Syntheses of natural bioactive 3-acyltetramic acids and derivatives

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"To boldly go where
no one has gone before"

Captain Jean-Luc Picard

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Abbreviations

δ	chemical shift
Δ	energy
Σ	protecting group
18-c-6	18-crown-6
abs.	absolute
Ac	acetyl
AC	adenylyl cyclase
Ac_2O	acetic anhydride
AcOH	acetic acid
AD-Mix α	asymmetric dihydroxylation-Mix α
AHL	*N*-acylhomoserine lactone
aq	aqueous solution
ATP	adenosine triphosphate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
br	broad
c	concentration
CAM	ceric ammonium molybdate
cAMP	cyclic adenosine-3′,5′-monophosphate
cat.	catalytic
Cbz	carboxybenzyl
$CDCl_3$	deuterated chloroform
CDI	1,1'-carbonyldiimidazole
^{c}Hex	cyclohexane
CoA	coenzyme A
cod	1,5-cyclooctadiene
conc.	concentrated
COSY	correlated spectroscopy
d	day
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	dichloroethane

DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
decomp.	decomposition
d_f	film thickness
DFG	Deutsche Forschungsgemeinschaft
DHP	3,4-dihydro-*2H*-pyran
DHU	dicyclohexylurea
DIBAL-H	Diisobutylaluminium hydride
DIP	direct insertion probe
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNA	desoxyribonucleic acid
DPEN	1,2-diphenyl-1,2-ethylenediamine
e.g.	*exempli gratia*; for example
EDC · HCl	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
EDTA	Ethylenediaminetetraacetic acid
EI	electron ionisation
eq.	equivalents
er	enantiomeric ratio
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
Exp. No.	experiment number
Fmoc	fluorenylmethyloxycarbonyl
GC	gas chromatography
HCA	hexachloroacetone
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography

HPPD	4-hydroxyphenylpyruvate dioxygenase
HRMS	high resolution mass specrometry
HSQC	heteronuclear single-quantum correlation
HWE	Horner-Wadsworth-Emmons
IC_{50}	half maximal inhibitory concentration
IPCF	isopropenyl chloroformate
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant
JMOD	J-modulated spin-echo
K/Li/NaHMDS	potassium/lithium/sodium hexamethyldisilazide
K_a	acid constant
kat.	katalytisch
KO^{t}Bu	potassium *tert*-butoxide
LD_{99}	lethal dose to kill 99% of the test population
LDA	lithium diisopropylamide
LG	leaving group
lit.	literature
LPS	lipopolysaccharide
M	metal
M	mole per litre
Me	methyl
MeCN	acetonitrile
MeI	methyl iodide
MeOD	deuterated methanol
MeOH	methanol
mol. sieves	molecular sieves
mp	melting point
MS	mass spectrometry
Ms	mesyl
NaOAc/KOAc	sodium/potassium acetate
NaOMe	sodium methoxide
^{n}BuLi	*n*-butyllithium
NEt_3	triethylamine

NHC	*N*-heterocylic carbene
^{n}Hex	*n*-hexane
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NPht	*N*-phthaloyl
NRPS	non-ribosomal peptide synthetase
obs.	observed
PAA	*para*-anisaldehyde
PAB	*para*-azidobenzyl
PAH	phenylalanine hydroxylase
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PKS	polyketide synthetase
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
Ppyz	piperazine
PS II	photosystem II
p-TosOH	*para*-toluenesulfonic acid
pub.	published
quant.	quantitative
RCM	ring closing metathesis
Red-Al®	sodium bis(2-methoxyethoxy) aluminium hydride
R_f	retention factor
rfx	reflux
RP	reversed-phase
rt	room temperature
SAMP/RAMP	(*S*)-(−)-/(*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine
sat.	saturated
®T3P	1-propanephosphonic acid cyclic anhydride
TA	tenuazonic acid

taut.	tautomerisation
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
^{t}BuOH	*tert*-butyl alcohol
^{t}BuOOH	*tert*-butyl hydroperoxide
TEG	triethylene glycol
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TFA	trifluoroacetic acic
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin-layer chromatography
TM	unregistered trademark
TNF	tumor necrosis factor
Tos/Ts	tosyl
TPAP	tetrapropylammonium perruthenate
t_R	retention time
UPPS	undecaprenyl pyrophosphate synthase
UV	ultraviolet

1 Introduction

1.1 Natural products and their role in drug and herbicide research

1.1.1 General ideas about drug development

Drug development is a very complex field of medicinal chemistry.[1] It involves a close cooperation of many different scientific fields. Biologists, biochemists and synthetic chemists all work together, not only to develop new drugs, but also to understand how new substances function. They explore the structure-activity relationship of a biologically active compound in order to find new hints on how the chemical structure is linked to its effect in a biological system.[2] Knowledge gained by such experiments lays the foundation for developing new active substances with similar or improved potentials against different diseases.

In the last decades, combinatorial chemistry has been used to find new compounds, which are expected to display physiological effects. The method is based upon molecular modelling for constructing entire libraries of such compounds. Many examples of combinatorial chemistry and ongoing research in this field have been published up to present.[3–5]

Nowadays, both routes can be taken to discover new biologically active compounds. The deduction of suitable structures, via a chemical-biological approach or computer modelling should lead to new structures with desired biological properties.[6]

1.1.2 Impact of natural products on new drugs

In general, natural products are chemical compounds, which are produced by a living organism, such as an animal, a plant or a microorganism. More precisely, most chemists define a natural product as a compound produced as a result of an organisms primary or secondary metabolism.[7] A medicinal chemist even excludes the products produced by the primary metabolism, only to define the non essential compounds, which are produced by the secondary metabolism (e.g.: antibiotics and pigments) to be called natural products. In many cases these substances are unique

to an organism or a group of organisms,[8] often influenced by the environment and the different challenges faced. It is these multiple and different environments and challenges caused by nature, which are responsible for the seemingly endless diversity of natural products. This is reflected in the chemical structure, which shows the same kind of diversity.

The term natural product is often associated with its properties. In many cases, newly extracted and purified compounds exhibit one or more pharmacological properties.

Statistically, many new approved drugs are either related to or inspired by natural products. In the last 30 years, approximately 1400 new drugs have been tested and introduced on the market.[9] 30% were based upon a natural product, excluding those that mimic certain structures of natural products. Entirely synthetic substances (29%) have almost the same impact in that field. In other research fields, such as in anticancer research, the contribution of natural products in the development of new drugs is even higher reaching up to 43%.[9–12]

These features can be understood, if one looks at the properties and sources of natural products. Produced in a natural habitat, nature had them undergo years of evolutionary change. Natural products have been altered and optimised to enable interaction with other biomolecular targets, such as proteins, nucleic acids and carbohydrates. Thus, they are able to naturally interact with receptors, DNA, etc.[13] In addition, they have taken up a function in living organisms. The chemical structure and their biological optimisation of these structures make them lead compounds for new drugs,[2,13] enabling the scientist to start from an advanced stage in drug development. A major drawback of natural products however is that they have not been developed to operate in a human body.

Predominantly natural products serve as a template for the synthetic chemist.[2,13] As in this thesis, the first aim is the total synthesis of a substance to create enough material for further study of its properties. The second aim is the creation of analogues of a given compound to explore structure-activity relationships and with this knowledge to tune its properties. Concerning drugs this would mean the suppression of undesired side effects or the increase of desired activities.

1.1.3 Impact of natural products on new herbicides

Basically, all the general ideas concerning the development of new drugs also apply in the field of herbicide research. Because of the fact that the requirement for effective drugs is much higher than for effective herbicides, many known natural products have not yet been tested as potential herbicides.[14,15]

Nevertheless, some natural products and their analogues are used as herbicides nowadays. Two examples, which are used commercially are shown in figure 1.1.: Bialaphos (**1**), a tripeptide produced by the microbes *Streptomyces hygroscopicus* and *Streptomyces viridochromogenes*, and its simpler derivative phosphinothricin (BASTA®) (**2**).[16]

Other natural products, isolated from different plants, are 1,4-cineole (**3**) and its analogue cinmethylin (**4**), which displays similar activity but lower volatility, due to its additional benzylether group (figure 1.1).[16]

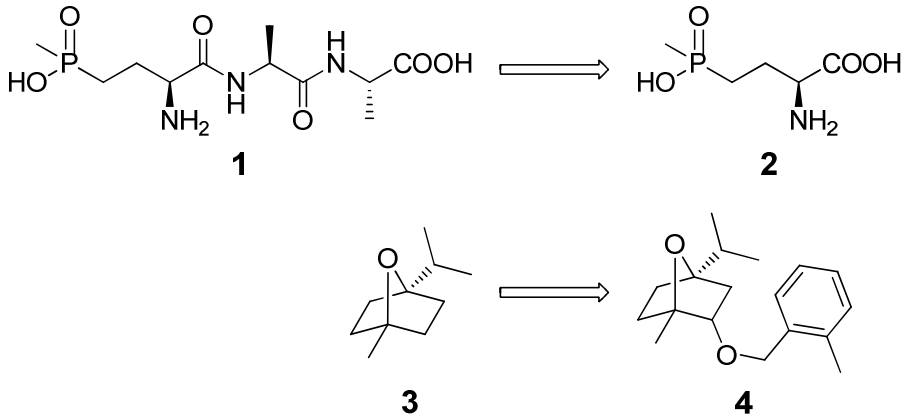
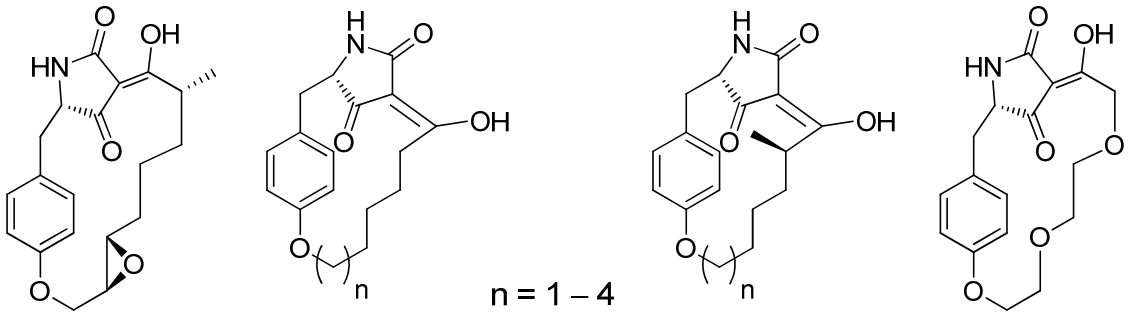


Figure 1.1 Examples for natural product herbicides and respective analogues

1.2 Objectives of this project

The aim of this project is the total synthesis of different natural products, all containing a tetramic acid moiety in one of the synthesis' stages.

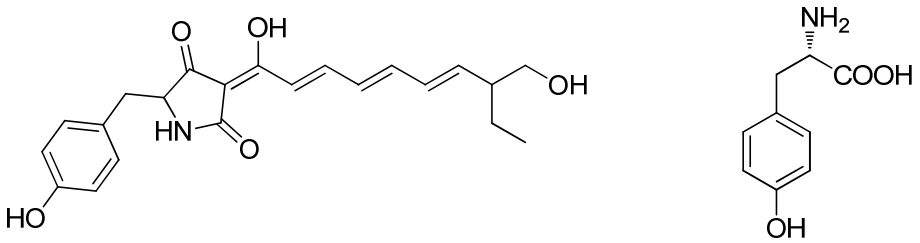
The primary objective is to synthesise macrocidin A (**5**), a cyclic tetramic acid, and to prepare distinct analogues with varying ring sizes, simplified side chains (**6** – **13**) and a polyether side chain (**14**) (figure 1.2).



5 **6 – 9** **10 – 13** **14**

Figure 1.2 Structures of macrocidin A (**5**) and its analogues (**6** – **14**)

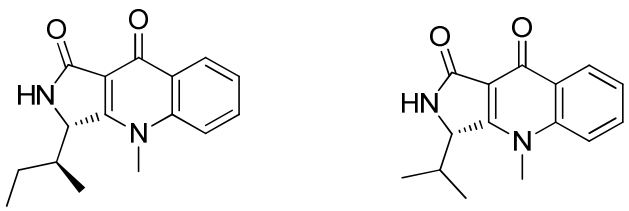
In addition, the first total synthesis of torrubiellone D (**15**) should be accomplished. It possesses the same tetramic acid core as macrocidin A (**5**), which derives from the natural amino acid L-tyrosine (**16**) (figure 1.3).



15 **16**

Figure 1.3 Structure of torrubiellone D (**15**) and L-tyrosine (**16**)

Furthermore, a short and direct route to quinolactacins A2 (**17**) and B2 (**18**) should be explored (figure 1.4).



17 **18**

Figure 1.4 Structures of quinolactacins A2 (**17**) and B2 (**18**)

Ultimately, different tetramic acid derivatives should be synthesised in order to test them as potential inhibitors for the adenylyl cyclase. This project was carried out in cooperation with Prof. C. Steegborn's group (biochemistry department). Different intermediates of the synthetic routes presented above as well as different structural analogues should be prepared on the basis of molecular modelling studies. Figure 1.5 shows the general structure of these molecules. The general tetramic acid core can be modified with different residues at the nitrogen and at C-5 (**19**). The same modifications can be made using the scaffold of a 3-acyltetramic acid, resulting in more variation, when looking at the residue R^3 (**20**).

19 **20**

Figure 1.5 General structures of potential adenylyl cyclase inhibitors

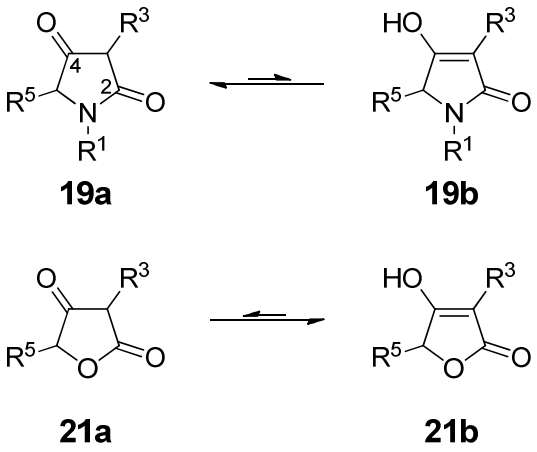
2 Theoretical Part

2.1 Tetramic acids

2.1.1 Structure and chemical properties

Compounds sharing the common motif of a pyrrolidine-2,4-dione unit (β-keto-γ-butyrolactam) are called tetramic acids. Numerous reviews about tetramic acids have been published, summarising most of the relevant facts about this class of compounds.[17–21]

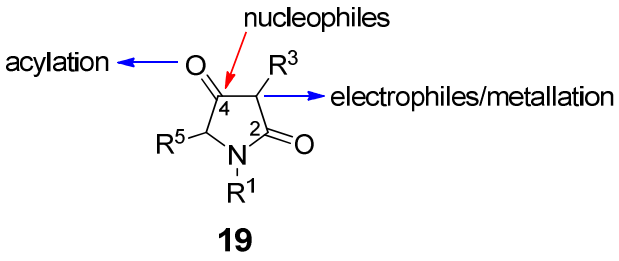
These heterocyclic compounds exist in two tautomeric forms (scheme 2.1) with the 2,4-diketo form (**19a**) usually being the predominant one.[18] When comparing the tetramic acids to their *O*-analogues (tetronic acids), observations concluded that for the tetronic acids the enolized tautomer (**21b**) is the favoured one. This is reflected in the different acidities of both compounds. In aqueous solution, the tetramic acids are usually much weaker acids (pK_a = 6.4) than the tetronic acids (pK_a = 3.8).[19]



Scheme 2.1 Tautomeric forms of tetramic acids (**19**) and tetronic acids (**21**)

The chemical properties of tetramic acids are based upon the stable C–N bond. The lactam is immensely stable towards treatment with strong acids and bases, therefore leaving a lot of possibilities to modify the tetramic acid core (**19**). Figure 2.1 shows that different positions possess unique reactivities. C-3 is prone to react with electrophiles or to undergo metallation by certain organometallic bases (e.g. *n*-butyllithium). The latter can for example be exploited to achieve a 3-arylation of

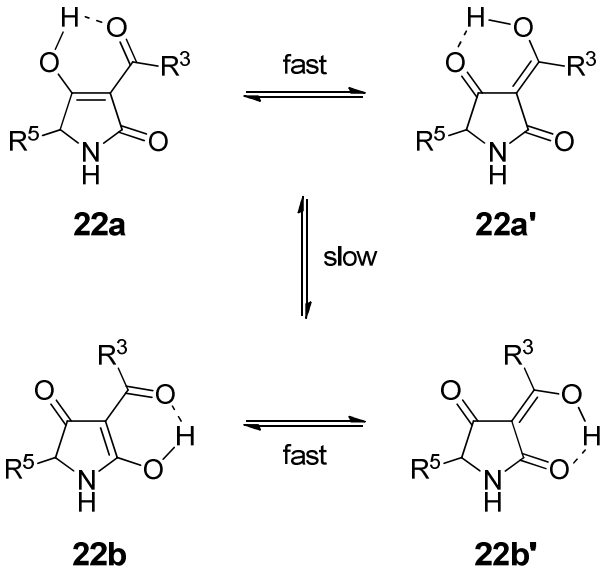
tetramic acids. In contrast, C-4 is susceptible to attacks by nucleophiles while O-4 can be reacted with acylation reagents.[18]



19

Figure 2.1 General reactivity of tetramic acids (**19**)

The most important tetramic acid derivatives are the 3-acyltetramic acids. When compared with tetramic acids, they show different properties. Their acidity is significantly higher with a pK_a ranging between 3.0 and 3.5 close to the value of tetronic acids.[19] This is a result of the complex tautomers, in which 3-acyltetramic acids exist. As with tetronic acids the enolized forms are predominant. Nine different tautomeric forms are possible, but only four can be observed (**22**).[19,22] To support this, highly correlated *ab initio* and density function calculations were carried out, also presenting four preferred structures of equally low energy.[23] NMR studies were conducted to identify the different forms and to analyse their importance. Scheme 2.2 shows the equilibrium between these forms.

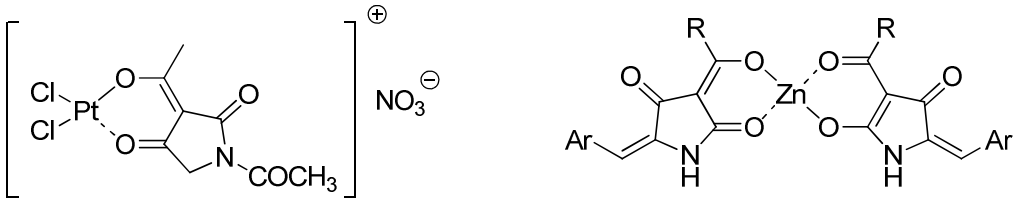


Scheme 2.2 Predominant tautomeric forms of 3-acyltetramic acids (**22**)

There are two different pairs of tautomers, the two internal tautomers a/a' and b/b' and the external tautomers a,a'/b,b'. The conversion between the internal tautomers occurs so fast that in NMR experiments only average chemical shifts are observed, whereas the slower conversion between the external tautomers shows a discernible pair of chemical shifts.[22,24] Further investigations revealed that from all four tautomers, b' is the most favoured one in most of the cases. For compounds with R^3 = Me and R^5 = Bn, ^{i}Pr, the ratio of the four tautomers is found to be a:a':b:b' = 5:15:0:80 (NMR in $CDCl_3$).[25] As with all tetramic acids, the solvent plays an important role upon the ratio of tautomers, as well as the substituents at the amide's nitrogen. If for example the nitrogen is acetylated, the hydrogen bond formed with the amides carbonyl is weakened significantly. In the case where R^3 = Pr and R^5 = H, 22a is the predominant tautomer.[26,27]

This always leads to complex NMR spectra, because more than one set of NMR signals is observed for a single compound.

Another fundamental property of 3-acyltetramic acids is their tendency to chelate metals.[20] The coordination takes place between the enolic oxygen of the 3-acyl group and the carbonyl oxygen either at C-2 or at C-4. Two examples, a cationic platinum complex (**23**) and a neutral zinc complex (**24**) with different modes of coordination, are shown in Figure 2.2. More examples and the biochemical significance of metal chelation will be discussed in detail in chapters 2.1.2, and 2.2.4.2.



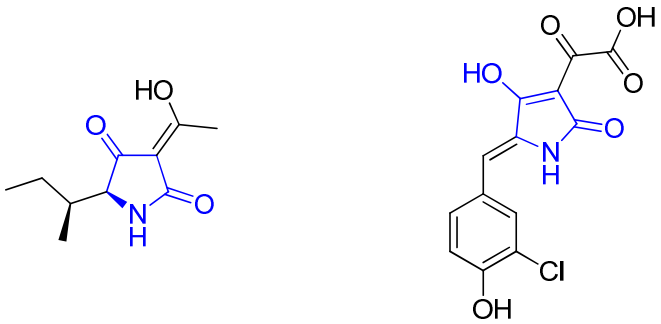
23 **24**

Figure 2.2 Metal chelate complexes with tetramic acid ligands

2.1.2 Natural occurrence and biological significance

Tetramic acids can be isolated from many natural sources such as bacteria, cyanobacteria, sponges, fungi and all kinds of marine species.[19] Their numerous occurrences in many different sources suggest that tetramic acid natural products play a significant role in biological processes. Their diverse activity spectrum encompasses antibiotic, antiviral and antiulcerative properties. They also display cytotoxicity, mycotoxicity and tumour inhibition, as well as fungicidal activity.[18] As mentioned before, nearly all of these compounds belong to the class of 3-acyltetramic acids. Two examples are shown in figure 2.3.

Tenuazonic acid (TA) (**25**) is perhaps one of the most simplest 3-acyltetramic acids, initially isolated from the fungus *Alternaria tenuis* auct.[28] It was studied thoroughly to reveal a diverse biological activity ranging from antibiotic activity[29] to inhibition against various viruses.[30] Synthesis was achieved by various routes over the years.[31,32] Pachydermin (**26**) is an unusual oxalylated tetramic acid, acquired from the New Zealand basidiomycete *Chamonixia pachydermis*. A degradation product of **26**, missing the 3-acylsubstituent, is the biological active substance, exhibiting antibacterial activity against *Bacillus subtilis*.[33]



25 **26**

Figure 2.3 Structures of tenuazonic acid (**25**) and pachydermin (**26**) which incorporate the tetramic acid motif (blue)

In many cases, the biological significant 3-acyltetramic acids cannot be isolated in their pure forms, but as metal complexes. Their high tendency to chelate metal atoms, leads to defined complexes with mono- or divalent metal cations. Two examples are shown in figure 2.4. TA (**25**) and pachydermin (**26**) were both isolated as metal salts. **25** was initially obtained as its magnesium and calcium salt (**27**, **28**).[34]

26, on the other hand, was found to exist as a salt containing sodium and potassium as counterions (**29**) (figure 2.4).[33]

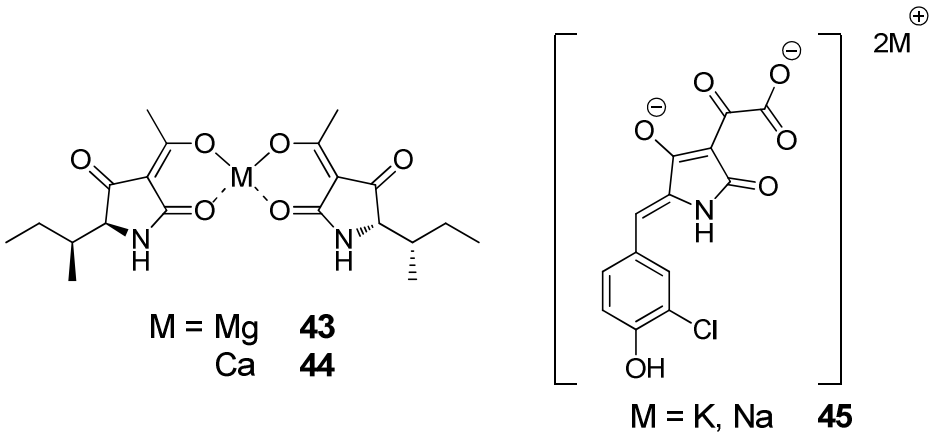


Figure 2.4 Isolated metal salts **27** – **29** of TA (**25**) and pachydermin (**26**)

This characteristic of 3-acyltetramic acids inspired many research groups to synthesise metal complexes of different tetramic acids in order to tune their biological properties and availability. Of **25**, complexes with Cu(II), Fe(III) and Ni(II) are known[35] and from various other compounds, even complexes with Zn(II), Ga(III), La(III) and Ru(II) have been prepared.[36]

There are other classes of natural occurring tetramic acids that exhibit unique structural motifs (figure 2.5). Gallinamide A (**30**) represents a *N*-acyl-4-*O*-alkyl-tetramic acid, produced by the marine cyanobacteria *Schizothrix* sp. It acts as an irreversible inhibitor of cathepsin L, an important lysosomal endopeptidase,[37,38] and shows antimalarial activity. It was first synthesised in 2009.[39]

Other unique compounds, recently isolated from the deep-sea-derived fungus *Cladosporium sphaerospermum* 2005-01-E3, are cladosins. The side chain of these compounds is connected to the C-3 of the tetramic acid by an enamine functionality. Of this group cladosin C (**31**), which exhibits antiviral activity, is shown.[40] Many enamine bearing tetramic acid derivatives have recently been synthesised to evaluate their biological potential.[41]

Additionally, two representatives of more complex tetramic acids are shown above: **32** stands for macrocyclic tetramic acids, whereas **33** represents the class of spirotetramic acids. The macrocycle cylindramide (**32**) was isolated from the marine

sponge *Halichondria cylindrate* and was found to exhibit cytotoxic activity against B16 melanoma cells.[42] A total synthesis was achieved by Laschat *et al*.[43,44]

Pyrroindomycin A (**33**) has a complex structure, unprecedented because of a macrocycle, which incorporates a spirotetramic acid, and a pyrroloindole group, connected by a deoxytrisaccharide bridge.[45] The stereochemical structure was predicted based upon a viable biochemical pathway[46] but no total synthesis has been achieved to date, which confirms the suggested structure. **49** was found in the extracts of the bacterium *Streptomyces rugosporus*, and exhibits widespread antibacterial activity against Gram-positive bacteria.[47]

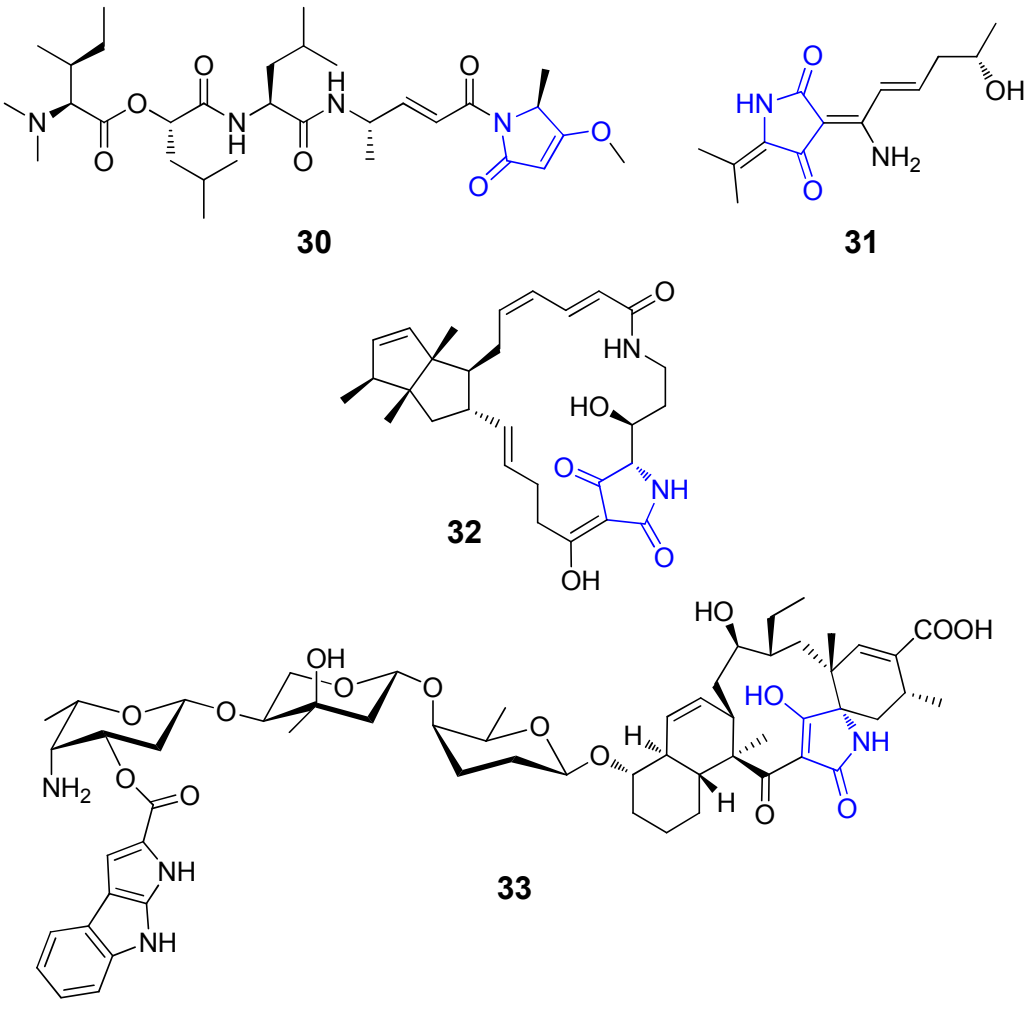


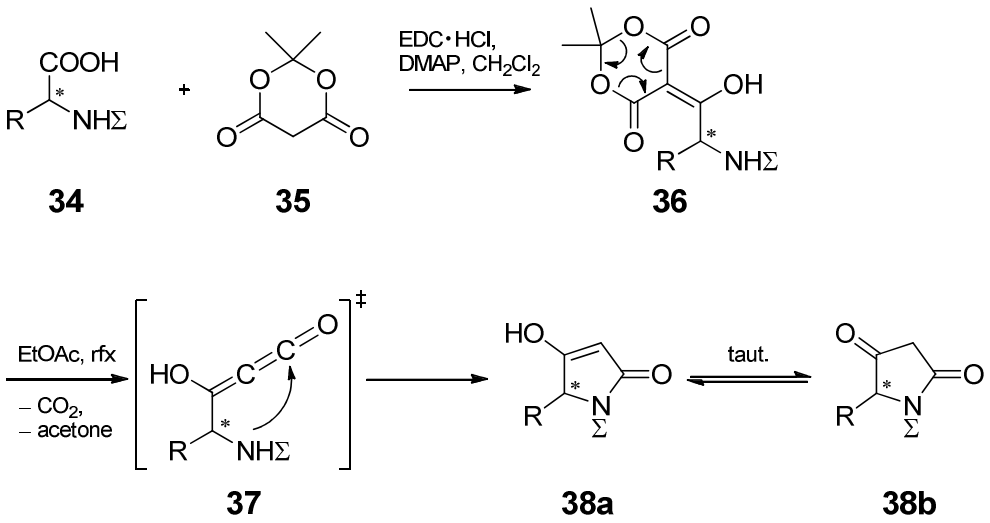
Figure 2.5 Structures of gallinamide A (**30**), cladosin C (**31**), cylindramide (**32**) and pyrroindomycin A (**33**), all incorporating the tetramic acid motif (blue)

2.1.3 Chemical syntheses - tetramic acids

2.1.3.1 Meldrum's acid approach

In 1987, Jouin *et al.* discovered a method to synthesise tetramic acids from *N*-protected amino acids (**34**) by applying Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (**35**).[48] With the help of condensation reagents, the carboxylic acid is activated and coupled to **35**, giving adduct **36**, which can be isolated. When **36** is heated to reflux in ethyl acetate (EtOAc), it decomposes, releasing acetone and CO_2 to give ketene intermediate **37**.[49] **37** is immediately nucleophillically attacked by the amino acids nitrogen, to form tetramic acid **38** (scheme 2.3). During this reaction sequence no racemisation of the stereocenter occurs, making this method a preferred one when stereochemistry is of importance. Originally, Jouin *et al.* used isopropenyl chloroformate (IPCF) as activating reagent for the acid.[48] Major drawbacks were high costs and the high toxicity of IPCF. Over the years studies to discover alternative reagents and reaction conditions were carried out.[50,51]

In 1996, Ma *et al.* succeeded in using the cheaper *N,N'*-dicyclohexylcarbodiimide (DCC) as a substitute for IPCF.[52] In doing so, a new difficulty arose: the separation of the desired product from the by-product dicyclohexylurea (DHU).



Scheme 2.3 Mechanism of the synthesis of tetramic acid **38** using Meldrum's acid (**35**) according to Hosseini *et al.*[53]

Later, in 2006, this problem was addressed by Hosseini *et al.*, who used *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC · HCl) instead of

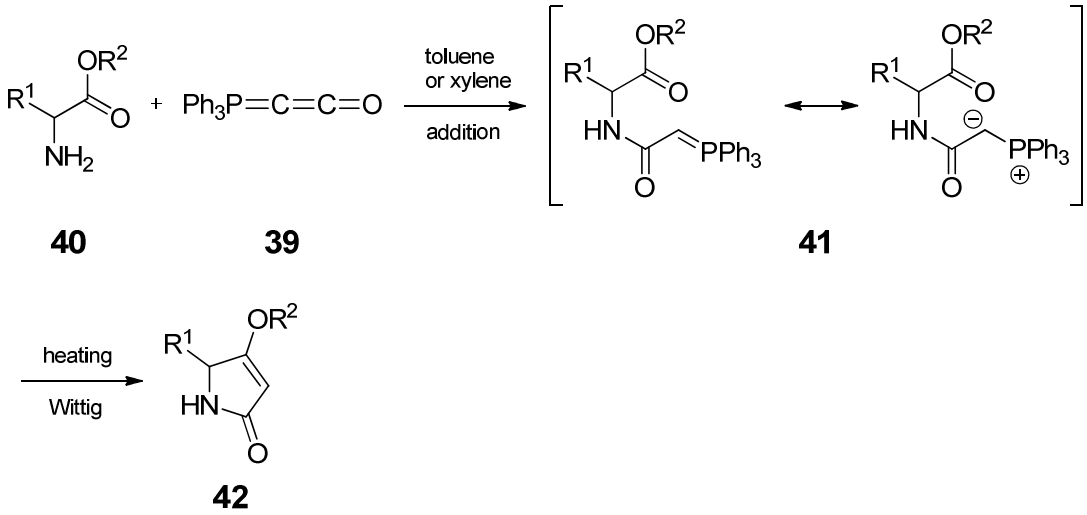
DCC. This reagent produces a urea derivative, which can be removed by acidic workup at the end of the reaction.[53] Therefore this procedure is preferred to date (scheme 2.3).

The general limitation of the synthesis of tetramic acids with Meldrum's acid lies in the fact that only *N*-protected α-amino carboxylic acids can be reacted in that manner to give **38**.

2.1.3.2 Domino synthesis using keteneylidene(triphenyl)phosphorane

In a very mild method to synthesise 4-*O*-alkyltetramates, the flexible reagent keteneylidene(triphenyl)phosphorane (Ph_3PCCO)[54,55] (**39**) is used as a means to facilitate the ring closure starting from different alkyl esters of α-amino-carboxylic acids (**40**) or their ammonium salts.[56] The whole reaction sequence can be carried out as a one-pot procedure and no racemisation at C-5 is observed.

The reaction can be understood as a domino reaction combining an addition and an intramolecular Wittig reaction (scheme 2.4).[57]



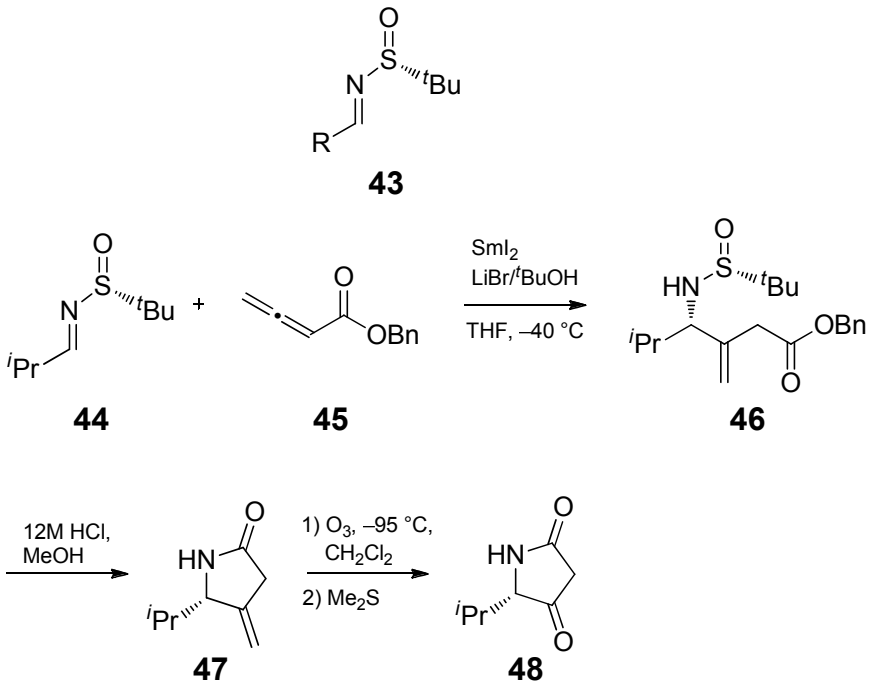
Scheme 2.4 Synthesis of tetramates (**42**) from α-aminoesters (**40**) and Ph_3PCCO (**39**)[56]

As starting materials, alkyl esters of α-amino-carboxylic acids (**40**) are used, which in a first step undergo an addition to the C-C double bond of **39** to give ester ylide **41**.

In a second step **41** reacts in an intramolecular Wittig reaction to give tetramate **42**. **42** is converted into the free tetramic acid by the removal of R^2. One problem of this method is the formation of triphenylphosphine oxide, which can be difficult to remove from the product. This can be avoided if polymer-bound Ph_3PCCO (**39**) is used. In this case, resulting triphenylphosphine oxide is removed by filtration. The methodology of employing **39** to form tetramic acids was frequently used in our group.[32,57–59]

2.1.3.3 Tetramic acid synthesis involving SmI_2

Another way to synthesise tetramic acids is by implementing a three step procedure, starting with chiral *tert*-butanesulfinyl imides (**43**),[60] which are easily prepared by reacting *tert*-butanesulfinamide with aldehydes or ketones (scheme 2.6).[61] These compounds are known to undergo SmI_2 mediated reductive cross-coupling reactions.[62]



Scheme 2.6 Synthesis of tetramic acids based upon chiral *tert*-butanesulfinyl imides (**43**)[60]

In this case according to Xu *et al*., *tert*-butanesulfinyl imide **44** was reacted with alleneoate **45** to give sulfinamide **46** via conjugate addition in a diasteromeric ratio of

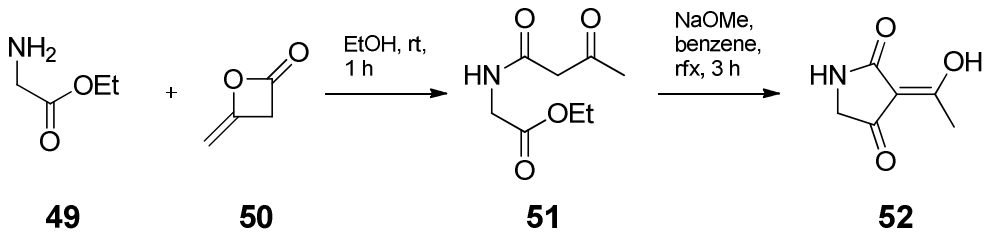
7:1. By treatment of **46** with HCl in methanol (MeOH), β-methylenyl-γ-lactam **47** was obtained and transformed into desired tetramic acid **48** by ozonolysis.[60]

2.1.4 Chemical syntheses – 3-acyltetramic acids

Due to the importance of 3-acyltetramic acids in nature, many strategies were developed to synthesise them beginning with different starting materials, in order to remain as flexible as possible. Owing to their historical relevance and their importance for this thesis, three important strategies will be discussed in the following chapters.

2.1.4.1 Lacey-Dieckmann condensation

The first synthesis developed to generate 3-acetyltetramic acids was published in 1954[63] and is related to the synthesis of 3-acetyltetronic acids.[64] Lacey *et al.* reported a two-step reaction sequence starting from α-amino ester **49**, which reacted with diketene (**50**) to give *N*-acetoacetyl-α-amino ester **51**. The following Dieckmann cyclisation was initiated by the addition of sodium methoxide (NaOMe) (later, potassium *tert*-butoxide (KO^{t}Bu) in *tert*-butanol was found to be the superior base[65]) and 3-acetyltetramic acid **52** was obtained in a yield of 96% (scheme 2.7).[63]



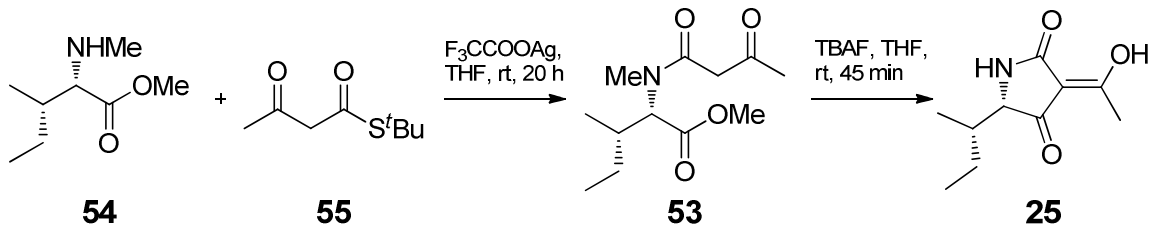
49 **50** **51** **52**

Scheme 2.7 Synthesis of 3-acetyltetramic acids via diketene (**50**) addition and Dieckmann cyclisation[63]

Due to its high yields, the Lacey-Dieckmann cyclisation became the most commonly used method to synthesise 3-acetyltetramic acids. If an appropriate α-amino ester is chosen, various groups can be introduced at C-5. When chiral α-amino esters are applied to create chiral products, racemisation at C-5 can be

observed. This major drawback is based upon the highly basic conditions during the cyclisation step.[66] Because of the use of **50**, another problem occurs: only 3-acetyltetramic acids can be prepared.

These problems were dealt with by Ley *et al.* They aimed to improve the flexibility and enantioselectivity of the Lacey-Dieckmann cyclisation (scheme 2.8).[67,68]



Scheme 2.8 Preparation of TA (**25**) according to Ley *et al.*[68]

β-ketothioesters are introduced as substitutes for **50**. These are reacted with silver(I)trifluoroacetate to give compounds, which are subjected to Dieckmann cyclisation conditions to furnish the desired 3-acetyltetramic acids.[67] The chance of racemisation is reduced by using the milder base tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) instead of alkoxy bases.[68] Scheme 2.8 shows an example of the stereoselective synthesis of TA (**25**) by cyclisation of β-ketoamide **53**, which was prepared by the reaction of chiral *N*-methyl-α-amino ester **54** and β-ketothioester **55**.

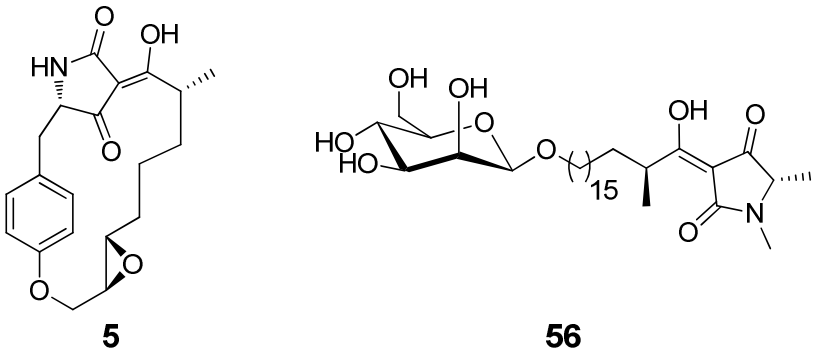


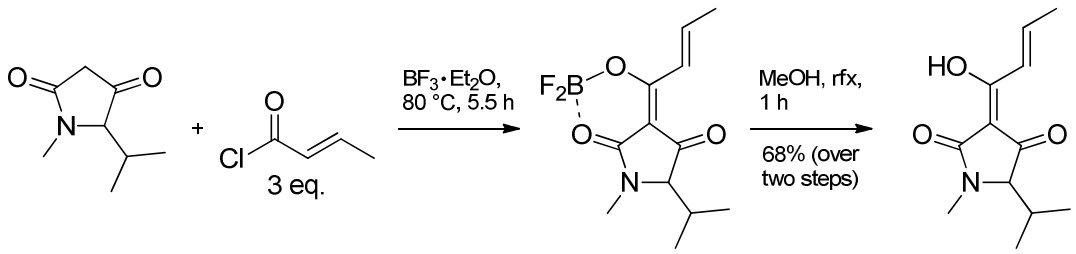
Figure 2.6 Structures of Macrocidin A (**5**) and Epicoccamide D (**56**)

The Lacey-Dieckmann cyclisation and its variants were used in natural product synthesis, to synthesise macrocidin A (**5**) (see chapter 2.2.1.2),[69] epicoccamide D (**56**)[70] (figure 2.6) and other complex 3-acyltetramic acids.[43,71]

2.1.4.2 Direct 3-acylation of tetramic acids using boron trifluoride

In 1990, Jones *et al.* experimented with different Lewis acids to facilitate the 3-acylation of acid chlorides with tetramic acids.[72,73] In preliminary studies, boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) and $TiCl_4$ surfaced as the reagents of choice.[65,72,74] Both approaches yielded the desired 3-acyltetramic acids in small to moderate yields of 19 – 70% ($BF_3 \cdot Et_2O$ showing better results). It was discovered that by isolating and purifying the 3-acyltetramic acids' BF_2-complexes, which are generated first, with subsequent methanolysis the desired products can generally be obtained with moderate yields ranging from 41 – 68% over two steps.

Giving an example, tetramic acid **57** was acylated with three equivalents of α,β-unsaturated acid chloride **58** in $BF_3 \cdot Et_2O$ to give BF_2-complex **59**. The free 3-acyltetramic acid **60** was liberated by heating **59** to reflux in MeOH (scheme 2.9).[73]



57 **58** **59** **60**

Scheme 2.9 Direct 3-acylation of tetramic acid **57** with acid chloride **58** and $BF_3 \cdot Et_2O$[73]

The method is flexible, allowing the application of various acid chlorides (alkyl, alkenyl and aryl acid chlorides) and tetramic acids. Due to the fact that BF_2-complexes of 3-acyltetramic acids are easy to handle and purify,[74] the products obtained are very pure. Drawbacks are the harsh conditions (heating and $BF_3 \cdot Et_2O$ as solvent) and the three equivalents of acid chloride required. In some cases, the acid chloride is not easily accessible and has to be synthesised with great effort.

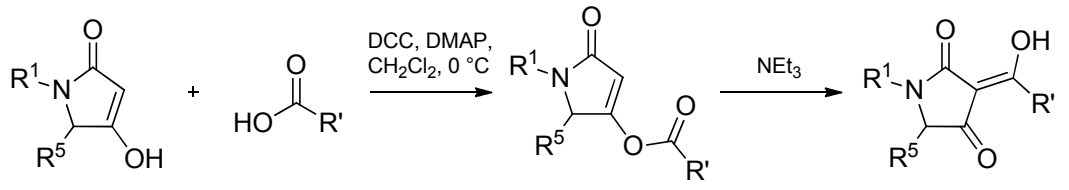
2.1.4.3 3-Acylation via 4-*O*-acyltetramic acids and subsequent rearrangement

3-Acyltetramic acids can also be synthesised by a two-step procedure. A tetramic acid (**61**) is reacted with a carboxylic acid (**62**) under conditions of a Steglich esterification,[75] employing an activating agent and an acyl transfer reagent, to synthesise a 4-*O*-acyltetramic acid (**63**). Several reagents were developed to initiate the acyl migration towards desired 3-acyltetramic acid **64** (scheme 2.10). This method is a mild alternative to the methods discussed before (chapters 2.1.4.1 and 2.1.4.2).

In 1987, Yoshii *et al.* used the standard Steglich esterification conditions, employing DCC as activating reagent and 4-dimethylaminopyridine (DMAP) as acyl transfer reagent. When 4-*O*-acylation was complete, triethylamine (NEt_3) was added to facilitate the rearrangement to the 3-acyl compound.[76]

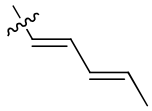
Scheme 2.10 highlights the results and shows the limitation of this method. The yields, when using alkyl carboxylic acids are satisfying, although this is not the case when α,β-unsaturated carboxylic acids or branched carboxylic acids are used. If the branched carboxylic acids inherit a stereocenter in α-position to the carboxyl functionality, some degree of racemisation is observed. Furthermore, the residues R^1, R^5 and R' significantly influence the outcome of the reaction.[77] Nevertheless, no precise prediction on the outcome of new reactions is possible, because the underlying mechanism of the acyl shift has not yet been uncovered.

Another problem is that carboxylic acids without an α-H (e.g. aromatic carboxylic acids) do not undergo acyl migration at all. The methods' flexibility can be expanded by the isolation of 4-*O*-acyltetramic acids **63** and by using other methods to initiate and control the acyl migration step. The original one-pot synthesis is often dismissed, because **63** can more easily be purified than **64** and the excess DHU can be removed more smoothly. Another way to avoid the DHU problem concerning the one-step procedure is by using EDC · HCl instead of DCC.[78]



61 **62** **63** **64**

R^1	R^5	R'	Yield (%)
H	Bn	^{n}pentyl	95
H	Bn	^{i}Pr	58
H	Bn	C_5H_7*	50
H	^{i}Pr	^{n}pentyl	88
H	^{i}Pr	C_5H_7*	50
Me	^{i}Pr	^{n}pentyl	89
Bn	H	^{n}pentyl	72
Bn	H	C_5H_7*	49

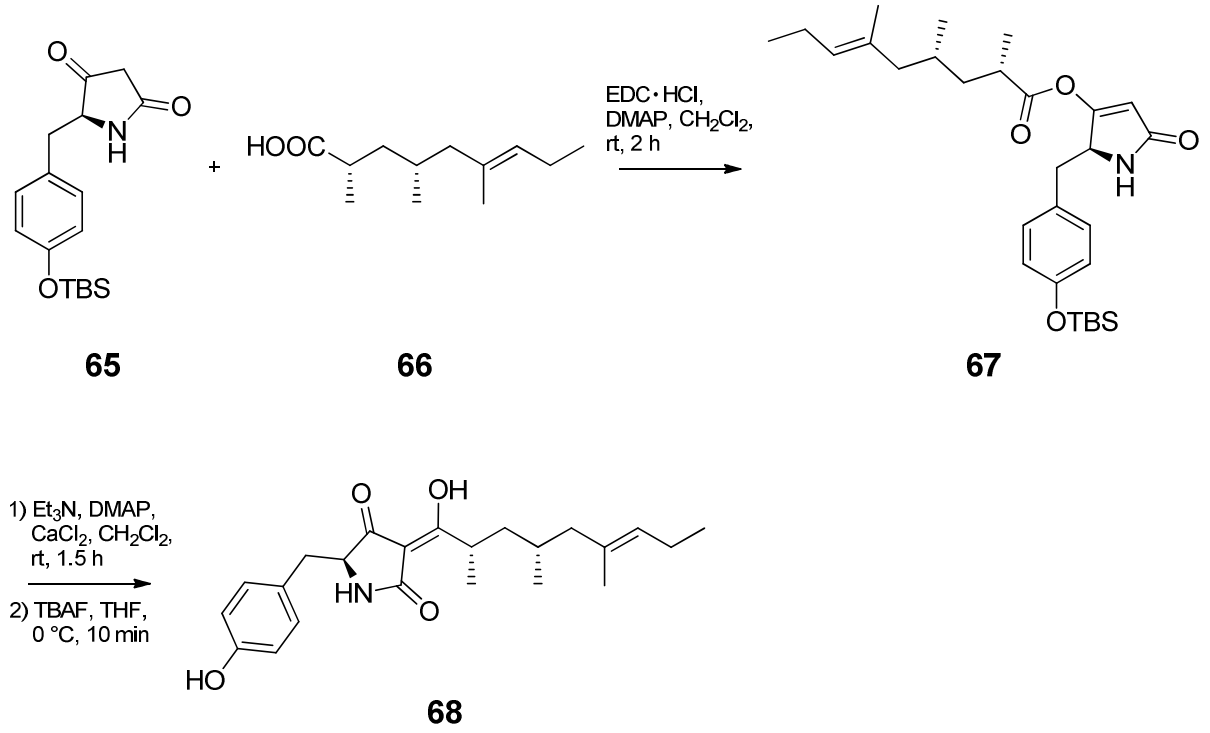
C_5H_7* = 

Scheme 2.10 Synthesis of various 3-acyltetramic acids (**64**) using the protocol of Yoshii *et al.*[76]

Yoda *et al.* circumvented the problem of low yields when using branched carboxylic acids by using $CaCl_2$ as an additive for the acyl migration.[79] Other metal salts were tested but only NaI showed effects similar to $CaCl_2$.[80] They even reported stereoselectivity when α-chiral carboxylic acids were used.[78–80] It is presumed that chelation of the calcium ion with the tetramic acid promotes the 3-acyl rearrangement.

For example, L-tyrosine derived tetramic acid **65** was reacted with chiral carboxylic acid **66** to 4-*O*-acyl compound **67**, rearranged and deprotected to give epicoccarine A (**68**) in a yield of 38% over both steps (scheme 2.11).

In addition, 3-acylation with carboxylic acids, lacking an α-H, was achieved by the same academic group,[80] allowing an even broader application of this method.



Scheme 2.11 Stereoselective synthesis of epicoccarine A (**68**) using the two-step 3-acylation strategy presented by Yoda *et al.*[78]

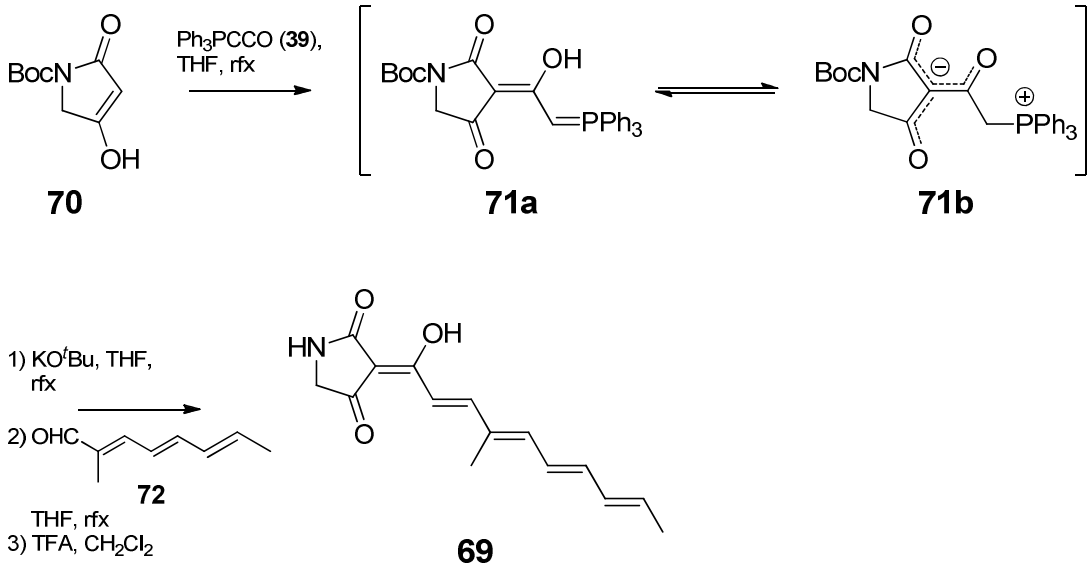
The acyl migration can also be triggered by using acetone cyanohydrin and NEt_3.[81] This method was studied in detail by Moloney *et al*.[77] It was concluded that the efficiency of this procedure strongly depends on the tetramic acid's *N*-substituent (R^1) (**61**) and the residue introduced by the carboxylic acid (R') (**62**). Even so, it is a powerful alternative, especially if aromatic carboxylic acids are used for 3-acylation. In this thesis, this fact was exploited for the total synthesis of quinolactacins A2 (**17**) and B2 (**18**) (chapter 3.3.3).

2.1.4.4 Synthesis of 3-enoyl- and 3-polyenoyltetramic acids

As described in the previous chapters, the synthesis of 3-enoyl- and 3-polyenoyltetramic acids cannot be achieved by standard 3-acylation methodology or only in very low yields. Therefore specialised reactions were developed to address this problem.[82–84]

2.1.4.4.1 3-Acylation using ketenylidene(triphenyl)phosphorane

The same reagent (**39**) mentioned in chapter 2.1.3.2 for the synthesis of tetramic acids can be used to prepare 3-enoyltetramic acids in a two-step procedure. This method was used to synthesise ravenic acid (**69**) for the first time (scheme 2.12).[85] In the first step of the mechanism Boc-protected tetramic acid **70** protonated **39** and then the protonated species of **39** is nucleophillically attacked by the tetramate anion. This formal addition produced 3-acylylide **71**, which was readily purified. As well known, it is stable because of the delocalisation of its electrons.[86] In the second step, **71** was activated to undergo a Wittig reaction with aldehyde **72** by heating it with KO^{t}Bu. After deprotection with trifluoroacetic acid (TFA), **69** was synthesised in a yield of 61% starting from **70**.



Scheme 2.12 Synthesis of ravenic acid (**69**) by 3-acylation via Ph_3PCCO (**39**) and subsequent Wittig olefination[85]

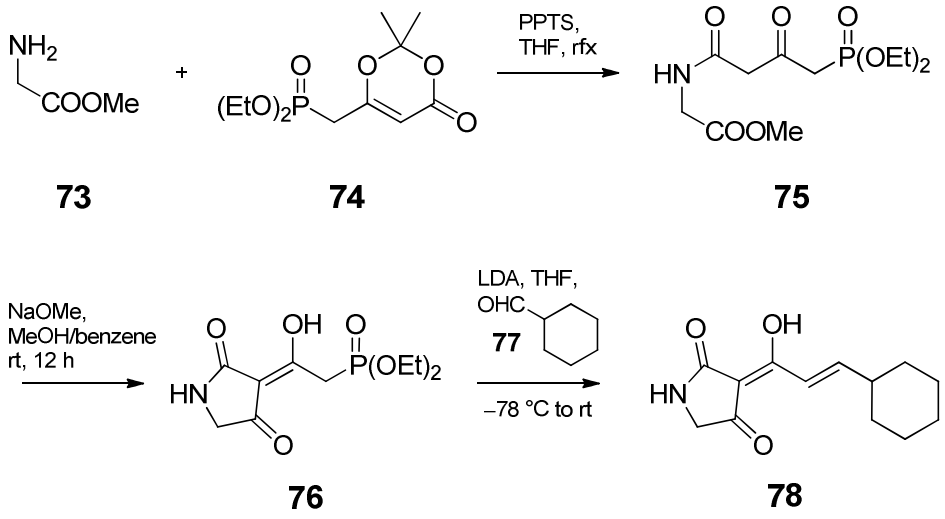
2.1.4.4.2 Specialised Lacey-Dieckmann condensation

In general, Lacey-Dieckmann cyclisations generate 3-acyltetramic acids (chapter 2.1.4.1). This variant uses a β-ketoamide, which is modified to incorporate a phosphonate for a subsequent HWE reaction following the Dieckmann cyclisation.[87]

Scheme 2.13 shows an example, starting with glycine methyl ester (**73**) and phosphonate **74** to give modified β-ketoamide **75**. **75** was converted to phosphonate

substituted 3-acyltetramic acid **76** via Dieckmann cyclisation. In the next step, a HWE reaction was performed, using cyclohexanal (**77**), yielding enoyltetramic acid **78** in a yield of 71%.

The method was modified over the years,[88] and due to the mild conditions and flexibility, used extensively for the synthesis of natural products.[89,90]



Scheme 2.13 Lacey-Dieckmann condensation of modified β-ketoamide **75** and subsequent HWE reaction

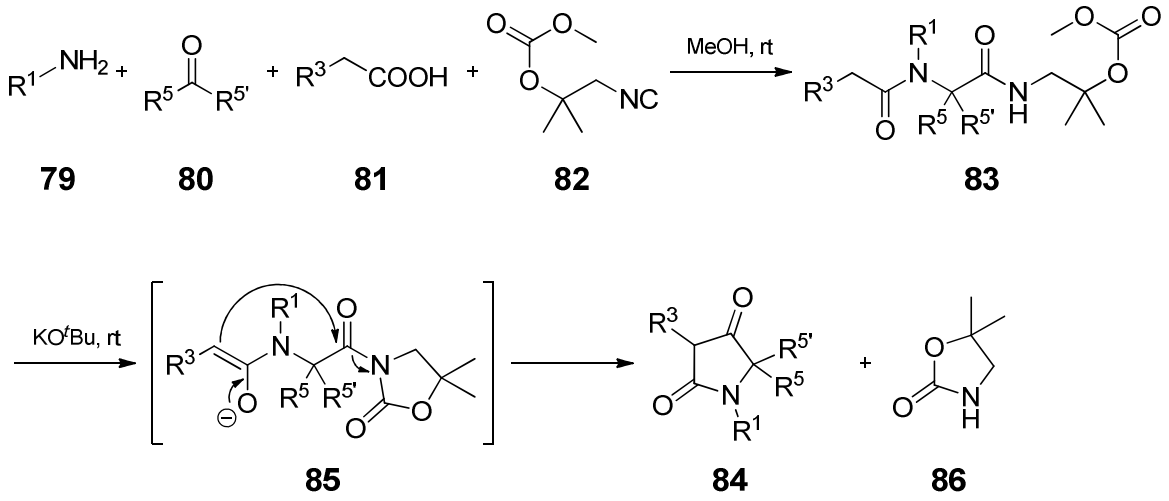
2.1.5 Chemical syntheses - special syntheses of tetramic acid derivatives

2.1.5.1 Polyfunctional tetramic acids synthesised via Ugi-Dieckmann reaction

A versatile and combinatorial synthesis of tetramic acid derivatives can be achieved by an Ugi reaction and subsequent Dieckmann condensation.[91] The advantage of the Ugi reaction is that it is a modular multi-component reaction. Many different residues can be introduced simultaneously.[92]

The variant of this reaction to synthesise tetramic acids starts with four typical components: amine **79**, carbonyl compound **80**, α-CH acidic carboxylic acid **81** and isocyanide **82** (1,1-dimethyl-2-isocyano-ethyl-methylcarbonate) (scheme 2.14). They are combined to form the desired Ugi product **83**. Similar to the Lacey-Dieckmann

cyclisation, the conversion of **83** to tetramic acid **84** is induced by adding a strong base. This leads to intermediate **85**, which loses 5,5-dimethyl-oxazolidin-2-one (**86**) by a nucleophilic attack of the enolate, in a Dieckmann like cyclisation. Different tetramic acid derivatives are obtained using this methodology in low to excellent yields.[91]



79 **80** **81** **82** **83** **85** **84** **86**

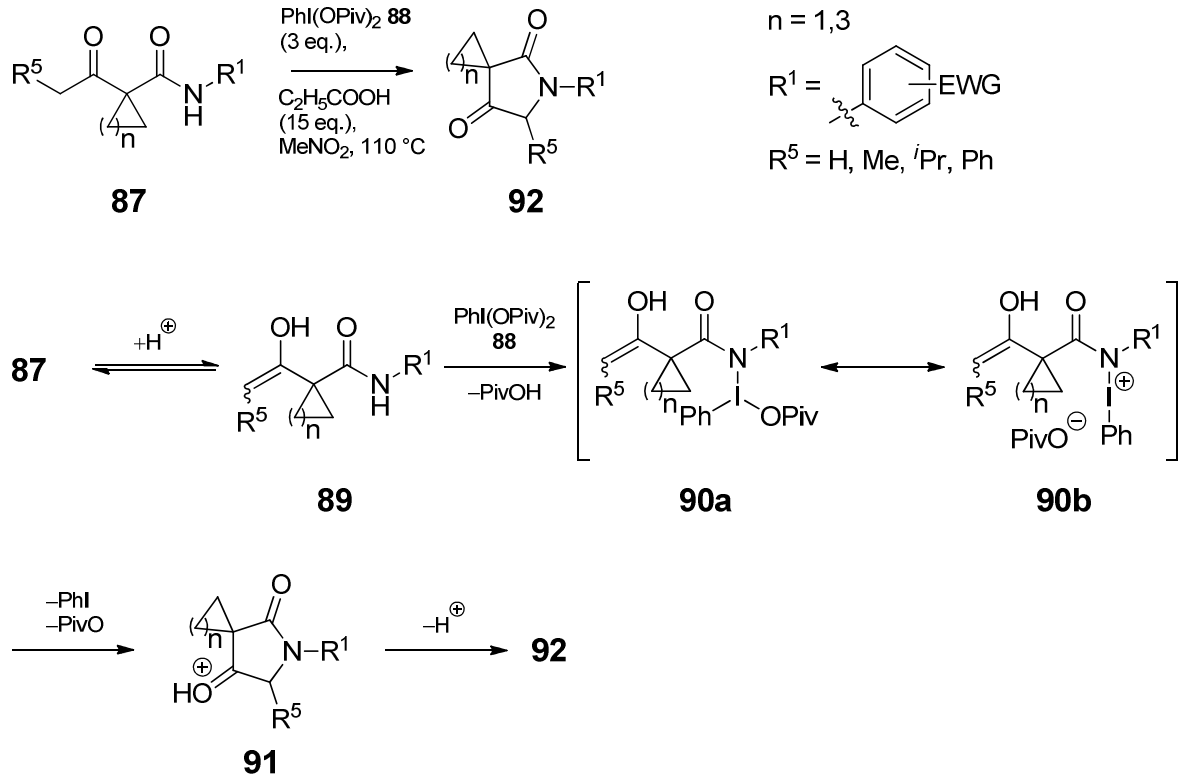
R^1	R^3	R^5	$R^{5'}$	Yield (%)
Bn	H	^{i}Pr	H	54
Bn	Ph	Me	H	84
Bn	Ph	Me	Me	23
C_7H_7O †	Ph	Me	Me	11
C_3H_7O*	Ph	^{i}Pr	H	88

Scheme 2.14 Modular synthesis of tetramic acid derivatives using an Ugi-Dieckmann multi-component reaction;[91] †4-$CH_3OC_6H_4$; *$(CH_2)_2OCH_3$

Due to its modular nature and the mild conditions applied, this approach is a valuable alternative to other synthetic methods. A drawback is that not all residues are tolerated. As shown above, the wrong combination of residues leads to a significant decrease in yield. Moreover, the stereocenter at C-5 cannot be set.

2.1.5.2 Synthesis of *N*-aryl-3-spirotetramic acids

A new synthesis of *N*-aryl-3-spirotetramic acids using hypervalent iodine (III) reagents was published by Mao *et al.* in 2013.[93]



Scheme 2.15 Synthesis of *N*-aryl-3-spirotetramic acids **92** according to Mao *et al.*[93]

The general reaction sequence shown in scheme 2.15 starts with the use of different 1-acetyl-*N*-aryl carboxamides (**87**), incorporating either a cyclopropane or a cyclopentane moiety. It is important that the aryl component of **87** bears an electron withdrawing substituent. The carboxamides **87** are reacted with the hypervalent iodine (III) compound bis(*tert*-butylcarbonyloxy)iodobenzene (**88**) and propionic acid. Under acidic conditions **87** undergoes keto-enol tautomerism to enol **89**. Reaction with **88** leads to intermediate **90**, which, in the next step, forms the tetramic acid core structure **91**. By deprotonation desired *N*-aryl-3-spirotetramic acid **92** is obtained.[93]

This reaction is the first example of a synthesis of tetramic acids via metal-free intramolecular sp^3 C−H amination. It shows that several residues at C-5 can be introduced but without the ability to control the stereochemistry.

2.2 Projects of the thesis

2.2.1 Macrocidins A and B

2.2.1.1 Structure and biological properties

Herbicides are important compounds in protecting agricultural crop from pest plants and other parasitic plants. Therefore it is essential that a herbicide selectively targets a pest plant, without interfering with the desired growth of a crop plant.

Some tetramic acid natural products are known to exhibit phytotoxicity and therefore could potentially be used as herbicides.[94] Two prominent representatives are macrocidin A (**5**) and macrocidin B (**93**) (figure 2.7).

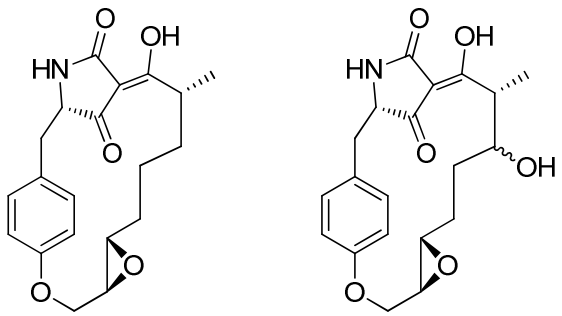


Figure 2.7 Structures of macrocidin A (**5**) and B (**93**)

The macrocidins were the first macrocyclic 3-acyltetramic acids to incorporate a tyrosine unit. They were isolated from the fungus *Phoma macrostoma* Montagne by Graupner *et al.* in 2003.[95] This fungus causes chlorotic leaf spots and necrosis on woody and herbaceous plants and black rot of artichoke leaves. **5** and **93** were isolated as major metabolites and their structure was determined by a combination of 1D- and 2D-NMR spectroscopic and mass spectrometric methods. In the case of **5**, this was supported by its crystal structure. The stereocenter of the hydroxyl group of **93** is not yet determined, whereas the coupling constants suggest a synclinal position of the respective hydrogen towards the hydrogen, situated at the neighbouring tertiary carbon.

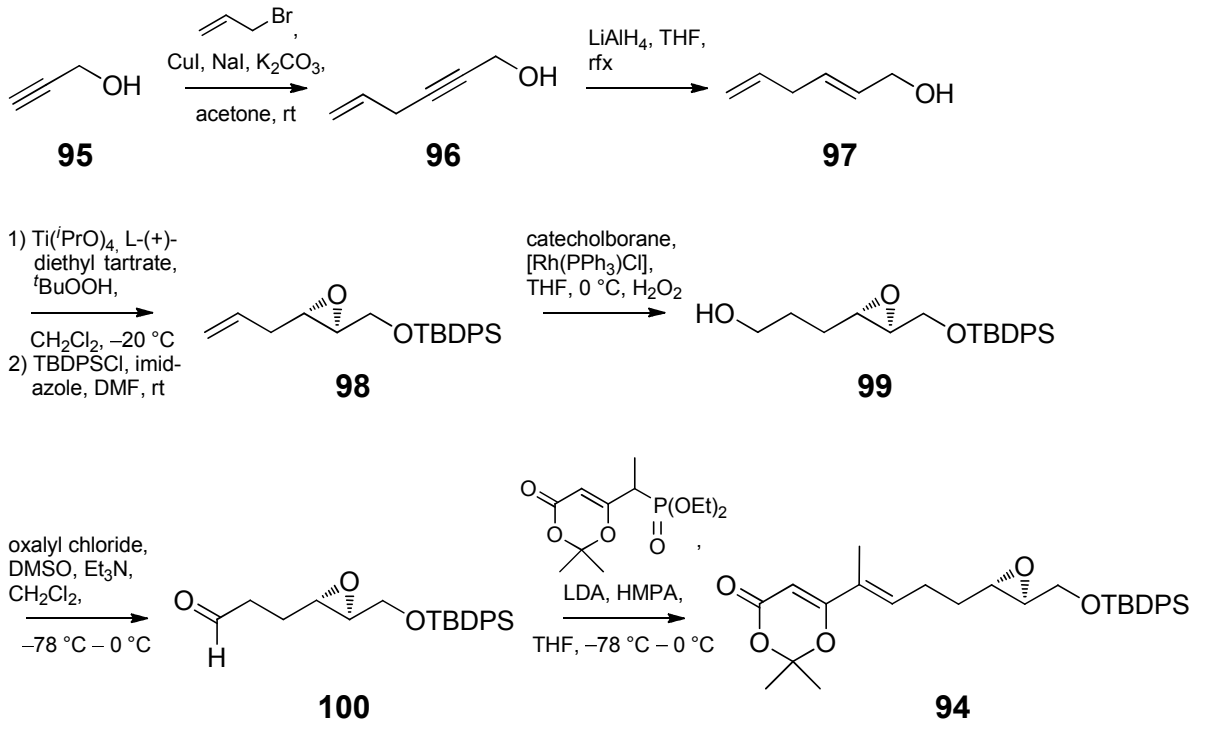
The purified samples of **5** and **93** were tested for any effects on plants. If the soil was treated preemergently with *Phoma macrostoma*, emerging leaves of a Canada

thistle showed strong signs of chlorosis and bleaching. The plant's growth was severely impaired. When applying the samples postemergently to other plants, it was observed that only broadleaf weeds were gravely affected, partly leading to the plants' death, whereas the grass weeds were left completely unharmed. The mode of action of these compounds is still unknown, although a unique mode of distribution inside the plant has been suggested.[95] This selectivity and possible mode of distribution make the macrocidins interesting for the beginning of the development of new herbicides. **5** and **93** are patented as usable herbicides since 2010.[16,96]

To date, only one total synthesis[69] and two partial syntheses[97,98] of **5** have been achieved (see chapter 2.2.1.2), whereas there has been no publication of a synthesis of **93**.

2.2.1.2 Strategies for the synthesis of macrocidin A

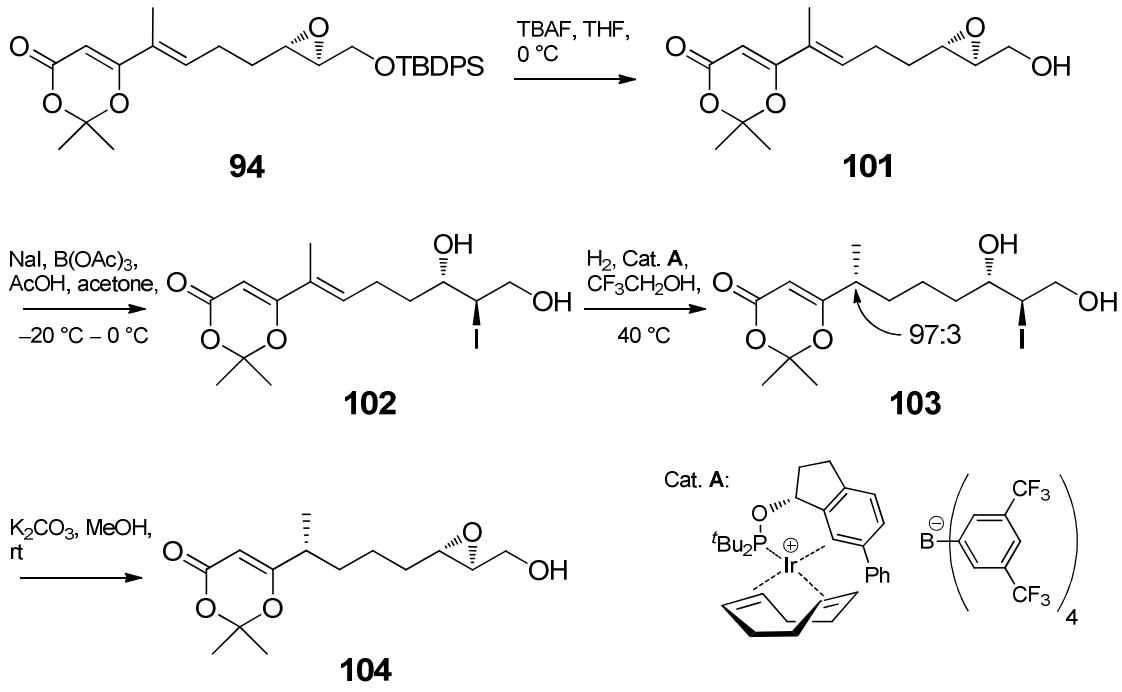
The only total synthesis to date, was published by Suzuki and Pfaltz *et al*. in 2010.[69] The key steps of this synthesis involved a stereoselective hydrogenation, a macrolactamisation and a Lacey-Dieckmann cyclisation to generate the 3-acyltetramic acid moiety.



Scheme 2.16 Synthesis of trisubstituted olefin building block **94**

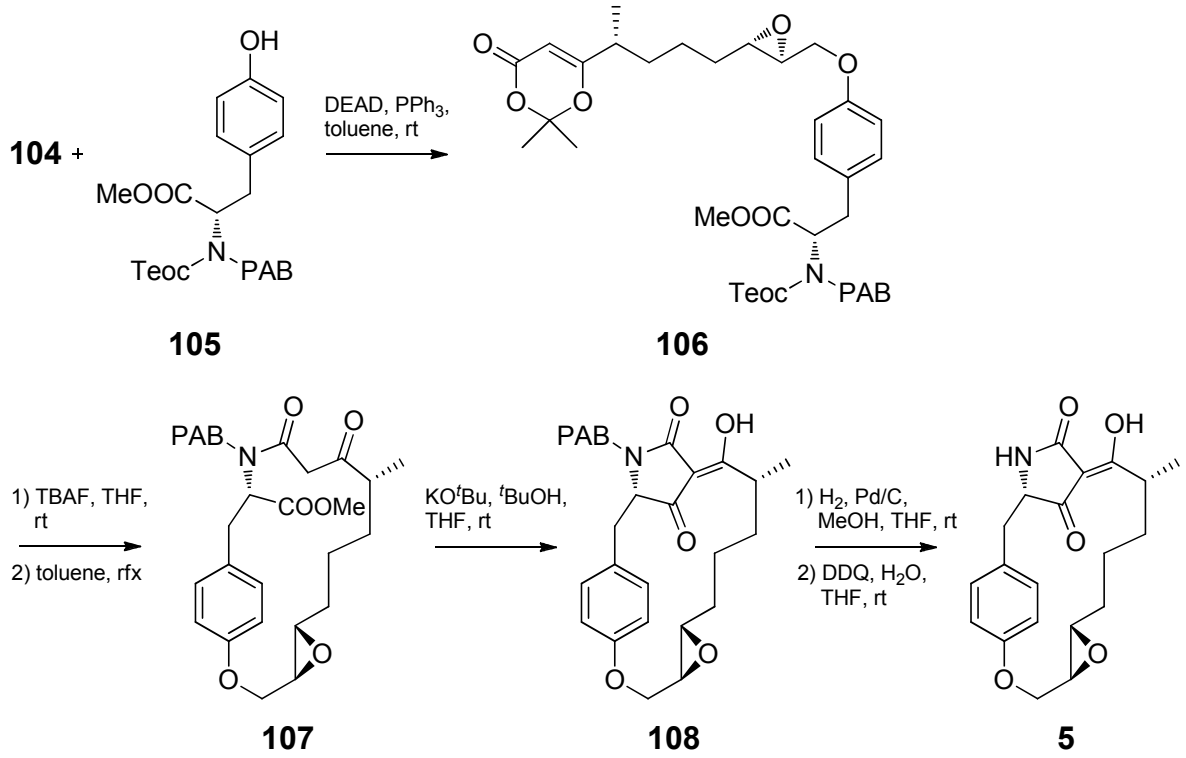
Scheme 2.16 shows the preparation of trisubstituted olefin building block **94**, incorporating the required epoxide. Propargyl alcohol (**95**) was transformed into compound **96** by copper mediated coupling with allyl bromide and alkine **96** was subsequently reduced with lithium aluminium hydride ($LiAlH_4$) to allylic alcohol **97**. The epoxide of **98** was introduced by asymmetric Katsuki-Sharpless epoxidation followed by silyl protection. Hydroboration of **98** to alcohol **99** and Swern oxidation to aldehyde **100** was followed by Horner-Wadsworth-Emmons (HWE) reaction to furnish olefin **94**.

The next step, being stereoselective hydrogenation of the trisubstituted olefin could not be achieved using substrate **94**. Therefore, a detour was necessary (scheme 2.17), starting with silyl deprotection to generate **101**. The epoxide was opened to give 1,3-diol **102** with excellent regioselectivity, before the hydrogenation was carried out to give **103** with formidable stereoselectivity (97:3). For this process iridium catalyst **A** was used successfully. In the last step, the epoxide was regenerated and **104** was obtained.



Scheme 2.17 Detour of stereoselective hydrogenation of **94** to **104**

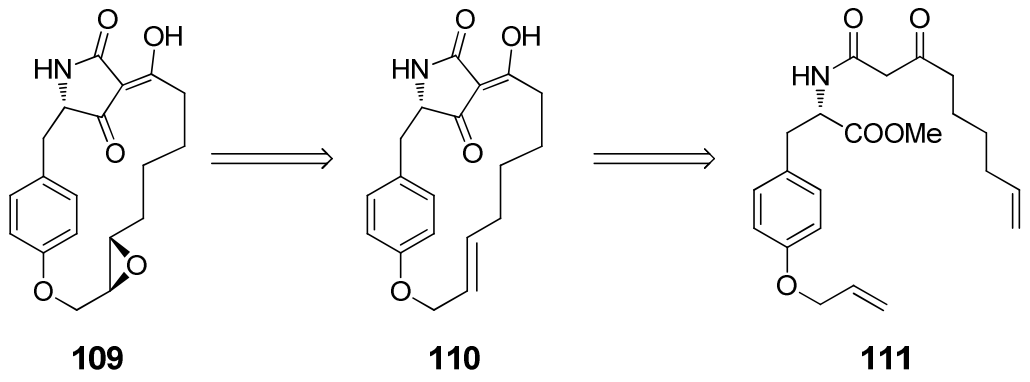
The final reactions (scheme 2.18) of the synthesis involved the coupling of building block **104** with tyrosine building block **105** via Mitsunobu reaction to **106**.



Scheme 2.18 Final steps in the preparation of macrocidin A (**5**) according to Yoshinari *et al.*[69]

From **106** the Teoc group (2-(trimethylsilyl)ethoxycarbonyl) was removed, to prepare the molecule for the subsequent macrolactamisation, which generated **107**. Lacey-Dieckmann cyclisation furnished **108** and in the last step the PAB group (*para*-azidobenzyl) was cleaved applying a two-step procedure. Overall, **5** was synthesised in a yield of 15% over 17 steps.

Papers on two other partial syntheses have been published to date.[97,98]

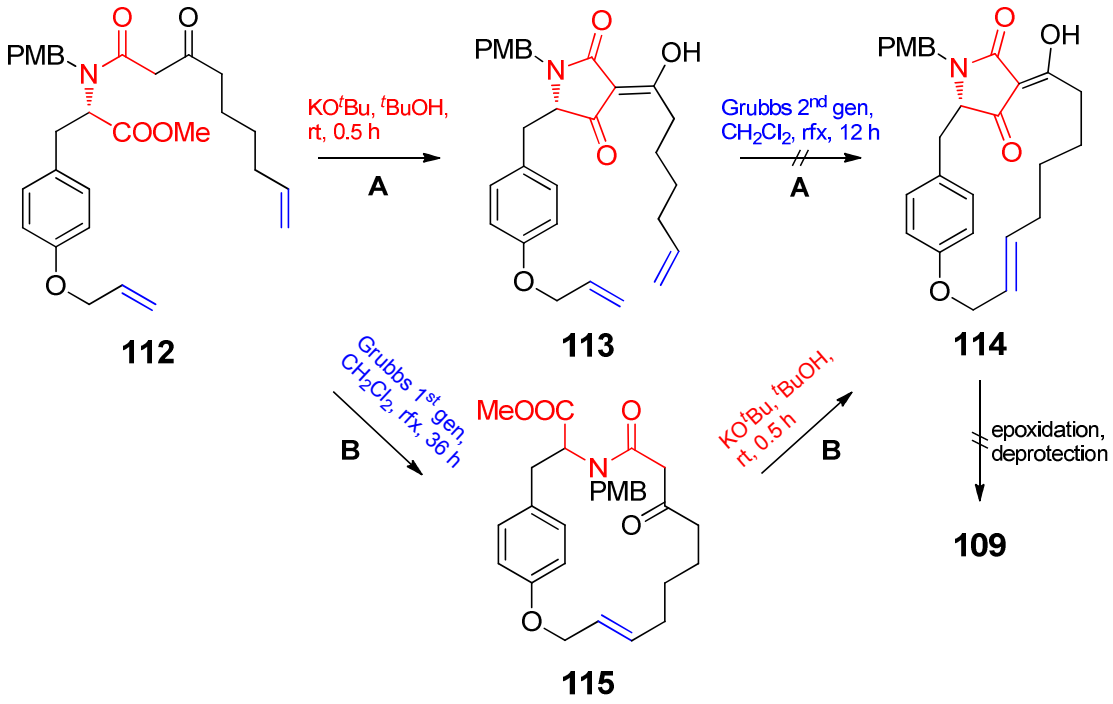


Scheme 2.19 Retrosynthetic approach to synthesise Nor-macrocidin A (**109**) according to Ramana *et al.*[97]

In the first publication of 2006 by Ramana *et al.,*[97] nor-macrocidin A (**109**), a simplified derivative of **5,** should have been synthesised (scheme 2.19). The key steps of the strategy presented were a Lacey-Dieckmann cyclisation to form the tetramic acid and a ring closing metathesis (RCM) to form the macrocycle. The epoxide should have been introduced in the last step via epoxidation of macrocycle **110**. Starting from β-ketoamide **111** Ramana *et al.* investigated whether it would be best to first generate the 3-acyltetramic acid and then to close the macrocycle (route A) or *vice versa* (route B), on the way to **110**.

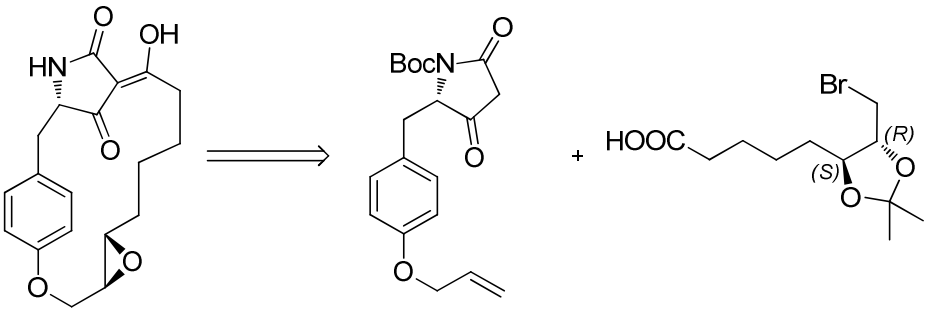
In general, they concluded that both ways could only be pursued if the amide's nitrogen remained unprotected. The critical step of both routes was the synthesis of the 3-acyltetramic acid.

As a result, both routes were tested with PMB protected β-ketoamide **112**, as shown in scheme 2.20. Route A was rejected because although 3-acyltetramic acid **113** was obtained in excellent yields of 91%, only traces of the desired product **114** were found after the RCM. On the other hand, the synthesis succeeded via route B, first generating RCM product **115** (63% yield) and then forming the tetramic acid core of **114** (56% yield). However, the final epoxidation step of the *E*-olefin could not be achieved. Only decomposition of the tetramic acid was observed.



Scheme 2.20 Attempts to synthesise nor-macrocidin A (**109**)[97]

The second partial synthesis was published in 2010 by Barnickel *et al*.[98] The synthesis was centred around a macrocyclisation via Williamson etherification. Again, Nor-macrocidin A (**109**) was the target of choice. Herein, two major building blocks were utilised, L-tyrosine derived tetramic acid **116** and ω-bromo acid **117** (scheme 2.21).

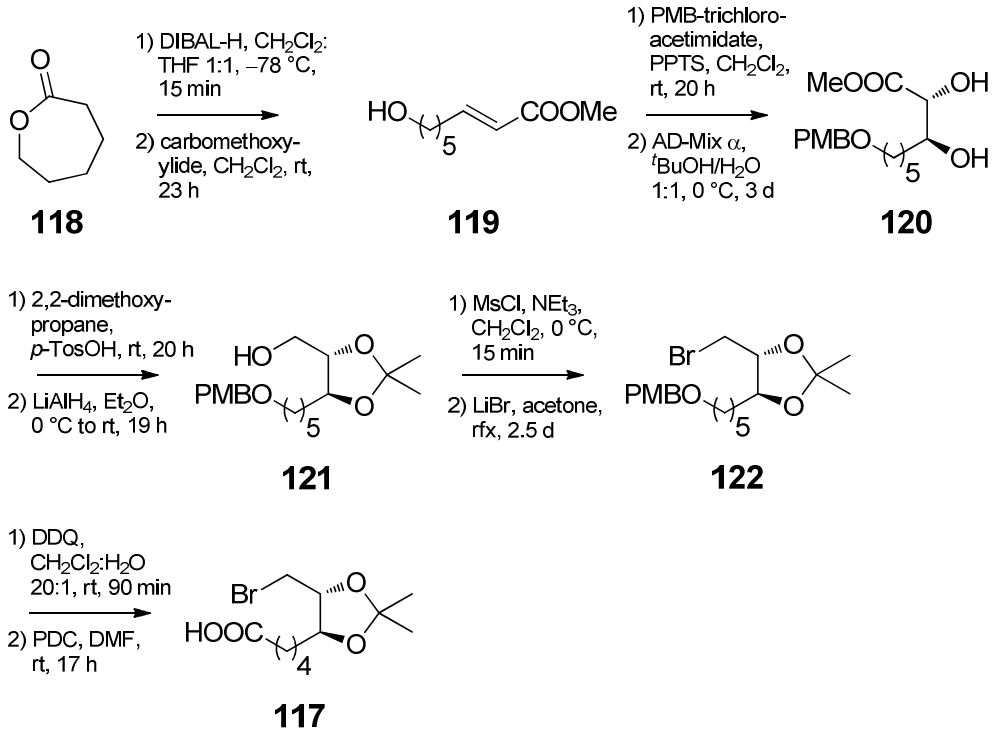


109 **116** **117**

Scheme 2.21 Retrosynthetic approach to synthesise Nor-macrocidin A (**109**) following Barnickel *et al.*[98]

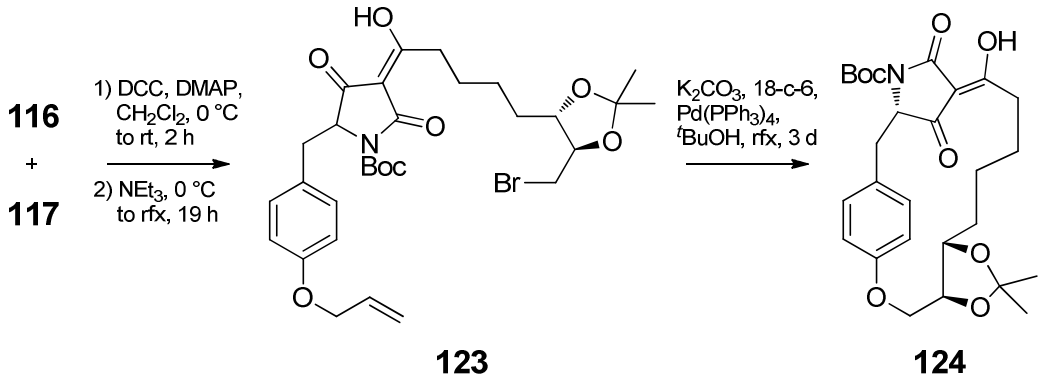
116 was synthesised following standard amino acid and tetramic acid chemistry. Boc-protection of the amino group of L-tyrosine[99], followed by allyl-protection of the phenolic alcohol[100] gave the precursor, to form **116** using the Meldrum's acid protocol (chapter 2.1.3.1).[48]

The side chain building block **117** was synthesised from ε-caprolactone (**118**) in 10 steps (scheme 2.22). In the beginning lactone **118** was opened to the respective aldehyde using diisobutylaluminium hydride (DIBAL-H) and was converted to olefin **119** via Wittig reaction. The alcohol was PMB-protected and the olefin dihydroxylated using the Sharpless dihydroxylation protocol to give diol **120**. **120** was then protected as an acetonide and the ester reduced to alcohol **121**, which was converted into bromide **122** by mesylation and subsequent bromination. The PMB-protecting group was oxidatively removed and the alcohol oxidised to form desired ω-bromo acid **117**.



Scheme 2.22 Synthesis of side chain building block **117**

The coupling of **116** with **117** was accomplished by 3-acylation using Yoshii conditions[76] (chapter 2.1.4.3) to generate 3-acyltetramic acid **123** (58% yield) (scheme 2.23). To initiate the macrocyclisation, an unprecedented palladium mediated tandem deallylation-Williamson etherification reaction was carried out. At first, the allyl-protecting group was removed using $Pd(PPh_3)_4$, followed by the nucleophilic attack of the liberated phenolate on the bromide to form macrocycle **124** (25% yield).

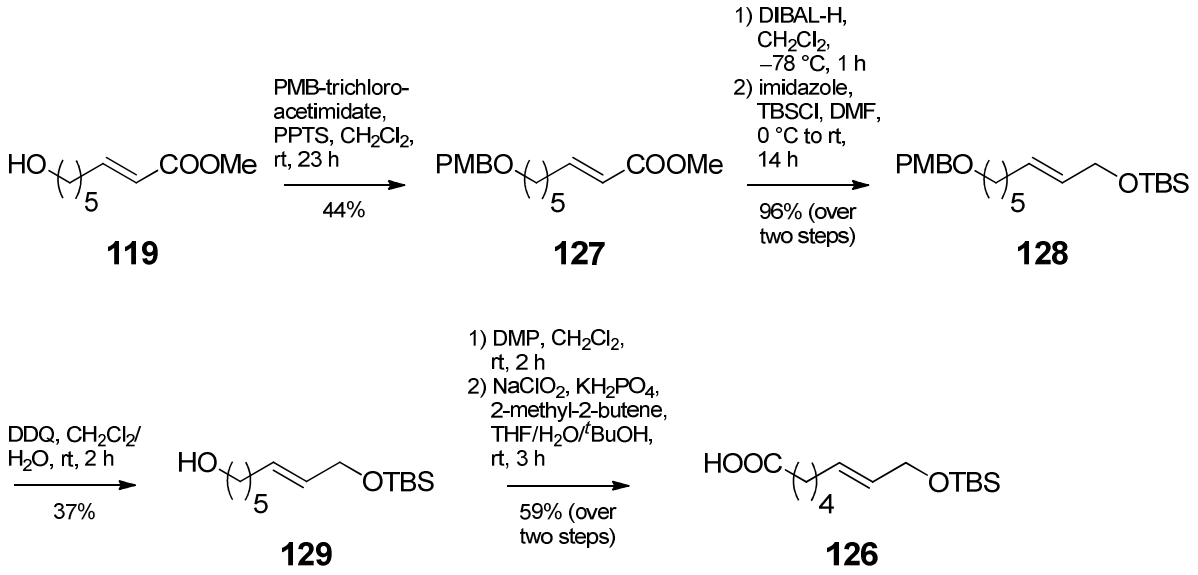


Scheme 2.23 3-Acylation and macrocyclisation to **124**

Further transformations, such as Boc-deprotection, acetonide cleavage and epoxide installation were not achieved.

A different approach to synthesise **109** was devised in M.Sc. Benjamin Christen's master's thesis, who was part of our group.[101] The main difference in his approach was that the epoxide was to be introduced after the 3-acylation occured, but before executing the macrocyclisation. At this point, the olefin of **125** should either be epoxidised directly (e.g. Sharpless,[102] Shi[103]) or dihydroxylated[104] and epoxidised in a two-step procedure.

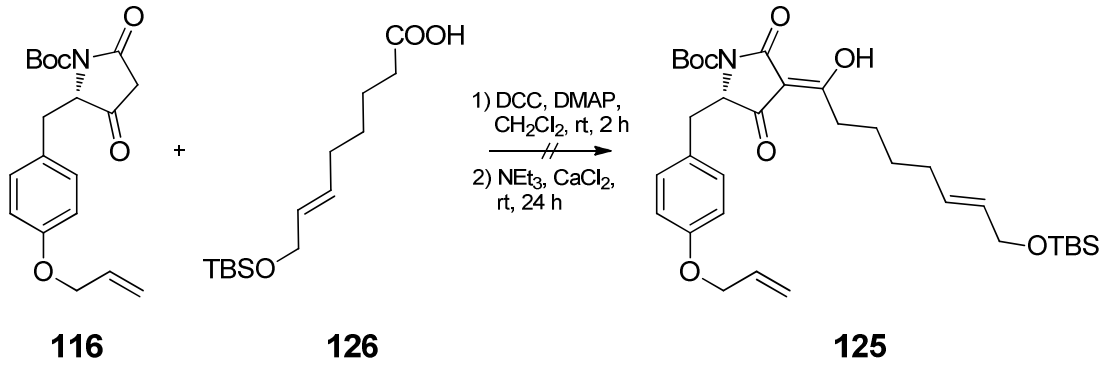
The respective side chain **126** was prepared over six steps with a yield of 9% starting from the known intermediate **119** (scheme 2.24).



Scheme 2.24 Synthesis of TBS-protected carboxylic acid **126** according to Christen[101]

This involved PMB-protection to **127**, reduction of the methyl ester moiety to the respective alcohol and subsequent TBS-protection to give **128**. The sequence was concluded by PMB-deprotection to **129** and a two-step oxidation, applying Dess-Martin-periodinane (DMP)[105] and a Pinnick oxidation[106,107] to generate **126**.

In the end the 3-acylation of **126** with tetramic acid **116** could not be accomplished (scheme 2.25).



116 **126** **125**

Scheme 2.25 Unsuccessful attempt to couple tetramic acid **116** with side chain **126** using the protocol of Yoda *et al.*[79]

2.2.1.3 Comparison of the macrocidins with other phytotoxic compounds

The macrocidins A and B are not the only tetramic acid derivatives that display phytotoxic activities.[94] Their structural diversity is as interesting as the different modes of action. Figure 2.8 shows four tetramic acids known to have an impact on biochemical processes within plants.

L-Tenuazonic acid (TA) (**25**) displays an activity spectrum ranging from growth inhibition of crop plants, such as rice plant seedlings, mung bean and radish,[108] to disruption of the metabolism of weed plants such as *Striga hermonthica*.[109] Due to its diverse activities, **25** also displays different modes of action such as the inhibition of the protein- and nucleic acid synthesis,[108] the inhibition of 4-hydroxy-phenylpyruvate dioxygenase (HPPD) (an enzyme vital to the catabolism of tyrosine in the cell)[110] and the interruption of the photosynthetic process by interfering with photosystem II (PS II).[111]

The compounds trichosetin (**130**) and equisetin (**131**) are structurally related. Nevertheless, **130** destroys cell membranes and mitochondria and thereby inhibits the growth of a variety of infected plants,[112] whereas **131** primarily suppresses germination and inhibits growth by causing necrosis, which affects the roots.[113]

A mode similar to **25** is postulated for fischerellin A (**132**), which also inhibits growth by the interaction with PS II, but not in the same manner as **25**.[114]

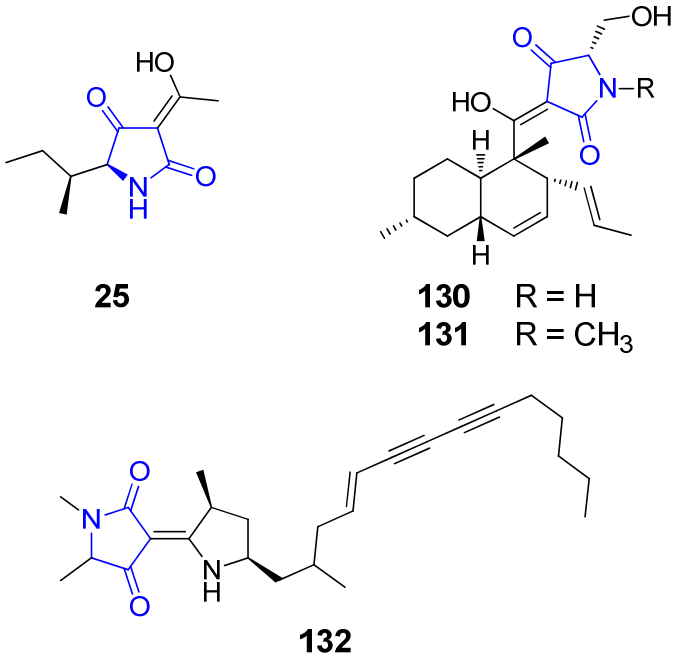


Figure 2.8 Structures of TA (**25**), trichosetin (**130**), equisetin (**131**) and fischerellin A (**132**)

If these four examples and their modes of action and selectivities are compared to the ones of the macrocidins (chapter 2.2.1.1), it can be concluded that the distinction between weed and crop plants is one of the major advantages of the macrocidins. Additionally, their unique mode of transportation inside the plant[95] makes the macrocidins a promising beginning towards developing new herbicides.

2.2.2 Torrubiellone D

2.2.2.1 Structure and biological properties

In 2010, Isaka *et al.* published a series of novel alkaloids called torrubiellone A – D (**133** – **135**, **15**) (figure 2.9).[115] These compounds were isolated from the fungus *Torrubiella* sp. BCC 2165 which targets spiders and scale insects.[116] In this thesis, a total synthesis of the tetramic acid incorporating compound torrubiellone D (**15**) was attempted. As shown in figure 2.9, **15** is a 3-polyenoyltetramic acid that can be divided into a tetramic acid part, based upon tyrosine, and a polyunsaturated side chain. Both the tyrosine part and the side chain possess a stereocenter, whose configuration is still unknown. It is likely that L-tyrosine (**16**) is used in the construction of **15** due to its availability from the chiral pool.

This group of novel alkaloids is quite similar to the class of militarinones, which were isolated in 2002[117] and 2003.[118] Militarinone C (**136**) in particular resembles **15**. The tetramic acid part is identical, only the side chain of **136** is more complex.

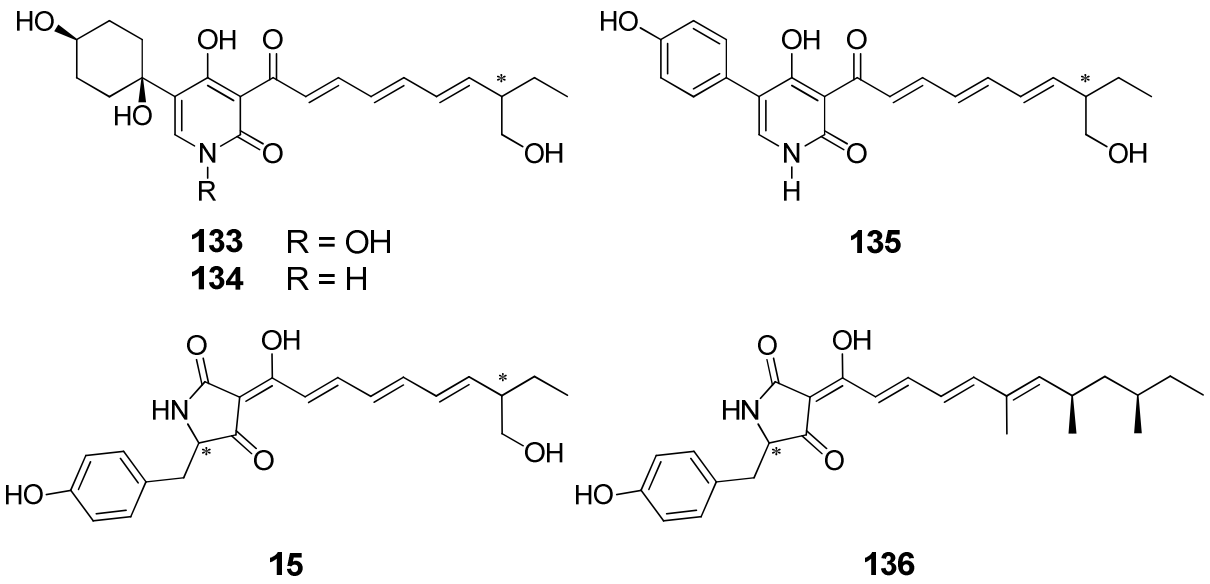


Figure 2.9 Structures of torrubiellone A (**133**), B (**134**), C (**135**) and D (**15**) and militarinone C (**136**)

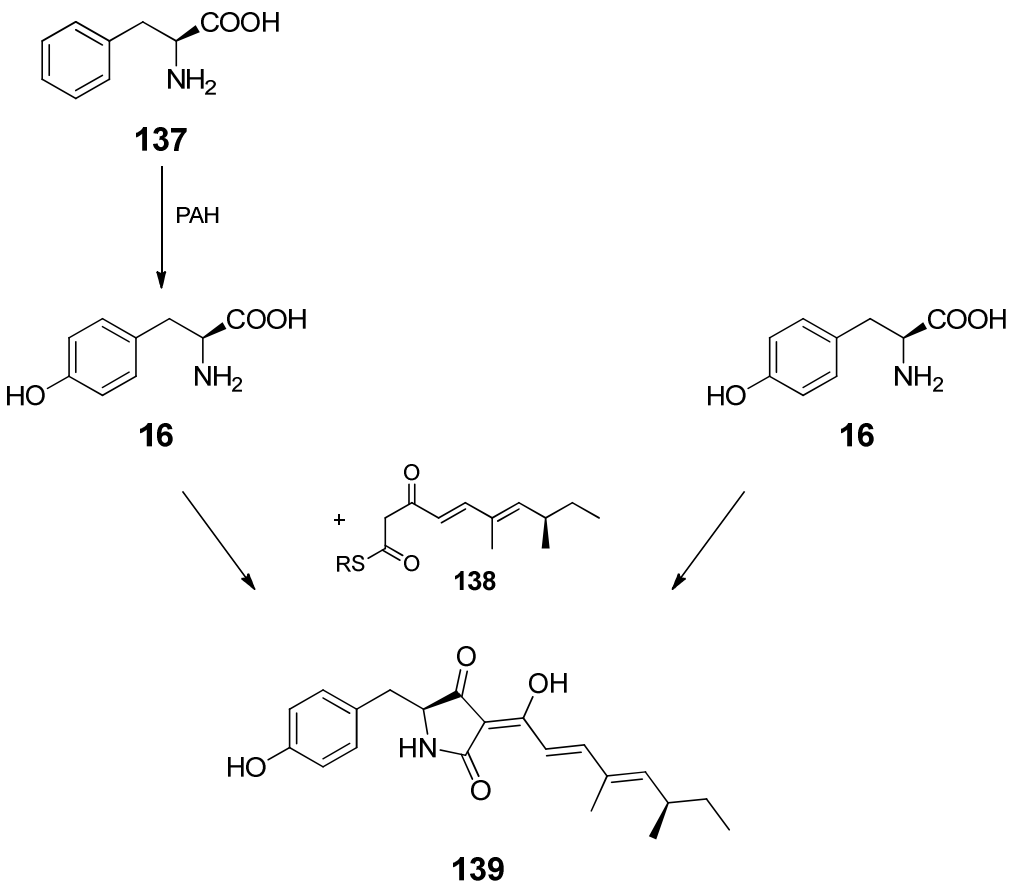
The torrubiellones were not thoroughly tested for their biological potential. **133** displays weak antimalarial activity and weak activity against cancer cell line NCI-187 and Varo cells, whereas **15** displays a weak cytotoxicity against the cancer cell line KB (IC_{50} = 44 µM).[115] The other two torrubiellones did not show any biological activity.

