t, C-22), 43.2 (d, C-19), 43.4 (t, C-38), 48.9 (d, C-16), 50.0 (d, C-4), 52.6 (q, C-47), 55.1 (d, C-45), 55.3 (q, C-31), 56.7 (d, C-34), 67.1 (t, C-10), 68.2 (t, C-10‘), 69.5 (d, C-3), 70.8 (t, C-50), 74.2 (d/t, C-2, C-26), 74.6 (d, C-48), 85.4 (d, C-20), 113.9 (d, C-29), 127.3 (d, C-14/C-42), 127.6 (d, C-52), 127.8 (d, C-14/C-42), 127.9 (d, C-28), 128.1 (d, C-12, C-54), 128.4 (d, C-12‘), 128.4 (d, C-53), 128.4 (d, C-13/C-41), 128.5 (d, C-13/C-41), 128.7 (d, C-13‘), 128.8 (d, C-14‘), 129.2 (d, C-40), 130.1 (s, C-27), 134.6 (s, C-11), 136.7 (s, C-11‘), 137.6 (s, C-51), 139.1 (s, C-39), 153.8 (s, C-9), 156.2 (s, C-8), 159.3 (s, C-30), 163.5 (s, C-9‘), 170.0 (s, C-33), 170.2 (s, C-46), 173.3 (s, C-37), 175.1 (s, C-15), 175.5 (s, C-1), 176.2 (s, C-18).

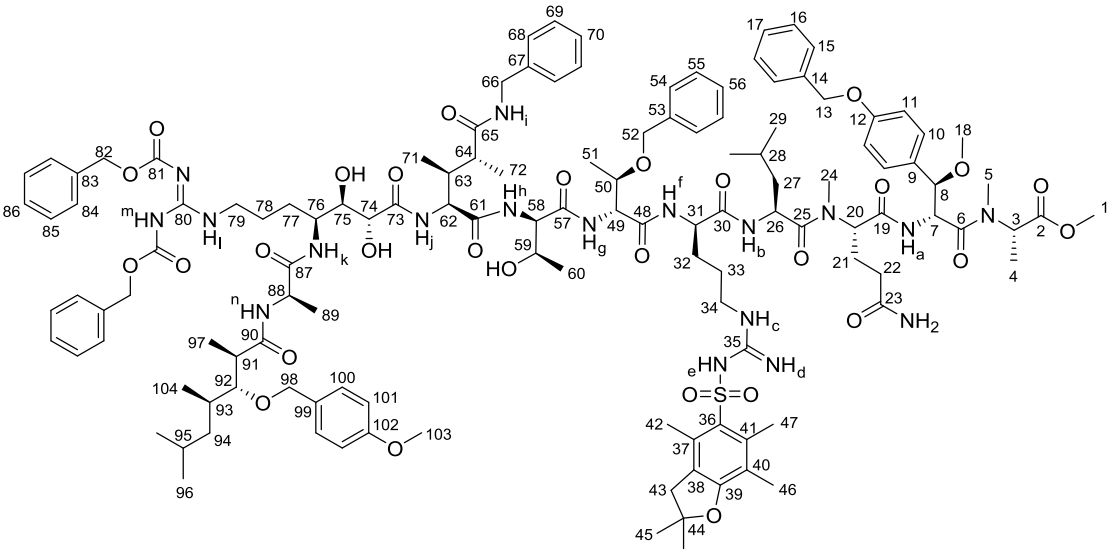
Optical rotation: $[\alpha]_D^{20}$ = –55.1 (c = 1.0, $CHCl_3$)

HRMS (ESI):	Calculated	Found
$C_{71}H_{95}N_8O_{16}$ $[M+H]^+$	1315.6861	1315.6892

methyl *N*-((2*R*,3*R*)-2-((*S*)-5-amino-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-((2*R*,3*R*)-2-((2*S*,3*S*,4*R*)-5-(benzylamino)-2-((2*R*,3*R*,4*S*)-7-((Z)-2,3-bis((benzyloxy)carbonyl)guanidino)-2,3-dihydroxy-4-((*R*)-2-((2*R*,3*R*,4*R*)-3-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanamido)propanamido) heptanamido)-3,4-dimethyl-5-oxopentanamido)-3-hydroxybutanamido)-3-(benzyloxy) butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino) pentanamido)-*N*,4-dimethylpentanamido)-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (141)

Alloc-protected peptide **131** (472 mg, 328 µmol) was deprotected with Et_2NH (171 µL, 1.64 mmol, 5.0 equiv.), TPPTS (7.5 mg, 13.0 µmol, 4 mol%) and $Pd(OAc)_2$ (328 µL, 6.55 µmol, 0.02 M in MeCN, 2 mol%) according to **GP-7**.

The free amine (135 mg, 98.7 µmol, 1.2 equiv.) was dissolved in DMF (1.70 mL) and carboxylic acid **138** (92.1 mg, 82.8 µmol, 1.0 equiv.) was added. After cooling to 0 °C, DIPEA (31.8 µL, 182 µmol, 2.2 equiv.) and PyAOP (51.8 mg, 98.5 µmol, 1.2 equiv.) were added and the reaction was stirred at room temperature overnight. The reaction mixture was absorbed onto isolute® and purified by rapid reversed-phase chromatography (C-18, H_2O/MeCN 95:5 → 0:100) and preparative HPLC (C-18, H_2O/MeCN 95:5 → 0:100) to afford protected callipeltin C **141** (134 mg, 55.4 µmol, 79%) as a white amorphous solid.



^{1}H-NMR (500 MHz, DMSO-d_6): δ = 0.60 (d, $^{3}J_{71,63}$ = 6.6 Hz, 3 H, 71-H), 0.77 (d, $^{3}J_{96,95}$ = 6.4 Hz, 3 H, 96-H), 0.81 (d, $^{3}J_{29,28}$ = 7.2 Hz, 3 H, 29-H), 0.82 (d, $^{3}J_{29',28}$ = 7.2 Hz, 3 H, 29-H'), 0.84 (d, $^{3}J_{96',95}$ = $^{3}J_{104,93}$ = 6.6 Hz, 6 H, 96-H', 104-H), 0.93 (d, $^{3}J_{97,91}$ = 6.9 Hz, 3 H, 97-H), 1.05 (d, $^{3}J_{51,50}$ = 6.1 Hz, 3 H, 51-H), 1.08 (m, 2 H, 94-H), 1.09 (d, $^{3}J_{60,59}$ = 6.0 Hz, 3 H, 60-H), 1.14 (d, $^{3}J_{72,64}$ = 6.4 Hz, 3 H, 72-H), 1.18 (d, $^{3}J_{89,88}$ = 6.9 Hz, 3 H, 89-H), 1.23 (m, 2 H, 77-H), 1.29 (d, $^{3}J_{4,3}$ = 7.2 Hz, 3 H, 4-H), 1.30 (m, 1 H, 27-H_a), 1.36 (m, 1 H, 21-H_a), 1.39 (s, 6 H, 45-H), 1.48 (m, 8 H, 27-H_b, 28-H, 32-H, 33-H_a, 78-H, 95-H), 1.65 (m, 5 H, 21-H_b, 22-H, 33-H_b, 93-H), 2.00 (s, 3 H, 46-H), 2.09 (m, 1 H, 64-H), 2.18 (m, 1 H, 63-H), 2.42 (s, 3 H, 47-H), 2.47 (s, 3 H, 42-H), 2.57 (m, 1 H, 91-H), 2.70 (s, 3 H, 24-H), 2.95 (s, 2 H, 43-H), 2.99 (s, 3 H, 5-H), 3.00 (m, 2 H, 34-H), 3.04 (s, 3 H, 18-H), 3.27 (m, 2 H, 79-H), 3.46 (dd, $^{3}J_{92,91}$ = 8.5 Hz, $^{3}J_{92,93}$ = 1.8 Hz, 1 H, 92-H), 3.56 (m, 1 H, 74-H/75-H), 3.60 (s, 3 H, 1-H), 3.68 (s, 3 H, 103-H), 3.86 (m, 4 H, 50-H, 59-H, 74-H/75-H, 76-H), 4.24 (m, 5 H, 31-H, 66-H, 88-H, 98-H_a), 4.35 (d, $^{3}J_{8,7}$ = 9.3 Hz, 1 H, 8-H), 4.42 (m, 2 H, 52-H_a, 58-H), 4.49 (m, 2 H, 52-H_b, 98-H_b), 4.64 (m, 2 H, 26-H, 49-H), 4.71 (m, 1 H, 62-H), 4.76 (dd, $^{3}J_{20,21a}$ = 9.7 Hz, $^{3}J_{20,21b}$ = 4.8 Hz, 1 H, 20-H), 4.90 (q, $^{3}J_{3,4}$ = 7.2 Hz, 1 H, 3-H), 4.95 (t, $^{3}J_{7,8/NH}$ = 9.5 Hz, 1 H, 7-H), 5.01 (s, 2 H, 82-H), 5.07 (s, 2 H, 13-H), 5.10 (d, $^{3}J_{OH,59}$ = 4.6 Hz, 1 H, OH), 5.16 (d, $^{3}J_{OH,74/75}$ = 2.0 Hz, 1 H, OH), 5.19 (s, 2 H, 82-H'), 5.75 (d, $^{3}J_{OH,74/75}$ = 5.2 Hz, 1 H, OH), 6.39 (bs, 2 H, NH_2), 6.60 (bs, 1 H, NH), 6.74 (s, 1 H, NH_d), 6.81 (d, $^{3}J_{101,100}$ = 8.7 Hz, 2 H, 101-H), 6.94 (d, $^{3}J_{11,10}$ = 8.7 Hz, 2 H, 11-H), 7.07 (bs, 1 H, NH_e), 7.18 (m, 5 H, 17-H, 85-H, 100-H), 7.26 (m, 8 H, 10-H, 54-H, 68-H, 70-H, 86-H), 7.29 (m, 2 H, 55-H), 7.34 (m, 4 H, 69-H, 84-H), 7.40 (m, 10 H, 15-H, 16-H, 56-H, 84-H', 85-H', 86-H'), 7.76 (d, $^{3}J_{NH,49}$ = 8.2 Hz, 1 H, NH_g), 7.95 (d, $^{3}J_{NH,88}$ = 5.8 Hz, 1 H, NH_n), 7.99 (d, $^{3}J_{NH,62}$ = 7.3 Hz, 1 H, NH_j), 8.08 (d, $^{3}J_{NH,7}$ = 9.2 Hz, 1 H, NH_a), 8.15 (m, 1 H, NH), 8.28 (t, $^{3}J_{NH,66}$ = 5.6 Hz, 1 H, NH_l), 8.33 (d, $^{3}J_{29,28}$ = 8.3 Hz, 1 H, NH), 8.37 (t, $^{3}J_{NH,34}$ = 5.2 Hz, 1 H, NH_c), 11.58 (s, 1 H, NH_m).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 12.3 (q, C-46), 12.4 (q, C-71), 14.1 (q, C-4), 15.0 (q, C-97), 15.5 (q, C-51), 16.2 (q, C-72), 17.0 (q, C-104), 17.6 (q, C-42), 18.2 (q, C-89), 18.9 (q, C-47), 20.3 (q, C-60), 21.1 (q, C-96), 21.3 (q, C-29), 23.1 (q, C-29'), 24.1 (t, C-21), 24.3 (q, C-96'), 24.6 (d, C-28, C-95), 25.5 (t, C-78), 28.3 (q, C-45), 29.0 (t, C-77), 29.5 (t, C-32, C-33), 30.1 (q, C-24), 31.6 (t, C-22), 31.7 (d, C-93), 32.1 (q, C-5), 38.3 (d, C-63), 38.9 (t, C-94), 39.9 (t, C-34), 40.2 (t,

