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Total synthesis of naturally occurring glycosylated tetramic acids

Dissertation to obtain the degree

Doctor of natural scienes (Dr. rer. nat.)

Submitted by

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"The biggest problem on being successful is that it looks quite easy."

Prof. Dr. Jean-Jacques Dordain, General Director of the European Space Agency (ESA) in an interview 12.11.2014 concerning the Rosetta mission.

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I. ABSTRACT

The first synthesis of a naturally occurring 3-acyl tetramic acid glycoconjugate was investigated. An endofungal metabolite called epicoccamide D (see Figure I.1.) was synthesized for the first time. This was accomplished in 19 steps resulting in a 17% overall yield. The total synthesis was built on a modular base to possibly adapt the concept to other natural products.

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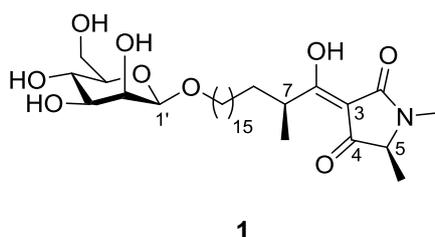
Figure I.1. Epicoccamide D with the assigned stereocenters being 5*S* and 7*S* configurated.

The key steps of the synthesis were: a β-selective glycosylation followed by a C-2 epimerisation reaction of the sugar moiety, a HWE olefination, an aminolysis reaction to install the *L*-alanine residue, followed by a Lacey-Dieckman cyclisation. The 7*S* stereocenter was established using a rhodium based homogeneous catalyst and applying a high-pressure hydrogenation to the tetramic acid. Stable BF$_2$-chelate complexes are here utilized to disarm its metal chelating properties. This procedure allowed assignment of the hitherto unknown absolute configuration of the natural product by comparison of NMR data and optical rotation.

Additional side chains of other naturally occurring 3-acyl tetramic acids were synthesized by applying similar retrosynthetic approaches used for epicoccamide D total synthesis. The dissacharide terminated alkyl chain of ancorinoside B bearing a galactose and a glucuronic acid (see Figure I.2. A) was successfully synthesized including two consecutive β-selective glycosylations and a C-6 oxidation protection procedure.

Also a more substituted side chain for the total synthesis of virgeneone (see Figure I.2. B) was synthesized ready to couple it to a β-mannose as elaborated for epicoccamide D total synthesis. Assembly of this side chain included an ozonolysis reaction and involved a Grignard reaction.

With both side chains in hand, the total synthesis of the two compounds ancorinoside B and virgineone can be performed by applying the protocol derived for epicoccamide D total

synthesis. All additional and new steps of these two side chains have been carried out within this thesis.

Additionally, chemical *N*-glycosylation was investigated to allow access to aurantosides (see Figure I.2. C) by employing a Fukayama-Mitsunobu reaction. The behaviour of the tetramic acids, 3-acyl tetramic acids and their boron complexes towards Lewis-acidic glycosylation conditions was examined as well.
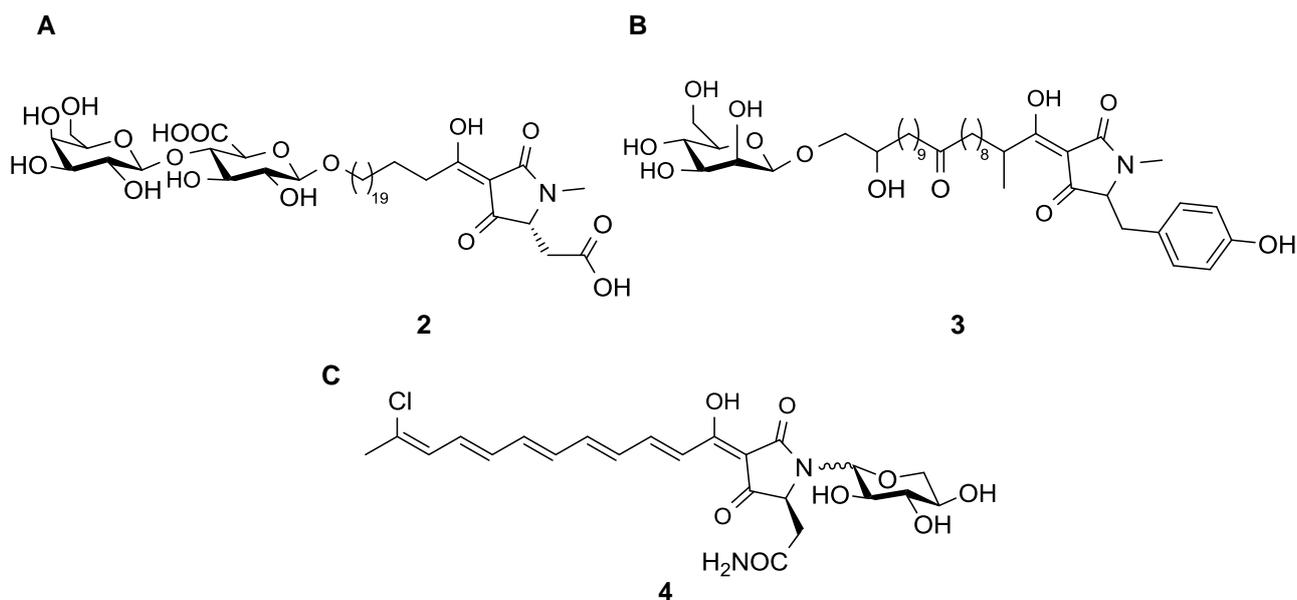
Figure I.2. Naturally occurring 3-acyl tetramic acid glycoconjugates: A) ancorinoside B; B) virgineone; C) aurantoside G/J.

The last section of this thesis deals with the stereoinduction of the successfully applied BF_2-complexes in terms of their behavior heterogeneous hydrogenations. This process is briefly investigated by building a diethyl boron complex of a tetramic acid.

II. INTRODUCTION

Infectious diseases, their overall behaviour, and potential threat towards human health, have changed dramatically over the last two decades. Not only have emerging resistances[1–4] of various human pathogens[5] to medicines become a major issue, but also mortality from cancer is on the increase[6]. These problems give rise to the need for new drugs to counter the potentially huge impact on global human health.

Techniques to find such drugs underwent a period of remarkable development in recent years. Different screening techniques like fragment-based drug discovery[7,8] or combinatorial compound library screening[9] combined with high-throughput analyzing methods have undergone much development and are highly efficient. Computational methods[10] can determine potentially effective binding sites and drug like molecules to target these identified sites can be modelled *in silico*. Their limitation, however, is that only known targets can be challenged with different compounds in established screenings. Natural products and their derivatives have therefore returned into sharp focus over the last few years.[11,12] Improved screening techniques allow the application of extracts from natural sources[11], the mentioned compound libraries are extended by bio-inspired derivatives[13] and natural products can lead to an important identification of new druggable targets[12]. After identifying a potential drug candidate, total synthesis is still required to eventually confirm the absolute configuration and to get higher amounts of the desired pure compound in hand.

There are several natural product lead compound classes[14] usable as inspiration for derivatives, target identification, or even directly as a drug. Most of the natural products, besides primary metabolites like peptides, nucleic acids and saccharides, are secondary metabolites bearing various additional functional groups[14]. The largest of these naturally occurring compound classes can be divided into alkaloids, polyketides, phenolic products, terpenes including steroids and poylenes. A reoccurring motif in most of these natural product classes is a so called tetramic acid[15] also referred to as pyrroldine-2,4-dione system.

II.1. Tetramic acid derivatives and their structural diversity

Tetramic acids, in addition to their oxygen based analogues called tetronic acids[16,17] are an important and persistent motif found in many natural product classes. The common structural feature of this compound class is the 5-membered ring system called pyrroldine-2,4-dione (**6**).

Most naturally occurring tetramic acids are acylated in the C-3 position and can have an additional moiety at the C-5 being derived from natural amino acids as shown in Figure II.1.D.[15,18–20] A tetramic acid of natural origin can also be 4-*O*-alkylated in some cases. Tetronic acids are also an important part in many natural products. One of the most famous and very well studied representative is called ascorbic acid better referred to as vitamin C (see Figure II.1.A).
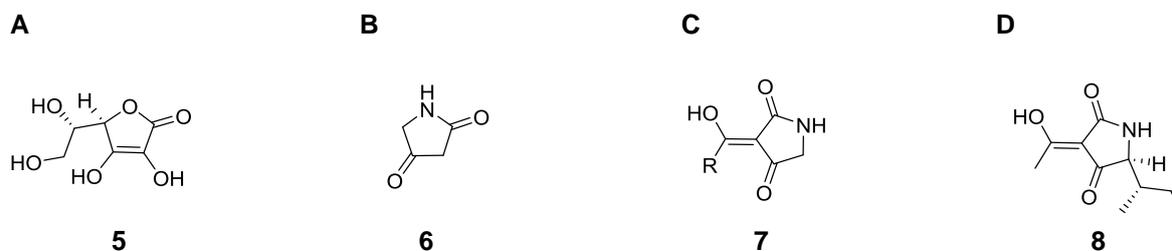
Figure II.1. Examples of tetramic and tetronic acids. A) *L*-ascorbic acid[17], the widely known tetronic acid derivative better referred to as vitamin C; B) core pyrrolidine-2,4-dione structure of tetramic acids; C) most frequent occurring 3-acylated tetramic acid derivative shown in their *exo*-enol form. The variable residue R can be a polyene, a fatty acid or incorporated in a ring system normally ending at the C-5 position of the tetramic acid heterocycle. D) tenuazonic acid[21,22].

The tetramic acid core pyrrolidine-2,4-dione system **6** was first synthesized 1911 by Benary[23]. It took almost fifty years until Thomas *et al.*[21] found the first example of a natural occurring tetramic acid called tenuazonic acid (**8**) and one year later the structure was elucidated by Stickings *et al.*[22]. Since then nearly 200 other tetramic acid derivatives have been isolated, their structures determined, and total syntheses performed[18]. These descriptions and findings are published in more than 600 articles (SciFinder 05/2015).

II.1.1. 3-Acyl tetramic acids

The most important and biggest subfamily of tetramic acids are 3-acyl derivatives since most other classes can are derived directly from them. Simple representatives of this class are, beside the mentioned tenuazonic acid, melophlins and penicillenoles.[18,20] Both of these groups bear an *N*-methylated pyrrolidine-2,4-dione system derived from either glycine or alanine (in the case of melophlins[24–26]), or from threonine including its possible elimination product (in the case of penicillenols[27]). Beside these minor differences their C-3 position is always acylated with a fatty acid chain comprising of various methylation patterns. It is possible to add glycosylated tetramic acids such as epicoccamide D[28] to this compound class but these, and other sugar bearing tetramic acids, are discussed later in this thesis in more

detail. The most important structural features of these compounds are exemplarily shown in Figure II.2.

A   **B**   **C**

9   **10**   **1**
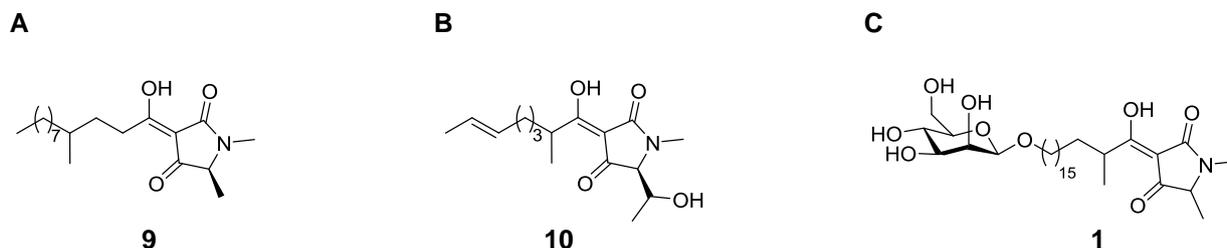
Figure II.2. Structure of three linear 3-acylated tetramic acids. A) melophlin B[24]; B) penicillenol C$_1$[27]; C) epicoccamide D[28].

Melophlins[24–26] (**9**) include the largest numbers of compounds in their family (19), whereas only six representatives of penicillenols[27] (**10**) and four in case of the epicoccamides[28,29] (**1**) are known to date. These three examples of 3-acylated tetramic acids, shown in Figure II.1., have numerous different biological activities reaching from antibacterial over antifungal to cytotoxic properties.

The first synthesis of one of the shown compounds was carried out in 2005 by Schobert *et al.*[30] using immobilized Ph$_3$PCCO in a domino style acylation Wittig reaction to gain access to melophlins. They achieved the first synthesis of several melophlin derivatives. Five years later Yoda *et al.*[31] found an approach to get penicillenols synthesized by a 4-*O*-acylation rearrangement procedure. Total synthesis of epicoccamide D was again achieved by Schobert *et al.*[32] in 2013. This particular synthesis is the major part of this thesis utilizing a Lacey-Dieckman approach to get the desired 3-acyl tetramic acid moiety in place.

II.1.2. 3-Polyenoyl tetramic acids

Derived from these 3-acyl tetramic acids, the next compound class that will be investigated are the 3-di- or 3-polyenoyl tetramic acids. In contrast to the above mentioned compounds they bear two or more double bonds in conjugation with the 3-*exo* enol double bond making this tautomer even more favourable. Examples of open chained 3-polyenoyl tetramic acids are shown in Figure II.3. However, hybrids of the later discussed 3-decalinoyl or macrocyclic tetramic acids with a polyene side chain also occur.

Ravenic acid (**11**) was first isolated by Michael *et al.*[33] and eight years later synthesized by Schobert *et al.*[34] using Ph$_3$PCCO for building up the tetramic acid moiety itself and again the same reagent for a 3-acylation Wittig reaction procedure. Harzenic acid (**12**) has been known for over 25 years and was originally isolated by Casser *et al.*[35], but it took until early 2015 to

develop a synthetic access to this tetramic acid. Healy *et al.*[36] published a smart synthesis using a known[37] lactone also occurring in 3-decanoylic tetramic acids[37] with all the desired stereocenters already in place. The alkaline conditions of the Lacey-Dieckman cyclisation deprotonated the *β*-keto amide moiety, as usual, and then opened the lactone to establish the desired tetramic acid moiety, yielding the desired C-5 substitution pattern shown in Figure II.3.B.
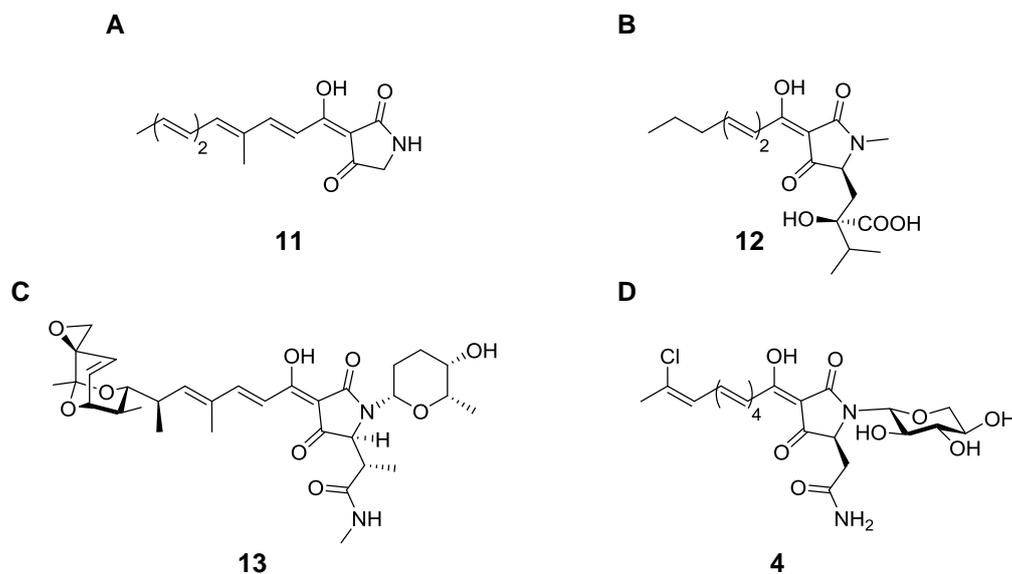
Figure II.3. Structure of 3-polyenoyl tetramic acids. A) ravenic acid[33]; B) harzianic acid[35]; C) streptolydigin[38]; D) aurantoside G[39].

Streptolydigin (**13**) has been known since 1963[38] and extracts with high amounts of this tetramic acids were intensively studied for their biological properties such as a strong *E. coli* RNA polymerase inhibition first discussed by McClure[40]. Starting from the early 1980s many suggestions concerning the biosynthetic pathway[41,42] of this compound have been published and recent results were able to almost show the complete path. From the first assessment of the structure of streptolydigin, it took nearly fifty years until Pronin *et al.*[43] facilitated the first total synthesis. Their outstanding synthetic approach utilized cross-metathesis, Evans auxiliary techniques, selective and easy to perform *N*-glycosylation with rhodinose, HWE olefination and again a Lacey-Dieckman cyclisation step at the very end of their synthesis. This approach was also the first known synthesis of a naturally occurring glycotetramic acid and by the start of this project the only one as far as the non-standard bacterial hexose rhodinose can be described as a sugar derivative.

Aurantosides (**4**) form another large compound class with currently eleven known members[39,44–48]. Their general structure has an *N*-glycosylation in common with streptolydigin being connected to *D*-xylose or a trisaccharide starting with xylose and all derivatives bear a polyene 3-acyl side chain. Another uncommon feature is their chlorination

on the polyene side chain. Total synthesis is currently in focus of intense research[49] but has not yielded any publications to date.

II.1.3. 3-Decanoyl tetramic acids

Another large group belonging to the group of 3-acyl tetramic acids are showing a decalinic acid moiety attached by acylation at the C-3. Again numerous representatives of this large tetramic acid family are currently known and some examples will be shown herein. Most of them differ in their absolute configuration, and the length of their substituents mainly around the decalin system. Structural variety of the 3-decanoyl tetramic acid groups is shown in Figure II.4. including a highly functionalized hexacyclic 3-decanoyl tetramic acid called integramycin[50] (Figure II.4.C), bearing various groups like a spiro acetal or an aromatic residue on the decalin system.
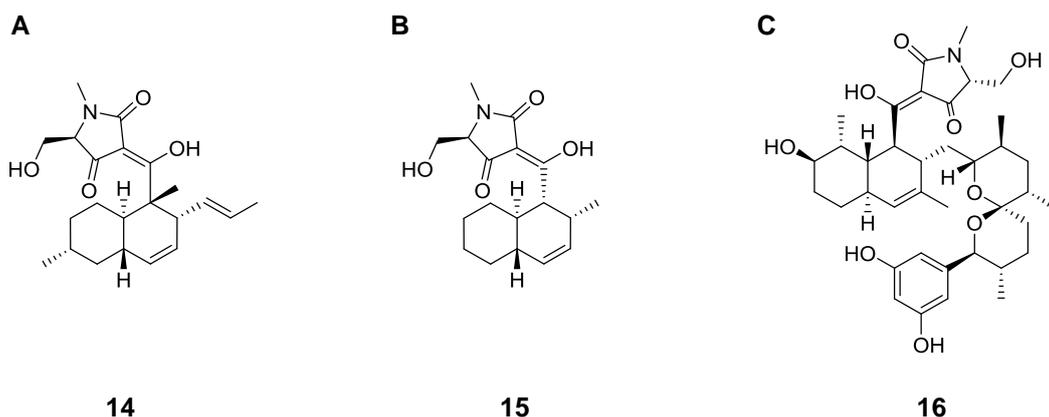
Figure II.4. Structural diversity of 3-decanoyl tetramic acids. A) equisetin[51]; B) methiosetin[52]; C) integramycin[50].

The first synthesis of equisetin[51] (**14**) was carried out by Turos together with Danishefsky *et al.*[53] which was later improved by Yuki *et al.*[54], Burke together with Ley *et al.*[55,56] and Yin *et al.*[57] all using a Diels-Alder approach and later again a Lacey-Dieckman cyclisation step. A similar approach might be useful for the recently found methiosetin[52] (**15**) but no synthesis has been published yet.

Integramycin[50] (**16**) has also been a reoccurring subject of research, but so far total synthesis remains elusive. Only two groups have currently published their results on setting up the bicyclic spiro moiety[58,59] of the molecule. Their contribution combined with the above mentioned methodology should make total synthesis reachable in the near future.

II.1.4. Macrocyclic tetramic acids

The last group of tetramic acids to discuss in detail are the macrocylic tetramic acids. Their macrocycles can be built up featuring all above mentioned possible derivatives. The macrocycle of these tetramic acid representatives are, in many cases, built as a 3-acyl residue ending at the C-5 position. The tetramic acid moiety is normally derived from a natural occurring amino acid. In contrast to the above shown 3-decanoyl tetramic acids this compound class often bears a pentalene system incorporated into the macrocyclic ring. Most representatives show an amide bond in the ring system closing the ring over a tetramic acid moiety derived from *L*-ornithine which, in turn, is a common metabolite from the urea cycle[60]. Examples of some macrocyclic tetramic acids are summarized in Figure II.5.

A   **B**   **C**

17   **18**   **19**
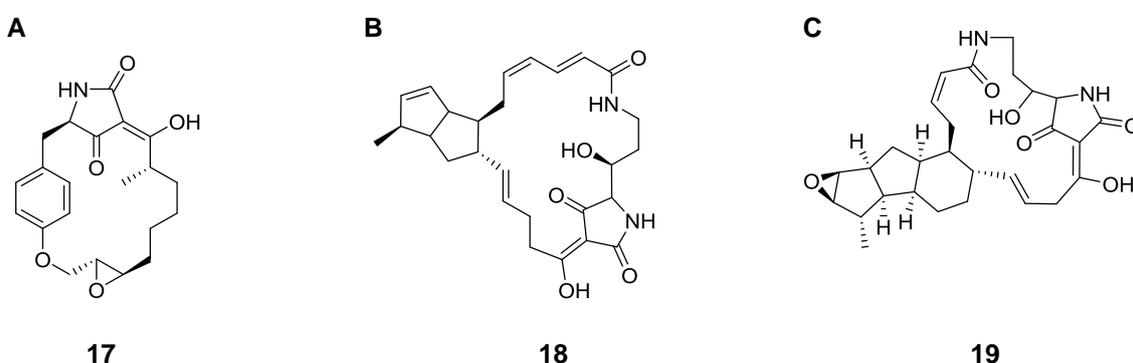
Figure II.5. Exemplary representatives of macrocyclic tetramic acids. A) macrocidin A[61]; B) cylindramid[62]; C) discodermid[63].

Macrocidin A[61] (**17**), a 17-membered macrocyclic tetramic acid, displays strong herbicidal activity compared to most tetramic acids being active against bacteria or fungi. The first and only known total synthesis was achived by Yoshinari *et al.*[64] Their approach combines a HWE olefination, an asymmetric homogeneous catalytic hydrogenation using a Crabtree's catalyst, a macrolactamization using a protected *β*-enol carboxylic acid derived phosphonate[65] and again a Lacey-Dieckman cyclisation.

Also the remarkable total synthesis of the 20-membered ring tetramic acid macrocycle cylindramid[62] (**18**) established by Cramer *et al.*[66] in 2005 needs to be mentioned. He not only synthesized the pentalen system, he also published the above mentioned macrolactamization using a tetrazoylsulfone, utilized a Suzuki cross-coupling and finishing his synthesis off with the common Lacey-Dieckman cyclisation to build the desired 5-membered tetramic acid ring. His synthesis was also stereoselective.

Discodermide[63] (**19**), again a 17-membered macrocycle, is yet another tetramic acid derivative that should be mentioned. The pentalen system is here connected to another

6-membered ring and the 3-acyl side chain connecting the tricyclus to the tetramic acid moiety is shorter compared to the moiety at the C-3 position in cylindramid. No total synthesis has appeared so far in the literature.

II.1.5. Additional tetramic acids

Besides those major classes of tetramic acids outlined above, there are several smaller classes of these compounds which, whilst they will not be discussed in detail here, deserve a brief mention. Tetramic acids can also be *N*-acylated[67,68], bear a spirocyclic moiety at the carbon at 5-position[69], can be derived from alkaloids[70], polyketides like the huge lydiamycin[71] (**20**) and even peptides like the proline rich dolastatin[72], the newly found janolusimide[73], or cyclic peptides[74] as summerazied in some review articles[15,18,20]. The spirotetramic acids are an example for a quickly growing tetramic acid class[20]. This set of diverse tetramic acids is completed by a recently discovered compound where even tetramic acid hetereoatoms are changed. Cladosins[75] bear a 3-*exo* enamine unit where normally the 3-acyl enol functionality is placed. The structure shown below is the mentioned lydicamycin[71] (**20**) which should display and sum up the huge structural variety of tetramic aicds.

20
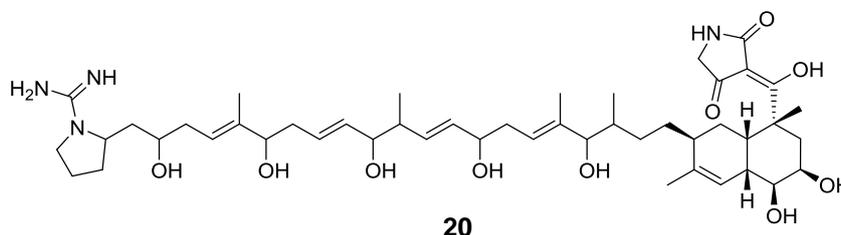
Figure II.6. Structural variety of tetramic acids: Lydicamycin.

The speed of discovery of tetramic acids is increasing and it is certain that more and more derivatives of these important groups or their hybrids are to be found in the future.
Their diversity in biological activities is as diverse as their shown structural omnifariousness.

II.2. Biological function of tetramic acids

One of the most important principles in nature is the fact that structure leads to function. Therefore the biological functions of tetramic acids found in diverse microorganisms of terrestrial and marine origin can turn out to be as diverse as their structure. However, most of

the above mentioned tetramic acids can be grouped by one of the following broad functions: They can be antibacterial, antifungal, antiherbal or cytotoxic.[15,18,20] These activities are widely investigated using state-of-the-art screening techniques. Several targets are now identified and can be inhibited or activated by individual tetramic acids selectively.

Reutericyclin[76,77] interferes in the pH difference between the membranes of gram-positive bacteria[78,79] and therefore interfers directly with the biosynthesis of ATP (more of which below – section II.2.1.). It is not only an effective antibacterial agent against *S. aureus* but also for disarming its major virulence factor toxin-1 which interacts strongly with the human interleukin-8 in a phosphate dependent manner.[80,81]

Tetramic acids are also known to selectively inhibit chitin synthase making them in addition to their other biological activities a candidate for an anti-insectile agent.[69]

Additional specific functions have also been discovered. The *N*-acyl tetramic acid eliamid was found to be active against diverse fungi and strongly cytotoxic. Its mode of action was revealed by Höfle *et al.* to be a NADH complex I inhibitor which disrupts the eukaryotic respiratory chain.[68]

HIV integrase inhibitory activity was also found among the class of tetramic acids. Integramycin (Figure II.4.C) was discovered to inhibit this enzyme being critical for viral replication.[50]

Streptolydigin (Figure II.3.C) was found to have similar effects on the RNA polymerase[40] of *E. coli.* It seems to bind to the initiation complex of the polymerase and thereby prohibiting the substrate nucleotide, which can be referred to as the elongation triphosphate like UTP, from binding to the complex. Streptolydigin aborts the formation of the complexes necessary for the polymerase initiation phase right before an elongation step can start.

II.2.1. Cell wall interaction of tetramic acids and quorum sensing

It is worth noting that one general aspect of the antimicrobial functionality of tetramic acids is their interaction with cell walls of bacteria. Most natural occurring tetramic acids are highly active against gram-positive bacteria[15,18,20]. This fact is mainly due to a lack of penetration of some tetramic acids through the inner cellular membrane of bacteria having a negative gram staining. In these[78,79] as well as other related studies[82,83] the tetramic acid is altering the chemical potential of the cellular membrane being again involved in bacterial ATP synthesis and ATP dependent processes. This shift of membrane potential is not only involved in

shutting down the cellular energy supply but is also directly responsible for disrupting membrane cohesion and stability.[79,82]

Another effect of this alteration of the bacterial cell wall is the inhibitory potency of tetramic acids on an inter-cell communication and interaction possessed by many human pathogens called quorum sensing[84]. This system describes the behaviour of bacteria changing their expression pattern completely when a critical cell density is passed. Triggered by small molecules (inducers) binding to receptors of a neighboured cell, the expression of certain genes are activated leading to effects like biofilm formation, production and release of virulence factors or expression of channels for active and controlled antibiotic agent efflux leading to resistances.[84] This quorum sensing system is also affected by many tetramic acids. An example of further investigations concerning quorum sensing suppression can be seen from the 2014 study published by Murray *et al.*[81] An autoinducer peptide (AIP) from *S. aureus* interacts with a transmembrane histidine kinase AgrC which phosphorylates AgrA. This phosphorylation is ultimately leading to reengineering of the transcriptional profile by AgrA induced expression of a promoter and RNAIII, an effector of downstream signalling events.[85] The tetramic acids tested were found to be a competitive inhibitor of the AIP/AgrC complex.[81] Assayed tetramic acids can be accounted for as a rearrangement product of a known inhibitor derived from a 3-oxo homoserine lactone. However Kaufmann *et al.*[86] found out in 2005 that the pH dependent ring opening of this lactone is undergoing an intramolecular rearrangement in a Lacey-Dieckman styled condensation to form a vinylogous product, a tetramic acid.[86] This formed tetramic acid was found to be the active inhibitor of the above mentioned interaction.[86] Additionally, homoserine derived tetramic acids showed even stronger inhibition.[81] Indeed, this inhibition was increased even further when the 3-acyl fatty acid chain was extended, which might have led on to higher intercalation of the tetramic acid into the membrane where AgrC is located.[81]

It is shown that the above mentioned results can be transferred to other organisms. One example for a proof of principle showed similar homoserine derived tetramic acids are active against *C. difficile* quorum sensing[87] besides their general antibacterial properties leading to cell lysis for example.

II.2.2. Tetramic acids as nucleotide or pyrophosphate mimics

The implications here are that of a tetramic acid moiety being a good mimic of nucleotides, and therefore potentially inhibit nucleotide dependent enzymes. Their mode of action is often

referred to competing with ATP, UTP[40,50], UDP[69] or even NADH[68]. Some studies[88,89] suggest that this fact can be explained by the overall electronical properties of tetramic acids being similar to nucleotides and especially regarding their phosphate residues. Peukert *et al.*[89,90] really emphasized this statement. These effects are acknowledged by molecular modelling when a target structure was known. Most people refer to this effect when asked for the biological activities of tetramic acids and their mode of action.

However four different studies supported by various 3-dimensional protein structures with 3-acyl tetramic acids crystallized as inhibitors[91–95] have been published which contest this position. In the case of streptolydigin RNA polymerase inhibition, an x-ray crystal structure is available where a nucleotide and the tetramic acid derived inhibitor are cocrystallized[94]. This, and other structures, showed the very narrow similar binding motif of a phosphate residue and the 3-acyl tetramic acid anion often binding to positive charged residues like arginine, glutamine and sometimes histidine, as well. And yet, in all the published cases, no colocalization of substrate and tetramic acid residue is confirmed. Streptolydigin, for instance, disrupts protein-protein interactions or protein-RNA interactions in case of the RNA polymerase, but is never colocalized with any nucleotidic substrate nor residue.

II.3. Chemical and structural properties of tetramic acids

The core pyrrolidine-2,4-dione system is normally present in the 2,4-diketo form. The pK_a value of the core structure of tetramic acids is around 6.4 in aqueous solution. The core structure of the comparable furane-2,4-dione tetronic acid is far more acidic with a pK_a of roughly 3.7 mostly showing the 4-enol form.[15]

The 3-acylated derivatives are more acidic than the core structure itself in both cases with a pK_a value in the range of 3.0 – 3.5.[15] The NMR spectra and other techniques like HPLC purification of the acylated derivatives are rather complex since they usually appear as a mixture of four stable tautomers.[15,18,20] Not This mixture is very heterogenous and their ratio can widely differ dependent on the electronic nature of the whole 3-acyl substituent as well as the substitution pattern at the C-5. Scheme II.1. is showing the four stable tautomers and their conversion into each other.[15]

Each groups of the two *exo*-enol tautomers (**21** together with **23**) on the left hand side of Scheme II.1. and the two enol forms on the right handed side (**22** and **24**) can be referred to as internal tautomers.[15] Single crystal structures of 3-acyl tetramic acid also confirmed the

predominant form in solution[96] and crystalline state[97] of the 3-acyl tetramic acid being the *exo*-enol tautomer **23**.[15,18] Metal chelate complexes utilizing boron trifluoride as strong Lewis-acid revealed chelate complexes of the same tautomer only.[98]
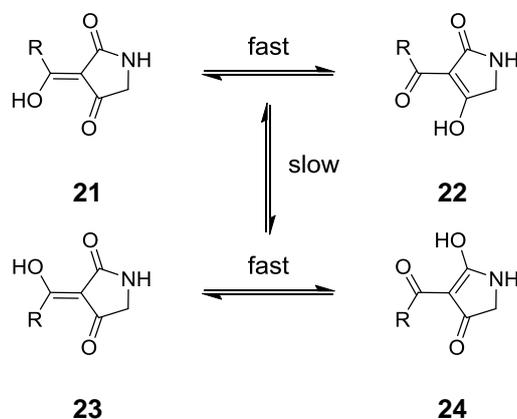
Scheme II.1. Tautomerism of 3-acyl tetramic acids. Tautomerism between *exo*-enol forms (**21**, **23**) on the left side and either the 4-enol form **22** or the corresponding amide enol **24** on the right side happens faster than directly between the two *exo*-enol forms.

The metal chelating propensity of 3-acyl tetramic acids is also worth noting. Some natual compounds could be isolated as their corresponding magnesium complexes exclusively[99,100] and their metal chelating power can overcome those of EDTA. Many studies suggest that the metal chelating properties of the 3-acyl tetramic acids are partly responsible for their biological activity.[18,20] It is also suggested that this effect is part of the proposed phosphate mimicry theorem but again, no structure mentioned above revealed a bivalent ion near the tetramic acid moiety of the tested inhibitors[91–95]. However, the function of the metal chelates might also be involved in transportation.[20,99,100]

The chemical reactivity of tetramic acids can be as versatile as their structural variations. Their overall structural and chemical features make many chemical substitutions on the pyrrolidine-2,4-dione system possible including olefination, arylation, amination, acylation, glycosylation and many places for potential alkylation attempts. This is outlined in Figure II.7.
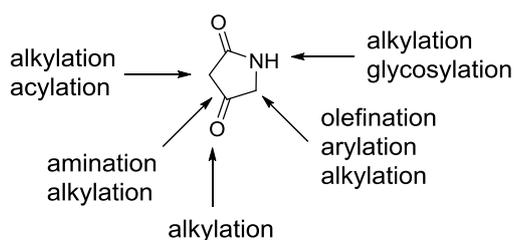
Figure II.7. Potential chemical substitution positions on tetramic acids.

Most of these possible modifications are represented within many natural products as explained in chapter II.1. To investigate the origin of these chemical modifications in nature, it will be necessary to take a closer look at the biosynthesic pathways of this extensive, natural product class.

II.4. Biosynthesis of tetramic acids

One rather seldom used biosynthetic pathway to 3-acyl tetramic acids is mentioned in chapter II.2.1. The quorum sensing molecules *N*-acylhomoserine lactones are converted into the corresponding 3-acyl tetramic acids under physiological conditions.[86] The thus formed tetramic acid is hence a competitive inhibitor to the normally occurring activating peptide for AgrC, a transmembrane histidine kinase.
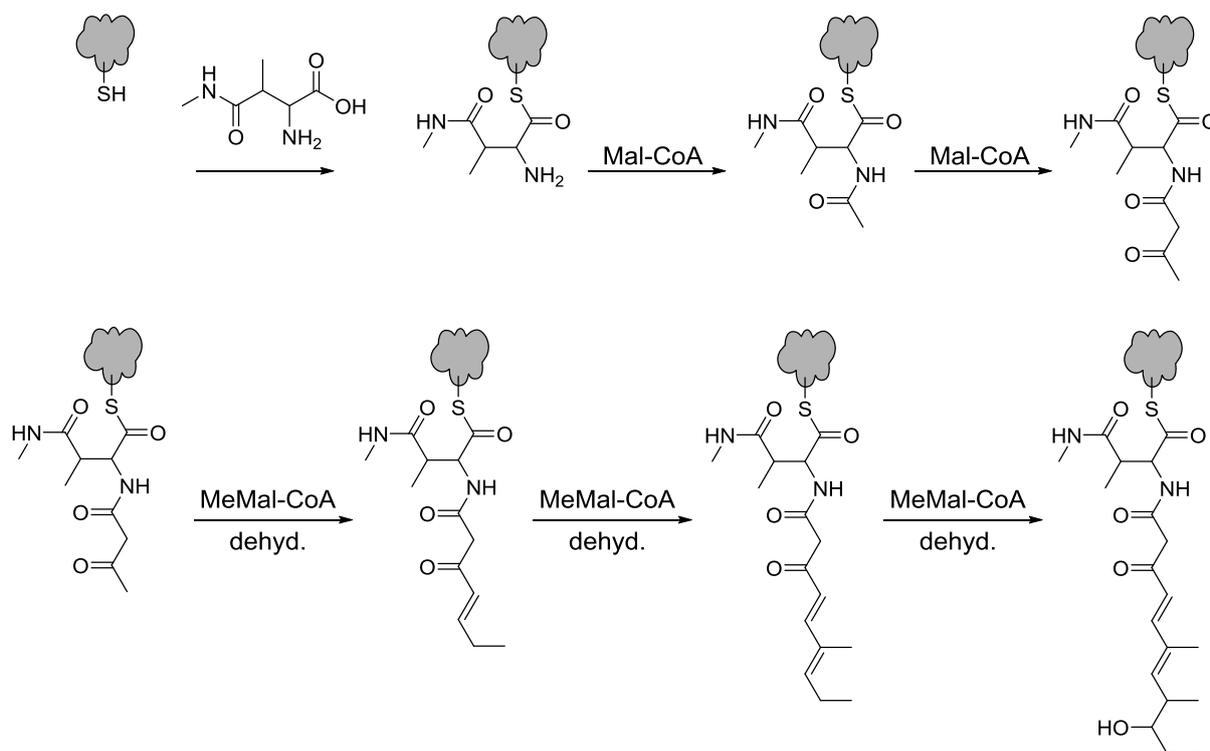
Scheme II.2. First biosynthetic steps to streptolydigin. The product is bound to an enzyme shown as grey cloud during most steps of the biosynthesis.

The standard *in vivo* biosynthetic pathway for 3-acyl tetramic acids normally involves a multiple domain bearing gene cluster encoding for multiple protein complexes involved in the biosynthesis of tetramic acids. These proteins or protein complexes might have tasks such as eventual necessary manipulation of a natural occurring amino acid like, for example: methylation, inversion of the C-5 and acylation carried out by non-ribosomal peptide

synthases, *N*-acylation, side chain elongation accomplished by polyketide synthases, cyclisation or functionalization of the finalized natural product. The biosynthesis of streptolydigin has been extensively covered in literature[41,42,101,102]. The biosynthesis of streptolydigin is a process which requires from malonyl coenzyme A (Mal-CoA) for four steps, methylmalonyl coenzyme A (MeMal-CoA)[41,42] also for four steps, besides N^2-methyl-β-methyl asparagine and the desoxysaccharide rhodinose[91].

The first set of biosynthetic steps are common in polyketide biosynthesis. The substrate amino acid is attached to an enzyme by thioester bond formation. Elongation of the open chain is achieved by incorporation of all C_3 (derived from MeMal-CoA) and three out of four C_2 (Mal-CoA) parts including several steps of reduction and dehydration carried out by additional enzymes. It is not known precisely when the actual methylation steps of the corresponding amino acid occur. However, it likely happens in later steps of the biosynthetic pathway.
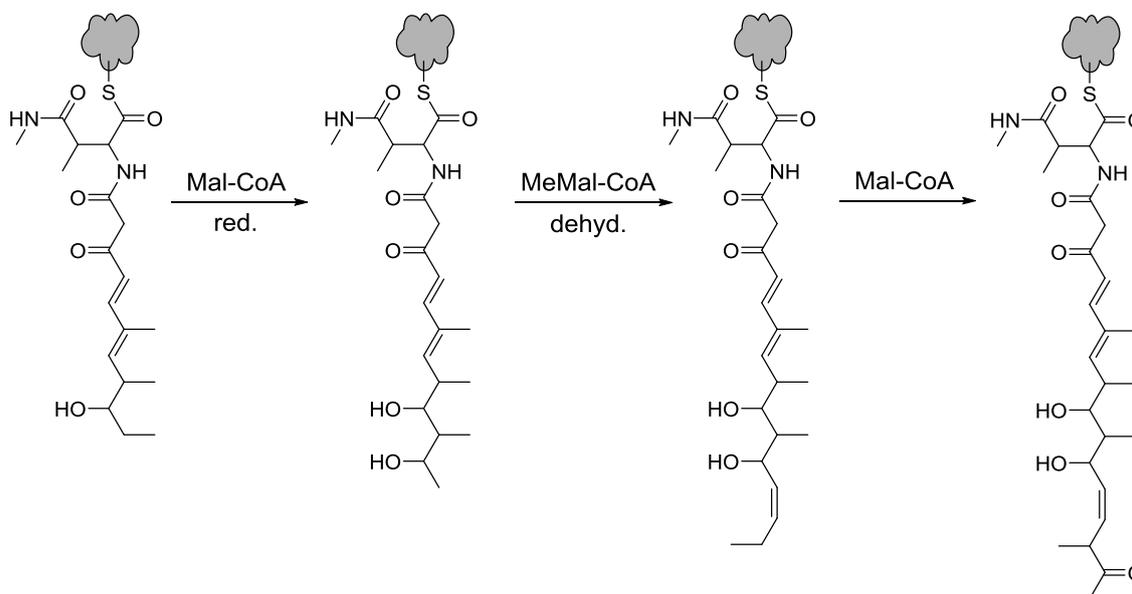
Scheme II.3. Second part of the biosynthesis of streptolydigin showing additional elongation steps.

After the last attachement of a C_2 unit the heterocycle is closed by spontaneous or enzymatic formation of a hemiacetal followed by formation of a full acetal. This step is not well studied and the sequence of acetal formation and the enzymes involved remain unclear. Nevertheless this step is followed by an oxidative epoxidation which forms the spirocenter on the heterocycle.

Biosynthesis is completed by closing the tetramic acid moiety and cleaving the product molecule from the enzyme. This step can spontaneously occur within the cytosol but recent literature[102] suggests that various Lacey-Dieckman cyclases may be catalysing this step. The

terminal step of the biosynthesis is thought to be the cytosolic glycosylation with the deoxysugar rhodinose.
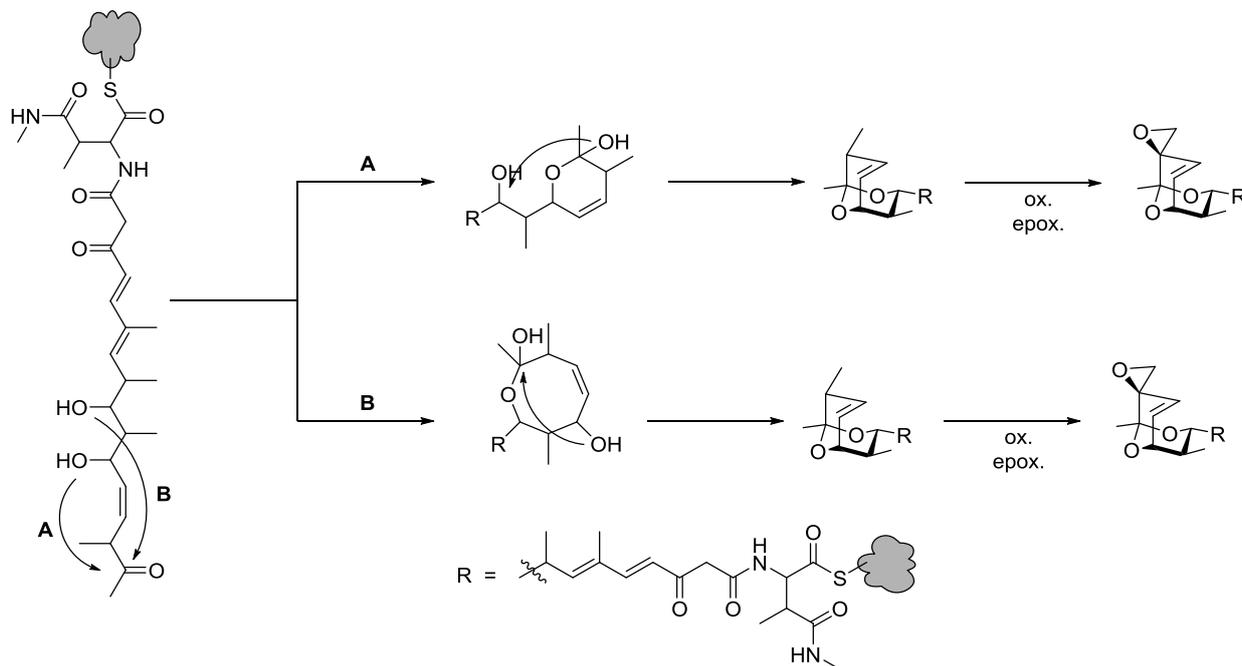
Scheme II.4. Third set of biosynthetic steps to streptolydigin including formation of the heterocyclic acetal residue. It is not known which path for acetal formation is used in biosynthesis and whether it is a spontaneous or catalyzed step.[42] Route A shows first the hemiacetal closure from the "inner" hydroxyl group to form a six-membered ring before the eight-membered ring is closed. Route B shows acetal formation in a reversed way.
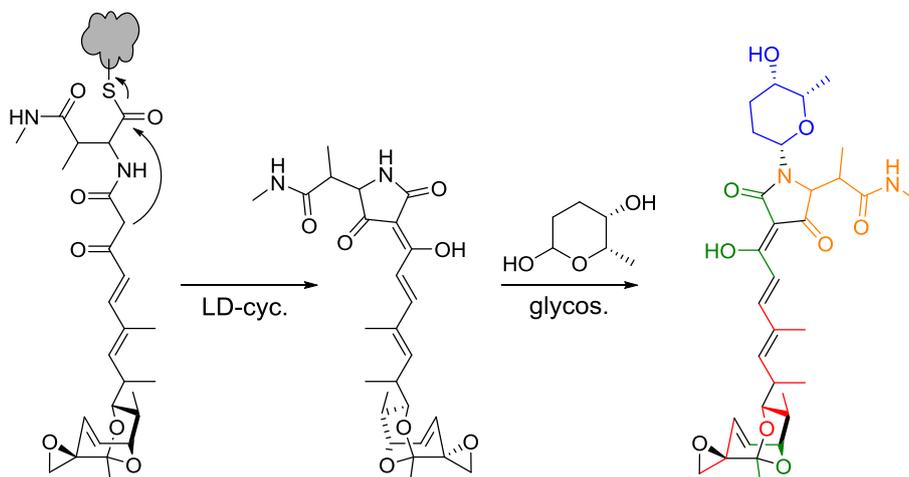
Scheme II.5. Terminal biosynthetic steps to streptolydigin. Colors in the last structure indicating the origin of the carbon[41] and some of the oxygen[42] atoms. The orange part is derived from dimethylated asparagine, the blue part is the desoxysugar rhodinose attached by terminal glycosylation, the green parts are C_2 units derived from Mal-CoA and the red parts are C_3 units with MeMal-CoA origin.

Another important class of enzymes involved in the biosynthesis of tetramic acids are Diels-Alderases[101] occurring in the synthesis of terpene derived tetramic acids like equisetin.

Many published syntheses of these types of compounds are recorded as utilizing similar steps to the streptolydigin biosynthetic pathway. Very recent results published by Kakule *et al.*[103] confirm this position through their descriptions of the biosynthesis of an equisetin analogue bearing a 4-hydroxy-4-methyl glutamate residue.

II.5. Chemical synthesis of tetramic acids

Methods to synthesize tetramic acids can be divided into two categories: Those that form the core structure of the tetramic acids followed by later acylation steps and methods that synthesize the 3-acyl tetramic acid directly. Both methods are shown below summarizing various approaches. An approach to perform a later C-5 oxidation complements the other methods.

II.5.1. Synthetic methods to form the core pyrrolidine-2,4-dione system

Synthesis of pyrrolidine-2,4-diones via Meldrum's acid

Nisato *et al.*[104] developed a method to directly convert *N*-Boc protected amino acids into their corresponding tetramic acid by the use of Meldrum's acid (**26**)[105] under acylation, thermic elimination of CO_2 as well as acetone and cyclisation. Additional methods were found to exchange the expensive and sensitive isopropenyl chloroformate with dicyclohexylcarbodiimide (DCC)[106] and later with less toxic water-soluble 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDCI)[107].
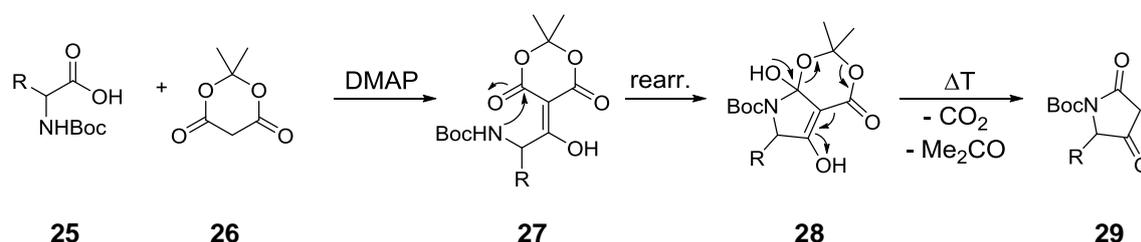
Scheme II.6. Tetramic acid synthesis via Meldrum's acid. R = various substitutions mainly derived from naturally occurring amino acids.

The protected amino acid or derivative **25** is attached to the Meldrum's acid **26** by an acylation supported by the above mentioned substances. The nucleophilic nitrogen of the amino acid then attacks one of the carbonyl carbons on the Meldrum's acid via **28** and thermic elimination occurs to form the tetramic acid **29**.

Synthesis of pyrrolidine-2,4-diones via domino-Wittig reaction

Another broadly used method to form tetramic acids, or in this case 4-*O*-protected tetramates, is the usage of ketenylidentriphenylphosphorane (Ph3PCCO) often referred to as Bestmann's ylide[108]. This method was later further improved by Schobert *et al.*[109] through using the stable ketenylide (**31**) as acyl donor to form the desired tetramic acid.
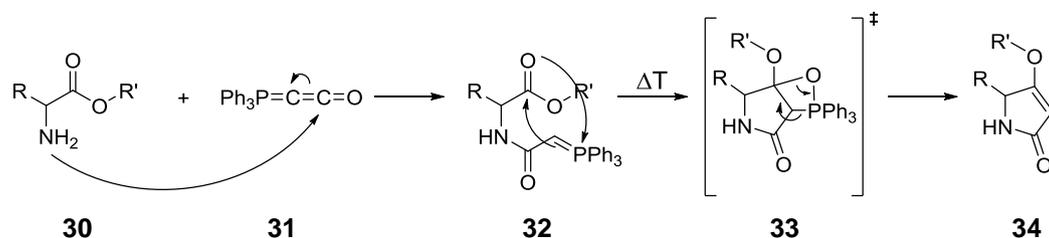
Scheme II.7. Mechanism of tetramate synthesis with Bestmann's ylide[108]. R = various substitutions mainly derived from naturally occurring amino acids; R' = methyl, ethyl, *t*butyl, benzyl.

In the first step the amino acid ester **30** attacks the ylide **31** to form a *N*-acyl yilide **32**. The subsequent intramolecular Wittig reaction between the ylide and the ester group via the formation of either a betain (not shown) or an oxaphosphetane structure (**33**) forms the desired tetramate **34** under thermodynamic conditions. The tetramate **34** is deprotected to yield the desired pyrrolidine-2,4-dione.

To simplify purification of the desired tetramic acids and to separate the product from triphenylphosphine oxide, an immobilized derivative of Bestmann's ylide was synthesized and tested successfully[110] in synthesis.

Synthesis of 3-methylated pyrrolidine-2,4-diones via SmI2

A rather new method established by Bai *et al.*[111] uses *N*-2-bromopropionated amino acid esters, cyclizes them by the use of samarium iodide and traps the product with diazomethane to yield a 3-methylated 4-*O*-methyl tetramate (**36**). The educt for the cyclisation is prepared by *N*-acylation of a protected amino acid with *n*BuLi and 2-bromopropionyl bromide.
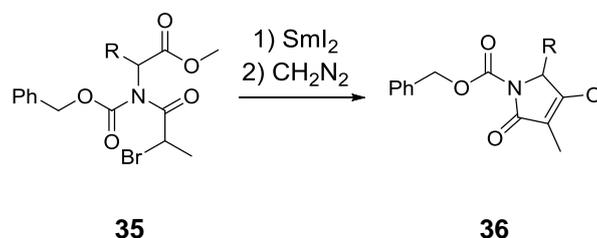
Scheme II.8. Tetramate synthesis with SmI2 and CH2N2 via a 2-bromopropionated and protected amino acid derivative. R = various substitutions mainly derived from naturally occurring amino acids.

Their synthetic approach seems to be limited in terms of the products possible but their method is quite new and it might be worth investigating other variants by attaching longer

N-acyl residues. It is worth noting that this synthetic possibility works better when unprotected proline is used[111] to yield the corresponding bicyclic tetramic acid.

Synthesis of 3-arylated pyrrolidine-2,4-diones via silver and CO_2 incorporation

Another recently published method for tetramic acid synthesis elaborated by Ishida *et al.*[112] uses catalytic amounts of silver(I) salts to incorporate CO_2 into an existing amino alkine and then utilizing an intramolecular rearrangement. The base used to catalyze this type of reaction was DBU.
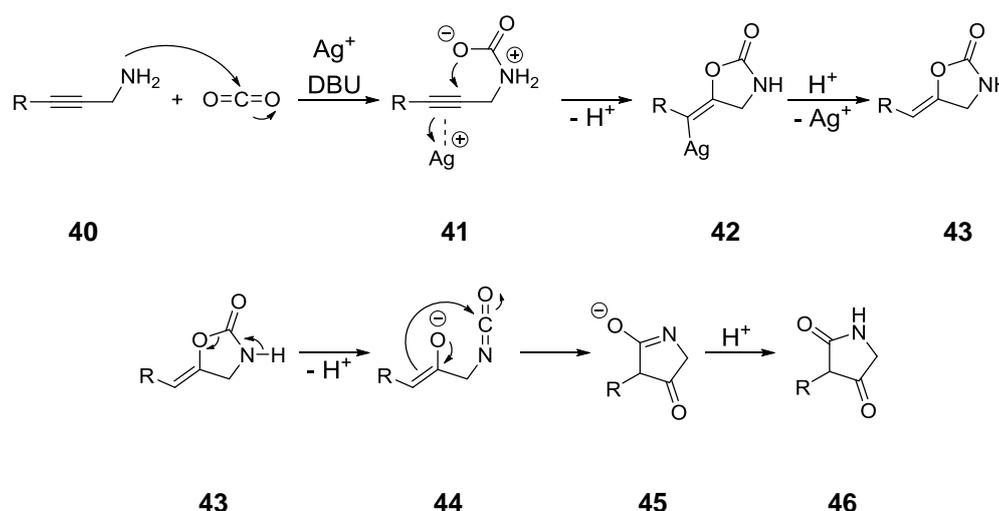
Scheme II.9. Tetramic acid synthesis via CO_2 incorperation catalyzed by silver(I) salt and DBU. Proposed mechanism[112] shown. R = any (branched) alkyl chain, cyclohexyl.

Firstly the carbon dioxide is attacked by an amino alkine **40**, to form an acylated alkine **41**. Then the electron densitiy on the double bond is reduced by complexation of silver(I) to allow the attack of the negatively charged oxygen and subsequent formation of an oxazolidinone **42** followed by reprotonation. This reprotonated oxazolidinone **43** is deprotonated again by DBU to form a charged isocyanate (**44**). This is attacked by the double bond again forming the desired tetramic acid **46** over an enamide (**45**).

Their first published studies were limited to 3-aryl compounds with various electron rich or poor aromats. The C-5 was tested to yield an glycine derived tetramic acid or to have an cyclohexyl residue on the corresponding alkine to yield C-5 spiro tetramic acids which are a growing class of tetramic acids.

II.5.2. 3-Acylation of the tetramic acid core

3-Acylation via 4-*O*-acylation and rearrangement

A more frequently used method for 3-acylation of the above gained pyrroldine-2,4-dione system is to first perform a 4-*O*-acylation and *in situ* rearrangement sequence. Several groups, including, Yoda *et al.*[31], Moloney *et al.*[79] and Yoshii *et al.*[113] studied this rearrangement tactic, leading to good yields of the desired tetramic acids.

47   **48**   **49**
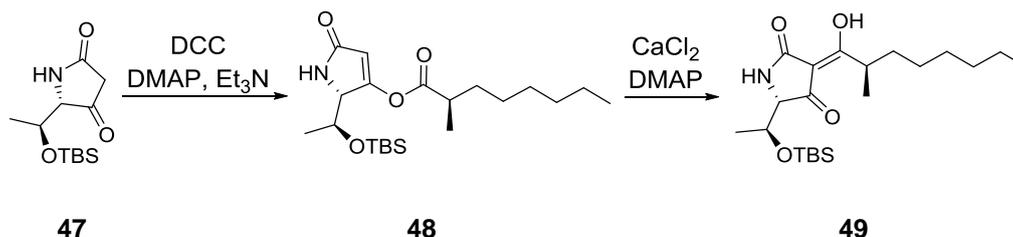
Scheme II.10. 3-Acylation by a 4-*O*-acylation rearrangement strategy using Ca^{2+} as published by Yoda *et al.*[31] in their stereoselective total synthesis of penicillenol A_1.

The mildest, and eventually most usable, method to induce the rearrangement is published by Yoda *et al.*[31] utilizing Ca^{2+} instead of high amounts of Et_3N to induce acyl migration *in situ* right after 4-*O*-acylation. The tetramic acid **47** used in their synthesis was derived from threonine and utilizing the above shown Meldrum's acid methodology. The remaining steps after isolation of the 3-acyl tetramic acid **49** are *N*-methylation and TBS deprotection.

3-Acylation via acylation with Bestmann's ylide and subsequent Wittig reaction

Schobert *et al.*[34] figured out that the Bestmann's ylide can directly act as an acylation reagent to selectively attack the C-3 position on pyrrolidine-2,4-dione systems.

50   **51**   **52**
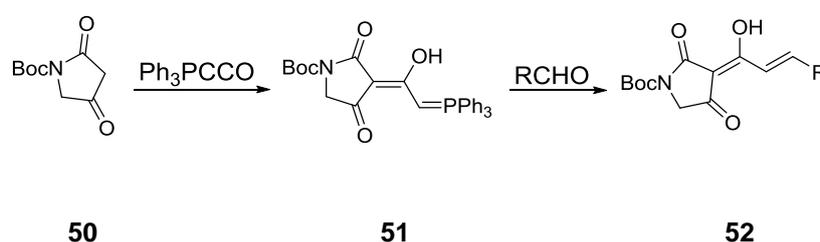
Scheme II.11. 3-Acylation by Bestmann's ylide acylation and Wittig olefination published by Schobert *et al.*[34] for the total synthesis of ravenic acid. R = any alkyl chain.

This shown synthesis (Scheme II.11.) is part of a published[34] total synthesis of ravenic acid. An accordingly protected amino acid **50** is acylated by addition of the ketenylidentriphenylphosphorane to yield a 3-acyl ylide **51**. This step normally proceeds quantitatively. The ylide can then undergo a Wittig reaction without further purification to

yield the desired 3-acylated tetramic acid **52**. The ylide needs to be activated by a base and only KO*t*Bu proved to accomplish[34] this activation.

Direct 3-acylation with acyl chloride and BF₃ etherate

Schobert *et al.*[30] used also carboxylic acid chlorides and converted tetramic acids diretctly into the corresponding 3-acyl tetramic acid complex derivatives by heating the educts in the microwave. The solvent was $BF_3 \cdot OEt_2$ and these aggressive reaction conditions are also directly the limitation of this type of acylation reaction. These conditions were successfully applied to the total synthesis of several melophlins[30].

3-Acylation by lithiated tetramic acids and subsequent oxidation

Another worth noticing method to perform a 3-acylation was investigated by the group around Jones *et al.*[114] but this method is less favoured because of the used strongly basic conditions. They were able to lithiate a tetramic acid selectively in the 3-position and isolating the corresponding 3-alkylated hydroxyl tetramic acid (**55**).

53   **54**   **55**   **56**
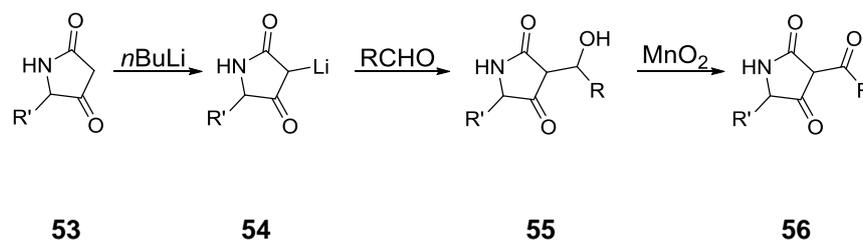
Scheme II.12. Published[114] 3-acylation by lithiation, aldehyde addition and oxidation. R = any alky chain; R' = various substitutions mainly derived from naturally occurring amino acids.

The mentioned hydroxyl tetramic acid **55** can be oxidized by MnO_2 to yield the desired 3-acylated tetramic acid **56**. The limitation within this 3-acylation procedure is again the strongly basic reaction conditions resulting in lots of C-5 isomerized product.

II.5.3. Aldol reaction for C-5 alkylation

This short chapters shows the synthesis of 3-methylated pyrrolidine-2,4-diones via aldol reaction as a C-5 alkylation. David *et al.*[115] figured out that similar products as above mentioned can be obtained by forming various pyrrols as a TMS enol ether and then performing a diastereoselective catalytic vinylogous aldol reaction using catalytic amounts of $SnCl_4$ and an aldehyde to introduce various residues on the tetramic acid C-5.

The protected amino acid **37** is again protected as a TMS enol ether. This enol ether pyrrol derivative **38** then undergoes the desired aldol reaction when the necessary aldehyde is added alongside a catalytic amount of SnCl$_4$.
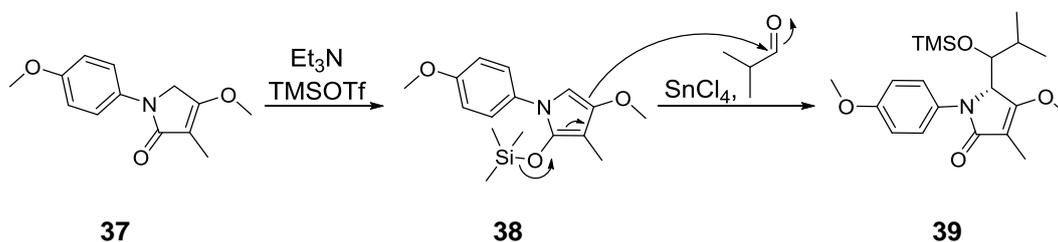
Scheme II.13. Mechanism of tetramate synthesis with an aldol reaction via a PMP protected amino acid derivative.

This reaction sequence formed also a limited set of simple 4-*O*-methylated tetramic acids (**39**) and further investigation is necessary to figure out the limitations of this reaction. However, David *et al.*[115] reported an enantiomeric excess of 20:1.

II.5.4. Direct synthesis of 3-acyl tetramic acids

Lacey-Dieckman cyclisation

Besides many reactions to form the core pyrrolidine-2,4-dione system and subsequent 3-acylation in the shown manner, there's currently one very important reaction to directly form 3-acyltetramic acids. The Lacey[116,117] group improved the Dieckman condensation so as to have direct access to 3-acyltetramic and -tetronic acids derived from β-keto amides or the corresponding esters. Since nature is also using the nucleophilic properties of a β-keto carbonyl precursor in the biosynthetic path to close the heterocycle as shown in chapter II.4., this synthetic approach can be considered as biomimetic.
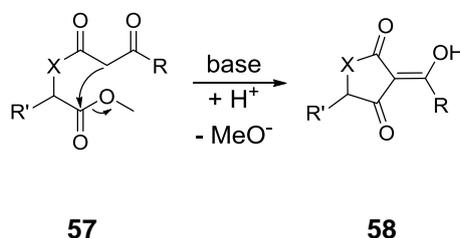
Scheme II.14. Mechanism of a Lacey-Dieckman cyclisation to directly yield 3-acyl tetramic acids. X is NH (tetramic acid) or O (tetronic acid), R is any side chain including aromatic derivatives, polyene chains and branched chains and R' is another side chain normally derived from naturally occurring amino acids.