Up to date, a total synthesis of **135** has been published (chapter 2.2.2.3).[119] The tetramic acid part derived from L-tyrosine (**16**) was successfully synthesised in different publications,[78,98] but no 3-polyenoyltetramic acid of tyrosine has been published to date.

2.2.2.2 Proposed biosynthesis

It has been postulated that tetramic acid incorporating compound **136** is a biosynthetic intermediate towards the other militarinones.[118] Therefore it is not hard to presume that the same holds true for the torrubiellones, meaning that **15** is also a

biosynthetic intermediate on the way to **133** – **135**. This biosynthetic transformation is comprised of an oxidative ring expansion of tetramic acids to 2-pyridones.[120]

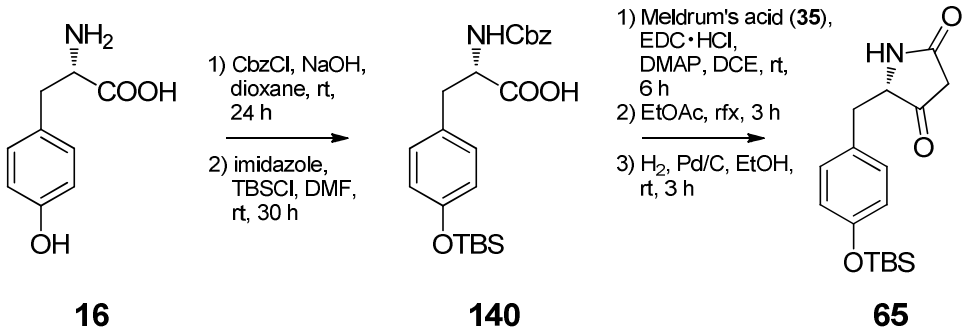


Scheme 2.26 Biosynthetis of tyrosine based 3-acyltetramic acids

The biosynthesis of the tetramic acid intermediates have been studied in detail over the last decades (see also chapter 2.2.4.1).[121,122] Scheme 2.26 shows that either L-phenylalanine (**137**) or L-tyrosine (**16**) can be included in the synthesis of tyrosine tetramic acids.[122] **16** can be used directly, whereas **137** has to be converted into **16** by a phenylalanine hydroxylase (PAH). Biosynthetic intermediate **138** (R = connectivity to the respective domain of the involved protein) is coupled with **16** to form desired tetramic acid **139**. From there, **139** can be transformed into 2-pyridones (like the ones in **133** – **135**) by an oxidative ring expansion.[120]

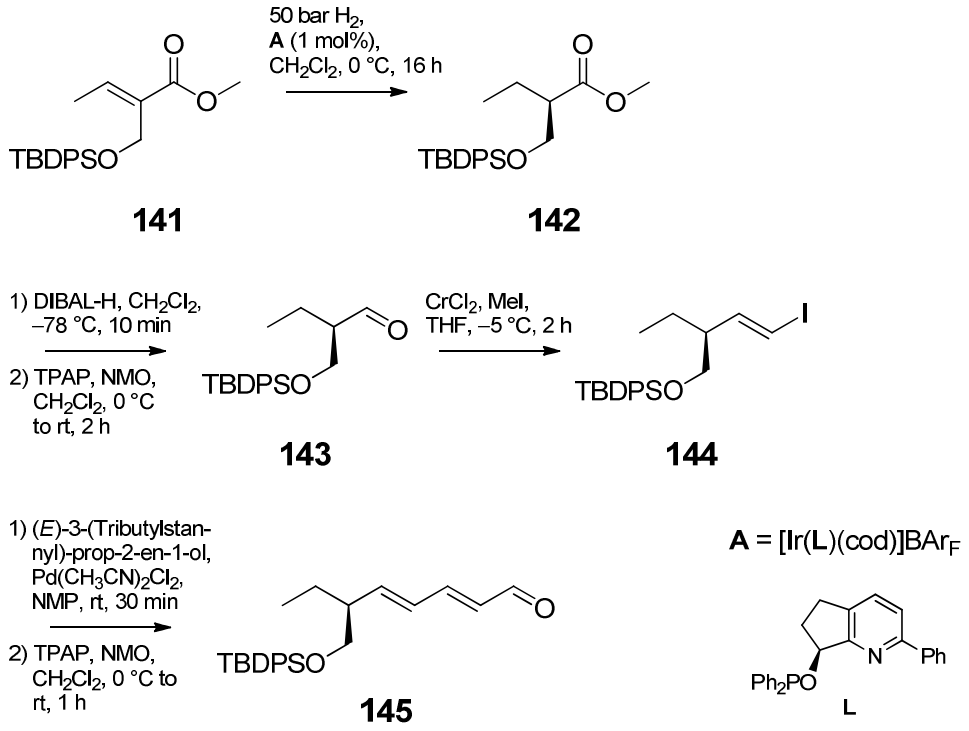
2.2.2.3 Synthetic strategies towards the torrubiellones

Since a total synthesis of **15** does not exist to date, only the syntheses of the different parts of **15** are known. In chapter 2.2.1.2, a straight forward synthesis of a tetramic acid derived from L-tyrosine (**16**) is described.[98] Another synthesis of a similar compound utilised a different protecting group strategy (scheme 2.27),[78] but in general the synthetic route is identical. L-Tyrosine (**16**) was protected twice, firstly the amine was protected with the Cbz-protecting group and secondly the phenol with the TBS-protecting group (*tert*-butyldimethylsilyl) to give precursor **140**, which was transformed into the respective tetramic acid applying the Meldrum's acid method. Cbz cleavage by palladium catalysed hydrogenation gave tetramic acid **65**.



Scheme 2.27 Exemplary synthesis of L-tyrosine derived tetramic acid **65**[78]

The side chain of torrubiellone D (**15**) was synthesised as a part of the total synthesis of **135** (scheme 2.28).[119] In the first step, the double bond of educt **141** was stereoselectively hydrogenated by the use of a specifically optimised iridium catalyst (**A**). In the next step methyl ester **142** was reduced with DIBAL-H and the alcohol transformed into aldehyde **143** by TPAP oxidation. The side chain was elongated via Takai olefination to give iodoolefin **144**. **144** was subjected to a Stille coupling with (*E*)-3-(tributyl-stannyl)-prop-2-en-1-ol to give an allylic alcohol which was oxidised to aldehyde **145** with TPAP. **145** was used in the final stages of the synthesis to be coupled to the desired core building block by HWE reaction. The same building block was used in the synthesis of torrubiellone B (**134**).[123]



Scheme 2.28 Part of the total synthesis of torrubiellone C[119]

In this thesis, the possibility of combining the two methods to develop the first total synthesis of torrubiellone D (**15**) was investigated.

2.2.3 Quinolactacins A – D

2.2.3.1 Structure and biological properties

The quinolactacins are a class of compounds isolated from *Penicillium* sp. EPF-6 by Nakagawa's group in 2000.[124,125] Three different compounds were isolated: quinolactacins A (**146**, **17**), B2 (**18**) and C2 (**147**). One year later, they discovered that quinolactacin A exists in two diastereomeric forms, called quinolactacin A1 (**146**) and A2 (**17**).[126] Both forms were isolated from *Penicillium citrinum* 90648.

In 2006, more members of this family were isolated from the same organism, namely quinolactacins B1 (**148**), C1 (**149**), D1 (**150**) and D2 (**151**).[127]

As shown in figure 2.10 the quinolactacins are closely related because they all exhibit the same core structure. A *N*-methylated quinolone frame fused with a pyrollidin-2-one unit that carries different substituents at C-5. In its entirety, the unique core structure element can be named pyrrolo[3,4-*b*]quinolone. The

diastereomeric forms **146** and **17** and compounds **147** and **149** possess a *sec*-butyl group at C-5. **147** and **149** contain an additional hydroxyl group in the same position. **148** and **18** on the other hand show an *iso*-propyl group and a hydrogen at C-5 and **150** and **151** display an *iso*-butyl group and a hydroxyl group, similar to **147** and **149**.

Studies of the pathway of decomposition of these compounds suggest that only quinolactacins A and B are real natural products, whereas C and D are decomposition products of the former two.[127]

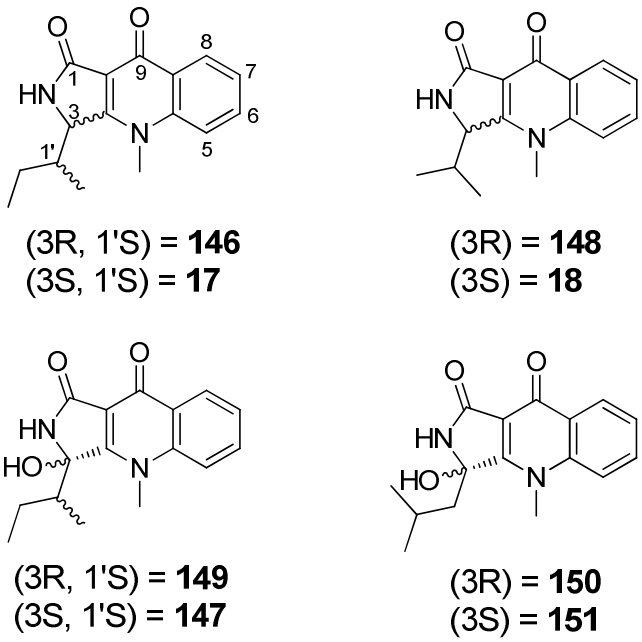


Figure 2.10 Structures of quinolactacins A1 (**146**), A2 (**17**), B1 (**148**), B2 (**18**) and C1 (**149**), C2 (**147**), D1 (**150**), D2 (**151**)

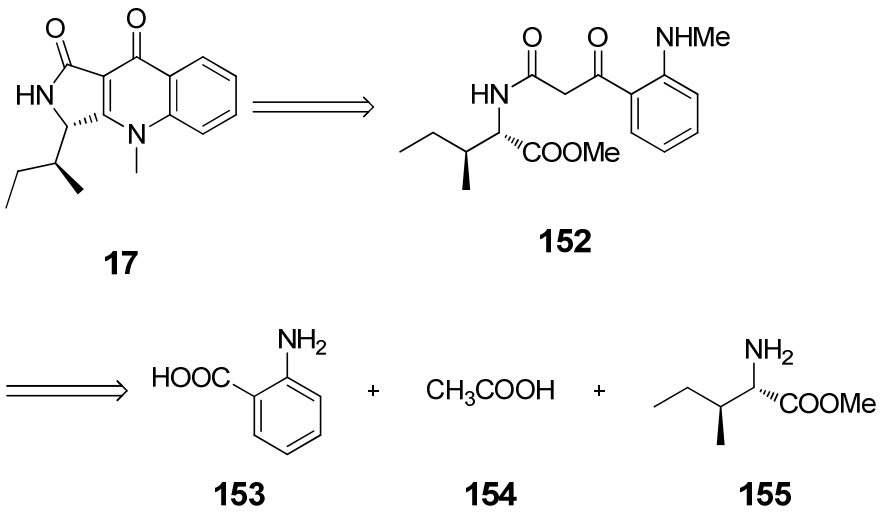
As for their biological properties, it has been reported that quinolactacins A1 (**146**) and A2 (**17**) both inhibit acetylcholinesterase,[126] which is involved in the signal transduction of neurons. This could give access to a treatment of Alzheimer-type dementia[126] because the deficit of acetylcholine is known to be one cause for this illness. It is noteworthy that the inhibitory effect of **17** (IC_{50} = 19.8 µM) is much higher than the effect of **146** (IC_{50} = 280 µM), only due to its distinct stereochemistry. In addition, **17** is proven to inhibit LPS-induced TNF production (LPS = lipopoly-saccharide, TNF = tumour necrosis factor) of murine macrophages (IC_{50} = 12.2 µM) and macrophage-like J774.1 cells.[124] TNF is one factor that causes the endotoxic shock syndrome,[128] an illness that can be fatal.

The compounds **149**, **147** and a racemic mixture of **150** and **151** were evaluated concerning their cytotoxicities against the mouse NS-1 cell line. **149** and **147** displayed moderate cytotoxicities (LD_{99} = 40 µM) and the racemic mixture (**150**, **151**) a high cytotoxicity (LD_{99} = 7.5 µM).[127] Of **148** and **18** no significant biological activities were reported.

Several total syntheses of the quinolactacins have been published to date,[129–132] and are shown in chapter 2.2.3.3.

2.2.3.2 Biosynthesis

The first assumption of how the biosynthesis of the quinolactacins might work was made in 2001.[129] A biomimetic approach to synthesise **17** and **18** lead to suggest that nature may take the same route. Scheme 2.29 depicts the retrosynthetical approach to generate **17**. Intermediate **152** is composed of anthranilic acid (**153**), acetic acid (AcOH) (**154**) and L-isoleucine methyl ester (**155**).

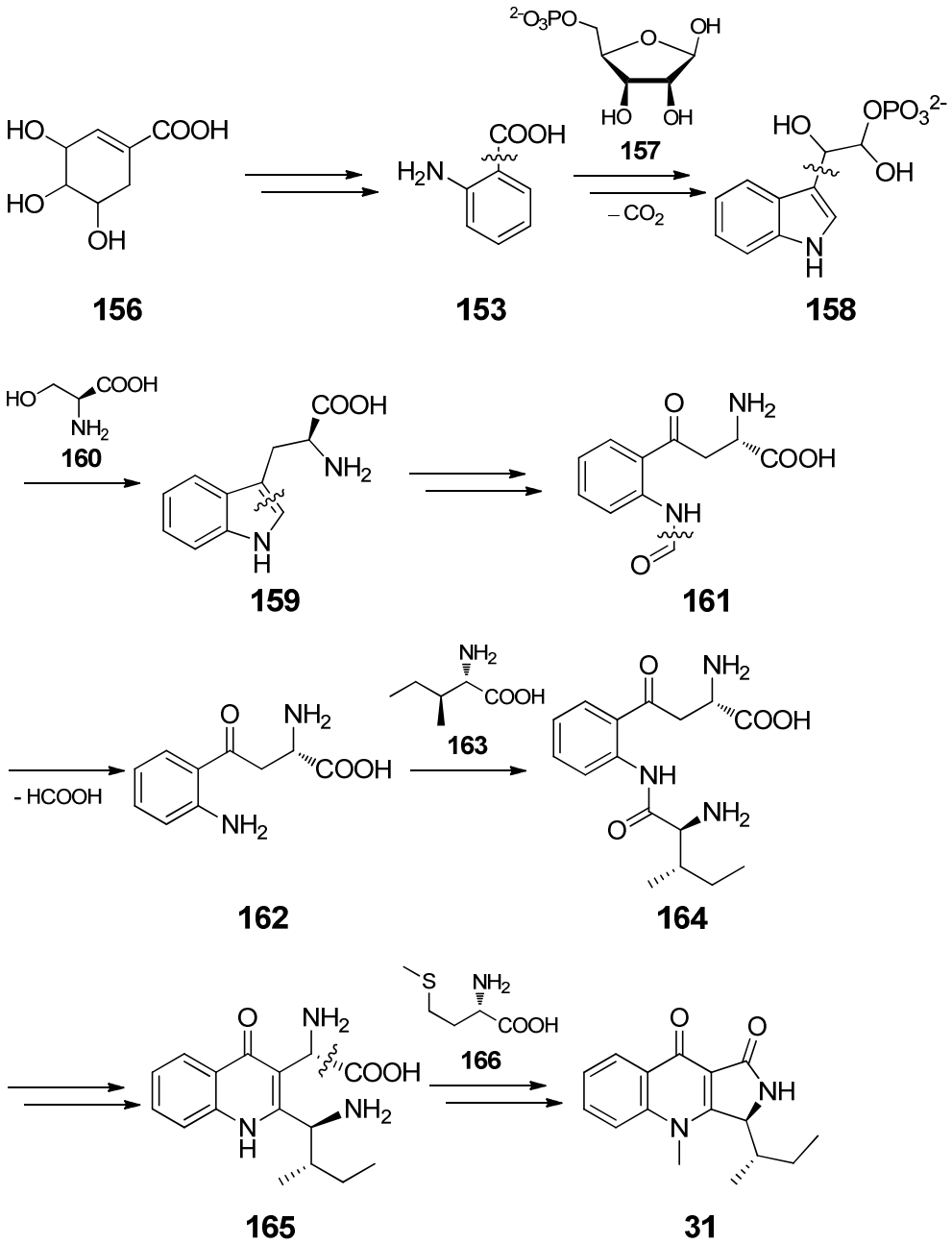


17 **152** **153** **154** **155**

Scheme 2.29 Retrosynthetic approach of a biomimetic synthesis of **17**[129]

By feeding experiments using ^{13}C labelled D-glucose and other precursor molecules Sasaki *et al.* proposed a different biosynthetic pathway.[133] As shown in scheme 2.30 anthranilic acid (**153**) was used as a starting point, being synthesised from shikimic acid (**156**) by the shikimate pathway. It was reacted with phosphorylated ribose (**157**) to form indole compound **158**. **158** was transformed into

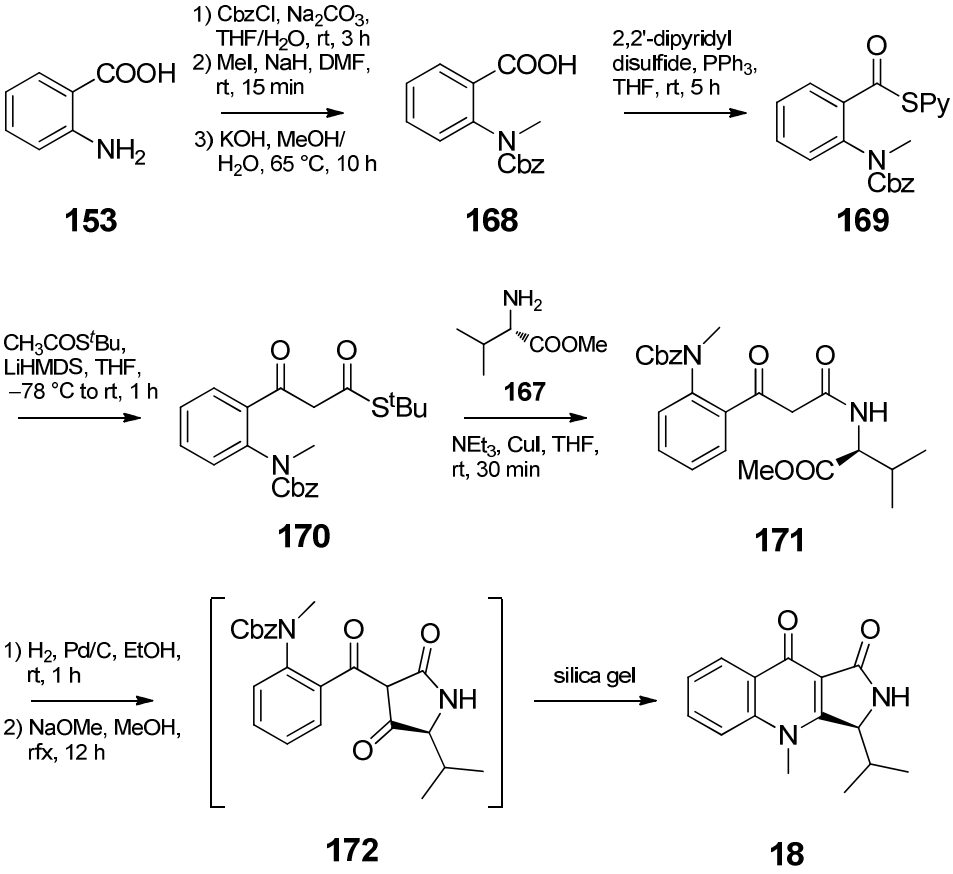
L-tryptophan (**159**) by condensation with L-serine (**160**) and catalysis by tryptophan synthetase. From there, an oxidative C-C cleavage took place to form intermediate **161** followed by *N*-deformylation to give compound **162**, known as kynurenine. In the next step, **162** was meant to undergo condensation with L-isoleucine (**163**) to **164** before cyclisation to quinolone **165** occurred. Oxidative decarboxylation lead to the formation of the lactam. To finish the process, the amine was methylated by L-methionine (**166**) as a methyl donor to create **17**.



Scheme 2.30 Biosynthesis of quinolactacin A2 (**17**)[133]

2.2.3.3 Total syntheses

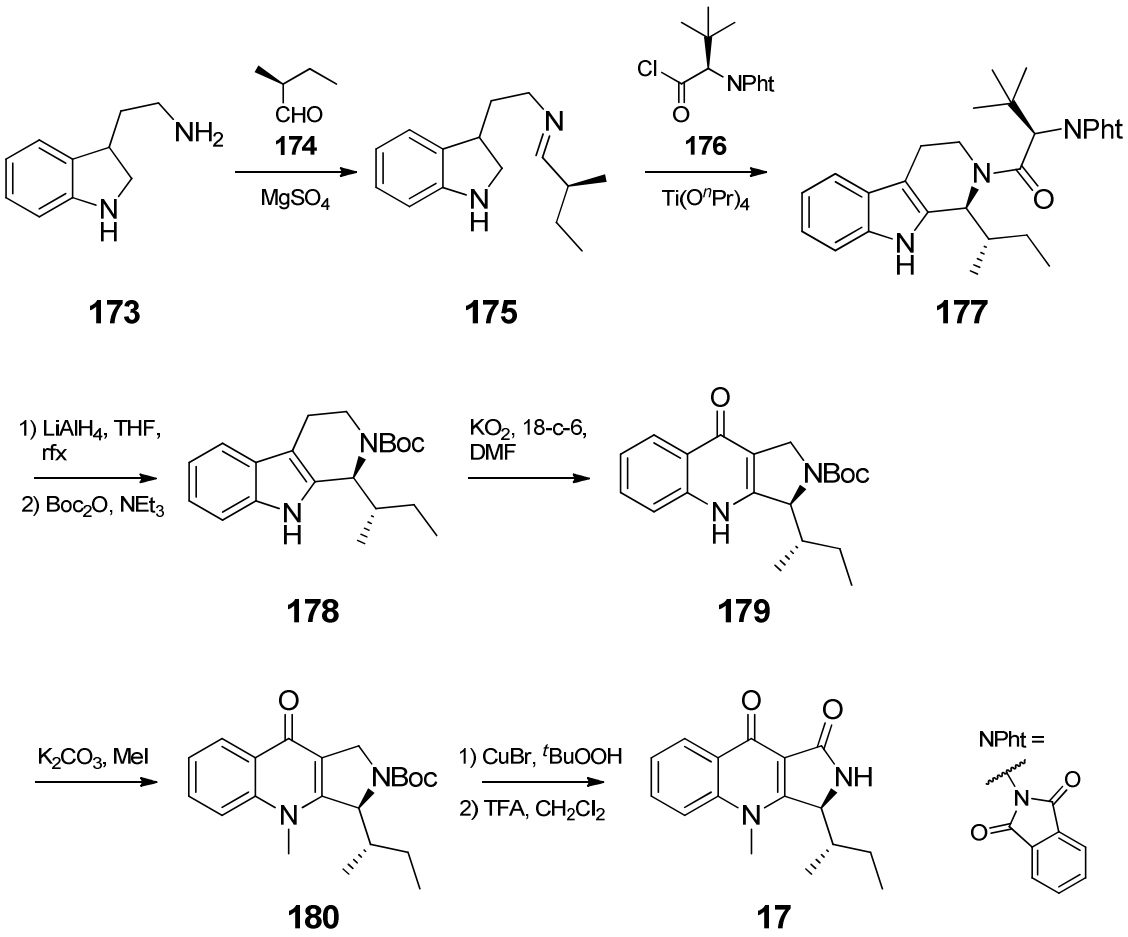
The first quinolactacin synthesised was quinolactacin B2 (**18**).[129] A biomimetic approach was chosen (as is shown for quinolactacin A2 (**17**) in scheme 2.29), using anthranilic acid (**153**), AcOH (**154**) and L-valine methyl ester (**167**).



Scheme 2.31 Total synthesis of quinolactacin B2 (**18**) by Tatsuta *et al.*[129]

Scheme 2.31 shows the synthetic route, starting with a three step procedure to convert **153** into *N*-methylated and Cbz-protected compound **168**. In the next step, the carboxylic acid was activated as its thioester analogue **169** and transformed into β-ketothioester **170** using *tert*-butyl thioacetate. Then **167** was added to generate β-ketoamide **171**, aided by copper(I)iodide and NEt_3. To obtain desired product **18**, the protecting group was removed via hydrogenolysis and a Lacey-Dieckmann cyclisation was performed to create 3-acyltetramic acid **172**, which was cyclised to **18** *in situ* by treating it with silica gel. **18** was obtained in a yield of 15% over nine steps.

The next total syntheses of quinolactacins A1 (**146**), A2 (**17**) and B2 (**18**) were accomplished by Zhang *et al.* (scheme 2.32).[130]

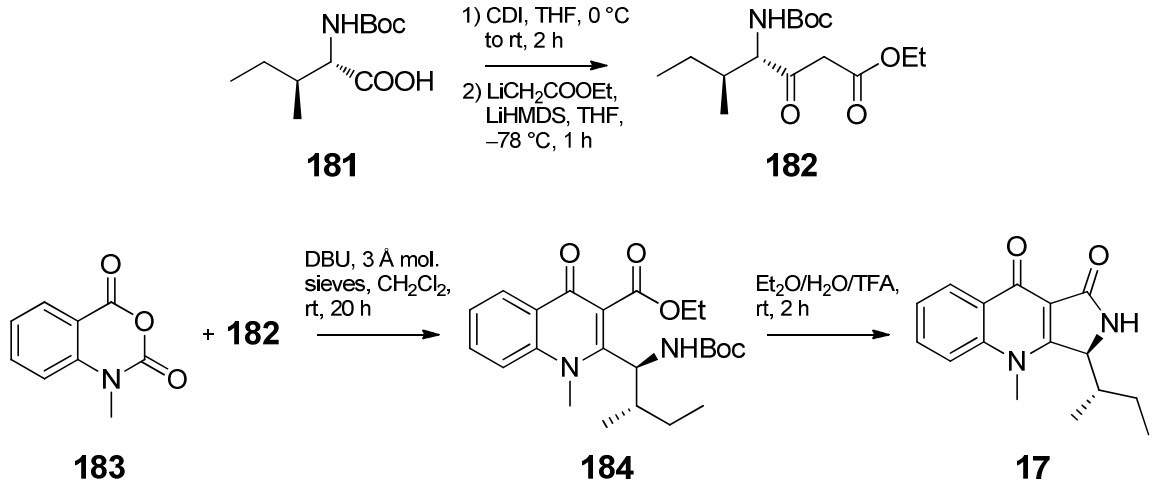


Scheme 2.32 Synthetis of quinolactacin A2 (**17**) according to Zhang *et al.*[130]

In the case of **17**, the synthesis began with the condensation of tryptamine (**173**) with (*S*)-(+)-2-methylbutanal (**174**) to Schiff base **175**. From there an asymmetric Pictet-Spengler reaction using chiral auxiliary **176** was carried out to give β-carboline **177** as the major product (*S* configuration at C-3) besides its diastereomer (*R* configuration at C-3) in a ratio of 4:1. The auxiliary was cleaved to form an amine, which was Boc-protected to give tricycle **178**. A modified Winterfeldt oxidation with potassium superoxide (KO_2) in the presence of 18-crown-6 and DMF created quinolone **179**. The following methylation of **179** gave the *N*-methylated compound **180**, which in the last steps was subjected to allylic oxidation and Boc-deprotection. **17** was obtained in 8% yield over eight steps.

Besides **17**, **18** was synthesised accordingly in 16% yield over eight steps. **146** was synthesised in small quantities, to determine the diastereomeric relationship between **146** and **17** (see chapter 2.2.3.4).

The third total synthesis was published by Park *et al*. in 2004.[131] The compound of interest was quinolactacin A2 (**17**). The synthesis is shown in scheme 2.33. Boc-protected L-isoleucine (**181**) was reacted with 1,1'-carbonyldiimidazole (CDI) to give a mixed anhydride, which was reacted *in situ* with lithio ethyl acetate to yield β-ketoester **182**.[134] The key step of this sequence was the following Friedländer annulation of **182** with *N*-methylisatoic anhydride (**183**). The resulting 4-oxoquinoline **184** was Boc-deprotected and the cyclisation to **17** took place spontaneously. Overall, **17** was obtained in a yield of 30% over three steps.

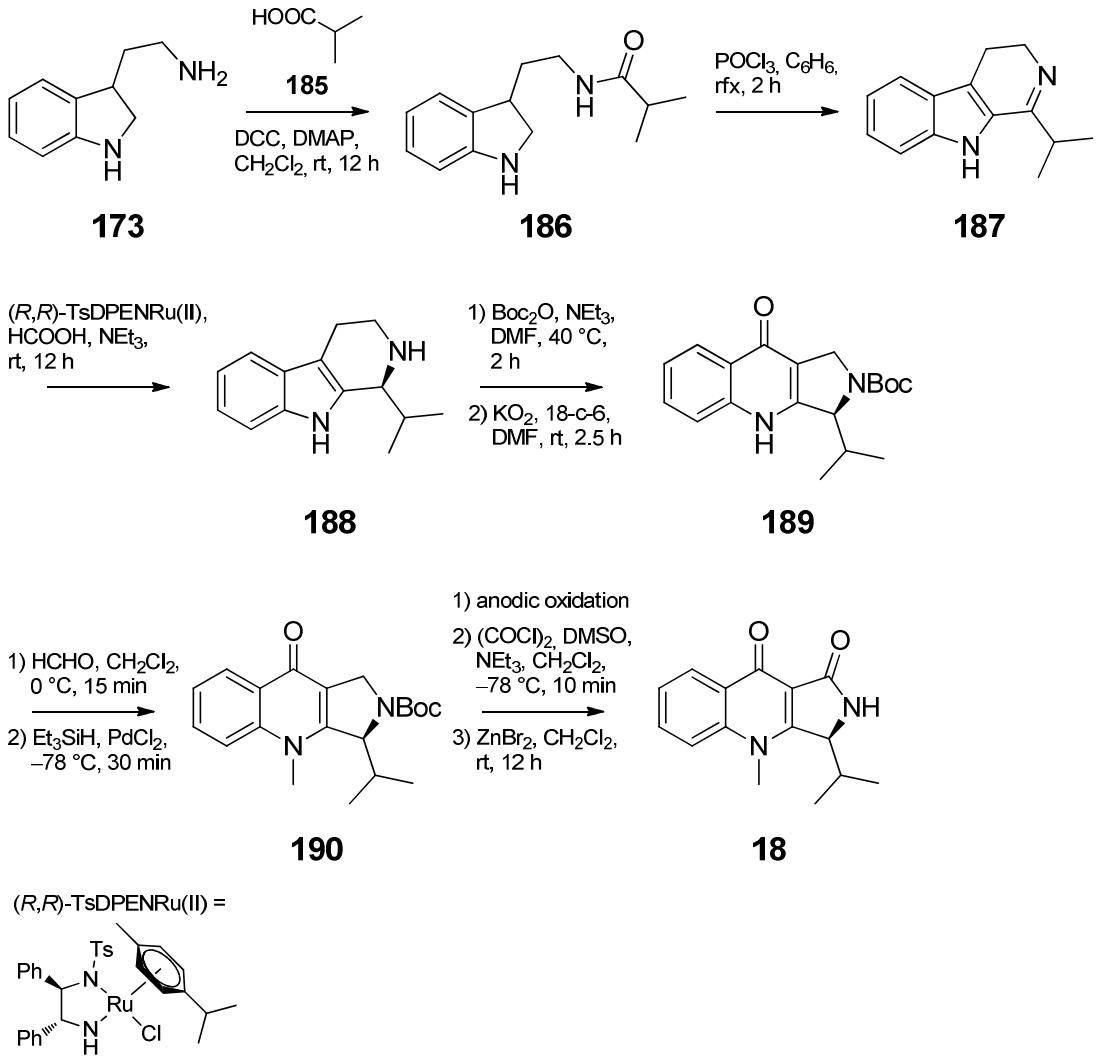


Scheme 2.33 Total synthesis of quinolactacin A2 (**17**) according to Park *et al.*[131]

The last total synthesis dealt with the synthesis of quinolactacin B2 (**18**) and was published by Shankaraiah *et al.* in 2008.[132] The key steps of this synthesis were a Noyori asymmetric hydrogenation, a Bischler-Napieralsky cyclisation and a Winterfeldt oxidation (scheme 2.34).

The synthesis began with tryptamine (**173**), which was coupled with isobutyric acid (**185**) using standard Steglich conditions to amide **186**. The next step was a Bischler-Napieralsky cyclisation to generate imine **187**. The stereocenter was installed using a hydrogenation catalyst invented by Noyori *et al.*,[135] to give compound **188** in good enantioselectivity (> 90%). Boc-protection and Winterfeldt oxidation yielded intermediate **189**, which was methylated by formylation and

reduction. From methylated compound **190**, the amide was introduced by anodic oxidation followed by a Swern oxidation and desired product **18** was liberated by deprotection with $ZnBr_2$ in an overall yield of 32% over ten steps.



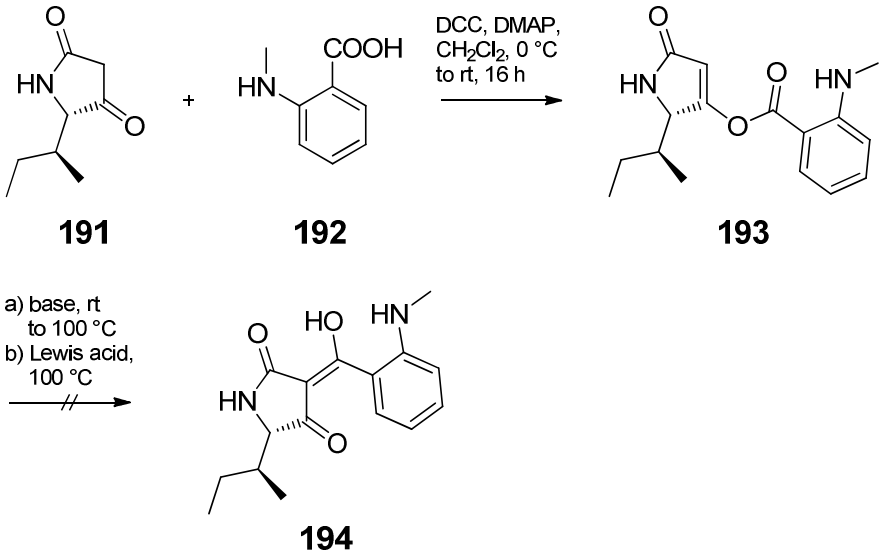
Scheme 2.34 Total synthesis of quinolactacin B2 (**18**) following Shankaraiah *et al.*[132]

2.2.3.4 Quinolactacine research in our group

In our group, Dipl. Chem. G. Rapp, Dr. C. Jagusch[136] and M.Sc. B. Christen[101] dealt with the synthesis of **17** and **18** but remained unsuccessful.

Dr. C. Jagusch synthesised unprotected L-isoleucine tetramic acid **191** using polymer bound ketenylidene(triphenyl)phosphorane (**39**).[32] 3-Acylation was carried out after the Jones acylation protocol[72,137] but the required acid chloride of

N-methylanthranilic acid (**192**) could not be obtained. 3-Acylation with **192** according to Yoshii *et al*.[76] was tested but the rearrangement of 4-*O*-acylated compound **193** to 3-acyl compound **194** was not achieved (scheme 2.35).[136]



Scheme 2.35 Attempt at the synthesis of 3-acyltetramic acid **194** according to Jagusch[136]

In another attempt, M.Sc. B. Christen used the Boc-protected version of **191** as a starting point.[101] The respective tetramic acid was created by the method of Jouin *et al.* (chapter 2.1.3.1).[48] From there, the same approach described in the section before was applied, with the same results as before. Only the 4-*O*-acylated species could be found whereas the desired 3-acyltetramic acid could not be isolated. Different approaches were attempted in achieving the Fries-rearrangement, including the use of NEt_3 and multiple Lewis acids. Additionally, one-step procedures were applied using $CaCl_2$ according to Yoda *et al.*[79] and the *N*-heterocylic carben (NHC) 1,3-dimethyl-*1H*-imidazole-2-ylidene.[138]

2.2.3.5 Detailed insight into the stereochemistry of quinolactacins

The stereochemistry of the quinolactacins has been discussed intensively over the last decade, especially the relation between the two diastereomers of quinolactacin A1 (**146**) and A2 (**17**).

When the first quinolactacins were described in 2000, only quinolactacin A2 (**17**) was isolated[124,125] but the stereochemistry was not mentioned. One year later, quinolactacin A1 (**146**) was isolated and described as a diastereomer of **17**.[126] The stereochemistry of both compounds was determined based upon NOESY spectroscopy. As a consequence, the stereochemistry of A1 (**146***) was described as *S*,*R* (C-3, C-1') and of A2 (**17**) as *S*,*S* (C-3, C-1'). Figure 2.11 shows quinolactacin A2 (**17**) and its possible two diastereomers **146** and **146***.

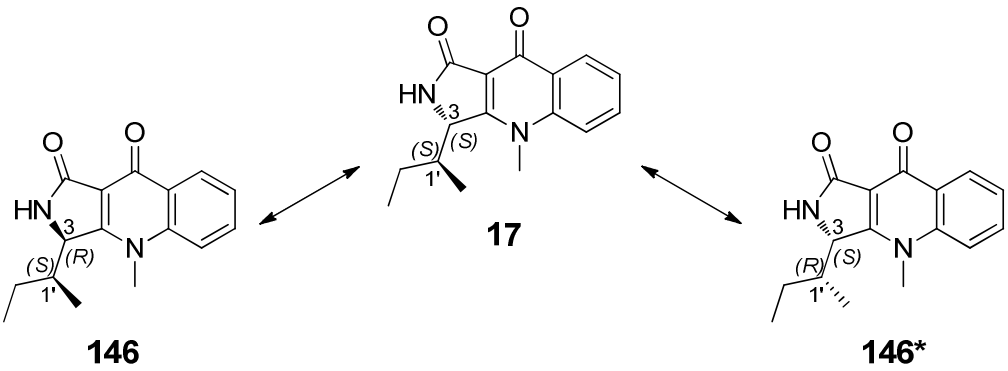
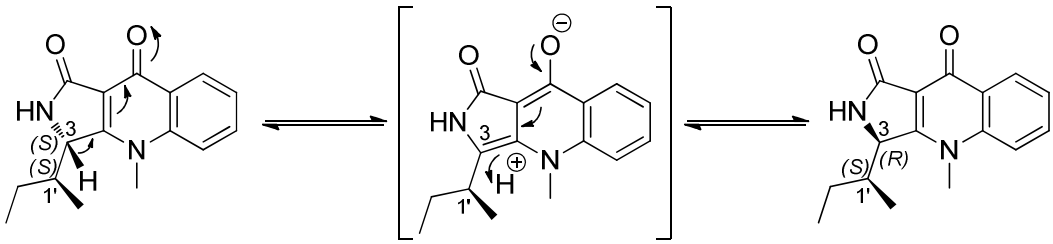


Figure 2.11 Structure of quinolactacin A2 (**17**) and its two possible diastereomeric structures of quinolactacin A1 (**146**, **146***)

In 2003, Zhang *et al.* tried to determine the stereochemistry of **17** and **146** by total synthesis (see scheme 2.33).[130] The stereocenter at C-1' was introduced by using pure (*S*)-(+)-2-methylbutanal (**174**) and set to be *S* configured. By choosing the appropriate chiral auxiliary, it was presumed that the second stereocenter at C-3 was synthetically installed as the *S*-configuration. The product's spectroscopical data was compared to the published data of **17** and found to be identical. In the following, the synthesis was repeated by using *rac*-2-methylbutanal. In doing so, C-1' diastereomers were created, which were separated by chiral HPLC. The ^{1}H-NMR data of the detected C-1' diastereomer matched the data of **146** published before. Therefore, it was concluded that **17** and **146** were C-1' diastereomers of each other and the structure was thought to be **146***.

In 2004, Park *et al.* published another stereoselective synthesis of **17** and the data was again matched with the published data of **17**.[131] It was discovered that when **17** was brought into contact with silica gel, protic solvents or acidic media, it formed its C-3 epimer **146**. The mechanism for this epimerisation and the ionic intermediate **195** are shown in scheme 2.36. The diastereomeric mixture was separated by chiral

HPLC and the desired diastereomer's spectroscopical data was identical to the published values. It was concluded that **17** and **146** must be C-3 diastereomers of each other. For the first time, structure **146** was favoured.



17 **195** **146**

Scheme 2.36 Proposed mechanism for the epimerisation of quinolactacin A2 (**17**)

The latter theory was confirmed by Clark *et al*. in 2006.[127] The quinolactacins were studied biochemically and it was concluded that both diastereomers are derived from L-isoleucine. The involvement of L-*allo*-isoleucine (required to create the structure of **146***) was denied. Furthermore, the relationship between all quinolactacins was examined. It was discovered that the two quinolactacin C epimers (**149**/**147**) can be viewed as oxidative decomposition products of the quinolactacins A1 (**146**) and A2 (**17**). Starting from **17**, all four compounds were identified after a matter of time, **146** by epimerisation and **149** and **147** by decomposition of **146** or **17** respectively. This relationship indicated that **146** was the correct structure of quinolactacin A1.

In summary, the quinolactacin diastereomeric pairs A, B, C and D can most likely be regarded as C-3 epimers of each other.

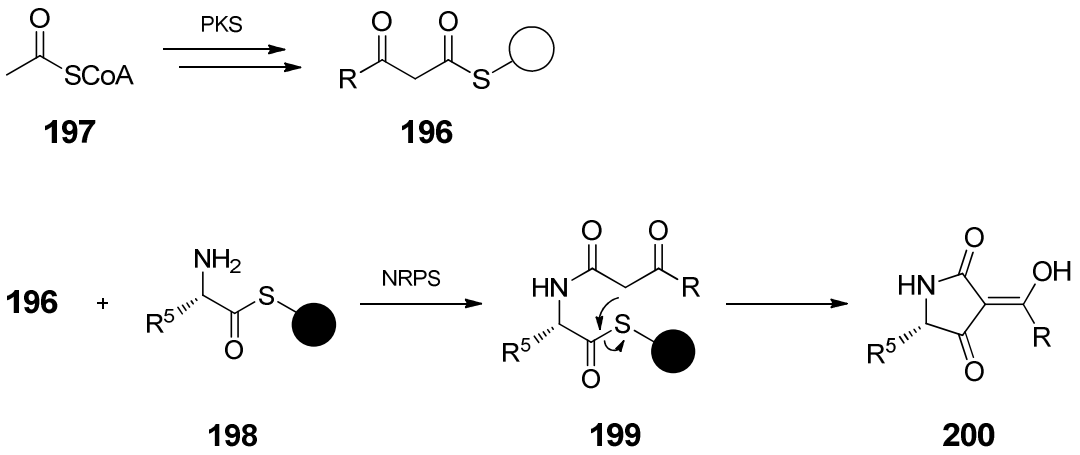
2.2.4 Biochemical role of tetramic acids and adenylyl cyclases

2.2.4.1 Biosynthesis of tetramic acids

Tetramic acids are found in many organisms and display various activities, as discussed in chapter 2.1.2. To increase the understanding of these compounds, one has to understand their origin, meaning their biosynthesis.

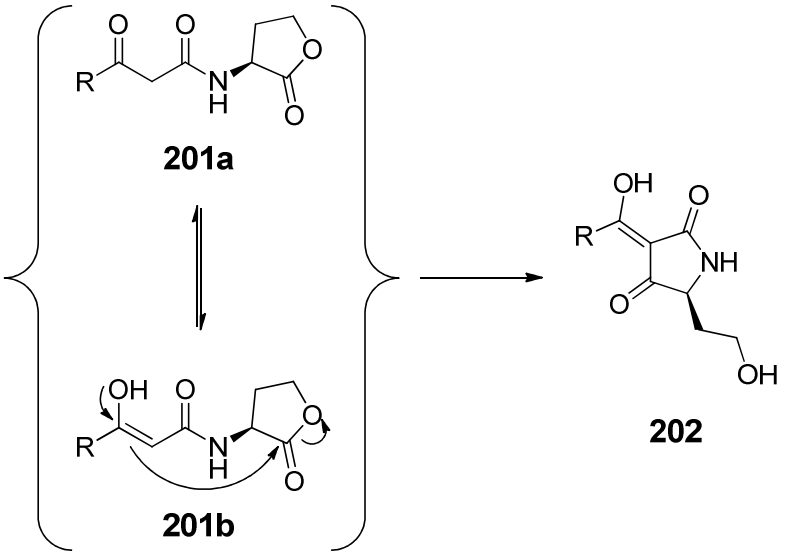
Tetramic acids are hybrid secondary metabolites. Two major pathways to produce tetramic acid metabolites in nature have so far been discovered.[19] The first one being

the combination of a polyketide building block and an α-amino acid. The whole process was studied in detail in the case of fungal tetramic acids (scheme 2.37).



Scheme 2.37 Biosynthetic pathway of tetramic acids involving PKS and NRPS[19]

The side chain of a 3-acyltetramic acid is prepared by multiple alterations, which is carried out by polyketide synthetases (PKS). The enzyme linked intermediate **196** is assembled by coupling multiple acetyl-CoA (coenzyme A) (**197**) units. **196** is joined with intermediate **198**, an enzyme coupled α-amino acid, by non-ribosomal peptide synthetases (NRPS) to compound **199**. Another enzymatic domain catalyses a Dieckmann-type cyclisation to release 3-acyltetramic acid **200**.[19,139]



Scheme 2.38 Degradation of 3-oxo-AHLs (**201**) to respective tetramic acids **202**[140]

The second way tetramic acids are synthesised in nature is by degradation of certain compounds called *N*-acylhomoserine lactones (AHLs), specifically of 3-oxo-AHLs (**201**). These substances play an essential role in the process of quorum sensing (see chapter 2.2.4.2). Scheme 2.38 depicts the process of AHL degradation. The degradation can be viewed as an irreversible, nonenzymatic Claisen-like reaction, which leads to 3-acyltetramic acids **202**.[140]

2.2.4.2 Quorum sensing - the role of tetramic acids

Quorum sensing is defined as the bacterial cell-to-cell communication using chemical signalling molecules.[141] These molecules, called autoinducers, have the purpose of coordinating actions between a large group of bacterial cells. The whole process of quorum sensing encompasses the production, release, detection and response to these autoinducers. It even enables communication between prokaryotes and eukaryotes.

A prominent class of autoinducers, produced by Gram-negative bacteria, are AHLs. If one looks at the role of tetramic acids in quorum sensing, the 3-oxo-AHLs play a fundamental role. This can be understood because tetramic acids originate from 3-oxo-AHLs (see chapter 2.2.4.1).[140] The well studied and derived from 3-oxo-AHL tetramic acid **203**, is shown in figure 2.12.

203 exhibits bactericidal activity against Gram-positive bacteria but also against its Gram-negative parent cells. This activity is based upon the ability to destabilise cell walls of target cells (this interaction is attributed to the highly lipophilic side chain of **203**).[142,143] In a broader view, this ability prevents competing bacterial cells from invading the occupied space. Furthermore, it is suggested that the self-killing effect of **203** is used to control cell population.[144] This knowledge can provide new impulses in developing new antibacterial drugs, based upon the structure of **203**.

Another ability of **203** is to complex iron in the bacteria's surroundings nearly as efficiently as other bacterial siderophores by increasing the availability of Fe^{3+} for the organism. The mode of complexation is based upon the bidentate chelation of 3-acyltetramic acids. Owing to the octahedral structure of the Fe(III) complex (**204**), the ratio between metal and ligand equals 1:3 (figure 2.12).[144]

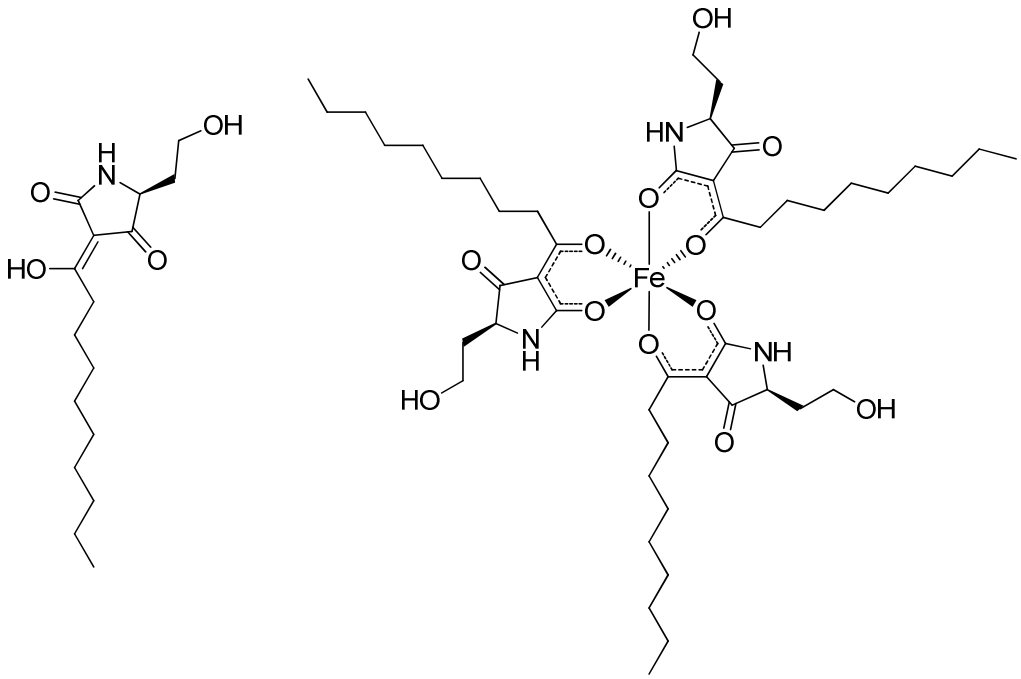
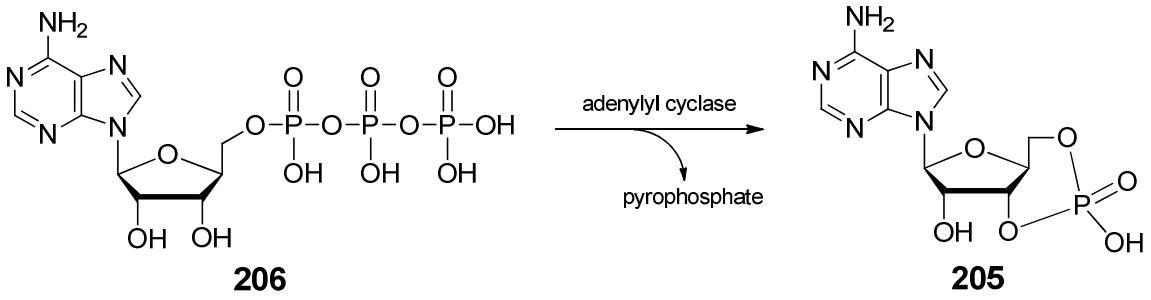


Figure 2.12 Structure of quorum sensing active tetramic acid **203** and its Fe^{3+} complex **204**[144]

2.2.4.3 cAMP, adenylyl cyclases and their connection to tetramic acids

Cyclic adenosine-3′,5′-monophosphate (cAMP) (**205**) is an important second messenger - an intracellular compound which triggers specific cellular mechanisms (figure 2.13). cAMP is involved in cell-to-cell communication and regulatory effects within a cell. It can be found in many organisms and tissues and its structure has been conserved through evolution, although its function varies when looking at different biological systems.[145]

cAMP is synthesised from adenosine triphosphate (ATP) (**206**) (scheme 2.39) catalysed by adenylyl cyclases (AC). These ACs are a large group of enzymes that can be classified into classes I – VI, whereas classes IV – VI are not well-studied. The different classes are grouped by specific sequence motifs, found in the active sites. Most ACs belong to class III and they are present in all kinds of species and organisms.[146]

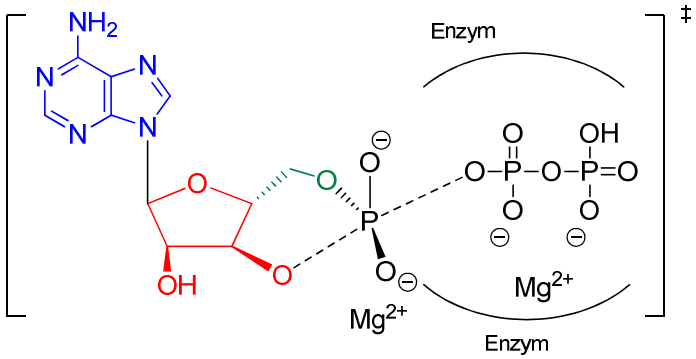


206 **205**

Scheme 2.39 Transformation of ATP (**206**) into cAMP (**205**) catalysed by adenylyl cyclase

Knowing the exact structure of the active site of class III ACs and the exact positioning of the substrate and the products in the active site (X-ray structures),[147] docking studies can be carried out to find new potential AC inhibitors.

Recent docking studies show that 3-acyltetramic acids could function as potential inhibitors for AC class III. Figure 2.13 shows the pentavalent trigonal bipyramidal transition state (**277**) inside the active site[148] at the precise moment when **205** is synthesised from **206**. In the figure beneath, a potential 3-acyltetramic acid derived from tryptophan (**208**) is shown.



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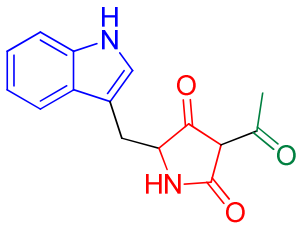


208

Figure 2.13 Transition state **207** of the transformation from ATP (**206**) into cAMP (**205**) inside the active site of AC class III and the structure of possible AC inhibitor **208**

The tryptophan part mimics the adenine portion, the tetramic acid core the ribose moiety and the 3-acyl side chain the phosphate section of the cAMP transition structure. Additionally, **208** is known for its importance as an intermediate in biochemical pathways.[149–151]

In this thesis various 3-acyltetramic acids were synthesised and handed in to be biochemically evaluated by the group of Prof. Dr. C. Steegborn. The results should reveal whether they represent potential AC inhibitors.

3 Results and Discussion

3.1 Contribution to the synthesis of macrocidin A and analogues

3.1.1 Overview

The major part of this thesis consisted of the chemistry towards and around macrocidin A (**5**). This compound (figure 3.1) was found to exhibit herbicidal activity and an interesting mode of transportation inside infected plants (see chapter 2.2.1.1.).[95] Based upon the work of B. Barnickel,[152] this part aimed for were the synthesis of a library of different compounds, all structurally related to **5**. The motivation was the attempt to generate different analogues and to compare their herbicidal activity against the activity of **5** in order to gain insight into the structure-activity relationship of **5**. The different molecules of interest (**6** – **14**) are shown in figure 3.1.

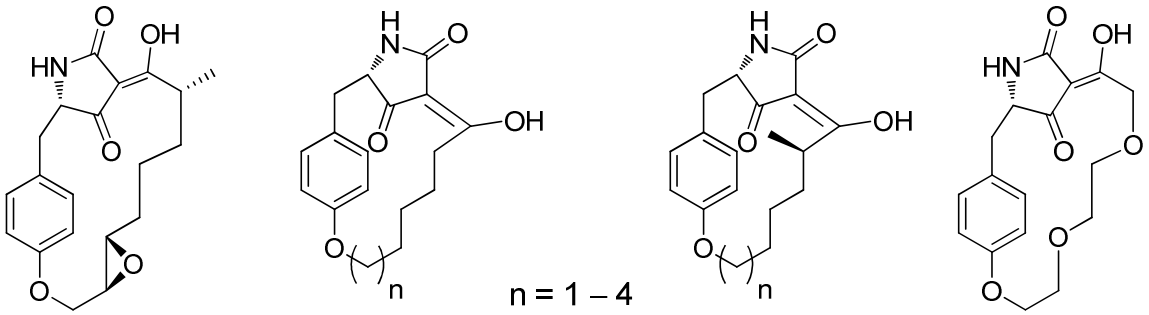


Figure 3.1 Structures of macrocidin A (**5**) and its analogues (**6** – **14**)

As can be seen above, the analogues of interest (**6** – **14**) all possess a simplified structure, lacking the epoxide in the side chain. It should be investigated whether the compounds still exhibit the same biological activity as the parent compound **5**. Another interesting feature is the size of the macrocycle itself. It can be assumed that different sizes of the ring might influence its interaction with the biological target.

Therefore, the simplest analogues envisioned are the macrocycles **6** – **9**, which do possess neither the epoxide nor the stereocenter in the side chain. The ring size is varied by the length of the side chain, starting with six carbon atoms (**6**) up to nine

carbon atoms (**9**). Compound **8** would represent the original ring size, similar to the natural product.

The second group of macrocidin A analogues (**10** – **13**) are a bit more complex than the group before, yet without the epoxide functionality but bearing a methyl group in the side chain. The methyl group should be introduced stereoselectively (*S*-configuration). Again the ring size should be modified to include side chains incorporating six (**10**) to nine (**13**) carbon atoms.

Another analogue (**14**) possesses a side chain containing two oxygen atoms (similar to a crownether). These two oxygens should provide additional centres which could interact with metals by chelation besides the standard 3-acyltetramic acids' donor atoms.

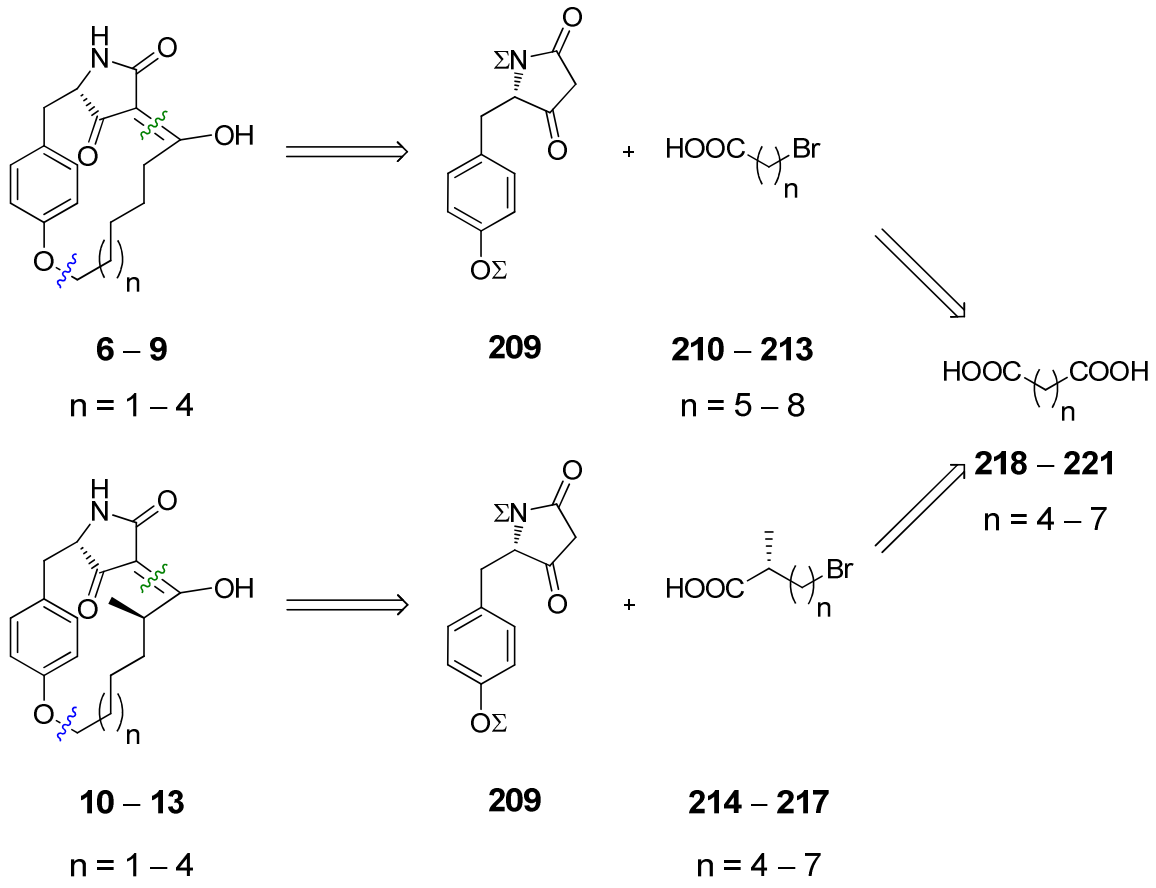
Finally, the total synthesis of **5** should be achieved, based upon the work of Barnickel,[152] who tried to synthesise nor-macrocidin A (**109**).[98]

3.1.2 Synthesis of simplified macrocidin A derived macrocycles

3.1.2.1 Retrosynthetic approach

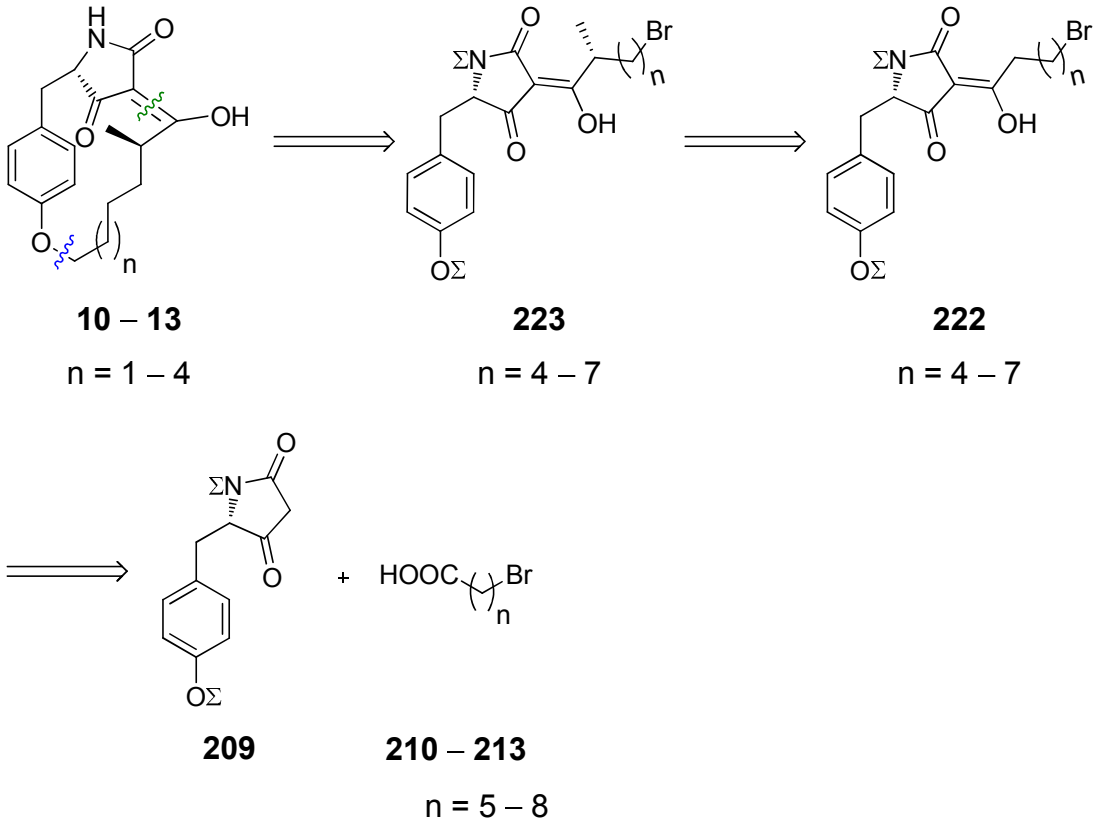
Macrocidin A can be retrosynthetically divided into two main fragments: a tetramic acid part and a side chain building block (scheme 3.1). The tetramic acid part **209** forms the core of all derivatives related to macrocidin A (**5**). It can be prepared from L-tyrosine (**16**), which must be equipped with adequate protecting groups. They are selected to be compatible with the remaining transformations, the coupling of **209** with the side chain and the macrocyclisation.

The structural diversity is introduced via the side chain, which has to be designed uniquely for each derivative. As for compounds **6** – **9**, the required side chains have to be less complex (**210** – **213**) than for compounds **10** – **13** (**214** – **217**) due to the lack of a stereocenter. To simplify matters, all eight side chains should be derived from only four dicarboxylic acids, namely adipic acid (**218**), pimelic acid (**219**), suberic acid (**220**) and azelaic acid (**221**).



Scheme 3.1 Retrosynthetic approach towards macrocidin A analogues **6** – **13**

An introduction of the α-methyl group at a later stage of the synthesis, should be investigated as well (scheme 3.2). The advantage of this route would be that only the simple bromo acids **210** – **213** would be needed and that the methyl group could be introduced stereoselectively after the 3-acylation of the tetramic acid takes place. A way should be found to convert 3-acylated compounds **222** into methylated substances **223** before carrying out the macrocyclisation. A drawback of this envisioned strategy could turn out to be the handling of compounds **222** and **223**, due to their high polarity.

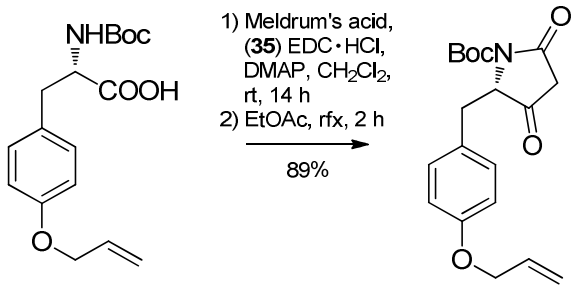


Scheme 3.2 Alternative retrosynthetic approach based upon late stage stereoselective methylation

3.1.2.2 Synthesis of an allyl-protected L-tyrosine derived tetramic acid

The L-tyrosine derived tetramic acid **116** was prepared according to a procedure of Barnickel.[152] As protecting groups, the Boc-protecting group was chosen to protect the amine of the amino acid and the allyl-protecting group to protect the phenolic hydroxyl group, because they should be compatible with the final macrocyclisation.

One drawback of this method[152] was the generation of DHU, which could not be removed entirely. Therefore, the tetramic acid formation was attempted using the protocol of Hosseini *et al.*[53], by which DCC is replaced by EDC · HCl (scheme 3.3). This procedure worked smoothly and the product obtained was more pure than the one received before.

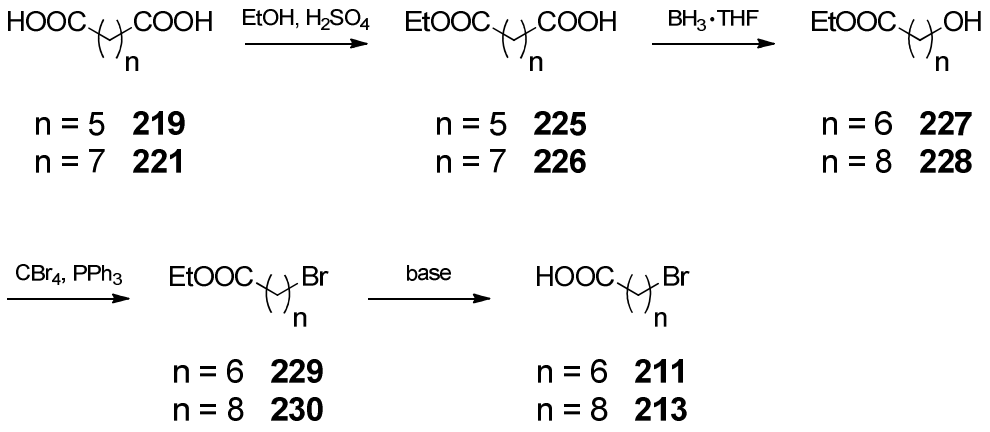


224 **116**

Scheme 3.3 Alternative tetramic acid formation using EDC · HCl[53]

3.1.2.3 Synthesis of simple bromo acids

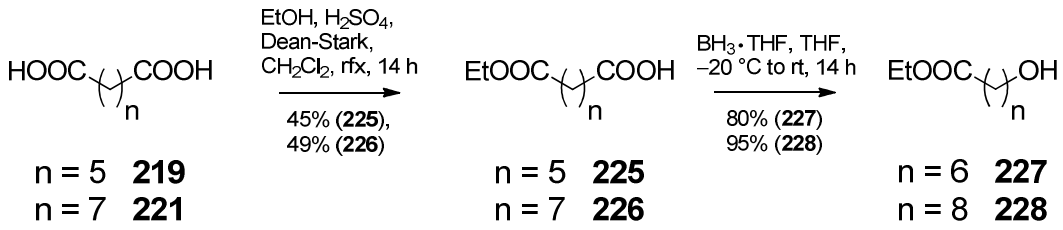
From the four bromo acids (**210** – **213**) needed as precursors for the coupling with tetramic acid **116**, two were commercially available (**210**, **212**), while the other two (**211**, **213**) needed to be synthesised. Scheme 3.4 shows the plan to synthesise **211** from pimelic acid (**219**) and **213** from azelaic acid (**221**).



Scheme 3.4 Synthetic plan to synthesise bromoacids **211** and **213**

In the first step, the dicarboxylic acids **219** and **221** were transformed into their respective monoethyl esters **225** and **226** (scheme 3.5). On account of the low price of both **219** and **221**, the maximal theoretical yield of 50% when using one equivalent of ethanol (EtOH) was not an issue (25% of diethyl ester and 25% of starting material were found as side products). The reaction was carried out using standard esterification conditions to give the desired monoethyl esters in 45% and 49% yields.

Experiments to increase the yields using Steglich conditions[153], modified Steglich conditions applying 1-propanephosphonic acid cyclic anhydride (®T3P) as coupling reagent[154] and a reaction based upon the Garreg-Samuelsson reaction[155], using imidazole, I_2 and triphenylphosphine (PPh_3)[156], were not successful.



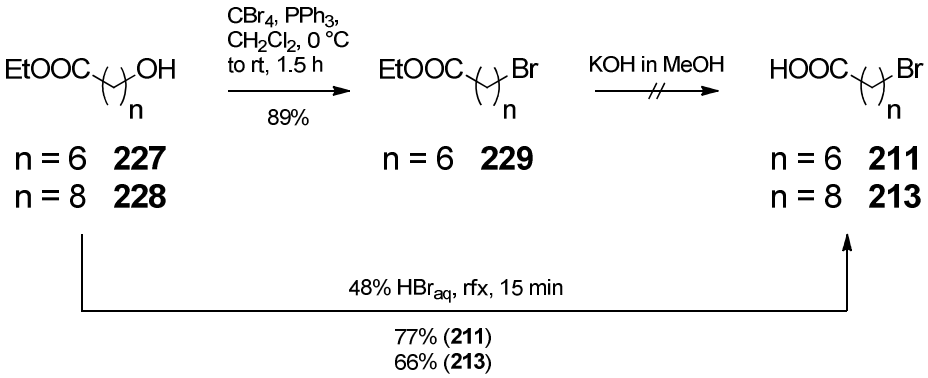
Scheme 3.5 Monoesterification of dicarboxylic acids **219** and **221** and selective reduction with borane

The free carboxylic acid functionalities of **225** and **226** were selectively reduced to the corresponding alcohols **227** and **228** in good to excellent yields with borane (as complex with THF) (scheme 3.5).[157,158] By using a syringe pump, the reagent was added with 1.5 mL/min at 0 °C. This assured stable and reproducible yields.

In the case of **227**, the hydroxyl group was brominated to form **229** using tetrabromomethane (CBr_4) and PPh_3 following a standard procedure (scheme 3.6).[159,160] However, the reaction only worked satisfactorily when the reagents were added at 0 °C and only when using 1 equivalent of both reagents, despite the use of more equivalents of both reagents in most of the literature.[161]

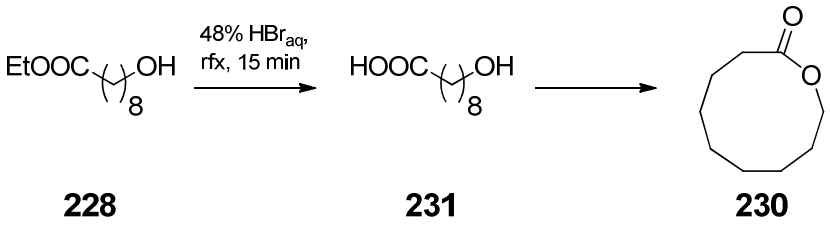
The saponification of the ester to liberate desired bromo acid **211** was tried with KOH in methanol.[162] The reaction produced multiple products. One may have been **211**, but the main product was identified as an alcohol, resulting from a nucleophilic attack of a hydroxide ion on the bromide. Hence, the reaction was dismissed.

To circumvent this problem, a one step procedure to transform ester alcohols **227** and **228** into the desired bromo acids **211** and **213** was employed (scheme 3.6). **227** and **228** were heated to reflux with 48% hydrogen bromide (HBr_{aq}) for 15 min.[163]



Scheme 3.6 Transformation of alcohol esters **227**/**228** with the goal of synthesising bromo acids **211**/**213**

211 was obtained in a yield of 77%, but in the case of **213**, the purified product was still a mixture of two substances. The ^{1}H-NMR spectrum lead to the conclusion that the second compound was lactone **230** (scheme 3.7), formed by esterification of hydroxy acid **231**. **231** could be an intermediate of the reaction. Purification attempts by column chromatography failed, due to the identical polarity of compounds **213** and **230**. In the end, the separation was managed by Kugelrohr distillation. Desired bromo acid **213** was obtained in 66% yield.

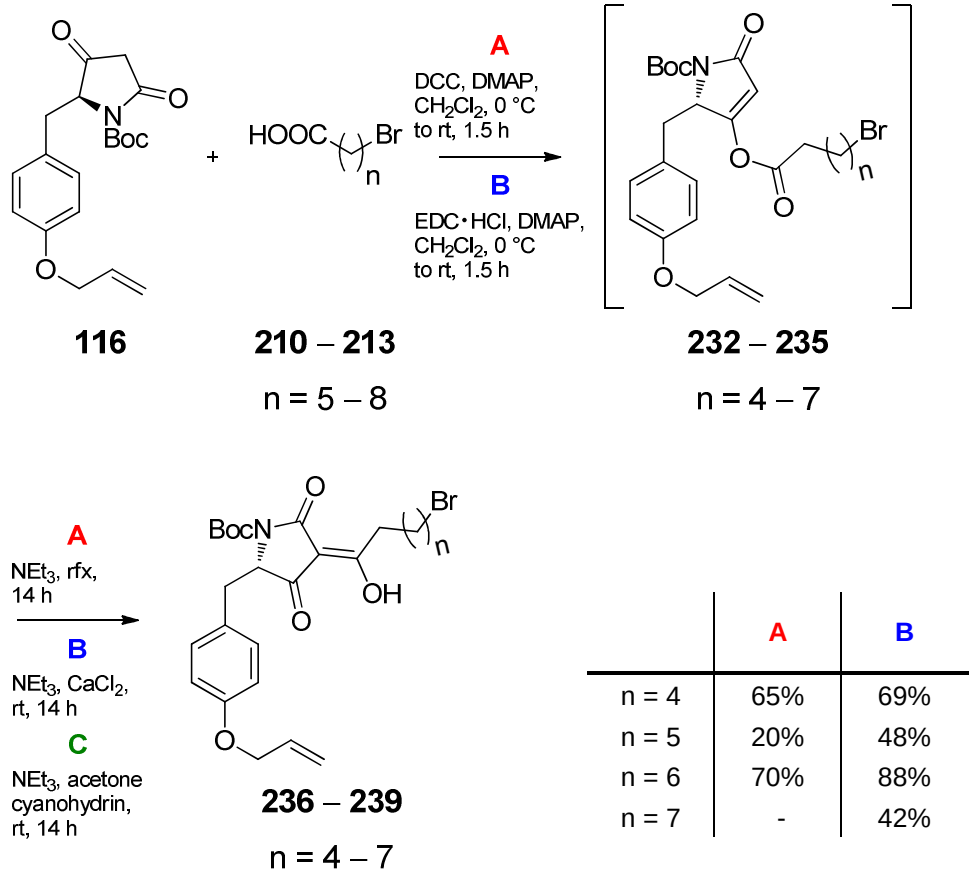


Scheme 3.7 Lactonisation of hydroxy acid **231** to **230** as a result of the reaction between **228** and HBr_{aq}

3.1.2.4 Synthesis of L-tyrosine derived 3-acyltetramic acids

With all four bromo acids in hand, the next step was the 3-acylation with L-tyrosine derived tetramic acid **116**. The 3-acylation was performed using the protocol of Yoshii *et al*. (scheme 3.8).[76] The 4-*O*-acylation and the subsequent rearrangement to the 3-acyl species were carried out as an one-pot reaction. Bromo acids **210** – **213** were coupled with tetramic acid **116** using DCC and DMAP to give 4-*O*-acyl

derivatives **232** – **235** *in situ*. NEt_3 is added to facilitate the rearrangement to furnish 3-acyl compounds **236** – **239**.



	A	B
n = 4	65%	69%
n = 5	20%	48%
n = 6	70%	88%
n = 7	-	42%

Scheme 3.8 3-Acylation of tetramic acid **116** with different bromo acids following the protocols of Yoshii *et al.* (**A**),[76] Yoda *et al.* (**B**)[78,79] (with respective yields over two steps) or Moloney *et al.* (**C**)[77]

The reaction gave compounds **236** – **238** in moderate yields ranging between 20% and 70%. The ^{1}H-NMR spectra of **236** – **238** showed leftover DHU originating from the use of DCC. The polarity of the products were similar to the polarity of the urea. The separation proved difficult, especially because column chromatography is always challenging, due to the affinity of 3-acyltetramic acids towards the metals in the silica gel.

Therefore, an alternative method by Yoda *et al.*[79] was tried. $CaCl_2$ was added during the step of the 4-*O*-acyl to 3-acyl rearrangement. The reaction worked smoothly and the general purity of products **236** – **239** and the milder reaction conditions (reaction is carried out at room temperature instead of heating to reflux) were convincing, although the yields were not higher than before (scheme 3.8).

To further improve the yields and the purity of the 3-acyl compounds, another method, presented by Yoda *et al.* was used, in which DCC was replaced by EDC · HCl.[78] Additionally the 4-*O*-acyl compounds were purified before the rearrangement was initiated because they could be purified easily by column chromatography.

Starting from the 4-*O*-acyl compounds, another way to initiate the rearrangement was tried, which is based upon the work of Moloney *et al*.[77] Acetone cyanohydrin was used as an additive besides NEt_3 (scheme 3.8). The method was a good alternative due to the mild reaction conditions and easy purification (acid/base extraction), although no yields are presented, because they fluctuated between 40% and 80%.

3.1.2.5 Synthesis of simple macrocidin A analogues

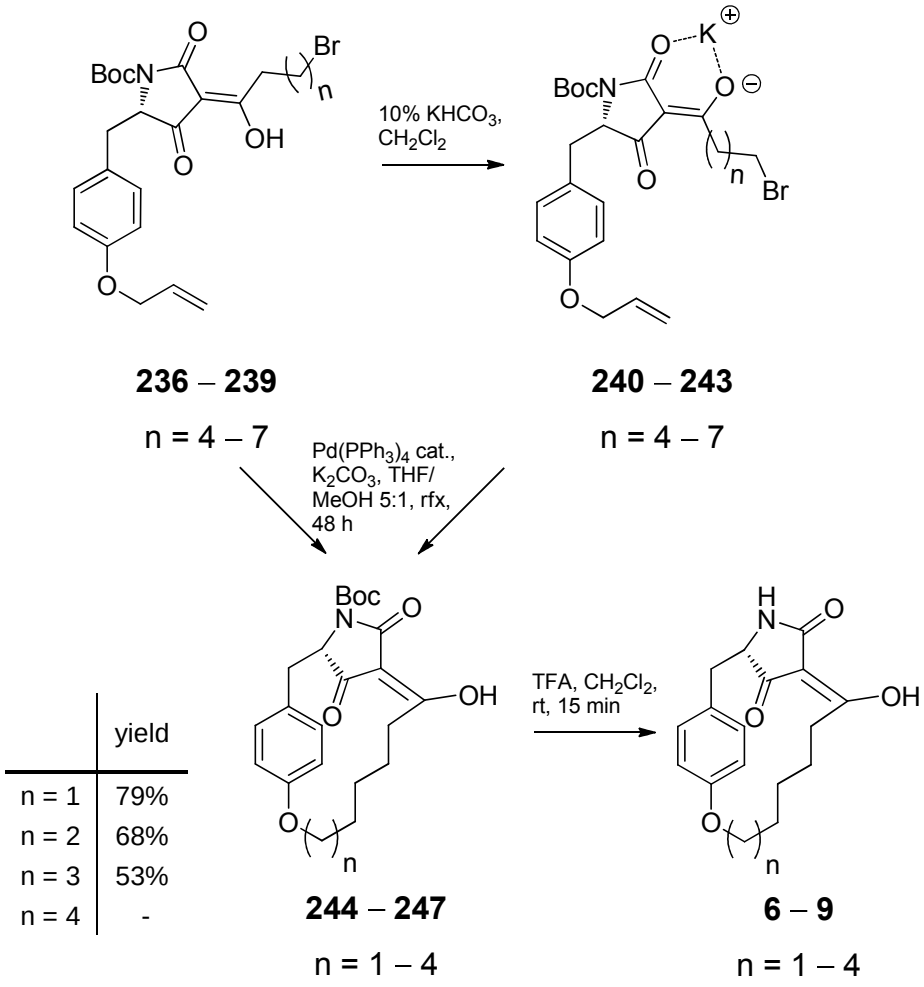
Once all 3-acyltetramic acids **236** – **239** were prepared, macrocycles **6** – **9** could be synthesised.

The macrocyclisation was performed by a tandem palladium catalysed allyl-deprotection and intramolecular Williamson etherification, followed by Boc-deprotection, according to a procedure of Barnickel *et al.*[98,152] (scheme 3.9).

It is noteworthy that either 3-acyltetramic acids **236 – 239** were used as starting materials or their respective potassium salts **240** – **243**. The potassium salts were easier to handle because they are solids, whereas the pure 3-acyltetramic acids are thick oily substances.

The conversion of the 3-acyltetramic acids into their respective potassium salts was achieved by dissolving compounds **236 – 239** in CH_2Cl_2 and treating them with $KHCO_{3aq}$.[152] The macrocyclisation progressed without problems, with the exception of derivative **247**, in which case a macrocycle could not be obtained. This might be an indication for a maximum ring size, based upon the rigidity of the molecule. These findings were supported by Barnickel's results,[152] who described that 3-acyltetramic acids synthesised with 10-bromodecanoic acid, could not be cyclised.

With macrocycles **244** – **246** in hand, the deprotection using TFA was carried out. The reaction often lead to a mixture of products. In the case of **245**, after two attempts, nothing could be found but unidentifiable side products.



	yield
n = 1	79%
n = 2	68%
n = 3	53%
n = 4	-

	yield
n = 1	36%
n = 2	-
n = 3	67%
n = 4	-

Scheme 3.9 Synthesis of macrocycles **6** – **9** starting from 3-acyltetramic acids **236** – **239**

Figure 3.2 shows an analytical HPLC spectrum of the crude reaction mixture for the deprotection of **244** to macrocycle **6**. Three fractions (**A** – **C**) were separated by preparative HPLC and tested by NMR spectroscopy. Fraction **A** showed tyrosine signals but no signals of the side chain, whereas **B** seemed to be the allyl-deprotected compound (perhaps a leftover intermediate before the macrocyclisation could take place). Fraction **C** looked promising, although one methylene group of the side chain seemed to be missing.

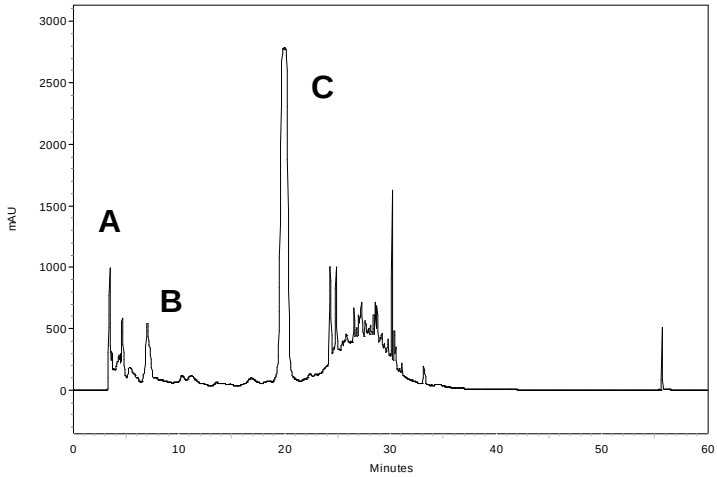


Figure 3.2 HPLC spectrum of the crude product from the reaction of **244** with TFA (288 nm, 50% MeOH in H_2O + 0.1% HCOOH; after 15 min in 10 min up to 100% MeOH)

Figure 3.3 shows the ^{1}H-NMR spectrum of fraction **C**. By checking the 2D-NMR, spectra it was concluded that the broad multiplet between 2.0 ppm and 2.5 ppm can be assigned to the missing methylene group 15. The fact that the corresponding integral summed up to 0.78 instead of 2.00 could not be explained.
Summing up, the spectrum shown in figure 3.3 and a fitting mass spectrometry prove that the desired macrocycle **6** was synthesised successfully.

One detail worth mentioning is that whilst trying to reproduce the results, only once was a different compound isolated with a similar HPLC retention time and HRMS produced the correct mass of m/z = 302.1403 ([M]+H^+). Additionally, all required signals were present in the NMR-spectra. Figure 3.5 compares the ^{1}H-NMR spectra of **6** and of the unknown compound.

Four distinctive discrepancies were observed. Firstly, the aromatic region of macrocycle **6** showed four signals (the two in the middle merge to appear as one), revealing that in the closed macrocycle the aromatic hydrogens are not chemically equivalent. This was not observed for the unknown compound, giving rise to an open structure. This assumption is fortified by the ^{13}C-NMR spectrum, which shows four tertiary aromatic signals for **6** and only two for the unknown compound.

Secondly, the complex multiplet between 4.10 – 4.33 ppm, assigned to the methylene group next to the phenolic oxygen, shifted to a higher field (triplet at 3.56 ppm). The new shift is similar to the one observed prior to the macrocyclisation

(methylene group next to the bromine in the acyl side chain). This indicated that the macrocycle was possibly reopened.

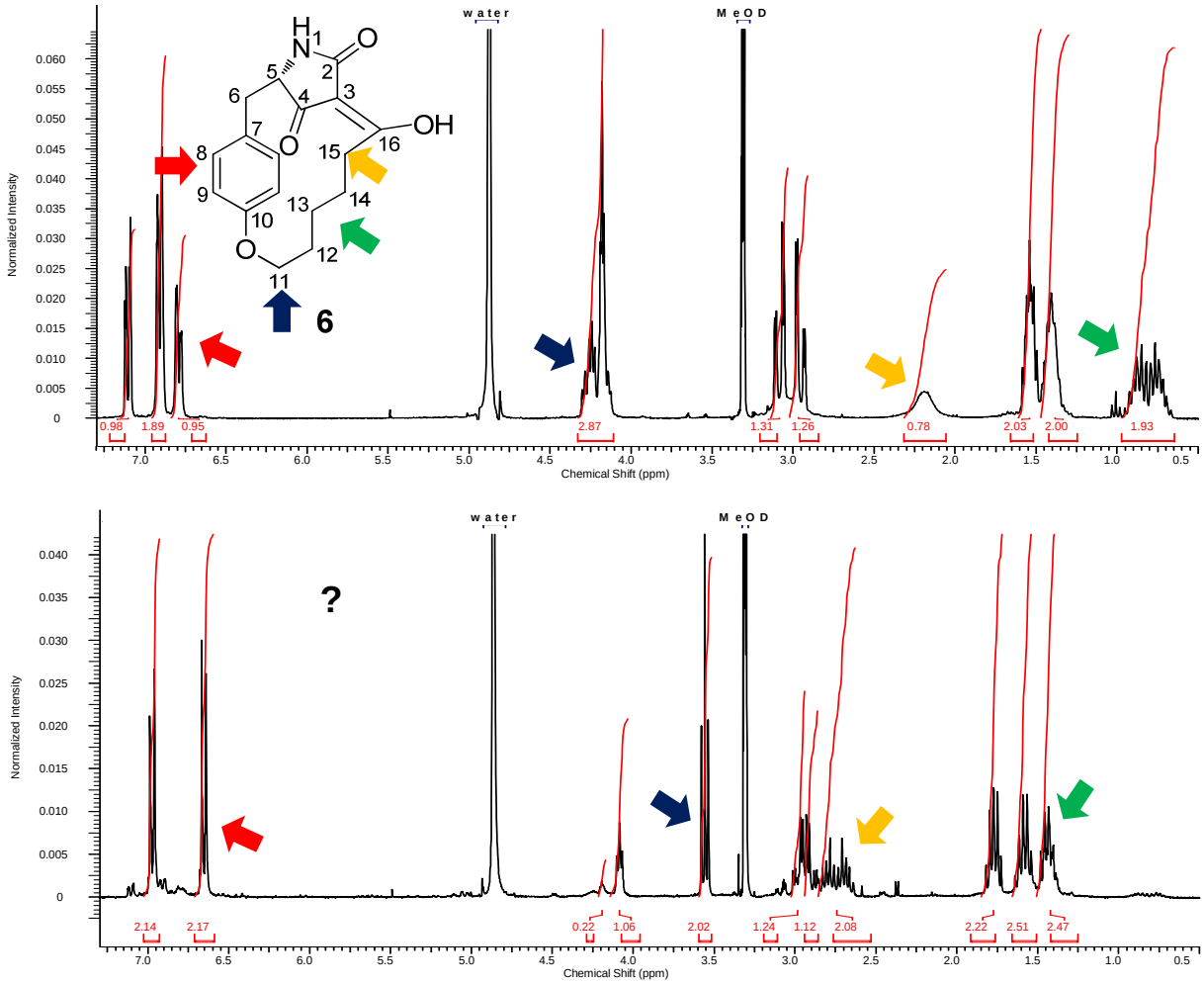
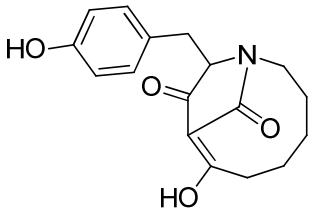


Figure 3.3 Comparison of the ^{1}H-NMR spectra of macrocycle **6** (upper spectrum) and an unidentified compound (**?**) (lower spectrum)

Thirdly, the broad multiplet between 2.07 – 2.32 ppm (assigned to methylene group 15) experienced a shift to a lower field and displayed a more complex multiplicity. The reason for this behaviour remained unclear.

Fourthly, the multiplet assigned to methylene group 13 shifted to a lower field and the aliphatic signals of the side chain converged. This supported the assumption that the ring was reopened, because the influence of the phenolic oxygen on the shifts of the aliphatic protons disappeared.



248

Figure 3.4 Theoretical structure of the unknown compound (**248**), generated by TFA deprotection of **244**

Figure 3.4 shows the theoretical structure of a compound, which would match most of the spectroscopical and spectrometrical data (**248**), regardless of how the transformation might have occurred. Structure **248** explains most of the discrepancies, but in the end, the structure belonging to the unknown compound could not be determined. Nevertheless, it is important to consider possible side reactions when carrying out the deprotection of the macrocycles with TFA.

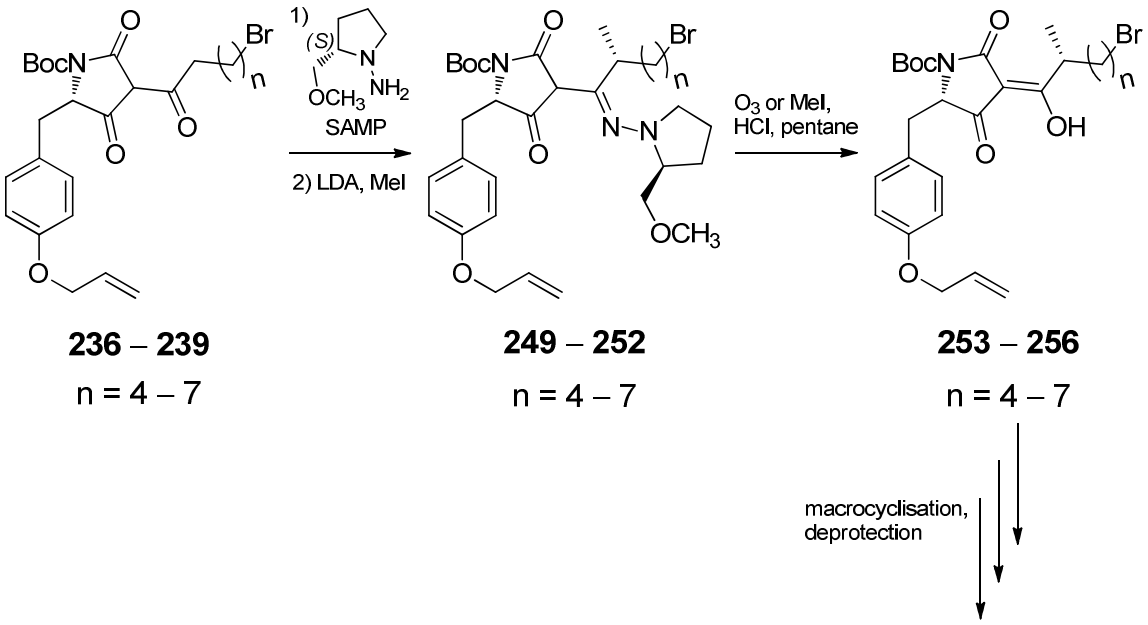
3.1.2.6 Attempted side chain α-methylation of 3-acyltetramic acids

The next aim was to synthesise the more complex macrocycles **10** – **13**. Starting from 3-acyltetramic acids **236** – **239**, the direct path would be α-methylation of **236** – **239**.

In this case the employment of the SAMP/RAMP methodology was considered.[164–167] The envisioned process is displayed in scheme 3.10. To be able to introduce the methyl group in its (*R*)-configuration, (*S*)-1-amino-2-methoxy-methylpyrrolidine (SAMP) should be employed. The chiral auxiliary should be reacted with **236** – **239** to give the corresponding hydrazones, which can be stereoselectively methylated to compounds **249** – **252**. Afterwards, the auxiliary must be cleaved either by ozonolysis or hydrolysis, liberating intermediates **253** – **256**, which need to be converted into final macrocycles **10** – **13** by palladium-catalysed macrocyclisation and Boc-deprotection (see chapter 3.1.2.5).

The success of this synthetic plan would depends on a regioselective hydrazone formation. Due to the fact that 3-acyltetramic acids incorporate three carbonyl functionalities, an assessment whether the hydrazine could form a hydrazone with

the desired exocyclic carbonyl group is required. The amide's carbonyl group at C-2 should not pose problems, whereas some competition might be expected from the isolated carbonyl group at C-4. This potential side reaction would have to be avoided or suppressed.



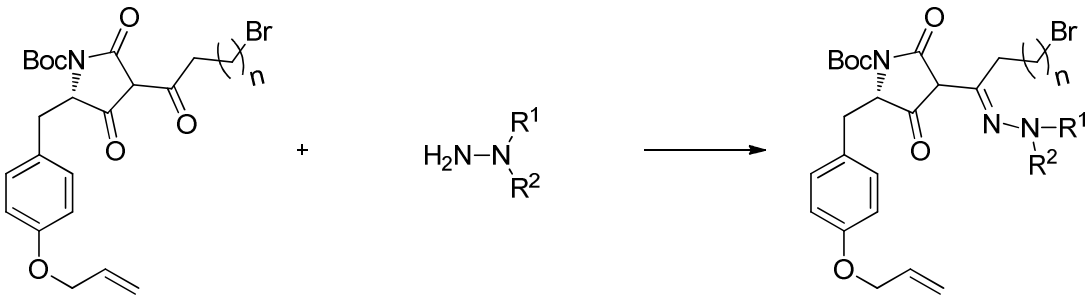
236 – **239**
n = 4 – 7

249 – **252**
n = 4 – 7

253 – **256**
n = 4 – 7

Scheme 3.10 Synthetic plan towards macrocycles **10** – **13** via side chain α-methylated 3-acyltetramic acid **253** – **256** using SAMP as chiral auxiliary

In order to check the regioselectivity of the hydrazone formation, experiments were conducted using simplified hydrazines **257** – **259** which were reacted with **236** and **238**. Scheme 3.11 sums up the reactions and table 3.1 displays the results.



n = 4 **236**
n = 6 **238**

R^1=H, R^2=C_6H_5 **257**
R^1=H, R^2=$C_6H_5NO_2$ **258**
R^1=R^2=CH_3 **259**

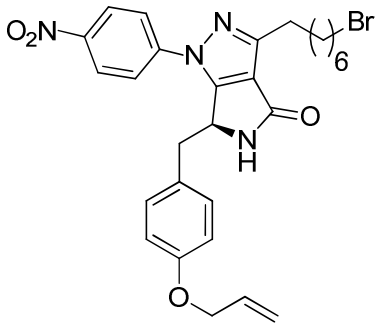
n = 4,6

Scheme 3.11 Hydrazone formation experiments with 3-acyltetramic acids **236** and **238**

In the beginning, phenylhydrazine hydrochloride (**257**) was used in a standard procedure to form hydrazones (exp. 7 – 9).[168] In experiments 1, 10 and 11 *para*-nitro-phenylhydrazine (**258**) was used instead of **257**.[169] It is known to be more reactive than **257** and was introduced neatly, without an additive.

Table 3.1 Hydrazone formation experiments with 3-acyltetramic acids **236** and **238** and different hydrazones **257** – **259** under different conditions; structure of undesired side product **260**[17]

Exp.	educt	hydrazine	eq. hydazine	additive	temp.	solvent	result
1	**236**	**258**	1.1		rfx	EtOH	-
2	**236**	**258**	1.1	H_2SO_4	rfx	EtOH	-
3	**236**	**259**	1.1		rfx	MeOH	< 3%
4	**236**	**259**	1.1		0° C to rt	MeOH	15%
5	**236**	**259**	1.1		0° C to rt	EtOH	-
6	**236**	**259**	1.1		rfx	*p*-Xylol	decomp.
7	**238**	**257**	1.0	NaOAc	rt	MeOH	-
8	**238**	**257**	1.0	NaOAc	rfx	MeOH	-
9	**238**	**257**	1.5	NaOAc	rfx	MeOH	-
10	**238**	**258**	1.0		rfx	EtOH	< 3%
11	**238**	**258**	1.0		rfx	CH_2Cl_2	-
12	**238**	**258**	1.1	H_2SO_4	rfx	EtOH	**260**
13	**238**	**258**	1.1		0° C to rt	EtOH	-
14	**238**	**259**	1.1		0° C to rt	EtOH	-
15	**238**	**259**	1.1	H_2SO_4	0° C to rt	EtOH	-
16	**238**	**259**	1.1		0° C to rt	MeOH	24%



260

In another effort, sulphuric acid was added in a catalytic amount to increase the rate of condensation. In experiments 2 and 15 no reaction could be observed. Experiment 12 yielded a single pure product, which could with high certainty be

identified as a condensation product (**260**) of the desired product with the 4-carbonyl group.[17] Furthermore, it was considered that there may have been a sterical problem involved when using aromatic hydrazines. This lead to the substitution of **258** with a smaller and simpler hydrazine, *N*,*N*-dimethylhydrazine (**259**),[169] but no product was obtained. Additionally, the solvent and the reaction temperature were varied but no satisfying result was generated.

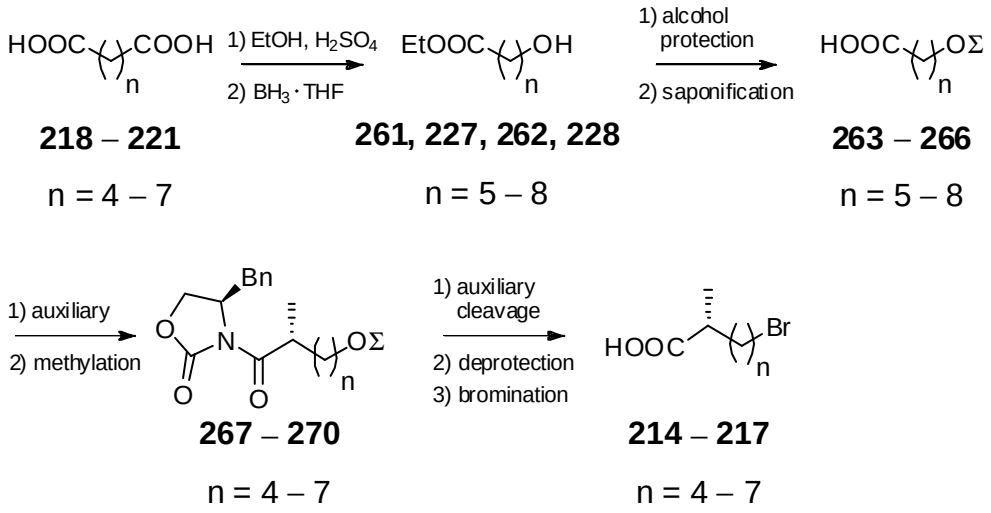
In summary, this approach was abandoned and another strategy had to be developed.

3.1.2.7 Synthesis of α-methylated bromo acids from dicarboxylic acids

On account of the failed attempt of a late stage α-methylation of 3-acyltetramic acids **236** – **239** (chapter 3.1.2.6), the α-methylation needed to be performed before the 3-acylation. This means that the methyl group had to be incorporated into the bromo acids (**214** – **217**). This strategy seemed unlikely, due to the fact that racemisation at the α-carbon was reported to have occurred when using 3-acylation conditions by Yoshii *et al*.[77,79] Yoda *et al.* circumvented this problem by adding $CaCl_2$ as an additive to retain the stereochemistry of the bromo acids employed.[78–80]

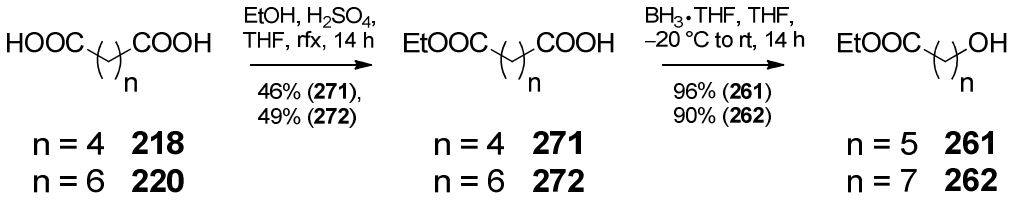
After thinking about a way to synthesise **214** – **217,** the way to synthesise bromo acids **211** and **213** came back into focus (chapter 3.1.2.3). In general, the synthetic route could be adapted to become the basis for the synthesis of **214** – **217** (scheme 3.12).

Starting from dicarboxylic acids **218** – **221** monesterification and reduction of carboxylic acid should be carried out to form **261**, **227**, **262** and **228** as shown in chapter 3.1.2.3. Deviating from the former strategy the alcohol should be protected and the carboxylic acid liberated to **263** – **266**. The Evans auxiliary should be attached and the methylation performed (**267** – **270**) before auxiliary cleavage, deprotection and bromination of the liberated alcohol should then furnish desired products **214** – **217**.