C-27), 40.5 (t, C-79), 41.9 (t, C-66), 42.5 (t, C-43), 42.9 (d, C-64), 42.9 (d, C-91), 47.1 (d, C-26), 48.8 (d, C-88), 49.5 (d, C-76), 51.5 (d, C-62), 51.8 (q, C-1), 52.0 (d, C-31), 52.2 (d, C-7), 52.9 (d, C-3), 54.9 (q, C-103), 55.1 (d, C-20), 55.3 (d, C-49), 56.5 (q, C-18), 58.1 (d, C-58), 66.3 (t, C-82), 67.4 (d, C-59), 67.5 (t, C-82'), 69.2 (t, C-13), 69.8 (t, C-52), 71.1 (d, C-74/C-75), 73.3 (t, C-98), 73.6 (d, C-74/C-75), 73.9 (d, C-50), 82.7 (d, C-8), 84.7 (d, C-92), 86.3 (s, C-44), 113.3 (d, C-101), 114.2 (d, C-11), 116.2 (s, C-37), 124.3 (s, C-41), 126.6 (d, C-70), 127.1 (d, C-68), 127.2 (d, C-17), 127.6 (d, C-54), 127.7 (d, C-15), 127.8 (d, C-56/C-86), 127.8 (d, C-56/C-86), 128.0 (d, C-84), 128.0 (d, C-86'), 128.2 (d, C-69), 128.3 (d, C-84'), 128.4 (d, C-16/C-55/C-85), 128.5 (d, C-16/C-55/C-85), 128.5 (d, C-16/C-55/C-85), 129.0 (d, C-10), 129.2 (d, C-100), 129.9 (s, C-9), 131.3 (s, C-99), 131.4 (s, C-40), 134.2 (s, C-38), 135.1 (s, C-83), 136.9 (s, C-83'), 137.1 (s, C-14), 137.3 (s, C-36), 138.4 (s, C-53), 139.6 (s, C-67), 152.6 (s, C-81), 155.0 (s, C-80), 156.0 (s, C-35), 157.4 (s, C-39), 158.2 (s, C-12), 158.4 (s, C-102), 163.0 (s, C-81'), 169.0 (s, C-19), 169.3 (s, C-48), 170.3 (s, C-6), 170.5 (s, C-57/C-61), 170.9 (s, C-57/C-61), 170.9 (s, C-23/C-30), 171.5 (s, C-2), 172.4 (s, C-25), 173.2 (s, C-73), 173.5 (s, C-23/C-30), 173.6 (s, C-87), 174.8 (s, C-90), 175.2 (s, C-65).

Optical rotation: $[\alpha]_D^{20}$ = –41.2 (c = 1.0, $CHCl_3$)

HRMS (ESI):	Calculated	Found
$C_{127}H_{175}N_{18}O_{29}S$ $[M+H]^+$	2448.2488	2448.2501

6.4 NMR Spectra

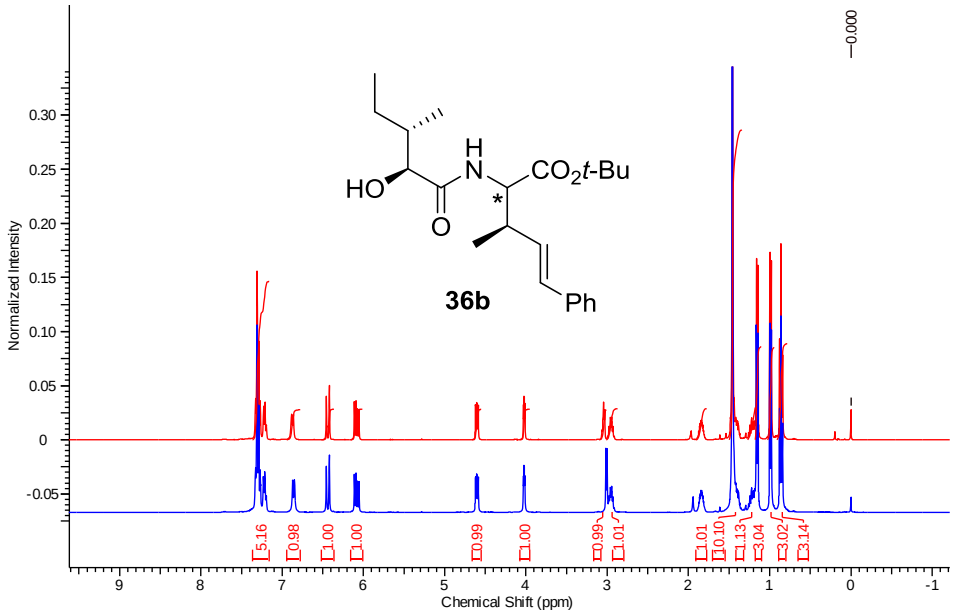


Fig. 9: NMR comparison of allylation product **36b** obtained under LDA (red) and LHMDS (blue) conditions.

7. Literature

[1] World Health Organization, “The top 10 causes of death,” https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death, **2020**, accessed 15.03.2022.

[2] J. L. Lau, M. K. Dunn, *Bioorg. Med. Chem.* **2018**, *26*, 2700–2707.

[3] T. Dang, R. D. Süssmuth, *Acc. Chem. Res.* **2017**, *50*, 1566–1576.

[4] Research Transparency Market, “Peptide Therapeutics Market—Global Industry Analysis, Size, Share, Growth, Trends and Forcast 2016–2024,” https://www.transparencymarketresearch.com/peptide-therapeutics-market.html, **2019**, accessed 15.03.2022.

[5] R. J. Malonis, J. R. Lai, O. Vergnolle, *Chem. Rev.* **2020**, *120*, 3210–3229.

[6] A. Mullard, *Nat. Rev. Drug Discov.* **2013**, *12*, 329–332.

[7] G. S. Hamilton, *Biologicals* **2015**, *43*, 318–332.

[8] K. C. Nicolaou, S. Rigol, *Angew. Chem. Int. Ed.* **2019**, *58*, 11206–11241.

[9] G. M. Suarez-Jimenez, A. Burgos-Hernandez, J. M. Ezquerra-Brauer, *Mar. Drugs* **2012**, *10*, 963–986.

[10] A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, *61*, 1382–1414.