This method is the most used synthetic tool to gain access to 3-acyl tetramic acids. The reaction tolerates most functional groups and is not limited to size or electronic properties of

the substituents. The scope of the Lacey-Dieckman cyclisation is limited, though. The use of strongly basic conditions to achieve the cyclisation step normally leads to a noteworthy isomerisation at the C-5 position. Lots of attempts have been carried out recently to prevent this unwanted side reaction by either changing the base to milder ones like tetra-*n*butylammonium fluoride (TBAF)[118] or using smaller amounts of sodium methoxide decreasing isomerisation to a minimum of less than 4%[32].

II.6. Glycosylated tetramic acids

Since this work is focussed on glycosylated 3-acyltetramic acids, the known derivatives as well as their origin and biological function will be discussed. Members of this class can be divided into two subfamilies: Tetramic acids being 3-acylated with a saturated fatty acid chain which is terminally glycosylated or *N*-glycosylated tetramic acids having a polyene 3-acyl side chain. Members of both families are described as follows.

II.6.1. Ancorinosides

Ancorinosides were isolated by Ikegami *et al*[119]. in 1997, its magnesium salt four years later by the same workgroup[100] and three additional representatives of this compound class by Fusetani *et al.*[120] also in 2001. All four derivatives were isolated from marine sponges like *Ancorina* (A) or *Penares sollasi* (B-D). Their structural motif consists of three major parts: A disaccharide with a *β*(1-4) linkage either being galactose and glucose or vice versa having the sugar moiety on the reducing end oxidized at the C-6 to the corresponding uronic acid. The second part is a C_{22} or C_{24} fatty acid chain with no or single substitutions. The third section of all ancorinoside species is a tetramic acid moiety derived from *D*-aspartic acid. Their structural variations are summarized in Figure II.8.

Ancorinoside A and its magnesium salt were tested for their inhibitory potency on embryonic development using fertilized starfish eggs. Both substances allow initial cellular divisions and formation of a morula, but development was inhibited and no further cell division was observed at a state of 256-512 cells where normally the formation of a blastula occurs.[100,119]

Ancorinosides were tested for their potency to inhibit matrix metalloproteinases (MMP) revealing a moderate effect on MMP type 2 and a weak effect on transmembrane MMP type 1 while maintaining very weak cytotoxic side effects.[120]
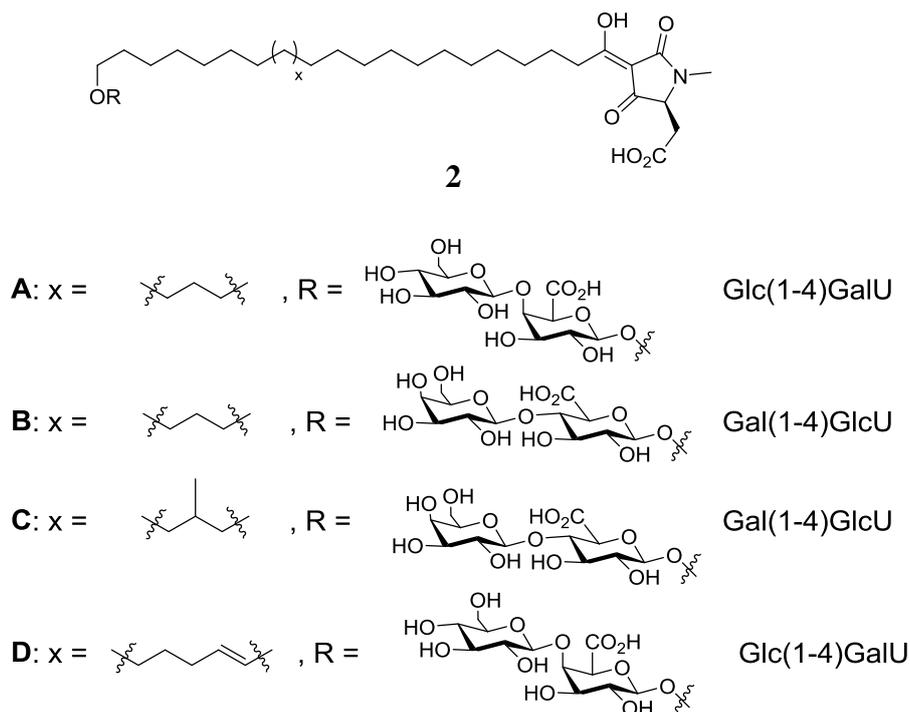
Figure II.8. Ancorinosides A-D derived from marine sponges.

Since this tetramic acid is derived from *N*-methyl-*D*-aspartic acid (NMDA) it might be worth testing[121] the behaviour of nerve cells towards ancorinosides since NMDA is a known agonist of the well studied NMDA receptor ion channels[122] which are known to be involved in learning deficiencies and eventually Alzheimer's disease.

II.6.2. Epicoccamides

Six years after the first isolation of ancorinosides by Ikegami *et al.* epicoccamide A was first isolated by the workgroup around G. König *et al.*[29] in 2003. This glycosylated tetramic acid was found in extracts of cultures derived from the fungi *Epicoccum purpurascens*. This fungi is of marine origin and is normally associated with the common moon jellyfish (*Aurelia aurita*).

Four years later Hertweck *et al.*[28] found three additional representatives of epicoccamides (B-D). These compounds were isolated from a terrestrial *Epicoccum* species living associated with a tree fungus called *Pholiota squarrosa*. All four tetramic acids share the same motif of a natural product similar to ancorinosides consisting of three major parts: A *β*-branched mannose, a long (C_{18}) and unsubstituted fatty acid chain and a tetramic acid derived from alanine. These structural features are summarized in Figure II.9.
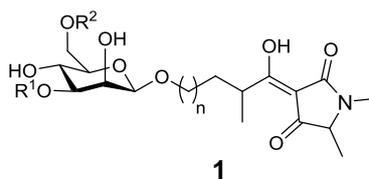
A: n = 13, R^1 = R^2 = H

B: n = 13, R^1 = Ac, R^2 = H

C: n = 13, R^1 = H, R^2 = Ac

D: n = 15, R^1 = R^2 = H

Figure II.9. Epicoccamides A-D derived of marine and terrestrial origin.

Hertweck *et al.* found identical structures compared to the epicoccamide derived from marine fungi with different acetylation patterns. Epicoccamide A was the major metabolite in their extracts as well but epicoccamide D proved the most active and showed notable cytotoxic and good antiproliferative effects.

The absolute configuration concerning the two methyl substituted stereocenters within the aglycon part of the molecule remained unclear, because no total synthesis was available for this compound class when the work on this thesis started.

The absolute configuration 5*S* and 7*S* suggested in this work was later acknowledged by a total synthesis performed by Yajima *et al.* [123] yielding epicoccamide A and D. They used Meldrum's acid to build up the alanine derived tetramic acid, a tandem 4-*O*-acylation rearrangement setup to build the 3-acyl tetramic acid moiety with approximately half the length of the fatty acid side chain, a *β*-selective glycosylation and a final cross-metathesis. Since their synthetic approach is similar to the one published by the same group[124] concerning virgineone aglycon synthesis, which is outlined below (Scheme II.15.), their key steps of their synthesis are not shown here.

II.6.3. Virgineone

Singh *et al.*[125] isolated another member of the glycosylated tetramic acid family in 2009 called virgineone. This compound was isolated from the fungus *Lachnum virgineum* belonging to the class of natural decomposers. The overall structural motif is similar to the two already mentioned classes. A *β*-mannosylated fatty acid chain being oxidized to a ketone in almost the middle and connected via 3-acylation to a tetramic acid derived from tyrosine. The fatty acid chain is additionally methylated in the same position as epiccoccamides and

bears a hydroxyl functionality neighboured to the glycosidic bond. These structural features are shown in Figure II.10.

3
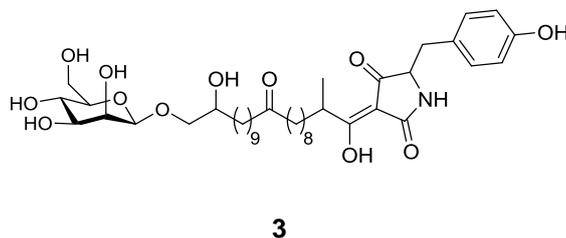
Figure II.10. Virgineone produced by the fungus *Lachnum virgineum*.

Virgineone was tested more extensively than the two already mentioned families of glycosylated 3-acyl tetramic acids. Singh *et al.* investigated the biochemical activity of the isolated compound with a *Candida albicans* fitness test. They tested[125] the effect of the compound on roughly 2900 deletion strains of the fungus *C. albicans* eventually elucidating the mode of action of virgineone. This showed the origin of the molecule's antifungal activity was connected to the stress response system. They also tested for the activity of the aglycon in their assays revealing that the mannose residue is absolutely necessary to show any biological activity.

It is worth noting that Yajima *et al.*[124] published a synthesis of the virgineone aglycon similar to their published work on epicoccamides. The key intermediates of their synthesis are shown in Scheme II.15.

59   **60**   **61**

61   **62**   **63**
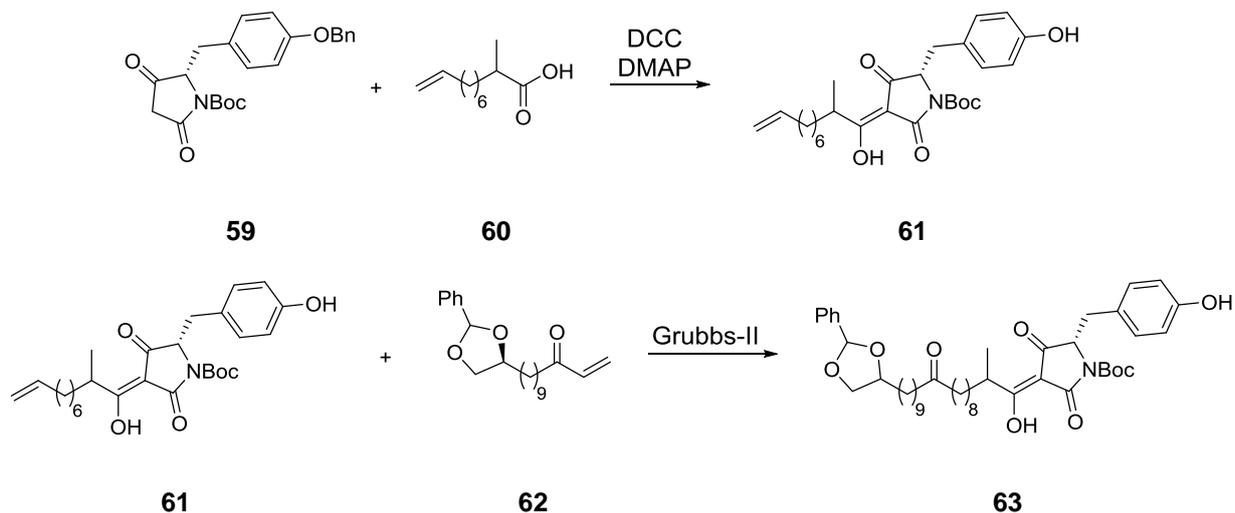
Scheme II.15. Published[124] synthesis of the virgineone aglycon. A tyrosine derived tetramic acid prepared by the shown method utilizing Meldrum's acid is acylated by a 4-*O*-acylation rearrangement strategy. The second part of the side chain including the ketone and the hydroxyl groups where the primary is *β*-mannosylated in the natural product is attached by Grubbs generation II catalyzed olefin cross metathesis.

Their preliminary synthetic steps revealed the configuration of the hydroxyl group next to the glycoside needs to be most likely *R*-configurated. They also propose that the stereocenter of the tyrosine moiety on the C-5 of the tetramic acid seems to bear the natural *S*-configuration. Concerning the C-7 methyl group their data suggest a racemic configuration.

The central steps of the published aglycon synthesis are assembly of the tetramic acid moiety **59** via the method utilizing Meldrum's acid, a 4-*O*-acylation rearrangement reaction between the tetramic acid, an olefinic side chain **60** and a cross metathesis to attach the diol **62** for glycosylation to the other half of the side chain bearing the tetramic acid.

II.6.4. Streptolydigin

The first member of the general class of gylcosylated tetramic acids to be isolated, and one of the most extensively studied, is streptolydigin, which was originally described by Rinehart *et al.*[38] in 1963. However, streptolydigin is not referred to as glycosylated tetramic acid in the literature. This is possibly due to the uncommon origin of the saccharide moiety. Because of having the nitrogen of the tetramic acid glycosylated with *L*-rhodinose streptoglydin can be accounted for to be a member of the *N*-glycosylated tetramic acid subfamily. The tetramic acid moiety of streptolydigin is derived from N^2-methyl-β-methyl asparagine connected to a diene side chain via 3-acylation. The side chain terminates with a complex acetal heterocycle including a spiro epoxide. The overall structural features of streptolydigin was shown in Figure II.3. and Scheme II.5.

Streptomyces lydicus strains were found to produce high amounts of streptolydigin beside several other antifungal and antibacterial agents released by these actinomycetes[126] of marine or terrestrial origin.

The most important biological activity of streptolydigin is the selective inhibition of bacterial RNA polymerases[40,91] as mentioned above. This strongly antibacterial compound is thought to bind to the polymerase and prohibit association of the next nucleotide by destroying the initiative complex necessary to start RNA elongation, thereby not allowing the DNA template strain to move along the polymerase. This theory is supported by a published crystal structure of the complete polymerase with UTP (elongation triphosphate) and streptolydigin showing the compound prohibits the binding of UTP or another triphosphate to the RNA chain 3'-terminus[91,92,94].
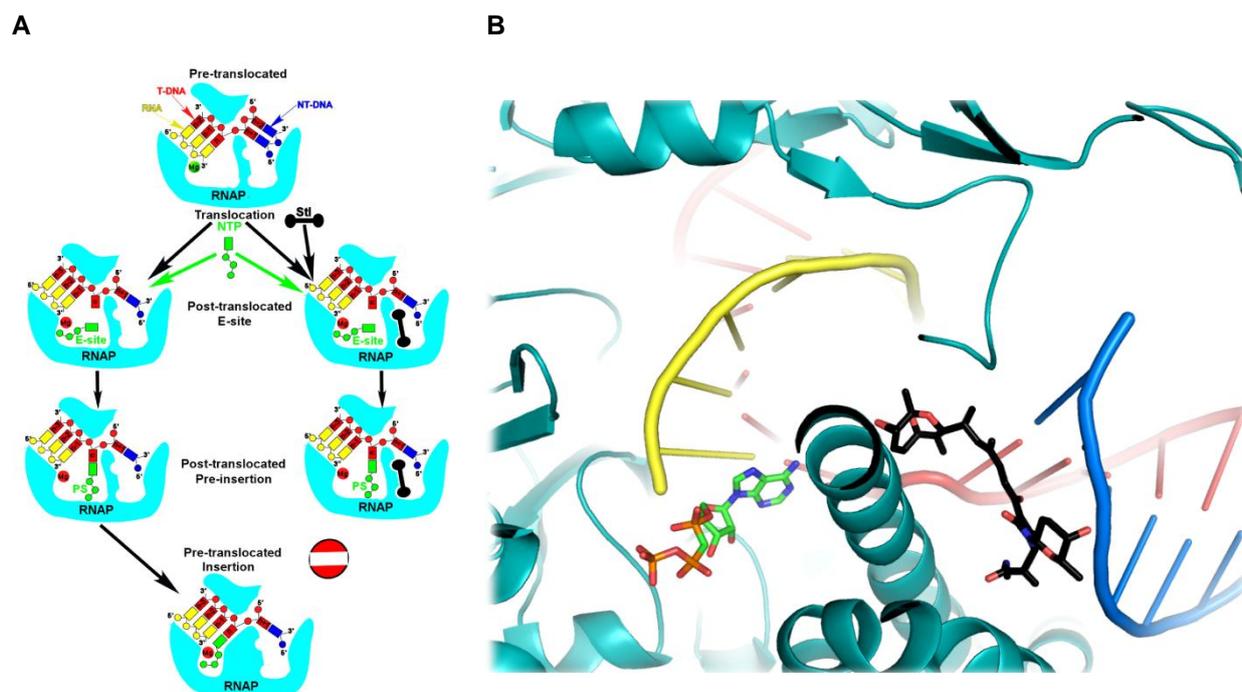
Figure II.11. Mode of bacterial RNA polymerase inhibition by streptoglydin. A) Within the protein (cyan) the DNA template binds to the polymerase. The unused strand (blue) is separated from the template strain (red). Without inhibitor (left side) another nucleotide triphosphate NTP (green) binds, aligns to its paired base from the template strain and is attached via phosphate linkage. The last step is the movement of the next base of the template DNA from the separation domain to the elongation domain. When streptolydigin (black) is bound, this movement is prevented. Used with kind permission from Elsevier[92]. B) Structure of *E. coli* RNA polymerase derived from published structural data[94] (PDB code: 2PPB). The structure shows the mechanism of inhibition shown in A) in more detail. The unused DNA strain is shown in blue, the template DNA strain in red, the formed new RNA strain in yellow, the nucleotide (here UTP) in green and the inhibitor streptolydigin in black. Protein (cyan) and the DNA/RNA strains are shown in cartoon presentation and the organic molecules in stick presentation.

Pronin *et al.*[43] achieved the first, and only, total synthesis in 2010, nearly 50 years after its structure was determined. Their key steps are a ring closure metathesis catalyzed by Grubbs catalyst, an acetalization over a Weinreb amide, a Wittig reaction, epoxidation, easy to facilitate *N*-glycosylation, aminolysis and HWE olefination. The key steps of their synthesis are shown in Scheme II.16. and Scheme II.17.

The two shown precursors **64** and **65** were derived by Sharpless dihydroxylation (**64**) and stereoselective aldol reaction followed by Evans-Tishchenk reaction (**65**) respectively. Both educts were coupled by standard Steglich conditions for esterification.
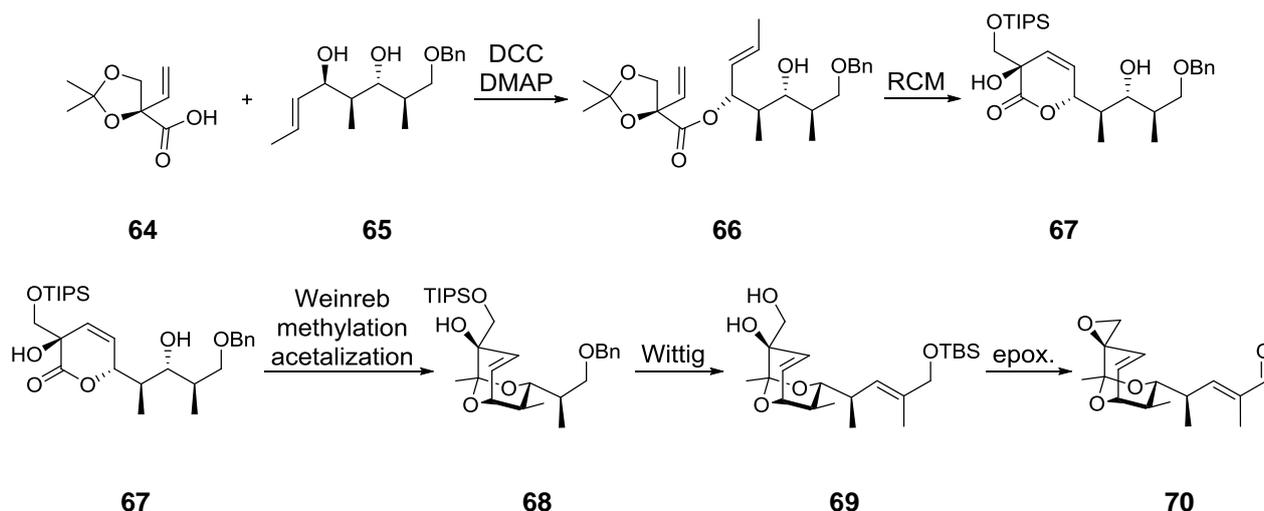
Scheme II.16. Published[43] synthesis of streptolydigin showing the key steps.

The lactone **67** was formed by ring closing metathesis catalyzed by a Grubbs 2nd generation catalyst. This lactone was then transferred into its Weinreb amide, methylated and the acetal was closed to form the desired product **68**. The side chain was elongated by a Wittig olefination and after protective group manipulation, an epoxidation was carried out and later formation of the desired aldehyde **70**.
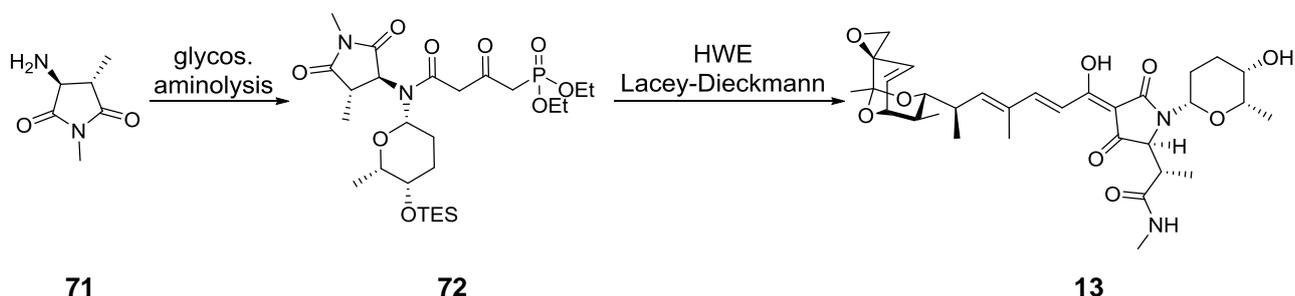
Scheme II.17. 2nd part of the published[43] synthesis of streptolydigin showing additional key steps.

The amine **71** was derived from a chiral acid utilizing Evans auxiliary technique to prepare an azide which was converted into the corresponding amine and cyclized in an oxidative TEMPO catalyzed manner. The *L*-rhodinose was attached by simply stirring it with the cyclic amine **71**. A known[56] phosphonate was introduced to this *N*-glycoside by aminolysis using the corresponding *β*-keto thioester. This phosphonate **72** was attached to the heterocycle by HWE olefination. The last step of the synthesis before global deprotection was the Lacey-Dieckman cyclisation. This cyclisation step yielded the desired tetramic acid **13** by lactam opening during Lacey-Dickman cyclisation instead of ester cleavage.

II.6.5. Aurantosides

Another class of *N*-acylated tetramic acids are called aurantosides. Currently eleven members[39,44–48] of this compound class are known and their first representative was isolated 1991 by Matsunaga *et al.*[44] Their origins are marine sponges like *Theonella*, *Homophymia conferta*, *Siliquariaspongia japonica* and the melophlins producing *Melophlus* family. These compounds are normally responsible for the slight orange to dark red color of the sponges. Besides the mentioned *N*-glycosylation with xylose or a trisaccharide starting from xylose, they all share a polyene side chain bearing at least one chlorine atom. The general structural features of aurantosides are summarized in Figure II.12.

4
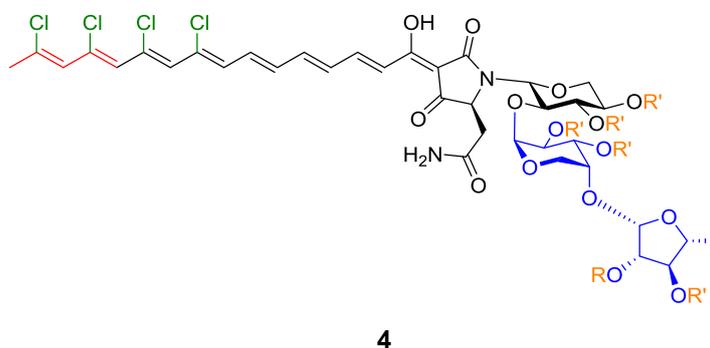
Figure II.12. Overview of possible aurantoside structures. R can be H, Me or Ac, R' only H or Ac (orange). The length of the polyene chain can vary from the shortest (black) to the longest (red) C_{16} derivative. The saccharide can either be xylose (black) or a trissaccharide starting with xylose (blue). The chlorination pattern (green) can be one or more in 1,3- or 1,5-distance.

Aurantosides A, B and D-F revealed significant cytotoxicity towards leukemia cells and are shown to be antifungal on *C. albicans* and *A. fumigates*.[46] Their activity was demonstrated to be 100 fold higher under the test conditions compared to other tetramic acid glycoconjugates. Interestingly aurantosides G, H and J did not show any significant biological activity[39,47] whatsoever, whereas aurantosides I and K exhibited significant antifungal effects[47,48]. Unfortunately the applied assays did not allow to determine any structure-activity relationship (SAR) between the compounds. The most efficient natural product had the shown trisaccharide unit together with a monochlorinated C_{12} polyene side chain in common. No total synthesis of aurantosides is known to date.

II.6.6. Rubrosides

The last subfamily of the *N*-glycosylated tetramic acid class is built up from compounds called rubrosides, found by Sata *et al.*[127] in 1999. Currently eight members are known[127],

and their overall structural motif is identical to the shown variation of aurantosides (Figure II.12.). The only difference between the two molecule classes is that all rubrosides have a terminal heterocycle at the end of the polyene 3-acyl chain. This hetereocycle is derived from tetrahydrofuran (THF), attached by its C-1 carbon to the side chain, *R*-methylated at C-4 and *S*-chlorinated at the C-2 position. This hereocycle is eventually attached to the above shown aurantosides as described in Figure II.13.
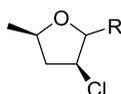
73

Figure II.13. Heterocycle attached to aurantosides. The C-1 stereocenter for attachment to the polyene side chain derived from aurantosides can be *R*- or *S*-configurated.

Chlorination and chain length can have additional variations compared to aurantosides. All rubrosides showed significant cytotoxicity against leukemia cells and comparable but higher antifungal activity compared to aurantosides.[127]

Since no total synthesis for aurantosides is published so far, rubrosides bearing an almost identical substitution pattern also lack of synthetic access to natural or synthetic derivatives for studies of an eventually occuring structure-activity relationship.

III. PROJECT AIMS

The aim of this work was to first establish an approach to the natural product compound class of glycosyl tetramic acids. The eventually established total synthesis should then be adopted to another class of glycoconjugated tetramic acids to verify its generality. Epicoccamide D (see Figure III.1.) was chosen to be the first candidate for total synthesis since it bears an uncommon β-mannosyl sugar residue together with two stereocenters of unknown configuration and a simple tetramic acid residue derived from alanine. It was necessary to find an approach which could potentially give rise to the four possible isomers concerning the tetramic acid C-5 and its acyl C-7 position, in order to gain insight into the absolute configuration of epicoccamides. As next natural products in the focus of this thesis ancorinoside B and virgineone were chosen. Their side chains should be synthesised with respect to differences in the substititution pattern, the sugar residue and the eventually found synthetic procedure for epicoccamide synthesis should be applied when possible.
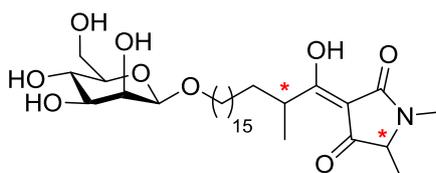
1

Figure III.1. Epicoccamide D and the two stereocenters of unknown configuration shown in red.

This will be the first total synthesis of a member of this product class bearing the 3-acyl tetramic acid motif on one end of a fatty acid chain, and a β-branched mannose on the other. Additionally, a route to synthesize *N*-glycosylated tetramic acids as in the natural product group of aurantosides or rubrosides should be investigated.

IV. RESULTS

IV.1. Total synthesis of epicoccamide D

Epicoccamides can be fragmented into three major parts which is shown in Figure IV.1.[28,29] The sugar moiety is connected by a *β*-glycosidic linkage to a fatty acid chain. The fatty acid chain is terminated by a tetramic acid moiety derived from alanine via 3-acylation. Epicoccamide D was selected for total synthesis because it is said to have the highest cytotoxic and antiproliferative effects in initial cellular based tests.[28] More material is also required to perform additional biochemical tests on possible drug-like properties and to potentially find a mode of action of this compound class.
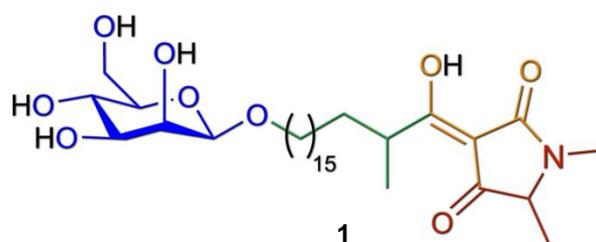
Figure IV.1. Epicoccamide D (**1**) consists of three major parts: A *β*-mannose (blue) connected to a fatty acid chain (green) by which an alanine derived tetramic acid (red/orange) is 3-acylated.

The first attempt to synthesize epicoccamides started from a peracetylated trichloroacetimidate glucose donor in order to benefit from the *β*-directing effect of a 2-*O*-acetyl participating group and after glycosylation changing the protective group pattern to a 2-*O*-unprotected sugar residue. This approach allows performing the necessary 2-*O*-epimerisation. The protective group pattern was chosen to be 4,6-*O*-benzylidene[128,129] together with a selective 3-protection[130–132] but failed on selective introduction of any protective group on 2- or 3-position after benzylidene protection due to proposed sterical hinderance by backflipping (backfolding)[133] of the alkyl chain. Starting from a mannose lacks *β*-stereoselectivity in a synthetic approach for a total synthesis[124].

The first trials also included a 3-acylation method developed by Schobert *et al.*[34,134] starting from a tetramic acid[110]. The 3-acylation would be followed by a new methylation procedure of the 3-acylylide. This methylation was also not successful.

IV.1.2. Retrosynthesis of epicoccamide D

It was evident from these first trials of synthesis that the protective groups of the sugar residue must be in place right before glycosylation and the sugar must bear an orthogonal protection at the 2-position. The assembly of the tetramic acid moiety was planned to be done in a very late step of synthesis to avoid purification problems concerning the 3-acyl tetramic acid with its metal chelating properties[20,99,100]. Closure of the tetramic acid moiety should be carried out by a Lacey-Dieckmann cyclisation[117] to avoid these problems. With that information in hand an approach to epicoccamide D seems possible. This retrosynthetic plan was developed with regards to the three major parts of the target molecule and is summarized in Scheme IV.1.
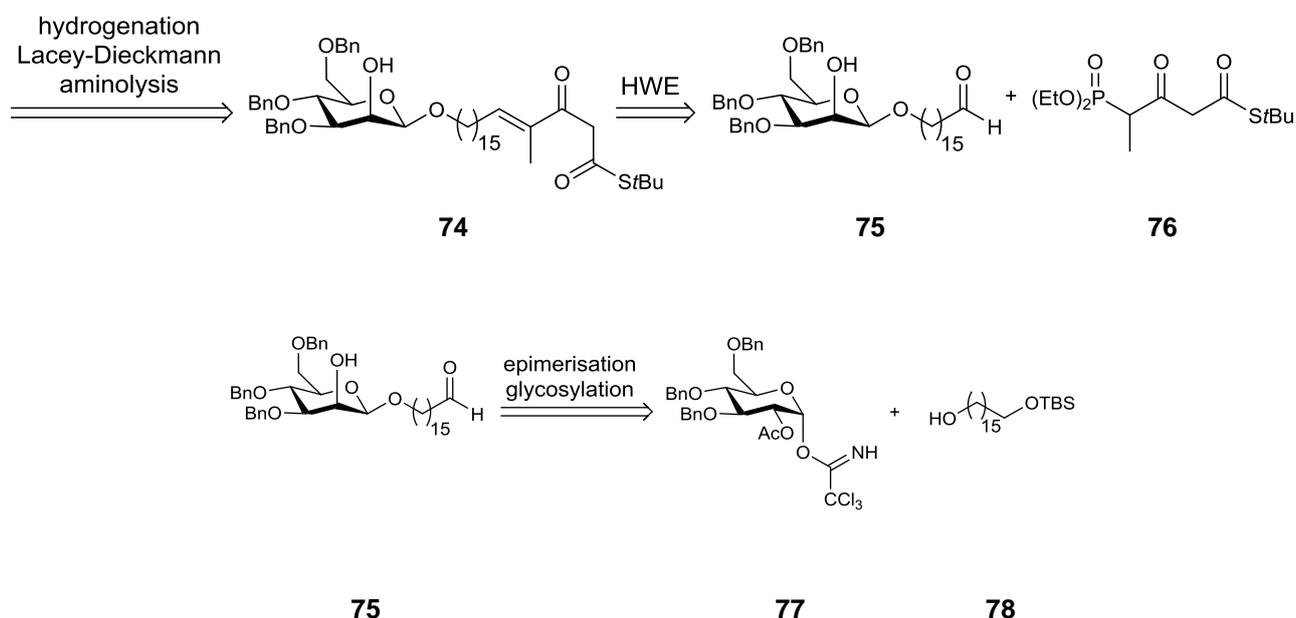
Scheme IV.1. Retrosynthetic approach to epicoccamide D.

The retrosynthesis started with a stereoselective hydrogenation of a double bond formed by HWE reaction (Horner-Wadsworth-Emmons). This step allows access to both diastereomers which can prove useful to get insight into the hitherto unknown absolute configuration. Retrosynthesis continued with a Lacey-Dieckmann cyclisation[117] which is a common method for tetramic acid formation at a late step of synthesis.[64,66] The educt for this cyclisation step was built by aminolysis of the HWE product **74**[56] using a thioester functionality and the corresponding amino acid methyl ester. The necessary aldehyde **75** for this olefination step was to be formed from a corresponding diol **78** by oxidation which was introduced via glycosylation of trichloracetimidate **77**. The β-configuration of the glycosidic bond was formed by glycosylation utilising a donor derived from D-glucose bearing a 2-O-participating

34

protective group. Other donors like a diacetylated sugar[135], a 1-hydroxy donor[136], a α-bromide under Koenigs-Knorr conditions[137] or directly from an orthoester[138,139] failed. To gain access to the *manno*-configuration of the desired natural product an epimerisation reaction was carried out right after glycosylation. The donor **77** for glycosylation was built with a 2-*O*-protecting group which should be participating and orthogonal to the other protective groups for the sugar moiety. A standardized trichloroacetimidate donor should be used for glycosylation as a first test.

IV.1.3. Total Synthesis

The forward synthesis started from *D*-glucose which was first peracetylated with acetic acid anhydride in pyridine with a 96% yield.[140] The peracetylated glucose **80** was transferred into a known ethoxy-orthoester **81**[141,142] by a newer I_2/Et_3SiH mediated reaction procedure[143] in over 99% yield. This orthoester allowed manipulation of the protecting groups in 3-, 4- and 6-position.
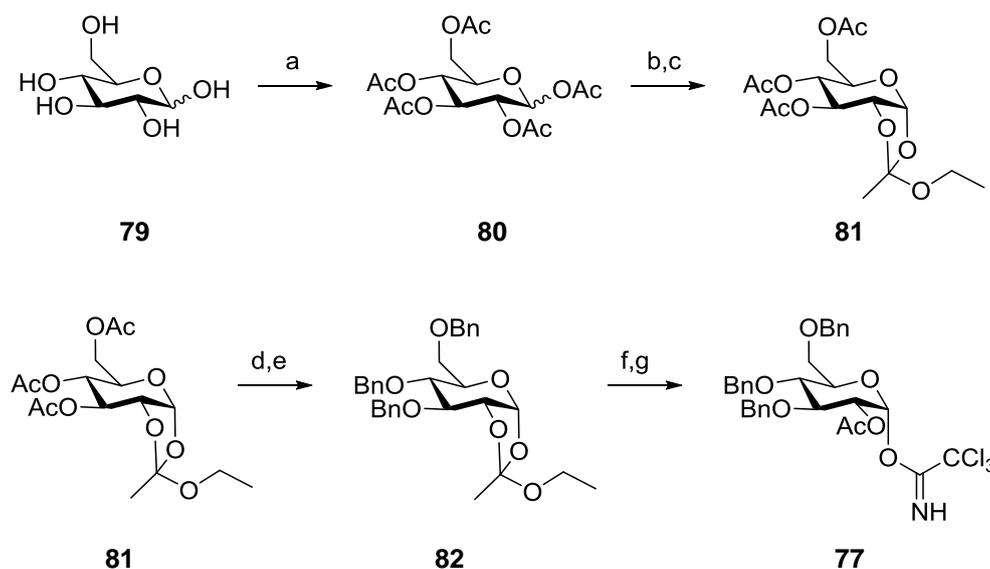
Scheme IV.2. Synthesis of the glycosyl donor. Reagents and conditions: a) 3:2 pyridine:Ac$_2$O, RT, overnight, 96%; b) I$_2$ (1.4 equiv), Et$_3$SiH (1.4 equiv), CH$_2$Cl$_2$, reflux, 1 h; c) 2,6-lutidine (4 equiv), EtOH (6 equiv), TBAI (0.25 equiv), reflux, 3 h, >99% over two steps; d) NaOMe (0.2 equiv), MeOH, RT, 45 min; e) BnBr (4.5 equiv), NaH (4 equiv), DMF, RT, 1 h, 91% over 2 steps; f) *p*-TsOH (0.5 equiv), dimethoxyethane:H$_2$O 10:1, RT, 2 h; g) Cl$_3$CCN (8 equiv), DBU (0.2 equiv), CH$_2$Cl$_2$, RT, 90 min, 83% over 2 steps.

The acetates where exchanged with benzyl ethers by a known[144–146] ester interchange method and protecting procedure using first sodium methoxide in methanol and then benzyl bromide and sodium hydride to yield 91% of the benzylated product **82**. To open the formed orthoester selectively, different methods were evaluated. While methods via aqueous acetic acid[147] or

sulfuric acid[145] failed and a method via a 1,2-O-diacetate[148] included one more step, a procedure using p-TsOH in a mixture of dimethoxyethane and water (10:1) yielded the desired 2-O-acetyl hemiacetal which was directly transferred into the imidate **77** with DBU and trichloroacetonitrile under standard conditions.[149] The yield for this reaction was 83% over two steps. All the steps to form the desired glycosyl donor are summarized in Scheme IV.2.

The desired glycosyl acceptor **78** consisting of a monoprotected C_{16} alkyl chain diol was synthesized by starting from hexadecanolide **83**. The free diol was prepared by nearly quantitative reduction of **83** using LiAlH$_4$ in THF.[150,151] The monoprotection was carried out under improved standard conditions[88] with imidazole and TBSCl to get the desired monoprotected diol **78** in 63% yield. Other methods using sodium hydride as base to make the sodium alcoholate and take the advantage of a phase transfer as reported[152,153] for shorter alkyl chains normally yielding high amounts of the desired monosilylated diol failed. The reason for this fact might be the alkyl chain being too long to distinguish between the two alcohol groups. The synthetic procedure to form the glycosyl acceptor **78** can be seen in Scheme IV.3.

83   **84**   **78**
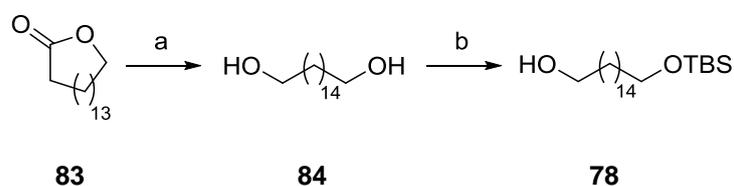
Scheme IV.3. Synthesis of the monoprotected diol **78**. Reagents and conditions: a) LiAlH$_4$ (2.5 equiv), THF, reflux, 1 h, then RT, 12 h, 99%; b) TBS-Cl (1 equiv), imidazole (2 equiv), THF, RT, 12 h, 63%.

The educt phosphonate **76** for the key step HWE reaction was prepared corresponding to a procedure published by Burke *et al.*[56] with higher yields. The first step of this reaction sequence was to install the β-ketothioester moiety by mixing bromopropionyl bromide with Meldrum's acid and after acidic extraction adding 2-methylpropane-2-thiol. This reaction yielded the bromo β-ketothioester **86** in 81% yield over two steps.

85   **26**   **86**   **76**
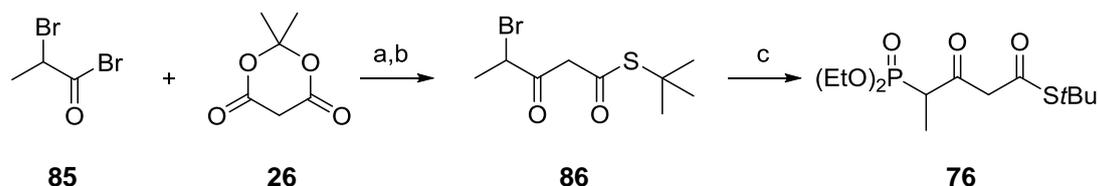
Scheme IV.4. Synthesis of the phosphonate **76**. Reagents and conditions: a) pyridine (2 equiv), 0 °C, 1 h; b) 2-methylpropane-2-thiol (TBM, 3 equiv), toluene, reflux, 1 h, 81% over 2 steps; c) NaH (1.1 equiv), THF, -20 °C, 10 min then Na (1.3 equiv), diethylphosphite (1.2 equiv), THF, RT, 16 h, 97%.

In the next step the actual phosphonate **86** was built by an Arbuzov reaction of **26** with diethylphosphite and sodium hydride[56]. The desired phosphonate **76** was assembled by this reaction in 97% yield without purification in sufficient quality and can be stored for up to four weeks. This procedure is shown in Scheme IV.4.

Assembly of the starting material for the actual total synthesis continued by forming *N*-methylated alanine methylesters **89** for aminolysis and Lacey-Dieckmann cyclisation[56,117] (see Scheme IV.1.). Cheap *t*butoxycarbonyl (BOC) protected alanine was first methylated using MeI and sodium hydride.[56,154–156] The methylation yielded 98% of the corresponding pure *S*-enantiomer of the *N*-methyl amino acid **88** or its racemic mixture depending on the starting material. It is not understandable why examples in literature[157,158] first deprotect the amine with aqueous HCl and in the next do an esterification in methanol by SO_2Cl_2. The liberation of HCl during esterification should be sufficient for BOC-deprotection in one single step. For this reason a one pot esterification and BOC-deprotection procedure was applied as stated in Scheme IV.5. The procedure was very close to the published ones[157,158] used to form the actual methyl ester starting from the deprotected *N*-methyl amino acid. This reaction gave the desired ester **89** in 88% yield concerning the *S*-enantiomer or 72% for the racemate.

(*S*)-**87**   (*S*)-**88**   (*S*)-**89**

(*R/S*)-**87**   (*R/S*)-**88**   (*R/S*)-**89**
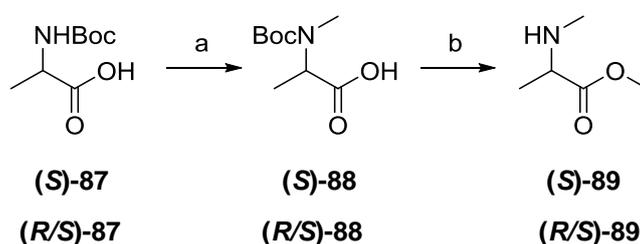
Scheme IV.5. Synthesis of amino acid derivatives. Reagents and conditions: a) NaH (3 equiv, 60% in mineral oil), MeI (8 equiv), THF, RT, 20 h, 98%; b) SOCl₂ (4 equiv), MeOH, RT, 24 h, 72-88%.

With all the necessary starting material for total synthesis in hand, the first key step of the actual synthesis of epicoccamide D was the glycosylation. First trials showed that the 2-*O*-participating acetyl group works as anticipated[159–161] during glycosylation of donor **77** with 1.1 equiv. of the acceptor alkyl chain **78** yielding only the *β*-configured product. No trace of the corresponding α-product in crude thin layer chromatography, ¹H and ¹³C NMR could be found. The initial yields were slighty above 60% at -20 °C. The lack of a good yield was explained by isolating a side product which was identified to be acetylated alkyl chain **78**. The product was formed by transferring the 2-*O*-acetyl group from the sugar to the alkyl chain under Lewis-acidic conditions. To get less of this side product it was possible to decrease glycosylation temperature to -78 °C due to the reactivity of linear alkyl chains in glycosylations. This increased the initial yield to above 70% but still the fully protected alkyl

chain was a major side product. Since the side chain can be generated in two steps with good yields (see Scheme IV.3.) the equivalence of the acceptor side chain **78** was increased step by step to 1.7 yielding 84% of the desired glycosylation product **90** (see Scheme IV.6.). Roughly 0.5 equivalence of the side chain could be reisolated after glycosylation and again be used.

The next challenge was the epimerisation reaction to form the desired *manno*-configurated glycoside **93**. For that purpose a standard procedure for deacytelation[144,146] was applied to form the 2-hydroxy product **91** in nearly quantitative yield. Since first trials with the Cornforth reagent pyridinium dichromate[162] failed, Swern oxidation and variations were tested to oxidize the sugar which could in a next step be reduced stereoselectively. A standard Swern oxidation using DMSO and oxalyl chloride[163,164] or trifluoroacetic anhydride[163,165–167] failed also like the variants established by Pfitzner-Moffat utilizing DMSO and dicyclocarbodiimide[168], the mild Albright-Goldman procedure with DMSO and acetic anhydride[169,170] often used for sugar oxidation[168,171–173] and the Corey-Kim type reaction with dimethyl sulfide and *N*-chlorosuccinimide[174–176]. Where the other reactions showed no conversion, the Corey-Kim procedure also used for sterically hindered products[177] and sugars[178] yielded a 2-*O*-methylsulfonated product. At the end the oxidation was successful by switching to the Dess-Martin periodinane (DMP)[179] which was applied in sugar oxidation as well[180]. Oxidation of the sugar moiety with DMP yielded in 96% yield the desired sugar ketone **92**. Due to the mentioned backfolding of the alkyl chain (see chapter IV.1) 3 equiv. of DMP were necessary. The selective reduction could be carried out easily with NaBH$_4$ yielding the desired *manno*-configurated product **93** in 97% yield. The only side product of the reaction was 3% of the *gluco*-configurated product **91** which could be separated by chromatography. The glycosylation and epimerisation sequence is shown in Scheme IV.6.

To prepare the desired aldehyde for HWE reaction, TBS deprotection was necessary first which was carried out using a TBAF solution in THF[181]. This step yielded 98% of the desired diol **94**.

For the following steps of synthesis the sterical blockage of the sugar moiety by the alkyl chain was helpful, because no 2-*O*-protecting group was necessary. The free axial 2-*O*-hydroxy functionality did neither disturb the oxidation of the alkyl chain to an aldehyde nor was able to catch away base for the HWE reaction. However, it can be protected e.g. with sodium hydride and benzyl bromide in 68% yield but it was evident that the overall yield with this additional step might be less.
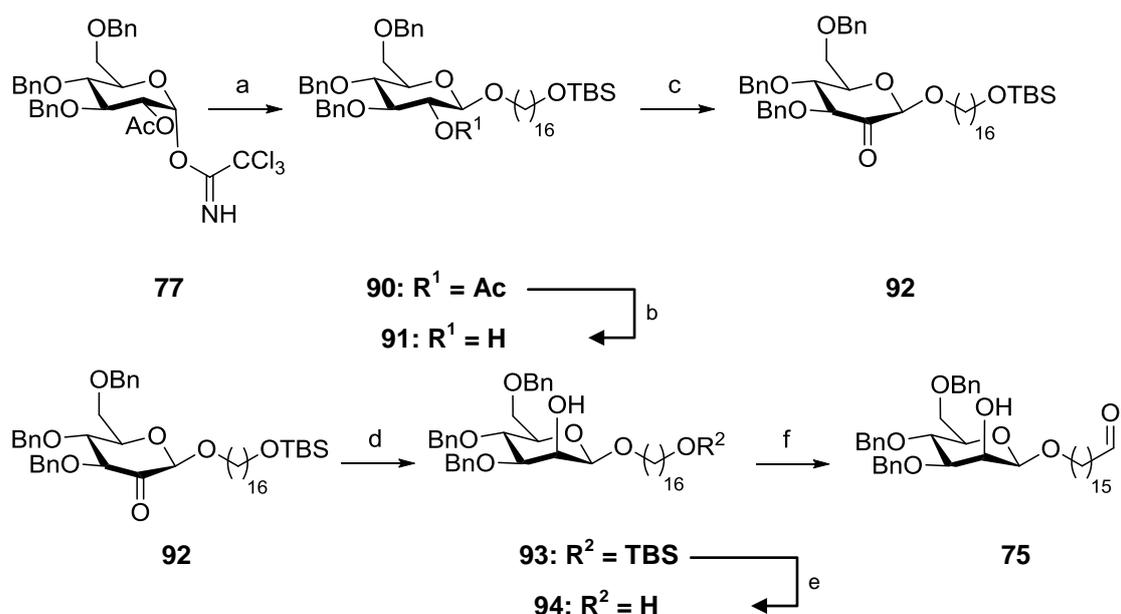
Scheme IV.6. Synthesis of glycoside **90**, epimerisation and oxidation. Reagents and conditions: a) **78** (1.7 equiv), BF$_3$·OEt$_2$ (0.15 equiv), 4 Å mol. sieves, CH$_2$Cl$_2$, -78 °C, 2 h, 84%; b) NaOMe (2 equiv), MeOH, RT, 12 h, 99.2%; c) DMP (3 equiv), CH$_2$Cl$_2$, RT, 16 h, 96%; d) NaBH$_4$ (10 equiv), MeOH:CH$_2$Cl$_2$ 1:1, RT, 12 h, 97%; e) TBAF (1 M in THF, 2 equiv), THF, RT, 12 h, 98%; f) DMP (1.15 equiv), CH$_2$Cl$_2$, 0°C to RT, 3 h, 70%.

The actual oxidation of the primary hydroxy group on the alkyl chain was carried out again with DMP[179]. To avoid the possible reoxidation of the sugar moiety the reaction was started at 0 °C and with no huge excess of oxidation reagent. This oxidation yielded in 70% the desired aldehyde for Horner-Wadsworth-Emmons olefination **75** and about 22% of recovered dialcohol **94**.
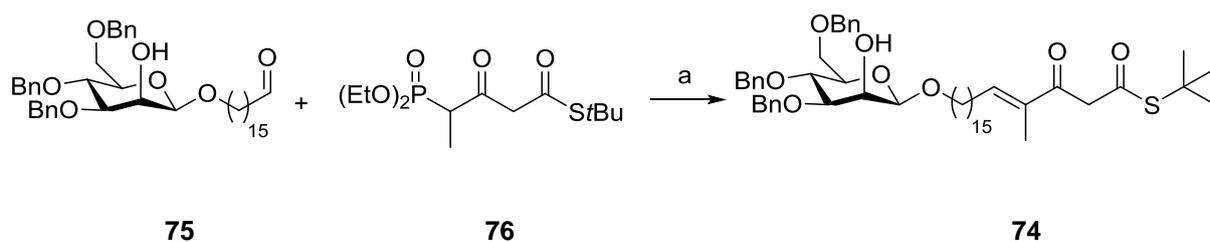
Scheme IV.7. Subsequent HWE olefination. Reagents and conditions: a) **76** (1.4 equiv), *n*BuLi (2.8 equiv), THF, -78 °C to RT, 4 h, 80%.

The following HWE reaction[182,183] was carried out to install a *β*-ketothioester unit which in turn enabled access to an aminolysis reaction where the corresponding amino acid from the natural chiral pool was connected. This olefination step needed a good tuning in reaction parameters as well as screening for the most efficient base. The work of Ley *et al.*[56] where the used phosphonate **76** is derived from, KHMDS is proposed to give good yields and satisfactorily E/Z rates. Other publications[184–186] showed a wide set of different bases and the influence of lithium salts[185] for higher Z-selectivity than the HWE normally provides[183].

Trials with different bases are summarized in Table IV.1. For these initial trials, a test system with the same phosphonate **76** and hexanal was established which was also applied for tests of catalysts later on.

Table IV.1. Overview of the tested bases screened in the HWE olefination step.

Entry	Base[a]	Additive[b]	Yield[c]	E:Z[d]	Notice
1	KHMDS	--	80%	4:3	Slow addition of base by syringe pump
2	KHMDS	--	79%	5:1	Fast addition of base
3	KHMDS	LiCl	65%	5:6	Slow addition of base by syringe pump
4	NaHMDS	--	60%	1:1	Slow addition of base by syringe pump
5	LiHMDS	--	25%[e]	10:11	Slow addition of base by syringe pump
6	NaH	--	72%	4:3	
7	LDA	--	< 5%	1:1	Nearly no conversion[e]
8	DBU	--	< 5%	7:5	Decomposition
9	DBU	LiCl	< 5%	10:11	Strong decomposition
10	*t*-BuOK	--	14%	7:5	Nearly no conversion
11	*t*-BuOK	LiCl	8%	11:10	Decomposition
12	*n*-BuLi	--	88%	6:5	Slow addition of base by syringe pump
13	*n*-BuLi	--	82%	12:5	Fast addition of base

[a] always 2 equiv based on the phosphonate **76** used; [b] 1:1 ratio concearning the base used; [c] based on the aldehyde **75**, [d] determined by NMR, [e] old reagent used.

Table IV.1 shows that the usage of KHMDS yields the highest *E*-selectivity as supposed by the results of Ley *et al.*[56] It was also evident that slow addition of the base via syringe pump worsened the *E*-selectivity of the used KHMDS possibly due to equilibration of different ylide species. The two highest yielding bases KHMDS and *n*butyl lithium were then tested in the complete system with aldehyde **75** and phosphonate **76**. In these experiments the silazane base failed to give good yields but *n*butyl lithium gave stable yields around 80% with the mentioned bad *E/Z*-selectivity of 2.4:1. It was suprising that the *E/Z*-selectivity of *n*butyl lithium did not play any role in the subsequent synthesis since the double bond seems to isomerize only to the *E*-derivative during Lacey-Dieckman cyclisation which will be described later on. The HWE olefination step was therefore carried out with *n*butyl lithium, because it had always the highest and most reproducible yields.

To attach the desired amino acid methyl ester **89**, the aminolysis protocol from the equisetin total synthesis[56] was adapted. The amount of base used was increased to account for the direct usage of the HCl salt gained from esterification with $SOCl_2$ (see Scheme IV.5.). Since the methyl ester salt **89** dissolved slowly in CH_2Cl_2 and the sterical demanding thioester **74** slowed the reaction speed down, reaction time was increased and the reaction was carried out

in complete darkness to avoid reduction of the silver salt[187,188] $F_3CCOOAg$. Triofluoroacetate was used as anion because it dissolves in organic solvents[189]. Since the configuration of the two additional stereocenters beside the sugar moiety was unclear[28,29], it was likely that nature might have used the *S*-isomer concerning the tetramic acid C-5 for biosynthesis. Therefore aminolysis was carried out using the *S*-configurated ester (*S*)-**89** and the racemic mixture (*R/S*)-**89** for comparison to gain a *β*-ketoamide **95** necessary for Lacey-Dieckmann cyclisation. Both reactions yielded 89% of the desired ketoamide.

74   (2*S*)-**95**

(2*R/S*)-**95**
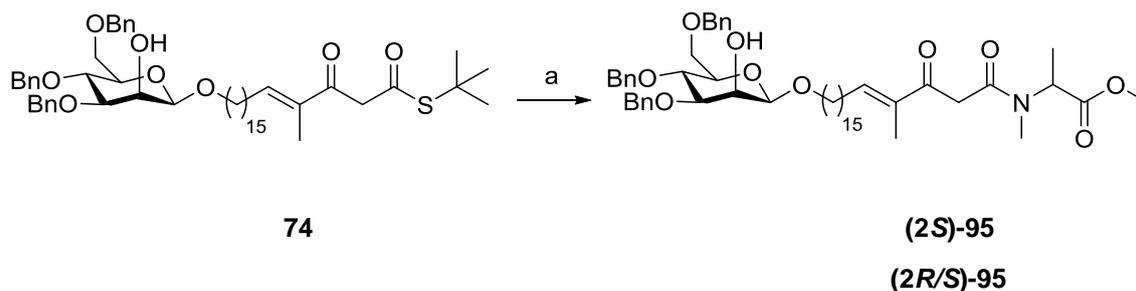
Scheme IV.8. Aminolysis. Reagents and conditions: a) **89** (2.5 equiv), NEt_3 (3.5 equiv), $F_3CCOOAg$ (2 equiv), CH_2Cl_2, light exclusion, 0 °C, 5 h, 89%.

The standard procedure of the Lacey-Dieckmann cyclisation[117] step was slightly changed by reducing the used base sodium methoxide to a minimum (2 equiv instead of 5 equiv) to avoid racemisation of the formed tetramic acid moiety by C-5 epimerisation[34] and also reducing stirring time (20 min instead of 45 min).

(2*S*)-**95**   (5*S*)-**96**

(2*R/S*)-**95**   (5*R/S*)-**96**
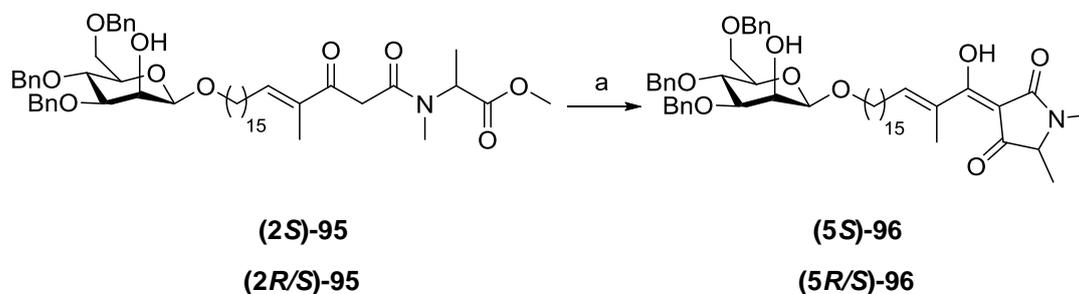
Scheme IV.9. Lacey-Dieckmann cyclisation. Reagents and conditions: a) NaOMe (2 equiv), MeOH, RT, 20 min, quant.

With these changes epimerization could be decreased to less than 4% which was checked by again using the phosphonate **76** with (*4S*)-methylhexanal, going through the above illustrated reaction sequence and analyzing the Lacey-Dieckmann adduct by chiral HPLC. In respect of the educt aldehyde purity of 98% this value is acceptable. It was surprising that these reaction conditions isomerized the double bond which was only 70% *E*-configurated to 90% of the *E*-isomer. Later BF_2-complexation steps isomerized the double bond further to only *E*-configurated isomer exclusively. This cyclisation step yielded the desired tetramic acid

quantitatively without purification which can be used directly in the following steps of synthesis.
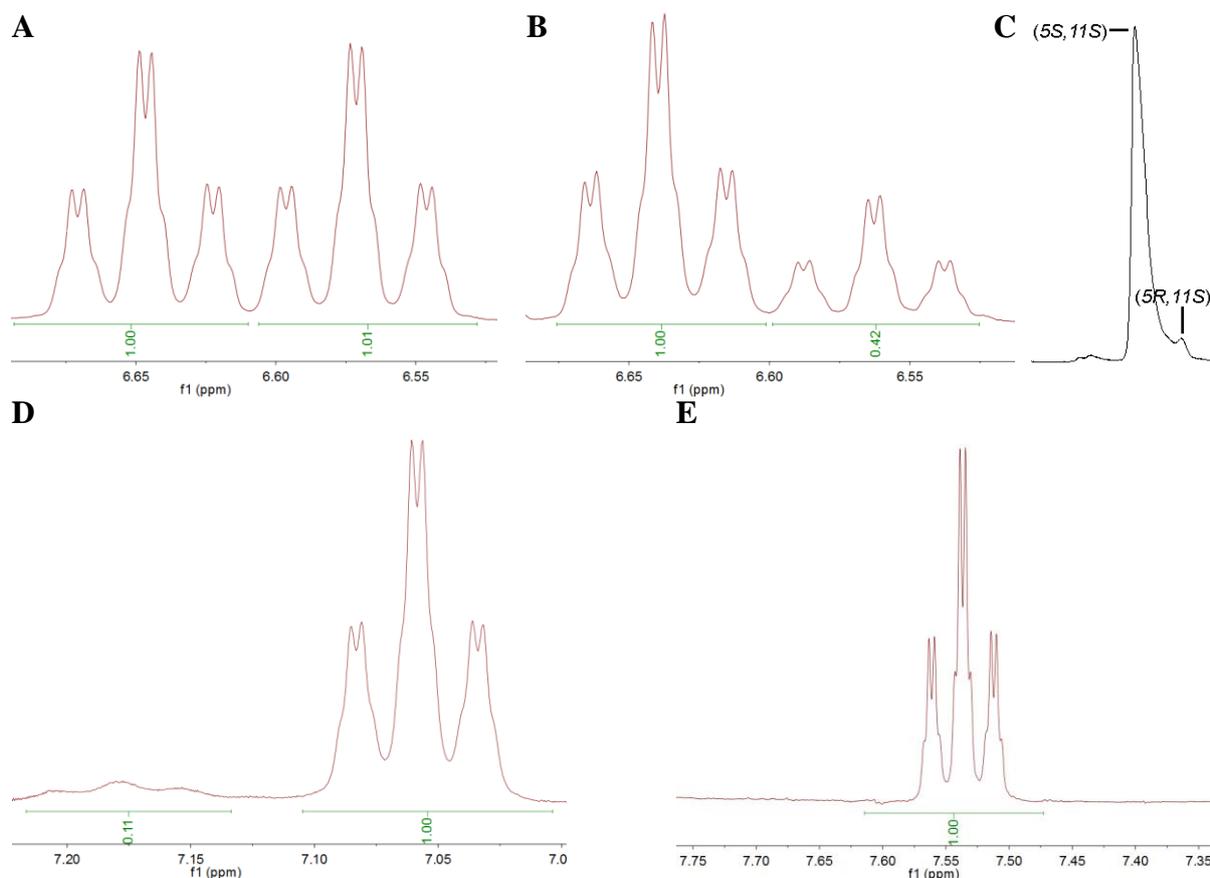
Figure IV.2. Base dependent *E/Z*-selectivity in HWE olefination step. A) HWE reaction of phosphonate **76** with hexanal and NaHMDS as base; B) HWE reaction of phosphonate **76** with hexanal and *n*-BuLi as base added fast; C) chiral HPLC profile of the Lacey-Dieckmann cyclisation product derived from the phosphonate **76** and (*4S*)-methylhexanal; D) Lacey-Dieckmann cyclisation product of the auxiliary **97** (see Scheme IV.10.); E) product of BF_2-complexation of **97**.

The final step of synthesis right before global deprotection needed to be an asymmetric hydrogenation to establish the second methyl substituted stereocenter in the side chain as selectively as possible. This step would also open access to both isomers. To test the different possible catalysts for asymmetric homogeneous hydrogenation the above mentioned test system also used for screening of bases concerning the HWE reaction was again applied. It was evident from first trials of the homogeneous hydrogenation with the corresponding 3-octenoyl tetramic acid shown in Scheme IV.10. (**97**) that the metal chelating propensities of 3-acyl tetramic acid traps the catalyst and therefore prohibits the actual reaction. 2-Octenic acid was also not reactive under similar conditions but its ethyl ester reacted well. This provided evidence that the metal chelating properties of the tetramic acid needed to be somewhat disarmed. For this reason the corresponding BF_2-complex was formed which is a well known[30,98,134], easy to handle and stable storage form of tetramic acids. The same

methodology as for the complete system shown in Scheme IV.7. and Scheme IV.8. was applied.
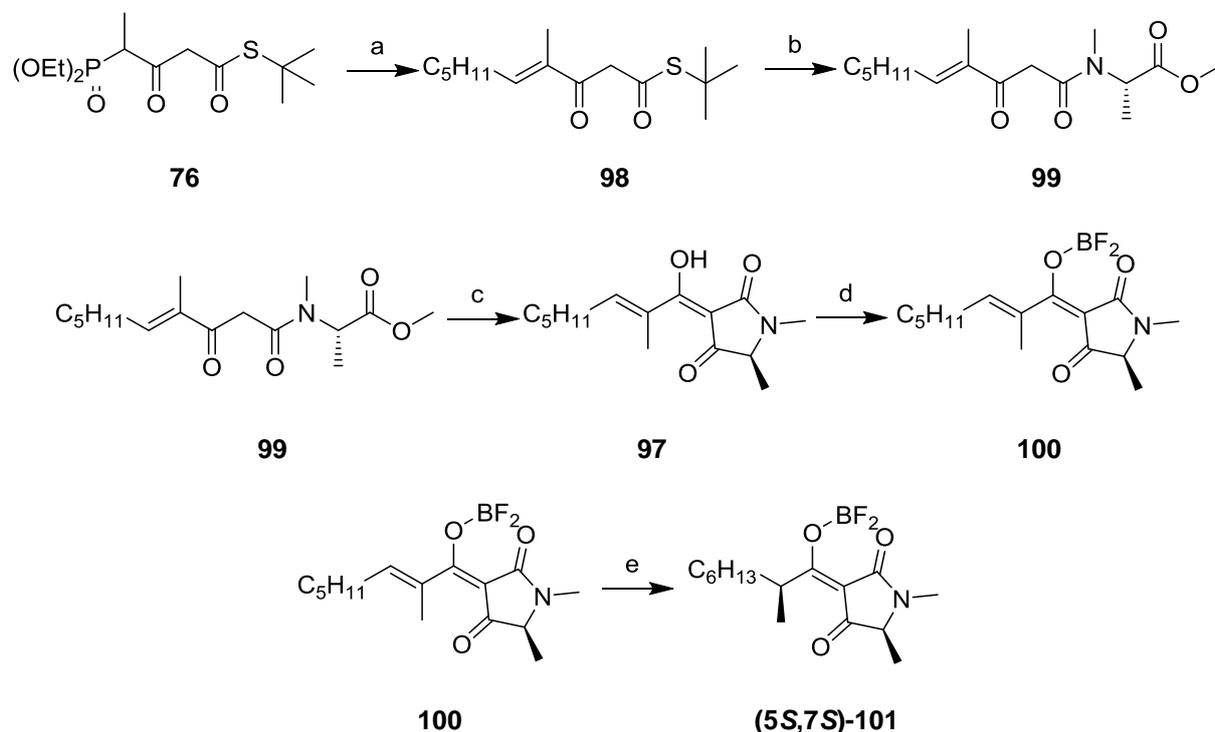
Scheme IV.10. Synthesis of a test system auxiliary. Reagents and conditions: a) Hexanal (1.0 equiv), **76** (1.4 equiv), *n*-BuLi (2.8 equiv), THF, -78 °C to RT, 1.5 h, 87%; b) **(S)-89** (2.5 equiv), NEt$_3$ (3.5 equiv), F$_3$CCOOAg (2 equiv), CH$_2$Cl$_2$, light exclusion, 0 °C, 2 h, 83%; c) NaOMe (2 equiv), MeOH, RT, 20 min, quant.; d) BF$_3$•OEt$_2$ (5 equiv), CH$_2$Cl$_2$, RT, 12 h, 90%; e) [(R,R)-Rh-Et-DUPHOS]$^+$ BF$_4$$^-$ (4 mol%), 100 bar H$_2$, CH$_2$Cl$_2$, 35 °C, 16 h, 97%.