Scheme 3.12 Synthetic route towards α-methylated bromo acids **214** – **217** starting from dicarboxylic acids **218** – **221**

The first task was to synthesise monoethyl esters **271** and **272** from adipic acid (**218**) and suberic acid (**220**) by following the instructions outlined in chapter 3.1.2.3. The same held true for the borane reduction to alcohols **261** and **262** (scheme 3.13).[157,158] The only difference was that the esterification was carried out in THF instead of CH_2Cl_2. The yields were similar to the ones observed when synthesising alcohol esters **227** and **228**.

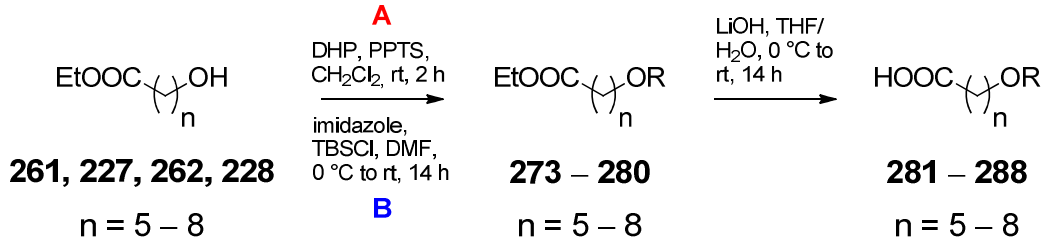


Scheme 3.13 Synthesis of alcohols **261** and **262** by monoesterification and borane reduction

As possible protecting groups for the alcohol the 2-tetrahydropyranyl (THP) group and the *tert*-butyldimethylsilyl (TBS) protecting group were taken into consideration. Both should remain stable under the basic conditions, applied in the next steps.

Both strategies were pursued to investigate whether one route was superior (scheme 3.14). The THP-protection was carried out, following a standard procedure. The alcohol was treated with 3,4-dihydro-*2H*-pyran (DHP) in CH_2Cl_2 with a catalytic amount of *para*-toluenesulfonic acid (*p*-TosOH).[170] The yield and purity of products

273 – **276** were not satisfying. Therefore an alternate protocol was tried by substituting *p*-TosOH with pyridinium *para*-toluenesulfonate (PPTS).[171] The reaction worked in good to excellent yields and for many cases products **273** – **276** can be used in further experiments without further purification (scheme 3.14). The TBS-protection of the same alcohols was carried out using imidazole and TBSCl in dimethylformamide (DMF).[172] The reaction worked efficiently and gave protected esters **277** – **280** in good yields (scheme 3.14).



n	R = THP (**A**) (yield)	R = TBS (**B**) (yield)	n	R = THP (yield)	R = TBS (yield)
5	86% (**273**)	86% (**277**)	5	80% (**281**)	51% (**285**)
6	82% (**274**)	90% (**278**)	6	45% (**282**)	75% (**286**)
7	86% (**275**)	88% (**279**)	7	69% (**283**)	71% (**287**)
8	95% (**276**)	93% (**280**)	8	52% (**284**)	92% (**288**)

Scheme 3.14 THP- (**A**)[171] and TBS-protection (**B**)[172] to **273** – **280** and subsequent saponification[173] to acids **281** – **288**

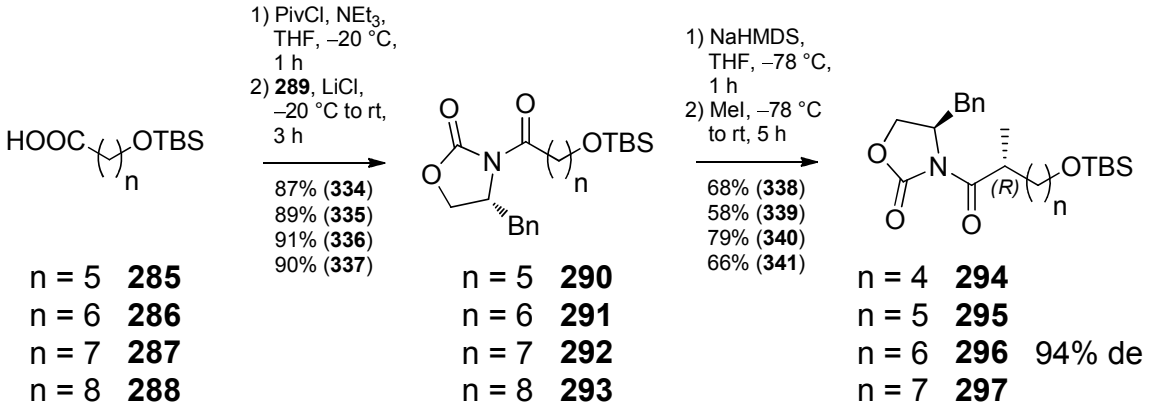
With all these protected esters in hand (**273** – **280**), the next objective was the saponification of the ester moiety. Therefore, different base/solvent mixtures were tested, ranging from KOH in MeOH,[162] NaOH in MeOH,[174] LiOH in THF/H_2O[173] and NEt_3 in acetonitrile (MeCN).[175] It could be concluded that each method lead to the desired products, but the last two methods provided the highest yields of **281** – **288**. Another problem with all of these methods was their reproducibility. High fluctuations in yield and purity were observed. The most stable reactions were achieved when using the LiOH protocol (scheme 3.14).

Having created the eight carboxylic acids **281** – **288**, the Evans auxiliary (*R*)-4-benzyl-2-oxazolidinone (**289**) was to be attached by using standard methodology.[176] Oxalyl chloride should be applied to generate the respective acid

chlorides, which should be added to a flask charged with **289** and *n*-butyllithium (^{n}BuLi).

However, no products were isolated when using THP-protected carboxylic acids **281** – **284** and only small amounts of product were found when working with TBS-protected carboxylic acids **285** – **288**. It is known that during the process of the acid chloride generation by oxalyl chloride, HCl is formed as a by-product. Most likely both acid labile protecting groups were cleaved and the reaction was ruined. Due to the high lability of the THP-protection group, the THP-route was abandoned henceforth.

To circumvent the problem of the HCl formation, alternative strategies to attach **289** to the carboxylic acids were tried. This involved the use of DCC and DMAP in a Steglich-type reaction to form the acyl carbamate[177] or the use of pivaloyl chloride to form a mixed anhydride, to which, in a one-pot procedure, **289** along with NEt_3 and dry LiCl is added.[178,179] The first method left the protecting groups untouched, however purification proved difficult because of leftover DHU. The second approach worked, producing high and reproducible yields of **290** – **293** (scheme 3.15).



n = 5 **285**
n = 6 **286**
n = 7 **287**
n = 8 **288**

n = 5 **290**
n = 6 **291**
n = 7 **292**
n = 8 **293**

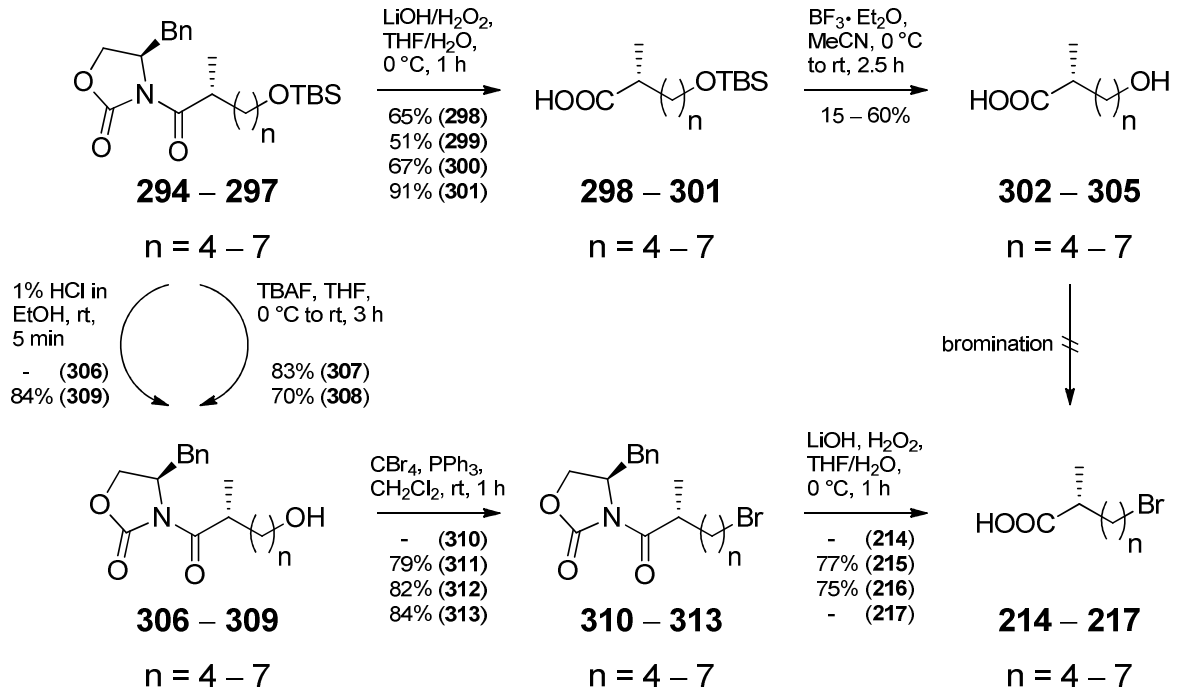
n = 4 **294**
n = 5 **295**
n = 6 **296** 94% de
n = 7 **297**

Scheme 3.15 Mild coupling of **289** with carboxylic acids **285** – **288** and stereoselective methylation to compounds **294** – **297**

The methylation of compounds **290** – **293** was performed according to literature (scheme 3.15).[178,179] The two diastereomers were separated by column chromatography using flash silica gel. Although the diasteromeric separation worked perfectly, the diastereomeric ratio of the reaction was calculated based upon GC analysis of the crude mixture of **296**. Two separate experiments showed that the diastereomeric excess (de) of the reaction of **292** to **296** was 94%.

Following the initial strategy the auxiliary was removed to form **298** – **301** by a standard procedure with $LiOH/H_2O_2$.[180,181] The results are summarised in scheme 3.16 showing that the yields of the reaction were not as high as stated in literature. Reasons for this might be the instability of the product during the harsh work up or during purification.

The next experiments involved the TBS-deprotection of compounds **298** – **301**. Three different approaches were tried. The methods employed used 1% HCl in EtOH,[182] boron trifluoride etherate ($BF_3 \cdot Et_2O$) in MeCN[183,184] and tetra-*n*-butyl-ammonium fluoride (TBAF) in THF.[185,186] The second method was superior to the other two, although only irreproducible yields ranging from 15% to 60%, were achieved (scheme 3.30). As a side reaction, lactonisation of the desired products **302** – **305** was observed and the pure products were prone to lactonisation and decomposition, even if stored at low temperatures.



Scheme 3.16 Abandoned route via compounds **298** – **301** and synthetic pathway starting from α-methylated compounds **294** – **297** leading to α-methylated bromo acids **214** – **217**

To avoid the polar intermediates **302** – **305**, the synthetic plan was altered (scheme 3.16). Instead of removing the auxiliary, the TBS-protecting group should be removed first, followed by the bromination of the hydroxyl group. The removal of the auxiliary should conclude the reaction sequence.

The deprotection of the TBS-protecting group was carried out using TBAF[185,186] or 1% HCl in EtOH (scheme 3.16).[182] The first method gave better results when synthesising **307** and **308** and the second method when applied to the synthesis of **309**. **306** had not yet been synthesised.

Having access to deprotected compounds **307** – **309**, the bromination of the free hydroxyl group was conducted, employing an Appel reaction to give **311** – **313** in good yields (scheme 3.16).[187]

The conclusion of the synthesis was the oxidative removal of the Evans auxiliary, as shown before in this chapter.[180,181,188] The reaction was carried out to give **215** and **216**, but the yields reported in literature were not achieved. Again, this gave rise to a high instability of **215** and **216** during work up and purification (scheme 3.16).

Nevertheless, the synthesis was completed in the case of **215** and **216**. The yields, starting from dicarboxylic acids **219** and **220**, are 6% and 9% respectively over nine steps.

The synthesis of **214** and **217** remained unfinished and the 3-acylation of tetramic acid **116** with **215** and **216** was not carried out in the course of this thesis.

3.1.3 Attempt at the synthesis of a crown ether incorporating analogue based upon macrocidin A

3.1.3.1 Motivation

Looking at the macrocyclic derivatives **6** – **13**, it can be noted that all of them represent simplified versions of the parent compound macrocidin A (**5**). The next target substance of this thesis depicts a different kind of macrocidin A analogue. The side chain of the natural product should be substituted by a crown ether side chain, leading to structure **14** (figure 3.5).

A large part of the work presented in this chapter is based upon B.Sc. Hendrik Hessefort's research for his bachelor's thesis.[189] The idea resulted from a DFG cooperation with the group of Prof. Dr. S. Laschat (University of Stuttgart).

The general motivation for synthesising **14** was to study its capabilities to chelate metals compared to **5**. The complexation of different metals is a significant property of natural 3-acyltetramic acids, which allows them to unfold their various effects in biological systems (see chapters 2.1.1, 2.1.2 and 2.2.4.2). In addition to the standard

"outer complexation" at the 3-acyl functionality of **5** (**314**), **14** possesses two additional donor atoms in the side chain. This might lead to a whole new type of coordination. The hypothetical metal complexes **315** – **317,** illustrated in figure 3.5, should exhibit different coordination patterns, including an "inner complexation" within the molecule. Furthermore, the new structural possibilities (complexation of different metal cations at the same time or the incorporation of the aromatic ring as potential ligand) might have an impact on the biological properties of the substance. An evaluation of the compounds' chemical and biological properties could prove to be interesting.

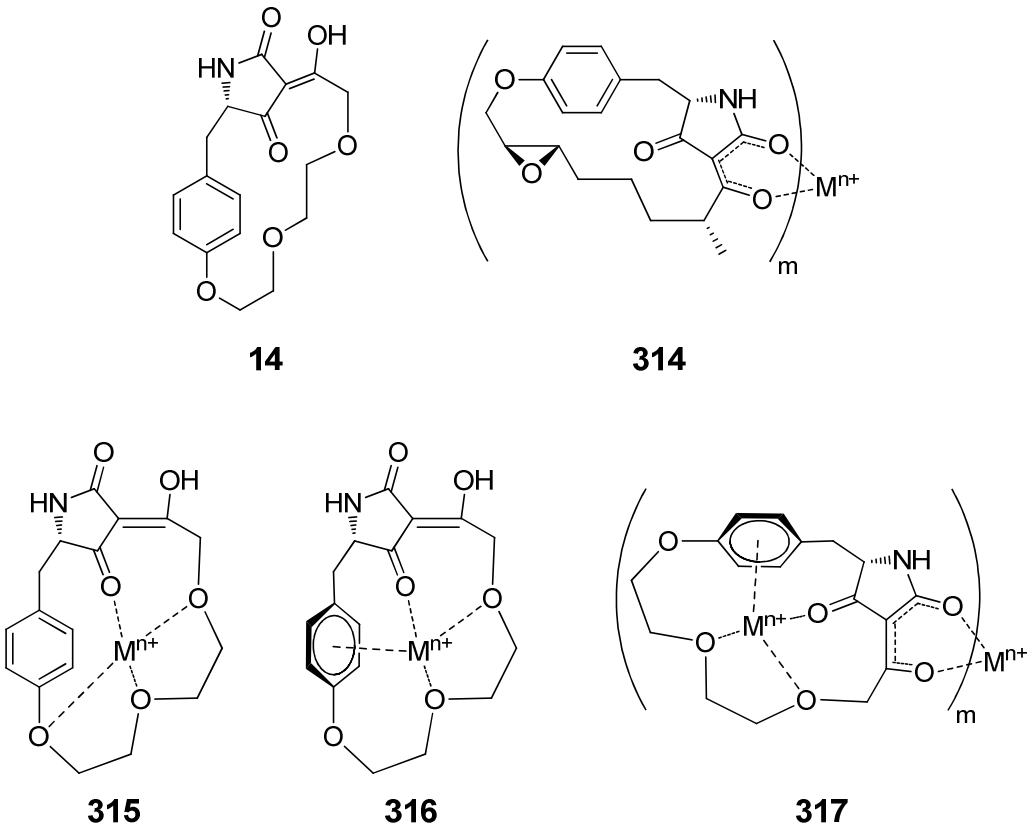


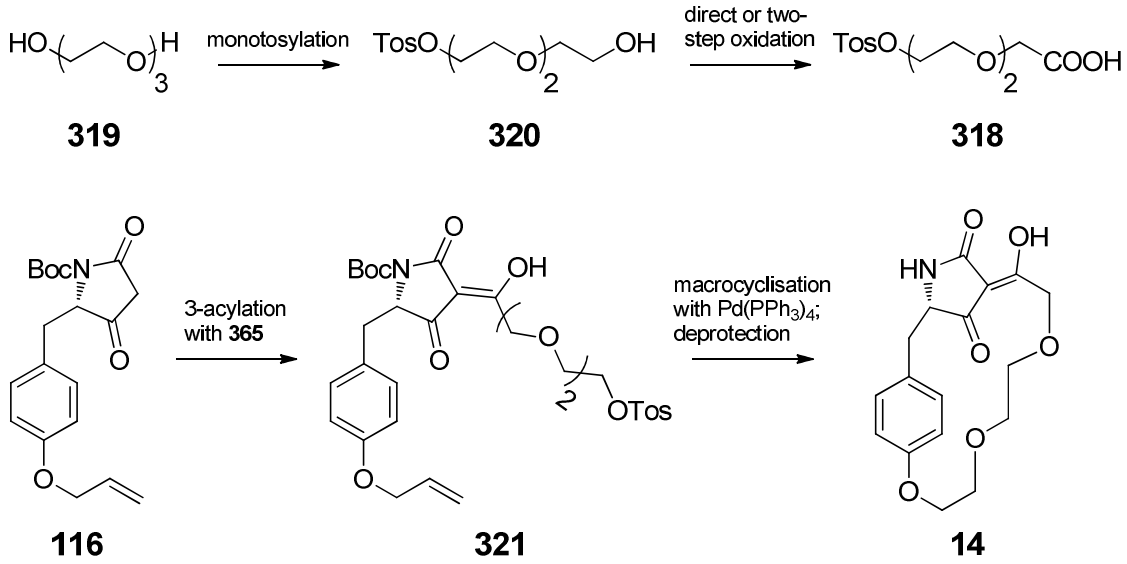
Figure 3.5 Structure of macrocidin A crown ether analogue **14** and hypothetical coordination patterns (**315** – **317**) in comparison to the coordination pattern of macrocidin A (**314**); n = 1 – 3, m = 1 – 3, M = metal

3.1.3.2 Attempted synthesis of a polyether analogue of macrocidin A

The retrosynthetic approach was similar to the ones discussed in the previous chapters. Macrocycle **14** could be hypothetically split into two major fragments: the tetramic acid fragment **116** and a polyether side chain **318** (scheme 3.17). **318** contains a leaving group and a carboxylic acid functionality and should be derived from the cheap and commercially available precursor triethylene glycol (TEG) (**319**).

Without any alterations, the synthesis of **116** starting from L-tyrosine (**16**) was adopted from the synthesis performed in chapter 3.1.2.2. The Boc- and allyl-protecting groups of **116** should be suitable for the synthesis of **14**.

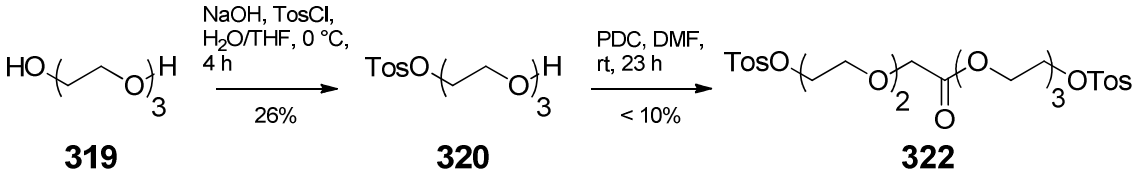
Due to experience in polyether chemistry of our DFG-cooperation group from Stuttgart (Prof. Dr. S. Laschat), the tosyl group was considered as a potent leaving group (scheme 3.17). The monotosylated alcohol **320** should be oxidised to respective carboxylic acid **318** and the transformation to **14** should be achieved by 3-acylation of tetramic acid **116** with **318** to **321** and subsequent macrocyclisation and deprotection.



Scheme 3.17 Synthetic plan starting from TEG (**319**) to generate polyether macrocycle **14**

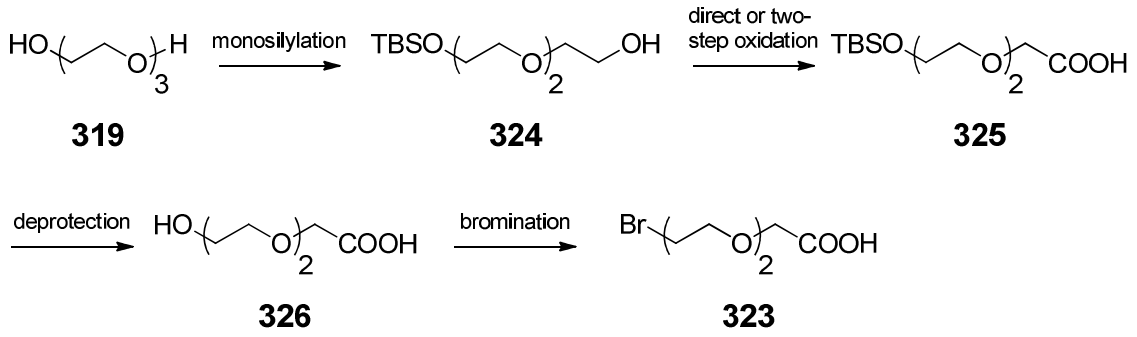
The first task was the synthesis of polyether side chain **318**. The first step is the monotosylation of TEG (**319**), which was carried out by following a protocol from Ouchi *et al*.[190] Only 26% of desired compound **320** and 38% of bisprotected

compound were obtained (scheme 3.18). Furthermore, intended oxidation of **320** to **318** by pyridinium dichromate (PDC)[191] afforded no desired product. In traces, the ester of **320** and **318** was identified (**322**) (scheme 3.18), whereas mostly decomposition was detected.



Scheme 3.18 Monotosylation of TEG (**319**)[190] and attempted PDC oxidation[191]

On account of the low yields and the instability of intermediate **320**, an alternative side chain (**323**) was proposed (scheme 3.19), containing a bromide instead of the labile tosyl-group. Desymmetrisation of TEG (**319**) should be carried out by mono-TBS-protection to **324**. Oxidation of **324** to carboxylic acid **325** should be followed by TBS-deprotection and bromination of alcohol **326** to give polyether bromo acid **323**.

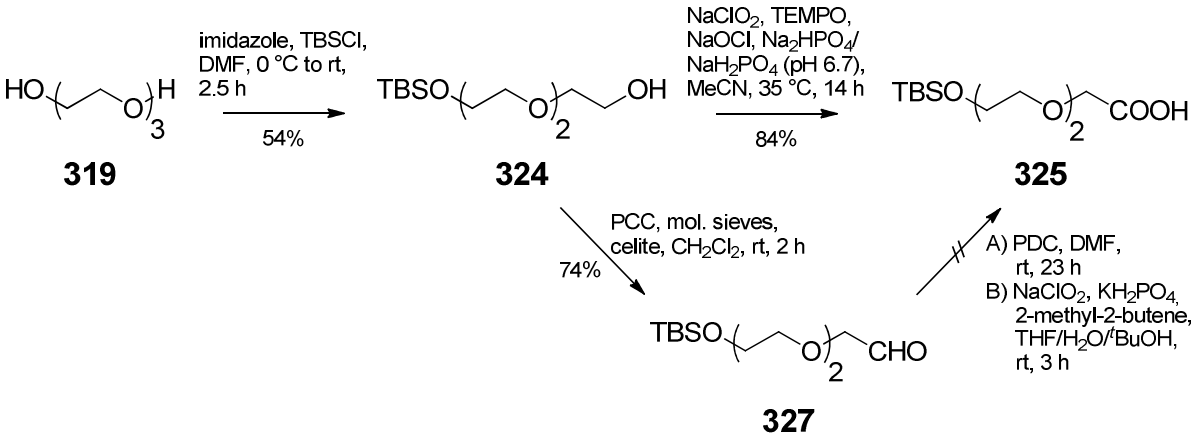


Scheme 3.19 Strategy to synthesise polyether bromo acid **323**

The alternative pathway began with the mono-TBS-protection. Three different protocols were tried: firstly, ^{n}BuLi was employed as a base[192] together with TBSCl and secondly, imidazole[172] was used; thirdly, the reaction was conducted in pyridine with a high excess of TEG (**319**) and catalytic quantities of DMAP.[193] All three ways furnished very pure products with the second method producing the highest yield (54%) (scheme 3.20).

The next step was the oxidation of alcohol **324** to carboxylic acid **325**. At first the direct oxidation using PDC[191] was tried again, leading to the same negative result as

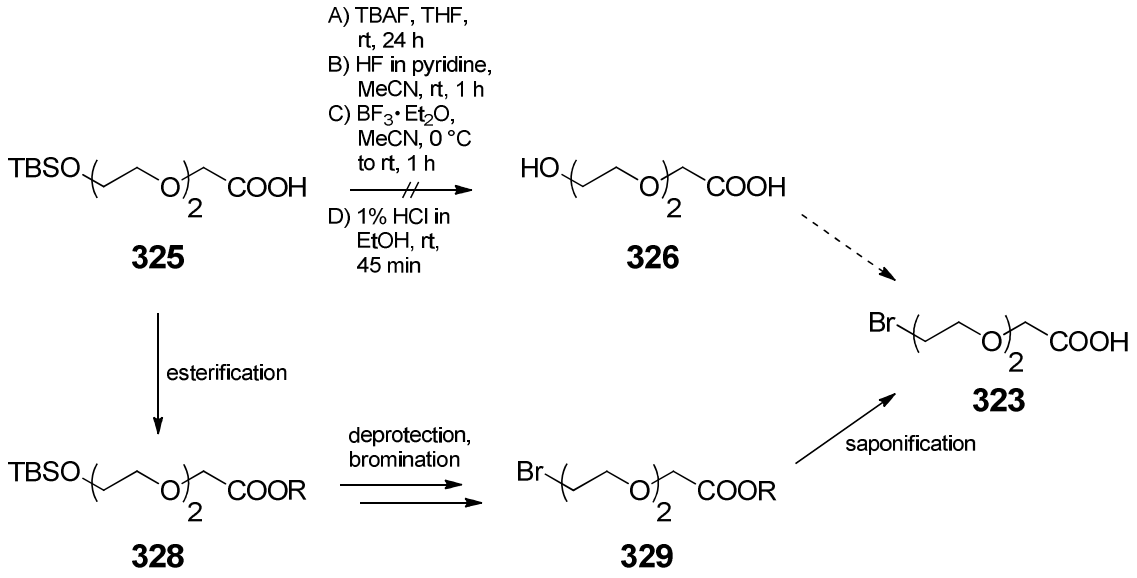
before. Then a two-step approach was attempted (scheme 3.20). The transformation of **324** into aldehyde **327** was achieved by PCC oxidation,[194,195] but the subsequent oxidation of **327** to **325** was not successful. Neither PDC nor a Pinnick oxidation[106,107] produced **325**. In the end, a one step oxidation, using sodium chlorite, sodium hypochlorite and (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO)[196] generated desired intermediate **325** (scheme 3.20). The most important feature of this reaction is that it had to be carried out at a pH of 6.7 (phosphate buffer) to be most effective.



Scheme 3.20 Mono-TBS-protection of TEG (**319**)[172] and one- and two-step oxidation attempts to synthesise carboxylic acid **325** from alcohol **324**

With protected carboxylic acid **325** in hand, four procedures were tested to achieve silyl-deprotecting to furnish **326** (scheme 3.21). As reagents TBAF,[197] HF in pyridine,[198] $BF_3 \cdot Et_2O$ in MeCN[199] and 1% HCl in EtOH were used.[200] Either no product was obtained because of complete decomposition or the very polar product could not be extracted from the aqueous phases during work up.

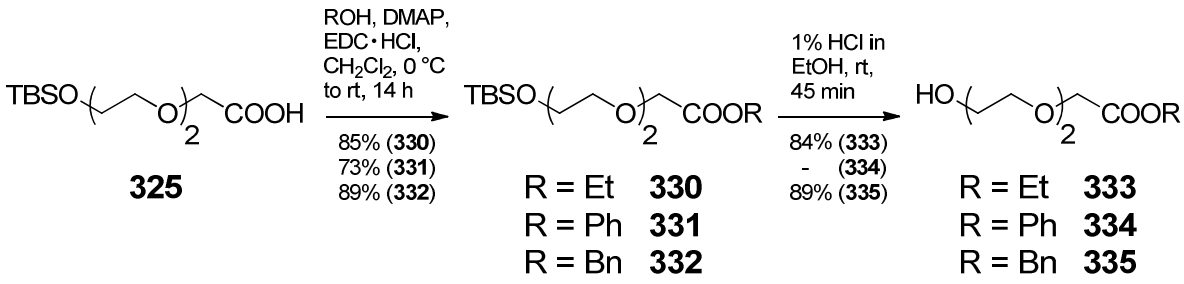
In order to circumvent the labile and polar intermediate **326**, a detour was suggested (scheme 3.21), based upon the idea of reducing the compounds polarity. Therefore, in the beginning, the free carboxylic acid functionality should be transformed into an ester (**328**). Then the TBS-protecting group should be cleaved to liberate the alcohol, which should be brominated to compound **329**. Saponification should finally lead to **323**.



Scheme 3.21 Attempts to deprotect **325** and proposed detour to synthesise bromo acid **323**

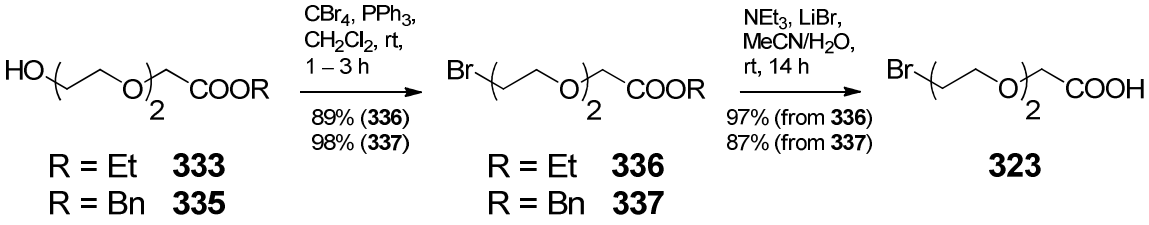
Three different esters were selected to reduce the polarity of **325**: an ethyl ester (**330**), a phenyl ester (**331**) and a benzyl ester (**332**). The three esters **330** – **332** were prepared under Steglich conditions, using DCC and DMAP.[75] Due to the mediocre yields, another protocol was tested by substituting DCC with EDC · HCl (scheme 3.22).[201] This lead to higher yields and purer products.

Again, the TBS-deprotection was performed, using TBAF[197] or 1% HCl in EtOH[182] as reagents. No products were detected using TBAF, but the reaction employing HCl furnished the desired alcohols **333** and **335** in good yields, with the exception of **334**, which was not obtained (scheme 3.22). The phenyl ester proved to be unstable under these conditions and the respective route was abandoned.



Scheme 3.22 Esterification of **325** using EDC · HCl[201] and TBS-deprotection experiments[182]

The conversion of alcohols **333** and **335** into respective bromo compounds **336** and **337** was achieved by an Appel reaction with CBr_4 and PPh_3 in excellent yields (scheme 3.23).[187] A reaction to transform **333** and **335** to bromo acid **323** in a one-pot reaction by applying triphenylphosphine dibromide (PPh_3Br_2) and zinc bromide (catalytically)[202] had to be discarded.



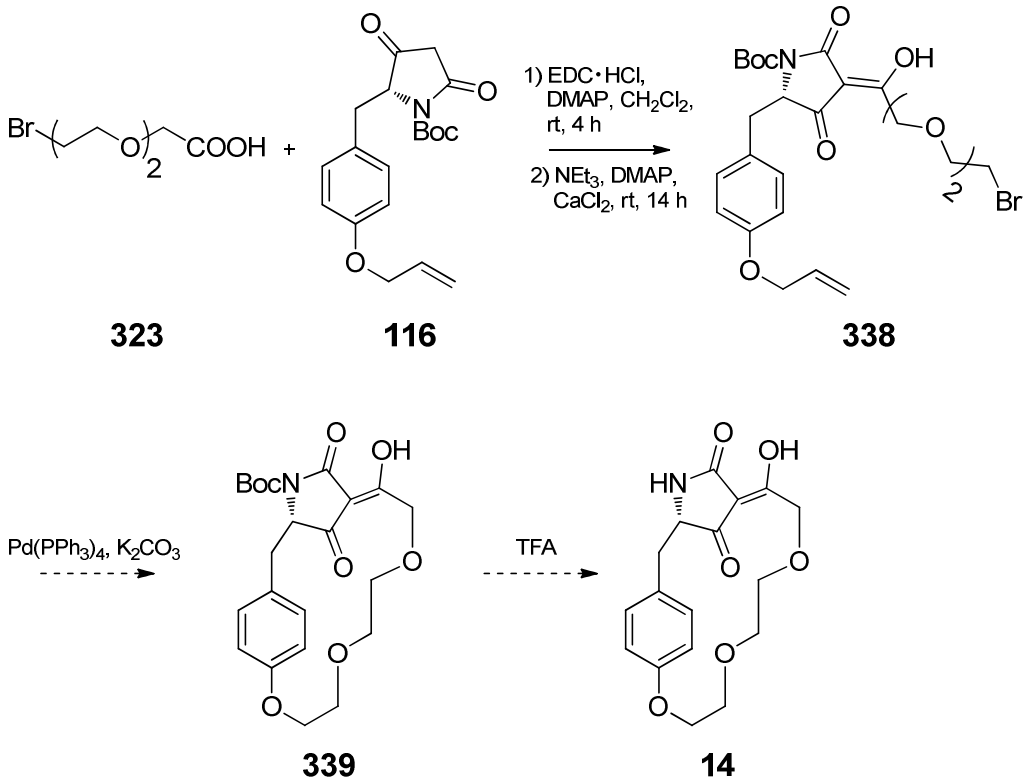
Scheme 3.23 Appel reaction to transform alcohols **333** and **335** into bromides **336** and **337**

To finalise the side chain, the ester had to be cleaved without harming the bromide (scheme 3.23). In the case of the benzyl ester **337**, hydrogenolysis was chosen, but the results were not promising. Concentrating on the ethyl ester compound **336**, a mild, lithium mediated ester hydrolysis employing NEt_3 and LiBr was tested.[175] The experiment not only gave desired bromo acid **323** in a yield of 98% but also furnished **323** from benzyl ester **337** in a yield of 84% (scheme 3.23).

Next, side chain **323** and tetramic acid building block **116** were coupled (scheme 3.24) by a 3-acylation procedure from Yoda *et al.*[78] **323** and **116** were reacted with EDC · HCl and DMAP to form the 4-*O*-acyltetramic acid. The rearrangement towards 3-acyl compound **338** was initiated in a one-pot procedure by adding NEt_3, DMAP and $CaCl_2$. According to the crude NMR spectra, the reaction worked but the purification of **338** was not achieved. Crystallisation and preparative HPLC were unsuccessful: the latter most likely because the formic acid in the HPLC solvent (essential when working with 3-acyltetramic acids) caused the decomposition of the side chain. Column chromatography produced no better results.

No solution to this problem was found during the course of this thesis. Different strategies could be attempted. Firstly, the 4-*O*-acyl intermediate could be purified before initiating the rearrangement, which will hopefully lead to a cleaner 3-acyltetramic acid **337**. Secondly, the crude product of **338** could be converted into its respective BF_2-complex by subjecting it to $BF_3 \cdot Et_2O$. These complexes are more easy to handle and should present a potential purification possibility.[58,137,203] Another

more direct pathway suggests the transformation of the crude product of **338** into respective macrocycle **339** without purification, followed by Boc-deprotection. Purification should be performed on desired product **14**.



Scheme 3.24 3-Acylation of tetramic acid **116** with polyether side chain **323** according to Yoda *et al.*[78] and missing steps towards macrocycle **14**

Initial experiments showed that neither the BF_2-complex nor the closed macrocycle could be detected with certainty. In the end, the purification of **338** and the synthesis of the desired macrocycle **14** remained unfinished, due to the lack of time and material.

3.1.4 Attempt at the total synthesis of macrocidin A

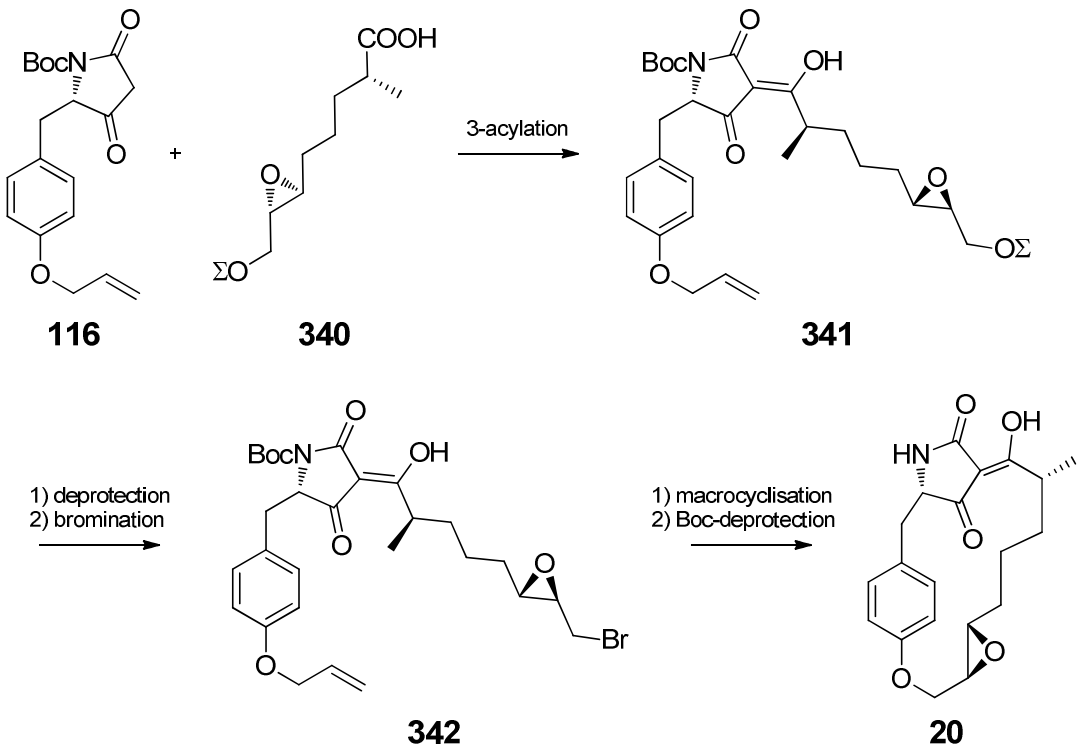
3.1.4.1 Previous work

In chapter 2.2.1.2 a synthesis of nor-macrocidin A (**109**) is shown,[98] depicting the work done prior to this work. In this thesis the main goal was to synthesise macrocidin A (**5**), which incorporates an additional stereocenter in comparison to **109**.

If one looks at the syntheses of **109**, the introduction of the epoxide was not achieved. As shown in literature,[97] the epoxide could not be installed when the macrocycle possessed an olefin. Therefore, the synthesis of Barnickel *et al*.,[98] shown in schemes 2.22 and 2.23, focused on introducing the stereocenters for the epoxide in an early stage of the synthesis via Sharpless dihydroxylation. Nevertheless, **109** was not obtained. The last attempt to synthesise **109** was made by M.Sc. Benjamin Christen,[101] who failed to facilitate the epoxidation of 3-acyltetramic acid **125**, which incorporated an olefin as a part of the 3-acyl side chain, because **125** could not be synthesised (scheme 2.25).

3.1.4.2 Plan to synthesise macrocidin A

The challenge to synthesise **20** involved the stereoselective installation of the epoxide and the stereoselective incorporation of the methyl group in the side chain. To achieve both goals, the former strategies should be merged with the synthetic routes employed for the generation of the macrocidin A analogues **10** – **13** in chapter 3.1.2.7.

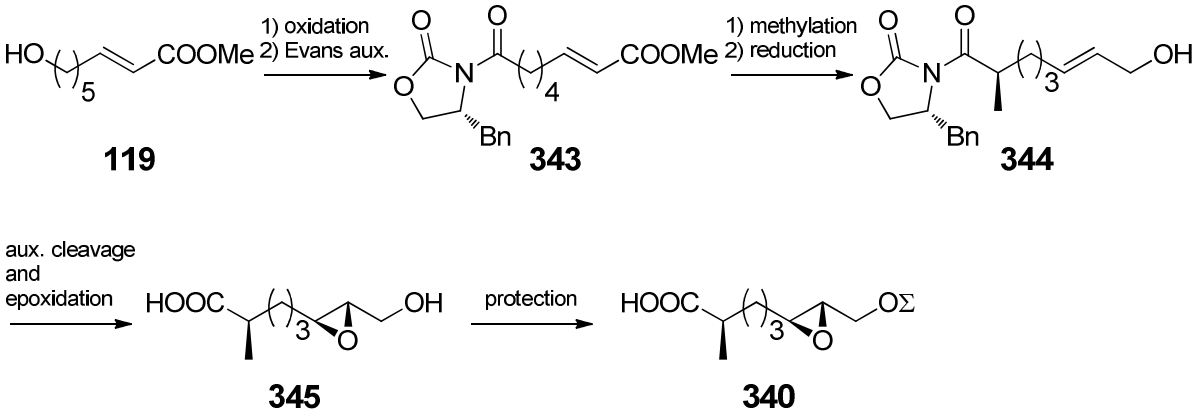


Scheme 3.25 Synthetic plan to synthesise macrocidin A (**5**) by using side chain **340**

When looking at the epoxide, the last possibility that remains unexplored is the introduction of the epoxide prior to the 3-acylation. Concerning the introduction of the methyl group, the Evans auxiliary strategy should be applied once more. The required building block **340** is shown in the synthetic plan in scheme 3.25.

3-Acylation according to Yoda *et al*.[79] should lead to compound **341** (the stereochemistry of the sidechain should be preserved) and the liberation of the hydroxyl group and the bromination should give molecule **342**. The last steps should involve the Pd-catalysed macrocyclisation followed by Boc-deprotection.

Scheme 3.26 shows the synthetic plan to synthesise side chain **340**. Well known compound **119**[152,204] should be oxidised and reacted with Evans auxiliary **289** to form **343**. From there, stereoselective methylation and reduction of the methyl ester should give allylic alcohol **344**. To generate intermediate **345**, either the auxiliary could be cleaved followed by stereoselective epoxidation or *vice versa*. Most likely, the alcohol functionality should be protected before proceeding to the 3-acylation.

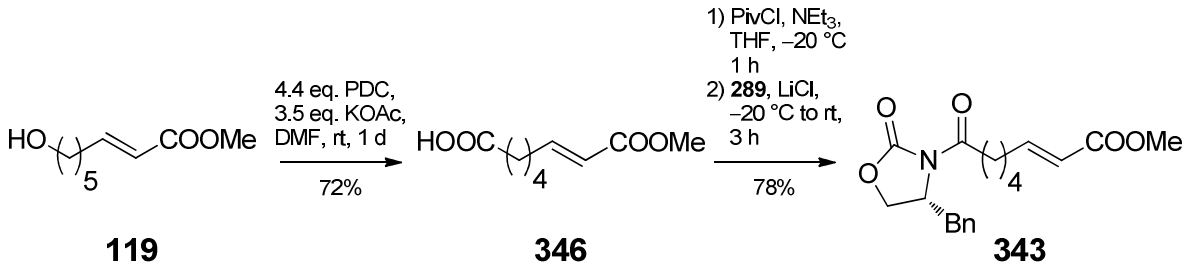


Scheme 3.26 Synthetic plan towards side chain **340**

3.1.4.3 First attempts to synthesise the macrocidin A side chain

The synthetic route started with the oxidation of building block **119**. First experiments were carried out using PDC as a reagent,[191,205,206] but the results were similar to the ones described before (chapter 3.1.3.2, scheme 3.18). As the major product, the ester of **119** with desired product **346** was detected. To suppress the esterification KOAc was tested as an additive to counteract the acidity of PDC. When

4.4 equivalents of PDC and 3.5 equivalents of KOAc were used, **346** was obtained in a yield of 72% (scheme 3.27).

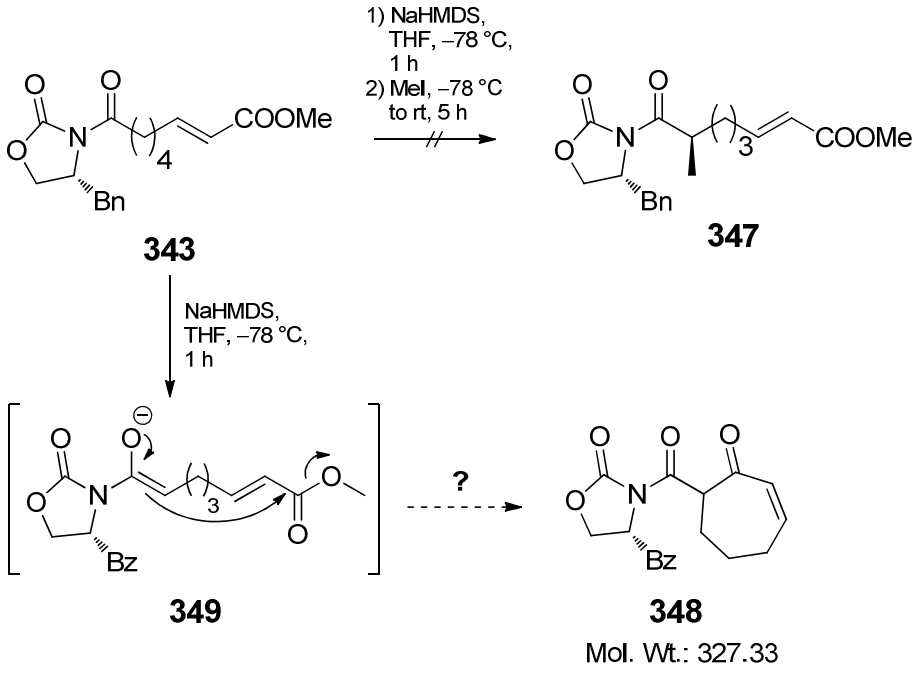


119 **346** **343**

Scheme 3.27 Optimised reaction condition for the oxidation of **119** towards carboxylic acid **346** and coupling of **346** with Evans auxiliary **289** according to Yadav *et al.*[178,179]

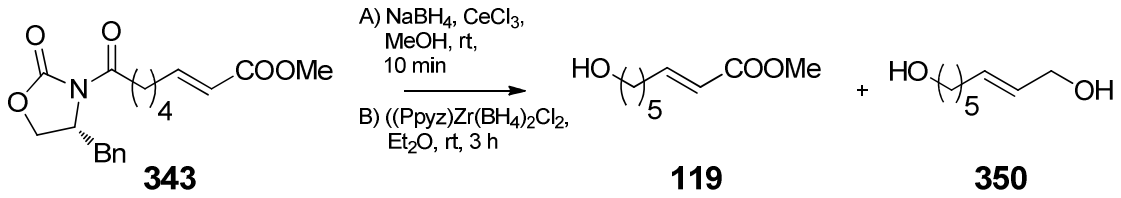
With carboxylic acid **346** in hand, **343** was synthesised in a yield of 78% using the same mild procedure shown in chapter 3.1.2.7.[178,179]

The next stage of the synthesis should be the stereoselective methylation of **343** to compound **347,**[178,179] but no product was found (scheme 3.28). The main isolated product, showed a mass of 327 g/mol. An explanation could be an intramolecular cyclisation to **348** as a result of an attack of enolate **349** on the methyl ester (scheme 3.66). Reducing the time of deprotonation from 1 h to 5 min proved to be ineffective.



Scheme 3.28 Attempted methylation of **343** and hypothetical side reaction

After encountering this obstacle, the original synthetic pathway was altered. If the methyl ester is not stable under methylation conditions, it should be removed prior to the methylation. Therefore, **343** should be reduced to the respective allylic alcohol. After the protection of the free alcohol, methylation should be attempted. Due to the fact, that the auxiliary might be unstable under reductive conditions, mild reduction methods were considered: a cerium mediated Luche reduction with sodium borohydride ($NaBH_4$)[207,208] and a reduction with a zirconium borohydride piperazine complex.[209] None of these experiments yielded the desired allylic alcohol, because the auxiliary did not survive the transformation (scheme 3.29). Only **119** and diol **350** were found. As a last resort, a two-step reaction, incorporating saponification of the methyl ester and subsequent borane reduction, was suggested, but without success. Ultimately the complete pathway had to be abandoned.



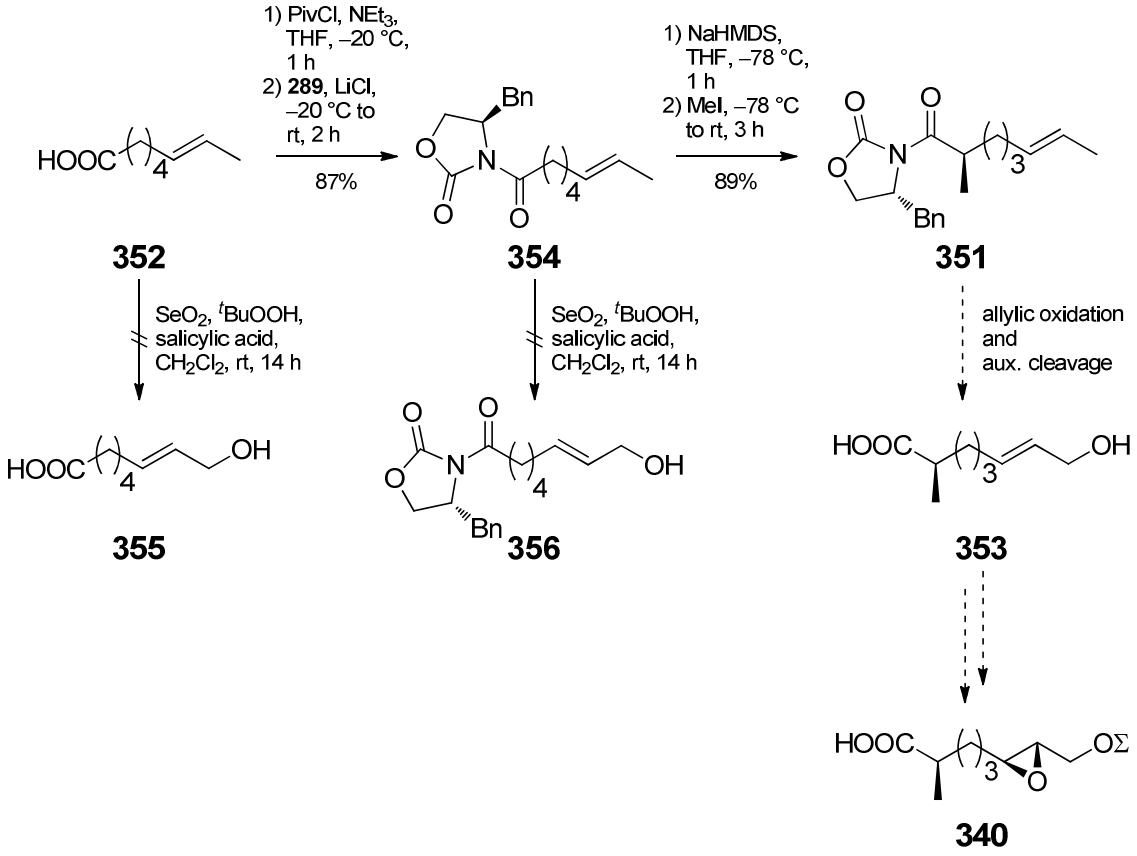
Scheme 3.29 Unsuccessful trials to reduce **343** without harming the auxiliary[207,209,210]

3.1.4.4 Attempt to synthesise the macrocidin A side chain via allylic oxidation

Due to the fact that the problems encountered were based upon the ester moiety in **119**, the next strategy encompassed the introduction of the allylic alcohol at a later stage of the synthesis.

While synthesising of penicillenol C1 in our group,[211] the stereoselective methylation, using Evans auxiliary **289**, was applied to synthesise compound **351** (scheme 3.30). This was achieved in two steps, starting from unsaturated acid **352**. Concerning our target **340**, **351** should be subjected either to a selenium dioxide (SeO_2) mediated allylic oxidation,[212–214] followed by an auxiliary cleavage or *vice versa*. This should give intermediate **353**, which could be converted into **340** in a few more steps.

To check whether the allylic oxidation would work in our case, two separate reactions were tried. Employing literature procedures, **352** and intermediate **354** were subjected to allylic oxidation conditions but without success (Scheme 3.30). No reaction to proposed products **355** or **356** was observed. Therefore, this plan was also dismissed.

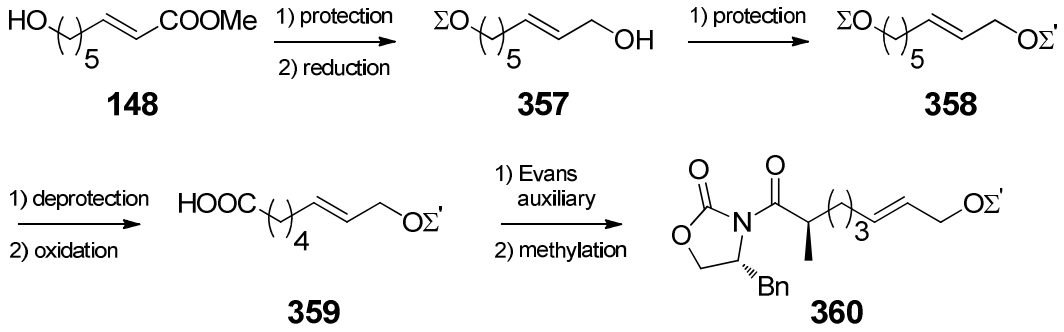


Scheme 3.30 Synthetic plan to synthesise **340** via allylic alcohol **353** applying a SeO_2 mediated allylic oxidation strategy[212–214] based upon the work of Kempf *et al.*[211] and unsuccessful experiments to convert **352** or **354** into allylic alcohols **355** or **356**

3.1.4.5 Modified strategy to synthesise the macrocidin A side chain

The next strategy was a combination of the strategies of Barnickel[152] and Christen.[101] In order to circumvent the problems with the methyl ester during stereoselective methylation, the new strategy should involve straight forward protecting group chemistry. Scheme 3.31 outlines this process, starting with

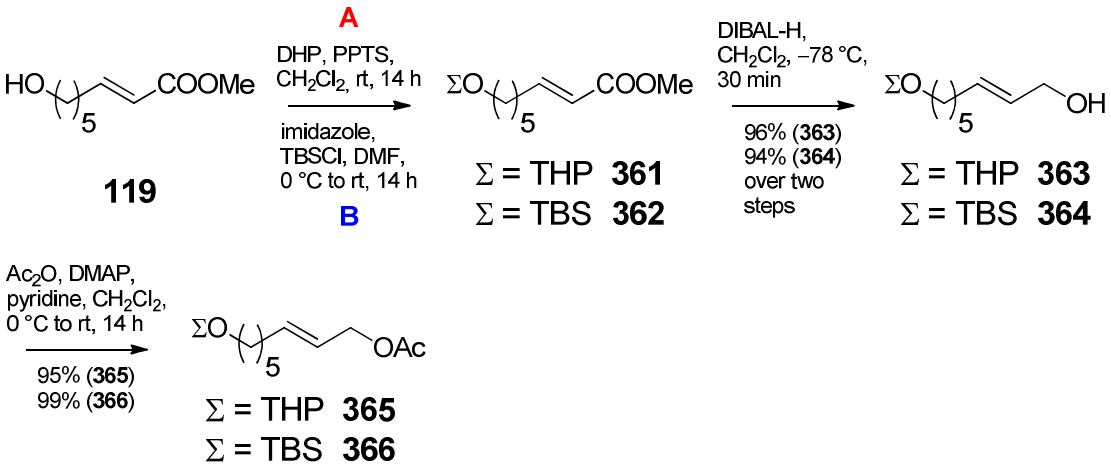
compound **119**. The alcohol should be protected and the methyl ester reduced to allylic alcohol **357**. From there, **357** should be reacted with a protecting group orthogonal to the first one to give **358**. Then, the first alcohol should be deprotected and oxidised to carboxylic acid **359**. Again the Evans auxiliary should be used to introduce the methyl group in two steps and to yield **360**.



Scheme 3.31 Synthetic plan to synthesise intermediate side chain **360**

The selection of the right protecting groups was essential for the success of this route. Therefore, two parallel pathways were pursued, with two different protecting group patterns.

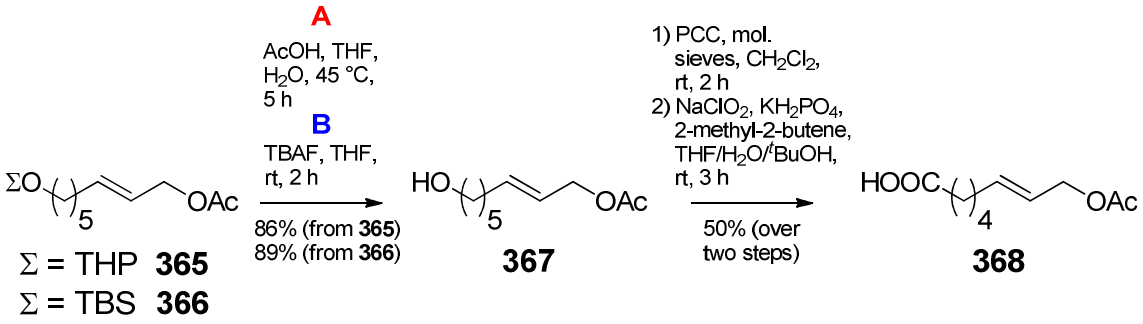
In the beginning, alcohol **119** was protected by applying the THP- or the TBS-protecting group (scheme 3.32).[172]



Scheme 3.32 THP- (**A**) and TBS-protection (**B**) of **119**, subsequent DIBAL-H reduction and Ac-protection of allylic alcohols **363** and **364**[215]

Well known literature procedures gave desired compounds **361**[171] and **362**, before both were reduced to the respective allylic alcohols **363** and **364** using DIBAL-H[152,216]. For the protection of liberated allylic alcohols **363** and **364**, the acetyl (Ac) group was chosen, because it should be stable under THP- and TBS-cleavage conditions. The protection to **365** and **366** proceeded as planned using acetic anhydride (Ac_2O) and DMAP in pyridine (scheme 3.32).[215]

The following steps involved the removal of the THP-/TBS-protecting group to form **367** and the oxidation of the liberated alcohol to carboxylic acid **368**. Standard THP-deprotection conditions employing *p*-TosOH in MeOH[217] gave two products in a ratio of 1:1. By NMR-spectroscopy, one was identified as desired product **367** and the other as its cis isomer. Somehow, the reaction conditions triggered the isomerisation of the double bond. Finally, clean THP-deprotection was achieved by reaction with AcOH in THF and H_2O (scheme 3.33).[170] In parallel experiments, TBS-compound **366** was deprotected using TBAF to synthesise **367** (scheme 3.33).[184]

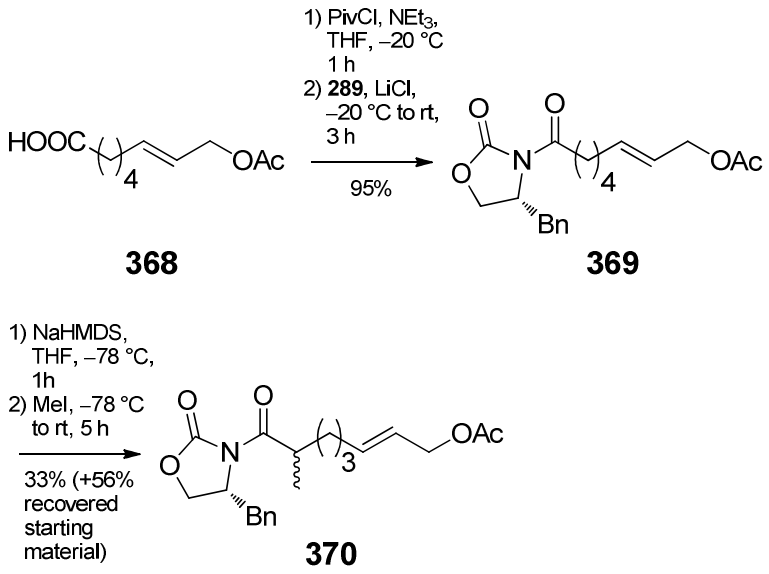


Scheme 3.33 Generation of alcohol **367** via THP- (**A**) and TBS-deprotection (**B**) of **365** and **366** respectively[170,184] and two-step oxidation of **367** to carboxylic acid **368**[107,195]

The next task was the transformation of the liberated alcohol moiety of **367** into carboxylic acid **368** by oxidation. Once again, the one-step procedure applying PDC produced negative results, giving a mixture of the respective aldehyde and acid **368** in low yields. However, the two-step procedure succeeded in preparing **368** in mediocre yields of 50% over two steps (scheme 3.33). PCC oxidation[195] furnished the respective aldehyde and Pinnick oxidation[106,107] carboxylic acid **368**.

Then, the same procedure as before was applied to facilitate the reaction between **368** and Evans auxiliary **289**,[178,179] generating product **369** in a superb yield of 95% (scheme 3.34). With **369** in hand, the stereoselective methylation was conducted as

before (scheme 3.34).[178,179] Although methylated compound **370** was isolated, next to a large amount of unreacted educt, only low stereoinduction was detected. In addition, Ac-deprotected compound was isolated, giving rise to the fact that the Ac-group was too labile.



Scheme 3.34 Coupling of Evans auxiliary **289** with Ac-protected compound **368**[178,179] and stereoselective methylation attempt of **369**

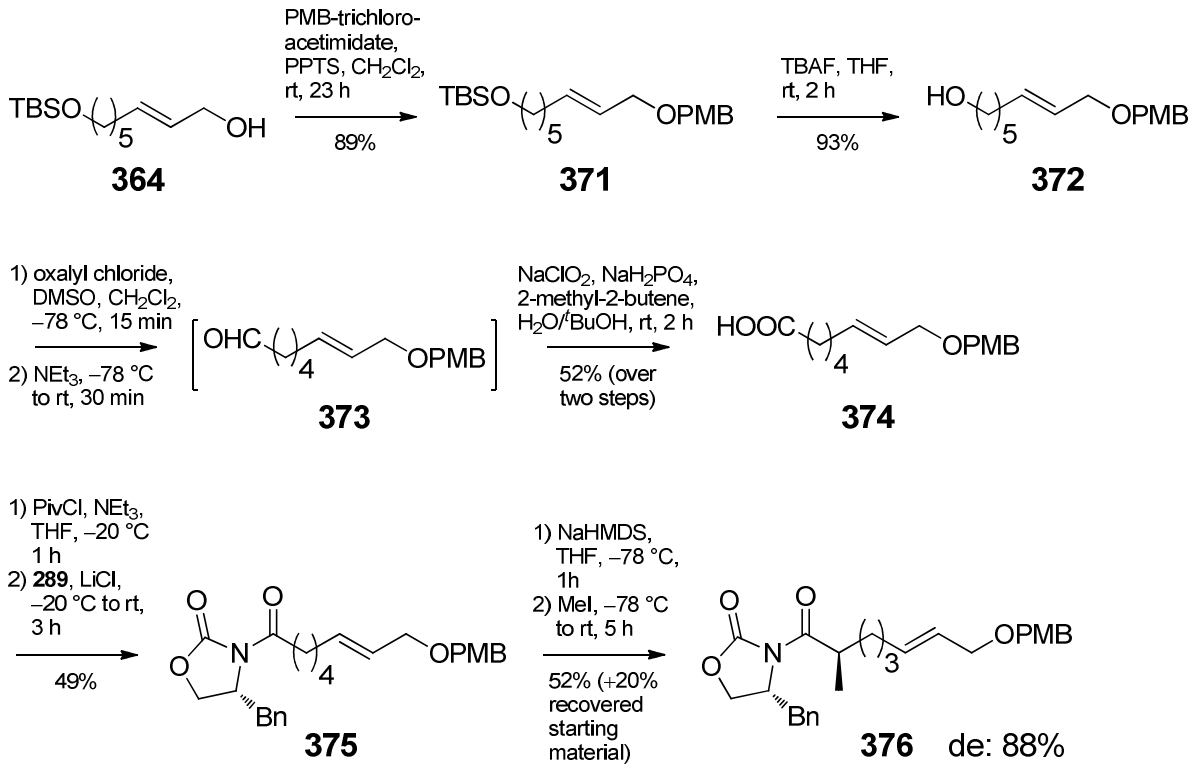
Due to the presumption that the instability of the Ac-protecting group could exhibit a disrupting effect on the stereoselective methylation, a new protecting group strategy was developed. The PMB-protecting group should be used instead of the Ac-group. It should not be susceptible to a nucleophilic attack by the enolate involved in the methylation process.

For this reason, the whole sequence was replicated using the PMB-protecting group (scheme 3.35). Starting from compound **364**, two methods for the PMB-protection were tested. The first one applied *para*-methoxybenzyl chloride (PMBCl) with NaH and catalytic amounts of tetrabutylammonium iodide (TBAI)[218] and the second one PMB-trichloroacetimidate and PPTS.[219] The latter proved superior in producing **371**, because of the high yields and easy purification.

From there the next four steps were performed according to the same protocols presented before (scheme 3.35). TBS-deprotection[184] of **371** to **372** was followed by a two-step oxidation via aldehyde **373** to carboxylic acid **374**. In this case the oxidation to aldehyde **373** was conducted by rapid Swern oxidation[220] due to the

higher crude yields (96%). The coupling of **374** with Evans auxiliary **289** lead to precursor **375**.

Next, the stereoselective methylation was tested using standard conditions.[178,179] Scheme 3.35 shows that the synthesis of **376** worked according to plan. From GC measurements the de of the reaction was calculated to be 88% and as a by-product about 20% of unreacted starting material was reisolated.



Scheme 3.35 Preparation of side chain **375**, incorporating the PMB-protecting group, for the subsequent stereoselective methylation

3.1.4.6 Outlook

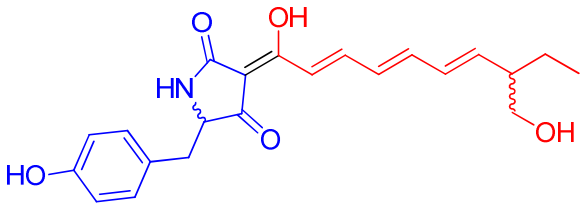
The main question that remains to be addressed is when to introduce the epoxide. The finalisation of the side chain should incorporate PMB-deprotection to liberate allylic alcohol **344** to achieve good enantioselectivity when performing the epoxidation. Then, either the epoxidation should be carried out followed by oxidative auxiliary cleavage or *vice versa* to give intermediate **345** (scheme 3.26). After Protection of the alcohol and 3-acylation with tetramic acid **116** should give **341** (see chapter 3.1.4.2, scheme 3.25). The last steps to synthesise macrocidin A (**5**) would

involve bromination of the liberated allylic alcohol to **342**, Pd-mediated macrocyclisation and deprotection.

3.2 Contributions to the synthesis of torrubiellone D

3.2.1 Overview

The second part of this thesis dealt with the synthesis of torrubiellone D (**15**), a polyenoyl tetramic acid that has not been totally synthesised to date. It exhibits biological activity and is a member of an entire torrubiellone family (see chapter 2.2.2).[115] Figure 3.6 illustrates its structure which is comprised of a tetramic acid part (blue), derived from tyrosine, not unlike the one that can be found in macrocidin A (**5**) and a polyunsaturated side chain (red).



15

Figure 3.6 Structure of torrubiellone D (**15**)

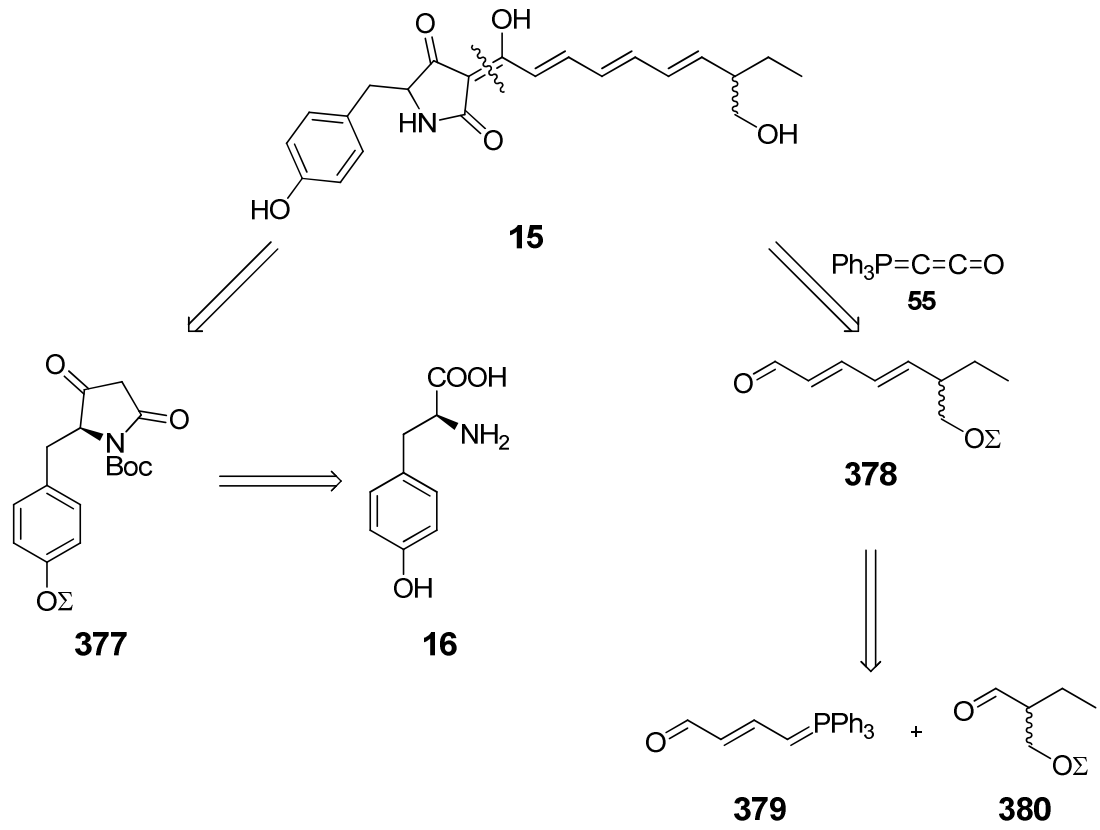
The work presented in the following chapters was carried out in close cooperation with M.Sc. Julia Stöckl[221] and B.Sc. Sebastian Bruckner[222] during the course of their bachelor's theses.

3.2.2 Retrosynthetic approach

Torrubiellone D (**15**) was split into two main fragments (scheme 3.36). The first one being L-tyrosine tetramic acid fragment **377** which was similar to the one synthesised for macrocidin A (**5**).

The second fragment was bisunsaturated aldehyde **378**, which should be coupled to the tetramic acid core by Wittig reaction. Aldehyde **378** should be derived from two

smaller intermediates, **379** and **380**, again combined by Wittig reaction. As shown in scheme 3.36, a racemic approach should be attempted, because the configuration of the stereocenter of the side chain is not known.



Scheme 3.36 Retrosynthetic approach to assemble torrubiellone D (**15**) from fragments **16**, **379** and **380**

There are known syntheses for fragments **379**[223,224] and **380**.[192,225] If the synthesis works as planned, a stereoselective synthesis of **380** should allow the generation of **15** in a stereoselective manner.

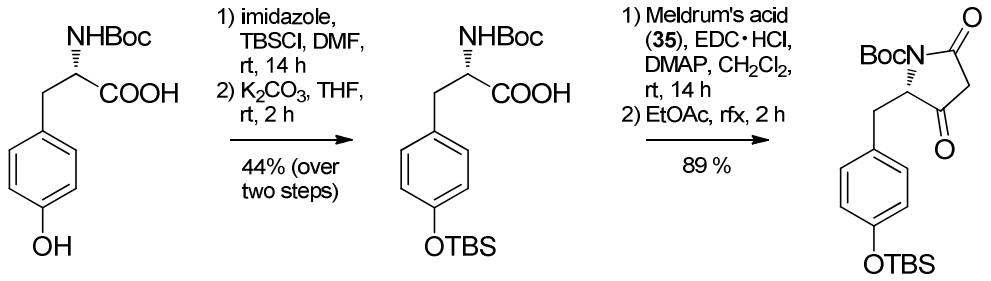
3.2.3 Synthesis of the tetramic acid part

The tetramic acid part for the total synthesis of torrubiellone D (**15**) was similar to the one used for the synthesis of macrocidin A (**5**) and its analogues **6** – **14**.

The only difference was the protecting group of the phenolic hydroxyl group. Instead of applying the allyl-protecting group, the TBS-protecting group was utilised (scheme 3.37), because the side chain fragment should also contain a TBS-

protecting group (chapter 3.2.4). After the coupling of both major fragments it should be possible to execute a global deprotection.

At first, Boc-protected L-tyrosine (**381**) was TBS-protected to give **382**. The reaction was carried out as a two-step procedure.[226] This involves the protection of the phenolic hydroxyl functionality and the carboxylic acid moiety and the subsequent hydrolysis of the undesired silyl ester with K_2CO_3 besides the silyl ether. Then, tetramic acid **383** was formed using EDC · HCl, DMAP and Meldrum's acid (**35**).[53] Starting from **381**, the complete sequence to **383** was achieved in a total yield of 39% (scheme 3.37).



381 **382** **383**

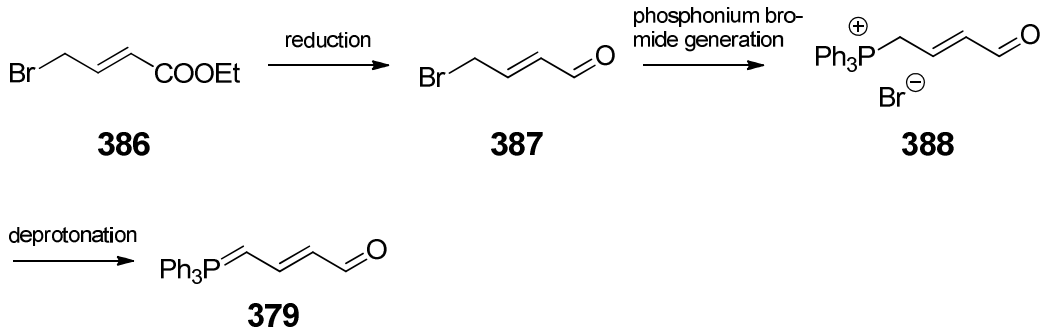
Scheme 3.37 Synthesis of tetramic acid **383** as a building block for the total synthesis of torrubiellone D (**15**)

3.2.4 Synthesis of the side chain

3.2.4.1 Synthetic plans to generate the side chain

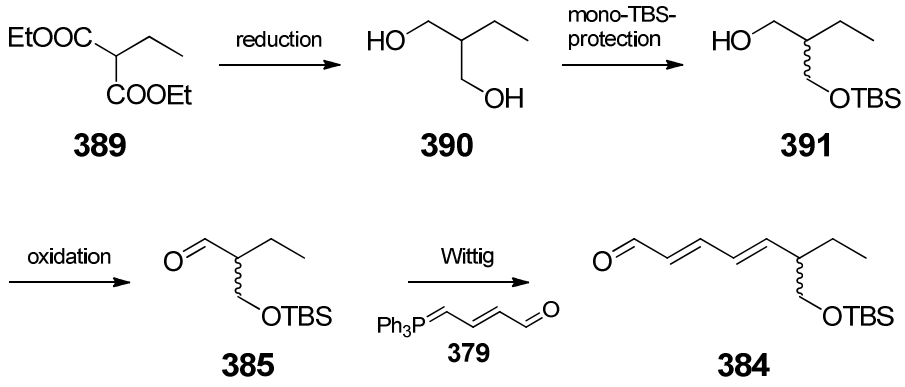
As referred to in the last chapter, the TBS-protecting group was chosen as the preferred protecting group during the synthesis of **15**. Therefore it was once again used for the synthesis of desired side chain **384**.

384 is comprised of two smaller fragments **379** and **385**, which were synthesised separately (scheme 3.38 and 3.39). C4-fragment **379** should be synthesised in three steps starting from ethyl 4-bromocrotonate (**386**) (scheme 3.38). The sequence should start by reduction of **386** to respective aldehyde **387**. The next two steps would involve the generation of phosphonium bromide **388** and the deprotonation of **388** to target ylide **379**, according to literature procedures.[223,224]



Scheme 3.38 Synthetic plan to synthesise C4-fragment **379**

The second fragment required for the synthesis of side chain **384** was branched compound **385**. **385** should be derived from commercially available diethyl ethylmalonate (**389**) (scheme 3.39). First of all, **389** should be reduced to symmetrical diol **390**, before one hydroxyl group should be TBS-protected to give **391**. From this stage on, the work should be continued with a racemic mixture of **391** for the rest of the synthesis. Final oxidation to aldehyde **385** should precede the coupling of fragment **379** with fragment **385** by Wittig reaction to complete the synthesis of side chain **384**.

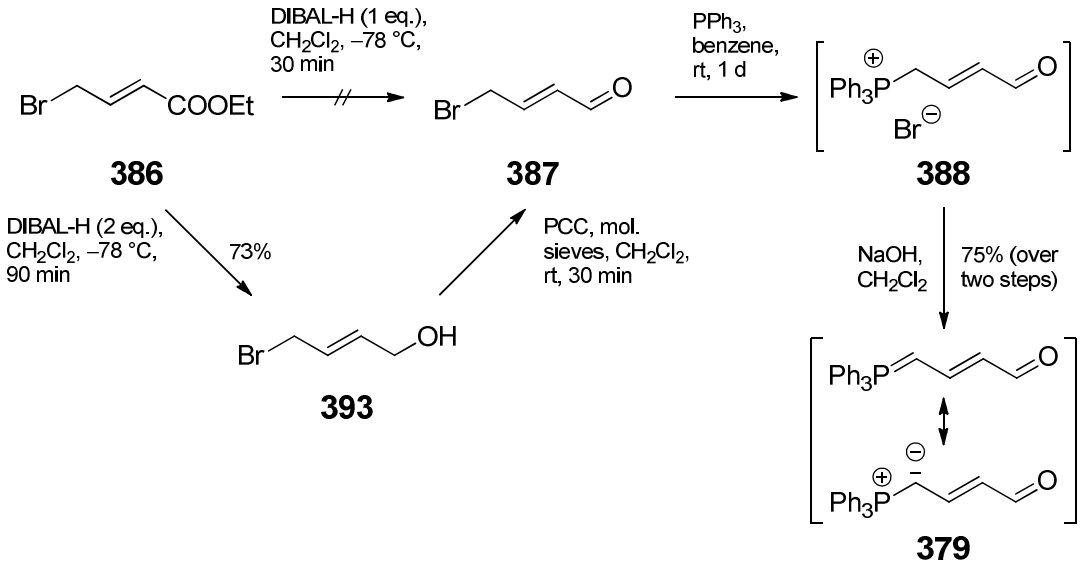


Scheme 3.39 Synthetic plan to synthesise building block **385** and combination with **379** to construct complete side chain **384**

3.2.4.2 Synthesis of two different C4-fragments

Two different C4-fragments were synthesised. In addition to originally proposed side chain **379**, alternative building block **392** was prepared to be more flexible in the following reactions.

The sequence to synthesise **379** started with commercially available ethyl 4-bromocrotonate (**386**). In the beginning, the possibility of reducing the ethyl ester of **386** to aldehyde **387** was tested (scheme 3.40).[227] DIBAL-H was used as the reducing agent.[152,216] Simultaneously, two products were detected: desired aldehyde **387** and allylic alcohol **393**. Since the overreduction of **386** to **393** could not be avoided, **386** was entirely transformed into alcohol **393** and oxidised from there by applying PCC, to desired compound **387** (scheme 3.40).[194,195] **387** was very labile when exposed to air and easily decomposed, which made the determination of the exact yield more complicated.

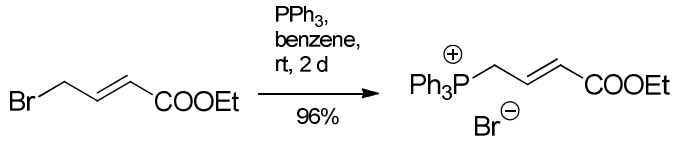


Scheme 3.40 Selective transformation of ethyl ester **386** to aldehyde **387** in a two-step reduction/ oxidation sequence[152,195,216] and finalisation of the synthesis of unsaturated C4-fragment **379**[223,224,228]

With aldehyde **387** in hand, the two-step conversion into ylide **379** was undertaken (scheme 3.40). As described in literature,[223,224,228] **387** was reacted with PPh_3 in benzene to give phosphonium bromide **388**, which displayed a similar instability as observed for aldehyde **387**. Therefore, the deprotonation to ylide **379** was performed without delay upon treatment with 1M NaOH. Ylide **379** was obtained as a deep red solid in a yield of approximately 75%.

To avoid isolation and purification of unstable intermediates **393** and **387**, the whole sequence starting from **386** to give **379** was carried out in quick succession under argon atmosphere. **379** was produced in a yield of 30% over four steps.

As a safeguard, unsaturated compound **392** was synthesised directly from **386** by reaction with PPh_3 (scheme 3.41).[229,230] **392** has such a high stability, that the deprotonation to form the ylide should be carried out *in situ*, prior to the Wittig reaction.



386 **392**

Scheme 3.41 Formation of phosphonium bromide **392** from ethyl 4-bromocrotonate (**386**)[229,230]

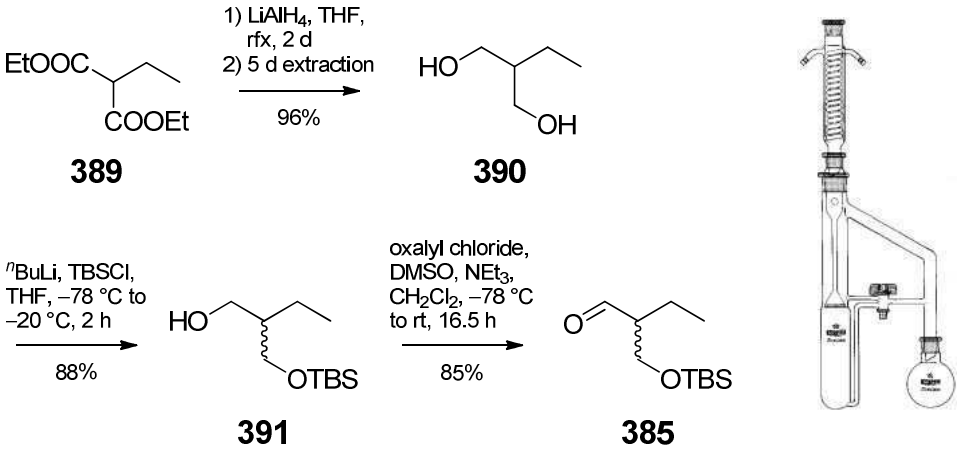
In the end, two potential coupling partners were generated (**379** and **392**), which could be reacted with fragment **385** in a Wittig reaction to either form unsaturated building block **384** or a precursor that in turn could be transformed into **384** in two steps. The coupling experiments are presented in chapter 3.2.4.4.

3.2.4.3 Synthesis of the racemic aldehyde fragment

The synthesis of second building block **385** for the creation of building block **384** started with diethyl ethylmalonate (**389**) according to a literature procedure[192]. The first step was a simple reduction of both ethyl esters functionalities to respective diol **390**. Different methods to achieve the reduction, either by using lithium aluminium hydride ($LiAlH_4$)[192,231] or $NaBH_4$,[232] were found but none produced **390** in yields higher than 12%. It was discovered that the reasons for this were the low boiling point of **390** and its low solubility in low boiling solvents. In the end, the yields reported in literature, were reproduced by the use of $LiAlH_4$ and a continuous extraction apparatus for five days (scheme 3.42).[231]

The next step to desired aldehyde **385** was the mono-TBS-protection of diol **390**. Statistically, only a maximum yield of 50% of **391** was to be expected. Three different alternatives were tried, employing imidazole at room temperature[172], ^{n}BuLi at −78 °C[192] and sodium hydride (NaH) at room temperature.[233] Together with TBSCl, imidazole generated desired mono-protected compound **391** in 22% yield. The

experiment with ^{n}BuLi showed the best results with 88% yield (scheme 3.42) and the last one with NaH gave **391** in a yield of 76%. Again, after work up, the evaporation of the solvents used was performed gently because of the high volatility of **391**.



Scheme 3.42 Synthetic route towards aldehyde **385** by reduction of **389** to diol **390**,[231] mono-TBS-protection[192] and oxidation of alcohol **391**[192,234]; picture of a continuous extraction apparatus for solvents with a higher density than water

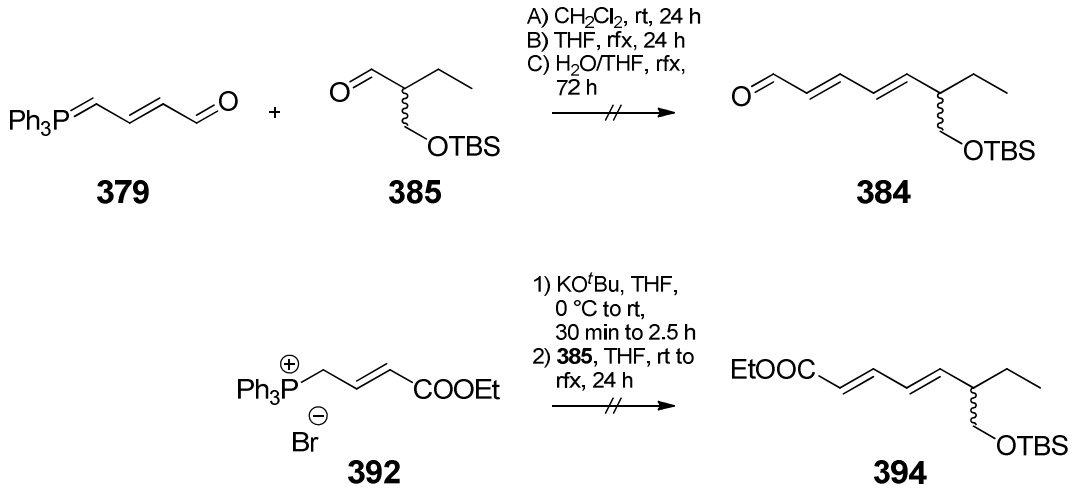
Continuing with **391**, the oxidation to corresponding aldehyde **385** was the last step to conclude the synthesis of the building block. Different methods were screened to determine the optimal procedure. In the beginning, a PCC oxidation was tested[194,195] but no desired product could be isolated due to complete decomposition of **391**. The same negative result was achieved when using tetrapropylammonium perruthenate (TPAP)[235,236] and *N*-methylmorpholine-*N*-oxide (NMO) as oxidant and co-oxidant. Positive results were provided by applying either Swern oxidation conditions (oxalyl chloride, dimethylsulfoxide (DMSO) and NEt_3)[192,234] or DMP as an oxidant.[105]. The Swern oxidation turned out to be superior and generated **385** in a yield of 85% instead of only 50% when DMP was utilised.

In the end **385** was constructed in an overall yield of 72% over three steps and was available for the combination via Wittig reaction with **379** or **392**.

3.2.4.4 Synthesis of the aldehyde side chain

With ylide **379** and aldehyde **385** in hand, the synthesis of unsaturated aldehyde building block **384** was undertaken. Both fragments were subjected to standard Wittig conditions. The reaction was carried out according to Rodriguez *et al.*[237] who also used **379** as a means of introducing a C4 fragment (scheme 3.43), but no product could be isolated. Neither the change from CH_2Cl_2 to THF as a solvent nor the increase in reaction temperature gave desired product **384**. Another method was tried, carrying out the reaction in a mixture of H_2O and THF but without success.[238]

Alternatively, the olefination was repeated with second C4 building block **392** instead of **379** (scheme 3.43). Phosphonium bromide **392** was transformed into the corresponding ylide *in situ* by the use of KO^{t}Bu. In a second step, aldehyde **385** was added.[230] Although both educts were consumed in the course of the reaction desired product **394** was only isolated in a yield of 3%. Alterations of the reaction conditions[225] did not improve the result.

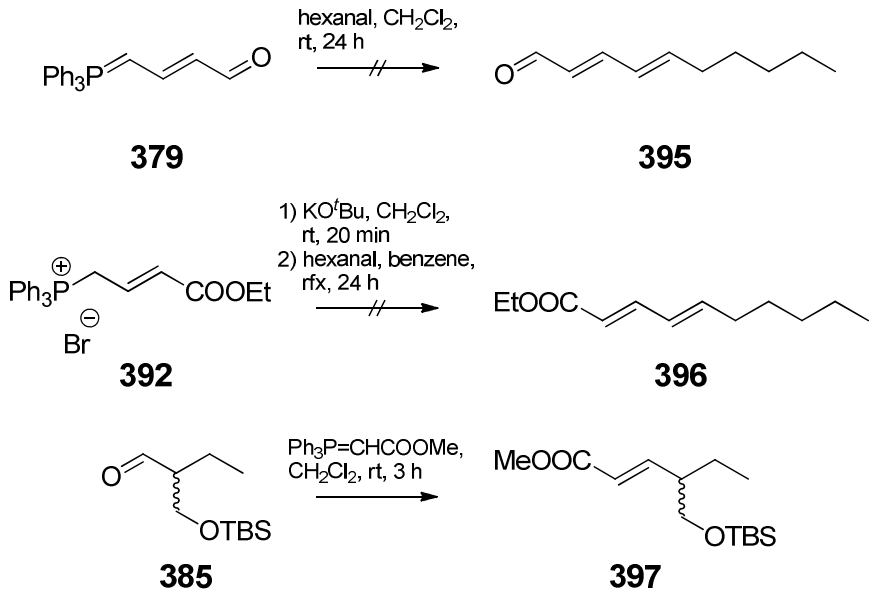


Scheme 3.43 Unsuccessful Wittig olefinations of ylide **379** or alternative C4 fragment **392** and aldehyde **385**[225,230,237,238]

At this stage, the reason for the failure of the Wittig reaction was examined to determine the cause of the problems. Therefore, a series of control experiments were carried out to check whether one of the fragments **379**, **392** or **385** was responsible for the disappointing results.

379 and **392** were reacted with commercially available hexanal in the same manner as described before and **385** was combined with model ylide

Ph_3P=CHCOOMe (scheme 3.44). The results showed that the problems could be traced back to both C4 fragments. The olefinations to products **395** and **396** were not achieved, whereas the Wittig reaction to form **397** worked well.

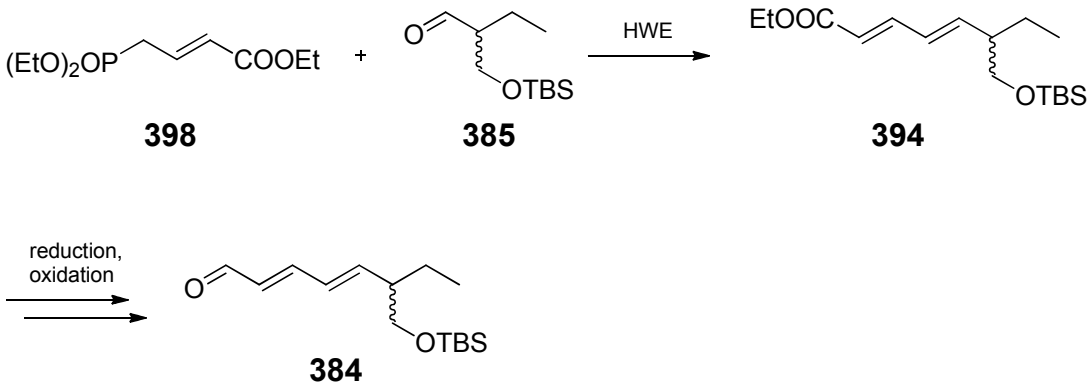


Scheme 3.44 Model reactions of the different fragments **379**, **392** and **385** to determine their reactivity under Wittig reaction conditions

All facts combined, it was necessary to think of an alternative strategy to synthesise side chain **384**.

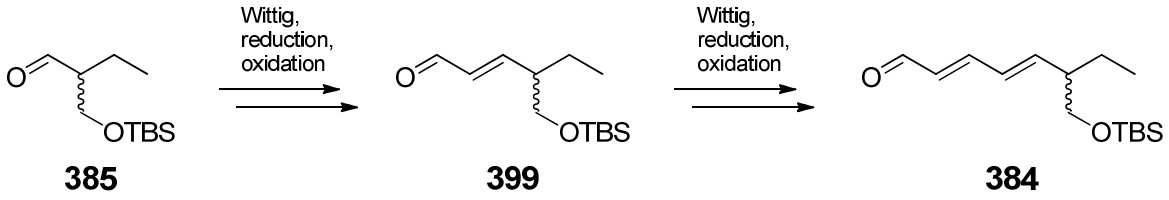
3.2.4.5 Alternative strategies to synthesise the elongated aldehyde side chain

Due to the fact that the Wittig reaction to form side chain **384** had to be abandoned, two alternative strategies were devised. The first approach should involve a Horner-Wadsworth-Emmons reaction (HWE) instead of a Wittig olefination (scheme 3.45). Instead of using an ylide, phosphonate **398** should be employed to produce intermediate **394**, which should be reduced and selectively oxidised to give desired aldehyde **384**.



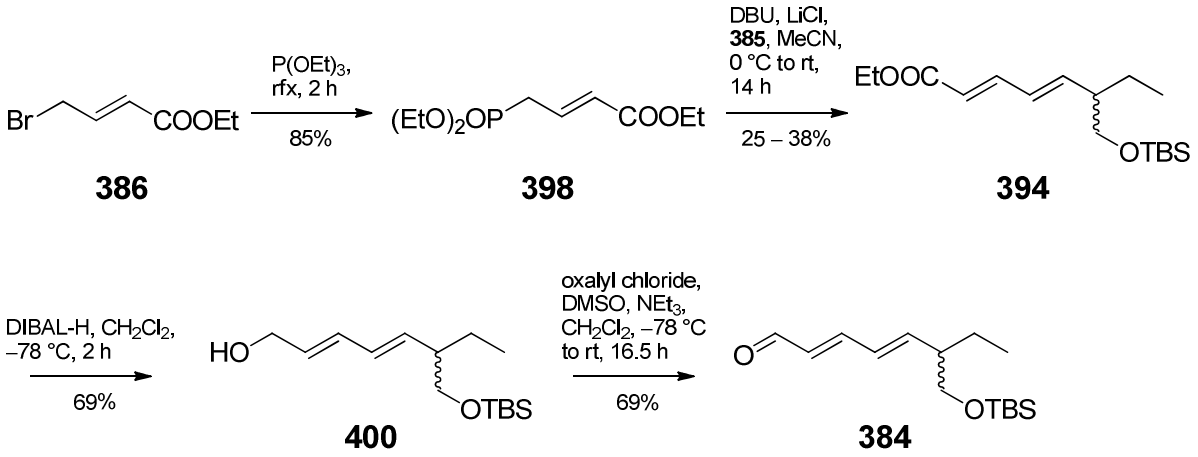
Scheme 3.45 First alternative route to generate side chain **384** employing the HWE olefination

The second method should be comprised of a step by step elongation of aldehyde **385** by two consecutive Wittig reaction, reduction and oxidation sequences (scheme 3.46). Using the simple ylide Ph_3P=CHCOOMe the first sequence should give intermediate **399** and the second should yield desired product **384**. This route is based upon a pathway described by Irlapati *et al*.[225]



Scheme 3.46 Stepwise elongation of **385** applying two consecutive three reaction sequences

Starting with the first approach, the initial task was the synthesis of phosphonate **398** by an Arbuzov reaction of ethyl 4-bromocrotonate (**386**) with triethyl phosphite ($P(OEt)_3$).[239,240] The reaction gave desired phosphonate **398** in 85% yield (scheme 3.47). The following step was the execution of the HWE olefination of phosphonate **398** and aldehyde **385**. The first experiments used LiHMDS as a base to activate the phosphonate,[239] but only a yield of 10% of **394** was achieved. The substitution of LiHMDS by NaHMDS or KHMDS[241] could not improve the results. Then, another procedure utilising the non-nucleophilic 1,8-diazabicycloundec-7-ene (DBU) as a base and LiCl as an additive was tested (scheme 3.47).[242] The reproducibility turned out to be a problem, but the yields now ranged from 25 – 38% and enough material of **394** could be produced to continue along the envisioned route.



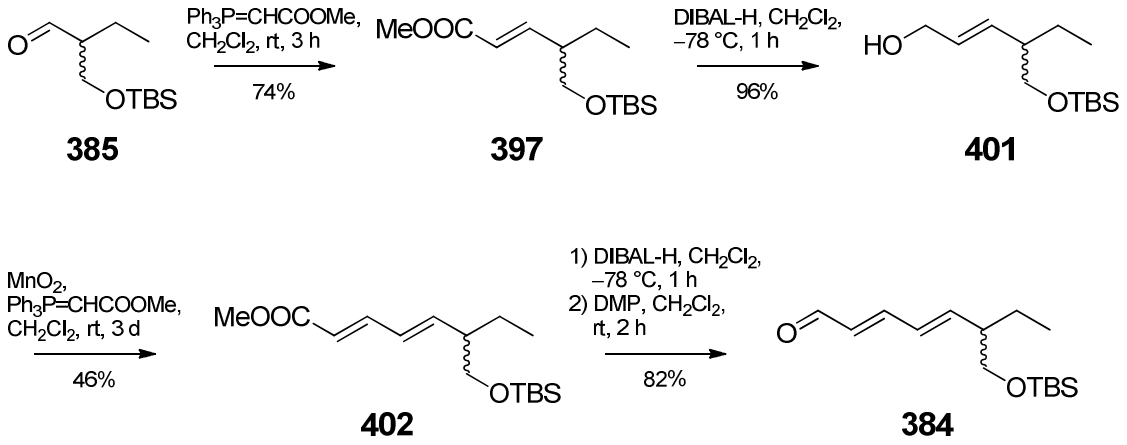
Scheme 3.47 First pathway to synthesise aldehyde **384** by Arbuzov reaction[239,240], HWE reaction[242], DIBAL-H reduction and Swern oxidation[225]

From there, the next two steps were well described in literature.[123,225,243] First a DIBAL-H reduction lead to allylic alcohol **400**, which was subsequently transformed into desired aldehyde **384** by Swern oxidation (scheme 3.47). **384** was obtained in a yield of 48% over two steps.

In summary the synthesis of desired aldehyde **384** by the first alternative route was managed in four steps, starting from ethyl 4-bromocrotonate (**386**) in an overall yield of 15%.

The second alternative pathway to synthesise aldehyde **384** was a step by step elongation (scheme 3.48),[225] similar to the last two steps of the HWE sequence. Building block **385** underwent a Wittig reaction with stabilised ylide Ph_3P=CHCOOMe to form compound **397**. Methyl ester **397** was reduced with DIBAL-H to allylic alcohol **401**[216] and instead of a two-step Swern oxidation/Wittig reaction sequence with the same ylide as before, a one step procedure was carried out. *In situ* oxidation of **401** to the corresponding aldehyde was accomplished by employing manganese(IV)oxide (MnO_2). Ph_3P=CHCOOMe was subsequently added to initiate the Wittig olefination to **402**.[244] Methyl ester **402** is isolated in a mediocre yield of 47%. An additional DIBAL-H reduction, followed by Dess-Martin oxidation[245] produced desired product **384** in 82% yield over the last two steps.

Summing up the details of this second route, another way to synthesise aldehyde side chain **384** was accomplished. The sequence involved five steps and furnished **384** in a yield of 27% starting from aldehyde building block **385**.



385 **397** **401**

402 **384**

Scheme 3.48 Step by step elongation sequence to synthesise aldehyde **384** from **385**

When comparing both alternatives, the HWE route contained less steps but the total yield was higher when the step by step elongation route was performed.

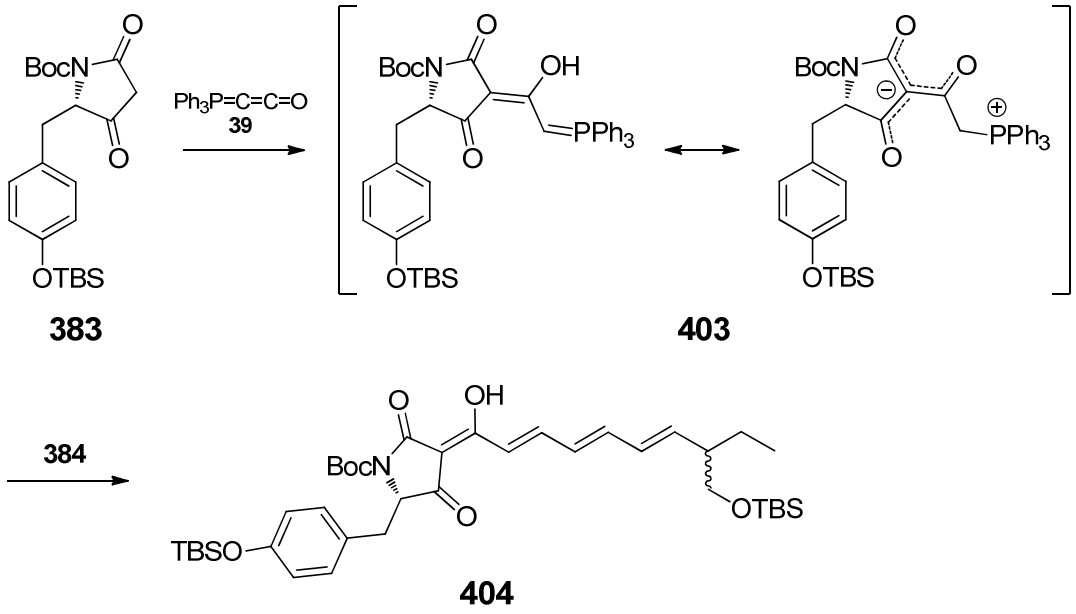
With fragments **383** (tetramic acid) and **384** (aldehyde) in hand, the next step towards the total synthesis of **15** can be attempted.

3.2.5 Attempts at the combination of tetramic acid and side chain

Finally the coupling of tetramic acid fragment **383** with unsaturated aldehyde **384** could be attempted. Previous work in our group suggested that a coupling of tetramic acid **383** with aldehyde **384** should be possible by carrying out the 3-acylation with ketenylidene(triphenyl)phosphorane (**39**).[85]

Scheme 3.49 shows the planned coupling of tetramic acid **383** with aldehyde fragment **384**. Betaine structure **403**/acylylide should be formed by reaction of **383** with **39** before Wittig olefination with aldehyde **384** should produce precursor **404**, which represents a mixture of diastereomers. This might offer an opportunity to separate the diastereomers by column chromatography or preparative HPLC.

According to established protocol,[85,203,246] phosphorane **39** was reacted with tetramic acid **383**.



Scheme 3.49 Synthetic plan to form torrubiellone D precursor **404** according to Schlenk *et al.*[85]

Reaction control by ^{31}P-NMR showed the formation of ylide **403** (figure 3.7).