[11] K. Fosgerau, T. Hoffmann, *Drug Discov. Today* **2015**, *20*, 122–128.

[12] B. G. de la Torre, F. Albericio, *Molecules* **2020**, *25*, 1–3.

[13] O. Al Musaimi, D. Al Shaer, F. Albericio, B. G. de la Torre, *Pharmaceuticals* **2021**, *14*, 145.

[14] A. Zorzi, K. Deyle, C. Heinis, *Curr. Opin. Chem. Biol.* **2017**, *38*, 24–29.

[15] N. Qvit, S. J. S. Rubin, T. J. Urban, D. Mochly-Rosen, E. R. Gross, *Drug Discov. Today* **2017**, *22*, 454–462.

[16] A. F. B. Räder, M. Weinmüller, F. Reichart, A. Schumacher-Klinger, S. Merzbach, C. Gilon, A. Hoffman, H. Kessler, *Angew. Chem. Int. Ed.* **2018**, *57*, 14414–14438.

[17] X. Jing, K. Jin, *Med. Res. Rev.* **2020**, *40*, 753–810.

[18] A. A. Vinogradov, Y. Yin, H. Suga, *J. Am. Chem. Soc.* **2019**, *141*, 4167–4181.

[19] C. T. Walsh, R. V. O’Brien, C. Khosla, *Angew. Chem. - Int. Ed.* **2013**, *52*, 7098–7124.

[20] J. N. DeGruyter, L. R. Malins, P. S. Baran, *Biochemistry* **2017**, *56*, 3863–3873.

[21] Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441–4482.

[22] S. Wang, G. Dong, C. Sheng, *Chem. Rev.* **2019**, *119*, 4180–4220.

[23] Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441–4482.

[24] R. W. Hoffmann, *Synthesis (Stuttg.)* **2006**, *2006*, 3531–3541.

[25] I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193–205.

[26] K. C. Nicolaou, S. A. Snyder, *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

[27] M. A. Hardy, B. A. Wright, J. L. Bachman, T. B. Boit, H. M. S. Haley, R. R. Knapp, R. F.

Lusi, T. Okada, V. Tona, N. K. Garg, R. Sarpong, *ACS Cent. Sci.* **2020**, *6*, 1017–1030.

[28] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.

[29] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943.

[30] B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1–14.

[31] B. M. Trost, *Org. Process Res. Dev.* **2012**, *16*, 185–194.

[32] Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297.

[33] Y. Matsushima, K. Onitsuka, T. Kondo, T. Mitsudo, S. Takahashi, *J. Am. Chem. Soc.* **2001**, *123*, 10405–10406.

[34] B. M. Trost, M. Rao, A. P. Dieskau, *J. Am. Chem. Soc.* **2013**, *135*, 18697–18704.

[35] N. Kanbayashi, K. Hosoda, M. Kato, K. Takii, T. Okamura, K. Onitsuka, *Chem. Commun.* **2015**, *51*, 10895–10898.

[36] Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen, S.-L. You, *Chem. Rev.* **2019**, *119*, 1855–1969.

[37] X. J. Liu, S. Jin, W. Y. Zhang, Q. Q. Liu, C. Zheng, S. L. You, *Angew. Chem. Int. Ed.* **2020**, *59*, 2039–2043.

[38] R. Takeuchi, N. Shiga, *Org. Lett.* **1999**, *1*, 265–268.

[39] B. W. H. Turnbull, P. Andrew Evans, *J. Org. Chem.* **2018**, *83*, 11463–11479.

[40] D. K. Leahy, P. A. Evans, *Mod. Rhodium-Catalyzed Org. React.* Wiley-VCH, **2005**, 191–214.

[41] T. Hayashi, A. Okada, T. Suzuka, M. Kawatsura, *Org. Lett.* **2003**, *5*, 1713–1715.

[42] M. Sidera, S. P. Fletcher, *Nat. Chem.* **2015**, *7*, 935–939.

[43] U. Kazmaier, D. Stolz, *Angew. Chem. Int. Ed.* **2006**, *45*, 3072–3075.

[44] D. Ghorai, À. Cristòfol, A. W. Kleij, *Eur. J. Inorg. Chem.* **2022**, *2022*, e202100820.

[45] L. Süsse, B. M. Stoltz, *Chem. Rev.* **2021**, *121*, 4084–4099.

[46] Y. Kita, R. D. Kavthe, H. Oda, K. Mashima, *Angew. Chem. Int. Ed.* **2016**, *55*, 1098–1101.

[47] Y. Weng, C. Zhang, Z. Tang, M. Shrestha, W. Huang, J. Qu, Y. Chen, *Nat. Commun.* **2020**, *11*, 392.

[48] B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104–1105.

[49] O. Belda, C. Moberg, *Acc. Chem. Res.* **2004**, *37*, 159–167.

[50] C. Moberg, *Org. React.* **2014**, 1–74.

[51] B. M. Trost, K. Dogra, *J. Am. Chem. Soc.* **2002**, *124*, 7256–7257.

[52] B. M. Trost, J. R. Miller, C. M. Hoffman, *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.

[53] B. Plietker, *Angew. Chem. Int. Ed.* **2006**, *45*, 1469–1473.

[54] B. Plietker, A. Dieskau, K. Möws, A. Jatsch, *Angew. Chem. Int. Ed.* **2008**, *47*, 198–201.

[55] G. C. Lloyd-Jones, A. Pfaltz, *Angew. Chem. Int. Ed.* **1995**, *34*, 462–464.

[56] J.-B. Langlois, A. Alexakis, in (Ed.: U. Kazmaier), Springer Berlin Heidelberg, Berlin,

Heidelberg, **2012**, pp. 235–268.

[57] J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

[58] J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *6*, 4387–4388.

[59] J. Tsuji, *Acc. Chem. Res.* **1969**, *2*, 144–152.

[60] K. E. Atkins, W. E. Walker, R. M. Manyik, *Tetrahedron Lett.* **1970**, *11*, 3821–3824.

[61] G. Hata, K. Takahashi, A. Miyake, *J. Chem. Soc. D Chem. Commun.* **1970**, 1392–1393.

[62] B. M. Trost, P. E. Strege, *J. Am. Chem. Soc.* **1977**, *99*, 1649–1651.

[63] B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292–294.

[64] B. M. Trost, *Tetrahedron* **2015**, *71*, 5708–5733.

[65] J. Vercauteren, B. M. Trost, *Tetrahedron Lett.* **1985**, *26*, 131–134.

[66] B. M. Trost, M. L. Crawley, C. B. Lee, *J. Am. Chem. Soc.* **2000**, *122*, 6120–6121.

[67] B. M. Trost, Chul Bom Lee, *J. Am. Chem. Soc.* **2001**, *123*, 3687–3696.

[68] B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11852–11853.

[69] B. M. Trost, R. Koller, B. Schäffner, *Angew. Chem. Int. Ed.* **2012**, *51*, 8290–8293.

[70] B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.

[71] B. M. Trost, B. Breit, M. G. Organ, *Tetrahedron Lett.* **1994**, *35*, 5817–5820.

[72] I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3199–3202.

[73] J. James, M. Jackson, P. J. Guiry, *Adv. Synth. Catal.* **2019**, *361*, 3016–3049.

[74] P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz, I. Marek, *J. Am. Chem. Soc.* **2017**, *139*, 9615–9620.

[75] B. Stoltz, *Jacs* **2012**, 19050.

[76] J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985**, *50*, 1523–1529.

[77] J. Tsuji, H. Kataoka, Y. Kobayashi, *Tetrahedron Lett.* **1981**, *22*, 2575–2578.

[78] B. M. Trost, G. A. Molander, *J. Am. Chem. Soc.* **1981**, *103*, 5969–5972.

[79] B. M. Trost, T. R. Verhoeven, *J. Org. Chem.* **1976**, *41*, 3215–3216.

[80] B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743.

[81] U. Kazmaier, Ed. , *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, Springer Verlag, Berlin, Heidelberg, **2012**.

[82] S.-C. Sha, J. Zhang, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2013**, *135*, 17602–17609.

[83] M. Braun, F. Laicher, T. Meier, *Angew. Chem. Int. Ed.* **2000**, *39*, 3494–3497.

[84] U. Kazmaier, F. L. Zumpe, *Angew. Chem. Int. Ed.* **1999**, *38*, 1468–1470.

[85] B. M. Trost, A. R. Sudhakar, *J. Am. Chem. Soc.* **1987**, *109*, 3792–3794.

[86] T. Nagano, S. Kobayashi, *J. Am. Chem. Soc.* **2009**, *131*, 4200–4201.

[87] K. Takahashi, A. Miyake, G. Hata, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230–236.

[88] B. M. Trost, E. J. McEachern, *J. Am. Chem. Soc.* **1999**, *121*, 8649–8650.

[89] P. R. Auburn, J. Whelan, B. Bosnich, *J. Chem. Soc. Chem. Commun.* **1986**, 146–147.

[90] B. J. Lüssem, H.-J. Gais, *J. Org. Chem.* **2004**, *69*, 4041–4052.