With this test system in hand different rhodium based catalysts were tested, analyzed via chiral HPLC and the reaction conditions (pressure and temperature) were optimized. The solvent was changed to CH$_2$Cl$_2$ since protic solvents dissolve the BF$_2$-complex in a few hours. Rhodium catalysts with chiral mono- and bidendate phosphine ligands[190–195] had been found to be active in other electron deficient systems[196]. Conditions were derived from the Nobel prize lecture 2001 (Prof. William S. Knowles)[197] and others[195,198]. Beside different homogeneous catalysts also including a Crabtree like Ir-based catalyst[199,200] the MacMillan organocatalyst *S*-Mac-H[201] was used as well as Pd/C[202,203] as reference. It is worth mentioning that the heterogeneous catalyst showed a certain stereoinduction which might be caused by the fact that tetramic acid BF$_2$-complexes are generally not totally flat[98] but have the boron atom elevated over the plain of the normally flat tetramic acid motif. This might give a heterogeneous hydrogenation using a catalyst like Pd/C a certain induction[204] possibly also due to the slightly imposed methyl group attached to the C-5. These results are summarized in Table IV.2.

Table IV.2. Catalysts and conditions for asymmetric hydrogenation. The individual catalysts tested are shown in Figure IV.3 below.

Entry	Catalyst	Anion	Conditions[a]	Yield	de[b]
1	Pd/C	--	10 wt% catalyst, MeOH, 1 bar	99%	42%
2	Pd/C	--	free tetramic acid[c], 10 wt% catalyst, MeOH, 1 bar	99%	4%
3	*S*-Mac-H	--	10 mol% catalyst, RT	0%	--
4	Ir-ThrePHOX	BARF	4 mol% catalyst, 180 bar	0%	--
5	Rh-BINAP[d]	BF$_4$	4 mol% catalyst, 8mol% BINAP[e]	30%	18%
6	Rh-MONOPHOS[d]	BF$_4$	4 mol% catalyst, 8mol% MONOPHOS[e]	50%	19%
7	Rh-*i*Pr-FERPHOS	BF$_4$	4 mol% catalyst, 80 bar	85%	40%
8	Rh-Me-DUPHOS	BF$_4$	4 mol% catalyst, 80 bar	48%	52%
9	Rh-Et-DUPHOS	OTf	4 mol% catalyst, 100 bar	10%	82%
10	Rh-Et-DUPHOS	BF$_4$	4 mol% catalyst, 100 bar	97%	82%
11	Rh-*i*Pr-DUPHOS	BF$_4$	4 mol% catalyst, 120 bar	56%	69%

[a] 35 °C, CH$_2$Cl$_2$, 16 h, 80 bar H$_2$ pressure as indicated; [b] determined by chiral HPLC analysis and NMR spectra; [c] instead of the corresponding BF$_2$-complex the free tetramic acid was used for comparison; [d] pre-catalyst [Rh(cod)$_2$]$^+$ BF$_4^-$ used; [e] BINAP and MONOPHOS ligands added to pre-catalyst.

A   **B**   **C**

D   **E**   **F**   **G**

H   **I**   **J**
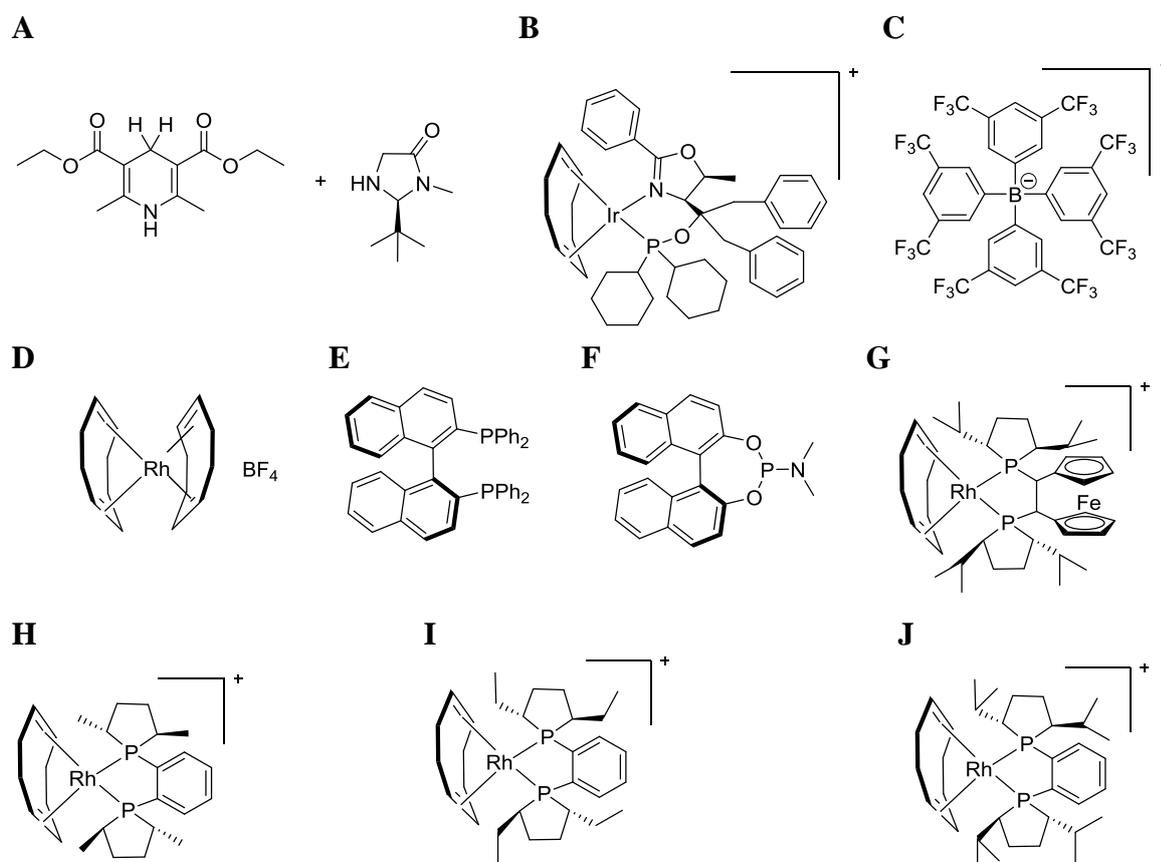
Figure IV.3. Ligands tested for stereoselectivity in catalytic hydrogenation. A) Mac-Millan catalyst[201] with Hantzsch-Ester and 10 mol% of a imidazolidinone derivative; B) Crabtree like catalyst[199,200]; C) BARF anion[199]; D) [Rh(cod)$_2$] BF$_4$ pre-catalyst; E) BINAP[190,195]; F) MONOPHOS[192–194]; G) Rh-*i*Pr-FERPHOS[191]; H) Rh-Me-DUPHOS[191,194]; I) Rh-Et-DUPHOS[191]; J) Rh-*i*Pr-DUPHOS[191].

To apply these results to the total synthesis, the method of BF_2-complex formation needed to be changed. The amount of $BF_3 \cdot OEt_2$ used and temperature was decreased to a minimum since the strong Lewis-acidic BF_3 degraded the glycosidic bond due to its strong sugar activating properties[160] when the conditions for the auxiliary were adopted. The amount of $BF_3 \cdot OEt_2$ was minimized from 5 equiv to 1.2 equiv and the temperature was decreased to 0 °C. Below that temperature complex formation was prevented nearly completely.

With the appropriate BF_2-complex in hand asymmetric hydrogenation was carried out under the same conditions as for the auxiliary and yielded exactly the same results as can be seen in Table IV.2. concerning yield and stereoselectivity and in Figure IV.4. below showing again stereoselectivity and purity.
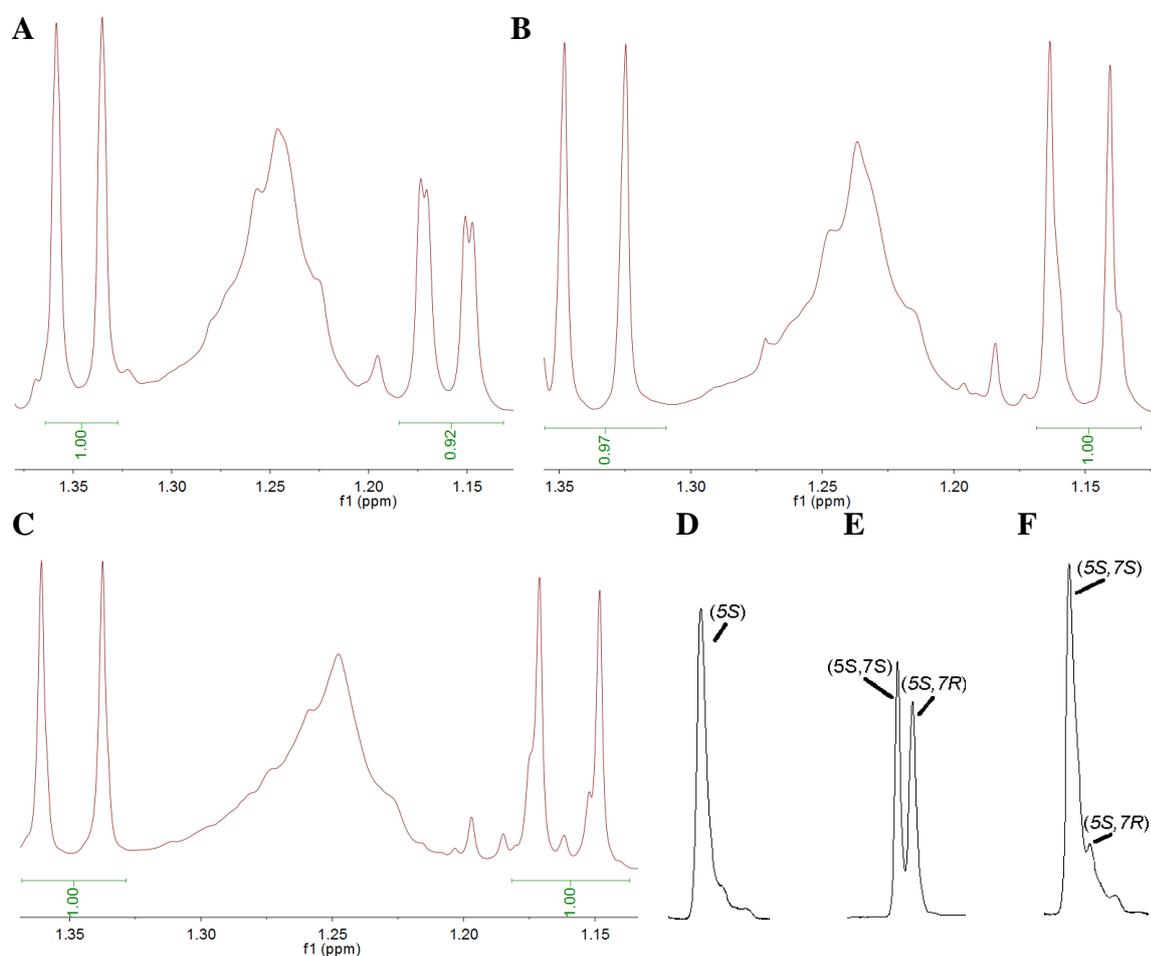
Figure IV.4. NMR and HPLC data showing purity and stereoselectivity of the hydrogenation products where Rh-Et-DUPHOS[191] was used. A) Pd/C catalyzed hydrogenation and BF_2-complexation thereafter to compare retention times and NMR spectra; B) (*R,R*)-configurated Rh-Et-DUPHOS catalyst used establishing a 7*S* stereocenter; C) (*S,S*)-configurated Rh-Et-DUPHOS catalyst used establishing a 7*R* stereocenter; D) HPLC profile of the BF_2-complex educt used for hydrogenation; E) nearly racemic mixture of the Pd/C hydrogenated and afterwards complexed product; F) HPLC profile of the product hydrogenated using the (*R,R*)-configurated Rh-Et-DUPHOS catalyst. In D, E, and F the chromatogram shows the retention time (x-axis) plotted against the absorption in mAU (y-axis).

The final step of the total synthesis of epicoccamide D was a global deprotection step where the BF$_2$-complex was also removed. Standard Pd/C hydrogenation was applied to remove the benzyl protecting groups. Methanol[30] was employed as solvent in which BF$_2$-chelate complexes are not stable[134]. The product (**5R/S**)-**96** using the racemic amino acid methyl ester (**R/S**)-**89** was directly hydrogenated to yield "racemic" epicoccamide with regard to the unknown absolute configuration of the C-5 and C-7 stereocenter.
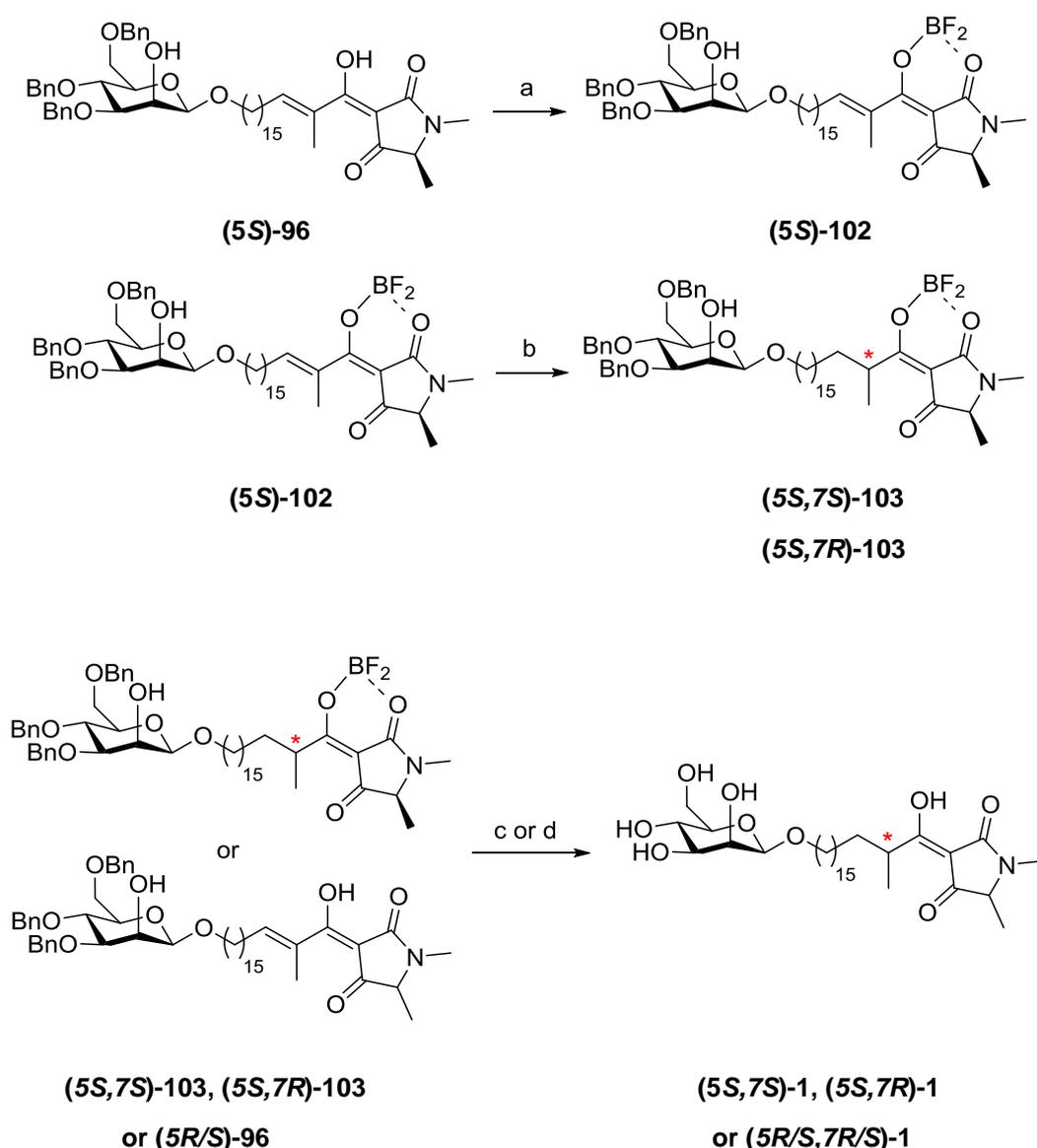
Scheme IV.11. Final global deprotection step of the total synthesis of epicoccamide D. Reagents and conditions: a) BF$_3$•OEt$_2$ (1.2 equiv), CH$_2$Cl$_2$, 0 °C to RT, 12 h, 62%; b) (S,S)- or (R,R)-Rh-Et-DUPHOS (0.04 equiv), 80 bar H$_2$, CH$_2$Cl$_2$, 35 °C, 16 h, 97%; c) Pd/C (5%, 100 wt%), 1 bar H$_2$, MeOH, 35 °C, 4 h, 97%; d) Pd/C (5%, 10 wt%), 1 bar H$_2$, MeOH, RT, 4 h, 97%.

With the different final products of total synthesis in hand assignment of the stereocenter established by the catalyst was necessary as a final working step to compare raised data with

published[28] results and eventually figure out the absolute configuration of natural epicoccamide D.

IV.1.4. Assignment and absolute configuration of synthetic products

The model compound **100** shown in Scheme IV.10. was subjected to hydrogenation with both (*S,S*)- and (*R,R*)-Et-DUPHOS configured catalysts and afterwards compared to the same model compound made by another route with a known stereocenter at C-7. NMR shifts as well as optical rotation were consulted to assign the stereoinduction of the used catalyst Rh Et-DUPHOS[191] and with this information in hand the absolute configuration at the C-7 methyl group on the side chain. The model compound was synthesized via 3-acylation of a free tetramic acid using the method described by Yoda *et al.*[205] and afterwards BF$_2$-complex formation was applied. The starting compounds required for this model compound were available in the work group made from octanoic acid α-methylated by the Evans auxiliary technique[206,207] and tetramic acid formation of the corresponding *N*-Boc-protected amino acid benzyl ester using ketenylidentriphenylphosphorane[34,110,134,208,209] and hydrogenolytic deprotection[30].

(2S)-104   **(5S)-105**   **(5S,7S)-101**
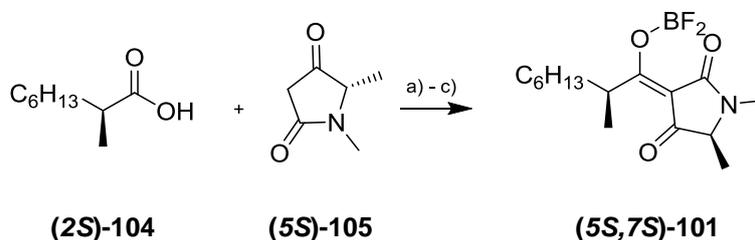
Scheme IV.12. Alternative access to the model compound to assign the stereocenters. Reagents and conditions: a) tetramic acid **105** (1 equiv), EDCI (2 equiv), DMAP (2 equiv), CH$_2$Cl$_2$, 0 °C to RT, 4 h; b) CaCl$_2$ (1.5 equiv), DMAP (0.3 equiv), NEt$_3$ (1.2 equiv), CH$_2$Cl$_2$, RT, 90 min; c) BF$_3$•OEt$_2$ (5 equiv), CH$_2$Cl$_2$, RT, 16 h, 52% over three steps.

The tetramic acid **(5S,7S)-101** obtained from the 3-acylation with a known stereocenter was then compared to the one obtained from a HWE olefination, aminolysis, Lacey-Dieckmann cyclisation and asymmetric hydrogenation sequence in regard to their HPLC- and NMR-data shown in Figure IV.4. The mentioned tetramic acid **(5S,7S)-101** had ^{1}H and ^{13}C NMR shifts and a retention time in agreement with the tetramic acid gained from the developed reaction set by usage of the (*R,R*)-Rh-Et-DUPHOS catalyst. These results lead to the assumption that the (*R,R*)-catalyst is building a *S*-configured stereocenter and a (*S,S*)-catalyst gave rise to a *R*-configured stereocenter. The shown data gave all the information necessary to assign the stereocenters in natural epicoccamide D.

IV.1.5. Comparison of synthetic products with natural epicoccamide D

The specific rotation of the synthetic products were compared to the one from natural epicoccamide D[28] besides their ^{13}C chemical shift in respect of the carbon at position 5 and 7 to assign the absolute configuration of natural epicoccamide. These results are summarized in Figure IV.5. and Table IV.3.
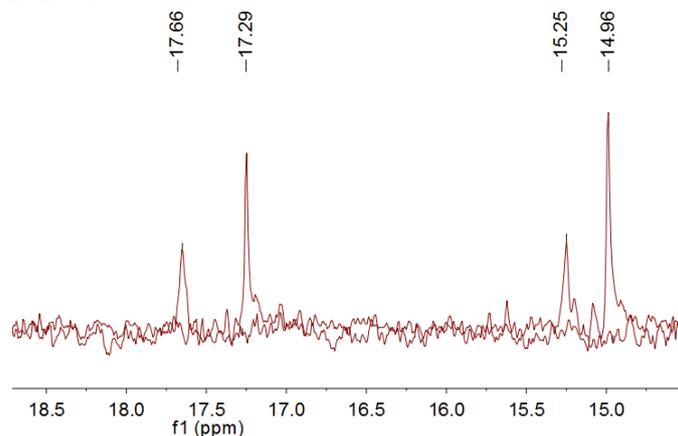
Figure IV.5. ^{13}C NMR shifts of two synthetic epicoccamide D isomers yielded from usage of the (*R*,*R*)- and (*S*,*S*)-Et-DUPHOS catalyst.

An overview concerning these results is given in Table IV.3.

Table IV.3. Comparison of the specific optical rotation[a] and ^{13}C NMR shifts[b] of natural and synthetic epicoccamide D beside another epicoccamide isomer.

Entry		Natural **1**	**(5S,7S)-1**	**(5S,7R)-1**
1	$[\alpha]_D^{25}$ [°]	-40	-39	-30
2	^{13}C-NMR: C-5 [ppm]	14.8	15.0	15.3
3	^{13}C-NMR: C-7 [ppm]	17.0	17.3	17.7

[a] recorded in MeOH with c = 0.2 g cm^{-3}; [b] 75 MHz in CDCl$_3$.

These results gave strong evidence that the absolute configuration of natural epicoccamide D is *5S* and *7S* respectively and that the right product was synthesized. This assumption was confirmed by Yajima *et al.*[123] after publication[32] of the shown data.

IV.2. Total synthesis of ancorinoside B diglycoside

A similar fragmentation for ancorsinosides[100,119,120] as for epicoccamides[28,29] is possible. The major difference to epicoccamides is a disaccharide unit at one end of the fatty acid chain in contrast to a single mannose. In case the of ancorinosides the tetramic acid moiety is derived from *D*-aspartic acid and the side chain is longer and can be substituted with a methyl group near the middle (ancorinoside C)[120] or a *Z*-configurated double bond (ancorinoside D)[120]. The disaccharide unit consists either of a Glc-*β*(1-4)GalU unit (ancorinoside A and D)[100,119,120] or a vice versa configurated Gal-*β*(1-4)GlcU unit (ancorinoside B and C)[120]. Ancorinoside B was chosen for total synthesis since it shares a simple side chain with ancorinoside A and was tested in more detail revealing interesting properties like a quite selective inhibition of MMP2[120], a matrix metalloprotease connected to disease by its angiogenic effect[210,211] in tumor growth. The target structure of ancorinoside B is shown in Figure IV.6. displaying its three major parts: The disaccharide unit, the fatty acid chain and the tetramic acid moiety.
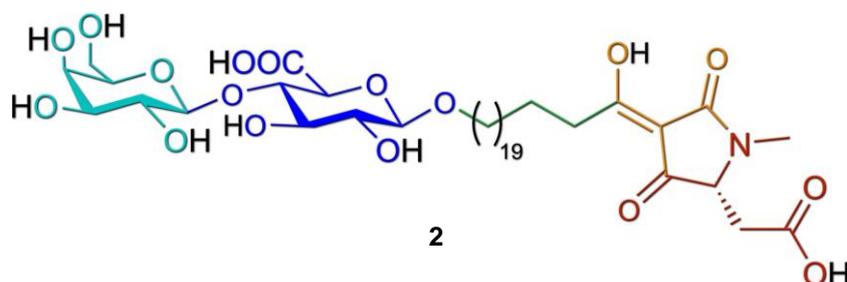
Figure IV.6. Ancorinosid B (**2**) consists of three parts: The blue dissacharide with a light blue galactose and a dark blue glucuronic acid connected by a *β*(1-4) linkage again *β*-connected to a fatty acid chain (green). The fatty acid chain is attached via 3-acylation to an aspartic acid derived tetramic acid (red).

IV.2.2. Retrosynthesis of ancorinoside B

Retrosynthesis commenced with similar steps as for the synthesis of epicoccamides as stated above (Scheme IV.1.). No asymmetric hydrogenation was necessary to build up ancorinoside B since the side chain of the chosen target molecule has no substitution. Additional differences to epicoccamide are the two *β*-configurated glycosidic bonds and a glucose residue oxidised to the corresponding glucuronic acid. The disaccharide bearing a lactose pattern should be build up by either using a readily oxidised glucuronic acid acceptor with a galactose donor or by utilizing a accordingly protected glucose acceptor and oxidize

right after the first or second glycosylation step. With respect to these differences the following retrosynthetic plan was developed.
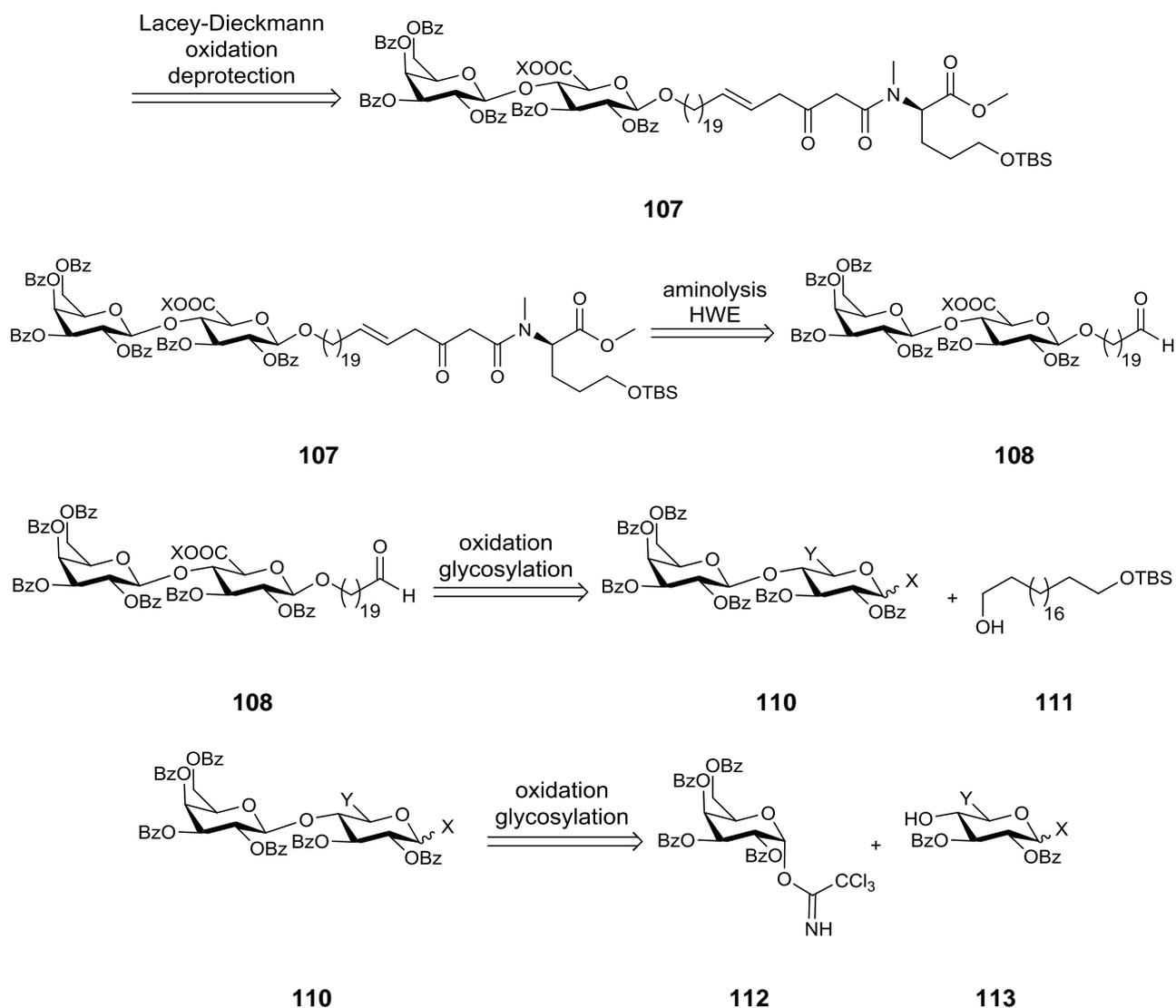
Scheme IV.13. Retrosynthetic approach to ancorinoside B. X = *β*-SPh or OAllyl (converted to *α*-trichloroacetimidate); Y = COOBn, COOMe or CH₂OTBS.

The retrosynthetic goal for the total synthesis of ancorinoside B was again to build up the tetramic acid moiety as late as possible, because of its metal chelating propensity. This part was therefore assembled by a Lacey-Dieckmann cyclisation[117] of the product gained from an aminolysis reaction with a protected homoserine which was converted into the actual aspartic acid derivative by deprotection and oxidation right after the cyclisation step. This was carried out to avoid formation of a 6-membered ring side product which might turn out to be hardly removed once the polar tetramic acid is established. Expensive *D*-homoserine can be derived from cheap *D*-methionine.[212] In front of the cyclisation step the necessary connection between the diketo moiety and the fatty acid glycoside was formed by a HWE olefination reaction[32,56]. The aldehyde **108** was to be build by glycosylation of an adequate disaccharide

50

donor **110** and the corresponding side chain acceptor **111** which was in turn assembled via reduction of eicosanedioic acid[213] and monoprotection. The desired glycosyl donor **110** should be assembled by glycosylation of a perbenzoylated donor **112** and either a readily oxidized and accordingly protected glucoronic acid ester acceptor **113** or, since the oxidized sugars are difficult to handle[214] and often oxidized right after glycosylation[215], an accordingly 6-*O*-protected acceptor **113** which can be deprotected and oxidized directly after one of the glycosylation steps. The actual functional group for gylcosylation was to be elaborated in preliminary experiments. Both Fischer[216] and Schmidt[217,218] donors (thioglycosides and trichloroacetimidates respectively) should be considered. Lactose bearing the same substitution pattern (Gal-*β*(1-4)Glc) could also be used and needed to be oxidized at the C-6 of the glucose unit. This approach is a highly specialized approach which wouldn't complement a set building blocks for assembly of glucuronic acid bearing saccharides and it also needs a longer reaction sequence to manipulate the protecting groups accordingly[219–223].

IV.2.3. Disaccharide unit of ancorinoside B via glucuronic acid

Glucuronic acids are well investigated concerning their properties as donors in glycosylation reactions[214,215,220,224–226] but there's a lack of knowledge using them first as acceptors[227], especially in the case of even more electron deficient acceptors. The following chapter describes the different used donor and acceptor combinations.
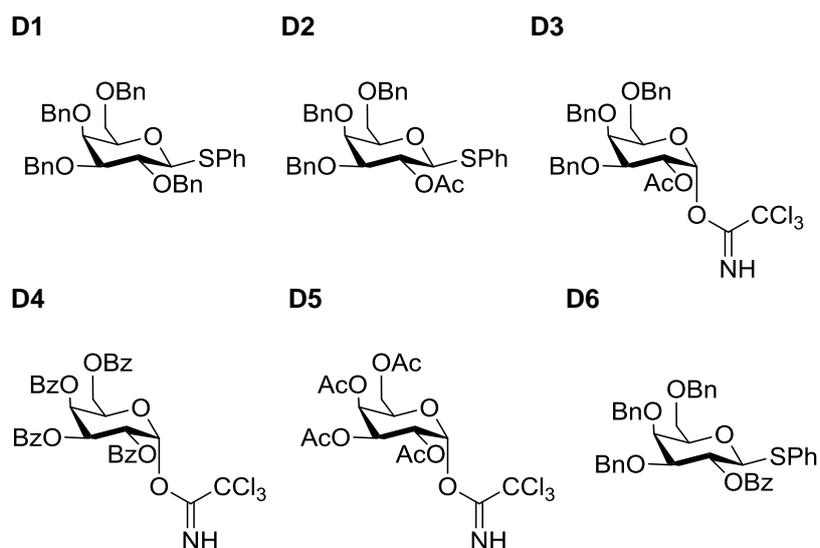
Figure IV.7. Tested donors for glycosylation. D1) perbenzylated thioglycoside donor; D2) perbenzylated and 2-*O*-acylated thioglycoside donor to have an participating group effect; D3) perbenzylated and 2-*O*-acylated trichloroacetimidate donor; D4) perbenzoylated trichloroacetimidate donor; D5) peracetylated trichloroacetimidate donor; D6) perbenzylated and 2-*O*-benzoylated thioglycoside donor.

Actual synthesis of these glycosylation educts is not shown, because these synthetic steps mainly consisted of known chemistry and protective group manipulations.

These donors were combined with different acceptors in different generations shown afterwards. The different combinations were tested to find some hints about the sterical and electronical behaviour of the tested acceptors. The actual procedure of this process and the evolving of these generations will be described after the actual overview over exemplary results shown in Table IV.4.

A1 **A2** **A3**

A4 **A5** **A6**
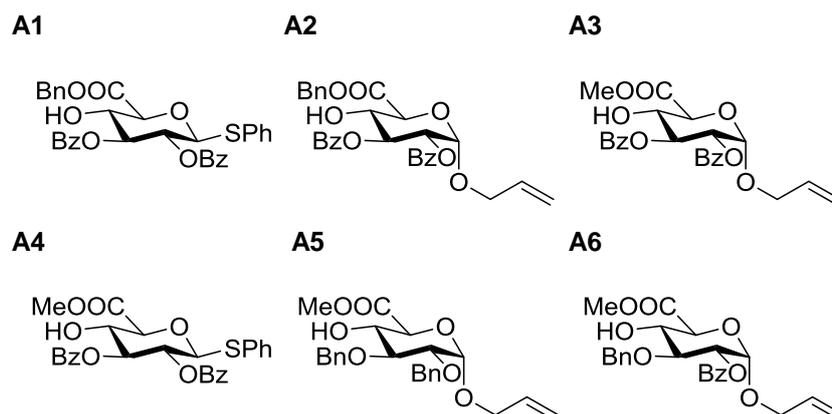
Figure IV.8. Tested acceptors for glycosylation. A1) C-6 benzyl ester protected thioglycoside acceptor; A2) C-6 benzyl ester and 1-*O*-allyl protected acceptor; A3) C-6 methyl ester and 1-*O*-allyl protected acceptor; A4) C-6 methyl ester protected thioglycoside acceptor; A5) C-6 methyl ester, 2,3-*O*-dibenzylated and 1-*O*-allyl protected acceptor; A6) C-6 methyl ester, 3-*O*-dibenzylated, 2-*O*-benzoylated and 1-*O*-allyl protected acceptor to have subsequent participating group effects for the next glycosylation and maintaining a minimum of electron richness.

The following Table IV.4. gives an overview over the tested donor-acceptor combinations shown in Figure IV.7. and Figure IV.8. as well as the tested reaction conditions and a short summary of their outcome. Not all tested conditions are shown since some only varied in the promoter (e.g. TMSOTf vs. $BF_3 \cdot OEt_2$) or in temperature and stirring time. Always the best result or at least a representative example is given in the following table.

Two different 2,3-*O*-benzoylated acceptors were used in the first set of experiments which were either 1-*O*-allyl protected or the corresponding 1-*S*-phenyl thioglycoside was employed. Both acceptors A1 and A2 were oxidized selectively by the use of a catalytic amount of TEMPO and stoichiometric BAIB (Diacetoxyiodobenzene)[224,225] while their 4,6-diol functionality was unprotected followed by a subsequent benzyl protection step under standard conditions. Another oxidation procedure with periodic acid and chromium(VI)oxide[228] was also tested in some experiments but the TEMPO catalyzed oxidation remained superior in all experiments. This complete set of experiments with acceptor A1 and A2 and five different donors (entry 1-9) remained unsuccessful or gave the corresponding α-product only probably due to some sterical hindrance caused by the C-6 benzyl ester which might shield the

4-hydroxy group from attacking the donor. No reaction was observed in most trials until the reaction was warmed up to room temperature step by step and only decomposition or hydrolysis of the donor was then observed. This is the reason why the benzyl ester was exchanged with its methyl derivative in the next set of experiments.

Table IV.4. Overview of different donor-acceptor combinations tested to build the disaccharide for ancorinoside B total synthesis.

Entry	Donor	Acceptor	Conditions[a]	Outcome
1	D1	A1	1.1 equiv NIS, 0.11 equiv TfOH, -45 °C, 3 h	54%, α-product
2	D2	A1	1.1 equiv NIS, 0.1 equiv TfOH, -40 °C, 3 h	No reaction
3	D2	A1	1.1 equiv NIS, 0.1 equiv TfOH, 0 °C to RT, 3 h	No reaction
4	D2	A1	1.1 equiv NIS, 0.1 equiv TMSOTf, -40 °C to RT, 3 h	First no reaction then decomposition
5	D3	A1	0.1 equiv BF$_3$•OEt$_2$, -15 °C, 3 h	No reaction
6	D4	A1	0.15 equiv BF$_3$•OEt$_2$, -40 °C, 2 h	No reaction
7	D3	A2	0.15 equiv BF$_3$•OEt$_2$, -40 °C, 2 h	No reaction
8	D3	A2	0.1 equiv BF$_3$•OEt$_2$, -20 °C, 2 h	No reaction
9	D5	A2	0.1 equiv TMSOTf, -20 °C, 2 h	No reaction
10	D2	A3	2 equiv NIS, 0.1 equiv TMSOTf, -78 °C to -20 °C, 3 h	12%, α-product
11	D3	A3	0.1 equiv BF$_3$•OEt$_2$, -40 °C, 2 h	No reaction
12	D4	A3	0.1 equiv BF$_3$•OEt$_2$, -78 °C, 3 h	33%, α-product
13	D3	A4	0.1 equiv BF$_3$•OEt$_2$, -40 °C, 3 h	No reaction
14	D4	A4	0.1 equiv TMSOTf, -0 °C to RT, 2 h	Decomposition
15	D4	A4	0.1 equiv BF$_3$•OEt$_2$, -40 °C to 0 °C, 3 h	40% β-product, next glycosylation failed
16	D5	A4	0.1 equiv BF$_3$•OEt$_2$, -40 °C, 3 h	No reaction
17	D4	A5	0.12 equiv BF$_3$•OEt$_2$, -40 °C, 2 h	70%, α:β = 45:55, next glycosylation α-product only
18	D3	A6	0.12 equiv BF$_3$•OEt$_2$, -40 °C, 3 h	No reaction
19	D4	A6	0.1 equiv BF$_3$•OEt$_2$, -78 °C, 3 h	No reaction
20	D4	A6	0.1 equiv TMSOTf, -40 °C, 3 h	Decomposition

[a] Reactions were carried out with 1.1 equiv donor, in CH$_2$Cl$_2$ and with 4 Å molecular sieves.

Two analogous methyl esters A3 and A4 were used as acceptors in the next set of experiments (entry 10-16) revealing that the attack of the acceptor might not only be a steric but an electronic problem as well. This was obvious, because again most reactions showed either no reaction or mainly the α-product in bad yield. The only exception to that was the combination of the very electron deficient donor D4 in combination with the thioglycoside acceptor A4. This reaction yielded 40% of the desired β-product as major product in the first shot. The next glycosylation to the side chain failed due to the known very poor activity of thioglucuronic acids[214].

The mentioned knowledge of a steric and electronic problem was combined to form the next acceptor A5 which was designed to be much more electron rich to allow a faster reaction with the electrophilic and activated donors (entry 17). The reaction went quite well when only the yield (70%) is considered showing that the thoughts about the electronic and steric problems of the donor were correct. Looking more into detail revealed a bad α/β-selectivity with a near 1:1 ratio and hard to separate isomeric mixtures. However, the reaction sequence was continued with allyl deprotection and imidate formation[229]. Glycosylation with $BF_3 \bullet OEt_2$ to get the desired diglycoside yielded the α-linked product only. The reason was apparently the missing participating 2-O-protecting group.

An acceptor A6 was designed which should combine all the knowledge about the electronic system and the important participating group at the 2-hydroxy position mentioned above for the last set of experiments (entry 18-20). The 1-O-allyl glucose was protected at the 4,6-position with benzylidene acetal[230] and afterwards selectively 2-O-benzoylated[231]. After 3-O-benzoylation under standard conditions with pyridine and benzoyl chloride, the sugar latter was oxidized as usual with TEMPO and BAIB[224,225] to yield the desired acceptor A6. This acceptor was unfortunately again too electron poor to react under any temperature with the tested donors D3 and D4.

IV.2.4. Total synthesis of ancorinoside B diglycoside

The next synthetic approach changed the acceptor to a 6-O-TBS protected glucose to carry out the first glycosylation, performing the C-6 oxidation and after protection trying to get the second glycosylation done. For this approach an 1-O-allyl-2,3-O-benzoyl-6-O-TBS protected donor was synthesized via a 4,6-O-benzylidene acetal, benzoylation and selective TBS protection. All steps were high yielding including the first glycosylation as well as the

oxidation step (data not shown) but the second glycosylation failed again on *β*-stereoselectivity using the readily oxidized disaccharide.

Since the synthetic trials to this point failed due to the problematic reactivity concerning the used glucuronic acid building blocks and their properties as donors and acceptors, the retrosynthetic plan in terms of the diglycoside was changed to account for these problems and avoid them eventually by establishing the desired diglycoside and performing the oxidation right after the 2nd glycosylation. The plan regarding the diglycoside was now as follows:
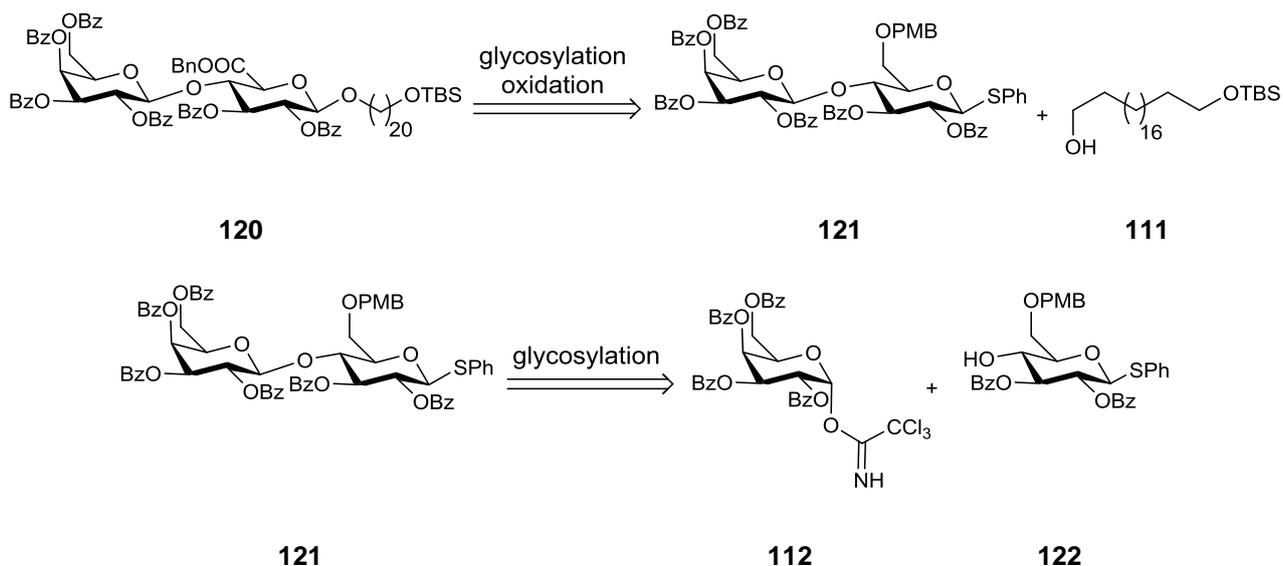
Scheme IV.14. 2nd retrosynthetic approach to the diglycoside for ancorinoside B synthesis.

The other difference in this approach beside the late oxidation step at the C-6 position of the glucose moiety was the use of a Fischer donor in the 2nd glycosylation to avoid additional protecting group manipulation.

The C$_{20}$ fatty acid chain for ancorinoside B was synthesized in a comparable manner as for epicoccamide D. Buyable eicosanedioic acid **117** was reduced with LiAlH$_4$ in THF[213] yielding 89% of the corresponding diol **118**. The TBS monoprotection was difficult in that case, because diol **118** did not dissolve in acceptable quantities in any organic solvent applicable for TBS protection. The reaction was carried out by partly dissolving the diol in hot 1,4-dioxane and fast addition of first TBSCl and the imidazole. This procedure gave the monoprotected C-20 diol **111** in 52% yield. The yield for setting up the same reaction in hot THF, other solvents or their mixtures and just let the reaction slowly take place by dissolving the educt stepwise was always below 10%. The reaction was also carried out in a solvent free manner by melting all educts in a preheated flask using the almost identical melting points (roughly 110 °C) and letting the reaction take place for about 5 min before standard workup. This attempt yielded 28% of the desired monoprotected diol **111**.

117   **118**   **111**
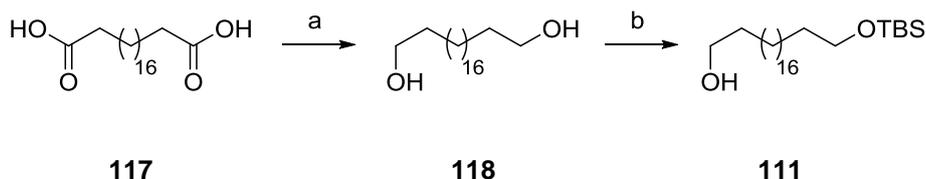
Scheme IV.15. Synthesis of the monoprotected diol side chain of ancorinoside B. Reagents and conditions: a) LiAlH$_4$ (3 equiv), THF, 0 °C 3 h then reflux 12 h, 89%, b) TBSCl (1 equiv), imidazole (2 equiv), 1,4-dioxane, reflux, 10 h, 52%.

Glycosylation with a 1-*O*-allyl-2,3-*O*-dibenzoyl-6-*O*-TBS protected glucose had no special requirements concerning the donor. A perbenzoylated imidate donor D4 (see Figure IV.7.) was chosen for this purpose. Galactose was first perbenzoylated[232] with BzCl and pyridine.

114   **115**   **112**
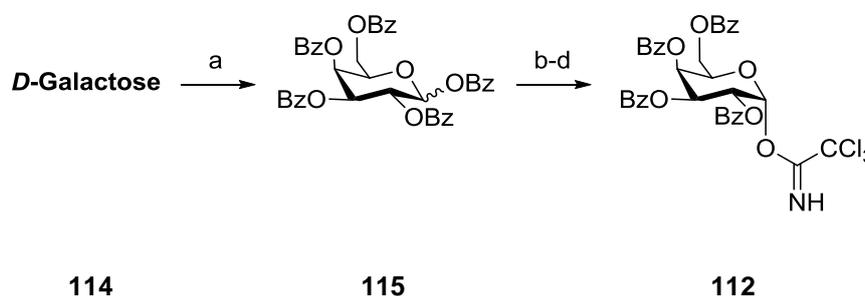
Scheme IV.16. Synthesis of the donor for disaccharide assembly. Reagents and conditions: a) BzCl (5.5 equiv), pyridine, 0 °C to RT, 12 h, quant.; b) HBr in ethyl acetate, 0 °C, 2 h; c) Ag$_2$CO$_3$ (0.5 equiv), acetone:H$_2$O = 19:1, RT, 12 h; d) Cl$_3$CCN (7 equiv), DBU (1.1 equiv), CH$_2$Cl$_2$, RT, 3 h, 57% over three steps.

Tetra-*O*-benzoyl galactose trichloroacetimidate **112** was formed by perbenzoylation, anomeric deprotection via the corresponding α-halide followed by treatment with Ag$_2$CO$_3$[233,234] and imidate formation[233]. The corresponding α-halide and the hemiacetal were used in consecutive steps without purification. This known[235] and more expansive route compared to deprotection with MeNH$_2$[236] gave pure donor **112**. Deprotection with hydrazine acetate[237] was not tested.

80   **123**   **124**
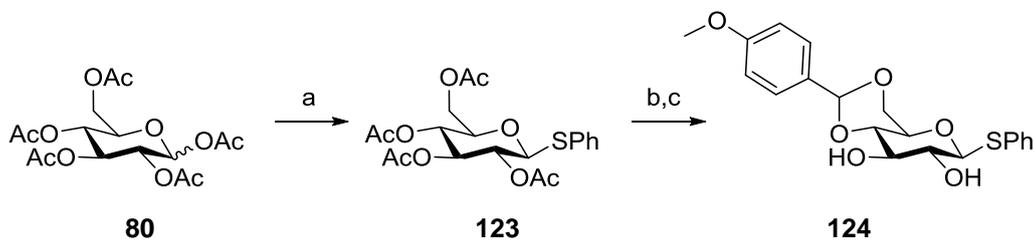
Scheme IV.17. Anisaldehyde acetal formation. Reagents and conditions: a) BF$_3$•OEt$_2$ (3.5 equiv), PhSH (1.8 equiv), CH$_2$Cl$_2$, reflux, 72 h, 52%; b) NaOMe (0.5 equiv), MeOH, RT, 45 min; c) *p*-TsOH (6.5 equiv), anisaldehyde dimethyl acetal (2 equiv), DMF, 50 °C, 8 h, 86% (two steps).

The necessary thioglycoside donor **122** was assembled starting from peracetylated glucose[32]. Penta-*O*-acetyl glucose was transformed into the corresponding thiophenyl glycoside **123** by

the use of BF$_3$•OEt$_2$.[238] To form the selective 6-*O*-PMB protected alcohol the thioglycoside was converted into a 4,6-*O*-anisol acetal **124** right after ester interchange. This was achieved by a known method[230,239,240] with ansialdehyde dimethyl acetal and *p*toluenesulfonic acid in DMF.

Reaction sequence continued with benzoylation of the diol **124** under standard conditions[241] with BzCl and pyridine. The last step for donor synthesis was a reductive acetal opening to form the desired 6-*O*-PMB protected donor with a free alcohol function at the 4-*O*-position. This was accomplished by the use of NaBH$_3$CN and TFA[242]. A slightly changed method published for similar glycosyl acceptors[243] was used.
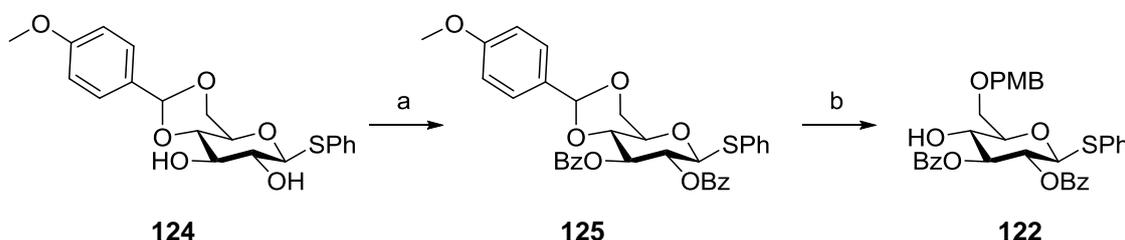
Scheme IV.18. Assembly of the monosaccharide acceptor. Reagents and conditions: a) BzCl (3 equiv), pyridine, 0 °C to RT, 12 h, 76%; b) NaBH$_3$CN (5 equiv), TFA (10 equiv), 4 Å mol. sieves, DMF, 0 °C to RT, 12 h, 88%.

With donor **112** and acceptor **122** in hand the first glycosylation was carried out using BF$_3$•OEt$_2$ at -40 °C. This procedure gave about 40% of the wrong configurated α-glycosidic linkage. Switching from BF$_3$•OEt$_2$ to TMSOTf as lewis acid to activate the Schmidt donor at again -40 °C yielded the desired β-branched disaccharide **121** in 62% yield.
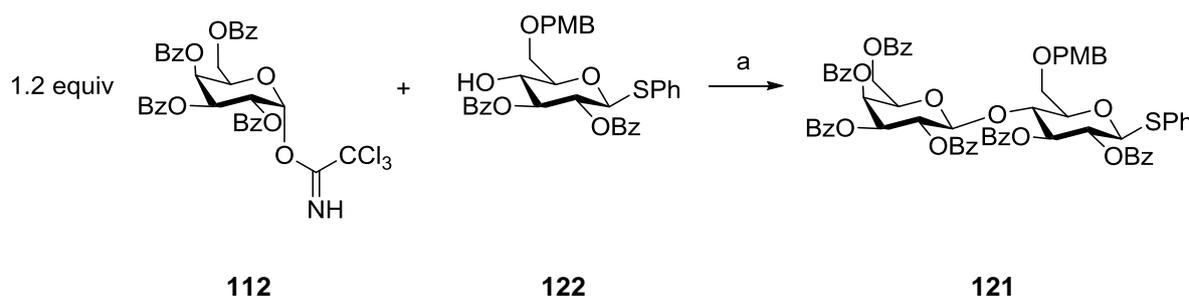
Scheme IV.19. First glycosylation with PMB protected acceptor. Reagents and conditions: a) **112** (1.2 equiv), TMSOTf (0.1 equiv), CH$_2$Cl$_2$, -40 °C, 3 h, 62%.

The advantage of using a thioglycoside as acceptor came now into play, because no further protecting group manipulation was necessary before the 2nd glycosylation was carried out. By the use of a Fischer type donor for this purpose, NIS and firstly TfOH was used under standard conditions[244,245] for this kind of glycosylation. These reaction conditions and the Brønsted-Lowry acidic TfOH showed TBS deprotection as major product during reaction monitoring which in turn gave rise to several side products. The desired diglycoside **126** was

only isolated in about 40% yield. Since other Lewis acids like $BF_3 \cdot OEt_2$ or TMSOTf can also be used as activating agents both were tested and both gave unsatisfying yields around 20% of the β-product caused by the lower activation rate of these Lewis acids and the therefore higher reaction temperature which lead to more α-configurated product. The mixture of both Lewis acids in a 2:1 fashion of TMSOTf and $BF_3 \cdot OEt_3$ led to a very high Lewis acidity caused by a $BF_2OTF \cdot OEt_2$ species as published[246]. This procedure gave 58% of the desired diglycoside **126** which was formed at -40 °C, with only a small excess of the monoprotected acceptor side chain **111** and without any oberservation of the corresponding and unwanted α-side product.

121   **126**
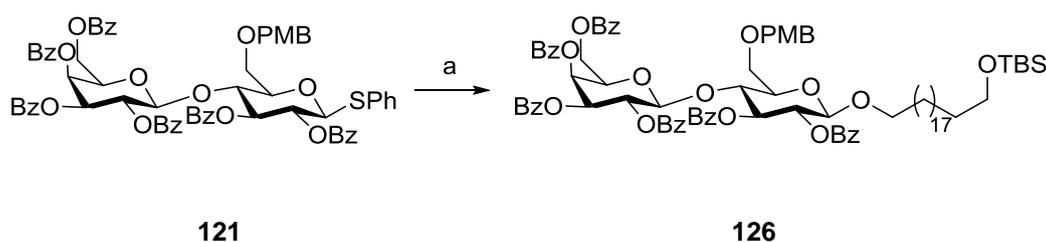
Scheme IV.20. Second glycosylation with PMB protected acceptor to attach the fatty acid chain. Reagents and conditions: a) **111** (1.05 equiv), TMSOTf (0.1 equiv), $BF_3 \cdot OEt_2$ (0.05 equiv), NIS (1.8 equiv) CH_2Cl_2, −40 °C, 3.5 h, 58%.

The next crucial step of the synthesis of the desired diglycoside for the ancorinsoside B total synthesis was the selective deprotection of the 6-hydroxy functionality by removal of the PMB ether. Standard oxidative conditions utilizing CAN[247] or DDQ[248,249] in various amounts[250] and temperatures always led to TBS protection on the side chain first. This undesired deprotection always occurred even before PMB deprotection started to take place as strict reaction control by tlc indicated. This effect was known for CAN under certain conditions but not known in literature for DDQ. Another deprotection trial was carried out under mild Lewis acidic conditions utilizing $MgBr_2 \cdot OEt_2$ and Me_2S which is a known method[251] allowing PMB deprotection by specifically mentioned TBS retention. These conditions showed nearly no reaction (about 10% conversion), even after three days. Another more acidic deprotection condition was tested using a catalytic amount of $SnCl_2$, an excess of TMSCl and anisole as scavenger.[252] Tin chloride dihydrate was used and therefore 4 Å molecular sieves were added to this reaction to trap the water and prevent accidental TBS deprotection. This quite fast reaction yielded the desired alcohol **127** in 99.6% yield after 90 min with no observed side reaction.

The last two steps of the reaction sequence for setting up the diglycoside **120** were the oxidation to the corresponding glucuronic acid derivative and afterwards the installation of a reasonable protecting group like a benzyl ester which can eventually be cleaved by

hydrogenation to remove also the formed double bond from the HWE olefination in later steps of the synthesis.

126 → **127**

127 → **120**
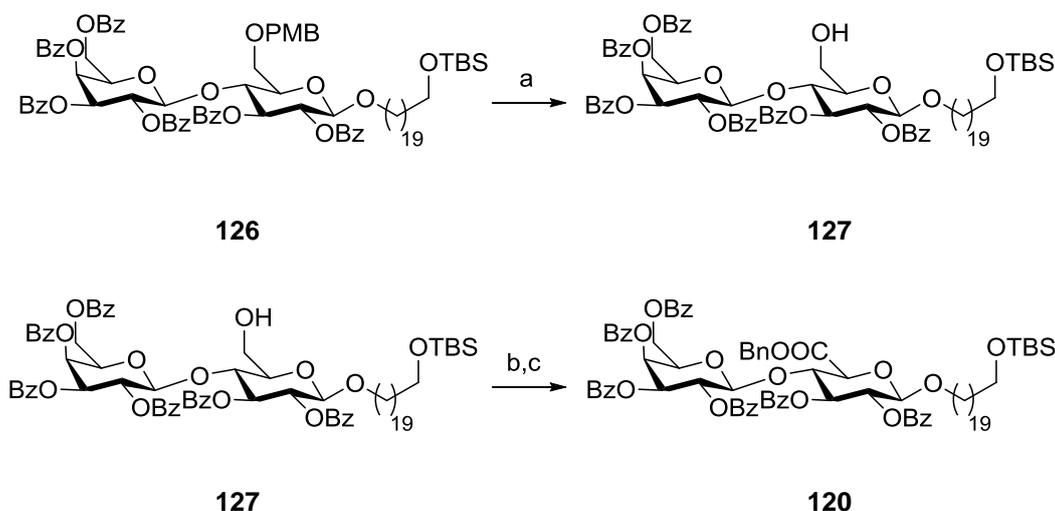
Scheme IV.21. Oxidation of the full diglycoside. Reagents and conditions: a) SnCl$_2$•2H$_2$O (0.1 equiv), TMSCl (3 equiv), anisole (1.5 equiv), 4 Å mol. sieves, CH$_2$Cl$_2$, RT, 90 min, 99.6%; b) PDC (2 equiv), Ac$_2$O (10 equiv), CH$_2$Cl$_2$, RT, 6 h; c) BnOH (20 equiv), CH$_2$Cl$_2$, RT, 3 h, 71% (over two steps).

The first trial to achieve this goal was a TEMPO catalyzed oxidation with BAIB as reoxidation reagent in a phase transfer like reaction. Since this reaction conditions proved successful not only for the synthesis of the monosaccharide glucuronic acid building blocks (see Table IV.4.) it was obvious to test this oxidation protection cascade with the side chain already attached. Since this attempt proved unsuccessful with no reaction shown by tlc and crude NMR analysis under different conditions[225,253,254], other TEMPO based methods (e.g. with NaClO, NaHCO$_3$, (C$_4$H$_9$)$_4$NBr and NaBr[226] or NaClO, NaHCO$_3$ and KBr[255]) were also tested with no success. Conditions utilizing TEMPO and periodic acid[228] or Jones reagent[256] were not tested, because of their acidic nature and therefore likely occuring TBS deprotection. Another sometimes used method for carbohydrate oxidation[257,258] is the use of the Cornforth reagent[259] pyridinium dichromate (PDC) often referred to as Corey-Schmidt oxidation[260]. The free carboxylic acid is either directly isolated[258] or transferred into its *t*butyl ester by direct addition of *t*butanol[257] which cannot be oxidized by PDC. In both cases acetic anhydride (Ac$_2$O) was added to speed up the reaction as published by Corey *et al.*[261] for the use of carbohydrate oxidation utilizing Collins reagent without isolating the aldehyde intermediate. In the case of the ancorinoside B total synthesis the mentioned benzyl ester **120** was in focus so only the oxidation part was first carried out as mentioned in literature[257,258]. After tlc and crude NMR analysis showed complete conversion to a lower running spot and the appearance of an additional quaternary carbon signal at 165.6 ppm together with a large shift of the C-5 proton, changing the signal form from a doublet triplet signal to a singulet

signal accompanied by disappearance of the protons at the C-6 position a complete and clean oxidation was assured. The oxidation was stopped by addition of large excess of benzyl alcohol to trap the remaining PDC. This addition produced reaction conditions where benzyl esterification took place over 3 h. The shown oxidation esterification yielded the desired glucuronic acid bearing diglycoside in 71% yield.

With the knowledge how to synthesize the diglycoside moiety of ancorinoside B in hand, the remaining steps of the synthesis will be carried out and published soon. These necessary steps will be shown and discussed in the conclusion section.

IV.3. Contribution to virgineone total synthesis

Another natural product total synthesis should be initialized with all the knowledge mentioned in the last two chapters. The next natural product named virgineone[125] shares some structural features with epicoccamides. Virgineone is a tetramic acid which is 3-acylated with a long fatty acid chain (C_{22}) attached to a mannose residue by β-linkage (see Figure IV.9.). This chain is also methylated at the same position as epicoccamides are. Additional features are a ketone within the side chain and a hydroxyl group next to the glycosidic linkage. Virgineone whose tetramic acid moiety is derived from tyrosine has only one representative member to date. Its biological mode of activity is not known but virginieone is more characterized in terms of a possible target being associated with the stress response pathway and the respiratory chain.[125] The structure of the mannosylated tetramic acid is shown in Figure IV.9. It is worth noting that upon start of this project the configuration of the three stereocentres besides those from the sugar residue were unknown.