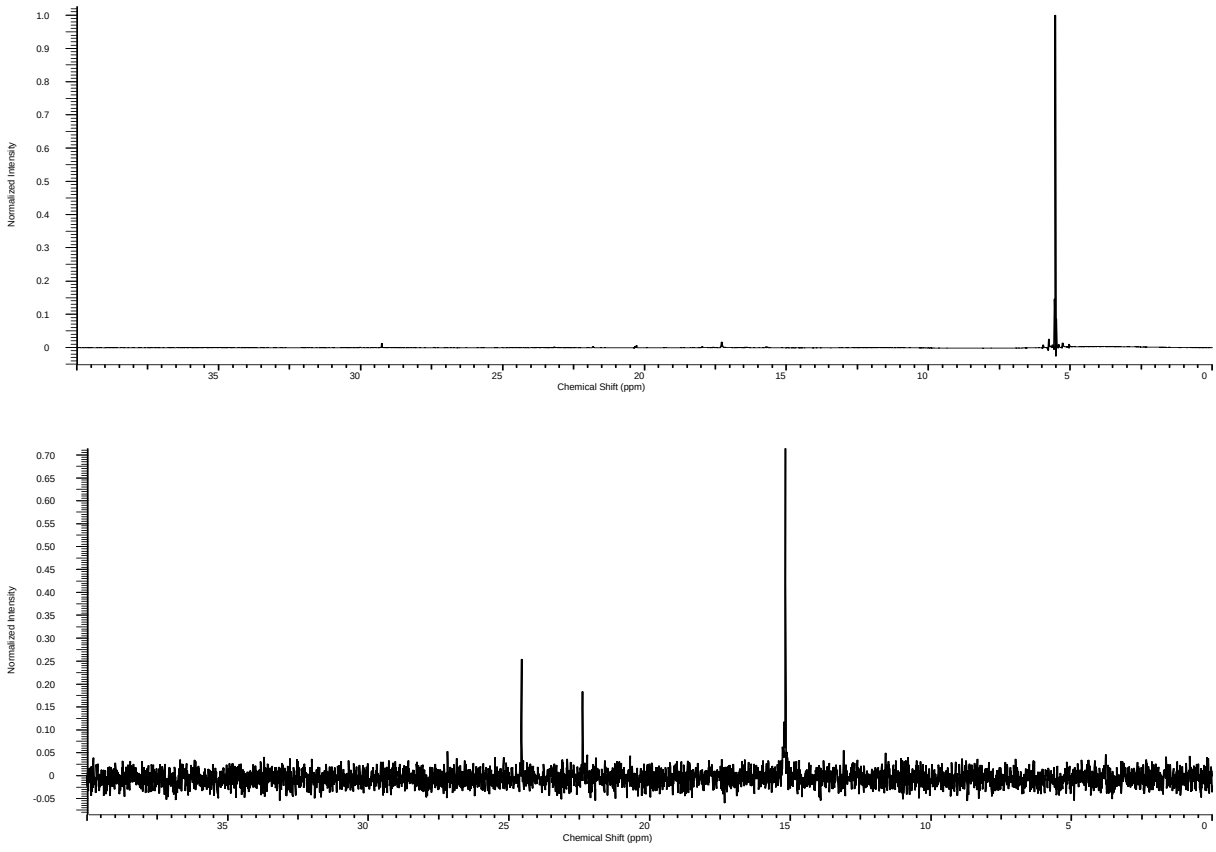


Figure 3.7 ^{31}P-NMR spectra of phosphorane **39** (upper) and ylide/betaine **403** in toluene (lower)

The signal of **39** can be found at 5.5 ppm, the most prominent signal of **403** at 15.2 ppm represents the ylidal structure. 22.4 ppm belongs to the betaine structure of **403** and the signal at 24.6 ppm shows some triphenylphosphine oxide, a decomposition product from **39** (a small amount of **403** was isolated, in order to be tested biochemically (chapter 3.4.3); isolation was accomplished by solvent evaporation of the reaction mixture).

During the next step, compound **403** was treated with KO^{t}Bu and aldehyde **384**. ^{31}P-NMR showed that the ylide and betaine signals vanished and a signal at 24.1 ppm could be observed, which was attributed to the presence of triphenylphosphine oxide (figure 3.8).

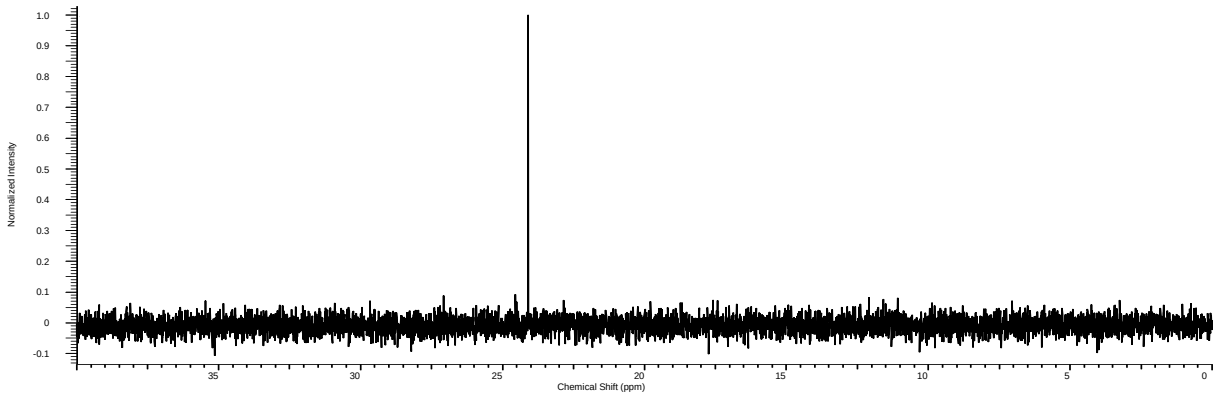


Figure 3.8 ^{31}P-NMR spectrum of the reaction control after the intended Wittig olefination of **403** with aldehyde **384**

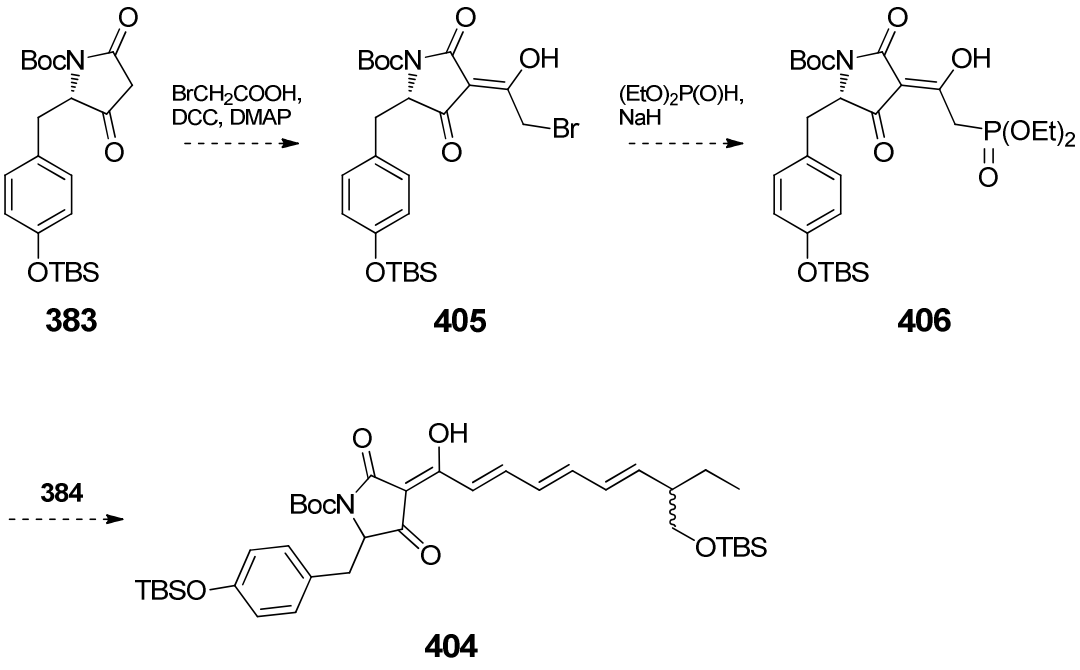
After work up however, no product could be isolated. Although the crude ^{1}H-NMR spectrum gave rise to the formation of desired coupling product **404**, after multiple purification attempts no traces of **404** were found. Neither purification as described by Schlenk *et al.*[85] using an ion exchange column nor purification by standard column chromatography was successful.

It is known that compounds with cumulated double bonds are prone to decomposition when exposed to different light sources. Therefore, the reaction was run in the dark and the whole purification process (ion exchange column and column chromatography) was repeated with columns that were covered with aluminium foil but the results remained the same.

3.2.6 Outlook

Due to the fact that the desired coupling product **404** could not be isolated from the crude reaction mixture, new means of purification will have to be tried. First of all a RP column chromatography should be carried out by trying different solvent systems with methanol or acetonitrile with and without formic acid as an additive. A treatment of the crude product with TFA, to remove the Boc- and presumably the TBS-protecting groups should also be taken into consideration. Purification of the natural product itself (**15**) could be accomplished.

If all these approaches fail, an alternative method of coupling aldehyde **384** with tetramic acid fragment **383** will have to be found. One possibility is illustrated in scheme 3.50. It should be based upon work done by Tan *et al.*[247] and instead of applying a Wittig olefination, a HWE reaction should be used for the coupling. 3-Acylation of **383** should lead to precursor **405**, which is transformed to phosphonate **406**. **406** can undergoe a HWE reaction with **384** to give desired compound **404**. A drawback might be that if the problem of isolating **404** is based upon purification, the same problems as before might arise again. In that case, an approach via Lacey-Dieckmann cyclisation could prove to be more promising.

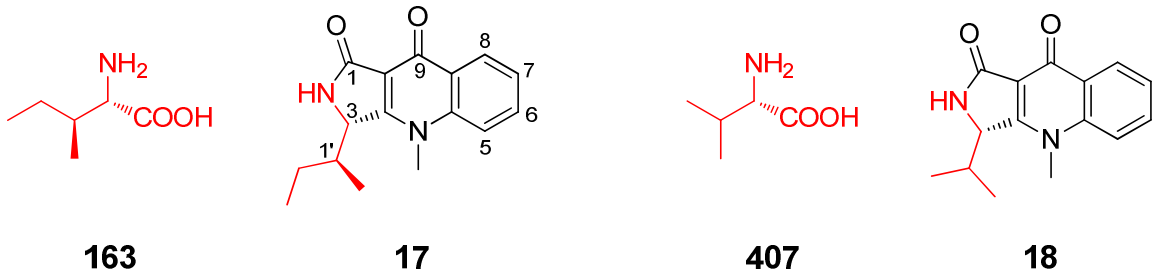


Scheme 3.50 Alternative pathway to synthesise torrubiellone D precursor **404** from tetramic acid **383** and aldehyde **384**[247]

3.3 Synthesis of quinolactacin A2 and contributions to the synthesis of quinolactacin B2

3.3.1 Overview

Quinolactacins A2 (**17**) and B2 (**18**) are both members of a larger quinolactacin family (chapter 2.2.3.1).[124–132] **17** and **18** are, unlike most of the targets presented in this thesis, no tetramic acids (figure 3.9). However, the synthetic strategies utilised tetramic acid chemistry to generate **17** and **18**. The different side chains of **17** and **18** should be introduced either by L-isoleucine (**163**) or by L-valine (**407**) respectively.



163 **17** **407** **18**

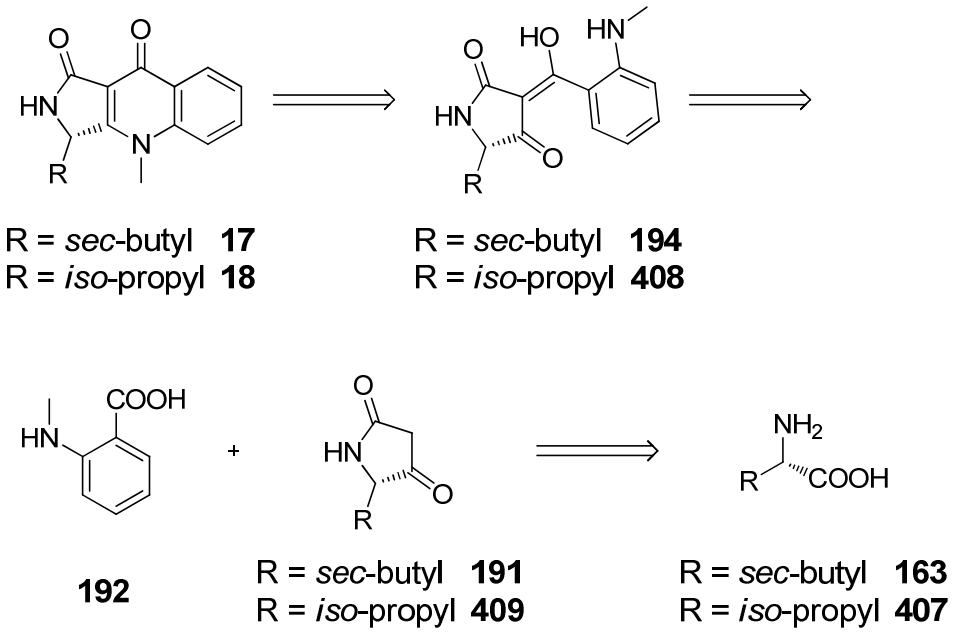
Figure 3.9 Structures of quinolactacins A2 (**17**) and B2 (**18**) and their biological precursors **163** and **407**

3.3.2 Retrosynthetic analysis

The attempt to synthesise the quinolactacins using tetramic acid chemistry was ongoing for years prior to this thesis. The motivation was to find a short, efficient and atom economic alternative to the syntheses known to date.[129–132] With the exception of one synthesis[131] all others were comprised of a minimum of eight steps and in many cases complex and expensive auxiliaries or catalysts were used to install the stereocenters.

Based upon the work of Abe *et al.*,[81] Yoda *et al.*[80] and Moloney *et al.*[77] a new strategy was envisioned to generate **17** and **18**. The pyrrolo[3,4-*b*]quinolone core is planned to be generated in the last step from 3-acyltetramic acids **194** or **408**. Both should be formed by 3-acylation of *N*-methylanthranilic acid (**192**) with corresponding tetramic acids **191** or **409**. The tetramic acids themselves should be derived from the respective essential amino acids **163** or **407** from the chiral pool by using Meldrum's

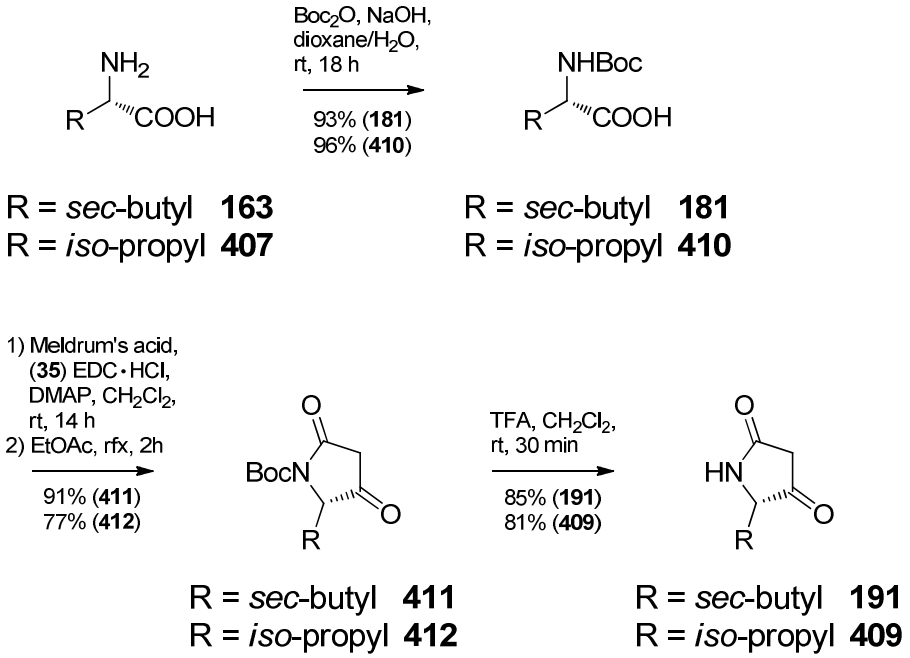
acid (**35**) (chapter 2.1.3.1) (scheme 3.51).[48] Due to the fact, that a similar approach by Christen[101] failed when protected tetramic acids were used, it is of importance to carry out the following route with the deprotected derivatives **191** and **409**.



Scheme 3.51 Retrosynthetic approach to synthesise quinolactacins A2 (**17**) and B2 (**18**)

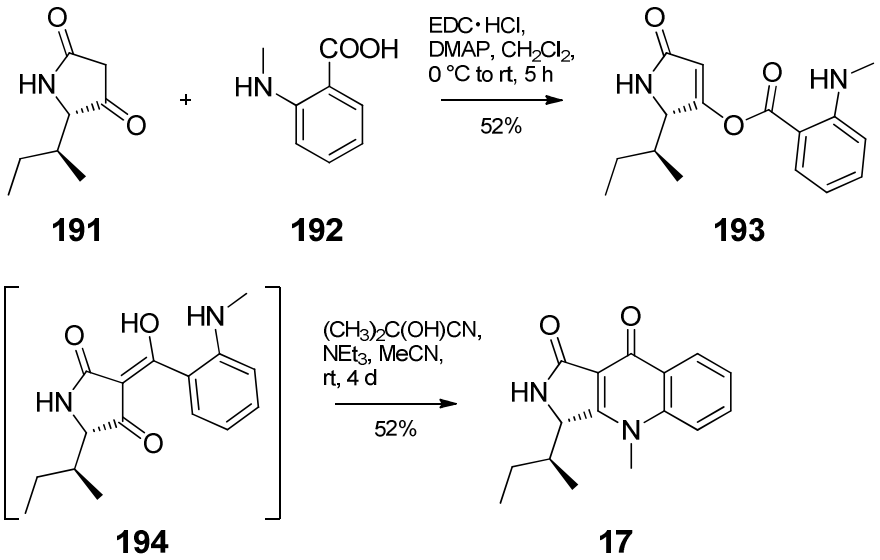
3.3.3 Synthesis of quinolactacins A2 and quinolactacin B2 precursors

The synthetic sequence commenced with Boc-protection of L-isoleucine (**163**) and L-valine (**407**) to compounds **181** and **410**.[99,152] By using EDC · HCl instead of DCC, the syntheses of tetramic acids **411** and **412** with Meldrum's acid (**35**) were improved.[53] The Boc-protecting group was cleaved during the next reaction by exposure of **411** and **412** to TFA to give desired products **191** and **409**. The products were crystallised to yield **191** and **409** as glittering white solids in yields of 72% and 60% respectively over three steps (scheme 3.52).



Scheme 3.52 Synthesis of L-isoleucine and L-valine derived tetramic acids **191** and **409** according to Hosseini *et al*.[53]

To prove the validity of the new strategy, the following steps were carried out only with tetramic acid **191**. 4-*O*-Acylation of **191** with *N*-methylanthranilic acid (**192**) was achieved following the procedure of Yoda *et al.* (scheme 3.53).[78]



Scheme 3.53 Synthesis of quinolactacin A2 (**17**) using tetramic acid **191** and *N*-methylanthranilic acid (**192**)[77,78]

The purification at this stage of the synthesis was crucial for the rest of the synthesis. Compound **193** is still unpolar enough to be purified by silica gel column chromatography and the outcome of the following steps depended upon the purity of 4-*O*-acyl precursor **193**.

The critical steps of this synthesis were the following acyl rearrangement to form 3-acyltetramic acid **194** and the subsequent cyclisation towards natural product **17**. For the initiation of the rearrangement acetone cyanohydrin was used in combination with NEt_3 (scheme 3.53).[77]

The reaction is monitored closely by analytical HPLC (figure 3.10). After 4 h still much starting material (t_R = 34 min) and two products (t_R = 10 min; t_R = 11 min) were observed. When looking at the spectrum 2 h later, only the second product signal grew stronger, although there was still starting material to be seen. After 47 h, the spectrum remained unchanged. Despite leftover starting material, the crude product was purified by preparative HPLC.

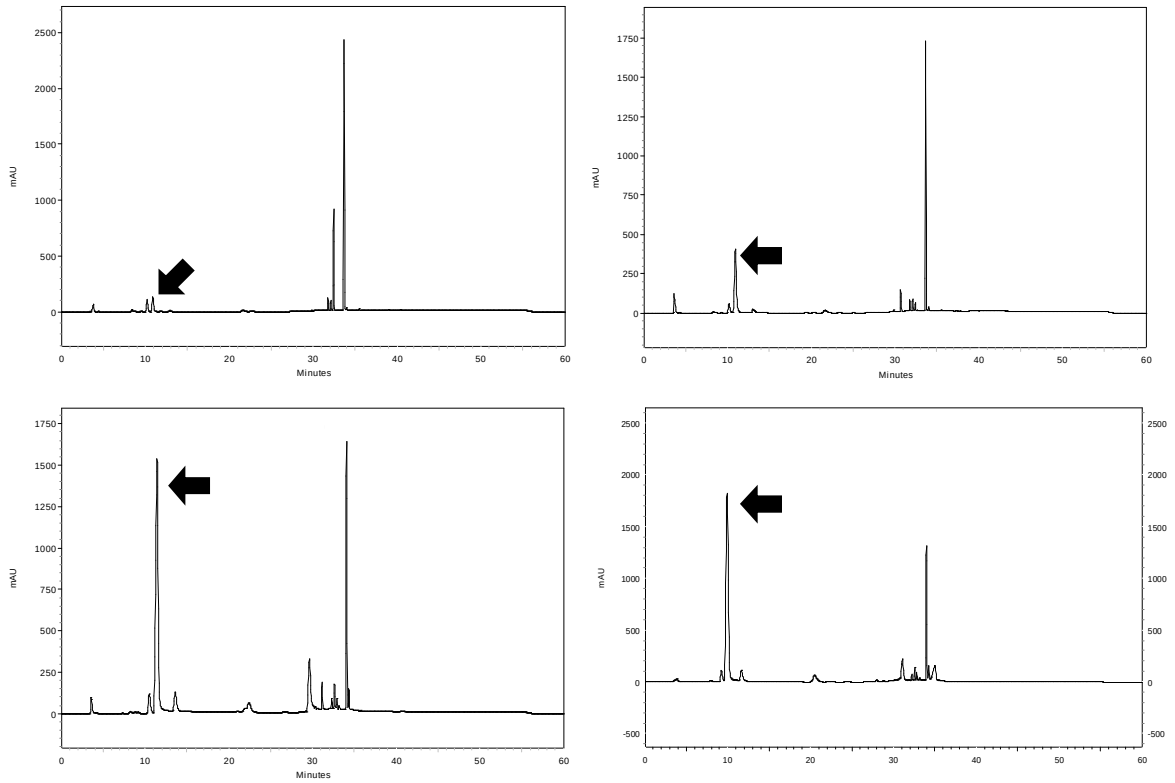


Figure 3.10 Analytical HPLC spectra after 4 h (top left), 6 h (top right), 30 h (bottom left) and 47 h (bottom right) of the formation of natural product **17** from 4-*O*-acyltetramic acid **193**

The two products were separated and analysed. The NMR-spectra of the small peak (10 min) showed that it belonged to 3-acyltetramic acid **194**. The second

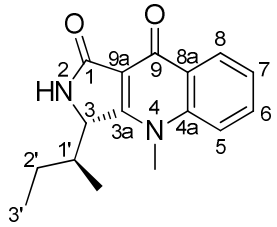
substance (11 min) was identified as the desired natural product **17**. An explanation was that 3-acyltetramic acid **194** underwent spontaneous cyclisation to **17**.

The published values of the physiochemical and spectral properties of **17** were compared with literature.[125] The appearance (white powder), the R_f value (0.75 (obs.) vs. 0.73 (pub.) in $CHCl_3$/MeOH 4:1), the decomposition point (256 °C (obs.) vs. 262 °C (pub.)) and the IR spectroscopical data matched the published values. Mass spectrometry confirmed the desired mass of 270 g/mol. The specific rotation was the only value, which did not match. Literature claims the value to be +17.9° (c = 0.13) when measured in DMSO.[127,130,131] The value found for the synthesised compound when measured in DMSO is −17.1° (c = 0.2). This observation could not be explained due to the fact that both stereocenters were not introduced chemically but were set by commercially available L-isoleucine (**163**). Furthermore, if one of the reactions carried out would have caused a stereocenter to collapse, racemisation would have been expected. At this point, a complete inversion of the specific rotation was seen, which could not be understood when looking at the reactions involved in the synthesis, which are mostly known from literature. That only left the rearrangement as the cause of the mismatched stereochemistry.

The only thing that might have happened was the epimerisation at C-3, which was described in detail (chapter 2.2.3.5).[127] This would cause **17** to epimerise to quinolactacin A1 (**146**) (scheme 2.36), but this would not explain the mismatched specific rotation. The specific rotation of **146** is reported to be +10.8° (c = 0.39)[131] and +30.3° (c = 0.16),[127] both in DMSO. Both values did not match the negative value observed for the synthesised product. In addition, the chemical shifts in the NMR spectra of **146**[126] differ in some important points from the shifts of **17**, making the assumption that **146** was synthesised instead of **17** all the more implausible. Moreover, a mixture of both epimers should result in signal doubling in NMR and should also be detected in the analytical HPLC.

Table 3.2 shows the published ^{1}H- and ^{13}C-NMR values of **17** compared to the ones observed.

Table 3.2 Comparison of the ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR chemical shifts of quinolactacin A2 (**17**) in DMSO-d_6[125]



17

	^{1}H-NMR (δ)			**^{13}C-NMR (δ)**	
	observed	published		observed	published
1			1	168.4	168.3
2-NH	8.13 (1H)	8.17 (1H)	2-NH		
3	4.82 (1H)	4.84 (1H)	3	58.9	58.9
3a			3a	164.2	164.0
4a			4a	141.2	141.2
5	7.82 – 7.83 (1H)	7.83 (1H)	5	117.1	117.0
6	7.79 – 7.82 (1H)	7.81 (1H)	6	132.5	132.4
7	7.45 – 7.51 (1H)	7.48 (1H)	7	124.3	124.2
8	8.23 – 8.27 (1H)	8.26 (1H)	8	125.8	125.8
8a			8a	128.1	128.0
9			9	171.5	171.5
9a			9a	110.4	110.3
4-Me	3.84 (3H)	3.86 (3H)	4-Me	36.1	36.0
3-OH			3-OH		
1'	2.18 (1H)	2.19 (1H)	1'	35.8	35.7
2'	0.71 – 0.95 (2H)	0.83 (1H)	2'	20.8	20.8
		0.88 (1H)			
3'	0.65 (3H)	0.65 (3H)	3'	11.5	11.4
1'-Me	1.13 (3H)	1.14 (3H)	1'-Me	17.6	17.5

The whole rearrangement/cyclisation reaction was repeated and after purification by preparative HPLC the isolated product was analysed by analytical HPLC again, showing a single peak. After dissolving the product in methanol and storing it for one week, the analytical process was repeated using the standard C-18 column and a chiral HPLC column. Two peaks were detected (figure 3.11), acknowledging that epimerisation takes place after prolonged exposure to protic solvents.

The only possibilities remaining were the complete conversion of both stereocenters or the conversion of the stereocenter in the side chain. Both scenarios were not very likely. Whereas the hydrogen at C-3 is quite acidic and might be prone to racemisation, the hydrogen at C-1' is not.

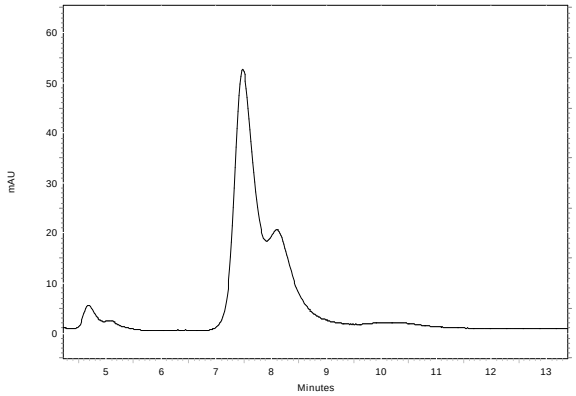
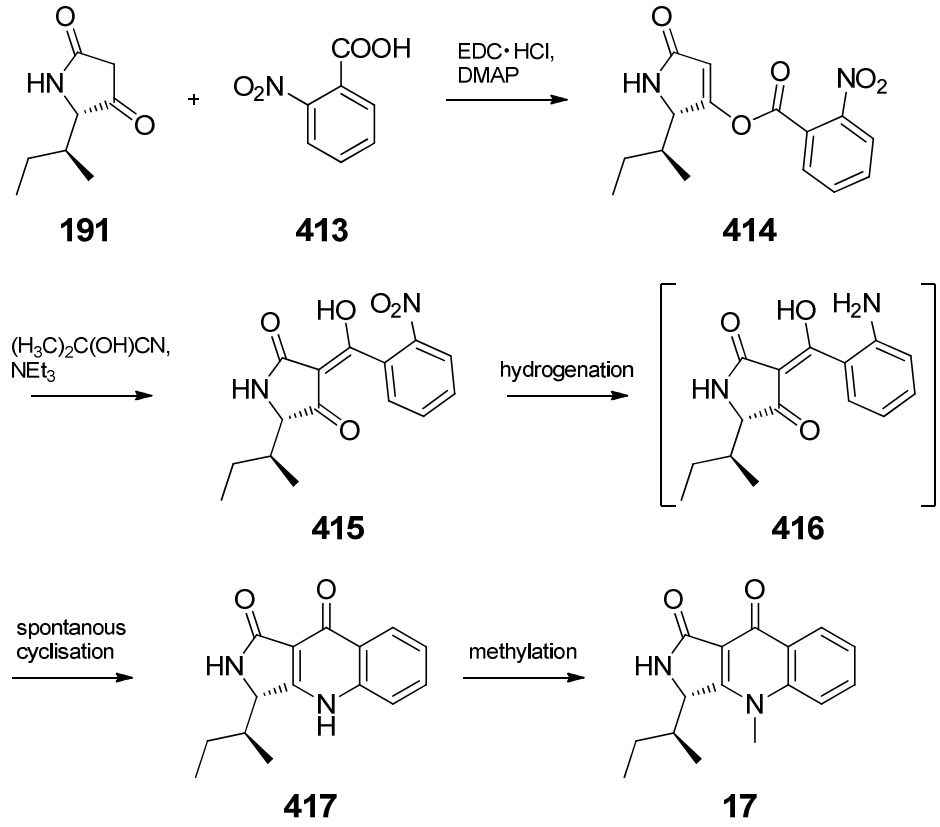


Figure 3.11 HPLC chromatogram of synthesised compound **17** on a chiral analytical HPLC column after prolonged exposure in methanol (15% MeCN, after 20 min in 10 min to 100% MeCN)

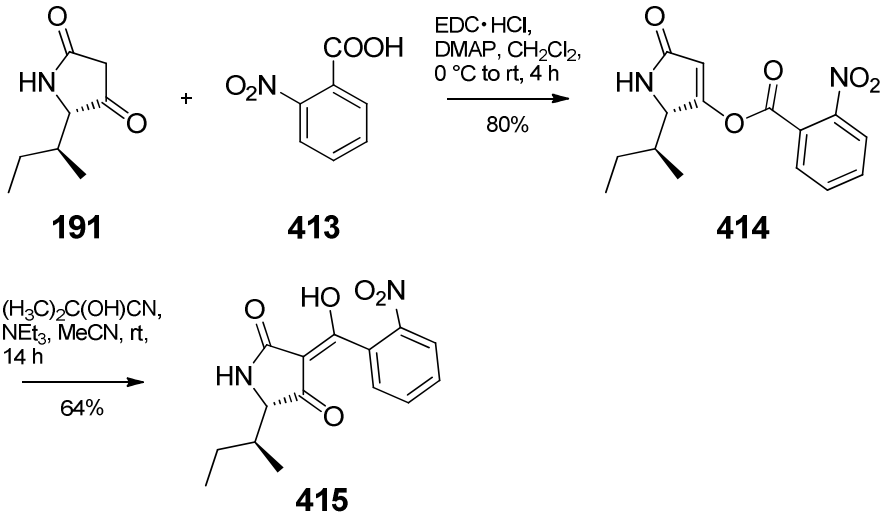
In order to validate the results, a second way to synthesise **17** was suggested. The alternative pathway (scheme 3.54) was inspired by the total synthesis of quinolactacide, a compound related to the quinolactacins.[81,248] Instead of using *N*-methylanthranilic acid (**192**), *ortho*-nitrobenzoic acid (**413**) was employed. The process should be carried out via 4-*O*-acylation to **414** and by initiation of the rearrangement with acetone cyanohydrin to form **415**. Thereafter, the nitro compound should be reduced by hydrogenation to amine **416**, which should cyclise to quinolactacin A2 precursor **417**. Subsequent methylation of enamine **417** should generate **17**.

To realise this strategy, **413** had to be synthesised. Two different approaches known from literature were performed. The first one was a $KMnO_4$ oxidation of *ortho*-nitrotoluene in H_2O,[249] which gave **413** in yields up to 30%. The second method was an oxidation of *ortho*-nitrobenzaldehyde, employing oxone® (potassium peroxomono-sulfate) as an oxidant.[250] **413** was produced in a yield of 82%.



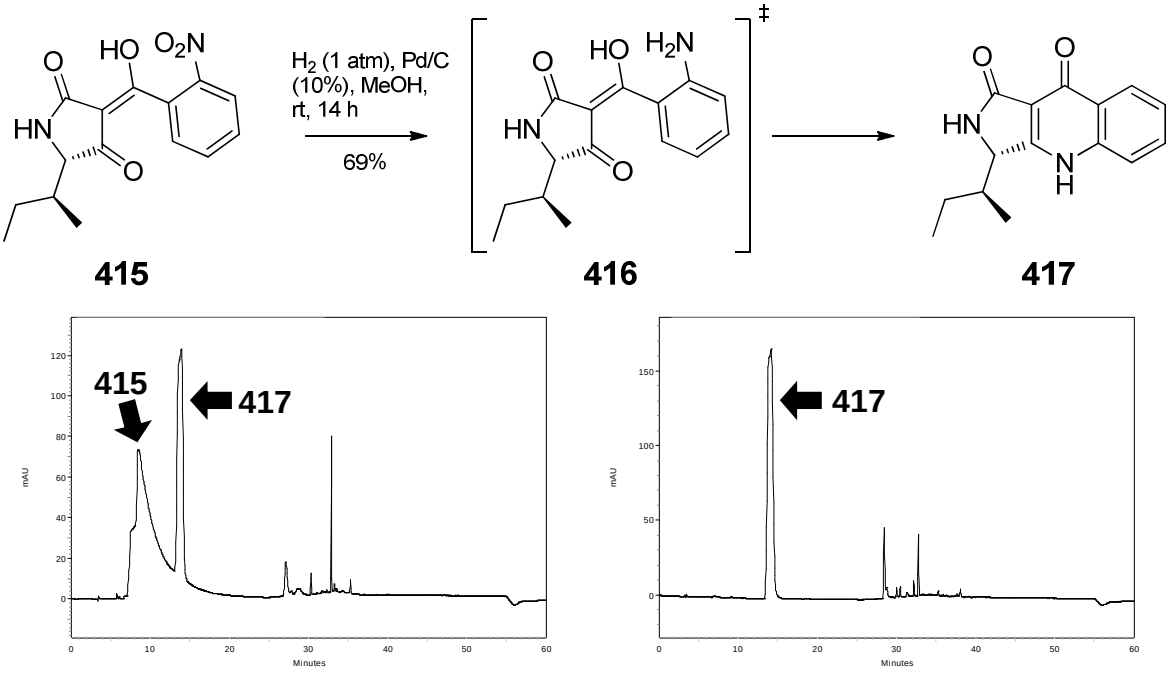
Scheme 3.54 Alternative sequence to synthesise quinolactacin A2 (**17**) using *ortho*-nitrobenzoic acid (**413**) instead of *N*-methylanthranilic acid (**192**)

With **413** in hand, the 4-*O*-acylation was undertaken, utilising the same procedure as before (scheme 3.55). 4-*O*-Acyltetramic acid **414** was obtained after careful purification in a yield of 80%. The next step was the Fries-rearrangement of **414** to 3-acyltetramic acid **415** with acetone cyanohydrin (scheme 3.55). The same procedure as before[77] was employed and target molecule **415** was isolated in a yield of 64%. Purification was carried out by RP column chromatography and confirmed by HPLC.



Scheme 3.55 4-*O*-Acylation of L-isoleucine derived tetramic acid **191** with *ortho*-nitrobenzoic acid (**413**)[78] and subsequent rearrangement to 3-acyl compound **415**[77]

The reductive hydrogenation of the nitro-group in **415** to amine **416** was monitored closely by analytical HPLC, due to the fact that the cyclisation to **417** could have occurred spontaneously. As a catalyst palladium on charcoal (10%) was used (scheme 3.56).[81]

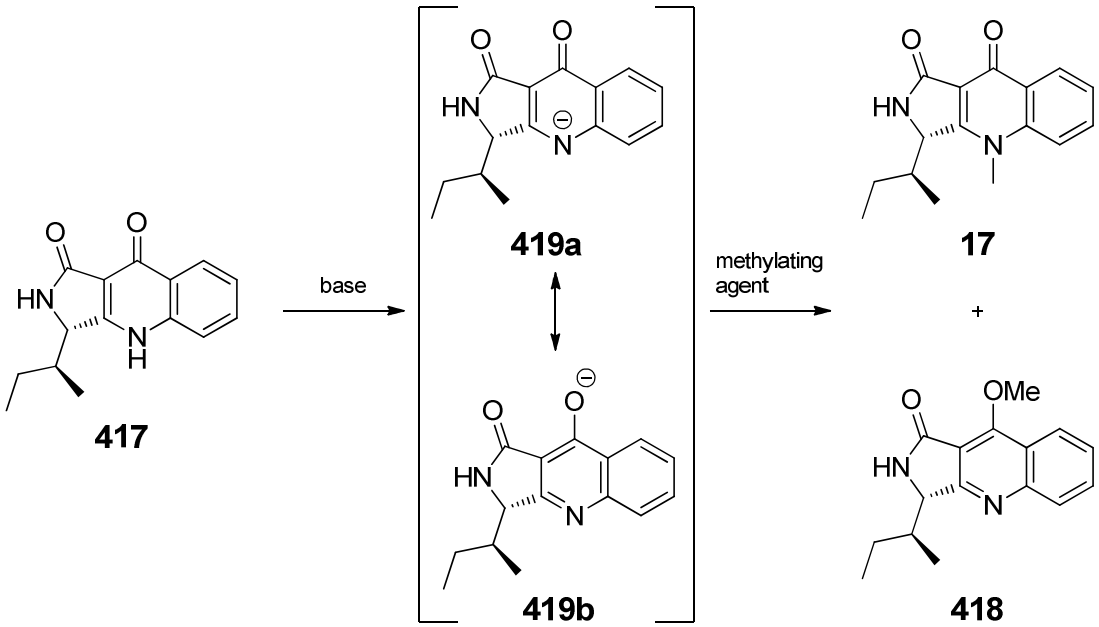


Scheme 3.56 Palladium catalysed hydrogenation of 3-acyltetramic acid **415** and spontaneous cyclisation to quinolactacin A2 precursor **417**[81] and analytical HPLC spectra (288 nm, 40% MeOH, after 20 min in 10 min to 100% MeOH) of the reaction after 2.5 h (left) and 14 h (right)

It was observed, that there was still starting material left after 2.5 h (scheme 3.56). After 14 h the reaction was terminated because analytical HPLC showed one major product. NMR spectroscopy revealed that the isolated solid represented the cyclised form **417**. No traces of intermediate 3-acyl compound **416** were found.

The last step to finish the synthesis of **17** was the methylation of the enamine in **417**. This transformation had to be achieved selectively next to the amide moiety. Another problem which needed to be addressed was the possibility of a side reaction, discussed by Zhang *et al.* during their synthesis of quinolactacin B2 (**18**).[130] Besides desired product **18**, the *O*-methylated product was isolated when the methylation was carried out using potassium carbonate (K_2CO_3) and methyl iodide (MeI). Shankaraiah *et al.* performed the same methylation with NaHMDS and MeI in yields above 90% without mentioning the existence of a side product.[132]

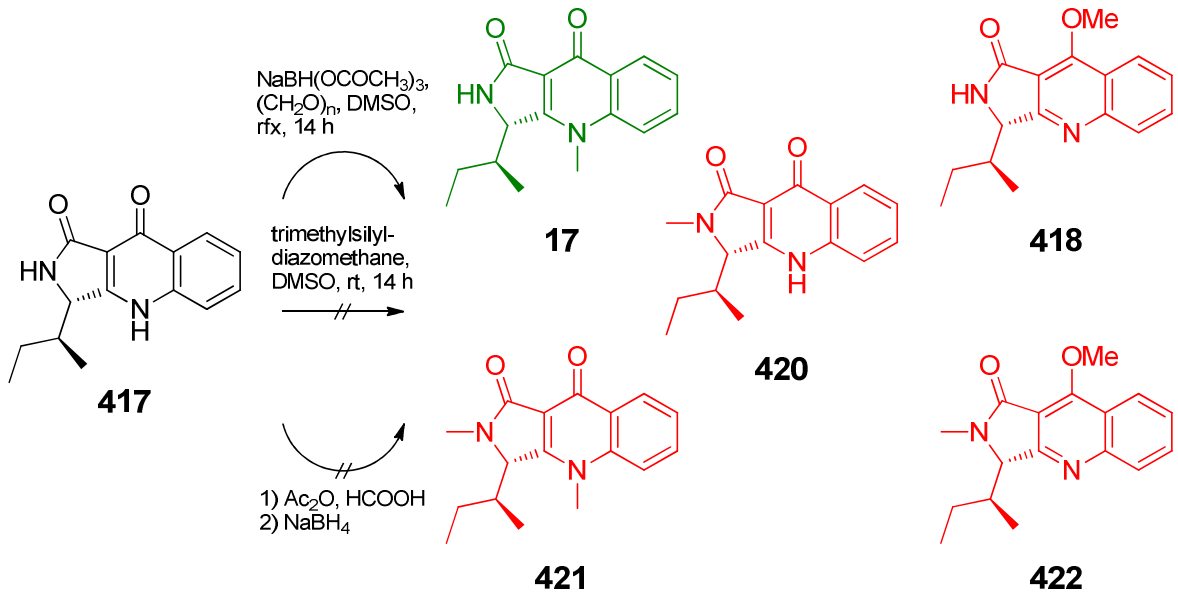
Scheme 3.57 shows desired product **17** and undesired side product **418**. The reason for the existence of the side product is mesomeric structure **419b** and the driving force of this side reaction is the installation of another aromatic ring.



Scheme 3.57 Possible products when trying to methylate **417** by the use of base and a methylating agent

To circumvent this problem a reductive amination reaction was suggested. Possible reagents to facilitate this reaction should be cyanoborohydride ($NaBH_3CN$) or sodium triacetoxyborohydride ($NaBH(OCOCH_3)_3$). Following a well described

procedure,[251,252] precursor **417** was reacted with paraformaldehyde and $NaBH(OCOCH_3)_3$ but no reaction could be witnessed. The change of solvent from DMF to DMSO remained ineffective. However, when the temperature was raised from room temperature to 80 °C, a reaction was observed (scheme 3.58).



Scheme 3.58 Trials for the methylation of **501** using different reagents and the structure hypothetical products

Analytical HPLC showed many products (figure 3.12), from which five can be thought of in advance (**17**, methylated aromatic compound **418**, methylated amide **420**, dimethylated compound **421** and dimethylated aromatic compound **422**) (scheme 3.58). No selectivity for one single product was observed. The reaction was set aside, although some possibilities like the use of other formaldehyde sources (*in situ* generated formaldehyde, formalin solution, trioxane) could still be explored.

In a second attempt, trimethylsilyldiazomethane[253] was employed to initiate direct methylation of the enamine, but no reaction was observed. The same negative result was found when a step by step approach was applied. The plan was to carry out the formylation of the enamine with the help of Ac_2O and formic acid. Subsequent reduction by the use of $NaBH_4$ should yield desired product **17**.

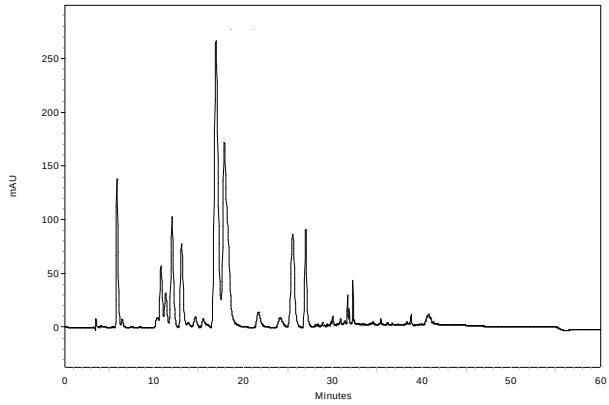
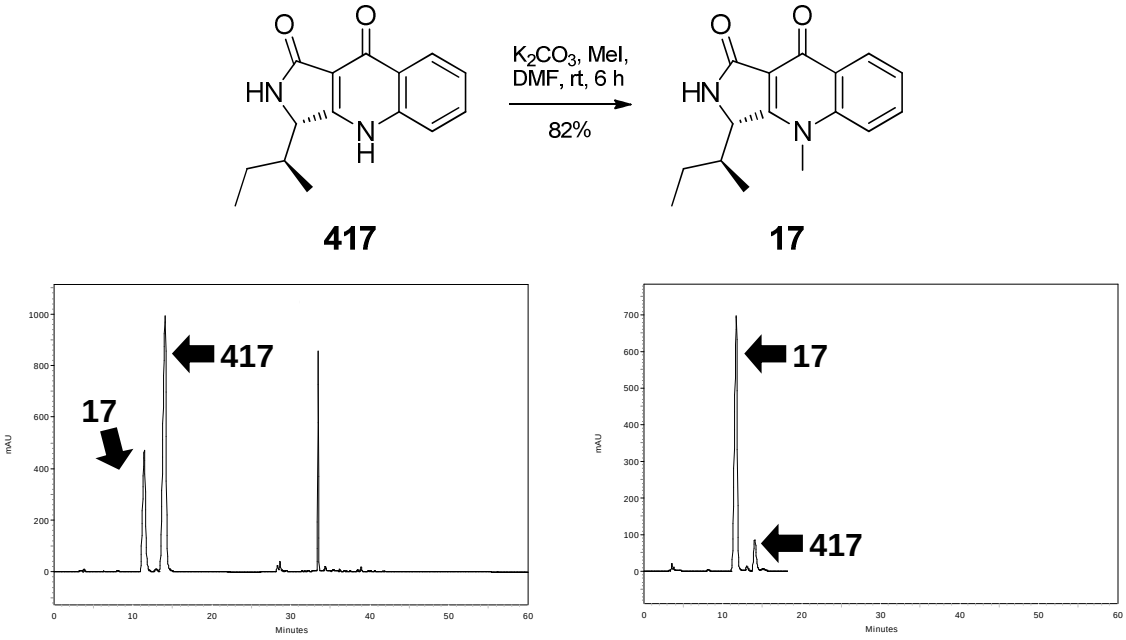


Figure 3.12 Analytical HPLC spectrum (288 nm, 40% MeOH, after 20 min in 10 min to 100% MeOH) of the unselective reaction of **417** with sodium triacetoxyborohydride and paraformaldehyde

As a last resort, the simple method of Zhang *et al.* was used (scheme 3.59).[130] After 1 h, analytical HPLC showed one major product peak besides educt **417**, belonging to a product which possessed the anticipated retention time of 11 min (scheme 3.59). After 5 h nearly all of **417** was consumed. Analytical HPLC of the purified substance displayed one single peak. In the end, desired product **17** was isolated in a yield of 82%.



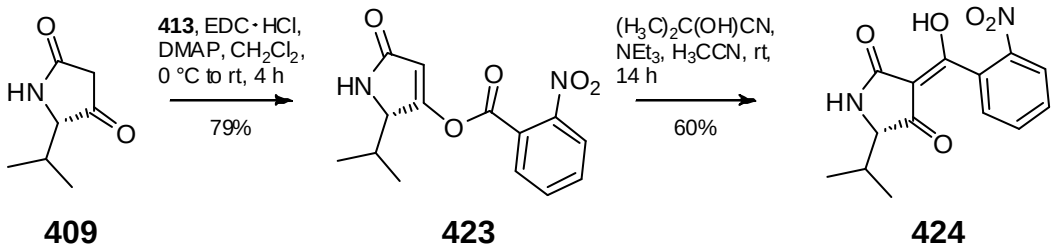
Scheme 3.59 Finalisation of the second route towards quinolactacin A2 (**17**) by selective methylation[130] and analytical HPLC spectra (288 nm, 40% MeOH, after 20 min in 10 min to 100% MeOH) of the reaction mixture after 1 h (left) and 5 h (right)

To be able to compare the substance isolated when following the first route with the one synthesised by the second route, the analytics were repeated. NMR spectra, decomposition point, R_f value, IR spectra and mass spectra were identical. The interesting fact was the value of the specific rotation. As before the value is −17.1° (c = 0.2) in DMSO. On the one hand, the result was satisfying because it confirms that in both cases the same product was produced. However, on the other hand the wrong specific rotation suggested that in both cases the wrong product was synthesised. To dispel all remaining doubts the melting point and specific rotation of L-isoleucine (**163**) was checked. Both values match the published ones. Additionally, the specific rotations were measured at two separate polarimeters. The mystery of the wrong specific rotation remains unsolved.

Both procedures described in the last section for the synthesis of **17** were then applied to the generation of **18**. It should be interesting to check the specific rotation of **18**, because it contains one less stereocenter.

As a starting point, L-valine (**407**) was used. The synthesis of tetramic acid **409** is shown in scheme 3.111. From there, 4-*O*-acylations with *N*-methylanthranilic acid (**192**) and *ortho*-nitrobenzoic acid (**413**) were carried out (scheme 3.60), but only nitro compound **423** could be isolated in a yield of 79%.

The last compound prepared in the course of this thesis was the 3-acyltetramic **424** by Fries-rearrangement from **423** (scheme 3.60). Again acetone cyanohydrin paired with NEt_3 was used to facilitate the acyl shift and product **424** was isolated in 60% yield.



Scheme 3.60 4-*O*-Acylation experiments of tetramic acid **409** with *ortho*-nitrobenzoic acid (**413**) and synthesis of 3-acyltetramic acid **424** via acyl rearrangement

3.3.4 Conclusion and outlook

In general, the synthesis of quinolactacin A2 (**17**) was accomplished by two separate synthetical pathways. The only piece that remained unsolved was the value of the specific rotation. Most of the sources of error were investigated, without success. The mystery remains as to why the value was the complete reverse, instead of a different value, as should be the case when racemisation of a stereocenter would have occurred. The error had to be located at the stereocenter of the side chain, because the change in the stereochemical configuration at C-3 was ruled out. Furthermore, it cannot be ruled out, that the value of the specific rotation presented in literature is incorrect. The way to determine the exact stereochemistry would be by X-ray crystallography, but to date crystallisation efforts remain in vain.

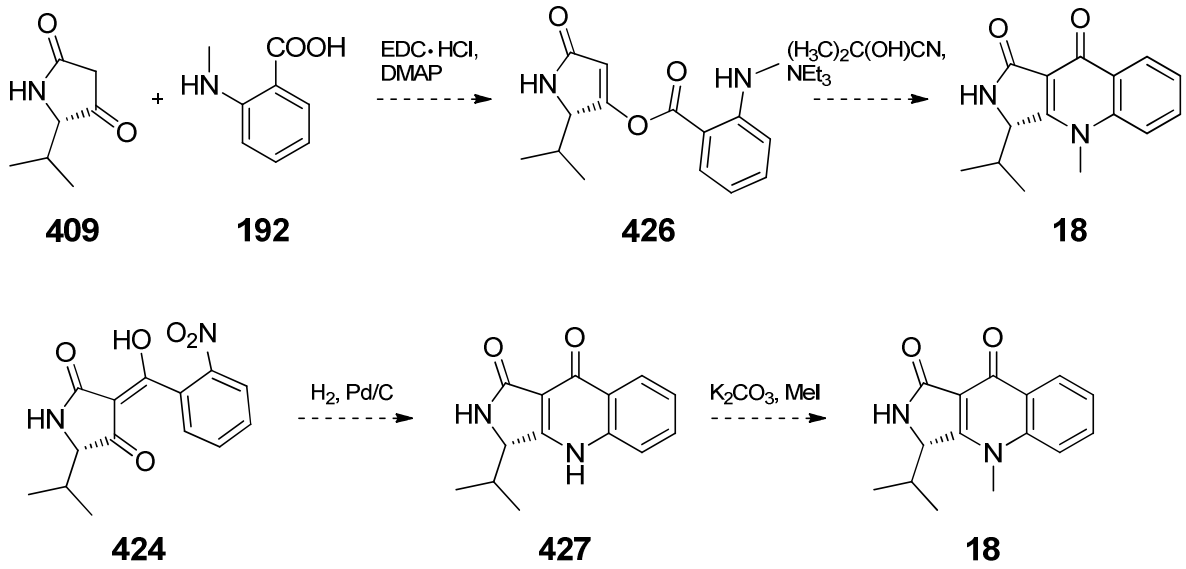
And yet, the synthesis should be repeated using L-alloisoleucine (**425**) instead of L-isoleucine (**163**) so as to compare the generated optical rotation value (figure 3.13).

163 **425**

Figure 3.13 Comparison of the structures of L-isoleucine (**163**) and L-alloisoleucine (**425**)

It remains to be seen whether the synthesis of quinolactacin B2 (**18**) will demonstrate the same problems due to the application of the same chemical transformations. If the value of the specific rotation should fit, it can be assumed that there is a problem with the side chain stereocenter of **17** during the reaction with acetone cyanohydrin, since all other steps are well described in literature.

Therefore, the remaining challenges are the repetition of the synthetic route and the finalisation of the syntheses of **18** (scheme 3.61) and the comparison of the analytical parameters of the synthesised compounds to the published ones.



Scheme 3.61 Remaining steps of the two separate routes towards quinolactacin B2 (**18**)

Generally speaking, it has to be emphasised that the basis of the successful synthesis of **17** and **18** was the use of unprotected tetramic acids **191** and **409**. All attempts to achieve the synthesis using Boc-protected derivatives **411** and **412** failed. This information could prove valuable when planning new total syntheses of compounds incorporating a tetramic acid moiety. It could indeed be used to alter the synthetic strategies towards macrocidin A (**5**) and torrubiellone D (**15**).

3.4 Synthesis of potential adenylyl cyclase inhibitors

3.4.1 Overview and synthetical objective

The last part of the thesis focused on the synthesis of possible inhibitors for the enzyme adenylyl cyclase. The enzyme is required to synthesise cyclic adenosine-3′,5′-monophosphate (cAMP) (**205**), which plays an important role as a second messenger in cell-to-cell communication and regulates different processes within the cell (chapter 2.2.4.3).[145]

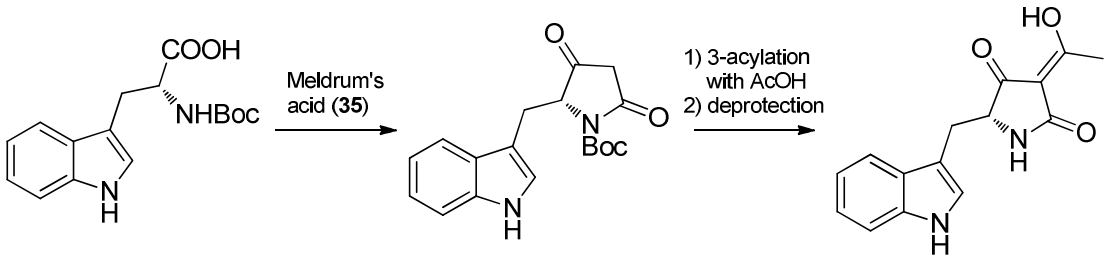
Computational studies revealed that L-tryptophan derived 3-acyltetramic acid **208** might act as a potential inhibitor for the adenylyl cyclase. In addition it is known that tetramic and tetronic acids were found to exhibit an inhibitory effect upon undecaprenyl pyrophosphate synthase (UPPS)[254] and phosphatases[255] by occupying

the phosphate binding site. Therefore, it should be investigated whether a similar mode of action can be identified when working with cyclases, such as the human soluble adenylyl cyclase.

The first objective of this biochemical project was the synthesis of **208** and to subject it to biochemical testing. The biochemical testing was carried out by Dr. S. Kleinbölting of Prof. C. Steegborn's group (biochemistry department). The second part of this project was comprised of the generation of more compounds, which could present potential candidates for the adenylyl cyclase inhibition.

3.4.2 Synthesis of a L-tryptophan derived 3-acyltetramic acid

The first approach to synthesise potential inhibitor **208** was planned as done before by tetramic acid generation via Meldrum's acid (**35**)[48] and subsequent 3-acylation with the respective acid (scheme 3.62).[76,79,80] The sequence should start from commercially available Boc-L-tryptophan (**427**). **427** should be transformed into the corresponding tetramic acid **428** and subsequent 3-acylation and Boc-deprotection should give target molecule **208**. Whether standard tetramic acid chemistry can be performed without any interference of the enamine moiety present in the side chain of **427** still requires exploration.



427 **428** **208**

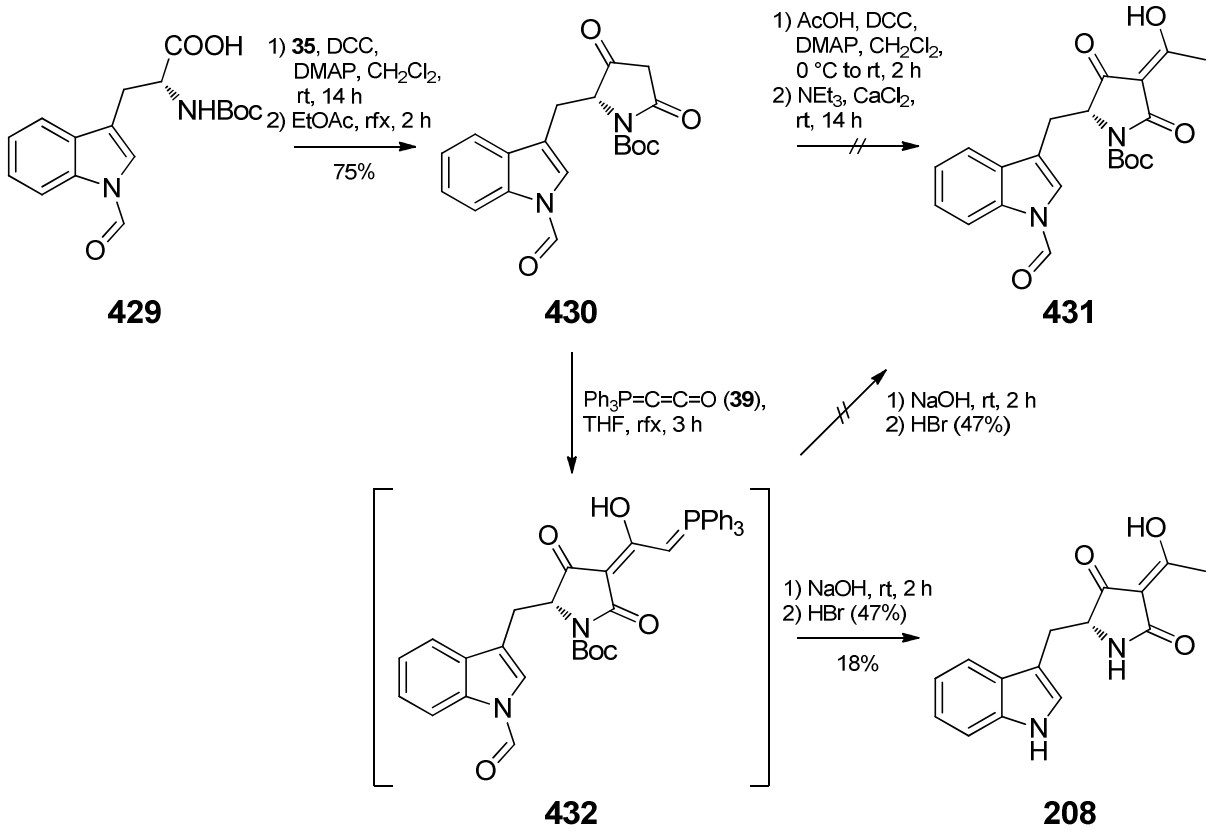
Scheme 3.62 Synthetic plan to form potential inhibitor **208** starting from Boc-L-tryptophan (**427**)

The first step of the synthetic route was the formation of the tetramic acid core by applying the protocol of Jouin *et al.*[48] using Meldrum's acid (**35**), DCC and DMAP. No definable product could be isolated. The same discouraging result was obtained when, instead of DCC and DMAP, the condensation agent T3P® is used.[154]

It was suggested that the free enamine might disrupt the desired reaction. Experiments to protect the moiety by introducing either an allyl-[256] or a fluorenyl-methyloxycarbonyl-protecting group[257] (Fmoc) were unsuccessful.

As an alternative, commercially available formylated compound **429** was envisioned to serve as the new educt for the synthesis of corresponding tetramic acid **430**. The tetramic acid synthesis was achieved in a yield of 75% (scheme 3.63).

The next step involved the 3-acetylation of tetramic acid **430**. The first attempt was made employing AcOH and following the Yoda protocol.[79] Desired product **431** could not be obtained. Therefore, an alternative acetylation method was tested, utilising ketenylidene(triphenyl)phosphorane (**39**) to introduce the required 3-acetyl substituent (scheme 3.63).[203,246]



Scheme 3.63 Tetramic acid synthesis starting from formyl-protected compound **429**, 3-acetylation attempts of **430** and the one-pot synthesis of target molecule **208**[79,203,246]

Tetramic acid **430** was reacted with **39** and resulting ylide **432** was hydrolysed by the addition of NaOH in a one-pot procedure. In fact, the anticipated product **431** was not obtained. Instead, target molecule **208** was isolated. The basic hydrolysis of ylide

432 and the acidic work up, using hydrogen bromide (HBr), did not only liberate the 3-acetyl moiety but also lead to a global Boc- and formyl-deprotection. After purification by preparative HPLC, the compound was ready to be used in biochemical experiments.

The biochemical evaluation by the group of Prof. C. Steegborn, did not display any relevant inhibitory effect of **208** (figure 3.14).[258] In order to measure the magnitude of the inhibitory effect of **208**, an adenylyl cyclase activity assay is performed.[259] A buffered solution of the cyclase was incubated with the test substance and ATP at 37 °C. The reaction was then terminated by flash freezing the mixture in liquid nitrogen before the protein was denatured and the remaining solution analysed by HPLC. The amount of generated cAMP was recorded and compared to the amount of cAMP generated in a control sample, without test substance **208**. With these values the relative activity of the adenylyl cyclase was calculated. As shown in figure 3.20, the relative activity of the protein still amounts to almost 80%. This means that the inhibitory effect of tetramic acid **208** is only minimal with respect to the high concentration (100 µM), which was used.

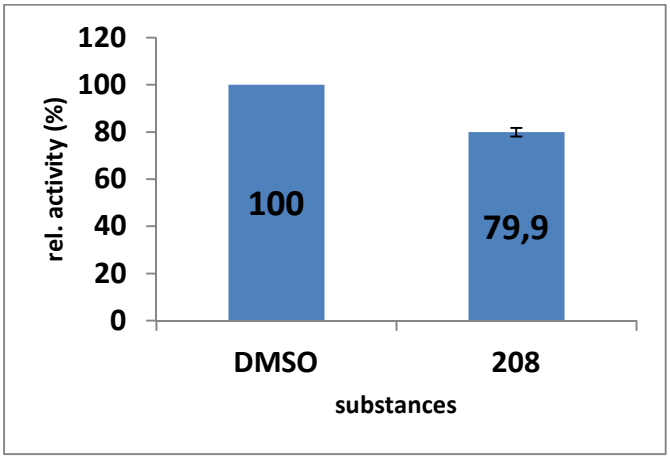


Figure 3.14 Relative activity (%) of adenylyl cyclase in the absence (DMSO) or presence of tetramic acid **208** (100 µM) and in the presence of ATP (5 mM); the amount of generated cAMP measured by HPLC was calculated in respect to DMSO-treated controls set to 100% +- standard deviation.

3.4.3 Synthesis of an extended substance library

After these results, a broader approach was suggested. Due to the lack of fundamental knowledge as to which chemical moiety might be responsible for a potential inhibition of the enzyme, different substances were discussed, which should be tested in further experiments.

Different classes of tetramic acids were thought of, with varying substituents at the positions 1, 3 and 5 of the tetramic acid core. Figure 3.15 shows the ten candidates, which should be synthesised and biochemically evaluated.

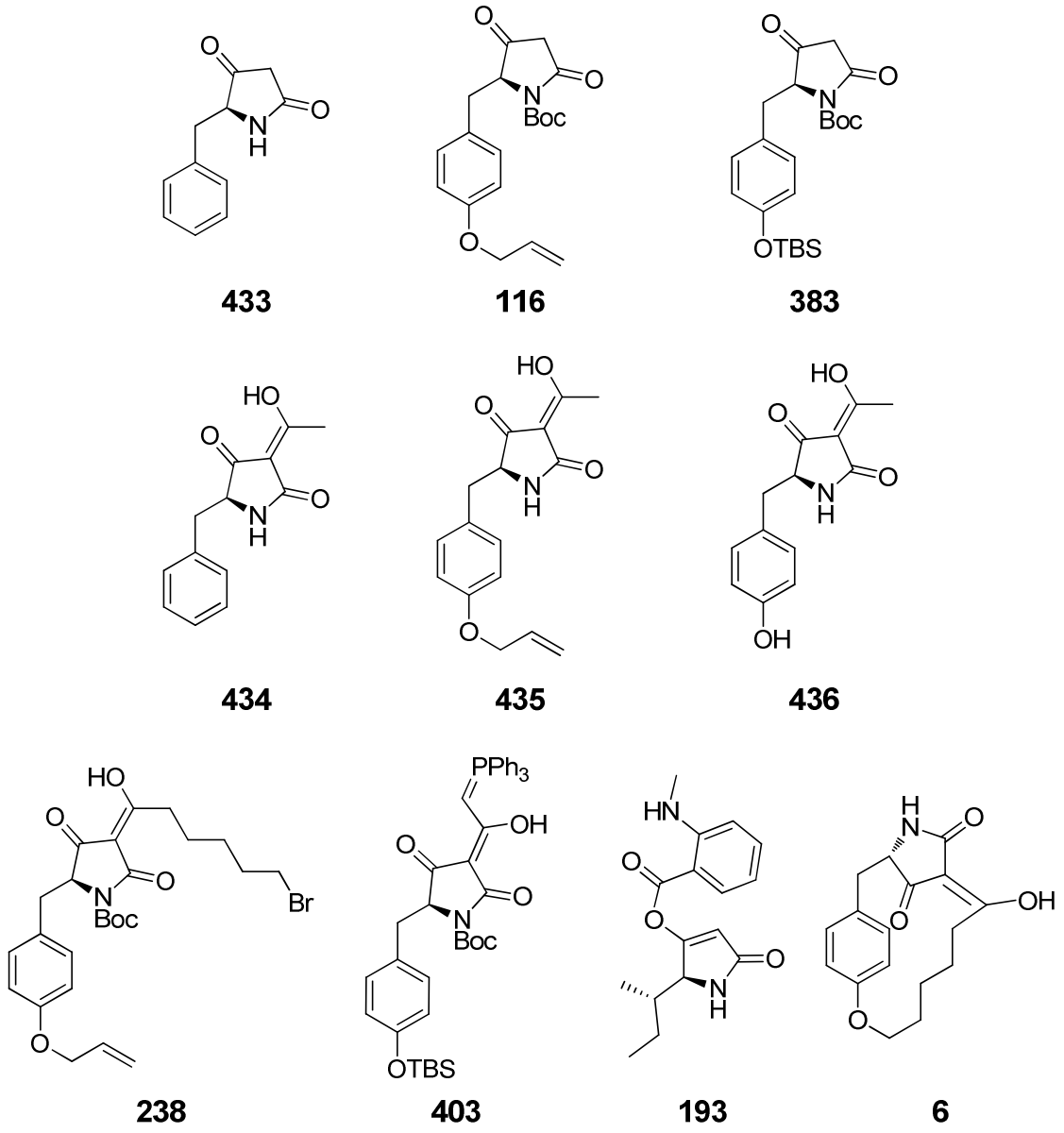
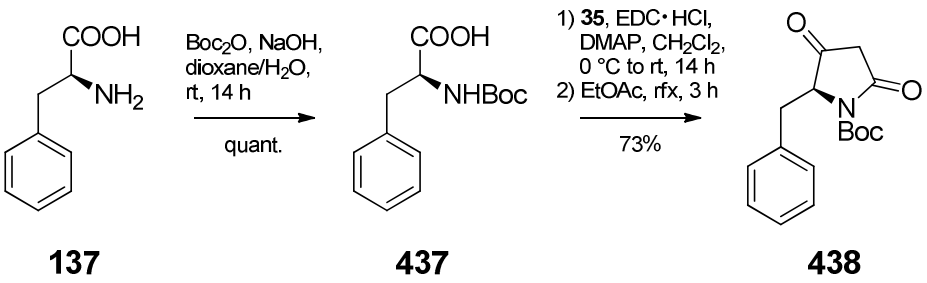


Figure 3.15 Library of substances for biological evaluation as potential cAMP cyclase inhibitor

In the first row, three tetramic acids are shown, without any substituent at C-3. **433** should be derived from L-phenylalanine (**137**), whereas **116** and **383** should be derived from L-tyrosine (**16**). The second row consists of 3-acetyltetramic acids, derived from the same two amino acids (**434** – **436**). The last four molecules illustrated should represent a miscellaneous mixture of different structural features, namely: a 3-acyltetramic acid bearing an unpolar 3-acyl chain (**238**), an acetylylide at C-3 (**403**), a 4-*O*-acyltetramic acid (**193**) and a macrocyclic compound (**6**).

From the ten compounds displayed in figure 3.21, six were already synthesised in the course of this thesis (**116**: chapter 3.1.2.2; **383**: chapter 3.2.3; **238**: chapter 3.1.2.4; **403**: chapter 3.2.5 (intermediate on the way to **404**); **193**: chapter 3.3.3; **6**: chapter 3.1.2.5). This means that only L-phenylalanine derived compounds **433** and **434** and L-tyrosine derived substances **435** and **436** needed to be synthesised.

At first, the synthesis of **433** and **434** was undertaken. The sequence started without problems, transforming amino acid **137** into its corresponding Boc-protected compound **437**.[152,260] The generation of tetramic acid **438** was achieved by applying EDC · HCl, DMAP and Meldrum's acid (**35**).[53] Over both steps a yield of 73% was obtained (scheme 3.64).



137 **437** **438**

Scheme 3.64 Two-step sequence to transform L-phenylalanine (**137**) into respective Boc-protected tetramic acid **438**[53,152,260]

Crystallisation of **438** produced crystals, which were measured by X-ray crystallography. The result is shown in figure 3.16. Few crystal structures of amino acid derived tetramic acids are known. Its crystal system can be described as simple orthorhombic.

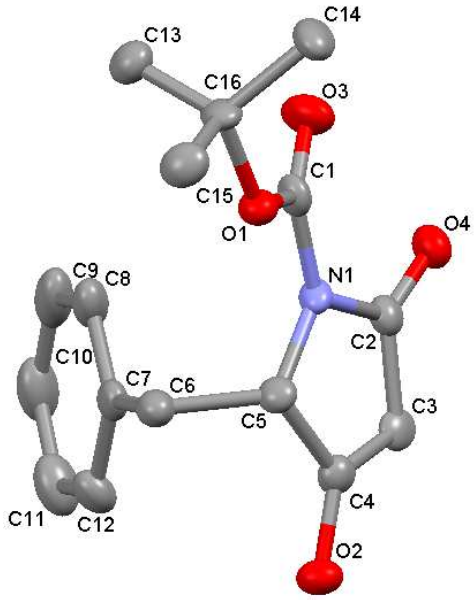
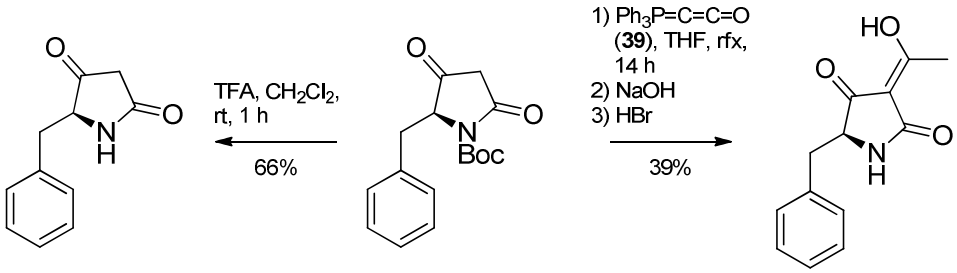


Figure 3.16 Molecular structure of *N*-(*tert*-butoxycarbonyl)-(5*S*)-(5-benzyl)-pyrrolidine-2,4-dione (**438**) as ellipsoid representations showing the atomic numbering schemes (H-atoms omitted). Selected bond lengths [Å] and angles [°]: O2—C4 1.341, O4—C2 1.238, N1—C1 1.411, N1—C2 1.381, N1—C5 1.462, C2—C3 1.456, C3—C4 1.332, C4—C5 1.497; O2—C4—C5 117.9, O4—C2—N1 125.3, O4—C2—C3 127.7, N1—C5—C6 113.9, C2—N1—C5 111.7, C3—C4—O2 130.1, C4—C3—C2 108.5, C4—C5—C6 113.4.

After that, the synthetic pathways deviated. To generate unprotected tetramic acid **433**, **438** was subjected to TFA in CH_2Cl_2 (scheme 3.65).[53] By crystallisation the product was obtained in a yield of 66%.

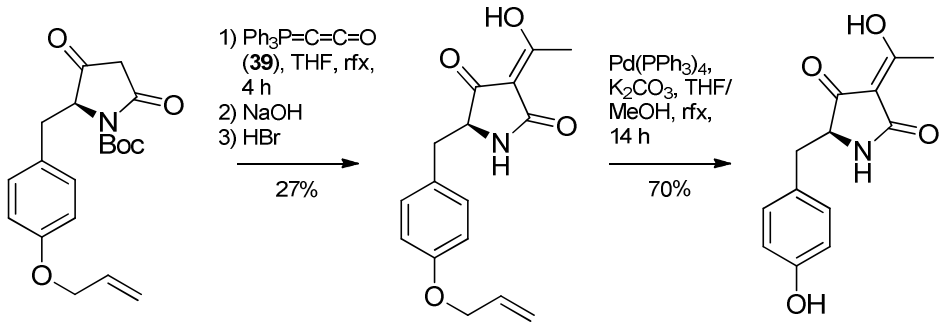


433 **438** **434**

Scheme 3.65 Transformation of Boc-protected tetramic acid **438** either into deprotected tetramic acid **433**[53] or into deprotected 3-acetyltetramic acid **434**[203,246]

In contrast, to produce 3-acetylated product **434**, **438** was reacted with phosphorane **55** and the resulting ylide was hydrolysed.[203,246] Acidic work up with HBr and preparative HPLC gave desired compound **434** in a yield of 39% (scheme 3.65).

The last two substances that were prepared for the biochemical evaluation are L-tyrosine derived compounds **435** and **436**. Both compounds were prepared from parent compound **116** (scheme 3.66).



116 **435** **436**

Scheme 3.66 Synthesis of target molecules **435**[203,246] and **436**[261] starting from L-tyrosine derived tetramic acid **116**

According to the procedures shown before, **116** was subjected to phosphorane **39**, the resulting ylide hydrolysed and the Boc-protecting group cleaved in an one-pot procedure to give **435** in a yield of 27%.[203,246] The allyl-deprotection was carried out utilising tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) and K_2CO_3.[152,261] Desired product **436** was obtained in a yield of 70% (scheme 3.66).

With all ten substances in hand, the biochemical evaluation was performed. The results generated by Dr. S. Kleinbölting from Prof. C. Steegborn's group, including the results with tryptophan derived compound **208**, were disillusioning. Figure 3.17 illustrates the results.[258] Most of the compounds showed no significant activity. Only compounds **403** and **193** displayed slight activity. Furthermore, the interaction of ylide **403** could simply be a result of ionic interactions between the substrate and the enzyme. Interestingly, the only 4-*O*-acyltetramic acid **193** showed more activity than all the other tetramic acids and 3-acyltetramic acids.

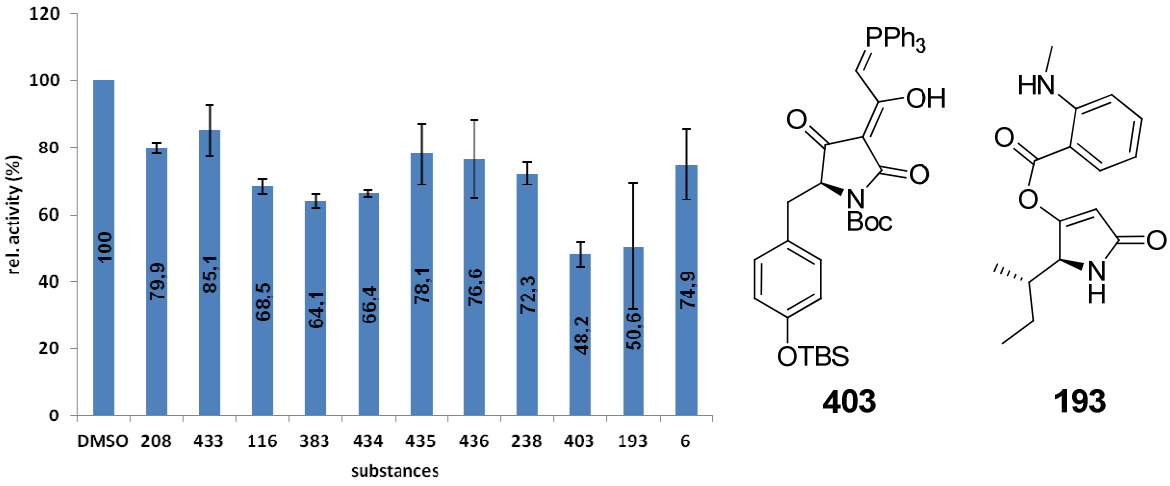


Figure 3.17 Relative activity (%) of adenylyl cyclase in the absence (with DMSO control) or presence of various tetramic acids (100 µM) and in the presence of ATP (5 mM); the amount of generated cAMP measured by HPLC was calculated in respect to DMSO-treated controls set to 100% +- standard deviation; structure of the most promising two compounds **403** and **193**

3.4.4 Conclusions

Ultimately, no feasible conclusions can be drawn from the biochemical information gathered. The tetramic acids and tetramic acid derivatives prepared could not *per se* be regarded as inhibitors for the adenylyl cyclase. Their general activity was very low and even the compounds displaying the best results were far from being promising candidates.

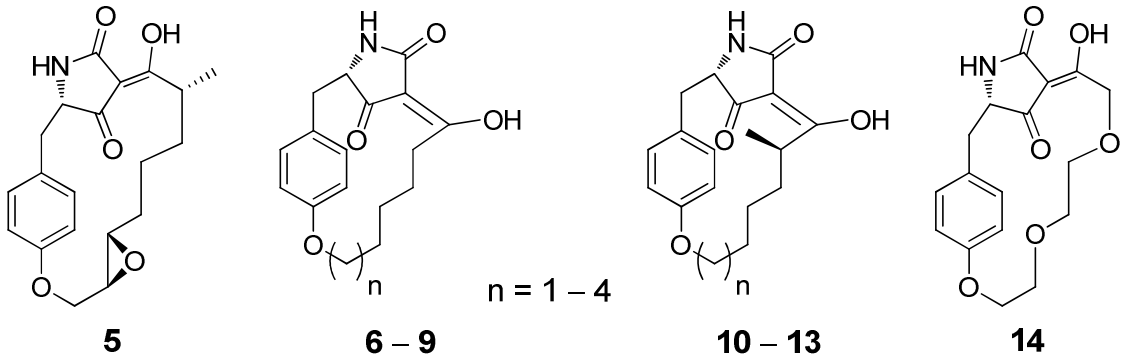
Nevertheless, some tendencies could be detected. For example, the TBS-protecting group seemed to decrease the activity compared to the allyl-protecting group, whereas the acetyl functionalisation seemed to improve the activity. Also the syntheses themselves could prove valuable in the course of future tetramic acid based projects, such as possible new total syntheses.

All in all, more effort will have to be put into this project, although doubtful whether the tetramic acid scaffold really is an auspicious starting point for further studies.

4 Summary

This thesis was divided into four major parts. The first three parts were dedicated to the syntheses of macrocidin A (**5**) and related analogues (**6** – **14**), to the synthesis of torrubiellone D (**15**) and to the syntheses of quinolactacin A2 (**17**) and B2 (**18**). The last part involved the synthesis of potential adenylyl cyclase inhibitors and their biochemical evaluation.

The main tasks of this thesis revolved around the natural product macrocidin A (**5**) and its analogues (**6** – **14**) (figure 4.1).[95]

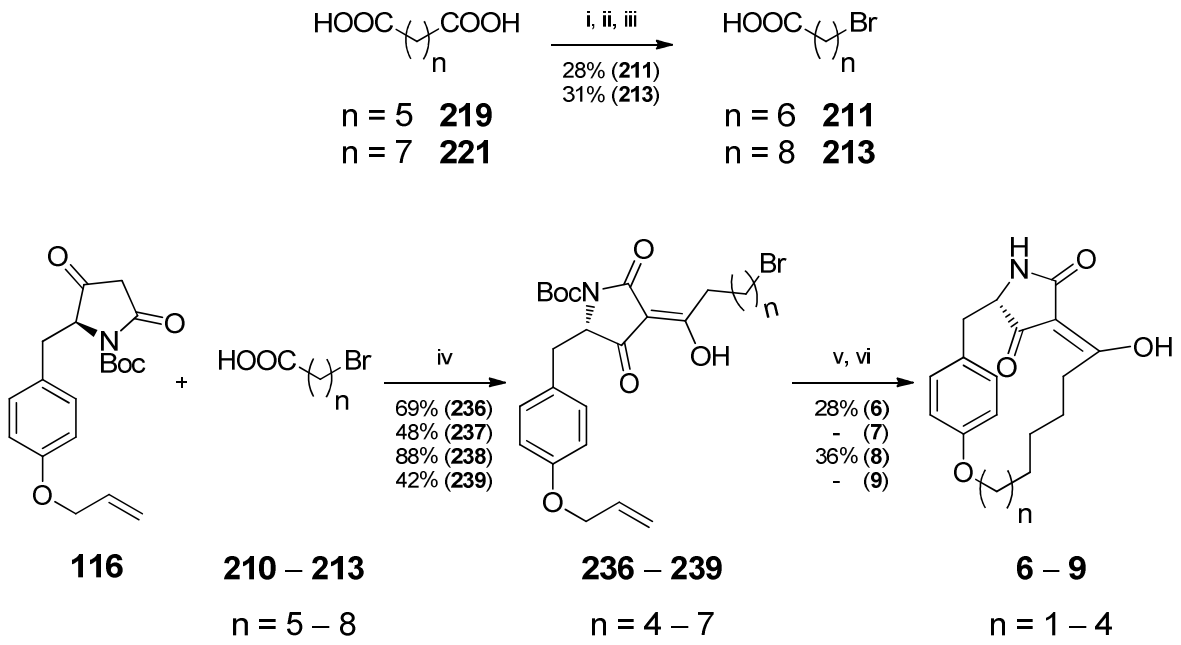


5 **6** – **9** **10** – **13** **14**

Figure 4.1 Structures of macrocidin A (**5**) and macrocidin A derived target molecules **6** – **14**

From the four different side chains (**210** – **213**) required to synthesise **6** – **9**, two (**211** and **213**) were synthesised in three steps (esterification, borane reduction and HBr mediated bromination and ester hydrolysis) (scheme 4.1), whereas the others (**210** and **212**) were commercially available.

Literature known L-tyrosine derived tetramic acid **116**[98,152] was coupled to side chains **210** – **213** by applying 3-acylation condition of Yoshii *et al.*[76] and Yoda *et al*.[79] Macroetherification via palladium catalysis[98,152] and subsequent deprotection provided **6** and **8** over two steps. The synthesis of **7** and **9** is yet to be completed.



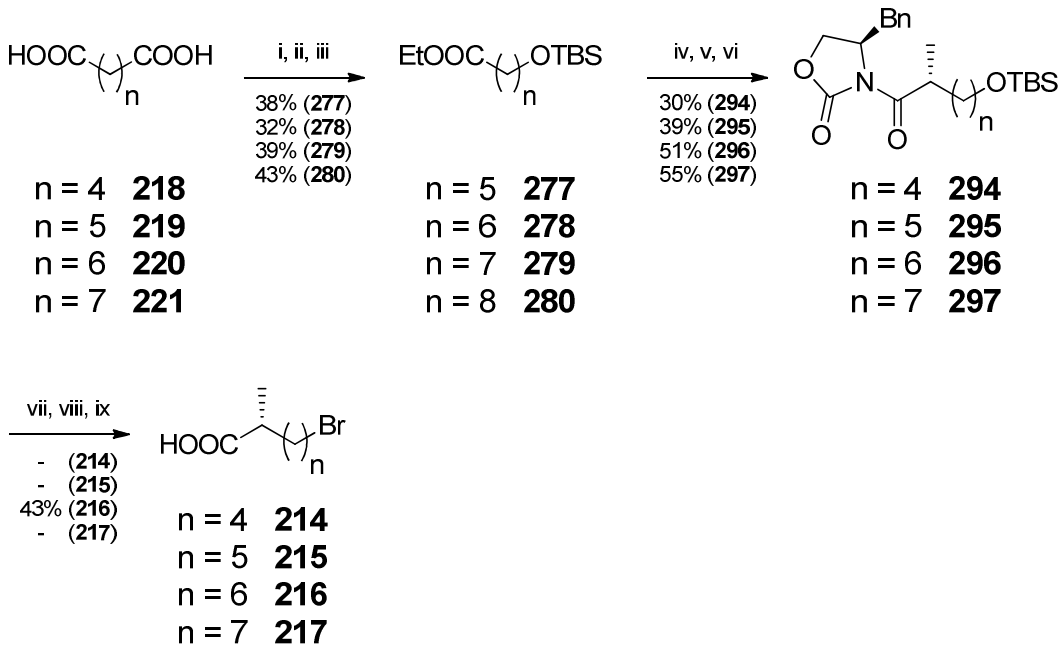
Scheme 4.1 Synthesis of analogues **6** – **9**; reagents and conditions: (i) EtOH, H_2SO_4, CH_2Cl_2, rfx, 14 h; (ii) $BH_3 \cdot THF$, THF, −20 °C to rt, 14 h; (iii) 48% HBr_{aq}, rfx, 15 min; (iv) a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 1.5 h; b) NEt_3, $CaCl_2$, rt, 14 h; (v) $Pd(PPh_3)_4$ cat., K_2CO_3, THF/MeOH, rfx, 48 h; (vi) TFA, CH_2Cl_2, rt, 15 min.

The second group of macrocidin A derivatives (**10** – **13**) possessed the original methyl group in the side chain, which was introduced stereoselectively during the synthesis of the variable side chains. The synthesis of these side chains (**214** – **217**), especially the stereoselective introduction of the methyl group was studied thoroughly.

Scheme 4.2 summarises the nine step procedure from dicarboxylic acids **218** – **221** towards the desired side chains **214** – **217**.

It included the desymmetrisation of **218** – **221** to TBS-protected esters **277** – **280** via esterification, borane reduction and TBS-protection. Saponification, stereo-selective methylation using Evans auxiliary **289**, transformation of the TBS-protected alcohol into the bromide and auxiliary cleavage finalised the sequence.

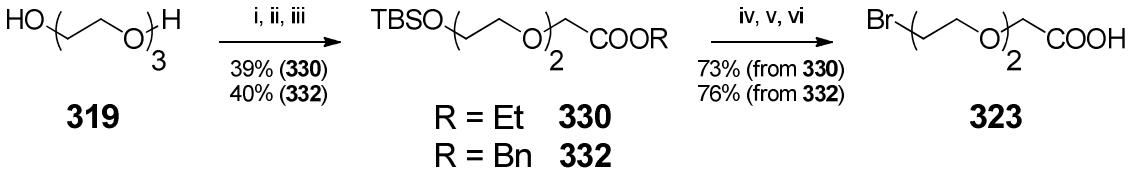
The route was completely established and optimised, although it was only carried out to the final stage for compounds **215** and **216**. Furthermore, the syntheses of target macrocycles **10** – **13** are still pending.



Scheme 4.2 Synthesis of α-methylated bromo acids **214** – **217**; reagents and conditions: (i) EtOH, H_2SO_4, CH_2Cl_2, rfx, 14 h; (ii) $BH_3 \cdot THF$, THF, −20 °C to rt, 14 h; (iii) imidazole, TBSCl, DMF, 0 °C to rt, 14 h; (iv) LiOH, THF/H_2O, 0 °C to rt, 14 h; (v) a) PivCl, NEt_3, THF, −20 °C, 1 h; b) (*R*)-4-benzyloxazolidinone (**289**), LiCl, −20 °C to rt, 3 h; (vi) a) NaHMDS, THF, −78 °C, 1 h; b) MeI, −78 °C to rt, 5 h; (vii) I) TBAF, THF, 0 °C to rt, 3 h; II) 1% HCl in EtOH, rt, 5 min; viii) CBr_4, PPh_3, CH_2Cl_2, rt, 1 h; ix) LiOH, H_2O_2, THF/H_2O, 0 °C, 1 h.

The third macrocidin A (**5**) inspired target molecule was a crownether analogue (**14**). Again, the synthesis of required side chain **323** was accomplished (scheme 4.3), but only initial experiments were carried out to produce macrocycle **14**.

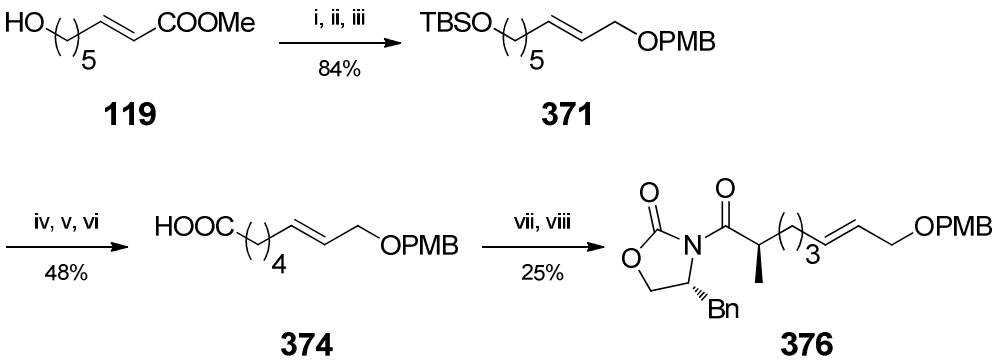
The appropriate side chain was synthesised in six steps, starting with a mono-TBS-protection of triethylene glycol (**319**) followed by a TEMPO oxidation and esterification of the generated carboxylic acid to ethyl ester **330** or benzyl ester **332**. Liberation of the remaining alcohol, bromination and hydrolysis of the respective ester finally generated desired side chain **323** over six steps. During the course of this synthesis many problems concerning the work up and handling of the very polar and unstable polyethers were solved.



Scheme 4.3 Preparation of polyether side chain **323**; reagents and conditions: (i) imidazole, TBSCl, DMF, 0 °C to rt, 2.5 h; (ii) $NaClO_2$, TEMPO, NaOCl, Na_2HPO_4, NaH_2PO_4, MeCN, 35 °C, 14 h; (iii) ROH, EDC · HCl, DMAP, CH_2Cl_2, 0 °C to rt, 14 h; (iv) 1% HCl in EtOH, rt, 45 min; (v) CBr_4, PPh_3, CH_2Cl_2, rt, 1 – 3 h; (vi) NEt_3, LiBr, MeCN/H_2O, rt, 14 h.

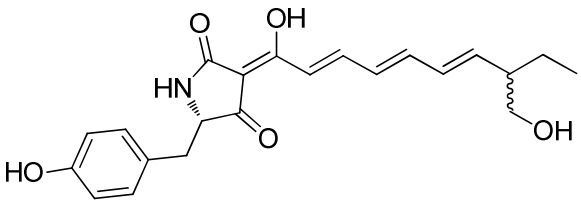
Another task was generating a side chain which should be used to synthesise macrocidin A (**5**). Many setbacks were encountered before arriving at a promising route (scheme 4.4).

It began with standard TBS-protection of known intermediate **119**, DIBAL-H reduction of the methyl ester and PMB-protection of the allylic alcohol to **371**. Subsequent TBS cleavage and stepwise oxidation to carboxylic acid **374** was then succeeded by Evans auxiliary (**289**) mediated stereoselective methylation to **376** scheme 4.4). In the future, the work presented, could lead to a way to introduce the epoxide stereoselectively and to ultimately synthesise **5**.



Scheme 4.4 Partial side chain synthesis for the total synthesis of macrocidin A (**5**); reagents and conditions: (i) imidazole, TBSCl, DMF, 0 °C to rt, 14 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) PMB-trichloroacetimidate, PPTS, CH_2Cl_2, rt, 23 h; (iv) TBAF, THF, rt, 2 h; (v) a) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 15 min; b) NEt_3, −78 °C to rt, 30 min; (vi) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/H_2O/^{t}BuOH, rt, 2 h; (vii) a) PivCl, NEt_3, THF, −20 °C, 1 h; b) (*R*)-4-benzyloxazolidinone (**289**), LiCl, −20 °C to rt, 3 h; (viii) a) NaHMDS, THF, −78 °C, 1 h; b) MeI, −78 °C to rt, 5 h.

The second target natural product of this thesis was torrubiellone D (**15**) (figure 4.2).[115] The synthesis consisted of two major parts: the preparation of tetramic acid core **383** and of unsaturated aldehyde fragment **384,** needed to install the 3-acyl side chain.



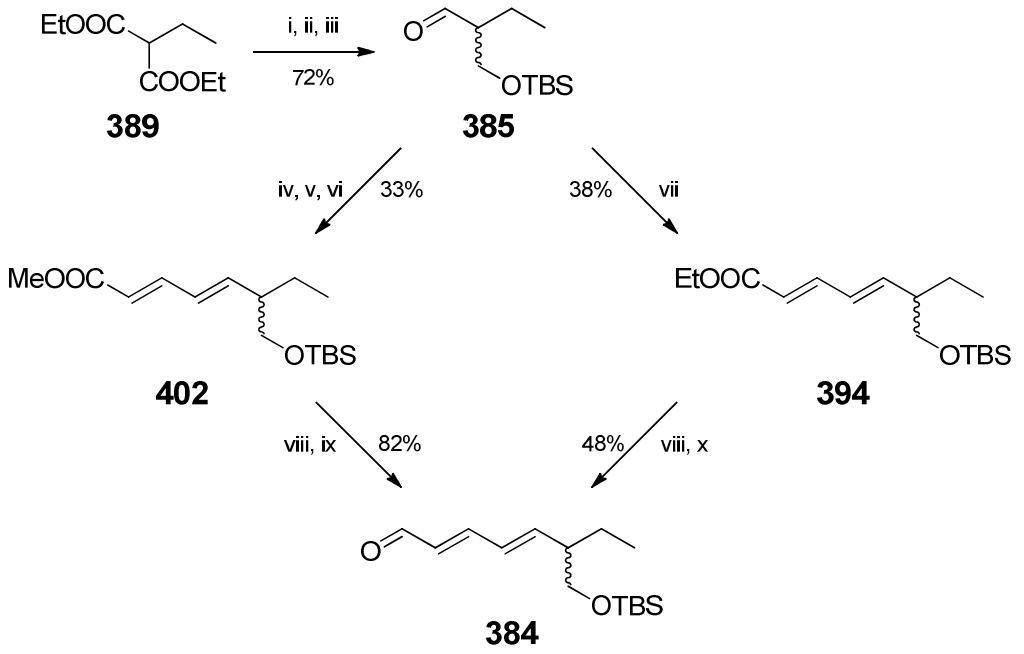
15

Figure 4.2 Structure of torrubiellone D (**15**)

The tetramic acid fragment **383** was generated following literature procedures.[53,152,226]

The side chain was synthesised in two ways (scheme 4.5). Both started with the transformation of diethyl ethylmalonate (**389**) into racemic TBS-protected aldehyde **385** via reduction, mono-protection and Swern-oxidation.[192] One path utilised a step by step elongation strategy,[225] incorporating a Wittig reaction, a DIBAL-H reduction and an oxidation-Wittig one step procedure to methyl ester **402**. This intermediate was converted into desired aldehyde side chain **384** by DIBAL-H reduction and Dess-Martin oxidation.

The second pathway employs a HWE reaction with phosphonate **398** to generate ethyl ester **394** in one step.[242] It is transformed into aldehyde **384** by applying DIBAL-H and Swern oxidation conditions.

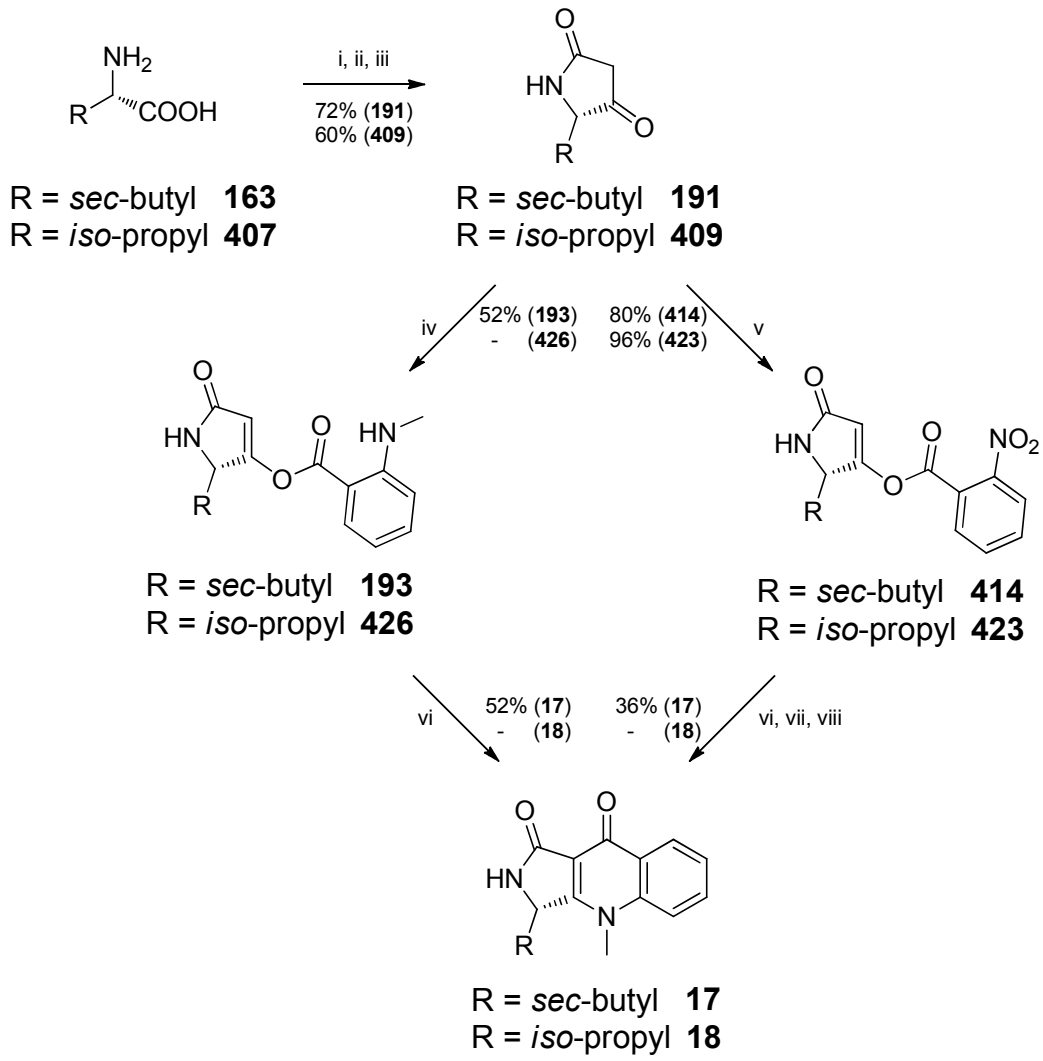


Scheme 4.5 Synthetic routes to aldehyde side chain **384**; reagents and conditions: (i) a) $LiAlH_4$, THF, rfx, 2 d; b) 5 d extraction; (ii) ^{n}BuLi, TBSCl, THF, −78 °C to −20 °C, 2 h; (iii) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, 16.5 h; (iv) Ph_3P=CHCOOMe, CH_2Cl_2, rt, 3 h; (v) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (vi) MnO_2, Ph_3P=CHCOOMe, CH_2Cl_2, rt, 3 d; (vii) $(EtO)_2OPCH_2CHCHCOOEt$ (**398**), DBU, LiCl, MeCN, 0 °C to rt; 14 h; (viii) DIBAL-H, CH_2Cl_2, −78 °C, 1 – 2 h; (ix) DMP, CH_2Cl_2, rt, 2 h; (x) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, 16.5 h.

The coupling of fragment **383** with **384** by ketenylidene(triphenyl) phosphorane (**39**) mediated 3-acylation has been tested multiple times,[203,246] but the desired product could not be purified and isolated to date.

The last natural products covered in this thesis were quinolactacins A2 (**17**) and B2 (**18**).[124,125] **17** was synthesised in a new and efficient way employing two different routes (scheme 4.6). Starting with L-isoleucine (**163**), tetramic acid **62** was produced following standard methodology. In one case, **62** was reacted with *N*-methyl-anthranilic acid (**192**) and in the other with *ortho*-nitrobenzoic acid (**413**) to give 4-*O*-acylated compounds **193** and **414**.[78] The 4-*O*-acyl to 3-acyl rearrangement was initiated using acetone cyanohydrine and NEt_3.[77] In the first case, the 3-acyl compound spontaneously cyclised to desired natural product **17** in an overall yield of 19% over five steps, whereas in the second case the nitro functionality was reduced by hydrogenation before the cyclisation occurred.[81] In order to produce **17**, an

additional selective methylation was performed to give **17** in a yield of 21% over seven steps.



Scheme 4.6 Synthetic route towards quinolactacins A2 (**17**) and B2 (**18**); reagents and conditions: (i) Boc_2O, NaOH, dioxane/H_2O, rt, 18 h; (ii) a) Meldrum's acid (**35**), EDC · HCl, DMAP, CH_2Cl_2, rt, 14 h; b) EtOAc, rfx, 2 h; (iii) TFA, CH_2Cl_2, rt, 30 min; (iv) *N*-methylanthranilic acid (**192**), EDC · HCl, DMAP, CH_2Cl_2, 0 °C to rt, 5 h; (v) *o*-nitrobenzoic acid (**413**), EDC · HCl, DMAP, CH_2Cl_2, 0 °C to rt, 4 h; (vi) $(CH_3)_3C(OH)CN$, NEt_3, MeCN, rt, 14 h – 4 d; (vii) H_2 (1 atm), Pd/C (10%), MeOH, rt, 14 h; (viii) K_2CO_3, MeI, DMF, rt, 6 h.

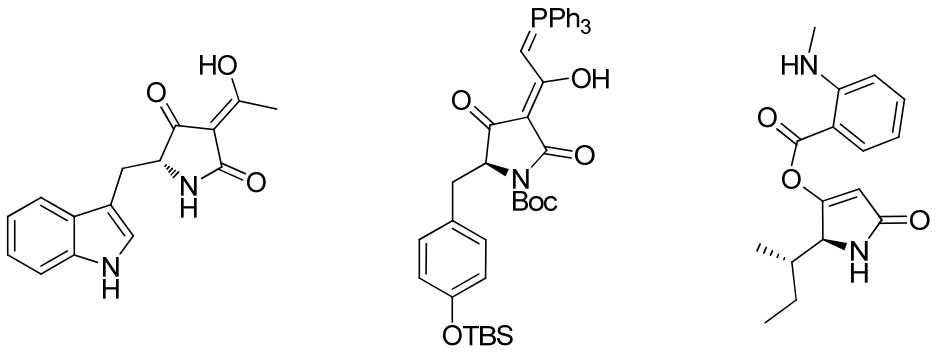
The major part of the analytical data suggested that **17** was synthesised successfully. Solely the wrong value of the specific optical rotation remained inexplicable (−17.1 ° (c = 0.2) instead of +17.9 ° (c = 0.13)[125]). Due to the facts that both independent pathways gave the same result and all stereocenters originated from the chiral pool, incorrect literature values cannot be ruled out.

The same sequence was carried out to generate **18**, by replacing **163** by L-valine (**407**) as the starting material. 4-*O*-Acyl compound **423** was synthesised, but the rest of the route could not be completed to date (scheme 4.6).

In the last part of the thesis, potential inhibitors for the adenylyl cyclase (an enzyme, responsible for the transformation of ATP into cAMP[145]) were synthesised and biochemically evaluated. This project was carried out in close cooperation with Dr. S. Kleinbölting from the group of Prof. C. Steegborn (biochemistry department), who performed all the biochemical tests.[258,259]

On the basis of computational studies, L-tryptophan derived compound **208** surfaced as the first candidate (figure 4.3). The synthesis was achieved in two steps, starting from Boc- and formyl-protected L-tryptophan (**429**). The tetramic acid was generated using Meldrum's acid (**35**)[48] and the 3-acetylation was accomplished by applying ketenylidene(triphenyl) phosphorane (**39**).[203,246]

Ten more tetramic acids and 3-acyltetramic acids were synthesised for biochemical evaluation, derived from L-phenylalanine, L-tyrosine and L-isoleucine. Figure 4.3 shows the two most promising representatives: compounds **403** and **193**.



208 **403** **193**

Figure 4.3 Potential tetramic acid incorporating inhibitors for the adenylyl cyclase

In the end, **208** shows no significant activity and even compounds **403** and **193** only show an inhibition of about 50%, when used in high concentrations of 100 µM.[258]

In summary, no definite proof could be found to confirm the theory that tetramic acid derivatives can serve as new leads to powerful adenylyl cyclase inhibitors. However, the synthesis of various different tetramic acids based upon L-tryptophan and L-phenylalanine could be synthetically relevant and biochemically interesting.

5 Zusammenfassung

Diese Arbeit war in vier Hauptbereiche aufgeteilt. Die ersten drei Teile beschäftigten sich mit den Synthesen von Macrocidin A (**5**) und den dazugehörigen Analoga (**6** – **14**), mit der Synthese von Torrubiellon D (**15**) und mit den Synthesen von Quinolactacin A2 (**17**) und B2 (**18**). Der abschließende Teil befasste sich mit der Synthese potentieller Adenylylcyclase Inhibitoren und deren biochemischer Evaluation.