[91] B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093.

[92] T. Hayashi, M. Konishi, K. Yokota, M. Kumada, *J. Chem. Soc. Chem. Commun.* **1981**, 313–314.

[93] N. Miyaura, T. Yano, A. Suzuki, *Tetrahedron Lett.* **1980**, *21*, 2865–2868.

[94] H. Matsushita, E. Negishi, *J. Am. Chem. Soc.* **1981**, *103*, 2882–2884.

[95] P. S. Pregosin, R. Salzmann, *Coord. Chem. Rev.* **1996**, *155*, 35–68.

[96] N. Solin, K. J. Szabó, *Organometallics* **2001**, *20*, 5464–5471.

[97] U. Kazmaier, F. L. Zumpe, *Angew. Chem. Int. Ed.* **2000**, *39*, 802–804.

[98] U. Kazmaier, M. Pohlman, *Synlett* **2004**, *2004*, 623–626.

[99] U. Kazmaier, K. Krämer, *J. Org. Chem.* **2006**, *71*, 8950–8953.

[100] J.-E. Bäckvall, K. L. Granberg, A. Heumann, *Isr. J. Chem.* **1991**, *31*, 17–24.

[101] C. P. Butts, E. Filali, G. C. Lloyd-Jones, P.-O. Norrby, D. A. Sale, Y. Schramm, *J. Am. Chem. Soc.* **2009**, *131*, 9945–9957.

[102] K. L. Granberg, J. E. Baeckvall, *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863.

[103] A. Guerrero, F. A. Jalón, B. R. Manzano, A. Rodríguez, R. M. Claramunt, P. Cornago, V. Milata, J. Elguero, *Eur. J. Inorg. Chem.* **2004**, *2004*, 549–556.

[104] F. A. Jalón, B. R. Manzano, B. Moreno-Lara, *Eur. J. Inorg. Chem.* **2005**, *2005*, 100–109.

[105] V. Montoya, J. Pons, J. García-Antón, X. Solans, M. Font-Bardía, J. Ros, *Organometallics* **2007**, *26*, 3183–3190.

[106] K. Itami, T. Koike, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 6957–6958.

[107] G. R. Cook, H. Yu, S. Sankaranarayanan, P. S. Shanker, *J. Am. Chem. Soc.* **2003**, *125*, 5115–5120.

[108] B. Aakermark, S. Hansson, B. Krakenberger, A. Vitagliano, K. Zetterberg, *Organometallics* **1984**, *3*, 679–682.

[109] B. Aakermark, B. Krakenberger, S. Hansson, A. Vitagliano, *Organometallics* **1987**, *6*, 620–628.

[110] B. Goldfuss, *J. Organomet. Chem.* **2006**, *691*, 4508–4513.

[111] D. A. Lange, B. Goldfuss, *Beilstein J. Org. Chem.* **2007**, *3*, 36.

[112] P. von Matt, A. Pfaltz, *Angew. Chem. Int. Ed.* **1993**, *32*, 566–568.

[113] J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769–1772.

[114] R. Prétôt, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 323–325.

[115] J. C. Fiaud, J. L. Malleron, *Tetrahedron Lett.* **1981**, *22*, 1399–1402.

[116] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1996**, *118*, 235–236.

[117] G. C. Lloyd-Jones, S. C. Stephen, *Chem. Eur. J.* **1998**, *4*, 2539–2549.

[118] T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Am. Chem. Soc.* **1998**, *120*, 1681–1687.

[119] B. Goldfuss, U. Kazmaier, *Tetrahedron* **2000**, *56*, 6493–6496.

[120] P. Fristrup, M. Ahlquist, D. Tanner, P.-O. Norrby, *J. Phys. Chem. A* **2008**, *112*, 12862–12867.

[121] M. D. K. Boele, P. C. J. Kamer, M. Lutz, A. L. Spek, J. G. de Vries, P. W. N. M. van Leeuwen, G. P. F. van Strijdonck, *Chem. Eur. J.* **2004**, *10*, 6232–6246.

[122] T. Hayashi, M. Kawatsura, Y. Uozumi, *Chem. Commun.* **1997**, 561–562.

[123] J. C. Fiaud, J. Y. Legros, *J. Org. Chem.* **1990**, *55*, 4840–4846.

[124] B. M. Trost, N. Asakawa, *Synthesis (Stuttg.)* **1999**, *1999*, 1491–1494.

[125] X.-C. He, B. Wang, G. Yu, D. Bai, *Tetrahedron: Asymmetry* **2001**, *12*, 3213–3216.

[126] B. M. Trost, J. D. Oslob, *J. Am. Chem. Soc.* **1999**, *121*, 3057–3064.

[127] B. M. Trost, M. L. Crawley, *J. Am. Chem. Soc.* **2002**, *124*, 9328–9329.

[128] A. Boto, C. C. González, D. Hernández, I. Romero-Estudillo, C. J. Saavedra, *Org. Chem. Front.* **2021**, *8*, 6720–6759.

[129] V. M. Lechner, M. Nappi, P. J. Deneny, S. Folliet, J. C. K. Chu, M. J. Gaunt, *Chem. Rev.* **2021**, DOI 10.1021/acs.chemrev.1c00357.

[130] J.-Q. Liu, A. Shatskiy, B. S. Matsuura, M. D. Kärkäs, *Synthesis (Stuttg.)* **2019**, *51*, 2759–2791.

[131] C. Bottecchia, T. Noël, *Chem. – A Eur. J.* **2019**, *25*, 26–42.

[132] P. Servatius, L. Junk, U. Kazmaier, *Synlett* **2019**, *30*, 1289–1302.

[133] F. J. Aguilar Troyano, K. Merkens, K. Anwar, A. Gómez-Suárez, *Angew. Chem. Int. Ed.* **2021**, *60*, 1098–1115.

[134] A. A. H. Ahmad Fuaad, F. Azmi, M. Skwarczynski, I. Toth, *Mol.* **2013**, *18*, 13148-13174.

[135] G. Apitz, W. Steglich, *Tetrahedron Lett.* **1991**, *32*, 3163–3166.

[136] G. Apitz, M. Jäger, S. Jaroch, M. Kratzel, L. Schäffeler, W. Steglich, *Tetrahedron* **1993**, *49*, 8223–8232.

[137] W. Steglich, M. Jager, P. Zistler, *Pure Appl. Chem.* **1994**, *66*, 2167–2170.

[138] C. Paulitz, W. Steglich, *J. Org. Chem.* **1997**, *62*, 8474–8478.

[139] H. Xu, A. Nazli, C. Zou, Z.-P. Wang, Y. He, *Chem. Commun.* **2020**, *56*, 14243–14246.

[140] S. P. Roche, *Synthesis (Stuttg.)* **2021**, *53*, 2767–2776.

[141] A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867.

[142] X. Fang, M. Johannsen, S. Yao, N. Gathergood, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1999**, *64*, 4844–4849.

[143] M. Schleusner, H.-J. Gais, S. Koep, G. Raabe, *J. Am. Chem. Soc.* **2002**, *124*, 7789–7800.

[144] D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury, L. Ryzhkov, A. E. Taggi, T. Lectka,

J. Am. Chem. Soc. **2002**, *124*, 67–77.

[145] C. Ogawa, M. Sugiura, S. Kobayashi, *Angew. Chem. Int. Ed.* **2004**, *43*, 6491–6493.

[146] S. J. T. Jonker, C. Diner, G. Schulz, H. Iwamoto, L. Eriksson, K. J. Szabó, *Chem. Commun.* **2018**, *54*, 12852–12855.

[147] S. Kobayashi, R. Matsubara, Y. Nakamura, H. Kitagawa, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 2507–2515.

[148] M. Wasa, R. Y. Liu, S. P. Roche, E. N. Jacobsen, *J. Am. Chem. Soc.* **2014**, *136*, 12872–12875.

[149] A. J. Bendelsmith, S. C. Kim, M. Wasa, S. P. Roche, E. N. Jacobsen, *J. Am. Chem. Soc.* **2019**, *141*, 11414–11419.

[150] D. Elad, J. Sinnreich, *Chem. Commun.* **1965**, 471–472.

[151] D. Elad, M. Schwarzberg, J. Sperling, *J. Chem. Soc. D Chem. Commun.* **1970**, 617–618.

[152] D. Elad, J. Sperling, *J. Am. Chem. Soc.* **1971**, *93*, 3839–3840.

[153] C. J. Easton, *Chem. Rev.* **1997**, *97*, 53–82.

[154] C. Wang, M. Guo, R. Qi, Q. Shang, Q. Liu, S. Wang, L. Zhao, R. Wang, Z. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 15841–15846.

[155] X. Hu, X. Chen, B. Li, G. He, G. Chen, *Org. Lett.* **2021**, *23*, 716–721.

[156] C. Che, Y.-N. Li, X. Cheng, Y.-N. Lu, C.-J. Wang, *Angew. Chem. Int. Ed.* **2021**, *60*, 4698–4704.