3
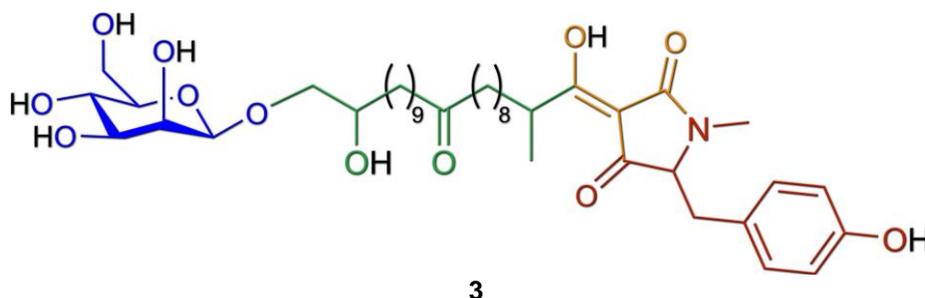
Figure IV.9. Virgineone (**3**) consists of three parts: The blue β-linked mannose residue connected to a fatty acid chain showing three different substitutions (green). This side chain is connected to a tyrosine derived tetramic acid (red/orange) by 3-acylation.

Only the retrosynthesis for the substituted side chain and the trials of forward synthesis are described in the following chapters since virgineone shares its major motifs with epicoccamides and therefore the retrosynthetic approach for assembly of the whole molecule is similar having the same key steps like glycosylation, epimerisation, HWE olefination and Lacey-Dieckmann cyclisation once the side chain is assembled. The difference in synthesis concerning the tyrosine derived tetramic acid is meant to be trivial and there should only be an additional deprotection oxidation step for the ketone in the side chain.

IV.3.2. Retrosynthesis of the virgineone side chain

The following retrosynthetic approach was elaborated using a Grignard reaction beside a Sharpless dihydroxylation as key steps in the side chain synthesis which allowed breaking the synthesis down into two cheap starting materials. Scheme IV.22. shows the general approach for the synthesis of the virgineone side chain. The exact pattern of protecting groups is not stated in the retrosynthetic scheme, because the three groups needed to be orthogonal and it was attempted to tune their reactivity during the following synthetic trials when necessary. The first introduced protecting group was set as TBS to start with.

Scheme IV.22. Retrosynthetic approach to the virgineone side chain. X, Y, Z = orthogonal protecting groups.

The retrosynthetic approach commenced from selectively protected diol **129** which was in turn made from the a similar molecule bearing a double bond via asymmetric Sharpless dihydroxylation[262,263]. This step might open access to both stereoisomers to potentially gain insight into the absolute configuration which was unclear[125] when this project was. The ketone in almost the middle of the side chain came from a protected alcohol bearing aldehyde **131**. The right time in synthesis when to deprotect and oxidize needs to be evaluated during total synthesis. The aldehyde necessary for the HWE olefination step[32] to connect the glycosylated side chain to the tetramic acid moiety is also derived from a protected alcohol **132** which can be deprotected and oxidized when required. The molecule is then cut into two parts next to the middle alcohol. These two parts are connected via a Grignard reaction[264] since a certain stereoselectivity is not required at that position. Bromide **133** and aldehyde **134** are needed starting materials for this Grignard reaction. The bromide is buyable and the aldehyde **134** can be made from cheap alcohol **135** by protection and direct ozonolysis.

IV.3.3. Synthesis of the virgineone side chain

The first starting material necessary for the planned synthesis of the virgineone side chain was aldehyde **134** (9-[(*t*butyldimethylsilyl)oxy)]nonanal). This educt was formed by protecting buyable 9-decen-1-ol (**135**) with TBSCl and imidazole in THF in quantitative yield.

135   **136**   **134**

Scheme IV.23. Synthesis of the aldehyde **134** for Grignard reaction. Reagents and conditions: a) TBSCl (1.25 equiv), imidazole (2 equiv), THF, RT, 16 h, quant.; b) O_3 (6% in O_2), CH_2Cl_2, -78 °C, 30 min; c) PPh_3 (2.5 equiv), CH_2Cl_2, RT, 2 h, 81% (two steps).

The protected alcohol **136** was converted into the desired aldehyde **134** by Crigee's ozonolysis[265] under standard conditions. The hereby formed trioxolan was intercepted under reductive conditions. Using PPh_3[266] instead of dimethylsulfide[267] increased the yield from 60% to 81% forming less side products.

The formed aldehyde **134** was reacted with buyable 11-bromoundec-1-ene **133** in a Grignard reaction under standard conditions[268] with roughened magnesium to yield 82% of the desired racemic alcohol **137** as a transparent oil.

Since the racemic alcohol formed by the Grignard reaction above should be deprotected and oxidized late in total synthesis, THP was chosen as protective group, because it is acid labile like TBS but the silyl protecting group can be removed orthogonally with F⁻ salts earlier in synthesis. Moreover a THP acetal can also be converted into the corresponding ketone under oxidative conditions[269]. This protection step was achieved by using dihydropyrane (DHP) and PPTS[270] yielding 86% of the diprotected diol **138**. MOM or MEM protection was tested as well but proved too unstable for later steps of synthesis.

133   **137**   **138**   **139**
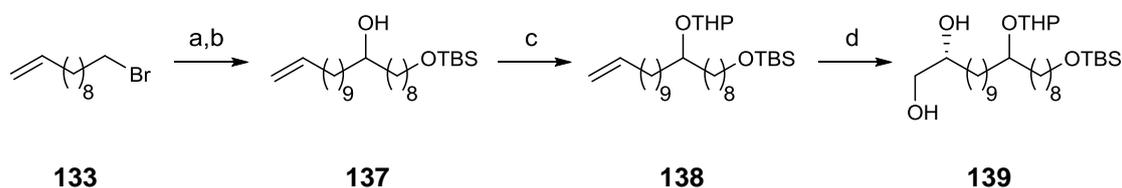
Scheme IV.24. Grignard reaction and protection. Reagents and conditions: a) Mg (2 equiv), **133** (1.5 equiv), THF, reflux, 1 h; b) **134** (1 equiv), THF, 50 °C, 2 h, 82%; c) DHP (5 equiv), PPTS (0.1 equiv), CH_2Cl_2, RT, 8 h, 86%; d) K_2CO_3 (3 equiv), $K_3Fe(CN)_6$ (3 equiv), $(DHQD)_2PHAL$ (1 mol%), $K_2OsO_2(OH)_4$ (2 mol%), *t*-butanol:water = 1:1, 4 °C, 4 d, 92%.

The next step of synthesis was the important asymmetric Sharpless dihydroxylation[263] of the double bond to have access to both isomers concerning the C-2 alcohol since its absolute configuration remained unclear in the natural product[125] so far but there was some

evidence[124] that this alcohol is *S*-configured. With a Sharpless dihydroxylation one might access both isomers to clarify this suggestion. The reaction was carried out under conditions[262,263] which are known to form the corresponding *R*-isomer using the (DHQD)$_2$PHAL ligand to compare the results to the published[124] data. Later access to the *S*-configured isomer should then be possible by using the (DHQ)$_2$PHAL ligand[263,271]. The actually used conditions[271] were utilizing $K_3Fe(CN)_6$ to reoxidize the catalyst, the above mentioned ligand (1 mol%) as well as $K_2OsO_2(OH)_4$ (2 mol%) in a 1:1 mixture of *t*butanol:water and allowing the two phase mixture to stirr at 4 °C for four days. This procedure yielded 92% of the desired *R*-configured diol **139**. The diastereomeric excess of this reaction was found to be above 90% by chiral HPLC analysis.

The most challenging step was now the protection of the secondary alcohol selectively or trying to first protect the primary alcohol with another protecting group if selectivity turned out to be a problem. The goal was to protect the secondary alcohol as a benzyl ether, because once this particular ether is formed it need not to be changed until deprotection and the benzyl ether will thus be cleaved in the final global deprotection step together with the sugar protecting groups.

One attempt was to first protect the primary alcohol selectively with a trityl group[272], introducing the benzyl protecting group and directly afterwards cleave again the bulky trityl group. Cleavage of the bulky trityl group failed with PPTS which removed first the TBS and then the THP protecting group before cleavage of the trityl group was observed. Other attempts with $ZnCl_2$, $ZnBr_2$, $CeCl_3$[273] and $BF_3 \cdot OEt_2$[274] gave either no conversion or even more complex product mixtures.

An obvious trial to achieve this goal was the protection of the 1,2-diol as a benzylidene acetal to open it under reductive conditions directly after protection to the desired secondary benzyl ether as published in many cases[275–277] for instance within the first trials of total synthesis of virgineone[124]. Selective deprotection failed in this case as well after several tests with reducing agents like DIBAL-H[124,275,277] or BH_3 together with $Cu(OTf)_2$[278].

The last attempt was to selectively form a primary pivaloyl ester and then execute the benzyl ether protection on the secondary alcohol as stated above. This procedure should leave the other protecting groups untouched during cleavage since the ester deprotection is done under basic conditions. Pivaloyl ester protection of diol **139** was carried out with the corresponding ester chloride and pyridine[279] and gave 32% of the corresponding ester **140**. The benzyl protection with benzyl bromide and sodium hydride and pivaloyl deprotection can be carried out in one single step, because stopping the protecting reaction with water delivers enough

hydoxide to hydrolyze the ester. This was only achieved with unsatisfactory yield of 13%. The benzyl protection without ester hydrolysis gave the desired fully protected alkyl chain **141** only in 10% yield. The following ester hydrolysis can be done with an unsatisfying yield of 8% of the desired glycosyl acceptor **142**. The poor yields resulted maybe from the lack of educt for these protection trials and therefore the hard to handle small scale of these reactions. These synthetic attempts are shown in Scheme IV.25. Coupling the alkyl chain to the necessary glucose donor was not tested because of the limited time for the whole project and lack of starting material.
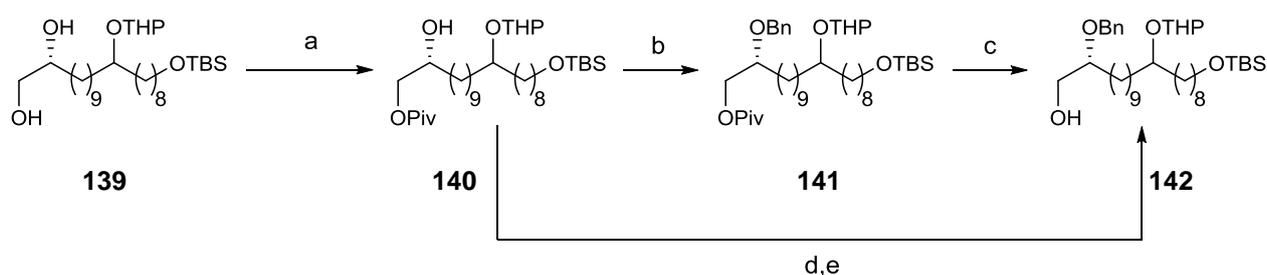
Scheme IV.25. Trials of selective secondary alcohol protection. Reagents and conditions: a) PivCl (1.05 equiv), pyridine (2.5 equiv), CH_2Cl_2, RT, 16 h, 32%; b) BnBr (1.5 equiv), NaH (2 equiv), TBAI (cat.), DMF, RT, 2 h, 10%; c) NaH (2 equiv), H_2O (1 equiv), DMF, RT, 4 h, 8%; d) BnBr (1.5 equiv), NaH (3 equiv), TBAI (5 mol%), DMF, RT, 24 h; e) H_2O (20 equiv), DMF, RT, 12 h 13% (two steps).

This work on the virgineone side chain was carried out with two bachelor students[280,281] and yielded the fully protected side chain of virgineone which can be glycosylated and conntected to a tetramic acid moiety followed by the necessary deprotection, oxidation and reduction steps. The missing steps for the total synthesis of virgineone are summarized in the conclusion section.

IV.4. Contribution to aurantoside G and J total synthesis

Aurantosides are another big class of glycosylated tetramic acids with currently eleven known members (A-K)[39,44–48]. The first member was found in 1991 and the last one 2012 so far. Unique in their structure is that the sugar residue (either xylose or a xylose containing trisaccharide) is not linked via a side chain to the tetramic acid moiety but is rather directly linked to the acid by *N*-glycosylation. The tetramic acid moiety is derived from *D*-aspartic acid in the case of the aurantosides. The overall structural motif is similar to that of the rubrosides A-H[127] whose polyenoyl side chain ends up with an additional heterocycle and whose tetramic acid is derived from asparagine. Again, this type of tetramic acids showed several biological activities reaching from a certain cytotoxicity towards cancer cells[44] to antibacterial or antifungal properties.

4
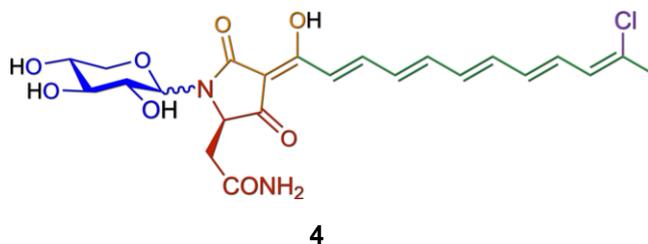
Figure IV.10. Aurantosides G and J (**4**) revealing again three typical parts for tetramic acid glycoconjugates: The blue *N*-glycosylated xylose residue, a tetramic acid derived from asparagine (orange/red) and a polyene 3-acyl side chain in green with an uncommon chlorine in purple at the end.

The conjugated side chain can be longer than shown in Figure IV.10. and bear additional chlorine atoms. The focus of the first attempts of total synthesis should be carried out on model systems similar to aurantoside G and J since both natural products are very similar and only differ in the configuration of the *N*-glycosidic linkage[39,47]. Since stereoinduction on this type of chemical *N*-glycosylation is unknown, both isomers can eventually be synthesized and separated in subsequent steps of synthesis.

IV.4.2. Retrosynthesis of aurantoside G and J

The planned synthesis of aurantosides is shown below and focuses on the *N*-glycosylation. The shown retrosynthetic approach where the sugar moiety of the aurantosides is attached via *N*-glycosylation or Fukuyama-Mitsunobu reaction[282,283] before the actual tetramic acid is formed, this project was mainly focussed on the behaviour of tetramic acids and their 3-acyl derivatives in terms of the capability being a *N*-glycosyl acceptor.
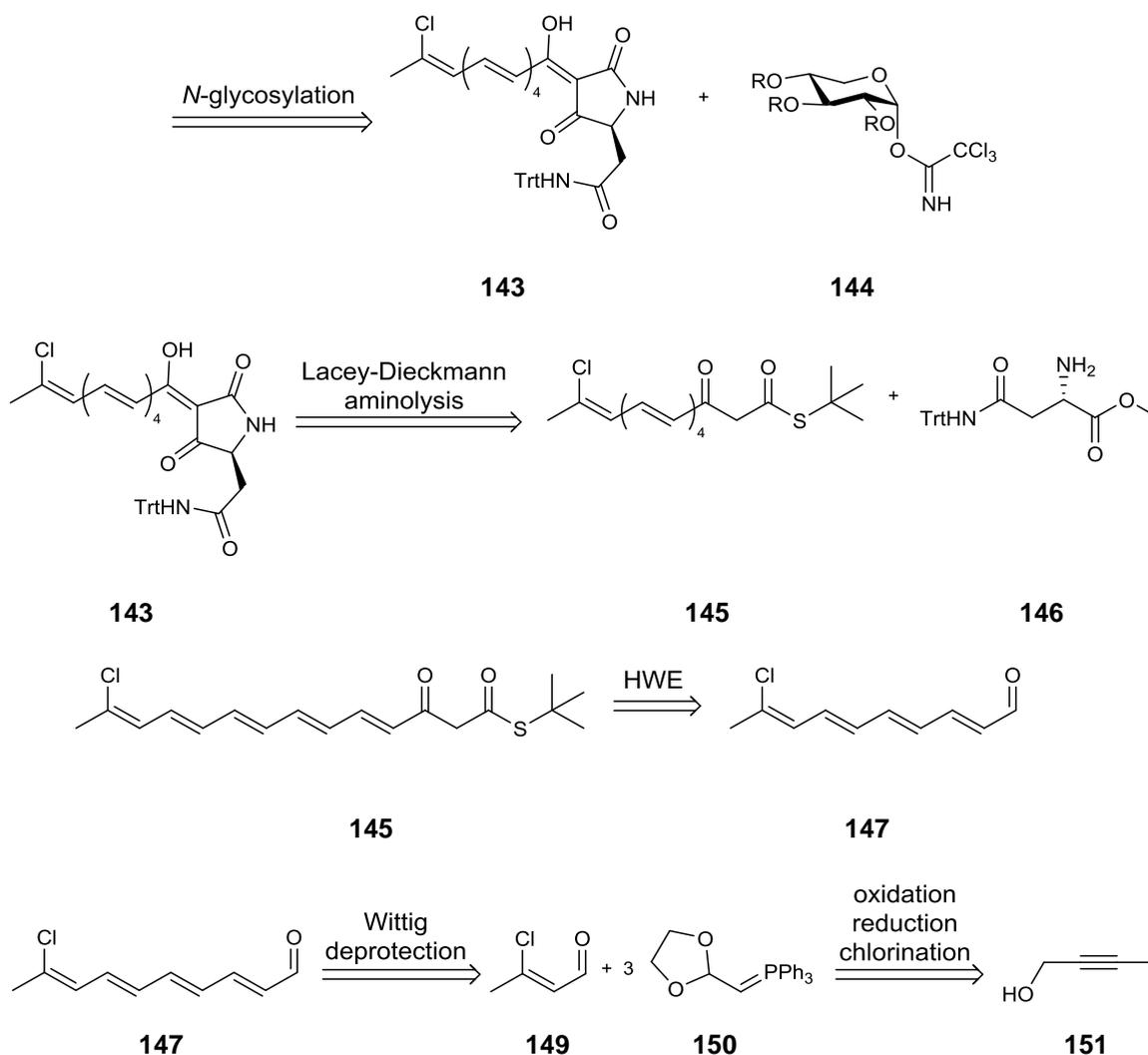
Scheme IV.26. Retrosynthetic approach to aurantoside G and J; R = Ac, Bn, Bz, PMB.

Retrosynthesis for this project started with the *N*-glycosylation as keystep of the synthesis. The donor for this step should be a trichloracetimidate since this type of donors are generally proved more active[159] than e.g. the corresponding thioglycosides and they have been published for use in amide glycosylation[284] with TMSOTf as promoter. The most useful protective groups on the xylose donor should be elaborated in a later step of this project to gain insight into possibly occurring 2-*O*-protective group participation or the electronic influence of the protective group pattern onto the actual glycosylation process. The necessary tetramic acid was again planned to be synthesized by a Lacey-Dieckmann cyclisation. Trityl protected asparagine can be purchased and esterified with methanol. The shown *β*-ketothioester **145** can be assembled by a HWE olefination as before. Phosphonate **148** (not shown) can be derived by the protocol from Ley *et al.*[56] starting from bromoacetyl bromide. The polyene aldehyde **147** can be made by repetitive usage of a Wittig olefination with the buyable dioxolane **150**[285] for instance. The chlorine bearing aldehyde **149** can be derived

from cheap 2-butyn-1-ol by reductive radical chlorination after a known[286] method and DMP mediated oxidation.

The mentioned retrosynthesis via *N*-glycosylation before tetramic acid formation is shown below as an alternative if the direct glycosylation of an already established 3-acyl tetramic acid fails.
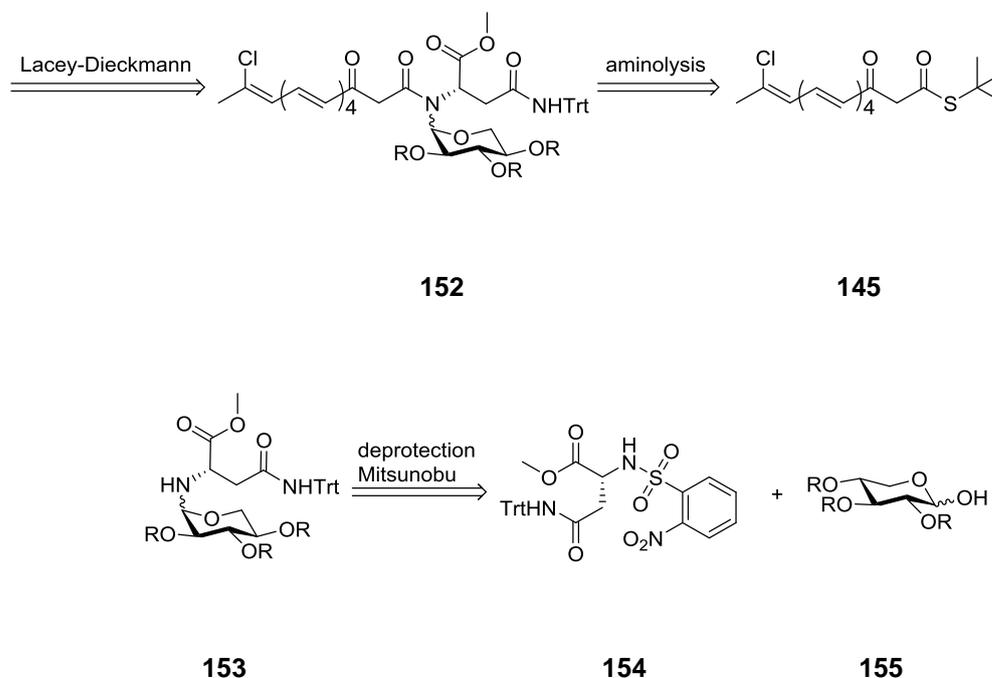
Scheme IV.27. Retrosynthetic approach to aurantosides via Mitsunobu reaction; R = Ac, Bn, Bz, PMB. For the upper aminolysis the lower sugar amino acid derivative **153** is used.

This alternative retrosynthetic plan should be applied whenever direct *N*-glycosylation attempts of the 3-acyl tetramic acid fail.

Starting again from a Lacey-Dieckmann cyclisation step, the necessary glycosylated *β*-ketoamide **152** was to be established by aminolysis of the readily glycosylated amino acid **153** and the corresponding *β*-ketothioester **145** mentioned in the retrosynthetic plan before. The sugar moiety can therefore be introduced by a Mitsunobu reaction (Fukuyama type[287]) of an accordingly protected hemiacetal and a nosyl protected amino acid methyl ester. Nosyl protection was said to be necessary for this Mitsunobu reaction.[43,283,288–290] The actual protective group pattern on the monosaccharide needs again to be evaluated depending on the requirements of the Mitsunobu reaction[43].

IV.4.3. Direct *N*-glycosylation trials with tetramic acids

The first attempt of chemical *N*-glycosylation of a tetramic acid was to attach the sugar moiety before the actual 3-acylation process was to be carried out. This was done by first synthesizing a rather unfunctionalized tetramic acid derived from isoleucine since it was available in our workgroup and synthesized by a known method[291] by Yoda *et al.* using Meldrum's acid, EDCI and DMAP. The Boc-protected tetramic acid was deprotected as mentioned in the same publication. The published[32] imidate for epicoccamide D synthesis **77** was again used in this test system, because it is said to be moderately armed[160] and it bears a 2-*O*-participating group.

156   **77**   **157**
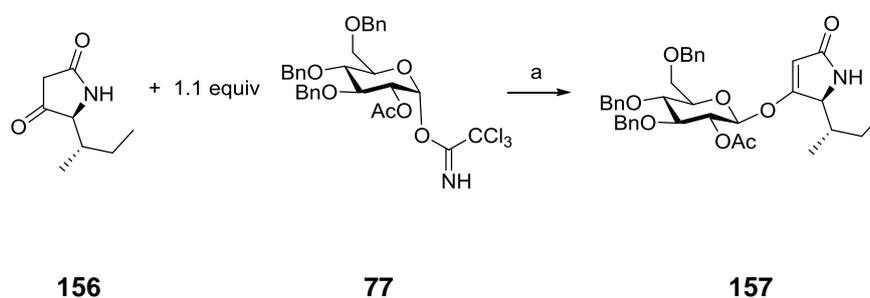
Scheme IV.28. Glycosylation of a tetramic acid: *O*-glycosylation. Reagents and conditions: a) **77** (1.1 equiv), TMSOTf (0.2 equiv), CH_2Cl_2, -45 °C, 1 h then -20 °C, 2 h, 42%.

Reaction of the isoleucine derived tetramic acid **156** with the already applied imidate **77** yielded only a 4-*O*-glycosylated product **157** in 42% yield. The anomeric center was built as a *β*-only product due to the possible side group effect of the 2-*O*-acetyl group. No *N*-glycosylation was observed and the only additional side product was the hydrolyzed donor. The ^{13}C NMR spectra confirmed this assumption showing an anomeric carbon atom at 98.5 ppm, a C-4 at 173.8 ppm and a C-3 at 99.3 ppm indicating an existing 4-*O*-enol derivative. An anomeric *N*-glycoside would have a C-1 shift of smaller than 90 ppm which will be shown afterwards.

To avoid this possible side reaction, a corresponding 4-*O*-protected tetramate was synthesized with two different protecting groups to account for the different electronic requirements for this *N*-glycosylation. The two tested tetramates bearing a 4-*O*-benzyl or a 4-*O*-(2-trimethylsilylethyl) group (TMSE) proved unsuccessful in the *N*-glycosylation and only hydrolyzed donor was isolated.

The same tetramic acid **156** was transferred into its 3-oct-2-enoyl derivative by treatment with ketylidenetriphenylphosphorane[109] (Ph3PCCO). The formed 3-acyl ylide **158** was transformed into the corresponding 3-acyl derivative by addition of hexanal and $KOC(CH_3)_3$

in a Wittig-like reaction developed by Schobert *et al.*[34] Since this 3-acyl tetramic acid **159** showed no reaction with the used imidate **77** under different temperatures and only hydrolysis and decomposition of the donor was observed, the 3-acyl tetramic acid was transferred into the corresponding BF$_2$-complex **160** by standard methods[32] to push the reaction to *N*-glycosylation and avoid other possible side products like a 3'-*O*-acyl glycosylation.
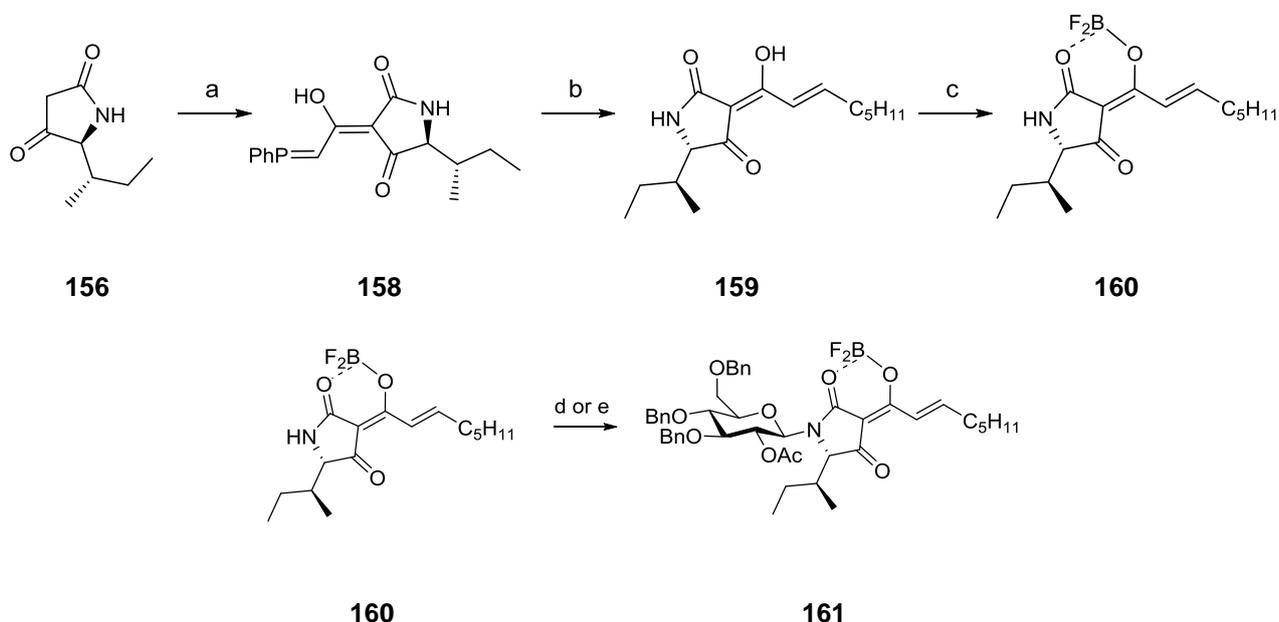
Scheme IV.29. Glycosylation of a 3-acyl tetramic acid. Reagents and conditions: a) Ph$_3$PCCO (1 equiv), THF, reflux, 2.5 h, quant; b) KOC(CH$_3$)$_3$ (1 equiv); THF, reflux, 20 min then hexanal (1 equiv), THF, reflux, 6 h, 15%; c) BF$_3$•OEt$_2$ (5 equiv), THF, RT, 24 h, 32%; d) **77** (1.1 equiv), BF$_3$•OEt$_2$ (0.15 equiv), CH$_2$Cl$_2$, -40 °C to RT, 2 h, 8%; e) **77** (1.1 equiv), TMSOTf (0.1 equiv), CH$_2$Cl$_2$, -40 °C, 1 h, 7%.

On one hand the direct chemical *N*-glycosylation of a 3-acyl tetramic acid BF$_2$-complex was successful. On the other hand the reproducible unsatisfying yield of this reaction showed its limitations already. For this reason, the 2nd retrosynthetic approach (Scheme IV.27.) via a Mitsunobu type reaction was tested.

IV.4.4. *N*-Glycosylated tetramic acids via Fukuyama-Mitsunobu reaction

The Fukuyama-Mitsunobu reaction was always said to be a good choice for chemical *N*-glycosylation in literature.[43,283,288–290] The known[290,292] 2-nosyl protected alanine methyl ester derived from alanine methyl ester hydrochloride[32] was reacted with anomeric unprotected 2,3,4,6-tetraacetyl galactose which was available in the lab and prepared by a known[288,293] standard method. This Mitsunobu variant yielded 94% of the desired *N*-glycoside **163**.

154   **162**   **163**
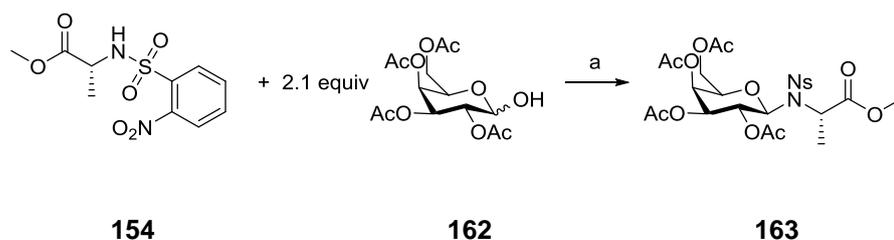
Scheme IV.30. Fukuyama-Mitsunobu reaction for *N*-glycosylation. Reagents and conditions: a) **162** (2.1 equiv), PPh$_3$ (2.1 equiv), DIAD (2.1 equiv), THF, -78 °C, 2 h, then RT 8 h, 94%.

The anomeric linkage was roughly 1:3 *α:β* but with this *N*-glycosylated product **163** in hand, the synthesis can be continued as stated in Scheme IV.27. to get both natural products aurantoside G and J which only differ in the anomeric linkage. Similar conditions were used in a test with 2,3,4-triacetyl xylose[294] **164**. These conditions yielded only 50% of the desired *N*-glycoside **165** due to the hard purification of the products. In this case the diastereomeric ratio was about 1:4 *α:β*. These problems could be avoided when nosyl deprotection was carried out direct after glycosylation without further purification steps in 69% yield over two steps as shown by M. Petermichl[49]. Similar conditions were applied with different protected sugars and the corresponding buyable *N*-trityl and protected *L*-asparagine which was methyl esterified and nosyl protected. All tested variants gave comparable good yields.[49]

154   **164**   **165**
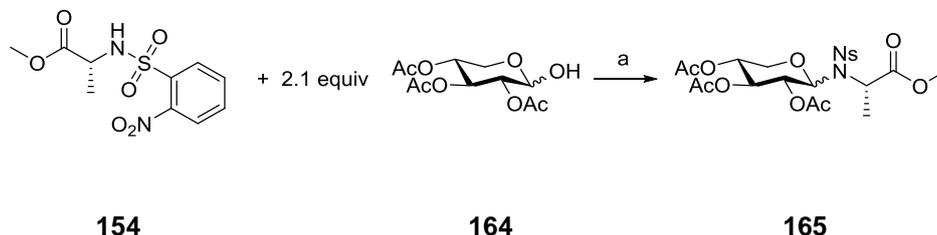
Scheme IV.31. Fukuyama-Mitsunobu reaction with xylose. Reagents and conditions: a) **164** (2.1 equiv), PPh$_3$ (2.1 equiv), DIAD (2.1 equiv), THF, -78 °C, 2 h, then RT 8 h, 50%.

This part of the project was carried out by M. Petermichl who continued the total synthesis of the aurantosides successfully[49] using the herein elaborated Fukayama-Mitsunobu reaction. The results of his total synthesis will be published soon.

IV.5. Stereoinduction by tetramic acid boron complexes

It is worth to shortly note that tetramic acid 3-acyl BF_2-complexes showed a significant stereoinduction in terms of the hydrogenation of a double bond which is in conjugation with the 3-acyl *exo*-enol double bond (see Scheme IV.10.) as shown for epicoccamide D total synthesis. This induction gave a diastereomeric excess of 42% when a non-chiral and heterogenous catalyst was used (see Table IV.2.).

This behaviour is explainable by a closer look on the 3-dimensional structure of tetramic acid BF_2-complexes. Jones *et al.*[98] found a BF_2-chelate complex in one certain orientation building a chelate with the oxygen of the 3'-enoyl function and the C-2 amide oxygen as shown in Figure IV.11. Residues on the tetramic acid C-5 are said to be the only moieties sticking out of the 3-acyl tetramic acid plane besides a potentially existing modification starting at the C-7 and the mentioned BF_2-complex.[98,295]
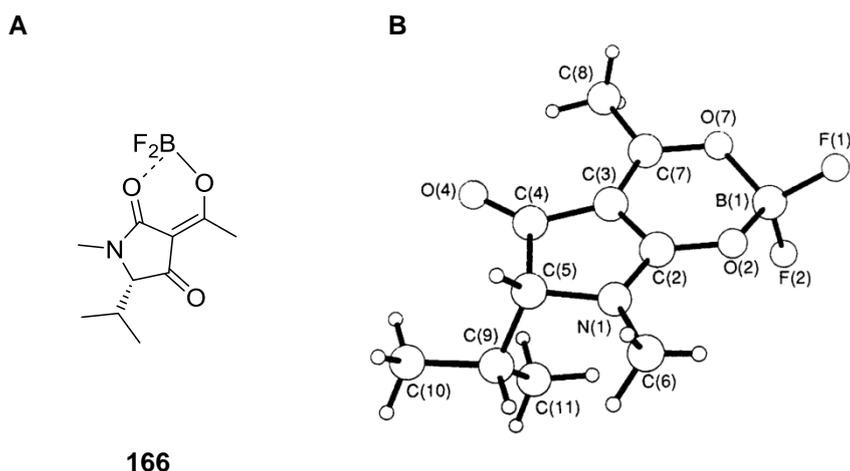
Figure IV.11. Jones *et al.*[98] showed the 3-dimensional structure of a 3-acyl tetramic acid BF_2-chelate complex derived from valine. A) Tetramic acid used for crystallization studies. B) 3-dimensional structure of **166** showing the whole 3-acyl tetramic acid in one plane except the C-5 isopropyl residue derived from valine and the BF_2 itself. The boron atom is 0.37 Å below the other carbon and oxygen atoms forming the 6-membered BF_2-chelate ring. The only found tautomer in their complexation trials was the shown 3-*exo*-enol form **166**. Adopted from Jones *et al.*[98] with permission from The Royal Society of Chemistry.

In case of the stereoinduction concerning the used epicoccamide auxiliary BF_2-chelate complex it looks like the heterogeneous and therefore very bulky catalyst is hindered in attacking from one side by the C-5 residue and the BF_2 atoms. This effect might lead to the mentioned diastereomeric excess of 42%.

To account for this assumption different 3-acyl tetramic acid boron chelates were in focus of synthesis. The tetramic acid derived auxiliary **97** used in the epicoccamide test system should

be converted into the corresponding boron complex by utilizing diethyl boron fluoride which was thankfully provided by the group of Wrackmeyer *et al.*[296]

97   **167**   **168**
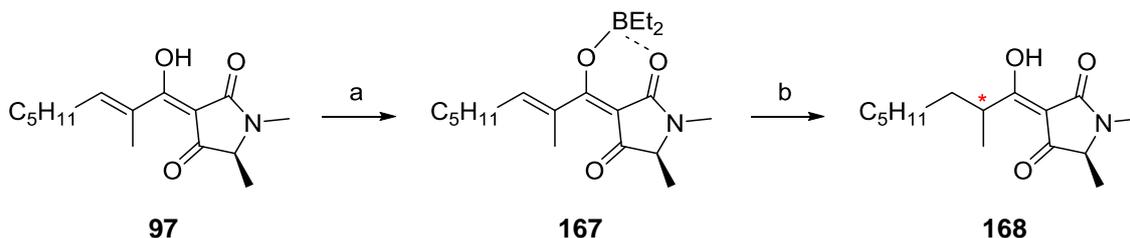
Scheme IV.32. Alternative boron 3-acyl tetramic acid complex for trials of the stereoinduction of homogeneous catalysts in catalytic hydrogenation of **167**. Reagents and conditions: a) BEt$_2$F•pyridine[296] (5 equiv), CH$_2$Cl$_2$, RT, 12 h, 65%; b) Pd/C (5%, 10 wt%), 1 bar H$_2$, CH$_2$Cl$_2$, RT, 4 h, 34%.

This conversion was carried out in the same manner as for the auxiliary of the epicoccamide D total synthesis[32]. The free 3-acyl tetramic acid **97** was transferred into its BEt$_2$-complex by the use of BEt$_2$F•pyridine derived from B. Wrackmeyer's group[296]. This procedure yielded the desired BEt$_2$-complex **167** in 65% yield.

The complex was subjected to identical conditions of hydrogenation (see Table IV.2.) as the BF$_2$-complex. This boron-dialkyl complex of a 3-acyl tetramic acid was not stable under standard hydrogenation conditions using palladium on charcoal. Since the complex decomposed rapidly during reaction, the hydrogenation stopped after roughly 35% conversion. The resulting product mixture contained the educt **97** and the reduced diethylboron complex of the 3-acyl tetramic acid **168**. This mixture was analyzed again by chiral HPLC which revealed a diastereomeric excess of about 60%. Exact numbers were not accessible since the educt eluted in the middle of the two possible diastereomers and without baseline separation.

These preliminary results looked promising and additional work needs to be carried out at least with more stable boron complexes.

V. CONCLUSION

V.1. Total synthesis of epicoccamide D

The secondary metabolite epicoccamide D, derived from fungal sources, was synthesized for the first time. The overall yield was 17% over 19 steps in the longest linear sequence starting from *D*-glucose. These high yielding steps included a C-2 glucose epimerisation reaction, a HWE olefination and a Lacey-Dieckman cyclisation as key steps of the total synthesis.

Another key step was the stereoselective hydrogenation of the corresponding 3-acyl tetramic acid BF$_2$-complex, which not only enabled access to all four possible configurations in terms of the unknown configuration of the stereocenters on the tetramic acid moiety, but also allowed the assignment of the absolute configuration of the natural product. An auxiliary technique was applied comparing NMR spectra and optical rotation of a synthetic tetramic acid derivative prepared by two different protocols. The auxiliaries were chosen to have similar substitutions as the natural product. The auxiliary was, on one hand, derived from the same methodology applied for the epicoccamide D total synthesis, and on the other hand prepared by an acylation method having a known absolute configuration[28,29]. Subsequent experiments showed that the same catalyst employed for both the auxiliary and the natural product synthesis had identical stereoinduction. Applying the other enantiomer of the catalyst (*R*,*R* instead of *S*,*S*-DUPHOS derived catalyst) revealed full inversion of the formed stereocenter (no match-mismatch), and showed that the stereocontrol in this homogeneous hydrogenation was only accomplished by the chiral catalyst with no observed substrate control. This hydrogenation step, using a cheap rhodium based chiral catalyst revealed the absolute configuration of natural epicoccamide D to be (5*S*,7*S*). The suggested absolute configuration was later confirmed by the Yajima group.[123] The hydrogenation step was achieved by employing a known[30,98,134] BF$_2$-chelate complex forming procedure.

The described method establishing the C-7 stereocenter complements other routes with similar synthetic *C*-7-branched targets using the Evans auxiliary technique[207]. After this selective alkylation a 4-*O* to C-3 acylation rearrangement protocol[123,205], developed by Yoshii *et al.*[113], and improved by Yoda *et al.*[31,205], was carried out. This method can also referred to be a direct C-3 acylation[297]. Additionally this total synthesis clears the way for the synthesis of members from the large glycotetramate family including ancorinosides and virgineone.

It is also worth noting that the access to *N*-methylated amino acid methyl esters was improved by direct usage of the Boc-protected amino acid and a two steps *N*-methylation esterification procedure. The second step liberated enough HCl to remove the Boc-group *in situ* without purification in between as it is usually described in literature[157,158].

The shown total synthesis of epiccoccamide D was of a modular character and allows access to additional natural derivatives and synthetic ones inspired by nature. Synthesizing such compounds in future might deliver an insight into the importance of the *β*-configurated glycosidic linkage, in which improvements, in terms of biological activities of another sugar moiety, can be made. Potentially other biological functions can be revealed by changing the alanine derived tetramic acid moiety to other (natural) amino acids. All this information might show an overall structure-activity relationship. Preliminary work has been carried out together with D. Linder[298] finding access to *α*-branched epiccoccamide derivatives. Having an adequate amount of material, not only of natural occurring epiccoccamide D, but also of other non-natural derivatives, in hand will allow extensive biochemical assays to be performed in order to find the mode of action of epiccoccamides, and eventually reveal their biological target to elucidate their antimicrobial and cytotoxic effects.

To the best of our knowledge the published[32] epiccoccamide D total synthesis was the first total synthesis of a naturally occurring glycosylated tetramic acid beside a synthesis by Pronin *et al.*[43]. In their synthetic approach no common hexose or pentose was attached to the 3-acyl fatty acid residue of a tetramic acid rather than a hexose named *L*-rhodinose[299,300] (2,3,6-trideoxy-*L*-galactose) which only occurs in gram-negative bacteria[301].

V.2. Total synthesis of the ancorinoside B diglycoside

The synthesis of the ancorinoside B diglycoside using either a readily C-6 oxidized acceptor for the first glycosylation or performing a convenient oxidation stept right before the second one failed. Many different donor-acceptor combinations were tested and temperature, promoter load and type of promoter (TMSOTf vs. BF$_3$•OEt$_2$) were changed with no positive result.

The diglycoside Gal-*β*(1-4)GlcU (part of ancorinoside B and C) was synthesized with 7.6% overall yield over 10 steps, starting from *D*-glucose. The total amount of steps was 16 to gain the desired diglycoside. This synthesis utilized a new glycosylation acceptor (or donor in case

of the 2nd glycosylation), two subsequent glycosylation steps and a high yielding late oxidation protection procedure.

This synthesis needs to be continued using the methodology also used for epicoccamide D total synthesis. The goal to get access to ancorinoside B should be reachable with this methods and the diglycoside already in hand. The only difference compared to epicoccamides might be a problem arising from two occuring esters, one from aspartic acid side chain and one amino acid methyl ester, close to each other during Lacey-Dieckmann cyclisation. In respect to this fact the necessary remaining steps of the total synthesis are shown below starting from the fully protected diglycoside. The remaining steps start with regard to the later oxidation of the C-5 tetramic acid side chain to install the aspartic acid functionality from the synthesis of a fully protected N-methyl homoserine[212,302] methyl ester derivative which can be derived from affordable D-methionine.

Additionally another phosphonate needs to be synthesized since ancorinosides do not bear a methyl group on the side chain. This can be accomplished using the method from Ley et al.[56] but starting with bromoacetyl bromide rather than bromopropionly bromide.

With all that material in hand, the total synthesis of ancorinoside B can be commenced in future with similar steps as for the epicoccamide D synthesis. The primary TBS group on the side chain will be deprotected, oxidized and transferred into the corresponding β-ketoamide via HWE olefination and aminolysis. The synthesis will be finalized by removal of the silyl protective group on the amino acid side chain from the above mentioned homoserine derivative after the mentioned cyclisation followed by oxidation.

107   R = CH$_2$OTBS

169   R = CH$_2$OTBS

170   R = CH$_2$OH

171   R = COOH
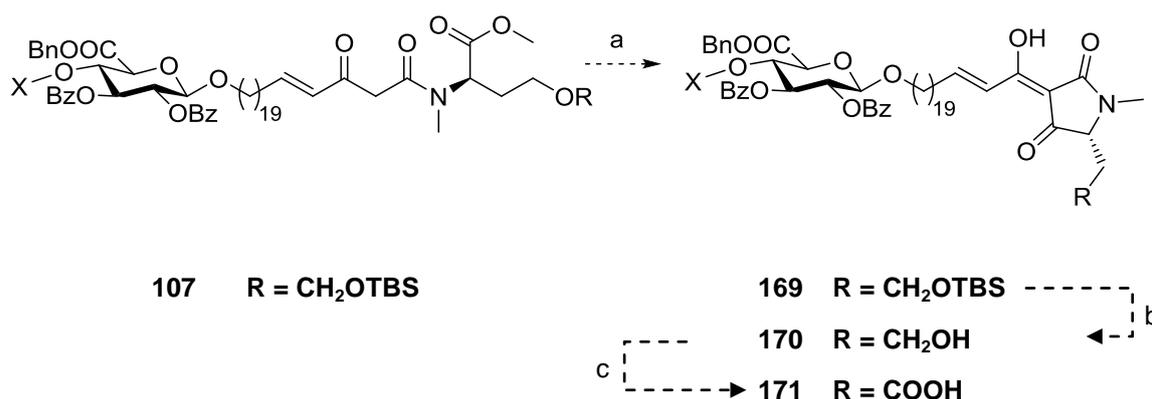
Scheme V.1. Suggested cyclisation, deprotection and oxidation step of the aminolysis product **107** to finalize ancorinoside B total synthesis. X = perbenzoylated β-D-galactose. Suggested reagents and conditions: a) NaOMe (1 equiv), MeOH, 0 °C, 6 h; b) TBAF (4 equiv), THF, RT, 12 h; c) TEMPO (0.1 equiv), BAIB (2.5 equiv), CH$_2$Cl$_2$:H$_2$O = 2:1, RT, 2 h.

The last step will be a global deprotection step by hydrogenation since all functional groups are protected by benzylic esters and can therefore be cleaved, also reducing the double bond

derived from the HWE olefination step. Ancorinosides do not possess a methyl substitution at the C-7 and hence no stereoselective hydrogenation is necessary during synthesis.

With this natural product in hand, biochemical evaluation can again be carried out, not only to find similarities or differences between ancorinoside B and epicoccamide D, but also eventually find additional information concerning the mode of action of the type-1 matrix metalloproteinase (MT1-MMP) inhibition which was found[120] in the case of the ancorinoside B. It is assumed that tetramic acids derived from different amino acids strongly differ in their biological activity.

Since ancorinosides have a tetramic acid moiety derived from *N*-methyl *D*-aspartic acid (NMDA), it might also be worth to test[121] for occurring activating behaviour of nerve cells. NMDA is a known agonist for receptors bound in the postsynaptic membrane regulating ion in- and efflux normally in a voltage-dependent manner.[122] The function of this receptor is directly connected to the process of learning and disfunction of the receptor leading to depression, including several other mood disorders[303], or is involved in Alzheimer's disease[304].

V.3. Contribution to virgineone total synthesis

The protected side chain of virgineone was synthesized in nine steps with a poor overall yield of 2.2%. This yield issue was caused by the problematic selective protection of the 1,2-diol gained from Sharpless dihydroxylation. It might be worth performing the synthesis, to this point, anew, since at least the selective pivaloyl esterification should give yields better than 32%. If this particular route still returns poor yields it might be useful to protect the starting material for this synthesis (dec-9-en-1-ol) with a more stable triisopropylsilyl (TIPS) group, which can possibly sustain trityl deprotection and still maintaining orthogonality to the THP protective group.

If these changes to the synthesis of the virgineone side chain prove successful the remaining steps for total synthesis can be then derived from epicoccamide D total synthesis. The only three differences compared to these synthetic routes are the missing *N*-methylation, the usage of an accordingly protected *L*-tyrosine derivative, and the required THP deprotection and oxidation late in synthesis. The oxidation step needs to be carried out at any point after the HWE olefination step to avoid side reactions and possibly before the actual Lacey-Dieckman cyclisation step in order to circumvent purification problems which might occur once the

corresponding tetramic acid is in place. A suitably protected tyrosine derivative (**172**) for aminolysis is shown in Figure V.1. as well as the step where THP deprotection and oxidation seems most reasonable (**173**).

172

173
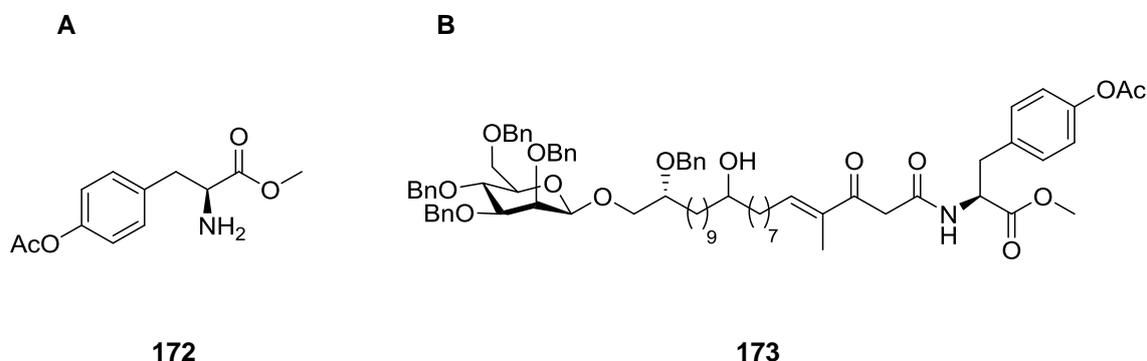
Figure V.1. Suggested tyrosine derivative and educt for oxidation. A) *O*-acetyl protected tyrosine derivative usable for the aminolysis reaction during the virgineone total synthesis. B) Key step and educt for the oxidation process to get the desired ketone which also arises in the natural product.

The acetyl protective group might be a clever choice since the conditions necessary to perform the Lacey-Dieckman cyclisation are conform to the normal standard conditions for removing an acetyl-group. It is also worth noting that the 2-hydroxyl group on the sugar moiety again needs to be protected right after the epimerisation has been performed.

With all these tools in hand a virgineone total synthesis should be reachable. If all these methods fail there is still the possibility to combine the knowledge of establishing the *β*-glycosidic linkage between mannose and its side chain with the published virgineone aglycon synthesis by Yajima *et al.*[124] It might be possible to use their methodology to install the long oxidized fatty acid by cutting it into two pieces with one bearing the ketone from a retrosynthetic view and later connect both parts by cross metathesis. The required glycoside **174** is shown in Figure V.2. besides the second reaction partner **175** for cross metatesis.

174

175

Figure V.2. Possible educts for cross metathesis. A) Necessary glycoside synthesized by the epicoccamide methodology. B) 3-acyl tetramic acid bearing also a terminal double bond for cross metathesis.

If a cross metathesis is performed to bring both the glycoside and the tetramic acid together, a C-2 protection of the sugar moiety might not be necessary. It is obvious that the cross metathesis is best performed right before the Lacey-Dieckman cyclisation step in order to have the product easily purified and avoid catching of the cross metathesis catalyst by the

tetramic acid. It might also be necessary to build up the tetramic acid moiety by a HWE-, Lacey-Dieckman- and aminolysis reaction sequence in order to have access to both stereoisomers at the C-7 methyl group.

It is imaginable, and indeed beneficial to perform this total synthesis in collaboration with Prof. Arata Yajima (*personal communication*). That might combine different approaches in a helpful way and can be important for future projects.

After successful total synthesis of virgineone biochemical tests and comparisons can be performed to eventually find a target where virgineone interacts with the calmodulin-dependent stress response system[125] and potentially explain its antifungal behaviour[125].

V.4. *N*-Glycosylation for aurantoside G and J synthesis

The first trial of chemical *N*-glycosylation using a tetramic acid derivative which was not 3-acylated and a trichloroacetimidate derived Schmidt donor yielded 42% of a selective 4-*O*-glycosylation product. From the current point of view other donors might react in a similar way since no other products or side reactions were observed. This reaction was not useful in terms of the planned aurantoside total synthesis but can potentially be used to synthesize tetramic acid 4-*O*-glycosides and investigate their biological behaviour. The sugar moiety of this new compound class might either be cleaved once transported into a cell or retained and partly involved into the biological function. Both compounds are worth to test for potential antibacterial, antifungal or cytotoxic properties.

The desired *N*-glycosylation was successful albeit with poor yields, using a readily available BF_2-complex of a 3-acyl tetramic acid with a Schmidt donor. Both $BF_3 \bullet OEt_2$ and TMSOTf were tested as promoter for this type of reaction. Since both activating reagents gave comparable yields below 10% the actual route for direct *N*-glycosylation of a tetramic acid was discarded and an approach using the Fukayama-Mitsunobu reaction to gain access to the desired *N*-glycoside was explored. The direct glycosylation tested might still be a reasonable approach for this type of reaction. Literature suggests changing the solvent for a direct *N*-glycosylation utilizing a Schmidt type donor from CH_2Cl_2 to nitromethane as shown by Takahashi *et al.*[284] In their studies this change increased the yield from 46% to 98%. To optimize this reaction might still be useful: It can be used to build up a small compound library of *N*-glycosylated tetramic acids fast and eventually get some insight into structure-function relationships (SAR) of this compound class.

The tested approach using the mentioned Mitsunobu type reaction yielded a *N*-glycoside of an amino acid in excellent yields (94%) but was not very stereoselective (*α:β* 1:3 or 1:4 respectively) since the participating group effect cannot play a role in this reaction as can be seen from the mechanism[282]. This reaction opened a possible approach for the aurantoside total synthesis and after altering electronic properties of the donor as well as some changes in the reaction sequence proved to be a successful advancement. The full synthetic record of this approach can be seen in the Master thesis of M. Petermichl.[49]

V.5. Stereoinduction by tetramic acid boron complexes

Substrate controlled asymmetric hydrogenation was not observed in terms of the applied homogeneous catalysis as shown by the results for epicoccamide synthesis using the rhodium based Et-DUPHOS catalyst. Utilizing palladium on charcoal on the same substrate (the BF_2-complex) revealed a detectable stereoinduction (42%).

In this hetereogeneous hydrogenation the stereoinduction is definitely substrate controlled. This is because not only the catalyst bears no stereogenic information, but also an increase of diastereomeric excess during some trials using different substrates was discovered. Whereas a non-complexed 3-acyl tetramic acid had a barely detectable stereoinduction of 4% possibly due to the elevated methyl group standing over the tetramic acid plane[98], the corresponding BF_2-chelate complex had already a stereoinduction of 42%. This induction was increased by changing the chelate from a difluoroboron to a diethylboron complex. This complex showed a diastereomeric excess of 60% during hetereogeneous catalytic hydrogenation, but was not stable during the reaction revealing only 35% conversion until the tetramic acid complex was hydrolyzed which additionally induced deactivation of the catalyst. The evidence of deactivated catalyst was supported by the fact that hydrolyzed tetramic acid was barely (and unselectively) hydrogenated and a high amount of educt was found during chiral HPLC analysis. A fast hydrolysis rate is explainable by the fact that the used diethylboron complex is by far not as Lewis-acidic as the BF_2 derivative and therefore not strongly bound and complexed by the tetramic acid.

To circumvent this fast hydrolysis rate during hydrogenation a more Lewis-acidic, therefore more stable and maybe even larger boron complex, can be supposed. A boron complex derived from a dialky boronic acid ester can be synthesized and used in the hetereogeneous hydrogenation step. Synthesis from literature of dialkyl or diaryl boronic acid ester fluorides

was performed by A. Meller *et al.*[305] utilizing a corresponding alcoholate (e.g. 2,2-dimethylpropanol or 2,6-di-*t*butylphenol) lithium salt together with BF$_3$•OEt$_2$. A second approach in literature is the synthesis of various large alkyl boronic acid esters published by Medrano *et al.*[306] as shown below.
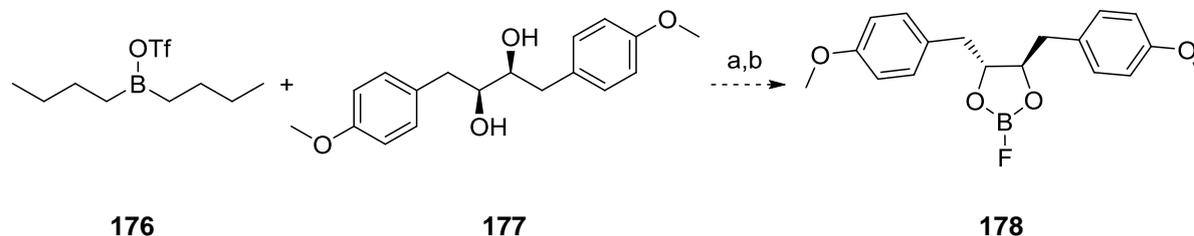
Scheme V.2. Synthesis of a chiral dialkyl boronic acid ester fluoride taken from Medrano *et al.*[306] Reagents and conditions: a) RT, 30 min, 0.1 torr; b) TBAF (1 equiv), THF, RT, 14 h.

The shown chiral diol **177** is cheap since it is used as educt for chiral catalyst synthesis and easily accessible by Sharpless dihydroxylation.

Another thing that can be changed in terms of the hetereogeneous hydrogenation, is the solid support of the used palladium species. It is known that the used solid support for a given hydrogenation catalyst has a huge influence on kinetics of the hydrogenation[307]. Beside palladium on charcoal, which is meant to be a more "dirty" catalyst bearing a varying number of functional groups on its surface, silica, alumina or a polymeric support[308,309] can be applied. The catalysing metal atom can be changed as well by employing e.g. platinum.

VI. EXPERIMENTAL SECTION

VI.1. General remarks

All chemicals and solvents were purchased from ABCR, Acros Organics, Alfa Aesar, Carbolution Chemicals, Fisher Scientific, Merck, Sigma-Aldrich and Strem Chemicals. The used solvents were dried under standard conditions for the corresponding solvent or directly used in p.a. quality as purchased. CH_2Cl_2 and DMF were dried over CaH_2, THF over sodium and methanol over phosphorous pentoxide. Solvents for chromatography and extraction were purchased in technical grade and destilled prior to use or also directly used in p.a. quality.

An inert atmosphere was applied using nitrogen (technical grade) with a standard pressure of 1 bar when not stated otherwise. When argon was necessary, the gas was used in a purity of 4.8 and dried prior to use with $CaCl_2$ and blue silica gel. The gases were purchased from Riessner gas.

Analytical tlc was performed on silica gel 60 F_{254} foil plates purchased from Merck. The retention factor was measured in relation to the complete way and the substances were made visible using either UV-light (254 nm or 366 nm) or stained using acidified ceric ammonium molybdate (1 g $Ce(SO_4)_2$, 2.5 g $(MoO_3)_{12} \cdot H_3PO_4$, 6 ml H_2SO_4, 94 ml H_2O). Silica gel based column chromatography was performed over a mesh of 63-200 nm and for flash chromatography a silica gel with a particle size of 25-40 nm was applied.

IR-spectra were recorded on a PerkinElmer ONE FT-IR spectrometer equipped with an ATR sampling module. The absorption was noted as spectroscopic wavenumer in cm^{-1}. The given peaks were labelled with s (strong), m (medium), w (weak), br (broad).

Specific rotation was measured using a PerkinElmer Polarimeter 241 and applying a 1 ml cuvette with a beam path of 10 cm. All measurements were carried out at 589 nm and with a given concentration and temperature.

Melting points were recorded on a Büchi M-565 melting point apparatus and noted uncorrectedly.

High resolution mass spectrometry was performed on either a UPLC/Q-TOF MS from Bruker or a Thermo Scientific Q Exactive Obritrap connected to a Dionex UltiMate 300 UPLC unit. All spectra were recorded in ESI$^+$ mode, the mass to charge ratio (m/z) of a given substance was detected and compared to the calculated value.

Analytical HPLC was performed on a Beckman system with solvent module 126 and a diode array detector module 168. For standard analytics a Phenomenex Gemini NX 5 μm C-18 reversed phase column sized 250•4.6 mm or a Phenomenex Kinetex 5 μm C-18 reversed phase column with the same size. Chiral HPLC was performed using a Macharey-Nagel Nucleodex CD β-OH column sized 150•4.0 mm.

NMR spectrometry was performed on either a Bruker Avance 300 or a Bruker Avance DRX-500 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) downfield from a Me_4Si signal as internal standard. Coupling constants are noted in Hertz (Hz). Spectra were standardized using the given signal of the deuterated solvents in which the substances were measured. These shifts[310] were $\delta(^1H)CDCl_3 = 7.26$ ppm, $\delta\ (^1H)D_2O = 4.79$ ppm, $\delta(^1H)CD_3OD = 3.31$ ppm, $\delta(^{13}C)CDCl_3 = 77.16$ ppm and $\delta(^{13}C)CD_3OD = 49.00$ ppm. Signals are indicated to be s (singlet), d (doublet), t (triplet), q (quartet), qui (quintet), m (multiplet) or combinations thereof.

VI.2. Epicoccamide D

VI.2.1. Glycosyl donor (imidate 77)

1,2,3,4,6-Penta-*O*-acetyl-*D*-glucopyranose (80)
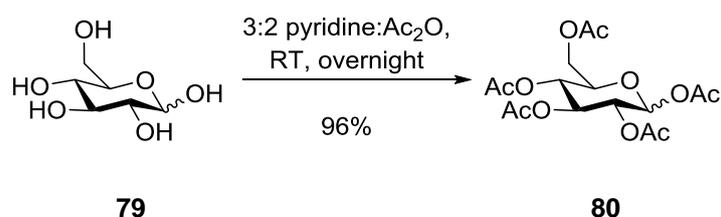
Scheme VI.1. Synthesis of peracetylated *D*-glucose **80**.

D-Glucose **79** (5.80 g, 32.36 mmol) was dissolved in 125 mL of a 3:2 mixture of pyridine and Ac_2O and stirred at room temperature overnight. All volatiles were removed by repeated use of toluene as an azeotropic entraining agent. The remainder was dissolved in EtOAc and washed with sat. aqueous $CuSO_4$, brine, sat. $NaHCO_3$ and again brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica gel; 50% EtOAc in *c*-hexane) to yield **80** (12.01 g, 96%) as a white solid; mixture of isomers $\alpha{:}\beta = 6.5{:}1$.

R_f =0.70 (ethyl acetate/cyclohexane 1:1);

m.p. 107 °C;

$[\alpha]_D^{22} = 82.9$ ($c = 1.0$ g cm^{-3}, chloroform);

HRMS (ESI) calcd for $C_{16}H_{22}O_{11}Na$ [M+Na]$^+$ 413.1026, found: 413.1012.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-α-*D*-glucopyranose (81)[145]
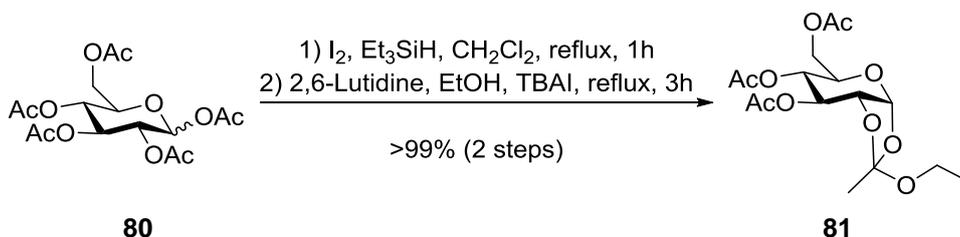
Scheme VI.2. Synthesis of orthoester **81** from peracetylated *D*-glucose **80**.

A solution of **80** (5.07 g, 13.0 mmol) in CH$_2$Cl$_2$ (60 mL) was treated with I$_2$ (4.6 g, 18.2 mmol) and Et$_3$SiH (2.9 mL, 18.2 mmol). The mixture was heated at reflux for 1 h, cooled to RT and treated with 2,6-lutidine (6.0 mL, 51.9 mmol), EtOH (4.6 mL, 77.9 mmol) and NEt$_4$I (1.20 g, 3.3 mmol). The mixture was heated at reflux for 3 h, the volatiles were removed under reduced pressure and the residue was purified by flash chromatography (silica gel; 15% EtOAc in *c*-hexane) to give **81** as transparent hygroscopic crystals (5.10 g, quantitative).