Das Hauptaugenmerk dieser Arbeit lag auf dem Naturstoff Macrocidin A (**5**) und seinen Analoga (**6** – **14**) (Abb. 5.1).

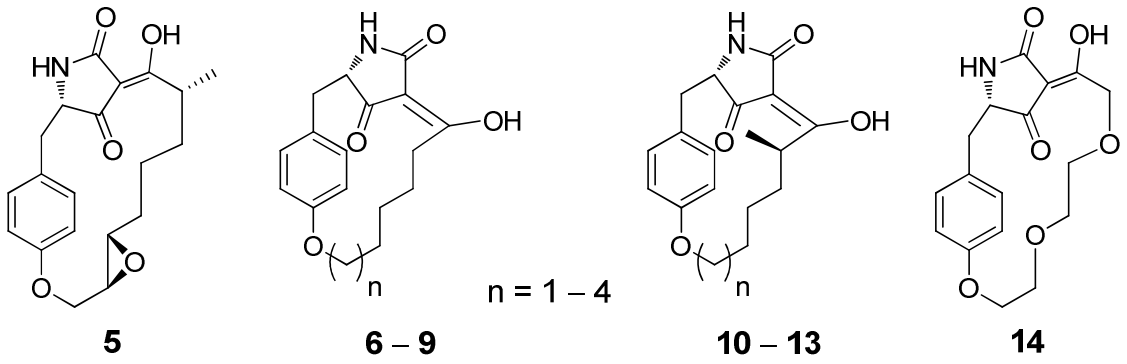
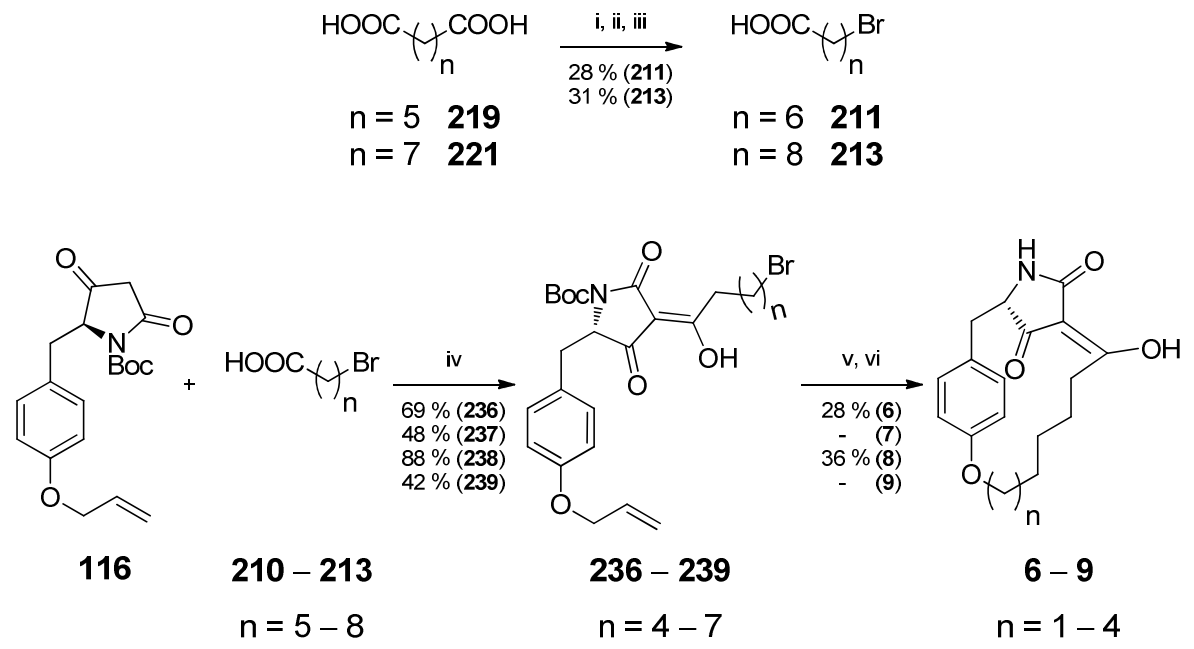


Abbildung 5.1 Strukturen von Macrocidin A (**5**) und Macrocidin Derivaten **6** – **14**

Von den vier benötigten Seitenketten (**210** – **213**) die für die Synthese von **6** – **9** notwendig waren, wurden zwei (**211** und **213**), in je drei Schritten, synthetisiert (Veresterung, Boran Reduktion und HBr vermittelte Bromierung und Esterhydrolyse) (Schema 5.1), wobei die anderen beiden Seitenketten (**210** und **212**) kommerziell erwerblich waren.

Die literaturbekannte L-Tyrosin abgeleitete Tetramsäure **116**[98,152] wurde nach den Vorschriften von Yoshii *et al.*[76] und Yoda *et al.*[79] mit den Seitenketten **210** – **213** gekoppelt. Makroveretherung unter Palladium Katalyse[98,152] und darauffolgende Entschützung lieferten **6** und **8** über zwei Stufen. Die Synthese von **7** und **9** wurde noch nicht vollständig abgeschlossen.



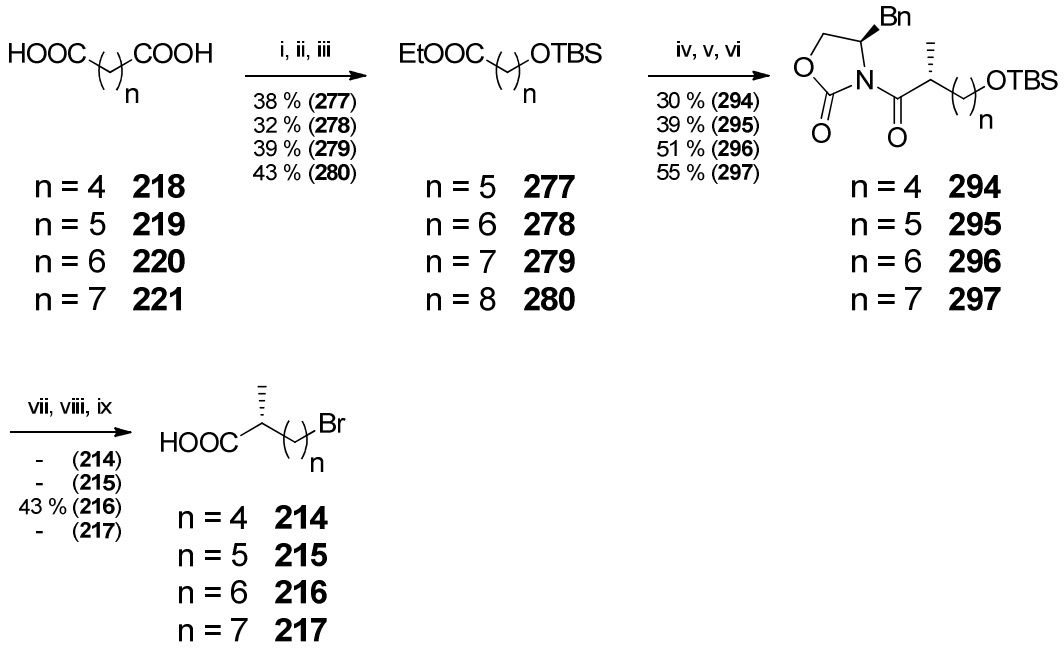
Schema 5.1 Synthese der Analoga **6** – **9**; Reagenzien und Bedingungen: (i) EtOH, H_2SO_4, CH_2Cl_2, RF, 14 h; (ii) $BH_3 \cdot THF$, THF, −20 °C auf RT, 14 h; (iii) 48 % HBr_{aq}, RF, 15 min; (iv) a) DCC, DMAP, CH_2Cl_2, 0 °C auf RT, 1.5 h; b) NEt_3, $CaCl_2$, RT, 14 h; (v) $Pd(PPh_3)_4$ kat., K_2CO_3, THF/MeOH, RF, 48 h; (vi) TFA, CH_2Cl_2, RT, 15 min.

Die zweite Gruppe von Macrocidin A Derivaten (**10** – **13**) trugen die ursprüngliche Methylgruppe in der Seitenkette, welche stereoselektiv bei der Synthese der verschiedenen Seitenketten eingebaut wurde. Die Synthese eben dieser Seitenketten (**214** – **217**) und vor allem die stereoselektive Einführung der Methylgruppe wurde intensiv untersucht.

Schema 5.2 fasst die optimierte neun Stufen Synthese der gewünschten Seitenketten **214** – **217** ausgehend von den Dicarbonsäuren **218** – **221** zusammen.

Diese beinhaltete die Desymmetrisierung von **218** – **221** zu den TBS-geschützten Estern **277** – **280** durch Veresterung, Boran Reduktion und TBS-Schützung. Weiterhin wurde die Reaktionssequenz durch Esterverseifung, stereoselektive Methylierung mit Hilfe von Evans Auxiliar **289**, Transformation des TBS-geschützten Alkohols zum Bromid und Auxiliar Abspaltung komplettiert.

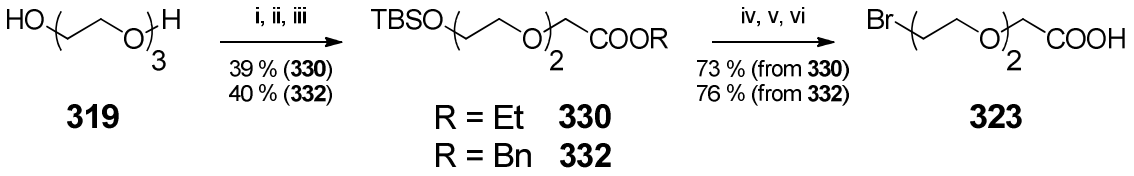
Die komplette Route wurde verifiziert und optimiert, auch wenn sie nur im Falle von Verbindung **226** bisher bis zum Ende durchgeführt wurde. Weiterhin stehen noch die Synthesen der entsprechenden Makrozyklen **10** – **13** aus.



Schema 5.2 Synthese der α-methylierten Bromsäuren **214** – **217**; Reagenzien und Bedingungen: (i) EtOH, H_2SO_4, CH_2Cl_2, RF, 14 h; (ii) $BH_3 \cdot THF$, THF, −20 °C auf RT, 14 h; (iii) Imidazol, TBSCl, DMF, 0 °C auf RT, 14 h; (iv) LiOH, THF/H_2O, 0 °C auf RT, 14 h; (v) a) PivCl, NEt_3, THF, −20 °C, 1 h; b) (*R*)-4-Benzyloxazolidinon (**289**), LiCl, −20 °C auf RT, 3 h; (vi) a) NaHMDS, THF, −78 °C, 1 h; b) MeI, −78 °C to rt, 5 h; (vii) I) TBAF, THF, 0 °C auf RT, 3 h; II) 1 % HCl in EtOH, RT, 5 min; viii) CBr_4, PPh_3, CH_2Cl_2, RT, 1 h; ix) LiOH, H_2O_2, THF/H_2O, 0 °C, 1 h.

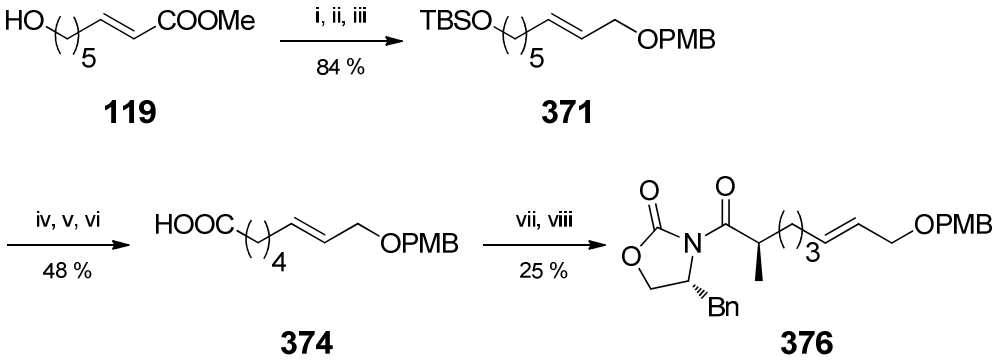
Das dritte von Macrocidin A (**5**) abgeleitete Zielmolekül entsprach einem Kronenether Analogon (**14**). Erneut wurde die Synthese der dafür benötigten Seitenkette **323** fertiggestellt (Schema 5.3), wobei aber bisher nur initiale Experimente durchgeführt wurden um Makrozyklus **14** zu generieren.

Die entsprechende Seitenkette wurde in sechs Schritten hergestellt, beginnend mit einer einfachen TBS-Schützung von Triethylenglykol (**319**) gefolgt von einer TEMPO Oxidation und einer Veresterung der entstandenen Carbonsäure zu entweder Ethylester **330** oder Benzylester **332**. Entschützung des verbleibenden Alkohols, Bromierung und die Hydrolyse des entsprechenden Esters liefert abschließend die gewünschte Seitenkette **323** über sechs Stufen. Im Laufe dieser Synthese wurden viele Probleme, die Aufarbeitung und den generellen Umgang mit derart polaren und instabilen Polyethern betreffend, gelöst.



Schema 5.3 Herstellung der Polyether Seitenkette **323**; Reagenzien und Bedingungen: (i) Imidazol, TBSCl, DMF, 0 °C auf RT, 2,5 h; (ii) $NaClO_2$, TEMPO, NaOCl, Na_2HPO_4, NaH_2PO_4, MeCN, 35 °C, 14 h; (iii) ROH, EDC · HCl, DMAP, CH_2Cl_2, 0 °C auf RT, 14 h; (iv) 1 % HCl in EtOH, RT, 45 min; (v) CBr_4, PPh_3, CH_2Cl_2, RT, 1 – 3 h; (vi) NEt_3, LiBr, MeCN/H_2O, RT, 14 h.

Eine weiteres Ziel der Arbeit war die Herstellung einer Seitenkette, die zur Synthese von Macrocidin A (**5**) selbst verwendet werden sollte. Viele Rückschläge mussten hierbei in Kauf genommen werden bevor eine vielversprechende Route ausgearbeitet werden konnte (Schema 5.4).

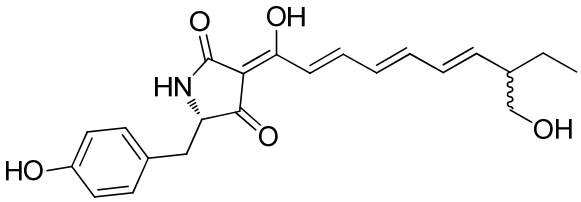


Schema 5.4 Teilsynthese der Seitenkette zur Totalsynthese von Macrocidin A (**5**); Reagenzien und Bedingungen: (i) Imidazol, TBSCl, DMF, 0 °C auf RT, 14 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) PMB-Trichloracetimidat, PPTS, CH_2Cl_2, RT, 23 h; (iv) TBAF, THF, RT, 2 h; (v) a) Oxalylchlorid, DMSO, CH_2Cl_2, −78 °C, 15 min; b) NEt_3, −78 °C auf RT, 30 min; (vi) $NaClO_2$, NaH_2PO_4, 2-Methyl-2-buten, THF/H_2O/^{t}BuOH, RT, 2 h; (vii) a) PivCl, NEt_3, THF, −20 °C, 1 h; b) (*R*)-4-Benzyloxazolidinon (**289**), LiCl, −20 °C auf RT, 3 h; (viii) a) NaHMDS, THF, −78 °C, 1 h; b) MeI, −78 °C auf RT, 5 h.

Die Synthese startete mit einer Standard TBS-Schützung des bekannten Intermediats **119**, einer DIBAL-H Reduktion des Methylesters und einer PMB-Schützung des so entstandenen Allylalkohols zu **371**. Anschließend standen die TBS-Entschützung und eine schrittweise Oxidation zu Carbonsäure **374** an, gefolgt von einer stereoselektiven Methylierung zu **376** mit Hilfe von Evans Auxiliar **289**

(Schema 5.4). In der Zukunft könnte die gezeigte Synthese der Seitenkette die stereoselektive Einführung des Epoxids und letzendlich die Synthese von **5** ermöglichen.

Der zweite Naturstoff, der Ziel dieser Arbeit war, war Torrubiellon D (**15**) (Abb. 5.2).[115] Die Synthese setzt sich aus zwei Hauptteilen zusammen, die Herstellung des Tetramsäure Grundkörpers **383** und die des ungesättigten Aldehydfragments **384**, welches für die Einführung der 3-Acylseitenkette benutzt werden soll.



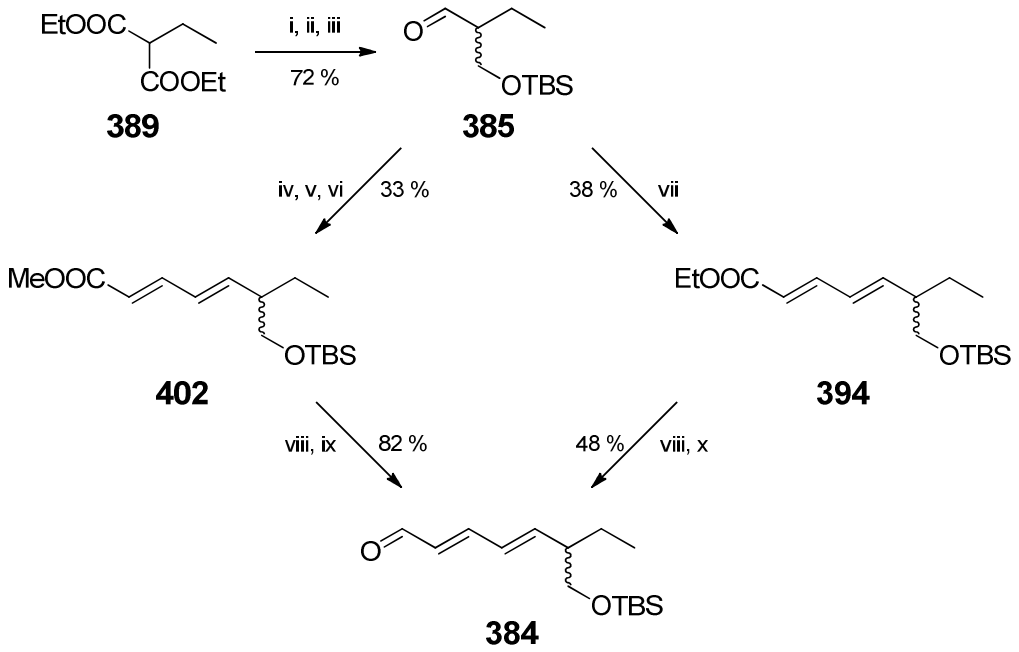
15

Abbildung 5.2 Struktur von Torrubiellon D (**15**)

Das Tetramsäurefragment **383** wurde Literatursynthesen folgend aufgebaut.[53,152,226]

Die Seitenkettensynthese erfolgte über zwei Wege (Schema 5.5). Beide begannen mit der Umwandlung von Diethylethylmalonat (**389**) zum racemischen TBS-geschütztem Aldehyd **385**. Dies wurde durch Reduktion, einfache Schützung und Swern Oxidation bewerkstelligt.[192] Ein Weg verfolgte dann eine schrittweise Verlängerungsstrategie,[225] die eine Wittig Reaktion, eine DIBAL-H Reduktion und eine einstufige Oxidations-Wittig Methode umfasste, um zu Methylester **402** zu gelangen. Diese Zwischenstufe wurde dann durch erneute DIBAL-H Reduktion und Dess-Martin Oxidation in die gewünschte Aldehydseitenkette **384** umgewandelt.

Der zweite Pfad wendete eine HWE-Reaktion mit Phosphonat **398** an um Ethylester **394** in einem Schritt zu erzeugen.[242] Dieser wurde dann durch DIBAL-H Reduktion und Swern Oxidation in den Aldehyd **384** überführt.

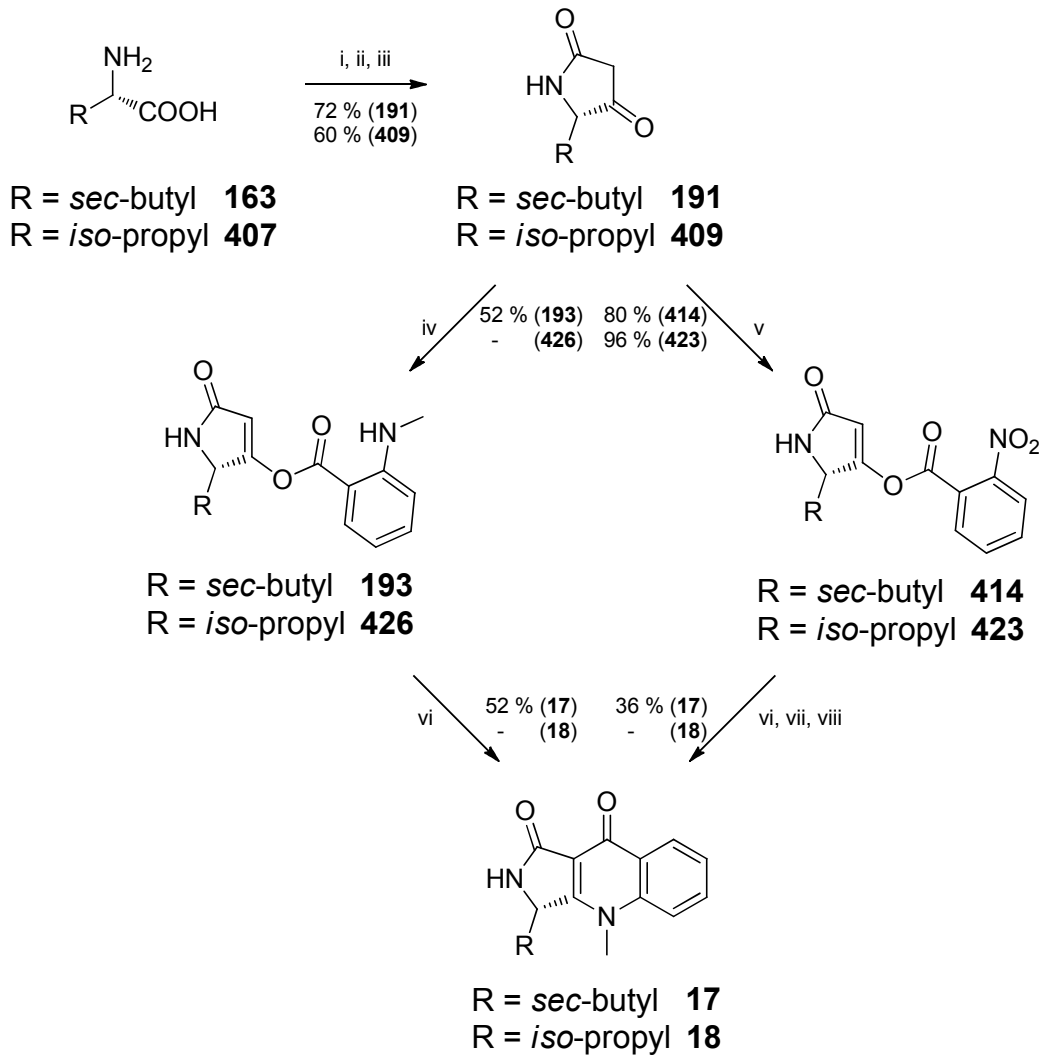


Schema 5.5 Syntheseroute zum Aldehydbaustein **384**; Reagenzien und Bedingungen: (i) a) $LiAlH_4$, THF, RF, 2 d; b) 5 d Extraktion; (ii) ^{n}BuLi, TBSCl, THF, −78 °C auf −20 °C, 2 h; (iii) Oxalylchlorid, DMSO, NEt_3, CH_2Cl_2, −78 °C auf RT, 16,5 h; (iv) Ph_3P=CHCOOMe, CH_2Cl_2, RT, 3 h; (v) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (vi) MnO_2, Ph_3P=CHCOOMe, CH_2Cl_2, RT, 3 d; (vii) $(EtO)_2OPCH_2CHCHCOOEt$ (**398**), DBU, LiCl, MeCN, 0 °C auf RT; 14 h; (viii) DIBAL-H, CH_2Cl_2, −78 °C, 1 – 2 h; (ix) DMP, CH_2Cl_2, RT, 2 h; (x) Oxalylchlorid, DMSO, NEt_3, CH_2Cl_2, −78 °C auf RT, 16,5 h.

Die Kopplung beider Fragmente **383** und **384** durch Ketenylidentriphenylphosphoran (**39**) vermittelte 3-Acylierung wurde mehrmals durchgeführt,[203,246] jedoch konnte das gewünschte Produkt bisher noch nicht sauber isoliert werden.

Die letzten in dieser Arbeit behandelten Naturstoffe waren Quinolactacin A2 (**17**) und B2 (**18**).[124,125] **17** wurde auf zwei verschiedenen Routen neu und effizient synthetisiert (Schema 5.6). Beginnend bei L-Isoleucin (**163**) wurde Tetramsäure **62** nach Standardvorschriften erhalten. Einerseits wurde **62** mit *N*-Methylanthranilsäure (**192**) und andererseits mit *ortho*-Nitrobenzoesäure (**413**) umgesetzt um 4-*O*-Acylverbindungen **193** und **414** herzustellen.[78] Die Umlagerung der 4-*O*-Acyl- zur 3-Acylverbindung wurde durch Acetoncyanhydrin und Triethylamin eingeleitet.[77] Im ersten Fall zyklisierte das 3-Acyl-Produkt von selbst und lieferte damit das gewünschte Naturprodukt **17** in einer Gesamtausbeute von 19 % über fünf Stufen, während im zweiten Fall die Nitro-Gruppe hydrogenolytisch reduziert wurde bevor die spontane Zyklisierung stattfand[81]. Um nun ebenfalls **17** zu synthetisieren war noch

eine selektive Methylierung nötig. Dieser Weg lieferte **17** in einer Ausbeute von 21 % über sieben Stufen.



Schema 5.6 Syntheseweg zu Quinolactacin A2 (**17**) and B2 (**18**); Reagenzien und Bedingungen: (i) Boc_2O, NaOH, Dioxan/H_2O, RT, 18 h; (ii) a) Meldrumsäure (**35**), EDC · HCl, DMAP, CH_2Cl_2, RT, 14 h; b) EtOAc, RF, 2 h; (iii) TFA, CH_2Cl_2, RT, 30 min; (iv) *N*-Methylanthranilsäure (**192**), EDC · HCl, DMAP, CH_2Cl_2, 0 °C auf RT, 5 h; (v) *o*-Nitrobenzoesäure (**413**), EDC · HCl, DMAP, CH_2Cl_2, 0 °C auf RT, 4 h; (vi) $(CH_3)_3C(OH)CN$, NEt_3, MeCN, RT, 14 h – 4 d; (vii) H_2 (1 atm), Pd/C (10 %), MeOH, RT, 14 h; (viii) K_2CO_3, MeI, DMF, RT, 6 h.

Der Hauptteil der analytischen Daten lässt darauf schließen, dass **17** erfolgreich synthetisiert wurde. Einzig und allein der falsche spezifische Drehwert (−17.1 ° (c = 0.2)) anstatt +17.9 ° (c = 0.13)[125]) bleibt bislang unerklärlich. Aufgrund der Tatsachen das beide Synthesewege unabhängig voneinander das selbe Ergebnis

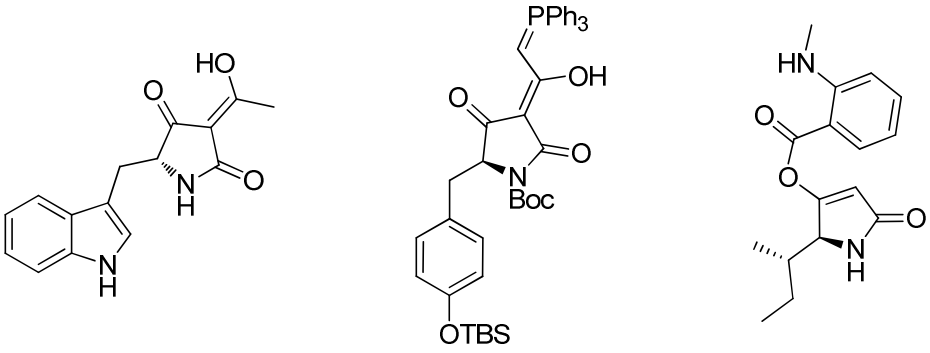
zeigten und alle Stereozentren aus dem chiralen Pool stammten, kann nicht ausgeschlossen werden, dass die Literaturwerte falsch sind.

Die gleiche Reaktionssequenz kann angewendet werden um **18** herzustellen, indem **163** durch L-Valin (**478**) ersetzt wird. Bislang wurde diese Route noch nicht vollständig durchgeführt aber erste Experimente zeigen vielversprechende Resultate (Schema 5.7).

Im letzten Teil dieser Arbeit wurden potentielle Inhibitoren für die Adenylylcyclase (ein Enzym, verantwortlich für die Umwandlung von ATP zu cAMP[145]) synthetisiert und biochemisch untersucht. Dieses Projekt wurde in enger Kooperation mit Dr. S. Kleinbölting der Arbeitsgruppe von Prof. C. Steegborn realisiert, die alle biochemischen Tests durchführte.[258,259]

Auf der Basis von computerbasierten Berechnungen kam L-Tryptophan Derivat **208** als erster Kandidat zum Vorschein (Abb. 5.3). Die Synthese von **208** wurde in zwei Schritten verwirklicht, beginnend von Boc- und Formyl-geschütztem L-Tryptophan (**517**). Die Bildung der Tetramsäure wurde mit Meldrumsäure (**35**)[48] und die 3-Acetylierung mit Ketenylidentriphenylphosphoran (**39**)[203,246] verwirklicht.

Zehn weitere Verbindungen auf der Basis von L-Phenylalanin, L-Tyrosin und L-Isoleucin abgeleiteten Tetramsäuren und 3-Acyltetramsäuren wurden synthetisiert um biochemisch getestet. Abb. 5.3 zeigt die zwei wirkungsvollsten Vertreter: Verbindungen **403** und **193**.



218 **475** **485**

Abbildung 5.3 Potentielle Inhibitoren der Adenylylcyclase die das Motiv einer Tetramsäure enthalten

Am Ende zeigte **208** keine wesentliche Aktivität und sogar Verbindungen **403** und **193** zeigten nur eine Inhibition von rund 50 % wenn sie in einer hohen Konzentration eingesetzt wurden.[258]

Zusammenfassend lässt sich sagen, dass kein eindeutiger Beweis erbracht werden konnte dass Tetramsäuren als leistungsfähige neue Adenylylcyclase Inhibitoren fungieren können. Trotzdem könnte die Synthese von verschiedenartigen, L-Tryptophan und L-Phenylalanin abgeleiteten Tetramsäuren von synthetischem Nutzen oder von biochemischem Intresse sein.

6 Experimental Part

6.1 General methods

All non-aqueous reactions were carried out under argon or nitrogen atmosphere using Schlenk technique unless noted otherwise. Flasks were dried in an oven or manually with a heat gun under vacuum. In these cases only freshly dried and readily distilled solvents (abs.) were used. In cases when no shielding gas is required, solvents with the purification grade p.a. or freshly distilled technical solvents were employed.

Solvents/chemicals: Standard solvents for extraction and column chromatography (cyclohexane, *n*-hexane, dichloromethane, chloroform, ethyl acetate, diethyl ether, methyl *tert*-butyl ether, tetrahydrofuran, ethanol, methanol) were distilled from technical sources prior to their use.

If dry solvents/reagents were used they were dried according to literature procedures[262] and freshly distilled before use. Dichloromethane, dimethylformamide, dimethyl sulfoxide and triethylamine were dried over calcium hydride, diethyl ether and tetrahydrofuran over sodium/benzophenone and methanol over magnesium. Acetonitrile was dried over potassium carbonate and phosphorus pentoxide.

Chemicals were obtained by various suppliers (*ABCR, Acros Organics, AK Scientific, Alfa Aesar, Carbolution, Fisher Scientific, Fluka, Grüssing, Merck, Sigma-Aldrich, Roth, VWR*) and used without further purification unless noted otherwise.

Analytical TLC: TLC was carried out using silica gel plates (either TLC silica gel 60 F_{254} foil plates from *Merck* or TLC silica gel 60 RP-18 F_{254}s foil plates from Merck). Besides UV-light (254 and 366 nm), for visualisation a variety of stains were used:

- iodine on fine silica gel;
- potassium permanganate (1 g $KMnO_4$, 2 g Na_2CO_3, 100 mL H_2O);
- *para*-anisaldehyde (PAA) (100 mL EtOH, 5 mL H_2SO_4, 5 mL *para*-anisaldehyde);
- ceric ammonium molybdate (CAM) (6 mL H_2SO_4, 1 g $Ce(SO_4)_2$, 2.5 g 12 $MoO_3 \times H_3PO_4$, 94 mL H_2O).

In the case of 3-acyltetramic acid, two R_f -values might by reported, representing two tautomers of the same compound.

Column chromatography: Column chromatography was performed using silica gel with the particle size of 63 – 200 µm or flash silica gel with the particle size of 25 – 40 µm from *Macherey-Nagel*. The column length was 30 cm and the diameter of the column was adjusted to the amount of silica gel needed. For a standard separation a mass ratio of 20:1 (silica gel/substance) is applied, for a more challenging separation a mass ratio of 100:1 (silica gel/substance) is applied.[262]

HPLC: Analytical HPLC measurements were carried out with a *Beckman System Gold Programmable Solvent Module 126* either using a *Kinetex*™ C18-HPLC-column (250 × 4.6 mm, pore size 100 Å, particle size 5 µm) by *Phenomenex* or a *Prontosil*™ RP 200-5-C18 column (250 × 4.0 mm, particle size 5 µm) by *Bischoff*. Detection was performed by the use of a *Diode Array Detection Module 168* from *Beckman Instruments*.

Preparative HPLC was carried out with a *Knauer WellChrom K-1800* either using a *Kinetex*™ C18-HPLC-column (250 × 21.2 mm, pore size 100 Å, particle size 5 µm) by *Phenomenex* or a *Prontosil*™ RP 200-5-C18 column (250 × 20.0 mm, particle size 5 µm) by *Bischoff*. Detection was performed by the use of a *WellChrom UV-detector K-2600* from *Knauer*.

NMR spectroscopy: All ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were recorded on a Bruker DRX 300 or DRX 500. Coupling constants are recorded in [Hz] and chemical shifts in [ppm] in reference to the respective deuterated solvent which is employed (chloroform-d_1 ($CDCl_3$) ($\delta(^1H)$ = 7.26 ppm, $\delta(^{13}C)$ = 77.16 ppm), methanol-d_4 (MeOD) ($\delta(^1H)$ = 3.31 ppm, $\delta(^{13}C)$ = 49.00 ppm), acetone-d_6 ($\delta(^1H)$ = 2.05 ppm, $\delta(^{13}C)$ = 29.84, 206.26 ppm) and dimethyl sulfoxide-d_6 (DMSO-d_6) ($\delta(^1H)$ = 2.50 ppm, $\delta(^{13}C)$ = 39.52 ppm)).[263,264] In order to describe the spin multiplicity the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad). The assignment of the signals to the corresponding atoms was conducted with the help of advanced ^{13}C-NMR spectra (JMOD) and 2D-NMR spectra (HSQC, HMBC).

If signals are interchangeable, and therefore cannot be assigned with certainty, the atoms are marked with "†". If multiple stereoisomers are visible, resulting in multiple signals for one atom, the major signal is marked with "*". If one multiplet can

be assigned to multiple atoms, the atoms concerned are separated with ",". If an assignment cannot be made, all atoms concerned are separated with "/".

Gas chromatography: All GC spectra are recorded on a *Carlo Erba HRGC 5160 Mega Series* gas chromatograph employing a DB-5ms silica column (l = 30 m, *ø* = 0.25 mm, d_f = 0.25 µm, *J & W Scientific*). The GC spectra were measured with two major heating protocols:

- program 0: the base temperature was 80 °C and was raised to 280 °C with 5 °C/min and was kept there for 15 min.
- program 4: the base temperature was 150 °C and was raised to 280 °C with 5 °C/min and was kept there for 30 min.

The retention times (t_R) are shown in [min].

Mass spectrometry: EI mass spectra were obtained on a *Thermo Finnigan MAT 8500* spectrometer with a *MAT SS 300* data system and the measurements were carried out using 70 eV of ionisation energy (positive ion mode). The measurements were carried out by direct insertion probe-mass spectroscopy (DIP-MS).

GC-MS spectra were obtained on a *Thermo Finnigan MAT 95* spectrometer coupled to a GC-unit (*Hewlett Packard 5890 Series II*).

HRMS spectra were obtained on a *Thermo Scientific Q Exactive Orbitrap* mass spectrometer connected to a *Dionex UltiMate 3000 RS* UHPLC unit. The measurements were carried out applying electrospray ionisation (ESI).

The peak values represent the mass-to-charge ratio (*m/z*) and their relative intensity [%] is reported in brackets in reference to the base peak which represents 100%. Furthermore, when dealing with halogens, the respective *m/z* values are marked to which isotope they belong (e.g. ^{79}Br vs. ^{81}Br).

IR-spectroscopy: The IR spectra were recorded on a *PerkinElmer Spectrum One* FT-IR-spectrometer. The absorption wavelength (λ) of the bands is reported as their spectroscopic wavenumbers ($\tilde{\nu}$) in [cm^{-1}]. The intensity of the bands is labelled with s (strong), m (medium) or w (weak).

Melting point measurements: The melting points of solids were measured with a *BÜCHI M-565* melting point apparatus and remain uncorrected.

Polarimetry: The specific rotation ($[\alpha]_D$) of substances was measured with a *PerkinElmer polarimeter 343* at 24 °C and/or with a *Jasco P-1020* polarimeter (λ = 589 nm, c = 1.0 ≡ 1 mg/mL) (OC1/2).

X-Ray: Crystal structures were obtained on a *STOE-IPDS II* diffractometer and were measured and calculated by M.Sc. Johannes Obenauf from the group of Prof. R. Kempe (inorganic chemistry II).

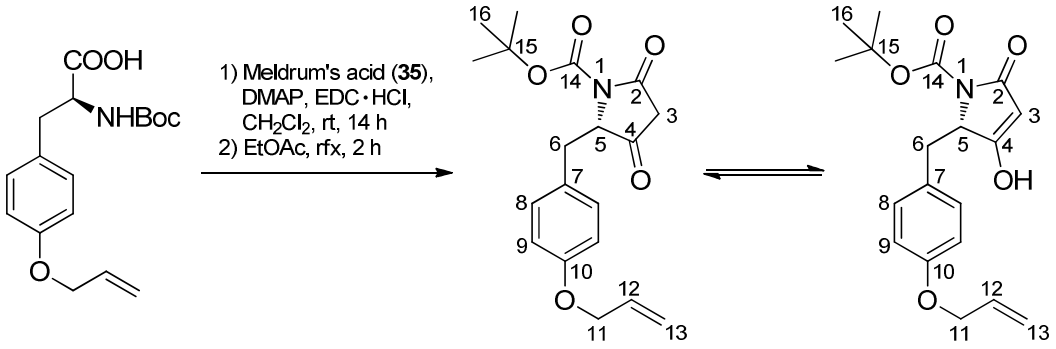
6.2 Macrocidin A and analogues

6.2.1 Synthesis of an allyl-protected L-tyrosine derived tetramic acid

6.2.1.1 General method to prepare tetramic acids from protected amino acids

According to procedures of Jouin *et al*.[48] and Hosseini *et al.*,[53] to a 0.15M solution of a protected amino acid (1.0 eq.) in CH_2Cl_2 abs. at 0 °C are added Meldrum's acid (**35**) (1.1 eq.), EDC · HCl (1.2 eq.) and DMAP (1.4 eq.) and the mixture is stirred for 14 h at room temperature. The mixture is diluted with EtOAc (20 mL/mmol) and the organic phase is washed with brine (2 × 10 mL/mmol), 5% citric acid (3 × 10 mL/mmol) and brine (10 mL/mmol). It is dried over Na_2SO_4, filtered and heated to reflux for 2 h before the solvent is evaporated. After drying *in vacuo* the crude tetramic acid is obtained.

6.2.1.2 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-5-((4-allyloxy) benzyl)-pyrrolidine-2,4-dione (116)



224 **116**

$C_{19}H_{23}NO_5$
Mol. Wt.: 345.39

Compound **116** is prepared applying the general method of 6.2.1.1. The use of bisprotected L-tyrosine derived amino acid **224** (prepared from L-tyrosine over two steps according to literature procedures of Barnickel[152], Bose *et al*.[99] and Kane *et al*.[100]) (10.2 g, 31.9 mmol) yields the product as a yellow foam (9.8 g, 28.5 mmol, 89%) without further purification.

R_f 0.38 (33% EtOAc in ^{c}Hex + two drops of acetic acid)

^{1}H-NMR (300 MHz, $CDCl_3$): tautomeric ratio: (keto : enol) 90% : 10% (calculated from NMR) (only keto form recorded, because enol form to weak and indistinct), assignment differs from literature.[152]

1.62 (s, 9H, H-16), 2.27 (dd, *J* = 22.3, 1.7 Hz, 1H, H-3a), 2.85 (d, *J* = 22.3 Hz, 1H, H-3b), 3.15 (dd, *J* = 14.1, 3.1 Hz, 1H, H-6a), 3.33 (dd, *J* = 14.1, 5.1 Hz, 1H, H-6b), 4.48 (ddd, *J* = 5.4, 1.5, 1.4 Hz, 2H, H-11), 4.60 (ddd, *J* = 5.1, 3.1, 1.7 Hz, 1H, H-5), 5.28 (ddt, *J* = 10.6, 1.6, 1.4 Hz, 1H, H-13_Z), 5.39 (ddt, *J* = 17.3, 1.6, 1.5 Hz, 1H, H-13_E), 6.02 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H, H-12), 6.82 (d, *J* = 8.7 Hz, 2H, H-9), 6.92 (d, *J* = 8.7 Hz, 2H, H-8).

^{13}C-NMR (75 MHz, $CDCl_3$): assignment differs from literature.[152]
28.2 (CH_3, C-16), 35.8 (CH_2, C-6), 43.5 (CH_2, C-3), 68.6 (CH, C-5), 69.0 (CH_2, C-11), 84.4 (C_{quart}, C-15), 115.3 (CH, C-9), 117.9 (CH_2, C-13), 125.9 (C_{quart}, C-7), 131.0 (CH, C-8), 133.2 (CH, C-12), 149.2 (C_{quart}, C-14), 158.2 (C_{quart}, C-10), 167.6 (C_{quart}, C-2), 204.6 (C_{quart}, C-4).

DIP-MS The MS spectrum of **116** is in good agreement with literature.[152]

mp 68.4 °C

$[\alpha]_D^{24}$ +77.4 ° (c = 1.0, $CHCl_3$), [lit.: +75.3 ° (c = 1.0, $CHCl_3$)][152]

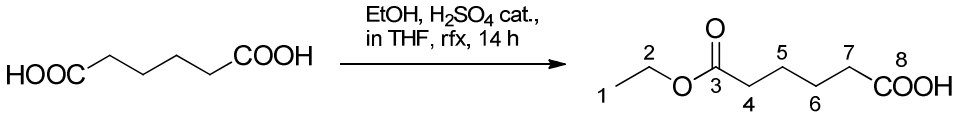
IR (cm^{-1}) The IR spectrum of **116** is in good agreement with literature.[152]

6.2.2 Synthesis of unbranched and α-methylated bromo acids

6.2.2.1 General method to prepare monoethyl esters from dicarboxylic acids

To a suspension of dicarboxylic acid (1.00 eq.) in a suitable solvent (0.5 mL/mmol) are added ethanol p.a. (1.01 eq.) and conc. H_2SO_4 (0.4 drops/mmol) and the mixture is heated to reflux for 14 h. The reaction is left to cool to room temperature before diluting the mixture with Et_2O (0.5 mL/mmol) and H_2O (0.5 mL/mmol). The phases are separated and the aqueous phase is extracted with Et_2O (3 × 0.5 mL/mmol). The combined organic phases are washed with H_2O (0.5 mL/mmol), before they are dried over $MgSO_4$, filtered and the solvent evaporated to give the crude product which is purified by column chromatography (20% → 67% Et_2O in ^{c}Hex→ Et_2O).

6.2.2.2 Preparation of adipic acid monoethyl ester (271)



218 **271**

$C_8H_{14}O_4$
Mol. Wt.: 174.19

Compound **271** is prepared applying the general method of 6.2.2.1. The use of adipic acid (**218**) (15.0 g, 102.6 mmol) and THF as a solvent yields the product as a colourless oil (8.2 g, 47.0 mmol, 46%).

R_f 0.27 (50% Et_2O in ^{c}Hex), tailing observed

^{1}H-/^{13}C-NMR The NMR spectra of **271** are in good agreement with literature.[265,266]

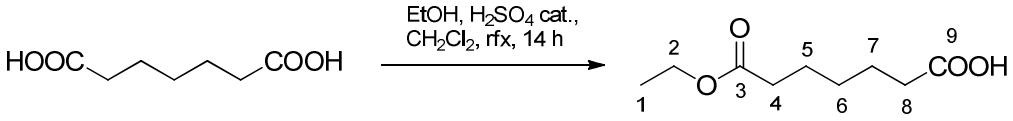
GC (t_R) 15.36 min (program 0)

GC-MS (EI):

175 (1), 156 (4), 129 (90), 115 (22), 111 (57), 101 (65), 88 (58) [$C_4H_8O_2^+$] (McL), 83 (45), 73 (58), 60 (42) [$C_2H_4O_2^+$] (McL), 55 (100).

IR (cm^{-1}) 2960 (w, br), 2934 (w), 1731 (s), 1704 (s), 1416 (m), 1373 (m), 1179 (s), 1142 (s), 1096 (m), 1077 (m), 1028 (m), 919 (m), 854 (m), 758 (m).

6.2.2.3 Preparation of pimelic acid monoethyl ester (225)



219 **225**

$C_9H_{16}O_4$
Mol. Wt.: 188.22

Compound **225** is prepared applying the general method of 6.2.2.1. The use of pimelic acid (**219**) (10.0 g, 62.4 mmol) and CH_2Cl_2 as a solvent yields the product as a colourless oil (5.3 g, 27.9 mmol, 45%).

R_f 0.16 (25% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
1.23 (t, *J* = 7.2 Hz, 3H, H-1), 1.29 – 1.42 (m, 2H, H-6), 1.56 – 1.70 (m, 4H, H-5, H-7), 2.27 (t, *J* = 7.5 Hz, 2H, H-8), 2.32 (t, *J* = 7.4 Hz, 2H, H-4), 4.10 (q, *J* = 7.2 Hz, 2H, H-2), 11.02 (br s, 1H, COOH-9).

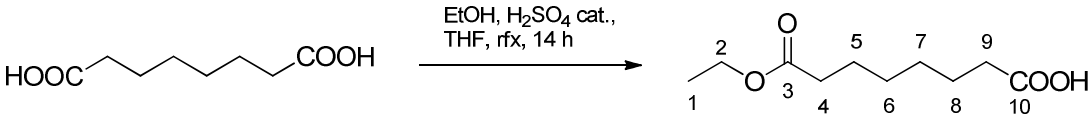
^{13}C-NMR (75 MHz, $CDCl_3$):
14.3 (CH_3, C-1), 24.4 (CH_2, C-7), 24.6 (CH_2, C-5), 28.6 (CH_2, C-6), 33.9 (CH_2, C-8), 34.2 (CH_2, C-4), 60.4 (CH_2, C-2), 173.8 (C_{quart}, C-3), 179.9 (C_{quart}, C-9).

GC (t_R) 18.85 min (program 0)

GC-MS (EI):
170 (3), 143 (78), 129 (28), 125 (59), 114 (38), 101 (32), 97 (49), 88 (91), 83 (37) [$C_4H_8O_2^+$] (McL), 73 (64), 69 (100), 60 (78), 55 (65).

IR (cm^{-1}) 3197 (w, br), 2939 (w), 2869 (w), 1728 (s), 1706 (s), 1462 (w), 1415 (w), 1373 (m), 1240 (m), 1181 (s), 1087 (m), 1028 (m), 936 (w), 860 (m), 737 (w).

6.2.2.4 Preparation of suberic acid monoethyl ester (272)



220 **272**

$C_{10}H_{18}O_4$
Mol. Wt.: 202.25

Compound **272** is prepared applying the general method of 6.2.2.1. The use of suberic acid (**220**) (15.0 g, 86.1 mmol) and THF as a solvent yields the product as a colourless oil (7.7 g, 38.0 mmol, 44%).

R_f 0.48 (50% EtOAc in ^{c}Hex), tailing observed

^{1}H-/^{13}C-NMR The NMR spectra of **272** are in good agreement with literature.[266]

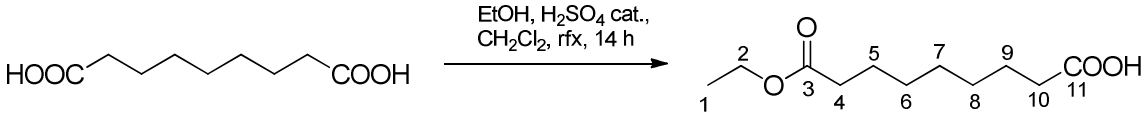
GC (t_R) 20.20 min (program 0)

GC-MS (EI):

185 (4) [M^+-OH], 157 (100), 143 (23), 138 (83), 128 (14), 111 (41), 97 (46), 88 (96) [$C_4H_8O_2^+$] (McL), 83 (54), 73 (46), 69 (69), 60 (61), 55 (52).

IR (cm^{-1}) 3058 (w, br), 2935 (m), 2858 (w), 1732 (s), 1704 (s), 1415 (m), 1373 (m), 1177 (s), 1095 (m), 1031 (m), 938 (w), 856 (w), 730 (w).

6.2.2.5 Preparation of azelaic acid monoethyl ester (226)



221 **226**

$C_{11}H_{20}O_4$
Mol. Wt.: 216.27

Compound **226** is prepared applying the general method of 6.2.2.1. The use of azelaic acid (**221**) (10.0 g, 53.1 mmol) and CH_2Cl_2 as a solvent yields the product as a colourless oil (5.6 g, 26.1 mmol, 49%).

R_f 0.38 (33% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):

1.23 (t, *J* = 7.1 Hz, 3H, H-1), 1.26 – 1.39 (m, 6H, H-6, H-7, H-8), 1.51 – 1.69 (m, 4H, H-5, H-9), 2.26 (t, *J* = 7.5 Hz, 2H, H-4), 2.32 (t, *J* = 7.5 Hz, 2H, H-10), 4.10 (q, *J* = 7.2 Hz, 2H, H-2), 11.04 (br s, 1H, COOH-11).

^{13}C-NMR (75 MHz, $CDCl_3$):

14.3 (CH_3, C-1), 24.7 (CH_2, C-9), 25.0 (CH_2, C-5), 28.9 (2 × CH_2, C-6/C-7/C-8), 29.0 (CH_2, C-6/C-7/C-8), 34.1 (CH_2, C-10), 34.4 (CH_2, C-4), 60.4 (CH_2, C-2), 174.1 (C_{quart}, C-3), 180.2 (C_{quart}, C-11).

GC (t_R) 23.26 min (program 0)

GC-MS (EI):

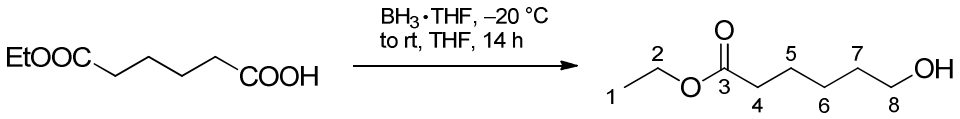
199 (2), 171 (64), 152 (76), 124 (27), 111 (23), 101 (25), 97 (29), 88 (100) [$C_4H_8O_2^+$] (McL), 83 (51), 73 (34), 69 (25), 60 (48), 55 (64).

IR (cm^{-1}) The IR spectrum of **226** is in good agreement with literature.[267]

6.2.2.6 General method to prepare ethyl hydroxyalkanoates from dicarboxylic acid monoethyl esters

According to procedures of Yoon *et al.*[157] and Gung *et al.*,[158] a solution of dicarboxylic acid monoethyl ester (1.00 eq.) in THF abs. (1.3 mL/mmol) is cooled to −20 °C in an ice/salt bath and borane (complex with THF, 1M in THF) (1.13 eq.) is added dropwise by the use of a syringe pump (1.5 mL/min). The reaction is left to slowly warm to room temperature and is stirred for 14 h. The mixture is cooled to 0 °C, diluted with H_2O (1 mL/mmol) and K_2CO_3 (0.2 g/mmol) is added. Et_2O (1.5 mL/mmol) is added and the phases are separated. The aqueous phase is extracted with Et_2O (3 × 1 mL/mmol) and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (50% EtOAc in ^{c}Hex).

6.2.2.7 Preparation of ethyl 6-hydroxyhexanoate (261)



271 **261**

$C_8H_{16}O_3$
Mol. Wt.: 160.21

Compound **261** is prepared applying the general method of 6.2.2.6. The use of monoester **271** (7.6 g, 43.8 mmol) yields the product as a colourless oil (6.7 g, 42.1 mmol, 96%).

R_f 0.58 (67% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **261** are in good agreement with literature.[268]

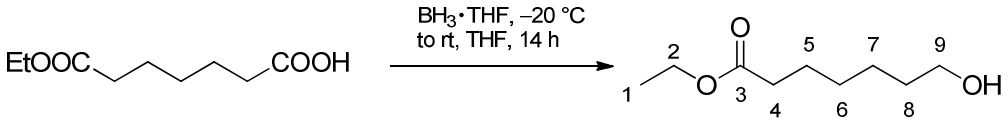
GC (t_R) 11.72 min (program 0)

GC-MS (EI):

130 (12), 115 (40), 101 (67) [M^+-C_3H_7O], 97 (45), 88 (94) [$C_4H_8O_2^+$] (McL), 73 (58) [M^+-$C_4H_7O_2$], 69 (100), 60 (51), 55 (64).

IR (cm^{-1}) 3349 (w, br), 2934 (m), 2871 (w), 1734 (s), 1463 (w), 1419 (m), 1374 (m), 1338 (m), 1183 (m), 1071 (m), 1053 (m), 1030 (s), 951 (w), 847 (w), 737 (w), 669 (m).

6.2.2.8 Preparation of ethyl 7-hydroxyheptanoate (227)[269]



225 **227**

$C_9H_{18}O_3$
Mol. Wt.: 174.24

Compound **227** is prepared applying the general method of 6.2.2.6. The use of monoester **225** (4.6 g, 24.5 mmol) yields the product as a colourless oil (3.4 g, 19.6 mmol, 80%).

R_f 0.55 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.10 (t, *J* = 7.0 Hz, 3H, H-1), 1.14 – 1.29 (m, 4H, H-6, H-7), 1.33 – 1.55 (m, 4H, H-5, H-8), 2.14 (t, *J* = 7.5 Hz, 2H, H-4), 3.06 (br s, 1H, OH), 3.43 (t, *J* = 6.6 Hz, 2H, H-9), 3.97 (q, *J* = 7.1 Hz, 2H, H-2).

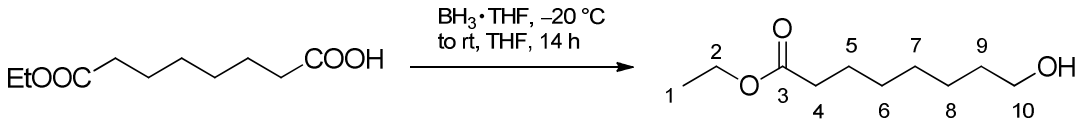
^{13}C-NMR (75 MHz, $CDCl_3$):
14.0 (CH_3, C-1), 24.7 (CH_2, C-5), 25.3 (CH_2, C-7), 28.7 (CH_2, C-6), 32.3 (CH_2, C-8), 34.1 (CH_2, C-4), 60.0 (CH_2, C-2), 62.2 (CH_2, C-9), 173.8 (C_{quart}, C-3).

GC (t_R) 13.90 min (program 0)

GC-MS (EI):
144 (12) [M^+-C_2H_5], 129 (17) [M^+-C_2H_5O], 111 (18), 101 (42) [M^+-$C_3H_5O_2$], 88 (100) [$C_4H_8O_2^+$] (McL), 83 (32), 73 (33) [$C_3H_5O_2^+$], 69 (38), 60 (42), 55 (67).

IR (cm^{-1}) 3392 (w, br), 2934 (m), 2861 (w), 1733 (s), 1463 (w), 1420 (w), 1372 (m), 1343 (w), 1300 (w), 1252 (m), 1179 (m), 1096 (m), 1076 (m), 1055 (m), 1029 (s), 914 (w), 857 (w), 729 (w).

6.2.2.9 Preparation of ethyl 8-hydroxyoctanoate (262)



272 **262**

$C_{10}H_{20}O_3$
Mol. Wt.: 188.26

Compound **262** is prepared applying the general method of 6.2.2.6. The use of monoester **272** (1.5 g, 7.4 mmol) yields the product as a colourless oil (1.3 g, 6.6 mmol, 90%).

R_f 0.39 (66.7% EtOAc in ^{c}Hex)

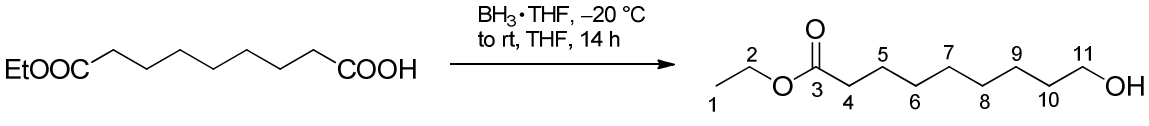
^{1}H-/^{13}C-NMR The NMR spectra of **262** are in good agreement with literature.[270,271]

GC (t_R) 17.10 min (program 0)

GC-MS (EI):
158 (18) [M^+-C_2H_5;-H], 143 (22) [M^+-C_2H_5O], 125 (22), 124 (23), 115 (21) [M^+-$C_3H_5O_2$], 101 (53), 96 (28), 88 (100) [$C_4H_8O_2^+$] (McL), 83 (28), 73 (36) [M^+-$C_6H_{11}O_2$], 70 (43), 60 (43), 55 (79).

IR (cm^{-1}) 3422 (w, br), 2932 (m), 2858 (w), 1733 (s), 1462 (w), 1418 (w), 1371 (m), 1339 (w), 1300 (w), 1248 (m), 1179 (m), 1095 (m), 1033 (m), 939 (w), 858 (w), 726 (w), 667 (w).

6.2.2.10 Preparation of ethyl 9-hydroxynonanoate (228)



226 **228**

$C_{11}H_{22}O_3$
Mol. Wt.: 202.29

Compound **228** is prepared applying the general method of 6.2.2.6. The use of monoester **226** (2.5 g, 11.6 mmol) yields the product as a colourless oil (2.2 g, 10.9 mmol, 95%).

R_f 0.36 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.23 (t, *J* = 7.1 Hz, 3H, H-1), 1.25 – 1.39 (m, 8H, H-6, H-7, H-8, H-9), 1.47 – 1.66 (m, 4H, H-5, H-10), 1.96 (br s, 1H, OH), 2.26 (t, *J* = 7.5 Hz, 2H, H-4), 3.61 (t, *J* = 6.6 Hz, 2H, H-11), 4.10 (q, *J* = 7.1 Hz, 2H, H-2),

^{13}C-NMR (75 MHz, $CDCl_3$):
14.4, (CH_3, C-1), 25.0 (CH_2, C-5), 25.8 (CH_2, C-9), 29.1 (CH_2, C-6/C-7/C8), 29.3 (2 × CH_2, C-6/C-7/C-8), 32.8 (CH_2, C-10), 34.5 (CH_2, C-4), 60.3 (CH_2, C-2), 63.0 (CH_2, C-11), 174.0 (C_{quart}, C-3).

GC (t_R) 20.32 min (program 0)

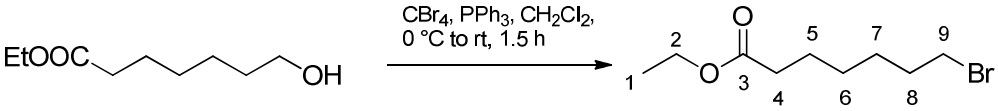
GC-MS (EI):
172 (8), 157 (5) [$M^+-OC_2H_5$], 138 (14), 129 (7) [$M^+-COOC_2H_5$], 115 (7), 110 (9), 101 (45), 97 (29), 88 (100) [$C_4H_8O_2^+$] (McL), 84 (29), 73 (31), 69 (47), 60 (30), 55 (77).

IR (cm^{-1}) 3342 (w, br), 2929 (m), 2856 (m), 1734 (s), 1465 (w), 1373 (m), 1301 (w), 1241 (m), 1180 (m), 1097 (m), 1034 (m), 940 (w), 858 (w), 724 (w).

6.2.2.11 General method for the Appel bromination of alcohols

According to procedures of Wang *et al.*[161] and Oikawa *et al.*,[187] to a 0.01 – 0.05M suspension of alcohol (1.0 eq.) in CH_2Cl_2 abs. at 0 °C are added PPh_3 (1.0 – 2.0 eq.) and CBr_4 (1.0 – 3.0 eq.) and the mixture is left to warm to room temperature. The reaction mixture is stirred for 1 h – 3 h before solvent evaporation gives the crude product.

6.2.2.12 Preparation of ethyl 7-bromoheptanoate (229)



227 **229**

$C_9H_{17}BrO_2$
Mol. Wt.: 237.13

Compound **229** is prepared applying the general method of 6.2.2.11. The use of alcohol **227** (100 mg, 0.57 mmol) and purification of the crude product by column chromatography (67% → 80% EtOAc in ^{c}Hex) yields the product as a yellow oil (121 mg, 0.51 mmol, 89%).

R_f 0.74 (80% EtOAc in ^{c}Hex)

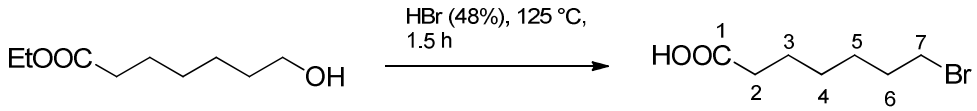
^{1}H-NMR (300 MHz, $CDCl_3$): only a vague ^{1}H-NMR spectrum is mentioned in the literature.[272]

1.24 (t, *J* = 7.1 Hz, 3H, H-1), 1.28 – 1.51 (m, 4H, H-6, H7), 1.62 (tt, *J* = 7.6, 7.4 Hz, 2H, H-5), 1.85 (tt, *J* = 7.4, 6.7 Hz, 2H, H-8), 2.28 (t, *J* = 7.4 Hz, 2H, H-4), 3.39 (t, *J* = 6.7 Hz, 2H, H-9), 4.11 (q, *J* = 7.1 Hz, 2H, H-2).

6.2.2.13 General method to prepare bromoalkanoic acids from ethyl hydroxyalkanoates

According to a procedure of Höfling *et al.*,[163] HBr (48%) (3 – 6 mL/mmol) is degassed with argon and the ethyl hydroxyalkanoate (1.0 eq.) is added dropwise. The mixture is heated to 125 °C for 2 h and left to cool down to room temperature before pouring the reaction mixture into H_2O (1 mL/mmol).The aqueous phase is extracted with EtOAc (4 × 1 mL/mmol) and the combined organic phases are washed with H_2O (1 mL/mmol) and brine (1 mL/mmol). Drying of the organic phases over $MgSO_4$, filtration and solvent evaporation yields the crude product.

6.2.2.14 Preparation of 7-bromoheptanoic acid (211)



227 **211**

$C_7H_{13}BrO_2$
Mol. Wt.: 209.08

Compound **211** is prepared applying the general method of 6.2.2.13. The use of monoester **227** (600 mg, 3.4 mmol) and purification of the crude product by column chromatography (33% EtOAc in ^{c}Hex) yields the product as a yellow oil (548 mg, 2.6 mmol, 76%) which solidifies in the refrigerator.

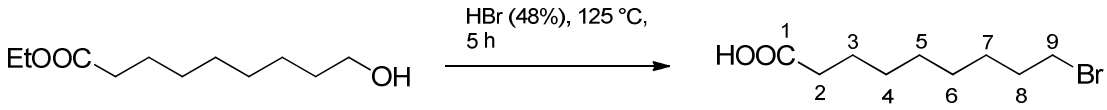
R_f 0.41 (50% EtOAc in ^{c}Hex)

^{1}H-NMR The ^{1}H-NMR spectrum of **211** is in good agreement with literature.[273]

^{13}C-NMR (75 MHz, $CDCl_3$):
24.5 (CH_2, C-3), 27.9 (CH_2, C-5), 28.3 (CH_2, C-4), 32.6 (CH_2, C-6), 33.8 (CH_2, C-7), 34.0 (CH_2, C-2), 180.3 (C_{quart}, C-1).

DIP-MS (EI):
208 (1) [M^+, ^{79}Br], 151 [M^+-CH_2COOH, ^{81}Br], 149 [M^+-CH_2COOH, ^{79}Br], 129 (68) [M^+-Br], 111 (90), 83 (55), 73 (56), 69 (94), 60 (100), 55 (78), 41 (97).

6.2.2.15 Preparation of 9-bromononanoic acid (213)



228 **213**

$C_9H_{17}BrO_2$
Mol. Wt.: 237.13

Compound **213** is prepared applying the general method of 6.2.2.13. The use of monoester **228** (2.0 g, 9.9 mmol) and purification of the crude product by Kugelrohr distillation yields the product as a colourless oil (1.6 g, 6.6 mmol, 66%) which solidifies in the refrigerator.

R_f 0.41 (50% EtOAc in ^{c}Hex)

^{1}H-NMR The ^{1}H-NMR spectrum of **213** is in good agreement with literature.[274]

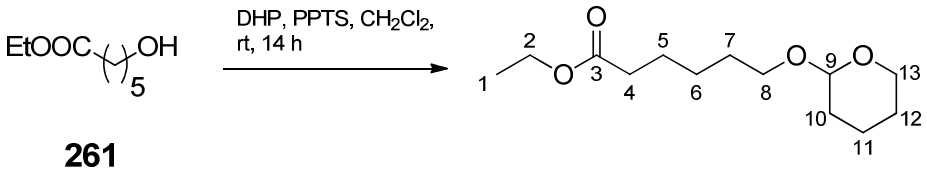
^{13}C-NMR (75 MHz, $CDCl_3$): literature spectrum misses one carbon.[275]
24.7 (CH_2, C-3), 28.2 (CH_2, C-7), 28.7 (CH_2, C-6), 29.0 (CH_2, C-4), 29.1 (CH_2, C-5), 32.9 (CH_2, C-8), 34.0 (CH_2, C-9), 34.2 (CH_2, C-2), 180.4 (C_{quart}, C-1).

DIP-MS (EI):
238 (5) [M^+, ^{81}Br], 236 (5) [M^+, ^{79}Br], 195 (11), 193 (10), 179 (10) [M^+−CH2COOH, ^{81}Br], 177 (11) [M^+−CH_2COOH, ^{79}Br], 157 (15) [M^+−Br], 139 (38), 97 (40), 73 (66) [$C_2H_4COOH^+$], 69 (27), 60 (100), 55 (61), 41 (54), 39 (16).

6.2.2.16 General method for the THP-protection of alcohols

According to a procedure of Miyashita *et al.*,[171] to a 0.1 – 0.5M solution of alcohol (1.0 eq.) in CH_2Cl_2 abs. are added PPTS (0.1 eq.) and DHP (1.5 – 3.0 eq.) and the reaction is left to stir for 14 h at room temperature. The reaction mixture is diluted with brine (3 mL/mmol) and Et_2O (3 mL/mmol). The phases are separated and the aqueous phase is extracted with Et_2O (3 × 3 mL/mmol). The combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.17 Preparation of ethyl 6-((tetrahydro-2*H*-pyran-2-yl)oxy) hexanoate (273)



261

273

$C_{13}H_{24}O_4$
Mol. Wt.: 244.33

Compound **273** is prepared applying the general method of 6.2.2.16. The use of alcohol **261** (3.0 g, 18.7 mmol) and purification of the crude product by column chromatography (9% EtOAc in ^{c}Hex) yields the product as a colourless oil (3.2 g, 13.2 mmol, 71%).

R_f 0.72 (67% EtOAc in ^{c}Hex)

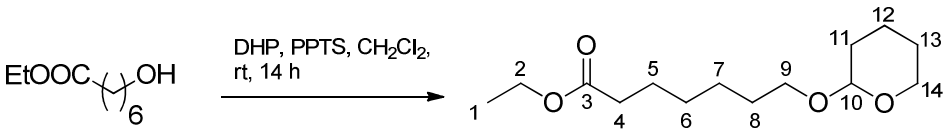
^{1}H-NMR (300 MHz, $CDCl_3$):
1.22 (t, *J* = 7.1 Hz, 3H, H-1), 1.31 – 1.44 (m, 2H, H-6), 1.44 – 1.71 (m, 9H, H-5, H-7, H-10, H-11a, H-12), 1.71 – 1.86 (m, 1H, H-11b), 2.27 (t, *J* = 7.5 Hz, 2H, H-4), 3.35 (dt, *J* = 9.6, 6.5 Hz, 1H, H-8a), 3.41 – 3.51 (m, 1H, H-13a), 3.70 (dt, *J* = 9.6, 6.7 Hz, 1H, H-8b), 3.77 – 3.88 (m, 1H, H-13b), 4.09 (q, *J* = 7.1 Hz, 2H, H-2), 4.51 – 4.56 (m, 1H, H-9).

^{13}C-NMR (75 MHz, $CDCl_3$):
14.3 (CH_3, C-1), 19.8 (CH_2, C-11), 24.9 (CH_2, C-4), 25.6 (CH_2, C-12), 25.9 (CH_2, C-6), 29.5 (CH_2, C-7), 30.9 (CH_2, C-10), 34.4 (CH_2, C-4), 60.2 (CH_2, C-2), 62.4 (CH_2, C-13), 67.4 (CH_2, C-8), 98.9 (CH, C-9), 173.8 (C_{quart}, C-3).

DIP-MS (EI):
159 (12) [M^+−THP], 143 (52) [M^+−OTHP], 115 (57), 101 (38) [$OTHP^+$], 97 (45), 85 (100) [THP^+], 73 (12) [$COOC_2H_5^+$], 69 (41), 67 (12), 55 (17), 41 (31).

IR (cm^{-1}) 2940 (m), 2869 (w), 1734 (s), 1455 (w), 1371 (w), 1352 (w), 1323 (w), 1259 (w), 1233 (m), 1200 (m), 1161 (m), 1136 (s), 1119 (s), 1077 (s), 1032 (s), 1022 (s), 972 (m), 906 (m), 869 (m), 814 (m), 741 (w).

6.2.2.18 Preparation of ethyl 7-((tetrahydro-2*H*-pyran-2-yl)oxy) heptanoate (274)



227 **274**

$C_{14}H_{26}O_4$
Mol. Wt.: 258.35

Compound **274** is prepared applying the general method of 6.2.2.16. The use of alcohol **227** (900 mg, 5.2 mmol) and purification of the crude product by column chromatography (9% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.1 g, 4.2 mmol, 82%).

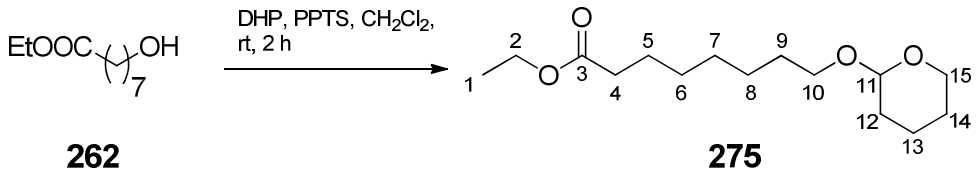
No experimental data is available, although a synthesis of compound **274** has been published.[276]

R_f 0.66 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.20 (t, *J* = 7.2 Hz, 3H, H-1), 1.24 – 1.40 (m, 4H, H-6, H-7), 1.40 – 1.70 (m, 9H, H-5, H-8, H-11, H-12a, H-13), 1.69 – 1.87 (m, 1H, H-12b), 2.24 (t, *J* = 7.5 Hz, 2H, H-4), 3.32 (dt, *J* = 9.6, 6.5 Hz, 1H, H-9a), 3.39 – 3.50 (m, 1H, H-14a), 3.67 (dt, *J* = 9.6, 6.8 Hz, 1H, H-9b), 3.75 – 3.87 (m, 1H, H-14b), 4.07 (q, *J* = 7.2 Hz, 2H, H-2), 4.49 – 4.55 (m, 1H, H-10).

6.2.2.19 Preparation of ethyl 8-((tetrahydro-2*H*-pyran-2-yl)oxy) octanoate (275)



262 **275**

$C_{15}H_{28}O_4$
Mol. Wt.: 272.38

Compound **275** is prepared applying the general method of 6.2.2.16. The use of alcohol **262** (400 mg, 2.1 mmol) and purification of the crude product by column chromatography (9% EtOAc in ^{c}Hex) yields the product as a colourless oil (498 mg, 1.8 mmol, 86%).

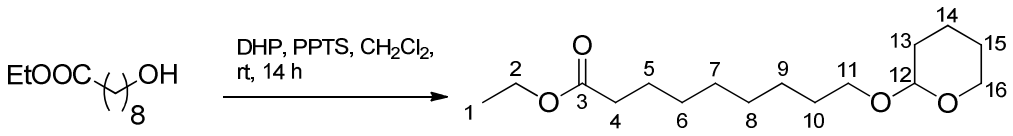
R_f 0.70 (67% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **275** are in good agreement with literature.[277]

DIP-MS (EI):
187 (3) [M^+−THP], 171 (10) [M^+−OTHP], 143 (5), 125 (23), 101 (28) [$OTHP^+$], 97 (15), 85 (100) [THP^+], 55 (19), 41 (13).

IR (cm^{-1}) 2935 (m), 2857 (w), 1734 (s), 1454 (w), 1371 (w), 1351 (w), 1322 (w), 1251 (w), 1200 (m), 1181 (m), 1135 (m), 1119 (s), 1077 (m), 1022 (s), 984 (m), 905 (m), 868 (m), 814 (w), 727 (w).

6.2.2.20 Preparation of ethyl 9-((tetrahydro-2*H*-pyran-2-yl)oxy) nonanoate (276)



228 **276**

$C_{16}H_{30}O_4$
Mol. Wt.: 286.41

Compound **276** is prepared applying the general method of 6.2.2.16. The use of alcohol **228** (2.0 g, 9.9 mmol) and purification of the crude product by column chromatography (9% EtOAc in ^{c}Hex) yields the product as a colourless oil (2.70 g, 9.4 mmol, 95%).

R_f 0.83 (50% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **276** are in good agreement with literature.[277]

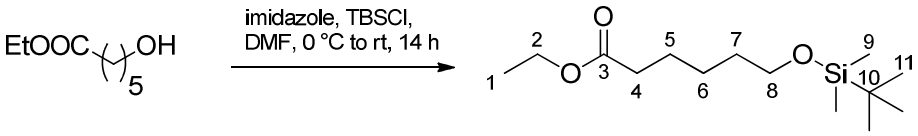
DIP-MS (EI):
386 (2) [M^+], 202 (5), 186 (17), 158 (7), 140 (30), 101 (23) [M^+−OTHP], 85 (28) [M^+−THP], 69 (84), 67 (50), 57 (52), 55 (100), 43 (50), 41 (100).

IR (cm^{-1}) 2931 (m), 2856 (m), 1735 (s), 1455 (w), 1371 (w), 1352 (w), 1323 (w), 1244 (w), 1200 (m), 1181 (m), 1136 (m), 1120 (s), 1078 (m), 1031 (s), 987 (m), 971 (m), 905 (w), 869 (m), 814 (w), 725 (w).

6.2.2.21 General method for the TBS-protection of alcohols

According to a procedure of Wright *et al.*,[172] a 0.33M solution of alcohol (1.0 eq.) in DMF abs. is cooled to 0 °C and imidazole (2.0 eq.) and TBSCl (1.1 – 1.2 eq.) are added. The reaction is left to slowly warm to room temperature and is stirred for 14 h. The reaction mixture is diluted with H_2O (2 mL/mmol) and extracted with EtOAc (3 × 2 mL/mmol). The combined organic phases are washed thoroughly with H_2O (3 × 2 mL/mmol) and brine (2 × 2 mL/mmol) before they are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.22 Preparation of ethyl 6-((*tert*-butyldimethylsilyl)oxy)hexan -oate (277)[278]



261 **277**

$C_{14}H_{30}O_3Si$
Mol. Wt.: 274.47

Compound **277** is prepared applying the general method of 6.2.2.21. The use of alcohol **261** (6.7 g, 42.1 mmol) and purification of the crude product by column chromatography (14% EtOAc in ^{c}Hex) yields the product as a colourless oil (9.9 g, 32.8 mmol, 86%).

R_f 0.90 (33% EtOAc in ^{c}Hex)

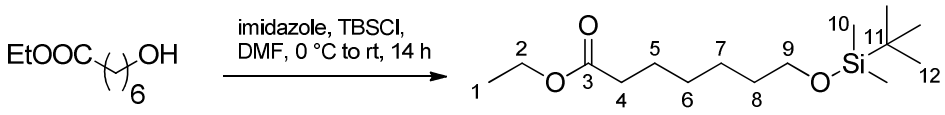
^{1}H-/^{13}C-NMR The NMR spectra of **277** are in good agreement with literature.[278]

GC (t_R) 20.48 min (program 0)

GC-MS (EI):
259 (8) [M^+-CH_3], 229 (41) [M^+-C_2H_5O], 217 (97) [M^+-^{t}Bu], 171 (100), 129 (19), 115 (8) [TBS^+], 103 (27), 101 (17), 97 (14), 75 (67) [$C_2H_7OSi^+$], 73 (37), 69 (45), 55 (14).

IR (cm^{-1}) 2930 (m), 2858 (w), 1737 (s), 1470 (w), 1463 (w), 1387 (w), 1372 (w), 1253 (m), 1159 (m), 1096 (s), 1035 (m), 1006 (w), 938 (w), 915 (w), 832 (s), 773 (s), 712 (w), 661 (w).

6.2.2.23 Preparation of ethyl 7-((*tert*-butyldimethylsilyl)oxy) heptanoate (278)



227 **278**

$C_{15}H_{32}O_3Si$
Mol. Wt.: 288.50

Compound **278** is prepared applying the general method of 6.2.2.21. The use of alcohol **227** (2.3 g, 13.4 mmol) and purification of the crude product by column chromatography (14% EtOAc in ^{c}Hex) yields the product as a colourless oil (3.5 g, 12.0 mmol, 90%).

R_f 0.91 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.03 (s, 6H, H-10), 0.88 (s, 9H, H-12), 1.24 (t, *J* = 7.1 Hz, 3H, H-1), 1.28 – 1.37 (m, 4H, H-6, H-7), 1.44 – 1.55 (m, 2H, H-8), 1.55 – 1.68 (m, 2H, H-5), 2.27 (t, *J* = 7.5 Hz, 2H, H-4), 3.58 (t, *J* = 6.4 Hz, 2H, H-9), 4.11 (q, *J* = 7.1 Hz, 2H, H-2).

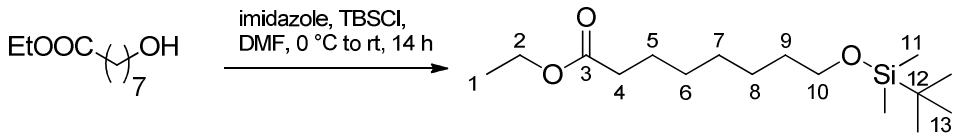
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.2 (CH_3, C-10), 14.4 (CH_3, C-1), 18.5 (C_{quart}, C-11), 25.1 (CH_2, C-5), 25.6 (CH_2, C-6/C-7), 26.1 (CH_3, C-12), 29.1 (CH_2, C-6/C-7), 32.8 (CH_2, C-8), 34.5 (CH_2, C-4), 60.3 (CH_2, C-2), 63.3 (CH_2, C-9), 173.9 (C_{quart}, C-3).

GC (t_R) 23.32 min (program 0)

GC-MS (EI):
273 (5) [M^+-CH_3], 243 [$M^+-OC_2H_5$], 231 (71) [$M^+-{}^{t}Bu$], 185 (100), 157 (3) [M^+−OTBS], 143 (7), 129 (8), 115 (9) [TBS^+], 103 (18), 83 (23), 75 (51) [$C_2H_7OSi^+$], 73 (37), 55 (20).

IR (cm^{-1}) 2930 (m), 2857 (m), 1737 (s), 1463 (w), 1372 (w), 1304 (w), 1253 (m), 1179 (m), 1158 (m), 1095 (s), 1034 (m), 1005 (m), 938 (w), 834 (s), 773 (s), 711 (w), 661 (w).

6.2.2.24 Preparation of ethyl 8-((*tert*-butyldimethylsilyl)oxy)octanoate (279)



262 **279**

$C_{16}H_{34}O_3Si$
Mol. Wt.: 302.52

Compound **279** is prepared applying the general method of 6.2.2.21. The use of alcohol **262** (1.5 g, 8.0 mmol) and purification of the crude product by column chromatography (20% EtOAc in ^{c}Hex) yields the product as a colourless oil (2.1 g, 7.0 mmol, 88%).

R_f 0.82 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-11), 0.89 (s, 9H, H-13), 1.25 (t, *J* = 7.1 Hz, 3H, H-1), 1.28 – 1.36 (m, 6H, H-6, H-7, H-8), 1.50 (quin, *J* = 6.5 Hz, 2H, C-9), 1.61 (quin, *J* = 7.2 Hz, 2H, H-5), 2.28 (t, *J* = 7.5 Hz, 2H, H-4), 3.59 (t, *J* = 6.5 Hz, 2H, H-10), 4.12 (q, *J* = 7.1 Hz, 2H, H-2).

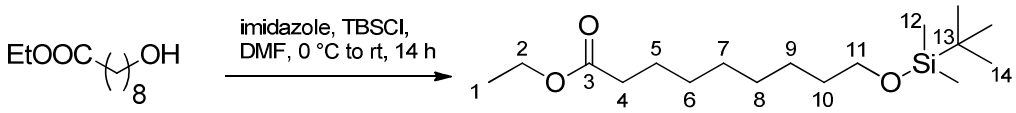
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-11), 14.4 (CH_3, C-1), 18.5 (C_{quart}, C-12), 25.1 (CH_2, C-5), 25.8 (CH_2, C-8), 26.1 (CH_3, C-13), 29.2 (CH_2, C-6/C-7), 29.3 (CH_2, C-6/C-7), 33.0 (CH_2, C-9), 34.5 (CH_2, C-4), 60.3 (CH_2, C-2), 63.4 (CH_2, C-10), 174.0 (C_{quart}, C-3).

GC (t_R) 24.91 min (program 0)

GC-MS (EI):
287 (5) [M^+-CH_3], 257 (16) [$M^+-C_2H_5O$], 245 (61) [$M^+-{}^{t}$Bu], 200 (29) [$M^+-{}^{t}$Bu; $-C_2H_5O$], 199 (100), 115 (11) [$C_6H_{15}Si^+$], 103 (19), 75 (56) [$C_2H_7OSi^+$], 73 (32), 55 (40).

IR (cm^{-1}) 2929 (m), 2857 (m), 1737 (s), 1463 (w), 1372 (w), 1252 (m), 1178 (m), 1095 (s), 1037 (m), 1006 (w), 939 (w), 832 (s), 812 (m), 773 (s), 711 (w), 661 (w).

6.2.2.25 Preparation of ethyl 9-((*tert*-butyldimethylsilyl)oxy) nonanoate (280)



228 **280**

$C_{17}H_{36}O_3Si$
Mol. Wt.: 316.55

Compound **280** is prepared applying the general method of 6.2.2.21. The use of alcohol **228** (1.0 g, 4.9 mmol) and purification of the crude product by column chromatography (20% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.4 g, 4.5 mmol, 93%).

R_f 0.84 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-12), 0.88 (s, 9H, H-14), 1.25 (t, *J* = 7.1 Hz, 3H, H-1), 1.25 – 1.37 (m, 8H, H-6, H-7, H-8, H-9), 1.42 – 1.55 (m, 2H, C-10), 1.55 – 1.68 (m, 2H, H-5), 2.28 (t, *J* = 7.5 Hz, 2H, H-4), 3.58 (t, *J* = 6.6 Hz, 2H, H-11), 4.11 (q, *J* = 7.1 Hz, 2H, H-2).

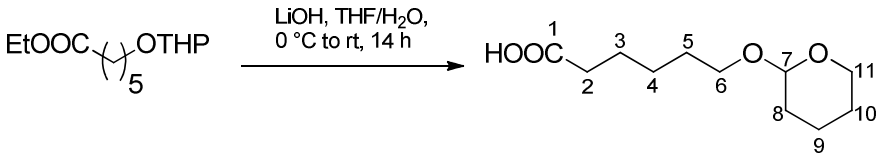
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-12), 14.4 (CH_3, C-1), 18.5 (C_{quart}, C-13), 25.1 (CH_2, C-5), 25.9 (CH_2, C-9), 26.1 (CH_3, C-14), 29.2 (CH_2, C-6, C-7, C-8), 29.4 (2 × CH_2, C-6, C-7, C-8), 33.0 (CH_2, C-10), 34.5 (CH_2, C-4), 60.2 (CH_2, C-2), 63.4 (CH_2, C-11), 174.0 (C_{quart}, C-3).

DIP-MS (EI):
315 (2) [M^+−H], 301 (9) [M^+−CH_3], 287 (73) [M^+−C_2H_5], 273 (13), 271 (11) [M^+−OC_2H_5], 259 (86) [M^+−^{t}Bu], 241 (82), 227 (13), 213 (100) [M^+−$COOC_2H_5$, −2 × CH3], 171 (10), 131 (11) [$OTBS^+$], 121 (15), 115 (10) [TBS^+], 103 (16), 95 (18), 81 (26), 75 (100) [$C_2H_7OSi^+$], 73 (43) [$COOC_2H_5^+$], 69 (42), 56 (36), 42 (19).

6.2.2.26 General method for the saponification of protected ethyl hydroxyalkanoates

According to a procedure of Kobayashi *et al.*,[173] a solution of protected ethyl hydroxyalkanoate (1.0 eq.) in THF (4 mL/mmol) is cooled to 0 °C and H_2O (3 mL/mmol) and LiOH (2M in H_2O) (3.2 – 3.5 eq.) are added dropwise. The suspension is left to slowly warm to room temperature and is stirred for 14 h, until the mixture becomes clear. THF is evaporated and the pH of the aqueous phase is carefully adjusted to 5 with 2M HCl_{aq}. The aqueous phase is extracted with EtOAc (3 × 8 mL/mmol) and the combined organic phases are washed with H_2O (2 × 8 mL/mmol) before they are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.27 Preparation of 6-((tetrahydro-2*H*-pyran-2-yl)oxy)hexanoic acid (281)



273 **281**

$C_{11}H_{20}O_4$
Mol. Wt.: 216.27

Compound **281** is prepared applying the general method of 6.2.2.26. The use of alcohol **273** (1.0 g, 4.1 mmol) and purification of the crude product by column chromatography (6% → 9% → 50% EtOAc in ^{c}Hex) yields the product as a colourless oil (704 mg, 3.3 mmol, 80%).

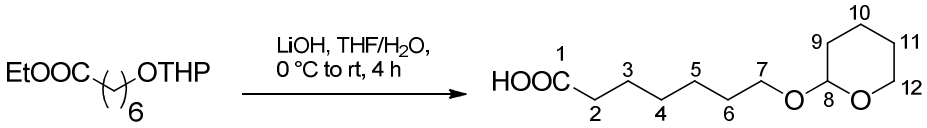
R_f 0.50 (75% EtOAc in ^{c}Hex), tailing observed

^{1}H-/^{13}C-NMR The NMR spectra of **281** are in good agreement with literature.[279]

DIP-MS (EI):
215 (1) [M^+−H], 143 (4) [M^+−C_2H_4COOH], 131 (5) [M^+−THP], 115 (55) [M^+−OTHP], 101 (31) [$OTHP^+$], 97 (41), 85 (100) [THP^+], 73 (17), 69 (50), 67 (15), 55 (30), 41 (47).

IR (cm^{-1}) 3001 (w, br), 2942 (m), 2869 (m), 1732 (m), 1707 (s), 1455 (w), 1441 (w), 1412 (w), 1353 (w), 1260 (m), 1233 (m), 1200 (m), 1184 (m), 1166 (m), 1136 (m), 1118 (s), 1075 (s), 1021 (s), 973 (m), 904 (m), 868 (m), 804 (m), 740 (w).

6.2.2.28 Preparation of 7-((tetrahydro-2*H*-pyran-2-yl)oxy)heptanoic acid (282)



274 **282**

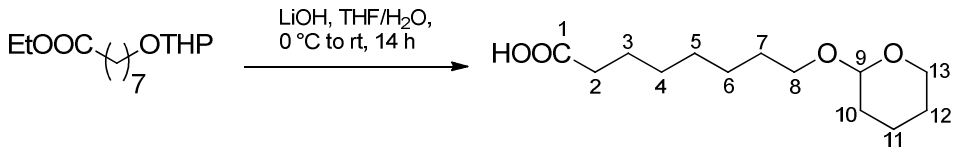
$C_{12}H_{22}O_4$
Mol. Wt.: 230.30

Compound **282** is prepared applying the general method of 6.2.2.26. The use of alcohol **274** (905 mg, 3.5 mmol) and purification of the crude product by column chromatography (6% → 9% → 50% EtOAc in ^{c}Hex) yields the product as a colourless oil (366 mg, 1.6 mmol, 45%).

R_f 0.30 (25% EtOAc in ^{c}Hex), tailing observed

The complete spectral data (NMR, MS, IR) of **282** is in good agreement with literature.[280]

6.2.2.29 Preparation of 8-((tetrahydro-2*H*-pyran-2-yl)oxy)octanoic acid (283)



275 **283**

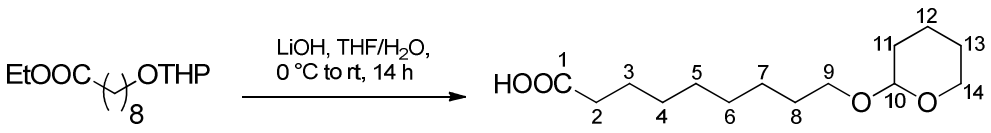
$C_{13}H_{24}O_4$
Mol. Wt.: 244.33

Compound **283** is prepared applying the general method of 6.2.2.26. The use of alcohol **275** (299 mg, 1.1 mmol) and purification of the crude product by column chromatography (6% → 13% → 17% EtOAc in ^{c}Hex) yields the product as a colourless oil (186 mg, 0.76 mmol, 69%).

R_f 0.42 (50% EtOAc in ^{c}Hex), tailing observed

The complete spectral data (NMR, MS, IR) of **283** is in good agreement with literature.[280]

6.2.2.30 Preparation of 9-((tetrahydro-2*H*-pyran-2-yl)oxy)nonanoic acid (284)



276 **284**

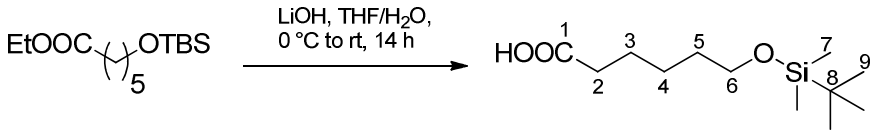
$C_{14}H_{26}O_4$
Mol. Wt.: 258.35

Compound **284** is prepared applying the general method of 6.2.2.26. The use of alcohol **276** (2.9 g, 10.0 mmol) and purification of the crude product by column chromatography (6% → 13% → 17% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.3 g, 5.2 mmol, 52%).

R_f 0.33 (25% EtOAc in ^{c}Hex), tailing observed

The complete spectral data (NMR, MS, IR) of **284** is in good agreement with literature.[280]

6.2.2.31 Preparation of 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid (285)



277 **285**

$C_{12}H_{26}O_3Si$
Mol. Wt.: 246.42

Compound **285** is prepared applying the general method of 6.2.2.26. The use of alcohol **277** (3.0 g, 10.9 mmol) and purification of the crude product by column chromatography (6% → 9% → 17% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.4 g, 5.6 mmol, 51%).

R_f 0.62 (25% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$): only a vague ^{1}H-NMR spectrum is mentioned in the literature.[281]

0.04 (s, 6H, H-7), 0.89 (s, 9H, H-9), 1.33 – 1.45 (m, 2H, H-4), 1.48 – 1.59 (m, 2H, C-5), 1.65 (quin, *J* = 7.6 Hz, 2H, H-3), 2.36 (t, *J* = 7.6 Hz, 2H, H-2), 3.61 (t, *J* = 6.3 Hz, 2H, H-6), 10.63 (br s, 1H, COOH-1).

^{13}C-NMR The ^{13}C-NMR spectrum of **285** is in good agreement with literature.[281]

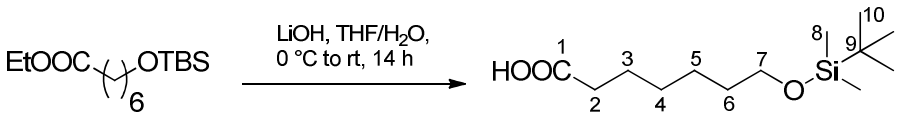
GC (t_R) 21.02 min (program 0)

GC-MS (EI):

213 (4), 189 (22) [$M^+ - {}^{t}Bu$], 171 (92), 131 (3) [$M^+ - TBS$], 129 (12), 115 (3) [TBS^+], 75 (100) [$C_2H_7OSi^+$], 73 (22), 69 (51), 55 (16).

IR (cm^{-1}) 3000 (w, br), 2929 (m), 2858 (m), 1708 (s), 1472 (w), 1463 (w), 1412 (w), 1388 (w), 1361 (w), 1283 (w), 1252 (m), 1097 (s), 1005 (w), 938 (m), 832 (s), 773 (s), 711 (m), 660 (m).

6.2.2.32 Preparation of 7-((*tert*-butyldimethylsilyl)oxy)heptanoic acid (286)



278 **286**

$C_{13}H_{28}O_3Si$
Mol. Wt.: 260.45

Compound **286** is prepared applying the general method of 6.2.2.26. The use of alcohol **278** (4.5 g, 15.6 mmol) and purification of the crude product by column chromatography (6% → 9% → 17% EtOAc in ^{c}Hex) yields the product as a colourless oil (3.1 g, 11.7 mmol, 75%).

R_f 0.58 (33% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR The ^{1}H-NMR spectrum of **286** is in good agreement with literature.[282]

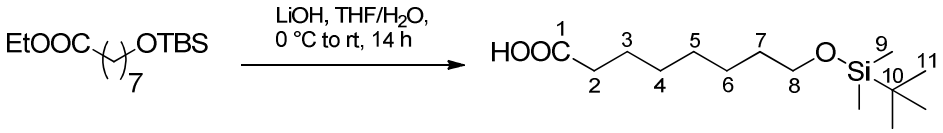
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-8), 18.5 (C_{quart}, C-9), 24.8 (CH_2, C-3), 25.6 (CH_2, C-4/C-5), 26.1 (CH_3, C-10), 29.0 (CH_2, C-4/C-5), 32.7 (CH_2, C-6), 34.2 (CH_2, C-2), 63.3 (CH_2, C-7), 180.2 (C_{quart}, C-1).

GC (t_R) 23.52 min (program 0)

GC-MS (EI):
227 (6), 203 (14) [$M^+ - {}^{t}Bu$], 185 (100) [$M^+ - C_2H_7OSi^+$], 129 (9) [M^+−OTBS], 111 (7), 93 (9), 83 (17), 75 (81) [$C_2H_7OSi^+$], 73 (19), 55 (24).

IR (cm^{-1}) The IR spectrum of **286** is in good agreement with literature.[282]

6.2.2.33 Preparation of 8-((*tert*-butyldimethylsilyl)oxy)octanoic acid (287)



279 **287**

$C_{14}H_{30}O_3Si$
Mol. Wt.: 274.47

Compound **287** is prepared applying the general method of 6.2.2.26. The use of alcohol **279** (2.2 g, 7.4 mmol) and purification of the crude product by column chromatography (6% → 9% → 17% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.4 g, 5.2 mmol, 71%).

R_f 0.56 (25% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-9), 0.89 (s, 9H, H-11), 1.28 – 1.36 (m, 6H, H-4, H-5, H-6), 1.51 (quin, *J* = 6.6 Hz, 2H, H-7), 1.63 (quin, *J* = 7.3 Hz, 2H, H-3), 2.34 (t, *J* = 7.3 Hz, 2H, H-2), 3.59 (t, *J* = 6.6 Hz, 2H, H-8), 10.69 (br s, 1H, COOH-1).

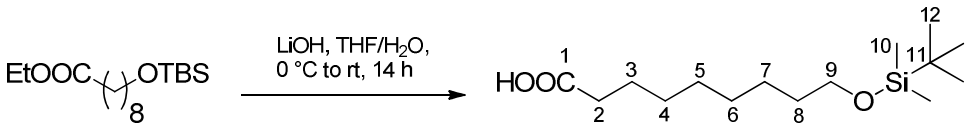
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-9), 18.5 (C_{quart}, C-10), 24.8 (CH_2, C-3), 25.8 (CH_2, C-6), 26.1 (CH_3, C-11), 29.2 (CH_2, C-4/C-5), 32.9 (CH_2, C-4/C-5), 34.2 (CH_2, C-2), 63.4 (CH_2, C-8), 180.3 (C_{quart}, C-1).

GC (t_R) 24.46 min (program 0)

GC-MS (EI):
241 (10), 217 (14) [M^+−^{t}Bu], 200 (29) [M^+−^{t}Bu; −OH], 199 (100) [M^+−C_2H_7OSi], 131 (6) [$C_6H_{15}OSi^+$], 115 (7) [$C_6H_{15}Si^+$], 75 (74) [$C_2H_7OSi^+$], 73 (26), 55 (42).

IR (cm^{-1}) 2929 (m), 2856 (m), 1708 (s), 1463 (w), 1412 (w), 1388 (w), 1361 (w), 1253 (m), 1095 (s), 1005 (w), 938 (m), 832 (s), 773 (s), 728 (w), 661 (m).

6.2.2.34 Preparation of 9-((*tert*-butyldimethylsilyl)oxy)nonanoic acid (288)



280 **288**

$C_{15}H_{32}O_3Si$
Mol. Wt.: 288.50

Compound **288** is prepared applying the general method of 6.2.2.26. The use of alcohol **280** (4.0 g, 12.6 mmol) and purification of the crude product by column chromatography (10% → 20% EtOAc in ^{c}Hex) yields the product as a colourless oil (3.4 g, 11.6 mmol, 92%).

R_f 0.63 (25% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR The ^{1}H-NMR spectrum of **288** is in good agreement with literature.[283]

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-10), 18.5 (C_{quart}, C-11), 24.8 (CH_2, C-3), 25.9 (CH_2, C-7), 26.1 (CH_3, C-12), 29.2 (CH_2, C-4/C-5/C-6), 29.4 (2 × CH_2, C-4/C-5/C-6), 34.2 (CH_2, C-2), 33.0 (CH_2, C-8), 63.4 (CH_2, C-9), 180.3 (C_{quart}, C-1).

GC (t_R) 26.65 min (program 0)

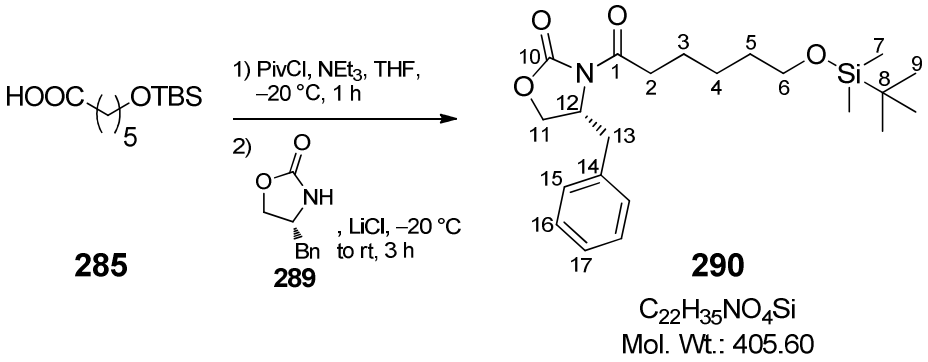
GC-MS The MS spectrum of **288** is in good agreement with literature.[283]

IR (cm^{-1}) 2929 (m), 2896 (w, br), 2856 (m), 1709 (s), 1464 (w), 1416 (w), 1387 w), 1361 (w), 1251 (m), 1096 (s), 1005 (w), 938 (m), 832 (s), 773 (s), 733 (w), 661 (m).

6.2.2.35 General method to prepare (*R*)-4-benzyl-3-(alkanoyl)oxazolidin-2-ones

According to a procedure of Yadav *et al.*,[178,179] a solution of carboxylic acid (1.0 eq.) in THF abs. (10 mL/mmol) is cooled to −20 °C in an ice/salt bath and NEt_3 abs. (2.5 eq.) and PivCl (1.0 eq.) are added. The mixture is stirred for 1 h at −20 °C before dry LiCl (1.5 eq.) and (*R*)-4-benzyloxazolidinone (**289**) (1.0 eq.) are added. The stirring is continued for 1 h at −20 °C and 2 h at room temperature before the reaction is terminated by the addition of sat. NH_4Cl_{aq} (10 mL/mmol) and EtOAc (15 mL/mmol). The phases are separated and the aqueous phase is extracted with EtOAc (3 × 10 mL/mmol) and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.36 Preparation of (*R*)-4-benzyl-3-(6-((*tert*-butyldimethylsilyl) oxy)hexanoyl)oxazolidin-2-one (290)



285 **289** **290**

$C_{22}H_{35}NO_4Si$
Mol. Wt.: 405.60

Compound **290** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **285** (770 mg, 3.1 mmol) and purification of the crude product by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.1 g, 2.7 mmol, 87%).

R_f 0.58 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.05 (s, 6H, H-7), 0.89 (s, 9H, H-9), 1.37 – 1.50 (m, 2H, H-4), 1.51 – 1.63 (m, 2H, H-5), 1.65 – 1.78 (m, 2H, H-3), 2.76 (dd, *J* = 13.2, 9.6 Hz, 1H, H-13a), 2.90 (dt, *J* = 17.1, 7.4 Hz, 2H, H-2b), 2.99 (dt, *J* = 16.9, 7.7 Hz, 2H, H-2a), 3.29 (dd, *J* = 13.2, 3.3 Hz, 1H, H-13b), 3.62 (t, *J* = 6.3 Hz, 2H, H-6), 4.07 – 4.27 (m, 2H, H-11), 4.62 – 4.73 (m, 1H, H-12), 7.17 – 7.41 (m, 5H, H-15, H-16, H-17).

^{13}C-NMR (75 MHz, $CDCl_3$):

−5.1 (CH_3, C-7), 18.5 (C_{quart}, C-8), 24.3 (CH_2, C-3), 25.6 (CH_2, C-4), 26.1 (CH_3, C-9), 32.8 (CH_2, C-5), 35.7 (CH_2, C-2), 38.1 (CH_2, C-13), 55.3 (CH_2, C-12), 63.2 (CH_2, C-6), 66.3 (CH_2, C-11), 127.5 (CH, C-17), 129.1 (CH, C-16), 129.6 (CH, C-15), 135.5 (C_{quart}, C-14), 153.6 (C_{quart}, C-10), 173.5 (C_{quart}, C-1).

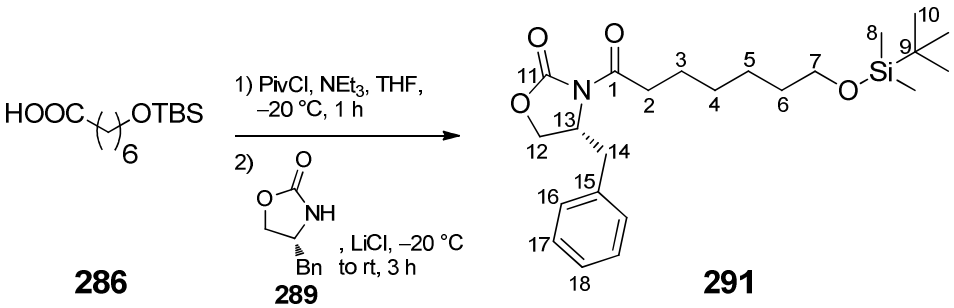
GC (t_R) 24.25 min (program 4)

GC-MS (EI):

405 (1) [M^+], 390 (4) [M^+-CH_3], 348 (100) [$M^+-{}^t$Bu], 229 (13) [$M^+-C_{10}H_{10}NO_2$], 171 (36), 141 (7), 129 (7), 117 (12), 91 (20) [$C_7H_7^+$], 75 (22) [$C_2H_7OSi^+$], 73 (10).

IR (cm^{-1}) 2928 (m), 2855 (w), 1783 (s), 1701 (m), 1472 (w), 1454 (w), 1385 (m), 1351 (m), 1287 (w), 1250 (m), 1207 (m), 1197 (m), 1095 (s), 1052 (m), 1005 (m), 937 (w), 915 (w), 833 (s), 774 (s), 740 (m), 701 (s), 661 (w).

6.2.2.37 Preparation of (*R*)-4-benzyl-3-(7-((*tert*-butyldimethylsilyl) oxy)heptanoyl)oxazolidin-2-one (291)



286 **289** **291**

$C_{23}H_{37}NO_4Si$
Mol. Wt.: 419.63

Compound **291** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **286** (1.4 g, 5.4 mmol) and purification of the crude product by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) yields the product as a colourless oil (2.0 g, 4.8 mmol, 89%).