[157] R. Qi, C. Wang, Y. Huo, H. Chai, H. Wang, Z. Ma, L. Liu, R. Wang, Z. Xu, *J. Am. Chem. Soc.* **2021**, *143*, 12777–12783.

[158] X. Zhao, B. Li, J. Xu, Q. Tang, Z. Cai, X. Jiang, *Chem. Eur. J.* **2021**, *27*, 12540–12544.

[159] G.-Z. Wang, D.-G. Liu, M.-T. Liu, Y. Fu, *Green Chem.* **2021**, *23*, 5082–5087.

[160] Q. Wei, Y. Ma, Y. Dong, G. Liu, *Org. Lett.* **2020**, *22*, 5796–5800.

[161] Z.-P. Yang, D. J. Freas, G. C. Fu, *J. Am. Chem. Soc.* **2021**, *143*, 8614–8618.

[162] H. Tian, W. Xu, Y. Liu, Q. Wang, *Org. Lett.* **2020**, *22*, 5005–5008.

[163] J. Wang, Y. Su, Z. Quan, J. Li, J. Yang, Y. Yuan, C. Huo, *Chem. Commun.* **2021**, *57*, 1959–1962.

[164] Z. Liang, B. Oliver, L. Chao-Jun, *Proc. Natl. Acad. Sci.* **2009**, *106*, 4106–4111.

[165] S. Li, X. Yang, Y. Wang, H. Zhou, B. Zhang, G. Huang, Y. Zhang, Y. Li, *Adv. Synth. Catal.* **2018**, *360*, 4452–4456.

[166] Z. Yuan, X. Liu, C. Liu, Y. Zhang, Y. Rao, *Mol.* **2020**, *25*, 5270.

[167] H. Jia, B. Qiao, J. Zhiyong, *Acta Chim. Sin.* **2021**, *79*, 1477–1480.

[168] G. Wu, J. Wang, C. Liu, M. Sun, L. Zhang, Y. Ma, R. Cheng, J. Ye, *Org. Chem. Front.* **2019**, *6*, 2245–2249.

[169] A. F. M. Noisier, M. A. Brimble, *Chem. Rev.* **2014**, *114*, 8775–8806.

[170] S.-I. Yamada, T. Oguri, T. Shioiri, *J. Chem. Soc. Chem. Commun.* **1976**, 136–137.

[171] T. Oguri, T. Shioiri, S. Yamada, *Chem. Pharm. Bull. (Tokyo)* **1977**, *25*, 2287–2291.

[172] J. M. McIntosh, P. Mishra, *Can. J. Chem.* **1986**, *64*, 726–731.

[173] J. M. Mcintosh, K. C. Cassidy, *Can. J. Chem.* **1988**, *66*, 3116–3119.

[174] U. Schöllkopf, U. Groth, *Angew. Chem. Int. Ed.* **1981**, *20*, 977–978.

[175] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem. Int. Ed.* **1981**, *20*, 798–799.

[176] U. Schöllkopf, W. Hartwig, U. Groth, *Angew. Chem. Int. Ed.* **1979**, *18*, 863–864.

[177] D. Seebach, H. Bossler, H. Gründler, S.-I. Shoda, R. Wenger, *Helv. Chim. Acta* **1991**, *74*, 197–224.

[178] M. Koeck, H. Kessler, D. Seebach, A. Thaler, *J. Am. Chem. Soc.* **1992**, *114*, 2676–2686.

[179] D. Seebach, A. Thaler, A. K. Beck, *Helv. Chim. Acta* **1989**, *72*, 857–867.

[180] A. Thaler, D. Seebach, F. Cardinaux, *Helv. Chim. Acta* **1991**, *74*, 628–643.

[181] D. Seebach, A. K. Beck, H. G. Bossler, C. Gerber, S. Y. Ko, C. W. Murtiashaw, R. Naef, S.-I. Shoda, A. Thaler, M. Krieger, R. Wenger, *Helv. Chim. Acta* **1993**, *76*, 1564–1590.

[182] J. Michaux, G. Niel, J.-M. Campagne, *Chem. Soc. Rev.* **2009**, *38*, 2093–2116.

[183] T. B. Wright, P. A. Evans, *Chem. Rev.* **2021**, *121*, 9196–9242.

[184] D. J. Ager, D. E. Froen, R. C. Klix, B. Zhi, J. M. McIntosh, R. Thangarasa, *Tetrahedron* **1994**, *50*, 1975–1982.

[185] U. Kazmaier, *Angew. Chem. Int. Ed. English* **1994**, *33*, 998–999.

[186] U. Kazmaier, *J. Org. Chem.* **1994**, *59*, 6667–6670.

[187] U. Kazmaier, A. Krebs, *Angew. Chem. Int. Ed. English* **1995**, *34*, 2012–2014.

[188] C. Schneider, U. Kazmaier, *Eur. J. Org. Chem.* **1998**, *1998*, 1155–1159.

[189] U. Kazmaier, C. Schneider, *Tetrahedron Lett.* **1998**, *39*, 817–818.

[190] C. Quirin, U. Kazmaier, *Eur. J. Org. Chem.* **2009**, *2009*, 371–377.

[191] P. Servatius, U. Kazmaier, *Org. Biomol. Chem.* **2018**, *16*, 3464–3472.

[192] T. Konno, T. Daitoh, T. Ishihara, H. Yamanaka, *Tetrahedron: Asymmetry* **2001**, *12*, 2743–2748.

[193] A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939–3002.

[194] I. Mizota, K. Tanaka, M. Shimizu, *Tetrahedron Lett.* **2012**, *53*, 1847–1850.

[195] M. Mohamed, M. A. Brook, *Tetrahedron Lett.* **2001**, *42*, 191–193.

[196] T. J. Fulton, A. Q. Cusumano, E. J. Alexy, Y. E. Du, H. Zhang, K. N. Houk, B. M. Stoltz, *J. Am. Chem. Soc.* **2020**, *142*, 21938–21947.

[197] R. Grandel, U. Kazmaier, B. Nuber, *Liebigs Ann.* **1996**, *1996*, 1143–1150.

[198] J. Alam, T. H. Keller, T.-P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 9546–9548.

[199] L. He, G. S. C. Srikanth, S. L. Castle, *J. Org. Chem.* **2005**, *70*, 8140–8147.

[200] S. Kappler, L. Karmann, C. Prudel, J. Herrmann, G. Caddeu, R. Müller, A. M. Vollmar, S. Zahler, U. Kazmaier, *Eur. J. Org. Chem.* **2018**, *2018*, 6952–6965.

[201] L. Karmann, K. Schultz, J. Herrmann, R. Müller, U. Kazmaier, *Angew. Chem. Int. Ed.* **2015**, *54*, 4502–4507.

[202] U. Kazmaier, J. Deska, A. Watzke, *Angew. Chem. Int. Ed.* **2006**, *45*, 4855–4858.

[203] J. Deska, U. Kazmaier, *Angew. Chem. Int. Ed.* **2007**, *46*, 4570–4573.

[204] J. Deska, U. Kazmaier, *Chem. Eur. J.* **2007**, *13*, 6204–6211.

[205] S. Datta, U. Kazmaier, *Org. Biomol. Chem.* **2011**, *9*, 872–880.

[206] A. Kiefer, D. Gawas, U. Kazmaier, *Eur. J. Org. Chem.* **2015**, *2015*, 5810–5816.

[207] K. Huwig, K. Schultz, U. Kazmaier, *Angew. Chem. Int. Ed.* **2015**, *54*, 9120-9123.

[208] U. Kazmaier, D. Stolz, *Angew. Chem. Int. Ed.* **2006**, *45*, 3072–3075.

[209] D. Stolz, U. Kazmaier, *Synthesis (Stuttg.)* **2008**, *2008*, 2288–2292.

[210] A. Bayer, U. Kazmaier, *Org. Lett.* **2010**, *12*, 4960–4963.

[211] P. Servatius, U. Kazmaier, *Synlett* **2015**, *26*, 2001–2005.

[212] B. M. Trost, X. Ariza, *Angew. Chem. Int. Ed. English* **1997**, *36*, 2635–2637.

[213] L. Wei, X. Chang, C.-J. Wang, *Acc. Chem. Res.* **2020**, *53*, 1084–1100.

[214] M. Zhu, Q. Zhang, W. Zi, *Angew. Chem. Int. Ed.* **2021**, *60*, 6545–6552.

[215] X. Huo, J. Zhang, J. Fu, R. He, W. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2080–2084.

[216] L. Wei, Q. Zhu, S.-M. Xu, X. Chang, C.-J. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 1508–1513.

[217] X. Huo, R. He, J. Fu, J. Zhang, G. Yang, W. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9819–9822.

[218] J. Wang, Z. Dai, C. Xiong, J. Zhu, J. Lu, Q. Zhou, *Adv. Synth. Catal.* **2019**, *361*, 5105–5111.

[219] M. Ke, Z. Liu, G. Huang, J. Wang, Y. Tao, F. Chen, *Org. Lett.* **2020**, *22*, 4135–4140.