R$_f$=0.56 (EtOAc/*c*-hexane 1:1);

m.p. 82-85 °C;

$[\alpha]_D^{23} = 44.6$ ($c = 1.0$ g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=5.69 (d, ^3J(H,H)=5.2 Hz, 1H, 1-H), 5.17 (t, ^3J(H,H)=2.8 Hz, 1H, 3-H), 4.90 (ddd, ^3J(H,H)=9.6 Hz, 2.8 Hz, 0.9 Hz, 1H, 4-H), 4.32 (ddd, ^3J(H,H)=5.2 Hz, 2.8 Hz, 0.9 Hz, 1H, 2-H), 4.20 (dd, ^3J(H,H)=5.0 Hz, 2.8 Hz, 2H, 6-H), 3.95 (ddd, ^3J(H,H)=9.2 Hz, 5.0 Hz, 2.8 Hz, 1H, 5-H), 3.54 (q, ^3J(H,H)=7.1 Hz, 2H, OCH$_2$), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 1.72 (s, 3H, CH$_3$), 1.18 (t, ^3J(H,H)=7.1 Hz, 3H, OCH$_2$C*H$_3$*);

^{13}C NMR (75 MHz, CDCl$_3$): δ=170.8, 169.8, 169.3, 121.4, 97.0, 73.2, 70.3, 68.3, 67.0, 63.2, 59.3, 20.9, 20.9, 15.4;

IR (thin film) ṽ=2976 (w), 2944 (w), 1741 (s), 1732 (s), 1447 (w), 1367 (s), 1295 (w), 1223 (s), 1205 (s), 1175 (s), 1157 (s), 1121 (m), 1105 (s), 1081 (m), 1034 (s), 983 (s), 952 (s), 906 (s), 875 (s), 805 (m), 733 (m) cm^{-1};

HRMS (ESI) Calcd for $C_{16}H_{24}O_{10}Na$ [M+Na]$^+$ 399.1267, found: 399.1213.

3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-*α*-D-glucopyranose (82)[145,149]
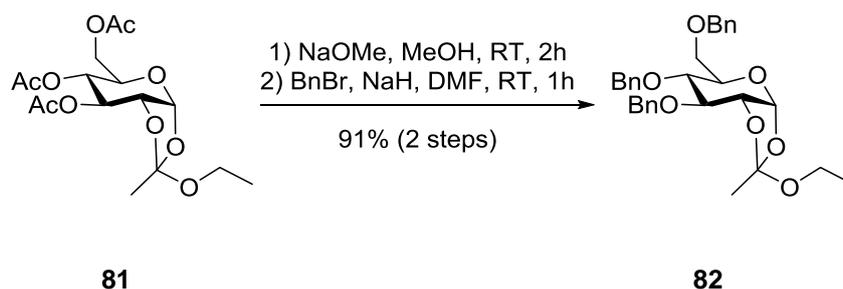
Scheme VI.3. Protective group manipulation for synthesis of benzylated orthoester **82**.

A solution of **81** (2.07 g, 5.5 mmol) in MeOH (21 mL) was treated with NaOMe (60 mg, 1.10 mmol) in one portion and the resulting mixture was stirred at RT until consumption of the starting material (ca. 45 min). The volatiles were removed under reduced pressure and the residue was dissolved in dry DMF (21 mL). The mixture was cooled to 0 °C and NaH (1.0 g, 22.0 mmol, 60% in mineral oil) was added in one portion. $C_6H_5CH_2Br$ (2.9 ml, 24.8 mmol) was added via syringe and the resulting mixture was stirred for 1 h at RT. The reaction was quenched with 50 g of ice and extracted twice with EtOAc. The combined organic phases were washed with brine, dried, concentrated and the residue was purified by flash chromatography (silica gel; 5% EtOAc in *c*-hexane) to afford **82** (2.6 g, 91%) as a clear oil.

R*f*=0.88 (EtOAc/*c*-hexane 1:1);

$[α]_D^{23}$ = 16.3 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.38-7.19 (m, 15H, H^{ar}), 5.79 (d, ^3J(H,H)=5.3 Hz, 1H, 1-H), 4.73 (d, ^2J(H,H)=11.7 Hz, 1H, 3O-CH^a), 4.62 (d, ^2J(H,H)=11.7 Hz, 2H, 3O-CH^b, 4O-CH^a), 4.61 (d, ^2J(H,H)=12.2 Hz, 1H, 6O-CH^a), 4.52 (d, ^2J(H,H)=12.2 Hz, 1H, 6O-CH^a), 4.45 (dd, ^3J(H,H)=5.3 Hz, 3.9 Hz, 1H, 2-H), 4.41 (d, ^2J(H,H)=11.7 Hz, 1H, 4O-CH^b), 3.90 (t, ^3J(H,H)=3.9 Hz, 1H, 3-H), 3.82 (dt, ^3J(H,H)=9.4 Hz, 3.0 Hz, 1H, 5-H), 3.74 (dd, ^3J(H,H)=9.4 Hz, 3.9 Hz, 1H, 4-H), 3.69 (m, 2H, 6-H), 3.57 (q ^3J(H,H)=7.1 Hz, 2H, OCH$_2$), 1.69 (s, 3H, CH$_3$), 1.22 (t, ^3J(H,H)=7.1 Hz, 3H, OCCH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=138.2 (6O-C*C*^{ipso}), 138.1 (4O-C*C*^{ipso}), 137.9 (3O-C*C*^{ipso}), 128.6 (3xCH^{ar}), 128.4 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.05 (3xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.7 (CH^{ar}), 121.1 (*C*(OR)$_3$), 97.9 (C-1), 78.9 (C-3), 75.9 (C-2), 75.0 (C-4), 73.5 (6O-CH$_2$), 73.1 (4O-CH$_2$), 72.0 (3O-CH$_2$), 70.6 (C-5), 69.3 (C-6), 58.8 (OCH$_2$), 22.0 (Me), 15.5 (OC*C*H$_3$);

IR (thin film) ṽ=3030 (w), 2978 (w), 2932 (w), 2868 (w), 1496 (w), 1454 (m), 1382 (m), 1364 (m), 1308 (w), 1252 (m), 1207 (m), 1094 (s), 1045 (s), 1027 (s), 988 (s), 951 (s), 907 (s), 731 (s), 695 (s) cm^{-1};

HRMS (ESI) Calcd for $C_{31}H_{36}O_7Na$ [M+Na]$^+$ 543.2359, found: 543.2294.

3,4,6-Tri-*O*-benzyl-2-*O*-acetyl-*α*-D-glucosyl trichloroimidate (77)[149]
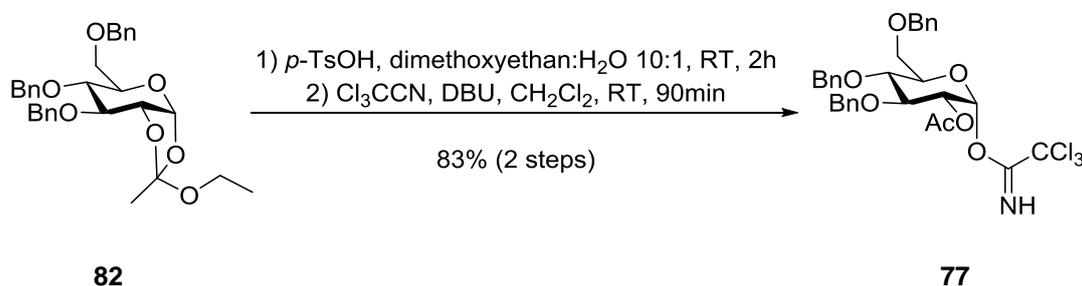
Scheme VI.4. Synthesis of benzylated imidate **82** for glycosylation.

A solution of **82** (885 mg, 1.70 mmol) in 20 mL of a mixture of 10% H_2O in DME was treated with *p*TosOH•H_2O (162 mg, 0.85 mmol) and stirred for 2 h. The reaction was quenched with sat. aqueous NaHCO$_3$, extracted three times with EtOAc, and the combined organic layers were washed with H_2O and brine, dried over Na$_2$SO$_4$ and concentrated. The crude product was dissolved in dry CH$_2$Cl$_2$ (35 mL), treated with CCl$_3$CN (1.6 mL, 16.1 mmol) and DBU (60 μL, 0.40 mmol) and stirred at RT for 1.5 h. The solvent was stripped off and the brownish remainder was purified by column chromatography (silica gel; 15% EtOAc in *c*-hexane) to remove the 1-*O*-acetyl-2-trichloroimidate by-product and to leave **77** (940 mg, 87%) as a colourless oil.

R$_f$=0.58 (EtOAc/*c*-hexane 1:2);

$[\alpha]_D^{22}$ = 67 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=8.56 (s, 1H, NH), 7.38-7.19 (m, 15H, H^{ar}), 6.53 (d, ^3J(H,H)=3.6 Hz, 1H, 1-H), 5.06 (dd, ^3J(H,H)=10.0 Hz, 3.6 Hz, 1H, 2-H), 4.86 (d, ^2J(H,H)=11.5 Hz, 1H, 3O-CH^a), 4.83 (d, ^2J(H,H)=10.6 Hz, 1H, 4O-CH^a), 4.76 (d, ^2J(H,H)=11.5 Hz, 1H, 3O-CH^b), 4.63 (d, ^2J(H,H)=12.0 Hz, 1H, 6O-CH^a), 4.57 (d, ^2J(H,H)=10.6 Hz, 1H, 4O-CH^b), 4.50 (d, ^2J(H,H)=12.0 Hz, 1H, 6O-CH^b), 4.09 (t, ^3J(H,H)=10.0 Hz, 1H, 4-H), 4.01 (ddd, ^3J(H,H)=10.0 Hz, 2.8 Hz, 1.8 Hz, 1H, 5-H), 3.87 (t, ^3J(H,H)=10.0 Hz, 1H, H-3), 3.81 (dd, ^2J(H,H)=12.5, ^3J(H,H)=2.8 Hz, 1H, 6-H^a), 3.72 (dd, ^2J(H,H)=12.5 Hz, ^3J(H,H)=1.8 Hz, 1H, 6-H^b), 1.92 (s, 3H, CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=169.8 (COO), 160.8 (CNH) 138.1 (6O-CC^{ipso}), 137.7 (4*O*-CC^{ipso}), 137.6 (3O-CC^{ipso}), 128.3 (3xCH^{ar}), 128.3 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.0 (2xCH^{ar}), 127.9 (2xCH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 127.6 (CH^{ar}), 127.6 (CH^{ar}), 93.9 (C-1), 79.3 (C-3), 76.9 (C-4), 75.2 (3O-CH$_2$), 75.2 (4O-CH$_2$), 73.3 (C-5, 6*O*-CH$_2$), 72.2 (C-2), 67.7 (C-6), 20.4 (CH$_3$);

IR (thin film) ṽ=3338 (w), 3031 (w), 2870 (w), 1737 (s), 1673 (m), 1497 (w), 1454 (m), 1368 (m), 1291 (m), 1228 (s), 1045 (s), 1027 (s), 968 (s), 913 (m), 832 (m), 794 (s), 734 (s), 696 (s) cm^{-1};

HRMS (ESI) Calcd for $C_{31}H_{32}O_7NCl_3Na$ [M+Na]$^+$ 658.1142, found: 658.1263.

All data in accordance with literature.[149]

VI.2.2. Synthesis of the C_{16} alkyl chain

1,16-Hexadecanediol (84)[311]
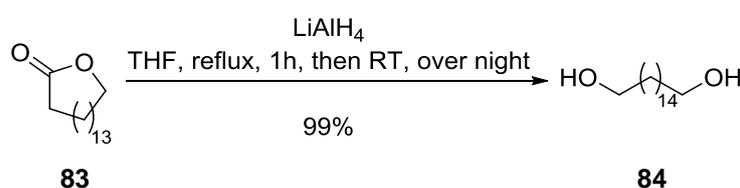
Scheme VI.5. Synthesis of diol **84**.

A solution of LiAlH$_4$ (783 mg, 20.64 mmol) in THF (80 mL) was kept at 0 °C and treated dropwise over a period of 30 min with a solution of hexadecanolide **83** (2.10 g, 8.25 mmol) in THF (70 mL). The resulting solution was heated at reflux for 2 h, then stirred over night at RT and finally quenched by with sat. aqueous Na/K-tartrate. The mixture was extracted twice with Et$_2$O, the combined organic layers were washed with brine, dried, and concentrated to leave pure **84** (2.13 g, 99.8%) as colourless crystals.

R$_f$=0.36 (EtOAc/c-hexane 1:2);

m.p. 92 °C;

^{1}H NMR (300 MHz, CD$_3$OD): δ=3.54 (t, ^3J(H,H)=6.6 Hz, 4H, 1-H, 16-H), 1.51 (qui, ^3J(H,H)=6.6 Hz, 4H, 2-H, 15-H), 1.37-1.27 (m, 24H);

^{13}C NMR (75 MHz, CD$_3$OD): δ=63.0 (C-1, C-16), 33.7 (C-2, C-15), 30.8 (7×CH$_2$), 30.7 (2×CH$_2$), 30.6 (2×CH$_2$), 27.0 (2×CH$_2$);

IR (thin film) ṽ=3411 (m), 3345 (m), 2919 (s), 2848 (s), 1480 (w), 1461 (m), 1356 (m), 1333 (w), 1051 (s), 1017 (s), 996 (w), 971 (m), 727 (m) cm^{-1}.

16-[(*t*Butyldimethylsilyl)oxy]hexadecane-1-ol (78)
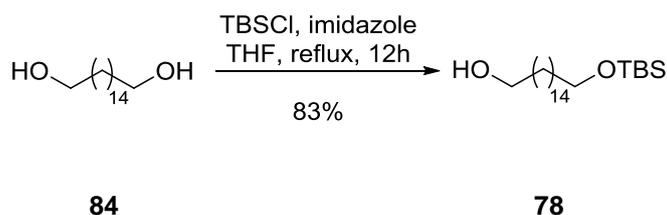
Scheme VI.6. Monoprotection of diol **84**.

A solution of diol **84** (440 mg 1.70 mmol) in THF (12 mL) was treated with imidazole (232 mg, 3.40 mmol) and TBSCl (256 mg, 1.70 mmol), stirred at RT for 12 h, quenched with sat. aqueous $NaHCO_3$, and extracted three times with Et_2O. The combined organic layers were dried, concentrated, and the residue was purified by column chromatography (silica gel; 35% EtOAc in *c*-hexane) to afford **78** (312 mg, 0.85 mmol, 63%) as a colourless oil.

R_f=0.57 (EtOAc/*c*-hexane 1:3);

^{1}H NMR (300 MHz, CD_3OD): δ=3.64 (t, ^3J(H,H)=6.6 Hz, 2H, *CH$_2$OH*), 3.61 (t, ^3J(H,H)=6.6 Hz, 2H, *CH$_2$OTBS*), 1.63-1.47 (m, 4H, 2-H, 15-H), 1.39-1.23 (m, 24H), 0.91 (s, 9H, C(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$);

^{13}C NMR (75 MHz, CD_3OD): δ=63.6 (*C*OTBS), 63.3 (*C*OH), 33.1 (C-15), 33.0 (C-2), 29.9 (C-7 to C-10), 29.9 (C-13), 29.8 (C-4), 29.7 (C-6, C-11), 27.1 (C-12, C-5), 26.2 (C(*CH$_3$*)$_3$), 26.0 (C-14), 26.0 (C-3), 18.6 (Si*C*^{q}), -5.0 (Si(*CH$_3$*)$_2$);

IR (thin film) ṽ=3335 (br), 2924 (s), 2854 (s), 1470 (m), 1463 (m), 1388 (w), 1361 (w), 1254 (m), 1099 (s), 1005 (m), 938 (w), 833 (s), 812 (m), 773 (s), 734 (m), 661 (m) cm^{-1};

HRMS (ESI) Calcd for $C_{22}H_{49}O_2Si$ [M+H]$^+$ 373.3502, found: 373.3490.

VI.2.3. Phosphonate (76)[56]

S-*t*Butyl-4-bromo-3-oxopentanethioate (76)
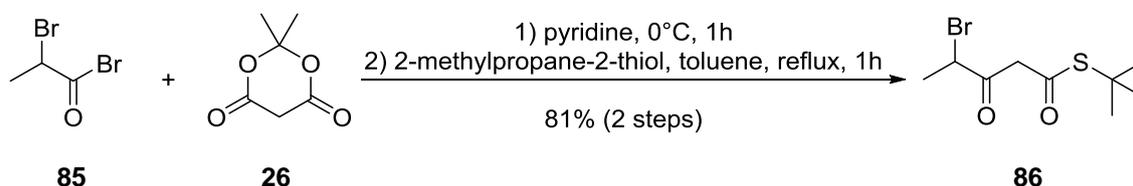
Scheme VI.7. Synthesis of thioester **86** for Arbuzov reaction.

A solution of Meldrum's acid **26** (2.9 g, 20.2 mmol) in CH_2Cl_2 (30 mL) was treated with pyridine (3.3 mL, 40.45 mmol) while stirring, then cooled to 0 °C, treated slowly with bromopropionyl bromide **85** (2.3 mL, 22.3 mmol) via a syringe, and left to stir at 0 °C for 1 h. The mixture was separated between CH_2Cl_2 and 2 M aqueous HBr solution and extracted

two times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, concentrated, and the residue was dissolved in toluene (30 mL). 2-Methylpropane-2-thiol (6.8 mL, 60.7 mmol) was slowly added and the mixture was heated at reflux for 1 h. Removal of the volatiles and column chromatography (silica gel; 5% EtOAc in c-hexane) yielded **86** (4.35 g, 81%) as a red oil which was a 3:2 mixture of keto and enol tautomers.

R_f=0.77 (EtOAc/c-hexane 1:4);

Major Tautomer (keto): ^{1}H NMR (300 MHz, CDCl$_3$): δ=4.59 (q, ^3J(H,H)=6.7 Hz, 1H; CHBr), 4.00 (d, ^2J(H,H)=15.0 Hz, 1H; COCHH^aCO), 3.73 (d, ^2J(H,H)=15.0 Hz, 1H; COCHH^bCO), 1.74 (d, ^3J(H,H)=6.7 Hz, 3H; HCCH_3), 1.47 (s, 9H; C(CH$_3$)$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=196.0 (CO), 192.7 (COS), 54.2 (CH$_2$), 49.5 (C(CH$_3$)$_3$), 47.5 (CH), 29.8 (C(CH$_3$)$_3$), 19.6 (CH$_3$);

Minor tautomer (enol): ^{1}H NMR (300 MHz, CDCl$_3$): δ=12.80 (s, 1H; C(OH)CHCO), 5.53 (s, 1H; C(OH)CHCO), 4.35 (q, ^3J(H,H)=6.9 Hz, 1H; CHBr), 1.82 (d, ^3J(H,H)=6.9 Hz, 3H; HCCH_3), 1.51 (s, 9H; C(CH_3)$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=197.1 (COS), 171.3 (COH), 98.7 (C^{enol}), 49.0 (C(CH$_3$)$_3$), 44.1 (CH), 30.1 (C(CH$_3$)$_3$), 22.4 (CH$_3$);

IR (thin film) $\tilde{\nu}$=2964 (m), 2925 (m), 1726 (m), 1672 (m), 1618 (s), 1476 (w), 1455 (m), 1401 (w), 1364 (m), 1310 (m), 1193 (m), 1159 (s), 1086 (s), 1062 (s), 1048 (s), 973 (s), 816 (s), 780 (m), 706 (m) cm^{-1}.

All data in accordance with literature.[56]

S-*t*Butyl-4-(diethoxyphosphoryl)-3-oxopentanethioate (76)[56]
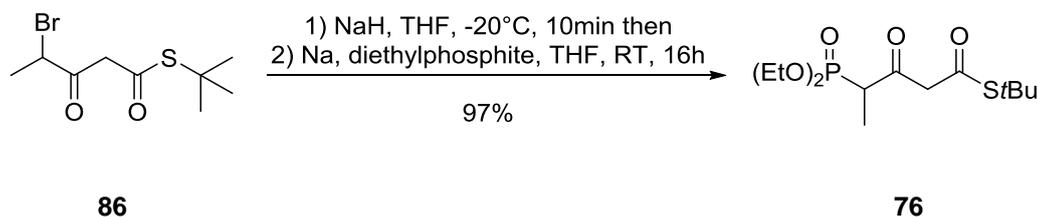
Scheme VI.8. Arbuzov reaction to form the phosphonate **76**.

Na (336 mg, 14.6 mmol) layered with dry THF (20 mL) was slowly treated via a syringe with diethylphosphite (1.74 ml, 13.49 mmol). The resulting mixture was heated at reflux for 2 h. By that time the sodium had been completely consumed. In another flask a suspension of NaH (494 mg, 12.4 mmol, 60% in mineral oil) in dry THF (30 mL) was cooled to 0 °C and treated slowly with a solution of **86** (3.0 g, 11.1 mmol) in THF (20 mL). The phosphate containing solution was cooled to RT and slowly added to the solution of **86**. The resulting mixture was

stirred at RT for 16 h, quenched with a sat. aqueous NH$_4$Cl and extracted three times with Et$_2$O. The organic layers were washed twice with water and brine, dried over Na$_2$SO$_4$ and concentrated to leave **76** (3.51 g, 97%) as a red oil of sufficient purity; 6:1 mixture of keto and enol tautomers, storable at −18 °C for ca. two weeks without decomposition.

R$_f$=0.20 (EtOAc/*c*-hexane 2:3);

Major tautomer (keto): ^{1}H NMR (300 MHz, CDCl$_3$): δ=4.08 (dq, ^3J(H,H)=15.2 Hz, 7.0 Hz, 4H, OCH$_2$), 4.01 (d, ^2J(H,H)=15.1 Hz, 1H, COC*H*^{a}HCO), 3.70 (d, ^2J(H,H)=15.1 Hz, 1H, COCH*H*^{b}CO), 3.42 (dq, ^2J(P,H)=26.1 Hz, ^3J(H,H)=7.0 Hz, 1H, PCH), 1.42 (s, 9H, C(CH$_3$)$_3$), 1.34 (d, ^3J(H,H)=7.0 Hz, 3H, HCC*H*$_3$), 1.32-1.25 (m, 3H; OCH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=197.9 (CO), 192.6 (COS), 100.8 (d, ^3J(P,C)=7.5 Hz, CH$_2$), 62.7 (dd, ^2J(P,C)=11.9 Hz, 6.7 Hz, 2xCH$_2$), 58.1 (OCH$_2$), 48.3 (*C*(CH$_3$)$_3$), 47.1 (d, ^1J(P,C)=125.9 Hz, CH), 16.3 (d, ^3J(P,C)=5.9 Hz, OCH$_2$*C*H$_3$), 10.6 (d, ^2J(P,C)=6.3 Hz, CH$_3$);

^{31}P NMR (120 MHz, CDCl$_3$): δ=22.15;

Minor tautomer (enol): ^{1}H NMR (300 MHz, CDCl$_3$): δ=13.01 (s, 1H, C(O*H*)CHCO), 5.43 (d, ^2J(H,H)=3.0 Hz, 1H, C(OH)C*H*CO), 4.08 (dq, ^3J(H,H)=15.3 Hz, 7.3 Hz, 4H, OCH$_2$), 2.65 (dq, ^2J(P,H)=23.3 Hz, ^3J(H,H)=7.3 Hz, 1H, PCH), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.32-1.25 (m, 3H, OCC*H$_3$*), 1.30 (d, ^3J(H,H)=7.0 Hz, 3H, HCC*H$_3$*);

^{13}C NMR (75 MHz, CDCl$_3$): δ=198.0 (COS), 171.5 (d, ^3J(P,C)=6.9 Hz, C^{enol}), 62.4 (dd, ^2J(P,C)=11.9 Hz, 6.7 Hz, 2xCH$_2$), 58.0 (OCH$_2$), 48.3 (*C*(CH$_3$)$_3$), 38.7 (d, ^1J(P,C)=135.9 Hz, CH), 30.0, 16.3 (d, ^3J(P,C)=5.9 Hz, OCH$_2$*C*H$_3$), 12.5 (d, ^2J(P,C)=5.9 Hz, CH$_3$);

^{31}P NMR (120 MHz, CDCl$_3$): δ=25.18;

IR (thin film): ṽ=2963 (m), 2924 (m), 1722 (m), 1674 (m), 1614 (m), 1456 (m), 1393 (m), 1365 (m), 1313 (m), 1251 (m), 1162 (m), 1017 (s), 960 (s), 836 (m), 789 (m), 688 (m) cm^{-1}; All data in accordance with literature.[56]

VI.2.4. Synthesis of alanine derivatives (89)

N-*t*Butoxycarbonyl-*N*-methyl-L-alanine ((*S*)-**88**)

(*S*)-**87**   (*S*)-**88**
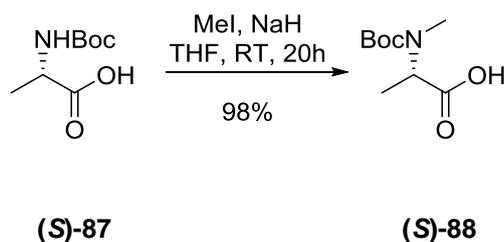
Scheme VI.9. *N*-Methylation procedure of (*S*)-**87**.

A solution of *N-t*butoxycarbonyl-L-alanine (1.43 g, 7.54 mmol) in THF (25 mL) was slowly treated at 0 °C with NaH (60% in mineral oil, 905 mg, 22.61 mmol). After the release of H_2 had ceased CH_3I (3.9 mL, 60.3 mmol) was added, the reaction mixture was stirred at RT for 24 h and then partitioned between H_2O and Et_2O. The organic layer was washed with a little sat. aqueous $NaHCO_3$ and the combined aqueous layers were acidified to pH 3 with 5 M HCl and then extracted twice with EtOAc. The combined organic phases were washed twice with sat. aqueous $Na_2S_2O_3$, dried over Na_2SO_4 and concentrated to leave (*S*)-**88** (1.44 g, 98%) as a clear oil; unspecified 1:1 mixture of rotamers A and B.

^{1}H NMR (300 MHz, CD_3OD): δ=4.67 (q, ^3J(H,H)=6.5 Hz, 1H, CH_3CH^a), 4.38 (q, ^3J(H,H)=6.5 Hz, 1H, CH_3CH^b), 2.84 (s, 6H, NCH_3), 1.44 (s, 18H, $(CH_3)_3$), 1.40 (d, ^3J(H,H)=6.5 Hz, 6H, $HCCH_3$);

^{13}C NMR (75 MHz, CD_3OD): δ=175.4 (CO_2H), 157.6 (C^aON), 157.3 (C^bON), 81.7 (C^aMe_3), 81.4 (C^bMe_3), 56.7 (CH_3C^aH), 54.9 (CH_3C^bH), 32.1 (NC^aH_3), 31.2 (NC^bH_3), 28.6 ($C(CH_3)_3$), 15.5 (CHC^aH_3), 15.1 (CHC^bH_3);

IR (thin film) ṽ=2978 (m), 2939 (m), 1731 (s), 1625 (s), 1488 (s), 1442 (m), 1410 (s), 1398 (s), 1321 (s), 1256 (m), 1207 (s), 1156 (s), 1098 (s), 1052 (m), 995 (m), 867 (s), 853 (s), 821 (m), 779 (s), 764 (s), 744 (m) cm^{-1}; HRMS (ESI) Calcd for $C_9H_{17}NO_4Na$ [M+Na]$^+$ 226.1050, found: 226.1032.

All data in accordance with a product prepared by a different protocol.[156]

(±)-*N-t*Butoxycarbonyl-*N*-methyl-alanine ((*R/S*)-**88**)
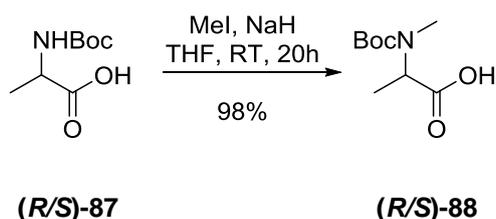
Scheme VI.10. *N*-Methylation procedure of **87**.

Analogously to (*S*)-**88** racemic (*R/S*)-**88** (1.80 g, 99.6%) was obtained as a colourless solid from (±)-*N-t*butoxycarbonylalanine (1.68 g, 8.9 mmol), NaH (1.07 g, 26.7 mmol), and CH_3I (4.6 mL, 71.1 mmol) as unspecified 1:1 mixture of rotamers A and B.

^{1}H NMR (300 MHz, CD_3OD): δ=4.68 (q, *J*=6.9 Hz, 1H, CH_3CH^a), 4.38 (q, *J*=6.8 Hz, 1H, CH_3CH^b), 2.85 (s, 6H, NCH_3), 1.44 (s, 18H, $(CH_3)_3$), 1.40 (d, *J*=7.2 Hz, 6H, $HCCH_3$);

^{13}C NMR (75 MHz, CD$_3$OD): δ=175.4 (CO$_2$H), 157.7 (C^{a}ON), 157.3 (C^{b}ON), 81.7 (C^{a}Me$_3$), 81.4 (C^{b}Me$_3$), 56.7 (CH$_3$C^{a}H), 54.9 (CH$_3$C^{b}H), 32.1 (NC^{a}H$_3$), 31.2 (NC^{b}H$_3$), 28.6 (C(CH$_3$)$_3$), 15.6 (CHC^{a}H$_3$), 15.1 (CHC^{b}H$_3$);

IR (thin film) ṽ=2977 (m), 2940 (m), 1733 (s), 1626 (s), 1489 (s), 1451 (m), 1443 (m), 1407 (s), 1398 (s), 1368 (s), 1321 (s), 1266 (s), 1256 (m), 1209 (s), 1156 (s), 1099 (s), 1050 (m), 996 (m), 867 (s), 854 (s), 821 (m), 780 (s), 767 (s), 745 (m), 663 (s), 564 (s), 541 (m) cm^{-1};

HRMS (ESI) Calcd for C$_9$H$_{17}$NO$_4$Na [M+Na]$^+$ 226.1050, found: 226.1034.

Methyl *N*-methyl-L-alaninate hydrochloride ((*S*)-89)
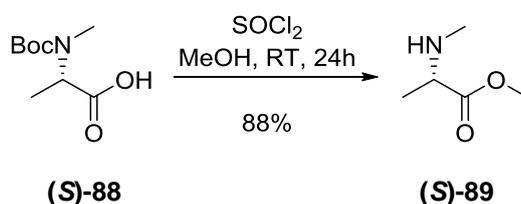
Scheme VI.11. Methyl esterification to form (*S*)-**89**.

A solution of (*S*)-**88** (2.29 g, 11.26 mmol) in CH$_3$OH (50 mL) was treated dropwise with SOCl$_2$ (3.3 mL, 45.1 mmol) and stirred at RT for 24 h. The volatiles were evaporated and residual traces of acid were removed by repeated azeotropic entrainment with toluene. The crude product was recrystallized from Et$_2$O/EtOH to yield a white crystalline hydrochloride of (*S*)-**89** (1.51 g, 88%).

m.p. 92°C;

[α]$_D^{22}$ = 4.0 (*c* = 2.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, D$_2$O): δ=4.13 (q, ^{3}J(H,H)=7.3 Hz, 1H, CH$_3$C*H*), 3.85 (s, 3H, OCH$_3$), 2.77 (s, 3H, NCH$_3$), 1.58 (d, ^{3}J(H,H)=7.3 Hz, 1H; CHC*H*$_3$);

^{13}C NMR (75 MHz, D$_2$O): δ=170.9 (C^q), 57.4 (CH), 53.9 (OMe), 31.7 (NCH$_3$), 14.6 (CH$_3$);

IR (thin film) ṽ=3398 (br) 2950 (m), 2676 (m), 2463 (m), 2434 (m), 2404 (m), 2048 (w), 1744 (s), 1575 (w), 1567 (w), 1465 (m), 1434 (m), 1375 (w), 1350 (m), 1309 (m), 1230 (s), 1203 (m), 1183 (m), 1157 (m), 1100 (s), 1071 (m), 1046 (m), 1011 (m), 966 (m), 906 (m), 875 (m), 836 (w), 817 (m), 753 (m) cm^{-1};

HRMS (ESI) Calcd for C$_5$H$_{12}$O$_2$N [M+H]$^+$ 118.0863, found: 118.0867;

All data in accordance with a product prepared by a different protocol.[158]

(±)-Methyl *N*-methyl-alaninate hydrochloride ((*R/S*)-89)
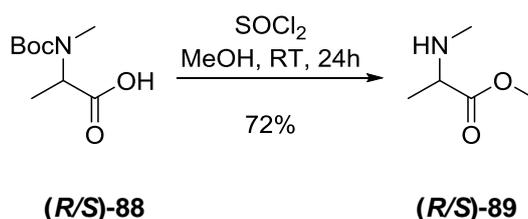
Scheme VI.12. Methyl esterification to form **89**.

Analogously to (*S*)-**89** racemic (*R/S*)-**89** (1.0 g, 74%) was obtained as a transparent oil from (*R/S*)-**88** (1.8 g, 8.86 mmol) and SOCl$_2$ (3 mL, 4.9 g, 41.13 mmol).

^{1}H NMR (300 MHz, CD$_3$OD): δ=9.21 (s, 1H, NH), 4.14 (q, *J*=7.2, 1H, CH$_3$C*H*), 3.86 (s, 3H, OMe), 2.76 (s, 3H, NCH$_3$), 1.59 (d, *J*=7.2 Hz, 1H, CHC*H*$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=170.9 (C^q), 57.4 (CH), 53.9 (OCH$_3$), 31.7 (NCH$_3$), 14.6 (CH$_3$);

IR (thin film) ṽ=3392 (br) 2962 (m), 2699 (m), 2458 (m), 2432 (m), 1743 (s), 1572 (w), 1460 (m), 1439 (m), 1385 (w), 1351 (m), 1308 (m), 1233 (s), 1204 (m), 1104 (s), 1074 (m), 1045 (m), 1013 (m), 976 (m), 875 (m), 834 (w), 754 (m) cm^{-1};

HRMS (ESI) Calcd for C$_5$H$_{12}$O$_2$N [M+H]$^+$ 118.0863, found: 118.0859.

VI.2.5. Synthesis of epicoccamide D ((*5S,7S*)-1) and derivatives

1'-*β*-[16-(*t*Butyldimethylsilyloxy)hexadecyl]-3',4',6'-tri-*O*-benzyl-2-*O*-acetyl-*D*-gluco-pyranoside (90)
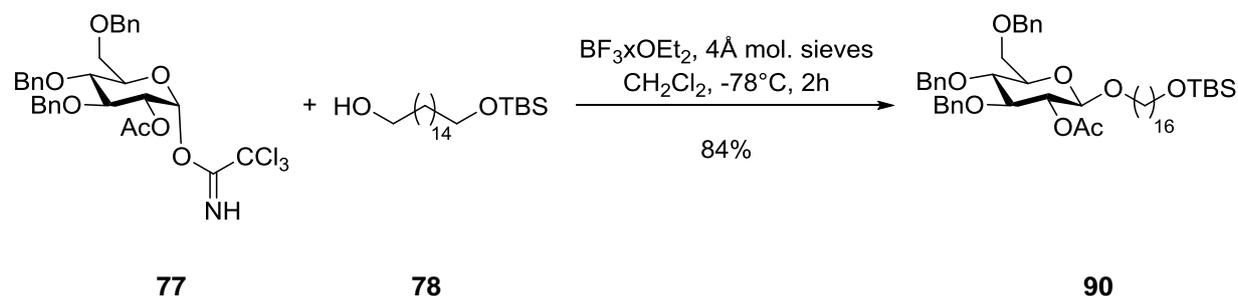
Scheme VI.13. Glycosylation procedure of **77** with **90**.

A mixture of 2 g powdered 4 Å molecular sieves, dried under vacuum at 600 °C for 20 min, alcohol **78** (2.19 g, 5.86 mmol), and CH$_2$Cl$_2$ (70 mL) was treated at RT with imidate **77** (2.2 g, 3.45 mmol), then cooled to -78 °C and treated with BF$_3$•OEt$_2$ (64 µL, 0.52 mmol). Vigorous[312] stirring was continued at -78 °C until completion (tlc control; approx. 2 h). The reaction mixture was filtered over celite, the celite pad was rinsed several times with CH$_2$Cl$_2$

and the combined organic phases were washed with sat. NaHCO$_3$. The aqueous layer was reextracted with CH$_2$Cl$_2$, the organic phases were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude product thus obtained was purified by flash chromatography (flash silica gel; 5% EtOAc in *c*-hexane) yielding 2.45 g of **90** (84%) as a clear oil.

R$_f$=0.85 (EtOAc/*c*-hexane 1:3);

$[\alpha]_D^{25}$ = -1.1 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.39-7.19 (m, 15H, H^{ar}), 5.05-4.96 (m, 1H, 2'-H), 4.80 (d, ^2J(H,H)=10.9 Hz, 2H, 6'O-CH$_2$), 4.68 (d, ^2J(H,H)=11.7 Hz, 1H, 4'O-CH^a), 4.64 (d, ^2J(H,H)=12.1 Hz, 1H, 3'O-CH^a), 4.57 (d, ^2J(H,H)=11.7 Hz, 1H, 4'O-CH^b), 4.56 (d, ^2J(H,H)=12.1 Hz, 1H, 3'O-CH^b), 4.37 (d, ^3J(H,H)=8.0 Hz, 1H, 1'-H), 3.89 (dt, ^3J(H,H)=6.3 Hz, ^2J(H,H)=9.6 Hz, 1H, 1'O-CH^a), 3.78 (dd, ^3J(H,H)=2.3 Hz, ^2J(H,H)=10.9 Hz, 1H, 6'-H^a), 3.75 (dd, ^3J(H,H)=4.6 Hz, 1.4 Hz, 1H, 4'-H), 3.70 (dd, ^3J(H,H)=10.9 Hz, 1.4 Hz, 1H, 5'-H), 3.70 (dd, ^3J(H,H)=4.6 Hz, 1.3 Hz, 1H, 3'-H), 3.63 (t, ^3J(H,H)=6.6 Hz, 2H, CH$_2$OSi), 3.51 (dd, ^3J(H,H)=2.3 Hz, ^2J(H,H)=10.9 Hz, 1H, 6'-H^b), 3.46 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.6 Hz, 1H, 1'O-CH^b), 1.99 (s, 3H, CH$_3$CO), 1.60-1.49 (m, 4H, 2×CH$_2$), 1.35-1.26 (m, 24H, 12×CH$_2$), 0.93 (s, 9H, C(CH$_3$)$_3$), 0.08 (s, 6H, Si(CH$_3$)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=169.6 (CH$_3$*C*O), 138.4 (4'O-C*C*^{ipso}), 138.3 (3'O-C*C*^{ipso}), 138.1 (6'O-C*C*^{ipso}), 128.6 (3×CH^{ar}), 128.5 (2×CH^{ar}), 128.2 (2×CH^{ar}), 128.0 (2×CH^{ar}), 127.9 (4×CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 101.2 (C-1'), 83.2 (C-3'), 78.2 (C-4'), 75.4 (C-5'), 75.2 (3'O-CH$_2$), 75.1 (4'O-CH$_2$), 73.7 (6'O-CH$_2$), 73.4 (C-2'), 69.8 (1'O-CH$_2$), 69.0 (C-6'), 63.5 (CH$_2$OSi), 33.0 (2×CH$_2$), 29.8 (6×CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 27.1 (CH$_2$), 26.15 (CH$_2$), 26.1 (C(*C*H$_3$)$_3$), 26.0 (CH$_2$), 21.0 (*C*H$_3$CO), 18.5 (SiC), -5.1 (Si(*C*H$_3$)$_2$);

IR (thin film): ṽ=2925 (m), 2853 (m), 1751 (m), 1497 (w), 1461 (m), 1454 (m), 1361 (m), 1229 (s), 1147 (m), 1090 (s), 1058 (s), 1028 (m), 1005 (m), 938 (w), 906 (w), 834 (m), 814 (m), 774 (m), 733 (m), 696 (s), 602 (w) cm^{-1};

HRMS (ESI) Calcd for C$_{51}$H$_{78}$O$_8$SiK [M+K]$^+$ 885.5103, found: 885.5081.

1'-*β*-[16-(*t*Butyldimethylsilyloxy)hexadecyl]-3',4',6'-tri-*O*-benzyl-*D*-glucopyranoside (91)
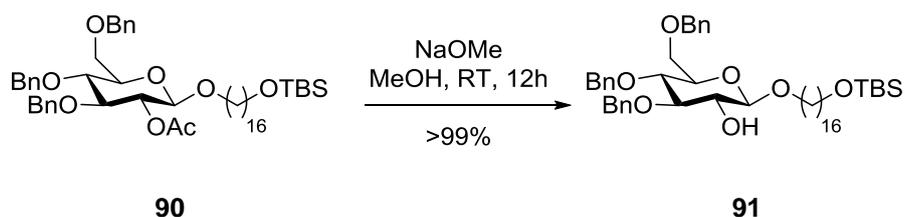
Scheme VI.14. Acetyl deprotection by ester interchange.

A solution of **90** (0.80 g, 0.94 mmol) in MeOH (10 mL) was treated with NaOMe (102 mg, 1.88 mmol) in one portion, stirred until completion of reaction by tlc (approx. 12 h), then quenched with HOAc (81 µL, 1.39 mmol), and finally concentrated in vacuum. The residue was purified by column chromatography (flash silica gel; 5% EtOAc in *c*-hexane) to afford 0.75 g **91** (99.2%) as a clear oil.

R_f=0.76 (EtOAc/*c*-hexane 1:3);

$[\alpha]_D^{25}$ = -3.1 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.43-7.18 (m, 15H, H^{ar}), 4.98 (d, ^2J(H,H)=11.2 Hz, 1H, 4'O-CH^a), 4.87 (d, ^2J(H,H)=10.1 Hz, 2H, 6'O-CH$_2$), 4.65 (d, ^2J(H,H)=12.2 Hz, 1H, 3'O-CH^a), 4.58 (d, ^2J(H,H)=12.2 Hz, 1H, 3'O-CH^b), 4.57 (d, ^2J(H,H)=11.2 Hz, 1H, 4'O-CH^b), 4.28 (d, ^3J(H,H)=7.3 Hz, 1H, 1'-H), 3.95 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.5 Hz, 1H, 1'O-CH^a), 3.78 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.70 (dd, ^3J(H,H)=7.3 Hz, 1.8 Hz, 1H, 2'-H), 3.63 (t, ^3J(H,H)= 6.6 Hz, 2H, CH$_2$OSi), 3.62 (dd, ^3J(H,H)=1.8 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.61 (dd, ^3J(H,H)=7.3 Hz, 1.8 Hz, 1H, 3'-H), 3.55 (dt, ^3J(H,H)=10.8 Hz, 1.8 Hz, 1H, 4'-H), 3.53 (ddd, ^3J(H,H)=10.8 Hz, 2.1 Hz, 1.8 Hz, 1H, 5'-H), 3.51 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.5 Hz, 1H, 1'O-CH^b), 1.67 (m, 2H, CH$_2$), 1.55 (m, 2H, CH$_2$), 1.42-1.27 (m, 24H, CH$_2$), 0.93 (s, 9H, C(CH$_3$)$_3$), 0.09 (s, 6H, Si(CH$_3$)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=138.8 (4'O-CC^{ipso}), 138.3 (3'O-CC^{ipso}), 138.2 (6'O-CC^{ipso}), 128.6 (3xCH^{ar}), 128.5 (2xCH^{ar}), 128.4 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.0 (2xCH^{ar}), 127.9 (CH^{ar}), 127.85 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 102.9 (C-1'), 84.7 (C-3'), 77.7 (C-4'), 75.3 (C-5'), 75.2 (3'O-CH$_2$), 75.1 (4'O-CH$_2$), 74.9 (C-2'), 73.6 (6'O-CH$_2$), 70.3 (C-6'), 69.0 (1'O-CH$_2$), 63.5 (CH$_2$OSi), 33.0 (CH$_2$), 29.8 (10×CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 26.1 (C(CH$_3$)$_3$), 25.9 (CH$_2$), 18.5 (SiC^q), -5.1 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=3481 (br), 2924 (m), 2853 (m), 1497 (w), 1463 (w), 1454 (m), 1360 (m), 1254 (m), 1208 (w), 1098 (s), 1059 (s), 1027 (m), 910 (w), 834 (m), 774 (m), 732 (m), 695 (s), 660 (m), 619 (w), 602 (w), 600 (w) cm^{-1};

HRMS (ESI) Calcd for C$_{49}$H$_{76}$O$_7$SiNa [M+Na]$^+$ 827.5258, found: 827.5235.

16-*O*-(*t*Butyldimethylsilyl)hexadecane-3',4',6'-tri-*O*-benzyl-*β*-D-arabinohexapyranosid-2-ulose (92)
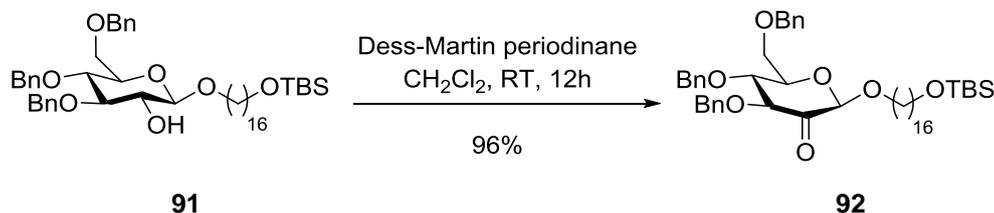
Scheme VI.15. First step of epimerisation reaction by sugar oxidation.

A solution of **91** (0.75 g, 0.93 mmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin periodinane (1.19 g, 2.79 mmol) in one portion. The resulting suspension was stirred under argon for 16 h, then treated with 50% sat. aqueous $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic layers were dried, concentrated, and the remainder was purified by column chromatography (silica gel; 10% EtOAc in *c*-hexane) to afford 714 mg (96%) of **92** as a transparent oil.

R_f=0.49-0.72 (due to formation of hydrates; EtOAc/*c*-hexane 1:3);

$[\alpha]_D^{25}$ = -18.4 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.44-7.17 (m, 15H, H^{ar}), 5.00 (d, ^2J(H,H)=11.4 Hz, 1H, 3'O-CH^a), 4.87 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.79 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.60 (d, ^2J(H,H)=9.4 Hz, 2H, 6'O-CH$_2$), 4.60 (d, ^2J(H,H)=11.4 Hz, 1H, 3'O-CH^b), 4.56 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.24 (d, ^3J(H,H)=7.9 Hz, 1H, 3'-H), 3.91 (dd, ^3J(H,H)=1.7 Hz, ^2J(H,H)=11.0 Hz, Hz, 1H, 6'-H^a), 3.87 (dt, ^3J(H,H)=3.6 Hz, ^2J(H,H)=9.5 Hz, 1H, 1'O-CH^a), 3.77 (dd, ^3J(H,H)=7.9 Hz, 5.0 Hz, 1H, 4'-H), 3.64 (ddd, ^3J(H,H)=11.0 Hz, 5.0 Hz, 1.7 Hz, 1H, 5'-H), 3.61 (t, ^3J(H,H)=6.6 Hz, 2H, CH$_2$OSi), 3.58 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.5 Hz, 1H, 1'O-CH^b), 3.51 (dd, ^3J(H,H)=1.7 Hz, ^2J(H,H)=11.0 Hz, 1H, 6'-H^b), 1.68 (m, 2H, CH$_2$), 1.52 (m, 2H, CH$_2$), 1.39-1.24 (m, 24H, CH$_2$), 0.91 (s, 9H, C(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=197.4 (C-2'), 138.1 (4'O-C*C*^{ipso}), 137.8 (3'O-C*C*^{ipso}), 137.5 (6'O-C*C*^{ipso}), 128.6 (3xCH^{ar}), 128.6 (2xCH^{ar}), 128.5 (CH^{ar}), 128.3 (CH^{ar}), 128.2 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 99.4 (C-1'), 85.7 (C-3'), 80.2 (C-4'), 75.9 (C-5'), 75.0 (4'O-CH$_2$), 73.7 (3'O-CH$_2$), 73.6 (6'O-CH$_2$), 70.0 (C-6'), 69.2 (CH$_2$), 63.5 (CH$_2$OSi), 33.0 (CH$_2$), 29.8 (9×CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 26.1 (C(*C*H$_3$)$_3$), 26.0 (CH$_2$), 25.9 (CH$_2$), 18.5 (SiC^q), -5.1 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=2925 (m), 2854 (m), 1742 (m), 1497 (w), 1462 (m), 1454 (m), 1371 (m), 1360 (m), 1247 (m), 1207 (w), 1145 (w), 1096 (s), 1047 (s), 1027 (s), 938 (w), 910 (w), 834

(s), 774 (m), 733 (m), 696 (s) cm^{-1};

HRMS (ESI) Calcd for $C_{49}H_{74}O_7SiNa$ [M+Na]$^+$ 825.5102, found: 825.5125.

1'-β-[16-(tButyldimethylsilyloxy)hexadecyl]3',4',6'-tri-O-benzyl-D-mannopyranoside (93)
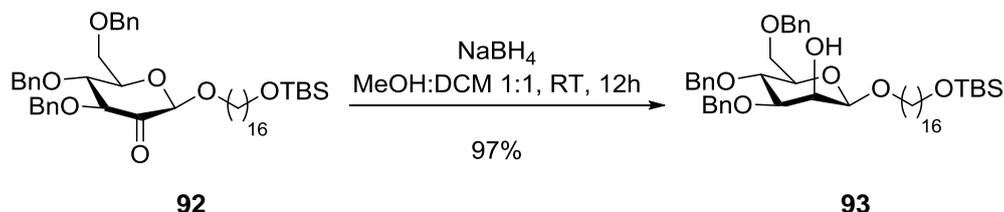
Scheme VI.16. Second step of epimerisation reaction by stereoselective reduction.

A solution of **92** (714 mg, 0.89 mmol) in 10 mL of a 1:1 mixture of CH_2Cl_2 and MeOH was treated with $NaBH_4$ (336 mg, 8.88 mmol) and the resulting mixture was stirred for 12 h and then concentrated. The remainder was submitted to column chromatography (silica gel; 10% EtOAc in c-hexane) to separate 3% of the *gluco*-configured by-product and to afford 688 mg (97%) of pure **93**.

R_f=0.47 (EtOAc/c-hexane 1:3);

$[\alpha]_D^{25}$ = -9.4 (c = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.19 (m, 15H, H^{ar}), 4.89 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.54 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.10 (dd, ^3J(H,H)=3.1 Hz, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=6.7 Hz, ^2J(H,H)=9.4 Hz, 1H, 1'O-CH^a), 3.86 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.78 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.3 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.60 (t, ^3J(H,H)=6.6 Hz, 2H, CH$_2$OSi), 3.57 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.50 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.4 Hz, 1H, 1'O-CH^b), 3.43 (ddd, ^3J(H,H)=10.8 Hz, 5.3 Hz, 2.1 Hz, 1H, 5'-H), 1.68-1.56 (m, 2H, CH$_2$), 1.54-1.45 (m, 2H, CH$_2$), 1.36-1.24 (m, 24H, 12×CH$_2$), 0.90 (s, 9H, C(CH$_3$)$_3$), 0.05 (s, 6H, Si(CH$_3$)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=138.4 (4'O-CC^{ipso}), 138.4 (3'O-CC^{ipso}), 138.0 (6'O-CC^{ipso}), 128.6 (3xCH^{ar}), 128.5 (2xCH^{ar}), 128.4 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.0 (2xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 99.9 (C-1'), 81.8 (C-4'), 75.5 (C-5'), 75.3 (4'O-CH$_2$), 74.5 (C-3'), 73.6 (6'O-CH$_2$), 71.5 (3'O-CH$_2$), 70.0 (1'O-CH$_2$), 69.5 (C-6'), 68.5

(C-2'), 63.5 (CH$_2$OSi), 33.0 (CH$_2$), 29.8 (6×CH$_2$), 29.8 (CH$_2$), 29.8 (2×CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 26.2 (CH$_2$), 26.1 (C(CH$_3$)$_3$), 25.9 (CH$_2$), 18.5 (SiC^q), -5.1 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=3440 (br), 2924 (m), 2853 (m), 1497 (w), 1462 (m), 1454 (m), 1385 (w), 1361 (m), 1313 (w), 1253 (m), 1207 (w), 1097 (s), 1074 (s), 1027 (m), 1006 (m), 939 (w), 909 (w), 834 (s), 812 (w), 774 (m), 732 (s), 695 (s) cm^{-1}.

HRMS (ESI) Calcd for C$_{49}$H$_{76}$O$_7$SiK [M+K]$^+$ 843.4997, found: 843.5018.

16-Hydroxyhexadecyl-3',4',6'-tri-*O*-benzyl-*β*-D-mannopyranoside (94)
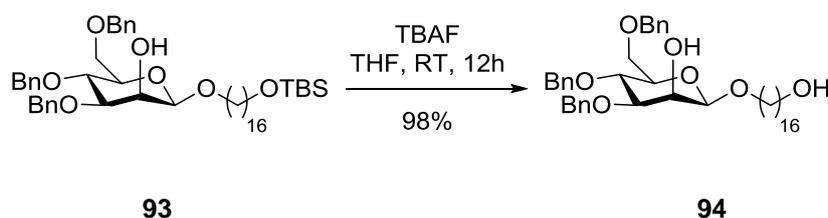
Scheme VI.17. TBS deprotection.

A solution of **93** (550 mg, 0.68 mmol) in dry THF (7 mL) was treated with a 1 M solution of TBAF in THF (1.4 mL, 1.4 mmol) and the resulting mixture was stirred at RT for 12 h, then quenched with sat. aqueous. NaHCO$_3$ and extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with aqueous NaHCO$_3$, dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography (silica gel; 20% EtOAc in *c*-hexane) to leave **94** (457 mg, 95%) as white crystals.

m.p. 63 °C;

R$_f$=0.42 (EtOAc/*c*-hexane 2:3);

[α]$_D^{25}$ = -13.9 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.41-7.19 (m, 15H, H^{ar}), 4.90 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.66 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.62 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.54 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.40 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=3.1 Hz, 0.8 Hz, 1H, 2'-H), 3.94 (dt, ^3J(H,H)=6.6 Hz, ^2J(H,H)=9.2 Hz, 1H, 1'O-CH^a), 3.87 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.78 (dd, ^3J(H,H)=2.2 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.2, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.57 (t, ^3J(H,H)=6.7 Hz, 2H, C*H*$_2$OH), 3.56 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.50 (dt, ^3J(H,H)=6.6 Hz, ^2J(H,H)=9.2 Hz, 1H, 1'O-CH^b), 3.43 (ddd, ^3J(H,H)=9.4 Hz, 5.2 Hz, 2.2 Hz, 1H, 5'-H), 1.69-1.58 (m, 2H, CH$_2$), 1.58-1.49 (m, 2H, CH$_2$), 1.34-1.25 (m, 24H, 12×CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=138.2 (4'O-CC^{ipso}), 138.2 (3'O-CC^{ipso}), 137.9 (6'O-CC^{ipso}), 128.4 (3xCH^{ar}), 128.4 (2xCH^{ar}), 128.3 (2xCH^{ar}), 128.0 (2xCH^{ar}), 127.8 (3xCH^{ar}), 127.7 (CH^{ar}), 127.6 (CH^{ar}), 127.5 (CH^{ar}), 99.8 (C-1'), 81.6 (C-4'), 75.2 (C-5'), 75.1 (4'O-CH$_2$), 74.3 (C-3'), 73.4 (6'O-CH$_2$), 71.2 (3'O-CH$_2$), 69.8 (CH$_2$), 69.2 (C-6'), 68.3 (C-2'), 62.7 (CH$_2$OH), 32.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (13×CH$_2$), 29.5 (CH$_2$), 29.45 (CH$_2$), 29.4 (CH$_2$), 26.0 (CH$_2$), 25.8 (CH$_2$);

IR (thin film) ṽ=3458 (br), 2924 (m), 2853 (m), 1496 (w), 1454 (m), 1368 (m), 1312 (w), 1265 (m), 1242 (w), 1207 (w), 1177 (w), 1099 (s), 1057 (s), 1027 (m), 909 (m), 874 (w), 834 (w), 789 (w), 731 (s), 696 (s) cm^{-1}.

HRMS (ESI) Calcd for C$_{43}$H$_{62}$O$_7$K [M+K]$^+$ 729.4133, found: 729.4118.

16-Oxohexadecyl-3',4',6'-tri-*O*-benzyl-*β-D*-mannopyranoside (75)
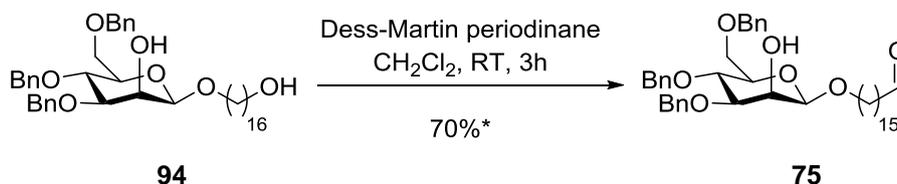
Scheme VI.18. Dess-Martin periodinane mediated selective oxidation to form aldehyde **75**. * 92% based on recovered starting material.

A mixture of alcohol **94** (321 mg, 0.47 mmol), Dess-Martin periodinane (227 mg, 0.54 mmol) and CH$_2$Cl$_2$ (10 mL) at 0 °C was allowed to warm up to RT over 3 h, treated with 50% sat. aqueous NaHCO$_3$ (15 mL) and extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with water, dried over Na$_2$SO$_4$ and concentrated in vacuum. The residue was purified by flash chromatography (flash silica gel; 25% EtOAc in *c*-hexane) to yield **75** (215 mg, 70%) as a transparent oil aside of 69 mg (0.10 mmol, 22%) of recovered alcohol **94**.

R$_f$=0.49 (EtOAc/*c*-hexane 1:2);

[α]$_D^{25}$ = -16.8 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=9.76 (t, ^3J(H,H)=1.9 Hz, 1H, HC=O), 7.42-7.20 (m, 15H, H^{ar}), 4.92 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^a), 4.80 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.68 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.64 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.58 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.56 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^b), 4.43 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 4.13 (dd, ^3J(H,H)=3.1 Hz, 0.9 Hz, 1H, 2'-H), 3.96 (dt, ^3J(H,H)=6.6 Hz, ^2J(H,H)=9.7 Hz, 1H, 1'O-CH^a), 3.89 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.80 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.9 Hz, 1H, 6'-H^a), 3.73 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=10.9 Hz, 1H, 6'-H^b), 3.59 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.52 (dt, ^3J(H,H)=6.6 Hz,

^2J(H,H)=9.7 Hz, 1H, 1'O-CH^b), 3.45 (ddd, ^3J(H,H)=9.4 Hz, 5.2 Hz, 2.1 Hz, 1H, 5'-H), 2.41 (td, ^3J(H,H)=7.3 Hz, 1.9 Hz, 2H, CH$_2$C=O), 1.69-1.55 (m, 4H, 2×CH), 1.39-1.24 (m, 22H, 11×CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=202.9 (C=O), 138.3 (4'O-CC^{ipso}), 138.3 (3'O-CC^{ipso}), 137.9 (6'O-CC^{ipso}), 128.5 (3xCH^{ar}), 128.4 (2xCH^{ar}), 128.3 (2xCH^{ar}), 128.1 (2xCH^{ar}), 127.9 (2xCH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 127.6 (CH^{ar}), 99.8 (C-1'), 81.6 (C-4'), 75.3 (C-5'), 75.2 (4'O-CH$_2$), 74.3 (C-3'), 73.5 (6'O-CH$_2$), 71.3 (3'O-CH$_2$), 69.9 (1'O-CH$_2$), 69.3 (C-6'), 68.4 (C-2'), 43.9 (CC=O), 29.7 (2×CH$_2$), 29.6 (CH$_2$), 29.6 (3×CH$_2$), 29.5 (CH$_2$), 29.4 (2×CH$_2$), 29.2 (CH$_2$), 26.0 (CH$_2$), 22.9 (CH$_2$);

IR (thin film): ṽ=3499 (br), 2923 (m), 2853 (m), 1723 (m), 1496 (w), 1464 (w), 1454 (m), 1366 (m), 1312 (w), 1242 (w), 1207 (w), 1177 (w), 1099 (s), 1072 (s), 1027 (m), 910 (w), 874 (w), 790 (w), 734 (s), 696 (s) cm^{-1};

HRMS (ESI) Calcd for C$_{43}$H$_{60}$O$_7$K [M+K]$^+$ 727.3976, found: 727.3991.

[17-Methyl-18-oxo-19-(*S-t*butylthiocarbonyl)-eicosa-16-enyl]-3',4',6'-tri-*O*-benzyl-*β-D*-mannopyranoside (74)
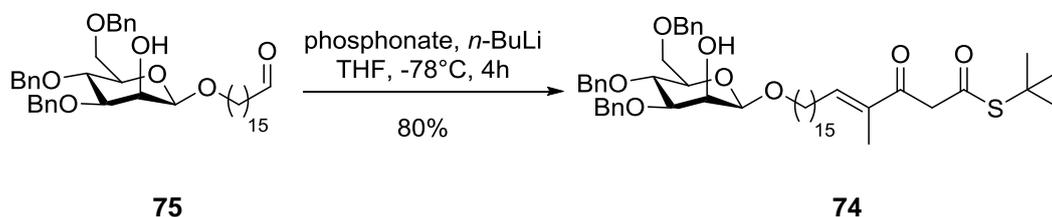
Scheme VI.19. HWE reaction of aldehyde **75** and phosphonate **76**.

A solution of phosphonate **76** (76 mg, 0.234 mmol) in dry THF (3 mL) at -78°C was treated dropwise with a 1.6 M solution of *n*BuLi in hexanes (290 µL, 0.47 mmol) and stirred at -78 °C for 15 min. Aldehyde **75** (115 mg, 0.167 mmol) dissolved in 3 mL THF was added dropwise, the resulting mixture was stirred for 30 min, then warmed up to RT and stirring was continued for a further 3 h. The reaction was quenched with sat. aqueous NH$_4$Cl, extracted three times with Et$_2$O and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography (silica gel; 10% EtOAc in *c*-hexane) affording **74** (114 mg, 80%) as a transparent oil; 3:1:1 mixture of a major keto-*E*-isomer, a minor enol-*E*-isomer (A) and a minor keto-*Z*-isomer (B).

[α]$_D^{25}$ = -14.5 (*c* = 1.0 g cm^{-3}, chloroform);

IR (thin film) $\tilde{v}$=3482 (br), 2923 (s), 2853 (m), 1688 (w), 1660 (m), 1641(m), 1584 (m), 1497 (w), 1454 (m), 1364 (m), 1301 (m), 1208 (m), 1159 (m), 1100 (s), 1064 (s), 1027 (m), 992 (w), 907 (w), 875 (w), 788 (w), 735 (m), 697 (m) cm^{-1};

HRMS (ESI) Calcd for $C_{52}H_{74}O_8SNa$ [M+Na]$^+$ 881.4997, found: 881.5006.

Major *E*-keto-isomer:

R_f=0.72 (EtOAc/*c*-hexane 1:2);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.41-7.19 (m, 15H, H^{ar}), 6.66 (td, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.3 Hz, 1H, 16-H), 4.90 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.54 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=3.1 Hz, 0.9 Hz, 1H, 2'-H), 3.94 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.8 Hz, 1H, 1'O-CH^a), 3.85 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.84 (s, 2H, OCCH$_2$CO), 3.79 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.3 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.57 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.50 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.6 Hz, 1H, 1'O-CH^b), 3.43 (ddd, ^3J(H,H)=9.4 Hz, 5.3 Hz, 2.1, 1H, 5'-H), 2.27 (qui, ^3J(H,H)=6.8 Hz, 2H, 15-H), 1.79 (d, ^4J(H,H)=1.3 Hz, 3H, C*H$_3$*C=C), 1.63 (q, ^3J(H,H)=6.9 Hz, 2H, OCH$_2$C*H$_2$*), 1.47 (s, 9H, *E-t*Bu), 1.37-1.24 (m, 24H; 12×CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.8 (C$_2$*C*=O), 193.4 (COS), 146.3, (H$_3$CC=*C*), 138.4 (4'O-C*C*^{ipso}), 138.3 (3'O-C*C*^{ipso}), 137.9 (6'O-C*C*^{ipso}), 128.6 (3xCH^{ar}), 128.5 (2xCH^{ar}), 128.4 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.0 (2xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.6 (CH^{ar}), 99.8 (C-1'), 81.7 (C-4'), 75.4 (C-5'), 75.3 (4'O-CH$_2$), 74.4 (C-3'), 73.6 (6'O-CH$_2$), 71.4 (3'O-CH$_2$), 69.9 (1'O-CH$_2$), 69.4 (C-6'), 68.5 (C-2'), 54.0 (OC*C*H$_2$CO), 48.9 (*C*Me$_3$), (C(*C*H$_3$)$_3$), 29.8 (CH$_2$), 29.7 (CH$_2$CH$_2$C=C), 29.7, 29.6, 29.5 (8×CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.0 (*C*H$_2$C=CCH$_3$), 28.6 (CH$_2$), 26.1 (*C*H$_2$CH$_2$C=C), 11.4 (*C*H$_3$C=C).