R_f 0.62 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.05 (s, 6H, H-8), 0.89 (s, 9H, H-10), 1.31 – 1.46 (m, 4H, H-4, H-5), 1.47 – 1.61 (m, 2H, H-6), 1.63 – 1.77 (m, 2H, H-3), 2.76 (dd, *J* = 13.2, 9.6 Hz, 1H, H-14a), 2.89 (dt, *J* = 16.9, 7.4 Hz, 1H, H-2b), 2.98 (dt, *J* = 16.9, 7.5 Hz, 1H, H-2a), 3.30 (dd, *J* = 13.4, 3.3 Hz, 1H, H-14b), 3.61 (t, *J* = 6.6 Hz, 2H, H-7), 4.12 – 4.24 (m, 2H, H-12), 4.62 – 4.72 (m, 1H, H-13), 7.17 – 7.37 (m, 5H, H-16, H-17, H-18).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-8), 18.5 (C_{quart}, C-9), 24.4 (CH_2, C-3), 25.8 (CH_2, C-4/C-5), 26.1 (CH_3, C-10), 29.1 (CH_2, C-4/C-5), 32.8 (CH_2, C-6), 35.7 (CH_2, C-2), 38.1 (CH_2, C-14), 55.3 (CH, C-13), 63.3 (CH_2, C-7), 66.3 (CH_2, C-12), 127.5 (CH, C-18), 129.1 (CH, C-17), 129.6 (CH, C-16), 135.5 (C_{quart}, C-15), 153.6 (C_{quart}, C-11), 173.5 (C_{quart}, C-1),

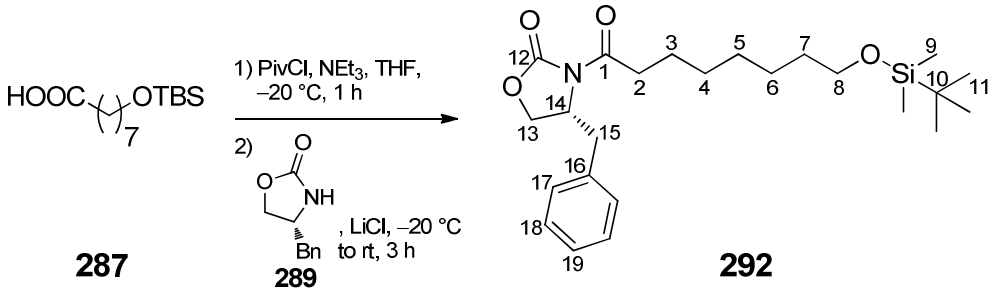
GC (t_R) 25.80 min (program 4)

GC-MS (EI):

419 (1) [M^+], 404 (2) [M^+-CH_3], 362 (100) [$M^+-{}^tBu$], 243 (5) [$M^+-C_{10}H_{10}NO_2$], 185 (21), 117 (19), 91 (21) [$C_7H_7^+$], 75 (37) [$C_2H_7OSi^+$], 73 (10).

IR (cm^{-1}) 2927 (m), 2855 (m), 1783 (s), 1740 (w), 1700 (m), 1605 (w), 1498 (w), 1474 (w), 1454 (w), 1385 (m), 1351 (m), 1249 (m), 1197 (m), 1096 (s), 1050 (m), 1030 (m), 1005 (m), 937 (w), 834 (s), 773 (s), 744 (m), 700 (s), 661 (m).

6.2.2.38 Preparation of (*R*)-4-benzyl-3-(8-((*tert*-butyldimethylsilyl) oxy)octanoyl)oxazolidin-2-one (292)



287 **289** **292**

$C_{24}H_{39}NO_4Si$
Mol. Wt.: 433.66

Compound **292** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **287** (700 mg, 2.6 mmol) and purification of the crude product by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) yields the product as a colourless oil (979 mg, 2.3 mmol, 91%).

R_f 0.52 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.05 (s, 6H, H-9), 0.89 (s, 9H, H-11), 1.28 – 1.42 (m, 6H, H-4, H-5, H-6), 1.52 (quin, *J* = 6.6 Hz, 2H, H-7), 1.69 (quin, *J* = 7.5 Hz, 2H, H-3), 2.76 (dd, *J* = 13.2, 9.6 Hz, 1H, H-15a), 2.89 (dt, *J* = 16.9, 7.5 Hz, 1H, H-2b), 2.97 (dt, *J* = 16.9, 7.5 Hz, 1H, H-2a), 3.30 (dd, *J* = 13.2, 3.3 Hz, 1H, H-15b), 3.60 (t, *J* = 6.6 Hz, 2H, H-8), 4.12 – 4.23 (m, 2H, H-13), 4.62 – 4.72 (m, 1H, H-14), 7.17 – 7.37 (m, 5H, H-17, H-18, H-19).

^{13}C-NMR (75 MHz, $CDCl_3$):

−5.1 (CH_3, C-9), 18.5 (C_{quart}, C-10), 24.4 (CH_2, C-3), 25.8 (CH_2, C-6), 26.1 (CH_3, C-11), 29.3 (CH_2, C-4/C-5), 29.4 (CH_2, C-4/C-5), 33.0 (CH_2, C-7), 35.7 (CH_2, C-2), 38.1 (CH_2, C-15), 55.3 (CH, C-14), 63.4 (CH_2, C-8), 66.3 (CH_2, C-13), 127.5 (CH, C-19), 129.1 (CH, C-18), 129.6 (CH, C-17), 135.5 (C_{quart}, C-16), 153.6 (C_{quart}, C-12), 173.5 (C_{quart}, C-1).

GC (t_R) 30.21 min (program 4)

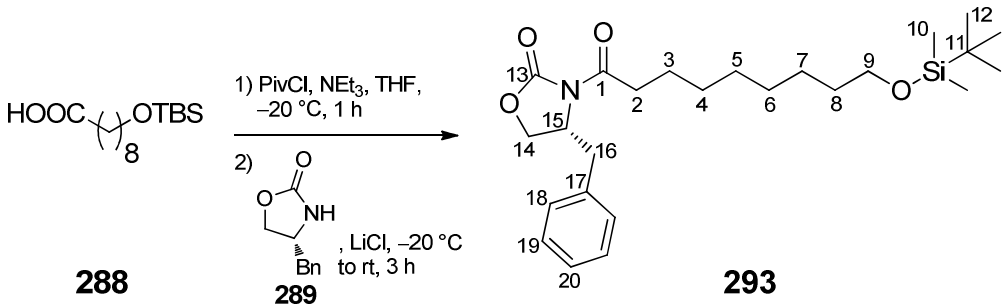
GC-MS (EI):

433 (1) [M^+], 418 (9) [M^+-CH_3], 376 (100) [$M^+-{}^t$Bu], 302 (1) [$M^+-C_6H_{15}OSi$], 257 (9) [$M^+-C_{10}H_{10}NO_2$], 117 (26), 91 (30) [$C_7H_7^+$], 75 (37) [$C_2H_7OSi^+$], 73 (21), 55 (21).

IR (cm^{-1}) 2929 (m), 2856 (m), 1781 (s), 1708 (s), 1463 (m), 1412 (m), 1388 (s), 1351 (m), 1253 (m), 1212 (s), 1095 (s), 1005 (m), 938 (m), 832 (s), 773 (s), 728 (s), 700 (s), 661 (m).

$[\alpha]_D^{24}$ −23.0 ° (c = 1.0, EtOH)

6.2.2.39 Preparation of (*R*)-4-benzyl-3-(9-((*tert*-butyldimethylsilyl) oxy)nonanoyl)oxazolidin-2-one (293)



Compound **293** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **288** (423 mg, 1.5 mmol) and purification of the crude product by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) yields the product as a colourless oil (590 mg, 1.3 mmol, 90%).

R_f 0.57 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.05 (s, 6H, H-10), 0.89 (s, 9H, H-12), 1.25 – 1.41 (m, 8H, H-4, H-5, H-6, H-7), 1.44 – 1.57 (m, 2H, H-8), 1.61 – 1.77 (m, 2H, H-3), 2.76 (dd, *J* = 13.3, 9.6 Hz, 1H, H-16a), 2.88 (dt, *J* = 16.9, 7.5 Hz, 1H, H-2b), 2.97 (dt, *J* = 16.9, 7.5 Hz, 1H, H-2a), 3.30 (dd, *J* = 13.3, 3.3 Hz, 1H, H-16b), 3.60 (t, *J* = 6.6 Hz, 2H, H-9), 4.12 – 4.24 (m, 2H, H-14), 4.62 – 4.72 (m, 1H, H-15), 7.17 – 7.38 (m, 5H, H-18, H-19, H-20).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-10), 18.5 (C_{quart}, C-11), 24.4 (CH_2, C-3), 25.9 (CH_2, C-7), 26.1 (CH_3, C-12), 29.2 (CH_2, C-4/C-5/C-6), 29.4 (CH_2, C-4/C-5/C-6), 29.5 (CH_2, C-4/C-5/C-6), 33.0 (CH_2, C-8), 35.7 (CH_2, C-2), 38.1 (CH_2, C-16), 55.3 (CH, C-15), 63.4 (CH_2, C-9), 66.3 (CH_2, C-14), 127.5 (CH, C-20), 129.1 (CH, C-19), 129.6 (CH, C-18), 135.5 (C_{quart}, C-17), 153.6 (C_{quart}, C-13), 173.6 (C_{quart}, C-1).

DIP-MS (EI):
447 (1) [M^+], 432 (3) [M^+-CH_3], 418 (3), 390 (100) [$M^+-{}^t$Bu], 271 (3) [$M^+-C_{10}H_{10}NO_2$], 143 (9), 131 (6) [$OTBS^+$], 117 (36), 115 (13) [TBS^+], 91 (33), 75 (69) [$C_2H_7OSi^+$], 73 (27), 69 (14), 55 (19), 42 (15).

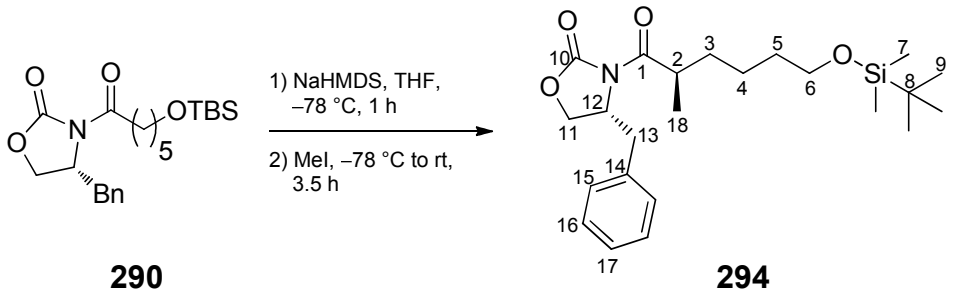
IR (cm^{-1}) 2928 (m), 2855 (m), 1783 (s), 1701 (m), 1455 (w), 1385 (m), 1351 (m), 1290 (w), 1251 (m), 1210 (m), 1198 (m), 1095 (s), 1052 (m), 1006 (m), 939 (w), 834 (s), 774 (s), 744 (m), 701 (s), 662 (w), 620 (w).

6.2.2.40 General methylation method to prepare (*R*)-4-benzyl-3-(2-methylalkanoyl)oxazolidin-2-ones from (*R*)-4-benzyl-3-(alkanoyl)oxazolidin-2-ones

According to a procedure of Yadav *et al.*,[178,179] THF abs. (5 – 20 mL/mmol) is cooled to −78 °C in an acetone/dry ice bath and NaHMDS (1.5M in hexanes) (1.1 eq.) is added dropwise before a solution of (*R*)-4-benzyl-3-(alkanoyl)oxazolidin-2-one (1.0 eq.) in THF abs. (1 – 5 mL/mmol) is added dropwise. The mixture is stirred for 1 h at −78 °C before MeI (3.0 eq.) is added dropwise and the stirring is continued for 3.5 h, leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of sat. NH_4Cl_{aq} (20 mL) and the phases are

separated. The aqueous phase is extracted with EtOAc (3 × 35 mL) and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.41 Preparation of (*R*)-4-benzyl-3-(6-((*tert*-butyldimethylsilyl) oxy)-2-methylhexanoyl)oxazolidin-2-one (294)



290 **294**

$C_{23}H_{37}NO_4Si$
Mol. Wt.: 419.63

Compound **294** is prepared applying the general method of 6.2.2.40. The use of unmethylated compound **290** (1.6 g, 4.0 mmol) and purification of the crude product by column chromatography (flash silica, 5% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.1 g, 2.7 mmol, 68%).

R_f 0.68 (25% EtOAc in ^{c}Hex)

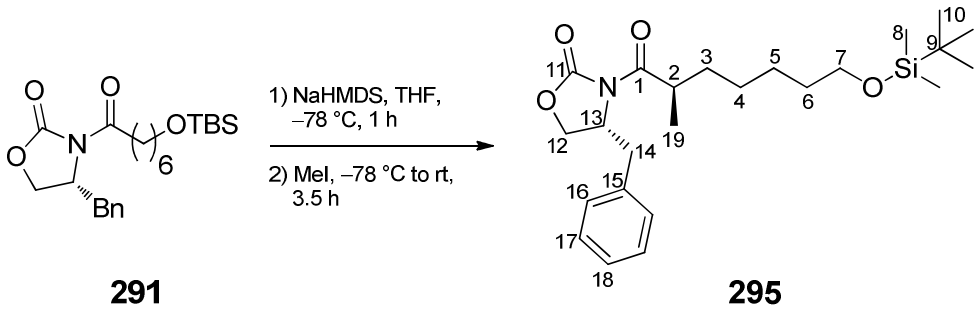
^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-7), 0.88 (s, 9H, H-9), 1.29 – 1.58 (m, 5H, H-3a, H-4, H-5), 1.22 (d, *J* = 6.9 Hz, 3H, H-18), 1.69 – 1.83 (m, 1H, H-3b), 2.77 (dd, *J* = 13.2, 9.6 Hz, 1H, H-13a), 3.27 (dd, *J* = 13.3, 3.2 Hz, 1H, H-13b), 3.60 (t, *J* = 6.4 Hz, 2H, H-6), 3.65 – 3.78 (m, 1H, H-2), 4.13 – 4.23 (m, 2H, H-11), 4.67 (dddd, *J* = 9.8, 6.7, 3.4, 3.4 Hz, 1H, H-12), 7.17 – 7.37 (m, 5H, H-15, H-16, H-17).

GC (t_R) 24.36 min (program 4)

GC-MS (EI):
419 (1) [M^+], 362 (100) [$M^+ - {}^t$Bu], 243 (24) [$M^+ - C_{10}H_{10}NO_2$], 234 (33), 185 (32), 117 (24), 91 (26) [$C_7H_7^+$], 75 (36) [$C_2H_7OSi^+$], 73 (23), 55 (15).

$[\alpha]_D^{24}$ −41.8 ° (c = 1.0, $CHCl_3$)

6.2.2.42 Preparation of (*R*)-4-benzyl-3-(7-((*tert*-butyldimethylsilyl) oxy)-2-methylheptanoyl)oxazolidin-2-one (295)



291 **295**

$C_{24}H_{39}NO_4Si$
Mol. Wt.: 433.66

Compound **295** is prepared applying the general method of 6.2.2.40. The use of unmethylated compound **291** (584 mg, 1.4 mmol) and purification of the crude product by column chromatography (flash silica, 5% EtOAc in ^{c}Hex) yields the product as a colourless oil (351 mg, 0.81 mmol, 58%).

R_f 0.62 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-8), 0.89 (s, 9H, H-10), 1.22 (d, *J* = 6.9 Hz, 3H, H-19), 1.28 – 1.38 (m, 4H, H-4, H-5), 1.41 – 1.58 (m, 3H, H-3a, H-6), 1.63 – 1.83 (m, 1H, H-3b), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H, H-14a), 3.27 (dd, *J* = 13.3, 3.2 Hz, 1H, H-14b), 3.59 (t, *J* = 6.6 Hz, 2H, H-7), 3.63 – 3.77 (m, 1H, H-2), 4.12 – 4.24 (m, 2H, H-12), 4.63 – 4.72 (m, 1H, H-13), 7.18 – 7.37 (m, 5H, H-16, H-17, H-18).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-8), 17.5 (CH_3, C-19), 18.5 (C_{quart}, C-9), 2 × 26.1 (CH_2, C-5), (CH_3, C-10), 27.2 (CH_2, C-4), 32.9 (CH_2, C-6), 33.6 (CH_2, C-3), 37.9 (CH, C-2), 38.1 (CH_2, C-14), 55.5 (CH, C-13), 63.3 (CH_2, C-7), 66.2 (CH_2, C-12), 127.5 (CH, C-18), 129.1 (CH, C-17), 129.6 (CH, C-16), 135.5 (C_{quart}, C-15), 153.2 (C_{quart}, C-11) ,177.4 (C_{quart}, C-1).

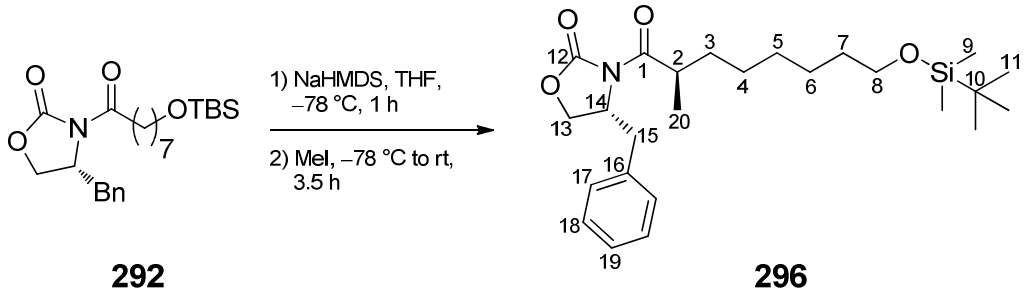
GC (t_R) 26.13 min (program 4)

DIP-MS (EI):

433 (2) [M^+], 418 (3) [M^+-CH_3], 376 (100) [$M^+-{}^tBu$], 257 (12) [$M^+-C_{10}H_{10}NO_2$], 199 (15), 117 (17), 91 (13) [$C_7H_7^+$], 75 (28) [$C_2H_7OSi^+$], 73 (15), 55 (14).

IR (cm^{-1}) 2929 (m), 2857 (w), 1779 (s), 1697 (m), 1455 (w), 1384 (m), 1349 (m), 1290 (w), 1236 (m), 1208 (s), 1195 (m), 1093 (s), 1051 (m), 1007 (m), 971 (m), 832 (s), 773 (s), 745 (m), 701 (s), 661 (m).

6.2.2.43 Preparation of (*R*)-4-benzyl-3-(8-((*tert*-butyldimethylsilyl) oxy)-2-methyloctanoyl)oxazolidin-2-one (296)



292 **296**

$C_{25}H_{41}NO_4Si$
Mol. Wt.: 447.68

Compound **296** is prepared applying the general method of 6.2.2.40. The use of unmethylated compound **292** (645 mg, 1.5 mmol) and purification of the crude product by column chromatography (flash silica, 5% EtOAc in ^{c}Hex) yields the product as a colourless oil (525 mg, 1.2 mmol, 79%).

R_f 0.36 (14% EtOAc in ^{c}Hex)

de 94% (calculated from GC)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.04 (s, 6H, H-9), 0.89 (s, 9H, H-11), 1.22 (d, *J* = 6.9 Hz, 3H, H-20), 1.25 – 1.35 (m, 6H, H-4, H-5, H-6), 1.41 – 1.56 (m, 3H, H-3, H-7), 1.66 – 1.81 (m, 1H, H-3), 2.76 (dd, *J* = 13.3, 9.6 Hz, 1H, H-15b), 3.27 (dd, *J* = 13.3, 3.3 Hz, 1H, H-15a), 3.59 (t, *J* = 6.4 Hz, 2H, H-8), 3.64 – 3.77 (m, 2H, H-2), 4.13 – 4.24 (m, 2H, H-13), 4.67 (dddd, *J* = 9.8, 6.7, 3.3, 3.3 Hz, 1H, H-14), 7.18 – 7.37 (m, 5H, H-17, H-18, H-19).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-9), 17.5 (CH_3, C-20), 18.5 (C_{quart}, C-10), 25.8 (CH_2, C-6), 26.1 (CH_3, C-11), 27.4 (CH_2, C-4/C-5), 29.6 (CH_2, C-4/C-5), 33.0 (CH_2, C-7), 33.5 (CH_2, C-3), 37.9 (CH, C-2), 38.1 (CH_2, C-15), 55.5 (CH, C-14), 63.4 (CH_2, C-8), 66.1 (CH_2, C-13), 127.5 (CH, C-19), 129.1 (CH, C-18), 129.6 (CH, C-17), 135.5 (C_{quart}, C-16), 153.2 (C_{quart}, C-12), 177.4 (C_{quart}, C-1).

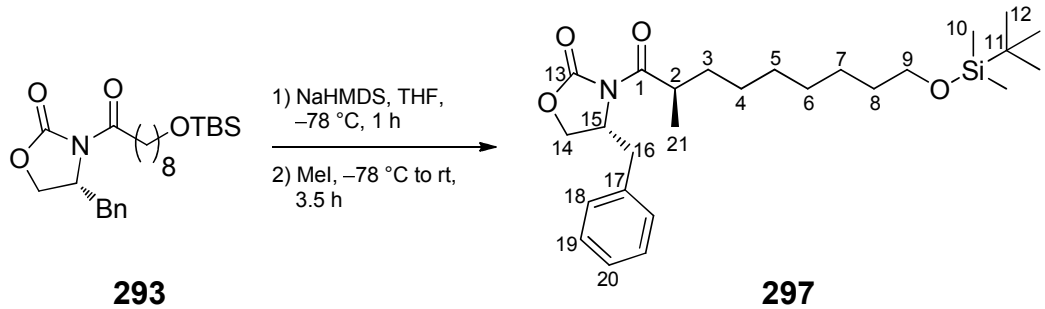
GC (t_R) 29.09 min (program 4)

GC-MS (EI):
447 (1) [M^+], 432 (3) [M^+-CH_3], 390 (100) [$M^+-{}^t$Bu], 271 (8) [$M^+-C_{10}H_{10}NO_2$], 117 (15), 91 (13) [$C_7H_7^+$], 75 (18) [$C_2H_7OSi^+$], 69 (11), 55 (5).

IR (cm^{-1}) 2929 (m), 2857 (w), 1779 (s), 1698 (m), 1462 (w), 1384 (m), 1349 (m), 1290 (w), 1247 (m), 1208 (m), 1195 (m), 1095 (s), 1051 (m), 1007 (m), 971 (m), 925 (w), 834 (s), 773 (s), 756 (s), 701 (s), 665 (m).

$[\alpha]_D^{24}$ −43.7 ° (c = 1.0, $CHCl_3$)

6.2.2.44 Preparation of (*R*)-4-benzyl-3-(9-((*tert*-butyldimethylsilyl) oxy)-2-methylnonanoyl)oxazolidin-2-one (297)



293 **297**

$C_{26}H_{43}NO_4Si$
Mol. Wt.: 461.71

Compound **297** is prepared applying the general method of 6.2.2.40. The use of unmethylated compound **293** (1.0 g, 2.2 mmol) and purification of the crude product by column chromatography (flash silica, 5% EtOAc in ^{c}Hex) yields the product as a colourless oil (677 mg, 1.5 mmol, 66%).

R_f 0.66 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.04 (s, 6H, H-10), 0.89 (s, 9H, H-12), 1.22 (d, *J* = 6.9 Hz, 3H, H-21), 1.25 – 1.35 (m, 8H, H-4, H-5, H-6, H-7), 1.43 – 1.56 (m, 3H, H-3a, H-8), 1.67 – 1.81 (m, 1H, H-3b), 2.76 (dd, *J* = 13.3, 9.6 Hz, 1H, H-16a), 3.27 (dd, *J* = 13.3, 3.3 Hz, 1H, H-16b), 3.59 (t, *J* = 6.6 Hz, 2H, H-9), 3.64 – 3.77 (m, 1H, H-2), 4.13 – 4.25 (m, 2H, H-14), 4.63 – 4.72 (m, 1H, H-15), 7.18 – 7.36 (m, 5H, H-18, H-19, H-20).

^{13}C-NMR (75 MHz, $CDCl_3$):

−5.1 (CH_3, C-10), 17.5 (CH_3, C-21), 18.5 (C_{quart}, C-11), 25.9 (CH_2, C-7), 26.1 (CH_3, C-12), 27.3 (CH_2, C-4), 29.4 (CH_2, C-5/C-6), 29.8 (CH_2, C-5/C-6), 33.0 (CH_2, C-8), 33.5 (CH_2, C-3), 37.8 (CH, C-2), 38.1 (CH_2, C-16), 55.5 (CH, C-15), 63.4 (CH_2, C-9), 66.1 (CH_2, C-14), 127.5 (CH, C-20), 129.1 (CH, C-19), 129.6 (CH, C-18), 135.5 (C_{quart}, C-17), 153.2 (C_{quart}, C-13), 177.5 (C_{quart}, C-1).

GC (t_R) 30.39 min (program 4)

DIP-MS (EI):

461 (3) [M^+], 446 (3) [M^+-CH_3], 404 (100) [$M^+-{}^t$Bu], 131 (4) [$OTBS^+$], 117 (12), 113 (34), 75 (17) [$C_2H_7OSi^+$].

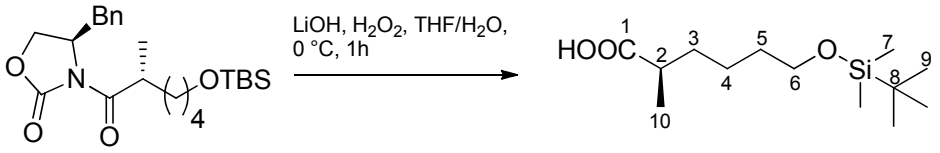
IR (cm^{-1}) 2929 (m), 2856 (m), 1780 (s), 1698 (m), 1456 (w), 1385 (m), 1349 (m), 1289 (w), 1247 (m), 1209 (m), 1196 (m), 1095 (s), 1051 (m), 1007 (m), 970 (m), 939 (w), 917 (w), 833 (s), 774 (s), 734 (m), 701 (s), 661 (w), 624 (w).

6.2.2.45 General method to facilitate the oxidative removal of the Evans auxiliary (I)

According to a procedure of Wang *et al.*,[181] a 0.05M solution of a compound containing an Evans auxiliary (1.0 eq.) in a mixture of THF/H_2O (3:1) is cooled to 0 °C and H_2O_2 (30%) (0.75 mL/mmol) and LiOH (2.0 eq.) are added. The mixture is stirred for 1 h at 0 °C before the THF is evaporated. The pH of the aqueous phase is adjusted to pH 3 with 2M HCl_{aq}. CH_2Cl_2 (15 mL/mmol) is added and the phases are separated. The aqueous phase is extracted with CH_2Cl_2 (3 × 15 mL/mmol) and the

combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.46 Preparation of (*R*)-6-((*tert*-butyldimethylsilyl)oxy)-2-methylhexanoic acid (298)



294 **298**

$C_{13}H_{28}O_3Si$
Mol. Wt.: 260.45

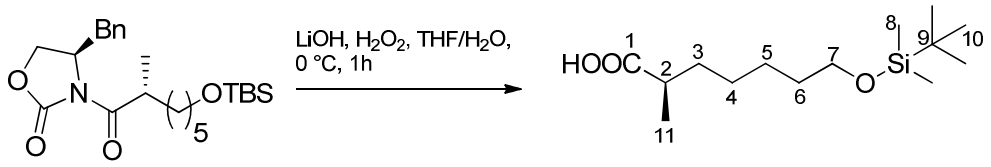
Compound **298** is prepared applying the general method of 6.2.2.45. The use of alcohol **294** (300 mg, 0.71 mmol) and purification of the crude product by column chromatography (20% EtOAc in ^{c}Hex) yields the product as a colourless oil (121 mg, 0.46 mmol, 65%).

R_f 0.38 (25% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, C-7), 0.89 (s, 9H, H-9), 1.18 (d, *J* = 6.9 Hz, 3H, H-10), 1.31 – 1.58 (m, 5H, H-3a, H-4, H-5), 1.63 – 1.77 (m, 1H, H-3b), 2.40 – 2.53 (m, 1H, H-2), 3.60 (t, *J* = 6.3 Hz, 2H, H-6), 11.29 (br s, 1H, COOH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.2 (CH_3, C-7), 16.9 (CH_3, C-10), 18.5 (C_{quart}, C-8), 23.6 (CH_2, C-4), 26.1 (CH_3, C-9), 32.8 (CH_2, C-5), 33.4 (CH_2, C-3), 39.5 (CH, C-2), 63.1 (CH_2, C-6), 183.2 (C_{quart}, C-1).

6.2.2.47 Preparation of (*R*)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylheptanoic acid (299)



295 **299**

$C_{14}H_{30}O_3Si$
Mol. Wt.: 274.47

Compound **299** is prepared applying the general method of 6.2.2.45. The use of alcohol **295** (810 mg, 1.9 mmol) and purification of the crude product by column chromatography (20% EtOAc in ^{c}Hex) yields the product as a colourless oil (262 mg, 0.95 mmol, 51%).

R_f 0.43 (25% EtOAc in ^{c}Hex), tailing observed

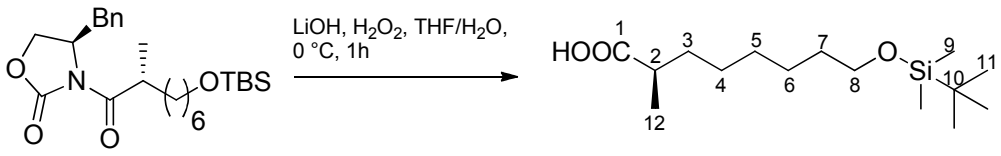
^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-8), 0.89 (s, 9H, H-10), 1.18 (d, *J* = 7.1 Hz, 3H, H-11), 1.29 – 1.39 (m, 4H, H-4, H-5), 1.39 – 1.58 (m, 3H, H-3a, H-6), 1.61 – 1.76 (m, 1H, H-3b), 2.39 – 2.52 (m, 1H, H-2), 3.60 (t, *J* = 6.4 Hz, 2H, H-7), 11.26 (br s, 1H, COOH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH3, C-8), 17.0 (CH3, C-11), 18.5 (Cquart, C-9), 25.9 (CH2, C-5), 26.1 (CH3, C-10), 27.1 (CH2, C-4), 32.8 (CH2, C-6), 33.7 (CH2, C-3), 39.5 (CH, C-2), 63.3 (CH2, C-7), 183.2 (Cquart, C-1).

GC (t_R) 24.89 min (program 0)

GC-MS (EI):
241 (8), 217 (22) [$M^+ - {}^{t}Bu$], 199 (100) [M^+−COOH, −2 × CH_3], 143 (13) [M^+−OTBS], 129 (6) [$M^+ - CH_2OTBS$], 115 (8) [TBS^+], 105 (11), 75 (97) [$C_2H_7OSi^+$], 73 (32), 55 (76).

6.2.2.48 Preparation of (*R*)-8-((*tert*-butyldimethylsilyl)oxy)-2-methyloctanoic acid (300)



296 **300**

$C_{15}H_{32}O_3Si$
Mol. Wt.: 288.50

Compound **300** is prepared applying the general method of 6.2.2.45. The use of alcohol **296** (156 mg, 0.35 mmol) and purification of the crude product by column chromatography (25% EtOAc in ^{c}Hex) yields the product as a colourless oil (67 mg, 0.23 mmol, 67%).

R_f 0.53 (33% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-9), 0.89 (s, 9H, H-11), 1.17 (d, *J* = 7.1 Hz, 3H, H-12), 1.24 – 1.40 (m, 6H, H-4, H-5, H-6), 1.40 – 1.57 (m, 3H, H-3a, H-7), 1.60 – 1.76 (m, 1H, H-3b), 2.38 – 2.52 (m, 1H, H-2), 3.59 (t, *J* = 6.6 Hz, 2H, H-8), 10.89 (br s, 1H, COOH-1).

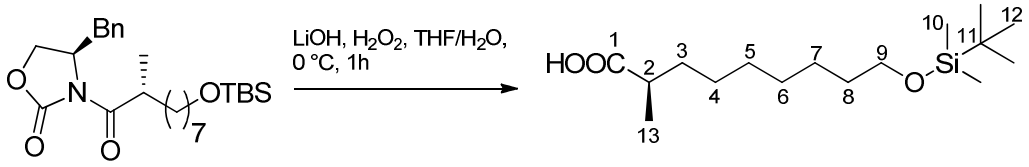
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-9), 17.0 (CH_3, C-12), 18.5 (C_{quart}, C-10), 25.8 (CH_2, C-6), 26.1 (CH_3, C-11), 27.3 (CH_2, C-4), 29.5 (CH_2, C-5), 32.9 (CH_2, C-7), 33.6 (CH_2, C-3), 39.5 (CH, C-2), 63.4 (CH_2, C-8), 183.1 (C_{quart}, C-1).

GC (t_R) 26.39 min (program 0)

GC-MS (EI):
255 (13), 231 (25) [$M^+ - {}^{t}Bu$], 213 (100) [$M^+ - C_2H_7OSi^+$], 171 (10), 157 (5) [M^+−OTBS], 143 (17), 111 (20), 105 (19), 89 (13), 75 (81) [$C_2H_7OSi^+$], 69 (71), 55 (47).

IR (cm^{-1}) 3065 (w, br), 2930 (m), 2858 (m), 1706 (s), 1464 (m), 1417 (w), 1387 (w), 1361 (w), 1291 (w), 1254 (m), 1096 (s), 1006 (w), 938 (m), 833 (s), 812 (m), 773 (s), 711 (w), 661 (m).

6.2.2.49 Preparation of (*R*)-9-((*tert*-butyldimethylsilyl)oxy)-2-methylnonanoic acid (301)



297 **301**

$C_{16}H_{34}O_3Si$
Mol. Wt.: 302.52

Compound **301** is prepared applying the general method of 6.2.2.45. The use of alcohol **297** (380 mg, 0.82 mmol) and purification of the crude product by column chromatography (25% EtOAc in ^{c}Hex) yields the product as a colourless oil (226 mg, 0.75 mmol, 91%).

R_f 0.40 (20% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-10), 0.89 (s, 9H, H-12), 1.17 (d, *J* = 7.1 Hz, 3H, H-13), 1.24 – 1.39 (m, 8H, H-4, H-5, H-6, H-7), 1.40 – 1.56 (m, 3H, H-3a, H-8), 1.61 – 1.75 (m, 1H, H-3b), 2.38 – 2.52 (m, 1H, H-2), 3.59 (t, *J* = 6.6 Hz, 2H, H-8), 11.13 (br s, 1H, COOH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-10), 17.0 (CH_3, C-13), 18.5 (C_{quart}, C-11), 25.9 (CH_2, C-7), 26.1 (CH_3, C-12), 27.2 (CH2, C-4), 29.4 (CH_2, C-5/C6), 29.6 (CH_2, C-5/C-6), 33.0 (CH_2, C-8), 33.7 (CH_2, C-3), 39.5 (CH, C-2), 63.4 (CH_2, C-9), 183.1 (C_{quart}, C-1).

GC (t_R) 27.98 min (program 0)

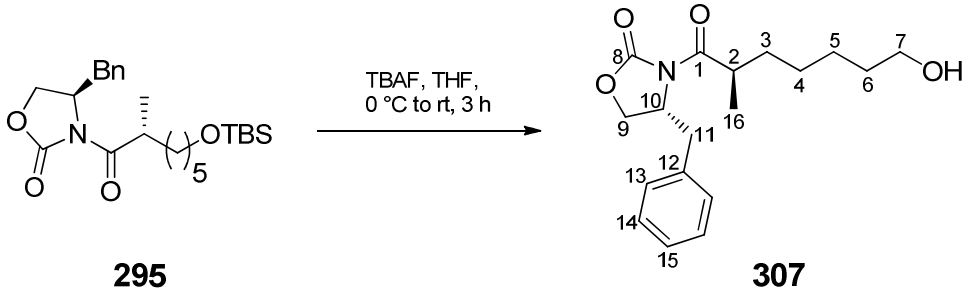
GC-MS (EI):
269 (4), 245 (11) [M^+–^{t}Bu], 227 (100) [M^+−C_2H_7OSi], 171 (3) [M^+−OTBS], 105 (10), 83 (38), 75 (88) [$C_2H_7OSi^+$], 69 (72), 55 (41).

$[\alpha]_D^{24}$ −7.9 ° (c = 1.0, EtOAc)

6.2.2.50 General method for TBAF mediated TBS-deprotection

According to procedures of Zhang *et al*.,[184] Pelliciari *et al.*[185] and Das *et al.*,[186] a 0.05 – 0.1M solution of TBS-protected compound (1.0 eq.) in THF is cooled to 0 °C and TBAF (1M in THF) (1.7 – 2.1 eq.) is added dropwise. The mixture is stirred for 3 h leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of sat. NH_4Cl_{aq} (10 mL/mmol) and is diluted with EtOAc (10 mL/mmol). The phases are separated and the aqueous phase is extracted with EtOAc (3 × 10 mL/mmol) and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.51 Preparation of (*R*)-4-benzyl-3-((*R*)-7-hydroxy-2-methyl-heptanoyl)oxazolidin-2-one (307)



295 **307**

$C_{18}H_{25}NO_4$
Mol. Wt.: 319.40

Compound **307** is prepared applying the general method of 6.2.2.50. The use of TBS-protected compound **295** (250 mg, 0.58 mmol) and purification of the crude product by column chromatography (33% EtOAc in ^{c}Hex) yields the product as a colourless oil (152 mg, 0.47 mmol, 83%).

R_f 0.10 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

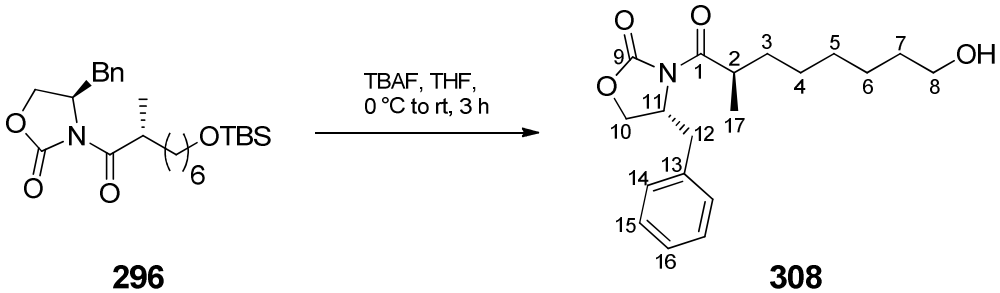
1.22 (d, *J* = 6.9 Hz, 3H, H-16), 1.29 – 1.46 (m, 4H, H-4, H-5), 1.46 – 1.64 (m, 3H, H-3a, H-6), 1.70 – 1.83 (m, 1H, H-3b), 2.76 (dd, *J* = 13.2, 9.6 Hz, 1H, H-11a), 3.26 (dd, *J* = 13.2, 3.3 Hz, 1H, H-11b), 3.63 (t, *J* = 6.6 Hz, 2H, H-7), 3.65 – 3.77 (m, 1H, H-2), 4.13 – 4.25 (m, 2H, H-9), 4.63 – 4.72 (m, 1H, H-10), 7.16 – 7.37 (m, 5H, H-13, H-14, H-15).

^{13}C-NMR (75 MHz, $CDCl_3$):

17.5 (CH_3, C-16), 25.8 (CH_2, C-5), 27.1 (CH_2, C-4), 32.7 (CH_2, C-6), 33.4 (CH_2, C-3), 37.7 (CH, C-2), 38.0 (CH_2, C-11), 55.5 (CH, C-10), 63.0 (CH_2, C-7), 66.2 (CH_2, C-9), 127.5 (CH, C-15), 129.1 (CH, C-14), 129.6 (CH, C-13), 135.4 (C_{quart}, C-12), 153.2 (C_{quart}, C-8), 177.4 (C_{quart}, C-1).

IR (cm^{-1}) 3414 (w, br), 2933 (m), 2862 (w), 1773 (s), 1694 (s), 1455 (m), 1385 (s), 1349 (s), 1289 (m), 1209 (s), 1097 (m), 1074 (m), 1051 (m), 1015 (m), 971 (m), 925 (w), 838 (w), 762 (m), 746 (s), 701 (s).

6.2.2.52 Preparation of (*R*)-4-benzyl-3-((*R*)-8-hydroxy-2-methyl-octanoyl)oxazolidin-2-one (308)



296 **308**

$C_{19}H_{27}NO_4$

Mol. Wt.: 333.42

Compound **308** is prepared applying the general method of 6.2.2.50. The use of TBS-protected compound **296** (644 mg, 1.4 mmol) and purification of the crude product by column chromatography (33% EtOAc in ^{c}Hex) yields the product as a colourless oil (337 mg, 1.0 mmol, 70%).

R_f 0.19 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.21 (d, *J* = 6.6 Hz, 3H, H-17), 1.26 – 1.41 (m, 6H, H-4, H-5, H-6), 1.47 – 1.62 (m, 3H, H-3a, H-7), 1.67 – 1.83 (m, 1H, H-3b), 2.76 (dd, *J* = 13.2, 9.6 Hz, 1H, H-12a), 3.26 (dd, *J* = 13.3, 3.2 Hz, 1H, H-12b), 3.62 (t, *J* = 6.6 Hz, 2H, H-8), 3.64 – 3.77 (m, 2H, H-2), 4.13 – 4.24 (m, 2H, H-10), 4.67 (dddd, *J* = 9.8, 6.6, 3.3, 3.3 Hz, 1H, H-11), 7.16 – 7.37 (m, 5H, H-14, H-15, H-16).

^{13}C-NMR (75 MHz, $CDCl_3$):

17.4 (CH_3, C-17), 25.6 (CH_2, C-6), 27.2 (CH_2, C-4/C-5), 29.4 (CH_2, C-4/C-5), 32.8 (CH_2, C-7), 33.4 (CH_2, C-3), 37.8 (CH, C-2), 38.0 (CH_2, C-12), 55.4 (CH, C-11), 63.0 (CH_2, C-8), 66.1 (CH_2, C-10), 127.4 (CH, C-16), 129.0 (CH, C-15), 129.5 (CH, C-14), 135.4 (C_{quart}, C-13), 153.2 (C_{quart}, C-9), 177.4 (C_{quart}, C-1).

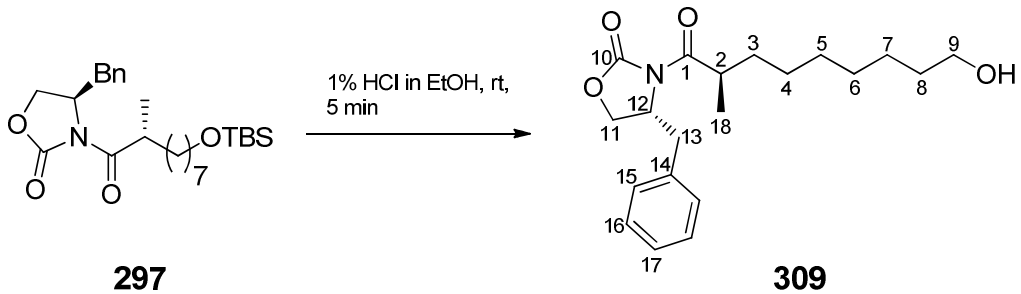
GC (t_R) 43.85 min (program 0)

GC-MS (EI):

333 (16) [M^+], 233 (17) [$C_{13}H_{15}NO_3^+$] (McL), 178 (32), 157 (100) [$M^+ - C_{10}H_{10}NO_2$], 139 (19), 129 (12) [$M^+ - C_{11}H_{10}NO_3$], 117 (29), 111 (39), 91 (43) [$C_7H_7^+$], 86 (23), 69 (86), 55 (37).

IR (cm^{-1}) 3396 (w, br), 2930 (m), 2857 (w), 1774 (s), 1694 (s), 1454 (m), 1384 (s), 1349 (m), 1289 (m), 1236 (m), 1209 (s), 1095 (m), 1074 (m), 1051 (m), 1030 (m), 1015 (m), 970 (m), 920(w), 839 (w), 761 (m), 745 (m), 701 (s).

6.2.2.53 Preparation of (*R*)-4-benzyl-3-((*R*)-9-hydroxy-2-methyl-nonanoyl)oxazolidin-2-one (309)



297 **309**

$C_{20}H_{29}NO_4$
Mol. Wt.: 347.45

According to a method of Cunico *et al.*,[182] to a solution of TBS-protected compound **297** (677 mg, 1.5 mmol, 1.0 eq.) in EtOH (30 mL) is added conc. HCl (0.3 mL) and the mixture is stirred for 5 min at room temperature. The reaction is terminated by the addition of sat. $KHCO_{3aq}$ (30 mL). The aqueous phase is extracted with EtOAc (4 × 30 mL) and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (33% → 50% EtOAc in ^{c}Hex) to yield the product as a colourless oil (428 mg, 1.2 mmol, 84%).

R_f 0.21 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.21 (d, *J* = 6.9 Hz, 3H, H-18), 1.26 – 1.38 (m, 8H, H-4, H-5, H-6, H-7), 1.48 – 1.62 (m, 3H, H-3a, H-8), 1.67 – 1.82 (m, 1H, H-3b), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H, H-13a), 3.26 (dd, *J* = 13.4, 3.3 Hz, 1H, H-13b), 3.63 (t, *J* = 6.6 Hz, 2H, H-9), 3.64 – 3.76 (m, 1H, H-2), 4.11 – 4.24 (m, 2H, H-11), 4.63 – 4.72 (m, 1H, H-12), 7.17 – 7.36 (m, 5H, H-15, H-16, H-17).

^{13}C-NMR (75 MHz, $CDCl_3$):
17.4 (CH_3, C-18), 25.6 (CH_2, C-7), 27.1 (CH_2, C-4), 29.2 (CH_2, C-5/C-6), 29.5 (CH_2, C-5/C-6), 32.7 (CH_2, C-8), 33.3 (CH_2, C-3), 37.7 (CH, C-2), 37.9 (CH_2, C-13), 55.3 (CH, C-12), 63.0 (CH_2, C-9), 66.0 (CH_2, C-11), 127.3 (CH, C-17), 128.9 (CH, C-16), 129.4 (CH, C-15), 135.3 (C_{quart}, C-14), 153.1 (C_{quart}, C-10), 177.3 (C_{quart}, C-1).

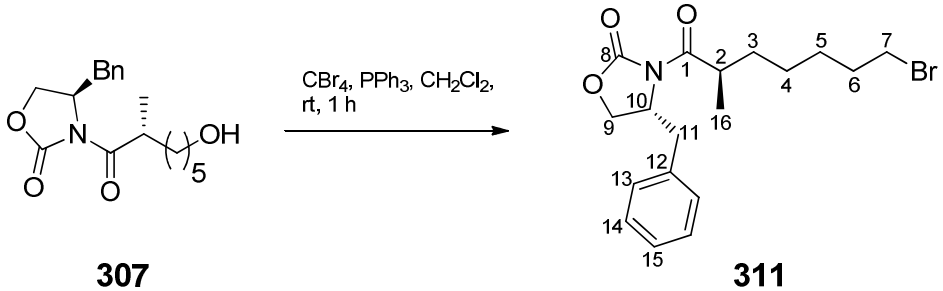
GC (t_R) 40.03 (program 0)

GC-MS (EI):

347 (7) [M^+], 233 (20), 178 (27), 171 (88) [$M^+-C_{10}H_{10}NO_2$], 153 (31), 143 (21) [$M^+-C_{11}H_{10}NO_3$], 134 (15), 117 (29), 91 (37) [$C_7H_7^+$], 83 (53), 69 (100), 55 (46).

IR (cm^{-1}) 3418 (w, br), 2927 (m), 2855 (w), 1775 (s), 1695 (s), 1455 (m), 1385 (s), 1349 (m), 1209 (s), 1097 (m), 1074 (m), 1050 (m), 1015 (m), 970 (m), 762 (m), 746 (m), 702 (s), 622 (m).

6.2.2.54 Preparation of (*R*)-4-benzyl-3-((*R*)-7-bromo-2-methyl-heptanoyl)oxazolidin-2-one (311)



307 **311**

$C_{18}H_{24}BrNO_3$
Mol. Wt.: 382.29

Compound **311** is prepared applying the general method of 6.2.2.11. The use of alcohol **307** (171 mg, 0.54 mmol) and purification of the crude product by column chromatography (flash silica, 25% EtOAc in ^{c}Hex) yields the product as a yellow oil (161 mg, 0.42 mmol, 79%).

R_f 0.83 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.23 (d, J = 6.8 Hz, 3H, H-16), 1.27 – 1.51 (m, 5H, H-3a, H-4, H-5), 1.71 – 1.82 (m, 1H, H-3b), 1.80 – 1.92 (m, 2H, H-6), 2.77 (dd, J = 13.3, 9.5 Hz, 1H, H-11a), 3.27 (dd, J = 13.3, 3.3 Hz, 1H, H-11b), 3.40 (t, J = 6.9 Hz, 2H, H-7), 3.72 (dq, J = 13.6, 6.8 Hz, 1H, H-2), 4.14 – 4.25 (m, 2H, H-9), 4.64 – 4.73 (m, 1H, H-10), 7.16 – 7.38 (m, 5H, H-13, H-14, H-15).

^{13}C-NMR (75 MHz, $CDCl_3$):

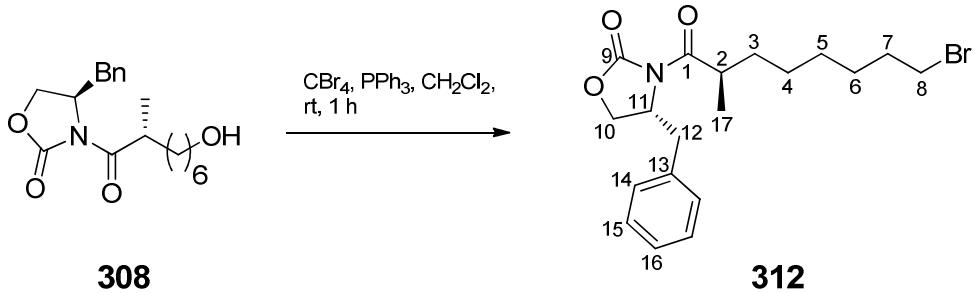
17.6 (CH_3, C-16), 26.5 (CH_2, C-4), 28.2 (CH_2, C-5), 32.7 (CH_2, C-6), 33.2 (CH_2, C-3), 33.9 (CH_2, C-7), 37.8 (CH, C-2), 38.1 (CH_2, C-11), 55.5 (CH, C-10), 66.2 (CH_2, C-9), 127.5 (CH, C-15), 129.1 (CH, C-14), 129.6 (CH, C-13), 135.4 (C_{quart}, C-12), 153.2 (C_{quart}, C-8), 177.2 (C_{quart}, C-1).

DIP-MS (EI):

383 (15) [M^+, ^{81}Br], 381 (16) [M^+, ^{79}Br], 292 (26) [$M^+-C_7H_7$, ^{81}Br], 290 (25) [$M^+-C_7H_7$, ^{79}Br], 277 (100), 233 (19), 207 (88) [$M^+-C_{10}H_{10}NO_2$, ^{81}Br], 205 (92) [$M^+-C_{10}H_{10}NO_2$, ^{79}Br], 201 (17), 199 (17), 179 (26) [$M^+-C_{11}H_{10}NO_3$, ^{81}Br], 177 (28) [$M^+-C_{11}H_{10}NO_3$, ^{79}Br], 133 (10), 117 (21), 97 (86), 91 (35) [$C_7H_7^+$], 86 (19), 77 (16) [$C_6H_5^+$], 69 (12), 55 (55), 41 (26).

IR (cm^{-1}) 2933 (w), 2859 (w), 1776 (s), 1695 (s), 1605 (w), 1585 (w), 1479 (w), 1455 (m), 1434 (m), 1384 (s), 1349 (m), 1289 (m), 1238 (m), 1209 (s), 1196 (m), 1102 (m), 1074 (m), 1049 (m), 1027 (m), 1015 (m), 971 (m), 918 (w), 839 (w), 742 (s), 695 (s).

6.2.2.55 Preparation of (*R*)-4-benzyl-3-((*R*)-8-bromo-2-methyl-octanoyl)oxazolidin-2-one (312)



308 **312**

$C_{19}H_{26}BrNO_3$
Mol. Wt.: 396.32

Compound **312** is prepared applying the general method of 6.2.2.11. The use of alcohol **308** (337 mg, 1.0 mmol) and purification of the crude product by column chromatography (flash silica, 20% EtOAc in ^{c}Hex) yields the product as a yellow oil (328 mg, 0.8 mmol, 82%).

R_f 0.48 (20% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.21 (d, *J* = 6.9 Hz, 3H, H-17), 1.26 – 1.49 (m, 7H, H-3a, H-4, H-5, H-6), 1.62 – 1.78 (m, 1H, H-3b), 1.78 – 1.89 (m, 2H, H-7), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H, H-12a), 3.25 (dd, *J* = 13.2, 3.3 Hz, 1H, H-12b), 3.39 (t, *J* = 6.7 Hz, 2H, H-8), 3.63 – 3.76 (m, 2H, H-2), 4.13 – 4.24 (m, 2H, H-10), 4.67 (dddd, *J* = 9.8, 6.7, 3.3, 3.3 Hz, 1H, H-11), 7.17 – 7.36 (m, 5H, H-14, H-15, H-16).

^{13}C-NMR (75 MHz, $CDCl_3$):

17.5 (CH_3, C-17), 27.2 (CH_2, C-4), 28.1 (CH_2, C-6), 28.9 (CH_2, C-5), 32.8 (CH_2, C-7), 33.4 (CH_2, C-3), 34.0 (CH_2, C-8), 37.8 (CH_2, C-2), 38.0 (CH_2, C-12), 55.5 (CH, C-11), 66.2 (CH_2, C-10), 127.5 (CH, C-16), 129.1 (CH, C-15), 129.6 (CH, C-14), 135.4 (C_{quart}, C-13), 153.2 (C_{quart}, C-9), 177.3 (C_{quart}, C-1).

GC (t_R) 46.10 min (program 0)

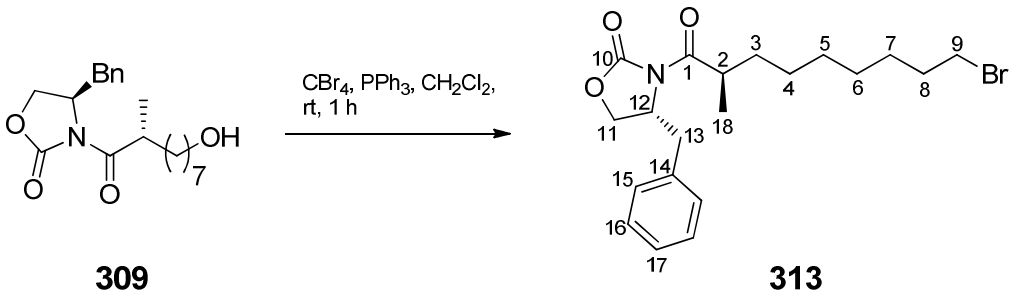
GC-MS (EI):

316 (1) [M^+−Br], 233 (13) [$C_{13}H_{15}NO_3^+$] (McL), 226 (16) [M^+−Br, −Bn], 178 (14), 141 (100) [M^+−Br, −$C_{10}H_{10}NO_2$], 113 (32) [M^+−Br, −$C_{11}H_{10}NO_3$], 91 (15) [$C_7H_7^+$], 86 (16), 71 (49) [$C_5H_{11}^+$], 57 (41) [$C_4H_9^+$].

IR (cm^{-1}) 2932 (w), 2857 (w), 1774 (s), 1694 (s), 1454 (w), 1383 (s), 1348 (m), 1289 (w), 1240 (s), 1207 (s), 1195 (s), 1099 (m), 1014 (m), 970 (m), 761 (m), 745 (m), 701 (s), 670 (m).

$[\alpha]_D^{24}$ −34.6 ° (c = 1.0, $CHCl_3$)

6.2.2.56 Preparation of (*R*)-4-benzyl-3-((*R*)-9-bromo-2-methyl-nonanoyl)oxazolidin-2-one (313)



309 **313**

$C_{20}H_{28}BrNO_3$
Mol. Wt.: 410.35

Compound **313** is prepared applying the general method of 6.2.2.11. The use of alcohol **309** (190 mg, 0.55 mmol) and purification of the crude product by column chromatography (flash silica, 20% EtOAc in ^{c}Hex) yields the product as a yellow oil (188 mg, 0.46 mmol, 84%).

R_f 0.74 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.21 (d, *J* = 6.8 Hz, 3H, H-18), 1.24 – 1.49 (m, 9H, H-3a, H-4, H-5, H-6, H-7), 1.67 – 1.80 (m, 1H, H-3b), 1.77 – 1.89 (m, 2H, H-8), 2.76 (dd, *J* = 13.3, 9.6 Hz, 1H, H-13a), 3.25 (dd, *J* = 13.3, 3.3 Hz, 1H, H-13b), 3.39 (t, *J* = 6.7 Hz, 2H, H-9), 3.70 (dq, *J* = 13.6, 6.8 Hz, 1H, H-2), 4.11 – 4.24 (m, 2H, H-11), 4.62 – 4.72 (m, 1H, H-12), 7.17 – 7.37 (m, 5H, H-15, H-16, H-17).

^{13}C-NMR (75 MHz, $CDCl_3$):
17.5 (CH_3, C-18), 27.2 (CH_2, C-4), 28.2 (CH_2, C-7), 28.7 (CH_2, C-5), 29.5 (CH_2, C-6), 32.8 (CH_2, C-8), 33.4 (CH_2, C-3), 34.1 (CH_2, C-9), 37.8 (CH, C-2), 38.0 (CH_2, C-13), 55.4 (CH, C-12), 66.1 (CH_2, C-11), 127.4 (CH, C-17), 129.0 (CH, C-16), 129.5 (CH, C-15), 135.4 (C_{quart}, C-14), 153.1 (C_{quart}, C-10), 177.3 (C_{quart}, C-1).

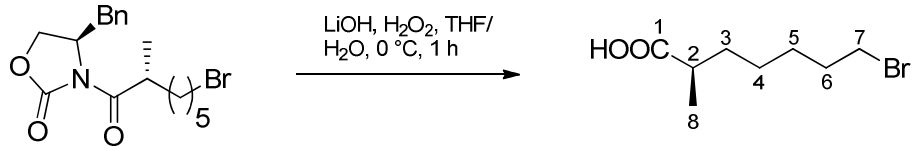
GC-MS (EI):
411 (4) [M^+, ^{81}Br], 409 (3) [M+, ^{79}Br], 320 (8) [$M^+-C_7H_7$, ^{81}Br], 318 (8) [$M^+-C_7H_7$, ^{79}Br], 235 (76) [$M^+-C_{10}H_{10}NO_2$, ^{81}Br], 233 (100) [$M^+-C_{10}H_{10}NO_2$, ^{79}Br], 207 (27) [$M^+-C_{11}H_{10}NO_3$, ^{81}Br], 205 (24) [$M^+-C_{11}H_{10}NO_3$, ^{79}Br], 178 (20), 165 (6), 163 (6), 153 (12), 125 (14), 117 (21), 91 (27) [$C_7H_7^+$], 86 (17), 83 (26), 71 (16), 69 (48), 57 (32), 55 (28).

IR (cm^{-1}) 2931 (m), 2856 (w), 1775 (s), 1695 (s), 1498 (w), 1455 (m), 1384 (s), 1349 (m), 1289 (m), 1237 (s), 1208 (s), 1196 (s), 1097 (m), 1075 (m), 1050 (m), 1015 (m), 970 (m), 916 (w), 838 (w), 761 (m), 746 (m), 701 (s), 640 (m).

6.2.2.57 General method to facilitate the oxidative removal of the Evans auxiliary (II)

According to procedures of Evans *et al.*[180] and Marimganti *et al.*,[226] a 0.08M solution of a compound containing an Evans auxiliary (1.0 eq.) in a mixture of THF/H_2O (3:1) is cooled to 0 °C and H_2O_2 (30%) (0.75 mL/mmol) and LiOH (2.0 eq.) are added. The mixture is stirred for 1 h leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of 1.5M Na_2SO_{3aq} (3.0 mL/mmol) and 0.5M $KHCO_{3aq}$ (9 mL/mmol). After 5 min of additional stirring, the THF is evaporated. The aqueous phase is diluted with H_2O (20 mL/mmol) and washed with CH_2Cl_2 (2 × 20 mL/mmol) before the pH of the aqueous phase is adjusted to pH 2 with 1M HCl_{aq}. The aqueous phase is extracted with EtOAc (4 × 20 mL/mmol) and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.2.58 Preparation of (*R*)-7-bromo-2-methylheptanoic acid (215)



311 **215**

$C_8H_{15}BrO_2$
Mol. Wt.: 223.11

Compound **215** is prepared applying the general method of 6.2.2.57. The use of alcohol **311** (161 mg, 0.42 mmol) and purification of the crude product by column chromatography (33% EtOAc in ^{c}Hex) yields the product as a yellow oil (72 mg, 0.32 mmol, 77%).

R_f 0.51 (50% EtOAc in ^{c}Hex), tailing observed

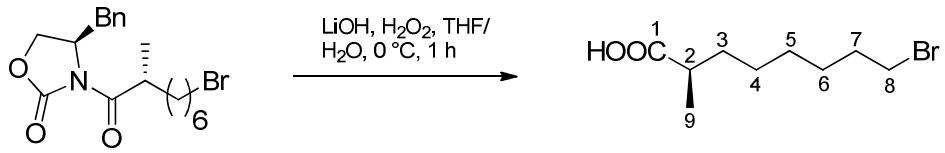
^{1}H-NMR (300 MHz, $CDCl_3$):
1.18 (d, *J* = 7.1 Hz, 3H, H-8), 1.21 – 1.51 (m, 5H, H-3a, H-4, H-5), 1.63 – 1.77 (m, 1H, H-3b), 1.86 (tt, *J* = 7.5, 6.7 Hz, 2H, H-6), 2.46 (dq, *J* = 13.2, 7.1 Hz, 1H, H-2), 3.40 (t, *J* = 6.7 Hz, 2H, H-7), 10.89 (br s, 1H, COOH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):
16.9 (CH_3, C-8), 26.3 (CH_2, C-4), 28.0 (CH_2, C-5), 32.6 (CH_2, C-6), 33.3 (CH_2, C-3), 33.7 (CH_2, C-7), 39.3 (CH, C-2), 183.1 (C_{quart}, C-1).

DIP-MS (EI):
224 (1) [M^+, ^{81}Br], 222 [M^+, ^{79}Br], 143 (6) [M^+−Br], 125 (7), 97 (10), 87 (15), 74 (100), 69 (9), 55 (27), 41 (28).

IR (cm^{-1}) 2961 (w, br), 2924 (m), 2855 (m), 1742 (w), 1705 (s), 1464 (m), 1378 (w), 1239 (m), 1116 (w), 1058 (w), 941 (w), 728 (w).

6.2.2.59 Preparation of (*R*)-8-bromo-2-methyloctanoic acid (216)



312 **216**

$C_9H_{17}BrO_2$
Mol. Wt.: 237.13

Compound **216** is prepared applying the general method of 6.2.2.57. The use of alcohol **312** (255 mg, 0.64 mmol) and purification of the crude product by column chromatography (33% EtOAc in ^{c}Hex) yields the product as a yellow oil (116 mg, 0.48 mmol, 75%).

R_f 0.53 (33% EtOAc in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
1.18 (d, *J* = 7.1 Hz, 3H, H-9), 1.28 – 1.51 (m, 7H, H-3a, H-4, H-5, H-6), 1.62 – 1.76 (m, 1H, H-3b), 1.78 – 1.91 (m, 2H, H-7), 2.38 – 2.52 (m, 1H, H-2), 3.40 (t, *J* = 6.9 Hz, 2H, H-8), 10.76 (br s, 1H, COOH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):
17.0 (CH_3, C-9), 27.1 (CH_2, C-4), 28.1 (CH_2, C-6), 28.8 (CH_2, C-5), 32.9 (CH_2, C-7), 33.5 (CH_2, C-3), 34.0 (CH_2, C-8), 39.5 (CH, C-2), 183.3 (C_{quart}, C-1).

GC (t_R) 20.51 min (program 0)

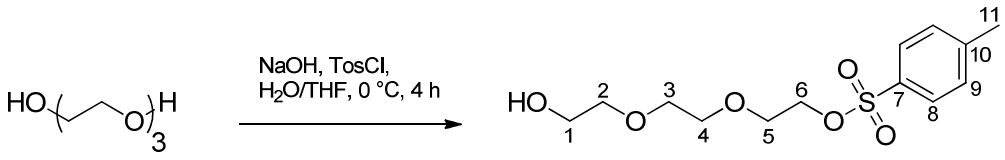
DIP-MS (EI):
236 (4) [M^+], 193 (15), 163 (6) [$M^+-C_3H_5O_2$], 157 (28) [M^+-Br], 140 (56) [M^+-Br, −OH], 129 (15), 111 (19), 87 (87), 74 (100) [$C_3H_6O_2^+$] (McL), 69 (37), 55 (47), 41 (55).

IR (cm^{-1}) 3001 (w, br), 2932 (m), 2858 (m), 1701 (s), 1464 (m), 1416 (w), 1379 (w), 1239 (m), 934 (m), 725 (w), 642 (m), 558 (m).

$[\alpha]_D^{24}$ −10.2 ° (c = 1.0, $CHCl_3$)

6.2.3 Synthesis of a polyether bromo acid

6.2.3.1 Preparation of 2-(2-(2-hydroxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (320)



319 **320**

$C_{13}H_{20}O_6S$
Mol. Wt.: 304.36

According to a method of Ouchi *et al.*,[190] a solution of TEG (**319**) (300 mg, 267 µL, 2.0 mmol, 1.0 eq.) in THF (3 mL) is cooled to 0 °C and 0.56M $NaOH_{aq}$ (5.0 mL, 2.8 mmol, 1.4 eq.) is added. *p*-TosOH (381 mg, 2.0 mmol, 1.0 eq.) is dissolved in THF (2 mL) and added dropwise over 2 h using a syringe pump. The mixture is stirred for 2 h at 0 °C before the reaction is terminated by the addition of ice water (20 mL). The mixture is extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases are washed with H_2O (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (67% EtOAc in ^{n}Hex → EtOAc) to yield the product as a colourless oil (153 mg, 0.50 mmol, 26%).

R_f 0.20 (33% EtOAc in ^{n}Hex)

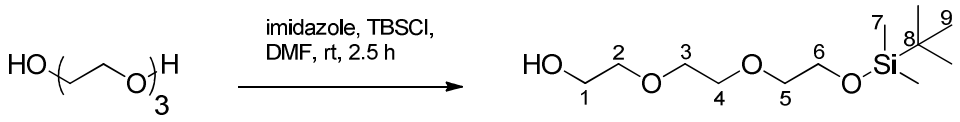
^{1}H-/^{13}C-NMR The NMR spectra of **320** are in good agreement with literature.[284]

GC-MS (EI):

216 (6), 186 (12), 173 (17) [$TosOH^+$], 155 (68), 91 (100), 89 (8), 65 (28).

IR (cm^{-1}) The IR spectrum of **320** is in good agreement with literature.[284]

6.2.3.2 Preparation of 2,2,3,3-tetramethyl-4,7,10-trioxa-3-sila-dodecan-12-ol (324)



319 **324**

$C_{12}H_{28}O_4Si$
Mol. Wt.: 264.43

Compound **324** is prepared applying the general method of 6.2.2.21. The use of TEG (**319**) (5.0 g, 4.5 µL, 33.3 mmol) and purification of the crude product by column chromatography (50% → 75% EtOAc in ^{n}Hex) yields the product as a colourless oil (4.7 g, 17.9 mmol, 54%).

R_f 0.48 (67% EtOAc in ^{n}Hex)

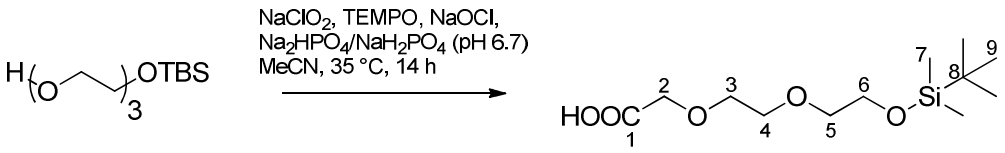
^{1}H-/^{13}C-NMR The NMR spectra of **324** are in good agreement with literature.[285]

GC (t_R) 20.31 min (program 0)

GC-MS (EI):
265 (23) [M^+], 207 (100) [$M^+ - {}^{t}Bu$], 163 (35), 159 (20), 147 (24), 119 (81), 115 (10) [$C_6H_{15}Si^+$], 103 (46), 89 (61), 75 (94) [$C_2H_7OSi^+$], 73 (31).

IR (cm^{-1}) 3425 (w), 2951 (w), 2929 (w), 2870 (w), 2857 (m), 1472 (w), 1463 (w), 1389 (w), 1361 (w), 1252 (m), 1100 (s), 1006 (w), 938 (m), 835 (s), 775 (s), 662 (m).

6.2.3.3 Preparation of 2,2,3,3-tetramethyl-4,7,10-trioxa-3-sila-dodecan-12-oic acid (325)



324 **325**

$C_{12}H_{26}O_5Si$

Mol. Wt.: 278.42

To a solution of TBS-protected compound **324** (5.5 g, 20.8 mmol, 1.0 eq.) in MeCN (105 mL) are added an aqueous 0.67M sodium phosphate buffer (5.6 g Na_2HPO_4 + 5.6 g NaH_2PO_4 in 111 mL H_2O; pH = 6.7) and (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (330 mg, 2.1 mmol, 0.1 eq.) and the mixture is heated to 35 °C. While stirring vigorously 2.2M $NaOCl_{2aq}$ (28.4 mL, 62.4 mmol, 3.0 eq.) and subsequently $NaOCl_{aq}$ (2.1 mL, 12% NaOCl diluted into 42.2 mL H_2O, 4.2 mmol, 0.2 eq.) are added slowly. The reaction mixture is stirred for 14 h at 35 °C before letting it cool down to room temperature and diluting it with H_2O (20 mL). 0.48M Na_2SO_{3aq} (precooled to 0 °C) is added until the red-brown solution stays colourless. The pH of the solution is adjusted to pH 8.5 with 1M $NaOH_{aq}$. MTBE (190 mL) is added and the mixture is stirred vigorously for 15 min. The phases are separated, the aqueous phase acidified to pH 3.5 with 2M HCl_{aq} and extracted with MTBE (4 × 100 mL). The combined organic phases are washed with H_2O (100 mL) and brine (100 mL) and are dried over Na_2SO_4 and filtered. The solvent is evaporated to give the product as a light yellow oil (4.9 g, 17.5 mmol, 84%), which can be used without further purification.

R_f 0.20 (67% EtOAc in ^{n}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):

0.02 (s, 6H, H-7), 0.84 (s, 9H, H-9), 3.54 (t, *J* = 5.2 Hz, 2H, H-5), 3.62 – 3.73 (m, 4H, H-3, H-4), 3.73 (t, *J* = 5.2 Hz, 2H, H-6), 4.13 (s, 2H, H-2), 8.87 (br s, 1H, COOH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.3 (CH_3, C-7), 18.0 (C_{quart}, C-8), 25.7 (CH_3, C-9), 61.5 (CH_2, C-6), 68.5 (CH_2, C-2), 70.3 (CH_2, C-4), 71.1 (CH_2, C-3), 72.6 (CH_2, C-5), 173.1 (C_{quart}, C-1).

GC (t_R) 24.78 (program 0)

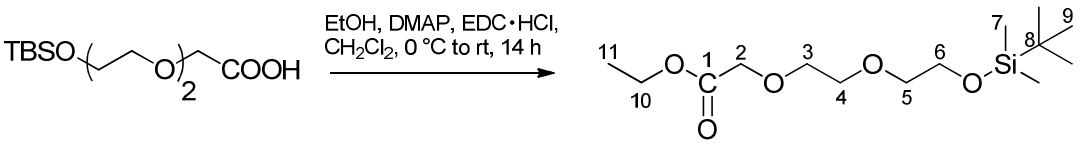
GC-MS (EI):
279 (1) [M^+], 221 (1) [$M^+ - {}^t$Bu], 189 (2), 163 (47), 147 (13) [M^+−TBS], 133 (4), [$M^+ - CH_2$TBS], 119 (42), 103 (28) [M^+−TBS, $-CO_2$], 101 (15), 89 (9), 75 (100) [$C_2H_7OSi^+$], 73 (24), 60 (2), 59 (13).

IR (cm^{-1}) 2952 (m), 2929 (m), 2871 (m), 2858 (m), 1737 (s), 1463 (w), 1470 (w), 1387 (w), 1361 (w), 1251 (s), 1214 (m), 1143 (s), 1105 (s), 1006 (w), 938 (m), 832 (s), 814 (s), 775 (s), 665 (m).

6.2.3.4 General method to facilitate an EDC · HCl promoted Steglich esterification

According to a procedure of Dhaon *et al.*,[201] a 0.1M solution of a carboxylic acid (1.0 eq.) in CH_2Cl_2 abs. (50 mL) is cooled to 0 °C and DMAP (0.75 eq.), an alcohol (2.0 eq.) and EDC · HCl (1.2 – 1.4 eq.) are added. The mixture is left to stir for 2 h at 0 °C before the mixture is stirred for 12 h at room temperature. The solvent is evaporated and the residue dissolved in EtOAc (20 mL/mmol). The organic phases are washed with H_2O (10 mL/mmol), sat. NH_4Cl_{aq} (3 × 10 mL/mmol), sat. $KHCO_{3aq}$ (2 × 10 mL/mmol) and H_2O (10 mL/mmol). The combined organic phases are dried over Na_2SO_4 and filtered. The solvent is evaporated to give the crude product.

6.2.3.5 Preparation of ethyl 2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-oate (330)



325 **330**

$C_{14}H_{30}O_5Si$
Mol. Wt.: 306.47

Compound **330** is prepared applying the general method of 6.2.3.4. The use of carboxylic acid **325** (2.0 g, 7.2 mmol) and ethanol p.a. (0.84 mL, 14.4 mmol) and purification of the crude product by column chromatography (20% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.9 g, 6.1 mmol, 84%).

R_f 0.40 (20% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.03 (s, 6H, H-7), 0.86 (s, 9H, H-9), 1.25 (t, *J* = 7.1 Hz, 3H, H-11), 3.52 (t, *J* = 5.5 Hz, 2H, H-5), 3.63 – 3.72 (m, 4H, H-3, H-4), 3.73 (t, *J* = 5.5 Hz, 2H, H-6), 4.12 (s, 2H, H-2), 4.18 (q, *J* = 7.1 Hz, 2H, H-10).

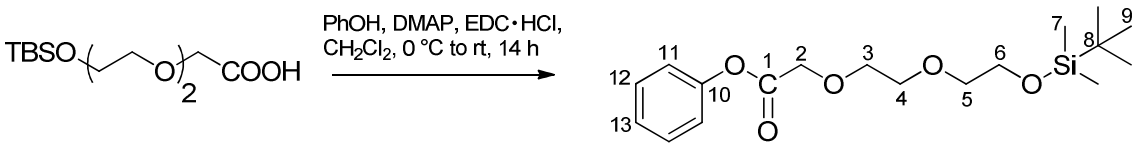
^{13}C-NMR (75 MHz, $CDCl_3$):
−5.2 (CH_3, C-7), 14.3 (CH_3, C-11), 18.4 (C_{quart}, C-8), 26.0 (CH_3, C-9), 60.8 (CH_2, C-10), 62.8 (CH_2, C-6), 68.8 (CH_2, C-2), 70.9 (CH_2, C-4), 71.0 (CH_2, C-3), 72.8 (CH_2, C-5), 170.6 (C_{quart}, C-1).

GC (t_R) 24.27 min (program 0)

GC-MS (EI):
307 (2) [M^+], 261 (1) [M^+−OC_2H_5], 249 (6) [M^+−^{t}Bu], 233 (5) [M^+−OC_2H_5, −CO], 161 (5) [M^+−CH_2OTBS], 159 (13) [M^+−C_2H_4OTBS], 131 (100), 117 (5), 103 (63), 75 (12) [$C_2H_7OSi^+$], 73 (10).

IR (cm^{-1}) 2952 (m), 2929 (m), 2871 (m), 2857 (m), 1755 (s), 1470 (w), 1463 (w), 1361 (w), 1252 (s), 1201 (s), 1144 (s), 1102 (s), 1032 (m), 1006 (w), 939 (m), 832 (s), 812 (s), 775 (s), 719 (w), 662 (m).

6.2.3.6 Preparation of phenyl 2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-oate (331)



325 **331**

$C_{18}H_{30}O_5Si$
Mol. Wt.: 354.51

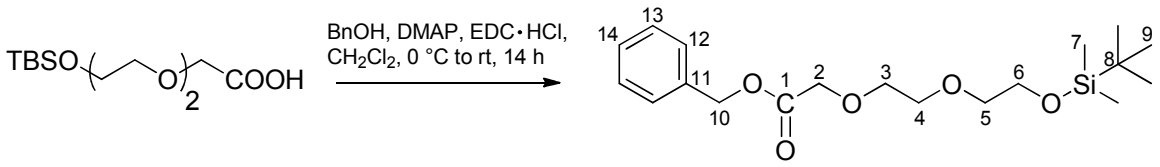
Compound **331** is prepared applying the general method of 6.2.3.4. The use of carboxylic acid **325** (140 mg, 0.50 mmol) and phenol (57 mg, 0.60 mmol) and purification of the crude product by column chromatography (5% EtOAc in ^{c}Hex) yields the product as a colourless oil (130 mg, 0.37 mmol, 73%).

R_f 0.81 (2.5% MeOH in CH_2Cl_2)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.07 (s, 6H, H-7), 0.90 (s, 9H, H-9), 3.58 (t, *J* = 5.4 Hz, 2H, H-5), 3.72 – 3.76 (m, 2H, H-4), 3.78 (t, *J* = 5.4 Hz, 2H, H-6), 3.80 – 3.85 (m, 2H, H-3), 4.43 (s, 2H, H-2), 7.08 – 7.14 (m, 2H, H-11), 7.20 – 7.27 (m, 1H, H-13), 7.34 – 7.42 (m, 2H, H-12).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-7), 18.5 (C_{quart}, C-8), 26.1 (CH_3, C-9), 62.9 (CH_2, C-6), 68.9 (CH_2, C-2), 71.0 (CH_2, C-4), 71.3 (CH_2, C-3), 72.9 (CH_2, C-5), 121.5 (CH, C-11), 126.1 (CH, C-13), 129.6 (CH, C-12), 150.3 (C_{quart}, C-10), 169.2 (C_{quart}, C-1).

6.2.3.7 Preparation of benzyl 2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-oate (332)



325 **332**

$C_{19}H_{32}O_5Si$
Mol. Wt.: 368.54

Compound **332** is prepared applying the general method of 6.2.3.4. The use of carboxylic acid **325** (1.2 g, 4.4 mmol) and benzyl alcohol (0.55 mL, 5.3 mmol) and purification of the crude product by column chromatography (15% EtOAc in ^{c}Hex) yields the product as a yellow oil (1.5 g, 6.1 mmol, 89%).

R_f 0.53 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.05 (s, 6H, H-7), 0.88 (s, 9H, H-9), 3.54 (t, J = 5.4 Hz, 2H, H-5), 3.66 – 3.75 (m, 4H, H-3, H-4), 3.75 (t, J = 5.4 Hz, 2H, H-6), 4.20 (s, 2H, H-2), 5.18 (s, 2H, H-10), 7.30 – 7.37 (m, 5H, H-12, H-13, H-14).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.2 (CH_3, C-7), 18.4 (C_{quart}, C-8), 26.0 (CH_3, C-9), 62.7 (CH_2, C-6), 66.5 (CH_2, C-10), 68.8 (CH_2, C-2), 70.9 (CH_2, C-4), 71.1 (CH_2, C-3), 72.7 (CH_2, C-5), 128.4 (CH, C-12/C-13/C-14), 128.5 (CH, C-12/C-13 /C-14), 128.6 (CH, C-12/C-13/C-14), 135.5 (C_{quart}, C-11), 170.4 (C_{quart}, C-1).

GC (t_R) 36.71 min (program 0)

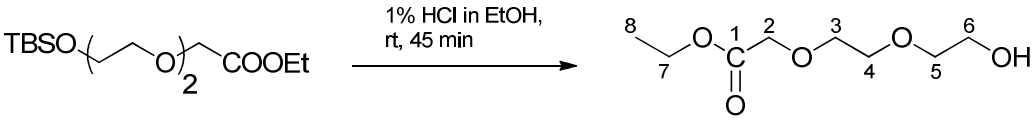
GC-MS (EI):
369 (1) [M^+], 311 (1) [M^+–^{t}Bu], 159 (2) [M^+−C_2H_4OTBS], 147 (1) [M^+−Bn, −OTBS], 103 (5), 92 (10), 91 (100) [$C_7H_7^+$], 75 (3) [$C_2H_7OSi^+$], 73 (6).

IR (cm^{-1}) 2952 (m), 2928 (m), 2884 (m), 2856 (m), 1756 (s), 1498 (w), 1472 (w), 1462 (w), 1388 (w), 1361 (w), 1251 (s), 1191 (m), 1143 (s), 1102 (s), 1050 (w), 1027 (w), 1006 (w), 939 (m), 832 (s), 812 (s), 775 (s), 751 (m), 735 (m), 696 (s), 662 (m).

6.2.3.8 General method to facilitate HCl promoted TBS-deprotection

According to a procedure of Cunico *et al.*,[182] to a 0.05M solution of a TBS-protected compound (1.0 eq.) in EtOH (5 mL) is added conc. HCl_{aq} (1% in EtOH) and the mixture is stirred for 45 min at room temperature. The reaction is terminated by the addition of sat. $KHCO_{3aq}$ (10 mL/mmol). The aqueous solution is extracted with EtOAc (4 × 10 mL/mmol) and the combined organic phases are dried over Na_2SO_4 and filtered. The solvent is evaporated to give the crude product.

6.2.3.9 Preparation of ethyl (2-(2-hydroxyethoxy)ethoxy)acetate (333)



330 **333**

$C_8H_{16}O_5$
Mol. Wt.: 192.21

Compound **333** is prepared applying the general method of 6.2.3.8. The use of TBS-protected compund **330** (55 mg, 0.18 mmol) yields the product as a colourless oil (29 mg, 0.15 mmol, 84%) without further purification.

R_f 0.26 (15% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.11 (t, *J* = 7.2 Hz, 3H, H-8), 3.17 (br s, 1H, OH), 3.39 – 3.45 (m, 2H, H-5), 3.48 – 3.59 (m, 6H, H-3, H-4, H-6), 3.97 (s, 2H, H-2), 4.03 (q, *J* = 7.2 Hz, 2H, H-7).

^{13}C-NMR (75 MHz, $CDCl_3$):
13.9 (CH_3, C-8), 60.5 (CH_2, C-7), 61.2 (CH_2, C-6), 68.3 (CH_2, C-2), 70.0 (CH_2, C-4), 70.6 (CH_2, C-3), 72.4 (CH_2, C-5), 170.2 (C_{quart}, C-1).

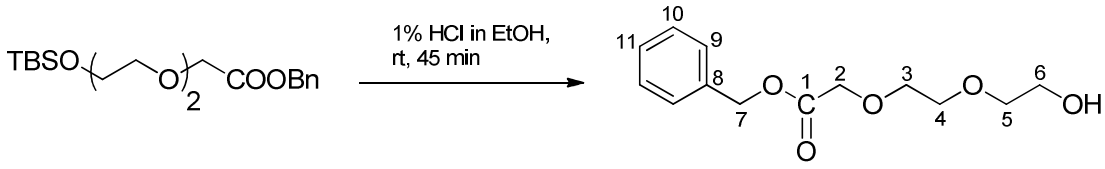
GC (t_R) 15.49 min (program 0)

GC-MS (EI):

193 (3) [M^+], 162 (12), 161 (3) [M^+-CH_2OH], 131 (85) [$M^+-C_2H_5O_2$], 130 (58), 119 (39) [$M^+-COOC_2H_5$], 117 (19), 103 (80), 102 (17), 89 (100) [$C_4H_9O_2^+$], 88 (77), 87 (34), 75 (45) [$C_3H_7O_2^+$], 73 (34), 70 (20), 61 (60), 60 (38), 59 (93), 58 (76), 57 (25).

IR (cm^{-1}) 3430 (w, br), 2910 (w), 2878 (w), 1749 (s), 1449 (w), 1427 (w), 1378 (w), 1355 (w), 1277 (m), 1203 (s), 1145 (s), 1111 (s), 1066 (s), 1028 (s), 929 (m), 888 (m), 847 (m), 705 (w).

6.2.3.10 Preparation of benzyl (2-(2-hydroxyethoxy)ethoxy) acetate (335)



332 **335**

$C_{13}H_{18}O_5$
Mol. Wt.: 254.28

Compound **335** is prepared applying the general method of 6.2.3.8. The use of TBS-protected compund **332** (1.4 g, 3.9 mmol) yields the product as a yellow oil (868 mg, 3.4 mmol, 89%) without further purification.

R_f 0.35 (80% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

2.39 (br s, 1H, OH), 3.57 – 3.62 (m, 2H, H-5), 3.66 – 3.76 (m, 6H, H-3, H-4, H-6), 4.18 (s, 2H, H-2), 5.19 (s, 2H, H-7), 7.27 – 7.39 (m, 5H, H-9, H-10, H-11).

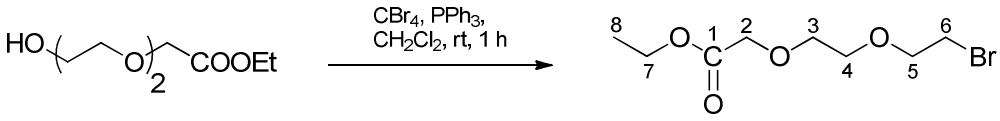
^{13}C-NMR (75 MHz, $CDCl_3$):

61.8 (CH_2, C-6), 66.8 (CH_2, C-7), 68.7 (CH_2, C-2), 70.5 (CH_2, C-4), 71.2 (CH_2, C-3), 72.7 (CH_2, C-5), 128.6 (CH, C-9/C-10/C-11), 128.6 (CH, C-9/C-10/C-11), 128.7 (CH, C-9/C-10/C-11), 135.4 (C_{quart}, C-8), 170.44 (C_{quart}, C-1).

GC (t_R) 29.81 min (program 0)

IR (cm^{-1}) 3453 (br), 2922 (m), 2853 (m), 1748 (s), 1634 (w), 1498 (w), 1455 (m), 1429 (w), 1390 (w), 1363 (w), 1259 (m), 1195 (s), 1144 (s), 1113 (s), 1067 (s), 1027 (m), 964 (w), 932 (w), 888 (w), 849 (w), 826 (w), 721 (m), 697 (s), 597 (w), 576 (w), 563 (w).

6.2.3.11 Preparation of ethyl (2-(2-bromoethoxy)ethoxy)acetate (336)



333 **336**

$C_8H_{15}BrO_4$
Mol. Wt.: 255.11

Compound **336** is prepared applying the general method of 6.2.2.11. The use of alcohol **333** (370 mg, 1.9 mmol) and purification of the crude product by column chromatography (12.5% → 17% → 33% EtOAc in ^{c}Hex) yields the product as a yellow oil (426 mg, 1.7 mmol, 89%).

R_f 0.44 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.28 (t, *J* = 7.1 Hz, 3H, H-8), 3.47 (t, *J* = 6.3 Hz, 2H, H-6), 3.69 – 3.76 (m, 4H, H-3, H-4), 3.82 (t, *J* = 6.3 Hz, 2H, H-5), 4.15 (s, 2H, H-2), 4.21 (q, *J* = 7.1 Hz, 2H, H-7).

^{13}C-NMR (75 MHz, $CDCl_3$):
14.3 (CH_3, C-8), 30.3 (CH_2, C-6), 60.9 (CH_2, C-7), 68.9 (CH_2, C-2), 70.7 (CH_2, C-4), 71.0 (CH_2, C-3), 71.3 (CH_2, C-5), 170.5 (C_{quart}, C-1).

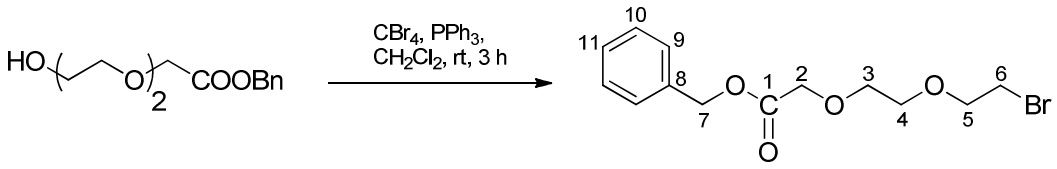
GC (t_R) 18.25 min (program 0)

GC-MS (EI):

257 (1) [M^+, ^{81}Br], 255 (1) [M^+, ^{79}Br], 183 (16) [M^+−COOBn, ^{81}Br], 181 (17) [M^+−COOBn, ^{79}Br], 153 (19), 152 (18), 151 (17), 150 (19), 139 (7), 137 (8), 131 (56) [M^+−C_2H_4OBr], 130 (35), 117 (23), 109 (99), 107 (100), 103 (29), 89 (31), 88 (6), 73 (16), 61 (37), 59 (58), 57 (11).

IR (cm^{-1}) 2981 (w), 2910 (w), 2869 (w), 1749 (s), 1445 (w), 1427 (w), 1376 (w), 1353 (w), 1276 (m), 1202 (s), 1143 (s), 1113 (s), 1028 (s), 954 (w), 934 (w), 911 (w), 847 (m), 801 (w), 721 (w), 698 (m), 664 (w), 574 (m).

6.2.3.12 Preparation of benzyl (2-(2-bromoethoxy)ethoxy)acetate (337)



335 **337**

$C_{13}H_{17}BrO_4$
Mol. Wt.: 317.18

Compound **337** is prepared applying the general method of 6.2.2.11. The use of alcohol **335** (868 mg, 3.4 mmol) and purification of the crude product by column chromatography (15% EtOAc in ^{c}Hex) yields the product as a yellow oil (1.1 g, 3.3 mmol, 98%).

R_f 0.38 (25% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.45 (t, *J* = 6.3 Hz, 2H, H-6), 3.68 – 3.77 (m, 4H, H-3, H-4), 3.80 (t, *J* = 6.3 Hz, 2H, H-5), 4.21 (s, 2H, H-2), 5.19 (s, 2H, H-7), 7.31 – 7.38 (m, 5H, H-9, H-10, H-11).

^{13}C-NMR (75 MHz, $CDCl_3$):

30.4 (CH_2, C-6), 66.7 (CH_2, C-7), 68.8 (CH_2, C-2), 70.7 (CH_2, C-4), 71.1 (CH_2, C-3), 71.3 (CH_2, C-5), 128.5 (CH, C-9/C-10/C-11), 128.6 (CH, C-9/C-10/C-11), 128.7 (CH, C-9/C-10/C-11), 135.5 (C_{quart}, C-8), 170.4 (C_{quart}, C-1).

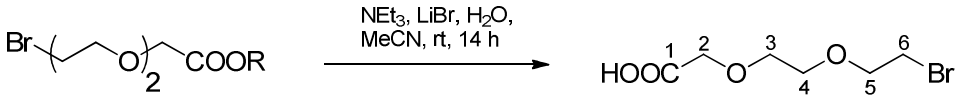
GC (t_R) 32.07 min (program 0)

GC-MS (EI):

318 (1) [M^+, ^{81}Br], 316 (1) [M^+, ^{79}Br], 193 (7) [$M^+-C_2H_4OBr$], 192 (11), 183 (18) [$M^+-COOBn$, ^{81}Br], 181 (19) [$M^+-COOBn$, ^{79}Br], 153 (37) [M^+-OCH_2COOBn, ^{81}Br], 152 (12), 151 (39) [M^+-OCH_2COOBn, ^{79}Br], 150 (10), 148 (26), 139 (6), 137 (7), 120 (21), 109 (93), 107 (100), 105 (20), 104 (16), 92 (48), 91 (50) [$C_7H_7^+$], 77 (11) [$C_6H_5^+$], 65 (23).

IR (cm^{-1}) 2879 (m, br), 1750 (s), 1498 (w), 1455 (m), 1426 (w), 1363 (w), 1275 (s), 1192 (s), 1142 (s), 1113 (s), 1026 (m), 1006 (m), 955 (m), 910 (w), 849 (w), 738 (m), 697 (s), 666 (s), 568 (m).

6.2.3.13 Preparation of (2-(2-(bromoethoxy)ethoxy)acetic acid (323)



R = Et **336**
R = Bn **337**

323

$C_6H_{11}BrO_4$
Mol. Wt.: 227.05

A: Synthesis starting from ethyl ester **336**:

According to a procedure of Mattsson *et al.*,[175] to a solution of ethyl ester **382** (116 mg, 0.45 mmol, 1.0 eq.) in MeCN (10 mL) with H_2O (2 vol%, 200 µL) are added NEt_3 (190 µL, 1.4 mmol, 3.0 eq.) and LiBr (399 mg, 4.6 mmol, 10.1 eq.) and the mixture is stirred for 14 h at room temperature. H_2O (10 mL) is added and the pH of the mixture is adjusted to pH 3 with 2M HCl_{aq}. EtOAc (50 mL) is added and the phases are separated before the aqueous phase is extracted with EtOAc (3 × 50 mL). The combined organic phases are washed with sat. NH_4Cl_{aq} (50 mL), dried over Na_2SO_4 and filtered. The solvent is evaporated and the product is obtained as a yellow oil (100 mg, 0.44 mmol, 97%).

B: Synthesis starting from benzyl ester **337**:

According to a procedure of Mattsson *et al*.,[175] to a solution of benzyl ester **383** (100 mg, 0.32 mmol, 1.0 eq.) in MeCN (10 mL) with H_2O (2 vol%, 200 µL) are added NEt_3 (131 µL, 0.95 mmol, 3.0 eq.) and LiBr (274 mg, 3.2 mmol, 10.0 eq.) and the mixture is stirred for 14 h at room temperature. H_2O (10 mL) is added and the mixture is washed with Et_2O (2 × 10 mL) before the pH of the aqueous phase is adjusted to pH 3 with 2M HCl_{aq}. EtOAc (10 mL) is added and the phases are separated before the aqueous phase is extracted with EtOAc (3 × 10 mL). The combined organic phases are washed with brine (10 mL), dried over Na_2SO_4 and filtered. The solvent is evaporated and the product is obtained as a yellow oil (62 mg, 0.27 mmol, 87%).

R_f 0.18 (67% EtOH in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, $CDCl_3$):
3.45 (t, *J* = 6.2 Hz, 2H, H-6), 3.67 – 3.77 (m, 4H, H-3, H-4), 3.80 (t, *J* = 6.2 Hz, 2H, H-5), 4.18 (s, 2H, H-2), 9.12 (br s, 1H, -COOH).

^{13}C-NMR (75 MHz, $CDCl_3$):
30.2 (CH_2, C-6), 68.4 (CH_2, C-2), 70.4 (CH_2, C-4), 71.0 (CH_2, C-3), 71.2 (CH_2, C-5), 174.6 (C_{quart}, C-1).

^{1}H-NMR (300 MHz, MeOD):
3.51 (t, J = 6.0 Hz, 2H, H-6), 3.66 – 3.75 (m, 4H, H-3, H-4), 3.81 (t, J = 6.0 Hz, 2H, H-5), 4.14 (s, 2H, H-2).

^{13}C-NMR (75 MHz, MeOD):
31.3 (CH_2, C-6), 69.2 (CH_2, C-2), 71.5 (CH_2, C-4), 71.8 (CH_2, C-3), 72.3 (CH_2, C-5), 174.1 (C_{quart}, C-1).

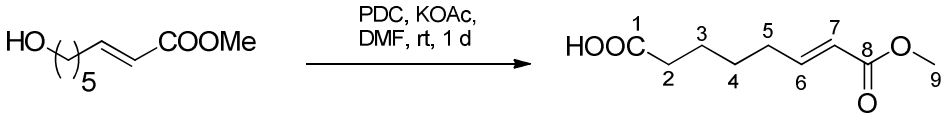
GC (t_R) 19.73 min (program 0)

GC-MS (EI):
229 (2) [M^+, ^{81}Br], 227 (2) [M^+, ^{79}Br], 210 (7), 208 (8), 183 (18) [M^+-CO_2, ^{81}Br], 181 (17) [M^+-CO_2, ^{79}Br], 152 (18), 151 (49), 150 (18), 149 (50), 139 (91), 137 (100), 133 (17) [M^+-CH_2Br], 109 (40), 107 (50), 103 (60), 102 (28), 89 (7), 61 (15), 59 (10), 46 (27), 44 (11).

IR (cm^{-1}) 2923 (m), 2854 (w), 1731 (s), 1460 (w), 1427 (w), 1359 (w), 1277 (m), 1229 (m), 1140 (s), 1101 (s), 1017 (s), 950 (w), 874 (m), 848 (m), 799 (m), 663 (m), 567 (m).

6.2.4 Partial syntheses of side chain fragments on the way to macrocidin A

6.2.4.1 Preparation of (*E*)-8-methoxy-8-oxooct-6-enoic acid (346)



119 **346**

$C_9H_{14}O_4$
Mol. Wt.: 186.21

According to procedures of Cornforth *et al*.[205] and Corey *et al.*,[191] to a solution of alcohol **119** (750 mg, 4.4 mmol, 1.0 eq.) in DMF p.a. (30 mL) are added KOAc (1.5 g, 15.3 mmol, 3.5 eq.) and PDC (7.2 g, 19.1 mmol, 4.4 eq.) and the reaction is left to stir for 1 d at room temperature. The pH of the reaction mixture is adjusted to pH 3 with 1M HCl_{aq} and EtOAc (40 mL) is added. The phases are separated and the aqueous phase is extracted with EtOAc (3 × 80 mL). The combined organic phases are washed with sat. NH_4Cl_{aq} (4 × 50 mL), H_2O (50 mL) and brine (50 mL) before they are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (25% → 50% EtOAc in ^{c}Hex). This yields the desired product as a colourless oil (585 mg, 3.1 mmol, 72%).

R_f 0.33 (50% EtOAc in ^{c}Hex), tailing observed

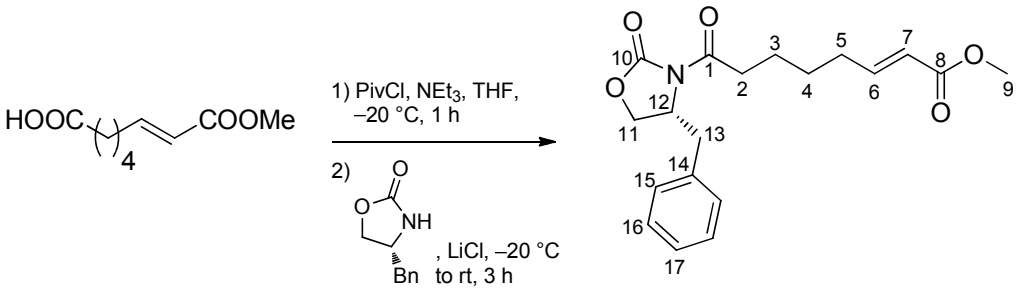
^{1}H-/^{13}C-NMR The NMR spectra of **346** are in good agreement with literature.[286]

GC (t_R) 19.97 min (program 0)

GC-MS (EI):
155 (17) [M^+-OCH_3], 136 (66), 127 (10) [$M^+-COOCH_3$], 113 (37) [$M^+-C_2H_4COOH$], 108 (69), 94 (18), 87 (23) [$C_3H_6COOH^+$], 81 (100), 72 (18), 67 (42), 59 (29) [$COOCH_3^+$], 56 (51), 42 (67).

IR (cm^{-1}) 2950 (m), 2862 (w), 1719 (s), 1655 (m), 1435 (m), 1273 (m), 1198 (s), 1177 (s), 1036 (m), 981 (m).

6.2.4.2 Preparation of (*R*,*E*)-methyl 8-(4-benzyl-2-oxooxazolidin-on-3-yl)-8-oxooct-2-enoate (343)



346 **289** **343**

$C_{19}H_{23}NO_5$
Mol. Wt.: 345.39

Compound **343** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **346** (342 mg, 1.8 mmol) and purification by column chromatography (flash silica, 14% → 25% EtOAc in ^{c}Hex) yields the product as a colourless oil (497 mg, 1.4 mmol, 78%).

R_f 0.38 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.46 – 1.60 (m, 2H, H-4), 1.64 – 1.77 (m, 2H, H-3), 2.24 (tdd, *J* = 7.2, 7.1, 1.5 Hz, 2H, H-5), 2.75 (dd, *J* = 13.3, 9.5 Hz, 1H, H-13a), 2.88 (dt, *J* = 17.1, 7.4 Hz, 1H, H-2a), 2.97 (dt, *J* = 17.1, 7.3 Hz, 1H, H-2b), 3.26 (dd, *J* = 13.3, 3.4 Hz, 1H, H-13b), 3.69 (s, 3H, H-9), 4.09 – 4.22 (m, 2H, H-11), 4.59 – 4.69 (m, 1H, H-12), 5.83 (dt, *J* = 15.6, 1.5 Hz, 1H, H-7), 6.95 (dt, *J* = 15.6, 7.1 Hz, 1H, H-6), 7.15 – 7.35 (m, 5H, H-15, H-16, H-17).

^{13}C-NMR (75 MHz, $CDCl_3$):
23.7 (CH_2, C-3), 27.4 (CH_2, C-4), 31.9 (CH_2, C-5), 35.2 (CH_2, C-2), 37.9 (CH_2, C-13), 51.4 (CH_3, C-9), 55.1 (CH, C-12), 66.3 (CH_2, C-11), 121.3 (CH, C-7), 127.4 (CH, C-17), 129.0 (CH, C-16), 129.4 (CH, C-15), 135.3 (C_{quart}, C-14), 148.9 (CH, C-6), 153.5 (C_{quart}, C-10), 167.0 (C_{quart}, C-8), 172.9 (C_{quart}, C-1).

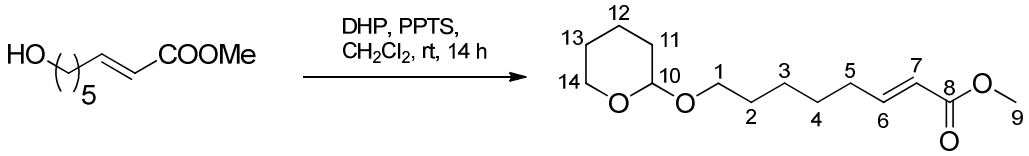
GC (t_R) 24.02 min (program 4)

GC-MS (EI):

345 (19) [M^+], 313 (23), 286 (17) [$M^+-COOCH_3$], 258 (28), 254 (9) [$M^+-C_7H_7$], 228 (23), 222 (14), 178 (60), 169 (45) [$M^+-C_{10}H_{10}NO_2$], 152 (19), 141 (40) [$M^+-C_{11}H_{10}NO_3$], 137 (100), 133 (39), 117 (68), 109 (87), 101 (49), 91 (66), 86 (27), 81 (77), 67 (28), 59 (16) [$COOCH_3^+$], 55 (25).

IR (cm^{-1}) 2948 (w), 2866 (w), 1776 (s), 1717 (s), 1697 (s), 1656 (m), 1481 (w), 1455 (m), 1436 (m), 1386 (s), 1351 (s), 1328 (m), 1274 (s), 1190 (s), 1153 (s), 1113 (m), 1097 (m), 1076 (m), 1048 (m), 1031 (m), 980 (s), 918 (w), 847 (m), 762 (m), 740 (m), 701 (s).

6.2.4.3 Preparation of (*E*)-methyl 8-((tetrahydro-*2H*-pyran-2-yl) oxy)oct-2-enoate (361)



119 **361**

$C_{14}H_{24}O_4$
Mol. Wt.: 256,34

Compound **361** is prepared applying the general method of 6.2.2.16. The use of alcohol **119** (1.5 g, 8.7 mmol) and purification of the crude product by column chromatography (25% EtOAc in ^{c}Hex) yields the product as a colourless oil (2.2 g, 8.5 mmol, 98%).

R_f 0.73 (50% EtOAc in ^{c}Hex)

Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-NMR The ^{1}H-NMR spectra of **361** is in good agreement with literature.[287]

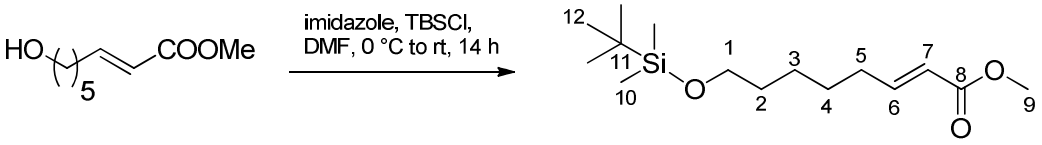
^{13}C-NMR (75 MHz, $CDCl_3$):

19.8 (CH_2, C-12), 25.6 (CH_2, C-13), 25.9 (CH_2, C-3), 28.0 (CH_2, C-4), 29.6 (CH_2, C-2), 30.9 (CH_2, C-11), 32.3 (CH_2, C-5), 51.5 (CH_3, C-9), 62.5 (CH_2, C-14), 67.5 (CH_2, C-1), 99.0 (CH, C-10), 121.1 (CH, C-7), 149.7 (CH, C-6), 167.3 (C_{quart}, C-8).