[220] H.-C. Liu, Y.-Z. Hu, Z.-F. Wang, H.-Y. Tao, C.-J. Wang, *Chem. Eur. J.* **2019**, *25*, 8681–8685.

[221] J. Zhang, X. Huo, B. Li, Z. Chen, Y. Zou, Z. Sun, W. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 1130–1139.

[222] A. Soheili, U. K. Tambar, *J. Am. Chem. Soc.* **2011**, *133*, 12956–12959.

[223] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

[224] K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028.

[225] T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656–5682.

[226] T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

[227] S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.

[228] M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.

[229] M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517.

[230] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

[231] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139–5151.

[232] M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2005**, *44*, 1549–1551.

[233] T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 2832–2834.

[234] R. Schettini, F. De Riccardis, G. Della Sala, I. Izzo, *J. Org. Chem.* **2016**, *81*, 2494–2505.

[235] D. Uraguchi, Y. Asai, T. Ooi, *Angew. Chem. Int. Ed.* **2009**, *48*, 733–737.

[236] C. Xu, Y. Qi, X. Yang, X. Li, Z. Li, L. Bai, *Org. Lett.* **2021**, *23*, 2890–2894.

[237] H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 792–795.

[238] C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355.

[239] Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832–1835.

[240] R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419–422.

[241] A. Shatskiy, M. D. Kärkäs, *Synlett* **2021**.

[242] K. Xu, Z. Wang, J. Zhang, L. Yu, J. Tan, *Org. Lett.* **2015**, *17*, 4476–4478.

[243] H.-H. Li, J.-Q. Li, X. Zheng, P.-Q. Huang, *Org. Lett.* **2021**, *23*, 876–880.

[244] S. Karmakar, A. Silamkoti, N. A. Meanwell, A. Mathur, A. K. Gupta, *Adv. Synth. Catal.* **2021**, *363*, 3693–3736.

[245] T. Qin, C. Josep, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, B. P. S., *Science* **2016**, *352*, 801–805.

[246] J. Wang, T. Qin, T.-G. Chen, L. Wimmer, J. T. Edwards, J. Cornella, B. Vokits, S. A. Shaw, P. S. Baran, *Angew. Chem. Int. Ed.* **2016**, *55*, 9676–9679.

[247] J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213–218.

[248] T. Kinsinger, U. Kazmaier, *Org. Lett.* **2018**, *20*, 7726–7730.

[249] T. Kinsinger, U. Kazmaier, *Org. Biomol. Chem.* **2019**, *17*, 5595–5600.

[250] M. Kohr, U. Kazmaier, *Org. Lett.* **2021**, *23*, 5947–5951.

[251] M. Wang, C. Wang, Y. Huo, X. Dang, H. Xue, L. Liu, H. Chai, X. Xie, Z. Li, D. Lu, Z. Xu, *Nat. Commun.* **2021**, *12*, 6873.

[252] L. Karmann, U. Kazmaier, *Eur. J. Org. Chem.* **2013**, *2013*, 7101–7109.

[253] J. Gorges, U. Kazmaier, *Eur. J. Org. Chem.* **2015**, *2015*, 8011–8017.

[254] M. Ahangarpour, I. Kavianinia, P. W. R. Harris, M. A. Brimble, *Chem. Soc. Rev.* **2021**, *50*, 898–944.

[255] A. Zampella, M. V. D'Auria, L. Gomez Paloma, A. Casapullo, L. Minale, C. Debitus, Y. Henin, *J. Am. Chem. Soc.* **1996**, *118*, 6202–6209.

[256] A. Zampella, A. Randazzo, N. Borbone, S. Luciani, L. Trevisi, C. Debitus, M. V. D'Auria, *Tetrahedron Lett.* **2002**, *43*, 6163–6166.

[257] A. Zampella, R. D'Orsi, V. Sepe, A. Casapullo, M. C. Monti, M. V. D'Auria, *Org. Lett.* **2005**, *7*, 3585–3588.

[258] C. Bassarello, A. Zampella, M. C. Monti, L. Gomez-Paloma, M. V. D'Auria, R. Riccio, G. Bifulco, *Eur. J. Org. Chem.* **2006**, 604–609.

[259] M. V. D'Auria, A. Zampella, L. G. Paloma, L. Minale, C. Debitus, C. Roussakis, V. Le Bert, *Tetrahedron* **1996**, *52*, 9589–9596.

[260] V. Sepe, R. D'Orsi, N. Borbone, M. Valeria D'Auria, G. Bifulco, M. C. Monti, A. Catania, A. Zampella, *Tetrahedron* **2006**, *62*, 833–840.

[261] M. V. D'Auria, V. Sepe, R. D'Orsi, F. Bellotta, C. Debitus, A. Zampella, *Tetrahedron* **2007**, *63*, 131–140.

[262] M. Stierhof, K. Ø. Hansen, M. Sharma, K. Feussner, K. Subko, F. F. Díaz-Rullo, J. Isaksson, I. Pérez-Victoria, D. Clarke, E. Hansen, M. Jaspars, J. N. Tabudravu, *Tetrahedron* **2016**, *72*, 6929–6934.

[263] N. Oku, K. R. Gustafson, L. K. Cartner, J. A. Wilson, N. Shigematsu, S. Hess, L. K. Pannell, M. R. Boyd, J. B. McMahon, *J. Nat. Prod.* **2004**, *67*, 1407–1411.

[264] Y. Yamano, M. Arai, M. Kobayashi, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4877–4881.

[265] T. D. Tran, N. B. Pham, G. Fechner, D. Zencak, H. T. Vu, J. N. A. Hooper, R. J. Quinn, *J. Nat. Prod.* **2012**, *75*, 2200–2208.

[266] M. J. Martin, R. Rodriguez-Acebes, Y. Garcia-Ramos, V. Martinez, C. Murcia, I. Digon, I. Marco, M. Pelay-Gimeno, R. Fernández, F. Reyes, A. M. Francesch, S. Munt, J. Tulla-Puche, F. Albericio, C. Cuevas, *J. Am. Chem. Soc.* **2014**, *136*, 6754–6762.

[267] L. Coello, R. Fernández, J. F. Reyes, A. Francesch, C. Cuevas, *WO 2010/070078 A1*, **2010**.

[268] M. Pelay-Gimeno, Y. García-Ramos, M. Jesús Martin, J. Spengler, J. M. Molina-Guijarro, S. Munt, A. M. Francesch, C. Cuevas, J. Tulla-Puche, F. Albericio, *Nat. Commun.* **2013**, *4*, 2352.

[269] A. Plaza, E. Gustchina, H. L. Baker, M. Kelly, C. A. Bewley, *J. Nat. Prod.* **2007**, *70*, 1753–1760.

[270] Z. Lu, R. M. Van Wagoner, M. K. Harper, H. L. Baker, J. N. A. Hooper, C. A. Bewley, C. M. Ireland, *J. Nat. Prod.* **2011**, *74*, 185–193.

[271] A. Zampella, V. Sepe, P. Luciano, F. Bellotta, M. C. Monti, M. V. D'Auria, T. Jepsen, S. Petek, M.-T. Adeline, O. Laprévôte, A.-M. Aubertin, C. Debitus, C. Poupat, A. Ahond, *J. Org. Chem.* **2008**, *73*, 5319–5327.

[272] A. Zampella, V. Sepe, F. Bellotta, P. Luciano, M. V. D'Auria, T. Cresteil, C. Debitus, S. Petek, C. Poupat, A. Ahond, *Org. Biomol. Chem.* **2009**, *7*, 4037–4044.

[273] H. J. Shin, M. A. Rashid, L. K. Cartner, H. R. Bokesch, J. A. Wilson, J. B. McMahon, K. R. Gustafson, *Tetrahedron Lett.* **2015**, *56*, 4215–4219.

[274] M. A. Rashid, K. R. Gustafson, L. K. Cartner, N. Shigematsu, L. K. Pannell, M. R. Boyd, *J. Nat. Prod.* **2001**, *64*, 117–121.

[275] P. W. Ford, K. R. Gustafson, T. C. McKee, N. Shigematsu, L. K. Maurizi, L. K. Pannell, D. E. Williams, E. Dilip de Silva, P. Lassota, T. M. Allen, R. Van Soest, R. J. Andersen, M. R.

Boyd, *J. Am. Chem. Soc.* **1999**, *121*, 5899–5909.

[276] P. Prasad, W. Aalbersberg, K.-D. Feussner, R. M. Van Wagoner, *Tetrahedron* **2011**, *67*, 8529–8531.

[277] A. S. Ratnayake, T. S. Bugni, X. Feng, M. K. Harper, J. J. Skalicky, K. A. Mohammed, C. D. Andjelic, L. R. Barrows, C. M. Ireland, *J. Nat. Prod.* **2006**, *69*, 1582–1586.

[278] A. Plaza, G. Bifulco, J. L. Keffer, J. R. Lloyd, H. L. Baker, C. A. Bewley, *J. Org. Chem.* **2009**, *74*, 504–512.