Minor *E*-enol-isomer A:

R_f=0.65 (EtOAc/*c*-hexane 1:2);

^{1}H NMR (300 MHz, CDCl$_3$): δ=13.00 (s, 1H, HC=CO*H* (enol)), 7.41-7.19 (m, 15H, H^{ar}), 6.66 (td, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.3 Hz, 1H, 16-H), 5.49 (s, 1H, *H*C=COH), 4.90 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.54 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=3.1 Hz, 0.9 Hz, 1H, 2'-H), 3.94 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.8 Hz, 1H, 1'O-CH^a), 3.85 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.79 (dd,

^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.3 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.57 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.50 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.6 Hz, 1H, 1'O-CH^b), 3.43 (ddd, ^3J(H,H)=9.4 Hz, 5.3 Hz, 2.1 Hz, 1H, 5'-H), 2.20 (qui, ^3J(H,H)=7.2 Hz, 2H, H$_3$CC=CHCH_2), 1.73 (d, ^4J(H,H)=1.3 Hz, 3H, CH_3C=C), 1.63 (q, ^3J(H,H)=6.9 Hz, 2H, OCH$_2$CH_2), 1.53 (s, 9H, Z-tBu), 1.37-1.24 (m, 24H, 12×CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.8 (C$_2$$C$=O), 193.4 (COS), 146.3, (H$_3$CC=C), 138.4 (4'O-CC^{ipso}), 138.3 (3'O-CC^{ipso}), 137.9 (6'O-CC^{ipso}), 137.1 (H$_3$CC=C), 128.6 (3xCH^{ar}), 128.5 (2xCH^{ar}), 128.4 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.0 (2xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.6 (CH^{ar}), 99.8 (C-1'), 97.4 (HC=COH), 81.7 (C-4'), 75.4 (C-5'), 75.3 (4'O-CH$_2$), 74.4 (C-3'), 73.6 (6'O-CH$_2$), 71.4 (3'O-CH$_2$), 69.9 (1'O-CH$_2$), 69.4 (C-6'), 68.5 (C-2'), 54.0 (OCCH_2CO), 48.3 (CMe$_3$) 30.28 (C(CH_3)$_3$), 29.8 (CH$_2$), 29.7 (CH$_2$$CH_2$C=C), 29.7, 29.6, 29.5 (8×CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.0 (CH_2C=CCH$_3$), 28.6 (CH$_2$), 26.1 (CH_2CH$_2$C=C), 11.4 (CH_3C=C).

Minor Z-keto-isomer B:

R$_f$=0.65 (EtOAc/c-hexane 1:2);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.41-7.19 (m, 15H, H^{ar}), 6.66 (td, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.3 Hz, 1H, 16-H), 4.90 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.54 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=3.1 Hz, 0.9 Hz, 1H, 2'-H), 3.94 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.8 Hz, 1H, 1'O-CH^a), 3.85 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.84 (s, 2H, OCCH$_2$CO), 3.79 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.3 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.57 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.50 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.6 Hz, 1H, 1'O-CH^b), 3.43 (ddd, ^3J(H,H)=9.4 Hz, 5.3 Hz, 2.1 Hz, 1H, 5'-H), 2.27 (qui, ^3J(H,H)=6.8 Hz, 2H, 15-H), 1.73 (d, ^4J(H,H)=1.3 Hz, 3H, CH_3C=C), 1.63 (q, ^3J(H,H)=6.9 Hz, 2H, OCH$_2$CH_2), 1.47 (s, 9H, E-tBu), 1.37-1.24 (m, 24H, 12×CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.8 (C$_2$$C$=O), 193.4 (COS), 138.4 (4'O-CC^{ipso}), 138.3 (3'O-CC^{ipso}), 137.9 (6'O-CC^{ipso}), 138.0 (H$_3$CC=C), 137.1 (H$_3$CC=C), 128.6 (3xCH^{ar}), 128.5 (2xCH^{ar}), 128.4 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.0 (2xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.6 (CH^{ar}), 99.8 (C-1'), 81.7 (C-4'), 75.4 (C-5'), 75.3 (4'O-CH$_2$), 74.4 (C-3'), 73.6 (6'O-CH$_2$), 71.4 (3'O-CH$_2$), 69.9 (1'O-CH$_2$), 69.4 (C-6'), 68.5 (C-2'), 54.0 (OCCH_2CO), 48.9 (CMe$_3$), 29.8 (C(CH_3)$_3$), 29.8 (CH$_2$), 29.7 (CH$_2$$CH_2$C=C), 29.7, 29.6, 29.5 (8×CH$_2$), 29.5

(CH$_2$), 29.4 (CH$_2$), 29.0, 28.8 (*CH$_2$*C=CCH$_3$), 28.6 (CH$_2$), 26.1 (*CH$_2$*CH$_2$C=C), 12.2 (*CH$_3$*C=C).

(22*S*)-[21-Aza-17,21,22-trimethyl-18,20,23-trioxo-pentacosa-16-enyl]-3',4',6'-tri-*O*-benzyl-*β*-D-mannopyranoside ((5*S*)-95)

74   **(2*S*)-95**
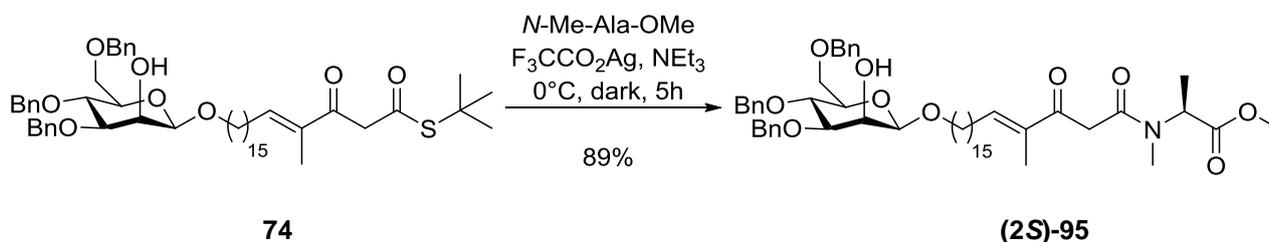
Scheme VI.20. Silver salt mediated aminolysis with (*S*)-**89**.

Under exclusion of moisture and light a solution of **74** (99 mg, 0.115 mmol) in CH$_2$Cl$_2$ (5.5 mL) at 0 °C was treated with amino ester (*S*)-**89** (hydrochloride, 44 mg, 0.289 mmol) in one portion. NEt$_3$ (56 µL, 0.403 mmol) was added dropwise, the reaction was initiated by addition of F$_3$CCO$_2$Ag (51 mg, 0.230 mmol), and the mixture was stirred at 0 °C for 5 h. The silver salt was filtered off, rinsed with CH$_2$Cl$_2$, and the combined filtrates were concentrated under reduced pressure. The crude product was purified by flash chromatography (flash silica gel; 15% EtOAc in *c*-hexane) to leave (5*S*)-**95** (91 mg, 89%) as a clear oil and a 3:1:1 mixture of a major (keto-*E*) isomer, a minor (enol-*E*) isomer (A) and a minor (keto-*Z*) isomer (B).

R$_f$=0.36 / 0.17 (keto and enol isomers; EtOAc/*c*-hexane 1:2);

$[\alpha]_D^{25}$ = -28.6 (*c* = 1.0 g cm^{-3}, chloroform);

IR (thin film) $\tilde{v}$=3490 (br), 2923 (s), 2853 (m), 1781 (m), 1742 (w), 1670 (m), 1645 (m), 1594 (m), 1454 (m), 1437 (w), 1391 (w), 1370 (m), 1315 (m), 1209 (m), 1177 (m), 1101 (s), 1078 (s), 1027 (m), 987 (m), 909 (w), 782 (w), 736 (m), 697 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{53}$H$_{75}$NO$_7$Na [M+Na]$^+$ 908.5283, found: 908.5288.

Major *E*-keto-isomer:

R$_f$=0.36(EtOAc/*c*-hexane 1:2);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.18 (m, 15H, H^{ar}), 6.72 (td, ^4J(H,H)=1.1 Hz, ^3J(H,H)=7.2 Hz, 1H; 8-H), 5.22 (q, ^3J(H,H)=7.3 Hz, 1H; 5-H), 4.89 (d, ^2J(H,H)=10.9 Hz, 1H; 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H; 3'O-CH^b), 4.62 (d, ^2J(H,H)=12.2 Hz, 1H; 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H; 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.9 Hz, 1H; 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.8 Hz, 1H; 1'-H), 4.10 (dd, ^3J(H,H)=3.1 Hz, 0.8 Hz, 1H; 2'-H), 3.93 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.4 Hz, 1H; 23-H^a), 3.85 (t, ^3J(H,H)=9.3 Hz, 1H; 4'-H), 3.84 (s, 2H; 3-H), 3.78 (dd, ^3J(H,H)=2.1 Hz,

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^2J(H,H)=10.8 Hz, 1H; 6'-H^a), 3.73 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=10.8 Hz, 1H; 6'-H^b), 3.71 (s, 3H; OCH$_3$), 3.56 (dd, ^3J(H,H)=9.3 Hz, 3.1 Hz, 1H; 3'-H), 3.49 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=11.0 Hz, 1H; 23-H^b), 3.42 (ddd, ^3J(H,H)=9.3 Hz, 5.2 Hz, 2.1 Hz, 1H; 5'-H), 2.93 (s, 3H; NCH$_3$), 2.25 (q, ^3J(H,H)=7.2 Hz, 2H; 9-H), 1.80 (d, ^4J(H,H)=1.1 Hz, 3H; 7-CH$_3$), 1.62 (qui, ^3J(H,H)=7.1 Hz, 2H; 22-H), 1.44 (m, 2H; 21-H), 1.41 (d, ^3J(H,H)=7.3 Hz, 3H; 5-CH$_3$), 1.36-1.22 (m, 22H; 11×CH$_2$);

^{13}C (75 MHz, CDCl$_3$): δ=207.0 (C-6), 188.6 (C-4), 170.3 (C-2), 148.0 (C-7), 145.9 (C-8), 138.4 (4'O-CC^{ipso}), 138.4 (3'O-CC^{ipso}), 138.0 (6'O-CC^{ipso}), 129.5 (3xCH^{ar}), 129.1 (2xCH^{ar}), 128.6 (2xCH^{ar}), 128.6 (CH^{ar}), 128.5 (CH^{ar}), 128.2 (CH^{ar}), 128.1 (CH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 99.9 (C-1'), 81.7 (C-4'), 75.5 (C-5'), 75.3 (4'O-CH$_2$), 74.5 (C-3'), 73.7 (6'O-CH$_2$), 71.5 (3'O-CH$_2$), 70.0 (C-5), 69.5 (C-6'), 68.5 (C-2'), 52.4 (OCH$_3$), 52.4 (C-5'), 44.8 (C-3), 32.4 (NCH$_3$), 29.9, 29.85 29.8, 29.75, 29.7, 29.65 (10×CH$_2$), 29.6 (C-21), 29.5 (C-9), 28.7 (C-22), 26.2 (C-10), 14.6 (7-CH$_3$), 11.4 (5-CH$_3$).

Minor *E*-enol-isomer A:

R$_f$=0.17 (EtOAc/*c*-hexane 1:2);

^{1}H NMR (300 MHz, CDCl$_3$): δ=13.2 (s, 1H, HC=CO*H*), 7.40-7.18 (m, 15H, H^{ar}), 6.87 (td, ^4J(H,H)=1.1 Hz, ^3J(H,H)=7.2 Hz, 1H, 8-H), 5.22 (q, ^3J(H,H)=7.3 Hz, 1H, 5-H), 4.89 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.62 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.10 (dd, ^3J(H,H)=3.1 Hz, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.4 Hz, 1H, 23-H^a), 3.85 (t, ^3J(H,H)=9.3 Hz, 1H, 4'-H), 3.84 (s, 2H, 3-H), 3.78 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.73 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.71 (s, 3H, OCH$_3$), 3.56 (dd, ^3J(H,H)=9.3 Hz, 3.1 Hz, 1H, 3'-H), 3.49 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=11.0 Hz, 1H, 23-H^b), 3.42 (ddd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=9.3 Hz, 2.1 Hz, 1H, 5'-H), 2.84 (s, 3H, NCH$_3$), 2.25 (q, ^3J(H,H)=7.2 Hz, 2H, 9-H), 1.77 (d, ^4J(H,H)=1.1 Hz, 3H, 7-CH$_3$), 1.62 (qui, ^3J(H,H)=7.1 Hz, 2H, 22-H), 1.44 (m, 2H, 21-H), 1.41 (d, ^3J(H,H)=7.3 Hz, 3H, 5-CH$_3$), 1.36-1.22 (m, 22H, 11×CH$_2$);

^{13}C (75 MHz, CDCl$_3$): δ=207.0 (C-6), 188.6 (C-4), 170.3 (C-2), 148.0 (C-7), 145.9 (C-8), 138.4 (4'O-CC^{ipso}), 138.4 (3'O-CC^{ipso}), 138.0 (6'O-CC^{ipso}), 129.5 (3xCH^{ar}), 129.1 (2xCH^{ar}), 128.6 (2xCH^{ar}), 128.6 (CH^{ar}), 128.5 (CH^{ar}), 128.2 (CH^{ar}), 128.1 (CH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 110.1 (HC=COH), 99.9 (C-1'), 81.7 (C-4'), 75.5 (C-5'), 75.3 (4'O-CH$_2$), 74.5 (C-3'), 73.7 (6'O-CH$_2$), 71.5 (3'O-CH$_2$), 70.0 (C-5), 69.5 (C-6'), 68.5

(C-2'), 52.4 (OCH$_3$), 52.4 (C-5'), 32.4 (NCH$_3$), 29.9, 29.85 29.8, 29.75, 29.7, 29.65 (10×CH$_2$), 29.6 (C-21), 29.5 (C-9), 28.7 (C-22), 26.2 (C-10), 14.6 (7-CH$_3$), 11.4 (5-CH$_3$).

Minor *Z*-keto-isomer B:

R$_f$=0.36(EtOAc/*c*-hexane 1:2);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.18 (m, 15H, H^{ar}), 6.53 (td, ^4J(H,H)=1.1 Hz, ^3J(H,H)=7.2 Hz, 1H, 8-H), 5.22 (q, ^3J(H,H)=7.3 Hz, 1H, 5-H), 4.89 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.62 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.10 (dd, ^3J(H,H)=3.1, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.4, 1H, 23-H^a), 3.85 (t, ^3J(H,H)=9.3 Hz, 1H, 4'-H), 3.84 (s, 2H, 3-H), 3.78 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8, 1H, 6'-H^a), 3.73 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=10.8, 1H, 6'-H^b), 3.71 (s, 3H, OCH$_3$), 3.56 (dd, ^3J(H,H)=9.3, 3.1 Hz, 1H, 3'-H), 3.49 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=11.0, 1H, 23-H^b), 3.42 (ddd, ^3J(H,H)=9.5, 5.2, 2.1 Hz, 1H, 5'-H), 2.93 (s, 3H, NCH$_3$), 2.25 (q, ^3J(H,H)=7.3 Hz, 2H, 9-H), 1.77 (d, ^4J(H,H)=1.1 Hz, 3H, 7-CH$_3$), 1.62 (qui, ^3J(H,H)=7.1 Hz, 2H, 22-H), 1.46 (d, ^3J(H,H)=7.3 Hz, 3H, 5-CH$_3$), 1.44 (m, 2H, 21-H), 1.36-1.22 (m, 22H, 11×CH$_2$);

^{13}C (75 MHz, CDCl$_3$): δ=207.0 (C-6), 188.6 (C-4), 170.3 (C-2), 148.0 (C-7), 147.0 (C-8), 138.4 (4'O-CC^{ipso}), 138.4 (3'O-CC^{ipso}), 138.0 (6'O-CC^{ipso}), 129.5 (3xCH^{ar}), 129.1 (2xCH^{ar}), 128.6 (2xCH^{ar}), 128.6 (CH^{ar}), 128.5 (CH^{ar}), 128.2 (CH^{ar}), 128.1 (CH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 99.9 (C-1'), 81.7 (C-4'), 75.5 (C-5'), 75.3 (4'O-CH$_2$), 74.5 (C-3'), 73.7 (6'O-CH$_2$), 71.5 (3'O-CH$_2$), 70.0 (C-5), 69.5 (C-6'), 68.5 (C-2'), 52.4 (OCH$_3$), 52.4 (C-5'), 44.8 (C-3), 32.4 (NCH$_3$), 29.9, 29.85 29.8, 29.75, 29.7, 29.7 (10×CH$_2$), 29.6 (C-21), 27.6 (C-9), 28.7 (C-22), 26.2 (C-10), 15.5 (7-CH$_3$), 11.4 (5-CH$_3$).

(5*R/S*)-**95**
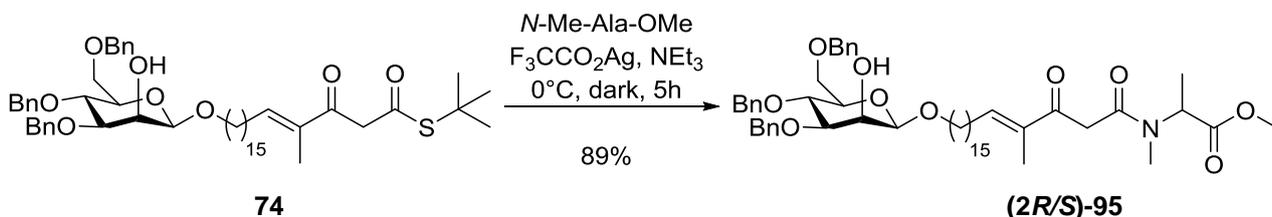
Scheme VI.21. Silver salt mediated aminolysis with (*R/S*)-**89**.

(5*R/S*)-**95** (53 mg, 89%) was obtained analogously to (5*S*)-**95** from **74** (58 mg, 0.063 mmol), *rac*-**89** (25 mg, 0.158 mmol), NEt$_3$ (31 µL, 0.222 mmol), and F$_3$CCO$_2$Ag (28 mg, 0.13 mmol) as a transparent oil.

R_f = 0.47 / 0.26 (EtOAc/c-hexane 1:2), keto:enol 6:1;

$[\alpha]_D^{25}$ = -12.7 (c = 1.0 g cm^{-3}, chloroform);

Only major isomer described:

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.17 (m, 15H, H^{ar}), 6.72 (td, ^4J(H,H)=1.1 Hz, ^3J(H,H)=7.3 Hz, 1H, 8-H), 5.22 (q, ^3J(H,H)=7.3 Hz, 1H, 5-H), 4.89 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^a), 4.77 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.62 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^b), 4.40 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.10 (dd, ^3J(H,H)=3.1 Hz, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=6.7 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^a), 3.85 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.84 (s, 2H, 3-H), 3.78 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=9.4 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.3 Hz, ^2J(H,H)=9.4 Hz, 1H, 6'-H^b), 3.71 (s, 3H, OCH$_3$), 3.56 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.49 (dt, ^3J(H,H)=6.7 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^b), 3.41 (ddd, ^3J(H,H)=9.4 Hz, 5.3 Hz, 2.1 Hz, 1H, 5'-H), 2.93 (s, 3H, NCH$_3$), 2.25 (q, ^3J(H,H)=7.3 Hz, 2H, 9-H), 1.79 (d, ^4J(H,H)=1.1 Hz, 3H, 7-CH$_3$), 1.60 (qui, ^3J(H,H)=6.7 Hz, 2H, 22-H), 1.44 (m, 2H, 21-H), 1.41 (d, ^3J(H,H)=7.3 Hz, 3H, 5-CH$_3$), 1.36-1.22 (m, 22H; 11×CH$_2$);

^{13}C (75 MHz, CDCl$_3$): δ=195.6 (C-6), 172.3 (C-4), 168.9 (C-2), 147.0 (C-7), 145.9 (C-8), 138.4 (4'O-CC^{ipso}), 138.4 (3'O-CC^{ipso}), 138.0 (6'O-CC^{ipso}), 128.6 (3xCH^{ar}), 128.6 (2xCH^{ar}), 128.5 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.0 (CH^{ar}), 129.0 (CH^{ar}), 127.9 (CH^{ar}), 127.7 (CH^{ar}), 99.9 (C-1'), 81.8 (C-4'), 75.4 (C-5'), 75.3 (4'O-CH$_2$), 74.5 (C-3'), 73.7 (6'O-CH$_2$), 71.5 (3'O-CH$_2$), 70.0 (1'O-CH$_2$), 69.4 (C-6'), 68.5 (C-2'), 52.5 (OCH$_3$), 52.4 (C-5), 44.8 (C-3), 32.4 (NCH$_3$), 29.8, 29.7, 29.6 (11×CH$_2$), 29.5 (C-9), 28.7 (C-22), 26.2 (C-10), 14.6 (7-CH$_3$), 11.4 (5-CH$_3$);

IR (thin film) ṽ=2924 (s), 2854 (m), 1743 (m), 1672 (m), 1643 (m), 1599 (w), 1591 (w), 1496 (m), 1454 (w), 1393 (m), 1371 (m), 1319 (m), 1211 (m), 1177 (w), 1101 (s), 1076 (s), 1028 (m), 949 (w), 790 (w), 737 (w), 697 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{53}$H$_{75}$NO$_7$Na [M+Na]$^+$ 908.5283, found: 908.5283.

(5''*S*, 16*E*)-18-(2''-Hydroxy-1'',5''-dimethyl-4''-oxo-4'',5''-dihydro-1''H-pyrrol-3''-yl)-17-methyl-18-oxooctadec-16-enyl 3',4',6'-tri-*O*-benzyl-*β*-D-mannopyranoside ((5*S*)-96)
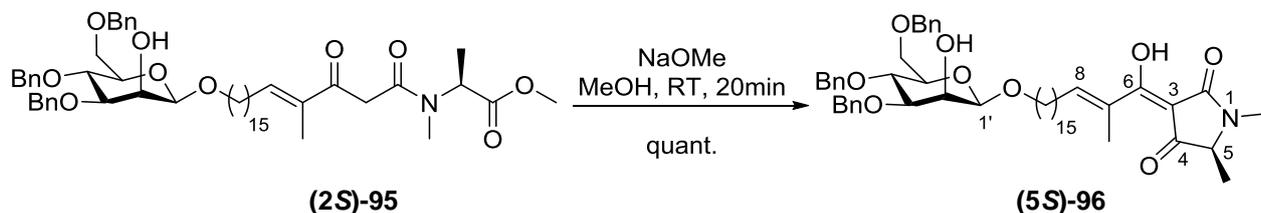
Scheme VI.22. Lacey-Dieckman cyclisation of enantiopure (*S*)-**95**. This scheme also shows the common numbering of 3-acyltetramic acids.

A mixture of (5*S*)-**95** (91 mg, 0.103 mmol), NaOMe (11.1 mg, 0.206 mmol) and dry MeOH (10 mL) was stirred for 20 min at RT, then quenched with 0.5 M aq. HCl. The aqueous phase was extracted five times with CH_2Cl_2, the combined extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure to leave pure (5*S*)-**96** (88 mg, quantitative) as a viscous oil.

R_f=0.51 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{25}$ = -37.7 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.18 (m, 15H, H^{ar}), 7.08 (tq, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.3 Hz, 1H, 8-H), 4.89 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=12.0 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=12.0 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=13.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=13.2 Hz, 1H, 6'O-CH^b), 4.54 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=3.0 Hz, 0.9 Hz, 1H, 2'-H), 3.92 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.4 Hz, 1H, 23-H^a), 3.85 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.78 (dd, ^3J(H,H)=2.0 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.71 (q, ^3J(H,H)=7.0 Hz, 1H, 5-H), 3.57 (dd, ^3J(H,H)=9.4 Hz, 3.0 Hz, 1H, 3'-H), 3.49 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.4 Hz, 1H, 23-H^b), 3.43 (ddd, ^3J(H,H)=9.4 Hz, 5.2 Hz, 2.0 Hz, 1H, 5'-H), 2.99 (s, 3H, NMe), 2.27 (qui, ^3J(H,H)=7.3 Hz, 2H, 9-H), 1.90 (d, ^4J(H,H)=1.3 Hz, 3H, 7-CH$_3$), 1.62 (qui, ^3J(H,H)=6.9 Hz, 2H, 22-H), 1.38-1.22 (m, 24H, 12×CH$_2$), 1.36 (d, ^3J(H,H)=7.0 Hz, 3H, 5-CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=195.1 (C-6), 192.8 (C-4), 184.4 (C-7), 175.0 (C-2), 146.1 (C-8), 138.4 (4'O-C*C*^{ipso}) 138.4 (3'O-C*C*^{ipso}), 138.0 (6'O-C*C*^{ipso}), 129.5 (3xCH^{ar}), 129.1 (2xCH^{ar}), 128.6 (CH^{ar}), 128.5 (CH^{ar}), 128.4 (CH^{ar}), 128.2 (2xCH^{ar}), 128.1 (CH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 128.7 (CH^{ar}), 99.9 (C-1'), 81.7 (C-4'), 75.4 (C-5'), 75.3 (4'-O*C*H$_2$), 74.5 (C-3'), 73.6 (6'-O*C*H$_2$), 71.5 (3'-O*C*H$_2$), 70.0 (C-23), 69.4 (C-6'), 68.5 (C-2'), 62.3 (NMe), 29.8, 29.7, 29.6, (11×CH$_2$), 29.3 (C-21), 28.5 (C-22), 26.7 (C-5), 26.2 (C-9), 15.2 (7-CH$_3$), 12.5 (5-CH$_3$);

IR (thin film) ṽ=3454 (br), 2924 (s), 2853 (m), 1742 (w), 1692 (w), 1646 (m), 1573 (m), 1494 (m), 1454 (m), 1403 (w), 1368 (m), 1313 (w), 1261 (m), 1209 (m), 1177 (w), 1100 (s), 1074 (s), 1027 (m), 931 (w), 872 (w), 794 (m) 735 (m), 697 (s) cm^{-1};

HRMS (ESI) Calcd for $C_{52}H_{71}NO_9Na$ $[M+Na]^+$ 876.5021, found: 876.5010.

(5R/S)-**96**
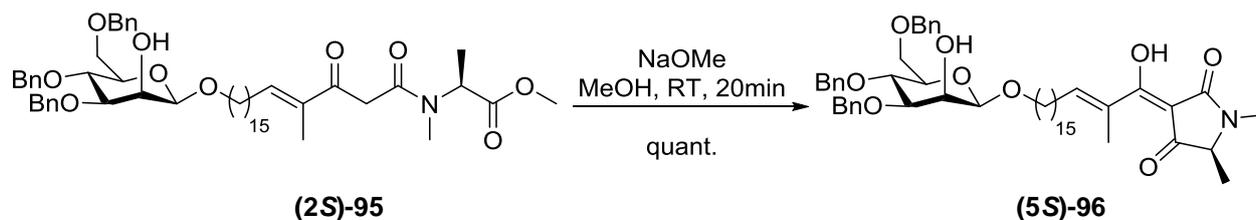
Scheme VI.23. Lacey-Dieckman cyclisation of (R/S)-**95**.

(5R/S)-**96** was obtained analogously to (5S)-**96** from (R/S)-**95** (53 mg, 0.06 mmol) and NaOMe (6.5 mg, 0.12 mmol). It was however stopped by neutralizing with DOWEX 50WX8 ion exchange resin. The resin was washed three times with 10 mL MeOH and the combined extracts were concentrated to leave pure (5R/S)-**96** (51 mg, quantitative).

R_f=0.31 (EtOAc/c-hexane 1:1);

$[\alpha]_D^{25}$ = -10.7 (c = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.18 (m, 15H, H^{ar}), 7.08 (tq, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.2 Hz, 1H, 8-H), 4.89 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.62 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.2 Hz, 1H, 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 4.10 (dd, ^3J(H,H)=3.1 Hz, 0.9 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=7.1 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^a), 3.86 (t, ^3J(H,H)=9.4 Hz, 1H, 4'-H), 3.78 (dd, ^3J(H,H)=2.2 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.71 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.66 (q, ^3J(H,H)=7.1 Hz, 1H, 5-H), 3.56 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.49 (dt, ^3J(H,H)=7.1 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^b), 3.42 (ddd, ^3J(H,H)=9.4 Hz, 5.2 Hz, 2.2 Hz, 1H, 5'-H), 2.99 (s, 3H, NCH$_3$), 2.28 (qui, ^3J(H,H)=7.2 Hz, 2H, 9-H), 1.90 (d, ^4J(H,H)=1.3 Hz, 3H, 7-CH$_3$), 1.62 (qui, ^3J(H,H)=7.1 Hz, 2H, 10-H), 1.51 (qui, ^3J(H,H)=7.1 Hz, 2H, 22-H), 1.38-1.21 (m, 22H, 11×CH$_2$), 1.36 (d, ^3J(H,H)=7.1 Hz, 3H, 5-CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=196.0 (C-6), 192.7 (C-4), 184.2 (C-7), 174.9 (C-2), 146.0 (C-8), 138.3 (4'O-CC^{ipso}) 138.2 (3'O-CC^{ipso}), 137.9 (6'O-CC^{ipso}), 128.5 (3xCH^{ar}), 128.4 (CH^{ar}), 128.3 (2xCH^{ar}), 128.1 (2xCH^{ar}), 127.9 (3xCH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.7

(CH^{ar}), 127.5 (CH^{ar}), 99.7 (C-1'), 81.6 (C-4'), 75.3 (C-5'), 75.2 (4'-OCH$_2$), 74.3 (C-3'), 73.5 (6'-OCH$_2$), 71.3 (3'-OCH$_2$), 69.9 (C-23), 69.3 (C-6'), 68.4 (C-2'), 62.1 (NMe), 29.8, 29.7, 29.6, 29.5 (10×CH$_2$), 29.4 (C-21), 29.2 (C-10), 28.4 (C-22), 26.6 (C-5), 26.0 (C-9), 15.1 (7-CH$_3$), 11.9 (5-CH$_3$);

IR (thin film) $\tilde{v}$=3031 (br), 2923 (s), 2853 (m), 1714 (m), 1702 (m), 1649 (m), 1569 (m), 1496 (w), 1462 (m), 1454 (m), 1405 (w), 1368 (m), 1312 (w), 1260 (w), 1209 (m), 1177 (w), 1103 (s), 1074 (s), 1027 (m), 930 (m), 792 (w) 735 (w), 697 (s) cm^{-1};

HRMS (ESI) Calcd for C$_{52}$H$_{71}$NO$_9$Na [M+Na]$^+$ 876.5021, found: 876.5061.

Difluoroboryl complex ((5*S*)-102)
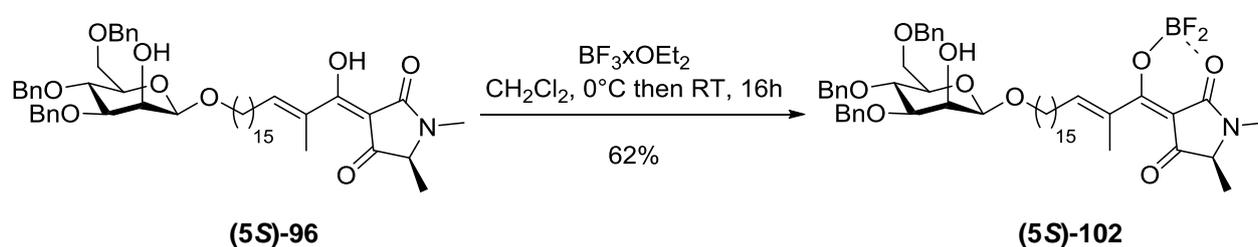
Scheme VI.24. BF$_2$-complex formation to avoid metal chelating of the hydrogenation catalyst later on.

A solution of (5*S*)-**96** (50 mg, 0.059 mmol) in CH$_2$Cl$_2$ (6 mL) was treated dropwise at 0 °C with BF$_3$×OEt$_2$ (9 μL, 0.073 mmol), allowed to warm up to RT, and stirred at this temperature for another 12 h. The solvent was then removed under reduced pressure and the remainder was purified by flash chromatography (flash silica gel; 40% EtOAc in *c*-hexane) yielding 33 mg (62%) of pure (5*S*)-**102**.

R$_f$=0.44 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{25}$ = -10.7 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.56 (tq, ^4J(H,H)=1.4 Hz, ^3J(H,H)=7.3 Hz, 1H, 8-H), 7.37-7.14 (m, 15H, H^{ar}), 4.87 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^a), 4.76 (d, ^2J(H,H)=12.0 Hz, 1H, 3'O-CH^a), 4.65 (d, ^2J(H,H)=12.0 Hz, 1H, 3'O-CH^b), 4.61 (d, ^2J(H,H)=12.3 Hz, 1H, 6'O-CH^a), 4.54 (d, ^2J(H,H)=12.3 Hz, 1H, 6'O-CH^b), 4.51 (d, ^2J(H,H)=10.9 Hz, 1H, 4'O-CH^b), 4.39 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.09 (dd, ^3J(H,H)=3.0 Hz, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.4 Hz, 1H, 23-H^a), 3.86 (dd, ^3J(H,H)=9.1 Hz, 5.4 Hz, 1H, 4'-H), 3.80 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.68 (dd, ^3J(H,H)=5.4 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.64 (q, ^3J(H,H)=7.1 Hz, 1H, 5-H), 3.55 (dd, ^3J(H,H)=9.1 Hz, 3.0 Hz, 1H, 3'-H), 3.47 (dt, ^3J(H,H)=6.9 Hz, ^2J(H,H)=9.4 Hz, 1H, 23-H^b), 3.41 (ddd, ^3J(H,H)=9.1 Hz, 5.4 Hz, 2.1 Hz, 1H, 5'-H), 3.14 (s, 3H, NCH$_3$), 2.28 (q, ^3J(H,H)=7.3 Hz, 2H, 9-H), 1.91 (d, ^4J(H,H)=1.4 Hz, 3H, 7-CH$_3$), 1.59 (qui, ^3J(H,H)=7.3 Hz, 2H, 10-H), 1.50 (qui,

^3J(H,H)=6.9 Hz, 2H, 22-H), 1.43 (d, ^3J(H,H)=7.1 Hz, 3H, 5-CH$_3$), 1.38-1.19 (m, 22H, 11×CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=196.2 (C-6), 189.5 (C-4), 178.1 (C-7), 172.7 (C-2), 151.8 (C-8), 138.6 (4'O-CC^{ipso}) 138.4 (3'O-CC^{ipso}), 138.1 (6'O-CC^{ipso}), 128.7 (3xCH^{ar}), 128.6 (2xCH^{ar}), 128.5 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.05 (3xCH^{ar}), 128.0 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 99.3 (C-1'), 80.5 (C-4'), 75.3 (4'-OCH$_2$), 74.5 (C-5'), 73.6 (6'-OCH$_2$), 72.1 (C-3'), 71.1 (3'-OCH$_2$), 69.1 (C-6'), 68.6 (C-2'), 68.0 (C-23), 64.1 (NMe), 30.0 (C-10), 29.8, 29.7, 29.6, (10×CH$_2$), 29.2 (C-21), 28.9 (C-11), 28.4 (C-22), 28.4 (C-5), 26.3 (C-9); 14.7 (7-CH$_3$), 12.4 (5-CH$_3$);

^{11}B NMR (100 MHz, CH$_2$Cl$_2$ + BF$_3$×OEt$_2$): δ=1.29;

IR (thin film) ṽ=3471 (br), 3031 (w), 2924 (s), 2853 (m), 1748 (w), 1710 (m), 1647 (m), 1582 (m), 1513 (s), 1454 (m), 1395 (w), 1372 (m), 1314 (w), 1262 (w), 1234 (w), 1207 (w), 1096 (m), 1054 (s), 1035 (s), 985 (w), 937 (w), 907 (w), 883 (w), 798 (w), 739 (w), 737 (m), 698 (s), 667 (s) cm^{-1};

HRMS (ESI) Calcd for C$_{52}$H$_{70}$BF$_2$NO$_9$Na [M+Na]$^+$ 924.5009, found: 924.5019.

Difluoroboryl complex ((5S,7S)-103)

(5S)-102   **(5S,7S)-103**
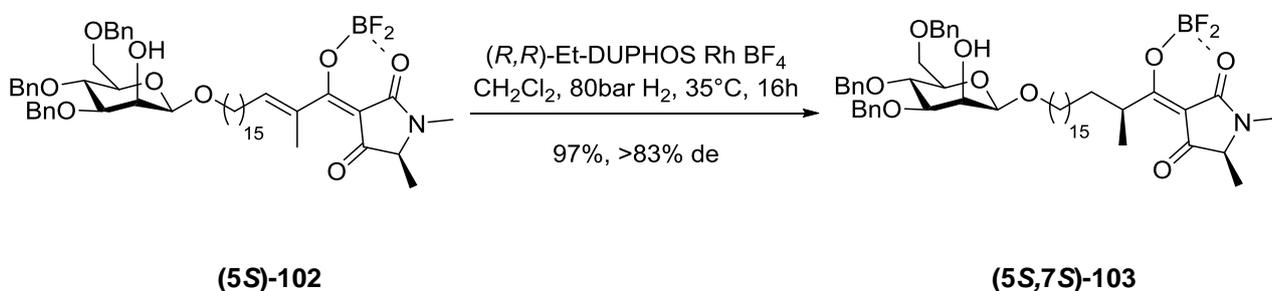
Scheme VI.25. Stereoselective hydrogenation with Rh based Et-DUPHOS catalyst to form the natural product configuration.

A glass vial was charged with complex (5S)-**102** (32 mg, 0.036 mmol), dry CH$_2$Cl$_2$ (3.6 mL), and (R,R)-Rh-Et-DUPHOS BF$_4$ (1 mg, 4 mol%,), and then put into a Parr high pressure autoclave which was sealed, pressurised with 80 bar H$_2$ gas, and heated at 35 °C for 16 h. After removal of all volatiles the crude product was purified by flash column chromatography on silica gel with 40% ethyl acetate in cyclohexane to leave (5S,7S)-**103** (31 mg, 97%; >83% de) as a colourless viscous oil.

R_f = 0.50 (ethyl acetate/cyclohexane 1/1);

[α]$_D^{24}$ = 1.7 (c = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$, 20°C, TMS): δ=7.40-7.15 (m, 15H, H^{ar}), 4.90 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=11.9 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=12.4 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.4, 1H, 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=2.8 Hz, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=7.0 Hz, ^2J(H,H)=9.2 Hz, 1H, 23-H^a), 3.86 (dd, ^3J(H,H)=9.1 Hz, 2.0 Hz, 1H, 4'-H), 3.79 (dd, ^3J(H,H)=2.2 Hz, ^2J(H,H)=11.4 Hz, 1H, 6'-H^a), 3.67 (dd, ^3J(H,H)=5.4 Hz, ^2J(H,H)=11.4 Hz, 1H, 6'-H^b), 3.66 (q, ^3J(H,H)=7.2 Hz, 1H, 5-H), 3.57 (dd, ^3J(H,H)=9.1 Hz, 2.8 Hz, 1H, 3'-H), 3.54 (m, 1H, 7-H), 3.50 (dt, ^3J(H,H)=7.0 Hz, ^2J(H,H)=9.2 Hz, 1H, 23-H^b), 3.43 (ddd, ^3J(H,H)=9.1 Hz, 5.4 Hz, 2.0 Hz, 1H, 5'-H), 3.14 (s, 3H, NMe), 1.66 (qui, ^3J(H,H)=6.9 Hz, 2H, 22-H), 1.45 (d, ^3J(H,H)=7.2 Hz, 3H, 5-CH$_3$), 1.44 (m, 2H, 8-H), 1.32-1.22 (m, 26H, 13×CH$_2$), 1.20 (d, ^3J(H,H)=6.8 Hz, 3H, 7-CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$, 20°C, TMS): δ=193.8 (C-6), 190.7 (C-4), 170.7 (C-2), 138.55 (4'OCC^{ipso}), 138.5 (3'OCC^{ipso}), 138.4 (6'OCC^{ipso}), 128.7 (3xCH^{ar}), 128.6 (2xCH^{ar}), 128.5 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.1 (3xCH^{ar}), 128.0 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 110.1 (C-3), 99.3 (C-1'), 80.5 (C-4'), 75.3 (4'OCH$_2$), 74.5 (C-5'), 73.6 (6'OCH$_2$), 72.1 (C-3'), 71.1 (3'OCH$_2$), 69.1 (C-6'), 68.6 (C-2'), 68.0 (C-23), 37.6 (C-7), 33.8 (NCH$_3$), 29.9, 29.8, 29.7, 29.65, 29.6, (13×CH$_2$), 28.1 (C-5), 27.3 (C-8), 26.3 (C-22); 17.0 (7-CH$_3$), 14.3 (5-CH$_3$);

^{11}B NMR (100 MHz, CH$_2$Cl$_2$, 20°C, BF$_3$×OEt$_2$): δ=0.45;

IR (film) ṽ=3496 (br), 2925 (s), 2853 (m), 1742 (w), 1721 (m), 1649 (s), 1574 (m), 1534 (m), 1456 (m), 1454 (m), 1209 (m), 1098 (s), 1054 (s), 1031 (s), 936 (m), 749 (m), 738 (m), 699 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{52}$H$_{72}$BF$_2$NO$_9$Na [M+Na]$^+$ 926.5166, found: 926.5184.

Difluoroboryl complex ((5S,7R)- 103)
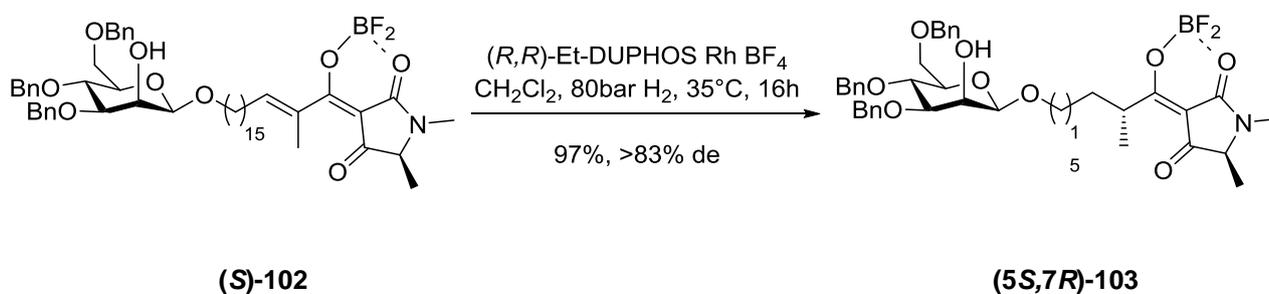
(S)-102 **(5S,7R)-103**

Scheme VI.26. Stereoselective hydrogenation with Rh based Et-DUPHOS catalyst.

Analogously to its (5*S*,7*S*)-diastereomer, (5*S*,7*R*)-**103** (25 mg, 97%) was obtained from hydrogenation of complex (5*S*)-**102** (26 mg, 0.029 mmol) in the presence of (*S*,*S*)-Rh-Et-DUPHOS BF$_4$ (1 mg, 4 mol%).

R$_f$=0.46 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{24}$ = -12.9 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.40-7.18 (m, 15H, H^{ar}), 4.89 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^a), 4.78 (d, ^2J(H,H)=12.0 Hz, 2H, 3'O-CH^a), 4.67 (d, ^2J(H,H)=12.0 Hz, 1H, 3'O-CH^b), 4.63 (d, ^2J(H,H)=12.3 Hz, 1H, 6'O-CH^a), 4.56 (d, ^2J(H,H)=12.3, 1H, 6'O-CH^b), 4.53 (d, ^2J(H,H)=10.8 Hz, 1H, 4'O-CH^b), 4.41 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 4.11 (dd, ^3J(H,H)=3.1 Hz, 0.8 Hz, 1H, 2'-H), 3.93 (dt, ^3J(H,H)=7.0 Hz, ^2J(H,H)=9.2 Hz, 1H, 23-H^a), 3.85 (dd, ^3J(H,H)=9.4 Hz, 5.4 Hz, 1H, 4'-H), 3.78 (dd, ^3J(H,H)=2.1 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^a), 3.67 (dd, ^3J(H,H)=5.4 Hz, ^2J(H,H)=10.8 Hz, 1H, 6'-H^b), 3.66 (q, ^3J(H,H)=7.2 Hz, 1H, 5-H), 3.57 (dd, ^3J(H,H)=9.4 Hz, 3.1 Hz, 1H, 3'-H), 3.54 (m, 1H, 7-H), 3.50 (dt, ^3J(H,H)=7.0 Hz, ^2J(H,H)=9.2 Hz, 1H, 23-H^b), 3.43 (ddd, ^3J(H,H)=9.4 Hz, 5.4 Hz, 2.1 Hz, 1H, 5'-H), 3.15 (s, 3H, NCH$_3$), 1.62 (qui, ^3J(H,H)=7.0 Hz, 2H, 22-H), 1.46 (d, ^3J(H,H)=7.2 Hz, 3H, 5-CH$_3$), 1.44 (m, 2H, 8-H), 1.32-1.22 (m, 26H, 13×CH$_2$), 1.20 (d, ^3J(H,H)=6.8 Hz, 3H, 7-CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.5 (C-6), 190.4 (C-4), 171.1 (C-2), 138.3 (4'O-C*C*^{ipso}) 138.2 (3'O-C*C*^{ipso}), 137.8 (6'O-C*C*^{ipso}), 128.4 (3xCH^{ar}), 128.3 (2xCH^{ar}), 128.2 (2xCH^{ar}), 128.0 (2xCH^{ar}), 127.9 (2xCH^{ar}), 127.8 (CH^{ar}), 127.8 (CH^{ar}), 127.7 (CH^{ar}), 127.5 (15×C^{ar}), 99.7 (C-1'), 81.6 (C-4'), 75.3 (C-5'), 75.1 (4'-OCH$_2$), 74.3 (C-3'), 73.5 (6'-OCH$_2$), 71,3 (3'-OCH$_2$), 69.8 (C-6'), 69.3 (C-23), 68.3 (C-2') 64.8 (NMe), 37.4 (C-7), 34.5 (C-8), 29.6, 29.5, 29.4 (13×CH$_2$), 28.0 (C-5), 27.1 (C-20), 26.0 (C-22), 16.8 (7-CH$_3$), 14.1 (5-CH$_3$);

^{11}B NMR (100 MHz, CH$_2$Cl$_2$): δ=0.38;

IR (thin film) ṽ=3522 (br), 2925 (s), 2854 (m), 1720 (m), 1648 (s), 1569 (m), 1533 (m), 1496 (w), 1454 (m), 1393 (w), 1367 (m), 1232 (m), 1205 (m), 1185 (m), 1175 (m), 1100 (s), 1070 (s), 1058 (s), 1032 (s), 936 (w), 737 (m), 698 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{52}$H$_{72}$BF$_2$NO$_9$Na [M+Na]$^+$ 926.5166, found: 926.5197.

(5*S*,7*S*)-**1d [Epicoccamide D]**
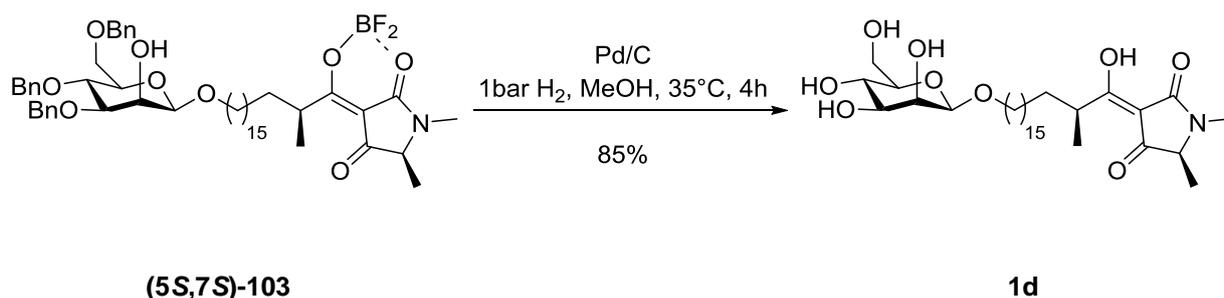
(5*S*,7*S*)-**103**   **1d**

Scheme VI.27. Global deprotection to form the natural product **1d**.

A mixture of (5*S*,7*S*)-**103** (10 mg, 0.011 mmol), 5% Pd on charcoal (10 mg), and dry methanol (2 mL) was saturated and pressurised with 1 bar of hydrogen gas. Stirring was maintained for 4 h at 35 °C. The mixture was filtered, the residue was thoroughly rinsed with methanol and CH_2Cl_2, and the combined filtrates were concentrated in vacuum to leave (5*S*,7*S*)-**1d** (6.9 mg, 97%) as a yellowish oil of ≥95% purity;

$[\alpha]_D^{24}$ = -39.0 (*c* = 0.2 g cm^{-3}, methanol);

^{1}H NMR (300 MHz, CD$_3$OD): δ=4.51 (d, ^3J(H,H)=0.9 Hz, 1H, 1'-H), 3.90 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^a), 3.87 (dd, ^3J(H,H)=2.4 Hz, ^2J(H,H)=12.0 Hz, 1H, 6'-H^a), 3.84 (dd, ^3J(H,H)=3.2 Hz, 0.9 Hz, 1H, 2'-H), 3.76-3.73 (m, 3H, 5-H, 4'-H, 6'-H^b), 3.55-3.53 (m, 2H, 7-H, 23-H^b), 3.45 (dd, ^3J(H,H)=9.4 Hz, 3.2 Hz, 1H, 3'-H), 3.21 (m, 1H, 5'-H), 2.86 (m, 3H, NCH$_3$), 1.62 (m, 4H, 8-H, 22-H), 1.40-1.26 (m, 26H, 13×CH$_2$), 1.32 (m, 3H, 5-CH$_3$), 1.15 (d, ^3J(H,H)=6.2 Hz, 3H, 7-CH$_3$);

^{13}C NMR (75 MHz, CD$_3$OD): δ=193.3 (C-6), 190.6 (C-4), 174.1 (C-2), 101.7 (C-1'), 100.7 (C-3), 78.3 (C-5'), 75.4 (C-3'), 72.6 (C-2'), 70.6 (C-23), 68.6 (C-4'), 68.6 (C-5), 62.9 (C-6'), 37.9 (C-7), 34.7 (NCH$_3$), 30.8, 30.7, 30.6, 30.5, 30.4 (12×CH$_2$), 28.3 (C-8), 27.2 (C-22), 23.7 (C-10), 17.4 (7-CH$_3$), 15.1 (5-CH$_3$);

IR (film) ṽ=3340 (br), 2921 (s), 2851 (s), 1740 (w), 1728 (m), 1710 (m), 1680 (m), 1647 (m), 1619 (s), 1466 (s), 1377 (m), 1365 (m), 1258 (m), 1203 (m), 1187 (m), 1173 (m), 1072 (s), 1032 (s), 925 (m), 798 (m), 722 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{31}$H$_{55}$NO$_9$Na [M+Na]$^+$ 608.3769, found: 608.3777.

(5*S*,7*R*)-**1e**
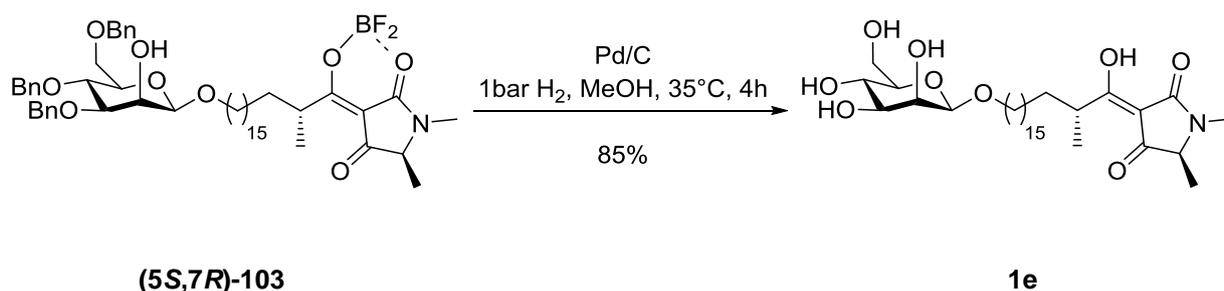
(5*S*,7*R*)-103   **1e**

Scheme VI.28. Global deprotection to form epicoccamide D derivative **1e**.

Analogously to its (5*S*,7*S*)-diastereomer, (5*S*,7*R*)-**1e** (22 mg, 85%) was obtained as a red oil of ≥ 97% purity as to HPLC. The product was formed from hydrogenation of (5*S*,7*R*)-**103** (39 mg, 0.043 mmol) in the presence of 40 mg of 5% Pd on charcoal catalyst in dry MeOH (5 mL); conditions, however, were: 1 bar H_2, stirring for 4 h at 35 °C.

$[\alpha]_D^{24}$ = -29.9 (*c* = 0.2 g cm^{-3}, methanol);

^{1}H NMR (300 MHz, CD$_3$OD): δ=4.49 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 3.91 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^a), 3.88 (dd, ^3J(H,H)=2.4 Hz, ^2J(H,H)=12.0 Hz, 1H, 6'-H^a), 3.84 (dd, ^3J(H,H)=3.2 Hz, 0.8 Hz, 1H, 2'-H), 3.71 (m, 3H, 5-H, 4'-H, 6'-H^b), 3.54 (m, 2H, 7-H, 23-H^b), 3.44 (dd, ^3J(H,H)=9.5 Hz, 3.2 Hz, 1H, 3'-H), 3.20 (ddd, ^3J(H,H)=9.5 Hz, 5.7 Hz, 2.4 Hz, 1H, 5'-H), 2.96 (s, 3H, NCH$_3$), 1.61 (m, 4H, 8-H, 22-H), 1.35-1.26 (m, 26H, 13×CH$_2$), 1.33 (d, ^3J(H,H)=7.0 Hz, 3H, 5-CH$_3$), 1.17 (d, ^3J(H,H)=6.9 Hz, 1H, 7-CH$_3$);

^{13}C NMR (75 MHz, CD$_3$OD): δ=193.3 (C-6), 190.6 (C-4), 174.4 (C-2), 101.7 (C-1'), 100.1 (C-3), 78.3 (C-5'), 75.4 (C-3'), 72.6 (C-2'), 70.6 (C-23), 68.6 (C-4'), 62.9 (C-5), 62.8 (C-6') 37.0 (C-7), 34.8 (NMe), 30.8, 30.7, 30.6 (12×CH$_2$), 28.3 (C-8), 27.2 (C-22), 26.5 (C-10), 17.5 (7-CH$_3$), 15.1 (5-CH$_3$);

IR (thin film) ṽ=3356 (br), 2922 (s), 2852 (m), 1740 (w), 1710 (m), 1690 (m), 1649 (m), 1615 (s), 1486 (w), 1460 (m), 1453 (m), 1399 (m), 1371 (m), 1343 (m), 1312 (m), 1266 (m), 1237 (m), 1173 (m), 1067 (s), 1027 (s), 926 (m), 879 (m), 797 (m), 733 (m), 723 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{31}$H$_{55}$NO$_9$Na [M+Na]$^+$ 608.3769, found: 608.3768.

(5*R/S,7R/S*)-**1f**

(5*R/S*,7*R/S*)-103   **1f**
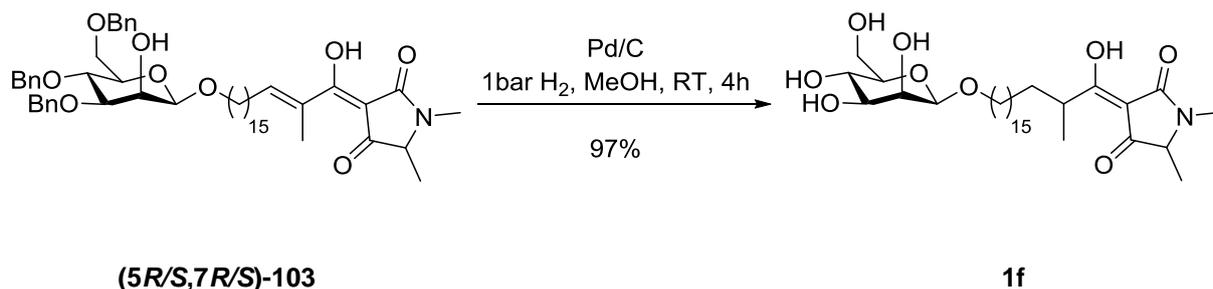
Scheme VI.29. Global deprotection to form racemic epicoccamide D derivative **1f**.

A mixture of (5*R/S*)-**96** (51 mg, 0.06 mmol), 5% Pd on charcoal catalyst (60 mg) and dry MeOH (6 mL) was saturated and pressurised with ca. 1 bar H_2, stirred for 4 h, then filtered, the residue was thoroughly rinsed with MeOH and CH_2Cl_2 and the combined filtrates were concentrated to leave a mixture of diastereomers of **1** (34 mg, 97%) as a viscous yellow oil of ≥98% purity as to HPLC.

$[\alpha]_D^{24}$ = -10.7 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (500 MHz, CD$_3$OD): δ=4.50 (d, ^3J(H,H)=0.8 Hz, 1H, 1'-H), 3.91 (dt, ^3J(H,H)=6.8 Hz, ^2J(H,H)=9.7 Hz, 1H, 23-H^a), 3.87 (dd, ^3J(H,H)=2.4 Hz, ^2J(H,H)=12.0 Hz, 1H, 6'-H^a), 3.84 (dd, ^3J(H,H)=3.2 Hz, 0.8 Hz, 1H, 2'-H), 3.72 (m, 3H, 5-H, 4'-H, 6'-H^b), 3.54 (m, 2H, 7-H, 23-H^b), 3.44 (dd, ^3J(H,H)=9.5 Hz, 3.2 Hz, 1H, 3'-H), 3.20 (ddd, ^3J(H,H)=9.5 Hz, 5.5 Hz, 2.4 Hz, 1H, 5'-H), 3.03 (s, 3H, NCH$_3$), 1.61 (m, 4H, 8-H, 22-H), 1.40-1.26 (m, 26H, 13×CH$_2$), 1.32 (d, ^3J(H,H)=6.5 Hz, 3H, 5-CH$_3$), 1.14 (d, ^3J(H,H)=6.2 Hz, 0.5H, 7-CH$_3$ of diastereomer A) / 1.05 (d, ^3J(H,H)=6.9 Hz, 0.5H, 7-CH$_3$ of diastereomer B);

^{13}C NMR (125 MHz, CD$_3$OD): δ=193.5 (C-6), 190.7 (C-4), 174.2 (C-2), 106.0 (C-1'),101.7 (C-3), 78.2 (C-5'), 75.3 (C-3'), 72.6 (C-2'), 70.7 (C-23), 68.6 (C-4'), 64.2 (C-5), 62.8 (C-6'), 36.5 (C-7), 33.1 (NMe), 30.8, 30.6, (12×CH$_2$), 28.0 (C-8), 27.2 (C-22), 23.7 (C-10), 19.3 (7-CH$_3$), 14.4 (5-CH$_3$);

IR (thin film) ṽ=3418 (br), 2953 (m), 2924 (s), 2853 (m), 1774 (w), 1733 (m), 1649 (w), 1579 (w), 1542 (w), 1522 (w), 1496 (w), 1464 (m), 1457 (m), 1411 (m), 1379 (m), 1353 (w), 1284 (m), 1270 (m), 1121 (s), 1074 (s), 953 (w), 941 (w) cm^{-1};

HRMS (ESI) Calcd for C$_{31}$H$_{55}$NO$_9$Na [M+Na]$^+$ 608.3769, found: 608.3774.

VI.2.6. Synthesis of model compounds

Route A: From 3-acylation[205] of (S)-**105** with (S)-**104**

Difluoroboryl complex ((5S,7S)-100)

Scheme VI.30. Synthesis of model compound: Via 3-acylation (protocol by Yoda *et al.*)[205].

A solution of (2S)-methyloctanoic acid **104**[30] (62 mg, 0.39 mmol) and tetramic acid (5S)-**105**[30] (50 mg, 0.39 mmol) in CH_2Cl_2 (6 mL) was treated with EDCI (91 mg, 0.47 mmol) and DMAP (95 mg, 0.79 mmol) and stirred for 1 h at RT before further EDCI (60 mg, 0.31 mmol) was added and stirring was continued for another hour. After addition of sat. aqueous NH_4Cl the crude 4-*O*-acyl tetramic acid was extracted three times with EtOAc. The combined organic extracts were washed twice with sat. aqueous NH_4Cl and brine, dried over Na_2SO_4 and concentrated.

The crude product thus obtained was dissolved in CH_2Cl_2 (4.5 mL) and treated with $CaCl_2$ (66 mg, 0.59 mmol), DMAP (14 mg, 0.12 mmol), and NEt_3 (66 μL, 0.47 mmol). The resulting suspension was stirred for 90 min at RT, diluted with EtOAc, acidified with 1 M aqueous HCl (5 mL), and extracted three times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated.

The crude material obtained was dissolved in CH_2Cl_2 (4 mL), treated with $BF_3 \times OEt_2$ (243 μL, 1.97 mmol), stirred for 16 h at RT, and concentrated by removal of all volatiles. Purification by column chromatography (silica gel; 40% EtOAc in *c*-hexane) furnished the desired BF_2-complex (5S,7S)-**100** (64 mg, 52% over 3 steps).

R$_f$=0.55 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{24}$ = -75.7 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=3.91 (q, ^3J(H,H)=7.1 Hz, 1H, 7-H), 3.53 (q, ^3J(H,H)=6.8 Hz, 1H, 5-CH), 3.16 (s, 3H, NCH$_3$), 1.81-1.65 (m, 1H, 8-H^a), 1.54-1.44 (m, 1H, 8-H^b), 1.46 (d, ^3J(H,H)=7.1 Hz, 3H, 7-CH$_3$), 1.25 (m, 8H, 4×CH$_2$), 1.19 (d, ^3J(H,H)=6.8 Hz, 3H, 5-CH$_3$), 0.89 (m, 3H, CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.7 (C-4), 190.6 (C-6), 171.3 (C-2), 98.2 (C-3), 65.0 (C-5), 37.6 (NMe), 33.8 (C-8), 31.7 (C-11), 29.3 (C-9), 28.1 (C-7), 27.2 (C-10), 22.7 (C-12), 16.9 (5-CH$_3$), 14.3 (7-CH$_3$), 14.2 (CH$_3$);

IR (thin film) ṽ=2956 (w), 2927 (m), 2857 (w), 1720 (m), 1644 (s), 1566 (m), 1530 (s), 1453 (m), 1417 (w), 1394 (m), 1375 (m), 1355 (m), 1270 (m), 1232 (m), 1183 (m), 1119 (m), 1074 (m), 1024 (s), 935 (m), 885 (m), 858 (m), 798 (m), 782 (m), 725 (s), 707 (m), 663 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{15}$H$_{24}$BF$_2$NO$_3$Na [M+Na]$^+$ 338.1710, found: 338.1712.

Route B: From hydrogenation of (5S)-**22** with (R,R)-Rh-Et-DUPHOS BF$_4$

S-tButyl 4-methyl-3-oxodec-4-enethioate (98)

Scheme VI.31. Synthesis of model compound via epicoccamide route: HWE olefination

A solution of phosphonate **76** (480 mg, 1.51 mmol,) dry THF (15 mL) was cooled to -78 °C, treated slowly via a syringe with nBuLi (1.9 mL, 1.6 M in hexanes, 3.02 mmol), stirred at -78 °C for 15 min, and finally treated slowly with hexanal (130 μL, 1.08 mmol) dissolved in 3 mL THF. This mixture was stirred for 30 min at -78 °C and 1 h at RT before being quenched with sat. aqueous NH$_4$Cl and extracted three times with Et$_2$O. The combined extracts were dried over Na$_2$SO$_4$, concentrated and purified by chromatography (silica gel; 5% EtOAc in c-hexane) yielding **98** (250 mg, 87%) as a red oil. 3:1:1 mixture of keto-E, enol-E, and keto-Z isomers.

Data only for the major keto-E isomer:

R$_f$=0.62-0.86 (EtOAc/c-hexane 1:19);

^{1}H NMR (300 MHz, CDCl$_3$): δ=6.64 (td, ^4J(H,H)=1.3 Hz, ^3J(H,H)=6.6 Hz, 1H, 5-H), 3.02 (s, 2H, 2-H), 2.24 (q, ^3J(H,H)=6.6, 2H, 6-H), 1.77 (d, ^4J(H,H)=1.3, 3H, 4-CH$_3$), 1.47 (m, 10H, CH$_2$), 0.88 (m, 3H, CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.7 (C-3), 193.4 (C-1), 146.2 (C-5), 137.2 (C-4), 54.0 (C-2), 48.3 ((CH$_3$)$_3$), 31.7 (C-6), 30.3 (CMe$_3$), 29.4 (C-8), 28.7 (C-9), 22.6 (C-7), 14.1 (CH$_3$), 11.4 (4-CH$_3$);

IR (thin film) ṽ=2959 (w), 2926 (m), 2859 (w), 1690 (m), 1661 (s), 1640 (s), 1582 (m), 1455 (m), 1389 (w), 1375 (w), 1364 (w), 1351 (w), 1324 (w), 1294 (w), 1248 (w), 1161 (m), 1099 (m), 1061 (s), 988 (m), 906 (m), 887 (m), 833 (m), 770 (s) cm^{-1}.