GC-MS (EI):

225 (2) [M^+-OCH_3], 197 (2) [$M^+-COOCH_3$], 169 (10), 156 (10), 140 (10), 113 (20) [$C_6H_9O_2^+$], 101 (15) [M^+-OTHP], 95 (50), 85 (100) [THP^+], 81 (20), 55 (32), 53 (10).

6.2.4.4 Preparation of (*E*)-methyl 8-((*tert*-butyldimethylsilyl)oxy) oct-2-enoate (362)



119 **362**

$C_{15}H_{30}O_3Si$
Mol. Wt.: 286.48

Compound **362** is prepared applying the general method of 6.2.2.21. The use of alcohol **119** (6.1 g, 35.1 mmol) and purification of the crude product by column chromatography (15% EtOAc in ^{c}Hex) yields the product as a colourless oil (10.0 g, 34.9 mmol, 99%).

R_f 0.93 (50% EtOAc in ^{c}Hex)

Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.02 (s, 6H, H-10), 0.87 (s, 9H, H-12), 1.27 – 1.40 (m, 2H, H-3), 1.40 – 1.56 (m, 4H, H-2, H-4), 2.19 (tdd, *J* = 7.2, 7.0, 1.5 Hz, 2H, H-5), 3.58 (t, *J* = 6.3 Hz, 2H, H-1), 3.70 (s, 3H, H-9), 5.80 (dt, *J* = 15.6, 1.5 Hz, 1H, H-7), 6.95 (dt, *J* = 15.6, 7.0 Hz, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$):

−5.2 (CH_3, C-10), 18.5 (C_{quart}, C-11), 25.5 (CH_2, C-3), 26.1 (CH_3, C-12), 27.9 (CH_2, C-4), 32.3 (CH_2, C-5), 32.7 (CH_2, C-2), 51.4 (CH_3, C-9), 63.1 (CH_2, C-1), 121.0 (CH, C-7), 149.6 (CH, C-6), 167.2 (C_{quart}, C-8).

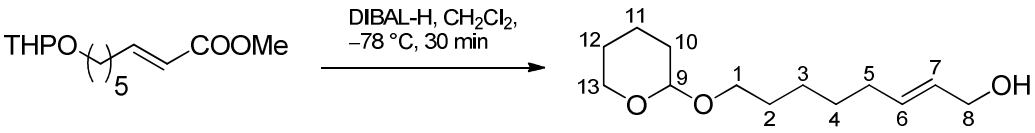
GC-MS (EI):
271 (2) [M^+-CH_3], 255 (5) [M^+-OCH_3], 230 (15), 229 (75) [$M^+-{}^t$Bu], 197 (35), 119 (5), 99 (11), 90 (65), 89 (100), 81 (34), 75 (45) [$C_2H_7OSi^+$], 73 (33), 67 (25), 59 (15), 55 (30), 53 (8).

IR (cm^{-1}) 2930, 2857, 1727, 1658, 1472, 1463, 1435, 1388, 1361, 1314, 1254, 1196, 1175, 1098, 1041, 1006, 978, 939, 832, 773, 716, 662.

6.2.4.5 General method for the reduction of esters to alcohols with DIBAL-H

According to procedures of Barnickel[152] and Fox *et al*.,[216] a 0.05M solution of an ester (1.0 eq.) in CH_2Cl_2 abs. is cooled to −78 °C in an acetone/dry ice bath and DIBAL-H (1M in hexanes) (2.0 eq.) is added dropwise using a syringe pump (0.5 mL/min). The mixture is stirred at −78 °C for 1 – 2 h. The reaction is terminated by the addition of H_2O (5 mL/mmol) and the remaing solid is dissolved with 2M HCl_{aq}. The phases are separated and the aqueous phase is extracted with CH_2Cl_2 (3 × 10 mL/mmol) before the combined organic phases are washed with H_2O (20 mL/mmol), dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product.

6.2.4.6 Preparation of (*E*)-8-((tetrahydro-*2H*-pyran-2-yl)oxy)oct-2-en-1-ol (363)



361 **363**

$C_{13}H_{24}O_3$
Mol. Wt.: 228.33

Compound **363** is prepared applying the general method of 6.2.4.5. The use of methyl ester **361** (2.2 g, 8.5 mmol) and purification of the crude product by column

chromatography (20% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.9 g, 8.4 mmol, 98%).

R_f 0.58 (50% EtOAc in ^{c}Hex)

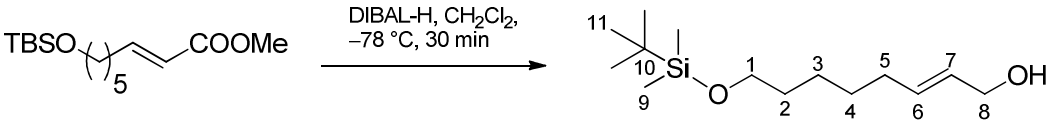
Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-NMR The ^{1}H-NMR spectra of **363** is in good agreement with literature.[287]

^{13}C-NMR (75 MHz, $CDCl_3$):
19.7 (CH_2, C-11), 25.5 (CH_2, C-12), 25.8 (CH_2, C-3), 29.0 (CH_2, C-4), 29.6 (CH_2, C-2), 30.8 (CH_2, C-10), 32.2 (CH_2, C-5), 62.4 (CH_2, C-13), 63.7 (CH_2, C-8), 67.6 (CH_2, C-1), 98.9 (CH, C-9), 129.2 (CH, C-7), 133.0 (CH, C-6).

GC-MS (EI):
227 (2) [M^+−H], 109 (7), 93 (7), 85 (100) [M^+−THP], 70 (15), 67 (39), 55 (72).

6.2.4.7 Preparation of (*E*)-8-((*tert*-butyldimethylsilyl)oxy)oct-2-en-1-ol (364)



362 **364**

$C_{14}H_{30}O_2Si$
Mol. Wt.: 258.47

Compound **364** is prepared applying the general method of 6.2.4.5. The use of methyl ester **362** (2.3 g, 8.1 mmol) yields the product as a colourless oil (2.0 g, 7.7 mmol, 95%) without further purification.

R_f 0.55 (33% EtOAc in ^{c}Hex)

Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-9), 0.89 (s, 9H, H-11), 1.24 – 1.43 (m, 4H, H-3, H-4), 1.43 – 1.60 (m, 2H, H-2), 2.00 – 2.12 (m, 2H, H-5), 3.59 (t, *J* = 6.4 Hz, 2H, H-1), 4.05 – 4.10 (m, 2H, H-8), 5.55 – 5.75 (m, 2H, H-6, H-7).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.1 (CH_3, C-9), 18.5 (C_{quart}, C-10), 25.5 (CH_2, C-3), 26.1 (CH_3, C-11), 29.0 (CH_2, C-4), 32.3 (CH_2, C-5), 32.8 (CH_2, C-2), 63.3 (CH_2, C-1), 64.0 (CH_2, C-8), 129.1 (CH, C-7), 133.5 (CH, C-6).

GC (t_R) 21.88 min (program 0)

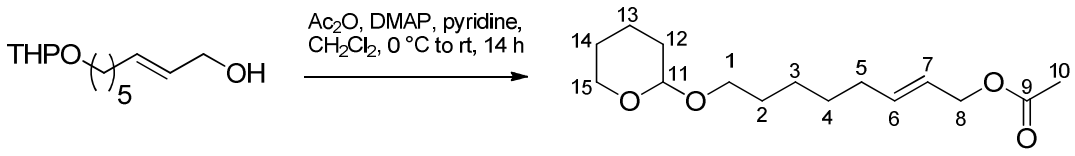
GC-MS (EI):
201 (2) [M^+–^{t}Bu], 183 (10), 169 (29), 155 (10), 115 (5) [M^+−TBS], 109 (30), 105 (15), 101 (5), 94 (5), 89 (5), 81 (18), 75 (100) [$C_2H_7OSi^+$], 73 (23), 67 (100), 57 (13) [^{t}Bu$^+$], 55 (25).

IR (cm^{-1}) 3339, 2929, 2856, 2335, 1670, 1471, 1462, 1437, 1388, 1361, 1253, 1218, 1097, 1004, 968, 938, 919, 832, 773, 711, 660.

6.2.4.8 General method for the acetyl-protection of alcohols

According to a procedure of Qian et al.,[215] a 0.05M solution of an alcohol (1.0 eq.) in a mixture of CH_2Cl_2 abs./pyridine abs. (1:1) is cooled to 0 °C and Ac_2O (1.0 eq.) and DMAP (catalytic amount) are added. The mixture is stirred for 14 h at room temperature before it is washed with 2M HCl_{aq} in quick succession until the separated aqueous phases' pH remains acidic. The aqueous phase is extracted with EtOAc (3 × 10 mL/mmol) before the combined organic phases are washed with brine (20 mL/mmol), dried over $MgSO_4$ and filtered. The solvent is evaporated to yield the crude product.

6.2.4.9 Preparation of (*E*)-8-((tetrahydro-*2H*-pyran-2-yl)oxy)oct-2-en-1-yl acetate (365)



363 **365**

$C_{15}H_{26}O_4$
Mol. Wt.: 270.36

Compound **365** is prepared applying the general method of 6.2.4.8. The use of alcohol **363** (1.1 g, 4.8 mmol) yields the product as a yellow oil (1.2 g, 4.5 mmol, 95%) without further purification.

R_f 0.51 (33% EtOAc in ^{c}Hex)

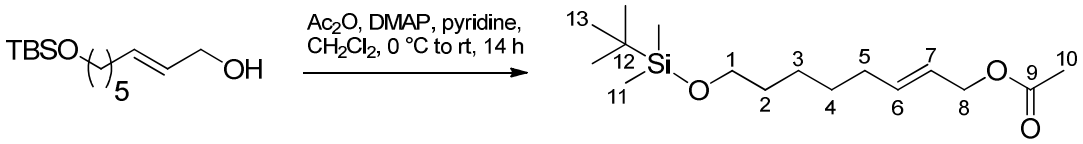
Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-/^{13}C-NMR The NMR spectra of **365** are in good agreement with literature.[288]

GC-MS (EI):
126 (12), 109 (29), 101 (19) [$OTHP^+$], 98 (21), 93 (35), 85 (100), 80 (46), 70 (30) [$M^+ - C_4H_8OTHP$, −Ac], 67 (58), 55 (61).

IR (cm^{-1}) 2937 (m), 2856 (w), 1739 (s), 1441 (w), 1381 (w), 1363 (m), 1322 (w), 1226 (s), 1200 (m), 1184 (w), 1136 (m), 1119 (m), 1076 (m), 1021 (s), 966 (s), 905 (m), 869 (m), 813 (m), 732 (w).

6.2.4.10 Preparation of (*E*)-8-((*tert*-butyldimethylsilyl)oxy)oct-2-en-1-yl acetate (366)



364 **366**

$C_{16}H_{32}O_3Si$
Mol. Wt.: 300.51

Compound **366** is prepared applying the general method of 6.2.4.8. The use of alcohol **364** (2.0 g, 7.6 mmol) yields the product as a yellow oil (2.3 g, 7.6 mmol, 99%) without further purification.

R_f 0.81 (25% EtOAc in ^{c}Hex)

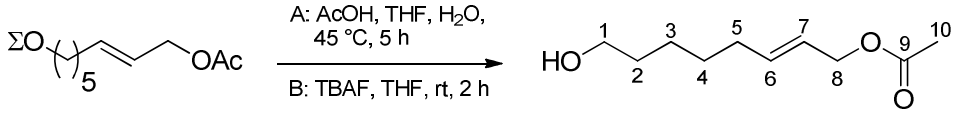
Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-11), 0.88 (s, 9H, H-13), 1.28 – 1.44 (m, 4H, H-3, H-4), 1.44 – 1.56 (m, 2H, H-2), 2.03 (s, 3H, H-10), 2.00 – 2.12 (m, 2H, H-5), 3.59 (t, *J* = 6.6 Hz, 2H, H-1), 4.49 (dd, *J* = 6.4, 1.0 Hz, 2H, H-8), 5.55 (dtt, *J* = 15.4, 6.4, 1.4 Hz, 1H, H-7), 5.76 (dtt, *J* = 15.4, 6.7, 1.0 Hz, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.2 (CH_3, C-11), 18.5 (C_{quart}, C-12), 21.2 (CH_3, C-10), 25.5 (CH_2, C-3), 26.1 (CH_3, C-13), 28.8 (CH_2, C-4), 32.4 (CH_2, C-5), 32.8 (CH_2, C-2), 63.3 (CH_2, C-1), 65.4 (CH2, C-8), 123.9 (CH, C-7), 136.6 (CH, C-6), 171.0 (C_{quart}, C-9).

GC-MS (EI):
159 (15) [$C_2H_4OTBS^+$], 133 (30), 115 (10) [TBS^+], 103 (5), 75 (100) [$C_2H_7OSi^+$], 73 (38), 59 (8) [$COOCH_3^+$], 47 (5).

6.2.4.11 Preparation of (*E*)-8-hydroxyoct-2-en-1-yl acetate (367)



Σ = THP **365**
Σ = TBS **366**

367

$C_{10}H_{18}O_3$
Mol. Wt.: 186.25

A: Synthesis starting from THP-protected compound **365**:

According to a procedure of Bernady *et al*.,[170] bisprotected compound **365** (1.2 g, 4.5 mmol, 1.0 eq.) is dissolved in a mixture of AcOH/THF/H_2O (4:2:1) (35 mL) and the mixture is stirred for 5 h at 45 °C. The reaction mixture is adjusted to pH 6 with 1M $NaOH_{aq}$. EtOAc (50 mL) is added and the phases are separated before the aqueous phase is extracted with EtOAc (3 × 50 mL). The combined organic phases are washed with brine (150 mL), dried over $MgSO_4$ and filtered. The solvent is evaporated and left over AcOH is removed by aceotropic evaporation with toluene. The crude product is purified by column chromatography (25% EtOAc in ^{c}Hex) to yield the product as a colourless oil (720 mg, 3.9 mmol, 86%).

B: Synthesis starting from TBS-protected compound **366**:

Compound **367** is prepared applying the general method of 6.2.2.50. The use of TBS-protected compound **366** (1.4 g, 4.7 mmol) and purification of the crude product by column chromatography (10% → 50% EtOAc in ^{c}Hex) yields the product as a colourless oil (781 mg, 4.2 mmol, 89%).

R_f 0.21 (33% EtOAc in ^{c}Hex)

Isom. ratio cis/trans = 1:10 (calculated from NMR)

^{1}H-NMR (300 MHz, $CDCl_3$): assignment differs from literature.[289]
1.21 – 1.41 (m, 4H, H-3, H-4), 1.43 – 1.55 (m, 2H, H-2), 1.99 (s, 3H, H-10), 1.95 – 2.06 (m, 2H, H-5), 2.29 (br s, 1H, OH), 3.55 (t, *J* = 6.6 Hz, 2H, H-1), 4.44 (dd, *J* = 6.4, 1.0 Hz, 2H, H-8), 5.49 (dtt, *J* = 15.4, 6.4, 1.4 Hz, 1H, H-7), 5.70 (dtt, *J* = 15.4, 6.7, 1.0 Hz, 1H, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$):

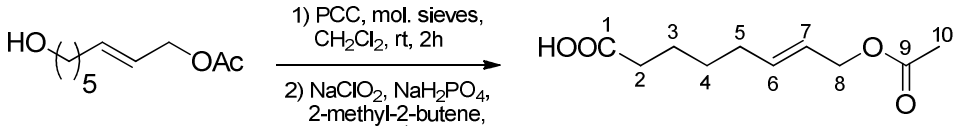
21.0 (CH_3, C-10), 25.3 (CH_2, C-3), 28.7 (CH_2, C-4), 32.2 (CH_2, C-5), 32.5 (CH_2, C-2), 62.6 (CH_2, C-1), 65.3 (CH_2, C-8), 123.9 (CH, C-7), 136.4 (CH, C-7), 171.0 (C_{quart}, C-9).

GC-MS (EI):

186 (2) [M^+], 169 (2) [M^+−OH], 143 (3) [M^+−$COCH_3$], 126 (15), 108 (85), 93 (60), 80 (100), 70 (40), 67 (55), 55 (30).

IR (cm^{-1}) 3404 (w, br), 2935 (m), 2857 (w), 1738 (s), 1442 (w), 1363 (m), 1228 (s), 1170 (w), 1137 (w), 1116 (w), 1075 (m), 1023 (s), 969 (s), 913 (m), 900 (m), 867 (w), 840 (w), 806 (w).

6.2.4.12 Preparation of (*E*)-8-acetoxyoct-6-enoic acid (368)



367 **368**

$C_{10}H_{16}O_4$
Mol. Wt.: 200.23

1) PCC oxidation:

According to a procedure of Herscovici *et al.*,[195] to a solution of alcohol **367** (1.4 g, 7.6 mmol, 1.0 eq.) in CH_2Cl_2 abs. (100 mL) are added carefully dried powdered molecular sieves (3Å) (3 g), Celite® (2 spatulas) and PCC (3.29 g, 15.3 mmol, 2.0 eq.) and the mixture is stirred for 2 h at room temperature. The reaction mixture is filtered over Celite® and the solvent is evaporated in the presence of flash silica gel. The dark solid is loaded onto a short silica gel column and the product is eluted with EtOAc/^{c}Hex (1:1). Solvent evaporation gives the crude aldehyde, which is immediately used in the next step.

2) Pinnick-oxidation:

According to procedures of Lindgren *et al.*[106] and Bal *et al.*,[107] to a solution of the crude aldehyde from **1**) (1.00 g, 0.54 mmol, 1.00 eq.) in a mixture of THF/*tert*-butanol/H_2O (1:1:0.25) (48 mL) are added 2-methyl-2-butene (5.18 mL, 48.9 mmol, 9.00 eq.), NaH_2PO_4 (352 mg, 2.9 mmol, 0.54 eq.) and $NaClO_2$ (1.77 g,

19.6 mmol, 3.60 eq.) and the mixture is stirred for 2 h at room temperature. The reaction is terminated by slow addition of sat. $Na_2S_2O_{3aq}$ (100 mL) at 0 °C. The pH is adjusted to pH 4 with 2M HCl_{aq} and the aqueous phase is extracted with EtOAc (3 × 150 mL). The combined organic phases are washed with 0.1M HCl (200 mL), dried over $MgSO_4$ and filtered. The solvent is evaporated and the crude product purified by column chromatography (25% → 33% → 50% EtOAc in ^{c}Hex → EtOAc) to yield the product as a colourless oil (769 mg, 3.8 mmol, 50% over two steps).

R_f 0.37 (50% EtOAc in ^{c}Hex), tailing observed

Isom. ratio cis/trans = 1:10 (calculated from NMR)

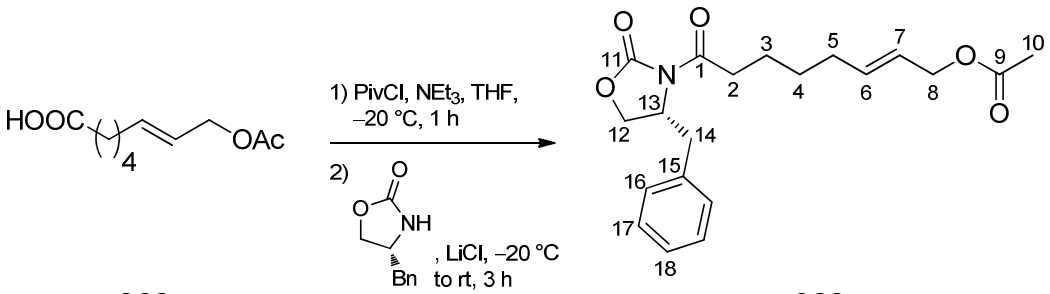
^{1}H-NMR (300 MHz, $CDCl_3$):
1.37 – 1.49 (m, 2H, H-4), 1.57 – 1.69 (m, 2H, H-3), 2.04 (s, 3H, H-10), 2.01 – 2.15 (m, 2H, H-5), 2.34 (t, *J* = 7.4 Hz, 2H, H-2), 4.49 (dd, *J* = 6.3, 1.0 Hz, 2H, H-8), 5.56 (dtt, *J* = 15.4, 6.3, 1.4 Hz, 1H, H-7), 5.74 (dtt, *J* = 15.4, 6.5, 1.0 Hz, 1H, H-6), 10.76 (br s, 1H, COOH).

^{13}C-NMR (75 MHz, $CDCl_3$):
21.1 (CH_3, C-10), 24.2 (CH_2, C-3), 28.3 (CH_2, C-4), 31.9 (CH_2, C-5), 33.9 (CH_2, C-2), 65.3 (CH_2, C-8), 124.4 (CH, C-7), 135.8 (CH, C-6), 171.1 (C_{quart}, C-9), 179.9 (C_{quart}, C-1).

GC-MS (EI):
141 (5) [$M^+-COOCH_3$], 140 (40), 122 (15), 113 (2) [$M^+-C_3H_6COOH$], 112 (17), 99 (5) [$M^+-C_4H_8COOH$], 94 (20), 80 (100), 79 (45), 73 (5), 70 (7), 68 (9), 67 (29), 60 (10), 59 (4) [$COOCH_3^+$], 55 (20), 54 (23).

IR (cm^{-1}) 2932 (w), 2920 (w, br), 2851 (w), 1778 (s), 1698 (m), 1612 (w), 1513 (m), 1455 (w), 1385 (m), 1352 (m), 1301 (m), 1246 (s), 1210 (m), 1740 (m), 1098 (m), 1033 (m), 972 (m), 908 (s), 821 (m), 726 (s), 702 (s), 647 (m).

6.2.4.13 Preparation of (*R*,*E*)-8-(4-benzyl-2-oxooxazolidinon-3-yl)-8-oxooct-2-en-1-yl acetate (369)



368 **289** **369**

$C_{20}H_{25}NO_5$
Mol. Wt.: 359.42

Compound **369** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **368** (617 mg, 3.1 mmol) and purification by column chromatography (flash silica, 33% EtOAc in ^{c}Hex) yields the product as a colourless oil (1.1 g, 2.9 mmol, 95%).

R_f 0.71 (50% EtOAc in ^{c}Hex)

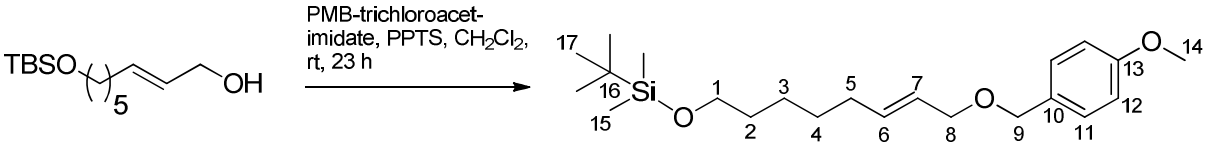
^{1}H-NMR (300 MHz, $CDCl_3$):
1.40 – 1.52 (m, 2H, H-4), 1.61 – 1.74 (m, 2H, H-3), 2.02 (s, 3H, H-10), 2.00 – 2.16 (m, 2H, H-5), 2.74 (dd, *J* = 13.3, 9.5 Hz, 1H, H-14a), 2.86 (dt, *J* = 17.1, 7.4 Hz, 1H, H-2a), 2.95 (dt, *J* = 17.1, 7.3 Hz, 1H, H-2b), 3.25 (dd, *J* = 13.4, 3.3 Hz, 1H, H-14b), 4.03 – 4.21 (m, 2H, H-12), 4.48 (dd, *J* = 6.3, 1.0 Hz, 2H, H-8), 4.57 – 4.69 (m, 1H, H-13), 5.56 (dtt, *J* = 15.4, 6.3, 1.4 Hz, 1H, H-7), 5.74 (dtt, *J* = 15.4, 6.5, 1.0 Hz, 1H, H-6), 7.14 – 7.33 (m, 5H, H-16, H-17, H-18).

^{13}C-NMR (75 MHz, $CDCl_3$):
21.0 (CH_3, C-10), 23.7 (CH_2, C-3), 28.3 (CH_2, C-4), 31.9 (CH_2, C-5), 35.3 (CH_2, C-2), 37.9 (CH_2, C-14), 55.1 (CH, C-13), 65.1 (CH_2, C-8), 66.2 (CH_2, C-12), 124.3 (CH, C-7), 127.3 (CH, C-18), 128.9 (CH, C-17), 129.4 (CH, C-16), 135.3 (C_{quart}, C-15), 135.8 (CH, C-6), 153.4 (C_{quart}, C-11), 170.8 (C_{quart}, C-9), 173.1 (C_{quart}, C-1).

GC-MS (EI):
299 (85), 232 (10), 219 (50), 178 (100), 134 (50), 123 (70), 117 (80), 91 (55), 91 (56) [$C_7H_7^+$], 79 (35), 67 (30), 55 (15).

IR (cm^{-1}) 2933 (w), 1777 (s), 1734 (s), 1697 (s), 1481 (w), 1454 (w), 1383 (s), 1352 (m), 1226 (s), 1099 (m), 1076 (m), 1049 (m), 1022 (m), 969 (m), 913 (m), 841 (w), 762 (m), 730 (s), 701 (s).

6.2.4.14 Preparation of (*E*)-*tert*-butyl((8-((4-methoxybenzyl)oxy) oct-6-en-1-yl)oxy)dimethylsilane (371)



364 **371**

$C_{22}H_{38}O_3Si$
Mol. Wt.: 378.62

According to procedures of Barnickel[152] and Nakajima *et al*.,[219] to a solution of PMB-2,2,2-trichloroacetimidate (1M in ^{n}hex) (7.0 mL, 7.0 mmol, 1.8 eq.) in a mixture of ^{n}hex/CH_2Cl_2 (2:1) (15 mL) are added allylic alcohol **364** (1.00 g, 3.9 mmol, 1.0 eq.) and PPTS (194 mg, 0.77 mmol, 0.2 eq.) and the mixture is stirred for 14 h at room temperature. The precipitated solid is removed by filtration and washed thoroughly with a mixture of ^{n}hex/CH_2Cl_2 (2:1). The filtrate is washed with sat. $KHCO_{3aq}$ (20 mL) and brine (20 mL) before the organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (flash silica, 5% EtOAc in ^{c}Hex) to yield the product as a colourless oil (1.3 g, 3.4 mmol, 89%).

R_f 0.50 (10% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.04 (s, 6H, H-15), 0.89 (s, 9H, H-17), 1.22 – 1.44 (m, 4H, H-3, H-4), 1.45 – 1.58 (m, 2H, H-2), 2.00 – 2.11 (m, 2H, H-5), 3.60 (t, *J* = 6.6 Hz, 2H, H-1), 3.80 (s, 3H, H-14), 3.94 (dd, *J* = 6.0, 1.0 Hz, 2H, H-8), 4.43 (s, 2H, H-9), 5.58 (dtt, *J* = 15.4, 6.0, 1.1 Hz, 1H, H-7), 5.70 (dtt, *J* = 15.4, 6.5, 1.0 Hz, 1H, H-6), 6.87 (d, *J* = 8.8 Hz, 2H, H-12), 7.26 (d, *J* = 8.8 Hz, 2H, H-11).

^{13}C-NMR (75 MHz, $CDCl_3$):

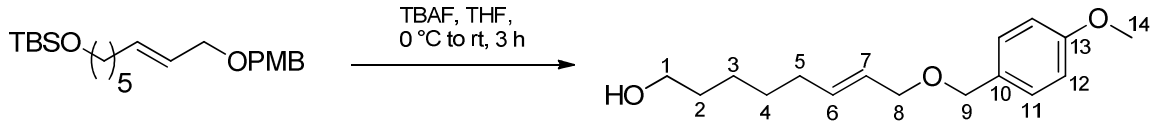
−5.1 (CH_3, C-15), 18.5 (C_{quart}, C-16), 25.5 (CH_2, C-3), 26.1 (CH_3, C-17), 29.0 (CH_2, C-4), 32.5 (CH_2, C-5), 32.8 (CH_2, C-2), 55.4 (CH_3, C-14), 63.4 (CH_2, C-1), 70.8 (CH_2, C-8), 71.7 (CH_2, C-9), 113.9 (CH, C-12), 126.5 (CH, C-7), 129.5 (CH, C-11), 130.7 (C_{quart}, C-10), 134.9 (CH, C-6), 158.9 (C_{quart}, C-13).

GC (t_R) 41.67 min (program 0)

GC-MS (EI):

185 (2), 137 (3) [$OPMB^+$], 121 (100) [PMB^+], 107 (3), 91 (4) [$C_7H_7^+$], 75 (13) [$C_2H_7OSi^+$], 55 (2).

6.2.4.15 Preparation of (*E*)-8-((4-methoxybenzyl)oxy)oct-6-en-1-ol (372)



371 **372**

$C_{16}H_{24}O_3$
Mol. Wt.: 264.36

Compound **372** is prepared applying the general method of 6.2.2.50. The use of TBS-protected compound **371** (3.2 g, 8.4 mmol) and purification of the crude product by column chromatography (50% EtOAc in ^{c}Hex) yields the product as a colourless oil (2.1 g, 7.8 mmol, 93%).

R_f 0.54 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.30 – 1.48 (m, 4H, H-3, H-4), 1.49 – 1.63 (m, 2H, H-2), 1.64 (br s, 1H, OH), 2.01 – 2.11 (m, 2H, H-5), 3.62 (t, *J* = 6.6 Hz, 2H, H-1), 3.79 (s, 3H, H-14), 3.93 (dd, *J* = 6.0, 1.0 Hz, 2H, H-8), 4.42 (s, 2H, H-9), 5.57 (dtt, *J* = 15.4, 6.0, 1.2 Hz, 1H, H-7), 5.70 (dtt, *J* = 15.4, 6.5, 1.0 Hz, 1H, H-6), 6.87 (d, *J* = 8.8 Hz, 2H, H-12), 7.26 (d, *J* = 8.8 Hz, 2H, H-11).

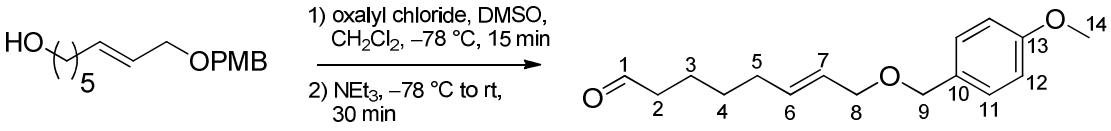
^{13}C-NMR (75 MHz, $CDCl_3$):
25.4 (CH_2, C-3), 28.9 (CH_2, C-4), 32.3 (CH_2, C-5), 32.7 (CH_2, C-2), 55.4 (CH_3, C-14), 63.0 (CH_2, C-1), 70.7 (CH_2, C-8), 71.7 (CH_2, C-9), 113.9 (CH, C-12), 126.6 (CH, C-7), 129.5 (CH, C-11), 130.6 (C_{quart}, C-10), 134.7 (CH, C-6), 159.3 (C_{quart}, C-13).

GC (t_R) 35.05 min (program 0)

GC-MS (EI):
263 (2) [M^+−H], 137 (27) [$OPMB^+$], 121 (100) [PMB^+], 107 (14), 91 (13), 77 (22), 67 (13).

IR (cm^{-1}) 3383 (w, br), 2931 (m), 2855 (m), 1737 (w), 1612 (m), 1586 (w), 1512 (s), 1462 (w), 1360 (w), 1301 (m), 1245 (s), 1173 (m), 1094 (m), 1052 (s), 1033 (s), 970 (m), 818 (s), 757 (w), 708 (w).

6.2.4.16 Preparation of (*E*)-8-((4-methoxybenzyl)oxy)oct-6-enal (373)



372 **373**

$C_{16}H_{22}O_3$
Mol. Wt.: 262.34

According to a procedure of Taillier *et al*.,[220] a solution of oxalyl chloride (0.42 mL, 4.8 mmol, 1.2 eq.) in CH_2Cl_2 abs. (18 mL) is cooled to −78 °C in an acetone/dry ice bath and DMSO abs. (0.32 mL, 4.4 mmol, 1.1 eq.) is added dropwise. After 5 min of stirring, alcohol **372** (1.1 g, 4.0 mmol, 1.0 eq.), dissolved in CH_2Cl_2 abs. (11 mL), is added dropwise and the mixture is stirred for 15 min. NEt_3 abs. (2.80 mL, 20.2 mmol, 5.0 eq.) is added dropwise and the stirring is continued for 30 min, leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of CH_2Cl_2 (20 mL) and sat. NH_4Cl_{aq} (40 mL). The phases are separated and the organic phase is washed with sat. NH_4Cl_{aq} (40 mL) and brine (2 × 40 mL) before being dried over $MgSO_4$ and filtered. The solvent is evaporated to give the

crude product as a yellow oil (1.0 g, 3.9 mmol, 96%) which is used in the next step without further purification.

R_f 0.56 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.32 – 1.49 (m, 4H, H-3, H-4), 1.58 – 1.79 (m, 2H, H-2), 2.01 – 2.13 (m, 2H, H-5), 2.43 (td, *J* = 7.3, 1.8 Hz, 2H, H-1), 3.80 (s, 3H, H-14), 3.93 (dd, *J* = 5.8, 0.8 Hz, 2H, H-8), 4.42 (s, 2H, H-9), 5.52 – 5.74 (m, 2H, H-6, H-7), 6.87 (d, *J* = 8.8 Hz, 2H, H-12), 7.26 (d, *J* = 8.8 Hz, 2H, H-11), 9.75 (t, *J* = 1.8 Hz, 1H, H-1).

^{13}C-NMR (75 MHz, $CDCl_3$):

21.7 (CH_2, C-3), 28.6 (CH_2, C-4), 32.1 (CH_2, C-5), 43.8 (CH_2, C-2), 55.4 (CH_3, C-14), 70.7 (CH_2, C-8), 71.7 (CH_2, C-9), 113.9 (CH, C-12), 127.1 (CH, C-7), 129.4 (C_{quart}, C-10), 129.5 (CH, C-11), 133.9 (CH, C-6), 159.3 (C_{quart}, C-13), 202.7 (CH, C-1).

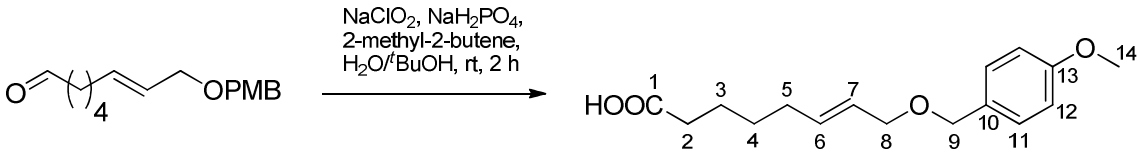
GC (t_R) 33.53 min (program 0)

GC-MS (EI):

122 (100), 107 (32), 91 (23), 79 (19), 77 (28).

IR (cm^{-1}) 2932 (w), 2853 (w), 1766 (w), 1722 (m), 1612 (m), 1586 (w), 1512 (s), 1462 (m), 1360 (w), 1301 (m), 1245 (s), 1172 (s), 1097 (m), 1064 (m), 1033 (s), 970 (m), 818 (s), 758 (m), 710 (w).

6.2.4.17 Preparation of (*E*)-8-((4-methoxybenzyl)oxy)oct-6-enoic acid (374)



373 **374**

$C_{16}H_{22}O_4$
Mol. Wt.: 278.34

According to procedures of Lindgren *et al*.[106] and Bal *et al*.,[107] to a solution of crude aldehyde **373** (300 mg, 1.1 mmol, 1.0 eq.) in a mixture of *tert*-butanol/H_2O (4:1)

(15 mL) are added 2-methyl-2-butene (1.1 mL, 10.3 mmol, 9.0 eq.), NaH_2PO_4 (357 mg, 2.3 mmol, 2.0 eq.) and $NaClO_2$ (414 mg, 4.6 mmol, 4.0 eq.) and the mixture is stirred for 2 h at room temperature. The reaction is terminated by the addition of sat. NH_4Cl_{aq} (20 mL) and EtOAc (20 mL). The phases are separated and the aqueous phase is extracted with EtOAc (2 × 20 mL). The combined organic phases are dried over $MgSO_4$ and filtered. The solvent is evaporated and the crude product purified by column chromatography (20% EtOAc in ^{c}Hex) to yield the product as a colourless oil (173 mg, 0.62 mmol, 54%).

R_f 0.26 (33% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.32 – 1.52 (m, 2H, H-4), 1.59 – 1.72 (m, 2H, H-3), 2.00 – 2.13 (m, 2H, H-5), 2.36 (t, *J* = 7.4 Hz, 2H, H-2), 3.80 (s, 3H, H-14), 3.94 (dd, *J* = 5.8, 0.8 Hz, 2H, H-8), 4.43 (s, 2H, H-9), 5.51 – 5.75 (m, 2H, H-6, H-7), 6.87 (d, *J* = 8.7 Hz, 2H, H-12), 7.26 (d, *J* = 8.7 Hz, 2H, H-11), 9.31 (br s, 1H, COOH).

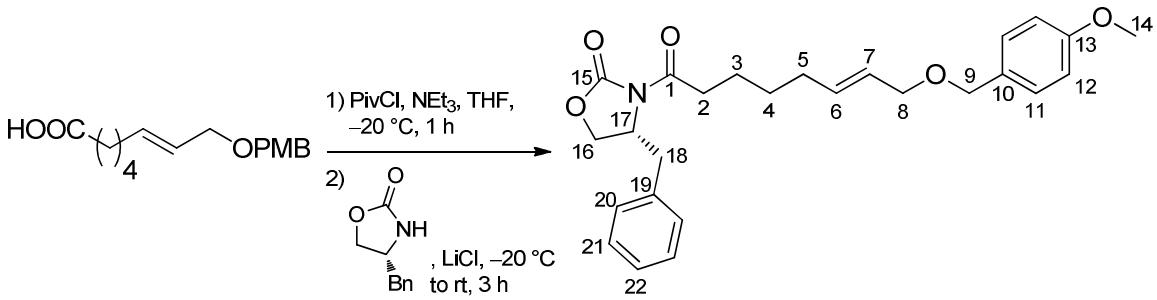
^{13}C-NMR (75 MHz, $CDCl_3$):
24.3 (CH_2, C-3), 28.5 (CH_2, C-4), 32.0 (CH_2, C-5), 33.9 (CH_2, C-2), 55.4 (CH_3, C-14), 70.6 (CH_2, C-8), 71.7 (CH_2, C-9), 113.9 (CH, C-12), 127.0 (CH, C-7), 129.6 (CH, C-11), 130.6 (C_{quart}, C-10), 134.1 (CH, C-6), 159.3 (C_{quart}, C-13), 179.4 (C_{quart}, C-1).

GC (t_R) 37.20 min (program 0)

GC-MS (EI):
152 (88), 135 (100), 121 (3) [PMB^+], 107 (13), 92 (11), 77 (20), 63 (8), 55 (6).

IR (cm^{-1}) 2950 (w, br), 2929 (m), 2852 (m), 1706 (s), 1612 (m), 1586 (w), 1513 (s), 1455 (m), 1421 (w), 1361 (w), 1302 (m), 1245 (s), 1172 (s), 1097 (m), 1033 (s), 970 (m), 848 (m), 818 (s), 776 (m), 758 (m), 709 (w), 636 (w).

6.2.4.18 Preparation of (*R*,*E*)-4-benzyl-3-(8-((4-methoxybenzyl) oxy)oct-6-enoyl)oxazolidin-2-one (375)



374 **289** **375**

$C_{26}H_{31}NO_5$
Mol. Wt.: 437.53

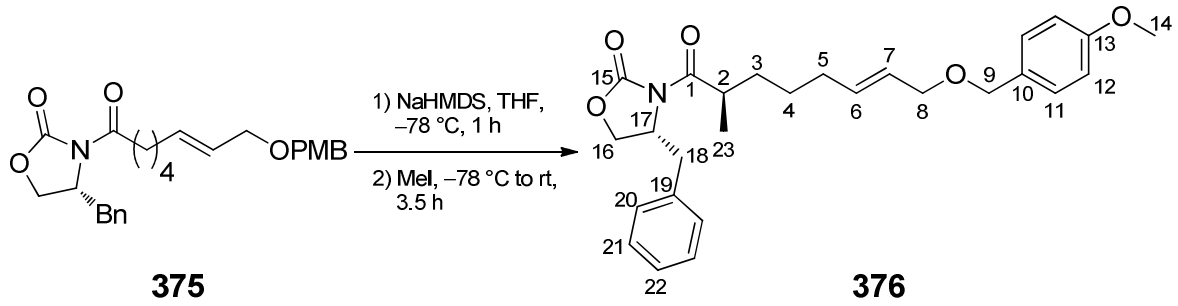
Compound **375** is prepared applying the general method of 6.2.2.35. The use of carboxylic acid **374** (173 mg, 0.62 mmol) and purification by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) yields the product as a colourless oil (133 mg, 0.30 mmol, 49%).

R_f 0.70 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):
1.43 – 1.56 (m, 2H, H-4), 1.65 – 1.78 (m, 2H, H-3), 2.06 – 2.17 (m, 2H, H-5), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H, H-18a), 2.90 (dt, *J* = 17.1, 7.4 Hz, 1H, H-2a), 2.98 (dt, *J* = 17.1, 7.4 Hz, 1H, H-2b), 3.30 (dd, *J* = 13.4, 3.3 Hz, 1H, H-18b), 3.80 (s, 3H, H-14), 3.95 (dd, *J* = 5.8, 0.8 Hz, 2H, H-8), 4.13 – 4.24 (m, 2H, H-16), 4.43 (s, 2H, H-9), 4.62 – 4.72 (m, 1H, H-17), 5.65 (m, 2H, H-6, H-7), 6.87 (d, *J* = 8.5 Hz, 2H, H-12), 7.17 – 7.37 (m, 5H, H-20, H-21, H-22), 7.27 (d, *J* = 8.5 Hz, 2H, H-11).

GC (t_R) 22.31 min (program 0)

6.2.4.19 Preparation of (*R*)-4-benzyl-3-((*R*,*E*)-8-((4-methoxybenzyl) oxy)-2-methyloct-6-enoyl)oxazolidin-2-one (376)



375 **376**

$C_{27}H_{33}NO_5$
Mol. Wt.: 451.55

Compound **376** is prepared applying the general method of 6.2.2.40. The use of unmethylated compound **375** (133 mg, 0.30 mmol) and purification of the crude product by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) yields the product as a colourless oil (71 mg, 0.16 mmol, 52%).

R_f 0.74 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$):

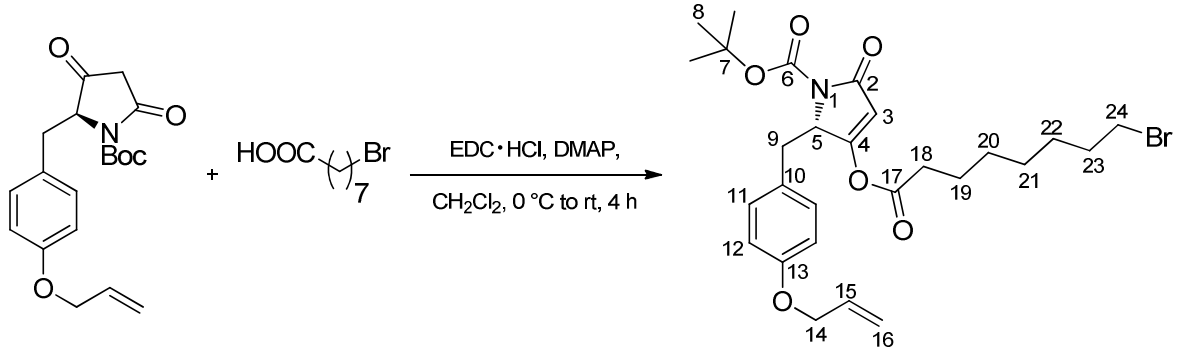
1.22 (d, *J* = 6.9 Hz, 3H, H-23), 1.34 – 1.51 (m, 2H, H-4), 1.68 – 1.84 (m, 2H, H-3), 2.02 – 2.13 (m, 2H, H-5), 2.77 (dd, *J* = 13.3, 9.5 Hz, 1H, H-18a), 3.25 (dd, *J* = 13.3, 3.3 Hz, 1H, H-18b), 3.64 – 3.78 (m, 1H, H-2), 3.79 (s, 3H, H-14), 3.94 (dd, *J* = 5.8, 0.8 Hz, 2H, H-8), 4.11 – 4.22 (m, 2H, H-16), 4.43 (s, 2H, H-9), 4.62 – 4.72 (m, 1H, H-17), 5.52 – 5.76 (m, 2H, H-6, H-7), 6.87 (d, *J* = 8.8 Hz, 2H, H-12), 7.17 – 7.38 (m, 5H, H-20, H-21, H-22), 7.26 (d, *J* = 8.8 Hz, 2H, H-11).

^{13}C-NMR (75 MHz, $CDCl_3$):

17.5 (CH_3, C-23), 26.8 (CH_2, C-4), 32.4 (CH_2, C-5), 33.1 (CH_2, C-3), 37.7 (CH_2, C-2), 38.1 (CH_2, C-18), 55.4 (CH_3, C-14), 55.5 (CH, C-17), 66.2 (CH_2, C-16), 70.7 (CH_2, C-8), 71.9 (CH_2, C-9), 113.9 (CH, C-12), 126.9 (CH, C-7), 127.5 (CH, C-22), 129.1 (CH, C-21), 2 × 129.6 (CH, C-11, C-20), 130.7 (C_{quart}, C-10), 134.3 (CH, C-6), 135.5 (C_{quart}, C-19), 153.2 (C_{quart}, C-15), 159.3 (C_{quart}, C-13), 177.3 (C_{quart}, C-1).

6.3 Syntheses of macrocidin A inspired macrocycles

6.3.1 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-4-(8-bromo-octanoyloxy)-5-(4-(allyloxy)benzyl)-1*H*-pyrrol-2(5*H*)-one (234)



116 **212** **234**

$C_{27}H_{36}BrNO_6$
Mol. Wt.: 550.48

According to a procedure of Yoda *et al.*,[78] to a solution of 8-bromooctanoic acid (**212**) (360 mg, 1.6 mmol, 1.1 eq.) in CH_2Cl_2 abs. (30 mL) at 0 °C are added EDC · HCl (310 mg, 1.6 mmol, 1.1 eq.) and DMAP (20 mg, 0.16 mmol, 0.11 eq.). The mixture is stirred for 5 min before bisprotected tetramic acid **116** (507 mg, 1.5 mmol, 1.0 eq.) is added and the mixture is left to stir for 4 h at room temperature. The mixture is diluted with EtOAc (100 mL) and the organic phases are washed with sat. NH_4Cl_{aq} (3 × 80 mL) and brine (80 mL). The organic phases are dried over Na_2SO_4, filtered and the solvent evaporated to give the crude product which is purified by column chromatography (25% → 50% EtOAc in ^{c}Hex → EtOAc). The product is obtained as a yellow oil (604 mg, 1.1 mmol, 75%).

R_f 0.15 (EtOAc)

^{1}H-NMR (300 MHz, $CDCl_3$):

1.30 – 1.52 (m, 6H, H-20/H-21/H-23), 1.60 (s, 9H, H-8), 1.61 – 1.73 (m, 2H, H-19), 1.80 – 1.92 (m, 2H, H-22), 2.47 (t, *J* = 7.4 Hz, 2H, H-18), 3.14 (dd, *J* = 14.1, 3.0 Hz, 1H, H-9a), 3.30 (dd, *J* = 14.1, 6.0 Hz, 1H, H-9b), 3.41 (t, *J* = 6.7 Hz, 2H, H-24), 4.48 (ddd, *J* = 5.3, 1.6, 1.2 Hz, 2H, H-14), 4.76 (ddd, *J* = 6.0, 3.0, 1.1 Hz, 1H, H-5), 5.27 (ddt, *J* = 10.5, 1.7, 1.2 Hz, 1H, H-16$_Z$), 5.39 (ddt, *J* = 17.3, 1.7, 1.6 Hz, 1H, H-16$_E$), 5.88 (d, *J* = 0.8 Hz, 1H, H-3), 6.03 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H, H-15), 6.78 (d, *J* = 7.8 Hz, 2H, H-12), 6.91 (*J* = 7.8 Hz, 2H, H-11).

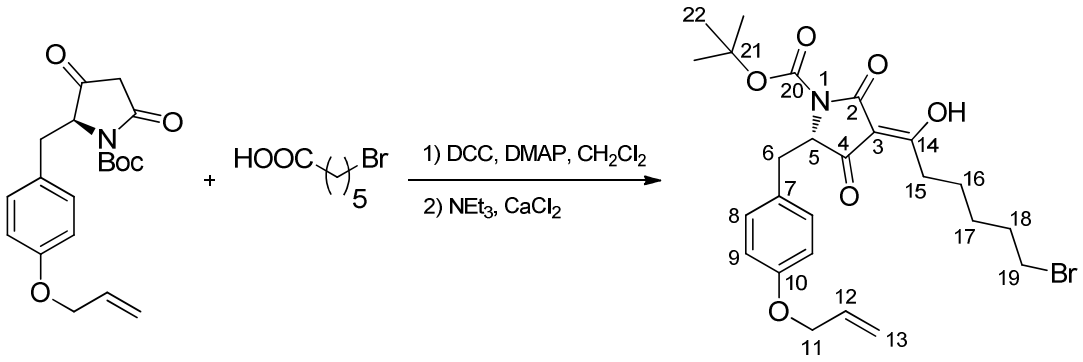
^{13}C-NMR (75 MHz, $CDCl_3$):

24.4 (CH_2, C-19), 28.0 (CH_2, C-23), 28.3 (CH_3, C-8), 28.5 (CH_2, C-21), 28.9 (CH_2, C-20), 32.8 (CH_2, C-22), 34.0 (CH_2, C-24), 34.4 (CH_2, C-18), 35.0 (CH_2, C-9), 60.7 (CH, C-5), 68.8 (CH_2, C-14), 83.3 (C_{quart}, C-7), 108.2 (CH, C-3), 114.7 (CH, C-12), 117.9 (CH_2, C-16), 126.1 (C_{quart}, C-10), 130.5 (CH, C-11), 133.3 (CH, C-15), 149.4 (C_{quart}, C-6), 157.8 (C_{quart}, C-13), 165.2 (C_{quart}, C-4), 168.3 (C_{quart}, C-2), 168.9 (C_{quart}, C-17).

6.3.2 General method for the 3-acylation of tetramic acids with carboxylic acids

According to procedures of Yoda *et al*.[79] and Barnickel,[152] to a 0.1M solution of tetramic acid (1.00 eq.) in CH_2Cl_2 abs. at 0 °C are added DMAP (0.33 eq.), a carboxylic acid (1.10 eq.) and DCC (1.2 eq.). The mixture is stirred for 1.5 h at room temperature before recooling the mixture to 0 °C and adding NEt_3 abs. (1.10 eq.) and dry $CaCl_2$ (1.50 eq.). The mixture is stirred for 14 h at room temperature before it is diluted with Et_2O (25 mL/mmol) and filtered over Celite®. The filtrate is washed with 2M HCl_{aq} (3 × 20 mL/mmol) and the aqueous phase is extracted with Et_2O (2 × 15 mL/mmol). The combined organic phases are dried over Na_2SO_4, filtered and the solvent evaporated. The crude product is covered with a layer of Et_2O and stored in the refrigerator for 14 h, in order for the left over urea to precipitate. The ethereal solution is carefully collected with a pipette and the solvent is evaporated to give the crude product.

6.3.3 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-3-(6-bromohexanoyl)-5-(4-(allyloxy)benzyl)-pyrrolidin-2,4-dione (236)



116 **210** **236**

$C_{25}H_{32}BrNO_6$
Mol. Wt.: 522.43

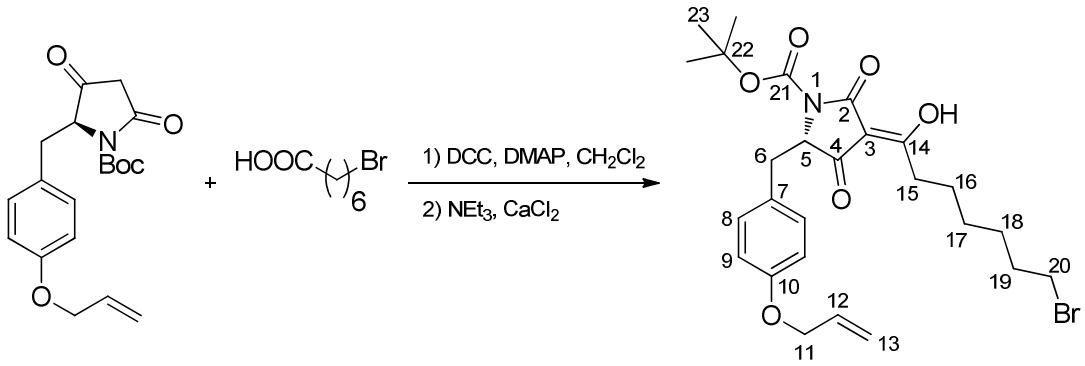
Compound **236** is prepared applying the general method of 6.3.2. The use of tetramic acid **116** (1.0 g, 2.9 mmol) and 6-bromohexanoic acid (**210**) (621 mg, 3.2 mmol) yields the product as a red oil (1.1 g, 2.0 mmol, 69%) without further purification.

R_f 0.79, 0.21 (EtOAc), tailing observed

^{1}H-NMR (300 MHz, MeOD): assignment differs from literature.[152]
1.30 – 1.55 (m, 4H, H-16, H-17), 1.62 (s, 9H, H-22), 1.73 – 1.91 (m, 2H, H-18), 2.65 – 2.78 (m, 2H, H-15), 3.16 (dd, *J* = 14.1, 2.6 Hz, 1H, H-6a), 3.36 (dd, *J* = 14.1, 5.4 Hz, 1H, H-6b), 3.40 (t, *J* = 6.8 Hz, 2H, H-19), 4.45 (ddd, *J* = 5.4, 1.6, 1.2 Hz, 2H, H-11), 4.55 (dd, *J* = 5.1, 2.6 Hz, 1H, H-5), 5.21 (ddt, *J* = 10.5, 1.7, 1.2 Hz, 1H, H-13$_Z$), 5.35 (ddt, *J* = 17.3, 1.7, 1.6 Hz, 1H, H-13$_E$), (ddt, *J* = 17.3, 10.5, 5.4 Hz, 1H, H-12), 6.76 (d, *J* = 8.8 Hz, 2H, H-9), 6.89 (d, *J* = 8.8 Hz, H-8).

^{13}C-NMR (75 MHz, MeOD): assignment differs from literature.[152]
25.7 (CH_2, C-16/C-17), 26.0 (CH_2, C-16/C-17), 28.4 (CH_3, C-22), 33.3 (CH_2, C-18), 34.1 (CH_2, C-19), 34.6 (CH_2, C-15), 35.8 (CH_2, C-6), 64.7 (CH, C-5), 69.6 (CH_2, C-11), 84.7 (C_{quart}, C-21), 105.3 (C_{quart}, C-3), 115.5 (CH, C-9), 117.5 (CH_2, C-13), 127.3 (C_{quart}, C-7), 131.8 (CH, C-8), 134.7 (CH, C-12), 150.6 (C_{quart}, C-20), 159.1 (C_{quart}, C-10), 177.1 (C_{quart}, C-2), 194.4 (C_{quart}, C-4), 194.8 (C_{quart}, C-14).

6.3.4 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-3-(7-bromo-heptanoyl)-5-(4-(allyloxy)benzyl)-pyrrolidin-2,4-dione (237)



116 **211** **237**

$C_{26}H_{34}BrNO_6$
Mol. Wt.: 536.46

Compound **237** is prepared applying the general method of 6.3.2. The use of tetramic acid **116** (500 mg, 1.5 mmol) and 7-bromoheptanoic acid (**211**) (333 mg, 1.6 mmol) and purification of the crude product by column chromatography (25% → 50% → 75% EtOAc in ^{c}Hex → 66% EtOH in ^{c}Hex → EtOH) gives the product as a complex with metals from the silica gel. After solvent evaporation, the product is redissolved in EtOAc (10 mL) and washed with 2M $EDTA_{aq}$ (2 × 10 mL), before drying over Na_2SO_4 and solvent evaporation, which yields the pure product as a red oil (370 mg, 0.69 mmol, 48%).

R_f 0.85, 0.25 (EtOAc), tailing observed

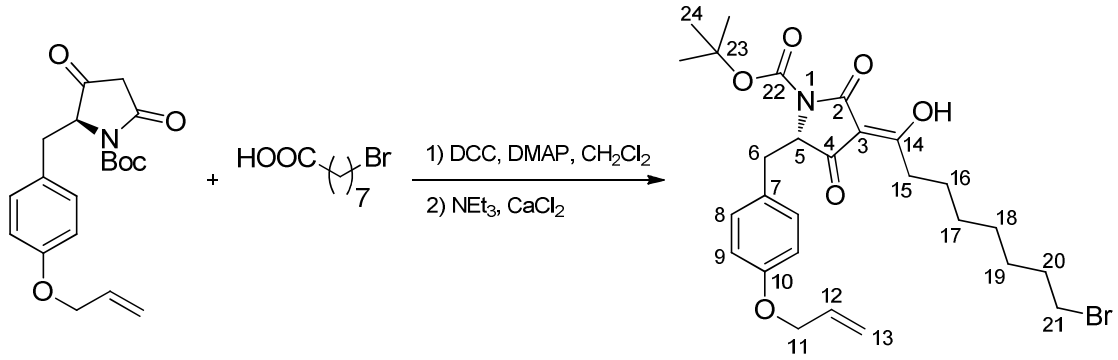
^{1}H-NMR (300 MHz, MeOD):

1.20 – 1.53 (m, 6H, H-16, H-17, H-18), 1.62 (s, 9H, H-23), 1.74 – 1.91 (m, 2H, H-19), 2.62 – 2.76 (m, 2H, H-15), 3.10 – 3.20 (m, 1H, H-6a), 3.25 – 3.36 (m, 1H, H-6b), 3.43 (t, *J* = 6.4 Hz, 2H, H-20), 4.38 – 4.47 (m, 2H, H-11), 4.46 – 4.53 (m, 1H, H-5), 5.17 – 5.26 (m, 1H, H-13a), 5.30 – 5.42 (m, 1H, H-13b), 5.93 – 6.11 (m, 1H, H-12), 6.70 (d, *J* = 8.0 Hz, 2H, H-9), 6.91 (d, *J* = 8.0 Hz, 2H, H-8).

DIP-MS (EI):

391 (28), 287 (11) [M^+−$C_{10}H_{11}O$, −COO^{t}Bu], 187 (9), 147 (100) [$C_{10}H_{11}O^+$], 119 (20), 107 (50), 91 (24), 69 (15), 57 (79), 44 (64), 41 (100), 39 (92).

6.3.5 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-3-(8-bromo-octanoyl)-5-(4-(allyloxy)benzyl)-pyrrolidin-2,4-dione (238)



116 **212** **238**

$C_{27}H_{36}BrNO_6$
Mol. Wt.: 550.48

Compound **238** is prepared applying the general method of 6.3.2. The use of tetramic acid **116** (500 mg, 1.5 mmol) and 8-bromoctanoic acid (**212**) (355 mg, 1.6 mmol) and purification of the crude product by column chromatography (25% → 50% → 75% EtOAc in ^{c}Hex → 66% EtOH in ^{c}Hex → EtOH) gives the product as a complex with metals from the silica gel. After solvent evaporation, the product is redissolved in EtOAc (10 mL) and washed with 2M $EDTA_{aq}$ (2 × 10 mL), before drying over Na_2SO_4 and solvent evaporation, which yields the pure product as a red oil (700 mg, 1.3 mmol, 88%).

R_f 0.83, 0.27 (EtOAc), tailing observed

^{1}H-NMR (300 MHz, MeOD): assignment differs from literature.[152]

1.21 – 1.54 (m, 8H, H-16, H-17, H-18, H-19), 1.62 (s, 9H, H-24), 1.76 – 1.90 (m, 2H, H-20), 2.73 (t, *J* = 7.4 Hz, 2H, H-15), 3.17 (dd, *J* = 14.1, 2.6 Hz, 1H, H-6a), 3.37 (dd, *J* = 14.1, 5.4 Hz, 1H, H-6b), 3.43 (t, *J* = 6.8 Hz, 2H, H-21), 4.46 (ddd, *J* = 5.1, 1.6, 1.4 Hz, 2H, H-11), 4.57 (dd, *J* = 5.4, 2.6 Hz, 1H, H-5), 5.22 (ddt, *J* = 10.5, 1.7, 1.4 Hz, 1H, H-13$_Z$), 5.35 (ddt, *J* = 17.3, 1.7, 1.6 Hz, 1H, H-13$_E$), 6.01 (ddd, *J* = 17.3, 10.5, 5.1 Hz, 1H, H-12), 6.76 (d, *J* = 8.7 Hz, 2H, H-9), 6.90 (d, *J* = 8.7 Hz, 2H, H-8).

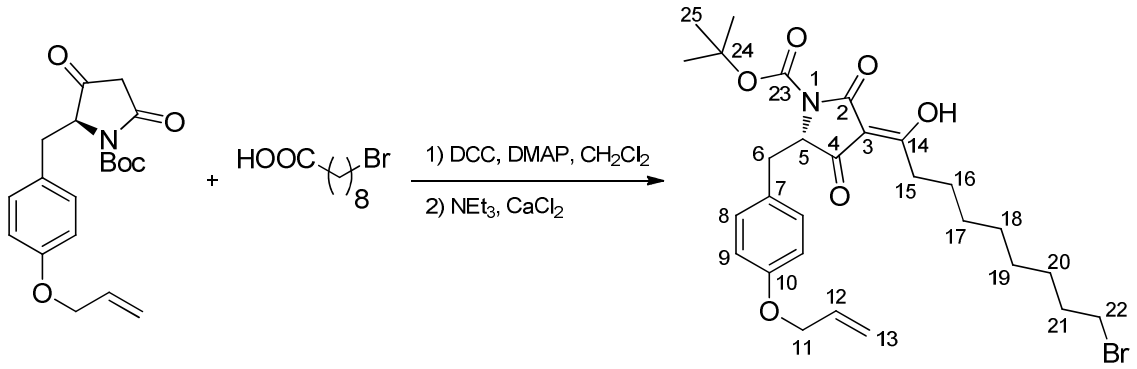
^{13}C-NMR (75 MHz, MeOD): assignment differs from literature.[152]

26.6 (CH_2, C-16/C-17/C-18/C-19), 28.4 (CH_3, C-24), 28.9 (CH_2, C-16/C-17/C-18/C-19), 29.3 (CH_2, C-16/C-17/C-18/C-19), 29.9 (CH_2, C-16/C-17/C-18/C-19), 33.9 (CH_2, C-20), 34.4 (CH_2, C-21), 34.8 (CH_2, C-15), 35.8 (CH_2, C-6), 64.9 (CH, C-5), 69.7 (CH_2, C-11), 84.8 (C_{quart}, C-23), 105.2 (C_{quart}, C-3), 115.6 (CH, C-9), 117.5 (CH_2, C-13), 127.4 (C_{quart}, C-7), 131.8 (CH, C-8), 134.8 (CH, C-12), 150.7 (C_{quart}, C-22), 159.2 (C_{quart}, C-10), 195.0 (C_{quart}, C-4/C-14), 195.1 (C_{quart}, C-4/C-14).

DIP-MS (EI):

550 (2) [M^+], 478 (3), 451 (21), 207 (4) [$C_8H_{15}BrO^+$−H, ^{81}Br], 205 (4) [$C_8H_{15}BrO^+$−H, ^{79}Br], 147 (100) [$C_{10}H_{11}O^+$], 119 (9), 107 (25), 91 (11), 57 (45), 41 (66).

6.3.6 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-3-(9-bromononanoyl)-5-(4-(allyloxy)benzyl)-pyrrolidin-2,4-dione (239)



116 **213** **239**

$C_{28}H_{38}BrNO_6$
Mol. Wt.: 564.51

Compound **239** is prepared applying the general method of 6.3.2. The use of tetramic acid **116** (1.1 g, 3.1 mmol) and 9-bromononanoic acid (**213**) (800 mg, 3.4 mmol) and purification of the crude product by column chromatography (50% EtOAc in ^{c}Hex → EtOAc → 50% EtOH in ^{c}Hex) gives the product as a complex with metals from the silica gel. After solvent evaporation, the product is redissolved in EtOAc (10 mL) and washed with 2M $EDTA_{aq}$ (2 × 10 mL), before drying over Na_2SO_4 and solvent evaporation, which yields the pure product as a red oil (721 mg, 1.3 mmol, 42%).

R_f 0.88, 0.27 (EtOAc), tailing observed

^{1}H-NMR (300 MHz, MeOD):

1.17 – 1.54 (m, 10H, H-16, H-17, H-18, H-19, H-20), 1.62 (s, 9H, H-25), 1.75 – 1.90 (m, 2H, H-21), 2.65 – 2.82 (m, 2H, H-15), 3.10 – 3.24 (m, 1H, H-6a), 3.32 - 3.39 (m, 1H, H-6b), 3.42 (t, *J* = 6.6 Hz, 2H, H-22), 4.38 – 4.50 (m, 2H, H-11), 4.52 – 4.64 (m, 1H, H-5), 5.16 – 5.26 (m, 1H, H-13a), 5.29 – 5.42 (m, 1H, H-13b), 5.92 – 6.09 (m, 1H, H-12), 6.75 (d, *J* = 7.8 Hz, H-9), 6.90 (d, *J* = 7.8 Hz, H-8).

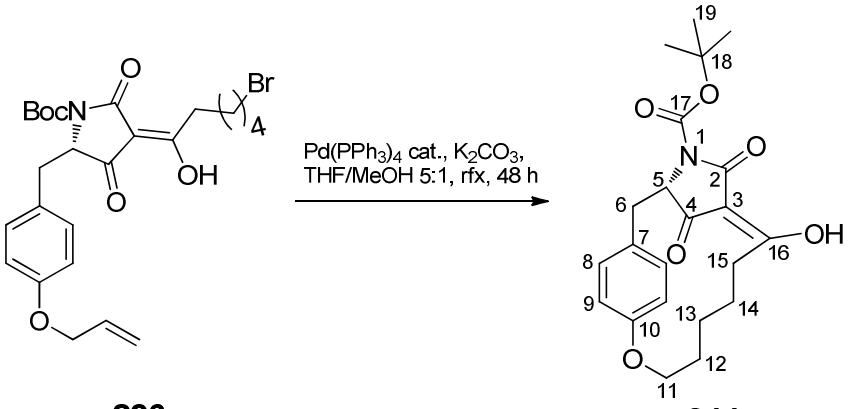
^{13}C-NMR (75 MHz, MeOD):

26.0 (CH_2, C-16/C-17/C-18/C-19/C-20), 28.6 (CH_3, C-25), 29.1 (CH_2, C-16/C-17/C-18/C-19/C-20), 29.6 (CH_2, C-16/C-17/C-18/C-19/C-20), (CH_2, C-16/C-17/C-18/C-19/C-20), 30.4 (CH_2, C-16/C-17/C-18/C-19/C-20), 33.9 (CH_2, C-21), 34.5 (CH_2, C-22), 34.9 (CH_2, C-15), 36.1 (CH_2, C-6), 64.2 (CH, C-5), 69.6 (CH_2, C-11), 83.8 (C_{quart}, C-24), 104.4 (C_{quart}, C-3), 115.2 (CH, C-9), 117.4 (CH_2, C-13), 128.3 (C_{quart}, C-7), 131.8 (CH, C-8), 134.8 (CH, C-12), 151.5 (C_{quart}, C-23), 159.7 (C_{quart}, C-10), 177.4 (C_{quart}, C-2), 197.5 (C_{quart}, C-4/C-14), 197.7 (C_{quart}, C-4/C-14).

DIP-MS (EI):

465 (7), 463 (7), 410 (10), 363 (4), 361 (3), 285 (4), 263 (5), 187 (6), 176 (6), 147 (100) [$C_{10}H_{11}O^+$], 107 (27), 91 (10), 56 (42), 41 (98).

6.3.7 Preparation of *N*-(*tert*-butoxycarbonyl)-(3*S*,6*Z*)-7-hydroxy-13-oxa-4-azatricyclo[12.2.2.1^{3,6}]nonadeca-1(16),6,14,17-tetraene-5,19-dione (244)[98,152]



236 **244**

$C_{22}H_{27}NO_6$
Mol. Wt.: 401.45

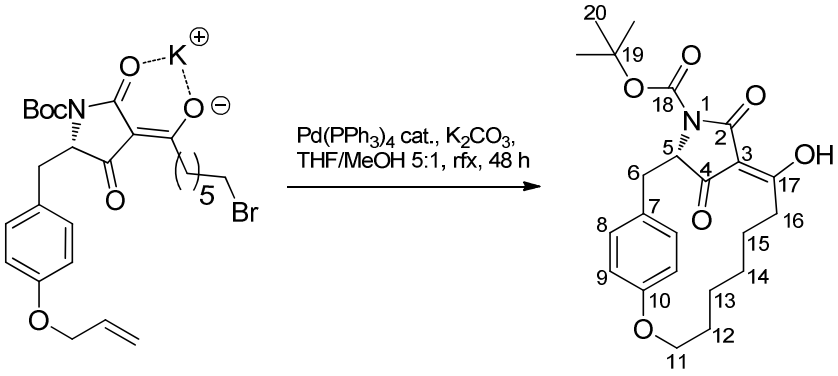
Macrocycle **244** is prepared applying a procedure of Barnickel.[152]

R_f 0.47 (33% EtOH in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, MeOD): assignment differs from literature.[152]
0.68 – 1.01 (m, 2H, H-13), 1.27 – 1.97 (m, 6H, H-12, H14, H15), 1.61, 1.63* (s, 9H, H-19), 3.08 (dd, *J* = 13.9, 3.3 Hz, 1H, H-6), 3.39 (dd, *J* = 13.9, 3.4 Hz, 1H, H-6b), 4.12 (dt, *J* = 12.9, 4.7 Hz, 1H, H-11a), 4.25 (dt, *J* = 12.9, 5.5 Hz, 1H, H-11b), 4.52 (br s, 1H, H-5), 4.61* (dd, *J* = 3.4, 3.3 Hz, 1H, H-5), 6.74 – 6.97 (m, 4H, H-8, H-9).

^{13}C-NMR (75 MHz, MeOD): assignment differs from literature.[152]
26.2 (CH_2, C-12), 26.5 (CH_2, C-13), 28.4 (CH_3, C-19), 31.7 (CH_2, C-14/C15), 33.3 (CH_2, C-14/C15), 36.6 (CH_2, C-6), 63.9 (CH, C-5), 70.8 (CH_2, C-11), 84.6 (C_{quart}, C-18), 107.3 (C_{quart}, C-3), 119.0 (CH, C-9a), 121.1 (CH, C-9b), 128.2 (C_{quart}, C-7), 131.2 (CH, C-8a), 132.6 (CH, C-8b), 150.9 (C_{quart}, C-17), 160.7 (C_{quart}, C-10), 172.9 (C_{quart}, C-2), 194.8 (C_{quart}, C-16), 198.1 (C_{quart}, C-4).

6.3.8 Preparation of *N*-(*tert*-butoxycarbonyl)-(3*S*,6*Z*)-7-hydroxy-14-oxa-4-azatricyclo[13.2.2.1^{3,6}]icosa-1(17),6,15,18-tetraene-5,20-dione (245)



241 **245**
$C_{23}H_{29}NO_6$
Mol. Wt.: 415.48

According to a procedure of Barnickel *et al*.,[98,152] to a solution of potassium salt **241** (150 mg, 0.26 mmol, 1.0 eq.) in a mixture of THF abs./MeOH abs. (5:1) (6 mL) is added $Pd(PPh_3)_4$ (6 mg, 2 mol%) and after 5 min of stirring, K_2CO_3 (108 mg, 0.78 mmol, 3.0 eq.) is added. The mixture is heated to reflux for 2 d before the solvent is evaporated. The residue is dissolved in 0.5M $NaOH_{aq}$ (25 mL) and washed

with Et_2O (2 × 30 mL). The pH of the aqueous phase is adjusted to pH 1 with conc. HCl_{aq} and the phase is extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases are dried over Na_2SO_4, filtered and the solvent evaporated. The product is obtained as an orange oil (74 mg, 0.18 mmol, 68%).

R_f 0.45 (33% EtOH in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, MeOD):

0.72 – 1.05 (m, 2H, H-13), 1.17 – 1.85 (m, 8H, H-12, H14, H15, H16), 1.62, 1.63* (s, 9H, H-20), 3.10 (dd, *J* = 13.9, 3.2 Hz, 1H, H-6), 3.42 (dd, *J* = 13.9, 3.7 Hz, 1H, H-6b), 4.11 – 4.25 (m, 2H, H-11), 4.55 (br s, 1H, H-5), 4.61* (dd, *J* = 3.7, 3.2 Hz, 1H, H-5), 6.54 – 7.14 (m, 4H, H-8, H-9).

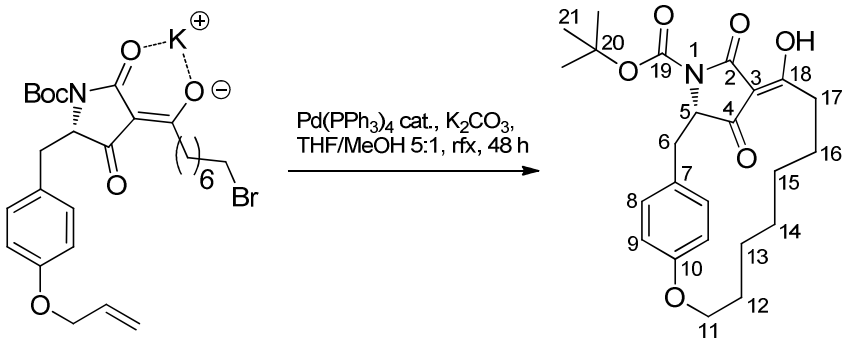
^{13}C-NMR (75 MHz, MeOD):

25.8 (CH_2, C-12), 27.0 (CH_2, C-13), 28.4 (CH_3, C-20), 29.7 (CH_2, C-14/C15), 32.0 (CH_2, C-14/C15), 35.8 (CH_2, C-16), 36.3 (CH_2, C-6), 63.7 (CH, C-5), 69.2 (CH_2, C-11), 84.6 (C_{quart}, C-19), 106.8 (C_{quart}, C-3), 117.6 (CH, C-9a), 117.9 (CH, C-9b), 127.1 (C_{quart}, C-7), 131.4 (CH, C-8a), 132.4 (CH, C-8b), 150.6 (C_{quart}, C-18), 160.5 (C_{quart}, C-10), 171.1 (C_{quart}, C-2), 194.4 (C_{quart}, C-17), 198.5 (C_{quart}, C-4).

DIP-MS (EI):

415 (36) [M^+], 342 (7) [M^+–O^{t}Bu], 315 (69), 209 (22), 175 (10), 141 (6), 125 (14), 107 (100), 91 (16), 77 (8), 57 (77) [^{t}Bu$^+$], 41 (30).

6.3.9 Preparation of *N*-(*tert*-butoxycarbonyl)-(3*S*,6*Z*)-7-hydroxy-15-oxa-4-azatricyclo[14.2.2.1^{3,6}]henicosa-1(18),6,16,19-tetraene-5,21-dione (246)[98,152]



242 **246**

$C_{24}H_{31}NO_6$
Mol. Wt.: 429.51

Macrocycle **246** is prepared applying a procedure of Barnickel.[152]

R_f 0.10 (86% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, MeOD): assignment differs from literature.[152]
0.76 – 1.00 (m, 2H, H-13), 1.12 – 1.81 (m, 10H, H-12, H14, H15, H16, H-17), 1.61, 1.64* (s, 9H, H-21), 3.11 (dd, *J* = 14.0, 2.7 Hz, 1H, H-6), 3.43 (dd, *J* = 14.0, 3.3 Hz, 1H, H-6b), 4.14 – 4.25 (m, 2H, H-11), 4.54 (br s, 1H, H-5), 4.65* (dd, *J* = 3.3, 2.7 Hz, 1H, H-5), 6.57 – 7.07 (m, 4H, H-8, H-9).

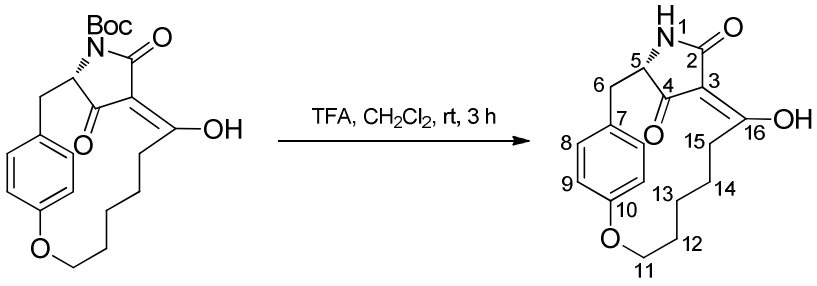
^{13}C-NMR (75 MHz, MeOD): assignment differs from literature.[152]
24.9 (CH_2, C-12), 26.6 (CH_2, C-13/C14/C15/C16), 27.2 (CH_2, C-13/C14/C15/C16), 28.3 (CH_2, C-13/C14/C15/C16), 28.4 (CH_3, C-21), 28.7 (CH_2, C-13/C14/C15/C16), 34.7 (CH_2, C-17), 35.8 (CH_2, C-6), 64.0 (CH, C-5), 68.0 (CH_2, C-11), 84.7 (C_{quart}, C-20), 106.4 (C_{quart}, C-3), 116.1 (CH, C-9a), 117.1 (CH, C-9b), 126.9 (C_{quart}, C-7), 131.2 (CH, C-8a), 131.8 (CH, C-8b), 150.9 (C_{quart}, C-19), 158.2 (C_{quart}, C-10), 168.4 (C_{quart}, C-2), 195.8 (C_{quart}, C-18), 196.9 (C_{quart}, C-4).

DIP-MS (EI):
429 (16) [M^+], 355 (10), 329 (41), 277 (100), 231 (9), 224 (12), 199 (17), 183 (16), 136 (13), 107 (39), 57 (38) [^{t}Bu$^+$], 43 (33).

6.3.10 General method for the Boc-deprotection of tetramic acids and derivatives

According to procedures of Hosseini *et al*.[53] and Barnickel,[152] to a 1M solution of a Boc-protected tetramic acid (1.0 eq.) in CH_2Cl_2 is added TFA (0.4 mL/mmol) dropwise and the mixture is stirred for 3 h at room temperature. The solvent is evaporated and toluene (6 × 10 mL/mmol) is added to remove residual TFA as an azeotrope with toluene. Et_2O (3 × 20 mL/mmol) is added and evaporated to remove residual toluene to give the crude product.

6.3.11 Preparation of (3*S*,6*Z*)-7-hydroxy-13-oxa-4-azatricyclo [12.2.2.1^{3,6}]nonadeca-1(16),6,14,17-tetraene-5,19-dione (6)



244 **6**

$C_{17}H_{19}NO_4$
Mol. Wt.: 301.34

Compound **6** is prepared applying the general method of 6.3.10. The use of Boc-protected macrocycle **244** (82 mg, 0.20 mmol) and purification by preparative HPLC (1:1 MeOH/H_2O + 1% HCOOH; after 15 min in 10 min to 100% MeOH) yields the product as an orange oil (22 mg, 0.07 mmol, 36%).

R_f 0.42 (33% EtOH in ^{c}Hex)

^{1}H-NMR (300 MHz, MeOD):

0.64 – 0.97 (m, 2H, H-13), 1.33 – 1.47 (m, 2H, H-14), 1.47 – 1.60 (m, 2H, H-12), 2.07 – 2.32 (m, 2H, H-15), 2.95 (dd, *J* = 13.7, 3.3 Hz, 1H, H-6a), 3.09 (dd, *J* = 13.7, 3.6 Hz, 1H, H-6b), 4.16 (dt, *J* = 12.5, 4.8 Hz, 1H, H-11a), 4.18 (dd, *J* = 3.6, 3.3 Hz, 1H, H-5), 4.26 (dt, *J* = 12.5, 5.0 Hz, 1H, H-11b), 6.79 (dd, *J* = 8.4, 2.2 Hz, 1H, H-9a), 6.87 – 6.96 (m, 2H, H-8a, H-9b), 7.11 (dd, *J* = 8.4, 2.2 Hz, 1H, H-8b).

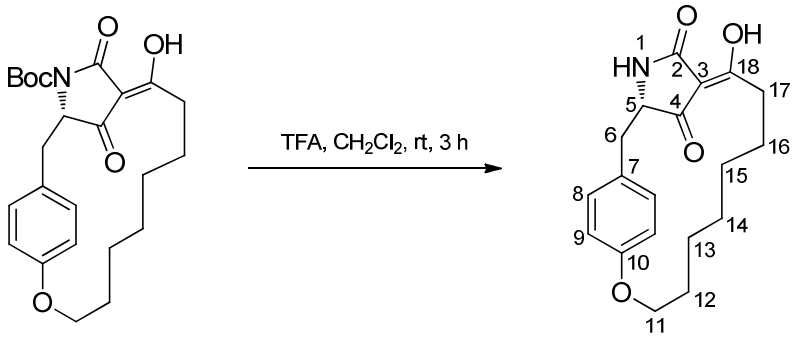
^{13}C-NMR (75 MHz, MeOD): quaternary carbons very faint

26.5 (2 × CH_2, C-13/C-14), 31.8 (CH_2, C-12), 32.3 (CH_2, C15), 37.7 (CH_2, C-6), 61.4 (CH, C-5), 70.9 (CH_2, C-11), 106.8 (C_{quart}, C-3), 118.5 (CH, C-9a), 120.4 (CH, C-9b), 128.5 (C_{quart}, C-7), 131.8 (CH, C-8a), 132.7 (CH, C-8b), 160.3 (C_{quart}, C-10), 172.2 (C_{quart}, C-2), 192.3 (C_{quart}, C-16), 201.0 (C_{quart}, C-4).

DIP-MS (EI):

301 (45) [M^+], 231 (36), 195 (63) [$M^+ - C_7H_6O$], 147 (28), 125 (23), 107 (100), 69 (12), 44 (27).

6.3.12 Preparation of (3*S*,6*Z*)-7-hydroxy-15-oxa-4-azatricyclo [14.2.2.1^{3,6}]henicosa-1(18),6,16,19-tetraene-5,21-dione (8)



246 **8**

$C_{19}H_{23}NO_4$

Mol. Wt.: 329.39

Compound **8** is prepared applying the general method of 6.3.10. The use of Boc-protected macrocycle **246** (39 mg, 0.09 mmol) yields the product as an orange oil (20 mg, 0.06 mmol, 67%) without further purification.

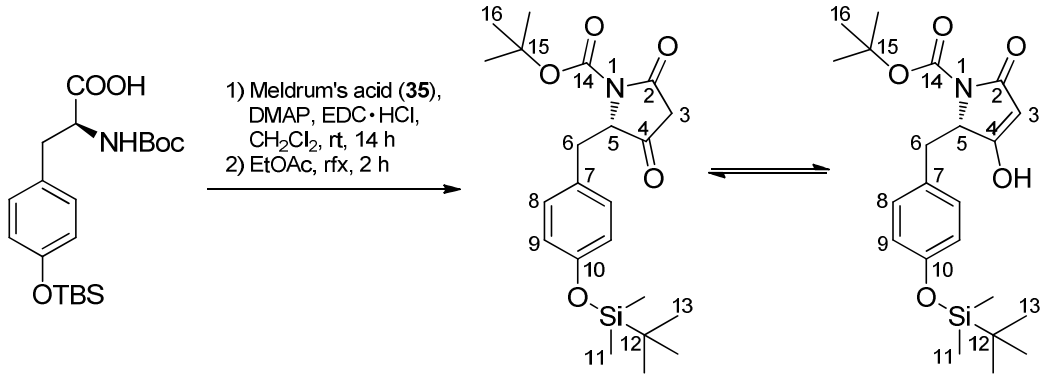
R_f 0.40 (33% EtOH in ^{c}Hex), tailing observed

^{1}H-NMR (300 MHz, MeOD):

0.65 – 1.68 (m, 10H, H12, H-13, H14, H15, H16), 2.23 – 2.36 (m, 2H, H-17), 2.96 (dd, *J* = 14.1, 3.6 Hz, 1H, H-6a), 3.09 (dd, *J* = 14.1, 3.6 Hz, 1H, H-6b), 4.05 – 4.28 (m, 2H, H-11), 4.16 – 4.23 (m, 1H, H-5), 6.61 – 6.69 (m, 1H, H-9a), 6.72 – 6.82 (m, 1H, H-9b), 6.91 – 7.01 (m, 1H, H-8a), 7.06 – 7.16 (m, 1H, H-8b).

6.4 Synthesis of precursors for the synthesis of torrubiellone D (15)

6.4.1 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-5-((4-*tert*-butyldimethylsilyl)oxy)benzyl)-pyrrolidin-2,4-dione (383)



382 **383**

$C_{22}H_{33}NO_5Si$
Mol. Wt.: 419.59

Compound **383** is prepared applying the general method of 6.2.1.1. The use of bisprotected L-tyrosine derived amino acid **382** (prepared from L-tyrosine over three steps according to literature procedures of Barnickel[152] and Marimganti *et al*.[226]) (5.5 g, 13.9 mmol) yields the product as a white foam (5.7 g, 13.6 mmol, 89%) without further purification.

R_f 0.30 (50% EtOAc in ^{c}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$): only keto form observed

0.16 (s, 6H, H-11), 0.96 (s, 9H, H-13), 1.62 (s, 9H, H-16), 2.22 (dd, *J* = 22.4, 1.7 Hz, 1H, H-3a), 2.84 (d, *J* = 22.4 Hz, 1H, H-3b), 3.13 (dd, *J* = 14.3, 3.0 Hz, 1H, H-6a), 3.33 (dd, *J* = 14.3, 4.9 Hz, 1H, H-6b), 4.60 (ddd, *J* = 4.9, 3.0, 1.6 Hz, 1H, H-5), 6.75 (d, *J* = 8.5 Hz, 2H, H-9), 6.88 (d, *J* = 8.5 Hz, 2H, H-8).

^{13}C-NMR (75 MHz, $CDCl_3$): only keto form observed (C-14 not observed)

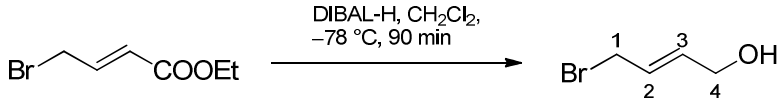
−4.5 (CH_3, C-11), 18.2 (C_{quart}, C-12), 25.6 (CH_3, C-13), 28.2 (CH_3, C-16), 35.7 (CH_2, C-6), 43.4 (CH_2, C-3), 68.3 (CH, C-5), 84.2 (C_{quart}, C-15), 120.3 (CH, C-9), 125.4 (C_{quart}, C-7), 130.4 (CH, C-8), 154.8 (C_{quart}, C-10), 166.5 (C_{quart}, C-2), 203.6 (C_{quart}, C-4).

DIP-MS (EI):
419 (5) [M^+], 346 (3) [M^+-O^tBu], 319 (4), 262 (9), 221 (100) [$M^+-C_9H_{12}NO_4$], 73 (25) [O^tBu^+], 58 (12), 45 (15).

mp 85 °C

6.4.2 Synthesis of different C4-fragments

6.4.2.1 Preparation of (*E*)-4-bromobut-2-en-1-ol (393)



386 **393**

C_4H_7BrO
Mol. Wt.: 151.00

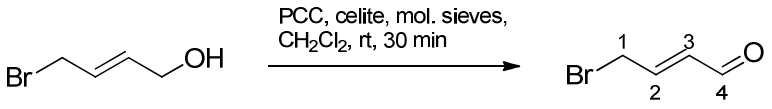
Compound **393** is prepared applying the general method of 6.2.4.5. The use of ethyl 4-bromocrotonate (**386**) (525 mg, 2.7 mmol) and purification of the crude product by column chromatography (10% → 17% EtOAc in ^{c}Hex) yields the product as a colourless oil (300 mg, 2.0 mmol, 73%). The product is stored in the refrigerator under argon atmosphere to prevent decomposition. Solvent evaporation is carried out very carefully due to the low boiling point of the product.

R_f 0.27 (25% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **393** are in good agreement with literature.[290]

GC-MS (EI):
151 (3) [M^+], 71 (100) [M^+-Br], 54 (12) [$M^+-Br, -OH$].

6.4.2.2 Preparation of (*E*)-4-bromobut-2-enal (387)



393 **387**

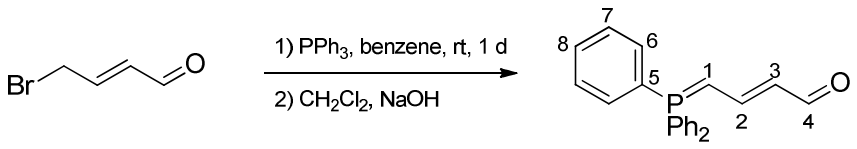
C_4H_5BrO
Mol. Wt.: 148.99

According to procedures of Herscovici *et al*.[195] and Corey *et al*.,[194] to a solution of allylic alcohol **393** (100 mg, 0.66 mmol, 1.0 eq.) in CH_2Cl_2 abs. (7 mL) are added powdered 3Å molecular sieves (220 mg), Celite® (2 spatulas) and PCC (186 mg, 0.86 mmol, 1.3 eq.) and the mixture is stirred for 30 min at room temperature. The reaction mixture is filtered over Celite® and the remaining solid is washed thoroughly with CH_2Cl_2. The solvent of the filtrate is evaporated in the presence of flash silica gel and the dark solid is loaded onto a short column of silica gel and the crude product is eluted with EtOAc/^{c}Hex (1:3). After purification by column chromatography (10% EtOAc in cHex) the product is obtained as a colourless oil. The determination of the yield is difficult due to the fast decomposition of the product during exposure to air. The product is stored in the refrigerator under argon atmosphere to prevent decomposition.

R_f 0.51 (25% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **387** are in good agreement with literature.[290]

6.4.2.3 Preparation of (*E*)-4-(triphenylphosphoranylidene)but-2-enal (379) from (*E*)-4-bromobut-2-enal (387)[223,224]



387 **379**

$C_{22}H_{19}OP$
Mol. Wt.: 330.36

According to procedures of Berenguer *et al*.[223] and Ernest *et al*.,[224] to a solution of aldehyde **387** (~60 mg, 0.40 mmol, 1.0 eq.) in benzene (7 mL) is added PPh_3 (106 mg, 0.40 mmol, 1.0 eq.) and the mixture is stirred for 1 d at room temperature. The reaction mixture is filtered, the remaining solid washed thoroughly with benzene and MeCN and the white phosphonium bromide is dried *in vacuo*. The solid is redissolved in CH_2Cl_2 and washed with 1M $NaOH_{aq}$. The now deep red organic phases are collected and dried over $MgSO_4$ and filtered. Solvent evaporation yields the product as a red solid (100 mg, 0.30 mmol, ~75% over two steps).

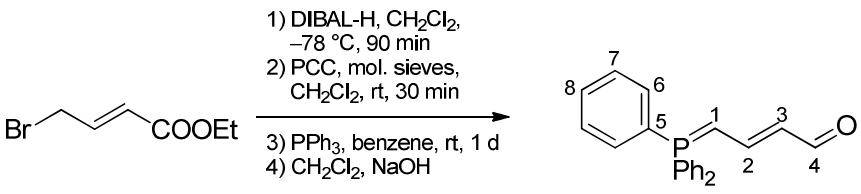
^{1}H-NMR (300 MHz, $CDCl_3$):
4.21 (dd, *J* = 22.5, 13.5 Hz, 1H, H-1), 5.72 (dd, *J* = 13.5, 9.3 Hz, 1H, H-2), 6.73 – 6.91 (m, 1H, H-3), 7.35 – 7.97 (m, 15H, H-6, H-7, H-8), 8.66 (d, *J* = 9.1 Hz, 1H, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$): partial signal doubling observed
57.1 (CH, C-1), 109.5 (CH, C-2), 128.5, 128.7, 129.5, 129.6, 132.1, 132.1, 133.3 (br) (C_{quart}, CH, C-5, C-6, C-7, C-8), 159.7 (CH, C-3), 186.6 (CH, C-4).

^{31}P-NMR (121 MHz, $CDCl_3$):
17.8 (PPh_3). [lit.: 18.1][228]

DIP-MS (EI):
330 (8) [M^+], 301 (4) [M+−CHO], 277 (100), 262 (72) [$P(C_6H_5)_3^+$], 201 (14), 199 (17), 183 (50), 152 (12), 108 (12), 77 (12) [$C_6H_5^+$], 52 (7)

6.4.2.4 Direct preparation of (*E*)-4-(triphenylphosphoranylidene) but-2-enal (379) from ethyl 4-bromocrotonate (386) without intermediary purification



386 **379**

$C_{22}H_{19}OP$
Mol. Wt.: 330.36

1) DIBAL-H reduction:

According to procedures of Barnickel *et al*.[152] and Fox *et al*.,[216] a solution of ethyl 4-bromocrotonate (**386**) (750 mg, 3.9 mmol, 1.0 eq.) in CH_2Cl_2 abs. (60 mL) is cooled to −78 °C in an acetone/dry ice bath and DIBAL-H (1M in hexanes) (7.8 mL, 7.8 mmol, 2.0 eq.) is added dropwise using a syringe pump (0.5 mL/min). The mixture is stirred at −78 °C for 90 min. The reaction is terminated by the addition of H_2O (15 mL) and the pH of the mixture is adjusted to pH 3 with 2M HCl_{aq}. The phases are separated and the aqueous phase is extracted with CH_2Cl_2 (3 × 40 mL) before the combined organic phases are washed with H_2O (2 × 70 mL), dried over $MgSO_4$ and filtered. The solvent is evaporated carefully (low boiling point of the product) to give the crude product.

2) PCC oxidation:

According to procedures of Herscovici *et al*.[195] and Corey *et al*.,[194] to a solution of crude allylic alcohol **393** from **1**) in CH_2Cl_2 abs. (50 mL) are added powdered 3Å molecular sieves (600 mg), Celite® (2 spatulas) and PCC (1.09 g, 5.1 mmol, 1.3 eq.) and the mixture is stirred for 30 min at room temperature. The reaction mixture is filtered over Celite® and the remaining solid is washed thoroughly with CH_2Cl_2. The solvent is evaporated in the presence of flash silica gel and the dark solid is loaded onto a short column of silica gel and the crude product is eluted with EtOAc/^{c}Hex (1:3). Solvent evaporation gives the crude aldehyde.

3) Phosphonium bromide generation:

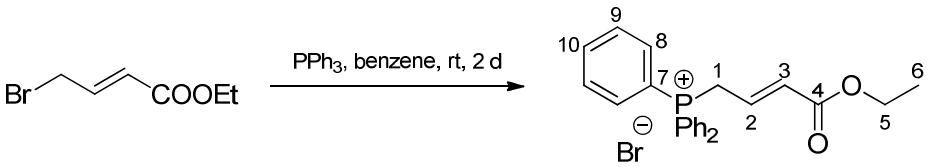
According to procedures of Berenguer *et al*.[223] and Ernest *et al*.,[224] to a solution of crude aldehyde **387** from **2**) in benzene (10 mL) is added PPh_3 (1.02 g, 3.9 mmol, 1.0 eq.) and the mixture is stirred for 1 d at room temperature. The reaction mixture is filtered, the remaining solid washed thoroughly with benzene and MeCN and the crude white phosphonium bromide is dried *in vacuo*.

4) Ylide preparation:

According to procedures of Berenguer *et al*.[223] and Ernest *et al*.,[224] the crude phosphonium bromide **388** from **3**) is dissolved in CH_2Cl_2 and washed with 1M $NaOH_{aq}$ (10 mL). The now deep red organic phases are collected and dried over $MgSO_4$ and filtered. Solvent evaporation yields the product as a red solid (385 mg, 1.2 mmol, 30% over four steps).

Analytical data shown in chapter 6.4.2.3.

6.4.2.5 Preparation of (*E*)-(4-ethoxy-4-oxobut-2-en-1-yl)triphenyl-phosphonium bromide (392)[229,230]



386 **392**

$C_{24}H_{24}BrO_2P$
Mol. Wt.: 455.32

According to procedures of Matsumoto *et al*.[229] and Dear *et al*.,[230] to a solution of ethyl 4-bromocrotonate (**386**) (1 g, 5.2 mmol, 1.0 eq.) in benzene (10 mL) is added PPh_3 (1.4 g, 5.4 mmol, 1.05 eq.) and the mixture is stirred for 2 d at room temperature. The reaction mixture is filtered, the remaining solid washed thoroughly with benzene and the resulting solid is dried *in vacuo* to give the product as a white solid (2.3 g, 5.0 mmol, 95%).

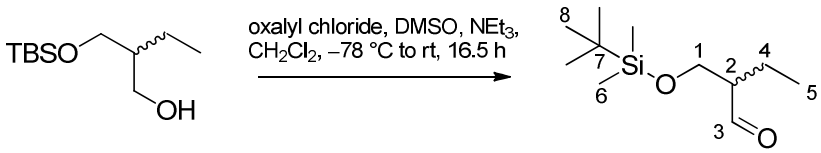
^{1}H-NMR The ^{1}H-NMR spectrum of **392** is in good agreement with literature.[230]

^{13}C-NMR (75 MHz, $CDCl_3$): partial signal doubling observed
14.1 (CH_3, C-6), 27.4, 28.0 (CH_2, C-3), 60.8 (CH_2, C-5), 117.0, 118.1 (C_{quart}, C-7), 130.5, 130.6 (CH, C-8), 130.7, 130.9 (CH, C-2), 132.3, 132.5 (CH, C-1), 134.0, 134.1 (CH, C-9), 135.3, 135.4 (CH, C-10), 165.1 (C_{quart}, C-4).

DIP-MS (EI):
375 (5) [M^+−Br], 279 (79), 277 (100), 262 (48) [PPh_3^+], 201 (20), 199 (23), 183 (58), 152 (13), 108 (16), 77 (19) [$C_6H_5^+$], 45 (21).

IR (cm^{-1}) 3644 (w), 3400 (w), 3009 (w), 2978 (w), 2874 (w), 2831 (w), 2766 (w), 1716 (m), 1642 (w), 1587 (w), 1481 (w), 1436 (m), 1396 (w), 1365 (w), 1326 (m), 1246 (m), 1208 (m), 1163 (m), 1112 (s), 1054 (m), 1027 (w), 995 (m), 983 (m), 889 (m), 839 (w), 758 (m), 750 (m), 734 (m), 719 (m), 690 (s).

6.4.3 Preparation of 2-(((*tert*-butyldimethylsilyl)oxy)methyl)butanal (385)



391 **385**

$C_{11}H_{24}O_2Si$
Mol. Wt.: 216.39

According to a procedure of Panek *et al*.,[192] a solution of oxalyl chloride (2.7 mL, 31.7 mmol, 2.0 eq.) in CH_2Cl_2 abs. (80 mL) is cooled to −78 °C in an acetone/dry ice bath and DMSO abs. (4.5 mL, 63.3 mmol, 4.0 eq.) is added dropwise. After 90 min of stirring, alcohol **391** (prepared over two steps according to literature procedures of Mirilashvili *et al*.[231] and Panek *et al*.[192]) (3.5 g, 15.8 mmol, 1.0 eq.), dissolved in CH_2Cl_2 abs. (40 mL), is added dropwise using a dropping funnel and the mixture is stirred for 1 h at −78 °C. NEt_3 abs. (13.2 mL, 95.0 mmol, 6.0 eq.) is added dropwise and the stirring is continued for 14 h, leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of CH_2Cl_2 (40 mL), H_2O

(80 mL) and sat. NH_4Cl_{aq} (80 mL). The phases are separated and the aqueous phase is extracted with EtOAc (3 × 70 mL). The combined organic phases are washed with H_2O (200 mL) and brine (90 mL) before being dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (12.5% EtOAc in ^{c}Hex) to yield the product as a yellow oil (2.9 g, 13.4 mmol, 85%).

R_f 0.77 (20% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **385** are in good agreement with literature.[225]

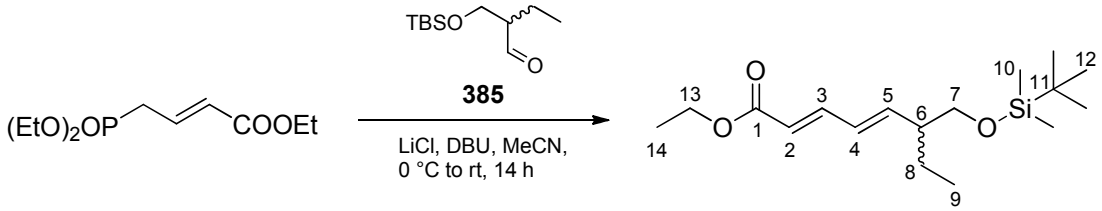
GC (t_R) 11.00 min (program 0)

GC-MS (EI):
159 (100) [M^+–^{t}Bu], 145 (16), 129 (70) [M^+–^{t}Bu, −2 × CH_3], 117 (67), 101 (38) [M^+−TBS], 89 (39), 75 (96) [$C_2H_7OSi^+$], 59 (27).

IR (cm^{-1}) 3407 (w), 2967 (m), 2937 (m), 2880 (w), 2001 (w), 1715 (m), 1462 (m), 1386 (w), 1260 (m), 1173 (m), 1137 (m), 1104 (m), 1042 (m), 776 (s).

6.4.4 Synthesis of a polyunsaturated aldehyde fragment

6.4.4.1 Preparation of (2*E*,4*E*)-ethyl 6-(((*tert*-butyldimethylsilyl) oxy)methyl)octa-2,4-dienoate (394)



398 **394**

$C_{17}H_{32}O_3Si$
Mol. Wt.: 312.52

According to a procedure of Jaschinski *et al*.,[242] a suspension of dry LiCl (156 mg, 3.7 mmol, 1.08 eq.) in MeCN abs. (50 mL) is cooled to 0 °C and phosphonate **398** (prepared according to literature procedures of Bennacer *et al*.[239] and Lee *et al*.[240]) (857 mg, 3.4 mmol, 1.00 eq.) and DBU (511 µL, 3.4 mmol, 1.00 eq.) are added dropwise. After 5 min of stirring, aldehyde **385** (800 mg, 3.7 mmol, 1.08 eq.), dissolved in MeCN abs. (5 mL), is added dropwise and the mixture is stirred for 14 h,

leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of sat. NH_4Cl_{aq} (70 mL) and EtOAc (100 mL). The phases are separated and the aqueous phase is extracted with EtOAc (3 × 100 mL). The combined organic phases are washed with sat. NH_4Cl_{aq} (2 × 100 mL) and brine (100 mL) before being dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (3% EtOAc in ^{c}Hex) to yield the product as a yellow oil (415 mg, 1.3 mmol, 38%).

R_f 0.73 (10% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **394** are in good agreement with literature.[123]

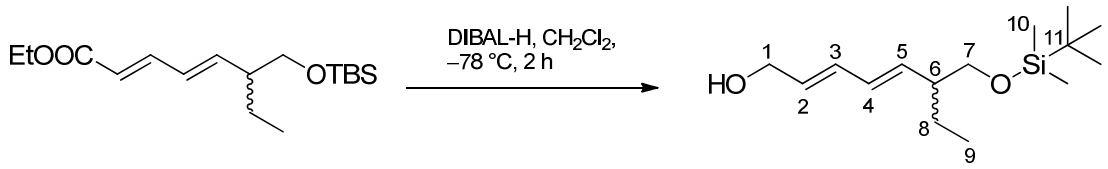
GC (t_R) 27.07 min (program 0)

GC-MS (EI):

311 (1) [M^+−H], 297 [M^+−CH_3], 282 (9) [M^+−2 × CH_3], 267 (9) [M^+−OC_2H_5], 255 (100) [M^+−^{t}Bu], 209 (23), 197 (5) [M^+−TBS], 183 (7), 133 (13), 122 (12), 115 (18), 107 (17), 103 (25), 89 (82), 79 (15), 75 (70) [$C_2H_7OSi^+$], 73 (80), 59 (12).

IR (cm^{-1}) 2959 (m), 2930 (m), 2858 (w), 1714 (s), 1643 (m), 1618 (w), 1463 (w), 1368 (w), 1301 (m), 1256 (s), 1220 (m), 1182 (m), 1139 (s), 1095 (s), 1045 (m), 1000 (s), 939 (w), 834 (s), 813 (m), 774 (s), 716 (w), 667 (m).