[279] L. Trevisi, S. Bova, G. Cargnelli, D. Danieli-Betto, M. Floreani, E. Germinario, M. V D'Auria, S. Luciani, *Biochem. Biophys. Res. Commun.* **2000**, *279*, 219–222.

[280] L. Trevisi, G. Cargnelli, G. Ceolotto, I. Papparella, A. Semplicini, A. Zampella, M. V. D'Auria, S. Luciani, *Biochem. Pharmacol.* **2004**, *68*, 1331–1338.

[281] R. Krishnamoorthy, B. L. Richardson, M. A. Lipton, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5136–5138.

[282] M. Kikuchi, Y. Watanabe, M. Tanaka, K. Akaji, H. Konno, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4865–4868.

[283] M. Kikuchi, H. Konno, *Biosci. Biotechnol. Biochem.* **2016**, *80*, 1066–1069.

[284] N. Okamoto, O. Hara, K. Makino, Y. Hamada, *J. Org. Chem.* **2002**, *67*, 9210–9215.

[285] D. B. Hansen, X. Wan, P. J. Carroll, M. M. Joullié, *J. Org. Chem.* **2005**, *70*, 3120–3126.

[286] M. A. Blaskovich, G. A. Lajoie, *J. Am. Chem. Soc.* **1993**, *115*, 5021–5030.

[287] C. J. Easton, C. A. Hutton, P. D. Roselt, E. R. T. Tiekink, *Tetrahedron* **1994**, *50*, 7327–7340.

[288] P. Marfey, *Carlsberg Res. Commun.* **1984**, *49*, 591.

[289] H. Konno, S. Aoyama, K. Nosaka, K. Akaji, *Synthesis (Stuttg.)* **2007**, *7*, 3666–3672.

[290] D. C. Cranfill, M. A. Lipton, *Org. Lett.* **2007**, *9*, 3511–3513.

[291] J. Tao, S. Hu, M. Pacholec, C. T. Walsh, *Org. Lett.* **2003**, *5*, 3233–3236.

[292] K. Makino, Y. Hiroki, Y. Hamada, *J. Am. Chem. Soc.* **2005**, *127*, 5784–5785.

[293] M. J. Martín, R. Rodríguez-Acebes, Y. García-Ramos, V. Martínez, C. Murcia, I. Digón, I. Marco, M. Pelay-Gimeno, R. Fernández, F. Reyes, A. M. Francesch, S. Munt, J. Tulla-Puche, F. Albericio, C. Cuevas, *J. Am. Chem. Soc.* **2014**, *136*, 6754–6762.

[294] B. Liang, P. J. Carroll, M. M. Joullié, *Org. Lett.* **2000**, *2*, 4157–4160.

[295] W. Oppolzer, *Pure Appl. Chem.* **1990**, *62*, 1241–1250.

[296] C. M. Acevedo, E. F. Kogut, M. A. Lipton, *Tetrahedron* **2001**, *57*, 6353–6359.

[297] S. Çalimsiz, M. A. Lipton, *J. Org. Chem.* **2005**, *70*, 6218–6221.

[298] N. Okamoto, O. Hara, K. Makino, Y. Hamada, *Tetrahedron Asymmetry* **2001**, *12*, 1353–1358.

[299] Y. Hamada, A. Kawai, Y. Kohno, O. Hara, T. Shioiri, *J. Am. Chem. Soc.* **1989**, *111*, 1525–1527.

[300] W. Xie, D. Ding, W. Zi, G. Li, D. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 2844–2848.

[301] Y. Tokairin, V. A. Soloshonok, H. Moriwaki, H. Konno, *Amino Acids* **2019**, *51*, 419–432.

[302] H. Konno, Y. Takebayashi, K. Nosaka, K. Akaji, *Heterocycles* **2010**, *81*, 79–89.

[303] S. Chandrasekhar, T. Ramachandar, B. V. Rao, *Tetrahedron Asymmetry* **2001**, *12*, 2315–2321.

[304] A. Ravi Kumar, B. Venkateswara Rao, *Tetrahedron Lett.* **2003**, *44*, 5645–5647.

[305] J. C. Thoen, Á. I. Morales-Ramos, M. A. Lipton, *Org. Lett.* **2002**, *4*, 4455–4458.

[306] S. Chandrasekhar, M. S. Reddy, G. S. Kiranbabu, A. S. K. Murthy, *Tetrahedron Lett.* **2006**, *47*, 7307–7309.

[307] L. Ermolenko, N. A. Sasaki, *J. Org. Chem.* **2006**, *71*, 693–703.

[308] J. Jeon, S. K. Hong, J. S. Oh, Y. G. Kim, *J. Org. Chem.* **2006**, *71*, 3310–3313.

[309] R. Yoshino, Y. Tokairin, H. Konno, *Tetrahedron Lett.* **2017**, *58*, 1604–1606.

[310] Y. Tokairin, K. Maita, S. Takeda, H. Konno, *Synthesis (Stuttg.)* **2015**, *47*, 351–358.

[311] V. Guerlavais, P. J. Carroll, M. M. Joullieé, *Tetrahedron Asymmetry* **2002**, *13*, 675–680.

[312] A. Zampella, M. Sorgente, M. V. D'Auria, *Tetrahedron Asymmetry* **2002**, *13*, 681–685.

[313] A. Zampella, M. V. D'Auria, *Tetrahedron-Asymmetr.* **2002**, *13*, 1237–1239.

[314] J. A. Turk, G. S. Visbal, M. A. Lipton, *J. Org. Chem.* **2003**, *68*, 7841–7844.

[315] K. A. Parker, Q. Xie, *Org. Lett.* **2008**, *10*, 1349–1352.

[316] G. Sabitha, K. Yadagiri, G. Chandrashekhar, J. S. Yadav, *Synthesis (Stuttg.)* **2010**, 4307–4311.

[317] Y. Tokairin, H. Konno, *Tetrahedron* **2017**, *73*, 39–45.

[318] D. C. Cranfill, Á. I. Morales-Ramos, M. A. Lipton, *Org. Lett.* **2005**, *7*, 5881–5883.

[319] S. Çalimsiz, Á. I. M. Ramos, M. A. Lipton, *J. Org. Chem.* **2006**, *71*, 6351–6356.

[320] M. Kikuchi, K. Nosaka, K. Akaji, H. Konno, *Tetrahedron Lett.* **2011**, *52*, 3872–3875.

[321] R. Krishnamoorthy, L. D. Vazquez-Serrano, J. A. Turk, J. A. Kowalski, A. G. Benson, N. T. Breaux, M. A. Lipton, *J. Am. Chem. Soc.* **2006**, *128*, 15392–15393.

[322] M. Kikuchi, H. Konno, *Org. Lett.* **2014**, *16*, 4324–4327.

[323] M. Winitz, L. Bloch-Frankenthal, N. Izumiya, S. M. Birnbaum, C. G. Baker, J. P. Greenstein, *J. Am. Chem. Soc.* **1956**, *78*, 2423–2430.

[324] S. C. Feifel, T. Schmiederer, T. Hornbogen, H. Berg, R. D. Süssmuth, R. Zocher, *ChemBioChem* **2007**, *8*, 1767–1770.

[325] S. Deechongkit, S.-L. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 497–500.

[326] Y. Zheng, J. Xu, *Tetrahedron* **2014**, *70*, 5197–5206.

[327] N. Valls, M. Vallribera, M. López-Canet, J. Bonjoch, *J. Org. Chem.* **2002**, *67*, 4945–4950.

[328] M. T. Crimmins, D. L. Jacobs, *Org. Lett.* **2009**, *11*, 2695–2698.

[329] S. M. Smith, G. L. Hoang, R. Pal, M. O. B. Khaled, L. S. W. Pelter, X. C. Zeng, J. M. Takacs, *Chem. Commun.* **2012**, *48*, 12180–12182.

[330] A. Horn, U. Kazmaier, *Org. Lett.* **2019**, *21*, 4595-4599.

[331] C. Prudel, K. Huwig, U. Kazmaier, *Chem. Eur. J.* **2020**, *26*, 3181–3188.

[332] N. P. S. Hassan, B. J. Naysmith, J. Sperry, M. A. Brimble, *Tetrahedron* **2015**, *71*, 7137–7143.

[333] R. C. Sawant, Y.-J. Liao, Y.-J. Lin, S. S. Badsara, S.-Y. Luo, *RSC Adv.* **2015**, *5*, 19027–19033.

[334] A. Kiefer, D. Gawas, U. Kazmaier, *Eur. J. Org. Chem.* **2015**, *2015*, 5810–5816.

[335] D. Stolz, U. Kazmaier, R. Pick, *Synthesis (Stuttg.)* **2006**, *2006*, 3341–3347.

[336] M. Kohr, U. Kazmaier, *Eur. J. Org. Chem.* **2019**, *2019*, 2843–2849.

[337] V. Rolland-Fulcrand, M. Rolland, M.-L. Roumestant, J. Martinez, *Eur. J. Org. Chem.* **2004**, *2004*, 873–877.

[338] S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136.

[339] C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya, P. Espinet, *ACS Catal.* **2015**, *5*, 3040–3053.