Corresponding amide (99)
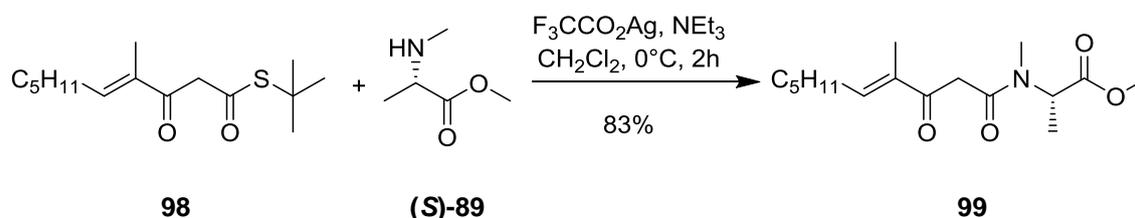
Scheme VI.32. Synthesis of model compound via epicoccamide route: Aminolysis

Analogously to (5S)-**95**, amide (S)-**99** (223 mg, 83%) was obtained from **98** (248 mg, 0.92 mmol), (S)-**89** (350 mg, 2.29 mmol), NEt$_3$ (0.5 mL, 3.67 mmol), and F$_3$CCO$_2$Ag (405 mg, 1.83 mmol); 3:1:1 mixture of keto-E, enol-E, and keto-Z isomers.

Data only for the major keto-E isomer:

R$_f$=0.53 (EtOAc/c-hexane 1:1);

$[\alpha]_D^{24}$ = -102.2 (c = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$; numbering scheme as for **95** (in Scheme VI.20.): δ=6.70 (td, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.3 Hz, 1H, 8-H), 5.22 (q, ^3J(H,H)=7.3 Hz, 1H, 5-H), 3.84 (s, 2H, 3-H), 3.68 (s, 3H, OCH$_3$), 2.91 (s, 3H, NCH$_3$), 2.22 (q, ^3J(H,H)=7.3 Hz, 2H, 9-H), 1.77 (d, ^4J(H,H)=1.3 Hz, 3H, 7-CH$_3$), 1.39 (d, ^3J(H,H)=7.3 Hz, 3H, 5-CH$_3$), 1.48-1.25 (m, 6H, 3×CH$_2$), 0.90 (m, 3H, CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=195.1 (C-6), 172.2 (C-4), 168.3 (C-2), 145.8 (C-7), 136.9 (C-5), 135.8 (C-6), 52.4 (C-5), 52.3 (OCH$_3$), 44.8 (C-3), 32.4 (C-8), 31.7 (NCH$_3$), 29.4 (C-10), 28.8 (C-12), 28.6 (C-13), 28.3 (C-11), 22.5 (C-9), 14.5 (7-CH$_3$), 11.4 (C-14);

IR (thin film) ṽ=2956 (w), 2928 (m), 2859 (w), 1742 (m), 1672 (m), 1643 (s), 1592 (m), 1548 (s), 1456 (m), 1443 (w), 1394 (w), 1373 (w), 1325 (w), 1211 (m), 1175 (m), 1083 (m), 1044 (s), 982 (m), 949 (m), 851 (m), 881 (m), 725 (s) cm^{-1}.

(5*S*)-3-((2′*E*)-1′-Hydroxy-2′-methylocten-1′-ylidene)-1,5-dimethylpyrrolidine-2,4-dione (97)
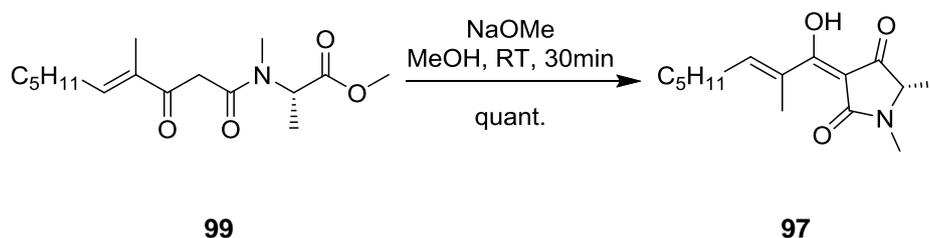
Scheme VI.33. Synthesis of model compound via epicoccamide route: Lacey-Dieckmann cyclisation

Analogously to **96**, tetramic acid (5*S*)-**97** (196 mg, quantitative) was obtained from amide **99** (220 mg, 0.74 mmol) and NaOMe (80 mg, 1.48 mmol) as a colourless oil which was submitted to complexation without further purification.

R_f=0.22 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{24}$ = -73.0 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.07 (tq, ^4J(H,H)=1.2 Hz, ^3J(H,H)=7.3 Hz, 1H, 8-H), 3.72-3.61 (m, 1H, 5-H), 2.96 (s, 3H, NCH$_3$), 2.26 (dq, ^4J(H,H)=1.2 Hz, ^3J(H,H)=7.3 Hz, 2H, 9-H), 1.89 (d, ^4J(H,H)=1.2 Hz, 3H, 7-CH$_3$), 1.49 (m, 2H, CH$_2$), 1.34 (d, ^3J(H,H)=7.0, 3H, 5-CH$_3$), 1.34-1.29 (m, 6H, 3×CH$_2$), 0.89 (m, 3H, CH$_3$);

^{13}C NMR (70 MHz, CDCl$_3$): δ=192.9 (C-4), 184.4 (C-6), 175.0 (C-2), 146.1 (C-8), 129.0 (C-7), 110.1 (C-3), 62.3 (C-5), 31.8 (NMe), 29.3 (C-11), 28.2 (C-9), 26.7 (C-10), 22.6 (C-12), 15.3 (5-CH$_3$); 14.2 (CH$_3$), 12.5 (7-CH$_3$);

IR (thin film) ṽ=2956 (w), 2928 (m), 2859 (w), 1716 (m), 1651 (s), 1607 (m), 1571 (s), 1464 (m), 1440 (w), 1384 (w), 1346 (w), 1311 (w), 1270 (w), 1259 (m), 1212 (m), 1161 (m), 1103 (m), 1078 (m), 1068 (s), 990 (m), 963 (m), 924 (m), 879 (m), 791 (w), 729 (s), 709 (m), 673 (m) cm^{-1}.

Difluoroboryl complex ((5*S*)-**100**)
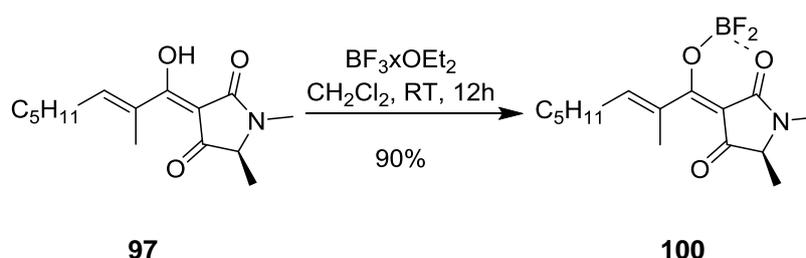
Scheme VI.34. Synthesis of model compound via epicoccamide route: Formation of corresponding BF$_2$ complex.

Analogously to (5*S*)-**102**, complex (5*S*)-**100** (202 mg, 90%) was obtained from **97** (190 mg, 0.72 mmol) and $BF_3 \times OEt_2$ (508 µL, 3.58 mmol).

R_f=0.58 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{24} = -10.4$ (c=1.0, CHCl₃);

¹H NMR (300 MHz, CDCl₃): δ=7.54 (tq, ⁴*J*(H,H)=1.3 Hz, ³*J*(H,H)=7.2 Hz, 1H, 8-H), 3.88 (q, ³*J*(H,H)=7.2 Hz, 1H, 5-H), 3.16 (s, 3H, NCH₃), 2.33 (dq, ³*J*(H,H)=7.2 Hz, 1.3 Hz, 2H, 9-H), 1.91 (d, ⁴*J*(H,H)=1.3 Hz, 3H, 7-CH₃), 1.52 (m, 2H, CH₂), 1.45 (d, ³*J*(H,H)=7.2, 3H, 5-CH₃), 1.33 (m, 4H, 2×CH₂), 0.89 (m, 3H; CH₃);

¹³C NMR (70 MHz, CDCl₃): δ=197.4 (C-6), 189.5 (C-4), 172.4 (C-2), 151.7 (C-8), 130.1 (C-7), 96.5 (C-3), 64.1 (C-5), 31.7 (NMe), 29.9 (C-11), 28.3 (C-10), 28.0 (C-9), 22.6, (C-12), 14.6 (5-CH₃), 14.1 (7-CH₃), 12.3 (CH₃);

IR (thin film) ṽ=2956, 2931, 2859, 1709, 1645, 1583, 1504, 1472, 1452, 1416, 1373, 1262, 1234, 11175, 1057, 1024, 937, 867, 874, 785, 730, 699, 655, 632 cm⁻¹.

Difluoroboryl complex ((5*S*,7*S*)-101)
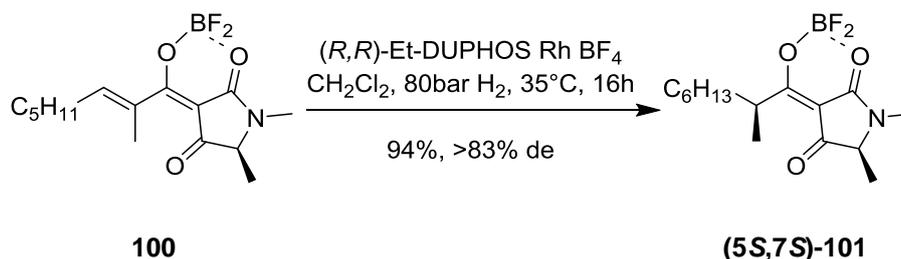
Scheme VI.35. Synthesis of model compound via epicoccamide route: Stereoselective hydrogenation to form the natural product configuration.

A mixture of freshly prepared (5*S*)-**100** (85 mg, 0.27 mmol), dry CH₂Cl₂ (8 mL), and (*R*,*R*)-Rh-Et-DUPHOS BF₄ (7 mg, 0.01 mmol) was placed in a Parr high pressure autoclave which was sealed, pressurised with 80 bar H₂ and heated to 35 °C for 16 h. After filtration through a plug of silica and removal of the volatiles (5S)-**101** (80 mg, 94%) was obtained as a colourless oil.

R_f=0.55 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{24} = -68.9$ (*c* = 1.0 g cm⁻³, chloroform);

¹H NMR (300 MHz, CDCl₃): δ=3.90 (q, ³*J*(H,H)=7.1 Hz, 1H, 7-H), 3.52 (q, ³*J*(H,H)=6.8 Hz, 1H, 5-H), 3.16 (s, 3H, NCH₃), 1.75-1.64 (m, 1H, 8-Hᵃ), 1.52-1.43 (m, 1H, 8-Hᵇ) 1.46 (d, ³*J*(H,H)=7.1 Hz, 3H, 7-CH₃), 1.25 (m, 8H, 4×CH₂), 1.19 (d, ³*J*(H,H)=6.8 Hz, 3H, 5-CH₃), 0.85 (m, 3H, CH₃);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.6 (C-4), 190.6 (C-6), 171.3 (C-2), 98.2 (C-3), 65.1 (C-5), 37.6 (NMe), 33.6 (C-8), 31.7 (C-11), 29.2 (C-9), 28.1 (C-7), 27.2 (C-10), 22.7 (C-12), 16.9 (5-CH$_3$), 14.3 (7-CH$_3$), 14.2 (CH$_3$);

IR (thin film) ṽ=2955 (w), 2931 (m), 2857 (w), 1720 (m), 1646 (s), 1568 (m), 1533 (s), 1453 (m), 1417 (w), 1395 (w), 1374 (w), 1357 (w), 1232 (m), 1214 (m), 1184 (m), 1058 (m), 1029 (s), 936 (m), 889 (m), 862 (m), 798 (w), 784 (w), 753 (m), 730 (s) cm^{-1};

HRMS (ESI) Calcd for C$_{15}$H$_{25}$BF$_2$NO$_3$Na [M+H]$^+$ 316.1890, found: 316.1917.

Difluoroboryl complex ((5*S*,7*R*)-101)

Scheme VI.36. Synthesis of model compound via epicoccamide route: Stereoselective hydrogenation.

Analogously to (5S,7S)-**101**, its diastereomer (5S,7R)-**101** was obtained by catalytic hydrogenation with (*S,S*)-Rh-Et-DUPHOS BF$_4$ with similar nearly quantitative yield (97%).

R$_f$=0.54 (EtOAc/*c*-hexane 1:1);

[α]$_D^{24}$ = -6.3 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=3.90 (q, ^3J(H,H)=7.1 Hz, 1H, 7-H), 3.51 (q, ^3J(H,H)=6.8 Hz, 1H, 5-H), 3.15 (s, 3H, NCH$_3$), 1.69 (m, 1H, 8-H^a), 1.51-1.41 (m, 1H, 8-H^b) 1.45 (d, ^3J(H,H)=7.1 Hz, 3H, 7-CH$_3$), 1.24 (m, 8H, 4×CH$_2$), 1.18 (d, ^3J(H,H)=6.8 Hz, 3H, 5-CH$_3$), 0.84 (m, 3H, CH$_3$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=193.5 (C-4), 190.6 (C-6), 171.2 (C-2), 98.2 (C-3), 65.0 (C-5), 37.5 (NMe), 33.6 (C-8), 31.7 (C-11), 29.2 (C-9), 28.1 (C-7), 27.1 (C-10), 22.6 (C-12), 16.9 (5-CH$_3$), 14.2 (7-CH$_3$), 14.1 (CH$_3$);

IR (thin film) ṽ=2955 (w), 2928 (m), 2857 (w), 1719 (m), 1644 (s), 1565 (m), 1531 (s), 1454 (m), 1417 (w), 1394 (w), 1375 (w), 1356 (w), 1268 (w), 1232 (m), 1181 (m), 1059 (m), 1026 (s), 935 (m), 910 (m), 861 (m), 798 (w), 784 (w), 730 (s), 707 (m) cm^{-1}.

HRMS (ESI) Calcd for C$_{15}$H$_{25}$BF$_2$NO$_3$Na [M+H]$^+$ 316.1890, found: 316.1908.

VI.3. Ancorinoside B

VI.3.1. Glycosyl donor

D-Galactopyranose pentabenzoate (115)[233,234]
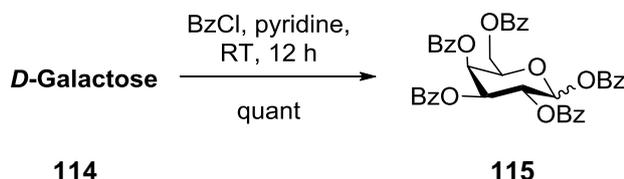
Scheme VI.37. Synthesis of perbenzoylated galactose **115**.

D-Glucose (5.39 g, 29.9 mmol) was suspended in 30 ml pyridine. The reaction was cooled to 0 °C. BzCl (164.5 mmol, 19.1 ml) was slowly added. The resulting mixture was heated to RT and stirred for 12 h. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (silica gel; 10% EtOAc in *c*-hexane) to yield perbenzoylated galactose (20.96 g, quantitative) as white crystals with α to β ratio of roughly 1:2.

All data in accordance with literature.[233,234]

2,3,4,6-Tetra-*O*-benzoyl-α-*D*-galactosyl trichloroimidate (112)[233]
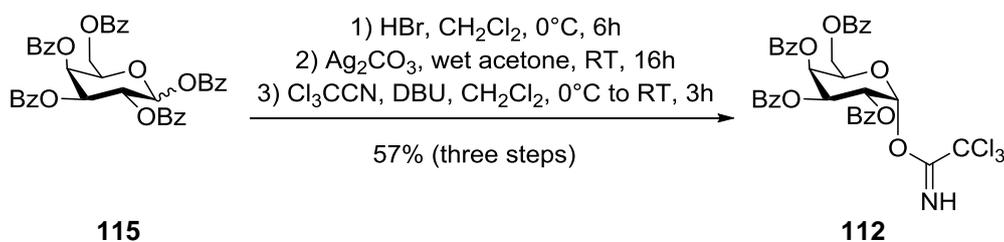
Scheme VI.38. Anomeric deprotection of perbenzoylated galactose.

Perbenzoylated galactose **115** (23.0 g, 29.9 mmol) was dissolved in 90 ml dry CH_2Cl_2. The solution was cooled to 0 °C and 45 ml of HBr in EtOAc (33 wt%) was slowly added. The reaction was stirred for 6 h. After complete consumption of the starting material, the reaction mixture was thrown on ice and diluted with diethylether. The organic layer was washed with H_2O, slowly with $NaHCO_3$, again H_2O and brine. The washed organic layer was dried over Na_2SO_4 and all volatiles were removed under reduced pressure. The crude material which was a colorless oil was directly subjected to the next step.

The remainder of the step above was redissolved in 120 ml acetone and 5 ml water was added. Ag_2CO_3 (4.5 g, 16.4 mmol) was added in one portion and stirring was maintained for 16 h. The remaining dark solution was filtered over celite and the celite was rinsed with three times 200 ml CH_2Cl_2. All organic fractions were combined, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The slightly yellow foam was directly used in the next step without further purification.

The crude hemiacetal (8.8 g, 14.75 mmol) was dissolved in 120 ml dry CH_2Cl_2. The resulting solution was cooled to 0 °C. DBU (16.63 mmol, 2.5 ml) and Cl_3CCN (103.3 mmol, 10.3 ml) were added in one portion. The reaction mixture was allowed to heat up to RT and stirring was maintained for 3 h. After complete consumption of the starting material all volatiles were removed under reduced pressure. The crude product was purified by column chromatography (silica gel; 25% EtOAc in *c*-hexane) to yield imidate **112** (6.22 g, 57% over three steps) as a slightly yellow foam.

R_f=0.44 (EtOAc/*c*-hexane 1:3);

^{1}H NMR (500 MHz, $CDCl_3$): δ=8.64 (s, 1H, NH), 8.13-7.25 (m, 20H, H^{ar}), 6.91 (d, ^3J(H,H)=3.7 Hz, 1H, 1-H), 6.15 (dd, ^3J(H,H)=3.7 Hz, 3.3 Hz, 1H, 4-H), 6.08 (dd, ^3J(H,H)=10.7 Hz, 3.3 Hz, 1H, 3-H), 5.96 (dd, ^3J(H,H)=10.7 Hz, 3.7 Hz, 1H, 2-H), 4.87 (dd, ^3J(H,H)=6.9 Hz, 6.1 Hz, 1H, 5-H), 4.62 (dd, ^3J(H,H)=11.4 Hz, 6.9 Hz, 1H, 6-H^a), 4.44 (dd, ^3J(H,H)=11.4 Hz, 6.1 Hz, 1H, 6-H^b);

^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1 (*C*OPh), 165.8 (*C*OPh), 165.7 (*C*OPh), 165.6 (*C*OPh), 160.7 (*C*NH), 133.9 (2xCH^{ar}), 133.7 (CH^{ar}), 133.5 (CH^{ar}), 133.4 (CH^{ar}), 130.3 (CH^{ar}), 130.2 (2xCH^{ar}), 130.1 (2×CH^{ar}), 130.0 (2×CH^{ar}), 129.9 (4×CH^{ar}), 129.8 (CH^{ar}), 129.4 (C_q^{ar}), 129.0 (C_q^{ar}), 128.9 (C_q^{ar}), 128.9 (2xCH^{ar}), 128.8 (C_q^{ar}), 128.6 (3xCH^{ar}), 128.5 (4xCH^{ar}), 93.8 (C-1), 69.8 (C-5), 68.6 (C-3), 68.5 (C-4), 67.9 (C-2), 62.3 (C-6);

All additional data in accordance with literature.[233,234]

VI.3.2. Synthesis of the C_{20} alkyl chain (111)

1,20-Eicosane diol (118)[213]
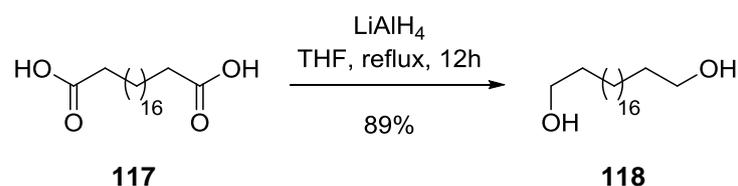
Scheme VI.39. Synthesis of C_{20} diol **118**.

755 mg of 1,20-eicosandioic acid **117** (2.20 mmol) was dissolved in 45 ml dry THF. The suspension was cooled to 0 °C and LiAlH$_4$ (251 mg, 6.61 mmol) was slowly added. The resulting suspension was heated up to reflux and stirred for 12 h. Tlc analysis showed complete consumption of the starting material (baseline) and one single spot by that time. The mixture was again cooled to 0 °C and the reaction was stopped by dropwise addition of Na/K-tartrate. The product was extracted three times with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the volatiles were removed under reduced pressure. This reaction gave 615 mg (1.96 mmol) of the desired product as a white solid in 89% yield.

R$_f$=0.18 (EtOAc/c-hexane 2:1);

m.p. 102 °C;

^{1}H NMR (300 MHz, CDCl$_3$): δ=3.54 (t, ^3J(H,H)=6.7 Hz, 4H, 2xOCH_2), 1.53 (pqui, ^3J(H,H)=6.7 Hz, 4H, OCH$_2$CH_2), 1.39-1.26 (m, 32H, CH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=63.0 (C-1, C-20), 33.7 (C-2, C-19), 30.8 (10×CH$_2$), 30.7 (2×CH$_2$), 30.6 (2×CH$_2$), 27.0 (2×CH$_2$);

IR (thin film) ṽ=3410 (m), 3342 (m), 2918 (s), 2850 (s), 1493 (w), 1460 (m), 1357 (m), 1333 (w), 1321 (w), 1050 (s), 1017 (s), 996 (w), 980 (w), 971 (m), 727 (m) cm^{-1}.

All data in accordance with literature.[213]

16-[(*t*Butyldimethylsilyl)oxy]octadecane-1-ol (111)
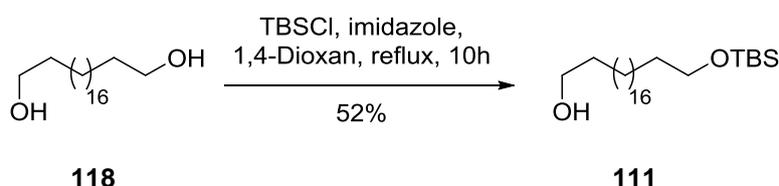
Scheme VI.40. Synthesis of the mono-TBS protected C$_{20}$ diol **111**.

1.21 g of the diol **118** (3.85 mmol) was suspended in 40 ml of 1,4-dioxan. The resulting mixture was heated to about 75 °C in order to dissolve the educt. TBSCl (580 mg, 3.85 mmol) and imidazol (524 mg, 7.70 mmol) was added in one portion. The mixture was heated to reflux for 10 h. The reaction was cooled to room temperature and then stopped by addition of saturated NaHCO$_3$ solution. The product mixture was extracted three times with ethyl acetate, the combined organic layers were washed two times with water and brine and dried over Na$_2$SO$_4$. The crude mixture was purified by silica chromatography (silica gel; 10% EtOAc in c-hexane) to yield **111** (845 mg, 52%) as a white waxy substance.

R$_f$=0.47 (EtOAc/c-hexane 1:3);

^{1}H NMR (500 MHz, CDCl$_3$): δ=3.63 (t, ^3J(H,H)=6.7, 2H, CH_2OH); 3.59 (t, ^3J(H,H)=6.7, 2H,

CH_2OTBS); 1.56 (pqui, ^3J(H,H)=6.7, 2H, CH_2CH_2OH); 1.50 (pqui, ^3J(H,H)=6.7, 2H, CH_2CH_2OTBS), 1.36-1.21 (m, 32H), 0.89 (s, 9H; C(CH_3)$_3$), 0.04 (s, 6H, Si(CH_3)$_2$);

^{13}C NMR (125 MHz, CDCl$_3$): δ=63.4 (COTBS), 63.1 (COH), 32.9 (C-19), 32.8 (C-2), 29.7 (C-6 to C-16), 29.7 (C-17), 29.7 (C-4), 29.6 (C-16), 29.5 (C-5), 26.0 (C(CH_3)$_3$), 25.8 (C-18), 25.7 (C-3), 18.4 (SiC^q), -5.2 (Si(CH_3)$_2$);

IR (thin film) ṽ=3375 (br), 2923 (s), 2853 (s), 1464 (m), 1367 (w), 1361 (w), 1254 (m), 1099 (s), 1058 (m), 1006 (w), 939 (w), 908 (w), 834 (s), 810 (m), 774 (s), 735 (m), 7020 (m), 662 (w) cm^{-1};

HRMS (ESI) Calcd for C$_{26}$H$_{56}$O$_2$SiNa [M+Na]$^+$ 451.3942, found: 451.3762.

VI.3.3. 6-*O*-PMB protected glycosyl acceptor (122)

1-*S*-Phenyl-2,3,4,6-tetra-*O*-acetyl-*β*-thio-*D*-glucopyranoside (123)[238]

80   **123**
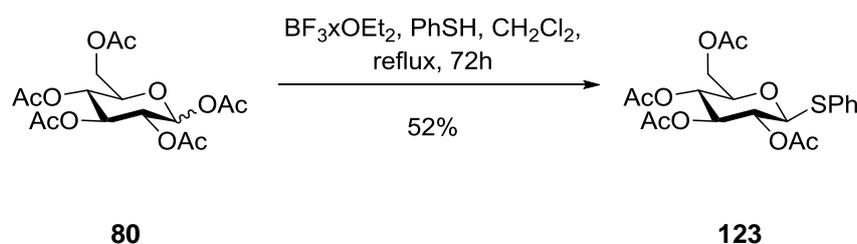
Scheme VI.41. Thioglycoside formation to yield **123**.

Peracetylated *D*-glycopyranose[32,140] **80** (2.55 g, 6.533 mmol) was dissolved in 65 ml CH$_2$Cl$_2$. BF$_3$•OEt$_2$ (2.82 ml, 22.86 mmol) and PhSH (12.0 ml, 11.76 mmol) were added via syringe. The reaction mixture was heated up to reflux for three days. After cooling the mixture to RT the reaction was stopped by addition of 100 ml 1 M NaOH. The aqueous phase was extracted three times using CH$_2$Cl$_2$. The combined organic layers were washed with NaHCO$_3$, H$_2$O and brine. The layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (silica gel; 12.5% EtOAc in *c*-hexane) to yield **123** (1.49 g, 52%) as a transparent oil.

R$_f$=0.42 (EtOAc/*c*-hexane 1:2);

^{1}H NMR (500 MHz, CDCl$_3$): δ=7.45-7.41 (m, 2H, H^{ar}), 7.27-7.23 (m, 3H, H^{ar}), 5.18 (pt, ^3J(H,H)=9.8 Hz, 1H, 4-H), 4.98 (dd, ^3J(H,H)=9.8 Hz, 9.4 Hz, 1H, 3-H), 4.91 (dd, ^3J(H,H)=10.1 Hz, 9.8 Hz, 1H; 2-H), 4.69 (d, ^3J(H,H)=10.1 Hz, 1H, 1-H), 4.17 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)=12.3 Hz, 1H, 6-CH^a), 4.12 (dd, ^3J(H,H)=2.4 Hz, ^2J(H,H)=12.3 Hz 1H, 6-CH^b), 3.70 (ddd, ^3J(H,H)=9.8 Hz, 5.2 Hz, 2.4 Hz, 1H, 5-H), 2.01 (s, 3H, CH$_3$), 1.96 (s, 3H, CH$_3$), 1.95 (s, 3H, CH$_3$), 1.92 (s, 3H, CH$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ=170.3 (*C*OPh), 169.9 (*C*OPh), 169.2 (*C*OPh), 169.0 (*C*OPh), 132.9 (2xCH^{ar}), 131.6 (C^{ar}), 128.8 (2xCH^{ar}), 128.2 (CH^{ar}), 85.4 (C-1), 75.6 (C-3), 73.8 (C-4), 69.8 (C-5), 68.1 (C-2), 60.1 (C-6), 20.5 (CH$_3$), 20.5 (CH$_3$), 20.4 (2xCH$_3$);

All additional data in accordance with literature.[313]

1-*S*-Phenyl-4,6-*O*-(methoxyphenyl)methylene-*β*-thio-*D*-glucopyranose (124)[239]
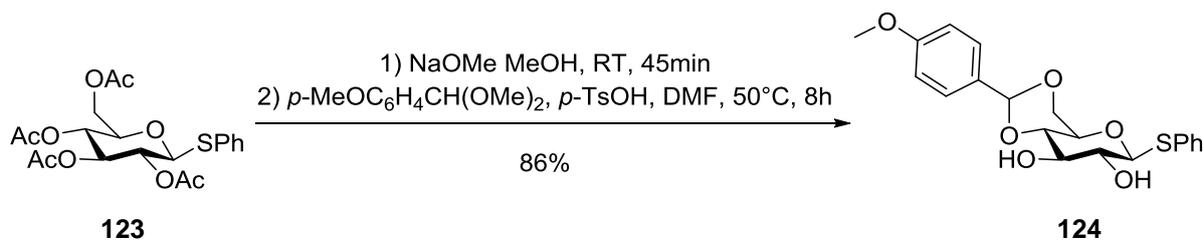
Scheme VI.42. Synthesis of anisaldehyde acetal **124**.

The peracetylated Schmidt-donor **123** (1.75 g, 3.973 mmol) was dissolved in 40 ml MeOH. Sodium methoxide (107 mg, 1.987 mmol) was added in one portion. The resulting suspension was stirred for 45 min (until complete consumption of the starting material). The solvents were removed under reduced pressure and the remainder was redissolved in 40 ml DMF. Toluenesulfonic acid (491 mg, 2.583 mmol) and anisaldehyde dimethyl acetal (1.35 ml, 7.946 mmol) were added. The resulting solution was heated up to 50 °C and stirring was maintained for 8 h. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (silica gel; 12.5% EtOAc in *c*-hexane) to yield **124** (1.33 g, 86% over two steps) as a white solid.

R$_f$=0.29 (EtOAc/*c*-hexane 1:3);

^{1}H NMR (500 MHz, CDCl$_3$): δ=7.56-7.52 (m, 2H, H^{ar}), 7.41-7.38 (m, 2H, H^{ar}), 7.35-7.32 (m, 3H, H^{ar}), 6.90-6.87 (m, 2H, H^{ar}), 5.49 (s, 1H, PhCH), 4.64 (d, ^3J(H,H)=9.7 Hz, 1H, 1-H), 4.36 (dd, ^3J(H,H)=10.6 Hz, 4.1 Hz, 1H, 6-CH^a), 3.84 (dd, ^3J(H,H)=9.4 Hz, 8.7 Hz, 1H, 4-H), 3.79 (s, 3H, OCH$_3$), 3.76 (dd, ^3J(H,H)=9.9 Hz, 9.4 Hz, 2.4 Hz ,1H, 3-H), 3.55 – 3.49 (m, 2H, 5-H, 6-CH^b), 3.47 (dd, ^3J(H,H)=9.9 Hz, 9.7 Hz, 1H, 2-H);

^{13}C NMR (100 MHz, CDCl$_3$): δ=160.4 (CH$_3$O*C*^{ar}), 133.2 (2xCH^{ar}), 131.4 (C^{ar}), 129.5 (C^{ar}), 129.3 (2xCH^{ar}), 128.6 (CH^{ar}), (2xCH^{ar}), 113.9 (2xCH^{ar}), 102.0 (Ph*C*H), 88.8 (C-1), 80.3 (C-4), 74.6 (C-3), 72.2 (C-2), 70.7 (C-5), 68.7 (C-6), 55.5 (OCH$_3$);

All additional data in accordance with literature.[239]

1-*S*-Phenyl-2,3-*O*-benzoyl-4,6-*O*-(methoxyphenyl)methylene-*β*-thio-*D*-glucopyranose (125)[241]
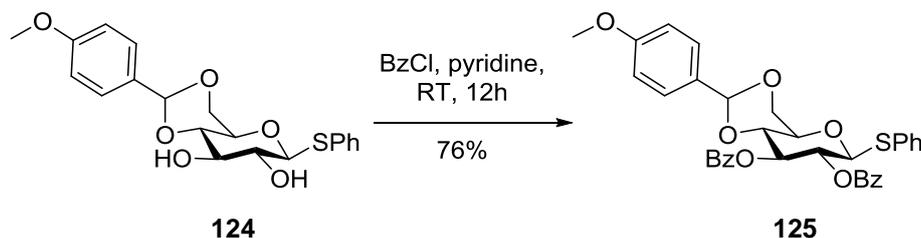
Scheme VI.43. Benzoyl protection of the acetal donor.

Diol **124** (1.33 g, 3.406 mmol) was dissolved in 40 ml pyridine. This solution was cooled to 0 °C. BzCl (1.2 ml, 10.22 mmol) was slowly added via syringe. The reaction mixture was allowed to heat up to RT and stirring was continued for 12 h. Tlc analysis showed complete consumption of the starting material by that time and the volatiles were removed under reduced pressure. The crude material was purified by column chromatography (silica gel; 10% EtOAc in *c*-hexane) to yield **125** (1.54 g, 76%) as a white foam.

R_f=0.69 (EtOAc/*c*-hexane 1:3);

^{1}H NMR (500 MHz, CDCl$_3$): δ=8.01-7.93 (m, 4H, H^{ar}), 7.55-7.45 (m, 4H, H^{ar}), 7.42-7.31 (m, 9H, H^{ar}), 6.86-6.82 (m, 2H, H^{ar}), 5.83 (dd, ^3J(H,H)=9.6 Hz, 9.4 Hz, 1H, 3-H), 5.52 (s, 1H, PhCH), 5.51 (dd, ^3J(H,H)=9.9 Hz, 9.4 Hz, 1H, 2-H), 5.07 (d, ^3J(H,H)=9.9 Hz, 1H, 1-H), 4.46 (dd, ^3J(H,H)=10.5 Hz, 4.9 Hz, 1H, 6-CH^a), 3.92 (dd, ^3J(H,H)=9.6 Hz, 8.7 Hz, 1H, 4-H), 3.88 (dd, ^3J(H,H)=10.5 Hz, 5.2 Hz, 1H, 6-CH^b), 3.77 (m, 5-H), 3.75 (s, 3H, OCH$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ=165.7 (*C*OPh C-2), 165.3 (*C*OPh C-3), 160.2 (CH$_3$O*C*^{ar}), 133.4 (CH^{ar}), 133.2 (CH^{ar}), 133.1 (2xCH^{ar}), 132.0 (C^{ar}), 130.0 (2xCH^{ar}), 129.9 (2xCH^{ar}), 129.4 (C^{ar}), 129.3 (C^{ar}), 129.2 (C^{ar}), 129.1 (2xCH^{ar}), 128.5 (2xCH^{ar}), 128.4 (CH^{ar}), 128.3 (2xCH^{ar}), 113.6 (2xCH^{ar}), 101.5 (Ph*C*H), 87.1 (C-1), 78.6 (C-4), 73.4 (C-3), 71.1 (C-2), 71.0 (C-5), 68.5 (C-6), 55.3 (OCH$_3$);

All additional data in accordance with literature.[241]

1-*S*-Phenyl-2,3-*O*-benzoyl-6-*O*-*p*methoxybenzyl-*β*-thio-D-glucopyranose (122)[242,243]
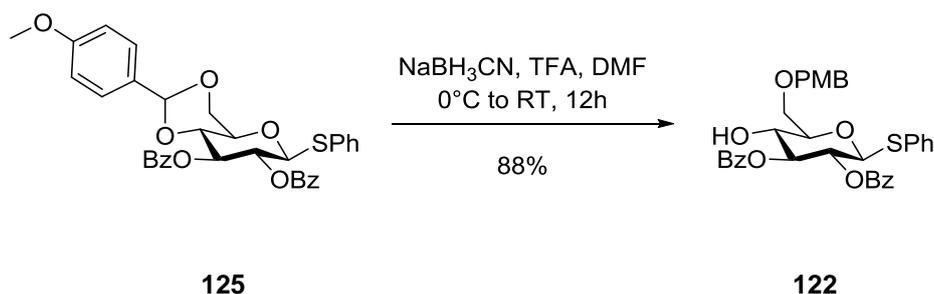
Scheme VI.44. Reductive acetal opening to yield the 6-*O*-PMB protected acceptor **122**.

The fully protected sugar **125** (3.4 g, 6.221 mmol) was dissolved in 50 ml DMF. The solution was cooled to 0 °C. Sodium cyanoborohydride (1.95 g, 31.103 mmol) was added in one portion. Trifluoroacetic acid (TFA, 4.8 ml, 62.21 mmol) was mixed with 35 ml DMF. This acidic solution was added dropwise to the reaction mixture while cooling was maintained. After completion of the TFA addition, the mixture was heated up to RT and stirring was continued for 12 h. Tlc analysis showed complete consumption of the starting material. The reaction mixture was filtrated over celite and neutralized using 100 ml sat. $NaHCO_3$ solution. The crude product was extracted three times with CH_2Cl_2 and the combined organic layers were washed again with sat. $NaHCO_3$ solution. The washed extracts were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude material was purified by column chromatography (silica gel; 10% EtOAc in *c*-hexane) to yield **122** (2.99 g, 88%) as a transparent oil.

R_f=0.58 (EtOAc/*c*-hexane 1:2);

$[\alpha]_D^{22}$ = 44.9 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (500 MHz, CDCl$_3$): δ=7.99-7.93 (m, 4H, H^{ar}), 7.54-7.48 (m, 4H, H^{ar}), 7.41-7.34 (m, 4H, H^{ar}), 7.31-7.24 (m, 5H, H^{ar}), 6.92-6.88 (m, 2H, H^{ar}), 5.49 (dd, ^3J(H,H)=9.5 Hz, 9.3 Hz, 1H, 3-H), 5.43 (pt, ^3J(H,H)=9.8 Hz, 1H, 2-H), 4.95 (d, ^3J(H,H)=9.9 Hz, 1H, 1-H), 4.58 (d, ^2J(H,H)=11.5 Hz, 1H, MPCH^a), 4.54 (d, ^2J(H,H)=11.5 Hz, 1H, MPCH^b), 3.95 (pt, ^3J(H,H)=9.3 Hz, 1H, 4-H), 3.86 (dd, ^3J(H,H)=4.3 Hz, ^2J(H,H)=5.4 Hz, 1H, 6-CH$_2$), 3.82 (s, 3H, OCH$_3$), 3.74 (dt, ^3J(H,H)=9.3 Hz, 4.3 Hz, 1H, 5-H), 3.30 (s, 1H, OH);

^{13}C NMR (100 MHz, CDCl$_3$): δ=167.2 (*C*OPh C-3), 165.4 (*C*OPh C-2), 159.5 (CH$_3$O*C*^{ar}), 133.5 (CH^{ar}), 133.4 (CH^{ar}), 132.8 (2xCH^{ar}), 132.5 (C^{ar}), 130.1 (2xCH^{ar}), 123.0 (2xCH^{ar}), 129.9 (C^{ar}), 129.5 (2xCH^{ar}), 129.4 (C^{ar}), 129.1 (C^{ar}) 129.0 (3xCH^{ar}), 128.5 (3xCH^{ar}), 128.2 (CH^{ar}), 114.0 (2xCH^{ar}), 86.3 (C-1), 78.9 (C-5), 77.8 (C-3), 73.5 (MP*C*H$_2$), 70.9 (C-4), 70.3 (C-2), 69.9 (C-6), 55.4 (OCH$_3$);

IR (thin film) ṽ=3463 (br), 2923 (w), 1725 (s), 1602 (w), 1588 (w), 1568 (w), 1513 (m), 1451

(m), 1440 (w), 1315 (m), 1275 (s), 1248 (s), 1177 (m), 1128 (m), 1104 (m), 1085 (s), 1067 (s), 1026 (m), 988 (w), 822 (w), 750 (m), 708 (s), 681 (m) cm^{-1};

HRMS (ESI) Calcd for $C_{34}H_{32}O_8SNa$ [M+Na]$^+$ 623.1710, found: 623.1700.

VI.3.4. Total synthesis of ancorinoside B diglycoside (120)

Phenyl *S*-(2,3,4,5-tetra-*O*-benzoyl-*β-D*-galactopyranosyl)-(1-4)-2,3-di-*O*-benzoyl-6-*O*-*p*methoxybenzyl-*β*-thio-*D* glucopyrandoside (121)
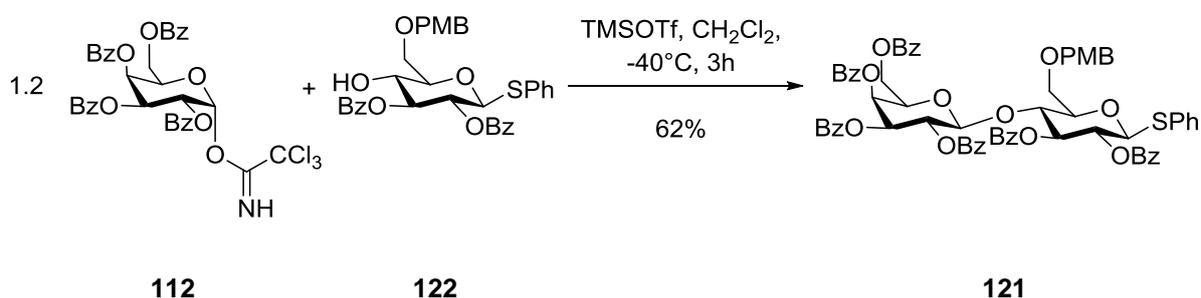
Scheme VI.45. 1st glycosylation with PMB-protected acceptor **122** and Schmidt-Donor **112**.

Alcohol **122** (852 mg, 1.418 mmol) and donor **112** (1.26 g, 1.702 mmol) were dissolved in 50 ml dry CH$_2$Cl$_2$ containing 1.3 g 4 Å molecular sieves. The suspension was cooled to -40 °C. TMSOTf (31 μl, 0.170 mmol) was added via syringe. The reaction mixture was stirred for 3 h at -40 °C until tlc analysis showed complete consumption of the donor. The reaction was stopped by addition of sat. NaHCO$_3$ solution. The crude glycosylation product was extracted three times using CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel; 5% EtOAc in *c*-hexane) to yield **121** (1.03 g, 88%) as a transparent oil.

R$_f$=0.29 (EtOAc/*c*-hexane 1:3);

[α]$_D^{22}$ = 23.1 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (500 MHz, CDCl$_3$): δ=8.03-8.00 (m, 2H, H^{ar}), 7.97-7.94 (m, 4H, H^{ar}), 7.87-7.84 (m, 3H, H^{ar}), 7.73-7.70 (m, 1H, H^{ar}), 7.63-7.57 (m, 2H, H^{ar}), 7.54-7.49 (m, 2H, H^{ar}), 7.48-7.43 (m, 6H, H^{ar}), 7.41-7.35 (m, 6H, H^{ar}), 7.32-7.27 (m, 4H, H^{ar}), 7.25-7.19 (m, 4H, H^{ar}), 7.16-7.11 (m, 2H, H^{ar}), 6.97-6.94 (m, 2H, H^{ar}), 6.91-6.88 (m, 1H, H^{ar}), 5.75 (pt, ^3J(H,H)=9.7 Hz, 1H, 3'-H), 5.71 (dd, ^3J(H,H)=9.1 Hz, 3.4 Hz, 1H, 4-H), 5.60 (dd, ^3J(H,H)=10.4 Hz, 8.0 Hz, 1H; 2-H), 5.44 (dd, ^3J(H,H)=9.9 Hz, 9.7 Hz, 1H, 2'-H), 5.36 (dd, ^3J(H,H)=10.4 HZ, 3.4 Hz, 1H, 3-H), 4.85 (d, ^3J(H,H)=9.9 Hz, 1H, 1'-H), 4.83 (d, ^3J(H,H)=8.0 Hz, 1H, 1-H), 4.64 (dd,

^3J(H,H)=3.2 Hz, ^2J(H,H)=11.7 Hz, 1H, 6'-H^a), 4.37 (dd, ^3J(H,H)=0.7 Hz, ^2J(H,H)=11.7 Hz, 1H, 6'-H^b), 4.27 (pt, ^3J(H,H)=9.7 Hz, 1H, 4'-H), 3.86 (ddd, ^3J(H,H)=9.1 Hz, 4.8 Hz, 3.4 Hz, 1H, 5-H), 3.78 (s, 3H, OCH$_3$), 3.77 (dd, ^3J(H,H)=4.8 Hz, ^2J(H,H)=11.5 Hz, 1H, 6-H^a), 3.77 (dd, ^3J(H,H)=3.4 Hz, ^2J(H,H)=11.5 Hz, 1H, 6-H^b), 3.64-3.59 (m, 2H, MPCH$_2$) 3.56 (ddd, ^3J(H,H)=9.7 Hz, 3.2 Hz, 0.7 Hz, 1H, 5'-H);

^{13}C NMR (100 MHz, CDCl$_3$): δ=165.8 (COPh C-6), 165.6 (2xCOPh C-2', C-3), 165.4 (COPh C-3'), 165.3 (COPh C-4), 164.7 (COPh C-2), 159.7 (CH$_3$OC^{ar}), 133.6 (CH^{ar}), 133.5 (2xCH^{ar}), 133.4 (CH^{ar}), 133.3 (CH^{ar}), 133.1 (CH^{ar}), 132.9 (3xCH^{ar}), 132.6 (C^{ar}), 130.1 (2×CH^{ar}), 130.0 (2×CH^{ar}), 129.9 (CH^{ar}), 129.9 (3xCH^{ar}), 129.8 (2×CH^{ar}), 129.7 (2×CH^{ar}), 129.6 (C^{ar}), 129.5 (C^{ar}), 129.3 (C^{ar}), 129.0 (C^{ar}), 129.0 (2xCH^{ar}), 128.9 (C^{ar}), 128.8 (CH^{ar}), 128.7 (2×CH^{ar}), 128.7 (2×CH^{ar}), 128.6 (2×CH^{ar}), 128.5 (2xCH^{ar}), 128.4 (2xCH^{ar}), 128.3 (2xCH^{ar}), 128.2 (CH^{ar}), 114.0 (2xCH^{ar}), 100.6 (C-1), 86.5 (C-1'), 79.0 (C-5'), 74.9 (C-4'), 74.5 (C-3'), 73.4 (C-6'), 71.9 (C-3), 71.2 (C-5), 70.7 (C-2'), 70.1 (C-2), 67.8 (C-4), 67.3 (MPCH$_2$), 61.1 (C-6), 55.5 (OCH$_3$);

IR (thin film) ṽ=1723 (s), 1602 (m), 1584 (w), 1513 (m), 1451 (m), 1315 (m), 1247 (s), 1177 (m), 1091 (s), 1068 (s), 1026 (s), 1001 (m), 847 (w), 820 (m), 804 (w), 752 (m), 706 (s), 687 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{68}$H$_{58}$O$_{17}$SNa [M+Na]$^+$ 1201.3287, found: 1201.3274.

[(tButyldimethylsilyloxy)-eicosyl] O-(2,3,4,5-tetra-O-benzoyl-β-D-galactopyranosyl)-(1-4)-2,3-di-O-benzoyl-6-O-pmethoxybenzyl -1-O-β-D-glucopyrandoside (126)
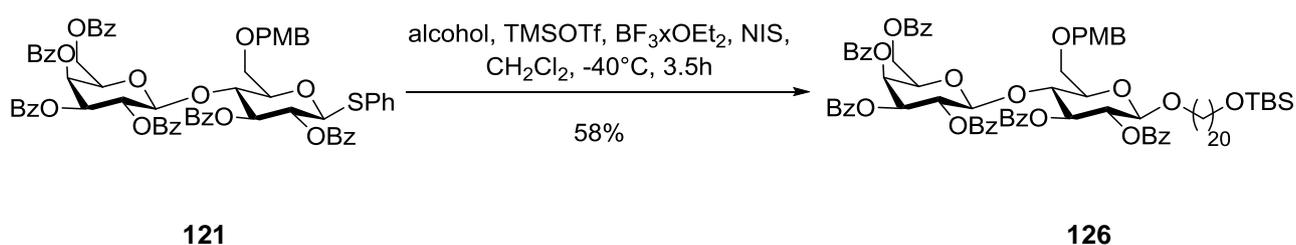
Scheme VI.46. 2nd glycosylation with PMB-protected disaccharide **121** and the TBS monoprotected side chain **111** to yield **126**.

Disaccharide donor **121** (1.02 g, 0.865 mmol) and monoprotected acceptor **111** (290 mg, 0.908 mmol) were dissolved in 15 ml dry CH$_2$Cl$_2$ containing 1 g 4 Å molecular sieves. The suspension was cooled to -40 °C. TMSOTf (15.7 μl, 0.086 mmol) and BF$_3$•OEt$_2$ (5.3 μl, 0.043 mmol) were added via syringe to get the *in situ* produced active donor species of BF$_2$OTF•OEt$_2$[246]. *N*-Ioduccinimide (350 mg, 1.557 mmol) was added in one portion. The reaction mixture was stirred for 3.5 h at -40 °C until tlc analysis showed complete

consumption of the donor. The reaction was stopped by addition of sat. NaHCO$_3$ solution. The crude glycosylation product was extracted three times using CH$_2$Cl$_2$. The combined organic layers were washed with 10 wt% Na$_2$S$_2$O$_3$ solution, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel; 5% EtOAc in *c*-hexane) to yield **126** (751 mg, 58%) as a transparent oil.

R$_f$=0.43 (EtOAc/*c*-hexane 1:3);

$[\alpha]_D^{22}$ = 2.1 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=8.08-7.93 (m, 6H, H^{ar}), 7.89-7.84 (m, 4H, H^{ar}), 7.76-7.71 (m, 2H, H^{ar}), 7.65-7.56 (m, 2H, H^{ar}), 7.54-7.43 (m, 6H, H^{ar}), 7.42-7.29 (m, 8H, H^{ar}), 7.25-7.11 (m, 4H, H$_{aromat.}$), 7.00-6.96 (m, 2H, H$_{aromat.}$), 5.71 (dd, ^3J(H,H)=7.1 Hz, 3.4 Hz 1H, 4-H), 5.70 (dd, ^3J(H,H)=9.9 Hz, 9.6 Hz, 1H, 3'-H), 5.61 (dd, ^3J(H,H)=10.4 Hz, 8.0 Hz, 1H, 2-H), 5.43 (dd, ^3J(H,H)=9.9 Hz, 8.0 Hz, 1H, 2'-H), 5.35 (dd, ^3J(H,H)=10.4 Hz, 3.4 Hz, 1H, 3-H), 4.79 (d, ^3J(H,H)=8.0 Hz, 1H, 1-H), 4.73 (dd, ^3J(H,H)=3.2 Hz, ^2J(H,H)=11.9 Hz, 1H, 6'-H^a), 4.59 (d, ^3J(H,H)=8.0 Hz, 1H, 1'-H), 4.35 (dd, ^3J(H,H)=0.7 Hz, ^2J(H,H)=11.9 Hz, 1H, 6'-H^b), 4.30 (pt, ^3J(H,H)=9.7 Hz, 1H, 4'-H), 3.89-3.80 (m, 1H, 5-H), 3.85 (dt, ^3J(H,H)=6.7 Hz, ^2J(H,H)=9.6 Hz, 1H, sugar-OCH^a), 3.78 (s, 3H, OCH$_3$), 3.75-3.66 (m, 3H, 6-CH$_2$, MPCH^a), 3.60 (t, ^3J(H,H)=6.7 Hz, 2H, SiOCH$_2$), 3.59 (d, ^2J(H,H)=10.6 Hz, 1H, MPCH^b), 3.51 (ddd, ^3J(H,H)=9.7 Hz, 3.2 Hz, 0.7 Hz, 1H, 5'-H), 3.42 (dt, ^3J(H,H)=6.7 Hz, ^2J(H,H)=9.6 Hz, 1H, sugar-OCH^b), 1.57-1.45 (m, 4H, 2×CH$_2$), 1.35-0.97 (m, 32H, 16×CH$_2$), 0.90 (s, 9H, C(*CH$_3$*)$_3$), 0.05 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=165.8 (*C*OPh C-6), 165.6 (*C*OPh C-3'), 165.5 (*C*OPh C-3), 165.4 (*C*OPh C-4), 165.3 (*C*OPh C-2'), 164.7 (*C*OPh C-2), 159.7 (CH$_3$O*C*^{ar}), 133.6 (CH^{ar}), 133.5 (CH^{ar}), 133.4 (CH^{ar}), 133.3 (CH^{ar}), 133.1 (3xCH^{ar}), 130.1 (C^{ar}), 130.1 (2×CH^{ar}), 129.8 (7×CH^{ar}), 129.8 (2xCH^{ar}), 129.7 (3xCH^{ar}), 129.6 (C^{ar}), 129.3 (2xC^{ar}), 129.1 (C^{ar}), 128.9 (C^{ar}), 128.7 (2xCH^{ar}), 128.7 (2xCH^{ar}), 128.6 (2×CH^{ar}), 128.4 (4×CH^{ar}), 128.2 (2xCH^{ar}), 114.2 (2xCH^{ar}), 101.4 (C-1'), 100.4 (C-1), 75.1 (C-4'), 74.8 (C-5'), 73.4 (C-6'), 73.3 (C-3'), 72.0 (C-2'), 71.9 (C-3), 71.2 (C-5), 70.2 (sugar-OCH$_2$), 70.2 (C-2), 67.9 (C-4), 67.1 (MP*C*H$_2$), 63.5 (SiOCH$_2$), 61.3 (C-6), 55.5 (OCH$_3$) 33.0 (CH$_2$), 29.9 (4×CH$_2$), 29.8 (3xCH$_2$), 29.8 (3×CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 26.1 (C(CH$_3$)$_3$), 25.9 (2xCH$_2$), 18.5 (Si*C*^{q}), −5.1 (Si(CH$_3$)$_2$);

IR (thin film) $\tilde{v}$=2925 (m), 2854 (m), 1729 (s), 1602 (m), 1583 (w), 1514 (m), 1491 (w), 1462 (m), 1452 (m), 1363 (m), 1315 (m), 1262 (s), 1253 (s), 1177 (m), 1094 (s), 1069 (s), 1028 (s), 1001 (m), 835 (m), 776 (m), 704 (s), 686 (m) cm^{-1};

HRMS (ESI) Calcd for $C_{88}H_{108}O_{19}SiNa$ [M+Na]$^+$ 1519.7146, found: 1519.7151.

[(*t*Butyldimethylsilyloxy)-eicosyl] *O*-**(2,3,4,5-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-** **(1-4)-2,3-di-*O*-benzoyl-1-*O*-*β*-D-glucopyrandoside (127)**[252]

126   **127**
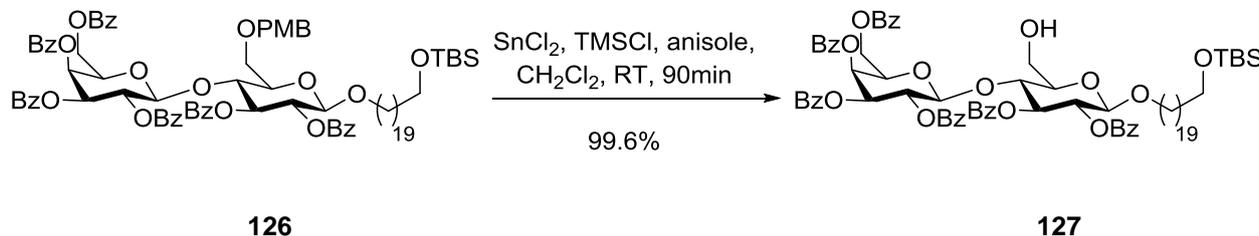
Scheme VI.47. Lewis acidic PMB-deprotection of **126** using SnCl$_2$, TMSCl and anisole to yield **127**.

Diglycoside **126** (166 mg, 0.111 mmol) was dissolved in 4 ml dry CH$_2$Cl$_2$ containing 150 mg 4 Å molecular sieves. SnCl$_2$ dihydrate (2.5 mg, 0.011 mmol) was added. To the resulting mixture TMSCl (42 µl, 0.332 mmol) and anisole (18 µl, 0.166 mmol) were added under argon. The reaction mixture was stirred at RT for 90 min until tlc analysis showed complete conversion of the starting material to a lower running spot. The reaction was stopped by addition of sat. NaHCO$_3$ solution. The crude product was extracted three times by the use of CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and all volatiles were removed under reduced pressure. The crude alcohol was purified by column chromatography (silica gel; 10% EtOAc in *c*-hexane) to yield **127** (152 mg, 99.6%) as a white solid.

R$_f$=0.39 (EtOAc/*c*-hexane 1:2);

$[\alpha]_D^{22}$ = 8.4 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (500 MHz, CDCl$_3$): δ=8.04-7.99 (m, 4H, H^{ar}), 7.97-7.92 (m, 4H, H^{ar}), 7.89-7.86 (m, 2H, H^{ar}), 7.76-7.72 (m, 2H, H^{ar}), 7.63-7.55 (m, 2H, H^{ar}), 7.54-7.44 (m, 6H, H^{ar}), 7.43-7.30 (m, 6H, H^{ar}), 7.24-7.20 (m, 2H, H^{ar}), 7.17-7.13 (m, 2H, H^{ar}), 5.76 (pd, ^3J(H,H)=3.4 Hz, 1H, 4-H), 5.70 (dd, ^3J(H,H)=9.9 Hz, 9.6 Hz, 1H, 3'-H), 5.67 (dd, ^3J(H,H)=10.2 Hz, 7.9 Hz, 1H, 2-H), 5.47 (dd, ^3J(H,H)=10.2 Hz, 3.4 Hz, 1H, 3-H), 5.35 (dd, ^3J(H,H)=9.9 Hz, 8.0 Hz, 1H, 2'-H), 5.02 (d, ^3J(H,H)=7.9 Hz, 1H, 1-H), 4.58 (d, ^3J(H,H)=8.0 Hz, 1H, 1'-H), 4.22 (pt, ^3J(H,H)=9.7 Hz, 1H, 4'-H), 3.91 (pdt, ^3J(H,H)=6.7 Hz, 3.4 Hz, 1H, 5-H), 3.84-3.72 (m, 5H, 6-CH$_2$, 6'-CH$_2$, sugar-OCH^a), 3.59 (t, ^3J(H,H)=6.7 Hz, 2H, SiOCH$_2$), 3.43 (m, 2H, 5'-H, sugar-OCH^b), 1.54-1.44 (m, 4H, 2×CH$_2$), 1.34-0.99 (m, 32H, 16×CH$_2$), 0.89 (s, 9H, C(*CH$_3$*)$_3$), 0.04 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (100 MHz, CDCl$_3$): δ=165.8 (*C*OPh C-6), 165.7 (2x*C*OPh C-2', C-3'), 165.4 (*C*OPh C-2), 165.3 (*C*OPh C-4), 164.8 (*C*OPh C-3), 133.6 (CH^{ar}), 133.5 (CH^{ar}), 133.4 (CH^{ar}), 133.4 (CH^{ar}), 133.1 (2xCH^{ar}), 130.1 (2×CH^{ar}), 130.1 (C^{ar}), 129.9 (2×CH^{ar}), 129.9 (2xCH^{ar}),

129.8 (5xCH^{ar}), 129.8 (C^{ar}), 129.6 (C^{ar}), 129.4 (C^{ar}), 129.1 (C^{ar}), 128.9 (C^{ar}), 128.7 (3xCH^{ar}), 128.7 (2xCH^{ar}), 128.6 (2×CH^{ar}), 128.4 (4×CH^{ar}), 128.3 (2xCH^{ar}), 101.1 (C-1), 100.7 (C-1'), 75.3 (C-5'), 74.9 (C-4'), 73.3 (C-3'), 72.1 (C-3), 72.1 (C-2'), 71.3 (C-5), 70.2 (C-2), 69.9 (sugar-OCH$_2$), 67.9 (C-4), 63.5 (SiOCH$_2$), 61.4 (C-6), 60.7 (C-6'), 33.0 (CH$_2$), 29.9 (4×CH$_2$), 29.8 (3×CH$_2$), 29.8 (3xCH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 27.1 (CH$_2$), 26.1 (C(CH$_3$)$_3$), 26.0 (CH$_2$), 25.9 (CH$_2$), 18.5 (SiC^q), −5.1 (Si(CH$_3$)$_2$);

IR (thin film) $\tilde{v}$=2925 (m), 2854 (m), 1727 (s), 1602 (m), 1586 (w), 1466 (m), 1451 (m), 1315 (m), 1260 (s), 1177 (m), 1158 (m), 1093 (s), 1069 (s), 1027 (s), 1001 (m), 836 (m), 776 (m), 707 (s), 686 (m) cm^{-1};

HRMS (ESI) Calcd for C$_{80}$H$_{100}$O$_{18}$SiNa [M+Na]$^+$ 1399.6571, found: 1399.6547.

Benzyl [*O*-(2,3,4,5-tetra-*O*-benzoyl-*β*-*D*-galactopyranosyl)-(1-4)-2,3-di-*O*-benzoyl-1-*O*-{(*t*butyldimethylsilyloxy)-eicosyl}-*β*-*D*-glucopyrandoside] uronate (120)[257,258]
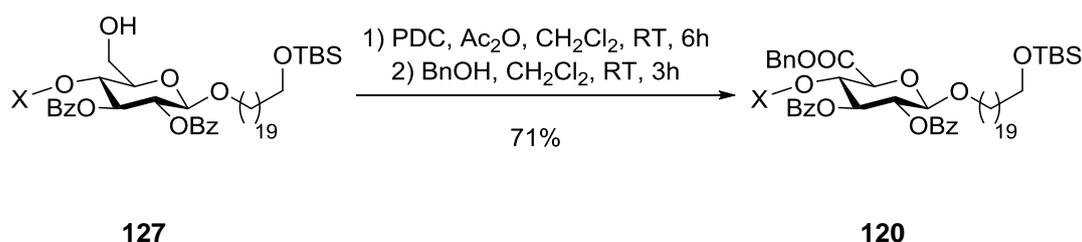
Scheme VI.48. C-6 oxidation and protection procedure to yield the desired glucuronic acid diglycoside **120**. X = perbonzoylated *β-D*-galactose.

Alcohol **127** (37 mg, 0.027 mmol) was dissolved in 1 ml dry CH$_2$Cl$_2$. Pyridinium dichromate (PDC, 22 mg, 0.058 mmol) was added. Acetic anhydride (28 μl, 0.290 mmol) was added via syringe. The resulting suspension was stirred at RT for 6 h until tlc analysis showed complete conversion of the starting material to a lower running blurry spot. Benzyl alcohol (60 μl, 0.581 mmol) was added dropwise. The benzyl protection was allowed to take place over 3 h. The reaction mixture was filtered over a small plug of silica gel. All volatiles were removed under reduced pressure. The crude desired diglycoside was purified by column chromatography (silica gel; 7.5% EtOAc in *c*-hexane) to yield **120** (28 mg, 71% over two steps) as a transparent oil.

R$_f$=0.63 (EtOAc/*c*-hexane 1:3);

[α]$_D^{22}$ = 8.0 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (500 MHz, CDCl$_3$): δ=8.01-7.89 (m, 8H, H^{ar}), 7.76-7.71 (m, 2H, H^{ar}), 7.65-7.55 (m, 2H, H^{ar}), 7.50-7.28 (m, 19H, H^{ar}), 7.25-7.20 (m, 2H, H^{ar}), 7.18-7.13 (m, 2H, H^{ar}), 5.74 (pd, ^3J(H,H)=9.6 Hz, 1H, 3'-H), 5.71 (pd, ^3J(H,H)=3.5 Hz, 1H, 4-H), 5.67 (dd, ^3J(H,H)=10.3 Hz,

8.0 Hz, 1H, 2-H), 5.38 (dd, ^3J(H,H)=9.6 Hz, 7.9 Hz, 1H, 2'-H), 5.36 (dd, ^3J(H,H)=10.3 Hz, 3.5 Hz, 1H, 3-H), 5.21 (d, ^2J(H,H)=12.0 Hz, 1H, 6'-OCH^a), 5.13 (d, ^2J(H,H)=12.0 Hz, 1H, 6'-OCH^b), 4.73 (d, ^3J(H,H)=8.0 Hz, 1H, 1-H), 4.60 (d, ^3J(H,H)=7.9 Hz, 1H, 1'-H), 4.13 (d, ^3J(H,H)=10.6 Hz, 1H, 5'-H), 3.80 (dt, ^3J(H,H)=6.4 Hz, ^2J(H,H)=10.1 Hz, 1H, sugar-OCH^a), 3.76-3.69 (m, 2H, 5-H, 6-CH^a), 3.66 (dd, ^3J(H,H)=10.6 Hz, 9.2 Hz, 1H, 4'-H), 3.59 (t, ^3J(H,H)=6.7 Hz, 2H, SiOCH$_2$), 3.55 (dd, ^3J(H,H)=6.7 Hz, ^2J(H,H)=10.6 Hz, 1H, 6-CH^b), 3.39 (dt, ^3J(H,H)=6.4 Hz, ^2J(H,H)=10.1 Hz, 1H, sugar-OCH^b), 1.52-1.41 (m, 4H, 2×CH$_2$), 1.32-0.98 (m, 32H, 16×CH$_2$), 0.89 (s, 9H, C(CH$_3$)$_3$), 0.05 (s, 6H, Si(CH$_3$)$_2$);

^{13}C NMR (100 MHz, CDCl$_3$): δ=165.7 (COPh C-6), 165.6 (COPh C-2'), 165.5 (COPh C-3'), 165.5 (COPh C-2), 165.4 (COPh C-4), 164.9 (COPh C-3), 154.8 (C-6'), 135.2 (C^{ar}), 133.7 (CH^{ar}), 133.6 (CH^{ar}), 133.5 (CH^{ar}), 133.4 (CH^{ar}), 133.3 (CH^{ar}), 133.2 (CH^{ar}), 130.2 (2×CH^{ar}), 130.1 (C^{ar}), 130.0 (2×CH^{ar}), 129.9 (3xCH^{ar}), 129.9 (2×CH^{ar}), 129.9 (3×CH^{ar}), 129.8 (2xCH^{ar}), 129.6 (C^{ar}), 129.5 (C^{ar}), 129.1 (C^{ar}), 129.1 (C^{ar}), 129.0 (CH^{ar}), 128.9 (C^{ar}), 128.9 (2xCH^{ar}), 128.9 (2xCH^{ar}), 128.7 (3×CH^{ar}), 128.7 (3×CH^{ar}), 128.7 (CH^{ar}), 128.4 (CH^{ar}), 128.4 (2xCH^{ar}), 101.2 (C-1), 101.1 (C-1'), 76.0 (C-5'), 73.0 (C-3'), 72.9 (C-4'), 71.9 (C-2'), 71.8 (C-3), 71.3 (C-5), 70.4 (sugar-OCH$_2$), 70.1 (BnCH$_2$), 70.1 (C-2), 67.6 (C-4), 63.5 (SiOCH$_2$), 61.0 (C-6), 33.1 (CH$_2$), 29.9 (2×CH$_2$), 29.9 (CH$_2$), 29.9 (CH$_2$), 29.8 (CH$_2$), 29.8 (2xCH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (2xCH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 26.2 (C(CH$_3$)$_3$), 26.0 (CH$_2$), 25.9 (CH$_2$), 18.6 (SiC^q), −5.1 (Si(CH$_3$)$_2$);

IR (thin film) $\tilde{v}$=2925 (m), 2853 (m), 1730 (s), 1602 (m), 1586 (w), 1452 (m), 1315 (m), 1259 (s), 1177 (m), 1092 (s), 1069 (s), 1026 (s), 807 (m), 755 (m), 707 (s) cm^{-1};

HRMS (ESI) Calcd for C$_{87}$H$_{104}$O$_{19}$SiNa [M+Na]$^+$ 1503.6833, found: 1503.6782.