6.4.4.2 Preparation of (2*E*,4*E*)-6-(((*tert*-butyldimethylsilyl)oxy) methyl)octa-2,4-dien-1-ol (400) from (2*E*,4*E*)-ethyl 6-(((*tert*-butyldimethylsilyl)oxy)methyl) octa-2,4-dienoate (394)



394 **400**

$C_{15}H_{30}O_2Si$
Mol. Wt.: 270.48

According to procedures of Ding *et al*.[123] and Irlapati *et al*.,[225] a solution of ethyl ester **394** (1.4 g, 4.5 mmol, 1.0 eq.) in CH_2Cl_2 abs. (20 mL) is cooled to −78 °C in an acetone/dry ice bath and DIBAL-H (1M in hexanes) (13.6 mL, 13.6 mmol, 3.0 eq.) is added dropwise using a syringe pump (0.5 mL/min). The mixture is stirred at −78 °C for 2 h. The reaction is terminated by slow addition of MeOH (6.5 mL) and EtOAc (65 mL). The resulting solid is dissolved by adding potassium sodium tartrate (30 mL) and stirring for 1 h. The phases are separated and the aqueous phase is extracted with EtOAc (3 × 40 mL) before the combined organic phases are washed with brine (50 mL) and dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (10% EtOAc in ^{c}Hex) to yield the product as a colourless oil (839 mg, 3.1 mmol, 69%).

R_f 0.30 (10% EtOAc in ^{c}Hex)

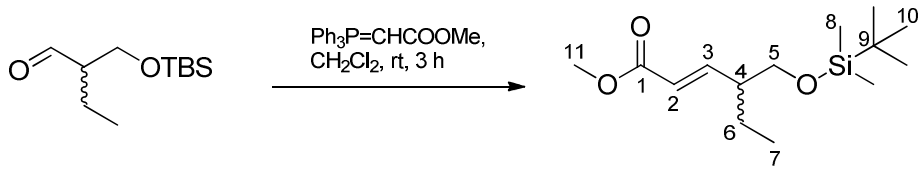
^{1}H-/^{13}C-NMR The NMR spectra of **400** are in good agreement with literature.[123]

GC (t_R) 21.70 min (program 0)

GC-MS (EI):
213 (18) [$M^+-{}^t$Bu], 195 (2) [$M^+-C_2H_7OSi$], 115 (11) [TBS^+], 108 (35), 105 (51), 95 (16), 93 (16), 89 (43), 79 (46), 75 (100) [$C_2H_7OSi^+$], 73 (81), 67 (20).

IR (cm^{-1}) 3350 (w, br), 2958 (m), 2928 (m), 2857 (m), 1472 (w), 1462 (w), 1380 (w), 1361 (w), 1252 (m), 1086 (s), 986 (s), 938 (w), 833 (s), 813 (m), 773 (s), 666 (m).

6.4.4.3 Preparation of (*E*)-methyl 4-(((*tert*-butyldimethylsilyl)oxy) methyl)hex-2-enoate (397)



385 **397**

$C_{14}H_{28}O_3Si$
Mol. Wt.: 272.46

According to a procedure of Irlapati *et al.*,[225] to a solution of ylide Ph_3P=CHCOOMe (201 mg, 0.57 mmol, 1.15 eq.) in CH_2Cl_2 abs. (10 mL) is added aldehyde **385** (108 mg, 0.50 mmol, 9.0 eq.) and the mixture is stirred for 3 h at room temperature. The solvent is evaporated and the crude mixture is loaded onto a short column of silica gel and the product is eluted with CH_2Cl_2 to remove left over triphenylphosphine oxide. Solvent evaporation yields the product as a colourless oil (100 mg, 0.37 mmol, 74%).

R_f 0.50 (5% EtOAc in ^{n}Hex)

^{1}H-NMR (300 MHz, $CDCl_3$): The ^{1}H-NMR spectrum of **397** is not completely in agreement with literature.[192]

0.02 (s, 6H, H-8), 0.87 (s, 9H, H-10), 0.88 (t, *J* = 7.5 Hz, 3H, H-7), 1.26 – 1.43 (m, 1H, H-6a), 1.51 – 1.67 (m, 1H, H-6b), 2.19 – 2.32 (m, 1H, H-4), 3.57 (dd, *J* = 6.0, 1.6 Hz, 2H, H-5), 3.73 (s, 3H, H-11), 5.85 (dd, *J* = 15.8, 1.1 Hz, 1H, H-2), 6.82 (dd, *J* = 15.9, 8.8 Hz, 1H, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$): The ^{13}C-NMR spectrum of **397** is not completely in agreement with literature.[192]

−5.3 (CH_3, C-8), 11.7 (CH_3, C-7), 18.4 (C_{quart}, C-9), 23.4 (CH_2, C-6), 26.0 (CH_3, C-10), 47.0 (CH, C-4), 51.5 (CH_3, C-11), 65.5 (CH_2, C-5), 121.9 (CH, C-2), 151.1 (CH, C-3), 167.2 (C_{quart}, C-1).

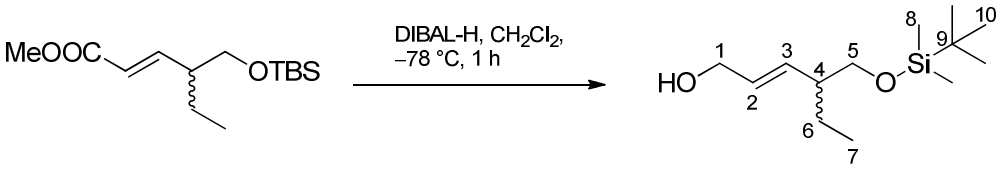
GC (t_R) 19.79 min (program 0) (GC shows a cis:trans ratio of 1:20)

GC-MS (EI):

257 (7) [M^+-CH_3], 242 (18) [$M^+-2\times CH_3$], 215 (63) [$M^+-{}^t$Bu], 183 (18), 145 (20) [CH_2OTBS^+], 119 (52), 89 (100), 75 (35) [$C_2H_7OSi^+$], 73 (65), 55 (17).

IR (cm^{-1}) 2955, 2930, 2858, 2183, 1727, 1658, 1463, 1435, 1384, 1361, 1311, 1253, 1175, 1145, 1099, 1006, 983, 938, 834, 774, 721, 666.

6.4.4.4 Preparation of (*E*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl) hex-2-en-1-ol (401)



397 **401**

$C_{13}H_{28}O_2Si$
Mol. Wt.: 244.45

Compound **401** is prepared applying the general method of 6.2.4.5. The use of methyl ester **397** (336 mg, 1.2 mmol) yields the product as a colourless oil (282 mg, 1.2 mmol, 96%) without further purification.

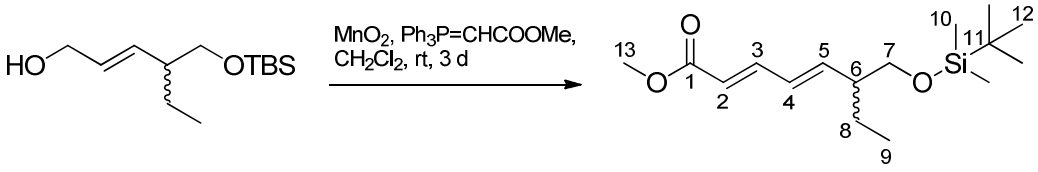
R_f 0.63 (5% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **401** are in good agreement with literature.[123]

GC (t_R) 17.59 min (program 0)

IR (cm^{-1}) 3333 (w, br), 2957 (m), 2929 (m), 2857 (m), 1471 (w), 1463 (m), 1383 (w), 1361 (w), 1253 (m), 1101 (m), 1005 (m), 971 (m), 938 (w), 833 (s), 813 (m), 772 (s), 666 (m).

6.4.4.5 (2*E*,4*E*)-methyl 6-(((tert-butyldimethylsilyl)oxy)methyl) octa-2,4-dienoate (402)



401 **402**

$C_{16}H_{30}O_3Si$
Mol. Wt.: 298.49

According to a procedure of Wei *et al*.,[244] to a solution of allylic alcohol **401** (287 mg, 1.2 mmol, 1.0 eq.) in CH_2Cl_2 abs. (30 mL) are added Ph_3P=CHCOOMe (589 mg, 1.8 mmol, 1.5 eq.), and MnO_2 (255 mg, 2.9 mmol, 2.5 eq.) and the mixture is stirred at room temperature. Within the next 24 h every 6 h is added another portion of MnO_2 (4 × 255 mg, 2.9 mmol, 2.5 eq.) and the stirring is continued for 24 h afterwards. More Ph_3P=CHCOOMe (393 mg, 1.2 mmol, 1.0 eq.) is added and the mixture is stirred for 24 h. The reaction mixture is filtered over Celite® and the remaining solid is washed thoroughly with CH_2Cl_2. The solvent of the filtrate is evaporated and the crude product is purified by column chromatography (flash silica, 10% EtOAc in ^{c}Hex) to yield the product as a colourless oil (160 mg, 0.54 mmol, 46%).

R_f 0.30 (4% Et_2O in ^{c}Hex)

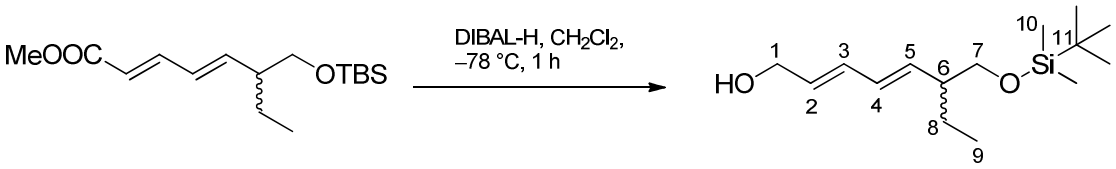
^{1}H-NMR (300 MHz, $CDCl_3$):
0.02 (s, 6H, H-10), 0.86 (t, *J* = 7.5 Hz, 3H, H-9), 0.87 (s, 9H, H-12), 1.21 – 1.39 (m, 1H, H-8a), 1.49 – 1.65 (m, 1H, H-8b), 2.13 – 2.27 (m, 1H, H-6), 3.48 – 3.60 (m, 2H, H-7), 3.74 (s, 3H, H-13), 5.81 (ddd, *J* = 15.4, 0.8, 0.8 Hz, 1H, H-2), 5.96 (dddd, *J* = 15.4, 8.8, 0.8, 0.8 Hz, 1H, H-5), 6.20 (dddd, *J* = 15.4, 10.8, 0.8, 0.8 Hz, 1H, H-4), 7.27 (ddd, *J* = 15.4, 10.8, 0.8 Hz, 1H, H-3).

^{13}C-NMR (75 MHz, $CDCl_3$):
−5.2 (CH_3, C-10), 11.8 (CH_3, C-9), 18.4 (C_{quart}, C-11), 23.9 (CH_2, C-8), 26.0 (CH_3, C-12), 47.7 (CH, C-6), 51.6 (CH_3, C-13), 65.9 (CH_2, C-7), 119.2 (CH, C-2), 129.4 (CH, C-4), 145.4 (CH, C-3), 146.3 (CH, C-5), 167.9 (C_{quart}, C-1).

GC (t_R) 26.60 min (program 0)

IR (cm^{-1}) 2956, 2930, 2857, 2166, 2132, 1977, 1720, 1644, 1617, 1463, 1435, 1383, 1361, 1308, 1257, 1220, 1178, 1141, 1096, 1000, 938, 914, 833, 774, 723, 667.

6.4.4.6 Preparation of (2*E*,4*E*)-6-(((*tert*-butyldimethylsilyl)oxy) methyl)octa-2,4-dien-1-ol (400) from (*E*)-4-(((*tert*-butyl-dimethylsilyl)oxy)methyl)hex-2-en-1-ol (402)



402 **400**

$C_{15}H_{30}O_2Si$
Mol. Wt.: 270.48

Compound **400** is prepared applying the general method of 6.2.4.5. The use of methyl ester **402** (160 mg, 0.54 mmol) yields the product as a colourless oil (126 mg, 0.47 mmol, 87%) without further purification.

Analytical data shown in chapter 6.4.4.2.

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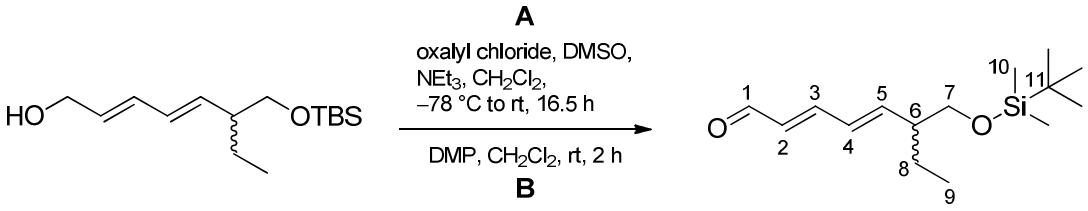
6.4.4.7 Preparation of (2*E*,4*E*)-6-(((*tert*-butyldimethylsilyl)oxy) methyl)octa-2,4-dienal (384)



400 **384**

$C_{15}H_{28}O_2Si$
Mol. Wt.: 268.47

A:

According to procedures of Panek *et al*.[192] and Irlapati *et al*.,[225] a solution of oxalyl chloride (0.52 mL, 6.1 mmol, 2.0 eq.) in CH_2Cl_2 abs. (10 mL) is cooled to −78 °C in an acetone/dry ice bath and DMSO abs. (0.86 mL, 12.1 mmol, 4.0 eq.), dissolved in CH_2Cl_2 abs. (2.5 mL), is added dropwise. After 90 min of stirring, alcohol **400** (820 mg, 3.0 mmol, 1.0 eq.), dissolved in CH_2Cl_2 abs. (7.5 mL), is added dropwise and the mixture is stirred for 1 h at −78 °C in an acetone/dry ice bath. NEt_3 abs. (2.10 mL, 15.2 mmol, 6.0 eq.) is added dropwise and the stirring is continued for 14 h, leaving the reaction mixture to slowly warm to room temperature. The reaction is terminated by the addition of CH_2Cl_2 (10 mL), H_2O (10 mL) and sat. NH_4Cl_{aq} (20 mL). The phases are separated and the aqueous phase is extracted with EtOAc (3 × 20 mL). The combined organic phases are washed with H_2O (50 mL) and brine (40 mL) before being dried over $MgSO_4$ and filtered. The solvent is evaporated to give the crude product which is purified by column chromatography (5% EtOAc in ^{c}Hex) to yield the product as a yellow oil (561 mg, 2.1 mmol, 69%).

B:

According to a procedure of Mitton-Fry *et al*.,[245] a solution of alcohol **400** (126 mg, 0.47 mmol, 1.0 eq.) in CH_2Cl_2 abs. (2.5 mL) is cooled to 0 °C and DMP (207 mg, 0.49 mmol, 1.05 eq.) is added and the mixture is stirred for 2 h at room temperature. The reaction mixture is filtered through a short column of Celite® and silica gel and the remaining solid is washed thoroughly with CH_2Cl_2. The filtrate is washed with sat. $KHCO_{3aq}$ (20 mL) and brine (20 mL) and the combined organic phases are dried

over $MgSO_4$ and filtered. The solvent is evaporated to yield the product as a colourless oil (118 mg, 0.44 mmol, 94%).

R_f 0.36 (5% Et_2O in ^{c}Hex), 0.59 (10% EtOAc in ^{c}Hex)

^{1}H-/^{13}C-NMR The NMR spectra of **384** are in good agreement with literature.[123]

GC (t_R) 21.70 min (program 0)

GC-MS (EI):

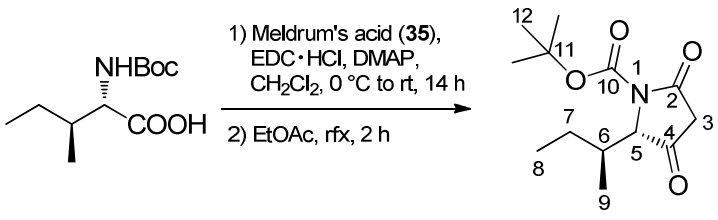
268 (1) [M^+], 253 (2) [M^+-CH_3], 238 (12) [$M^+-2\times CH_3$], 211 (51) [$M^+-{}^t$Bu], 193 (5) [$M^+-C_2H_7OSi^+$], 181 (5) [$M^+-{}^t$Bu, $-2\times CH_3$], 169 (9) [$M^+-{}^t$Bu, $-C_2H_2O$], 129 (10), 119 (10), 95 (18), 89 (40), 75 (100) [$C_2H_7OSi^+$], 73 (60), 59 (10).

IR (cm^{-1}) 2956 (m), 2929 (m), 2856 (m), 1684 (s), 1640 (s), 1462 (w), 1382 (w), 1361 (w), 1253 (m), 1164 (m), 1096 (s), 1008 (m), 987 (m), 938 (w), 834 (s), 813 (m), 774 (s), 667 (m), 610 (w).

6.5 Synthesis of quinolactacin A2 (17) and contributions to the synthesis of quinolactacin B2 (18)

6.5.1 Synthesis of quinolactacin A2 (17)

6.5.1.1 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-(5-*sec*-butyl)-pyrrolidine-2,4-dione (411)



181 **411**

$C_{13}H_{21}NO_4$
Mol. Wt.: 255.31

Compound **411** is prepared applying the general method of 6.2.1.1. The use of *N*-Boc-L-isoleucine (**181**) (prepared from L-isoleucine over three steps according to

literature procedures of Christen[101] and Umezawa *et al*.[291]) (10.8 g, 46.9 mmol) yields the product as an orange oil (10.9 g, 42.7 mmol, 91%) without further purification.

R_f 0.63 (*iso*-propanol)

^{1}H-NMR (300 MHz, $CDCl_3$): only keto form visible
0.89 (d, *J* = 7.2 Hz, 3H, H-9), 0.99 (t, *J* = 7.4 Hz, 3H, H-8), 1.35 – 1.71 (m, 2H, H-7), 1.55 (s, 9H, H-12), 2.11 (tqd, *J* = 14.5, 7.2, 3.3 Hz, 1H, H-6), 3.11 (s, 2H, H-3), 4.41 (d, *J* = 3.3 Hz, 1H, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$): only keto form visible
12.0 (CH_3, C-8), 14.0 (CH_3, C-9), 25.7 (CH_2, C-7), 28.1 (CH_3, C-12), 37.9 (CH, C-6), 44.5 (CH_2, C-3), 70.5 (CH, C-5), 84.4 (C_{quart}, C-11), 149.0 (C_{quart}, C-10), 168.2 (C_{quart}, C-2), 203.9 (C_{quart}, C-4).

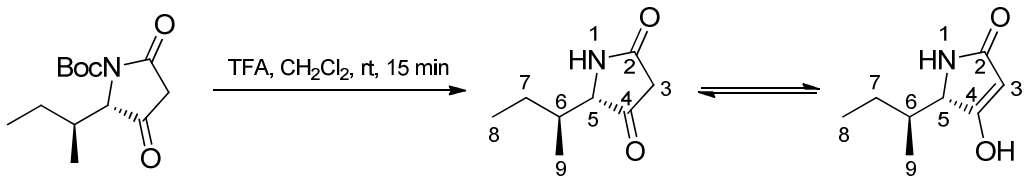
^{1}H-NMR (300 MHz, MeOD):
0.83 (d, *J* = 7.1 Hz, 3H, H-9), 0.99 (t, *J* = 7.4 Hz, 3H, H-8), 1.54 (s, 9H, H-12), 1.76 (dt, *J* = 14.7, 7.4 Hz, 2H, H-7), 2.09 (tqd, *J* = 14.7, 7.1, 2.5 Hz, 1H, H-6), 4.04 (d, *J* = 2.5 Hz, 1H, H-5).

^{13}C-NMR (75 MHz, MeOD):
12.9 (CH_3, C-8), 14.1 (CH_3, C-9), 26.7 (CH_2, C-7), 28.6 (CH_3, C-12), 38.2 (CH, C-6), 44.8 (CH_2, C-3), 67.2 (CH, C-5), 84.3 (C_{quart}, C-11), 149.2 (C_{quart}, C-10), 168.5 (C_{quart}, C-2), 204.0 (C_{quart}, C-4).

DIP-MS (EI):
240 (2) [M^+−Me], 199 (53), 182 (18) [M^+−O^{t}Bu], 171 (11), 155 (5), 143 (7), 127 (23), 112 (14), 99 (74), 84 (9), 70 (9) [$C_3H_2O_2^+$], 58 (100), 42 (33).

$[\alpha]_D^{24}$ +53.6 ° (c = 1.0, $CHCl_3$)

6.5.1.2 Preparation of (5*S*)-(5-*sec*-butyl)-pyrrolidine-2,4-dione (191)



411 **191**

$C_8H_{13}NO_2$
Mol. Wt.: 155.19

Compound **191** is prepared applying the general method of 6.3.10. The use of Boc-protected tetramic acid **411** (10.4 g, 40.7 mmol) yields the product as an orange oil. Et_2O is added to the oil multiple times, until the pure product precipitates from Et_2O and can be obtained by filtration as a glittering, white solid (5.4 g, 34.8 mmol, 85%).

R_f 0.86 (*iso*-propanol)

^{1}H-/^{13}C-NMR The $CDCl_3$ NMR spectra of **191** are in good agreement with literature.[32]

^{1}H-NMR (300 MHz, MeOD): tautomeric ratio: (keto : enol) 60% : 40% (calculated from NMR)

Keto: 0.92 (t, *J* = 7.5 Hz, 3H, H-8), 0.98 (d, *J* = 7.0 Hz, 3H, H-9), 1.29 (ddq, *J* = 13.2, 9.0, 7.5 Hz, 1H, H-7a), 1.42 (dqd, *J* = 13.2, 7.5, 4.9 Hz, 1H, H-7b), 1.84 (qddd, *J* = 9.0, 7.0, 4.9, 4.0 Hz, 1H, H-6), 3.94 (d, *J* = 4.0 Hz, 1H, H-5).

Enol: 0.92 (t, *J* = 7.5 Hz, 3H, H-8), 0.98 (d, *J* = 7.0 Hz, 3H, H-9), 1.19 (ddq, *J* = 13.2, 9.5, 7.5 Hz, 1H, H-7a), 1.42 (dqd, *J* = 13.2, 7.5, 4.9 Hz, 1H, H-7b), 1.85 (qddd, *J* = 9.5, 7.0, 4.9, 3.1 Hz, 1H, H-6), 4.04 (d, *J* = 3.1 Hz, 1H, H-5).

^{13}C-NMR (75 MHz, MeOD):

Keto: 12.1 (CH_3, C-8), 15.5 (CH_3, C-9), 25.6 (CH_2, C-7), 38.6 (CH_2, C-3), 39.0 (CH, C-6), 70.1 (CH, C-5), 174.5 (C_{quart}, C-2), 209.7 (C_{quart}, C-4).

Enol: 12.4 (CH_3, C-8), 15.8 (CH_3, C-9), 24.1 (CH_2, C-7), 37.4 (CH, C-6), 64.2 (CH, C-5), 95.0 (CH, C-3), 178.9 (C_{quart}, C-2/C-4), 179.0 (C_{quart}, C-2/C-4).

MS (EI):

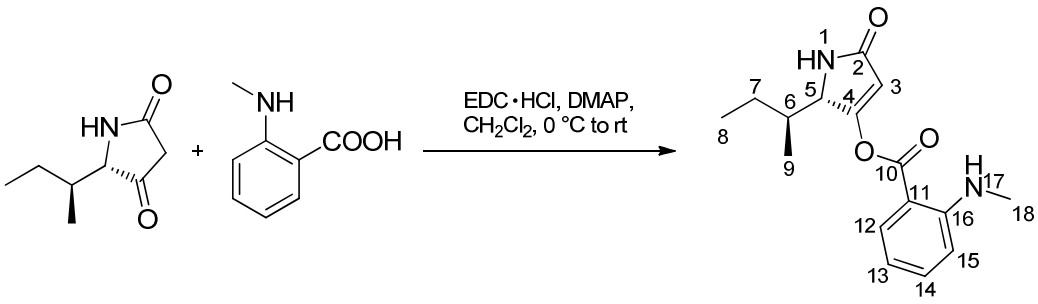
155 (3) [M^+], 139 (3), 127 (100) [M^+−CO], 112 (2) [M^+−CONH], 99 (93), 84 (35), 71 (24), 70 (32) [$C_3H_2O_2^+$], 58 (24), 42 (31).

mp 107 °C [lit.: 113 °C][32]

$[\alpha]_D^{24}$ −23.0 ° (c = 1.0, EtOH) [lit.: −38 ° (c = 1.0, MeOH)][32]

IR (cm^{-1}) 3176 (m, br), 3095 (m), 2974 (m), 2962 (m), 2938 (w), 2880 (m), 1771 (m), 1685 (s), 1655 (s), 1536 (w), 1465 (w), 1456 (w), 1385 (m), 1358 (s), 1301 (s), 1284 (m), 1247 (m), 1162 (w), 1125 (w), 969 (m), 779 (s), 760 (s), 712 (s).

6.5.1.3 Preparation of (5*S*)-4-((2-methylamino)benzoyloxy)-(5-*sec*-butyl)-1*H*-pyrrol-2(5*H*)-one (193)



191 **192** **193**

$C_{16}H_{20}N_2O_3$
Mol. Wt.: 288.34

According to a procedure of Yoda *et al.*,[78] to a solution of L-isoleucine tetramic acid (**191**) (1.0 g, 6.4 mmol, 1.00 eq.) and *N*-methylanthranilic acid (**192**) (1.1 g, 7.1 mmol, 1.10 eq.) in CH_2Cl_2 abs. (125 mL) at 0 °C are added EDC · HCl (1.4 g, 7.1 mmol, 1.10 eq.) and DMAP (86 mg, 0.71 mmol, 0.11 eq.) and the mixture is left to warm to room temperature. Stirring is continued until TLC showed complete consumption of the starting material. The mixture is diluted with EtOAc (200 mL) and washed with sat. NH_4Cl_{aq} (3 × 150 mL) and brine (150 mL) before the organic phases are dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product is

purified by column chromatography (silica gel, 25% → 50% EtOAc in ^{c}Hex → EtOAc) to give the product as a yellow oil. The product is precipitated from EtOAc with pentane to give the product as a pale yellow solid (970 mg, 3.4 mmol, 52%).

R_f 0.44 (EtOAc), 0.78 (20% MeOH in $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$): The ^{1}H-NMR spectrum of **193** is not completely in agreement with literature.[136]

0.91 (t, *J* = 7.5 Hz, 3H, H-8), 1.07 (d, *J* = 7.0 Hz, 3H, H-9), 1.23 (ddq, *J* = 14.1, 9.5, 7.5 Hz, 1H, H-7a), 1.42 (dqd, *J* = 14.1, 7.5, 4.3 Hz, 1H, H-7b), 1.95 (dqdd, *J* = 9.5, 7.0, 4.3, 3.2 Hz, 1H, H-6), 2.96 (s, 3H, H-18), 4.32 (ddd, *J* = 3.2, 1.2, 1.2 Hz, 1H, H-5), 6.17 (dd, *J* = 1.2, 1.2 Hz, 1H, H-3), 6.63 (ddd, *J* = 8.1, 7.0, 0.8 Hz, 1H, H-13), 6.72 (dd, *J* = 8.6, 0.8 Hz, 1H, H-15), 6.96 (br s, 1H, NH-1), 7.46 (ddd, *J* = 8.6, 7.0, 1.7 Hz, 1H, H-14), 7.58 (br s, 1H, NH-17), 7.87 (dd, *J* = 8.1, 1.7 Hz, 1H, H-12).

^{13}C-NMR (75 MHz, $CDCl_3$): The ^{13}C-NMR spectrum of **193** is not completely in agreement with literature.[136]

12.2 (CH_3, C-8), 16.2 (CH_3, C-9), 23.1 (CH_2, C-7), 29.7 (CH_3, C-18), 36.5 (CH, C-6), 63.2 (CH, C-5), 107.3 (C_{quart}, C-11), 107.9 (CH, C-3), 111.4 (CH, C-15), 114.8 (CH, C-13), 131.6 (CH, C-12), 136.3 (CH, C-14), 153.2 (C_{quart}, C-16), 164.0 (C_{quart}, C-10), 165.6 (C_{quart}, C-4), 174.3 (C_{quart}, C-2).

^{1}H-NMR (300 MHz, MeOD):

0.93 (t, *J* = 7.5 Hz, 3H, H-8), 1.04 (d, *J* = 7.0 Hz, 3H, H-9), 1.22 (ddq, *J* = 13.7, 9.3, 7.5 Hz, 1H, H-7a), 1.44 (dqd, *J* = 13.7, 7.5, 4.6 Hz, 1H, H-7b), 1.97 (dqdd, *J* = 9.3, 7.0, 4.6, 3.0 Hz, 1H, H-6), 2.95 (s, 3H, H-18), 4.41 (dd, *J* = 3.0, 0.9 Hz, 1H, H-5), 6.10 (d, *J* = 0.9 Hz, 1H, H-3), 6.64 (ddd, *J* = 8.1, 7.0, 0.8 Hz, 1H, H-13), 6.81 (dd, *J* = 8.6, 0.8 Hz, 1H, H-15), 7.48 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1H, H-14), 7.89 (dd, *J* = 8.1, 1.7 Hz, 1H, H-12).

^{13}C-NMR (75 MHz, MeOD):

12.5 (CH_3, C-8), 16.1 (CH_3, C-9), 24.4 (CH_2, C-7), 29.7 (CH_3, C-18), 37.7 (CH, C-6), 64.5 (CH, C-5), 107.9 (CH, C-3), 108.0 (C_{quart}, C-11), 112.5 (CH, C-15), 115.7 (CH, C-13), 132.4 (CH, C-12), 137.5 (CH, C-14), 154.6 (C_{quart}, C-16), 165.1 (C_{quart}, C-10), 167.9 (C_{quart}, C-4), 176.3 (C_{quart}, C-2).

DIP-MS (EI):

288 (58) [M^+], 134 (100) [$C_8H_8NO^+$], 120 (19), 116 (29), 106 (26) [$C_7H_8N^+$], 91 (24), 79 (22), 77 (41).

HRMS (ESI):

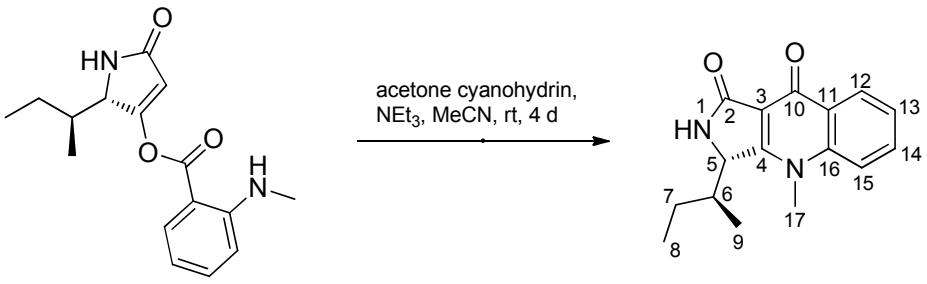
289.1544 [M + H] (calculated for $C_{16}H_{21}N_2O_3$: 289.1552).

mp 123 °C

$[\alpha]_D^{24}$ −2.1 ° (c = 1.0, EtOH)

IR (cm^{-1}) The IR spectrum of **193** is in good agreement with literature.[136]

6.5.1.4 Preparation of quinolactacin A2 (17) from (5*S*)-4-((2-methylamino)benzoyloxy)-(5-*sec*-butyl)-1*H*-pyrrol-2(5*H*)-one (193)



193 **17**

$C_{16}H_{18}N_2O_2$
Mol. Wt.: 270.33

According to a procedure of Moloney *et al*.,[77] to a solution of 4-*O*-acyltetramic acid (**193**) (122 mg, 0.42 mmol, 1.0 eq.) in MeCN abs. (7 mL) are added NEt_3 abs. (117 µL, 0.85 mmol, 2.0 eq.) and acetone cyanohydrin (39 µL, 0.42 mmol, 1.0 eq.) and the mixture is stirred for 4 d. During this time the progress of the reaction is monitored by analytical HPLC. The solvent is evaporated and the crude yellow oil is

purified by preparative HPLC (40% MeOH in H_2O/after 20 min gradient to 100% MeOH in 10 min) to yield the desired natural product as a white solid (60 mg, 0.22 mmol, 52%).

All spectral and experimental data of **17** is in good agreement with literature,[125] except the value of the optical rotation.

R_f 0.60 (20% MeOH in $CHCl_3$)

^{1}H-NMR (300 MHz, DMSO-d_6):
0.65 (t, *J* = 7.4 Hz, 3H, H-8), 0.71 – 0.95 (m, 2H, H-7), 1.13 (d, *J* = 6.9 Hz, 3H, H-9), 2.18 (dqdd, *J* = 8.9, 6.9, 4.5, 2.5 Hz, 1H, H-6), 3.84 (s, 3H, H-17), 4.82 (dd, *J* = 2.2, 1.4 Hz, 1H, H-5), 7.45 – 7.51 (m, 1H, H-13), 7.79 – 7.82 (m, 1H, H-14), 7.82 – 7.83 (m, 1H, H-15), 8.13 (br s, 1H, NH-1), 8.23 – 8.27 (m, 1H, H-12).

^{13}C-NMR (75 MHz, DMSO-d_6):
11.5 (CH_3, C-8), 17.6 (CH_3, C-9), 20.8 (CH_2, C-7), 35.8 (CH, C-6), 36.1 (CH_3, C-17), 58.9 (CH, C-5), 110.4 (C_{quart}, C-3), 117.1 (CH, C-15), 124.3 (CH, C-13), 125.8 (CH, C-12), 128.1 (C_{quart}, C-11), 132.5 (CH, C-14), 141.2 (C_{quart}, C-16), 164.2 (C_{quart}, C-4), 168.4 (C_{quart}, C-2), 171.5 (C_{quart}, C-10).

^{1}H-NMR (300 MHz, MeOD):
0.70 (t, *J* = 7.3 Hz, 3H, H-8), 0.76 – 1.06 (m, 2H, H-7), 1.23 (d, *J* = 6.9 Hz, 3H, H-9), 2.22 – 2.37 (m, 1H, H-6), 3.90 (s, 3H, H-17), 4.82 – 4.88 (m, 1H, H-5), 7.36 – 7.43 (m, 1H, H-13), 7.70 – 7.76 (m, 2H, H-14, H-15), 8.21 – 8.27 (m, 1H, H-12).

^{13}C-NMR (75 MHz, MeOD):
11.9 (CH_3, C-8), 18.1 (CH_3, C-9), 22.4 (CH_2, C-7), 37.1 (CH, C-6), 37.9 (CH_3, C-17), 61.7 (CH, C-5), 111.5 (C_{quart}, C-3), 117.9 (CH, C-15), 126.0 (CH, C-13), 127.2 (CH, C-12), 129.1 (C_{quart}, C-11), 134.3 (CH, C-14), 142.8 (C_{quart}, C-16), 166.0 (C_{quart}, C-4), 171.6 (C_{quart}, C-2), 174.8 (C_{quart}, C-10).

^{1}H-NMR (300 MHz, acetone-d_6):

0.69 (t, *J* = 7.4 Hz, 3H, H-8), 0.84 – 1.08 (m, 2H, H-7), 1.30 (d, *J* = 6.9 Hz, 3H, H-9), 2.27 – 2.40 (m, 1H, H-6), 3.93 (s, 3H, H-17), 4.94 (br s, 1H, H-5), 7.27 (ddd, *J* = 7.9, 6.6, 1.5 Hz, 1H, H-13), 7.60 (ddd, *J* = 8.5, 6.6, 1.5 Hz, 1H, H-14), 7.65 (dd, *J* = 8.5, 1.5 Hz, 1H, H-15), 8.18 (dd, *J* = 7.9, 1.5 Hz, 1H, H-12), 8.24 (br s, 1H, NH-1).

^{13}C-NMR (75 MHz, acetone-d_6):

12.0 (CH_3, C-8), 18.3 (CH_3, C-9), 22.0 (CH_2, C-7), 36.8 (CH_3, C-17), 37.3 (CH, C-6), 60.9 (CH, C-5), 111.8 (C_{quart}, C-3), 117.4 (CH, C-15), 124.8 (CH, C-13), 126.9 (CH, C-12), 129.3 (C_{quart}, C-11), 133.0 (CH, C-14), 142.4 (C_{quart}, C-16), 165.2 (C_{quart}, C-4), 170.3 (C_{quart}, C-2), 172.7 (C_{quart}, C-10).

MS (EI):

270 (62) [M^+], 229 (11), 213 (100) [$M^+ - C_4H_9$], 199 (9), 185 (10), 158 (11), 142 (3), 130 (7), 115 (3), 103 (3), 89 (3), 77 (4).

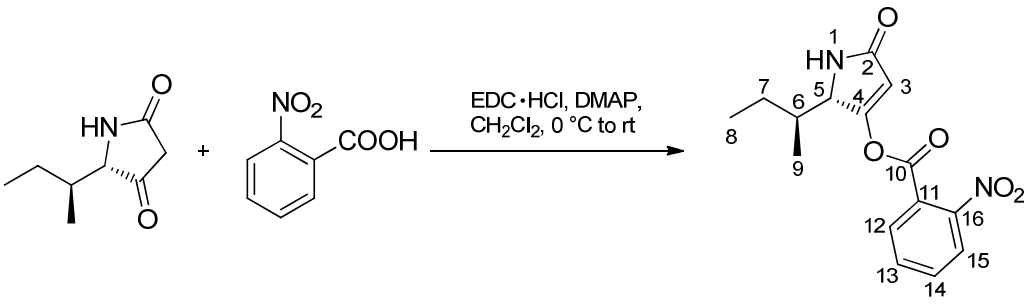
HRMS (ESI):

271.1441 [M + H] (calculated for $C_{16}H_{19}N_2O_2$: 271.1447).

mp 245.6 °C (decomposition) [lit.: 262 – 265 °C (decomposition)].[125]

$[\alpha]_D^{24}$ −27.0 ° (c = 0.4, DMSO-d_6, wet), −28.1 ° [OC1/2] (c = 0.4, DMSO-d_6, wet), −17.1 ° (c = 0.2, DMSO abs.), −16.8 ° [OC1/2] (c = 0.14, DMSO abs.) [lit.: +17.9 ° (c = 0.13, DMSO)].[125]

6.5.1.5 Preparation of (5*S*)-4-((2-nitro)benzoyloxy)-(5-*sec*-butyl)-1*H*-pyrrol-2(5*H*)-one (414)



191 **413** **414**

$C_{15}H_{16}N_2O_5$
Mol. Wt.: 304.30

According to a procedure of Yoda *et al*.,[78] to a solution of L-isoleucine tetramic acid (**191**) (800 mg, 5.2 mmol, 1.00 eq.) and *ortho*-nitrobenzoic acid (**413**) (prepared from *ortho*-nitrobenzaldehyde according to a literature procedure of Travis *et al*.[250]) (948 mg, 5.7 mmol, 1.10 eq.) in CH_2Cl_2 abs. (60 mL) at 0 °C are added EDC · HCl (1.1 g, 5.7 mmol, 1.10 eq.) and DMAP (69 mg, 0.57 mmol, 0.11 eq.) and the mixture is left to warm to room temperature. Stirring is continued for 4 h before the mixture is diluted with EtOAc (150 mL) and washed with sat. NH_4Cl_{aq} (3 × 60 mL) and brine (60 mL). The combined organic phases are dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product is purified by column chromatography (silica gel, 25% → 50% EtOAc in ^{c}Hex → EtOAc) to yield the product as a yellow oil (1.3 g, 4.1 mmol, 80%).

R_f 0.38 (EtOAc)

^{1}H-NMR (300 MHz, $CDCl_3$):
0.84 (t, *J* = 7.4 Hz, 3H, H-8), 1.00 (d, *J* = 7.1 Hz, 3H, H-9), 0.97 – 1.15 (m, 1H, H-7a), 1.19 – 1.41 (m, 1H, H-7b), 1.71 – 1.92 (m, 1H, H-6), 4.19 (ddd, *J* = 3.2, 1.4, 1.2 Hz, 1H, H-5), 6.22 (dd, *J* = 1.6, 1.4 Hz, 1H, H-3), 7.69 – 7.81 (m, 3H, H-12, H-13, H-14), 7.96 – 8.01 (m, 1H, H-15), 8.08 (br s, 1H, NH-1).

^{13}C-NMR (75 MHz, $CDCl_3$):

11.7 (CH_3, C-8), 16.1 (CH_3, C-9), 22.5 (CH_2, C-7), 35.8 (CH, C-6), 63.3 (CH, C-5), 109.3 (CH, C-3), 124.4 (CH, C-15), 125.8 (C_{quart}, C-11), 130.2 (CH, C-12), 133.0 (CH, C-14), 133.6 (CH, C-13), 147.9 (C_{quart}, C-16), 161.1 (C_{quart}, C-10), 164.9 (C_{quart}, C-4), 173.8 (C_{quart}, C-2).

DIP-MS (EI):

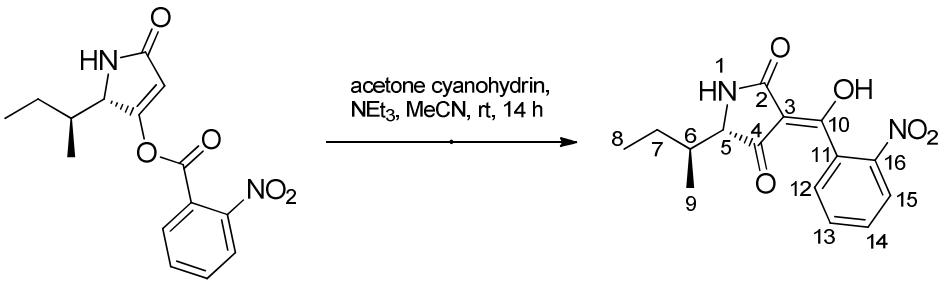
304 (1) [M^+], 258 (86) [M^+-NO_2], 248 (100), 202 (21), 175 (15), 170 (17), 158 (17), 150 (64) [$C_7H_4NO_3^+$], 134 (23), 130 (12), 121 (14), 104 (21), 86 (13), 76 (14), 69 (12), 62 (14), 51 (14), 41 (17).

HRMS (ESI):

305.1128 [M + H] (calculated for $C_{15}H_{17}N_2O_5$: 305.1137).

$[\alpha]_D^{24}$ +67.8 ° (c = 1.0, EtOH)

6.5.1.6 Preparation of (5*S*)-3-((2-nitro)benzoyl)-(5-*sec*-butyl) pyrrolidin-2,4-dione (415)



414 **415**

$C_{15}H_{16}N_2O_5$
Mol. Wt.: 304.30

According to a procedure of Moloney *et al*.,[77] to a solution of 4-*O*-acyltetramic acid **414** (500 mg, 1.6 mmol, 1.0 eq.) in MeCN abs. (8 mL) are added NEt_3 abs. (0.46 mL, 3.3 mmol, 2.0 eq.) and acetone cyanohydrin (150 µL, 1.6 mmol, 1.0 eq.) and the mixture is stirred for 4 h at room temperature. The solvent is evaporated and the residue is dissolved in 1M $NaOH_{aq}$ (30 mL) and the aqueous phase washed with Et_2O (2 × 30 mL). The pH of the aqueous phase is adjusted to pH 1 with 2M HCl_{aq} and the phase is extracted with EtOAc (3 × 20 mL). The combined organic phases are dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude product

as a deep orange oil. Purification is carried out by column chromatography (RP silica gel, 20% → 40% MeOH in H_2O → MeOH). The product obtained is dissolved in $CHCl_3$ (30 mL), washed with 2M HCl_{aq} (3 × 20 mL) (to get rid of chelated metal ions), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired product is obtained as an orange oil (319 mg, 1.1 mmol, 64%).

^{1}H-NMR (300 MHz, $CDCl_3$): tautomeric ratio: 57% : 43% (calculated from NMR)
major tautomer: 0.85 (t, *J* = 7.4 Hz, 3H, H-8), 0.95 (d, *J* = 7.1 Hz, 3H, H-9), 1.12 – 1.53 (m, 2H, H-7), 1.81 – 1.96 (m, 1H, H-6), 3.76 (d, *J* = 3.3 Hz, 1H, H-5), 7.37 (br s, 1H, NH-1), 7.59 (dd, *J* = 7.3, 1.8 Hz, 1H, H-12), 7.67 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H, H-14), 7.74 (ddd, *J* = 7.5, 7.3, 1.4 Hz, 1H, H-13), 8.15 (dd, *J* = 8.0, 1.4 Hz, 1H, H-15).
minor tautomer: 0.94 (t, *J* = 7.4 Hz, 3H, H-8), 1.02 (d, *J* = 6.9 Hz, 3H, H-9), 1.12 – 1.53 (m, 2H, H-7), 1.92 – 2.05 (m, 1H, H-6), 4.13 (d, *J* = 3.6 Hz, 1H, H-5), 6.95 (br s, 1H, NH-1), 7.51 (dd, *J* = 7.4, 1.6 Hz, 1H, H-12), 7.65 (ddd, *J* = 8.0, 7.7, 1.6 Hz, 1H, H-14), 7.74 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H, H-13), 8.16 (dd, *J* = 8.0, 1.1 Hz, 1H, H-15).

^{13}C-NMR (75 MHz, $CDCl_3$):
major tautomer: 11.8 (CH_3, C-8), 15.6 (CH_3, C-9), 23.4 (CH_2, C-7), 37.1 (CH, C-6), 67.2 (CH, C-5), 101.7 (C_{quart}, C-3), 124.6 (CH, C-15), 128.3 (C_{quart}, C-11), 130.4 (CH, C-12), 131.9 (CH, C-14), 133.5 (CH, C-13), 147.7 (C_{quart}, C-16), 176.2 (C_{quart}, C-2), 178.1 (C_{quart}, C-10), 193.4 (C_{quart}, C-4).
minor tautomer: 11.8 (CH_3, C-8), 15.5 (CH_3, C-9), 23.9 (CH_2, C-7), 37.1 (CH, C-6), 62.1 (CH, C-5), 106.4 (C_{quart}, C-3), 123.8 (CH, C-15), 128.1 (C_{quart}, C-11), 129.5 (CH, C-12), 131.5 (CH, C-14), 133.9 (CH, C-13), 147.7 (C_{quart}, C-16), 168.9 (C_{quart}, C-2), 189.2 (C_{quart}, C-10), 193.6 (C_{quart}, C-4).

^{1}H-NMR (300 MHz, MeOD):
0.88 (t, *J* = 7.4 Hz, 3H, H-8), 0.98 (d, *J* = 7.1 Hz, 3H, H-9), 1.10 – 1.29 (m, 1H, H-7a), 1.30 – 1.47 (m, 1H, H-7b), 1.80 – 1.97 (m, 1H, H-6), 3.90 (d, *J* = 3.3 Hz, 1H, H-5), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H, H-12), 7.67 (ddd, *J* = 8.2, 7.6, 1.5 Hz, 1H, H-14), 7.77 (ddd, *J* = 7.6, 7.5, 1.1 Hz, 1H, H-13), 8.14 (dd, *J* = 8.2, 1.1 Hz, 1H, H-15).

^{13}C-NMR (75 MHz, MeOD):

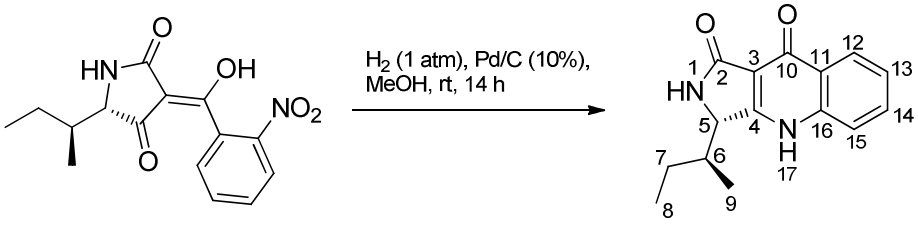
12.2 (CH_3, C-8), 15.9 (CH_3, C-9), 24.5 (CH_2, C-7), 38.1 (CH, C-6), 66.8 (CH, C-5), 102.8 (C_{quart}, C-3), 124.9 (CH, C-15), 130.4 (CH, C-12), 132.2 (CH, C-14), 133.6 (C_{quart}, C-11), 135.0 (CH, C-13), 148.3 (C_{quart}, C-16), 176.0 (C_{quart}, C-2), 186.6 (C_{quart}, C-10), 193.8 (C_{quart}, C-4).

DIP-MS (EI):

304 (1) [M^+], 258 (100) [M^+-NO_2], 248 (84), 202 (25), 175 (18), 170 (18), 158 (19), 150 (78), 134 (28), 130 (16), 121 (20), 104 (27), 86 (16), 76 (23) [$C_6H_4^+$], 69 (17), 57 (16) [$C_4H_9^+$], 51 (22), 42 (28).

$[\alpha]_D^{24}$ −44.2 ° (c = 1.0, EtOH)

6.5.1.7 Preparation of (3*S*)-(3-*sec*-butyl)-2,3-dihydro-1*H*-pyrrolo[3,4-b]quinoline-1,9-(4*H*)-dione (417)



415 **417**

$C_{15}H_{16}N_2O_2$
Mol. Wt.: 256.30

According to a procedure of Abe *et al*.,[81] to a solution of 3-acyltetramic acid **415** (319 mg, 1.1 mmol, 1.0 eq.) in MeOH abs. (15 mL) is added palladium on charcoal (10%, 32 mg, 10% w/w) and the mixture is stirred under hydrogen at atmospheric pressure for 14 h at room temperature, resulting in a green solution and precipitation of a white solid. The reaction mixture is filtered over Celite®, the Celite® is washed thoroughly with MeOH (30 mL) and $CHCl_3$ (30 mL) and the combined filtrates are concentrated *in vacuo*. The product is precipitated by the addition of cold MeOH and the solid is washed with Et_2O giving the product as a pale yellow solid (185 mg, 0.72 mmol, 69%).

[150 mg are purified by preparative HPLC to get better analytical data (40% MeOH in H_2O/after 20 min gradient to 100% MeOH in 10 min). This only yielded

9 mg of pure white product, possibly due to its high polarity and bad solubility in pure methanol]

R_f 0.41 (50% MeOH in H_2O, RP silica)

^{1}H-NMR (300 MHz, DMSO-d_6):

0.73 (t, *J* = 7.4 Hz, 3H, H-8), 0.87 – 1.02 (m, 2H, H-7), 1.10 (d, *J* = 7.1 Hz, 3H, H-9), 2.08 – 2.23 (m, 1H, H-6), 4.56 (d, *J* = 2.5 Hz, 1H, H-5), 7.39 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H, H-13), 7.64 (dd, *J* = 8.4, 1.1 Hz, 1H, H-15), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, H-14), 8.05 (br s, 1H, NH-1), 8.16 (dd, *J* = 8.2, 1.4 Hz, 1H, H-12), 12.37 (br s, 1H, NH-17).

^{13}C-NMR (75 MHz, DMSO-d_6):

11.8 (CH_3, C-8), 17.1 (CH_3, C-9), 21.3 (CH_2, C-7), 36.6 (CH, C-6), 58.8 (CH, C-5), 109.4 (C_{quart}, C-3), 118.8 (CH, C-15), 124.1 (CH, C-13), 125.6 (CH, C-12), 127.1 (C_{quart}, C-11), 132.3 (CH, C-14), 139.8 (C_{quart}, C-16), 162.7 (C_{quart}, C-4), 168.8 (C_{quart}, C-2), 172.2 (C_{quart}, C-10).

DIP-MS (EI):

256 (12) [M^+], 227 (10), 200 (100), 172 (6), 145 (13), 130 (5), 116 (4), 104 (6), 89 (5), 57 (4).

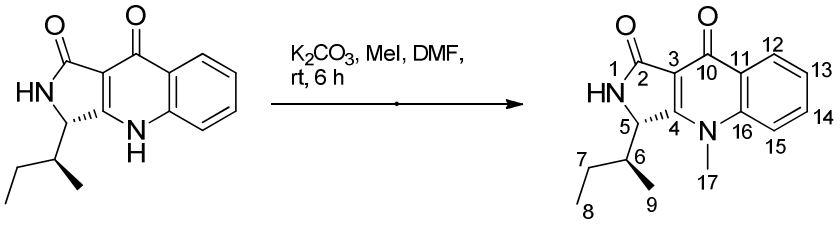
HRMS (ESI):

257.1281 [M + H] (calculated for $C_{15}H_{17}N_2O_2$: 257.1290).

$[\alpha]_D^{24}$ +52.3 ° (c = 1.0, DMSO abs.)

IR (cm^{-1}) 3209 (w), 3079 (w), 2961 (m), 2933 (m), 2874 (w), 2351 (w, br), 1675 (s), 1610 (s), 1568 (s), 1532 (s), 1471 (s), 1369 (m), 1383 (m), 1351 (m), 1305 (m), 1240 (m), 1208 (m), 1155 (m), 1121 (m), 1045 (m), 1025 (m), 861 (w), 815 (m), 792 (m), 755 (s), 709 (s), 675 (s), 657 (m).

6.5.1.8 Preparation of quinolactacin A2 (17) from (3*S*)-(3-*sec*-butyl)-2,3-dihydro-1*H*-pyrrolo[3,4-b]quinoline-1,9-(4*H*)-dione (417)



417 **17**

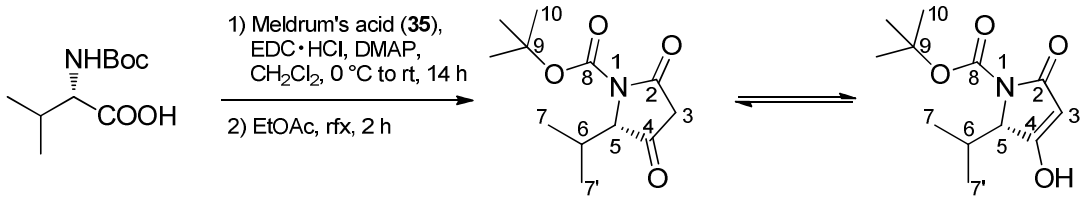
$C_{16}H_{18}N_2O_2$
Mol. Wt.: 270.33

According to a procedure of Zhang *et al*.,[130] to a solution of unmethylated quinolactacin A2 precursor **417** (16.3 mg, 64 µmol, 1.0 eq.) in DMF abs. (1 mL) are added K_2CO_3 (8.8 mg, 64 µmol, 1.0 eq.) and MeI (8 µL, 0.13 mmol, 2.0 eq.) and the mixture is stirred for 2 h at room temperature. More K_2CO_3 (8.8 mg, 64 µmol, 1.0 eq.) and MeI (8 µL, 0.13 mmol, 2.0 eq.) are added and the mixture is stirred for another 4 h at room temperature. The solvent is evaporated and the crude product is purified by preparative HPLC (40% MeOH in H_2O/after 20 min gradient to 100% MeOH in 10 min). The natural product is obtained as a white solid (14 mg, 52 µmol, 82%).

All spectral and experimental data of **17** is in good agreement with literature,[125] except the value of the optical rotation.
Analytical data shown in chapter 6.5.1.4.

6.5.2 Contributions to the synthesis of quinolactacin B2 precursors

6.5.2.1 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-(5-*iso*-propyl)-pyrrolidine-2,4-dione (412)



410 **412**

$C_{12}H_{19}NO_4$
Mol. Wt.: 241.28

Compound **412** is prepared applying the general method of 6.2.1.1. The use of *N*-Boc-L-valine (**410**) (prepared from L-valine according to literature procedures of Barnickel[152] and Caplar *et al*.[260]) (5.0 g, 23.0 mmol) yields the crude product. The mixture is concentrated *in vacuo* multiple times, redissolving the residue in between with Et_2O, until the product precipitates as a white solid (4.3 g, 17.7 mmol, 77%).

^{1}H-NMR (300 MHz, $CDCl_3$): only keto form visible
0.92 (d, *J* = 6.9 Hz, 3H, H-7†), 1.11 (d, *J* = 7.1 Hz, 3H, H-7'†), 1.54 (s, 9H, H-10), 2.35 (qqd, *J* = 7.1, 6.9, 3.8 Hz, 1H, H-6), 3.11 (s, 2H, H-3), 4.28 (d, *J* = 3.8 Hz, 1H, H-5).

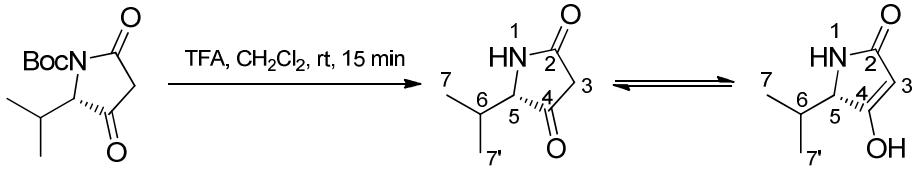
^{13}C-NMR (75 MHz, $CDCl_3$): only keto form visible
16.4 (CH_3, C-7†), 18.5 (CH_3, C-7'†), 28.1 (CH_3, C-10), 31.2 (CH, C-6), 44.3 (CH_2, C-3), 72.0 (CH, C-5), 84.4 (C_{quart}, C-9), 149.2 (C_{quart}, C-8), 168.0 (C_{quart}, C-2), 203.7 (C_{quart}, C-4).

^{1}H-NMR (300 MHz, MeOD): only enol form visible; the ^{1}H-NMR spectrum of **412** is not completely in agreement with literature.[48]
0.84 (d, *J* = 6.9 Hz, 3H, H-7†), 1.14 (d, *J* = 7.3 Hz, 3H, H-7†), 1.52 (s, 9H, H-10), 2.46 (qqd, *J* = 7.3, 6.9, 2.7 Hz, 1H, H-6), 4.37 (d, *J* = 2.7 Hz, 1H, H-5).

^{13}C-NMR (75 MHz, MeOD): only enol form visible
15.8 (CH_3, C-7†), 18.7 (CH_3, C-7'†), 28.4 (CH_3, C-10), 30.7 (CH, C-6), 66.2 (CH, C-5), 83.6 (C_{quart}, C-9), 95.7 (CH, C-3), 150.9 (C_{quart}, C-8), 173.7 (C_{quart}, C-2), 179.7 (C_{quart}, C-4).

$[\alpha]_D^{24}$ +80.0 ° (c = 1.0, EtOH) [lit.: +123 ° (c = 1.0, MeOH)].[48]

6.5.2.2 Preparation of (5*S*)-(5-*iso*-propyl)-pyrrolidine-2,4-dione (409)[53]



412 **409**

$C_7H_{11}NO_2$
Mol. Wt.: 141.17

Compound **409** is prepared applying the general method of 6.3.10. The use of Boc-protected tetramic acid **412** (2.5 g, 10.4 mmol) yields the product as an orange oil. Et_2O is added to the oil multiple times, until the pure product precipitates from Et_2O and can be obtained by filtration as a glittering, white solid (1.19 g, 8.4 mmol, 81%).

R_f 0.37 (EtOAc)

^{1}H-/^{13}C-NMR The $CDCl_3$ NMR spectra of **409** are in good agreement with literature.[53]

^{1}H-NMR (300 MHz, MeOD): tautomeric ratio: (keto : enol) 60% : 40% (calculated from NMR)
Keto: 0.91 (d, *J* = 6.9 Hz, 3H, H-7†), 1.01 (d, *J* = 7.1 Hz, 3H, H-7'†), 2.10 (qqd, *J* = 7.1, 6.9, 3.8 Hz, 1H, H-6), 3.88 (d, *J* = 3.8 Hz, 1H, H-5).
Enol: 0.82 (d, *J* = 6.9 Hz, 3H, H-7†), 1.04 (d, *J* = 7.1 Hz, 3H, H-7'†), 2.12 (qqd, *J* = 7.1, 6.9, 3.0 Hz, 1H, H-6), 3.98 (d, *J* = 3.0 Hz, 1H, H-5).

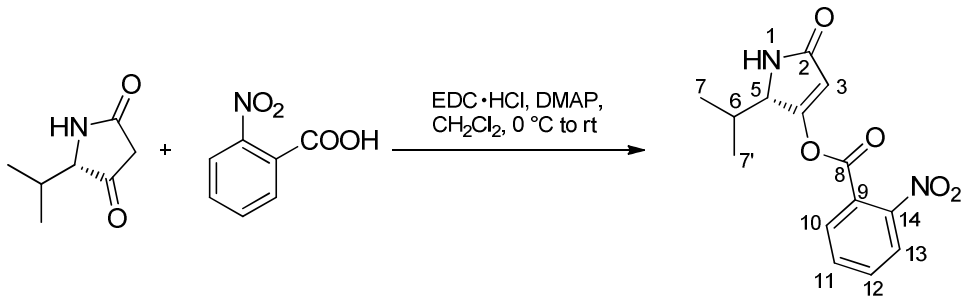
^{13}C-NMR (75 MHz, MeOD): tautomeric ratio: (keto : enol) 60% : 40% (calculated from NMR)

Keto: 17.1 (CH_3, C-7†), 19.0 (CH_3, C-7'†), 32.0 (CH, C-6), 41.7 (CH_2, C-3), 70.7 (CH, C-5), 174.5 (C_{quart}, C-2), 209.7 (C_{quart}, C-4).

Enol: 15.4 (CH_3, C-7†), 19.7 (CH_3, C-7'†), 30.2 (CH, C-6), 64.4 (CH, C-5), 94.8 (CH, C-3), 178.9 (C_{quart}, C-2/C-4), 179.1 (C_{quart}, C-2/C-4).

$[\alpha]_D^{24}$ −38.9 ° (c = 1.0, EtOH) [lit.: −46.4 ° (c = 1.0, EtOH)].[53]

6.5.2.3 Preparation of (5*S*)-4-((2-nitro)benzoyloxy)-(5-*iso*-propyl)-1*H*-pyrrol-2(5*H*)-one (423)



409 **413** **423**

$C_{14}H_{14}N_2O_5$
Mol. Wt.: 290.27

According to a procedure of Yoda *et al*.,[78] to a solution of L-valine tetramic acid (**409**) (100 mg, 0.71 mmol, 1.0 eq.) and *ortho*-nitrobenzoic acid (**413**) (prepared from 2-nitrobenzaldehyde according to a literature procedure of Travis *et al*.[250]) (130 mg, 0.77 mmol, 1.1 eq.) in CH_2Cl_2 abs. (9 mL) at 0 °C are added EDC · HCl (149 g, 0.77 mmol, 1.1 eq.) and DMAP (10 mg, 0.08 mmol, 0.11 eq.) and the mixture is left to warm to room temperature. Stirring is continued for 4 h before the mixture is diluted with EtOAc (25 mL) and washed with sat. NH_4Cl_{aq} (3 × 20 mL) and brine (20 mL) before the organic phases are dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product is purified by column chromatography (silica gel, 25% → 50% EtOAc in ^{c}Hex → EtOAc) to give the product as a yellow oil (162 mg, 0.56 mmol, 79%).

R_f 0.47 (EtOAc)

^{1}H-NMR (300 MHz, MeOD):

0.79 (d, *J* = 6.9 Hz, 3H, H-7†), 1.06 (d, *J* = 7.1 Hz, 3H, H-7'†), 2.11 (qqd, *J* = 7.1, 6.9, 3.0 Hz, 1H, H-6), 4.27 (dd, *J* = 3.0, 1.1 Hz, 1H, H-5), 6.16 (d, *J* = 1.1 Hz, 1H, H-3), 7.81 – 7.97 (m, 3H, H-10, H-11, H-12), 8.05 – 8.13 (m, 1H, H-13).

^{13}C-NMR (75 MHz, MeOD):

15.1 (CH_3, C-7†), 19.8 (CH_3, C-7'†), 30.2 (CH, C-6), 64.5 (CH, C-5), 109.0 (CH, C-3), 125.5 (CH, C-13), 126.7 (C_{quart}, C-9), 131.5 (CH, C-10), 134.6 (CH, C-12), 134.9 (CH, C-11), 149.4 (C_{quart}, C-14), 162.5 (C_{quart}, C-8), 167.3 (C_{quart}, C-4), 175.6 (C_{quart}, C-2).

DIP-MS (EI):

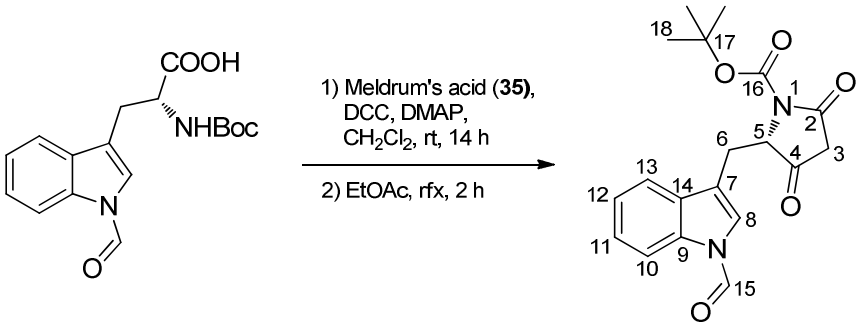
290 (1) [M^+], 244 (100) [M^+-NO_2], 202 (16), 174 (9), 156 (23), 149 (26), 135 (17), 121 (10), 104 (14) [$C_7H_4O^+$], 76 (12) [$C_6H_4^+$], 72 (18), 55 (19), 51 (10).

HRMS (ESI):

291.0972 [M + H] (calculated for $C_{14}H_{15}N_2O_5$: 291.0981).

6.6 Synthesis of potential adenylyl cyclase inhibitors

6.6.1 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-(5-(1-formyl-*1H*-indol-3-yl)methyl))-pyrrolidine-2,4-dione (430)



429 **430**

$C_{19}H_{20}N_2O_5$

Mol. Wt.: 356.37

According to procedures of Jouin *et al.*,[48] Fehrentz *et al.*[292] and Barnickel,[152] to a solution of Meldrum's acid (**35**) (239 mg, 1.7 mmol, 1.1 eq.) in CH_2Cl_2 abs. (25 mL) at

0 °C are added DMAP (368 mg, 3.0 mmol, 2.0 eq.), bisprotected L-tryptophane **429** (commercially purchased) (500 mg, 1.5 mmol, 1.0 eq.) and DCC (372 mg, 1.8 mmol, 1.2 eq.) and the mixture is stirred for 14 h at room temperature. The mixture is kept in the freezer for 1 d before the precipitated urea is removed by filtration. The solvent of the filtrate is evaporated and the residual oil is redissolved in EtOAc (30 mL) and the solution is washed with 2M HCl_{aq} (3 × 20 mL) and brine (20 mL). The organic phases are dried over Na_2SO_4, filtered and the solution is heated to reflux for 3 h. The mixture is concentrated *in vacuo* to give the crude product which is purified by column chromatography (flash silica, 7% → 10% → 20% EtOAc in ^{c}Hex) to yield the product as a white solid (404 mg, 1.1 mmol, 75%).

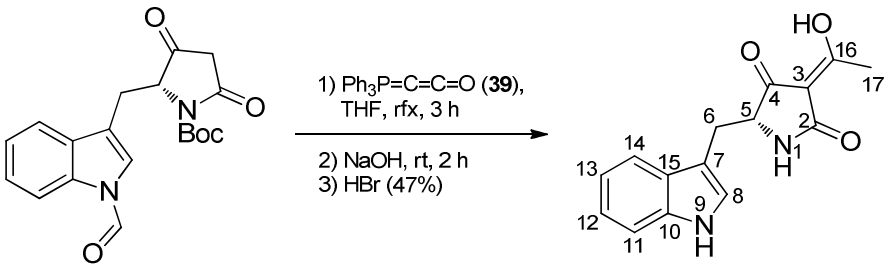
^{1}H-NMR (300 MHz, MeOD):
1.49 (s, 9H, H-18), 3.26 (dd, *J* = 14.8, 3.0 Hz, 1H, H-6a), 3.48 (dd, *J* = 14.8, 5.2 Hz, 1H, H-6b), 4.29 (dd, *J* = 5.2, 3.0 Hz, 1H, H-5), 7.04 – 7.69 (m, 4H, H-10, H-11, H-12, H-13), 7.74, 8.21* (br s, 1H, H-8), 9.03*, 9.40 (br s, 1H, H-15).

DIP-MS (EI):
158 (17) [$M^+ - C_9H_{12}NO_4$], 141 (10), 130 (100), 117 (14), 82 (12), 77 (11), 67 (15), 57 (31), 45 (71), 42 (45).

6.6.2 General method for the actetylation of tetramic acids employing ketenylidene(triphenyl)phosphorane

According to a procedure of Urbina-Gonzalez,[246] to a 0.05M solution of tetramic acid (1.0 eq.) in THF abs. is added ketenylidene(triphenyl)phosphorane (**39**) (1.1 eq.) and the mixture is heated to reflux for 3 h. To the cooled reaction mixture is added 2.5M $NaOH_{aq}$ (6 mL/mmol) dropwise and the stirring is continued for 2 h at room temperature. HBr (47%) (30 mL/mmol) and Et_2O (45 mL/mmol) are added carefully and the phases are separated. The aqueous phase is extracted with Et_2O (7 × 30 mL/mmol) and the combined organic phases are dried over Na_2SO_4 and filtered. Solvent evaporation gives the crude product.

6.6.3 Preparation of (5*S*)-3-acetyl-(5-(*1H*-indol-3-yl)methyl))-pyrrolidine-2,4-dione (208)



430 **208**

$C_{15}H_{14}N_2O_3$
Mol. Wt.: 270.28

Compound **208** is prepared applying the general method of 6.6.2. The use of bisprotected L-tryptophan tetramic acid **430** (400 mg, 1.1 mmol) and purification by preparative HPLC (55% MeOH in H_2O + 0.1% HCOOH/after 15 min gradient to 100% MeOH in 10 min) yields the product as a white solid (54 mg, 0.20 mmol, 18%).

^{1}H-NMR (300 MHz, MeOD): the ^{1}H-NMR spectrum of **208** is not completely in agreement with literature.[149]

2.28 (s, 3H, H-17), 3.07 (dd, *J* = 14.4, 6.4 Hz, 1H, H-6a), 3.24 (dd, *J* = 14.4, 4.0 Hz, 1H, H-6b), 4.13 (dd, *J* = 6.4, 4.0 Hz, 1H, H-5), 6.98 (dd, *J* = 8.0, 7.4 Hz, 1H, H-12), 7.03 (s, 1H, H-8), 7.06 (dd, *J* = 7.7, 7.4 Hz, 1H, H-13), 7.29 (d, *J* = 8.0 Hz, 1H, H-11), 7.54 (d, *J* = 7.7 Hz, 1H, H-14).

^{13}C-NMR (75 MHz, MeOD):

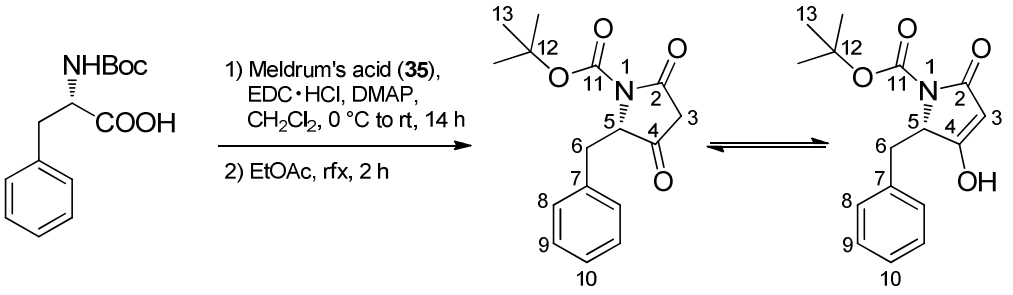
20.1 (CH_3, C-17), 28.4 (CH_2, C-6), 63.7 (CH, C-5), 103.4 (C_{quart}, C-3), 109.8 (C_{quart}, C-7), 112.2 (CH, C-11), 119.5 (CH, C-14), 119.8 (CH, C-12), 122.3 (CH, C-13), 128.8 (C_{quart}, C-10), 137.9 (C_{quart}, C-15), 173.3 (C_{quart}, C-2), 187.1 (C_{quart}, C-16), 198.8 (C_{quart}, C-4).

DIP-MS (EI):

270 (32) [M^+], 215 (10), 201 (8), 130 (100) [$M^+-C_6H_6NO_3$], 103 (33), 77 (37), 56 (42), 44 (56).

$[\alpha]_D^{24}$ −112.2 ° (c = 1.0, MeOH) [lit.: −117.8 ° (c = 1.0, MeOH)].[149]

6.6.4 Preparation of *N*-(*tert*-butoxycarbonyl)-(5*S*)-(5-benzyl-pyrrolidine-2,4-dione (438)



437 **438**

$C_{16}H_{19}NO_4$
Mol. Wt.: 289.33

Compound **438** is prepared applying the general method of 6.2.1.1. The use of *N*-Boc-L-phenylalanine (**437**) (prepared from L-phenylalanine according to a literature procedure of Barnickel[152] and Caplar *et al.*[260]) (1.3 g, 9.2 mmol) yields the crude product as an oil. The oil is dissolved in a little EtOAc and the mixture is put into the freezer for 2 d. The precipitated product is collected by filtration to yield the product as white crystalline solid (1.8 g, 6.2 mmol, 73%).

R_f 0.28 (EtOAc)

X-Ray data: Mol. Wt.: 289.33

Lattice system orthorombic

Symmetry space group $P\ 2_1\ 2_1\ 2_1$

Lattice parameters a = 8.8515 (8) Å

b = 9.7924 (10) Å

c = 16.9511 (15) Å

α = 90 °, β = 90 °, γ = 90 °

Volume of primitive cell [$Å^3$] 1469.3 (2)

No.of asymmetric units Z 4

Attenuation coefficient

μ(Mo-Kα) [mm^{-1}] 0.094

Mo-Kα radiation λ [Å] 0.71069

Temperature T [K] 133

Structure factor F(000) 616.0

Measured reflections 16878

Refinement of F^2 against all reflections

Least-square matrix: full

Reliability factor R[$F^2 > 2\sigma(F^2)$] 0.0591

Reliability factor wR2 0.0991

Goodness of fit S 0.972

For full details see appendix (chapter 8.1)

^{1}H-NMR (300 MHz, $CDCl_3$): only keto form visible

1.63 (s, 9H, H-13), 2.27 (dd, *J* = 22.5, 1.6 Hz, 1H, H-3a), 2.87 (d, *J* = 22.5 Hz, 1H, H-3b), 3.22 (dd, *J* = 13.9, 2.9 Hz, 1H, H-6a), 3.40 (dd, *J* = 13.9, 5.2 Hz, 1H, H-6b), 4.65 (ddd, *J* = 5.2, 2.9, 1.6 Hz, 1H, H-5), 6.99 – 7.07 (m, 2H, H-8), 7.24 – 7.36 (m, 3H, H-9, H-10).

^{13}C-NMR (75 MHz, $CDCl_3$): only keto form visible

28.4 (CH_3, C-13), 33.5 (CH_2, C-6), 37.6 (CH_2, C-3), 60.8 (CH_2, C-5), 79.9 (C_{quart}, C-12), 127.1 (CH, C-10), 128.7 (CH, C-9), 129.3 (CH, C-8), 136.3 (C_{quart}, C-7), 155.3 (C_{quart}, C-11), 166.9 (C_{quart}, C-2), 206.9 (C_{quart}, C-4).

^{1}H-NMR (300 MHz, MeOD): only enol form visible

1.61 (s, 9H, H-13), 3.16 (dd, *J* = 14.0, 2.7 Hz, 1H, H-6a), 3.47 (dd, *J* = 14.0, 5.5 Hz, 1H, H-6b), 4.69 (dd, *J* = 5.5, 2.7 Hz, 1H, H-5), 7.04 – 7.10 (m, 2H, H-8), 7.15 – 7.25 (m, 3H, H-9, H-10).

^{13}C-NMR (75 MHz, MeOD): only enol form visible

28.5 (CH_3, C-13), 35.8 (CH_2, C-6), 62.1 (CH_2, C-5), 83.9 (C_{quart}, C-12), 97.2 (CH_2, C-3), 128.0 (CH, C-10), 129.1 (CH, C-9), 130.9 (CH, C-8), 135.5 (C_{quart}, C-7), 150.9 (C_{quart}, C-11), 173.2 (C_{quart}, C-2), 178.1 (C_{quart}, C-4).

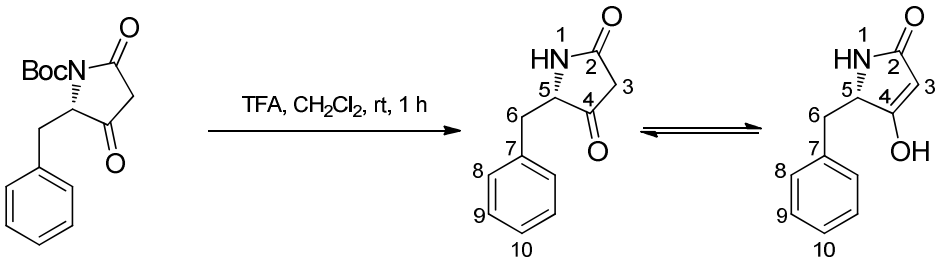
DIP-MS (EI):

289 (1) [M^+], 233 (27), 216 (17) [$M^+ - O^tBu$], 189 (34), 161 (45), 146 (9), 118 (12), 91 (63) [$C_7H_7^+$], 58 (100), 42 (16).

$[\alpha]_D^{24}$ +116.23 ° (c = 1.0, $CHCl_3$)

IR (cm^{-1}) The IR spectrum of **438** is in good agreement with literature.[293]

6.6.5 Preparation of (*S*)-5-benzylpyrrolidine-2,4-dione (433)[53]



438 **433**

$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

Compound **433** is prepared applying the general method of 6.3.10. The use of Boc-protected tetramic acid **438** (150 mg, 0.52 mmol) yields the crude product. The crude product is dissolved in a minimum of EtOAc and some Et_2O is added before the mixture is stored in the freezer for 14 h. The pure product precipitates and is collected by filtration and washing with cold Et_2O to yield the product as white solid (65 mg, 0.34 mmol, 66%).

R_f 0.33 (EtOAc)

^{1}H-NMR (300 MHz, $CDCl_3$): only keto form visible
2.73 (dd, *J* = 22.4, 1.7 Hz, 1H, H-3a), 2.84 (dd, *J* = 14.0, 8.2 Hz, 1H, H-6a), 2.94 (dd, *J* = 22.4, 0.5 Hz, 1H, H-3b), 3.17 (dd, *J* = 14.0, 4.0 Hz, 1H, H-6b), 4.24 (dddd, *J* = 8.2, 4.0, 1.7, 0.5 Hz, 1H, H-5), 7.13 – 7.19 (m, 2H, H-8), 7.24 – 7.37 (m, 3H, H-9, H-10).

^{13}C-NMR (75 MHz, $CDCl_3$): only keto form visible
38.5 (CH_2, C-5), 40.9 (CH_2, C-3), 65.3 (CH, C-5), 127.6 (CH, C-10), 129.2 (CH, C-9), 129.5 (CH, C-8), 135.3 (C_{quart}, C-7), 170.7 (C_{quart}, C-2), 206.6 (C_{quart}, C-4).

^{1}H-NMR The MeOD ^{1}H-NMR spectrum of **433** is in good agreement with literature.[53]

^{13}C-NMR (75 MHz, MeOD): tautomeric ratio: (keto : enol) 66% : 33% (calculated from NMR)
Keto: 38.6 (CH_2, C-6), 40.6 (CH_2, C-3), 66.5 (CH, C-5), 127.7 (CH, C-10), 129.6 (CH, C-9), 130.7 (CH, C-8), 137.0 (C_{quart}, C-7), 174.0 (C_{quart}, C-2), 209.1 (C_{quart}, C-4).

Enol: 38.2 (CH_2, C-6), 60.2 (CH, C-5), 94.3 (CH, C-3), 128.0 (CH, C-10), 129.4 (CH, C-9), 131.0 (CH, C-8), 136.8 (C_{quart}, C-7), 177.2 (C_{quart}, C-2/C-4), 178.5 (C_{quart}, C-2/C-4).

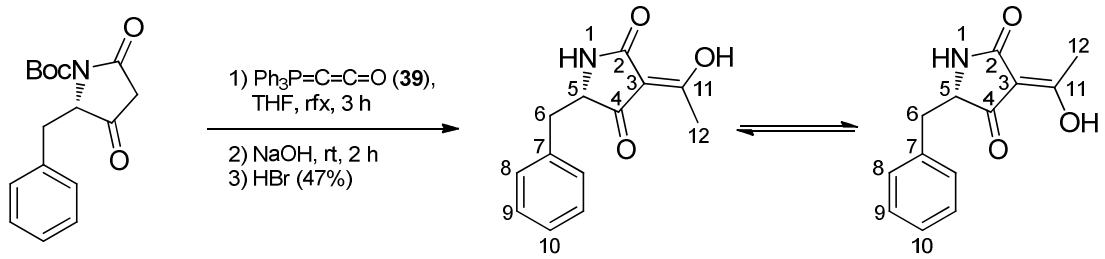
DIP-MS (EI):

189 (9) [M^+], 161 (1) [M^+-CO], 98 (3) [$M^+-C_7H_7$], 91 (100) [$C_7H_7^+$], 77 (3) [$C_6H_5^+$], 65 (10).

mp 159.5 °C

IR (cm^{-1}) The IR spectrum of **433** is in good agreement with literature.[53]

6.6.6 Preparation of (*S*)-3-acetyl-5-benzylpyrrolidine-2,4-dione (434)



438 **434**

$C_{13}H_{13}NO_3$
Mol. Wt.: 231.25

Compound **434** is prepared applying the general method of 6.6.2. The use of *N*-Boc-L-phenylalanine tetramic acid (**438**) (150 mg, 0.52 mmol) and purification by preparative HPLC (45% MeOH in H_2O + 0.1% HCOOH/after 25 min gradient to 100% MeOH in 10 min) yields the product as a white solid (47 mg, 0.20 mmol, 39%).

^{1}H-NMR The $CDCl_3$ ^{1}H-NMR spectrum of **434** is in agreement with literature.[137]

^{13}C-NMR (75 MHz, $CDCl_3$): tautomeric ratio: 83% : 17% (calculated from NMR), only major tautomer reported

19.9 (CH_3, C-12), 38.5 (CH_2, C-6), 63.7 (CH, C-5), 106.2 (C_{quart}, C-3), 127.4 (CH, C-10), 129.2 (2 × CH, C-8, C-9), 136.6 (C_{quart}, C-7), 174.7 (C_{quart}, C-2), 194.2 (C_{quart}, C-4/C-11), 195.9 (C_{quart}, C-4/C-11).

^{1}H-NMR (300 MHz, MeOD):
2.34 (s, 3H, H-12), 2.94 (dd, *J* = 14.0, 6.3 Hz, 1H, H-6a), 3.10 (dd, *J* = 14.0, 4.5 Hz, 1H, H-6b), 4.15 (dd, *J* = 6.3, 4.5 Hz, 1H, H-5), 7.13 – 7.29 (m, 5H, H-8, H-9, H-10).

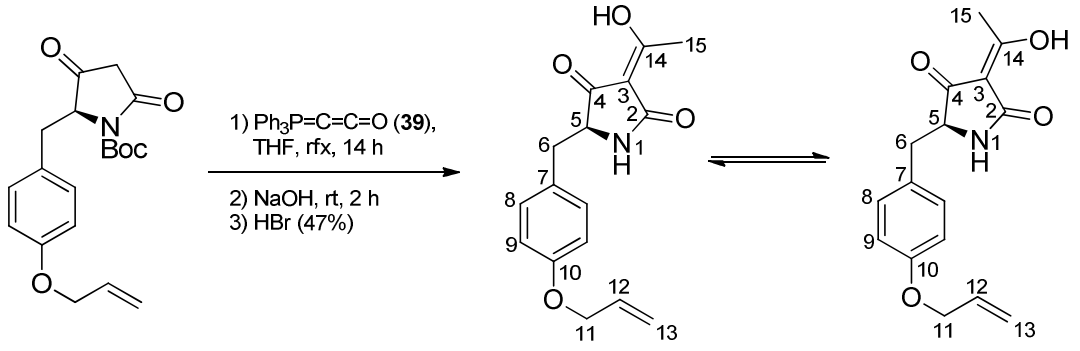
^{13}C-NMR (75 MHz, MeOD): quaternary carbons very faint
20.4 (CH_3, C-12), 38.3 (CH_2, C-6), 63.7 (CH, C-5), 104.9 (C_{quart}, C-3), 127.9 (CH, C-10), 129.3 (CH, C-9), 130.8 (CH, C-8), 137.1 (C_{quart}, C-7), 173.0 (C_{quart}, C-2), 193.6 (C_{quart}, C-4/C-11), 196.5 (C_{quart}, C-4/C-11).

DIP-MS (EI):
231 (43) [M^+], 214 (2) [M^+−OH], 189 (10), 140 (45) [M^+−C_7H_7], 120 (14), 98 (27), 91 (100) [$C_7H_7^+$], 65 (13), 43 (32).

mp 129.5 °C

IR (cm^{-1}) 3189 (m), 3034 (w), 2934 (w), 1711 (s), 1615 (s, br), 1496 (m), 1453 (s), 1424 (s), 1379 (s), 1316 (m), 1276 (s), 1227 (s), 1083 (m), 1029 (m), 1003 (m), 1003 (m), 962 (m), 919 (s), 884 (s), 840 (m), 781 (s), 757 (m), 727 (s), 695 (s).

6.6.7 Preparation of (*S*)-3-acetyl-5-((4-allyloxy)benzyl)-pyrrolidine-2,4-dione (435)



116 **435**

$C_{16}H_{17}NO_4$
Mol. Wt.: 287.31

Compound **435** is prepared applying the general method of 6.6.2. The use of tetramic acid **116** (345 mg, 1.0 mmol) and purification by preparative HPLC (45%

MeOH in H_2O + 0.1% HCOOH/after 25 min gradient to 100% MeOH in 10 min) yields the product as a white solid (78 mg, 0.27 mmol, 27%).

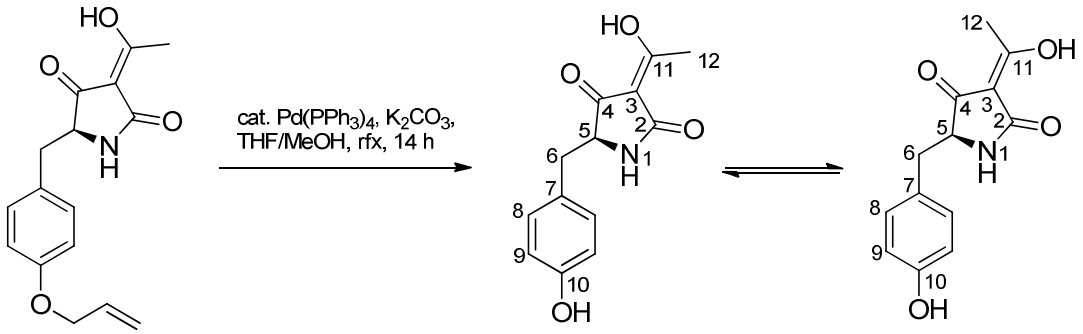
^{1}H-NMR (300 MHz, $CDCl_3$): tautomeric ratio: 77% : 13% (calculated from NMR), only major tautomer reported

2.46 (s, 3H, H-15), 2.60 (dd, *J* = 13.9, 10.3 Hz, 1H, H-6a), 3.23 (dd, *J* = 13.9, 3.4 Hz, 1H, H-6b), 3.98 (dd, *J* = 10.3, 3.4 Hz, 1H, H-5), 4.53 (ddd, *J* = 5.2, 1.5, 1.4 Hz, 2H, H-11), 5.30 (ddt, *J* = 10.6, 1.6, 1.4 Hz, 1H, H-13$_Z$), 5.41 (ddt, *J* = 17.3, 1.6, 1.5 Hz, 1H, H-13$_E$), 5.63 (br s, 1H, NH-1), 6.05 (ddt, *J* = 17.3, 10.6, 5.2 Hz, 1H, H-12), 6.87 (d, *J* = 8.7 Hz, 2H, H-9), 7.10 (d, *J* = 8.7 Hz, H-8).

^{13}C-NMR (75 MHz, $CDCl_3$): tautomeric ratio: 77% : 13% (calculated from NMR), only major tautomer reported

19.8 (CH_3, C-15), 37.6 (CH_2, C-6), 63.8 (CH, C-5), 69.0 (CH_2, C-11), 115.4 (CH, C-9), 117.9 (CH_2, C-13), 128.6 (C_{quart}, C-7), 130.2 (CH, C-8), 133.3 (CH, C-12), 158.0 (C_{quart}, C-10), 185.8 (C_{quart}, C-2), 194.3 (C_{quart}, C-4).

6.6.8 Preparation of (*S*)-3-acetyl-5-((4-hydroxy)benzyl)-pyrrolidine-2,4-dione (436)



435 **436**

$C_{13}H_{13}NO_4$
Mol. Wt.: 247.25

According to procedures of Barnickel *et al.*,[98,152] To a solution of 3-acyltetramic acid **435** (20 mg, 0.07 mmol, 1.0 eq.) in a mixture of THF abs./MeOH abs. (5:1)

(3 mL) is added $Pd(PPh_3)_4$ (~2 mg, 2 mol%) and after 5 min of stirring, K_2CO_3 (29 mg, 0.21 mmol, 3.0 eq.) is added. The mixture is heated to reflux for 14 h before the solvent is evaporated. The residue is dissolved in 0.5M $NaOH_{aq}$ (25 mL) and washed with Et_2O (2 × 30 mL). The pH of the aqueous phase is adjusted to pH 1 with conc. HCl_{aq} and the phase is extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases are dried over Na_2SO_4, filtered and the solvent evaporated. The product is obtained as an orange oil (12 mg, 0.05 mmol, 70%).

^{1}H-NMR (300 MHz, MeOD): the ^{1}H-NMR spectrum of **436** is not in agreement with literature.[294]

2.34 (s, 3H, H-12), 2.86 (dd, *J* = 14.1, 6.0 Hz, 1H, H-6a), 3.00 (dd, *J* = 14.1, 4.4 Hz, 1H, H-6b), 4.08 (dd, *J* = 6.0, 4.4 Hz, 1H, H-5), 6.67 (d, *J* = 8.2 Hz, 2H, H-9), 6.98 (d, *J* = 8.2 Hz, 1H, H-8).

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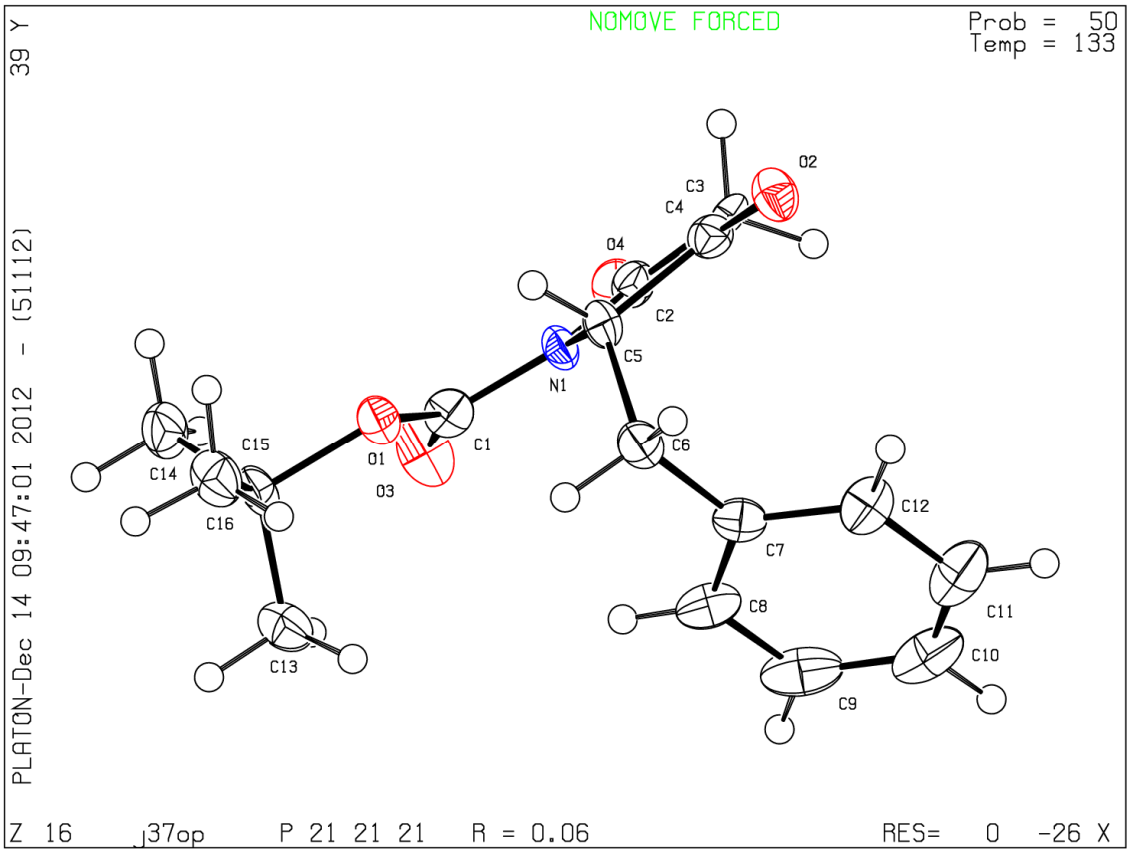
8 Appendix

8.1 X-Ray structural analysis of *N*-(*tert*-butoxycarbonyl)-(5S)-(5-benzyl)-pyrrolidine-2,4-dione (438)



Computing details:

Data collection: *X-AREA*-STOE; cell refinement: *X-AREA*-STOE; data reduction: *X-AREA*-STOE; program(s) used to solve structure: *SIR97*; program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008).

Crystal Data: (cell parameters from 16878 reflections)

Formula	$C_{16}H_{19}NO_4$
Molecular weight [g · mol^{-1}]	289.32
Lattice system	orthorombic
Appearance	block, colourless
Crystal size [mm]	0.107 × 0.103 × 0.099

Symmetry space group	*P* 21 21 21
Lattice parameters	a = 8.8515 (8) Å
	b = 9.7924 (10) Å
	c = 16.9511 (15) Å
	α = 90 °, β = 90 °, γ = 90 °
Volume of primitive cell [Å^3]	1469.3 (2)
No.of asymmetric units Z	4
Density ρ [g · cm^{-1}]	1.308
Attenuation coefficient μ(Mo-Kα) [mm^{-1}]	0.094
Mo-Kα radiation λ [Å]	0.71069
Temperature T [K]	133
Structure factor F(000)	616.0

Data collection:

Measurement device	STOE-IPDS II
Radiation source	fine-focus sealed tube
Radiation monochromator	graphite
Measurement method	ω-scan
Measured reflections	16878
Independent reflections	2481
Reflections with $I > 2\sigma(I)$	1744
Merging error R_{int}	0.0965
Maximal angle of incidence θ_{max}	24.79 °
Minimal angle of incidence θ_{min}	2.4 °
Miller indices	h = −10→10
	k = −11→11
	l = −19→20

Refinement:

Refinement of F^2 against all reflections	
Least-square matrix: full	
Reliability factor R[$F^2 > 2\sigma(F^2)$]	0.0591
Reliability factor wR2	0.0991

Goodness of fit S	0.972
Independent reflections	2481
No. of parameters	197

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0427P)^2 + 0.2522P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$	0.05
electron density in the crystal [e · Å^{-3}]	Δρmax = 0.343
	Δρmin = −0.268

Absolute structure: Flack H D (1983), Acta Cryst. A39, 876 – 881

Flack parameter	−2 (2)

Special details:

Geometry: All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.

Refinement: Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors (gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters [Å^2]

	x	y	z	U_{iso}*/U_{eq}
O1	0.1262(3)	0.5561(3)	0.76311(15)	0.0259(7)
O2	0.5234(3)	0.8257(3)	0.61682(15)	0.0289(7)
O3	0.0192(3)	0.4448(3)	0.65940(17)	0.0389(8)
O4	0.0953(3)	0.5848(3)	0.52091(16)	0.0306(7)
N1	0.2142(4)	0.5986(3)	0.64311(18)	0.0226(8)
C1	0.1080(5)	0.5231(4)	0.6873(2)	0.0247(9)
C2	0.1970(4)	0.6291(4)	0.5641(2)	0.0243(10)
C3	0.3178(4)	0.7233(4)	0.5432(2)	0.0247(10)
H3A	0.3819	0.6830	0.5014	0.030
H3B	0.2745	0.8098	0.5230	0.030
C4	0.4002(4)	0.7476(4)	0.6075(2)	0.0237(9)
C5	0.3440(5)	0.6693(4)	0.6774(2)	0.0233(9)
H5C	0.301(4)	0.725(4)	0.717(2)	0.037(12)
C6	0.4642(4)	0.5723(4)	0.7133(2)	0.0270(10)
H6A	0.5506	0.6273	0.7325	0.032
H6B	0.4198	0.5246	0.7592	0.032
C7	0.5210(4)	0.4680(4)	0.6554(2)	0.0261(9)
C8	0.4433(5)	0.3463(4)	0.6418(3)	0.0348(11)
H8	0.3538	0.3267	0.6706	0.042
C9	0.4959(6)	0.2539(5)	0.5864(3)	0.0473(13)
H9	0.4414	0.1719	0.5772	0.057
C10	0.6274(6)	0.2796(5)	0.5441(3)	0.0456(13)
H10	0.6620	0.2165	0.5056	0.055
C11	0.7060(6)	0.3966(5)	0.5585(3)	0.0449(13)
H11	0.7974	0.4136	0.5309	0.054
C12	0.6544(4)	0.4912(4)	0.6131(2)	0.0320(10)
H12	0.7101	0.5727	0.6218	0.038
C13	0.0709(5)	0.3349(4)	0.8226(2)	0.0326(11)
H13A	0.1805	0.3207	0.8234	0.049
H13B	0.0286	0.2958	0.7742	0.049

H13C	0.0254	0.2901	0.8686	0.049
C14	−0.1305(4)	0.5167(4)	0.8152(3)	0.0360(11)
H14A	−0.1644	0.4837	0.7636	0.054
H14B	−0.1467	0.6156	0.8185	0.054
H14C	−0.1880	0.4710	0.8569	0.054
C15	0.0982(5)	0.5494(4)	0.8993(2)	0.0331(10)
H15A	0.0826	0.6484	0.8974	0.050
H15B	0.2064	0.5299	0.9038	0.050
H15C	0.0452	0.5115	0.9451	0.050
C16	0.0374(4)	0.4856(4)	0.8253(2)	0.0271(9)

Atomic displacement parameters [Å^2]

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0248(16)	0.0284(16)	0.0244(15)	0.0031(12)	0.0028(12)	−0.0025(13)
O2	0.0298(17)	0.0300(16)	0.0269(15)	−0.0011(13)	0.0032(13)	−0.0075(13)
O3	0.0353(18)	0.053(2)	0.0287(16)	0.0015(15)	−0.0066(14)	−0.0150(16)
O4	0.0270(17)	0.0388(17)	0.0261(15)	0.0026(14)	−0.0035(14)	0.0019(15)
N1	0.0204(18)	0.0285(18)	0.0190(17)	0.0087(15)	0.0040(14)	0.0013(15)
C1	0.025(2)	0.031(2)	0.018(2)	−0.0007(18)	−0.0073(18)	0.003(2)
C2	0.022(2)	0.029(2)	0.022(2)	0.0003(18)	0.0000(19)	0.0054(19)
C3	0.025(2)	0.022(2)	0.027(2)	−0.0040(18)	0.0078(18)	0.0089(18)
C4	0.028(2)	0.021(2)	0.023(2)	−0.0029(18)	0.001(2)	0.002(2)
C5	0.026(2)	0.028(2)	0.016(2)	0.0015(18)	0.0031(18)	−0.0020(18)
C6	0.025(2)	0.030(2)	0.027(2)	0.0047(19)	0.0006(19)	−0.0017(18)
C7	0.026(2)	0.027(2)	0.025(2)	0.0042(18)	−0.0090(18)	0.0027(18)
C8	0.037(3)	0.027(2)	0.041(3)	−0.002(2)	−0.012(2)	0.007(2)
C9	0.059(3)	0.031(2)	0.052(3)	−0.002(2)	−0.026(3)	0.009(3)
C10	0.053(3)	0.041(3)	0.043(3)	−0.013(2)	−0.013(3)	0.020(3)
C11	0.042(3)	0.057(3)	0.036(3)	−0.009(3)	−0.002(2)	0.019(3)
C12	0.025(2)	0.037(3)	0.034(2)	−0.008(2)	−0.005(2)	0.0006(19)
C13	0.041(3)	0.030(2)	0.027(2)	0.0052(19)	−0.001(2)	−0.0032(19)
C14	0.022(2)	0.047(3)	0.039(3)	0.011(2)	0.005(2)	0.003(2)
C15	0.044(3)	0.036(2)	0.020(2)	−0.0018(19)	0.002(2)	−0.005(2)
C16	0.023(2)	0.033(2)	0.026(2)	0.0091(19)	0.0049(19)	−0.0064(18)

Geometric parameters

Bond length [Å]

O1—C1	1.335(4)	C8—H8	0.9500
O1—C16	1.486(4)	C9—C10	1.390(7)
O2—C4	1.341(4)	C9—H9	0.9500
O3—C1	1.196(5)	C10—C11	1.363(7)
O4—C2	1.238(5)	C10—H10	0.9500
N1—C1	1.411(5)	C11—C12	1.386(6)
N1—C2	1.381(5)	C11—H11	0.9500
N1—C5	1.462(5)	C12—H12	0.9500
C2—C3	1.456(6)	C13—C16	1.506(5)
C3—C4	1.332(5)	C13—H13A	0.9800
C3—H3A	0.9900	C13—H13B	0.9800
C3—H3B	0.9900	C13—H13C	0.9800
C4—C5	1.497(5)	C14—C16	1.527(5)
C5—C6	1.550(5)	C14—H14A	0.9800
C5—H5C	0.94(4)	C14—H14B	0.9800
C6—C7	1.503(5)	C14—H14C	0.9800
C6—H6A	0.9900	C15—C16	1.501(5)
C6—H6B	0.9900	C15—H15A	0.9800
C7—C8	1.396(5)	C15—H15B	0.9800
C7—C12	1.400(5)	C15—H15C	0.9800
C8—C9	1.385(6)		

Bond angle [°]

O1—C1—N1	107.7(3)	C8—C9—H9	119.6
O1—C16—C15	102.1(3)	C9—C8—C7	120.3(4)
O1—C16—C13	109.2(3)	C9—C8—H8	119.8
O1—C16—C14	110.0(3)	C9—C10—H10	120.4
O2—C4—C5	117.9(3)	C10—C9—H9	119.6
O3—C1—O1	128.0(4)	C10—C11—C12	120.9(5)

O3—C1—N1	124.3(3)	C10—C11—H11	119.6
O4—C2—N1	125.3(4)	C11—C10—C9	119.2(5)
O4—C2—C3	127.7(4)	C11—C10—H10	120.4
N1—C2—C3	107.0(4)	C11—C12—C7	120.8(4)
N1—C5—C4	100.9(3)	C11—C12—H12	119.6
N1—C5—C6	113.9(3)	C12—C7—C6	120.4(4)
N1—C5—H5C	104(3)	C12—C11—H11	119.6
C1—O1—C16	120.5(3)	C13—C16—C14	112.6(3)
C1—N1—C5	124.1(3)	C15—C16—C13	111.3(4)
C2—N1—C1	123.7(3)	C15—C16—C14	111.1(4)
C2—N1—C5	111.7(3)	C16—C13—H13A	109.5
C2—C3—H3A	110.0	C16—C13—H13B	109.5
C2—C3—H3B	110.0	C16—C13—H13C	109.5
C3—C4—O2	130.1(4)	C16—C14—H14A	109.5
C3—C4—C5	111.9(3)	C16—C14—H14B	109.5
C4—C3—C2	108.5(3)	C16—C14—H14C	109.5
C4—C3—H3A	110.0	C16—C15—H15A	109.5
C4—C3—H3B	110.0	C16—C15—H15B	109.5
C4—C5—C6	113.4(3)	C16—C15—H15C	109.5
C4—C5—H5C	114(3)	H3A—C3—H3B	108.4
C5—C6—H6A	109.0	H6A—C6—H6B	107.8
C5—C6—H6B	109.0	H13A—C13—H13B	109.5
C6—C5—H5C	110(2)	H13A—C13—H13C	109.5
C7—C6—C5	112.9(3)	H13B—C13—H13C	109.5
C7—C6—H6A	109.0	H14A—C14—H14B	109.5
C7—C6—H6B	109.0	H14A—C14—H14C	109.5
C7—C8—H8	119.8	H14B—C14—H14C	109.5
C7—C12—H12	119.6	H15A—C15—H15B	109.5
C8—C7—C6	121.6(4)	H15A—C15—H15C	109.5
C8—C7—C12	118.0(4)	H15B—C15—H15C	109.5
C8—C9—C10	120.9(5)		

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(Eidesstattliche) Versicherungen und Erklärungen

(§ 5 Nr. 4 PromO)

Hiermit erkläre ich, dass keine Tatsachen vorliegen, die mich nach den gesetzlichen Bestimmungen über die Führung akademischer Grade zur Führung eines Doktorgrades unwürdig erscheinen lassen.

(§ 8 S. 2 Nr. 5 PromO)

Hiermit erkläre ich mich damit einverstanden, dass die elektronische Fassung meiner Dissertation unter Wahrung meiner Urheberrechte und des Datenschutzes einer gesonderten Überprüfung hinsichtlich der eigenständigen Anfertigung der Dissertation unterzogen werden kann.

(§ 8 S. 2 Nr. 7 PromO)

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Ich habe die Dissertation nicht bereits zur Erlangung eines akademischen Grades anderweitig eingereicht und habe auch nicht bereits diese oder eine gleichartige Doktorprüfung endgültig nicht bestanden.

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Ort, Datum, Unterschrift