[340] A. Fürstner, J.-A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Commun.* **2008**, 2873–2875.

[341] L. Junk, U. Kazmaier, *Org. Biomol. Chem.* **2016**, *14*, 2916–2923.

[342] L. Junk, U. Kazmaier, *Synlett* **2016**, *27*, 1531–1536.

[343] K. C. Nicolaou, N. F. Jain, S. Natarajan, R. Hughes, M. E. Solomon, H. Li, J. M. Ramanjulu, M. Takayanagi, A. E. Koumbis, T. Bando, *Angew. Chem. Int. Ed.* **1998**, *37*, 2714–2716.

[344] M. H. Junttila, O. O. E. Hormi, *J. Org. Chem.* **2009**, *74*, 3038–3047.

[345] T. Planke, M. Moreno, S. Hüttel, J. Fohrer, F. Gille, M. D. Norris, M. Siebke, L. Wang, R. Müller, A. Kirschning, *Org. Lett.* **2019**, *21*, 1359–1363.

[346] H. Shao, M. Goodman, *J. Org. Chem.* **1996**, *61*, 2582–2583.

[347] Y. Nakamura, M. Hirai, K. Tamotsu, Y. Yonezawa, C. Shin, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1369–1377.

[348] J. Gorges, U. Kazmaier, *Org. Lett.* **2018**, *20*, 2033–2036.

[349] T. J. Michnick, D. S. Matteson, *Synlett* **1991**, 631–632.

[350] D. S. Matteson, E. C. Beedle, *Tetrahedron Lett.* **1987**, *28*, 4499–4502.

[351] O. C. Ho, R. Soundararajan, J. Lu, D. S. Matteson, Z. Wang, X. Chen, M. Wei, R. D. Willett, *Organometallics* **1995**, *14*, 2855–2860.

[352] D. S. Matteson, R. Soundararajan, O. C. Ho, W. Gatzweiler, *Organometallics* **1996**, *15*, 152–163.

[353] R. P. Singh, D. S. Matteson, *J. Org. Chem.* **2000**, *65*, 6650–6653.

[354] W. C. Hiscox, D. S. Matteson, *J. Org. Chem.* **1996**, *61*, 8315–8316.

[355] K. Feichtinger, C. Zapf, H. L. Sings, M. Goodman, *J. Org. Chem.* **1998**, *63*, 3804–3805.

[356] T. Fukuyama, S. C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.

[357] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

[358] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

[359] J. S. An, W. K. Shin, D. K. An, *Bull. Korean Chem. Soc.* **2015**, *36*, 2928–2931.

[360] C. L. Bailey, J. W. Clary, C. Tansakul, L. Klabunde, C. L. Anderson, A. Y. Joh, A. T. Lill, N. Peer, R. Braslau, B. Singaram, *Tetrahedron Lett.* **2015**, *56*, 706–709.

[361] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

[362] S. Czernecki, C. Georgoulis, C. Provelenghiou, *Tetrahedron Lett.* **1976**, *17*, 3535–3536.

[363] P. R. Skaanderup, C. S. Poulsen, L. Hyldtoft, M. R. Jørgensen, R. Madsen, *Synthesis (Stuttg.)* **2002**, *2002*, 1721–1727.

[364] T. W. Greene, P. G. M. Wuts, *Prot. Groups Org. Synth.* Wiley & Sons, New York. **1999**, 17–245.

[365] S. V Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke, D. J. Reynolds, *Chem. Rev.* **2001**, *101*, 53–80.

[366] T. Sun, W. Zhang, C. Zong, P. Wang, Y. Li, *J. Pept. Sci.* **2010**, *16*, 364–374.

[367] S. Lemaire-Audoire, M. Savignac, E. Blart, G. Pourcelot, J. P. Genêt, J.-M. Bernard, *Tetrahedron Lett.* **1994**, *35*, 8783–8786.

[368] S. Lemaire-Audoire, M. Savignac, E. Blart, J.-M. Bernard, J. P. Genêt, *Tetrahedron Lett.* **1997**, *38*, 2955–2958.

[369] F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino, S. A. Kates, *Tetrahedron Lett.* **1997**, *38*, 4853–4856.

[370] K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378–1382.

[371] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[372] J. R. Cochrane, D. H. Yoon, C. S. P. McErlean, K. A. Jolliffe, *Beilstein J. Org. Chem.* **2012**, *8*, 1344–1351.

[373] M. Hikota, H. Tone, K. Horita, O. Yonemitsu, *J. Org. Chem.* **1990**, *55*, 7–9.

[374] W. R. Roush, K. Koyama, M. L. Curtin, K. J. Moriarty, *J. Am. Chem. Soc.* **1996**, *118*, 7502–7512.

[375] M. Hikota, Y. Sakurai, K. Horita, O. Yonemitsu, *Tetrahedron Lett.* **1990**, *31*, 6367–6370.

[376] I. Paterson, R. D. Norcross, R. A. Ward, P. Romea, M. A. Lister, *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314.

[377] S. Mattsson, M. Dahlström, S. Karlsson, *Tetrahedron Lett.* **2007**, *48*, 2497–2499.

[378] B. Cornils, W. A. Herrmann, J.-H. Xu, H.-W. Zanthoff, *Catal. from A to Z: A Concise Encyclopedia*, Wiley-VCH, 2143–2146, **2020**.

[379] Y. Li, G. Manickam, A. Ghoshal, P. Subramaniam, *Synth. Commun.* **2006**, *36*, 925–928.

[380] H. Ji, Q. Jing, J. Huang, R. B. Silverman, *Tetrahedron* **2012**, *68*, 1359–1366.

[381] E. Alonso, D. J. Ramón, M. Yus, *Tetrahedron* **1997**, *53*, 14355–14368.

[382] A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053.

[383] M. Y. Kim, J. E. Starrett, S. M. Weinreb, *J. Org. Chem.* **1981**, *46*, 5383–5389.

[384] T. S. Rao, P. S. Pandey, *Synth. Commun.* **2004**, *34*, 3121–3127.

[385] T. Ohgi, S. M. Hecht, *J. Org. Chem.* **1981**, *46*, 1232–1234.

[386] P. Lei, Y. Ding, X. Zhang, A. Adijiang, H. Li, Y. Ling, J. An, *Org. Lett.* **2018**, *20*, 3439–3442.

[387] C. Y. Chern, Y. P. Huang, W. M. Kan, *Tetrahedron Lett.* **2003**, *44*, 1039–1041.

[388] L. Kuang, J. Zhou, S. Chen, K. Ding, *Synthesis (Stuttg.)* **2007**, 3129–3134.

[389] S. Takano, A. Kurotaki, M. Takahashi, K. Ogaswara, *Synthesis (Stuttg.)* **1986**, *1986*, 403–406.

[390] P. Bentler, N. Erdeljac, K. Bussmann, M. Ahlqvist, L. Knerr, K. Bergander, C. G. Daniliuc, R. Gilmour, *Org. Lett.* **2019**, *21*, 7741–7745.

[391] M. Dindaroğlu, S. Akyol Dinçer, H.-G. Schmalz, *Eur. J. Org. Chem.* **2014**, *2014*, 4315–4326.

[392] D. J. Blair, C. J. Fletcher, K. M. P. Wheelhouse, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 5552–5555.

Danksagung

Besonderer Dank gilt an dieser Stelle Herrn Prof. Dr. Uli Kazmaier für die interessante Themenstellungen und die hervorragende Betreuung. Weiterhin möchte ich mich speziell für die Freiheit bei der Bearbeitung meiner gesamten Arbeit bedanken.

Herrn Prof. Dr. J. Jauch danke ich für das Erstellen des Zweitgutachtens und die Begleitung als "Mentor" im Laufe des Studiums.

Dem gesamten Arbeitskreis danke ich für das angenehme Arbeitsklima und die spaßigen Mittagspausen und Feierabende. Besonderer Dank gilt meinem Laborkollegen Thorsten für die interessante und amüsante Zusammenarbeit und Michael für die interessanten Gespräche und Diskussionen. Für das zügige Korrekturlesen dieser Arbeit danke ich Andreas, Kevin und Lukas. Mein Dank gilt auch den ehemaligen Mitarbeitern Phil, Jan, Tanja, Cynthia und Sarah für feucht fröhlichen Spieleabende und sonstige amüsante Stunden.

Rudi Thomes danke ich für das Messen der hochaufgelösten Massen und die technische Hilfestellung an den HPLC- und MS-Apparaturen. Dr. Volker Huch danke ich für das Messen von Röntgenkristallstrukturen.

Spezieller Dank gilt Robert und Danjano für die Begleitung im Studium sowie all die spaßigen Abende im Laufe der Promotion und die noch vor uns liegenden „Abenteuer“.

Meinen Eltern und meinem kleinen Bruder danke ich für die Unterstützung und den Rückhalt in meinem gesamten Leben.

Zuletzt möchte ich Julia für die wunderschöne gemeinsame Zeit und die Unterstützung während des Studiums und der Doktorarbeit danken.