VI.4. Virgineone

VI.4.1. Synthesis of the C_{20}-alkene (138) for Sharpless dihydroxylation

10-(tButyldimethylsilyloxy)-1-decene (136)
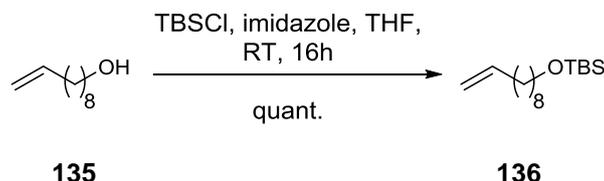
Scheme VI.49. TBS protection of C_{10} building block.

9-Decen-1-ol **135** (2.00 g, 12.80 mmol) was dissolved in 40 ml dry THF. TBSCl (2.18 mg, 16.00 mmol) and imidazole (3.86 g, 25.60 mmol) were added in one portion. The resulting solution was stirred at RT for 16 h until all starting material was consumed. The reaction was stopped by addition of sat. NaHCO$_3$ solution. The crude material was extracted three times using CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel; 20% EtOAc in c-hexane) to yield **136** (3.5 g, quant.) as a transparent oil.

R$_f$=0.89 (EtOAc/c-hexane 1:4);

^{1}H NMR (300 MHz, CDCl$_3$): δ=5.81 (ddt, ^3J(H,H)=17.1 Hz, 10.2 Hz, 6.7 Hz, 1H, CH), 4,99 (ddt, ^4J(H,H)=2.2 Hz, ^3J(H,H)=17.1 Hz, ^2J(H,H)=1.4 Hz, 1H, 1-CH[a]), 4,93 (ddt, ^4J(H,H)=2.3 Hz, ^3J(H,H)=10.2 Hz, ^2J(H,H)=1.4 Hz, 1H, 1-CH[b]), 3.60 (t, ^3J(H,H)=6.6 Hz, 2H, SiOCH$_2$), 2.08-2.00 (m, 2H, 3-CH$_2$), 1.51 (pqui, ^3J(H,H)=6.7 Hz, 2H, 9-CH$_2$), 1.42-1.25 (m, 10H, 5xCH$_2$), 0.90 (s, 9H, C(CH_3)$_3$), 0.05 (s, 6H, Si(CH_3)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=139.5 (CH), 114.4 (C-1), 63.6 (SiOCH$_2$), 34.2 (C-3), 33.3 (C-9), 29.9 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 26.3 (C(CH$_3$)$_3$), 26.2 (CH$_2$), 18.7 (SiC[q]), -4.9 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=2927 (w), 2856 (w), 1641 (m), 1472 (w), 1463 (m), 1388 (w), 1361 (m), 1254 (s), 1097 (s), 1005 (m), 990 (m), 938 (w), 908 (w), 833 (m), 812 (m), 773 (m), 710 (m), 661 (m) cm^{-1}.

9-(*t*Butyldimethylsilyloxy)-nonanal (134)[266]
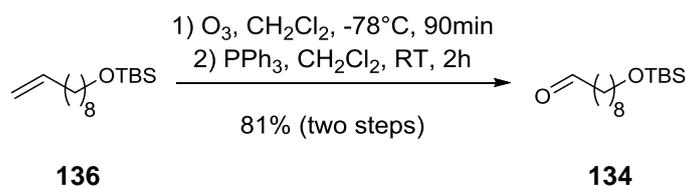
Scheme VI.50. Ozonolysis of the TBS protected C_{10} building block **136**.

Alkene **136** (2.76 g, 11.65 mmol) was dissolved in 130 ml dry CH_2Cl_2. The solution was cooled to -78 °C. Ozon (6% v/v) was bubbled through the solution for 20 min until the solution turned dark blue. The solution and the gaseous phase above were washed with oxygen. PPh_3 (7.64 g, 29.13 mmol) was added in one portion to stop the actual ozonolysis reductively and the mixture was allowed to heat up to RT. The resulting solution was stirred at RT for 2 h. 100 ml of water was added and the crude product was extracted three times using Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel; 2.5% EtOAc in *c*-hexane) to yield **134** (2.56 g, 81% over two steps) as a transparent oil.

R_f=0.49 (EtOAc/*c*-hexane 1:9);

^{1}H NMR (300 MHz, $CDCl_3$): δ=9.75 (t, ^3J(H,H)=1.9 Hz, 1H, CHO), 3.59 (t, ^3J(H,H)=6.4 Hz, 2H, SiOCH$_2$), 1.51 (dt, ^3J(H,H)=7.4 Hz 1,9 Hz, 2H, 2-CH$_2$), 1.62 (pqui, ^3J(H,H)=7.4 Hz, 2H, 3-CH$_2$), 1.50 (pqui, ^3J(H,H)=6.4 Hz, 2H, 8-CH$_2$), 1.35-1.26 (m, 8H, 4xCH$_2$), 0.89 (s, 9H, C(*CH$_3$*)$_3$), 0.04 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, $CDCl_3$): δ=202.9 (CHO), 63.5 (SiOCH$_2$), 44.1 (C-2), 33.1 (C-8), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 26.2 (C(CH$_3$)$_3$), 26.0 (CH$_2$), 18.6 (SiC^q), -5.0 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=2928 (w), 2855 (w), 1727 (s), 1462 (m), 1388 (w), 1360 (m), 1254 (s), 1094 (s), 1005 (m), 990 (w), 938 (m), 832 (m), 812 (m), 774 (m), 661 (m) cm^{-1}.

20-(*t*Butyldimethylsilyloxy)-12-hydroxy-1-icosene (137)
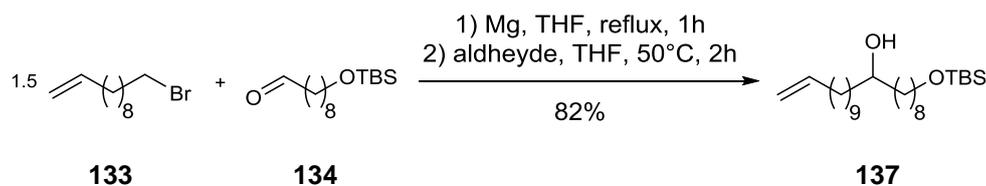
Scheme VI.51. Grignard reaction of the aldehyde **134** with 11-bromoundec-1-ene **133**.

Freshly roughened magnesium (271 mg, 11.17 mmol) and 11-bromoundec-1-ene **133** (1.90 ml, 8.82 mmol) were transferred into a flask containing 25 ml dry THF. The resulting

mixture was heated to reflux for 1 h until the suspension turned dark grey and the magnesium was mostly dissolved. The Grignard reagent containing solution was cooled to RT and aldehyde **134** (1.60 g, 5.88 mmol) was added as a solution in 12 ml dry THF. The reaction mixture was heated up to 50 °C and stirred for additional 2 h. The reaction was stopped by addition of ice. The pH was adjusted to below 6 by the use of 1 M hydrochloric acid. The crude product of this Grignard reaction was extracted three times with ethyl acetate. The combined organic layers were washed with a sat. $NaHCO_3$ solution, dried over Na_2SO_4 and all volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (silica gel; 10% EtOAc in *c*-hexane) to yield **137** (2.05 g, 82% over two steps) as a transparent oil.

R_f=0.24 (EtOAc/*c*-hexane 1:9);

^{1}H NMR (300 MHz, CDCl$_3$): δ=5.81 (ddt, ^3J(H,H)=17.1 Hz, 10.2 Hz, 6.7 Hz, 1H, 2-CH), 4,99 (ddt, ^4J(H,H)=2.2 Hz, ^3J(H,H)=17.1 Hz, ^2J(H,H)=1.6 Hz, 1H, 1-CH^a), 4,93 (ddt, ^4J(H,H)=2.3 Hz, ^3J(H,H)=10.2 Hz, ^2J(H,H)=1.3 Hz, 1H, 1-CH^b), 3.60 (t, ^3J(H,H)=6.6 Hz, 2H, SiOCH$_2$), 3.59 (m, 1H, HOC*H*), 2.08-1.99 (m, 2H, 3-CH$_2$), 1.55-1.22 (m, 30H, 15xCH$_2$), 0.89 (s, 9H, C(*CH$_3$*)$_3$), 0.04 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=139.5 (C-2), 114.4 (C-1), 72.3 (C-12), 63.6 (SiOCH$_2$), 37.8 (2xCH$_2$), 34.1 (CH$_2$), 33.2 (CH$_2$), 30.0 (2xCH$_2$), 29.9 (2xCH$_2$), 29.8 (CH$_2$), 29.7 (2xCH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 27.2 (CH$_2$), 26.3 (C(CH$_3$)$_3$), 26.0 (2xCH$_2$), 18.7 (SiC^q), -4.9 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=3362 (br), 2925 (m), 2854 (m), 1640 (m), 1463 (w), 1387 (w), 1360 (m), 1254 (s), 1097 (s), 1004 (m), 993 (m), 908 (m), 834 (m), 812 (m), 774 (m), 741 (w), 661 (m) cm^{-1}.

20-(*t*Butyldimethylsilyloxy)-12-(tetrahydropyran-2'-yloxy)-1-icosene (138)
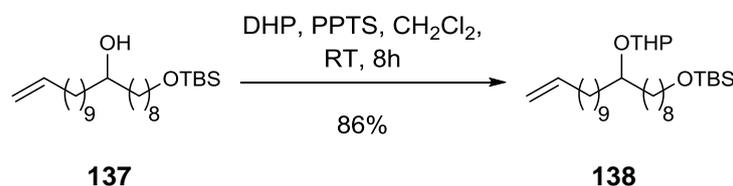
Scheme VI.52. THP-protection of the C$_{20}$ building block **137**.

Secondary alcohol **137** (2.05 g, 4.79 mmol) was dissolved in 100 ml CH$_2$Cl$_2$. Dihydropyrane (DHP, 2.02 ml, 23.97 mmol) and pyridinium *p*toluenesulfonate (PPTS, 120 mg, 0.48 mmol) were added to the above solution. The resulting mixture was stirred at RT for 8 h. The reaction was stopped using sat. NaHCO$_3$ solution and the crude product was extracted three

times with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$ and all volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (silica gel; 2.5% EtOAc in *c*-hexane) to yield **138** (2.05 g, 82%) as a transparent oil.

R$_f$=0.77 (EtOAc/*c*-hexane 1:19);

^{1}H NMR (300 MHz, CDCl$_3$): δ=5.81 (ddt, ^3J(H,H)=17.1 Hz, 10.2 Hz, 6.8 Hz, 1H, 2-CH), 4,99 (ddt, ^4J(H,H)=1.8 Hz, ^3J(H,H)=17.1 Hz, ^2J(H,H)=1.5 Hz, 1H, 1-CH^a), 4,92 (ddt, ^4J(H,H)=2.3 Hz, ^3J(H,H)=10.2 Hz, ^2J(H,H)=1.5 Hz, 1H, 1-CH^b), 4.64 (t, ^3J(H,H)=3.6 Hz, 1H, THP-CH), 3.91 (dt, ^3J(H,H)=4.9 Hz, ^2J(H,H)=10.5 Hz, 1H, THP-6-CH^a), 3.59 (t, ^3J(H,H)=6.6 Hz, 2H, SiOCH$_2$), 3.58 (m, 1H, THPOC*H*), 3.47 (dt, ^3J(H,H)=6.3 Hz, ^2J(H,H)=10.5 Hz, 1H, THP-6-CH^b), 2.03 (pq, ^3J(H,H)=6.8 Hz, 2H, 3-CH$_2$), 1.89-1.66 (m, 2H, THP-2-CH$_2$), 1.58-1.45 (m, 10H, THP-3-CH$_2$, THP-4-CH$_2$, 3xCH$_2$), 1.39-1.22 (m, 24H, 12xCH$_2$), 0.89 (s, 9H, C(*CH$_3$*)$_3$), 0.04 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=139.2 (C-2), 114.2 (C-1), 97.6 (THP-C-2), 76.9 (C-12), 63.5 (SiOCH$_2$), 62.8 (THP-C-6), 35.2 (CH$_2$), 34.0 (CH$_2$), 33.6 (CH$_2$), 33.1 (CH$_2$), 31.4 (THP-C-3), 30.0 (CH$_2$), 29.8 (2xCH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.1 (CH$_2$), 26.1 (C(CH$_3$)$_3$), 26.0 (CH$_2$), 25.8 (THP-C-5), 25.2 (CH$_2$), 20.1 (THP-C-4). 18.5 (SiC^q), -5.1 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=2926 (m), 2854 (m), 1641 (m), 1463 (w), 1385 (w), 1360 (m), 1254 (s), 1200 (s), 1097 (s), 1077 (s), 1004 (m), 907 (m), 868 (m), 835 (m), 813 (m), 773 (m), 721 (w), 661 (m) cm^{-1}.

VI.4.2. Dihydroxylation and selective protection

(2*R*)-20-(*t*Butyldimethylsilyloxy)-12-(tetrahydropyran-2'-yloxy)icosane-1,2-diol (139)[271]
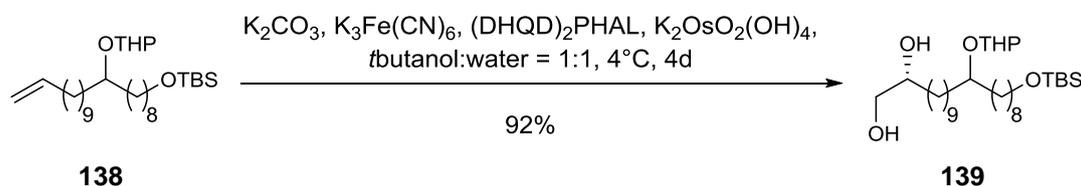
Scheme VI.53. Asymmetric Sharpless dihydroxylation of the C$_{20}$ building block **138**.

The fully protected alkene **138** (770 mg, 1.51 mmol) was dissolved in 15 ml of a 1:1 mixture of *t*butanol and water. The chiral ligand (DHQD)$_2$PHAL (12 mg, 0.015 mmol), potassium ferricyanide(III) (1.49 g, 4.54 mmol), potassium carbonate (627 mg, 4.54 mmol) and potassium osmate dihydrate (0.030 mmol, 11 mg) were all added in one portion. The resulting

two phase system was stirred at 4 °C for four days. The reaction was stopped by addition of a 1:1 mixture of sat. Na_2SO_3 and $Na_2S_2O_3$ aqueous solution. Stirring was maintained for another hour before the crude material was extracted five times with ethyl acetate. The combined organic layers were washed with sat. NaCl solution, dried over Na_2SO_4 and all volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (silica gel; 20% EtOAc in *c*-hexane) to yield **139** (760 mg, 92%) as a transparent oil.

R_f=0.41 (EtOAc/*c*-hexane 1:1);

$[\alpha]_D^{25}$ = 1.2 (*c* = 1.0 g cm^{-3}, chloroform);

^{1}H NMR (300 MHz, CDCl$_3$): δ=4.63 (t, ^3J(H,H)=3.6 Hz, 1H, THP-CH), 3.89 (dt, ^3J(H,H)=4.9 Hz, ^2J(H,H)=10.5 Hz, 1H, THP-6-CH^a), 3.73-3.63 (m, 2H, 1-CH^a, 2-CH), 3.60 (m, 1H, THPOC*H*), 3.58 (t, ^3J(H,H)=6.6 Hz, 2H, SiOCH$_2$), 3.48 (dt, ^3J(H,H)=6.3 Hz, ^2J(H,H)=10.5 Hz, 1H, THP-6-CH^b), 3.40 (dd, ^3J(H,H)=4.2 Hz, ^2J(H,H)=9.9 Hz, 1H, 1-CH^b), 2.43 (s, 2H, 2xOH), 1.87-1.62 (m, 2H, THP-2-CH$_2$), 1.59-1.36 (m, 14H, THP-3-CH$_2$, THP-4-CH$_2$, 5xCH$_2$), 1.33-1.22 (m, 22H, 11xCH$_2$), 0.89 (s, 9H, C(*CH$_3$*)$_3$), 0.03 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=97.6 (THP-C-2), 76.9 (C-12), 72.4 (C-2), 66.9 (C-1), 63.5 (SiOCH$_2$), 62.8 (THP-C-6), 35.2 (CH$_2$), 33.6 (CH$_2$), 33.3 (CH$_2$), 33.0 (CH$_2$), 31.3 (THP-C-3), 30.0 (CH$_2$), 29.8 (2xCH$_2$), 29.7 (2xCH$_2$), 29.6 (2xCH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 26.1 (C(CH$_3$)$_3$), 25.9 (CH$_2$), 25.8 (THP-C-5), 25.7 (CH$_2$), 25.1 (CH$_2$), 20.1 (THP-C-4). 18.5 (SiC^q), -5.1 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=3362 (br), 2926 (m), 2854 (m), 1463 (w), 1440 (m), 1385 (w), 1360 (m), 1320 (w), 1254 (s), 1200 (s), 1183 (m), 1098 (s), 1076 (s), 1022 (m), 1004 (m), 937 (s), 907 (m), 866 (m), 834 (m), 812 (m), 774 (m), 731 (w), 665 (m) cm^{-1}.

(2*R*)-20-(*t*butyldimethylsilyloxy)-2-hydroxy-12-(tetrahydropyran-2'-yloxy)icoyl pivalate (140)
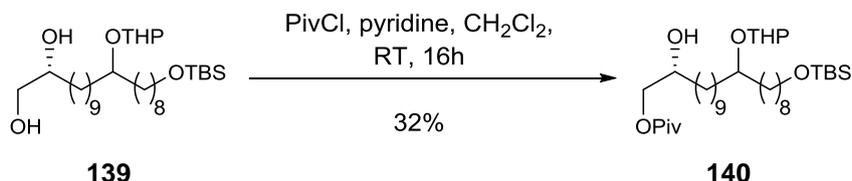
Scheme VI.54. Pivalate protection of the primary alcohol of diol **139**.

Diol **139** (760 mg, 1.395 mmol) was dissolved in 20 ml dry CH$_2$Cl$_2$. Pivaloyl chloride (180 µl, 1.464 mmol) and pyridine (282 µl, 3.487 mmol) were added. Stirring was maintained for 16 h. The starting material was completely consumed by that time. The reaction was

stopped by addition of sat. NH$_4$Cl solution. The crude product was extracted three times using Et$_2$O. The combined organic layers were washed with sat. CuSO$_4$ solution, water and brine. The washed layers were dried over Na$_2$SO$_4$ and all violatiles were removed *in vacuo*. The crude product was purified by flash chromatography (silica gel; 20% EtOAc in *c*-hexane) to yield **140** (279 mg, 32%) as a transparent oil.

R$_f$=0.85 (EtOAc/*c*-hexane 1:1);

^{1}H NMR (300 MHz, CDCl$_3$): δ=4.64 (t, ^3J(H,H)=3.5 Hz, 1H, THP-CH), 4.12 (dd, ^3J(H,H)=4.7 Hz, ^2J(H,H)=11.4 Hz, 1H, 1-CH^a), 3.97 (dd, ^3J(H,H)=7.0 Hz, ^2J(H,H)=11.4 Hz, 1H, 1-CH^b), 3.94-3.86 (m, 1H, 2-CH), 3.86-3.79 (m, 1H, THPO*C*H), 3.67 (dd, ^3J(H,H)=6.7 Hz, ^2J(H,H)=7.4 Hz, 1H, THP-6-CH^a), 3.62-3.55 (m, 1H, 12-CH), 3.59 (t, ^3J(H,H)=6.6 Hz, 2H, SiOCH$_2$), 3.46 (dt, ^3J(H,H)=4.5 Hz, ^2J(H,H)=11.0 Hz, 1H, THP-6-CH^b), 1.87-1.62 (m, 4H, THP-3-CH$_2$, THP-4-CH$_2$), 1.59-1.28 (m, 10H, THP-5-CH$_2$, 4xCH$_2$), 1.35-1.24 (m, 24H, 12xCH$_2$), 1.22 (s, 9H, C(*CH$_3$*)$_3$), 0.89 (s, 9H, SiC(*CH$_3$*)$_3$), 0.04 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=177.9 (CO), 97.8 (THP-C-2), 76.9 (C-12), 73.3 (C-1), 72.3 (C-2), 63.5 (SiOCH$_2$), 62.8 (THP-C-6), 38.6 (*t*BuC^q), 35.0 (CH$_2$), 33.4 (CH$_2$), 33.3 (CH$_2$), 33.0 (CH$_2$), 31.4 (THP-C-3), 30.1 (CH$_2$), 29.9 (2xCH$_2$), 29.7 (2xCH$_2$), 29.6 (2xCH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 27.1 (C(CH$_3$)$_3$) 26.1 (SiC(CH$_3$)$_3$), 25.9 (CH$_2$), 25.8 (THP-C-5), 25.7 (CH$_2$), 25.1 (CH$_2$), 20.1 (THP-C-4). 18.6 (SiC^q), -5.1 (Si(CH$_3$)$_2$).

(2*R*)-2-(benzyloxy)-20-(*t*butyldimethylsilyloxy)-12-(tetrahydropyran-2'-yloxy)icoyl pivalate (141)

Scheme VI.55. Benzyl protection of the pivaloate protected alcohol **140**.

Pivalate ester **140** (96 mg, 0.153 mmol) was dissolved in 3 ml dry DMF. Benzyl bromide (27 µl, 0.229 mmol), sodium hydride (12 mg, 0.305 mmol, 60% in mineral oil) and a catalytic amount of tetra-*n*butyl ammonium iodide (TBAI) were added. The resulting suspension was stirred for 2 h until tlc showed complete consumption of the starting material. The reaction was stopped with sat. NH$_4$Cl solution. The crude product was extracted three times using ethyl acetate. The combined organic layers were washed with water and brine. The washed layers were dried over Na$_2$SO$_4$ and all violatiles were removed *in vacuo*. The crude product

was purified by flash chromatography (silica gel; 5% EtOAc in *c*-hexane) to yield **140** (10 mg, 10%) as a transparent oil.

R_f=0.79 (EtOAc/*c*-hexane 1:3);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.38-7.27 (m, 5H, H$_{aromat.}$), 4.64 (t, [3]*J*(H,H)=3.5 Hz, 1H, THP-CH), 4.56 (s, 2H, PhCH$_2$), 4.13 (dt, [3]*J*(H,H)=3.2 Hz, [2]*J*(H,H)=11.4 Hz, 1H, 1-CH[a]), 3.97 (dt, [3]*J*(H,H)=7.0 Hz, [2]*J*(H,H)=11.4 Hz, 1H, 1-CH[b]), 3.94-3.86 (m, 1H, 2-CH), 3.86-3.77 (m, 1H, THP-6-CH[a]), 3.61-3.55 (m, 1H, 12-CH), 3.59 (t, [3]*J*(H,H)=6.6 Hz, 2H, SiOCH$_2$), 3.47 (dt, [3]*J*(H,H)=4.5 Hz, [2]*J*(H,H)=11.3 Hz, 1H, THP-6-CH[b]), 1.89-1.61 (m, 6H, THP-3-CH$_2$, THP-4-CH$_2$, CH$_2$), 1.59-1.38 (m, 12H, THP-5-CH$_2$, 5xCH$_2$), 1.32-1.24 (m, 22H, 11xCH$_2$), 1.22 (s, 9H, C(*CH$_3$*)$_3$), 0.89 (s, 9H, SiC(*CH$_3$*)$_3$), 0.04 (s, 6H, Si(*CH$_3$*)$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=177.9 (CO), 139.3 (C[ar]), 128.5 (CH[ar]), 128.4 (CH[ar]), 128.0 (CH[ar]), 127.7 (CH[ar]), 127.5 (CH[ar]), 97.8 (THP-C-2), 76.9 (C-12), 76.1 (C-2), 75.6 (BnCH$_2$), 70.3 (C-1), 63.5 (SiOCH$_2$), 62.8 (THP-C-6), 38.2 (*t*BuC[q]), 35.0 (CH$_2$), 33.4 (CH$_2$), 33.3 (CH$_2$), 33.0 (CH$_2$), 31.4 (THP-C-3), 30.0 (CH$_2$), 29.9 (2xCH$_2$), 29.7 (2xCH$_2$), 29.6 (2xCH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 27.0 (C(CH$_3$)$_3$) 26.1 (SiC(CH$_3$)$_3$), 25.8 (CH$_2$), 25.8 (THP-C-5), 25.7 (CH$_2$), 25.1 (CH$_2$), 20.1 (THP-C-4). 18.6 (SiC[q]), -5.1 (Si(CH$_3$)$_2$);

IR (thin film) ṽ=2928 (m), 2854 (m), 1463 (w), 1385 (w), 1361 (m), 1284 (m), 1254 (s), 1201 (s), 1161 (w), 1100 (s), 1078 (s), 1023 (m), 1004 (m), 836 (m), 775 (m), 699 (m), 665 (w) cm^{-1}.

(2*R*)-2-(benzyloxy)-20-(*t*butyldimethylsilyloxy)-12-(tetrahydropyran-2'-yloxy)icosan-1-ol (142)

Scheme VI.56. Benzyl protection of the alcohol **140** and direct hydrolysis of the pivaloate ester **141**.

Pivalate ester **140** (92 mg, 0.146 mmol) was dissolved in 3 ml dry DMF. Benzyl bromide (26 µl, 0.219 mmol), sodium hydride (18 mg, 0.439 mmol, 60% in mineral oil) and a catalytic amount of tetra-*n*butyl ammonium iodide (TBAI) were added. The resulting suspension was stirred for 24 h until tlc showed complete consumption of the starting material. Hydrolysis of the fully protected intermediate **141** was started by addition of water (53µl, 2.925 mmol). This suspension was stirred for additional 12 h. The reaction was stopped with sat. NH$_4$Cl solution. The crude product was extracted three times using ethyl acetate. The combined organic layers

were washed with water and brine. The washed layers were dried over Na_2SO_4 and all violatiles were removed *in vacuo*. The crude product was purified by flash chromatography (silica gel; 5% EtOAc in *c*-hexane) to yield **142** (12 mg, 13%) as a transparent oil.

R_f=0.76 (EtOAc/*c*-hexane 1:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ=7.39-7.27 (m, 5H, H[ar]), 4.64 (t, [3]J(H,H)=3.5 Hz, 1H, THP-CH), 4.56 (s, 2H, $PhCH_2$), 3.95-3.87 (m, 1H, 2-CH), 3.85-3.77 (m, 1H, THP-6-CH[a]), 3.64-3.54 (m, 1H, 12-CH), 3.59 (t, [3]J(H,H)=6.6 Hz, 2H, $SiOCH_2$), 3.51 (dd, [3]J(H,H)=3.0 Hz, [2]J(H,H)=9.4 Hz, 1H, 1-CH[a]), 3.47 (dt, [3]J(H,H)=4.5 Hz, [2]J(H,H)=11.3 Hz, 1H, THP-6-CH[b]), 3.32 (dd, [3]J(H,H)=8.0 Hz, [2]J(H,H)=9.4 Hz, 1H, 1-CH[b]), 1.88-1.65 (m, 4H, THP-3-CH_2, THP-4-CH_2), 1.59-1.38 (m, 12H, THP-5-CH_2, 5xCH_2), 1.35-1.19 (m, 24H, 21xCH_2), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$);

^{13}C NMR (75 MHz, $CDCl_3$): δ=138.2 (C[ar]), 128.6 (2xCH[ar]), 127.9 (CH[ar]), 127.9 (2xCH[ar]), 97.6 (THP-C-2), 76.9 (C-12), 74.8 ($PhCH_2$), 73.5 (C-1), 72.2 (C-2), 63.5 ($SiOCH_2$), 62.8 (THP-C-6), 37.7 (CH_2), 35.2 (CH_2), 33.3 (CH_2), 33.0 (CH_2), 31.4 (THP-C-3), 30.1 (CH_2), 29.8 (CH_2), 29.8 (2xCH_2), 29.7 (2xCH_2), 29.6 (CH_2), 29.5 (CH_2), 26.2 ($SiC(CH_3)_3$), 26.0 (CH_2), 25.8 (CH_2), 25.7 (THP-C-5), 25.7 (CH_2), 25.2 (CH_2), 20.1 (THP-C-4), 18.5 (SiC[q]), -5.1 ($Si(CH_3)_2$);

IR (thin film) ṽ=3453 (br), 2925 (m), 2853 (m), 1463 (w), 1454 (m), 1385 (w), 1361 (m), 1254 (s), 1200 (s), 1098 (s), 1077 (s), 1022 (m), 835 (m), 812 (w), 775 (m), 734 (w), 697 (m) cm^{-1}.

VI.5. Aurantoside G and J

VI.5.1. *O*-Glycosylation

(5*S*,6*S*)-4-(3',4',6'-tri-*O*-benzyl-2-*O*-acetyl)-5-*sec*butyl-1,5-dihydro-2*H*-pyrrol-2-one-*β*-D-glucopyranoside (157)
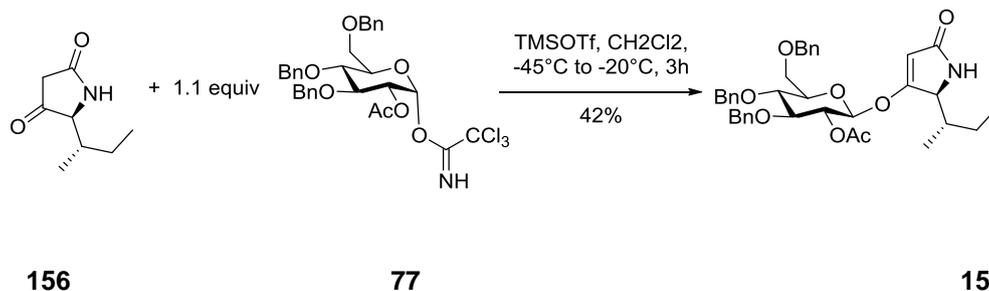
Scheme VI.57. Chemical 4-*O*-glycosylation of tetramic acid **156** derived from isoleucine with the Schmidt donor **77**.

Tetramic acid **156** (50 mg, 0.318 mmol) was dissolved in 6 ml dry DMF together with donor **77** (223 mg, 0.349 mmol) and 250 mg 4 Å molecular sieves. The suspension was cooled to -45 °C. TMSOTf (5.7 μl, 0.032 mmol) was added via syringe. The resulting suspension was stirred for 1 h at -45 °C and the warmed up to -20 °C. Stirring was maintained for additional 2 h until tlc analysis showed complete consumption of the donor. The reaction was stopped by the addition of NEt$_3$ (22 μl, 0.159 mmol). The crude product was filtrated over celite and the filter was washed thouroughly with CH$_2$Cl$_2$. All volatiles of the combined organic fractions were removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; 20% EtOAc in *c*-hexane) to yield **157** (84 mg, 42%) as a transparent oil.

R$_f$=0.38 (EtOAc/*c*-hexane 1:1);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.36-7.23 (m, 13H, H^{ar}), 7.22-7.17 (m, 2H, H^{ar}), 6.51 (d, ^4J(H,H)=4.9 Hz, 1H, NH), 5.20 (dd, ^3J(H,H)=8.1 Hz, 3.2 Hz, 1H, H'-2), 5.19 (dd, ^4J(H,H)=4.9 Hz, 3.3 Hz, 1H, 3-H), 4.89 (d, ^3J(H,H)=8.1 Hz, 1H, 1'-H), 4.81 (d, ^2J(H,H)=11.6 Hz, 1H, 4'O-CH^a), 4.79 (d, ^2J(H,H)=10.9 Hz, 1H, 6'O-CH^a), 4.68 (d, ^2J(H,H)=11.6 Hz, 1H, 4'O-CH^b), 4.60 (d, ^2J(H,H)=10.9 Hz, 1H, 6'O-CH^b), 4.59 (d, ^2J(H,H)=12.2 Hz, 1H, 3'O-CH^a), 4.51 (d, ^2J(H,H)=12.2 Hz, 1H, 3'O-CH^b), 4.01 (dd, ^4J(H,H)=3.3 Hz, 1H, 5-H), 3.83 (dd, ^3J(H,H)=9.6 Hz, 5.4 Hz, 1H, 4'-H), 3.72 (m, 1H, 6'-H), 3.71 (dd, ^3J(H,H)=5.4 Hz, 3.2 Hz, 1H, H'-3), 3.56 (ddd, ^3J(H,H)=9.6 Hz, 4.7 Hz, 3.0 Hz, 1H, H'-5), 1.95 (s, 3H, CH$_3$CO), 1.88-1.73 (m, 1H, H-6), 1.41 (ddq, ^3J(H,H)=7.4 Hz, 5.2 Hz,

^4J(H,H)=13.1 Hz, 1H, H-7^a), 1.20 (ddq, ^3J(H,H)=7.4 Hz, 5.9 Hz, ^4J(H,H)=13.1 Hz, 1H, H-7^b), 0.95 (d, ^3J(H,H)=6.9 Hz, 3H, H-9), 0.86 (t, ^3J(H,H)=7.4 Hz, 3H, H-8);

^{13}C NMR (75 MHz, CDCl$_3$): δ=174.2 (C-2), 173.8 (C-4), 169.3 (CH$_3$CO), 128.6 (3xCH^{ar}), 128.5 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.0 (CH^{ar}), 127.9 (CH^{ar}), 127.9 (2xCH^{ar}), 127.8 (2xCH^{ar}), 127.8 (2xCH^{ar}), 99.3 (C-3), 98.5 (C-1'), 82.5 (C-3'), 77.4 (C-4'), 76.0 (C-5'), 75.1 (6'-OCH$_2$), 75.0 (4'O-CH$_2$), 73.4 (3'-OCH$_2$), 72.2 (C-2'), 68.00 (C-6'), 62.3 (C-5), 36.4 (C-6), 23.2 (C-7), 20.9 (CH$_3$CO), 15.3 (C-9), 11.9 (C-8).

VI.5.2. *N*-Glycosylation

BF$_2$-complex of (5S,6S)-N-(3',4',6'-tri-O-benzyl-2-O-acetyl)-5-*sec*butyl-3-(2''E-octenyl)pyrrolidine-2,4-dione-$β$-D-glucopyranoside (161)

160   **161**
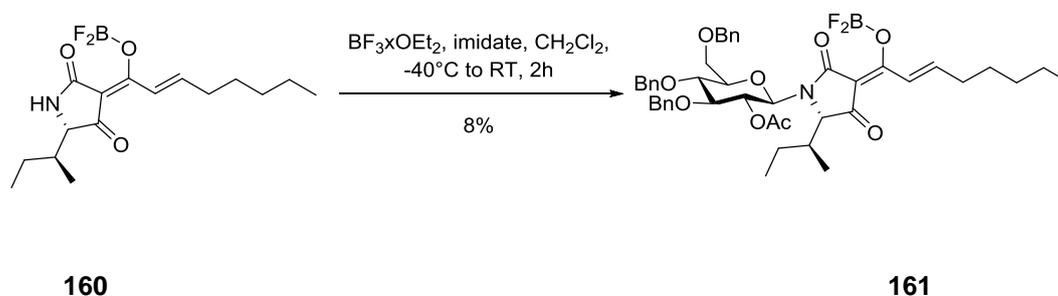
Scheme VI.58. *N*-Glycosylation of 3-acyl tetramic acid BF$_2$-complex **160**.

The known$^{[32,34,109]}$ difluoroboryl complex **160** (55 mg, 0.169 mmol) and imidate **77** (118 mg, 0.185 mmol) were dissolved in 3.5 ml dry CH$_2$Cl$_2$ containing 150 mg 4 Å molecular sieves. The resulting mixture was cooled to -40 °C. BF$_3$•OEt$_2$ (3 μl, 0.025 mmol) was added via syringe. The reaction was stirred for 2 h maintaining -40 °C. Tlc analysis showed complete consumption of the donor by that time. All volatiles were removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; 20% EtOAc in *c*-hexane) to yield **161** (11 mg, 8%) as a slightly yellow oil.

R$_f$=0.23 (EtOAc/*c*-hexane 1:4);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.54 (dt, ^4J(H,H)=15.5 Hz, ^3J(H,H)=7.1 Hz, 1H, 11-H), 7.37-7.25 (m, 13H, H^{ar}), 7.19-7.13 (m, 2H, H^{ar}), 7.05 (dt, ^3J(H,H)=7.1 Hz, 6.7 Hz, 1H, 12-H), 6.35 (d, ^3J(H,H)=3.6 Hz, 1H, 1'-H), 4.99 (dd, ^3J(H,H)=9.5 Hz, 1.6 Hz, 1H, 3'-H), 4.85-4.48 (m, 6H, 3xOCH$_2$Ph), 4.02 (d, ^3J(H,H)=3.1 Hz, 1H, 5-H), 3.81 (dd, ^3J(H,H)=9.6 Hz, 3.6, 1H, 2'-H), 3.77-3.72 (m, 1H, 5'-H), 3.65-3.59 (m, 1H, 4'-H), 3.42 (dd, ^3J(H,H)=3.7 Hz, 1.9 Hz, ^2J(H,H)=9.7 Hz, 1H, 6'-CH^a), 3.39 (dd, ^3J(H,H)=3.6 Hz, 1.9 Hz, ^2J(H,H)=9.7 Hz, 1H, 6'-CH^b), 2.36 (ddt, ^4J(H,H)=15.5 Hz, ^3J(H,H)=7.2 Hz, 6.7 Hz, 1H, 13-H), 2.03 (s, 3H,

CH₃CO), 2.01 (m, 1H, 6-H), 1.51 (pt, ^3J(H,H)=7.2 Hz, 1H, 14-H), 1.36-1.27 (m, 4H, 15-H, 16-H), 1.03 (d, ^3J(H,H)=7.0 Hz, 2H, 7-H), 0.90-0.85 (m, 6H, 8-H, 17-H), 0.82 (d, ^3J(H,H)=6.8 Hz, 3H, 9-H);

^{13}C NMR (75 MHz, CDCl₃): δ=190.7 (C-4), 174.2 (C-10), 171.2 (CO), 169.0 (C-2), 156.8 (C-11), 137.8 (3xC^{ar}), 128.6 (CH^{ar}), 128.6 (4xCH₂), 128.1 (2xCH^{ar}), 128.1 (2xCH^{ar}), 128.0 (CH^{ar}), 128.0 (2xCH^{ar}), 127.9 (CH^{ar}), 127.8 (CH^{ar}), 127.8 (CH^{ar}), 121.1 (C-12), 110.2 (C-3), 91.2 (C-1'), 82.7 (C-4'), 78.8 (C-2'), 74.9 (C-5', OCH₂), 73.4 (OCH₂), 73.0 (CH₂), 72.8 (C-3'), 72.2 (C-6'), 67.8 (C-5), 35.4 (C-6), 33.5 (C-13), 31.5 (CH₂), 27.5 (C-14), 22.2 (CH₂), 20.7 (CH₃CO), 15.4 (C-7), 14.0 (C-17), 12.8 (C-9), 11.8 (C-8);

^{11}B NMR (75 MHz, CDCl₃): δ=-2.47.

N-Nosyl-N-(2',3',4',6'-tetra-O-acetyl)-L-alanine methyl ester D-glucopyranoside (163)
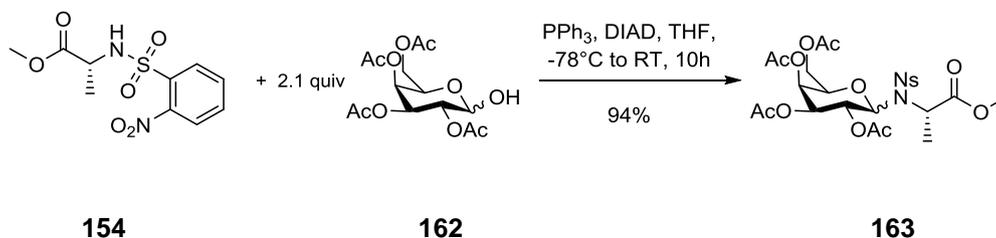
Scheme VI.59. *N*-Glycosylation via Fukayama-Mitsunobu reaction of acetylated galactose[288,293] **162** and *N*-nosyl protected *L*-alanine[290,292] **154**.

Peracetylated anomeric free galactose[288,293] **162** (90 mg, 0.336 mmol), nosyl protected alanine methyl ester[290,292] **154** (59 mg, 0.158 mmol) and PPh₃ (88 mg, 0.336 mmol) were dissolved in 3.5 ml dry THF. The resulting mixture was cooled to -78 °C. Diisopropyl azodicarboxylate (66 μl, 0.336 mmol) was added via syringe. The reaction was stirred for 1 h maintaining -78 °C and then allowed to react over 8 h at RT. All volatiles were removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; 30% EtOAc in *c*-hexane) to yield **163** (92 mg, 94%) as a white solid.

R$_f$=0.04 (EtOAc/*c*-hexane 1:2);

^{1}H NMR (300 MHz, CDCl₃): δ=8.21-8.13 (m, 2H, H^{ar}), 7.76-7.59 (m, 6H, H^{ar}), 5.39 (d, ^3J(H,H)=3.3 Hz, 1H, 1'-H^α), 5.36 (d, ^3J(H,H)=8.0 Hz, 1H, 1'-H^β), 5.29 (dd, ^3J(H,H)=9.4 Hz, 4.9 Hz, 2H, 3'-H), 5.16 (m, 2H, 5'-H), 5.05 (ddd, ^3J(H,H)=9.4 Hz, 8.0 Hz 3.2 Hz, 2H, 2'-H), 4.52 (q, ^3J(H,H)=7.4 Hz, 1H, 1-H^α), 4.29 (q, ^3J(H,H)=7.4 Hz, 1H, 1-H^β), 4.04 (m, 6H, 4'-H, 6'-H), 3.59 (s, 3H, OCH₃^α), 3.48 (s, 3H, OCH₃^β), 2.00 (s, 6H, CH₃CO), 1.97 (s, 6H, CH₃CO), 1.94 (s, 6H, CH₃CO), 1.92 (s, 6H, CH₃CO), 1.59 (d, ^3J(H,H)=7.4 Hz, 3H, 4-H^α), 1.59 (d, ^3J(H,H)=7.4 Hz, 3H, 4-H^β).

N-Nosyl-*N*-(2',3',4'-tri-*O*-acetyl)-*L*-alanine methyl ester *β*-*D*-xylopyranose (165)
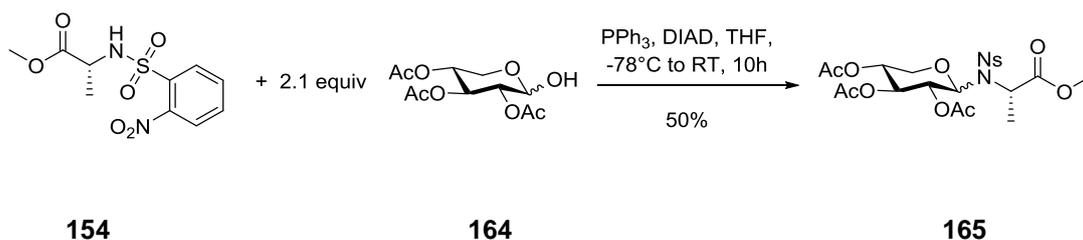
Scheme VI.60. *N*-Glycosylation via Fukayama-Mitsunobu reaction of acetylated xylose[294] **164** and *N*-nosyl protected *L*-alanine[290,292] **154**.

Peracetylated anomeric free xylose[294] **164** (488 mg, 1.767 mmol), nosyl protected alanine methyl ester[290,292] **154** (239 mg, 0.829 mmol) and PPh$_3$ (463 mg, 1.767 mmol) were dissolved in 20 ml dry THF. The resulting mixture was cooled to -78 °C. Diisopropyl azodicarboxylate (350 μl, 1.767 mmol) was added via syringe. The reaction was stirred for 1 h maintaining -78 °C and then allowed to react over 8 h at RT. All volatiles were removed under reduced pressure and the crude product was purified by flash chromatography (silica gel; 25% EtOAc in *c*-hexane) to yield **165** (223 mg, 50%) as a white solid.

R$_f$=0.26 (EtOAc/*c*-hexane 1:1);

Only the major *β*-anomer is described below:

^{1}H NMR (300 MHz, CDCl$_3$): δ=8.06-8.00 (m, 1H, H^{ar}), 7.66-7.49 (m, 3H, H^{ar}), 5.16 (dd, ^3J(H,H)=9.3 Hz, 9.2 Hz, 1H, 2'-H), 5.09 (pt, ^3J(H,H)=9.2 Hz, 1H, 3'-H), 4.96 (d, ^3J(H,H)=9.3 Hz, 1H, 1'-H), 4.87 (ddd, ^3J(H,H)=10.4 Hz, 5.8 Hz, 1.3 Hz, 1H, 4'-H), 4.41 (q, ^3J(H,H)=7.4 Hz, 1H, 1-H), 3.98 (dd, ^3J(H,H)=11.1 Hz, 5.8 Hz, 1H, 5'-CH^a), 3.38 (s, 3H, OCH$_3$), 3.27 (dd, ^3J(H,H)=11.1 Hz, 1.3 Hz, 1H, 5'-CH^b), 1.89 (s, 3H, CH$_3$CO), 1.87 (s, 3H, CH$_3$CO), 1.76 (s, 3H, CH$_3$CO), 1.45 (d, ^3J(H,H)=7.4 Hz, 3H, 4-H);

^{13}C NMR (75 MHz, CDCl$_3$): δ=170.6 (CO), 169.6 (CO), 169.1 (CO), 148.4 (C^{ar}NO$_2$), 134.0 (CH), 133.1 (C^{ar}), 131.5 (CH^{ar}), 131.1 (CH^{ar}), 123.8 (CH^{ar}), 85.5 (C-1'), 73.4 (C-3'), 69.1 (C-2'), 68.2 (C-4'), 64.8 (C-5'), 54.4 (C-1), 52.2 (OCH$_3$), 20.3 (2xCH$_3$CO), 20.3 (CH$_3$CO), 17.8 (C-4);

IR (thin film) ṽ=1740 (s), 1546 (s), 1439 (w), 1365 (s), 1246 (s), 1215 (s), 1169 (s), 1085 (s), 1036 (s), 989 (m), 940 (m), 909 (w), 853 (m), 770 (m), 742 (m), 729 (m), 689 (w), 655 (m) cm^{-1}.

VI.6. Tetramic acid boron complexes

Diethylboron complex of (5*S*)-3-((2′*E*)-1′-hydroxy-2′-methylocten-1′-ylidene)-1,5-dimethylpyrrolidine-2,4-dione (167)
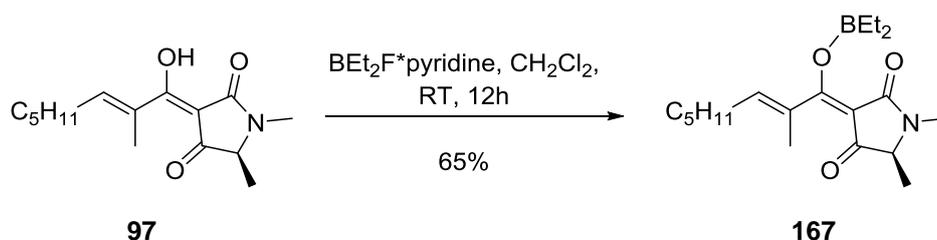
Scheme VI.61. Diethylboron complex formation of **97** by a known[32] method using BEt$_2$F•pyridine[296] to get **167**.

The 3-acyl tetramic acid used for auxiliary synthesis **97** (37 mg, 0.139 mmol) was dissolved in 2.8 ml dry CH$_2$Cl$_2$. Analogously to the normal[32] BF$_2$ complex formation, BEt$_2$F•pyridine from Wrackmeyer *et al.*[296] (117 mg, 0.697 mmol) was added at RT. The resulting mixture was stirred for at least 12 h. All volatiles were removed under reduced pressure. The crude material was purified utilizing column chromatography (silica gel; 15% EtOAc in *c*-hexane) to yield **167** (30 mg, 65%) as a slightly red oil.

R$_f$=0.63 (EtOAc/*c*-hexane 1:2);

$[\alpha]_D^{24}$ = 25.5 (c=1.0, CHCl$_3$);

^{1}H NMR (300 MHz, CDCl$_3$): δ=7.30 (tq, ^4J(H,H)=1.3 Hz, ^3J(H,H)=7.3 Hz, 1H, 8-H), 3.74 (q, ^3J(H,H)=7.0 Hz, 1H, 5-H), 3.06 (s, 3H, NCH$_3$), 2.29 (dq, ^3J(H,H)=7.3 Hz, 1.3 Hz, 2H, 9-H), 1.85 (d, ^4J(H,H)=1.3 Hz, 3H, 7-CH$_3$), 1.52 (m, 2H, CH$_2$), 1.40 (d, ^3J(H,H)=7.0, 3H, 5-CH$_3$), 1.33 (m, 4H, 2×CH$_2$), 0.89 (m, 3H, CH$_3$), 0.74 (t, ^3J(H,H)=7.8 Hz, 6H, BCH$_2$*CH$_3$*), 0.40 (q, ^3J(H,H)=7.8 Hz, 4H, BCH$_2$);

IR (thin film) ṽ=2954 (w), 2930 (m), 2860 (w), 1710 (m), 1651 (s), 1611 (s), 1488 (m), 1451 (m), 1396 (w), 1381 (w), 1342 (w), 1312 (w), 1264 (w), 1228 (m), 1092 (m), 927 (s), 798 (w) cm^{-1}.

Diethylboron complex of (5*S*)-3-(-1′-hydroxymethyloctan-1′-ylidene)-1,5-dimethylpyrrolidine-2,4-dione (168)
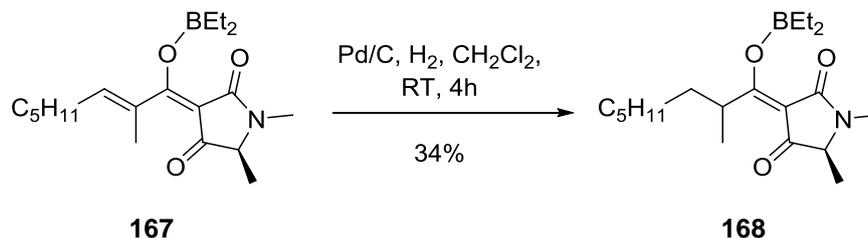
Scheme VI.62. Hydrogenation of the diethylboron complex **168**.

The diethylboron complex of **97** (30 mg, 0.090 mmol) was dissolved in 1 ml dry CH_2Cl_2. A catalytic amount of palladium on charcoal was added. Hydrogenation was carried at RT using H_2 gas at standard pressure of 1 bar for 4 h. The catalyst was filtered off and the filter was washed thouroughly with CH_2Cl_2. The solvent was removed under reduced pressure. The crude material was purified utilizing column chromatography (silica gel; 15% EtOAc in *c*-hexane) to yield **167** (10 mg, 34%) as a slightly red oil.

R_f=0.64 (EtOAc/*c*-hexane 1:2);

$[\alpha]_D^{24}$ = 37.2 (c=1.0, CHCl$_3$);

^{1}H NMR (300 MHz, CDCl$_3$): δ=3.74 (q, ^3J(H,H)=7.1 Hz, 1H; 7-H), 3.50 (q, ^3J(H,H)=7.2 Hz, 1H; 5-H), 3.04 (s, 3H; NCH$_3$), 1.67 (m, 2H, CH$_2$), 1.40 (d, ^3J(H,H)=7.1 Hz, 3H; 7-CH$_3$), 1.31-1.20 (m, 8H; 4×CH$_2$), 1.13 (d, ^3J(H,H)=7.2 Hz, 3H; 5-CH$_3$), 0.86 (m, 3H; CH$_3$), 0.73 (t, ^3J(H,H)=7.8 Hz, 6H, BCH$_2$*CH$_3$*), 0.39 (q, ^3J(H,H)=7.8 Hz, 4H, BCH$_2$);

^{13}C NMR (75 MHz, CDCl$_3$): δ=192.1 (C-4), 189.9 (C-6), 170.6 (C-2), 98.0 (C-3), 65.0 (C-5), 37.5 (NMe), 33.6 (C-8), 31.7 (C-11), 29.2 (C-9), 28.1 (C-7), 27.2 (C-10), 22.7 (C-12), 16.8 (5-CH$_3$), 14.2 (7-CH$_3$), 14.4 (2xBCH$_2$), 14.2 (CH$_3$), 7.6 (2xBCH$_2$*CH$_3$*);

IR (thin film) $\tilde{v}$=2947 (w), 2930 (m), 2869 (w), 1706 (m), 1629 (s), 1533 (s), 1459 (m), 1410 (w), 1372 (w), 1356 (w), 1298 (w), 1273 (w), 1239 (w), 1094 (w), 1060 (m), 938 (m), 866 (m), 795 (w) cm^{-1}.

VII. ABBREVIATIONS

Ac$_2$O	acetic anhydride
AIP	autoinducer peptide
approx.	approximately
ar	aromatic
ATP	adenosine triphosphate
BAIB	(diacetoxyiodo)benzene
Bn	benzyl
BnBr	benzyl bromide
BnOH	benzyl
BOC	*t*butoxycarbonyl
br	IR: broad
Bz	benzoyl
BzCl	benzoyl chloride
CAN	cer ammonium molybdate
cat.	catalytic
CCO	ketenylidentriphenylphosphorane
d	days
d	NMR: doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCC	N,N'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisopropylaluminium hydride, DIBAL-H
DMAP	4-dimethylaminopyridin
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
e.g.	example given
epox.	epoxidation

equiv	equivalence
ESA	european space agency
et al.	*et alii/et aliae*, and others
g	grams
glcos.	glycosylation
h	hours
HMDS	hexamethyldisilazane
HPLC	high pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons (reaction)
LDA	lithium diisopropyl amide
M	molar
m	IR: medium
m	NMR: multiplet
Mal-CoA	malonyl coenzyme A
MeMal-CoA	methylmalonyl coenzyme A
Min	minutes
MS	mass spectrometer
MMP	matrix metalloproteinases
NADH	nicotinamide adenine dinucleotide
NMDA	*N*-methyl-*D*-aspartic acid
NTP	nucleotide triphosphate
p	NMR: pseudo
PDC	pyridinium dichromate
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*toluenesulfonate
pyr	pyridine
q	NMR: quartet
Q-TOF	quadrupole time of flight
quant.	quantitative
qui	NMR: quintet
RT	room temperature
s	IR: strong
s	NMR: singulet
SAR	structure-activity relationship

t	time
t	NMR: triplet
TBAI	tetra-*n*butylammonium iodide
TBSCl	*t*butyldimethylsilyl chloride
TEMPO	(2,2,6,6-teramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPSCl	tri-*iso*propylsilyl chloride
TMSCl	trimethylsilyl chloride
TMSE	trimethylsilylethane
TrtCl	triphenylmethyl chloride, trityl chloride
TLC	thin layer chromatography
p-TsOH	*p*toluenesulfonic acid
UDP	uridine diphosphate
UPLC	ultra high pressure liquid chromatography
UTP	uridine triphosphate
v/v	volume by volume
vs.	versus
w	IR: weak
w/v	weight per volume
wt%	weight percent

VIII. LITERATURE

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IX. ACKNOWLEDGEMENTS

X. ABSTRACT (GERMAN VERSION)

Die Untersuchung eines synthetischen Zugangs zu natürlich vorkommenden Glycoconjugaten von 3-acylierten Tetramsäuren stand im Mittelpunkt dieser Arbeit. Der aus einem Pilz stammende Sekundärmetabolit Epicoccamid D (siehe Figure X.1.) wurde erstmals mit einer Gesamtausbeute von 17% über 19 Stufen synthetisiert. Die gezeigte Synthese hat einen modularen Charakter der es erlaubt, Teile der Totalsynthese auf andere ähnliche Naturstoffe zu übertragen und damit zugänglich zu machen.
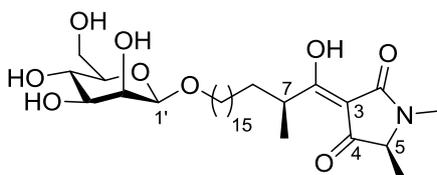
Figure X.1. Epicoccamid D. Die Abbildung zeigt die im Rahmen dieser Arbeit ermittelte absolute Konfiguration 5*S*,7*S* von Epicoccamid D.

Die Schlüsselschritte der Synthese beinhalteten eine β-selektive Glycosylierung gefolgt von einer Epimerisierung am C-2 des Zuckers, eine HWE-Olefinierung, eine Aminolyse um die Aminosäure *L*-Alanin einzuführen und eine Lacey-Dieckman Zyklisierung. Das 7*S* Stereozentrum wurde durch die Verwendung eines Rhodium basierten homogenen Katalysators sowie einer Hochduck-Hydrierung aufgebaut. Um eine Chelatisierung von Metallionen, wie beispielsweise des verwendeten Katalysators, zu unterbinden wurde die Tetramsäure als stabiler BF_2-Komplex verwendet. Da dieser synthetische Ansatz den Zugriff auf alle vier möglichen Isomere erlaubt war es möglich, die absolute Konfiguration des Naturstoffs durch Vergleich der NMR-Daten und des optischen Drehwertes zu bestimmen.

Der retrosynthetische Ansatz der Epicoccamid Totalsynthese wurde erneut angewendet um die Synthese weiterer Seitenketten von natürlich vorkommenden, glykosylierten und 3-acylierten Tetramsäuren zu ermöglichen. Ein Bespiel hierfür ist die erfolgreiche Synthese der Seitenketten von Ancorinosid B (siehe Figure X.2. A). Die Seitenkette dieses Naturstoffs ist aus einer C_{20} Alkylkette und einem Disaccharid bestehend aus Galactose und Glucuronsäure aufgebaut. Diese Seitenkette wurde erfolgreich mit Hilfe zweier aufeinanderfolgender sowie β-selektiver Glycosylierungen und einer Oxidation sowie gleichzeitiger Schützung des C-6 der Glucose synthetisiert.
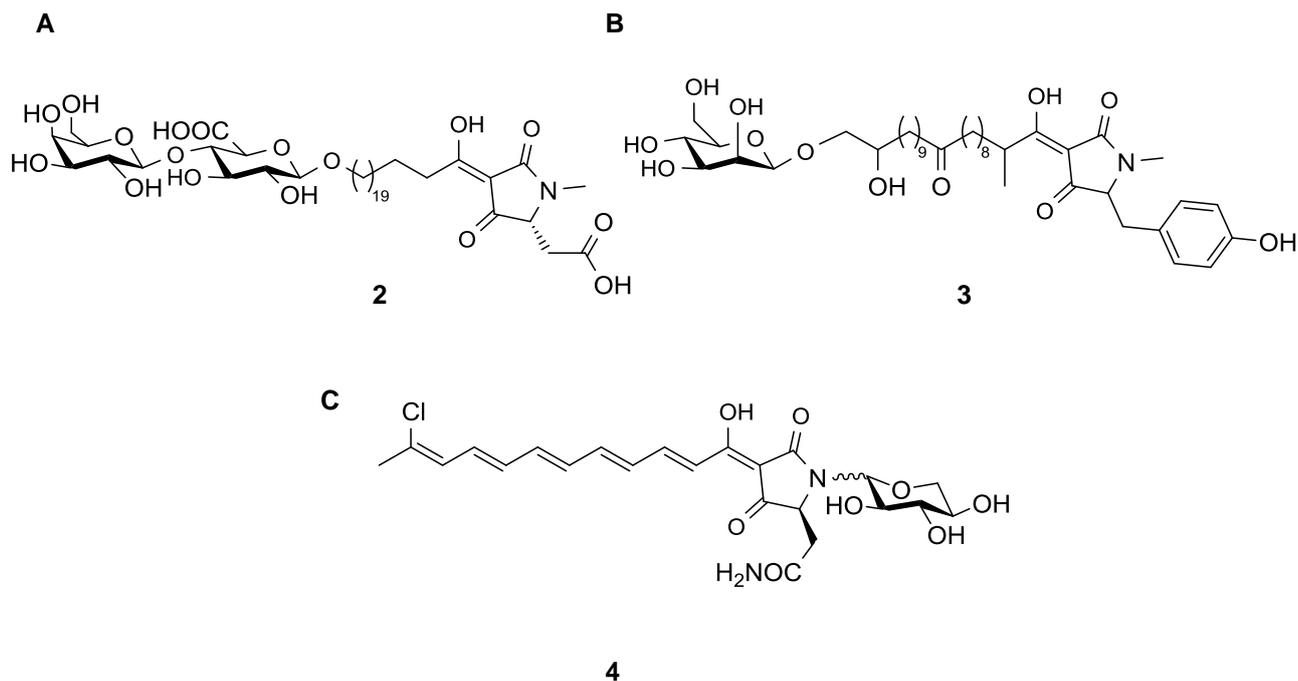
Figure X.2. Natürlich vorkommende 3-acylierte Glycoconjugate von Tetramsäuren: A) Ancorinosid B; B) Virgineon; C) die beiden aurantoside G und J.

Weiterhin wurde eine mehrfach substituierte Seitenkette für die Synthese von Virgineon (siehe Figure X.2. B) hergestellt. Diese Seitenkette muss ähnlich der Epicoccamid D Totalsynthese noch an einen Mannoserest gekoppelt und die *β*-konfigurierte glycosidische Bindung realisiert werden. Die Synthese dieser Seitenkette beinhaltete neben einer Ozonolyse auch eine Grignard-Reaktion.

Mit den dargestellten Seitenketten sollte die Synthese der beiden Naturstoffe Ancorinosid B und Virgineon mit Hilfe des für Epicoccamid D entwickelten Protokolls möglich sein, da alle zusätzlichen und neuen Schritte in Bezug auf die Totalsynthese dieser Verbindungen in dieser Arbeit untersucht wurden.

Zusätzlich wurde eine Vorschrift zur chemischen *N*-Glykosylierung etabliert um einen Zugang zur Stoffklasse der Aurantoside (siehe Figure X.2. C) zu erhalten. Diese *N*-Glykosylierung wurde mit Hilfe einer Fukayama-Mitsunobu-Reaktion erfolgreich bewerkstelligt. Hierbei wurde ebenfalls das Verhalten von Tetramsäuren, 3-acylierten Tetramsäuren und ihren Borkomplexen bei Lewis-sauren Bedingungen zur Glykosylierung untersucht.

Als Letzter Abschnitt dieser Arbeit wurde die Stereoinduktion der oben erwähnten, synthetisch wertvollen BF_2-chelat Komplexe analysiert und ihr Verhalten in einer heterogenen Hydrierung genauer untersucht. Für diesen Zweck wurde ein Diethylborkomplex einer Tetramsäure synthetisiert.

XI. EIDESSTATTLICHE VERSICHERUNG/ERKLÄRUNG

(§ 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.

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Hiermit erkläre ich eidesstattlich, dass ich die Dissertation selbständig verfasst und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt habe.

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Bayreuth, den 04.08.2015   _____
                                                    (Sebastian Loscher)